



Evergreen Perinatal Education
WHERE EXCELLENCE IN HEALTHCARE BEGINS

OUTCOMES OF BREASTFEEDING VERSUS FORMULA FEEDING

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Note to Readers

The original credit for this document goes to Jon Ahrendsen, MD, FAAFP who organized this material in a document called "Advantages of Breastfeeding." He was kind enough to share his work freely, and allowed me to update and publish it on the internet.

Evergreen Perinatal Education (EPE) now maintains this bibliography with abstracts. The articles are chosen from a PubMed monthly search for research or review articles comparing human milk to other food or drinks for infants. We update and publish it regularly. The purpose is to provide evidence-based information about the outcome differences between breastfeeding and formula-feeding, and their related impacts on maternal and child health.

We hope you find this comprehensive resource of great use in your everyday practice.
Ginna Wall, MN, IBCLC.

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Effects on the Infant

INFECTION

Candidiasis

Kadir, T., Uygun, B., & Akyüz, S. (2005). Prevalence of *Candida* species in Turkish children: relationship between dietary intake and carriage. *Archives of oral Biology*, 50(1), 33-37.

In this study, the prevalence and intensity of *Candida* species were evaluated in 300 healthy Turkish children aged between 0 and 12 years. Oral samples were cultured for fungal growth and *Candida* species. The results demonstrated that the prevalence of oral candidal carriage in 300 healthy children was 26.3%. *Candida albicans* was the most frequently isolated yeast (84.8% of the isolates). The other yeasts were identified as *Candida parapsilosis*, *Candida krusei*, *Candida kefyr*, *Candida famata*, and *Candida tropicalis*. It was also observed that the frequency of carriage varied as a function of age. The prevalence of carriage in children who were fed with both breast milk and bottle milk or other fluids was 18.5%, while in children fed only with breast milk was 0%. This finding supports previously reported observations that there may be intrinsic differences in oral carriage of *Candida* species between different ages and populations and type of dietary intake may affect frequency of carriage.

Diarrhea

Rebelo, F. M., & Caldas, E. D. (2016). Arsenic, lead, mercury and cadmium: Toxicity, levels in breast milk and the risks for breastfed infants. *Environmental research*, 151, 671-688.

At 12 months postpartum, women (n = 813; 62% response) completed a questionnaire that assessed sociodemographics, infant occurrence of otitis media and diarrhea, and the timing of starting/stopping feeding at the breast, expressed milk, and formula. Women who intended to “bottle feed” exclusively were not recruited. Logistic and negative binomial regressions were conducted in the full sample (n = 491) and no-formula (n = 106) and bottle-only (n = 49) subsamples. Longer duration of expressed milk feeding was associated with increased odds of experiencing otitis media (6-month OR [OR_{6-month}] 2.15, 95% CI 1.01-4.55) in the no-formula subsample. Longer durations of breast milk feeding (OR_{6-month} 0.70, 95% CI 0.54-0.92; 6-month incidence rate ratio [IRR_{6-month}] 0.74, 95% CI 0.63-0.91), and feeding at the breast (OR_{6-month} 0.70, 95% CI 0.54-0.89; IRR_{6-month} 0.74, 95% CI 0.63-0.88) were associated with less diarrhea, and longer formula feeding duration was associated with increased risk of diarrhea (IRR_{6-month} 1.34, 95% CI 1.13-1.54) in the full sample. Substance fed and mode of breast milk delivery have different contributions to infant health depending on the health outcome of interest. Feeding at the breast may be advantageous compared with expressed milk feeding for reducing the risk of otitis media, and breast milk feeding compared with formula may reduce the risk of diarrhea.

Hanieh, S., Ha, T. T., Simpson, J. A., Thuy, T. T., Khuong, N. C., Thoang, D. D., ... & Biggs, B. A. (2015). Exclusive breast feeding in early infancy reduces the risk of inpatient admission for

diarrhea and suspected pneumonia in rural Vietnam: a prospective cohort study. *BMC public health*, 15(1), 1166.

A prospective cohort study of 1049 infants, born to women who had previously participated in a cluster randomized controlled trial of antenatal micronutrient supplementation in rural Vietnam, was undertaken between 28th September 2010 and 8th Jan 2012. Infants were followed until 6 months of age, and the outcome measure was inpatient admission for suspected pneumonia or diarrheal illness during the first 6 months of life. Risk factors were assessed using univariable logistic regression and multiple logistic regression. Of the 1049 infants seen at 6 months of age, 8.8 % required inpatient admission for suspected pneumonia and 4 % of infants required inpatient admission for diarrheal illness. One third of infants (32.8 %) were exclusively breastfed at 6 weeks of age. Exclusive breastfeeding at 6 weeks of age significantly reduced the odds of inpatient admission for suspected pneumonia (Odds Ratio (OR) 0.39, 95 % Confidence Interval (CI) 0.20 to 0.75) and diarrheal illness (OR 0.37, 95 % CI 0.15 to 0.88). Exclusive breast feeding in early infancy reduces the risk of severe illness from diarrhea and suspected pneumonia. Public health programs to reduce the burden of inpatient admission from diarrheal and respiratory illness in rural Vietnam should address barriers to exclusive breastfeeding.

Turin, C. G., & Ochoa, T. J. (2014). The role of maternal breast milk in preventing infantile diarrhea in the developing world. *Current tropical medicine reports*, 1(2), 97-105.

Multiple interventions have been designed to decrease mortality and disability in children. Among these, breastfeeding is the most cost-effective intervention for protecting children against diarrhea and all causes of mortality. Human milk is uniquely suited to the human infant, both in its nutritional composition and in the non-nutritive bioactive factors that promote survival and healthy development. Suboptimal breastfeeding has been linked with numerous adverse child health outcomes including increased incidence of diarrhea and pneumonia. This review provides an update regarding recent studies on the effect of breastfeeding on diarrhea morbidity and mortality in children in developing countries, describes major human milk components responsible for this protective effect (oligosaccharides, secretory immunoglobulins, lactoferrin, bacterial microbiota, etc.), and highlights areas for future research in this topic. Breastfeeding promotion remains an intervention of enormous public health potential to decrease global mortality and promote better growth and neurodevelopment in children.

Coppa, G. V., Zampini, L., Galeazzi, T., Facinelli, B., Ferrante, L., Capretti, R., & Orazio, G. (2006). Human milk oligosaccharides inhibit the adhesion to Caco-2 cells of diarrheal pathogens: *Escherichia coli*, *Vibrio cholerae*, and *Salmonella typhi*. *Pediatric Research*, 59(3), 377.

Breast-fed children, compared with the bottle-fed ones, have a lower incidence of acute gastroenteritis due to the presence of several anti-infective factors in human milk. The aim of this work is to study the ability of human milk oligosaccharides to prevent infections related to some common pathogenic bacteria. Oligosaccharides of human milk were fractionated by gel filtration and characterized by thin-layer chromatography and high-performance anion exchange chromatography. Fractions obtained contained, respectively, 1) acidic oligosaccharides, 2) neutral high-molecular-weight oligosaccharides, and 3) neutral low-molecular-weight oligosaccharides. Experiments were carried out to study the ability of oligosaccharides in

inhibiting the adhesion of three intestinal microorganisms (enteropathogenic *Escherichia coli* serotype O119, *Vibrio cholerae*, and *Salmonella typhi*) to differentiated Caco-2 cells. The study showed that the acidic fraction had an antiadhesive effect on the all three pathogenic strains studied (with different degrees of inhibition). The neutral high-molecular-weight fraction significantly inhibited the adhesion of *E. coli* O119 and *V. cholerae*, but not that of *S. typhi*; the neutral low-molecular-weight fraction was effective toward *E. coli* O119 and *S. typhi* but not *V. cholerae*. Our results demonstrate that human milk oligosaccharides inhibit the adhesion to epithelial cells not only of common pathogens like *E. coli* but also for the first time of other aggressive bacteria as *V. cholerae* and *S. typhi*. Consequently, oligosaccharides are one of the important defensive factors contained in human milk against acute diarrheal infections of breast-fed infants.

Quigley, M. A., Cumberland, P., Cowden, J. M., & Rodrigues, L. C. (2006). How protective is breast feeding against diarrheal disease in infants in 1990s England? A case-control study. *Archives of disease in childhood*, 91(3), 245-250.

Case-control study of diarrheal disease cases presenting to 34 general practices in England. Data were available on 304 infants (167 cases and 137 controls). After adjustment for confounders, breastfeeding was associated with significantly less diarrheal disease. Associations were striking even in infants aged ≥ 6 months. They did not vary by social class but were greater in those living in rented council accommodation and in more crowded households. The effect of receiving no breast milk was stronger in more deprived areas than in less deprived areas. The effect of not receiving exclusive breast milk was stronger in more deprived areas than in less deprived areas. In formula fed infants, there was significantly more diarrheal disease in those not sterilizing bottles/teats with steam or chemicals. The protective effect of breast feeding did not persist beyond two months after breast feeding had stopped. Breastfeeding protects against diarrheal disease in infants in England although the degree of protection may vary across infants and wear off after breastfeeding cessation. Education about the benefits of breastfeeding and the risks of inadequate sterilization should be targeted at carers in deprived areas or households.

Newburg, D. S., Ruiz-Palacios, G. M., Altaye, M., Chaturvedi, P., Meinzen-Derr, J., Guerrero, M. D. L., & Morrow, A. L. (2003). Innate protection conferred by fucosylated oligosaccharides of human milk against diarrhea in breastfed infants. *Glycobiology*, 14(3), 253-263.

The relationship (1) between maternal Lewis blood group type and milk oligosaccharide expression, and (2) between variable oligosaccharide expression and risk of diarrhea in their infants, was studied in a cohort of 93 Mexican breastfeeding mother infant pairs. Milk of the 67 Le(a-b+) mothers contained more LNF-II (Le(a)) and 3-FL (Le(x)) (oligosaccharides whose fucose is exclusively α 1,3- or α 1,4-linked) than milk from the 24 Le(a-b-) mothers; milk from Le(a-b-) mothers contained more LNF-I (H-1) and 2'-FL (H-2), whose fucose is exclusively α 1,2-linked. The pattern of oligosaccharides varied among milk samples; in each milk sample, the pattern was summarized as a ratio of 2-linked to non-2-linked fucosyloligosaccharides. Milks with the highest ratios were produced primarily by Le(a-b-) mothers; those with the lowest ratios were produced exclusively by Le(a-b+) mothers ($p < 0.001$). Thus maternal genetic polymorphisms expressed as Lewis blood group types are expressed in

milk as varied fucosyloligosaccharide ratios. The four infants who developed diarrhea associated with stable toxin of *Escherichia coli* were consuming milk with lower ratios than the remaining infants. Furthermore, the 27 infants who developed moderate to severe diarrhea of any cause were consuming milk with lower ratios than the 26 who remained healthy. Thus, milk with higher 2-linked to non-2-linked fucosyloligosaccharide ratios affords greater protection against infant diarrhea. Conclusion: specific oligosaccharides constitute a major element of an innate immune system of human milk.

Baker, D., Taylor, H., & Henderson, J. (1998). Inequality in infant morbidity: causes and consequences in England in the 1990s. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Journal of Epidemiology & Community Health*, 52(7), 451-458. An episode of diarrhea was significantly less likely to last for six or more days if an infant was breastfed for three or more months.

Scariati, P. D., Grummer-Strawn, L. M., & Fein, S. B. (1997). A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States. *Pediatrics*, 99(6), e5-e5. The risk of developing diarrhea increases as the amount of breast milk an infant receives decreases. When compared with exclusively breastfed infants, infants who were exclusively formula-fed had an 80% increase in their risk of developing diarrhea.

Fuchs, S. C., Victora, C. G., & Martines, J. (1996). Case-control study of risk of dehydrating diarrhoea in infants in vulnerable period after full weaning. *Bmj*, 313(7054), 391-394. The type of milk consumed before the start of diarrhoea episode was strongly associated with dehydration. Compared with infants exclusively breastfed, bottle-fed infants were at higher risk (odds ratio for cow's milk = 6.0, for formula milk = 6.9). Compared with those still breastfeeding, children who stopped in the previous two months were more likely to develop dehydrating diarrhea.

Dewey, K. G., Heinig, M. J., & Nommsen-Rivers, L. A. (1995). Differences in morbidity between breast-fed and formula-fed infants. *The Journal of pediatrics*, 126(5), 696-702. In the first year of life the incidence of diarrheal illness among breastfed infants was half that of formula-fed infants.

Lerman, Y., Slepon, R., & Cohen, D. (1994). Epidemiology of acute diarrheal diseases in children in a high standard of living rural settlement in Israel. *The Pediatric infectious disease journal*, 13(2), 116-122. Children less than 12 months of age had a lower incidence of acute diarrheal disease during the months they were being breastfed than children that were fed with formula during the same period.

Long, K. Z., Wood, J. W., Gariby, E. V., Weiss, K. M., Mathewson, J. J., de la Cabada, F. J., ... & Wilson, R. A. (1994). Proportional hazards analysis of diarrhea due to enterotoxigenic *Escherichia coli* and breast feeding in a cohort of urban Mexican children. *American journal of epidemiology*, 139(2), 193-205.

Strictly formula-fed children had an incidence of diarrhea over three times that of strictly breast-fed infants and twice that of breast-fed and supplementally fed children.

Blake, P. A., Ramos, S., MacDonald, K. L., Rassi, V., Gomes, T. A. T., Ivey, C., ... & Trabulsi, L. R. (1993). Pathogen-specific risk factors and protective factors for acute diarrheal disease in urban Brazilian infants. *Journal of Infectious Diseases*, 167(3), 627-632.

In this study of 500 Brazilian infants ≤ 12 months old with diarrhea and 500 age-matched controls, breast-feeding infants < 6 months old (OR, 0.3) and boiling household drinking water (OR, 0.4) were protective. Breast-feeding was protective against enteropathogenic *Escherichia coli* infections (OR, 0.1).

Popkin, B. M., Adair, L., Akin, J. S., Black, R., Briscoe, J., & Flieger, W. (1990). Breast-feeding and diarrheal morbidity. *Pediatrics*, 86(6), 874-882.

This study used a unique longitudinal survey of more than 3000 mother-infant pairs observed from pregnancy through infancy. The sample is representative of infants from the Cebu region of the Philippines. The sequencing of breast-feeding and diarrheal morbidity events was carefully examined in a longitudinal analysis which allowed for the examination of age-specific effects of feeding patterns. Because the work controlled for a wide range of environmental causes of diarrhea, the results can be generalized to other populations with some confidence. The addition to the breast-milk diet of even water, teas, and other non-nutritive liquids doubled or tripled the likelihood of diarrhea. Supplementation of breast-feeding with additional nutritive foods on liquids further increased significantly the risk of diarrhea; most benefits of breast-feeding alone or in combination with nutritive foods/liquids became small during the second half of infancy. Benefits of breast-feeding were slightly greater in urban environments.

Enteroviruses

Sadeharju, K., Knip, M., Virtanen, S. M., Savilahti, E., Tauriainen, S., Koskela, P., ... & Finnish TRIGR Study Group. (2007). Maternal antibodies in breast milk protect the child from enterovirus infections. *Pediatrics*, 119(5), 941-946.

One hundred fifty infants who were prospectively followed up from birth were monitored for enterovirus infections. The duration of breastfeeding was recorded, and maternal breast milk and blood samples were regularly taken at 3-month intervals for the detection of enterovirus antibodies and RNA. Maternal serum was available from early pregnancy, delivery, and 3 months postpartum. Enterovirus infections were frequent and were diagnosed in 43% of infants before the age of 1 year and in 15% of the mothers during pregnancy. Infants exclusively breastfed for >2 weeks had fewer enterovirus infections by the age of 1 year compared with those exclusively breastfed for ≤ 2 weeks (0.38 vs 0.59 infections per child). High maternal antibody levels in serum and in breast milk were associated with a reduced frequency of infections. This effect was seen only in those infants breastfed >2 weeks, indicating that breast milk antibodies mediate this effect. Enterovirus RNA was not found in any of the breast milk samples. These results suggest that breastfeeding has a protective effect against enterovirus infections in infancy. This effect seems to be mediated primarily by maternal antibodies in breast milk.

Gastroenteritis

Ardıç, C., & Yavuz, E. (2018). Effect of breastfeeding on common pediatric infections: a 5-year prospective cohort study. *Arch Argent Pediatr*, 116(2), 126-132.

Introduction. The studies conducted revealed that breastfeeding duration has a reducing effect on common infectious diseases in the children during breastfeeding period. **Objective.** The aim of the present study was to address the association between breastfeeding duration and common infectious diseases in the children until 5 years of age to show long-term protective effects of the breast milk. **Population and Methods.** The study included 411 infants who were born in Rize (Turkey) between January 2011 and December 2011. The present prospective-cohort study lasted for 5 years and 11 interviews were conducted with each mother of the infants during this period. The infants were divided into two groups as those who were breastfed more and less than 12 months and the association between breastfeeding and infections such as acute otitis media, acute gastroenteritis, acute respiratory tract infections and acute urinary system infections was investigated. **Results.** Of 270 infants 193 (71.5%) were breastfed longer than 12 months and 77 (28.5%) were breastfed less than 12 months. Infants in the first group had less acute otitis media and acute gastroenteritis ($n=77$, 28.52%) when compared with the infants breastfed less than 12 months during the 5-year period ($p<0.05$). **Conclusions.** The present study detected that breastfeeding duration longer than 12 months significantly reduces the common childhood infections such as otitis media and gastroenteritis during the first 5 years of life.

Malik, W., Ashraf, S., & Malik, S. (2018). Relation of Bottlefeed versus Exclusive Breast Feeding Reduction of Acute Gastroenteritis related hospitalization in under 6 months infant. *PAKISTAN JOURNAL OF MEDICAL & HEALTH SCIENCES*, 12(1), 130-131.

Background: Acute gastroenteritis leads to greater number of physician visits and hospitalization. Breast feeding for at least 6 months can decrease infant mortality rate. **Aim:** To compare between intake of bottle feed and exclusive breast feed in reduction of acute gastroenteritis related hospital admissions in less than 6 months old healthy infant. **Methods:** It was a cross sectional study done in the Division of Paediatric Infectious Diseases, Department of Paediatrics, Services Hospital, Lahore. The demographic profile of infants recorded after fulfilling inclusion and exclusion criteria. Data analyzed through SPSS 20.0. Logistic regression technique applied for analysis. **Results:** The previous hospital admissions related to acute gastroenteritis in bottle feed were (66%) in boys and 60% in girls. Oral rehydration therapy for acute gastroenteritis in bottle feed was 71% in boys and 63% in girls. **Conclusion:** Breast feeding was protective against gastrointestinal diseases. This study promotes breast feeding for nourishment and nurturing a bond between mother and her child.

Bentley, J. P., Simpson, J. M., Bowen, J. R., Morris, J. M., Roberts, C. L., & Nassar, N. (2016). Gestational age, mode of birth and breastmilk feeding all influence acute early childhood gastroenteritis: a record-linkage cohort study. *BMC pediatrics*, 16(1), 55.

Acute gastroenteritis (AGE) is a leading cause of infectious morbidity in childhood. Clinical studies have implicated caesarean section, early birth and formula feeding in modifying normal

gut microbiota development and immune system homeostasis in early life. Rates of early birth and cesarean delivery are also increasing worldwide. This study aimed to investigate the independent and combined associations of the mode and timing of birth and breastmilk feeding with AGE hospitalisations in early childhood. Population-based record-linkage study of 893,360 singleton livebirths of at least 33 weeks gestation without major congenital conditions born in hospital, New South Wales, Australia, 2001–2011. Using age at first AGE hospital admission, Cox-regression was used to estimate the associations for gestational age, vaginal birth or caesarean delivery by labour onset and formula-only feeding while adjusting for confounders. There were 41,274 (4.6 %) children admitted to hospital at least once for AGE and the median age at first admission was 1.4 years. Risk of AGE admission increased with decreasing gestational age (37–38 weeks: 15 % increased risk, 33–36 weeks: 25 %), caesarean section (20 %), planned birth (17 %) and formula-only feeding (18 %). The rate of AGE admission was highest for children who were born preterm by modes of birth other than vaginal birth following the spontaneous onset of labour and who received formula-only at discharge from birth care (62–78 %). Vaginal birth following spontaneous onset of labour at 39+ weeks gestation with any breastfeeding minimised the risk of gastroenteritis hospitalisation in early childhood. Given increasing trends in early planned birth and caesarean section worldwide, these results provide important information about the impact obstetric interventions may have on the development of the infant gut microbiota and immunity.

Nassar, N., Bentley, J. P., Simpson, J. M., Bowen, J. R., Morris, J. M., & Roberts, C. L. (2014). O-171 The Combined Role Of Normal Birth And Breastfeeding In Acute Early Childhood Gastroenteritis.

Clinical studies have shown prematurity, birth via caesarean section (CS) and exposure to breastmilk impact the establishment of gut microbiota and immune system in early life and increase susceptibility to acute gut infections. This study aims to investigate the combined association of mode, timing of birth and breastfeeding with acute gastroenteritis (AGE) in early childhood. We conducted a population-based cohort study of 893,360 infants born in New South Wales, Australia, 2001–2011. Data was ascertained via record-linkage of administrative birth, hospital and death data. Follow-up was based on time between discharge at birth to first admission of AGE, sixth birthday, death or study end-date (30/06/2012). Multivariable Cox regression was used to estimate risk of AGE admission adjusted for maternal, obstetric and birth factors. In 2001–2011, there were 41,274 (4.6%) hospital admissions for AGE in childhood; two-thirds admitted. Findings support the biological hypothesis of the importance of mode, timing of birth and breastfeeding in development of gut microbiota and immune system in early life. Spontaneous vaginal birth at 39+ weeks gestation with any exposure to breastmilk at birth minimises the risk of AGE hospital admission in early childhood.

Rebhan, B., Kohlhuber, M., Schwegler, U., Fromme, H., Abou-Dakn, M., & Koletzko, B. V. (2009). Breastfeeding duration and exclusivity associated with infants' health and growth: data from a prospective cohort study in Bavaria, Germany. *Acta paediatrica*, 98(6), 974-980. Mothers delivering a baby in April 2005 were recruited throughout Bavaria, Germany, for a prospective birth cohort study. These mothers reported breastfeeding data, health and growth data of 1901 infants assessed by a physician in questionnaires on day 2-6, and in months 2, 4, 6 and 9. Subjects were healthy term infants with a birth weight > or =2500 g. We compared 475

infants breastfed exclusively for ≥ 6 months (group A), 870 infants breastfed fully/exclusively ≥ 4 months, but not exclusively ≥ 6 months (group B) and 619 infants not breastfed/breastfed or ≥ 6 months of exclusive breastfeeding reduced significantly the risk for ≥ 1 episode of gastrointestinal infection(s) during months 1-9 compared to no/ or ≥ 6 months of exclusive breastfeeding.

Abu-Ekteish, F., & Zahraa, J. (2002). Hypernatraemic dehydration and acute gastro-enteritis in children. *Annals of tropical paediatrics*, 22(3), 245-249.

Sixty-seven children aged 18 days to 18 months were admitted with hypernatraemic dehydration caused by acute gastroenteritis. Five hypernatraemic infants (7.5%) were breastfed compared with 40 (60%) isonatraemic controls ($p < 0.00001$). Six children from the hypernatraemic group developed convulsions and two died. Hypernatraemic dehydration remains an important and serious complication in infants with gastro-enteritis. Artificial milk feeding, particularly the use of evaporated cow's milk powder, is a predisposing factor for hypernatraemia in infantile gastroenteritis.

Giardia

Pereira, Q. L. C., Hara, C. D. C. P., Fernandes, R. T. S., Fagundes, D. L. G., do Carmo França-Botelho, A., Gomes, M. A., ... & Honorio-França, A. C. (2018). Human colostrum action against *Giardia lamblia* infection influenced by hormones and advanced maternal age. *Parasitology research*, 117(6), 1783-1791.

Children are more susceptible to *Giardia lamblia* infection. Cells and hormones contained in human colostrum have an immunoprotective action against giardiasis, but the effects of advanced maternal age on these components are poorly understood. This study analyzed the colostrum of older women to determine melatonin and cortisol levels besides the participation of these hormones on the functional activity of phagocytes against *G. lamblia*. Colostrum samples were collected from younger (18 to 35 years old) and older (over 36 years old) lactating women. Colostrum samples were subjected to melatonin and cortisol determination, immunophenotyping, quantification of superoxide release, and assessment of phagocytic rate and microbicidal activity of phagocytes treated with hormones and in the presence of *G. lamblia*. Colostrum from mothers of advanced age contained higher melatonin and cortisol levels and a lower rate of cells expressing CD14⁺ and CD15⁺. In the colostrum of these older mothers, melatonin increased superoxide release by phagocytes. In both groups, superoxide release by phagocytes treated with cortisol was higher in the presence of *G. lamblia*. In colostrum from mothers of advanced age, mononuclear (MN) phagocytes treated with melatonin showed higher phagocytosis of *G. lamblia* and higher microbicidal index. In younger mothers, MN and polymorphonuclear (PMN) colostrum phagocytes exhibited higher rates of *G. lamblia* elimination when treated with both melatonin and cortisol. In older mothers, cortisol and melatonin regulation for the functional activity of colostrum phagocytes against *G. lamblia* may represent an additional defense mechanism, relevant for the protection and treatment of parasitic infections in breastfed children.

Ignatius, R., Gahutu, J. B., Klotz, C., Steininger, C., Shyirambere, C., Lyng, M., ... & Mockenhaupt, F. P. (2012). High prevalence of *Giardia duodenalis* Assemblage B infection and association with underweight in Rwandan children. *PLoS neglected tropical diseases*, 6(6), e1677.

This study reported that breastfeeding reduced the odds of being infected with *G. duodenalis* ($P=0.04$) while a high number of siblings showed the opposite effect. In multivariate analysis, *G. duodenalis* remained positively associated with increasing age many siblings, and negatively with health facility attendance and breastfeeding

França-Botelho, A. C., Honório-França, A. C., França, E. L., Aparecida Gomes, M., & Costa-Cruz, J. M. (2006). Phagocytosis of *Giardia lamblia* trophozoites by human colostral leukocytes. *Acta Paediatrica*, 95(4), 438-443.

To determine the phagocytic activity of the polymorphonuclear and mononuclear cells present in human colostrum, and to verify the influence of opsonins in the adherence, ingestion and killing of *Giardia lamblia* trophozoites. *Methods*: Polymorphonuclear and mononuclear phagocytes were incubated with *G. lamblia* trophozoites, in the presence as well as the absence of supernatant of human colostrum (the source of opsonins) for 30, 60 and 120 min. The trophozoites/phagocytes ratio was 1:1, and the percentage of phagocytosed trophozoites was determined by microscopic examination of acridine orange-stained cells. *Results*: The mononuclear phagocytes presented more functional activity than the polymorphonuclear. The highest indexes of adherence (77.6 ± 5.1), ingestion (68.9 ± 5.5) and killing (48.5 ± 4.9) were obtained through the incubation of mononuclear cells in the presence of colostrum supernatant for 120 min. The phagocytes of human colostrum were able to ingest *G. lamblia* trophozoites and presented microbicidal activity *in vitro*, suggesting that these phagocytes may act as an additional mechanism of protection against infant giardiasis through breastfeeding.

Mahmud, M. A., Chappell, C. L., Hossain, M. M., Huang, D. B., Habib, M., & DuPont, H. L. (2001). Impact of breast-feeding on *Giardia lamblia* infections in Bilbeis, Egypt. *The American journal of tropical medicine and hygiene*, 65(3), 257-260.

A total of 152 infants were followed from birth to 1 year of age in a rural community of Egypt to document *Giardia lamblia* infection and to determine the effect of breast-feeding on enteric infections by this protozoan. The incidence of asymptomatic infection was 4.5 episodes per child-year. Exclusively breast-fed infants had lower risk for asymptomatic (odds ratio 0.66) and symptomatic infections (relative risk 0.50). Furthermore, breast-fed infants had fewer clinical manifestations, including mucus in stool (23.8% versus 76.2%), loss of appetite (17.6% versus 82.3%), and abdominal tenderness (17% versus 82.9%) compared with infants who were not exclusively breast-fed. Breast-feeding should be considered as an effective means to prevent *Giardia* infections and should be encouraged in regions where *G. lamblia* is highly endemic. Mahmud-MA et al. "Impact of breast feeding on *Giardia lamblia* infections in Bilbeis, Egypt." *American Journal of Tropical Medicine and Hygiene*. Sep 2001; 65 (3): 257-260.

Ignatius, R., Gahutu, J. B., Klotz, C., Steininger, C., Shyirambere, C., Lyng, M., ... & Mockenhaupt, F. P. (2012). High prevalence of *Giardia duodenalis* Assemblage B infection and

association with underweight in Rwandan children. *PLoS neglected tropical diseases*, 6(6), e1677.

Giardia duodenalis is highly endemic in East Africa but its effects on child health, particularly of submicroscopic infections, i.e., those below the threshold of microscopy, and of genetic subgroups (assemblages), are not well understood. We aimed at addressing these questions and at examining epidemiological characteristics of *G. duodenalis* in southern highland Rwanda. In 583 children <5 years of age from communities and health facilities, intestinal parasites were assessed by triplicate light microscopy and by PCR assays, and *G. duodenalis* assemblages were genotyped. Cluster effects of villages were taken into account in statistical analysis. The prevalence of *G. duodenalis* as detected by microscopy was 19.8% but 60.1% including PCR results. Prevalence differed with residence, increased with age, and was reduced by breastfeeding. In 492 community children without, with submicroscopic and with microscopic infection, underweight (weight-for-age z-score <-2 standard deviations) was observed in 19.7%, 22.1%, and 33.1%, respectively, and clinically assessed severe malnutrition in 4.5%, 9.5%, and 16.7%. Multivariate analysis identified microscopically detectable *G. duodenalis* infection as an independent predictor of underweight and clinically assessed severe malnutrition. Submicroscopic infection showed respective trends. Overall, *G. duodenalis* was not associated with gastrointestinal symptoms but assemblage A parasites (proportion, 13%) were increased among children with vomiting and abdominal pain. The prevalence of *G. duodenalis* in high-endemicity areas may be greatly underestimated by light microscopy, particularly when only single stool samples are analysed. Children with submicroscopic infections show limited overt manifestation, but constitute unrecognized reservoirs of transmission. The predominance of assemblage B in Rwanda may be involved in the seemingly unimposing manifestation of *G. duodenalis* infection. However, the association with impaired child growth points to its actual relevance. Longitudinal studies considering abundant submicroscopic infections are needed to clarify the actual contribution of *G. duodenalis* to morbidity in areas of high endemicity.

França-Botelho, A. C., Honório-França, A. C., França, E. L., Aparecida Gomes, M., & Costa-Cruz, J. M. (2006). Phagocytosis of *Giardia lamblia* trophozoites by human colostrum leukocytes. *Acta Paediatrica*, 95(4), 438-443.

The aim of this study was to determine the phagocytic activity of the polymorphonuclear and mononuclear cells present in human colostrum, and to verify the influence of opsonins in the adherence, ingestion and killing of *Giardia lamblia* trophozoites. Polymorphonuclear and mononuclear phagocytes were incubated with *G. lamblia* trophozoites, in the presence as well as the absence of supernatant of human colostrum (the source of opsonins) for 30, 60 and 120 min. The trophozoites/phagocytes ratio was 1:1, and the percentage of phagocytosed trophozoites was determined by microscopic examination of acridine orange-stained cells. The mononuclear phagocytes presented more functional activity than the polymorphonuclear. The highest indexes of adherence (77.6 ± 5.1), ingestion (68.9 ± 5.5) and killing (48.5 ± 4.9) were obtained through the incubation of mononuclear cells in the presence of colostrum supernatant for 120 min. The phagocytes of human colostrum were able to ingest *G. lamblia* trophozoites and presented microbicidal activity in vitro, suggesting that these phagocytes may act as an additional mechanism of protection against infant giardiasis through breastfeeding.

Haemophilus Influenza

Silfverdal, S. A., Bodin, L., Ulanova, M., Hahn-Zoric, M., Hanson, L. Å., & Olcen, P. (2002). Long term enhancement of the IgG2 antibody response to Haemophilus influenzae type b by breast-feeding. *The Pediatric infectious disease journal*, 21(9), 816-821.

Titers of IgG1, IgG2, IgA and IgM antibodies were determined in sera taken during the acute illness and during early and late convalescence in 30 children <6 years of age with invasive Haemophilus influenzae type b (Hib) infection and their mothers. Children 18 months or older with longer durations of exclusive breast-feeding (13 weeks or more) had higher Hib antibody concentrations of the IgG1, IgG2, IgA and IgM isotypes than those with a shorter duration of exclusive breast-feeding. This study indicates the presence of a long lasting enhancing effect of breast-feeding on the antibody response to Hib in children, in particular on IgG2 Hib antibody production.

Silfverdal, S. A., Bodin, L., Hugosson, S., Garpenholt, Ö., Werner, B., Esbjörner, E., ... & Olcén, P. (1997). Protective effect of breastfeeding on invasive Haemophilus influenzae infection: a case-control study in Swedish preschool children. *International journal of epidemiology*, 26(2), 443-450.

In Orebro County a 2.5-fold increase in the incidence of Haemophilus influenzae (HI) meningitis was found between 1970 and 1980, an observation that initiated the present study. MATERIALS AND METHODS: In order to search for associations between morbidity in invasive HI infection and possible risk factors, a case-control study was conducted over a 6-year period from 1987 to 1992, before general Hib vaccination was introduced in Sweden. Fifty-four cases with invasive HI infection 139 matched controls were studied for possible risk factors such as day-care outside the home, short duration of breastfeeding, passive smoking, low socioeconomic level of the household, many siblings in the family, allergy, frequent infections, repeated antibiotic treatments and immunoglobulin deficiency. RESULTS: Multivariate analysis showed a significant association between invasive HI infection and two independent factors, i.e. short duration (< 13 weeks) of exclusive breastfeeding, odds ratio (OR) 3.79 (95% confidence interval [CI] 1.6-8.8) and history of frequent infections, OR 4.49 (95% CI : 1.0-21.0). For the age at onset 12 months or older, the associations were stronger, OR 7.79 (95% CI : 2.4-26.6) and 5.86 (95% CI : 1.1-30.6), respectively. When breastfeeding duration in weeks was analysed as a continuous variable the OR was 0.95 (95% CI : 0.92-0.99), indicating a decreased risk with each additional week. Increased OR were observed for other risk factors as well but not of the magnitude found for short duration of breastfeeding. DISCUSSION: The association of decreased risk for invasive HI infection and long duration of breastfeeding was persisting beyond the period of breastfeeding itself. This finding supports the hypothesis of a long-lasting protective effect of breastfeeding on the risk for invasive HI infection. CONCLUSION: A decreased risk for invasive HI infection with long duration of breastfeeding was found. Our results do have implications for strategies in breastfeeding promotion, especially in countries where Hib vaccination is too costly and not yet implemented.

Harabuchi, Y., Faden, H., Yamanaka, N., Duffy, L., Wolf, J., & Krystofik, D. (1994). Human milk secretory IgA antibody to nontypeable Haemophilus influenzae: possible protective effects against nasopharyngeal colonization. *The Journal of pediatrics*, 124(2), 193-198.

The protective effects of human milk against otitis media may be due in part to inhibition of nasopharyngeal colonization with *H. influenzae* by specific secretory IgA antibody.

Arnold, C., Makintube, S., & Istre, G. R. (1993). Day care attendance and other risk factors for invasive *Haemophilus influenzae* type b disease. *American Journal of Epidemiology*, 138(5), 333-340.

Two hundred and ninety-five of 373 (79%) children with reported cases of invasive *Haemophilus influenzae* type b (Hib) occurring in the state of Oklahoma from January 1, 1986, through December 31, 1987, were matched according to birth date with two controls each. Conditional logistic regression was used to assess the independent roles of day care attendance, number of young children in the home, crowding, passive smoking, maternal education, household income, and race in Hib disease. Statistically significant odds ratios (ORs) were found for day care attendance (OR = 2.9), the presence of two or more children in the home under 6 years of age (OR = 2.4), crowding (ratio of number of people in the home to number of bedrooms ≥ 2) (OR = 2.0), and exposure to cigarette smoking in the home (OR = 1.4). Household income was independently associated with Hib disease. African Americans were at increased risk even after adjustment for income and crowding (OR = 4.1). Although there were no important differences in risk for other factors by type of Hib disease, there was a large and statistically significant difference in risk for day care attendance between meningitis (adjusted OR = 5.1, 95% confidence interval (CI) 3.1–8.2) and other types of Hib disease (combining non-meningitis cases, adjusted OR = 1.6, 95% CI 0.9–2.7). Increasing numbers of hours per week of daycare attendance and children per room were associated with increasing risk of Hib meningitis in a dose-response pattern. The highest day care ORs for meningitis were observed in the youngest (<6 months) and oldest (≥ 24 months) children. The adjusted OR for exposure to breast feeding was 0.5 (95% CI 0.3–0.8). A protective effect for Hib polysaccharide vaccination among children aged ≥ 18 months was suggested but did not reach statistical significance (OR = 0.4, 95% CI 0.2–1.1).

Petersen, G. M., Silimperi, D. R., Chiu, C. Y., & Ward, J. I. (1991). Effects of age, breast feeding, and household structure on *Haemophilus influenzae* type b disease risk and antibody acquisition in Alaskan Eskimos. *American journal of epidemiology*, 134(10), 1212-1221. Invasive *Haemophilus influenzae* type b (Hib) disease occurred at a mean age of 8.7 months. Breastfeeding was significantly less common among cases than controls (odds ratio = 0.53).

Cochi, S. L., Fleming, D. W., Hightower, A. W., Limpakarnjanarat, K., Facklam, R. R., Smith, J. D., ... & Broome, C. V. (1986). Primary invasive *Haemophilus influenzae* type b disease: a population-based assessment of risk factors. *The Journal of pediatrics*, 108(6), 887-896. In a population-based case-control study of risk factors for primary invasion of *haemophilus influenzae*, type B disease, breastfeeding was protective of infants less than 6 months of age.

HIV

Rollins, N. C., Ndirangu, J., Bland, R. M., Coutsooudis, A., Coovadia, H. M., & Newell, M. L. (2013). Exclusive breastfeeding, diarrhoeal morbidity and all-cause mortality in infants of HIV-

infected and HIV uninfected mothers: an intervention cohort study in KwaZulu Natal, South Africa. *PloS one*, 8(12), e81307.

Antiretroviral drug interventions significantly reduce the risk of HIV transmission to infants through breastfeeding. We report diarrhoea prevalence and all-cause mortality at 12 months of age according to infant feeding practices, among infants born to HIV-infected and uninfected mothers in South Africa. A non-randomised intervention cohort study that followed both HIV-infected and HIV-uninfected mothers and their infants until 18 months of age. Mothers were supported in their infant feeding choice. Detailed morbidity and vital status data were collected over the first year. At the time, only single dose nevirapine was available to prevent mother-to-child transmission of HIV. Among 2,589 infants, detailed feeding data and vital status were available for 1,082 HIV-exposed infants and 1,155 HIV non-exposed infants. Among exclusively breastfed (EBF) infants there were 9.4 diarrhoeal days per 1,000 child days (95%CI. 9.12-9.82) while among infants who were never breastfed there were 15.6 diarrhoeal days per 1,000 child days (95%CI. 14.62-16.59). Exclusive breastfeeding was associated with fewer acute, persistent and total diarrhoeal events than mixed or no breastfeeding in both HIV-exposed infants and also infants of HIV uninfected mothers. In an adjusted cox regression analysis, the risk of death among all infants by 12 months of age was significantly greater in those who were never breastfed (aHR 3.5, $p < 0.001$) or mixed fed (aHR 2.65, $p < 0.001$) compared with those who were EBF. In separate multivariable analyses, infants who were EBF for shorter durations had an increased risk of death compared to those EBF for 5-6 months [aHR 2.18 (95% CI, 1.56-3.01); $p < 0.001$]. In the context of antiretroviral drugs being scaled-up to eliminate new HIV infections among children, there is strong justification for financial and human resource investment to promote and support exclusive breastfeeding to improve HIV-free survival of HIV-exposed and non-exposed infants.

Infections in general (ear, respiratory, GI, urinary, conjunctivitis, thrush)

Victora, C. G., Bahl, R., Barros, A. J., França, G. V., Horton, S., Krasevec, J., ... & Group, T. L. B. S. (2016). Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *The Lancet*, 387(10017), 475-490.

The importance of breastfeeding in low-income and middle-income countries is well recognised, but less consensus exists about its importance in high-income countries. In low-income and middle-income countries, only 37% of children younger than 6 months of age are exclusively breastfed. With few exceptions, breastfeeding duration is shorter in high-income countries than in those that are resource-poor. Our meta-analyses indicate protection against child infections and malocclusion, increases in intelligence, and probable reductions in overweight and diabetes. We did not find associations with allergic disorders such as asthma or with blood pressure or cholesterol, and we noted an increase in tooth decay with longer periods of breastfeeding. For nursing women, breastfeeding gave protection against breast cancer and it improved birth spacing, and it might also protect against ovarian cancer and type 2 diabetes. The scaling up of breastfeeding to a near universal level could prevent 823 000 annual deaths in children younger than 5 years and 20 000 annual deaths from breast cancer. Recent epidemiological and biological findings from during the past decade expand on the known benefits of breastfeeding for women and children, whether they are rich or poor.

Ajetunmobi, O. M., Whyte, B., Chalmers, J., Tappin, D. M., Wolfson, L., Fleming, M., ... & Stockton, D. L. (2015). Breastfeeding is associated with reduced childhood hospitalization: evidence from a Scottish Birth Cohort (1997-2009). *The Journal of pediatrics*, 166(3), 620-625. The objective of this study was to evaluate the risk of childhood hospitalization associated with infant feeding patterns at 6-8 weeks of age in Scotland. A retrospective population level study based on the linkage of birth, death, maternity, infant health, child health surveillance, and admission records for children born as single births in Scotland between 1997 and 2009 (n = 502 948) followed up to March 2012. Descriptive analyses, Kaplan Meier tests, and Cox regression were used to quantify the association between the mode of infant feeding and risk of childhood hospitalization for respiratory, gastrointestinal, and urinary tract infections, and other common childhood ailments during the study period. Within the first 6 months of life, there was a greater hazard ratio (HR) of hospitalization for common childhood illnesses among formula-fed infants (HR 1.40; 95% CI 1.35-1.45) and mixed-fed infants (HR 1.18; 95% CI 1.11-1.25) compared with infants exclusively breastfed after adjustment for parental, maternal, and infant health characteristics. Within the first year of life and beyond, a greater relative risk of hospitalization was observed among formula-fed infants for a range of individual illnesses reported in childhood including gastrointestinal, respiratory, and urinary tract infections, otitis media, fever, asthma, diabetes, and dental caries. Using linked administrative data, we found greater risks of hospitalization in early childhood for a range of common childhood illnesses among Scottish infants who were not exclusively breastfed at 6-8 weeks of age.

Biesbroek, G., Bosch, A. A., Wang, X., Keijser, B. J., Veenhoven, R. H., Sanders, E. A., & Bogaert, D. (2014). The impact of breastfeeding on nasopharyngeal microbial communities in infants. *American journal of respiratory and critical care medicine*, 190(3), 298-308. Breastfeeding elicits significant protection against respiratory tract infections in infancy. Modulation of respiratory microbiota might be part of the natural mechanisms of protection against respiratory diseases induced by breastfeeding. To study the association between breastfeeding and nasopharyngeal microbial communities, including all cultivable and non-cultivable bacteria. In this observational study, we analyzed the microbiota of infants that had received exclusive breastfeeding (n = 101) and exclusive formula feeding (n = 101) at age 6 weeks and 6 months by 16S-based GS-FLX-titanium-pyrosequencing. At 6 weeks of age the overall bacterial community composition was significantly different between breastfed and formula-fed children (nonmetric multidimensional scaling, $P = 0.001$). Breastfed children showed increased presence and abundance of the lactic acid bacterium *Dolosigranulum* (relative effect size [RES], 2.61; $P = 0.005$) and *Corynebacterium* (RES, 1.98; $P = 0.039$) and decreased abundance of *Staphylococcus* (RES, 0.48; $P = 0.03$) and anaerobic bacteria, such as *Prevotella* (RES, 0.25; $P < 0.001$) and *Veillonella* (RES, 0.33; $P < 0.001$). Predominance (>50% of the microbial profile) of *Corynebacterium* and *Dolosigranulum* was observed in 45 (44.6%) breastfed infants compared with 19 (18.8%) formula-fed infants (relative risk, 2.37; $P = 0.006$). *Dolosigranulum* abundance was inversely associated with consecutive symptoms of wheezing and number of mild respiratory tract infections experienced. At 6 months of age associations between breastfeeding and nasopharyngeal microbiota composition had disappeared. Our data suggest a strong association between breastfeeding and microbial community composition in

the upper respiratory tract of 6-week-old infants. Observed differences in microbial community profile may contribute to the protective effect of breastfeeding on respiratory infections and wheezing in early infancy.

Li, R., Dee, D., Li, C. M., Hoffman, H. J., & Grummer-Strawn, L. M. (2014). Breastfeeding and risk of infections at 6 years. *Pediatrics*, 134(Supplement 1), S13-S20.

Previous studies have shown that breastfeeding is associated with reductions in the risk of common infections among infants; however, whether breastfeeding confers longer term protection is inconclusive. We linked data from the 2005–2007 IFPS II (Infant Feeding Practices Study II) and follow-up data collected when the children were 6 years old. Multivariable logistic regression was used, controlling for sociodemographic variables, to examine associations of initiation, duration, exclusivity of breastfeeding, timing of supplementing breastfeeding with formula, and breast milk intensity (proportion of milk feedings that were breast milk from age 0–6 months) with maternal reports of infection (cold/upper respiratory tract, ear, throat, sinus, pneumonia/lung, and urinary) and sick visits in the past year among 6-year-olds ($N = 1281$). The most common past-year infections were colds/upper respiratory tract (66%), ear (25%), and throat (24%) infections. No associations were found between breastfeeding and colds/upper respiratory tract, lung, or urinary tract infections. Prevalence of ear, throat, and sinus infections and number of sick visits differed according to breastfeeding duration, exclusivity, and timing of supplementing breastfeeding with formula ($P < .05$). Among children ever breastfed, children breastfed for ≥ 9 months had lower odds of past-year ear (adjusted odds ratio [aOR]: 0.69 [95% confidence interval (95% CI): 0.48–0.98]), throat (aOR: 0.68 [95% CI: 0.47–0.98]), and sinus (aOR: 0.47 [95% CI: 0.30–0.72]) infections compared with those breastfed >0 to <3 months. High breast milk intensity ($>66.6\%$) during the first 6 months was associated with lower odds of sinus infection compared with low breast milk intensity ($<33.3\%$) (aOR: 0.53 [95% CI: 0.35–0.79]). This prospective longitudinal study suggests that breastfeeding may protect against ear, throat, and sinus infections well beyond infancy.

Ghaemi, S., Navaei, P., Rahimirad, S., Behjati, M., & Kelishadi, R. (2014). Evaluation of preventive effects of colostrum against neonatal conjunctivitis: A randomized clinical trial. *Journal of education and health promotion*, 3.

Neonatal conjunctivitis leads to several ocular consequences in the affected neonates such as blindness. Currently available therapeutic options include NaNO₃, Gentamicin, Neomycin and so on, in which each of them has their own limitations. Regarding the immunologic content of colostrum and its safety and easy accessibility, we aimed to evaluate its preventive effects against neonatal conjunctivitis. In this clinical trial, conducted from November 2011 to July 2012, 300 preterm neonates, with culture negative eye swab, were enrolled and randomly assigned into three groups. The intervention group received two drops of colostrum. Control group received no treatment and other neonates were treated with topical Erythromycin ointment (0.5%). All neonates were followed for occurrence of clinical conjunctivitis for 28 days. Data analysis were performed by Chi-square test. Our data demonstrate the beneficial preventive effects of Colostrum against neonatal conjunctivitis ($P = 0.036$). Colostrum is suggested as an alternative prophylactic option for antibiotics against neonatal conjunctivitis. As colostrum is

easily accessible without cost, potential hazards and side effects, public education about its topical favorable effects is worthwhile.

Liu, B., & Newburg, D. S. (2013). Human milk glycoproteins protect infants against human pathogens. *Breastfeeding Medicine*, 8(4), 354-362.

Breastfeeding protects the neonate against pathogen infection. Major mechanisms of protection include human milk glycoconjugates functioning as soluble receptor mimetics that inhibit pathogen binding to the mucosal cell surface, prebiotic stimulation of gut colonization by favorable microbiota, immunomodulation, and as a substrate for bacterial fermentation products in the gut. Human milk proteins are predominantly glycosylated, and some biological functions of these human milk glycoproteins (HMGP) have been reported. HMGP range in size from 14 kDa to 2,000 kDa and include mucins, secretory immunoglobulin A, bile salt-stimulated lipase, lactoferrin, butyrophilin, lactadherin, leptin, and adiponectin. This review summarizes known biological roles of HMGP that may contribute to the ability of human milk to protect neonates from disease.

Duijts, L., Jaddoe, V. W., Hofman, A., & Moll, H. A. (2010). Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. *Pediatrics*, peds-2008. The objective of this study was to examine the associations of duration of exclusive breastfeeding with infections in the upper respiratory (URTI), lower respiratory (LRTI), and gastrointestinal tracts (GI) in infancy. METHODS: This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onward in the Netherlands. Rates of breastfeeding during the first 6 months (never; partial for <4 months, not thereafter; partial for 4–6 months; exclusive for 4 months, not thereafter; exclusive for 4 months, partial thereafter; and exclusive for 6 months) and doctor-attended infections in the URTI, LRTI, and GI until the age of 12 months were assessed by questionnaires and available for 4164 subjects. RESULTS: Compared with never-breastfed infants, those who were breastfed exclusively until the age of 4 months and partially thereafter had lower risks of infections in the URTI, LRTI, and GI until the age of 6 months (adjusted odds ratio [aOR]: 0.65 [95% confidence interval (CI): 0.51–0.83]; aOR: 0.50 [CI: 0.32–0.79]; and aOR: 0.41 [CI: 0.26–0.64], respectively) and of LRTI infections between the ages of 7 and 12 months (aOR: 0.46 [CI: 0.31–0.69]). Similar tendencies were observed for infants who were exclusively breastfed for 6 months or longer. Partial breastfeeding, even for 6 months, did not result in significantly lower risks of these infections. CONCLUSIONS: Exclusive breastfeeding until the age of 4 months and partially thereafter was associated with a significant reduction of respiratory and gastrointestinal morbidity in infants. Our findings support health-policy strategies to promote exclusive breastfeeding for at least 4 months, but preferably 6 months, in industrialized countries.

Ladomenou, F., Moschandreas, J., Kafatos, A., Tselentis, Y., & Galanakis, E. (2010). Protective effect of exclusive breastfeeding against infections during infancy: a prospective study. *Archives of disease in childhood*, 95(12), 1004-1008.

926 infants, followed for 12 months: feeding mode and all infectious episodes, including acute otitis media (AOM), acute respiratory infection (ARI), gastroenteritis, urinary tract infection, conjunctivitis and thrush, were recorded at 1, 3, 6, 9 and 12 months of life. Infants exclusively

breastfed for 6 months, as per WHO recommendations, presented with fewer infectious episodes than their partially breastfed or non-breastfed peers and this protective effect persisted after adjustment for potential confounders for ARI (OR 0.58, 95% CI 0.36 to 0.92), AOM (OR 0.37, 95% CI 0.13 to 1.05) and thrush (OR 0.14, 95% CI 0.02 to 1.02). Prolonged exclusive breastfeeding was associated with fewer infectious episodes ($r(s)=-0.07$, $p=0.019$) and fewer admissions to hospital for infection ($r(s)=-0.06$, $p=0.037$) in the first year of life. Partial breastfeeding was not related to protective effect. Several confounding factors, including parental age and education, ethnicity, presence of other siblings, environmental tobacco smoke exposure and season of birth were demonstrated to have an effect on frequency of infections during infancy. Findings from this large-scale prospective study in a well-defined infant population with adequate healthcare standards suggest that exclusive breastfeeding contributes to protection against common infections during infancy regarding and lessens the frequency and severity of infectious episodes. Partial breastfeeding did not seem to provide this protective effect.

Quigley, M. A., Kelly, Y. J., & Sacker, A. (2007). Breastfeeding and hospitalization for diarrheal and respiratory infection in the United Kingdom Millennium Cohort Study. *Pediatrics*, 119(4), e837-e842.

The objective of this study was to measure the effect of breastfeeding on hospitalization for diarrheal and lower respiratory tract infections in the first 8 months after birth in contemporary United Kingdom. The study was a population-based survey (sweep 1 of the United Kingdom Millennium Cohort Study). Data on infant feeding, infant health, and a range of confounding factors were available for 15890 healthy, singleton, term infants who were born in 2000–2002. The main outcome measures were parental report of hospitalization for diarrhea and lower respiratory tract infection in the first 8 months after birth. Seventy percent of infants were breastfed (ever), 34% received breast milk for at least 4 months, and 1.2% were exclusively breastfed for at least 6 months. By 8 months of age, 12% of infants had been hospitalized (1.1% for diarrhea and 3.2% for lower respiratory tract infection). Data analyzed by month of age, with adjustment for confounders, show that exclusive breastfeeding, compared with not breastfeeding, protects against hospitalization for diarrhea and lower respiratory tract infection. The effect of partial breastfeeding is weaker. Population-attributable fractions suggest that an estimated 53% of diarrhea hospitalizations could have been prevented each month by exclusive breastfeeding and 31% by partial breastfeeding. Similarly, 27% of lower respiratory tract infection hospitalizations could have been prevented each month by exclusive breastfeeding and 25% by partial breastfeeding. The protective effect of breastfeeding for these outcomes wears off soon after breastfeeding cessation. Breastfeeding, particularly when exclusive and prolonged, protects against severe morbidity in contemporary United Kingdom. A population-level increase in exclusive, prolonged breastfeeding would be of considerable potential benefit for public health.

Meningitis in Preterm Infants

Hylander, M. A., Strobino, D. M., & Dhanireddy, R. (1998). Human milk feedings and infection among very low birth weight infants. *Pediatrics*, 102(3), e38-e38.

The incidence of any infection and sepsis/meningitis are significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants.

Necrotizing Enterocolitis

Herrmann, K., & Carroll, K. (2014). An exclusively human milk diet reduces necrotizing enterocolitis. *Breastfeeding Medicine*, 9(4), 184-190.

This study tested the hypothesis that feeding an exclusively human milk (EHM) diet to premature infants reduces the incidence of necrotizing enterocolitis (NEC) associated with enteral feeding. An observational study for infants born at less than 33 weeks of gestational age was performed in a single neonatal intensive care unit. An EHM diet prospectively eliminated bovine-based artificial milk, including bovine-based fortifier, through 33 weeks postmenstrual age (PMA). The clinical data from a 2.5-year interval of the EHM diet were compared with data from the previous 6.5 years for similar infants who received bovine-based milk products before 33 weeks PMA. In the EHM diet cohort, 148 of 162 infants (91%) received EHM through 33 weeks PMA. In order to achieve an EHM diet, 140 of 162 infants (86%) received their own mother's milk, and 98 of 162 infants (60%) received donor human milk. The EHM cohort was also fed a human milk-based fortifier to truly eliminate bovine products. The distribution of NEC onset in the EHM cohort was significantly different from that in the control cohort for the day of onset ($p=0.042$) and the PMA at onset ($p=0.011$). In the control cohort, NEC onset after Day 7 of life occurred in 15 of 443 infants (3.4%), significantly more than in the EHM cohort where NEC occurred in two of 199 infants (1%) ($p=0.009$). In conclusion, changing to an EHM milk diet through 33 weeks PMA reduced the incidence of NEC associated with enteral feeding.

Cristofalo, E. A., Schanler, R. J., Blanco, C. L., Sullivan, S., Trawoeger, R., Kiechl-Kohlendorfer, U., ... & Abrams, S. (2013). Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. *The Journal of pediatrics*, 163(6), 1592-1595.

The objective of this study was to compare the duration of parenteral nutrition, growth, and morbidity in extremely premature infants fed exclusive diets of either bovine milk-based preterm formula (BOV) or donor human milk and human milk-based human milk fortifier (HUM), in a randomized trial of formula vs human milk. Multicenter randomized controlled trial. The authors studied extremely preterm infants whose mothers did not provide their milk. Infants were fed either BOV or an exclusive human milk diet of pasteurized donor human milk and HUM. The major outcome was duration of parenteral nutrition. Secondary outcomes were growth, respiratory support, and necrotizing enterocolitis (NEC). Birth weight (983 vs 996 g) and gestational age (27.5 vs 27.7 wk), in BOV and HUM, respectively, were similar. There was a significant difference in median parenteral nutrition days: 36 vs 27, in BOV vs HUM, respectively ($P=.04$). The incidence of NEC in BOV was 21% (5 cases) vs 3% in HUM (1 case), $P=.08$; surgical NEC was significantly higher in BOV (4 cases) than HUM (0 cases), $P=.04$. In extremely preterm infants given exclusive diets of preterm formula vs human milk, there was a significantly greater duration of parenteral nutrition and higher rate of surgical NEC in infants receiving preterm formula. This trial supports the use of an exclusive human milk diet to nourish extremely preterm infants in the neonatal intensive care unit.

Sullivan, S., Schanler, R. J., Kim, J. H., Patel, A. L., Trawöger, R., Kiechl-Kohlendorfer, U., ... & Laroia, N. (2010). An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *The Journal of pediatrics*, 156(4), 562-567.

The objective of this study was to evaluate the health benefits of an exclusively human milk-based diet compared with a diet of both human milk and bovine milk-based products in extremely premature infants. Infants fed their own mothers' milk were randomized to 1 of 3 study groups. Groups HM100 and HM40 received pasteurized donor human milk-based human milk fortifier when the enteral intake was 100 and 40 mL/kg/d, respectively, and both groups received pasteurized donor human milk if no mother's milk was available. Group BOV received bovine milk-based human milk fortifier when the enteral intake was 100 mL/kg/d and preterm formula if no mother's milk was available. Outcomes included duration of parenteral nutrition, morbidity, and growth. The 3 groups (total $n = 207$ infants) had similar baseline demographic variables, duration of parenteral nutrition, rates of late-onset sepsis, and growth. The groups receiving an exclusively human milk diet had significantly lower rates of necrotizing enterocolitis (NEC; $P = .02$) and NEC requiring surgical intervention ($P = .007$). For extremely premature infants, an exclusively human milk-based diet is associated with significantly lower rates of NEC and surgical NEC when compared with a mother's milk-based diet that also includes bovine milk-based products.

Meinzen-Derr, J., Poindexter, B., Wrage, L., Morrow, A. L., Stoll, B., & Donovan, E. F. (2009). Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *Journal of Perinatology*, 29(1), 57.

The objective of this study was to determine the association between human milk (HM) intake and risk of necrotizing enterocolitis (NEC) or death among infants 401 to 1000 g birth weight. Analysis of 1272 infants in the National Institute of Child Health and Human Development Neonatal Network Glutamine Trial was performed to determine if increasing HM intake was associated with decreased risk of NEC or death. HM intake was defined as the proportion of HM to total intake, to enteral intake and total volume over the first 14 days. Known NEC risk factors were included as covariates in Cox proportional hazard analyses for duration of survival time free of NEC. Among study infants, 13.6% died or developed NEC after 14 days. The likelihood of NEC or death after 14 days was decreased by a factor of 0.83 (95% confidence interval, CI 0.72, 0.96) for each 10% increase in the proportion of total intake as HM. Each 100 mL kg^{-1} increase in HM intake during the first 14 days was associated with decreased risk of NEC or death (hazard ratio, HR 0.87 (95% CI 0.77, 0.97)). There appeared to be a trend towards a decreased risk of NEC or death among infants who received 100% HM as a proportion to total enteral intake (HM plus formula), although this finding was not statistically significant (HR 0.85 (95% CI 0.60, 1.19)). These data suggest a dose-related association of HM feeding with a reduction of risk of NEC or death after the first 2 weeks of life among extremely low birth weight infants. Necrotizing enterocolitis (NEC) is a frequent cause of mortality and morbidity in very low birth weight (VLBW) infants. Human milk (HM) feeding has been associated with lower risk of NEC. However, mothers of VLBW infants often experience insufficient milk production, resulting in mixed feedings of HM and formula. Moreover, medical complications often limit the volume of feeding they can be given.

Sisk, P. M., Lovelady, C. A., Dillard, R. G., Gruber, K. J., & O'shea, T. M. (2007). Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *Journal of Perinatology*, 27(7), 428.

To determine if high proportions of (50% or greater) HM enteral feeding within the first 14 days of life are protective against NEC. This was a prospective cohort study of VLBW infants who were grouped according to the HM proportion of enteral feeding in the first 14 days: <50% (low human milk, LHM, $n=46$) and 50% (high human milk, HHM, $n=156$). The outcome of interest was development of NEC (Bell stage 2 or 3). Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) and to assess potential confounding due to perinatal risk factors. Two hundred and two infants were studied. Confirmed NEC occurred in 5/46 (10.6%) of the LHM group, as compared with 5/156 (3.2%) of the HHM. Gestational age was the only perinatal factor associated with risk of NEC. After adjustment for gestational age, HHM was associated with a lower risk of NEC ((OR=0.17, 95% CI: 0.04 to 0.68), $P=0.01$). Enteral feeding containing at least 50% HM in the first 14 days of life was associated with a sixfold decrease in the odds of NEC.

McGuire, W., & Anthony, M. Y. (2003). Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, 88(1), F11-F14.

Meta-analysis of randomised controlled trials. Four small trials, all initiated more than 20 years ago, fulfilled the prespecified inclusion criteria. None of the trials individually found any statistically significant difference in the incidence of NEC. However, meta-analysis found that feeding with donor human milk was associated with a significantly reduced relative risk (RR) of NEC. Infants who received donor human milk were three times less likely to develop NEC (RR 0.34), and four times less likely to have confirmed NEC (RR 0.25) than infants who received formula milk.

Schanler, R. J., Shulman, R. J., & Lau, C. (1999). Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics*, 103(6), 1150-1157.

The benefits of improved health (less sepsis and necrotizing enterocolitis) associated with the feeding of fortified human milk outweighed the slower rate of growth observed in this study of 108 preterm infants. Infants fed human milk were discharged an average of 15 days earlier than infants preterm formula.

Caplan, M. S., & Mackendrick, W. (1993). Necrotizing enterocolitis: a review of pathogenetic mechanisms and implications for prevention. *Pediatric pathology*, 13(3), 357-369.

Although no specific intervention for NEC treatment exists, preventive therapy using either enteral IgA supplementation, breast milk feeding, antibiotic prophylaxis, or exogenous steroid administration have reduced the incidence of this overwhelming disease in small randomized trials.

Buescher, E. S. (1994). Host defense mechanisms of human milk and their relations to enteric infections and necrotizing enterocolitis. *Clinics in perinatology*, 21(2), 247-262.

Based on both laboratory and clinical studies, human milk feeding appears to have protective effects against development of necrotizing enterocolitis.

Lucas, A., Cole, T.J. (1990). Breast Milk and Neonatal Necrotizing Enteral Colitis. *Lancet*, 336, 1519-23.

Among babies born at more than 30 weeks gestation, confirmed necrotizing enterocolitis was rare in those whose diet included breast milk; it was 20 times more common in those fed formula only.

Otitis Media (ear infection)

Bowatte, G., Tham, R., Allen, K. J., Tan, D. J., Lau, M. X. Z., Dai, X., & Lodge, C. J. (2015). Breastfeeding and childhood acute otitis media: a systematic review and meta-analysis. *Acta Paediatrica*, 104, 85-95.

The objective of this study was to synthesize the evidence on the association between duration and exclusivity of breastfeeding and the risk of acute otitis media (AOM). Systematic review and meta-analysis following searching of PubMed, CINAHL and EMBASE electronic databases. Twenty-four studies, all from the USA or Europe, met the inclusion criteria. In the pooled analyses, any form of breastfeeding was found to be protective for AOM in the first 2 years of life. Exclusive breastfeeding for the first 6 months was associated with the greatest protection (OR 0.57 95% CI 0.44, 0.75), followed by 'more vs less' breastfeeding (OR 0.67; 0.59, 0.76) and 'ever vs never' breastfeeding (OR 0.67; 0.56, 0.80). This systematic review and meta-analysis provides evidence that breastfeeding protects against AOM until 2 years of age, but protection is greater for exclusive breastfeeding and breastfeeding of longer duration. Exclusive breastfeeding during the first 6 months was associated with around a 43% reduction in ever having AOM in the first 2 years of life. After 2 years of age, there is no evidence that breastfeeding protects against AOM; however, there were few studies and the evidence quality was low.

Sabirov, A., Casey, J. R., Murphy, T. F., & Pichichero, M. E. (2009). Breast-feeding is associated with a reduced frequency of acute otitis media and high serum antibody levels against NTHi and outer membrane protein vaccine antigen candidate P6. *Pediatric research*, 66(5), 565.

Nontypeable *Haemophilus influenzae* (NTHi) causes acute otitis media (AOM) in infants. Breast-feeding protects against AOM and/or nasopharyngeal (NP) colonization; however, the mechanism of protection is incompletely understood. Children with AOM and healthy children were studied according to feeding status: breast-fed, breast/formula fed, or formula fed. Cumulative episodes of AOM, ELISA titers of serum IgG antibodies to whole-cell NTHi and vaccine candidate outer membrane protein P6, bactericidal titers of serum and NP colonization by NTHi were assessed. A lower incidence of AOM was found in breast- versus formula-fed children. Levels of specific serum IgG antibody to NTHi and P6 were highest in breast-fed,

intermediate in breast/formula fed, and lowest in formula-fed infants. Serum IgG antibody to P6 correlated with bactericidal activity against NTHi. Among children with AOM, the prevalence of NTHi in the NP was lower in breast- *versus* nonbreast-fed infants. We conclude that breast-feeding shows an association with higher levels of antibodies to NTHi and P6, suggesting that breast-feeding modulates the serum immune response to NTHi and P6. Higher serum IgG might facilitate protection against AOM and NP colonization in breast-fed children.

Scariati, P. D., Grummer-Strawn, L. M., & Fein, S. B. (1997). A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States. *Pediatrics*, 99(6), e5-e5.
The risk of developing an ear infection increases as the amount of breast milk an infant receives decreases. When compared with exclusively breastfed infants, infants who were exclusively formula-fed had a 70% increase in their risk of developing an ear infection.

Dewey, K. G., Heinig, M. J., & Nommsen-Rivers, L. A. (1995). Differences in morbidity between breast-fed and formula-fed infants. *The Journal of pediatrics*, 126(5), 696-702.
In infants who were breastfed until at least 12 months of age, the percentage of any otitis media was 19% lower, and of prolonged episodes (>10 days) was 80% lower than formula-fed infants. The mean duration of episodes of otitis media was longer in formula-fed than breastfed infants (8.8 vs 5.9 days, respectively).

Duncan, B., Ey, J., Holberg, C. J., Wright, A. L., Martinez, F. D., & Taussig, L. M. (1993). Exclusive breast-feeding for at least 4 months protects against otitis media. *Pediatrics*, 91(5), 867-872.
Infants exclusively breast-fed for 4 or more months had half the number of acute otitis media episodes as did those not breastfed at all, and 40% less than those infants whose diets were supplemented with other foods prior to 4 months. The recurrent otitis media rate in infants exclusively breast-fed for 6 months or more was 10% and was 20.5% in those infants who breast-fed for less than 4 months.

Alho, O. P., Koivu, M., Sorri, M., & Rantakallio, P. (1990). Risk factors for recurrent acute otitis media and respiratory infection in infancy. *International journal of pediatric otorhinolaryngology*, 19(2), 151-161.
Short duration of breastfeeding involved another significant risk of recurrent respiratory infections and otitis media.

Teele, D. W., Klein, J. O., Rosner, B., & Greater Boston Otitis Media Study Group. (1989). Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *Journal of infectious diseases*, 160(1), 83-94.
Significantly increased risk for acute otitis media as well as prolonged duration of middle ear effusion were associated with male gender, sibling history of ear infection and not being breast fed.

(See also: Duffy 1997, Aniansson 1994, Harabushi 1994, Paradise 1994, Sassen 1994, Owen 1993, Gulick 1986, Saarinen 1982)

Pneumococcal Disease

Levine, O. S., Farley, M., Harrison, L. H., Lefkowitz, L., McGeer, A., & Schwartz, B. (1999). Risk factors for invasive pneumococcal disease in children: a population-based case–control study in North America. *Pediatrics*, 103(3), e28-e28.

Among children 2 to 59 months, invasive pneumococcal disease was strongly associated with underlying disease and with day care attendance in the previous 3 months. Among 2- to 11-month-olds, current breastfeeding was associated with a decreased likelihood of invasive pneumococcal disease.

Respiratory Infections (general)

Henkle, E., Steinhoff, M. C., Omer, S. B., Roy, E., Arifeen, S. E., Raqib, R., ... & Zaman, K. (2013). The effect of exclusive breast-feeding on respiratory illness in young infants in a maternal immunization trial in Bangladesh. *The Pediatric infectious disease journal*, 32(5), 431-435.

Exclusive breast-feeding reduces the risk of respiratory illness in infants younger than 6 months of age in developing countries by approximately half. We evaluated the effect of exclusive breast-feeding on respiratory illness with fever (RIF) in Bangladeshi infants in the context of a randomized maternal influenza immunization trial. Infants in a maternal vaccine trial in Dhaka, Bangladesh, were prospectively assessed at weekly intervals for 6 months after birth for breast-feeding practices and RIF. We estimated the risk of an RIF episode for infants who were exclusively breast-fed the prior week compared with infants not exclusively breast-fed the prior week using generalized estimating equations. We followed a total of 331 infants from birth to 24 weeks of age. The median weeks infants were exclusively breast-fed was 15 (interquartile range, 6–21). The adjusted independent odds of respiratory illness for exclusively breast-fed infants compared with nonexclusively breast-fed infants was 0.59 (95% confidence interval: 0.45–0.77) for an RIF episode. After adjusting for exclusive breast-feeding, we confirmed the previous report that maternal immunization with influenza vaccine had an independent protective effect against RIF (odds ratio, 0.72; 95% confidence interval: 0.55–0.93). No significant difference in the protective effect of exclusive breast-feeding was seen by maternal influenza immunization status. Exclusive breast-feeding during the first 6 months of life and maternal immunization with influenza vaccine independently and substantially reduced respiratory illness with fever in infants.

Lamberti, L. M., Zakarija-Grković, I., Walker, C. L. F., Theodoratou, E., Nair, H., Campbell, H., & Black, R. E. (2013). Breastfeeding for reducing the risk of pneumonia morbidity and mortality in children under two: a systematic literature review and meta-analysis. *BMC public health*, 13(3), S18.

Suboptimal breastfeeding practices among infants and young children <24 months of age are associated with elevated risk of pneumonia morbidity and mortality. We conducted a systematic review and meta-analysis to quantify the protective effects of breastfeeding exposure against

pneumonia incidence, prevalence, hospitalizations and mortality. We conducted a systematic literature review of studies assessing the risk of selected pneumonia morbidity and mortality outcomes by varying levels of breastfeeding exposure among infants and young children <24 months of age. We used random effects meta-analyses to generate pooled effect estimates by outcome, age and exposure level. Suboptimal breastfeeding elevated the risk of pneumonia morbidity and mortality outcomes across age groups. In particular, pneumonia mortality was higher among not breastfed compared to exclusively breastfed infants 0-5 months of age (RR: 14.97; 95% CI: 0.67-332.74) and among not breastfed compared to breastfed infants and young children 6-23 months of age (RR: 1.92; 95% CI: 0.79-4.68). Our results highlight the importance of breastfeeding during the first 23 months of life as a key intervention for reducing pneumonia morbidity and mortality.

Lanari, M., Prinelli, F., Adorni, F., Di Santo, S., Faldella, G., Silvestri, M., & Musicco, M. (2013). Maternal milk protects infants against bronchiolitis during the first year of life. Results from an Italian cohort of newborns. *Early human development*, 89, S51-S57.

Bronchiolitis is one of the primary causes of hospitalization in infancy. We evaluated the effect of breastfeeding on the occurrence of hospitalization for bronchiolitis in the first year of life.

METHODS: In a prospective cohort study, 1,814 newborns of \approx 33 weeks of gestational age (wGA) were enrolled in 30 Italian Neonatology Units and followed-up for 1 year to assess hospitalizations for bronchiolitis. Children were grouped as 'never breastfed' and 'ever breastfed'; these latter were further divided into those 'exclusively breastfed' and 'breastfed associated with milk formula'. The risk of hospitalization for bronchiolitis was evaluated with survival analysis, and hazard ratios (HR) with 95% confidence interval [95% CI] were calculated.

RESULTS: Among enrolled newborns 22.9% were 'never breastfed'; in the breastfed group, 65% were 'exclusively breastfed' and 35% were 'breastfed with associated milk formula'. At 12 months of age, the risk of hospitalization for bronchiolitis was significantly higher in the 'never breastfed' group (HR: 1.57; 95% CI: 1.00-2.48). 'Breastfed associated with formula milk' and 'exclusively breastfed' groups were at similar risk of hospitalization for bronchiolitis. This observed protective effect of maternal milk was not explained by the higher prevalence of conditions able to increase the risk of bronchiolitis among 'never breastfed newborns'.

CONCLUSIONS: Breastfeeding, even in association with formula milk, reduces the risk of hospitalization for bronchiolitis during the first year of life. Encouraging breastfeeding might be an effective/inexpensive measure of prevention of lower respiratory tract infections in infancy.

Chantry, C. J., Howard, C. R., & Auinger, P. (2006). Full breastfeeding duration and associated decrease in respiratory tract infection in US children. *Pediatrics*, 117(2), 425-432.

The American Academy of Pediatrics recommends exclusive breastfeeding for an infant's first 6 months of life. When compared with exclusive breastfeeding for 4 months, greater protection against gastrointestinal infection, but not respiratory tract infection, has been demonstrated for the 6-month duration. The objective of this study was to ascertain if full breastfeeding of \geq 6 months compared with 4 to $<$ 6 months in the United States provides greater protection against respiratory tract infection. Secondary analysis of data from the National Health and Nutrition Examination Survey III, a nationally representative cross-sectional home survey conducted from 1988 to 1994, was performed. Data from 2277 children aged 6 to $<$ 24 months, who were

divided into 5 groups according to breastfeeding status, were compared. Children who required neonatal intensive care were excluded. In unadjusted analyses, infants who were fully breastfed for 4 to < 6 months (n = 223) were at greater risk for pneumonia than those who were fully breastfed for ≥ 6 months (n = 136) (6.5% vs 1.6%). There were not statistically significant differences in ≥ 3 episodes of cold/influenza (45% vs 41%), wheezing (23% vs 24%), ≥ 3 episodes of OM (27% vs 20%), or first OM at < 12 months of age (49% vs 47%). Adjusting for demographic variables, childcare, and smoke exposure revealed statistically significant increased risk for both pneumonia (odds ratio [OR]: 4.27) and ≥ 3 episodes of OM (OR: 1.95) in those who were fully breastfed for 4 to < 6 months compared with ≥ 6 months. This nationally representative study documents increased risk of respiratory tract infection including pneumonia and recurrent OM in children who were fully breastfed for 4 vs 6 months. These findings support current recommendations that infants receive only breast milk for the first 6 months of life.

Oddy, W. H., Sly, P. D., De Klerk, N. H., Landau, L. I., Kendall, G. E., Holt, P. G., & Stanley, F. J. (2003). Breast feeding and respiratory morbidity in infancy: a birth cohort study. *Archives of disease in childhood*, 88(3), 224-228.

In this prospective birth cohort study of 2602 Australian children: hospital, doctor, or clinic visits for four or more upper respiratory tract infections were significantly greater if predominant breast feeding was stopped before 2 months or partial breast feeding was stopped before 6 months. Predominant breast feeding for less than six months was associated with an increased risk for two or more hospital, doctor, or clinic visits and hospital admission for wheezing, lower respiratory illness. Breast feeding for less than eight months was associated with a significantly increased risk for two or more hospital, doctor, or clinic visits or hospital admissions because of wheezing lower respiratory illnesses.

Bachrach, V. R. G., Schwarz, E., & Bachrach, L. R. (2003). Breastfeeding and the risk of hospitalization for respiratory disease in infancy: a meta-analysis. *Archives of pediatrics & adolescent medicine*, 157(3), 237-243.

Data from 33 studies indicate a protective association between breastfeeding and the risk of respiratory disease hospitalization. Among generally healthy infants in developed nations, more than a tripling in severe respiratory tract illnesses resulting in hospitalizations was noted for infants who were not breastfed compared with those who were exclusively breastfed for 4 months.

César, J. A., Victora, C. G., Barros, F. C., Santos, I. S., & Flores, J. A. (1999). Impact of breastfeeding on admission for pneumonia during postneonatal period in Brazil: nested case-control study. *Bmj*, 318(7194), 1316-1320.

Infants who were not being breast fed were 17 times more likely than those being breast fed exclusively to be admitted to hospital for pneumonia.

Cushing, A. H., Samet, J. M., Lambert, W. E., Skipper, B. J., Hunt, W. C., Young, S. A., & McLaren, L. C. (1998). Breastfeeding reduces risk of respiratory illness in infants. *American journal of epidemiology*, 147(9), 863-870.

In a cohort of 1,202 healthy infants, born in Albuquerque, New Mexico, the daily occurrences of respiratory symptoms and breastfeeding status were reported by the mothers every 2 weeks during the first 6 months of life. After adjustment for potential confounding factors, full breastfeeding was associated with a reduction in lower respiratory illness risk (odds ratio=0.81) and significantly reduced the duration of respiratory illness.

de Duran, C. M. (1991). Cytologic diagnosis of milk micro aspiration. *Immunol Allerg Pract*, 8, 402-5.

The authors presented results found in infants with two or more episodes of acute chronic bronchitis. They found that approximately twice as many bottle-fed infants presented with the problem as those who were breastfed.

Respiratory Syncytial Virus

Somech, R., Tal, G., Gilad, E., Mandelberg, A., Tal, A., & Dalal, I. (2006). Epidemiologic, socioeconomic, and clinical factors associated with severity of respiratory syncytial virus infection in previously healthy infants. *Clinical pediatrics*, 45(7), 621-627.

195 previously healthy infants with confirmed respiratory syncytial virus (RSV) infection were enrolled into three subgroups according to disease severity: outpatients (82 patients), inpatients (100 patients), and intensive care unit patients (13 patients). Epidemiologic parameters such as gestational age, birth weight, chronologic age at presentation, and gender as well as socioeconomic factors such as ethnic origin, family history of asthma, exposure to cigarette smoke, number of family members, presence of pets at home, breast-feeding, and day-care attendance were not found to predict the severity of RSV illness in previously healthy infants. Our results emphasize the complexity of predicting disease severity in previously healthy infants with RSV infection and suggest that other parameters such as host genetic background might explain the clinical variability.

Bulkow, L. R., Singleton, R. J., Karron, R. A., & Harrison, L. H. (2002). Risk factors for severe respiratory syncytial virus infection among Alaska native children. *Pediatrics*, 109(2), 210-216. Breastfeeding was associated with a lower risk of RSV hospitalization (odds ratio: 0.34).

Holberg, C. J., Wright, A. L., Martinez, F. D., Ray, C. G., Taussing, L. M., Lebowitz, M. D., & Group Health Medical Associates. (1991). Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. *American journal of epidemiology*, 133(11), 1135-1151.

Breastfeeding was associated with a lower incidence of RSV infection during the first year of life.

Downham, M. A., Scott, R., Sims, D. G., Webb, J. K., & Gardner, P. S. (1976). Breast-feeding protects against respiratory syncytial virus infections. *Br Med J*, 2(6030), 274-276.

Eight out of 115 infants admitted to hospital with respiratory syncytial (RS) virus infection had been breast-fed compared with 46 out of 167 controls; this difference was statistically significant. Twenty-one specimens of human colostrum were examined, and all contained RS

virus neutralizing activity. Specific IgA and IgG were detected in 18 specimens, whereas IgM was detected in none. The titre of IgA antibody was usually higher and correlated more closely to the titre of neutralizing activity than that of IgG. Infants inhale milk feeds and regurgitate them through the nose, and the IgA collecting in the respiratory tract might protect against severe respiratory infection. Alternatively, if severe RS virus illness is a sign of hypersensitivity to the virus breast-feeding might protect the infant from an early sensitizing infection.

Rotavirus

Altameemi, D. Q. D. Y., & Chlaibawi, D. A. A. M. (2018). Role of breast feeding against infection with rotavirus among children with acute gastroenteritis. *International Journal of Development Research*, 8(11), 24277-24279.

Breast feeding during the first two years of life plays an important protective role against infection with rotavirus, although the practice of breast feeding is decreasing in the community.

Das, S., Sahoo, G. C., Das, P., Singh, U. K., Jaiswal, A. K., Singh, P., ... & Kumar, R. (2016). Evaluating the impact of breastfeeding on rotavirus antigenemia and disease severity in Indian children. *PloS one*, 11(2), e0146243.

Among the total 145 infants with diarrhea, the prevalence of breastfed infants was 23.4% (34 children) compared to 76.5% (111 children) prevalence of non-breastfed ones. Notably, RV-diarrhea was most common among the latter group.

Van Den Berg, J., & Berger, M. Y. (2011). Guidelines on acute gastroenteritis in children: a critical appraisal of their quality and applicability in primary care. *BMC family practice*, 12(1), 134.

There is a protective effect of breastfeeding against rotavirus infection in infants, particularly in children 6 months and younger

Salmonellosis

Turin, C. G., & Ochoa, T. J. (2014). The role of maternal breast milk in preventing infantile diarrhea in the developing world. *Current tropical medicine reports*, 1(2), 97-105.

Components of human milk inhibit the adhesion of *E. coli*, *Salmonella* *typhi* and *Vibrio cholera* to epithelial cells. Protection by human milk antibodies against specific virulence factors of enteric pathogens have been described for *Vibrio cholera*, *Campylobacter jejuni*, enteropathogenic *E. coli* (EPEC), *Shigella*, *Salmonella*, *Giardia lamblia*, among others.

Rowe, S. Y., Rocourt, J. R., Shiferaw, B., Kassenborg, H. D., Segler, S. D., Marcus, R., ... & Emerging Infections Program FoodNet Working Group. (2004). Breast-feeding decreases the risk of sporadic salmonellosis among infants in FoodNet sites. *Clinical Infectious Diseases*, 38(Supplement_3), S262-S270.

Among the population of the Foodborne Diseases Active Surveillance Network (FoodNet) surveillance areas ("FoodNet sites") in 1996, children under 12 months of age had the highest incidence of sporadic salmonellosis. We conducted a case-control study in 5 FoodNet sites to identify risk factors for sporadic infant salmonellosis. A case patient was a child under 12

months of age with a laboratory-confirmed, nontyphoidal serogroup B or D *Salmonella* infection. Twenty-two case patients were matched with 39 control subjects. In a multivariate analysis, case patients were more likely to have a liquid diet containing no breast milk than a liquid diet containing only breast milk (matched odds ratio, 44.5; $P=.04$). To decrease their infants' risk of salmonellosis, mothers should be encouraged to breast-feed their infants.

Sepsis in Preterm Infants

Patel, A. L., Johnson, T. J., Engstrom, J. L., Fogg, L. F., Jegier, B. J., Bigger, H. R., & Meier, P. P. (2013). Impact of early human milk on sepsis and health-care costs in very low birth weight infants. *Journal of Perinatology*, 33(7), 514.

The objective of this study was to study the incidence of sepsis and neonatal intensive care unit (NICU) costs as a function of the human milk (HM) dose received during the first 28 days post birth for very low birth weight (VLBW) infants. Prospective cohort study of 175 VLBW infants. The average daily dose of HM (ADDHM) was calculated from daily nutritional data for the first 28 days post birth (ADDHM-Days 1–28). Other covariates associated with sepsis were used to create a propensity score, combining multiple risk factors into a single metric. The mean gestational age and birth weight were 28.1 ± 2.4 weeks and 1087 ± 252 g, respectively. The mean ADDHM-Days 1–28 was 54 ± 39 ml $\text{kg}^{-1} \text{ day}^{-1}$ (range 0–135). Binary logistic regression analysis controlling for propensity score revealed that increasing ADDHM-Days 1–28 was associated with lower odds of sepsis (odds ratio 0.981, 95% confidence interval 0.967–0.995, $P=0.008$). Increasing ADDHM-Days 1–28 was associated with significantly lower NICU costs. A dose–response relationship was demonstrated between ADDHM-Days 1–28 and a reduction in the odds of sepsis and associated NICU costs after controlling for propensity score. For every HM dose increase of $10 \text{ ml kg}^{-1} \text{ day}^{-1}$, the odds of sepsis decreased by 19%. NICU costs were lowest in the VLBW infants who received the highest ADDHM-Days 1–28.

Hylander, M. A., Strobino, D. M., & Dhanireddy, R. (1998). Human milk feedings and infection among very low birth weight infants. *Pediatrics*, 102(3), e38-e38.

The incidence of any infection and sepsis/meningitis are significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants.

Tobacco smoke (protective effect against exposure to)

Karmaus, W., Dobai, A. L., Ogbuanu, I., Arshard, S. H., Matthews, S., & Ewart, S. (2008). Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. *Journal of Asthma*, 45(8), 688-695.

The effect of breastfeeding on asthma is controversial, which may be explained by related and interacting early childhood risk factors. We assessed the joint effects of a risk-triad consisting of maternal smoking during pregnancy, breastfeeding for less than 3 months, and recurrent lower respiratory tract infections (RLRTI) on physician-diagnosed childhood asthma. The association was assessed in the Isle of Wight birth cohort study (1989-1990) using a repeated measurement approach with data collection at birth, and at ages 1, 2, 4, and 10 years. The

population consists of 1,456 children recruited between January 1989 and February 1990. Prenatal smoking, breastfeeding for less than 3 months, and recurrent lower respiratory infections (RLRTI) were combined into eight risk-triads. Relative risks (RR) and 95% confidence intervals were estimated with a log-linear model. The risk-triad involving RLRTI in infancy, maternal smoking during pregnancy, and breastfeeding for less than 3 months showed a stronger association with asthma at ages 4 and 10 compared to other risk-triads (RR of 5.79 for any asthma at ages 1, 2, 4, and 10; and 3.1 for asthma at ages 4 and 10). Of the three individual risk factors, RLRTI appeared to be the major driver of the combined effects in the risk-triads. The effect of RLRTI on asthma was modified by breastfeeding. Breastfeeding for ≥ 3 months also attenuated the effect of prenatal smoking on asthma in children without RLRTI. A high proportion of asthma cases in childhood can be prevented by promoting breastfeeding, by preventing smoking during pregnancy, and by avoidance of recurrent lower respiratory tract infections in early childhood.

Yilmaz, G., Isik Agras, P., Hizli, S., Karacan, C., Besler, H. T., Yurdakok, K., & Coskun, T. (2009). The effect of passive smoking and breast feeding on serum antioxidant vitamin (A, C, E) levels in infants. *Acta Paediatrica*, 98(3), 531-536.

Toxic substances in tobacco smoke are known to have negative effects on the antioxidant capacity of the human body. In order to investigate the effect of passive smoking on serum antioxidant levels in infants, serum vitamin A, E, C levels and urinary cotinine/creatinine levels were measured in 254 infants at the age of 6 months. Methods: The information about infants' nutrition and exposure to tobacco smoke was obtained from the mothers by the help of a questionnaire. The infants were grouped according to both smoking status of mother and urinary cotinine/creatinine levels. Results: The mean serum vitamin A, C and E levels of infants of smoking mothers were significantly lower than those of non-smoking mothers ($p < 0.05$). Vitamin A, E and C levels were negatively correlated with urinary cotinine/creatinine levels ($p < 0.05$, r : -0.61, -0.42, -0.53, respectively). Multivariate analysis revealed independent factors determining the serum vitamin A, E and C levels of infants as maternal smoking and breastfeeding ($p < 0.05$). Conclusion: Tobacco smoke exposure of infants significantly decreases their serum antioxidant vitamin A, C and E levels. However, breastfeeding may help to prevent the decrement of antioxidant vitamin levels of passive smoking infants.

Karmaus, W., Dobai, A. L., Ogbuanu, I., Arshard, S. H., Matthews, S., & Ewart, S. (2008). Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. *Journal of Asthma*, 45(8), 688-695.

The effect of breastfeeding on asthma is controversial, which may be explained by related and interacting early childhood risk factors. We assessed the joint effects of a risk-triad consisting of maternal smoking during pregnancy, breastfeeding for less than 3 months, and recurrent lower respiratory tract infections (RLRTI) on physician-diagnosed childhood asthma. The association was assessed in the Isle of Wight birth cohort study (1989-1990) using a repeated measurement approach with data collection at birth, and at ages 1, 2, 4, and 10 years. The population consists of 1,456 children recruited between January 1989 and February 1990. Prenatal smoking, breastfeeding for less than 3 months, and recurrent lower respiratory infections (RLRTI) were combined into eight risk-triads. Relative risks (RR) and 95% confidence

intervals were estimated with a log-linear model. The risk-triad involving RLRTI in infancy, maternal smoking during pregnancy, and breastfeeding for less than 3 months showed a stronger association with asthma at ages 4 and 10 compared to other risk-triads (RR of 5.79 for any asthma at ages 1, 2, 4, and 10; and 3.1 for asthma at ages 4 and 10). Of the three individual risk factors, RLRTI appeared to be the major driver of the combined effects in the risk-triads. The effect of RLRTI on asthma was modified by breastfeeding. Breastfeeding for ≥ 3 months also attenuated the effect of prenatal smoking on asthma in children without RLRTI. A high proportion of asthma cases in childhood can be prevented by promoting breastfeeding, by preventing smoking during pregnancy, and by avoidance of recurrent lower respiratory tract infections in early childhood.

Chatzimichael, A., Tsalkidis, A., Cassimos, D., Gardikis, S., Tripsianis, G., Deftereos, S., ... & Tsanakas, I. (2007). The role of breastfeeding and passive smoking on the development of severe bronchiolitis in infants. *Minerva pediatrica*, 59(3), 199-206.

Bronchiolitis is an acute infectious disease of the lower respiratory tract which causes the obstruction of bronchioles in children younger than 2 years. The aim of this study was to investigate the effect of passive smoking alone and in conjunction with breastfeeding on the severity of acute bronchiolitis in infancy and the duration of hospitalisation. We studied 240 consecutive infants aged from 6 to 24 months (137 boys and 103 girls) median age 14 months, who required hospital admission for acute bronchiolitis at the Paediatric Department of Democritus University Hospital, Alexandroupolis, Greece. Among the entire cohort, 122 (50.8%) children presented a severe attack of bronchiolitis. Breastfeeding for less than four months (OR=6.1), exposure to environmental tobacco smoke (OR=2.2) and their combination (OR=16.2) showed significant association with severe bronchiolitis and prolonged hospitalisation. Passive smoking did not increase the risk of severe bronchiolitis, when infants breastfed for more than four months (OR=1.9). In conclusion, exposure to environmental tobacco smoke worsens the symptoms and the prognosis of bronchiolitis, while breastfeeding seems to have a protective effect even in children exposed to environmental tobacco smoke.

Jin, C., & Rossignol, A. M. (1993). Effects of passive smoking on respiratory illness from birth to age eighteen months, in Shanghai, People's Republic of China. *The Journal of pediatrics*, 123(4), 553-558.

Children who were not fed human milk had a 1.8-fold increased risk of respiratory disease at each level of exposure to passive cigarette smoke, in comparison with children who were fed human milk for at least 1 month.

Woodward, A., Douglas, R. M., Graham, N. M., & Miles, H. (1990). Acute respiratory illness in Adelaide children: breast feeding modifies the effect of passive smoking. *Journal of Epidemiology & Community Health*, 44(3), 224-230.

Odds of respiratory illness with maternal smoking were 7 times higher among children who were never breastfed than among those who were breastfed.

Urinary Tract Infections

Mårild, S., Hansson, S., Jodal, U., Oden, A., & Svedberg, K. (2004). Protective effect of breastfeeding against urinary tract infection. *Acta Paediatrica*, 93(2), 164-167.

Two children's hospitals and local child health centres in Sweden participated in a prospective case-control study. In total, 200 consecutive cases (89M, 111F), aged 0-6y, presenting with first-time febrile UTI were enrolled. The mean age was 0.98 years. As control subjects, 336 children (147M, 189F) were recruited from the child health centre, matched for age and gender and included consecutively for each case during the first days after diagnosis. The duration of exclusive breastfeeding was obtained from the case and controls by a standardized procedure. Results: Ongoing exclusive breastfeeding gave a significantly lower risk of infection. A longer duration of breastfeeding gave a lower risk of infection after weaning, indicating a long-term mechanism. The protective role of breastfeeding was strongest directly after birth, then decreased until 7 mo of age, after which age no effect was demonstrated. Conclusion: A protective role of breastfeeding against UTI was demonstrated. The study provides statistical support to the view that breast milk is a part of the natural defence against UTI.

Pisacane, A., Graziano, L., Mazzearella, G., Scarpellino, B., & Zona, G. (1992). Breast-feeding and urinary tract infection. *The Journal of pediatrics*, 120(1), 87-89.

Breastfed infants have a relative risk of developing a UTI of 0.38 compared to formula-fed infants.

Coppa, G. V., Gabrielli, O., Giorgi, P., Catassi, C., Montanari, M. P., Varaldo, P. E., & Nichols, B. L. (1990). Preliminary study of breastfeeding and bacterial adhesion to uroepithelial cells. *The Lancet*, 335(8689), 569-571.

The oligosaccharide content of breast-milk and urine from nursing mothers is very similar, and the pattern of oligosaccharides excreted by infants is also strongly correlated with that of breastmilk. The oligosaccharides cause inhibition of bacterial adhesion, suggesting that breastfeeding may have a preventive effect on urinary tract infection in both mother and infant.

INFANT AND CHILDHOOD ILLNESSES

Anemia and Iron Deficiency

Assis, A. M. O., Gaudenzi, E. N., Gomes, G., Ribeiro, R. D. C., Szarfarc, S. C., & de Souza, S. B. (2004). Hemoglobin concentration, breastfeeding and complementary feeding in the first year of life. *Revista de saude publica*, 38(4), 543-551.

In this cross-sectional study with 553 children under age 12 months who attended public healthcare facilities hemoglobin concentration was measured. Hemoglobin concentrations compatible with anemia were identified in 62.8% of the children, with greater occurrence among the 6-12 months age group (72.6%). Exclusive breastfeeding during the first six months of life was associated with the highest levels of hemoglobin. The remaining feeding regimes were associated with different levels of reduction in hemoglobin levels, which became compatible with anemia in children fed with formula ($p=0,009$). Tea and/or water consumption was associated with a reduction in hemoglobin concentration of 0.76 g/dl ($p< 0,001$) among children under age

6 months. For children aged 6-12 months, hemoglobin concentrations increased significantly with the consumption of sugar ($p=0.017$) and beans ($p=0.018$), and decreased significantly with the consumption of fruit ($p<0.001$). Conclusions: exclusive breastfeeding until age 6 months and continuation of breastfeeding after this age, combined with qualitatively and quantitatively appropriate feeding may contribute towards an increase in hemoglobin concentration in the first year of life.

Thorsdottir, I., Gunnarsson, B. S., Atladottir, H., Michaelsen, K. F., & Palsson, G. (2003). Iron status at 12 months of age—effects of body size, growth and diet in a population with high birth weight. *European journal of clinical nutrition*, 57(4), 505.

Longitudinal observational study. Weighed 2 day food records at the ages of 6, 9 and 12 months were used to analyse food and nutrient intake. Every fifth child was iron-deficient and 2.7% were also anaemic ($Hb<105\text{ g/l}$). Higher weight gain from 0 to 12 months was seen in infants who were iron-deficient at 12 months. Iron-deficient infants had shorter breast-feeding duration (5.3 ± 2.2 months) than non-iron-deficient (7.9 ± 3.2 months; $P = 0.001$). Iron status indices were negatively associated with cow's milk consumption at 9-12 months, but were positively associated with iron-fortified breakfast cereals, fish and meat consumption.

Autoimmune Thyroid Disease

Fort, P., Moses, N., Fasano, M., Goldberg, T., & Lifshitz, F. (1990). Breast and soy-formula feedings in early infancy and the prevalence of autoimmune thyroid disease in children. *Journal of the American College of Nutrition*, 9(2), 164-167.

Feeding practices in infancy may affect the development of various autoimmune diseases later in life. Thyroid alterations are among the most frequently encountered autoimmune conditions in children. A detailed history of feeding practices was obtained in 59 children with autoimmune thyroid disease, their 76 healthy siblings, and 54 healthy nonrelated control children. The frequency of feedings with soy-based milk formulas in early life was significantly higher in children with autoimmune thyroid disease (prevalence 31%) as compared with their siblings (prevalence 12%), and healthy nonrelated control children (prevalence 13%).

Constipation and Anal Fissures

Andıran, F., Dayı, S., & Mete, E. (2003). Cows milk consumption in constipation and anal fissure in infants and young children. *Journal of paediatrics and child health*, 39(5), 329-331.

Two groups of 30 children aged between 4 months and 3 years were evaluated retrospectively. Group I comprised children with chronic constipation and anal fissure in whom surgical causes were excluded, and group II comprised normal children. The daily consumption of cows milk, duration of breastfeeding and other clinical features of the children were investigated. The mean daily consumption of cows milk was significantly higher in group I than group II. Group I children were breastfed for a significantly shorter period (5.8 months) than group II (10.1 months). The odds ratios for the two factors - children consuming more than 200 mL of cows milk per day and breastfeeding for less than 4 months were calculated to be 8.6 and 5.7, respectively.

Cryptorchidism (undescended testicle)

MORI, M., DAVIES, T. W., TSUKAMOTO, T., KUMAMOTO, Y., & FUKUDA, K. (1992). Maternal and Other Factors of Cryptorchidism. *The Kurume medical journal*, 39(2), 53-60.

This case-controlled study showed a significant association of cryptorchidism and lack of breastfeeding.

Esophageal and Gastric Lesions

Benhamou, P. H., Francoual, C., Glangeaud, M. C., Barette, A., Dupont, C., & Bréart, G. (2000). Risk Factors for Severe Esophageal and Gastric Lesions in Term Neonates: A Case–Control Study. *Journal of pediatric gastroenterology and nutrition*, 31(4), 377-380.

This multicenter study of 137 case-control pairs searched for causes and risk factors related to severe upper digestive tract lesions. Case patients were full-term neonates with endoscopically confirmed severe bleeding or ulcerative lesions of the esophagus and/or stomach. Three factors were independently and significantly associated with esophageal and gastric lesions: use of antacid and antiulcer treatments (odds ratio [OR] 3.9), cardiac deceleration (OR 2.2), and breast-feeding (OR 0.5)..Breast-feeding may play a protective role against severe lesions in neonates.

Benhamou, P. H., Cheikh, A., Francoual, C., Kalach, N., De Boissieu, D., & Dupont, C. (1998). Possible Protection by Breast-Feeding against Severe Esophageal and Gastric Lesions in the Neonate. *Neonatology*, 73(5), 337-339.

The development of safe fiberoptic endoscopy in neonates led to the identification of the occurrence of severe esophageal and gastric lesions (EGL) in the first days of life. The cause of these early acute lesions, which are associated most of the time with severe clinical symptoms, remains unknown. 34 neonates with EGL were compared with controls born in the same maternity unit immediately after those enrolled in the EGL series. Clinical and obstetric data were not different in the 2 groups. Breast-feeding was less frequent ($p < 0.01$) and given later ($p = 0.0001$) in babies with EGL. This retrospective analysis yielded no indication relative to the causative phenomenon leading to such mucosal alterations. In contrast, it provides the first evidence of a possible protective role of breast-feeding.

Gastroesophageal Reflex

Heacock, H. J., Jeffery, H. E., Baker, J. L., & Page, M. (1992). Influence of breast versus formula milk on physiological gastroesophageal reflux in healthy, newborn infants. *Journal of pediatric gastroenterology and nutrition*, 14(1), 41-46.

Breastfed neonates demonstrate gastroesophageal reflux episodes of significantly shorter duration than formula fed neonates.

Inguinal Hernia

Pisacane, A., de Luca, U., Vaccaro, F., Valiante, A., Impagliazzo, N., & Caracciolo, G. (1995). Breast-feeding and inguinal hernia. *The Journal of pediatrics*, 127(1), 109-111.

Human milk contains gonadotropin releasing hormone, which may affect the maturation of neonatal testicular function. This case-control study showed breastfed infants had a significant dose response reduction in inguinal hernia.

Lactose Malabsorption

Rudzeviciene, O., Narkeviciute, I., & Eidukevicius, R. (2004). Lactose malabsorption in young Lithuanian children with atopic dermatitis. *Acta paediatrica (Oslo, Norway: 1992)*, 93(4), 482-486.

To determine the prevalence of lactose malabsorption in young Lithuanian atopic dermatitis children; to evaluate the relationship between lactose malabsorption and the duration of exclusive breastfeeding, and the relationship between lactose malabsorption and cow's milk intolerance in parents and grandparents. Methods: 144 children with atopic dermatitis aged 1.5-24 mo (study group) and 32 children without symptoms of allergic diseases (control group) were investigated. Lactose and glucose-galactose absorption tests based on serial blood glucose determination, culture of stool, latex agglutination test for rotavirus and microscopic examination of stool for parasites were performed. Lactose malabsorption was determined in 59 (40.9%) and glucose-galactose malabsorption in 17 (11.8%) children with atopic dermatitis. The risk of developing lactose malabsorption was higher in children fed exclusively on breast milk up to 1 month of age than in children fed exclusively on breast milk for 4 to 6 months (OR: 2.62). Lactose malabsorption was significantly more frequent in patients whose mothers did not tolerate cow's milk (66.7%) than in patients whose mothers were tolerant to it (41.1%). Conclusion: Lactose malabsorption was determined in 40.9% of Lithuanian atopic dermatitis children aged under 2 years. Lactose malabsorption appeared to be associated with brief duration of exclusive breastfeeding (less than 1 month) and mothers' milk intolerance.

Morbidity and Mortality

Khan, J., Vesel, L., Bahl, R., & Martines, J. C. (2015). Timing of breastfeeding initiation and exclusivity of breastfeeding during the first month of life: effects on neonatal mortality and morbidity—a systematic review and meta-analysis. *Maternal and child health journal*, 19(3), 468-479.

The purpose of this study was to review the evidence on the effect of initiation of breastfeeding early after birth and of exclusive breastfeeding during the first month in reducing neonatal mortality and morbidity. We searched Cochrane and PubMed databases for all available papers addressing our review questions and identified eleven papers. Data were extracted using a standard abstraction form. Evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation system. Meta-analysis was done using STATA 11.0. Early initiation of breastfeeding was associated with a reduced risk of neonatal mortality. Initiating breastfeeding after the first hour doubled the risk of neonatal mortality. Exclusively

breastfed neonates had a lower risk of mortality and infection-related deaths in the first month than partially breastfed neonates. Exclusively breastfed neonates also had a significantly lower risk of sepsis, diarrhea and respiratory infections compared with those partially breastfed. The pooled evidence indicates that substantial benefits in reducing neonatal mortality and morbidity can be achieved with effective promotion of early initiation of breastfeeding and exclusive breastfeeding during the first month of life.

Sankar, M. J., Sinha, B., Chowdhury, R., Bhandari, N., Taneja, S., Martinez, J., & Bahl, R. (2015). Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. *Acta paediatrica*, 104, 3-13.

To synthesize the evidence for effects of optimal breastfeeding on all-cause and infection-related mortality in infants and children aged 0–23 months. We conducted a systematic review to compare the effect of predominant, partial or nonbreastfeeding versus exclusive breastfeeding on mortality rates in the first six months of life and effect of no versus any breastfeeding on mortality rates between 6 and 23 months of age. A systematic literature search was conducted in PubMed, Cochrane CENTRAL and CABI. The risk of all-cause mortality was higher in predominantly (RR 1.5), partially (RR 4.8) and nonbreastfed (RR 14.4) infants compared to exclusively breastfed infants 0–5 months of age. Children 6–11 and 12–23 months of age who were not breastfed had 1.8- and 2.0-fold higher risk of mortality, respectively, when compared to those who were breastfed. Risk of infection-related mortality in 0–5 months was higher in predominantly (RR 1.7), partially (RR 4.56) and nonbreastfed (RR 8.66) infants compared to exclusive breastfed infants. The risk was twofold higher in nonbreastfed children when compared to breastfed children aged 6–23 months. The findings underscore the importance of optimal breastfeeding practices during infancy and early childhood.

Abrams, S. A., Schanler, R. J., Lee, M. L., Rechtman, D. J., & Prolacta Study Group. (2014). Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. *Breastfeeding Medicine*, 9(6), 281-285.

Provision of human milk has important implications for the health and outcomes of extremely preterm (EP) infants. This study evaluated the effects of an exclusive human milk diet on the health of EP infants during their stay in the neonatal intensive care unit. EP infants <1,250 g birth weight received a diet consisting of either human milk fortified with a human milk protein-based fortifier (HM) ($n=167$) or a diet containing variable amounts of milk containing cow milk-based protein (CM) ($n=93$). Principal outcomes were mortality, necrotizing enterocolitis (NEC), growth, and duration of parenteral nutrition (PN). Mortality (2% versus 8%, $p=0.004$) and NEC (5% versus 17%, $p=0.002$) differed significantly between the HM and CM groups, respectively. For every 10% increase in the volume of milk containing CM, the risk of sepsis increased by 17.9% ($p<0.001$). Growth rates were similar between groups. The duration of PN was 8 days less in the subgroup of infants receiving a diet containing <10% CM versus $\geq 10\%$ CM ($p<0.02$). An exclusive human milk diet, devoid of CM-containing products, was associated with lower mortality and morbidity in EP infants without compromising growth and should be considered as an approach to nutritional care of these infants.

Lauer, J. A., Betrán, A. P., Barros, A. J., & de Onís, M. (2006). Deaths and years of life lost due to suboptimal breast-feeding among children in the developing world: a global ecological risk assessment. *Public health nutrition*, 9(6), 673-685.

We estimate attributable fractions, deaths and years of life lost among infants and children 12 years of age due to suboptimal breast-feeding in developing countries. For infants, we consider deaths due to diarrhoeal disease and lower respiratory tract infections, and deaths due to all causes are considered in the second year of life. Outcome measures are attributable fractions, deaths, years of life lost and offsetting deaths potentially caused by mother-to-child transmission of HIV through breastfeeding. Attributable fractions for deaths due to diarrhoeal disease and lower respiratory tract infections are 55% and 53%, respectively, for the first six months of infancy, 20% and 18% for the second six months, and are 20% for all-cause deaths in the second year of life. Globally, as many as 1.45 million lives (117 million years of life) are lost due to suboptimal breastfeeding in developing countries. Offsetting deaths caused by mother-to-child transmission of HIV through breast-feeding could be as high as 242 000 (18.8 million years of life lost) if relevant World Health Organization recommendations are not followed. The size of the gap between current practice and recommendations is striking when one considers breast-feeding involves no out-of-pocket costs, that there exists universal consensus on best practices, and that implementing current international recommendations could potentially save 1.45 million children's lives each year.

Edmond, K. M., Zandoh, C., Quigley, M. A., Amenga-Etego, S., Owusu-Agyei, S., & Kirkwood, B. R. (2006). Delayed breastfeeding initiation increases risk of neonatal mortality. *Pediatrics*, 117(3), e380-e386.

10,947 breastfed singleton infants born in rural Ghana between July 2003 and June 2004.

Breastfeeding was initiated within the first day of birth in 71% of infants and by the end of day 3 in all but 1.3% of them; 70% were exclusively breastfed during the neonatal period. The risk of neonatal death was fourfold higher in children given milk-based fluids or solids in addition to breast milk. There was a marked dose response of increasing risk of neonatal mortality with increasing delay in initiation of breastfeeding from 1 hour to day 7; overall late initiation (after day 1) was associated with a 2.4-fold increase in risk. CONCLUSIONS: Promotion of early initiation of breastfeeding has the potential to make a major contribution to the achievement of the child survival millennium development goal; 16% of neonatal deaths could be saved if all infants were breastfed from day 1 and 22% if breastfeeding started within the first hour.

Breastfeeding-promotion programs should emphasize early initiation as well as exclusive breastfeeding. This has particular relevance for sub-Saharan Africa, where neonatal and infant mortality rates are high but most women already exclusively or predominantly breastfeed their infants.

Bahl, R., Frost, C., Kirkwood, B. R., Edmond, K., Martinez, J., Bhandari, N., & Arthur, P. (2005). Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study. *Bulletin of the World Health Organization*, 83, 418-426.

To determine the association of different feeding patterns for infants (exclusive breastfeeding, predominant breastfeeding, partial breastfeeding and no breastfeeding) with mortality and hospital admissions during the first half of infancy. Altogether, 9424 infants and their mothers

(2919 in Ghana, 4000 in India and 2505 in Peru) were enrolled when infants were 18-42 days old. Mother-infant pairs were visited at home every 4 weeks from the age of 6 weeks in Ghana and India and at the age of 10 weeks in Peru. At each visit, mothers were queried about what they had offered their infant to eat or drink during the past week. Information was also collected on hospital admissions and deaths occurring between the ages of 6 weeks and 6 months. The main outcome measures were all-cause mortality, diarrhoea-specific mortality, mortality caused by acute lower respiratory infections, and hospital admissions. Non-breastfed infants had a higher risk of dying when compared with those who had been predominantly breastfed. Conclusion: Finding that the risks of death are similar for infants who are predominantly breastfed and those who are exclusively breastfed suggests that in settings where rates of predominant breastfeeding are already high, promotion efforts should focus on sustaining these high rates rather than on attempting to achieve a shift from predominant breastfeeding to exclusive breastfeeding.

Chen, A., & Rogan, W. J. (2004). Breastfeeding and the risk of postneonatal death in the United States. *Pediatrics*, 113(5), e435-e439.

We evaluated the effect of breastfeeding on postneonatal mortality in United States using 1988 National Maternal and Infant Health Survey (NMIHS) data: 1204 infants who died between 28 days and 1 year from causes other than congenital anomaly or malignant tumor and 7740 children who were still alive at 1 year were included. Overall, children who were ever breastfed had 0.79 times the risk of never breastfed children for dying in the postneonatal period. Longer breastfeeding was associated with lower risk. Odds ratios by cause of death varied from 0.59 for injuries to 0.84 for sudden infant death syndrome. This large data set allowed robust estimates and control of confounding, but the effects of breast milk and breastfeeding cannot be separated completely from other characteristics of the mother and child. Assuming causality, however, promoting breastfeeding has the potential to save or delay ~720 postneonatal deaths in the United States each year.

Raisler, J., Alexander, C., & O'campo, P. (1999). Breast-feeding and infant illness: a dose-response relationship?. *American Journal of Public Health*, 89(1), 25-30.

The association between breastfeeding dose and illnesses in the first 6 months of life was analyzed for 7092 infants. Breastfeeding dose (ratio of breast-feedings to other feedings) was categorized as "full," "most," "equal," "less," or "no" breastfeeding. Compared with no breastfeeding, full breast-feeding infants had lower odds ratios of diarrhea, cough or wheeze, and vomiting and lower mean ratios of illness months and sick baby medical visits. "Most" breastfeeding infants had lower odds ratios of diarrhea and cough or wheeze, and "equal" breast-feeding infants had lower odds ratios of cough or wheeze. "Full," "most," and "equal" breastfeeding infants without siblings had lower odds ratios of ear infections and certain other illnesses, but those with siblings did not. "Less" breastfeeding infants had no reduced odds ratios of illness. Findings did not vary by income.

Hylander, M. A., Strobino, D. M., & Dhanireddy, R. (1998). Human milk feedings and infection among very low birth weight infants. *Pediatrics*, 102(3), e38-e38.

The incidence of any infection and sepsis/meningitis are significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants.

Jones, E. G., & Matheny, R. J. (1993). Relationship between infant feeding and exclusion rate from child care because of illness. *Journal of the American Dietetic Association*, 93(7), 809-811. During the first 6 months of life, breastfeeding has a protective effect against respiratory illnesses, gastrointestinal illnesses, and on all illnesses. Beaudry M et al. "Relation between infant feeding and infections during the first six months of life." *J Pediatr* 1995 Feb;126(2):191-7

Huygen, F. J. (1991). The relationship between breast-feeding and early childhood morbidity in a general population. *Family medicine*, 23(7), 510-515.

There is an inverse relationship to breastfeeding and morbidity. This was most prominent in the first year of life, but it was also present in the first three years.

Habicht, J. P., DaVanzo, J., & Butz, W. P. (1986). Does breastfeeding really save lives, or are apparent benefits due to biases?. *American journal of epidemiology*, 123(2), 279-290.

There is an association between breastfeeding up to 6 months of age and survival of infants throughout the first year of life. The younger the infant and the longer the breastfeeding, the greater the estimated benefits in terms of death averted.

Plagiocephaly

Not-breastfeeding predicted additional risks for developing plagiocephaly. Losee JE et al. Nonsynostotic occipital plagiocephaly: factors impacting onset, treatment, and outcomes. *Plast Reconstr Surg*. 2007 May;119(6):1866-73.

Bottle-feeding; always offering the feeding from the same side, was related to positional preference and asymmetry in children. Boere-Boonekamp M, van der Linden-Kuiper L. Positional preference: prevalence in infants and follow-up after two years. *Pediatrics*. 2001;107:3310-43.

Pyloric Stenosis

McAteer, J. P., Ledbetter, D. J., & Goldin, A. B. (2013). Role of bottle feeding in the etiology of hypertrophic pyloric stenosis. *JAMA pediatrics*, 167(12), 1143-1149.

Bottle feeding has been implicated in the etiology of hypertrophic pyloric stenosis (HPS). Further data are needed to define the nature of this relationship and the clinical variables that influence it. To determine if bottle feeding after birth is associated with the development of HPS in infants. We hypothesized that bottle feeding is associated with an increased risk of HPS and that this risk is modified by other risk factors. Population-based case-control study of births from January 1, 2003, to December 31, 2009, using Washington State birth certificates linked to hospital discharge data. Cases included all singleton infants born within the study period and subsequently admitted with both a diagnostic code for HPS and a procedure code for

pyloromyotomy (n = 714). Controls were randomly chosen among singleton infants who did not develop HPS and were frequency matched to cases by birth year. Hypertrophic pyloric stenosis incidence decreased over time, from 14 per 10 000 births in 2003 to 9 per 10 000 in 2009. Simultaneously, breastfeeding prevalence increased from 80% in 2003 to 94% in 2009. Compared with controls, cases were more likely to be bottle feeding after birth (19.5% vs 9.1%). After adjustment, bottle feeding was associated with an increased risk of HPS (odds ratio [OR], 2.31; 95% CI, 1.81-2.95). This association did not differ according to sex or maternal smoking status but was significantly modified by maternal age (<20 years OR, 0.98; 95% CI, 0.51-1.88; ≥35 years OR, 6.07; 95% CI, 2.81-13.10) and parity (nulliparous OR, 1.60; 95% CI, 1.07-2.38; multiparous OR, 3.42; 95% CI, 2.23-5.24). Bottle feeding is associated with an increased risk of HPS, and this effect seems to be most important in older and multiparous women. These data suggest that bottle feeding may play a role in HPS etiology, and further investigations may help to elucidate the mechanisms underlying the observed effect modification by age and parity.

Krogh, C., Biggar, R. J., Fischer, T. K., Lindholm, M., Wohlfahrt, J., & Melbye, M. (2012). Bottle-feeding and the risk of pyloric stenosis. *Pediatrics*, peds-2011.

Among 70,148 singleton infants, 65 infants had surgery for PS, of which 29 were bottle-fed before PS diagnosis. The overall HR of PS for bottle-fed infants compared with not bottle-fed infants was 4.62 (95% confidence interval [CI]: 2.78–7.65). Among bottle-fed infants, risk increases were similar for infants both breast and bottle-fed (HR: 3.36 [95% CI: 1.60–7.03]), formerly breastfed (HR: 5.38 [95% CI: 2.88–10.06]), and never breastfed (HR: 6.32 [95% CI: 2.45–16.26]) (P = .76). The increased risk of PS among bottle-fed infants was observed even after 30 days since first exposure to bottle-feeding and did not vary with age at first exposure to bottle-feeding. Bottle-fed infants experienced a 4.6-fold higher risk of PS compared with infants who were not bottle-fed. The result adds to the evidence supporting the advantage of exclusive breastfeeding in the first months after birth.

Pisacane, A., De Luca, U., Criscuolo, L., Vaccaro, F., Valiante, A., Inglese, A., ... & Pinto, L. (1996). Breast feeding and hypertrophic pyloric stenosis: population based case-control study. *BMJ*, 312(7033), 745-746.

Infants with pyloric stenosis were less likely to have been breastfed during the first week of life.

Retinopathy of Prematurity

Muneer, A., Attia Bari, S. N., & Ali, A. S. (2018). Is human milk feeding protective for Retinopathy of Prematurity?. *Pakistan Journal of Medical Sciences*, 34(6), 1534.

The objective of the study was to find the association between breast milk feeding with retinopathy of prematurity (ROP) in preterm infants. This was a cross sectional study to examine the effects of breast milk feeding on ROP. Premature newborns below 34 weeks from neonatal unit retinopathy of prematurity program during the years 2015 to 2017 of The Lahore General Hospital were included. We recorded the gestational age, birth weight, presence of ROP and the type of feeding (breastfeeding vs. formula milk). Out of 428 preterm babies 210 (49%) were males. More babies were between 32-34 weeks of gestation 229 (53.5%) as compared to < 32 weeks 199 (46.5%). Among all 428 preterm infants 19(4.4%) developed ROP. Majority 13

(68.4%) who developed ROP were <32 weeks of gestation ($p=0.042$). The mean birth weight of infants without ROP was 1.51 ± 0.36 kg (95%CI; 1.47-1.55), while it was 1.36 ± 0.29 kg (95%CI; 1.22-1.50) with ROP and all who developed ROP were < 2kg. The estimated odds ratio of developing ROP for breast fed versus top feeding was (ORs: 0.571, 95% CI; 0.222- 1.489). There was a trend toward lower incidence of ROP in the group of newborns who received breast-feeding (36.8%) as compared to top feeding (63.2%) but almost similar percentage who didn't develop ROP were breast fed or top fed with statistically insignificant results ($p= 0.24$). Slightly lesser percentage of preterm babies who were breastfed developed retinopathy of prematurity.

Zhou, J., Shukla, V. V., John, D., & Chen, C. (2015). Human milk feeding as a protective factor for retinopathy of prematurity: a meta-analysis. *Pediatrics*, 136(6), e1576-e1586.

The aim of this meta-analysis was to pool currently available data on incidence of ROP in infants fed human milk versus formula. Longitudinal studies comparing the incidence of ROP in infants who were fed human milk and formula were selected. Studies involving donor milk were not included. Two independent reviewers conducted the searches and extracted data. Meta-analysis used odds ratios (ORs), and subgroup analyses were performed. Five studies with 2208 preterm infants were included. Searches including various proportions of human milk versus formula, any-stage ROP, and severe ROP were defined to pool data for analyses. For any-stage ROP, the ORs (95% confidence intervals [CIs]) were as follows: exclusive human milk versus any formula, 0.29 (0.12 to 0.72); mainly human milk versus mainly formula, 0.51 (0.26 to 1.03); any human milk versus exclusive formula, 0.54 (0.15 to 1.96); and exclusive human milk versus exclusive formula, 0.25 (0.13 to 0.49). For severe ROP, they were 0.11 (0.04 to 0.30), 0.16 (0.06 to 0.43), 0.42 (0.08 to 2.18), and 0.10 (0.04 to 0.29), respectively. Based on current limited evidence, in very preterm newborns, human milk feeding potentially plays a protective role in preventing any-stage ROP and severe ROP.

Manzoni, P., Stolfi, I., Pedicino, R., Vagnarelli, F., Mosca, F., Pugni, L., ... & Borghesi, A. (2013). Human milk feeding prevents retinopathy of prematurity (ROP) in preterm VLBW neonates. *Early human development*, 89, S64-S68.

This is a secondary analysis of data collected during two multicenter RCTs performed consecutively (years 2004 through 2008) by a network of eleven tertiary NICUs in Italy. 314 infants received exclusively human maternal milk (group A), and 184 a preterm formula because their mothers were not expected to breastfeed. Overall, retinopathy of prematurity (ROP) incidence (any stage) was significantly lower in infants fed maternal milk (11 of 314; 3.5%) as compared to formula-fed neonates (29 of 184; 15.8%) (RR 0.14; 95% CI 0.12-0.62; $p = 0.004$). The same occurred for threshold ROP (1.3% vs. 12.3%, respectively; RR 0.19; 95% CI 0.05-0.69; $p = 0.009$). At multivariate logistic regression controlling for potentially confounding factors that were significantly associated to ROP (any stage) at univariate analysis (birth weight, gestational age, days on supplemental oxygen, systemic fungal infection, outborn, hyperglycaemia), type of milk feeding retained significance, human maternal milk being protective with $p = 0.01$. Exclusive human, maternal milk feeding since birth may prevent ROP of any stage in VLBW infants in the NICU.

Hylander, M. A., Strobino, D. M., Pezzullo, J. C., & Dhanireddy, R. (2001). Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants. *Journal of perinatology*, 21(6), 356.

The objective of this study was to examine the effect of human milk feedings on the incidence of ROP among VLBW infants. We identified 283 VLBW infants admitted to the Georgetown University Medical Center Neonatal Intensive Care Unit (NICU) from January 1992 through September 1993. All infants surviving to receive enteral feeding and ophthalmologic examinations for ROP (n=174) were included in the analysis. Type of feeding (human milk versus exclusive formula), presence of ROP, and potential confounding variables were abstracted retrospectively from medical records. ROP was present if any stage of ROP was diagnosed at any age during the initial NICU hospitalization; each case was counted once based on the worse severity of ROP in either eye. Multiple logistic regression was used to control for confounders. Major predictors of ROP were similar in both feeding groups including gestational age, days on mechanical ventilation, and total number of days on supplemental oxygen. The incidence of ROP differed significantly by type of feeding (human milk –41.0% vs. formula –63.5%, $p=0.005$). Human milk feeding independently correlated with a reduced odds of ROP (OR: 0.42, 95% CI: 0.19 to 0.93) ($p=0.03$), controlling for gestational age, duration of supplemental oxygen therapy, 5-minute Apgar score, and race. Human milk feeding independently correlated with a reduced odds of ROP (OR: 0.46, 95% CI: 0.18 to 0.91) ($p=0.03$), controlling for birthweight, duration of supplemental oxygen therapy, 5-minute Apgar score, and race. Human milk feeding among VLBW infants was associated with a lower incidence of ROP compared to exclusively formula-fed VLBW infants after adjusting for confounding variables.

Sudden Infant Death Syndrome (SIDS)

Thompson, J. M., Tanabe, K., Moon, R. Y., Mitchell, E. A., McGarvey, C., Tappin, D., ... & Hauck, F. R. (2017). Duration of breastfeeding and risk of SIDS: an individual participant data meta-analysis. *Pediatrics*, 140(5), e20171324.

Sudden infant death syndrome (SIDS) is a leading cause of postneonatal infant mortality. Our previous meta-analyses showed that any breastfeeding is protective against SIDS with exclusive breastfeeding conferring a stronger effect. The duration of breastfeeding required to confer a protective effect is unknown. To assess the associations between breastfeeding duration and SIDS. Breastfeeding variables, demographic factors, and other potential confounders were identified. Individual-study and pooled analyses were performed. A total of 2267 SIDS cases and 6837 control infants were included. In multivariable pooled analysis, breastfeeding for <2 months was not protective (adjusted odds ratio [aOR]: 0.91, 95% confidence interval [CI]: 0.68–1.22). Any breastfeeding ≥ 2 months was protective, with greater protection seen with increased duration (2–4 months: aOR: 0.60, 95% CI: 0.44–0.82; 4–6 months: aOR: 0.40, 95% CI: 0.26–0.63; and >6 months: aOR: 0.36, 95% CI: 0.22–0.61). Although exclusive breastfeeding for <2 months was not protective (aOR: 0.82, 95% CI: 0.59–1.14), longer periods were protective (2–4 months: aOR: 0.61, 95% CI: 0.42–0.87; 4–6 months: aOR: 0.46, 95% CI: 0.29–0.74). Breastfeeding duration of at least 2 months was associated with half the risk of SIDS. Breastfeeding does not need to be exclusive to confer this protection.

Alm, B., Wennergren, G., Möllborg, P., & Lagercrantz, H. (2016). Breastfeeding and dummy use have a protective effect on sudden infant death syndrome. *Acta Paediatrica*, 105(1), 31-38.

We conducted a literature review on the effect of breastfeeding and dummy (pacifier) use on sudden infant death syndrome (SIDS). From 4343 abstracts, we identified 35 relevant studies on breastfeeding and SIDS, 27 on dummy use and SIDS and 59 on dummy use versus breastfeeding. We found ample evidence that both breastfeeding and dummy use reduce the risk of SIDS. There has been a general reluctance to endorse dummy use in case it has a detrimental effect of breastfeeding. However, recent evidence suggests that dummy use might not be as harmful to breastfeeding as previously believed.

Hauck, F. R., Thompson, J. M., Tanabe, K. O., Moon, R. Y., & Vennemann, M. M. (2011). Breastfeeding and reduced risk of sudden infant death syndrome: a meta-analysis. *Pediatrics*, 128(1), 103-110.

A total of 18 studies out of a possible 288 were identified as of suitable quality to be included in this meta-analysis of the effect of breastfeeding on Sudden Infant Death Syndrome (SIDS). For infants who received any amount of breastmilk for any duration, the univariable SOR (summary odds ratio) was 0.40 (95% confidence interval [CI]: 0.35–0.44), and the multivariable SOR was 0.55 (95% CI: 0.44–0.69). For any breastfeeding at 2 months of age or older, the univariable SOR was 0.38 (95% CI: 0.27–0.54). The univariable SOR for exclusive breastfeeding of any duration was 0.27 (95% CI: 0.24–0.31). The authors conclude that breastfeeding is protective against SIDS, and this effect is stronger when breastfeeding is exclusive. They recommend that breastfeeding should be included with other SIDS risk-reduction messages to both reduce the risk of SIDS and promote breastfeeding for its many other infant and maternal health benefits.

Vennemann, M. M., Bajanowski, T., Brinkmann, B., Jorch, G., Yücesan, K., Sauerland, C., & Mitchell, E. A. (2009). Does breastfeeding reduce the risk of sudden infant death syndrome?. *Pediatrics*, 123(3), e406-e410.

In some countries the advice to breastfeed is included in the campaigns' messages, but in other countries it is not. The German Study of Sudden Infant Death is a case-control study of 333 infants who died of sudden infant death syndrome and 998 age matched controls. A total of 49.6% of cases and 82.9% of controls were breastfed at 2 weeks of age. Exclusive breastfeeding at 1 month of age halved the risk, partial breastfeeding at the age of 1 month also reduced the risk of sudden infant death syndrome, but after adjustment this risk was not significant. Being exclusively breastfed in the last month of life/before the interview reduced the risk, as did being partially breastfed. Breastfeeding survival curves showed that both partial breastfeeding and exclusive breastfeeding were associated with a reduced risk of sudden infant death syndrome. CONCLUSIONS: This study shows that breastfeeding reduced the risk of sudden infant death syndrome by approximately 50% at all ages throughout infancy. We recommend including the advice to breastfeed through 6 months of age in sudden infant death syndrome risk-reduction messages.

Hauck, F. R., Herman, S. M., Donovan, M., Iyasu, S., Moore, C. M., Donoghue, E., ... & Willinger, M. (2003). Sleep environment and the risk of sudden infant death syndrome in an

urban population: the Chicago Infant Mortality Study. *Pediatrics*, 111(Supplement 1), 1207-1214.

A population-based case-control study of 260 SIDS deaths that occurred in Chicago between 1993 and 1996 and an equal number of matched living controls. The racial/ethnic composition of the study groups was 75.0% black; 13.1% Hispanic white; and 11.9% non-Hispanic white. Several factors related to the sleep environment during last sleep were associated with higher risk of SIDS: placement in the prone position, soft surface, pillow use, face and/or head covered with bedding, bed sharing overall, bed sharing with parent(s) alone, and bed sharing in other combinations. Pacifier use was associated with decreased risk, as was breastfeeding either ever (OR: 0.2) or currently (OR: 0.2). In a multivariate model, several factors remained significant: prone sleep position, soft surface, pillow use, bed sharing other than with parent(s) alone, and not using a pacifier.

Alm, B., Wennergren, G., Norvenius, S. G., Skjaerven, R., Lagercrantz, H., Helweg-Larsen, K., & Irgens, L. M. (2002). Breastfeeding and the sudden infant death syndrome in Scandinavia, 1992–95. *Archives of Disease in Childhood*, 86(6), 400-402.

This analysis is based on data from the Nordic Epidemiological SIDS Study, a case-control study. After adjustment for smoking during pregnancy, paternal employment, sleeping position, and age of the infant, the adjusted odds ratio was 5.1 if the infant was exclusively breast fed for less than four weeks, 3.7 for 4-7 weeks, 1.6 for 8-11 weeks, and 2.8 for 12-15 weeks, with exclusive breastfeeding over 16 weeks as the reference. Mixed feeding in the first week post partum did not increase the risk.

McVea, K. L., Turner, P. D., & Pepler, D. K. (2000). The role of breastfeeding in sudden infant death syndrome. *Journal of Human Lactation*, 16(1), 13-20.

A meta-analysis and qualitative literature review were performed. Twenty-three studies were included in the meta-analysis. The studies were heterogeneous, and a majority (14) were of "fair" or "poor" quality. Crude ORs from 19 individual studies favored breastfeeding as protective against SIDS. The combined analysis indicated that bottle-fed infants were twice as likely to die from SIDS (pooled OR = 2.11). The results of the analysis show that there is an association between bottle-feeding and SIDS, but this may be related to confounding variables.

l'Hoir, M. P., Engelberts, A. C., Van Well, G. T. H. J., Bajanowski, T., Helweg-Larsen, K., & Huber, J. (1998). Sudden unexpected death in infancy: epidemiologically determined risk factors related to pathological classification. *Acta Paediatrica*, 87(12), 1279-1287.

Sixty-three infants who died suddenly and unexpectedly were classified into 3 groups: SIDS (19 cases), borderline SIDS (30 cases) and non-SIDS (14 cases). Non-SIDS cases received more breastfeeding, the parents hardly smoked during pregnancy and after birth, a firm mattress had been used, and more often signs of illness had been reported by the parents, compared with the SIDS and borderline SIDS cases.

Mitchell, A. (1991). Results from the First Year of The New Zealand Count Death Study. *N.Z. Med A.* 104:71-76

Not breastfeeding at discharge from an obstetric hospital at any stage of the infant's life was associated with an increased risk of SIDS.

Hoffmann, H. J. (1988). Results of the national institute of child health and human development SIDS cooperative epidemiological study. *Am. Nya. Cad. Sci.*, 533, 13.

A study indicated that breastfeeding was protective against SIDS, consistent with an effect mediated through the prevention of gastrointestinal and/or respiratory disease. Hoffman, H.J.,

Toddler Illnesses

Gulick, E. E. (1986). The effects of breast-feeding on toddler health. *Pediatric nursing*, 12(1), 51-54.

Mothers of 67 infants were questioned about the types and duration of illness episodes requiring medical care between 16 and 30 months of age. Breastfeeding was noted to decrease the number of infant illnesses and indirectly improve toddler health.

Wheezing

Azad, M. B., Vehling, L., Lu, Z., Dai, D., Subbarao, P., Becker, A. B., ... & Sears, M. R. (2017). Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. *European Respiratory Journal*, 49(5), 1602019.

The impact of breastfeeding on respiratory health is uncertain, particularly when the mother has asthma. We examined the association of breastfeeding and wheezing in the first year of life. We studied 2773 infants from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort. Caregivers reported on infant feeding and wheezing episodes at 3, 6 and 12 months. Breastfeeding was classified as exclusive, partial (supplemented with formula or complementary foods) or none. Overall, 21% of mothers had asthma, 46% breastfed for at least 12 months and 21% of infants experienced wheezing. Among mothers with asthma, breastfeeding was inversely associated with infant wheezing, independent of maternal smoking, education and other risk factors (adjusted rate ratio (aRR) 0.52; 95% CI 0.35–0.77 for ≥ 12 versus < 6 months breastfeeding). Compared with no breastfeeding at 6 months, wheezing was reduced by 62% with exclusive breastfeeding (aRR 0.38; 95% CI 0.20–0.71) and by 37% with partial breastfeeding supplemented with complementary foods (aRR 0.63; 95% CI 0.43–0.93); however, breastfeeding was not significantly protective when supplemented with formula (aRR 0.89; 95% CI 0.61–1.30). Associations were not significant in the absence of maternal asthma (p-value for interaction < 0.01). Breastfeeding appears to confer protection against wheezing in a dose-dependent manner among infants born to mothers with asthma.

Dong, G. H., Qian, Z. M., Liu, M. M., Wang, D., Ren, W. H., Bawa, S., ... & Simckes, M. (2013). Breastfeeding as a modifier of the respiratory effects of air pollution in children. *Epidemiology*, 24(3), 387-394.

Breastfeeding and air pollution are both important factors for respiratory symptoms and asthma in children. Few studies have examined possible interaction between them on respiratory outcomes. We studied 31,049 Chinese children, ages 2–14 years old, from 25 elementary

schools and 50 kindergartens in the Seven Northeastern Cities during 2008–2009. Parents or guardians completed questionnaires about the children's histories of respiratory conditions, risk factors, and feeding methods. Three-year average concentrations of particles with an aerodynamic diameter $\leq 10 \mu\text{m}$, sulfur dioxide, nitrogen dioxides, and ozone were calculated from monitoring stations in 25 study districts. We used two-level logistic regressions to examine the effects of exposure, controlling for covariates. Association of air pollution with childhood respiratory conditions was modified by breastfeeding. Compared with children who had been breastfed, those who were not exhibited consistently stronger effects of air pollution. Among non-breastfed children, odds ratios (ORs) per $10 \mu\text{g}/\text{m}^3$ increase in nitrogen dioxide were 1.40 (95% confidence interval = 1.19–1.64) for cough, 1.41 (1.16–1.71) for phlegm, 1.17 (1.00–1.36) for current wheeze, and 1.25 (1.07–1.46) for doctor-diagnosed asthma. For breastfed children, the ORs were 1.25 (1.09–1.43) for cough, 1.15 (0.99–1.34) for phlegm, 0.97 (0.87–1.08) for current wheeze, and 1.17 (1.05–1.32) for doctor-diagnosed asthma. Breastfeeding was more protective among younger children. Breastfeeding was also associated with reduced effects of passive smoke exposure in children. The authors concluded that breastfeeding is associated with smaller associations between air pollution and respiratory conditions in children, suggesting that breastfeeding reduces susceptibility to the respiratory effects of pollutants.

Guibas, G. V., Xepapadaki, P., Moschonis, G., Douladiris, N., Filippou, A., Tsirigoti, L., ... & Papadopoulos, N. G. (2013). Breastfeeding and wheeze prevalence in pre-schoolers and pre-adolescents: the Genesis and Healthy Growth studies. *Pediatric Allergy and Immunology*, 24(8), 772-781.

To date, extensive research has been undertaken on a potential link of breastfeeding (BF) to wheezing illnesses. Nevertheless, an association remains to be established, partly due to age-dependent discrepancies and different definitions of exposures/outcomes across studies. We thus investigated the relation of diverse infantile feeding patterns with wheeze/asthma prevalence in two cohorts of children of different ages (preschool and preadolescent). Wheeze ever/in the last 12 months (current) and doctor-diagnosed asthma were retrospectively reported by parents of the participants of two cross-sectional studies: the *Genesis* study (1871 children aged 1–5) and the *Healthy Growth* study (1884 children aged 9–13). Information on feeding practices (exclusive breastfeeding vs. mixed vs. formula feeding) and their duration (2 vs. 4 vs. 6 months) was recorded. Perinatal and anthropometric data were also collected. In pre-schoolers, regimes that did not entail exclusive BF were positively correlated to current/ever wheeze, both before and after adjustment for confounders. No differences between the associations of regimes with 2, 4 or 6 months of exclusive BF with current/ever wheeze were shown. Furthermore, there was no consistent correlation of feeding practices with physician-diagnosed asthma. In pre-adolescents, no association of infantile feeding patterns with the wheeze/asthma outcomes was observed. The authors concluded that exclusive BF is associated with reduced prevalence of current/ever wheeze in pre-schoolers; however, this appears to wane in older children. The association of a period of exclusive BF as low as 2 months with pre-school wheeze prevalence, appeared to be comparable with that of 6 months of exclusivity.

Soto-Ramírez, N., Karmaus, W., Zhang, H., Davis, S., Agarwal, S., & Albergottie, A. (2013). Modes of infant feeding and the occurrence of coughing/wheezing in the first year of life. *Journal of Human Lactation*, 29(1), 71-80.

The authors conducted prospective analyses of associations between the repeated ascertainment of feeding mode and wheezing in infancy. The Infant Feeding Practices Study II (2833 infants) provided data on coughing/wheezing episodes (CWEs) at 8 time points and feeding modes at 9 time points from months 1 to 12. Feeding modes were defined as direct breastfeeding, indirect breastfeeding (IBF, bottled breast milk), formula feeding (FF), and their combinations. In concurrent and delayed models using repeated measurements, the relative risks (RR) and their 95% confidence intervals (95% CI) of different feeding modes for CWEs were estimated. In the delayed models, only infants without symptoms were considered at risk for consequent CWE. In a model with a 1-month delay, compared to direct breastfeeding, any other feeding mode showed a statistically significant risk for CWEs (IBF: RR = 1.69, 95% CI [1.05, 2.72]; FF: RR = 1.26, 95% CI [1.08, 1.47]; mixed breast feeding plus FF: RR = 1.25, 95% CI [1.01, 1.55]; and FF and direct breastfeeding: RR = 1.38, 95% CI [1.14, 1.68]). In a concurrent effect model, FF, the combination of FF and IBF, and mixed breastfeeding plus formula were risk factors (RR = 1.38, 95% CI [1.19, 1.59], RR = 1.83, 95% CI [1.27, 2.63], and RR=1.35, 95% CI [1.11, 1.65]; respectively). Any mode of feeding that includes formula or bottled breast milk seems to be a moderate risk for cough or wheezing episodes in the first 12 months of life.

Garcia-Marcos, L., Mallol, J., Solé, D., Brand, P. L., & EISL Study Group. (2010). International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. *Pediatric Allergy and Immunology*, 21(5), 878-888.

Risk factors for wheezing during the first year of life (a major cause of respiratory morbidity worldwide) are poorly known in non-affluent countries. We studied and compared risk factors in infants living in affluent and non-affluent areas of the world. A population-based study was carried out in random samples of infants from centres in Latin America (LA) and Europe (EU). Parents answered validated questionnaires referring to the first year of their infant's life during routine health visits. Wheezing was stratified into occasional (1-2 episodes, OW) and recurrent (3 + episodes, RW). Among the 28687 infants included, the most important independent risk factors for OW and RW (both in LA and in EU) were having a cold during the first 3 months of life [OR for RW 3.12 (2.60-3.78) and 3.15 (2.51-3.97); population attributable fraction (PAF) 25.0% and 23.7%]; and attending nursery school [OR for RW 2.50 (2.04-3.08) and 3.09 (2.04-4.67); PAF 7.4% and 20.3%]. Other risk factors were as follows: male gender, smoking during pregnancy, family history of asthma/rhinitis, and infant eczema. Breast feeding for >3 months protected from RW [OR 0.8 (0.71-0.89) in LA and 0.77 (0.63-0.93) in EU]. University studies of mother protected only in LA [OR for OW 0.85 (0.76-0.95) and for RW 0.80 (0.70-0.90)]. Although most risk factors for wheezing are common in LA and EU; their public health impact may be quite different. Avoiding nursery schools and smoking in pregnancy, breastfeeding babies >3 months, and improving mother's education would have a substantial impact in lowering its prevalence worldwide.

Eneli, I. U., Karmaus, W. K., Davis, S., & Kuehr, J. (2006). Airway hyperresponsiveness and body mass index: the Child Health and Environment Cohort Study in Hesse, Germany. *Pediatric pulmonology*, 41(6), 530-537.

Increased body mass index has been linked to wheezing, a diagnosis of asthma, and morbidity. We investigated the association between body mass index (BMI), breastfeeding, and airway hyperresponsiveness (AHR) in 536 German schoolchildren. We analyzed consecutive surveys in 1994-1995 and 1997, conducted as part of the Child Health and Environment Cohort Study in Hesse, Germany. The questionnaire included questions adapted from the German version of the International Study of Asthma and Allergy in Childhood (ISAAC). A bronchial challenge test using 4.5% hypertonic saline was conducted during the 1997 survey. AHR was defined as a fall in forced expiratory volume in 1 sec (FEV1) of $\geq 15\%$. Of 536 children who participated in the 1997 survey (median age, 10.3 years), 82 (15%) tested positive for AHR. In a multivariate analysis, there was no association between AHR determined at age 10 years and the highest quintile of BMI compared to the lowest quintile at age 4 years (odds ratio (OR), 1.4; 95% confidence interval (CI), 0.5-3.6), 7-8 years (OR, 0.6; 95% CI, 0.1-2.5), or 10 years (OR, 1.1; 95% CI, 0.2-4.3). Breastfeeding for 12 weeks or longer protected against AHR (OR, 0.4; 95% CI, 0.2-0.9). However, when children in the highest quintile of BMI at age 4 years had been breastfed for 8 weeks or less, the prevalence of AHR at age 10 years was significantly increased (27.7%, $P = 0.01$). In conclusion, our results demonstrate a protective effect of breastfeeding against AHR, and reinforce the need to encourage breastfeeding. Although there was no association between BMI and AHR, our finding of an interactive effect of high BMI and short breastfeeding on AHR suggests a complex etiological pathway that needs to be further explored.

Baker, D., Taylor, H., & Henderson, J. (1998). Inequality in infant morbidity: causes and consequences in England in the 1990s. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Journal of Epidemiology & Community Health*, 52(7), 451-458. Infants who were breastfed for three or more months were significantly less likely to have three or more episodes of wheezing in the first six months after birth.

Burr, M. L., Limb, E. S., Maguire, M. J., Amarah, L., Eldridge, B. A., Layzell, J. C., & Merrett, T. G. (1993). Infant feeding, wheezing, and allergy: a prospective study. *Archives of Disease in Childhood*, 68(6), 724-728.

Children who had ever been breast fed had a lower incidence of wheeze than those who had not (59% and 74% respectively). The effect persisted to age 7 years in the non-atopics only, the risk of wheeze being halved in the breast fed children.

Porro, E., Indinnimeo, L., Antognoni, G., Midulla, F., & Criscione, S. (1993). Early wheezing and breastfeeding. *Journal of Asthma*, 30(1), 23-28.

Within the group who had had early wheezing, infants who had been breastfed for at least one month subsequently had less severe wheezing.

Wright, A. L., Holberg, C. J., Martinez, F. D., Morgan, W. J., & Taussig, L. M. (1989). Breastfeeding and lower respiratory tract illness in the first year of life. Group Health Medical Associates. *Bmj*, 299(6705), 946-949.

Breastfeeding seems to protect against wheezing respiratory tract illnesses in the first 4 months of life, particularly when other risk factors are present.

ALLERGIES

Allergies in general

Luccioli, S., Zhang, Y., Verrill, L., Ramos-Valle, M., & Kwegyir-Afful, E. (2014). Infant feeding practices and reported food allergies at 6 years of age. *Pediatrics*, 134(Supplement 1), S21-S28.

The goal of this study was to identify the frequency of physician-diagnosed food allergies among 6-year-old US children and study the impact of exclusive breastfeeding and complementary food introduction on this frequency. Data were analyzed from children who participated in the Infant Feeding Practices Study II Year 6 Follow-Up Study (Y6FU). Children with probable food allergy (pFA) were defined as children with report of physician-diagnosed food allergy at age 6 years. Subgroups of pFA included children who were not diagnosed before 1 year of age (new pFA) and those with atopic risk factors (high risk). Prevalence of total pFA in the Y6FU was 6.34%. The majority of these children had new pFA and high-risk factors. Higher maternal education, higher family income, family history of food allergy, and reported eczema before 1 year of age were significantly associated with higher odds of total or new pFA. Exclusive breastfeeding duration and timing of complementary food introduction were not significantly associated with total pFA. However, exclusive breastfeeding of ≥ 4 months compared with no breastfeeding was marginally associated with lower odds of new pFA (adjusted odds ratio: 0.51; $P = .07$); this effect was not observed with high-risk children. Analysis of infant and maternal variables in the Y6FU cohort of US children revealed that socioeconomic and atopic factors were the main predictors of pFA at age 6 years. Exclusive breastfeeding of ≥ 4 months may have a preventive effect on development of pFA after 1 year of age in non high-risk children.

Friedman, N. J., & Zeiger, R. S. (2005). The role of breast-feeding in the development of allergies and asthma. *Journal of Allergy and Clinical Immunology*, 115(6), 1238-1248.

Breastfeeding's role in the prevention of allergic disease remains controversial. Reasons for this controversy include methodological differences and flaws in the studies performed to date, the immunologic complexity of breast milk itself and, possibly, genetic differences among patients that would affect whether breast-feeding is protective against the development of allergies or is in fact sensitizing. The preponderance of evidence does suggest, however, that there would be much to lose by not recommending breast-feeding. In general, studies reveal that infants fed formulas of intact cow's milk or soy protein compared with breast milk have a higher incidence of atopic dermatitis and wheezing illnesses in early childhood. Consistent with these findings,

exclusive breast-feeding should be encouraged for at least 4 to 6 months in infants at both high and low risk of atopy and irrespective of a history of maternal asthma.

Stoney, R. M., Woods, R. K., Hosking, C. S., Hill, D. J., Abramson, M. J., & Thien, F. C. K. (2004). Maternal breast milk long-chain n-3 fatty acids are associated with increased risk of atopy in breastfed infants. *Clinical & Experimental Allergy*, 34(2), 194-200.

Australia has one of the highest prevalence rates internationally of allergic conditions, such as asthma and eczema. Atopy is one hallmark for the development of allergic disease and predisposes to allergic inflammation in the target organs. Omega-3 (n-3) fatty acids (FAs) are thought to act as precursors to the formation of less active inflammatory mediators, with the potential to reduce inflammation. To investigate whether increased n-3 FA levels in maternal breast milk are associated with a lower risk of developing atopy in infancy, 620 children born into families where at least one first-degree relative had an atopic disease were studied. Some 224 women provided either a colostrum (n=194) or 3-month expressed breast milk (EBM) sample (n=118). Maternal colostrum and 3-month EBM samples were analysed for FA content by gas chromatography. Skin prick tests (SPTs) to six common allergens were performed on infants at 6, 12 and 24 months of age and on mothers who agreed at study entry. For infants sensitized to foods at 6 months (n=29), the total n-3 FA level in the colostrum was significantly higher (P=0.004) as were levels of individual long-chain n-3 FAs, docosapentaenoic acid (DPA, C22:5, P=0.001) and docosahexaenoic acid (DHA, C22:6, P=0.002) than in non-sensitized infants. Infants with aero-allergen sensitization at 24 months (n=30) had higher levels of the n-3 FA, DPA (P=0.002) and DHA (P=0.007), and similarly higher total n-3 FA (P=0.009) in maternal colostrum than those infants who were not sensitized. Conclusion: Higher n-3 FA levels in the colostrum do not appear to confer protection against, but may be a risk factor for, the eventual development of atopy in high-risk breastfed infants.

Van Odijk, J., Kull, I., Borres, M. P., Brandtzaeg, P., Edberg, U., Hanson, L. Å., ... & Sundell, J. (2003). Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. *Allergy*, 58(9), 833-843.

The review concluded that breastfeeding seems to protect from the development of atopic disease. The effect appears even stronger in children with atopic heredity. If breast milk is unavailable or insufficient, extensively hydrolysed formulas are preferable to unhydrolysed or partially hydrolysed formulas in terms of the risk of some atopic manifestations.

Oddy, W. H., Holt, P. G., Sly, P. D., Read, A. W., Landau, L. I., Stanley, F. J., ... & Burton, P. R. (1999). Association between breastfeeding and asthma in 6 year old children: findings of a prospective birth cohort study. *Bmj*, 319(7213), 815-819.

2187 children were followed to age 6 years to study the association between duration of exclusive breastfeeding and asthma or atopy. After adjustment for confounders, the introduction of milk other than breastmilk before 4 months of age was a significant risk factor for all asthma and atopy related outcomes in children aged 6 years. A significant reduction in the risk of childhood asthma at age 6 years occurs if exclusive breast feeding is continued for at least the 4 months after birth.

Tariq, S. M., Matthews, S. M., Hakim, E. A., Stevens, M., Arshad, S. H., & Hide, D. W. (1998). The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *Journal of allergy and clinical immunology*, 101(5), 587-593.

A birth cohort was followed-up to age 4 years. By age 4 years, 27% of the children had symptoms of allergic disease. Family history of atopy was the single most important risk factor for atopy in children. Sibling atopy was a stronger predictor of clinical disease than maternal or paternal atopy. Formula-feeding before 3 months of age predisposed to asthma at age 4 years (OR: 1.8).

Marini, A., Agosti, M., Motta, G., & Mosca, F. (1996). Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years follow-up. *Acta Paediatrica*, 85, 1-21.

The factors most important in the pathogenesis of allergic symptoms were: (i) formula implementation begun in the first week of life; (ii) early weaning (< 4 months); (iii) feeding beef (< 6 months); (iv) early introduction of cow's milk (< 6 months); and (v) parental smoking in the presence of the babies and early day care admission (< 2 years of life). All the preventive measures used in this study (exclusive breastfeeding and/or hydrolyzed milk feeding, delayed and selective introduction of solid foods, and environmental advice) were effective at the third year of follow-up, greatly reducing allergic manifestations in high atopic Page 15 of 63 risk babies in comparison with those not receiving these interventions.

Merrett, T. G., Burr, M. L., Butland, B. K., Merrett, J., Miskelly, F. G., & Vaughan-Williams, E. (1988). Infant feeding and allergy: 12-month prospective study of 500 babies born into allergic families. *Annals of Allergy*, 61(6 Pt 2), 13-20.

Breastfeeding, even for short periods, was clearly associated with lower incidence of wheezing, prolonged colds, diarrhea, and vomiting.

Allergic Rhinitis

Bloch, A. M., Mimouni, D., Mimouni, M., & Gdalevich, M. (2002). Does breastfeeding protect against allergic rhinitis during childhood? A meta-analysis of prospective studies. *Acta Paediatrica*, 91(3), 275-279.

A systematic review was conducted of prospective studies that evaluated the association between exclusive breastfeeding during the first 3 mo after birth and allergic rhinitis. The summary odds ratio for the protective effect of breastfeeding was 0.74. The effect estimate in studies of children with a family history of atopy was 0.87. Exclusive breastfeeding during the first 3 months after birth protects against allergic rhinitis in children, both with and without a family history of atopy.

Asthma (see also “Wheezing”)

Abarca, N. E., Garro, A. C., & Pearlman, D. N. (2018). Relationship between breastfeeding and asthma prevalence in young children exposed to adverse childhood experiences. *Journal of Asthma*, 1-10.

The objective of this study was to investigate if duration of supplemental breastfeeding is associated with a lower asthma risk and whether adverse childhood experiences (ACEs) early in life influence this relationship in children ages 3 to 5 years. Methods: Data were from the 2011–2012 National Survey of Children's Health, a nationally representative cross-sectional survey. Modified Poisson regression models were used to estimate incident risk ratios (IRR) for lifetime and current asthma in young children aged 3 to 5 years ($n = 15,642$). We tested for effect measure modification using stratified analyses. Results: Exclusive breastfeeding for at least 6 months or supplemental breastfeeding for children ≥ 12 months significantly reduced the risk of lifetime asthma prevalence compared to never breastfed children (IRR 0.64; 95% CI: 0.46–0.88, $p = 0.007$; and IRR 0.68; 95% CI: 0.47–0.99, $p = 0.044$, respectively), adjusted for covariates. In stratified analyses, breastfeeding reduced the risk of lifetime asthma for children who experienced 1 ACE but not for children who experienced 2 or more ACEs. Conclusion: Exclusive breastfeeding for at least 6 months, with and without supplementation, appears to prevent asthma or delay its onset. The protective effect of breastfeeding was attenuated among children who experienced more than 2 ACEs. The known harmful effects that ACEs have on children's health may outweigh the benefits of breastfeeding in reducing the risk of a child developing asthma. Understanding how specific time periods in a child's life may be most affected by exposure to early life adversities, along with the protective effect of breastfeeding against asthma, are important areas of further study.

Huo, X., Chu, S., Hua, L., Bao, Y., Du, L., Xu, J., & Zhang, J. (2018). The effect of breastfeeding on the risk of asthma in high-risk children: a case-control study in Shanghai, China. *BMC pregnancy and childbirth*, 18(1), 341.

Increasing evidence shows that antibiotic use in pregnancy may increase the risk of childhood asthma but epidemiologic studies are still limited and findings are inconsistent. Meanwhile, exclusive and prolonged breastfeeding may prevent children from allergic diseases. We aimed to assess the association between prenatal antibiotic use and the risk of childhood asthma, and explore whether breastfeeding modifies the risk. We conducted a case-control study in Shanghai, China, from June 2015 to January 2016. A total of 634 asthma cases and 864 controls aged 3-12 years were included. Multiple logistic regressions were used to estimate crude and adjusted odds ratios (aOR). The prevalence of antibiotic use in pregnancy in the cases and controls was 7.1 and 3.5%, respectively. A significant association between prenatal antibiotic use and childhood asthma was observed (aOR: 1.7, 95% CI: 1.0-2.9), particularly in boys (aOR: 2.2, 95% CI: 1.1-4.4) and children with family history of allergic disorders (aOR: 3.1, 95% CI: 1.2-8.4). However, this association existed only in children who were not breastfed exclusively in the first six months of life (aOR 2.6, 95% CI 1.3-5.1) but not in children who were exclusively breastfed (aOR 0.9, 95% CI 0.4-2.1). Likewise, exclusive breastfeeding also decreased the association between antibiotic use in pregnancy and asthma in boys and in children with family histories of allergic diseases. Antibiotic use in pregnancy was a risk factor for childhood asthma. However, this risk may be attenuated by exclusive breastfeeding in the first six months of life, especially among high-risk children.

Moossavi, S., Miliku, K., Sepehri, S., Khafipour, E., & Azad, M. (2018). The prebiotic and probiotic properties of human milk: Implications for infant immune development and pediatric asthma. *Frontiers in pediatrics*, 6, 197.

The incidence of pediatric asthma has increased substantially in recent decades, reaching a worldwide prevalence of 14%. This rapid increase may be attributed to the loss of “Old Friend” microbes from the human microbiota resulting in a less diverse and “dysbiotic” gut microbiota, which fails to optimally stimulate immune development during infancy. This hypothesis is supported by observations that the gut microbiota is different in infants who develop asthma later in life compared to those who remain healthy. Thus, early life exposures that influence gut microbiota play a crucial role in asthma development. Breastfeeding is one such exposure; it is generally considered protective against pediatric asthma, although conflicting results have been reported, potentially due to variations in milk composition between individuals and across populations. Human milk oligosaccharides (HMOs) and milk microbiota are two major milk components that influence the infant gut microbiota and hence, development of the immune system. Among their many immunomodulatory functions, HMOs exert a selective pressure within the infant gut microbial niche, preferentially promoting the proliferation of specific bacteria including *Bifidobacteria*. Milk is also a source of viable bacteria originating from the maternal gut and infant oral cavity. As such, breastmilk has prebiotic and probiotic properties that can modulate two of the main forces controlling the gut microbial community assembly, i.e., dispersal and selection.

Huang, C., Liu, W., Cai, J., Weschler, L. B., Wang, X., Hu, Y., ... & Sundell, J. (2017).

Breastfeeding and timing of first dietary introduction in relation to childhood asthma, allergies, and airway diseases: a cross-sectional study. *Journal of Asthma*, 54(5), 488-497.

We investigated associations of breastfeeding (BF) durations and patterns and of timing of other dietary introductions with prevalence of asthma, wheeze, hay fever, rhinitis, pneumonia, and eczema among preschool children. *Methods*: During April 2011-April 2012, we conducted a cross-sectional study in 72 kindergartens from five districts of Shanghai, China and obtained 13,335 questionnaires of children 4–6-years-old. We used multiple logistic regression models to evaluate the target associations. *Results*: Compared to children who were never BF, children who were exclusively breastfed 3–6 months had the lowest risk of asthma (adjusted odds ratio and 95% confidence interval: 0.81, 0.72–0.91) and wheeze (0.93, 0.87–0.99); and exclusive BF >6 months was significantly associated with a reduced risk of hay fever (0.93, 0.89–0.97), rhinitis (0.97, 0.94–0.99), pneumonia (0.97, 0.94–0.99), and eczema (0.96, 0.93–0.99). No significant associations were found between the time when fruits or vegetables were introduced and the studied diseases. Associations were independent of the child's sex and parent's ownership of the current residence. Longer duration BF was only significantly protective when there was no family history of atopy. *Conclusions*: This study suggests that heredity, but not sex and socioeconomic status, may negatively impact the effect of BF on childhood airway and allergic diseases. Our findings support China's national recommendation that mothers provide exclusive BF for the first four months, and continue partial BF for more than 6 months.

den Dekker, H. T., Sonnenschein-van der Voort, A. M., Jaddoe, V. W., Reiss, I. K., de Jongste, J. C., & Duijts, L. (2016). Breastfeeding and asthma outcomes at the age of 6 years: The Generation R Study. *Pediatric Allergy and Immunology*, 27(5), 486-492.

Breastfeeding is associated with a lower risk of asthma symptoms in early childhood, but its effect at older ages remains unclear. We examined the associations of duration and exclusiveness of breastfeeding with asthma outcomes in children aged 6 years, and whether these associations were explained by atopic or infectious mechanisms. We performed a population-based prospective cohort study among 5675 children. Information about breastfeeding was collected by questionnaires. At age 6 years, we measured interrupter resistance (Rint) and fractional exhaled nitric oxide (FeNO). Information about wheezing patterns (early (≤ 3 years only), late (> 3 years only), persistent (≤ 3 and > 3 years)), and current asthma at 6 years was derived from repeated questionnaires. Compared to children who were ever breastfed, those who were never breastfed had lower FeNO levels (sympercent (95% CI): -16.0 (-24.5, -7.5)) and increased risks of late and persistent wheezing (OR(95% CI): 1.69 (1.06, 2.69) and 1.44 (1.00, 2.07), respectively). Shorter duration of breastfeeding was associated with early wheezing and current asthma (1.40 (1.14, 1.73) and 2.19 (1.29, 3.71), respectively). Less exclusive breastfeeding was associated with early wheezing (1.28 (1.08, 1.53)). Breastfeeding duration and exclusiveness were not associated with FeNO or Rint. The associations were not explained by inhalant allergies, partly by lower respiratory tract infections in early life, and to a lesser extent by lower respiratory tract infections in later life. The authors concluded that breastfeeding patterns may influence wheezing and asthma in childhood, which seems to be partly explained by infectious mechanisms.

Lodge, C. J., Tan, D. J., Lau, M. X. Z., Dai, X., Tham, R., Lowe, A. J., ... & Dharmage, S. C. (2015). Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatrica*, 104, 38-53.

The aim of this study was to systematically review the association between breastfeeding and childhood allergic disease. Predetermined inclusion/exclusion criteria identified 89 articles from PubMed, CINAHL and EMBASE databases. Meta-analyses performed for categories of breastfeeding and allergic outcomes. Meta-regression explored heterogeneity. More vs. less breastfeeding (duration) was associated with reduced risk of asthma for children (5–18 years), particularly in medium-/low-income countries and with reduced risk of allergic rhinitis ≤ 5 years, but this estimate had high heterogeneity and low quality. Exclusive breastfeeding for 3–4 months was associated with reduced risk of eczema ≤ 2 years (estimate principally from cross-sectional studies of low methodological quality). No association found between breastfeeding and food allergy (estimate had high heterogeneity and low quality). Meta-regression found differences between study outcomes may be attributable to length of breastfeeding recall, study design, country income and date of study inception. Some of the protective effect of breastfeeding for asthma may be related to recall bias in studies of lesser methodological quality. The authors concluded that there is some evidence that breastfeeding is protective for asthma (5–18 years). There is weaker evidence for a protective effect for eczema ≤ 2 years and allergic rhinitis ≤ 5 years of age, with greater protection for asthma and eczema in low-income countries.

Dogaru, C. M., Nyffenegger, D., Pescatore, A. M., Spycher, B. D., & Kuehni, C. E. (2014). Breastfeeding and childhood asthma: systematic review and meta-analysis. *American journal of epidemiology*, 179(10), 1153-1167.

Asthma and wheezing disorders are common chronic health problems in childhood.

Breastfeeding provides health benefits, but it is not known whether or how breastfeeding decreases the risk of developing asthma. We performed a systematic review and meta-analysis of studies published between 1983 and 2012 on breastfeeding and asthma in children from the general population. We searched the PubMed and Embase databases for cohort, cross-sectional, and case-control studies. We grouped the outcomes into asthma ever, recent asthma, or recent wheezing illness (recent asthma or recent wheeze). Using random-effects meta-analyses, we estimated pooled odds ratios of the association of breastfeeding with the risk for each of these outcomes. We performed meta-regression and stratified meta-analyses. We included 117 of 1,464 titles identified by our search. The pooled odds ratios were 0.78 (95% confidence interval: 0.74, 0.84) for 75 studies analyzing "asthma ever," 0.76 (95% confidence interval: 0.67, 0.86) for 46 studies analyzing "recent asthma," and 0.81 (95% confidence interval: 0.76, 0.87) for 94 studies analyzing recent wheezing illness. After stratification by age, the strong protective association found at ages 0–2 years diminished over time. We found no evidence for differences by study design or study quality or between studies in Western and non-Western countries. A positive association of breastfeeding with reduced asthma/wheezing is supported by the combined evidence of existing studies.

Kuiper, S., Muris, J. W., Dompeling, E., Kester, A. D., Wesseling, G., Knottnerus, J. A., & van Schayck, C. P. (2007). Interactive effect of family history and environmental factors on respiratory tract-related morbidity in infancy. *Journal of Allergy and Clinical Immunology*, 120(2), 388-395.

Family and environmental factors affect the development of respiratory morbidity. How these factors interact is unclear. We sought to clarify the interactive effect of family history of asthma and environmental factors on the occurrence of respiratory morbidity. Two hundred twenty-one infants with a positive family history of asthma (PFH) and 308 with a negative family history of asthma (NFH) were prenatally selected and followed until the age of 2 years. Exposure to environmental factors and the occurrence of respiratory morbidity were recorded. Infants with a PFH had more respiratory morbidity than infants with an NFH. Adjusted ORs ranged from 1.7 for expiratory wheezing to 4.9 for croup. Parental smoking increased the OR of a PFH for wheezing ever (OR, 5.8) and attacks of wheezing (OR, 6.8), as did Der p 1 (OR, 10.2 and OR, 7.1, respectively). Exposure to both parental smoking and Der p 1 further increased this OR (OR, 30.8 and OR, 26.2, respectively). Breastfeeding decreased the ORs of PFH for tonsillitis and acute otitis media. Parental smoking and Der p 1 increase the effect of a PFH on respiratory morbidity. Breast-feeding reduces this effect. Extra attention should be given to stimulate mothers to breast-feed their children in case they cannot stop smoking or taking sanitation measures.

Oddy, W. H., Peat, J. K., & de Klerk, N. H. (2002). Maternal asthma, infant feeding, and the risk of asthma in childhood. *Journal of allergy and clinical immunology*, 110(1), 65-67.

In a cohort study of 2602 West Australian children enrolled before birth and followed prospectively, we collected data on method of infant feeding, maternal asthma (as reported by parental questionnaire), atopy (as measured by skin prick test), and current asthma (defined as a physician's diagnosis of asthma and wheeze in the last year) at 6 years of age. The risk of childhood asthma increased if exclusive breast-feeding was stopped (other milk was introduced) before 4 months (odds ratio, 1.28), and this risk was not altered by atopy or maternal asthma status. After adjusting for covariates, exclusive breast-feeding for less than 4 months was a significant risk factor for current asthma (odds ratio, 1.35).

Dell, S., & To, T. (2001). Breastfeeding and asthma in young children: findings from a population-based study. *Archives of pediatrics & adolescent medicine*, 155(11), 1261-1265. A sample of 2184 Canadian children between the ages of 12 and 24 months, whose mother reported data on breastfeeding and asthma, were studied. Outcomes included parental report of physician-diagnosed asthma and wheeze in the previous year. The prevalence of asthma was 6.3%; and wheeze, 23.9%. After adjustment for smoking, low birth weight, low maternal education, and sex, a duration of breastfeeding for less than 9 months was found to be a risk factor for asthma (odds ratio 2.39) and wheeze (odds ratio 1.54). A dose-response effect was observed, with a longer breastfeeding duration being protective against the development of asthma and wheeze in young children.

Gdalevich, M., Mimouni, D., & Mimouni, M. (2001). Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *The Journal of pediatrics*, 139(2), 261-266.

Meta analysis of 12 prospective studies found the odds ratio (OR) for the protective effect of breast-feeding was 0.70. The effect estimate was greater in studies of children with a family history of atopy (OR = 0.52) than in studies of a combined population (OR = 0.73).

CONCLUSIONS: Exclusive breast-feeding during the first months after birth is associated with lower asthma rates during childhood. The effect, caused by immunomodulatory qualities of breast milk, avoidance of allergens, or a combination of these and other factors, strengthens the advantage of breast-feeding, especially if a family history of atopy is present.

Haby, M. M., Peat, J. K., Marks, G. B., Woolcock, A. J., & Leeder, S. R. (2001). Asthma in preschool children: prevalence and risk factors. *Thorax*, 56(8), 589-595.

Parents of children aged 3-5 years living in two cities in Australia were surveyed by questionnaire to ascertain the presence of asthma and various proposed risk factors for asthma in their children. Recent asthma was defined as ever having been diagnosed with asthma and having cough or wheeze in the last 12 months and having used an asthma medication in the last 12 months. Atopy was measured by skin prick tests to six common allergens. The prevalence of recent asthma was 18% to 22%. Factors which increased the risk of recent asthma were: atopy (odds ratio 2.35), having a parent with a history of asthma (OR 2.05), having had a serious respiratory infection in the first 2 years of life (OR 1.93), and a high dietary intake of polyunsaturated fats (OR 2.03). Breast feeding (OR 0.41) and having three or more older siblings (OR 0.16) decreased the risk of recent asthma. Of the factors tested, those

that have the greatest potential to be modified to reduce the risk of asthma are breast feeding and consumption of polyunsaturated fats.

Oddy, W. H., Holt, P. G., Sly, P. D., Read, A. W., Landau, L. I., Stanley, F. J., ... & Burton, P. R. (1999). Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *Bmj*, 319(7213), 815-819.

Introducing milk other than breast milk to infants younger than 4 months old increases the risk of asthma and atopy (a predisposition to certain allergies). The investigators followed 2,187 children from before birth through their 6th birthday. Children who were fed milk other than breast milk before 4 months of age experienced higher rates of all indicators of asthma and allergy. Such children were 25% more likely to be diagnosed with allergy and 30% more likely to have a positive skin test for allergies than were children who received only breast milk during their early months. The total duration of exclusive breastfeeding was less important, though longer breastfeeding was associated with less asthma and allergy. The researchers also found increased risks of asthma and atopy among boys, infants born prematurely, and children living in households where smoking took place.

Eczema

Chiu, C. Y., Liao, S. L., Su, K. W., Tsai, M. H., Hua, M. C., Lai, S. H., ... & Huang, J. L. (2016). Exclusive or partial breastfeeding for 6 months is associated with reduced milk sensitization and risk of eczema in early childhood: the PATCH Birth Cohort Study. *Medicine*, 95(15).

There is insufficient evidence to confirm the association between breastfeeding and allergic outcomes later in life. This study aimed to determine the relationships between different breastfeeding patterns and allergen sensitizations and risk of developing atopic diseases in early childhood. A total of 186 children from a birth cohort in the Prediction of Allergies in Taiwanese Children study for a 4-year follow-up period were enrolled. Total serum immunoglobulin E (IgE) levels and specific IgE antibodies against food and inhalant allergens were measured sequentially at 6 months as well as at 1, 1.5, 2, 3, and 4 years of age. A significantly lower prevalence of milk sensitization was found in children at ages 1 and 1.5 years who were exclusively or partially breastfed for ≥ 6 months. Breastfeeding ≥ 6 months was significantly associated with a reduced risk of developing eczema but not allergic rhinitis and asthma at ages 1 and 2 years. Compared with exclusive breastfeeding ≥ 6 months, partial breastfeeding < 6 months was significantly associated with an increased risk of developing eczema at ages 1 and 2 years. As with exclusive breastfeeding, partial breastfeeding for at least 6 months appears to be associated with a reduced prevalence of milk sensitization as well as a reduced risk of developing eczema in early childhood.

Stabell Benn, C., Wohlfahrt, J., Aaby, P., Westergaard, T., Benfeldt, E., Fleischer Michaelsen, K., ... & Melbye, M. (2004). Breastfeeding and risk of atopic dermatitis, by parental history of allergy, during the first 18 months of life. *American journal of epidemiology*, 160(3), 217-223.

The authors studied the association between breastfeeding and development of atopic dermatitis during the first 18 months of life among children with and without a parental history of allergy. A cohort study of 15,430 mother-child pairs enrolled in The Danish National Birth Cohort

was carried out between 1998 and 2000. Data on breastfeeding, atopic dermatitis, and potential confounders was obtained from telephone interviews conducted during pregnancy and when the children were 6 and 18 months of age. The cumulative incidence of atopic dermatitis was 11.5% at 18 months of age. Overall, current breastfeeding was not associated with atopic dermatitis (incidence rate ratio (IRR) = 0.91, 95% confidence interval (CI): 0.80, 1.04). Exclusive breastfeeding for at least 4 months was associated with an increased risk of atopic dermatitis in children with no parents with allergies (IRR = 1.29, 95% CI: 1.06, 1.55) but not for children with one (IRR = 1.11, 95% CI: 0.94, 1.31) or two (IRR = 0.88, 95% CI: 0.69, 1.13) parents with allergies (test for homogeneity, $p = 0.03$). The authors found no overall effects of exclusive or partial breastfeeding on the risk of atopic dermatitis. However, the effect of exclusive breastfeeding for 4 months or more depended on parental history of allergic diseases.

Gdalevich, M., Mimouni, D., David, M., & Mimouni, M. (2001). Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *Journal of the American Academy of Dermatology*, 45(4), 520-527.

This meta-analysis of 18 prospective studies evaluated the association between exclusive breast-feeding during the first 3 months after birth and atopic dermatitis. The odds ratio (OR) for the protective effect of breast-feeding in the studies analyzed was 0.68. This effect estimate was higher in the group of studies wherein children with a family history of atopy were investigated separately (OR = 0.58) than in those of combined populations (OR = 0.84). A small subset of studies of children without a history of atopy in first-degree relatives showed no association between breast-feeding and the onset of atopic dermatitis (OR = 1.43). Exclusive breast-feeding during the first 3 months of life is associated with lower incidence rates of atopic dermatitis during childhood in children with a family history of atopy. This effect is lessened in the general population and negligible in children without first-order atopic relatives. Breast-feeding should be strongly recommended to mothers of infants with a family history of atopy, as a possible means of preventing atopic eczema.

DEVELOPMENT AND INTELLIGENCE

Microbiome

Walker, W. A., & Iyengar, R. S. (2014). Breast milk, microbiota, and intestinal immune homeostasis. *Pediatric Research*, 77(1-2), 220.

Newborns adjust to the extrauterine environment by developing intestinal immune homeostasis. Appropriate initial bacterial colonization is necessary for adequate intestinal immune development. An environmental determinant of adequate colonization is breast milk. Although the full-term infant is developmentally capable of mounting an immune response, the effector immune component requires bacterial stimulation. Breast milk stimulates the proliferation of a well-balanced and diverse microbiota, which initially influences a switch from an intrauterine TH2 predominant to a TH1/TH2 balanced response and with activation of T-regulatory cells by breast milk-stimulated specific organisms (*Bifidobacteria*, *Lactobacillus*, and *Bacteroides*). As an example of its effect, oligosaccharides in breast milk are fermented by colonic bacteria

producing an acid milieu for bacterial proliferation. In addition, short-chain fatty acids in breast milk activate receptors on T-reg cells and bacterial genes, which preferentially mediate intestinal tight junction expression and anti-inflammation. Other components of breast milk (defensins, lactoferrin, etc.) inhibit pathogens and further contribute to microbiota composition. The breast milk influence on initial intestinal microbiota also prevents expression of immune-mediated diseases (asthma, inflammatory bowel disease, type 1 diabetes) later in life through a balanced initial immune response, underscoring the necessity of breastfeeding as the first source of nutrition.

Bedwetting

de Oliveira, D. M., Dahan, P., Ferreira, D. F., de Oliveira, L. F., de Paula, L. I. D. S., de Figueiredo, A. A., ... & Netto, J. M. B. (2016). Association between exclusive maternal breastfeeding during the first 4 months of life and primary enuresis. *Journal of pediatric urology*, 12(2), 95-e1.

Although the relationship between enuresis and breastfeeding is still poorly documented in the literature, a possible association is speculated as both are strongly associated with children's development. Therefore, the main objective of this study was to evaluate whether there is an association between primary enuresis and the duration of exclusive breastfeeding. This is an observational, case-control study, involving 200 children and adolescents from 6 to 14 years old, who were divided into two groups: the enuresis group (EG), composed of 100 children with primary enuresis; and the control group (CG) of 100 matched children without enuresis. The matching criteria were sex, age, and socioeconomic level. Adults responsible for each infant answered a structured questionnaire to identify biological and behavioral factor, as well as the duration of maternal breastfeeding. Children whose parents could not comprehend the questionnaire or children with neurological or psychiatric disorders or secondary enuresis were not included in the study. Evaluating the duration of exclusive breastfeeding, 72% of the subjects of the EG and 42% of the CG had been breastfed for less than 4 months ($p < 0.001$) (Figure). In bivariate analysis, there was a strong association between symptoms of enuresis with a positive family history of enuresis and duration of exclusive breastfeeding ($p < 0.001$), and also association with full breastfeeding duration ($p = 0.044$), number of children ($p = 0.045$), and parents' education ($p = 0.045$). After logistic regression, primary enuresis continued to be associated with duration of exclusive breastfeeding and family history of enuresis. The proportion of children that had been exclusively breastfed for more than 4 months was significantly higher in the CG 58% (58/100) than in the EG 28% (28/100) ($p < 0.001$, OR 4.35, 95% CI 1.99–9.50). This study confirmed the association between primary enuresis and various factors that have already been studied, with the addition of a new factor, duration of exclusive breastfeeding for less than 4 months, which is strongly associated with primary enuresis.

Barone, J. G., Ramasamy, R., Farkas, A., Lerner, E., Creenan, E., Salmon, D., ... & Schneider, D. (2006). Breastfeeding during infancy may protect against bed-wetting during childhood. *Pediatrics*, 118(1), 254-259.

A case-control study was conducted in a pediatric continence center and a general pediatric practice. Cases ($n = 55$) were recruited from the continence center and defined as children 5 to

13 years of age who experienced lifetime involuntary voiding of urine during nighttime sleep at least 2 times a week in the absence of defects of the central nervous system or urinary tract. Age- and gender-matched controls (n = 117) who did not exhibit bed-wetting were enrolled from a general pediatric practice. Infant feeding practices were measured as breastfeeding (yes/no) and, for those who were breastfed, by the duration of breastfeeding and the time of formula supplementation. Among the case subjects, 45.5% were breastfed, whereas among the controls 81.2% were breastfed. After adjusting for race, income, and family size, the odds ratio was 0.283, indicating that case subjects were significantly less likely than controls to be breastfed. Among all the study subjects who were breastfed, controls were breastfed for a significantly longer period than case subjects (an average of 3 months longer). Although breastfed controls were less likely to be supplemented with formula than breastfed case subjects, this difference was not statistically significant. Breastfeeding longer than 3 months may protect against bed-wetting during childhood. Breast milk supplemented with formula Page 17 of 63 did not make a difference in the rate of enuresis.

Brain Activity in Infants of Depressed Mothers

Jones, N. A., McFall, B. A., & Diego, M. A. (2004). Patterns of brain electrical activity in infants of depressed mothers who breastfeed and bottle feed: The mediating role of infant temperament. *Biological Psychology*, 67(1-2), 103-124.

The present study was designed to examine the association between breastfeeding and temperament in infants of depressed mothers. Seventy-eight mothers, 31 who were depressed, and their infants participated. Depressed mothers who had stable breastfeeding patterns were less likely to have infants with highly reactive temperaments. Infants of depressed mothers who breastfed did not show the frontal asymmetry patterns, i.e., left frontal hypoactivity, previously reported. Moreover, breastfeeding stability, even in depressed mothers, was related to more positive dyadic interactions. Finally, a model was supported, in which the effects of maternal depression on infant feeding are mediated by infant frontal EEG asymmetry and infant temperament. These findings could provide a foundation for developing intervention techniques, employing breastfeeding promotion and support, directed toward attenuating the affective and physiological dysregulation already noted in infants of depressed mothers.

Brainstem, Cognitive, and Motor Development in Preterm Infants

Hallowell, S. G., & Spatz, D. L. (2012). The relationship of brain development and breastfeeding in the late-preterm infant. *Journal of pediatric nursing*, 27(2), 154-162.

Late-preterm infants (34 0/7–36 6/7 weeks gestation) are physiologically and developmentally immature at birth. The relationship between brain development and feeding is important since adequate oral intake is imperative to prevent feeding-related morbidity and mortality associated with being late preterm. One third of brain growth occurs in the last 6–8 weeks of gestation. The ontogeny of coordinated oral feeding appears to follow a chronological, predictable pattern in preterm neonates. This suggests that neurodevelopmental maturation, rather than experience or learned behavior, is largely responsible for feeding behaviors. The aim of this article is to

provide a review of the literature that establishes the relationship between brain development and feeding in the late-preterm infant.

Vohr, B. R., Poindexter, B. B., Dusick, A. M., McKinley, L. T., Wright, L. L., Langer, J. C., & Poole, W. K. (2006). Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics*, 118(1), e115-e123.

Nutrition data including enteral and parenteral feeds were collected prospectively, and follow-up assessments of 1035 extremely low birth weight infants at 18 months' corrected age were completed at 15 sites that were participants in the National Institute of Child Health and Human Development Neonatal Research Network Glutamine Trial between October 14, 1999, and June 25, 2001. Total volume of breast milk feeds (mL/kg per day) during hospitalization was calculated. There were 775 (74.9%) infants in the breast milk and 260 (25.1%) infants in the no breast milk group. Infants in the breast milk group were similar to those in the no breast milk group in every neonatal characteristic and morbidity, including number of days of hospitalization. Mean age of first day of breast milk for the breast milk infants was 9.3 +/- 9 days. Infants in the breast milk group began to ingest non-breast milk formula later (22.8 vs 7.3 days) compared with the non-breast milk group. Age at achieving full enteral feeds was similar between the breast milk and non-breast milk groups (29.0 +/- 18 vs 27.4 +/- 15). Energy intakes of 107.5 kg/day and 105.9 kg/day during the hospitalization did not differ between the breast milk and nonbreast milk groups, respectively. At discharge, 30.6% of infants in the breast milk group still were receiving breast milk. Mothers in the breast milk group were significantly more likely to be white (42% vs 27%), be married (50% vs 30%), have a college degree (22% vs 6%), and have private health insurance (34% vs 18%) compared with the no breast milk group. Mothers who were black, had a low household income (< or = dollar 20000), or had higher parity were less likely to provide breast milk feeds. The analysis of outcomes between the any human milk and no human milk groups were adjusted for maternal age, maternal education, marital status, race/ethnicity, and the other standard covariates. Children in the breast milk group were more likely to have a Bayley Mental Development Index > or = 85, higher mean Bayley Psychomotor Development Index, and higher Bayley Behavior Rating Scale percentile scores for orientation/engagement, motor regulation, and total score. There were no differences in the rates of moderate to severe cerebral palsy or blindness or hearing impairment between the 2 study groups. There were no differences in the mean weight (10.4 kg vs 10.4 kg), length (80.5 cm vs 80.5 cm), or head circumference (46.8 cm vs 46.6 cm) for the breast milk and no breast milk groups, respectively, at 18 months. Multivariate analyses, adjusting for confounders, confirmed a significant independent association of breast milk on all 4 primary outcomes: the mean Bayley (Mental Development Index, Psychomotor Development Index, Behavior Rating Scale, and incidence of rehospitalization). For every 10-mL/kg per day increase in breast milk ingestion, the Mental Development Index increased by 0.53 points, the Psychomotor Development Index increased by 0.63 points, the Behavior Rating Scale percentile score increased by 0.82 points, and the likelihood of rehospitalization decreased by 6%. In an effort to identify a threshold effect of breast milk on Bayley Mental Development Index and Psychomotor Development Index scores and Behavior Rating Scale percentile scores, the mean volume of breast milk per kilogram per day during the hospitalization was calculated, and infants in the

breast milk group were divided into quintiles of breast milk ingestion adjusted for confounders. Overall, the differences across the feeding quintiles of Mental Development Index and Psychomotor Development Index were significant. There was a 14.0% difference in Behavior Rating Scale scores between the lowest and highest quintiles. For the outcomes (Mental Development Index, Psychomotor Development Index, Behavior Rating Scale, and Rehospitalization 80th percentile quintile of breast milk feeding were significantly different from the no breast milk values. In our adjusted regression analyses, every 10 mL/kg per day breast milk contributed 0.53 points to the Bayley Mental Development Index; therefore, the impact of breast milk ingestion during the hospitalization for infants in the highest quintile (110 mL/kg per day) on the Bayley Mental Development Index would be 10×0.53 , or 5.3 points.

CONCLUSIONS: An increase of 5 points potentially would optimize outcomes and decrease costs by decreasing the number of very low birth weight children who require special education services. The societal implications of a 5-point potential difference (one third of an SD) in IQ are substantial. The potential long-term benefit of receiving breast milk in the NICU for extremely low birth weight infants may be to optimize cognitive potential and reduce the need for early intervention and special education services.

Bier, J. A. B., Oliver, T., Ferguson, A. E., & Vohr, B. R. (2002). Human milk improves cognitive and motor development of premature infants during infancy. *Journal of Human Lactation*, 18(4), 361-367.

Thirty-nine premature infants, 29 of whom received human milk (HMG) and 10 of whom received formula only (FG), were enrolled in a study examining the effect of human milk on cognitive and motor development. Infants were assessed at 3, 7, and 12 months corrected ages; the Peabody Picture Vocabulary Test was administered to their mothers. HMG infants had higher motor scores than FG infants at 3 months (48 ± 20 vs 35 ± 12 , $P = .05$) and 12 months (63 ± 20 vs 46 ± 15 , $P < 0.05$) and higher cognitive scores at 12 months corrected age (101 ± 11 vs 90 ± 9 , $P < 0.05$) adjusting for oxygen requirement and maternal vocabulary score. Human milk is associated with improved development of premature infants at 3 and 12 months corrected age in this sample.

Amin, S. B., Merle, K. S., Orlando, M. S., Dalzell, L. E., & Guillet, R. (2000). Brainstem maturation in premature infants as a function of enteral feeding type. *Pediatrics*, 106(2), 318-322.

Brainstem maturation was measured by brainstem auditory-evoked responses (BAERs) in preterm infants born at 28 to 32 weeks' gestation, and cared for in the neonatal intensive care unit of a regional referral center in Upstate New York. Baseline and follow-up BAER measurements were compared, and the rates of change were calculated. Data from 37 study infants (17 fed breast milk and 20 fed commercial premature formula) revealed that infants fed breast milk have faster brainstem maturation, compared with infants fed formula.

Cognitive Development, Intelligence, IQ and Behaviour

Amiel Castro, R., Glover, V., Ehlert, U., & O'Connor, T. G. (2021). Breastfeeding, prenatal depression and children's IQ and behaviour: a test of a moderation model. *BMC pregnancy and childbirth*, 21(1), 1-12.

Background: We aimed to determine the associations between breastfeeding and children's neurodevelopment indexed by intelligence quotient (IQ) and emotional and behavioural problems through mid-childhood adjusting for prenatal and postnatal depression and multiple confounders; and to test the novel hypothesis that breastfeeding may moderate the effects of prenatal depression and anxiety on children's neurodevelopment. **Methods:** The study is based on women and their children from the longitudinal Avon Longitudinal Study of Parents and Children (n=11,096). Children's IQ was derived from standardized in-person testing; behaviour problems were assessed according to parent-report; information on breastfeeding, prenatal depression and anxiety and multiple confounders were derived from self-report questionnaires. We conducted hierarchical multiple regression adjusting for several covariates. **Results:** 43% women were exclusively breastfeeding at 1 month and an additional 16.8% were engaged in mixed or partial breastfeeding. Both exclusive breastfeeding ($B = 2.19$; $SD = 0.36$, $p = .00$) and mixed feeding ($B = 1.59$; $SD = 0.52$; $p = .00$) were positively associated with IQ at 8 years of age, after adjusting for covariates. Exclusive breastfeeding was negatively associated with hyperactivity/attention deficit at 4 years ($B = -.30$, $SD = .05$; $p < .01$); mixed feeding was related to hyperactivity/attention deficit at age 9 ($B = .20$; $SD = .08$; $p = .03$) after adjustments. There was no association between breastfeeding and emotional or conduct problems. Breastfeeding did not moderate the association between prenatal depression and anxiety and children's neurodevelopment. **Conclusions:** The selective association between breastfeeding and neurodevelopmental measures suggests a nutritional rather than broader beneficial psychological effect on child neurodevelopment. Breastfeeding did not moderate the associations between prenatal depression and anxiety and child neurodevelopment, suggesting separate mechanisms of action.

Belfort, M. B., Anderson, P. J., Nowak, V. A., Lee, K. J., Molesworth, C., Thompson, D. K., ... & Inder, T. E. (2016). Breast milk feeding, brain development, and neurocognitive outcomes: a 7-year longitudinal study in infants born at less than 30 weeks' gestation. *The Journal of pediatrics*, 177, 133-139.

The objective of this study is to determine the associations of breast milk intake after birth with neurological outcomes at term equivalent and 7 years of age in very preterm infants. We studied 180 infants born at <30 weeks' gestation or <1250 grams birth weight enrolled in the Victorian Infant Brain Studies cohort from 2001-2003. We calculated the number of days on which infants received >50% of enteral intake as breast milk from 0-28 days of life. Outcomes included brain volumes measured by magnetic resonance imaging at term equivalent and 7 years of age, and cognitive (IQ, reading, mathematics, attention, working memory, language, visual perception) and motor testing at 7 years of age. We adjusted for age, sex, social risk, and neonatal illness in linear regression. A greater number of days on which infants received >50% breast milk was associated with greater deep nuclear gray matter volume at term equivalent age (0.15 cc/d; 95% CI, 0.05-0.25); and with better performance at age 7 years of age on IQ (0.5 points/d; 95% CI, 0.2-0.8), mathematics (0.5; 95% CI, 0.1-0.9), working memory (0.5; 95% CI, 0.1-0.9), and motor

function (0.1; 95% CI, 0.0-0.2) tests. No differences in regional brain volumes at 7 years of age in relation to breast milk intake were observed. Predominant breast milk feeding in the first 28 days of life was associated with a greater deep nuclear gray matter volume at term equivalent age and better IQ, academic achievement, working memory, and motor function at 7 years of age in very preterm infants.

Stadler, D. D., Musser, E. D., Holton, K. F., Shannon, J., & Nigg, J. T. (2016). Recalled initiation and duration of maternal breastfeeding among children with and without ADHD in a well characterized case-control sample. *Journal of abnormal child psychology*, 44(2), 347-355.

Early environmental influences are increasingly of interest in understanding ADHD as a neurodevelopmental condition, particularly in light of recognition that gene by environmental interplay are likely involved in this condition. Breastfeeding duration predicts cognitive development, as well as development of brain white matter connectivity, in areas similar to those seen in ADHD. Prior studies show an association between breastfeeding and ADHD but without adequate evaluation of ADHD. A case control cohort of 474 children aged 7-13 years was examined, 291 with well characterized ADHD (71.5 % male) and the rest typically developing controls (51.9 % male). Mothers retrospectively reported on breastfeeding initiation and duration. Initiation of breastfeeding was not associated with child ADHD, but shorter duration of breastfeeding was associated with child ADHD with a medium effect size ($d = 0.40$, $p < 0.05$); this effect held after covarying a broad set of potential confounders, including child oppositional defiant and conduct problems and including maternal and paternal ADHD symptoms. Effects were replicated across both parent and teacher ratings of child ADHD symptoms. Shorter duration of breastfeeding is among several risk factors in early life associated with future ADHD, or else longer duration is protective. The direction of this effect is unknown, however. It may be that some children are more difficult to breastfeed or that breastfeeding provides nutrients or other benefits that reduce future chance of ADHD.

Horta, B. L., Loret de Mola, C., & Victora, C. G. (2015). Breastfeeding and intelligence: a systematic review and meta-analysis. *Acta paediatrica*, 104, 14-19.

This study was aimed at systematically reviewing evidence of the association between breastfeeding and performance in intelligence tests. Two independent searches were carried out using Medline, LILACS, SCIELO and Web of Science. Studies restricted to infants and those where estimates were not adjusted for stimulation or interaction at home were excluded. Fixed- and random-effects models were used to pool the effect estimates, and a random-effects regression was used to assess potential sources of heterogeneity. We included 17 studies with 18 estimates of the relationship between breastfeeding and performance in intelligence tests. In a random-effects model, breastfed subjects achieved a higher IQ [mean difference: 3.44 points (95% confidence interval: 2.30; 4.58)]. We found no evidence of publication bias. Studies that controlled for maternal IQ showed a smaller benefit from breastfeeding [mean difference 2.62 points (95% confidence interval: 1.25; 3.98)]. In the meta-regression, none of the study characteristics explained the heterogeneity among the studies. Breastfeeding is related to improved performance in intelligence tests. A positive effect of breastfeeding on cognition was also observed in a randomised trial. This suggests that the association is causal.

Cai, S., Pang, W. W., Low, Y. L., Sim, L. W., Sam, S. C., Bruntraeger, M. B., ... & Richmond, J. (2014). Infant feeding effects on early neurocognitive development in Asian children—. *The American journal of clinical nutrition*, 101(2), 326-336.

Breastfeeding has been shown to enhance global measures of intelligence in children. However, few studies have examined associations between breastfeeding and specific cognitive task performance in the first 2 y of life, particularly in an Asian population. We assessed associations between early infant feeding and detailed measures of cognitive development in the first 2 y of life in healthy Asian children born at term. In a prospective cohort study, neurocognitive testing was performed in 408 healthy children (aged 6, 18, and 24 mo) from uncomplicated pregnancies (i.e., birth weight >2500 and <4000 g, gestational age ≥37 wk, and 5-min Apgar score ≥9). Tests included memory (deferred imitation, relational binding, habituation) and attention tasks (visual expectation, auditory oddball) as well as the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Children were stratified into 3 groups (low, intermediate, and high) on the basis of breastfeeding duration and exclusivity. After potential confounding variables were controlled for, significant associations and dose-response relations were observed for 4 of the 15 tests. Higher breastfeeding exposure was associated with better memory at 6 mo, demonstrated by greater preferential looking toward correctly matched items during early portions of a relational memory task (i.e., relational binding task: P-trend = 0.015 and 0.050 for the first two 1000-ms time bins, respectively). No effects of breastfeeding were observed at 18 mo. At 24 mo, breastfed children were more likely to display sequential memory during a deferred imitation memory task (P-trend = 0.048), and toddlers with more exposure to breastfeeding scored higher in receptive language [+0.93 (0.23, 1.63) and +1.08 (0.10, 2.07) for intermediate- and high-breastfeeding groups, respectively, compared with the low-breastfeeding group], as well as expressive language [+0.58 (-0.06, 1.23) and +1.22 (0.32, 2.12) for intermediate- and high-breastfeeding groups, respectively] assessed via the BSID-III. Our findings suggest small but significant benefits of breastfeeding for some aspects of memory and language development in the first 2 y of life, with significant improvements in only 4 of 15 indicators. Whether the implicated processes confer developmental advantages is unknown and represents an important area for future research.

Belfort, M. B., Rifas-Shiman, S. L., Kleinman, K. P., Guthrie, L. B., Bellinger, D. C., Taveras, E. M., ... & Oken, E. (2013). Infant feeding and childhood cognition at ages 3 and 7 years: effects of breastfeeding duration and exclusivity. *JAMA pediatrics*, 167(9), 836-844.

The objective of this study was to examine relationships of breastfeeding duration and exclusivity with child cognition at ages 3 and 7 years and to evaluate the extent to which maternal fish intake during lactation modifies associations of infant feeding with later cognition. Prospective cohort study (Project Viva), a US prebirth cohort that enrolled mothers from April 22, 1999, to July 31, 2002, and followed up children to age 7 years, including 1312 Project Viva mothers and children. Child receptive language assessed with the Peabody Picture Vocabulary Test at age 3 years, Wide Range Assessment of Visual Motor Abilities at ages 3 and 7 years, and Kaufman Brief Intelligence Test and Wide Range Assessment of Memory and Learning at age 7 years. Adjusting for socio-demographics, maternal intelligence, and home environment in linear regression, longer breastfeeding duration was associated with higher Peabody Picture Vocabulary Test score at age 3 years (0.21; 95% CI, 0.03-0.38 points per month breastfed) and

with higher intelligence on the Kaufman Brief Intelligence Test at age 7 years (0.35; 0.16-0.53 verbal points per month breastfed; and 0.29; 0.05-0.54 nonverbal points per month breastfed). Breastfeeding duration was not associated with Wide Range Assessment of Memory and Learning scores. Beneficial effects of breastfeeding on the Wide Range Assessment of Visual Motor Abilities at age 3 years seemed greater for women who consumed 2 or more servings of fish per week (0.24; 0.00-0.47 points per month breastfed) compared with less than 2 servings of fish per week (-0.01; -0.22 to 0.20 points per month breastfed) ($P = .16$ for interaction). Our results support a causal relationship of breastfeeding duration with receptive language and verbal and nonverbal intelligence later in life.

Bernard, J. Y., De Agostini, M., Forhan, A., Alfaiate, T., Bonet, M., Champion, V., ... & EDEN Mother-Child Cohort Study Group. (2013). Breastfeeding duration and cognitive development at 2 and 3 years of age in the EDEN mother-child Cohort. *The Journal of pediatrics*, 163(1), 36-42. The objective of this study was to investigate the dose-response relationship between breastfeeding duration and cognitive development in French preschool children. In the French EDEN Mother-Child Cohort Study, we evaluated language ability with the Communicative Development Inventory (CDI) in 1387 2-year-old children and overall development with the Ages and Stages Questionnaire (ASQ) in 1199 3-year-old children. Assessments were compared between breastfed and non-breastfed children and also according to breastfeeding duration in multivariable linear models, controlling for a wide range of potential confounders. We tested departure from linearity. After adjustments, ever-breastfed children scored 3.7 ± 1.8 ($P = .038$) points higher than never-breastfed children on the CDI and 6.2 ± 1.9 ($P = .001$) points higher on the ASQ. Among breastfed children, exclusive and any-breastfeeding durations were positively associated with both CDI and ASQ scores. The fine motor domain of ASQ was associated with any-breastfeeding duration, and the problem solving domain with exclusive-breastfeeding duration. We did not observe significant departures from linearity. No interactions were found between the child's sex, parental education or socioeconomic status, and breastfeeding duration. The authors concluded that longer breastfeeding duration was associated with better cognitive and motor development in 2- and 3-year-old children and a dose-response relationship was suggested.

Deoni, S. C., Dean III, D. C., Piryatinsky, I., O'muircheartaigh, J., Waskiewicz, N., Lehman, K., ... & Dirks, H. (2013). Breastfeeding and early white matter development: a cross-sectional study. *Neuroimage*, 82, 77-86.

Does breastfeeding alter early brain development? The prevailing consensus from large epidemiological studies posits that early exclusive breastfeeding is associated with improved measures of IQ and cognitive functioning in later childhood and adolescence. Prior morphometric brain imaging studies support these findings, revealing increased white matter and sub-cortical gray matter volume, and parietal lobe cortical thickness, associated with IQ, in adolescents who were breastfed as infants compared to those who were exclusively formula-fed. Yet it remains unknown when these structural differences first manifest and when developmental differences that predict later performance improvements can be detected. In this study, we used quiet magnetic resonance imaging (MRI) scans to compare measures of white matter microstructure (mcDESPOT measures of myelin water fraction) in 133 healthy children

from 10 months through 4 years of age, who were either exclusively breastfed a minimum of 3 months; exclusively formula-fed; or received a mixture of breast milk and formula. We also examined the relationship between breastfeeding duration and white matter microstructure. Breastfed children exhibited increased white matter development in later maturing frontal and association brain regions. Positive relationships between white matter microstructure and breastfeeding duration are also exhibited in several brain regions that are anatomically consistent with observed improvements in cognitive and behavioral performance measures. While the mechanisms underlying these structural differences remain unclear, our findings provide new insight into the earliest developmental advantages associated with breastfeeding, and support the hypothesis that breast milk constituents promote healthy neural growth and white matter development.

Groen-Blokhuis, M. M., Franić, S., van Beijsterveldt, C. E., de Geus, E., Bartels, M., Davies, G. E., ... & Hudziak, J. J. (2013). A prospective study of the effects of breastfeeding and FADS2 polymorphisms on cognition and hyperactivity/attention problems. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 162(5), 457-465.

Breastfeeding has been associated with improved cognitive functioning. There is a beneficial effect on IQ, and possibly on associated phenotypes such as attention problems. It has been suggested that the effect on IQ is moderated by polymorphisms in the FADS2 gene, which is involved in fatty acid metabolism. In this study we tested the relation between breastfeeding and FADS2 polymorphisms on the one hand and IQ, educational attainment, overactivity, and attention problems on the other hand. IQ at age 5, 7, 10, 12, and/or 18 ($n = 1,313$), educational attainment at age 12 ($n = 1,857$), overactive behavior at age 3 ($n = 2,560$), and attention problems assessed at age 7, 10, and 12 years ($n = 2,479$, $n = 2,423$, $n = 2,226$) were predicted by breastfeeding and two SNPs in FADS2 (rs174575 and rs1535). Analyses were performed using structural equation modeling. After correction for maternal education, a main effect of breastfeeding was found for educational attainment at age 12 and overactive behavior at age 3. For IQ, the effect of breastfeeding across age was marginally significant ($P = 0.05$) and amounted to 1.6 points after correcting for maternal education. Neither a main effect of the FADS2 polymorphisms nor an interaction with breastfeeding was detected for any of the phenotypes. This developmentally informed study confirms that breastfeeding is associated with higher educational attainment at age 12, less overactive behavior at age 3 and a trend toward higher IQ after correction for maternal education. In general, the benefits of breastfeeding were small and did not interact with SNPs in FADS2.

Herba, C. M., Roza, S., Govaert, P., Hofman, A., Jaddoe, V., Verhulst, F. C., & Tiemeier, H. (2013). Breastfeeding and early brain development: the Generation R study. *Maternal & child nutrition*, 9(3), 332-349.

Breastfeeding during infancy is associated with a range of short- and long-term health benefits. We examine whether breastfeeding in the first 2 months of life is associated with structural markers of brain development in infants from the general population. This study was embedded within the Generation R study. Cranial ultrasounds were obtained at approximately 7 weeks post-natal age. The diameter of the gangliothalamic ovoid, corpus callosum length, ventricular volume and head circumference were measured. Maternal reports of breastfeeding were

obtained at 2 months of age. We examined associations in relation to current breastfeeding practices (exclusively breastfed, n = 318, breast- and bottle-fed, n = 119, and bottle-fed, n = 243). Analyses were adjusted for head size and relevant covariates. Secondary analyses were conducted for breastfeeding history (exclusively breastfed, n = 318, breast- and bottle-fed, n = 281, and never breastfed, n = 81). Exclusive breastfeeding was associated with more optimal brain development compared with babies who were bottle-fed or never breastfed. Results were most consistent for gangliothalamic ovoid diameter. Larger gangliothalamic ovoid diameters were evident in babies who were exclusively breastfed compared with bottle-fed babies [difference between means (95% confidence interval) = 0.21(0.02, 0.39), P = 0.02]. Smaller ventricular volume and larger head circumference were also found for exclusively breastfed babies. Breastfeeding was not significantly associated with corpus callosum length. Maternal reports of breastfeeding are associated with more mature brain development within the first 2 months of life. Results are most consistent for gangliothalamic ovoid diameter, a subcortical structure rich in docosahexaenoic acid. Findings also pointed to non-specific neural developmental advantage for exclusively breastfed babies.

Yorifuji, T., Kubo, T., Yamakawa, M., Kato, T., Inoue, S., Tokinobu, A., & Doi, H. (2014). Breastfeeding and behavioral development: a nationwide longitudinal survey in Japan. *The Journal of pediatrics*, 164(5), 1019-1025.

We used a large, nationwide Japanese population-based longitudinal survey that began in 2001. We restricted participants to term singletons with birth weight >2500 g (n = 41 188). Infant feeding practice was queried at age 6-7 months. Responses to survey questions about age-appropriate behaviors at age 2.5 and 5.5 years were used as indicators of behavioral development. We conducted logistic regression analyses, controlling for potential child and parental confounding factors, with formula feeding as the reference group. RESULTS: We observed a dose-response relationship between breastfeeding status and an inability to perform age-appropriate behaviors at both ages. With a single exception, all ORs for outcomes for exclusive breastfeeding were smaller than those for partial feeding of various durations. The protective associations did not change after adjustment for an extensive list of confounders or in the sensitivity analyses. CONCLUSION: We observed prolonged protective effects of breastfeeding on developmental behavior skills surveyed at age 2.5 and 5.5 years. Beneficial effects were most likely in children who were breastfed exclusively, but whether a biological ingredient in breast milk or extensive interactions through breastfeeding, or both, is beneficial is unclear.

Iacovou, M., & Sevilla, A. (2012). Infant feeding: the effects of scheduled vs. on-demand feeding on mothers' wellbeing and children's cognitive development. *The European Journal of Public Health*, 23(1), 13-19.

Many popular childcare books recommend feeding babies to a schedule, but no large-scale study has ever examined the effects of schedule-feeding. Here, we examine the relationship between feeding infants to a schedule and two sets of outcomes: mothers' wellbeing, and children's longer-term cognitive and academic development. We used a sample of 10 419 children from the Avon Longitudinal Study of Parents and Children, a cohort study of children born in the 1990s in Bristol, UK. Outcomes were compared by whether babies were fed to a

schedule at 4 weeks. Maternal wellbeing indicators include measures of sleep sufficiency, maternal confidence and depression, collected when babies were between 8 weeks and 33 months. Children's outcomes were measured by standardized tests at ages 5, 7, 11 and 14, and by IQ tests at age 8. Mothers who fed to a schedule scored more favourably on all wellbeing measures except depression. However, schedule-fed babies went on to do less well academically than their demand-fed counterparts. After controlling for a wide range of confounders, schedule-fed babies performed around 17% of a standard deviation below demand-fed babies in standardized tests at all ages, and 4 points lower in IQ tests at age 8 years. Feeding infants to a schedule is associated with higher levels of maternal wellbeing, but with poorer cognitive and academic outcomes for children.

Guxens, M., Mendez, M. A., Moltó-Puigmartí, C., Julvez, J., García-Esteban, R., Forns, J., ... & Sunyer, J. (2011). Breastfeeding, long-chain polyunsaturated fatty acids in colostrum, and infant mental development. *Pediatrics*, peds-2010.

A population-based birth cohort was established in the city of Sabadell (Catalonia, Spain) as part of the INMA-INfancia y Medio Ambiente Project. A total of 657 women were recruited during the first trimester of pregnancy. Information about parental characteristics and breastfeeding was obtained by using a questionnaire, and trained psychologists assessed mental and psychomotor development by using the Bayley Scales of Infant Development in 504 children at 14 months of age. A high percentage of breastfeeds among all milk feeds accumulated during the first 14 months was positively related with child mental development (0.37 points per month of full breastfeeding [95% confidence interval: 0.06-0.67]). Maternal education, social class, and intelligence quotient only partly explained this association. Children with a longer duration of breastfeeding also exposed to higher ratios between n-3 and n-6 PUFAs in colostrum had significantly higher mental scores than children with low breastfeeding duration exposed to low levels. Greater levels of accumulated breastfeeding during the first year of life were related to higher mental development at 14 months, largely independently from a wide range of parental psychosocial factors. LC-PUFA levels seem to play a beneficial role in children's mental development when breastfeeding levels are high.

McCorry, C., & Layte, R. (2011). The effect of breastfeeding on children's educational test scores at nine years of age: Results of an Irish cohort study. *Social science & medicine*, 72(9), 1515-1521.

A total of 8,226 9 year-old children were studied in Ireland as part of the 'Growing up in Ireland' study. Information relating to breastfeeding initiation and exposure duration was obtained retrospectively via parental recall. After controlling for a range of child, maternal, socio-economic and socio-environmental factors, children who were breastfed were found to have a 3.24 percentage point advantage on reading scores and a 2.23 percentage point advantage on mathematics scores using standardised reading and mathematics tests. Any amount of breastfeeding was associated with significantly higher test scores than no exposure, but evidence of a dose-response relationship was weak.

Isaacs, E. B., Fischl, B. R., Quinn, B. T., Chong, W. K., Gadian, D. G., & Lucas, A. (2010). Impact of breast milk on intelligence quotient, brain size, and white matter development. *Pediatric research*, 67(4), 357.

Although observational findings linking breast milk to higher scores on cognitive tests may be confounded by factors associated with mothers' choice to breastfeed, it has been suggested that one or more constituents of breast milk facilitate cognitive development, particularly in preterms. Because cognitive scores are related to head size, we hypothesized that breast milk mediates cognitive effects by affecting brain growth. We used detailed data from a randomized feeding trial to calculate the percentage of expressed maternal breast milk (%EBM) in the infant diet of 50 adolescents. MRI scans were obtained (mean age = 15 y 9 mo), allowing volumes of total brain (TBV) and white and gray matter (WMV, GMV) to be calculated. In the total group, %EBM correlated significantly with verbal intelligence quotient (VIQ); in boys, with all IQ scores, TBV and WMV. VIQ was, in turn, correlated with WMV and, in boys only, additionally with TBV. No significant relationships were seen in girls or with gray matter. These data support the hypothesis that breast milk promotes brain development, particularly white matter growth. The selective effect in males accords with animal and human evidence regarding gender effects of early diet. Our data have important neurobiological and public health implications and identify areas for future mechanistic study.

Kramer, M. S., Aboud, F., Mironova, E., Vanilovich, I., Platt, R. W., Matush, L., ... & Collet, J. P. (2008). Breastfeeding and child cognitive development: new evidence from a large randomized trial. *Archives of general psychiatry*, 65(5), 578-584.

To assess whether prolonged and exclusive breastfeeding improves children's cognitive ability at age 6.5 years, 17 046 healthy breastfeeding infants were enrolled in this study, of whom 13 889 (81.5%) were followed up at age 6.5 years. The experimental intervention led to a large increase in exclusive breastfeeding at age 3 months (43.3% for the experimental group Page 19 of 63 vs 6.4% for the control group) and a significantly higher prevalence of any breastfeeding at all ages up to and including 12 months. The experimental group had higher means on all of the intelligence measures, with cluster-adjusted mean differences of +7.5 for verbal IQ, +2.9 for performance IQ, and +5.9 for full-scale IQ. Teachers' academic ratings were significantly higher in the experimental group for both reading and writing. These results, based on the largest randomized trial ever conducted in the area of human lactation, provide strong evidence that prolonged and exclusive breastfeeding improves children's cognitive development.

Lawlor, D. A., Najman, J. M., Batty, G. D., O'callaghan, M. J., Williams, G. M., & Bor, W. (2006). Early life predictors of childhood intelligence: findings from the Mater-University study of pregnancy and its outcomes. *Paediatric and perinatal epidemiology*, 20(2), 148-162.

Growing evidence linking childhood intelligence with adult health outcomes suggests a need to identify predictors of this psychological characteristic. In this study, we have examined the early life determinants of childhood intelligence in a population-based birth cohort of individuals born in Brisbane, Australia between 1981 and 1984. In univariable analyses, family income in the year of birth, maternal and paternal education, maternal age at birth, maternal ethnicity, maternal smoking during pregnancy, duration of labour, birthweight, breastfeeding and childhood height, and body mass index were all associated with intelligence at age 14. In

multivariable analyses, the strongest and most robust predictors of intelligence were family income, parental education and breastfeeding, with these three variables explaining 7.5% of the variation in intelligence at age 14. Addition of other variables added little further explanatory power. Our results demonstrate the importance of indicators of socio-economic position as predictors of intelligence, and illustrate the need to consider the role of such factors in generating the association of childhood intelligence with adult disease risk.

Victora, C. G., Barros, F. C., Horta, B. L., & Lima, R. C. (2005). Breastfeeding and school achievement in Brazilian adolescents. *Acta Paediatrica*, 94(11), 1656-1660.

In a population-based birth cohort, they analysed the highest grade achieved in school of over 2,000 male 18-y-olds relative to breastfeeding information collected in early life. Analyses were adjusted for birthweight, family income, maternal and paternal schooling, household assets, number of siblings, social class, maternal smoking during pregnancy, and ethnicity. After adjustment for confounding variables, there was a highly significant trend in school achievement with increasing breastfeeding duration. Those breastfed for 9 mo or more were ahead by 0.5-0.8 school grades, relative to those breastfed for less than 1 mo. Data from a cross-sectional survey in the same population suggest that such a difference corresponds to a 10-15% difference in adult income levels. The duration of exclusive or predominant breastfeeding was also positively associated with schooling.

Smith, M. M., Durkin, M., Hinton, V. J., Bellinger, D., & Kuhn, L. (2003). Influence of breastfeeding on cognitive outcomes at age 6–8 years: follow-up of very low birth weight infants. *American Journal of Epidemiology*, 158(11), 1075-1082.

The relation between breastfeeding and childhood cognitive development was examined in 1991-1993 among 439 school-age children weighing <1,500 g when born. After covariate adjustment for home environment, maternal verbal ability, a composite measure of parental education and occupation, and length of hospitalization, the authors found that breastfed children evidenced an advantage only for measures specific to visual-motor integration (5.1 intelligence quotient (IQ) points). Differences in test scores between breastfed children and those who did not receive any breast milk feedings were 3.6 IQ points for overall intellectual functioning and 2.3 IQ points for verbal ability.

Oddy, W. H., Kendall, G. E., Blair, E., De Klerk, N. H., Stanley, F. J., Landau, L. I., ... & Zubrick, S. (2003). Breast feeding and cognitive development in childhood: a prospective birth cohort study. *Paediatric and perinatal epidemiology*, 17(1), 81-90.

A cohort study of 2393 term infants. Of these, complete infant feeding data in the first year of life and verbal cognitive IQ (Peabody Picture Vocabulary Test-PPVT-R) were available for 1450 children at 6 years, and a performance subtest (Perceptual organisation WISC-Block Design) for 1375 children at 8 years. Full breastfeeding was categorised as none, >0 to 6 months. Associations between breast-feeding duration and PPVT-R at 6 years and Block Design at 8 years were estimated before and after adjustment for gender, gestational age, maternal age, maternal education, parental smoking and the presence of older siblings. The early cessation of full breast feeding was associated with reduced verbal IQ and the performance subtest. After adjustment, mean PPVT-R scores were 3.56 points higher in children fully breastfed for >6

months compared with those children never breast fed ($P=0.003$). Interactions between maternal education (four levels) and breast feeding demonstrated a positive association of maternal education on verbal IQ ($F=2.64$; $P=0.005$) in children breastfed for longer but not on performance ($F=0.74$; $P=0.67$). The early introduction of milk other than breast milk was associated with reduced verbal IQ after adjustment for social and perinatal confounders.

Jacobson, J. L., & Jacobson, S. W. (2002). Association of prenatal exposure to an environmental contaminant with intellectual function in childhood. *Journal of Toxicology: Clinical Toxicology*, 40(4), 467-475.

Polychlorinated biphenyls are a family of synthetic hydrocarbon compounds that were used historically for a broad range of industrial purposes. Although banned in the 1970s, they continue to be ubiquitous in landfills, sediments, and wildlife. Prenatal polychlorinated biphenyl exposure was evaluated in a sample of children born to women who had eaten relatively large quantities of polychlorinated biphenyl-contaminated Lake Michigan fish. This exposure was found to be associated with poorer intellectual function after controlling statistically for a broad range of potential confounding variables. Deficits included poorer recognition memory in infancy, lower scores on a preschool IQ test, and poorer verbal IQ and reading comprehension at 11 years of age. Although breast-fed children were exposed postnatally to elevated levels of polychlorinated biphenyls from maternal milk, the adverse effects associated with prenatal exposure were markedly stronger in the children who were not breast-fed. It is not clear whether the adverse effects were attenuated in the breast-fed children due to certain nutrients in the breast milk or due to better quality of intellectual stimulation provided by the breast-feeding mothers. Virtually no adverse effects were found in relation to postnatal exposure to polychlorinated biphenyls from breast-feeding, indicating that the fetus is particularly vulnerable to this exposure.

Fewtrell, M. S., Morley, R., Abbott, R. A., Singhal, A., Isaacs, E. B., Stephenson, T., ... & Lucas, A. (2002). Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants. *Pediatrics*, 110(1), 73-82.

In this double-blind, randomized, controlled trial of preterm formula with and without long-chain polyunsaturated fatty acids (LCPUFA), the participants were 195 formula-fed preterm infants (birth weight < 1750 g, gestation <37 weeks) from 2 United Kingdom neonatal units and 88 breast milk-fed infants. Main outcome measures were Bayley Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) at 18 months and Knobloch, Passamanick and Sherrard's Developmental Screening Inventory at 9 months' corrected age. Safety outcome measures were anthropometry at 9 and 18 months, tolerance, infection, necrotizing enterocolitis, and death. There were no significant differences in developmental scores between randomized groups, although infants who were fed LCPUFA-supplemented formula showed a nonsignificant 2.6-point advantage in MDI and PDI at 18 months, with a greater (nonsignificant) advantage (MDI: 4.5 points; PDI: 5.8 points) in infants below 30 weeks' gestation. LCPUFA-supplemented infants were shorter than control infants at 18 months (difference in length standard deviation score: 0.44). No other significant short- or long-term differences in safety outcomes were observed. Breastfed infants had significantly higher developmental scores at 9

and 18 months than both formula groups and were significantly heavier and longer at 18 months than LCPUFA-supplemented but not control infants.

Mortensen, E. L., Michaelsen, K. F., Sanders, S. A., & Reinisch, J. M. (2002). The association between duration of breastfeeding and adult intelligence. *Jama*, 287(18), 2365-2371. Independent of a wide range of possible confounding factors, a significant positive association between duration of breastfeeding and intelligence was observed in 2 independent samples of young adults, assessed with 2 different intelligence tests. A sample of 973 men and women and a sample of 2280 men, all of whom were born in Copenhagen, Denmark, between 1959 and 1961, were divided into 5 categories based on duration of breastfeeding, as assessed by physician interview with mothers at a 1-year examination. Thirteen potential confounders were included as covariates: parental social status and education; single mother status; mother's height, age, and weight gain during pregnancy and cigarette consumption during the third trimester; number of pregnancies; estimated gestational age; birth weight; birth length; and indexes of pregnancy and delivery complications. Duration of breastfeeding was associated with significantly higher scores on the Verbal, Performance, and Full Scale IQs. With regression adjustment for potential confounding factors, the mean IQs were 99.4, 101.7, 102.3, 106.0, and 104.0 for breastfeeding durations of less than 1 month, 2 to 3 months, 4 to 6 months, 7 to 9 months, and more than 9 months, respectively. The corresponding mean scores on the BPP were 38.0, 39.2, 39.9, 40.1, and 40.1.

Rao, M. R., Hediger, M. L., Levine, R. J., Naficy, A. B., & Vik, T. (2002). Effect of breastfeeding on cognitive development of infants born small for gestational age. *Acta Paediatrica*, 91(3), 267-274.

Duration of exclusive breastfeeding and cognitive development were evaluated prospectively for 220 term children born SGA and 299 term children born appropriate for gestational age (AGA). Cognitive development was assessed using the Bayley Scale of Infant Development at 13 mo and Wechsler Preschool and Primary Scales of Intelligence at 5 y of age. Children born SGA and exclusively breastfed for 24 weeks were predicted to have an 11-point IQ advantage over those breastfed for 12 weeks, as opposed to a 3-point advantage for children born AGA with similar durations of breastfeeding. These data suggest that mothers should breastfeed exclusively for 24 wk to enhance cognitive development.

Angelsen, N. K., Vik, T., Jacobsen, G., & Bakketeig, L. S. (2001). Breastfeeding and cognitive development at age 1 and 5 years. *Archives of disease in childhood*, 85(3), 183-188.

In 345 Scandinavian children, data on breast feeding were prospectively recorded during the first year of life, and neuromotor development was assessed at 1 and 5 years of age. Main outcome measures were Bayley's Scales of Infant Development at age 13 months (Mental Index, MDI; Psychomotor Index, PDI), Wechsler Preschool and Primary Scales of Intelligence (WPPSI-R), and Peabody Developmental Scales at age 5. Children breast fed for less than 3 months had an increased risk, compared to children breast fed for at least 6 months, of a test score below the median value of MDI at 13 months and of WPPSI-R at 5 years. The increased risk of lower MDI and total IQ scores persisted after adjustment for maternal age, maternal intelligence Page 21 of 63 (Raven score), maternal education, and smoking in pregnancy.

Dewey, K. G., Cohen, R. J., Brown, K. H., & Rivera, L. L. (2001). Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. *The Journal of nutrition*, 131(2), 262-267.

To examine whether the duration of exclusive breastfeeding affects maternal nutrition or infant motor development, we examined data from two studies in Honduras: the first with 141 infants of low-income primiparous women and the second with 119 term, low birth weight infants. In both studies, infants were exclusively breastfed for 4 mo and then randomly assigned to continue exclusive breastfeeding (EBF) until 6 mo or to receive high-quality, hygienic solid foods (SF) in addition to breast milk between 4 and 6 mo. Maternal weight loss between 4 and 6 mo was significantly greater in the exclusive breastfeeding group (EBF) group than in the group(s) given solid foods (SF) in study 1 (-0.7 ± 1.5 versus -0.1 ± 1.7 kg, $P < 0.05$) but not in study 2. The estimated average additional nutritional burden of continuing to exclusively breastfeed until 6 mo was small, representing only 0.1–6.0% of the recommended dietary allowance for energy, vitamin A, calcium and iron. Women in the EBF group were more likely to be amenorrheic at 6 mo than women in the SF group, which conserves nutrients such as iron. In both studies, few women (10–11%) were thin (body mass index <19 kg/m²), so the additional weight loss in the EBF group in study 1 was unlikely to have been detrimental. Infants in the EBF group crawled sooner (both studies) and were more likely to be walking by 12 mo (study 1) than infants in the SF group. Taken together with our previous findings, these results indicate that the advantages of exclusive breastfeeding during this interval appear to outweigh any potential disadvantages in this setting.

Quinn, P. J., O'Callaghan, M., Williams, G. M., Najman, J. M., Andersen, M. J., & Bor, W. (2001). The effect of breastfeeding on child development at 5 years: a cohort study. *Journal of paediatrics and child health*, 37(5), 465-469.

A total of 3880 children were followed from birth. Breastfeeding duration was measured by questionnaire at 6 months of age and a Peabody Picture Vocabulary Test Revised (PPVT-R) was administered at 5 years. A strong positive relationship was demonstrated between breastfeeding and the PPVT-R scores with increasing scores with increased duration of breastfeeding. After adjusting for a wide range of biological and social factors, the adjusted mean for those breastfed for 6 months or more was 8.2 points higher for females and 5.8 points for males when compared to those never breastfed.

Anderson, J. W., Johnstone, B. M., & Remley, D. T. (1999). Breast-feeding and cognitive development: a meta-analysis—. *The American journal of clinical nutrition*, 70(4), 525-535.

A review of 20 published studies on the effects of breastfeeding on infant IQ found that breastfed babies' IQs may be 3 to 5 points higher than those of formula-fed babies. The longer a baby is breast-fed, the greater the benefits to his or her IQ. These benefits were seen from age 6 months through 15 years.

Paine, B. J., Makrides, M., & Gibson, R. A. (1999). Duration of breast-feeding and Bayley's Mental Developmental Index at 1 year of age. *Journal of paediatrics and child health*, 35(1), 82-85.

96 healthy term infants, aged between 10 and 14 months were assessed using the Bayley Scales of Infant Development. Duration of breast-feeding significantly predicted mental development scores for boys, but not for girls. Duration of breastfeeding did not predict psychomotor development scores.

Horwood, L. J., & Fergusson, D. M. (1998). Breastfeeding and later cognitive and academic outcomes. *Pediatrics*, 101(1), e9-e9.

Increasing duration of breastfeeding was associated with consistent and statistically significant increases in 1) intelligence quotient assessed at ages 8 and 9 years; 2) reading comprehension, mathematical ability, and scholastic ability assessed during the period from 10 to 13 years; 3) teacher ratings of reading and mathematics assessed at 8 and 12 years; and 4) higher levels of attainment in school leaving examinations. Breastfeeding is associated with small but detectable increases in child cognitive ability and educational achievement. These effects are 1) pervasive, being reflected in a range of measures including standardized tests, teacher ratings, and academic outcomes in high school; and 2) relatively long-lived, extending throughout childhood into young adulthood.

Riva, E., Agostoni, C., Biasucci, G., Trojan, S., Luotti, D., Fiori, L., & Giovannini, M. (1996). Early breastfeeding is linked to higher intelligence quotient scores in dietary treated phenylketonuric children. *Acta Paediatrica*, 85(1), 56-58.

School-age phenylketonuric children who had, as infants, been breastfed 20-40 days prior to dietary intervention scored significantly better (IQ advantage of 14.0 points, $p = 0.01$) than children who had been formula fed. A 12.9 point advantage persisted also after adjusting for social and maternal education status.

Lanting, C. I., Huisman, M., Boersma, E. R., Touwen, B. C. L., & Fidler, V. (1994). Neurological differences between 9-year-old children fed breast-milk or formula-milk as babies. *The Lancet*, 344(8933), 1319-1322.

The presence of minor neurological dysfunction is associated with behavioural and cognitive development at school age. We have previously shown a relation between minor neurological dysfunction and perinatal disorders, especially abnormal neonatal neurological conditions. We have now investigated the relation between breastfeeding and long-term neurological development. We studied 135 breastfed (for ≥ 3 weeks) and 391 formula-fed children, born at term in the University Hospital Groningen between 1975 and 1979. A standard neonatal neurological examination was used to classify the infants as normal (247), slightly abnormal (213), or frankly abnormal (66). At 9 years of age the children were re-examined. In 1993 their mothers were asked to complete a questionnaire about how the children were fed as infants. After adjustment for obstetric, perinatal, neonatal neurological, and social differences, a small advantageous effect of breastfeeding on neurological status at 9 years of age was found (odds ratio for neurological non-normality 0.54 [95% CI 0.30-0.97]). Although a retrospective design cannot lead to definite conclusions, our data suggest a beneficial effect of breast-feeding on

postnatal neurological development. Longer-chain polyunsaturated fatty acids, which are present in breast-milk but not in most formula-milks, may have a role since they are vital for brain development.

Lucas, A., Morley, R., Cole, T. J., Lister, G., & Leeson-Payne, C. (1992). Breast milk and subsequent intelligence quotient in children born preterm. *The Lancet*, 339(8788), 261-264. Children who had consumed mother's milk by tube in early weeks of life had a significantly higher IQ at 7.5 to 8 years, than those who received no maternal milk, even after adjustment for differences between groups and mothers' educational and social class.

Morrow-Tlucak, M., Haude, R. H., & Ernhart, C. B. (1988). Breastfeeding and cognitive development in the first 2 years of life. *Social science & medicine*, 26(6), 635-639. Supplementary regression analysis examining the strength of relationship between duration of breastfeeding and cognitive development show small but significant relationship between duration of breastfeeding and scores on the mental development index of the Bayley Scales at 1 and 2 years.

Morley, R., Cole, T. J., Powell, R., & Lucas, A. (1988). Mother's choice to provide breast milk and developmental outcome. *Archives of Disease in Childhood*, 63(11), 1382-1385. In 771 low birth weight infants, babies whose mothers chose to provide breast milk had an 8 point advantage in mean Bayley's mental developmental index over infants of mother choosing not to do so.

Gastrointestinal, Microbiome, and Immune Development (see also “Vaccine Response”)

Pannaraj, P. S., Li, F., Cerini, C., Bender, J. M., Yang, S., Rollie, A., ... & Bailey, A. (2017). Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. *JAMA pediatrics*, 171(7), 647-654.

Establishment of the infant microbiome has lifelong implications on health and immunity. Gut microbiota of breastfed compared with nonbreastfed individuals differ during infancy as well as into adulthood. Breast milk contains a diverse population of bacteria, but little is known about the vertical transfer of bacteria from mother to infant by breastfeeding. The objective of this study was to determine the association between the maternal breast milk and areolar skin and infant gut bacterial communities. In a prospective, longitudinal study, bacterial composition was identified with sequencing of the 16S ribosomal RNA gene in breast milk, areolar skin, and infant stool samples of 107 healthy mother-infant pairs. The study was conducted in Los Angeles, California, and St Petersburg, Florida, between January 1, 2010, and February 28, 2015. Amount and duration of daily breastfeeding and timing of solid food introduction. Bacterial composition in maternal breast milk, areolar skin, and infant stool by sequencing of the 16S ribosomal RNA gene. In the 107 healthy mother and infant pairs (median age at the time of specimen collection, 40 days; range, 1-331 days), 52 (43.0%) of the infants were male. Bacterial communities were distinct in milk, areolar skin, and stool, differing in both composition and diversity. The infant gut microbial communities were more closely related to an infant's mother's

milk and skin compared with a random mother (mean difference in Bray-Curtis distances, 0.012 and 0.014, respectively; $P < .001$ for both). Source tracking analysis was used to estimate the contribution of the breast milk and areolar skin microbiomes to the infant gut microbiome. During the first 30 days of life, infants who breastfed to obtain 75% or more of their daily milk intake received a mean (SD) of 27.7% (15.2%) of the bacteria from breast milk and 10.3% (6.0%) from areolar skin. Bacterial diversity (Faith phylogenetic diversity, $P = .003$) and composition changes were associated with the proportion of daily breast milk intake in a dose-dependent manner, even after the introduction of solid foods. The results of this study indicate that bacteria in mother's breast milk seed the infant gut, underscoring the importance of breastfeeding in the development of the infant gut microbiome.

Madan, J. C., Hoen, A. G., Lundgren, S. N., Farzan, S. F., Cottingham, K. L., Morrison, H. G., ... & Karagas, M. R. (2016). Association of cesarean delivery and formula supplementation with the intestinal microbiome of 6-week-old infants. *JAMA pediatrics*, 170(3), 212-219.

The intestinal microbiome plays a critical role in infant development, and delivery mode and feeding method (breast milk vs formula) are determinants of its composition. However, the importance of delivery mode beyond the first days of life is unknown, and studies of associations between infant feeding and microbiome composition have been generally limited to comparisons between exclusively breastfed and formula-fed infants, with little consideration given to combination feeding of both breast milk and formula. To examine the associations of delivery mode and feeding method with infant intestinal microbiome composition at approximately 6 weeks of life. Prospective observational study of 102 infants followed up as part of a US pregnancy cohort study. Delivery mode was abstracted from delivery medical records, and feeding method prior to the time of stool collection was ascertained through detailed questionnaires. Stool microbiome composition was characterized using next-generation sequencing of the 16S rRNA gene. There were 102 infants (mean gestational age, 39.7 weeks; range, 37.1-41.9 weeks) included in this study, of whom 70 were delivered vaginally and 32 by cesarean delivery. In the first 6 weeks of life, 70 were exclusively breastfed, 26 received combination feeding, and 6 were exclusively formula fed. We identified independent associations between microbial community composition and both delivery mode ($P < .001$; $Q < .001$) and feeding method ($P = .01$; $Q < .001$). Differences in microbial community composition between vaginally delivered infants and infants delivered by cesarean birth were equivalent to or significantly larger than those between feeding groups ($P = .003$). Bacterial communities associated with combination feeding were more similar to those associated with exclusive formula feeding than exclusive breastfeeding ($P = .002$). We identified 6 individual bacterial genera that were differentially abundant between delivery mode and feeding groups. The infant intestinal microbiome at approximately 6 weeks of age is significantly associated with both delivery mode and feeding method, and the supplementation of breast milk feeding with formula is associated with a microbiome composition that resembles that of infants who are exclusively formula fed. These results may inform feeding choices and shed light on the mechanisms behind the lifelong health consequences of delivery and infant feeding modalities.

Mueller, N. T., Bakacs, E., Combellick, J., Grigoryan, Z., & Dominguez-Bello, M. G. (2015). The infant microbiome development: mom matters. *Trends in molecular medicine*, 21(2), 109-117.

The infant microbiome plays an essential role in human health and its assembly is determined by maternal–offspring exchanges of microbiota. This process is affected by several practices, including Cesarean section (C-section), perinatal antibiotics, and formula feeding, that have been linked to increased risks of metabolic and immune diseases. Here we review recent knowledge about the impacts on infant microbiome assembly, discuss preventive and restorative strategies to ameliorate the effects of these impacts, and highlight where research is needed to advance this field and improve the health of future generations.

Thompson, A. L., Monteagudo-Mera, A., Cadenas, M. B., Lampl, M. L., & Azcarate-Peril, M. A. (2015). Milk-and solid-feeding practices and daycare attendance are associated with differences in bacterial diversity, predominant communities, and metabolic and immune function of the infant gut microbiome. *Frontiers in cellular and infection microbiology*, 5, 3.

The development of the infant intestinal microbiome in response to dietary and other exposures may shape long-term metabolic and immune function. We examined differences in the community structure and function of the intestinal microbiome between four feeding groups, exclusively breastfed infants before introduction of solid foods (EBF), non-exclusively breastfed infants before introduction of solid foods (non-EBF), EBF infants after introduction of solid foods (EBF+S), and non-EBF infants after introduction of solid foods (non-EBF+S), and tested whether out-of-home daycare attendance was associated with differences in relative abundance of gut bacteria. Bacterial 16S rRNA amplicon sequencing was performed on 49 stool samples collected longitudinally from a cohort of 9 infants (5 male, 4 female). PICRUSt metabolic inference analysis was used to identify metabolic impacts of feeding practices on the infant gut microbiome. Sequencing data identified significant differences across groups defined by feeding and daycare attendance. Non-EBF and daycare-attending infants had higher diversity and species richness than EBF and non-daycare attending infants. The gut microbiome of EBF infants showed increased proportions of Bifidobacterium and lower abundance of Bacteroidetes and Clostridiales than non-EBF infants. PICRUSt analysis indicated that introduction of solid foods had a marginal impact on the microbiome of EBF infants (24 enzymes overrepresented in EBF+S infants). In contrast, over 200 bacterial gene categories were overrepresented in non-EBF+S compared to non-EBF infants including several bacterial methyl-accepting chemotaxis proteins (MCP) involved in signal transduction. The identified differences between EBF and non-EBF infants suggest that breast milk may provide the gut microbiome with a greater plasticity (despite having a lower phylogenetic diversity) that eases the transition into solid foods.

Walker, W. A., & Iyengar, R. S. (2014). Breast milk, microbiota, and intestinal immune homeostasis. *Pediatric Research*, 77(1-2), 220.

Newborns adjust to the extrauterine environment by developing intestinal immune homeostasis. Appropriate initial bacterial colonization is necessary for adequate intestinal immune development. An environmental determinant of adequate colonization is breast milk. Although the full-term infant is developmentally capable of mounting an immune response, the effector immune component requires bacterial stimulation. Breast milk stimulates the proliferation of a well-balanced and diverse microbiota, which initially influences a switch from an intrauterine TH2 predominant to a TH1/TH2 balanced response and with activation of T-regulatory cells by

breast milk–stimulated specific organisms (Bifidobacteria, Lactobacillus, and Bacteroides). As an example of its effect, oligosaccharides in breast milk are fermented by colonic bacteria producing an acid milieu for bacterial proliferation. In addition, short-chain fatty acids in breast milk activate receptors on T-reg cells and bacterial genes, which preferentially mediate intestinal tight junction expression and anti-inflammation. Other components of breast milk (defensins, lactoferrin, etc.) inhibit pathogens and further contribute to microbiota composition. The breast milk influence on initial intestinal microbiota also prevents expression of immune-mediated diseases (asthma, inflammatory bowel disease, type 1 diabetes) later in life through a balanced initial immune response, underscoring the necessity of breastfeeding as the first source of nutrition.

Zivkovic, A. M., German, J. B., Lebrilla, C. B., & Mills, D. A. (2011). Human milk glycobiome and its impact on the infant gastrointestinal microbiota. *Proceedings of the National Academy of Sciences*, 108(Supplement 1), 4653-4658.

Human milk contains an unexpected abundance and diversity of complex oligosaccharides apparently indigestible by the developing infant and instead targeted to its cognate gastrointestinal microbiota. Recent advances in mass spectrometry-based tools have provided a view of the oligosaccharide structures produced in milk across stages of lactation and among human mothers. One postulated function for these oligosaccharides is to enrich a specific “healthy” microbiota containing bifidobacteria, a genus commonly observed in the feces of breast-fed infants. Isolated culture studies indeed show selective growth of infant-borne bifidobacteria on milk oligosaccharides or core components therein. Parallel glycoprofiling documented that numerous *Bifidobacterium longum* subsp. *infantis* strains preferentially consume small mass oligosaccharides that are abundant early in the lactation cycle. Genome sequencing of numerous *B. longum* subsp. *infantis* strains shows a bias toward genes required to use mammalian-derived carbohydrates by comparison with adult-borne bifidobacteria. This intriguing strategy of mammalian lactation to selectively nourish genetically compatible bacteria in infants with a complex array of free oligosaccharides serves as a model of how to influence the human supraorganismal system, which includes the gastrointestinal microbiota.

Donovan, S. M. (2006). Role of human milk components in gastrointestinal development: current knowledge and future needs. *The Journal of pediatrics*, 149(5), S49-S61.

Human milk (HM) is a complex physiological fluid with multifunctional roles within the gastrointestinal tract that facilitate the successful postnatal adaptation of the newborn by stimulating cellular growth and digestive maturation, the establishment of symbiotic microflora, and the development of gut-associated lymphoid tissues. An intricate mixture of bioactive proteins, lipids, and carbohydrates that is unique to milk supports these processes and provides important signals to the developing intestine. The complexity of HM composition and the potential interactions among milk components has hampered our understanding of how HM components affect gastrointestinal development. Furthermore, limited information exists about the fundamental mechanisms of postnatal intestinal growth of healthy infants, further hindering our ability to delineate the role of HM in regulating this process. In this paper, evidence for the role of HM components in early intestinal development is summarized, with a discussion of the limitations of existing data, and suggestions are made for future research that is needed to

delineate the biology of HM, the physiology of postnatal intestinal development, and the complexity of potential interactions that occur between HM components and the developing neonate.

Penders, J., Vink, C., Driessen, C., London, N., Thijs, C., & Stobberingh, E. E. (2005). Quantification of *Bifidobacterium* spp., *Escherichia coli* and *Clostridium difficile* in faecal samples of breast-fed and formula-fed infants by real-time PCR. *FEMS microbiology letters*, 243(1), 141-147.

To determine the influence of either exclusive breast-feeding or formula feeding on both composition and quantity of the gut microbiota in infants, we have developed real-time, quantitative PCR assays for the detection of *Bifidobacterium* spp. and *Clostridium difficile*. Furthermore, we have monitored the prevalence and counts of *Escherichia coli* by applying a previously described real-time PCR assay. We found all 100 infants tested to be colonized by *Bifidobacterium* spp. The bifidobacterial counts were comparable between the 50 breast-fed and 50 formula-fed infants with median values of 10.56 log (10) and 10.24 log(10) CFU g⁻¹ wet weight faeces, respectively. *C. difficile* was detected in 14% of the breast-fed and 30% of the formula-fed infants. In addition, the *C. difficile* counts were significantly lower in breast-fed infants than in the formula-fed group. The prevalence of *E. coli* in the breast-fed and formula-fed group was 80% and 94%, respectively. Also, the *E. coli* counts in colonized infants was significantly lower in the breast-fed infants than in the formula-fed group. We conclude that the prevalence and counts of *C. difficile* as well as *E. coli* are significantly lower in the gut microbiota of breast-fed infants than in that of formula-fed infants, whereas the prevalence and counts of *Bifidobacterium* spp. is similar among both groups.

Kelly, D., & Coutts, A. G. P. (2000). Early nutrition and the development of immune function in the neonate. *Proceedings of the Nutrition Society*, 59(2), 177-185.

The intestine is the largest immune organ in the body, and as such is the location for the majority of lymphocytes and other immune effector cells. The intestine is exposed to vast quantities of dietary and microbial antigens, and is the most common portal of entry for pathogens, some of which are potentially lethal. The development of normal immune function of the intestine is therefore vital for survival, and is dependent on appropriate antigen exposure and processing, and also an intact Page 22 of 63 intestinal barrier. In early life innate mechanisms of defence are probably more important than active or adaptive mechanisms in responding to an infectious challenge, since the healthy neonate is immunologically naive (has not seen antigen) and has not acquired immunological memory. During this period maternal colostrum and milk can significantly augment resistance to enteric infections. The mechanisms of enhancing disease resistance are thought to be passive, involving a direct supply of antimicrobial factors, and active, by promoting the development of specific immune function. A tolerance response to dietary and non-invasive antigens is generally induced in the gut. However, it must also be able to mount an adequate immune response to ensure clearance of foreign antigens. It is now recognized that regulation of tolerance and active immune responses is critical to health, and failure to regulate these responses can lead to recurrent infections, inflammatory diseases and allergies. The education of the immune system in early life is thought to be critical in minimizing the occurrence of these immune-based disorders. During this phase

of development maternal milk provides signals to the immune system that generate appropriate response and memory. One factor that has been proposed to contribute to the increase in the incidence of immune-based disorders, e.g. atopic diseases in Western countries, is thought to be the increased prevalence of formula-feeding. Early nutrition and the development of immune function in the neonate.

Orrhage, K., & Nord, C. E. (1999). Factors controlling the bacterial colonization of the intestine in breastfed infants. *Acta Paediatrica*, 88, 47-57.

This article summarizes the published data on the intestinal microflora in breastfed infants published during the last 15 y. Acetic acid is found in higher concentrations in breastfed than in formula-fed infants. Degradation of mucin starts later in breastfed than in formula-fed infants. The conversion of cholesterol to coprostanol is also delayed by breastfeeding.

Carver, J. D. (1999). Dietary nucleotides: effects on the immune and gastrointestinal systems. *Acta Paediatrica*, 88, 83-88.

Nucleotides (NT) and their related metabolic products play key roles in many biological processes. Most dietary NT are rapidly metabolized and excreted. However, some are incorporated into tissues, particularly at younger ages. Under conditions of limited NT intake, rapid growth or certain disease states, dietary NT may spare the cost of de novo NT synthesis and optimize the function of rapidly dividing tissues such as those of the gastrointestinal and immune systems. Animals fed NT-supplemented versus non-NT supplemented diets have enhanced gastrointestinal growth and maturation, and improved recovery following small and large bowel injury. Indices of humoral and cellular immunity are enhanced, and survival rates are higher following infection with pathogens. Infants receive NT in human milk, where they are present as nucleic acids, nucleosides, nucleotides and related metabolic products. The NT content of human milk is significantly higher than most cow's milk-based infant formulae. Dietary NT are reported to enhance the gastrointestinal and immune systems of formula-fed infants. Infants fed NT-supplemented versus non-supplemented formula have a lower incidence of diarrhea, higher antibody titers following *Haemophilus influenzae* type b vaccination and higher natural killer cell activity. These data suggest that human milk NT may contribute to the superior clinical performance of the breastfed infant.

Hanson, L. A. (1998). Breastfeeding provides passive and likely long-lasting active immunity. *Annals of Allergy, Asthma & Immunology*, 81(6), 523-537.

Protection against infections has been well evidenced during lactation against, e.g., acute and prolonged diarrhea, respiratory tract infections, otitis media, urinary tract infection, neonatal septicemia, and necrotizing enterocolitis. There is also interesting evidence for an enhanced protection remaining for years after lactation against diarrhea, respiratory tract infections, otitis media, *Haemophilus influenzae* type b infections, and wheezing illness. In several instances the protection seems to improve with the duration of breastfeeding. A few factors in milk like anti-antibodies (anti-idiotypic antibodies) and T and B lymphocytes have in some experimental models been able to transfer priming of the breastfed offspring. This together with transfer of numerous cytokines and growth factors via milk may add to an active stimulation of the infant's immune system. Such an enhanced function could also explain why breastfeeding may protect

against immunologic diseases like celiac disease and possibly allergy. Suggestions of protection against autoimmune diseases and tumors have also been published.

Fitzsimmons, S. P., Evans, M. K., Pearce, C. L., Sheridan, M. J., Wientzen, R., & Cole, M. F. (1994). Immunoglobulin A subclasses in infants' saliva and in saliva and milk from their mothers. *The Journal of pediatrics*, 124(4), 566-573.

Secretory IgA concentration increased more rapidly during the first 6 months after birth in infants exclusively breastfed than in those exclusively bottle fed

Koutras, A. K., & Vigorita, V. J. (1989). Fecal secretory immunoglobulin A in breast milk versus formula feeding in early infancy. *Journal of pediatric gastroenterology and nutrition*, 9(1), 58-61. Enhanced fecal SIgA in breastfed infants is not caused solely by the presence of IgA in breast milk; it represents a stimulatory effect of breast milk on the gastrointestinal humoral immunologic development.

Hormones

Savino, F., Benetti, S., Liguori, S. A., Sorrenti, M., & Cordero Di Montezemolo, L. (2013). Advances on human milk hormones and protection against obesity. *Cell Mol Biol*, 59(1), 89-98. Extensive research shows that breast milk could have positive health effects not limited to infancy, but extend into childhood and adulthood. Recently many studies have provided new evidence on the long-term positive effects of breastfeeding, in particular protection against obesity and type 2 diabetes, suggesting that breast milk may have a role in the programming of later metabolic diseases. The mechanism throughout breastfeeding that exerts these effects has been a major focus of interest for researchers and it is still not completely known. There are some hints for biological plausibility of beneficial effects of breastfeeding including macronutrient intake, hormonal and behavioural mechanisms related to breast milk composition. Breast milk biochemical components, such as protein quantity and quality, polyunsaturated fatty acids, oligosaccharides, cytokines and hormones, in particular leptin, adiponectin and resistin together with the breastfeeding practice itself can influence infants feeding behaviour and regulation of growth and appetite control later in life. Further research is needed to confirm the possibility that hormones present in breast milk exert a metabolic and beneficial effects.

Savino, F., Fissore, M. F., Liguori, S. A., & Oggero, R. (2009). Can hormones contained in mothers' milk account for the beneficial effect of breast-feeding on obesity in children?. *Clinical endocrinology*, 71(6), 757-765.

Nutrition and growth during infancy are an emerging issue because of their potential link to metabolic health disorders in later life. Moreover, prolonged breast-feeding appears to be associated with a lower risk of obesity than formula feeding. Human milk is a source of various hormones and growth factors, namely adipokines (leptin and adiponectin), ghrelin, resistin and obestatin, which are involved in food intake regulation and energy balance. These compounds are either not found in commercial milk formulas or their presence is still controversial. Diet-

related differences during infancy in serum levels of factors involved in energy metabolism might explain anthropometric differences and also differences in dietary habits between breast-fed (BF) and formula-fed (FF) infants later in life, and may thus have long-term health consequences. In this context, the recent finding of higher leptin levels and lower ghrelin levels in BF than in FF infants suggests that differences in hormonal values together with different protein intake could account for the differences in growth between BF and FF infants both during infancy and later in life. In this review, we examine the data related to hormones contained in mothers' milk and their potential protective effect on subsequent obesity and metabolic-related disorders.

Bernt, K. M., & Walker, W. A. (1999). Human milk as a carrier of biochemical messages. *Acta Paediatrica*, 88, 27-41.

Hormones, growth factors, cytokines and even whole cells are present in breast milk and act to establish biochemical and immunological communication between mother and child. In addition, milk nutrients such as nucleotides, glutamine and Page 23 of 63 lactoferrin have been shown to influence gastrointestinal development and host defense.

Murphy, M. S. (1998). Growth factors and the gastrointestinal tract. *Nutrition*, 14(10), 771-774. Human milk as well as the milk of several mammalian species contains a group of biologically active substances that directly influence the newborn's metabolism and promote growth and differentiation of organs and target tissues. The biological significance of hormones and growth factors in milk is an area of active research.

Kling, P. J., Sullivan, T. M., Roberts, R. A., Philipps, A. F., & Koldovsky, O. (1998). Human milk as a potential enteral source of erythropoietin. *Pediatric research*, 43(2), 216.

Erythropoietin stimulates production of red blood cells and is used in the treatment of anemia of prematurity. Human milk contains considerable amounts of erythropoietin which resist degradation after exposure to gastric juices at physiologic pH levels.

Lucas, A., Baker, B. A., & Cole, T. J. (1990). Plasma prolactin and clinical outcome in preterm infants. *Archives of disease in childhood*, 65(9), 977-983.

Prolactin may be important for lung maturation and surfactant synthesis, and may play a role in the growth of the gut and intestinal absorption of fluid and ions. In a study of 280 infants weighing less than 1850 grams at birth, higher plasma prolactin levels were associated with fewer days on ventilator, faster transition to full enteral feedings, and greater gain in length.

Neurological, Psychomotor and Social Development

Leventakou, V., Roumeliotaki, T., Koutra, K., Vassilaki, M., Mantzouranis, E., Bitsios, P., ... & Chatzi, L. (2015). Breastfeeding duration and cognitive, language and motor development at 18 months of age: Rhea mother-child cohort in Crete, Greece. *J Epidemiol Community Health*, 69(3), 232-239.

Breast feeding duration has been associated with improved cognitive development in children. However, few population-based prospective studies have evaluated dose-response

relationships of breastfeeding duration with language and motor development at early ages, and results are discrepant. The study uses data from the prospective mother–child cohort ('Rhea' study) in Crete, Greece. 540 mother–child pairs were included in the present analysis. Information about parental and child characteristics and breastfeeding practices was obtained by interview-administered questionnaires. Trained psychologists assessed cognitive, language and motor development by using the Bayley Scales of Infant Toddler Development (3rd edition) at the age of 18 months. Duration of breastfeeding was linearly positively associated with all the Bayley scales, except of gross motor. The association persisted after adjustment for potential confounders with an increase of 0.28 points in the scale of cognitive development ($\beta=0.28$; 95% CI 0.01 to 0.55), 0.29 points in the scale of receptive communication ($\beta=0.29$; 95% CI 0.04 to 0.54), 0.30 points in the scale of expressive communication ($\beta=0.30$; 95% CI 0.04 to 0.57) and 0.29 points in the scale of fine motor development ($\beta=0.29$; 95% CI 0.02 to 0.56) per accumulated month of breastfeeding. Children who were breast fed longer than 6 months had a 4.44-point increase in the scale of fine motor development ($\beta=4.44$; 95% CI 0.06 to 8.82) compared with those never breast fed. The authors concluded that longer duration of breastfeeding was associated with increased scores in cognitive, language and motor development at 18 months of age, independently from a wide range of parental and infant characteristics. Additional longitudinal studies and trials are needed to confirm these results.

Sacker, A., Quigley, M. A., & Kelly, Y. J. (2006). Breastfeeding and developmental delay: findings from the millennium cohort study. *Pediatrics*, 118(3), e682-e689.

The study sample included 14,660 term singletons. Almost half (47%) of the infants initially were exclusively breastfed, but only 3.5% of these infants were still being fed exclusively on breast milk after 4 months of age. Thirty-four % of infants were not breastfed at all; 9% of the infants were identified with delays in gross motor coordination and 6% with fine motor coordination delays at age 9 months. The proportion of infants who mastered the developmental milestones increased with duration and exclusivity of breastfeeding. Infants who had never been breastfed were 50% more likely to have gross motor coordination delays than infants who had been breastfed exclusively for at least 4 months (10.7% vs 7.3%). Any breast milk also was positively related to development: infants who had never been breastfed were 30% more likely to have gross motor delays than infants who were given some breast milk for up to 2 months (10.7% vs 8.4%). The odds ratios for gross motor delay were not attenuated after adjustment for biological, socioeconomic, or psychosocial factors. Infants who were never breastfed had at least a 40% greater likelihood of fine motor delay than infants who were given breast milk for a prolonged period. Results suggest that the protective effect of breastfeeding on the attainment of gross motor milestones is attributable to some component(s) of breast milk or feature of breastfeeding and is not simply a product of advantaged social position, education, or parenting style, because control for these factors did not explain any of the observed association. In contrast, the association between breastfeeding and fine motor delay was explained by biological, socioeconomic, and psychosocial factors.

Khedr, E. M. H., Farghaly, W. M. A., Amry, S. E. D., & Osman, A. A. A. (2004). Neural maturation of breastfed and formula-fed infants. *Acta paediatrica*, 93(6), 734-738.

The study included 53 normal, healthy infants (30 exclusively breastfed infants and 23 exclusively formula-fed infants) at the age of 1 year. Each infant was subjected to a full physical and neurological examination together with neurophysiological studies including flash visual evoked potential (FVEP), brainstem auditory evoked potential (BAEP) and somatosensory evoked potential (SSEP). There was significant prolongation of P-100 wave latency of FVEP in formula-fed infants, together with significant prolongation of absolute latency of waves I, III and V of BAEP in formula-fed infants compared with breastfed infants. There was significant prolongation in inter-peak latencies between cortical and Erb's components in formula-fed infants compared with breastfed infants. We can conclude that VEP, BAEP and SSEP are more mature in breastfed infants relative to formula-fed infants at 1 y of age, and thus breast milk helps earlier development and maturation of some aspects of the nervous system than milk formulas.

Morley, R., Fewtrell, M. S., Abbott, R. A., Stephenson, T., MacFadyen, U., & Lucas, A. (2004). Neurodevelopment in children born small for gestational age: a randomized trial of nutrient-enriched versus standard formula and comparison with a reference breastfed group. *Pediatrics*, 113(3), 515-521.

Many studies have shown that children born small for gestational age (SGA) are at a neurodevelopmental disadvantage. We have shown that nutrient enrichment of formula fed to term SGA infants improves their growth and hypothesized that it also would improve their neurodevelopmental outcome. A randomized, controlled trial of standard term-infant (n=147) or nutrient-enriched (n=152) formula for the first 9 months. A reference group of 175 breastfed SGA infants was also recruited in 5 maternity hospitals in the United Kingdom. There was no significant intergroup difference in Bayley Mental Development Index (MDI) or Psychomotor Development Index (PDI) scores at 18 months. However, at 9 months, children fed the enriched formula had a significantly lower developmental quotient (99.5 vs 102.0). A significant disadvantage was seen in girls but not in boys. Breastfed infants had significantly higher MDI and PDI scores at 18 months than formula-fed infants. Confounding factors accounted for 34% of the observed association between breastfeeding and MDI score and none of the association between breastfeeding and PDI score. Conclusions: The previously reported enhanced linear growth in SGA children fed enriched formula was not matched by a neurodevelopmental advantage. At 9 months, girls fed the enriched formula had a significant developmental disadvantage, although this was not seen at 18 months. Later follow-up will determine any long-term effects on health or development. Meanwhile, use of enriched formula for term SGA children should not be promoted. It seems that breastfeeding may be especially beneficial for neurodevelopment in children born SGA.

Hart, S., Boylan, L. M., Carroll, S., Musick, Y. A., & Lampe, R. M. (2003). Brief report: breast-fed one-week-olds demonstrate superior neurobehavioral organization. *Journal of pediatric psychology*, 28(8), 529-534.

Participants were infants of breast-feeding (N = 41) and formula-feeding (N = 42) mothers. Assessments on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) were conducted on the infants when they were 8.95 days of age. Breast-fed infants surpassed formula-fed infants on items of the orientation, motor, range of state, and state regulation

dimensions of the BNBAS. Breast-fed infants also exhibited fewer abnormal reflexes, signs of depression, and withdrawal. Infants of adolescent mothers did not differ from those of adult mothers, regardless of feeding method. These data provide compelling evidence that breast-feeding is advantageous to neonates' neurobehavioral organization.

Bouwstra, H., Boersma, E. R., Boehm, G., Dijck-Brouwer, D. A. J., Muskiet, F. A. J., & Hadders-Algra, M. (2003). Exclusive breastfeeding of healthy term infants for at least 6 weeks improves neurological condition. *The Journal of nutrition*, 133(12), 4243-4245.

To investigate the minimal duration of exclusive breastfeeding for optimal neurological outcome, the quality of general movements at 3 months was assessed in 147 breastfed healthy term infants. The quality of general movements is a sensitive marker of neurological condition. There was a positive association between breastfeeding duration and movement quality, with a saturation effect at the age of similar to 6 wk. In the group of infants breastfed for less than or equal to 6 wk ($n = 55$), 18% exhibited normal-optimal general movements, 47% normal-suboptimal, and 47% mildly abnormal. In contrast, in the group of infants breastfed for > 6 wk ($n = 92$), 43% exhibited normal-optimal general movements, 45% normal-suboptimal, and 12% mildly abnormal. Exclusive breastfeeding for >6 wk was therefore associated with markedly less abnormal and more normal-optimal GM. Thus, breastfeeding for > 6 wk might improve the neurological condition in infants.

Dewey, K. G., Cohen, R. J., Brown, K. H., & Rivera, L. L. (2001). Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. *The Journal of nutrition*, 131(2), 262-267.

Infants were exclusively breastfed for 4 months and then randomly assigned to continue exclusive breastfeeding until 6 months or to receive high-quality, hygienic solid foods in addition to breast milk between 4 and 6 months. Infants who were exclusively breastfed for 6 months crawled sooner and were more likely to be walking by 12 mo than infants who started solid foods at 4 months.

Agostoni, C., Marangoni, F., Lammardo, A. M., Giovannini, M., Riva, E., & Galli, C. (2001). Breastfeeding duration, milk fat composition and developmental indices at 1 year of life among breastfed infants. *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA)*, 64(2), 105-109.

The associations of breastfeeding duration and milk fat composition with the developmental outcome at 1 year of age were measured in 44 infants exclusively breastfed for 3 months, out of 95 recruited at birth. Pooled breast milk (hindmilk) of the mothers was analysed at colostrum, 1, 3, 6, 9, and 12 months for total fat and fatty acid content. Infants were examined at 12 months by means of the Bayley test. There was a progressive reduction of the number of breastfed babies after the introduction of solids to 29 (6 months), 17 (9 months) and 10 (12 months). After adjusting for major confounders, infants breastfed for 6 months or longer showed a trend to have an advantage at the Bayley psychomotor developmental index compared to those breastfed >3 and <6 months while the Bayley mental developmental index (MDI) was just 2.1 points higher. Among the milk fat components considered for each time-point, the total fat

content at 6 months showed the strongest association with the MDI at 12 months ($r=0.59$, $P=0.001$). Prolonging breastfeeding during the weaning process may result in a better developmental performance at 12 months, possibly due to the supply of fats affecting brain composition.

Gerrish, C. J., & Mennella, J. A. (2000). Short-term influence of breastfeeding on the infants' interaction with the environment. *Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology*, 36(1), 40-48.

Infants (4 to 6 months old) looked at a mobile significantly longer when tested after breastfeeding. This finding suggests that breastfeeding has a substantial effect on infants' attentiveness to and interaction with their environment.

Vestergaard, M., Obel, C., Henriksen, T. B., Sørensen, H. T., Skajaa, E., & Østergaard, J. (1999). Duration of breastfeeding and developmental milestones during the latter half of infancy. *Acta Paediatrica*, 88(12), 1327-1332.

Motor skills and early language development were evaluated in 1656 8-month-olds. The proportion of infants who mastered the specific milestones increased consistently with increasing duration of breastfeeding. The relative risk for the highest versus the lowest breastfeeding category was 1.3 for crawling, 1.2 for pincer grip and 1.5 for polysyllable babbling. Little change was found after adjustment for confounding factors. In conclusion, data support the hypothesis that breastfeeding benefits neurodevelopment.

Barros, F. C., Victora, C. G., Morris, S. S., Halpern, R., Horta, B. L., & Tomasi, E. (1997). Breast feeding, pacifier use and infant development at 12 months of age: a birth cohort study in Brazil. *Paediatric and perinatal epidemiology*, 11(4), 441-450.

Children breastfed for 9 months or more present significantly less suspected developmental delay (25.5%, measured by the Denver II test) than those breast fed for less than 1 month (42.4%).

Temboury, M. C., Otero, A., Polanco, I., & Arribas, E. (1994). Influence of breast-feeding on the infant's intellectual development. *Journal of pediatric gastroenterology and nutrition*, 18(1), 32-36.

A prospective study of measured psychomotor development between 18 and 29 months using the Bayley scales. Lower results on the Index of Mental Development were associated with bottle-fed infants.

Baumgartner, C. (1984). Psychomotor and social development of breast-fed and bottle-fed babies during their first year of life. *Acta Paediatrica Hungarica*, 25(4), 409-417.

The psychomotor and social development of breastfed babies clearly differs from that of bottle-fed ones and leads at the age of 12 months to significant advantages of the psychomotor and social capabilities.

Sleep Cycles and Arousal

Cubero, J., Valero, V., Sánchez, J., Rivero, M., Parvez, H., Rodríguez, A. B., & Barriga, C. (2005). The circadian rhythm of tryptophan in breast milk affects the rhythms of 6-sulfatoxymelatonin and sleep in newborn. *Neuroendocrinology Letters*, 26(6), 657-662.

The hormone melatonin regulates sleep and this pineal hormone is synthesized in the organism from the amino acid tryptophan. It is known that breast-fed babies have better sleep patterns and a better entrained sleep/wake cycle than bottle-fed babies. Sixteen infants of 12 weeks of age were studied, divided into two groups depending on their exclusively natural or artificial feeding. Tryptophan in the breast milk presented a circadian rhythm with acrophase at around 03:00. This affected the 6-sulfatoxymelatonin circadian rhythm with acrophase at 06:00 in the breast-fed infants, and also promoted nocturnal sleep. Assumed sleep, actual sleep, and sleep efficiency were significantly increased in the breast fed infants with respect to the formula-fed infants.

Horne, R. S. C., Parslow, P. M., Ferens, D., Watts, A. M., & Adamson, T. M. (2004). Comparison of evoked arousability in breast and formula fed infants. *Archives of disease in childhood*, 89(1), 22-25.

Arousal from sleep is believed to be an important survival mechanism that may be impaired in victims of SIDS. Previously it has been shown that arousability is impaired by the major risk factors for SIDS such as prone sleeping and maternal smoking. To establish whether arousability was altered by method of feeding, 43 healthy term infants were studied using daytime polysomnography on three occasions: 2-4 weeks post-term, 2-3 months post-term, and 5-6 months post-term. Multiple measurements of arousal threshold in response to nasal air jet stimulation applied alternately to the nares were made in both active sleep and quiet sleep while infants slept supine. Arousal thresholds were not different between breast fed and formula fed infants in quiet sleep. However, in active sleep breast fed infants were significantly more arousable than formula fed infants at 2-3 months of age. There was no difference between groups of infants when sleep period length was compared at any study. Conclusion: Breast fed infants are more easily aroused from active sleep at 2-3 months of age than formula fed infants. This age coincides with the peak incidence of SIDS.

Speech and Language Development

Smith, J. M. (2015). Breastfeeding and language outcomes: A review of the literature. *Journal of communication disorders*, 57, 29-40.

Many researchers have investigated the potential impact of breastfeeding in infancy on a child's subsequent development, but only a small subset of these studies considers language development and impairment. This paper reviews that literature, discussing postnatal neurodevelopment, potential mechanisms for dietary influences on communication outcomes, studies of typically developing children, and studies of children with communication concerns. For population based studies of language development, a modest but statistically robust relationship is seen across large samples that account for breastfeeding exclusivity. A similar protective relationship is seen in studies that evaluate the relationship between breastfeeding and language disorders; effect sizes are typically larger in these papers. Implications for researchers and service providers are reviewed.

Dee, D. L., Li, R., Lee, L. C., & Grummer-Strawn, L. M. (2007). Associations between breastfeeding practices and young children's language and motor skill development. *Pediatrics*, 119(Supplement 1), S92-S98.

Using cross-sectional data on 22399 children from the 2003 National Survey of Children's Health, we examined relationships between breastfeeding practices and children's language and motor skills development. Outcomes were based on each mother's response to questions regarding her level of concern (a lot, a little, not at all) about her child's development of expressive language, receptive language, fine motor skills, and gross motor skills.

Breastfeeding data were based on mothers' recall. Mean age of the sample was 2.79 years; 67% were non-Hispanic white, 16% were Hispanic, and 9% were non-Hispanic black.

Approximately 17% of mothers reported concerns about their child's expressive language development; approximately 10% had receptive language concerns; approximately 6% had concerns about fine motor skills; and 5% reported general motor skills concerns. Multivariate analysis revealed that mothers who initiated breastfeeding were less likely than mothers of never-breastfed children to be concerned a lot about their child's expressive and receptive language development and fine and general motor skills. Mothers of children breastfed 3 to 5.9 months were less likely than mothers of never-breastfed children to be concerned a lot about their child's expressive and receptive language and fine and general motor skills. As with all cross-sectional data, results should be interpreted with caution. Our findings suggest breastfeeding may protect against delays in young children's language and motor skill development. Fewer concerns about language and motor skill development were evident for children breastfed ≥ 3 months, and concerns generally decreased as breastfeeding continued ≥ 9 months.

Vestergaard, M., Obel, C., Henriksen, T. B., Sørensen, H. T., Skajaa, E., & Østergaard, J. (1999). Duration of breastfeeding and developmental milestones during the latter half of infancy. *Acta Paediatrica*, 88(12), 1327-1332.

Several studies have suggested that breastfeeding has a long-term influence on brain development. However, interpretation of these findings is complicated by the presence of many potential confounding factors. Only a few studies have examined infants before 1 y of age, although very early assessment might reduce the role of environmental influence. We investigated the association between exclusive breastfeeding and three developmental milestones related to general and fine motor skills and early language development at the age of 8 mo. We followed 1656 healthy, singleton, term infants, with a birthweight of at least 2500 g, born between May 1991 and February 1992 in Aarhus, Denmark. Information was collected at 16 wk gestation, at delivery and when the infant was 8 mo old. Motor skills were evaluated by measurement of crawling and pincer grip. Early language development was defined as the ability to babble in polysyllables. The proportion of infants who mastered the specific milestones increased consistently with increasing duration of breastfeeding. The relative risk for the highest versus the lowest breastfeeding category was 1.3 (95% CI: 1.0-1.6) for crawling, 1.2 (95% CI: 1.1-1.3) for pincer grip and 1.5 (95% CI: 1.3-1.8) for polysyllable babbling. Little change was found after adjustment for confounding. In conclusion, our data support the hypothesis that breastfeeding benefits neurodevelopment.

Obel, C., Henriksen, T. B., Hedegaard, M., Secher, N. J., & Ostergaard, J. (1998). Smoking during pregnancy and babbling abilities of the 8-month-old infant. *Paediatric and Perinatal Epidemiology*, 12(1), 37-48.

Animal experiments suggest that the fetal brain is sensitive to nicotine. Our study describes the relationship between maternal cigarette smoking during pregnancy and babbling abilities of the 8-month-old infant. In a longitudinal cohort, information was collected at the 16th week of gestation, at delivery and when the infant was about 8 months old. At this age babbling abilities of the infant were evaluated by a health visitor during a home visit. Complete follow-up was obtained for 1871 children. A dose-response-like relationship between number of cigarettes smoked per day during pregnancy and babbling abilities was found after controlling for potential confounders. Smoking 10 or more cigarettes per day during pregnancy almost doubled the risk (odds ratio 2.0) of the infant being a non-babbling at the examination at 8 months. Among children who were breastfed for less than 4 months this risk was even higher (OR = 2.7).

Broad, F. E., & Duganzich, D. M. (1983). The effects of infant feeding, birth order, occupation and socio-economic status on speech in six-year-old children. *The New Zealand medical journal*, 96(734), 483-486.

The relationship of breast-feeding to the incidence of clear speech at six years of age was examined for 319 New Zealand children of European descent in samples from Putaruru and West Coast. Children were more likely to be breast-fed if firstborn, and less likely if the father's occupational group was business or labouring. Differences in clear speech were associated with birth order and socio-economic status. Controlling for these effects, the association of breast-feeding with clear speech was different for the sexes. It was negligible for girls but strongly positive for boys.

Broad, F. E. (1975). Further studies on the effects of infant feeding on speech quality. *The New Zealand medical journal*, 82(553), 373-376.

A previous speech survey (Broad 1972) has been extended to include similar children in schools on the West Coast of the South Island, making a total of 319 for the two surveys. Both surveys were retrospective. The combined studies showed that: 1. Breastfeeding is associated strongly with improved speech clarity in the male child and the tendency for breastfeeding to be associated with improved tonal quality is sustained. 2. Reading ability is associated with breastfeeding for the entire group, boys showing the effect more clearly than girls. 3. A high degree of association was found between reading ability and speech clarity. 4. There is an association between breastfeeding and confidence. There is evidence that the feeding effect is different for both sexes and that differences exist between the two regions.

Thymus Development

Hsu, P., & Nanan, R. K. H. (2018). Breast feeding, thymus and immunity—what is the link?. *Frontiers in Pediatrics*, 6, 268.

Breastfeeding has been associated with improved infant outcomes in multiple aspects, including immune outcomes such as infections and potentially atopy and autoimmunity. However

associations do not necessarily implicate cause and effect and at this point, exactly how breast feeding and components of breast milk may modulate the infant's immune compartment remains unclear, especially in humans. Some lines of evidence suggest that breastfeeding affects the development of the infant's thymus, a critical organ for T cell development. This may be a direct effect mediated by breast milk components or alternatively, a secondary effect from the impact of breast feeding on the infant's gut microbiome. Here we discuss the potential mechanisms and impact of this association between breastfeeding and thymic development.

Jeppesen, D. L., Hasselbalch, H., Lisse, I. M., Ersbøll, A. K., & Engelmann, M. D. (2004). T-lymphocyte subsets, thymic size and breastfeeding in infancy. *Pediatric allergy and immunology*, 15(2), 127-132.

This study followed the changes in concentration of T-lymphocyte subsets (CD4+ and CD8+ cells) in peripheral blood, and thymus size during infancy. Two different populations of infants between birth and 1 year of age were examined. Study Group I: infants with a variable duration of breastfeeding. Study Group II: long-term breastfed infants. In both groups a correlation was found between T-lymphocyte subsets (CD8+ cells) and the thymic index at 10 months of age. In Group I, infants still breastfed at the 8-month examination had a higher CD8% than formula-fed infants, and infants breastfed at the 4-month examination had a higher CD4% at 10 months of age. Group II showed an increase in the absolute number of CD4+ and CD8+ cells from 8 to 10 months of age; and a positive correlation between the number of breastfeedings per day at 8 months of age, and an increase in CD4+ cells from 8 to 10 months of age. In conclusion, a correlation was found between thymus size and CD8+ cells. Breastfeeding might have both a current and long-term immune-modulating effect on the developing cellular immune system.

Hasselbalch, H., Engelmann, M. D. M., Ersbøll, A. K., Jeppesen, D. L., & Fleischer-Michaelsen, K. (1999). Breast-feeding influences thymic size in late infancy. *European journal of pediatrics*, 158(12), 964-967.

At 10 months the thymic index was significantly higher in those still being breast-fed compared to infants who had stopped breast-feeding between 8 and 10 months of age. In infants still breast-fed at 10 months there was a significant correlation between the number of breast-feeds per day and their thymic index.

Hasselbalch, H., Jeppesen, D. L., Esrboll, A. K., Engelmann, M. D. M., & Nielsen, M. B. (1997). Thymus size evaluated by sonography: a longitudinal study on infants during the first year of life. *Acta radiologica*, 38(2), 222-227.

Forty-seven healthy infants were examined as neonates and re-examined at 4 months of age. Thirty-seven of the infants were also re-examined at 8, 10, and 12 months of age. The thymus size was measured. Infants exclusively breast-fed during the first 4 months of their lives had a larger thymic index at 10 months than formula-fed infants. Infants with fever episodes from 10 to 12 months had a smaller thymic index at 12 months. The thymus size in healthy infants increases from birth to 4 and 8 months of age and then decreases.

Hasselbalch, H., Jeppesen, D. L., Engelmann, M. D. M., Michaelsen, K. F., & Nielsen, M. B. (1996). Decreased thymus size in formula-fed infants compared with breastfed infants. *Acta paediatrica*, 85(9), 1029-1032.

At 4 months the geometric mean thymic index was 38.3 in exclusively breastfed infants (n = 21), 27.3 in partially breastfed infants (n = 13) and 18.3 in formula fed infants (n = 13). This finding was independent of weight, length, sex and previous or current illness. There was no significant difference in mean thymic index at birth between the three feeding groups and thymic index had increased in all three groups from birth to 4 months. Conclusion: the thymus is considerably larger in breastfed than in formula-fed infants at the age of 4 months. The cause of this difference is unknown but human milk contains many immune modulating factors that might cause this effect.

Visual Acuity

Singhal, A., Morley, R., Cole, T. J., Kennedy, K., Sonksen, P., Isaacs, E., ... & Lucas, A. (2007). Infant nutrition and stereoacuity at age 4–6 y–. *The American journal of clinical nutrition*, 85(1), 152-159.

Breastfeeding has been reported to benefit visual development in children. A higher concentration of docosahexaenoic acid (DHA) in breast milk than in formula has been proposed as one explanation for this association and as a rationale for adding DHA to infant formula, but few long-term data support this possibility. The objectives of the study were, first, to test the hypothesis that breastfeeding benefits stereoscopic visual maturation and, second, if that benefit is shown, to ascertain whether it is mediated by the dietary intake of DHA. Stereoacuity was measured by using the random dot E test (primary outcome), and visual acuity was measured by using the Sonksen-Silver acuity system (secondary outcome) in previously breastfed (n = 78) or formula-fed (n = 184) children aged 4-6 y who had been followed prospectively from birth. In the formula-fed group, children were randomly assigned to receive formula with either DHA or arachidonic acid (n = 94) or a control formula (n = 90) for the first 6 mo. Breastfed children had a significantly (P = 0.001) greater likelihood of foveal stereoacuity than did formulafed children (odds ratio: 2.5) independent of potential confounding (P = 0.005). Stereoacuity did not differ significantly between children randomly assigned to DHA-supplemented or control formula. None of the groups differed in Sonksen-Silver visual acuity. These findings support the hypothesis that breastfeeding benefits long-term stereoscopic development. An effect of DHA cannot be excluded, but the lack of difference in stereoacuity between infants randomly assigned to DHA-containing and those assigned to control formula raises the hypothesis that factors in breast milk other than DHA account for the observed benefits.

Williams, C., Birch, E. E., Emmett, P. M., Northstone, K., & Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) Study Team. (2001). Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study–. *The American journal of clinical nutrition*, 73(2), 316-322. Observational studies suggested that breastfeeding benefits the visual development of preterm children, which has been attributed to the presence of docosahexaenoic acid (DHA) in breast

milk but not most formula milks. Randomized studies showed that preterm children require a dietary supply of DHA in the first few weeks of life for optimal visual development, but it is unclear whether full-term children experience similar benefits from breast milk or DHA supplements. The objective of this study was to compare stereoacuity at age 3.5 years in healthy, full-term children who were breast-fed and in similar children who had not been breast-fed after adjustment for socioeconomic status and maternal diet. Prospectively collected data on maternal diet during pregnancy (including intake of oily fish), the child's diet, and the socioeconomic status of the family were examined. Children who had been breast-fed for 4 mo were more likely to achieve high-grade stereopsis, or stereoscopic vision, than were children who had not been breast-fed (adjusted odds ratio: 2.77). The mother's antenatal blood DHA content was associated with her intake of oily fish ($P < 0.0001$). Children whose mothers ate oily fish during pregnancy were also more likely to achieve high-grade stereopsis than were children whose mothers did not eat oily fish (adjusted odds ratio: 1.57). The results of this study suggest that for full-term infants, breast-feeding is associated with enhanced stereopsis at age 3.5 years, as is a maternal DHA-rich antenatal diet, irrespective of later infant feeding practice.

PAIN AND PHYSIOLOGIC RESPONSE DURING FEEDINGS

Zhu, J., Hong-Gu, H., Zhou, X., Wei, H., Gao, Y., Ye, B., ... & Chan, S. W. C. (2015). Pain relief effect of breast feeding and music therapy during heel lance for healthy-term neonates in China: A randomized controlled trial. *Midwifery*, 31(3), 365-372.

Objectives to test the effectiveness of breastfeeding (BF), music therapy (MT), and combined breastfeeding and music therapy (BF+MT) on pain relief in healthy-term neonates during heel lance. Participants included among 288 healthy-term neonates recruited, 250 completed the trial. All neonates were undergoing heel lancing for metabolic screening, were breastfed, and had not been fed for the previous 30 minutes. All participants were randomly assigned into four groups – BF, MT, BF+MT, and no intervention – with 72 neonates in each group. Neonates in the control group received routine care. Neonates in the other three intervention groups received corresponding interventions five minutes before the heel lancing and throughout the whole procedure. Findings mean changes in NIPS scores from baseline over time was dependent on the interventions given. Neonates in the BF and combined BF+MT groups had significantly longer latency to first cry, shorter duration of first crying, and lower pain mean score during and one minute after heel lance, compared to the other two groups. No significant difference in pain response was found between BF groups with or without music therapy. The MT group did not achieve a significantly reduced pain response in all outcome measures. BF could significantly reduce pain response in healthy-term neonates during heel lance. MT did not enhance the effect of pain relief of BF.

Gabriel, M. Á. M., de Mendoza, B. D. R. H., Figueroa, L. J., Medina, V., Fernández, B. I., Rodríguez, M. V., ... & Malagón, L. M. (2013). Analgesia with breastfeeding in addition to skin-to-skin contact during heel prick. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, 2012.

The objective of this study was to investigate the analgesic effect (measured with Neonatal Infant Pain Scale (NIPS)) of breastfeeding (BF) in addition to skin-to-skin contact (SSC) versus other methods of non-pharmacological analgesia during blood sampling through heel lance in healthy term neonates. Patients included 136 healthy term newborns. Inclusion criteria: healthy term neonates, wish to breastfeed and absence of feeding during the previous 60 min. Intervention Neonates were randomly assigned to four groups: Group breastfed with SSC (BF+SSC Group) (n=35); Group sucrose with SSC (Sucrose+SSC Group) (n=35); SSC Group (n=33); or Sucrose Group (n=33). Babies were recorded with a video camera. Three observers watched the videos and measured NIPS score at three time points (t0: 2 min before heel prick; t1: During heel prick; and t2: 2 min after the heel prick). The influences of non-pharmacological methods on crying time, percentage of crying while sampling, heart rate, number of attempts and duration of sampling were also studied. BF+SSC Group achieved a significant lower median NIPS score (value=1) compared with other groups (value=2, 4 and 4, respectively). The percentage of neonates with moderate-to-severe pain was also lower in the BF+SSC Group. Both groups BF+SSC and Sucrose+SSC achieved a significant lower percentage of crying compared with SSC Group. This study suggests that BF in addition to SSC provides superior analgesia to other kinds of non-pharmacological analgesia in healthy term neonates during heel prick.

Modarres, M., Jazayeri, A., Rahnema, P., & Montazeri, A. (2013). Breastfeeding and pain relief in full-term neonates during immunization injections: a clinical randomized trial. *BMC anesthesiology*, 13(1), 22.

The aim of this study was to examine the effect of breastfeeding on pain relief in full-term neonates during injection of hepatitis B vaccine. This was a randomized clinical trial. A sample of full-term neonates was randomly allocated into two groups: the experimental group and the control group. Neonates in the experimental group were breastfed two minutes before, during, and after the hepatitis B immunization and the control group were held in mothers' arms but not fed. Pain was assessed using the Douleur Aiguë du Nouveau-né (DAN) scale measuring facial expressions, limb movements and vocal expressions. The assessments were carried out after hepatitis B immunization. One hundred thirty healthy full-term neonates were studied (65 in the experimental group and 65 in the control group). Gestational age, birth weight, Apgar score and gender did not differ between the two groups. The mean total pain score as measured by the DAN scale was 3.52 (SD = 1.37) for the experimental group and it was 6.78 (SD = 1.69) for the controls indicating a significant lower pain score for the experimental group ($P < 0.001$). Also, there were significant differences for the three measures of DAN scale that are facial expressions, limb movements and vocal expression, between the two study groups ($P < 0.001$). The findings confirm that breastfeeding reduces pain and is an effective way for pain relief during hepatitis B vaccine injection.

Efe, E., & Özer, Z. C. (2007). The use of breast-feeding for pain relief during neonatal immunization injections. *Applied nursing research*, 20(1), 10-16.

The objective of this study was to examine the pain-relieving effect of breast-feeding during immunization injections in healthy neonates. Sixty-six healthy infants returning to a clinic for their second-, third-, or fourth-month immunization with intramuscular diphtheria, tetanus, and

pertussis were randomized to be breast-fed before, during, and after the injection or to be given the injection according to routine clinic procedure (no breast-feeding). To assess the pain responses of the neonates during and after immunization, we noted their heart rates, oxygen saturation levels, and length of crying. The crying time was shorter in the experimental (breast-feeding) group (M +/- SD duration, 35.85 +/- 40.11 seconds) than in the control group (M +/- SD duration, 76.24 +/- 49.61 seconds; $p = .001$). The heart rate and oxygen saturation levels were almost the same in both groups. We concluded that breast-feeding, maternal holding, and skin-to-skin contact significantly reduced crying in infants receiving an immunization injection for diphtheria, tetanus, and pertussis.

Shah, P. S., Aliwalas, L. L., & Shah, V. S. (2006). Breastfeeding or breast milk for procedural pain in neonates. *Cochrane Database of Systematic Reviews*, (3).

Clinical studies have shown reduction in the changes in physiological parameters and pain score measurements following preemptive analgesic administration in situations where the neonate is experiencing pain or stress. Nonpharmacological measures (such as holding, swaddling, breastfeeding) and pharmacological measures (such as acetaminophen, sucrose and opioids) have been used for this purpose. The primary objective of this review was to evaluate the effectiveness of breastfeeding or supplemental breast milk in reducing procedural pain in neonates. Eleven eligible studies were identified. Neonates in the breastfeeding group had statistically significantly less increase in the heart rate, reduced proportion of crying time and reduced duration of crying compared to swaddled group or pacifier group. Neonates in the breastfeeding group had a significant reduction in duration of crying compared to fasting (no intervention) group, but there was no significant difference when compared to glucose group. Premature Infant Pain Profile scores were significantly different between the breastfeeding group when compared to placebo group and the group positioned in mother's arms. However, these scores were not statistically significantly different in the breastfeeding group when compared to the no treatment group and the glucose group. Douleur Aigue Nouveau-ne scores were significantly different in the breastfeeding group when compared to the placebo group and the group positioned in mother's arms, but not when compared to the glucose group. Neonates in the supplemental breast milk group had significantly less increase in the heart rate and Neonatal Facial Coding Score compared to the placebo group. The differences in the duration of crying time and oxygen saturation change between supplemental breast milk group and the placebo group were not statistically significant. Neonates in the supplemental breast milk group had significantly higher increase in the heart rate changes and duration of crying time compared to glucose/sucrose group. No study was identified that has evaluated safety/effectiveness of repeated administration of breastfeeding or supplemental breast milk for pain relief. If available, breastfeeding or breast milk should be used to alleviate procedural pain in neonates undergoing a single painful procedure compared to placebo, positioning or no intervention. Administration of glucose/sucrose had similar effectiveness as breastfeeding for reducing pain. The effectiveness of breast milk for repeated painful procedures is not established and further research is needed. These studies should include various control interventions including glucose/sucrose and should target preterm neonates.

Phillips, R. M., Chantry, C. J., & Gallagher, M. P. (2005). Analgesic effects of breast-feeding or pacifier use with maternal holding in term infants. *Ambulatory Pediatrics*, 5(6), 359-364.

Full-term breast-feeding infants scheduled for routine newborn screening blood test via heel stick (n = 96) were randomized to 3 groups for analgesia: 1) breast-feeding, 2) pacifier use while held by mothers, 3) pacifier use while held by research assistants (nonmothers). Primary outcome was crying (percent of infants who cried during the procedure and mean percent of procedure time that infants cried). Secondary outcomes were physiologic measures. Fewer breast-feeding infants cried than infants using a pacifier while held by nonmothers both during the procedure (69% vs 100%, $P < .01$) and after the procedure (28% vs 60%, $P = .03$). Those infants crying during the procedure cried for less time if held by their mothers either breast-feeding (33%, $P < .01$) or using a pacifier (45%, $P = .03$) than those using a pacifier while being held by nonmothers (66%). Breast-feeding is more analgesic than pacifier use with nonmaternal holding. Maternal holding with either breast-feeding or pacifier use is more analgesic than nonmaternal holding with pacifier use, suggesting that maternal holding itself has an analgesic effect. Breastfeeding and maternal holding should be considered as pain-control measures for the neonate during heel-stick procedures.

Bier, J. A. B., Ferguson, A. E., Morales, Y., Liebling, J. A., Oh, W., & Vohr, B. R. (1997). Breastfeeding infants who were extremely low birth weight. *Pediatrics*, 100(6), e3-e3.

Preterm infants demonstrated a higher oxygen saturation and a higher temperature during breastfeeding than during bottle feeding, and were less likely to desaturate to <90% oxygen during breastfeeding.

Marino, B. L., O'Brien, P., & LoRe, H. (1995). Oxygen saturations during breast and bottle feedings in infants with congenital heart disease. *Journal of pediatric nursing*, 10(6), 360-364.

In infants with congenital heart disease, oxygen saturations during breastfeeding were higher on average and less variable than during bottle feedings, indicating that there is less cardiorespiratory stress with breastfeeding.

Tully, S. B., Bar-Haim, Y., & Bradley, R. L. (1995). Abnormal tympanography after supine bottle feeding. *The Journal of pediatrics*, 126(6), S105-11.

Supine bottle feeding has a significant effect on middle-ear pressure dynamics, probably caused by the aspiration of milk into the ear.

LONG TERM EFFECTS

Autism

Boucher, O., Julvez, J., Guxens, M., Arranz, E., Ibarluzea, J., de Miguel, M. S., ... & O'Connor, G. (2017). Association between breastfeeding duration and cognitive development, autistic traits and ADHD symptoms: a multicenter study in Spain. *Pediatric research*, 81(3), 434.

Several studies have related longer breastfeeding duration to better intellectual performance in children. By contrast, few studies have investigated the potential protective effects of breastfeeding against behavioral problems such as attention deficit hyperactivity disorder

(ADHD) symptoms, and even fewer on autism spectrum disorders (ASD) traits. We examined the association between breastfeeding duration and cognitive development, attention, ADHD symptoms, and autistic traits using data from the INMA Project, a Spanish multicenter birth-cohort study, and taking into account the intensity of breastfeeding. Duration of any, predominant, and exclusive breastfeeding was documented during infancy through maternal questionnaires. Children (N = 1,346; mean age = 4.9 y) were assessed using the McCarthy Scales of Children's Abilities, Conners' Kiddie Continuous Performance Test, criteria of the DSM-ADHD symptoms form list, and the Childhood Autism Spectrum Test. After adjustment for several confounders, longer duration of breastfeeding was independently associated with better cognitive development and with fewer autistic traits. This study provides further evidence of a positive association of breastfeeding with cognitive function apart from socio-environmental factors, and also suggests a protective role against autistic traits. Results are in agreement with recommendations for prolonged breastfeeding duration to promote child development.

Penn, A. H., Carver, L. J., Herbert, C. A., Lai, T. S., McIntire, M. J., Howard, J. T., ... & Dobkins, K. R. (2016). Breast milk protects against gastrointestinal symptoms in infants at high risk for autism during early development. *Journal of pediatric gastroenterology and nutrition*, 62(2), 317. Parents of children with Autism spectrum disorders (ASD) often report gastrointestinal dysfunction in their children. The objectives of the current study were to: 1) determine if infants at high risk for developing ASD (i.e. siblings of children diagnosed with ASD) show greater prevalence of gastrointestinal problems, and 2) whether this prevalence is associated with diet and age at weaning from breast milk. Using questionnaires, diet history and gastrointestinal problems were tracked prospectively and retrospectively in 57 High-risk infants, and for comparison, in 114 Low-risk infants (infants from families without ASD history). In Low-risk infants, prevalence of GI symptoms, in aggregate, did not vary with diet or age of weaning. By contrast, High-risk infants with GI symptoms were weaned earlier than those without symptoms ($p < 0.04$), and High-risk infants showed greater prevalence of GI symptoms, in aggregate, on a no breast milk (NBM) diet than on an exclusive breast milk (EBM) diet ($p < 0.017$). Constipation, in particular, was more prevalent in High-risk infants compared to Low-risk infants ($p = 0.01$), especially on a NBM diet ($p = 0.002$). High-risk infants who completed weaning earlier than 6 months showed greater prevalence of constipation ($p = 0.001$) and abdominal distress ($p = 0.004$) than those fully weaned after 6 months. The authors concluded that late weaning and EBM were associated with protection against GI symptoms in High-risk infants.

Al-Farsi, Y. M., Al-Sharbati, M. M., Waly, M. I., Al-Farsi, O. A., Al-Shafae, M. A., Al-Khaduri, M. M., ... & Deth, R. C. (2012). Effect of suboptimal breast-feeding on occurrence of autism: A case-control study. *Nutrition*, 28(7-8), e27-e32.

To evaluate the association between suboptimal breast-feeding practices and autism spectrum disorders (ASDs). Methods: A case-control study was conducted in 102 ASD cases and 102 matched healthy controls. Results: Based on adjusted odds ratios from logistic regression models, ASD was found to be associated with the late initiation of breast-feeding (odds ratio 1.48, 95% confidence interval 1.01–3.1), a non-intake of colostrum (odds ratio 1.7, 95% confidence interval 1.03–4.3), prelacteal feeding, and bottle-feeding. The risk of ASD was found to decrease in a dose-response fashion over increasing periods of exclusive breast-feeding (P

for trend = 0.04) and continued breast-feeding (P for trend = 0.001). Conclusion: The study indicates that increased ASD risk is generally associated with suboptimal breast-feeding practices.

Schultz, S. T., Klonoff-Cohen, H. S., Wingard, D. L., Akshoomoff, N. A., Macera, C. A., Ji, M., & Bacher, C. (2006). Breastfeeding, infant formula supplementation, and Autistic Disorder: the results of a parent survey. *International breastfeeding journal*, 1(1), 16.

When 861 children with Autistic Disorder were compared with 123 control children, not breastfeeding was associated with a 2.5 times increase in the odds of having Autistic Disorder.

Tanoue, Y., & Oda, S. (1989). Weaning time of children with infantile autism. *Journal of autism and developmental disorders*, 19(3), 425-434.

Comparing the weaning times of 145 autistic infants in a control group of 224 neurotypical children, the children in the control group breastfed significantly longer than the autistic infants.

Appendicitis

Alves, J. G. B., Figueiroa, J. N., & Barros, I. (2008). Does breastfeeding provide protection against acute appendicitis? A case-control study. *Tropical doctor*, 38(4), 235-236.

Breastfeeding stimulates a more tolerant lymphoid tissue at the base of the appendix and this could provide protection against acute appendicitis. Two studies reported that children and adolescents with appendicitis were less likely to have been breastfed. In a case-control study of 200 children with histologically confirmed acute appendicitis matched by 200 siblings with the same sex and difference age - up to three-year-old - we found breast feeding in at least the first two months of life and for more than four months provides protection against acute appendicitis. These findings suggest that breastfeeding may possibly give protection against the development of appendicitis.

Pisacane, A., De Luca, U., Impagliazzo, N., Russo, M., De Caprio, C., & Caracciolo, G. (1995). Breastfeeding and acute appendicitis. *BMJ: British Medical Journal*, 310(6983), 836.

Bone mass

Blanco, E., Burrows, R., Reyes, M., Lozoff, B., Gahagan, S., & Albala, C. (2017). Breastfeeding as the sole source of milk for 6 months and adolescent bone mineral density. *Osteoporosis International*, 28(10), 2823-2830.

The aim of the study is to assess the role of breastfeeding BF on adolescent bone mineral density (BMD) in a cohort prospectively followed since infancy. We studied 679 participants from an infancy iron deficiency anemia preventive trial in Santiago, Chile, followed to adolescence. Breast and bottle feeding were ascertained weekly from 4 to 12 months. At 16 years, whole body BMD was assessed by DEXA. Using linear regression, we evaluated associations between BF duration and BF as the sole source of milk and adolescent BMD z-score, adjusting for possible infancy, adolescent, and background confounders. Mean birth

weight and length were 3.5 (0.3) kg and 50.7 (1.6) cm. For at least 6 months, BF was the sole source of milk for 26.3% and with supplementation for 36.7%. For 37%, BF was provided for less than 6 months. Mean 16-year BMD z-score was 0.25 (1.0). Covariates included male sex, birth length, and gestational age. BF as the sole source of milk ≥ 6 months, compared to BF < 6 months, was associated with higher adolescent BMD z-score adjusting for covariates ($\beta = 0.29$, $p < 0.05$). Mixed BF was not significantly related to adolescent BMD z-score ($\beta = 0.06$, $p = 0.47$). For every 30 days of BF as the sole source of milk, adolescent BMD z-score increased by 0.03 ($p = 0.01$). BF without formula supplementation for at least 6 months was associated with higher adolescent BMD z-score and a suggestive trend in the same direction for BMD suggests that exclusivity and duration of BF may play a role in adolescent bone health.

van den Hooven, E. H., Gharsalli, M., Heppe, D. H., Raat, H., Hofman, A., Franco, O. H., ... & Jaddoe, V. W. (2016). Associations of breast-feeding patterns and introduction of solid foods with childhood bone mass: The Generation R Study. *British Journal of Nutrition*, 115(6), 1024-1032.

Breast-feeding has been associated with later bone health, but results from previous studies are inconsistent. We examined the associations of breast-feeding patterns and timing of introduction of solids with bone mass at the age of 6 years in a prospective cohort study among 4919 children. We collected information about duration and exclusiveness of breast-feeding and timing of introduction of any solids with postnatal questionnaires. A total body dual-energy X-ray absorptiometry scan was performed at 6 years of age, and bone mineral density (BMD), bone mineral content (BMC), area-adjusted BMC (aBMC) and bone area (BA) were analysed. Compared with children who were ever breast-fed, those never breast-fed had lower BMD (-4.62 mg/cm²; 95 % CI -8.28 , -0.97), BMC (-8.08 g; 95 % CI -12.45 , -3.71) and BA (-7.03 cm²; 95 % CI -12.55 , -1.52) at 6 years of age. Among all breast-fed children, those who were breast-fed non-exclusively in the first 4 months had higher BMD (2.91 mg/cm²; 95 % CI 0.41 , 5.41) and aBMC (3.97 g; 95 % CI 1.30 , 6.64) and lower BA (-4.45 cm²; 95 % CI -8.28 , -0.61) compared with children breast-fed exclusively for at least 4 months. Compared with introduction of solids between 4 and 5 months, introduction <4 months was associated with higher BMD and aBMC, whereas introduction between 5 and 6 months was associated with lower aBMC and higher BA. Additional adjustment for infant vitamin D supplementation did not change the results. In conclusion, results from the present study suggest that ever breast-feeding compared with never breast-feeding is associated with higher bone mass in 6-year-old children, but exclusive breast-feeding for 4 months or longer was not positively associated with bone outcomes.

Calcagno, A., Pala, G., Allegri, A. E. M., Napoli, F., Fratangeli, N., Calevo, M. G., ... & Di, I. N. (2015, August). Intrauterine Growth Restriction, Gestational Age, Steroidal Prophylaxis and Breastfeeding Influence Bone Mass in Prepubertal Children. In *54th Annual ESPE* (Vol. 84). European Society for Paediatric Endocrinology.

In order to address this topic we evaluated bone mass in ex-preterm (PT) and born at term (BT) prepubertal children and potential risk factors for bone health. DXA measures of total body less head and lumbar spine mineral density (TB/L1-L4 BMD, g/cm² and z-score), bone mineral content (TB-BMC, g), fat mass (FM%, kg) and free fat mass (FFM kg) were obtained in 100 PT

(n=42 females, n=58 males, median age at study 6.7 ± 1.3 years; gestational age-GA-range 26–36 weeks) and 51 BT (n=28 females, n=23 males) healthy children. Patients underwent height (HT SDS), BMI SDS and biochemical measures of 25OHD, PTH, CTx, BAP. 27 subjects (n=21 PT, n=6 BT) were intrauterine growth restriction (IUGR) and 55 PT underwent prenatal steroid prophylaxis. Forty-three children (n=20 PT and n=23 BT) were breastfed. There were no significant differences in anthropometrics, DXA parameters and bone markers between PT and BT children. However, positive correlations were found between GA or birth weight and BMC, BMD or BMD z-score both at the TB and the L1–L4. Steroid prophylaxis and breast feeding were respectively negatively (r 's between -0.16 and -0.39 ; all P 's <0.04) and positively (r 's between 0.18 and 0.29 ; all P 's <0.02) associated to all bone parameters. The IUGR group (17.9%) was shorter and presented significantly lower DXA bone measures (all P 's <0.05) compared to no IUGR children. Multiple regression analyses showed that, independently of age at visit, gestational age was predictive of bone mass (4.8%) in PT but not in BT children. Our study demonstrates comparable bone mass parameters in PT and BT prepubertal children. Breastfeeding seems to have a positive impact on bone parameters, while gestational age, IUGR and steroid prophylaxis might represent long-lasting risk factors for bone health.

Muniz, L. C., Menezes, A. M. B., Assunção, M. C. F., Wehrmeister, F. C., Martínez-Mesa, J., Gonçalves, H., ... & Barros, F. C. (2015). Breastfeeding and bone mass at the ages of 18 and 30: prospective analysis of live births from the Pelotas (Brazil) 1982 and 1993 cohorts. *PLoS one*, 10(4), e0122759.

The objective of this study was to evaluate the effect of total breastfeeding, breastfeeding duration and type of breastfeeding at 3 months of age on bone mass at 18 and 30 years. A prospective, longitudinal study was conducted with two birth cohorts (1982 and 1993) in Pelotas, Southern Brazil. Measurements of bone mineral content (BMC) and bone mineral density (BMD) at 18 and 30 years of age were obtained by dual-energy X-ray absorptiometry (DXA). Information on breastfeeding was collected during the first 4 years of life. Analyses were performed by linear regression and stratified by sex. A total of 1109 and 3226 participants provided complete information on breastfeeding in early life and bone mass at 18 and 30 years, respectively. No association between breastfeeding and bone mass was observed in women at both ages nor among men at age 30. Among men at the age of 18, BMC and BMD were higher among those breastfed regardless of duration ($p=0.032$ and $p=0.043$, respectively). Despite a very weak positive effect of breastfeeding (yes/no) on BMC and BMD at age 18 in men, most findings pointed to a lack of association between breastfeeding and bone mass until young adulthood.

Jones, G., Riley, M., & Dwyer, T. (2000). Breastfeeding in early life and bone mass in prepubertal children: a longitudinal study. *Osteoporosis international*, 11(2), 146-152. In this study of 330 8-year-old children from Southern Tasmania, those who were breastfed had higher bone mineral density at the femoral neck, lumbar spine and total body compared with those who were bottle-fed. This association remained significant after adjustment for size, lifestyle factors and socioeconomic factors. Breastfeeding for less than 3 months was not associated with increased bone mass at any site.

Cancer

Breast Cancer in Adulthood

Potischman, N., & Troisi, R. (1999). In-utero and early life exposures in relation to risk of breast cancer. *Cancer Causes & Control*, 10(6), 561-573.

Having been breastfed as an infant has been associated with a 20-35% reduction in risk of premenopausal breast cancer in four of six studies evaluating this factor.

Freudenheim, J. L., Marshall, J. R., Graham, S., Laughlin, R., Vena, J. E., Bandera, E., ... & Nemoto, T. (1994). Exposure to breastmilk in infancy and the risk of breast cancer. *Epidemiology*, 324-331.

Women who were breastfed as infants, even if only for a short time, showed an approximate 25% lower risk of developing premenopausal or postmenopausal breast cancer, compared to women who were bottle-fed as an infant.

Childhood Cancer

Smulevich, V. B., Solionova, L. G., & Belyakova, S. V. (1999). Parental occupation and other factors and cancer risk in children: I. Study methodology and non-occupational factors. *International journal of cancer*, 83(6), 712-717.

In a case-controlled study of 593 cases of cancer in Moscow children 0 to 14 years of age, the positive trend of increased risk of cancer with decreasing duration of breastfeeding was significant for all cancer combined.

Davis, M., Savitz, D., & Graubard, B. (1988). Infant feeding and childhood cancer. *The Lancet*, 332(8607), 365-368.

Children who are artificially fed or breastfed for only 6 months or less, are at an increased risk of developing cancer before age 15. The risk of artificially-fed children was 1-8 times that of long-term breastfed children, and the risk for short term feeders was 1-9 times that of long term breast feeders.

Cancer due to DNA Damage

Dündaröz, R., Ulucan, H., Aydın, H. İ., Güngör, T., Baltacı, V., Denli, M., & Sanisoğlu, Y. (2003). Analysis of DNA damage using the comet assay in infants fed cow's milk. *Neonatology*, 84(2), 135-141.

Regarding DNA damage leading to cancer development in the absence of human milk protection, a comparison between infants fed human milk and cow's milk was performed. Each group consisted of 35 infants, whose ages ranged from 9 to 12 months. The level of DNA damage in the peripheral blood lymphocytes of infants was studied by the comet assay. A significant increase was found in the number of limited DNA-damaged ($p < 0.001$) and extensive DNA-damaged ($p < 0.001$) cells of infants fed cow's milk. These results suggest that there is some level of DNA damage in the lymphocytes of infants not breast-fed and this may lead to malignancy in childhood or later in life.

DÜndaröz, R., Aydın, H. İ., Ulucan, H., Baltacı, V., Denli, M., & Gökçay, E. (2002). Preliminary study on DNA damage in non breast-fed infants. *Pediatrics international*, 44(2), 127-130.

There are many advantages of human milk for infants, including protection against cancer development. In this study, the level of genetic damage in the peripheral blood lymphocytes of infants who were fed mainly by cow's milk and breast milk was studied by sister chromatid exchange (SCE) analysis, a sensitive measurement of chromosomal damage. Each group consisted of 30 infants, ranging from 9 to 12 months. A significant increase was found in the frequencies of SCE of infants not breastfed compared to those who were breast-fed.

Hodgkin's Disease

Davis, M. K. (1998). Review of the evidence for an association between infant feeding and childhood cancer. *International journal of cancer*, 78(S11), 29-33.

This review of 9 published case-control studies suggests that children who are never breast-fed or are breast-fed short-term have a higher risk than those breast-fed for > 6 months of developing Hodgkin's disease, but not non-Hodgkin's lymphoma or acute lymphoblastic leukemia.

Schwartzbaum, J. A., George, S. L., Pratt, C. B., & Davis, B. (1991). An exploratory study of environmental and medical factors potentially related to childhood cancer. *Medical and pediatric oncology*, 19(2), 115-121.

A statistically significant protective effect against Hodgkin's disease among children who are breastfed at least 8 months compared with children who were breastfed no more than 2 months.

Leukemia and Lymphoma

Gao, Z., Wang, R., Qin, Z. X., Dong, A., & Liu, C. B. (2018). Protective effect of breastfeeding against childhood leukemia in Zhejiang Province, PR China: a retrospective case-control study. *Libyan Journal of Medicine*, 13(1), 1508273.

This research investigated the relationship between childhood leukemia and breastfeeding in the P. R. of China. We conducted a retrospective case-control study from March 2008 to April 2017 at the Children's Hospital of Zhejiang University, Zhejiang province, P. R. of China, which reviewed 958 children who had been diagnosed with leukemia in case group and 785 healthy children in control group. Data were obtained from medical records, and if the medical records were incomplete, we called mothers of children by phone to complete the data. Breastfeeding reduces the risk of childhood leukemia; the effect is greater, if feeding continued for 7–9 months ($p = 0.002$). In addition, we suggest that some factors such as maternal age, smoking during pregnancy, abortion history, genetic factors, parents use of hair dye, and the history of using birth control pills before pregnancy can increase the risk of childhood leukemia. This study indicates that promoting breastfeeding for 7–9 months may help lower the childhood leukemia incidence. Our study firstly demonstrates that breastfeeding has protective effects against childhood leukemia in the P. R. of China.

Amitay, E. L., & Keinan-Boker, L. (2015). Breastfeeding and childhood leukemia incidence: a meta-analysis and systematic review. *JAMA pediatrics*, 169(6), e151025-e151025.

Childhood cancer incidence increases and although rare, it is a leading cause of mortality. Leukemia and lymphoma comprise 40% of all cancers in children but little is known of their etiology. In this study, we examined the associations of breastfeeding and other early life exposures with childhood leukemia and lymphoma. A population-based case-control study carried out in 2011–2013 comprised mothers of 190 incidents (2005–2013) of leukemia/lymphoma cases aged 1–19 yr at diagnosis and 384 population-based controls. Interviews based on a computerized structured questionnaire were conducted with the mothers. Multivariate logistic regression models adjusted for potential confounders assessed the association between breastfeeding patterns and childhood leukemia/lymphoma. Ever breastfeeding category was associated with a 64% decreased risk for childhood leukemia/lymphoma [odds ratio (OR) = 0.36, 95% confidence interval (CI): 0.22, 0.60]; and similar trends, with a dose-response effect, were observed for any breastfeeding (exclusive and/or partial) category for 6, 12, and 18+ mo. Other infant exposures associated with cancer risk were child iron supplementation (OR = 0.39, 95% CI: 0.26, 0.59), pet ownership (OR = 0.50, 95% CI: 0.33, 0.78), paternal smoking (OR = 1.93, 95% CI: 1.18, 3.15), and having older siblings (OR = 1.18, 95% CI: 1.05, 1.33). Breastfeeding—a controllable and modifiable exposure—is inversely associated with risk for childhood leukemia and lymphoma with a dose-response effect.

Greenop, K. R., Bailey, H. D., Miller, M., Scott, R. J., Attia, J., Ashton, L. J., ... & Milne, E. (2015). Breastfeeding and nutrition to 2 years of age and risk of childhood acute lymphoblastic leukemia and brain tumors. *Nutrition and cancer*, 67(3), 431-441.

Acute lymphoblastic leukemia (ALL) and childhood brain tumors (CBT) are 2 of the most common forms of childhood cancer, but little is known of their etiology. In 2 nationwide case-control studies we investigated whether breastfeeding, age of food introduction, or early diet are associated with the risk of these cancers. Cases aged 0–14 years were identified from Australian pediatric oncology units between 2003 and 2007 (ALL) and 2005 and 2010 (CBT) and population-based controls through nationwide random-digit dialing. Mothers completed questionnaires giving details of infant feeding up to the age of 2 yr. Data from 322 ALL cases, 679 ALL controls, 299 CBT cases, and 733 CBT controls were analysed using unconditional logistic regression. Breastfeeding was associated with a reduced risk of ALL [odds ratio (OR) = 0.52, 95% confidence interval (CI): 0.32, 0.84], regardless of duration. Introduction of artificial formula within 14 days of birth was positively associated with ALL (OR = 1.57, 95% CI: 1.03, 2.37), as was exclusive formula feeding to 6 mo (OR = 1.81, 95% CI: 1.07, 3.05). No associations were seen between breastfeeding or formula use and risk of CBT. Our results suggest that breastfeeding and delayed introduction of artificial formula may reduce the risk of ALL but not CBT.

Flores-Lujano, J., Perez-Saldivar, M. L., Fuentes-Pananá, E. M., Gorodezky, C., Bernaldez-Rios, R., Del Campo-Martinez, M. A., ... & Bolea-Murga, V. (2009). Breastfeeding and early infection in the aetiology of childhood leukaemia in Down syndrome. *British journal of cancer*, 101(5), 860.

For a child to develop acute leukaemia (AL), environmental exposure may not be sufficient: interaction with a susceptibility factor to the disease, such as Down syndrome (DS), may also be necessary. We assessed whether breastfeeding and early infection were associated with the risk of developing AL in children with DS. METHODS: Children with DS in Mexico City, and either with or without AL, were the cases (N=57) and controls (N=218), respectively. Population was divided in children with AL and with acute lymphoblastic leukaemia (ALL) and also in children < or = 6 and >6 years old. RESULTS: Breastfeeding and early infections showed moderate (but not significant) association for AL, whereas hospitalisation by infection during the first year of life increased the risk: odds ratios (confidence interval 95%) were 0.84 (0.43-1.61), 1.70 (0.82- 3.52); and 3.57 (1.59-8.05), respectively. A similar result was obtained when only ALL was analysed. CONCLUSION: We found that breastfeeding was a protective factor for developing AL and ALL, and during the first year of life, infections requiring hospitalisation were related to a risk for developing the disease in those children with DS >6 years of age. These data do not support the Greaves's hypothesis of early infection being protective for developing ALL.

Kwan, M. L., Buffler, P. A., Abrams, B., & Kiley, V. A. (2004). Breastfeeding and the risk of childhood leukemia: a meta-analysis. *Public health reports*, 119(6), 521-535.

The authors used a meta-analytic technique to (1) quantify the evidence of an association between duration of breastfeeding and risk of childhood acute lymphoblastic leukemia (ALL) or acute myeloblastic leukemia (AML), (2) assess the influence of socioeconomic status (SES) on any such associations, and (3) discuss the implications of these findings for the evaluation of 3 whether breastfeeding reduces the risk of childhood leukemia. Methods. A fixed effects model was employed to systematically combine the results of 14 case-control studies addressing the effect of short-term (less than or equal to 6 months) and long-term (>6 months) breastfeeding on the risk of childhood ALL and/or AML. Subgroup analyses of studies that did and did not adjust for SES were also performed. Results. A significant, negative association was observed between long-term breastfeeding and both ALL risk (odds ratio=0.76) and AML risk (OR=0.85). Short-term breastfeeding was similarly protective for ALL and AML. Results for studies that adjusted and did not adjust for SES were not significantly different from the results for the 14 studies combined. Conclusions. This meta-analysis showed that both short-term and long-term breastfeeding reduced the risk of childhood ALL and AML, suggesting that the protective effect of breastfeeding might not be limited to ALL as earlier hypothesized. Potential bias introduced by different participation rates for case and control samples that differed in SES can be minimized by implementing larger case-control studies with SES-matched, population-based controls.

Perrillat, F., Clavel, J., Auclerc, M. F., Baruchel, A., Leverger, G., Nelken, B., ... & Hémon, D. (2002). Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. *British journal of cancer*, 86(7), 1064.

This study included 280 cases (240 acute lymphoblastic leukaemia and 40 acute non-lymphoblastic leukaemia) and 288 controls. Data were obtained from standardised face-to-face interviews of the mothers. A statistically-significant inverse association was observed between childhood leukaemia and day-care attendance (odds ratio=0.6), repeated early common

infections (greater than or equal to 4 per year before age two, odds ratio=0.6), surgical procedures for ear-nose-throat infections before age two (odds ratio=0.5) and prolonged breast-feeding (greater than or equal to 6 months, odds ratio=0.5). All the above associations were observed both for acute lymphoblastic leukaemia and acute non-lymphoblastic leukaemia.

Bener, A., Denic, S., & Galadari, S. (2001). Longer breast-feeding and protection against childhood leukaemia and lymphomas. *European Journal of Cancer*, 37(2), 234-238.
This case-controlled study of 117 Bedouin Arab children showed that breastfeeding for less than six months was associated with an odds ratio of 2.79 for contracting a lymphoid malignancy compared with children breastfed longer than six months.

Shu, X. O., Linet, M. S., Steinbuch, M., Wen, W. Q., Buckley, J. D., Neglia, J. P., ... & Robison, L. L. (1999). Breast-feeding and risk of childhood acute leukemia. *Journal of the National Cancer Institute*, 91(20), 1765-1772.

A total of 1744 children with acute lymphoblastic leukemia (ALL) and 1879 matched control subjects, aged 1-14 years, and 456 children with acute myeloid leukemia (AML) and 539 matched control subjects, aged 1-17 years, were studied. Ever having breast-fed was found to be associated with a 21% reduction in risk of childhood acute leukemias. The inverse Page 31 of 63 associations were stronger with longer duration of breast-feeding.

Shu, X. O., Linet, M. S., Steinbuch, M., Wen, W. Q., Buckley, J. D., Neglia, J. P., ... & Robison, L. L. (1999). Breast-feeding and risk of childhood acute leukemia. *Journal of the National Cancer Institute*, 91(20), 1765-1772.

In interviews with the mothers of 2,200 children affected by either acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML), the infant-feeding history of each of these children was compared with that of over 2,400 healthy controls. The investigators found that a history of breastfeeding was associated with a reduction in risk of childhood acute leukemias. Babies who are breast-fed for as little as one month have a 20% lower risk of childhood leukemia than bottle-fed babies, and babies breast-fed for more than 6 months have an even lower risk -- 30% less..

Neuroblastoma

Daniels, J. L., Olshan, A. F., Pollock, B. H., Shah, N. R., & Stram, D. O. (2002). Breast-feeding and neuroblastoma, USA and Canada. *Cancer Causes & Control*, 13(5), 401-405.

In a large case-control study in the United States and Canada, maternal reports of breast-feeding were compared among 393 children six months or older who had neuroblastoma and 376 age-matched controls. Children with neuroblastoma were less likely to have breast-fed than control children (odds ratio = 0.6). The association between breast-feeding and neuroblastoma increased with breast-feeding duration (0-3 months OR = 0.7, 13+ months OR = 0.5).

Conclusion: Breast-feeding was inversely associated with neuroblastoma and should be encouraged among healthy mothers.

Testicular Cancer

Coupland, C. A., Forman, D., Chilvers, C. E., Davey, G., Pike, M. C., & Oliver, R. T. D. (2004). Maternal risk factors for testicular cancer: a population-based case-control study (UK). *Cancer Causes & Control*, 15(3), 277-283.

A population-based case-control study of testicular cancer. Mothers of participants completed a questionnaire about their reproductive and obstetric history. The risk of testicular cancer was approximately doubled for sons of mothers aged 15-19 years at conception compared with mothers with older ages at conception. Nausea or vomiting during the first trimester of pregnancy was associated with a reduced risk of testicular cancer (odds ratio of 0.73). There was also a reduction in risk in men who had been breastfed for 6 months or more (odds ratio 0.65). Men who had low birthweights (< 2500 g) or had been born two or more weeks early had slightly increased risks, as did men whose mothers had used oral contraception in the 12 months before their conception. These findings support previous reports of increased risks in men born early or with low birthweight, but the direction of the association with maternal age is contrary to some other studies. The suggestion of a protective effect of breastfeeding requires further confirmation.

Tumor growth

Wolf, J. S., Li, D., Taylor, R. J., & O'Malley Jr, B. W. (2003). Lactoferrin inhibits growth of malignant tumors of the head and neck. *ORL*, 65(5), 245-249.

Lactoferrin, a naturally occurring glycoprotein found in breast milk, has previously been shown to have antimicrobial properties and recently has been demonstrated to inhibit malignant tumor growth. Using an orthotopic murine model for both squamous cell carcinoma and fibrosarcoma of the floor of the mouth, the researchers administered lactoferrin directly into the tumors. Additionally, they performed in vitro experiments to assess whether the effects of lactoferrin are due to direct cytotoxicity. Results revealed growth inhibition of 50% ($p = 0.03$) and 54% ($p = 0.01$) as compared with controls for both human and murine tumor cells in immunodeficient and immunocompetent mice, respectively. Lactoferrin proved effective in reducing malignant tumor growth in a murine model. These properties offer hope for its use as a primary or adjuvant chemotherapeutic agent. Further investigation focused on mechanism and delivery is needed.

Cardiovascular Disease (Atherosclerosis, Cholesterol Concentration, Hypertension)

Kelishadi, R., & Farajian, S. (2014). The protective effects of breastfeeding on chronic non-communicable diseases in adulthood: A review of evidence. *Advanced biomedical research*, 3. This review concluded that a growing body of evidence suggests that breastfeeding has protective roles against obesity, hypertension, dyslipidemia, and type II diabetes mellitus during adulthood.

Kuklina, E. V. (2014). Breastfeeding and cardiometabolic profile in childhood: how infant feeding, preterm birth, socioeconomic status, and obesity may fit into the puzzle.

Martin, R. M., Patel, R., Kramer, M. S., Vilchuck, K., Bogdanovich, N., Sergeichick, N., ... & Gillman, M. W. (2014). Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. *Circulation*, 129(3), 321-329.

The duration and exclusivity of breastfeeding in infancy have been inversely associated with future cardiometabolic risk. We investigated the effects of an experimental intervention to promote increased duration of exclusive breastfeeding on cardiometabolic risk factors in childhood. We followed-up children in the Promotion of Breastfeeding Intervention Trial, a cluster-randomized trial of a breastfeeding promotion intervention based on the World Health Organization/United Nations Children's Fund Baby-Friendly Hospital Initiative. In 1996 to 1997, 17 046 breastfeeding mother-infant pairs were enrolled from 31 Belarusian maternity hospitals and affiliated polyclinics (16 intervention versus 15 control sites); 13 879 (81.4%) children were followed up at 11.5 years, with 13 616 (79.9%) who had fasted and did not have diabetes mellitus. The outcomes were blood pressure; fasting insulin, adiponectin, glucose, and apolipoprotein A1; and the presence of metabolic syndrome. Analysis was by intention to treat, accounting for clustering within hospitals/clinics. The intervention substantially increased breastfeeding duration and exclusivity in comparison with the control arm (43% versus 6% and 7.9% versus 0.6% exclusively breastfed at 3 and 6 months, respectively). Cluster-adjusted mean differences at 11.5 years between experimental versus control groups were as follows: 1.0 mm Hg (95% confidence interval, -1.1 to 3.1) for systolic and 0.8 mm Hg (-0.6 to 2.3) for diastolic blood pressure; -0.1 mmol/L (-0.2 to 0.1) for glucose; 8% (-3% to 34%) for insulin; -0.3 µg/mL (-1.5 to 0.9) for adiponectin; and 0.0 g/L (-0.1 to 0.1) for apolipoprotein A1. The cluster-adjusted odds ratio for metabolic syndrome, comparing experimental versus control groups, was 1.21 (0.85 to 1.72).

Kwok, M. K., Leung, G. M., & Schooling, C. M. (2013). Breastfeeding and adolescent blood pressure: evidence from Hong Kong's "Children of 1997" Birth Cohort. *American journal of epidemiology*, 178(6), 928-936.

Observationally, breastfeeding is associated with lower blood pressure in Western developed settings, whereas little association exists in developing settings. However, postnatal characteristics (e.g., breast milk substitutes, infection rates, underweight, and pubertal timing) differ between these settings. We examined the association of breastfeeding with blood pressure at ~13 years, using multivariable linear regression, in 5,247 term births in 1997 from a population-representative Hong Kong Chinese birth cohort where socioeconomic patterning of breastfeeding differs from that of Western and developing settings but standard of living, social infrastructure, and postnatal characteristics are similar to those of Western settings. Higher education is associated with short-term breastfeeding but recent migration with longer-term breastfeeding. Compared with never breastfeeding, exclusive breastfeeding for ≥3 months was not associated with blood pressure (systolic mean difference = 0.82 mm Hg, 95% confidence interval (CI): -0.46, 2.11 and diastolic mean difference = 0.49 mm Hg, 95% CI: -0.22, 1.21), nor was partial breastfeeding for any length of time or exclusive breastfeeding for <3 months (systolic mean difference = 0.01 mm Hg, 95% CI: -0.64, 0.66 and diastolic mean difference = 0.16 mm Hg, 95% CI: -0.20, 0.52), adjusted for socioeconomic position and infant

characteristics. Lack of association in a non-Western developed setting further suggests that observations concerning breastfeeding and blood pressure vary with setting, thereby casting doubt on causality.

van den Berg, G., van Eijsden, M., Galindo-Garre, F., Vrijkotte, T. G., & Gemke, R. J. (2013). Explaining socioeconomic inequalities in childhood blood pressure and prehypertension: the ABCD study. *Hypertension*, 61(1), 35-41.

Much remains to be understood about the socioeconomic inequalities in hypertension that continue to exist. We investigated the association of socioeconomic status with blood pressure and prehypertension in childhood. In a prospective cohort, 3024 five- to six-year-old children had blood pressure measurements and available information on potential explanatory factors, namely birth weight, gestational age, smoking during pregnancy, pregnancy-induced hypertension, familial hypertension, maternal body mass index, breastfeeding duration, domestic tobacco exposure, and body mass index. The systolic and diastolic blood pressures of children from mid-educated women were 1.0-mm Hg higher (95% CI, 0.4-1.7) and 0.9-mm Hg higher (95% CI, 0.3-1.4), and the blood pressures of children with low-educated women were 2.2-mm Hg higher (95% CI, 1.4-3.0) and 1.7- mm Hg higher (95% CI, 1.1-2.4) compared with children with high-educated women. Children with mid- (odds ratio, 1.50; 95% CI, 1.18-1.92) or low-educated mothers (odds ratio, 1.80; 95% CI, 1.35-2.42) were more likely to have prehypertension compared with children with high-educated mothers. Using path analyses, birth weight, breastfeeding duration, and body mass index were determined as having a role in the association of maternal education with offspring blood pressure and prehypertension. The socioeconomic gradient in hypertension appears to emerge from childhood as the results show a higher blood pressure and more prehypertension in children from lower socioeconomic status families. Socioeconomic disparities could be reduced by improving 3 factors in particular, namely birth weight, breastfeeding duration, and body mass index, but other factors might also play a role.

Labayen, I., Ortega, F. B., Ruiz, J. R., Loit, H. M., Harro, J., Villa, I., ... & Sjöström, M. (2012). Association of exclusive breastfeeding duration and fibrinogen levels in childhood and adolescence: the European Youth Heart Study. *Archives of pediatrics & adolescent medicine*, 166(1), 56-61.

To examine the association of exclusive breastfeeding (BF) duration on serum fibrinogen levels of children and adolescents from Estonia and Sweden, controlling for other potential confounding factors that could mediate in this relationship. A total of 704 children and 665 adolescents were studied. Exclusive BF duration was reported by the mother and categorized in the following 5 categories: never, less than 1 month, 1 to 3 months, more than 3 to 6 months, and more than 6 months. Fasting fibrinogen level was measured, and age, sex, pubertal status, country, adiposity (sum of 5 skin-fold thicknesses), total cholesterol and triglyceride levels, blood pressure, physical activity (accelerometry), birth weight, maternal education, body mass index, and age were considered confounders in the analyses. RESULTS: Longer duration of exclusive BF was associated with lower fibrinogen levels regardless of confounders ($P < .001$). Mean (SD) fibrinogen levels were lower in youth who were breastfed for more than 3 months (after adjusting for all confounders, $P < .01$) in children (2.55 [0.04] vs 2.77 [0.03] g/L), adolescents

(2.59 [0.06] vs 2.72 [0.03] g/L), boys (2.47 [0.04] vs 2.73 [0.04] g/L), and girls (2.60 [0.03] vs 2.75 [0.02] g/L), compared with groups who were not breastfed. The results did not change substantially after further adjustment for birth weight and maternal educational level.

CONCLUSIONS: Exclusive BF is associated with less low-grade inflammation, as estimated by serum fibrinogen levels, in healthy children and adolescents. These findings give further support to the notion that early feeding patterns could program cardiovascular disease risk factors later in life.

van Rossem, L., Wijga, A. H., de Jongste, J. C., Koppelman, G. H., Oldenwening, M., Postma, D. S., ... & Smit, H. A. (2012). Blood Pressure in 12-Year-Old Children Is Associated With Fatty Acid Composition of Human Milk: The Prevention and Incidence of Asthma and Mite Allergy Birth Cohort. *Hypertension*, HYPERTENSIONAHA-112.

Breastfed individuals have a lower blood pressure than formula-fed individuals.

Supplementation with n-3 long-chain polyunsaturated fatty acids in adults is also associated with a lower blood pressure. We studied whether children receiving human milk with a relatively high content of n-3 long-chain polyunsaturated fatty acids have a lower blood pressure at age 12 years, and, if so, whether this association is explained by the n-3 long-chain polyunsaturated fatty acids content in erythrocyte membranes at age 12 years. Within a 12-year follow-up of a population-based birth cohort, we compared blood pressure of 205 never-breastfed children and 109 children who had fatty acid composition of their mothers' breast milk measured during lactation. In addition, 973 children had information on erythrocyte fatty acid composition and blood pressure at age 12 years. Children who received human milk with an n-3 long-chain polyunsaturated fatty acids content above the median (ie, 0.51 weight percentage) had a 4.79-mm Hg lower systolic (95% CI, -7.64 to -1.94) and a 2.47-mm Hg lower diastolic (95% CI, -4.45 to -0.49) blood pressure at age 12 years than never-breastfed children. N-3 long-chain polyunsaturated fatty acids levels in human milk below the median value and current n-3 long-chain polyunsaturated fatty acid status were not associated with blood pressure at age 12 years. Thus, a relatively high content of n-3 long-chain polyunsaturated fatty acids in human milk is associated with a lower blood pressure in children at age 12 years, a finding not explained by current n-3 long-chain polyunsaturated fatty acids status.

Lugonja, N., Spasić, S. D., Laugier, O., Nikolić-Kokić, A., Spasojević, I., Oreščanin-Dušić, Z., & Vrvic, M. M. (2013). Differences in direct pharmacologic effects and antioxidative properties of mature breast milk and infant formulas. *Nutrition*, 29(2), 431-435.

Early-onset and exclusive breast-feeding provides a significant health benefit to infants compared with infant formulas. The aim of this study was to compare mature breast milk with standard infant formulas by examining their effects on non-vascular smooth muscle contraction and their antioxidative properties. The pharmacologic effects of breast milk and formulas were examined using a model system of the rat uterine smooth muscle contraction. Electron paramagnetic resonance spin-trapping spectroscopy was used to compare the antioxidative capacities of breast milk (obtained in the ninth week of lactation) with commercial infant formulas against hydroxyl radical production in the Fenton reaction. The activities of superoxide dismutase, glutathione peroxidase, and the sulfhydryl group were determined in the breast milk and infant formulas. In contrast to the infant formulas, breast milk exerted a relaxing effect on

isolated non-vascular smooth muscle. In general, breast milk showed higher antioxidative activity compared with the infant formulas. In all samples, the generation of hydroxyl radicals led to the formation of carbon-centered and ascorbyl radicals. Human milk exerts direct pharmacologic relaxation effects and provides better antioxidant protection compared with infant formulas because of the presence of specific enzymatic components, such as human superoxide dismutase. We propose that these effects should be advantageous to an infant's gastrointestinal tract by supporting the normal work of the smooth musculature and maintaining redox homeostasis and may represent one of the mechanisms by which breast-feeding benefits health.

Labayen, I., Ruiz, J. R., Ortega, F. B., Loit, H. M., Harro, J., Villa, I., ... & Sjostrom, M. (2012). Exclusive breastfeeding duration and cardiorespiratory fitness in children and adolescents—. *The American journal of clinical nutrition*, 95(2), 498-505.

Breastfeeding has been associated with a protective effect against cardiovascular disease. Higher cardiorespiratory fitness during childhood is associated with healthier cardiovascular profile later in life. The objective was to examine the association Page 33 of 63 of exclusive breastfeeding duration with fitness in children and adolescents and to test the role of body composition and sociodemographic factors in this relation. At the time of the study, exclusive breastfeeding duration was reported by mothers and grouped into 4 categories: exclusively formula fed or breastfed for 6 mo. Fitness was determined by a maximal cycle-ergometer test in 1025 children (aged 9.5 ± 0.4 y) and in 971 adolescents (aged 15.5 ± 0.5 y) from Estonia and Sweden. Longer duration of breastfeeding was associated with higher fitness regardless of confounders [$+5.1\%$ L/min; country, sex, age, pubertal status, and BMI (adjusted $P < 0.001$) or fat mass and fat-free mass (FFM) ($+3.3\%$; adjusted $P < 0.001$)]. Further adjustment for birth weight, physical activity, and maternal educational level did not change the results ($P = 0.001$). The results were consistent in children and adolescents with low ($P < 0.001$) or high ($P = 0.013$) FFM, in nonoverweight ($P < 0.001$) or overweight ($P = 0.002$) children and adolescents, in offspring of nonoverweight ($P < 0.001$) or overweight ($P = 0.003$) mothers, in mothers with a low ($P = 0.004$) or high ($P < 0.001$) educational level, and in participants born within upper ($P = 0.001$), middle ($P = 0.017$), or lower ($P = 0.007$) tertiles of birth weight. Longer exclusive breastfeeding has a beneficial effect on cardiorespiratory fitness in children and adolescents. Because early infant-feeding patterns are potentially modifiable, a better understanding of the possible programming effect of exclusive breastfeeding on cardiorespiratory fitness is of public health interest.

Evelein, A. M., Geerts, C. C., Visseren, F. L., Bots, M. L., van der Ent, C. K., Grobbee, D. E., & Uiterwaal, C. S. (2011). The association between breastfeeding and the cardiovascular system in early childhood. *The American journal of clinical nutrition*, 93(4), 712-718.

In 306 children, ultrasonographic measurements of the carotid artery were performed to obtain carotid intima-media thickness (CIMT), distensibility, and elastic modulus. At 5 y of age, children who had been exclusively breastfed in infancy for 3 to 6 mo had a CIMT that was $21.1 \mu\text{m}$ greater than that of exclusively formula-fed children (95% CI: 5.0, $37.2 \mu\text{m}$; $P = 0.01$, adjusted for confounders). CIMT was not significantly different between children exclusively breastfed for

either 6 mo and formula-fed children. The choice of infant feeding appears to have an effect on the vascular system already in early childhood.

Singhal, A. (2009). The early origins of atherosclerosis. In *Early Nutrition Programming and Health Outcomes in Later Life* (pp. 51-58). Springer, Dordrecht.

Atherosclerosis has a long pre-clinical phase with development of pathological changes in arteries of children and young adults decades before overt clinical manifestations of disease. Nutritional factors in both infancy and childhood have been shown to be important in this process and affect lifetime cardiovascular disease risk. Breast-feeding in particular is associated with benefits for long-term cardiovascular risk factors possibly as a consequence of a slower pattern of growth in breast-fed compared to formula-fed infants. In fact, the benefits of slower growth for later health and longevity, appears to be a fundamental biological phenomenon conserved across diverse animal species. The nutritional programming of atherosclerosis could therefore be regarded as a specific example of programming of human aging as seen previously in programming of lifespan and telomere length in animals. The critical window for these effects is unknown, but evidence is accumulating for programming effects of growth from very early in infancy.

Owen, C. G., Whincup, P. H., Kaye, S. J., Martin, R. M., Davey Smith, G., Cook, D. G., ... & Freudenheim, J. L. (2008). Does initial breastfeeding lead to lower blood cholesterol in adult life? A quantitative review of the evidence—. *The American Journal of Clinical Nutrition*, 88(2), 305-314.

The study consisted of a systematic review of published observational studies relating initial infant feeding status to blood cholesterol concentrations in adulthood (ie, aged >16 y). Data were available from 17 studies (17 498 subjects; 12 890 breastfed, 4608 formula-fed). Mean differences in total cholesterol concentrations (breastfed minus formula-fed) were pooled by using fixed-effect models. Effects of adjustment (for age at outcome, socioeconomic position, body mass index, and smoking status) and exclusion (of nonexclusive breast feeders) were examined. RESULTS: Mean total blood cholesterol was lower ($P = 0.037$) among those ever breastfed than among those fed formula milk (mean difference: -0.04 mmol/L; 95% CI: -0.08 , 0.00 mmol/L). The difference in cholesterol between infant feeding groups was larger ($P = 0.005$) and more consistent in 7 studies that analyzed "exclusive" feeding patterns (-0.15 mmol/L; -0.23 , -0.06 mmol/L) than in 10 studies that analyzed nonexclusive feeding patterns (-0.01 mmol/L; -0.06 , 0.03 mmol/L). Adjustment for potential confounders including socioeconomic position, body mass index, and smoking status in adult life had minimal effect on these estimates. CONCLUSIONS: Initial breastfeeding (particularly when exclusive) may be associated with lower blood cholesterol concentrations in later life. Moves to reduce the cholesterol content of formula feeds below those of breast milk should be treated with caution.

Rudnicka, A. R., Owen, C. G., & Strachan, D. P. (2007). The effect of breastfeeding on cardiorespiratory risk factors in adult life. *Pediatrics*, 119(5), e1107-e1115.

A total of 9377 persons born during 1 week in 1958 in England, Scotland, and Wales were followed-up periodically from birth into adulthood. Infant feeding was recorded from a parental questionnaire at 7 years old as never breastfed, breastfed partially or wholly for 1 month.

Breastfeeding for >1 month was associated with reduced waist circumference, waist/hip ratio, von Willebrand factor, and lower odds of obesity compared with formula feeding after adjustment for birth weight, prepregnancy maternal weight, maternal smoking during pregnancy, socioeconomic position in childhood and adulthood, region of birth, gender, and current smoking status. Infant feeding status was not associated with other cardiorespiratory risk factors after adjustment, except for lower fibrinogen and C-reactive protein levels in women.

Martin, R. M., Ebrahim, S., Griffin, M., Smith, G. D., Nicolaides, A. N., Georgiou, N., ... & Gunnell, D. (2005). Breastfeeding and atherosclerosis: intima-media thickness and plaques at 65-year follow-up of the Boyd Orr cohort. *Arteriosclerosis, thrombosis, and vascular biology*, 25(7), 1482-1488.

A historic cohort study based on a 65-year follow-up of the Carnegie survey of diet and health in prewar Britain, 1937 to 1939. A total of 732 eligible cohort members living in or around Aberdeen, Bristol, Dundee, Wisbech, and London were invited for follow-up examinations in 2002, and 405 (55%) participated. In models controlling for age and sex, breastfeeding was inversely associated with common carotid intima-media thickness (IMT), bifurcation IMT, carotid plaque, and femoral plaque, compared with bottle-feeding. controlling for socioeconomic variables in childhood and adulthood, smoking and alcohol made little difference to effect estimates. controlling for factors potentially on the causal pathway (blood pressure, adiposity, cholesterol, insulin resistance, and C-reactive protein) made little difference to observed associations. Conclusions Breastfeeding may be associated with a reduced risk of atherosclerosis in later life.

Martin, R. M., Gunnell, D., & Davey Smith, G. (2005). Breastfeeding in infancy and blood pressure in later life: systematic review and meta-analysis. *American Journal of Epidemiology*, 161(1), 15-26.

A systematic review has confirmed that breastfeeding confers a small reduction in blood pressure. Fifteen studies including 17,503 subjects were summarized. Breastfed infants had lower systolic and diastolic blood pressure than bottle-fed infants. The authors conclude that this could confer important benefits on cardiovascular health at a population level.

Lawlor, D. A., Najman, J. M., Sterne, J., Williams, G. M., Ebrahim, S., & Smith, G. D. (2004). Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University study of pregnancy and its outcomes. *Circulation*, 110(16), 2417-2423.

We examined the associations of a range of parental and early life characteristics with systolic blood pressure at 5 years of age. Information from 3864 children who were followed up prospectively from their mother's first antenatal clinic assessment was used. Children who had been breast fed until at least 6 months had lower systolic blood pressure than those who were breastfed for a shorter duration. Because childhood blood pressure tracks into adulthood, interventions aimed at early life risk factors, such as quitting smoking during pregnancy, breast feeding, and prevention of obesity in all family members, may be important for reducing the population distribution of blood pressure and thus cardiovascular disease risk.

Singhal, A., Cole, T. J., Fewtrell, M., & Lucas, A. (2004). Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. *The Lancet*, 363(9421), 1571-1578.

Breastfeeding is associated with reduced cholesterol concentration later in life, but previous studies have not used random assignment of infant diet with prospective follow-up. We tested the hypothesis that breastmilk feeding benefits the lipoprotein profile in adolescents born preterm, in whom randomization to different diets at birth is feasible. Infants born preterm were randomly assigned to receive (trial 1) donated banked breastmilk or preterm formula, or (trial 2) standard term formula or preterm formula, as sole diet or as supplements to mother's milk in both trials. We followed up 216 participants at age 13-16 years and measured ratio of low-density to high-density lipoprotein cholesterol (LDL to HDL), ratio of apolipoprotein B to apolipoprotein A-1 (apoB to apoA-1), and concentration of C-reactive protein (CRP; a measure of the inflammatory process associated with atherosclerosis). Adolescents who had been randomised to banked breastmilk had a lower CRP concentration and LDL to HDL ratio (mean difference 0.34 [14% lower]) than those given preterm formula. A greater proportion of human milk intake in infancy was associated with lower ratios of LDL to HDL and apoB to apoA-1— independent of gestation and potential confounding factors—and with lower CRP concentration. CRP concentration correlated with the two lipoprotein ratios. Our data provide experimental evidence for the long-term benefits of breastmilk feeding on the risk of atherosclerosis.

Martin, R. M., Ness, A. R., Gunnell, D., Emmett, P., & Smith, G. D. (2004). Does breast-feeding in infancy lower blood pressure in childhood?: the Avon Longitudinal Study of Parents and Children (ALSPAC). *Circulation*, 109(10), 1259-1266.

Breast-feeding in infancy has been associated with decreased coronary heart disease mortality, but the underlying mechanisms are unclear. In a prospective cohort study, a total of 7276 singleton, term infants born in 1991 and 1992 were examined at 7.5 years. Complete data were available for 4763 children. The systolic and diastolic blood pressures of breast-fed children were 1.2 mm Hg lower and 0.9 mm Hg lower, respectively, compared with children who were never breast-fed (models controlled for age, sex, room temperature, and field observer). Blood pressure differences were attenuated but remained statistically significant in fully adjusted models controlling for social, economic, maternal, and anthropometric variables. Blood pressure differences were similar whether breast-feeding was partial or exclusive. We examined the effect of breast-feeding duration. In fully adjusted models, there was a 0.2-mm Hg reduction (0.0 to 0.3) in systolic pressure for each 3 months of breast-feeding. Breast-feeding is associated with a lowering of later blood pressure in children born at term. If the association is causal, the wider promotion of breast-feeding is a potential component of the public health strategy to reduce population levels of blood pressure.

Owen, C. G., Whincup, P. H., Odoki, K., Gilg, J. A., & Cook, D. G. (2002). Infant feeding and blood cholesterol: a study in adolescents and a systematic review. *Pediatrics*, 110(3), 597-608. A total of 1532 individuals in 10 British towns were studied, and 37 studies with 52 observations on total cholesterol (TC) were reviewed. In infancy, mean TC was higher among those breastfed (mean TC difference = 0.64), whereas in adults, mean TC Page 35 of 63 was lower among those breastfed (mean TC difference = -0.18). Patterns for low-density lipoprotein (LDL) were

similar to those for TC throughout. These results suggest that breastfeeding may have long-term benefits for cardiovascular health and may have implications for the content of formula feed milks.

Singhal, A., Cole, T. J., & Lucas, A. (2001). Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *The Lancet*, 357(9254), 413-419.

Breastfeeding has been associated with lower blood pressure in later life, but previous studies have not controlled for possible confounding factors by using a randomized design with prospective follow-up. In this study, blood pressure was measured at age 13-16 years in 216 (23%) of a cohort of 926 children who were born prematurely and had participated at birth in two parallel randomised trials in five neonatal units in the UK. Dietary interventions were: donated banked breastmilk versus preterm formula and standard term formula versus preterm formula. Children followed up at age 13-16 years were similar to those not followed up in terms of social class and anthropometry at birth. Mean arterial blood pressure at age 13-16 years was lower in the 66 children assigned banked breastmilk (alone or in addition to mother's milk) than in the 64 assigned preterm formula (mean 81.9 vs 86.1 mm Hg; $p=0.001$). In non-randomised analyses, the proportion of enteral intake as human milk in the neonatal period was inversely related to later mean arterial pressure. No differences were found in the term formula ($n=44$) versus preterm formula ($n=42$) comparison. Breastmilk consumption was associated with lower later blood pressure in children born prematurely. This data provides experimental evidence of programming of a cardiovascular risk factor by early diet and further supports the long-term beneficial effects of breastmilk.

Ravelli, A. C. J., Van der Meulen, J. H. P., Osmond, C., Barker, D. J. P., & Bleker, O. P. (2000). Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. *Archives of disease in childhood*, 82(3), 248-252.

Exclusive breast feeding seems to have a protective effect against some risk factors for cardiovascular disease in later life. In this study of 625 adults aged 48-53 years, those who were bottle fed had a higher mean plasma glucose concentration after a standard oral glucose tolerance test than those who were exclusively breast fed. They also had a higher plasma low density lipoprotein (LDL) cholesterol concentration, a lower high density lipoprotein (HDL) cholesterol concentration, and a higher LDL/ HDL ratio. Systolic blood pressure and body mass index were not affected by the method of infant feeding.

Plancoulaine, S., Charles, M. A., Lafay, L., Tauber, M., Thibault, N., Borys, J. M., & Eschwege, E. (2000). Infant-feeding patterns are related to blood cholesterol concentration in prepubertal children aged 5–11 y: the Fleurbaix-Laventie Ville Sante study. *European journal of clinical nutrition*, 54(2), 114.

After adjustment for age, height, and sibship, and taking into account current diet and parental hypercholesterolemia, cholesterol concentration was lower in boys who had been breast fed. This study provides evidence that diet in infancy may have longstanding effect on lipid metabolism.

Celiac Disease

Ivarsson, A., Myléus, A., Norström, F., van der Pals, M., Rosén, A., Högborg, L., ... & Karlsson, E. (2013). Prevalence of childhood celiac disease and changes in infant feeding. *Pediatrics*, peds-2012.

Between 1984 and 1996, Sweden experienced an “epidemic” of clinical celiac disease in children <2 years of age, attributed partly to changes in infant feeding. Whether infant feeding affects disease occurrence and/or the clinical presentation remains unknown. We investigated and compared the total prevalence of celiac disease in 2 birth cohorts of 12-year-olds and related the findings to each cohort’s ascertained infant feeding. A 2-phase cross-sectional screening study was performed in which 13 279 children from 2 birth cohorts participated: children born during the epidemic (1993) and children born after the epidemic (1997). Previously diagnosed cases were reported and confirmed. Blood samples were analyzed for serological markers and children with positive values were referred for small intestinal biopsy. Infant feeding practices in the cohorts were ascertained via questionnaires. Prevalence comparisons were expressed as prevalence ratios. The total prevalence of celiac disease was 29 in 1000 and 22 in 1000 for the 1993 and 1997 cohorts, respectively. Children born in 1997 had a significantly lower risk of having celiac disease compared with those born in 1993 (prevalence ratio: 0.75; 95% confidence interval: 0.60–0.93; $P = .01$). The cohorts differed in infant feeding (specifically, in the proportion of infants introduced to dietary gluten in small amounts during ongoing breastfeeding). The authors concluded that a significantly reduced prevalence of celiac disease in 12-year-olds indicates an option for disease prevention. Our findings suggest that the present infant feeding recommendation to gradually introduce gluten-containing foods from 4 months of age, preferably during ongoing breastfeeding, is favorable.

Henriksson, C., Boström, A. M., & Wiklund, I. E. (2013). What effect does breastfeeding have on coeliac disease? A systematic review update. *Evidence-based medicine*, 18(3), 98.

The objective of this study was to update the evidence published in a previous systematic review and meta-analysis that compared the effect of breastfeeding on risk of coeliac disease (CD). **Material and methods** A systematic review of observational studies published between 1966 and May 2004 on the subject was conducted in 2005. This update is a systematic review of observational studies published between June 2004 and April 2011. Pubmed, EMBASE and Cinahl were searched for published studies that examined the association between breastfeeding and CD. **Results** After duplicates were removed 90 citations were screened. Four observational studies were included in the review. Two of three studies which had examined the duration of breastfeeding and CD reported significant associations between longer duration of breastfeeding and later onset of CD (OR ranged from 0.18 to 0.665). Breastfeeding during the introduction of gluten to the infant was reported to have a protective effect in two studies. **Conclusions** Our findings support previous published findings that breastfeeding seems to offer a protection against the development of CD in predisposed infants. Breastfeeding at time of gluten introduction is the most significant variable in reducing the risk. Timing of gluten introduction may also be a factor in the development of CD.

Akobeng, A. K., Ramanan, A. V., Buchan, I., & Heller, R. F. (2006). Effect of breastfeeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Archives of disease in childhood*, 91(1), 39-43.

Coeliac disease (CD) is a disorder that may depend on genetic, immunological, and environmental factors. Recent observational studies suggest that breastfeeding may prevent the development of CD. AIM: To evaluate articles that compared effects of breastfeeding on risk of CD. METHODS: Systematic review and meta-analysis of observational studies published between 1966 and June 2004 that examined the association between breast feeding and the development of CD. RESULTS: Six case-control studies met the inclusion criteria. With the exception of one small study, all the included studies found an association between increasing duration of breastfeeding and decreased risk of developing CD. Meta-analysis showed that the risk of CD was significantly reduced in infants who were breastfeeding at the time of gluten introduction (pooled odds ratio 0.48, 95% CI 0.40 to 0.59) compared with infants who were not breastfeeding during this period. CONCLUSIONS: Breast feeding may offer protection against the development of CD. Breast feeding during the introduction of dietary gluten, and increasing duration of breastfeeding were associated with reduced risk of developing CD. It is, however, not clear from the primary studies whether breast feeding delays the onset of symptoms or provides a permanent protection against the disease. Long term prospective cohort studies are required to investigate further the relation between breastfeeding and CD.

Ivarsson, A., Hernell, O., Stenlund, H., & Persson, L. Å. (2002). Breast-feeding protects against celiac disease. *The American journal of clinical nutrition*, 75(5), 914-921.

Celiac disease, or permanent gluten-sensitive enteropathy, is an immunologic disease strictly dependent on exposure to wheat gluten or related proteins. A questionnaire was used to assess patterns of food introduction to infants, 627 Swedish children with celiac disease and 1254 referents. The risk of celiac disease was reduced in children aged <2 y if they were still being breast-fed when dietary gluten was introduced (OR 0.59). This effect was even more pronounced in infants who continued to be breast-fed after dietary gluten was introduced (OR: 0.36). The risk was greater when gluten was introduced in the diet in large amounts than when introduced in small or medium amounts.

Peters, U., Schneeweiss, S., Trautwein, E. A., & Erbersdobler, H. F. (2001). A case-control study of the effect of infant feeding on celiac disease. *Annals of nutrition and metabolism*, 45(4), 135-142.

In this case-control study, 143 children with celiac disease and 137 randomly recruited gender- and age-matched control children were administered a standardized questionnaire. The risk of developing celiac disease decreased significantly by 63% for children breast-fed for more than 2 months (OR 0.37) as compared with children breast-fed for 2 months or less. The age at first gluten introduction had no significant influence on the incidence of celiac disease (OR 0.72 comparing first gluten introduction into infant diet >3 months vs. less than or equal to 3 months). Conclusion: A significant protective effect on the incidence of celiac disease was suggested by the duration of breast-feeding (partial breastfeeding as well as exclusive breastfeeding). The data did not support an influence of the age at first dietary gluten exposure on the incidence of

celiac disease. However, the age at first gluten exposure appeared to affect the age at onset of symptoms.

Auricchio, S., Follo, D., Giunta, A., Marzorati, D., Prampolini, L., Ansaldi, N., ... & Bossi, A. (1983). Does breastfeeding protect against the development of clinical symptoms of celiac disease in children?. *Journal of pediatric gastroenterology and nutrition*, 2(3), 428-433. Celiac disease is characterized by lethargy, megaloblastic anemia, malabsorption, and GI symptoms caused by allergy to gluten. Prolonged breastfeeding, at least until the 6th month, and gluten introduction started at least at the 5th month of life, significantly delay the onset of the disease. Gluten introduction should be done progressively and under breast feeding protection. Introduction of gluten 2 months before weaning has a protective effect. Bouguerra F et al. [Breast feeding effect relative to age of onset of celiac disease]. *Arch Pediatr* 1998 Jun;5(6):621-6 Children formula-fed from birth, or breast-fed for less than 30 days, were found to have a relative risk of developing symptoms of celiac disease four times higher than children breast-fed for more than 30 days.

Conduct Disorders

Rochat, T. J., Houle, B., Stein, A., Coovadia, H., Coutsooudis, A., Desmond, C., ... & Bland, R. M. (2016). Exclusive breastfeeding and cognition, executive function, and behavioural disorders in primary school-aged children in rural South Africa: a cohort analysis. *PLoS medicine*, 13(6), e1002044.

Exclusive breastfeeding (EBF) is associated with early child health; its longer-term benefits for child development remain inconclusive. We examine the associations between EBF, HIV exposure, and other maternal/child factors and the cognitive and emotional-behavioural development of children aged 7–11 y. The Vertical Transmission Study (VTS) supported EBF in HIV-positive and HIV-negative women; between 2012 and 2014, HIV-negative VTS children (332 HIV exposed, 574 HIV unexposed) were assessed in terms of cognition (Kaufman Assessment Battery for Children Second Edition [KABC-II]), executive function (Developmental Neuropsychological Assessment Second Edition [NEPSY-II]), and emotional-behavioural functioning (parent-reported Child Behaviour Checklist, [CBCL]). We developed population means by combining the VTS sample with 629 same-aged HIV-negative children from the local demographic platform. For each outcome, we split the VTS sample into scores above or at/below each population mean and modelled each outcome using logistic regression analyses, overall and stratified by child sex. There was no demonstrated effect of EBF on overall cognitive functioning. EBF was associated with fewer conduct disorders overall (adjusted odds ratio [aOR] 0.44 [95% CI 0.3–0.7], $p \leq 0.01$), and there was weak evidence of better cognition in boys who had been exclusively breastfed for 2–5 mo versus ≤ 1 mo (Learning subscale aOR 2.07 [95% CI 1.0–4.3], $p = 0.05$). Other factors associated with better child cognition were higher maternal cognitive ability (aOR 1.43 [95% CI 1.1–1.9], $p = 0.02$, Sequential; aOR 1.74 [95% CI 1.3–2.4], $p < 0.001$, Planning subscales) and crèche attendance (aOR 1.96 [95% CI 1.1–3.5], $p = 0.02$, Sequential subscale). Factors positively associated with executive function were home stimulation (aOR 1.36 [95% CI 1.0–1.8], $p = 0.04$, Auditory Attention; aOR 1.35 [95% CI 1.0–1.8], $p = 0.05$, Response Set) and crèche (aOR 1.74 [95% CI 1.0–3.0], $p = 0.05$, Animal

Sorting). Maternal mental health problems and parenting stress were associated with increased emotional-behavioural problems on the total CBCL (aOR 2.44 [95% CI 1.3–4.6], $p = 0.01$; aOR 7.04 [95% CI 4.2–11.9], $p < 0.001$, respectively). Maternal HIV status was not associated with any outcomes in the overall cohort. Limitations include the nonrandomised study design and lack of maternal mental health assessment at the child's birth. EBF was associated with fewer than average conduct disorders and weakly associated with improved cognitive development in boys. Efforts to improve stimulation at home, reduce maternal stress, and enable crèche attendance are likely to improve executive function and emotional-behavioural development of children.

Shelton, K. H., Collishaw, S., Rice, F. J., Harold, G. T., & Thapar, A. (2011). Using a genetically informative design to examine the relationship between breastfeeding and childhood conduct problems. *European child & adolescent psychiatry*, 20(11-12), 571-579.

While the physical health and nutritional benefits of breastfeeding for the mother and child are relatively well established, the evidence for psychological effects is less clear. This study aimed to examine whether there is an association between breastfeeding and later conduct problems in children. It also considered the extent to which any relationship is attributable to maternally-provided inherited characteristics that influence both likelihood of breastfeeding and child conduct problems. A prenatal cross-fostering design with a sample of 870 families with a child aged 4-11 years was used. Mothers were genetically related or unrelated to their child as a result of assisted reproductive technologies. The relationship between breastfeeding and conduct problems was assessed while controlling for theorised measured confounders by multivariate regression (e.g. maternal smoking, education, and antisocial behaviour), and for unmeasured inherited factors by testing associations separately for related and unrelated mother-child pairs. Breastfeeding was associated with lower levels of conduct disorder symptoms in offspring in middle childhood. Breastfeeding was associated with lower levels of conduct problems even after controlling for observed confounders in the genetically related group, but not in the genetically unrelated group. In contrast, maternal antisocial behaviour showed robust associations with child conduct problems after controlling for measured and inherited confounders. These findings highlight the importance of using genetically sensitive designs in order to test causal environmental influences.

Diabetes Mellitus

Lund-Blix, N. A., Stene, L. C., Rasmussen, T., Torjesen, P. A., Andersen, L. F., & Rønningen, K. S. (2015). Infant feeding in relation to islet autoimmunity and type 1 diabetes in genetically susceptible children: the MIDIA Study. *Diabetes care*, 38(2), 257-263.

We aimed to study the association of breast-feeding duration and age at the introduction of solid foods with the risk of islet autoimmunity and type 1 diabetes in genetically susceptible children. Newborns were recruited from the Norwegian general population during 2001–2007. After genetic screening of nearly 50,000 newborns, 908 children with the high-risk HLA genotype were followed up with blood samples and questionnaires at age 3, 6, 9, and 12 months and then annually. Complete infant diet data were available for 726 children. Any breast-feeding for 12 months or longer predicted a decreased risk of developing type 1 diabetes compared with any

breast-feeding for less than 12 months before and after adjusting for having a first-degree relative with type 1 diabetes, vitamin D supplementation, maternal education, sex, and delivery type (hazard ratio 0.37 [95% CI 0.15–0.93]). Any breast-feeding for 12 months or longer was not associated with islet autoimmunity but predicted a lower risk of progression from islet autoimmunity to type 1 diabetes (hazard ratio 0.35 [95% CI 0.13–0.94]). Duration of full breast-feeding was not significantly associated with the risk of islet autoimmunity or type 1 diabetes nor was age at introduction of solid foods or breastfeeding at the time of introduction of any solid foods. These results suggest that breastfeeding for 12 months or longer predicts a lower risk of progression from islet autoimmunity to type 1 diabetes among genetically predisposed children.

Pereira, P. F., Rita de Cássia, G. A., & Araújo, R. M. A. (2014). Does breastfeeding influence the risk of developing diabetes mellitus in children? A review of current evidence. *Jornal de pediatria*, 90(1), 7-15.

The aim of this study was to perform a review to investigate the influence of breastfeeding as a protective agent against the onset of diabetes in children. Sources included a non-systematic review of SciELO, LILACS, MEDLINE, Scopus, and VHL databases, and selection of the 52 most relevant studies. A total of 21 articles, specifically on the topic, were analyzed (nine related to type 1 diabetes and 12 to type 2 diabetes). The duration and exclusivity of breastfeeding, as well as the early use of cow's milk, have been shown to be important risk factors for developing diabetes. It is believed that human milk contains substances that promote the maturation of the immune system, which protect against the onset of type 1 diabetes. Moreover, human milk has bioactive substances that promote satiety and energy balance, preventing excess weight gain during childhood, thus protecting against the development of type 2 diabetes. Although the above mentioned benefits have not been observed by some researchers, inaccuracies on dietary habit reports during childhood and the presence of interfering factors have been considered responsible for the lack of identification of beneficial effects. The authors concluded that given the scientific evidence indicated in most published studies, it is believed that the lack of breastfeeding can be a modifiable risk factor for both type 1 and type 2 diabetes. Strategies aiming at the promotion and support of breastfeeding should be used by trained healthcare professionals in order to prevent the onset of diabetes.

Frederiksen, B., Kroehl, M., Lamb, M. M., Seifert, J., Barriga, K., Eisenbarth, G. S., ... & Norris, J. M. (2013). Infant exposures and development of type 1 diabetes mellitus: The Diabetes Autoimmunity Study in the Young (DAISY). *JAMA pediatrics*, 167(9), 808-815.

The incidence of type 1 diabetes mellitus (T1DM) is increasing worldwide, with the most rapid increase among children younger than 5 years of age. OBJECTIVE: To examine the associations between perinatal and infant exposures, especially early infant diet, and the development of T1DM. DESIGN: The Diabetes Autoimmunity Study in the Young (DAISY) is a longitudinal, observational study. SETTING: Newborn screening for human leukocyte antigen (HLA) was done at St. Joseph's Hospital in Denver, Colorado. First-degree relatives of individuals with T1DM were recruited from the Denver metropolitan area. PARTICIPANTS: A total of 1835 children at increased genetic risk for T1DM followed up from birth with complete prospective assessment of infant diet. Fifty-three children developed T1DM. EXPOSURES: Early (<4 months of age) and late (≥6 months of age) first exposure to solid foods compared

with first exposures at 4 to 5 months of age (referent). MAIN OUTCOME AND MEASURE: Risk for T1DM diagnosed by a physician. RESULTS: Both early and late first exposure to any solid food predicted development of T1DM (hazard ratio [HR], 1.91; 95% CI, 1.04-3.51, and HR, 3.02; 95% CI, 1.26-7.24, respectively), adjusting for the HLA-DR genotype, first-degree relative with T1DM, maternal education, and delivery type. Specifically, early exposure to fruit and late exposure to rice/oat predicted T1DM (HR, 2.23; 95% CI, 1.14-4.39, and HR, 2.88; 95% CI, 1.36-6.11, respectively), while breastfeeding at the time of introduction to wheat/barley conferred protection (HR, 0.47; 95% CI, 0.26-0.86). Complicated vaginal delivery was also a predictor of T1DM (HR, 1.93; 95% CI, 1.03-3.61). CONCLUSIONS AND RELEVANCE: These results suggest the safest age to introduce solid foods in children at increased genetic risk for T1DM is between 4 and 5 months of age. Breastfeeding while introducing new foods may reduce T1DM risk.

Owen, C. G., Martin, R. M., Whincup, P. H., Smith, G. D., & Cook, D. G. (2006). Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence—. *The American journal of clinical nutrition*, 84(5), 1043-1054.

A systematic review of published studies identified 1010 reports; 23 examined the relation between infant feeding and type 2 diabetes in later life or risk factors for diabetes. Subjects who were breastfed had a lower risk of type 2 diabetes in later life than did those who were formula fed (7 studies; 76 744 subjects; odds ratio: 0.61). Children and adults without diabetes who had been breastfed had marginally lower fasting insulin concentrations than did those who were formula fed (6 studies; 4800 subjects; percentage difference: -3%). Breastfed infants had lower mean preprandial blood glucose and insulin concentrations than did those who were formula fed. Breastfeeding in infancy is associated with a reduced risk of type 2 diabetes, with marginally lower insulin concentrations in later life, and with lower blood glucose and serum insulin concentrations in infancy.

Sadauskaitė-Kuehne, V., Ludvigsson, J., Padaiga, Ž., Jašinskienė, E., & Samuelsson, U. (2004). Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood. *Diabetes/metabolism research and reviews*, 20(2), 150-157. Early weaning diet, early introduction of breast milk substitution and cow's milk have been shown to increase the risk of type 1 diabetes later in life. It is also shown that older maternal age, maternal education, preeclampsia, prematurity, neonatal illness and neonatal icterus caused by blood group incompatibility, infections and stress might be risk factors for type 1 diabetes. Data from 517 children in south-east of Sweden and 286 children in Lithuania in the age group of 0 to 15 years with newly diagnosed type 1 diabetes mellitus were included into analysis. Three age- and sex-matched healthy controls were randomly selected. Information was collected via questionnaires. Exclusive breastfeeding longer than five months (odds ratio 0.54) and total breastfeeding longer than 7 (0.56) or 9 months (0.61) among Swedish children 5 to 9 years old and later than the seventh month (0.24) among all Swedish children is protective against diabetes when adjusted for all other above-listed risk factors. In Lithuania, exclusive breastfeeding longer than two months in the age group of 5 to 9 years is protective (0.58) when adjusted Page 37 of 63 for other factors. Conclusions; Longer exclusive and total breastfeeding appears as an independent protective factor against type 1 diabetes.

Young, T. K., Martens, P. J., Taback, S. P., Sellers, E. A., Dean, H. J., Cheang, M., & Flett, B. (2002). Type 2 diabetes mellitus in children: prenatal and early infancy risk factors among native Canadians. *Archives of pediatrics & adolescent medicine*, 156(7), 651-655.

A case-control study of 46 patients younger than 18 years, and 92 matched controls from a large Native population in Winnipeg, Manitoba. Information on exposure to prenatal and early infancy risk factors was obtained through questionnaires administered by a Native nurse-interviewer. Preexisting diabetes (odds ratio [OR], 14.4), gestational diabetes (OR, 4.40), and breastfeeding longer than 12 months (OR, 0.24) were significant independent predictors of diabetic status. Conclusion: breastfeeding reduces the risk of type 2 diabetes among Native Canadian children and should be promoted as a potential intervention to control the disease.

Monetini, L., Cavallo, M. G., Stefanini, L., Ferrazzoli, F., Bizzarri, C., Marietti, G., ... & IMDIAB group. (2001). Bovine β -casein antibodies in breast-and bottle-fed infants: their relevance in Type 1 diabetes. *Diabetes/metabolism research and reviews*, 17(1), 51-54.

Bovine beta-casein is a cow's milk protein that targets both humoral and cellular immune responses in patients with Type 1 diabetes and, to a lesser degree, also in normal subjects. This study aimed to determine whether the avoidance of cow's milk consumption early in life could prevent the development of antibody response to bovine beta-casein despite the mother being exposed on a daily basis to cow's milk consumption. The researchers measured the antibody response to bovine beta -casein in 28 healthy infants under 4 months of age, of whom 16 were exclusively breast-fed and 12 were bottle-fed with cow's milk. In addition, beta -casein antibodies were measured in 37 prepubertal children with Type 1 diabetes and in 31 healthy children who were exposed to cow's milk or dairy products to see whether differences in antibody titers exist in this young age group. Antibodies binding to beta -casein were also evaluated. Elevated levels of beta -casein antibodies were found in bottle-fed infants compared to breast-fed infants ($p < 0.0001$). Antibody levels to bovine -casein were also significantly higher in children with Type 1 diabetes compared to age-matched controls ($p = 0.03$). The authors confirmed specific binding to bovine beta-casein in bottle-fed infants, in children with Type 1 diabetes and in controls exposed to cow's milk, but not in infants who were exclusively breast-fed. The results of this study indicate that breastfeeding within the first 4 months of life prevents the generation of antibody response to bovine beta -casein despite the mothers' consumption of cow's milk during the breastfeeding period.

Kimpimäki, T., Erkkola, M., Korhonen, S., Kupila, A., Virtanen, S. M., Ilonen, J., ... & Knip, M. (2001). Short-term exclusive breastfeeding predisposes young children with increased genetic risk of Type I diabetes to progressive beta-cell autoimmunity. *Diabetologia*, 44(1), 63-69.

This study aimed to establish the relation between early infant nutrition and signs of beta-cell autoimmunity in young children. They identified and observed from birth 2949 infants with increased genetic risk of Type I (insulin-dependent) diabetes mellitus and monitored them for islet cell antibodies at 3 to 6 month intervals. This case-control study comprises the first 65 children who seroconverted to islet cell antibody positivity before the age of 4 years and 390 control children who were islet cell antibody-negative (six control children/case). Infants who had been breastfed exclusively for at least 4 months had lower risk of seroconversion to

positivity for IA-2A or all four autoantibodies [odds ratio 0.24] than those infants who had been breastfed exclusively for less than 2 months. The risk of seroconversion was higher in those younger than 2 months (OR 4.37) or aged 2 to 3.9 months (OR 5.50) when they first received cows' milk than in those aged 4 months or older. These observations suggest that short-term breastfeeding and the early introduction of cows' milk-based infant formula predispose young children who are genetically susceptible to Type I diabetes to progressive signs of beta-cell autoimmunity.

McKinney, P. A., Parslow, R., Gurney, K. A., Law, G. R., Bodansky, H. J., & Williams, R. (1999). Perinatal and neonatal determinants of childhood type 1 diabetes. A case-control study in Yorkshire, UK. *Diabetes Care*, 22(6), 928-932.

A population-based case-control study of 196 children with type 1 diabetes and 325 age- and sex-matched control subjects found a significantly raised risk for illnesses in the neonatal period (OR 1.61), the majority of which were infections and respiratory difficulties. Exclusive breastfeeding as the initial feeding method was significantly protective (OR 0.65).

Pettitt, D. J., & Knowler, W. C. (1998). Long-term effects of the intrauterine environment, birth weight, and breast-feeding in Pima Indians. *Diabetes care*, 21, B138.

Diabetes is less common among breast-fed children (6.9 and 30.1% among offspring of nondiabetic and diabetic women, respectively) than among bottle-fed children (11.9 and 43.6%, respectively).

Children who developed IDDM in New South Wales, Australia, were compared to healthy children of the same sex and age. Those who were exclusively breastfed during their first three months of life had a 34% lower risk of developing diabetes than those who were not breastfed. Children given cow's-milk-based formula in their first three months were 52% more likely to develop IDDM than those not given cow's milk formula. *Diabetes Care* 1994;17:1381-1389, 1488-1490.

Helicobacter pylori infection

Carreira, H., Bastos, A., Peleteiro, B., & Lunet, N. (2015). Breast-feeding and *Helicobacter pylori* infection: systematic review and meta-analysis. *Public health nutrition*, 18(3), 500-520.

The objective of this study was to quantify the association between breast-feeding and *Helicobacter pylori* infection, among children and adolescents. We searched MEDLINETM and ScopusTM up to January 2013. Summary relative risk estimates (RR) and 95 % confidence intervals were computed through the DerSimonian and Laird method. Heterogeneity was quantified using the I² statistic. We identified thirty-eight eligible studies, which is nearly twice the number included in a previous meta-analysis on this topic. Fifteen studies compared ever v. never breast-fed subjects; the summary RR was 0.87 (95 % CI 0.57, 1.32; I²=34.4 %) in middle-income and 0.85 (95 % CI 0.54, 1.34; I²=79.1 %) in high-income settings. The effect of breast-feeding for ≥4–6 months was assessed in ten studies from middle-income (summary RR=0.66; 95 % CI 0.44, 0.98; I²=65.7 %) and two from high-income countries (summary RR=1.56; 95 % CI 0.57, 4.26; I²=68.3 %). Two studies assessed the effect of exclusive breast-

feeding until 6 months (OR=0.91; 95 % CI 0.61, 1.34 and OR=1.71; 95 % CI 0.66, 4.47, respectively). Our results suggest a protective effect of breast-feeding in economically less developed settings. However, further research is needed, with a finer assessment of the exposure to breast-feeding and careful control for confounding, before definite conclusions can be reached.

Helicobacter pylori infection was examined among 356 asymptomatic white Hispanic and black children aged 2--16 years attending 13 licensed day care centers in Houston. Demographic information and socioeconomic factors were evaluated. H. Page 38 of 63 *pylori* status was determined by (13)C-urea breath testing. The prevalence of active H. *pylori* infection was 24% and increased with age. Prevalence was almost identical among white Hispanic and black children. Children living in the most crowded conditions were at the greatest risk for H. *pylori* acquisition, and an inverse correlation was seen between the mother's education and H. *pylori* positivity in children. Breast-feeding played a protective role against the acquisition of H. *pylori* infection. Malaty HM et al. *Helicobacter pylori* infection in preschool and school-aged minority children: effect of socioeconomic indicators and breast-feeding practices. *Clin Infect Dis* 2001 May 15;32(10):1387-92

Serum H *pylori* IgG antibodies were measured in 631 men and 389 women born during 1920-30. Independent of their current social class, subjects were more likely to be H *pylori* seropositive if they had large numbers of siblings, and if they had lived in a crowded house, or shared a bedroom or bed in childhood. Low weight at 1 year was associated with increased seropositivity rates in men, but not women. Men and women who were breast fed in infancy were less likely to be seropositive than those who were bottle fed. Fall CH, Goggin PM, Hawtin P, Fine D, Duggleby S. "Growth in infancy, infant feeding, childhood living conditions, and *Helicobacter pylori* infection at age 70." *Arch Dis Child* 1997 Oct;77(4):310-4

Haemophilus Influenzae Meningitis

Silfverdal, S. A., Bodin, L., & Olcén, P. (1999). Protective effect of breastfeeding: an ecologic study of *Haemophilus influenzae* meningitis and breastfeeding in a Swedish population.

International journal of epidemiology, 28(1), 152-156.

A strong negative correlation between breastfeeding and incidence of *Haemophilus influenzae* infection 5 to 10 years later.

Inflammatory Bowel Disease (Crohn's Disease, Ulcerative Colitis)

Rogier, E. W., Frantz, A. L., Bruno, M. E., Wedlund, L., Cohen, D. A., Stromberg, A. J., & Kaetzel, C. S. (2014). Secretory antibodies in breast milk promote long-term intestinal homeostasis by regulating the gut microbiota and host gene expression. *Proceedings of the National Academy of Sciences*, 111(8), 3074-3079.

Maintenance of intestinal homeostasis requires a healthy relationship between the commensal gut microbiota and the host immune system. Breast milk supplies the first source of antigen-

specific immune protection in the gastrointestinal tract of suckling mammals, in the form of secretory IgA (SIgA). SIgA is transported across glandular and mucosal epithelial cells into external secretions by the polymeric Ig receptor (pIgR). Here, a breeding scheme with polymeric Ig receptor-sufficient and -deficient mice was used to study the effects of breast milk-derived SIgA on development of the gut microbiota and host intestinal immunity. Early exposure to maternal SIgA prevented the translocation of aerobic bacteria from the neonatal gut into draining lymph nodes, including the opportunistic pathogen *Ochrobactrum anthropi*. By the age of weaning, mice that received maternal SIgA in breast milk had a significantly different gut microbiota from mice that did not receive SIgA, and these differences were magnified when the mice reached adulthood. Early exposure to SIgA in breast milk resulted in a pattern of intestinal epithelial cell gene expression in adult mice that differed from that of mice that were not exposed to passive SIgA, including genes associated with intestinal inflammatory diseases in humans. Maternal SIgA was also found to ameliorate colonic damage caused by the epithelial-disrupting agent dextran sulfate sodium. These findings reveal unique mechanisms through which SIgA in breast milk may promote lifelong intestinal homeostasis, and provide additional evidence for the benefits of breastfeeding.

Gearry, R. B., Richardson, A. K., Frampton, C. M., Dodgshun, A. J., & Barclay, M. L. (2010). Population-based cases control study of inflammatory bowel disease risk factors. *Journal of gastroenterology and hepatology*, 25(2), 325-333.

A population-based case-control study was carried out in Canterbury, New Zealand. Participants comprised 638 prevalent Crohn's disease (CD) cases, 653 prevalent ulcerative colitis (UC) cases and 600 randomly-selected sex and age matched controls. Exposure rates to environmental risk factors were compared. Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) are presented. Results: A family history of IBD (CD OR 3.06 [2.18-4.30], UC OR 2.52 [1.90-3.54]), cigarette smoking at diagnosis (CD OR 1.99 [1.48-2.68], UC OR 0.67 [0.48-0.94]), high social class at birth (CD and UC trend, $P < 0.001$) and Caucasian ethnicity (CD OR 2.04 [1.05-4.38], UC OR 1.47 [1.01-2.14]) were significantly associated with IBD. City living was associated with CD ($P < 0.01$). Being a migrant was associated with UC. Having a childhood vegetable garden was protective against IBD (CD OR 0.52 [0.36-0.76], UC OR 0.65 [0.45-0.94]) as was having been breastfed (CD OR 0.55 [0.41-0.74], UC OR 0.71 [0.52-0.96]) with a duration-response effect. Appendicectomy, tonsillectomy, infectious mononucleosis and asthma were more common in CD patients than controls ($P < 0.01$). Conclusions: The importance of childhood factors in the development of IBD is confirmed. The duration-response protective association between breast-feeding and subsequent development of IBD requires further evaluation, as does the protective effect associated with a childhood vegetable garden.

Barclay, A. R., Russell, R. K., Wilson, M. L., Gilmour, W. H., Satsangi, J., & Wilson, D. C. (2009). Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. *The Journal of pediatrics*, 155(3), 421-426.

A total of 79 articles were identified, 20 of which were found describing breastfeeding in relation to the development of IBD; 8 of these articles included separate early-onset groups. One study did not describe "any exposure" to breast milk for the early onset group, so 7 studies were

included in the meta-analysis. Breast milk exposure had a significant protective effect (OR, 0.69; 95% CI, 0.51-0.94; $P = .02$) in developing early-onset IBD. A non-significant difference was demonstrated for ulcerative colitis and Crohn's disease individually (OR, 0.72; 95% CI, 0.51-1.02; $P = .06$; OR, 0.64; 95% CI, 0.38-1.07; $P = .09$, respectively).

Klement, E., Cohen, R. V., Boxman, J., Joseph, A., & Reif, S. (2004). Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *The American journal of clinical nutrition*, 80(5), 1342-1352.

The aim of this meta-analysis was to examine the role of breastfeeding in preventing inflammatory bowel disease and to summarize the evidence gathered about this subject. Studies showed heterogeneous results. The pooled odds ratios of all the 17 reviewed studies, calculated according to the random-effects model, were 0.67 (95% CI: 0.52, 0.86) for Crohn disease and 0.77 (0.61, 0.96) for ulcerative colitis. However, only 4 studies for Crohn disease and 4 for ulcerative colitis were eventually included in the highest quality group. In this group, the pooled odds ratio was 0.45 (0.26, 0.79) for Crohn disease and 0.56 (0.38, 0.81) for ulcerative colitis. The results of this meta-analysis support the hypothesis that breastfeeding is associated with lower risks of Crohn disease and ulcerative colitis. However, because only a few studies were graded to be of high quality, we suggest that further research, conducted with good methodology and large sample sizes, should be carried out to strengthen the validity of these observations.

Thompson, N. P., Montgomery, S. M., Wadsworth, M. E., Pounder, R. E., & Wakefield, A. J. (2000). Early determinants of inflammatory bowel disease: use of two national longitudinal birth cohorts. *European journal of gastroenterology & hepatology*, 12(1), 25-30.

Twenty-six cases of Crohn's disease and 29 cases of ulcerative colitis were matched for gender and social class with controls. There was a trend that those with Crohn's disease were more likely not to have been breast-fed (OR 0.4). The prevalence of inflammatory bowel disease was 5.12/1000 by the age of 43 years.

Corrao, G., Tragnone, A., Caprilli, R., Trallori, G., Papi, C., Andreoi, A., ... & Mansi, C. (1998). Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study. *International journal of epidemiology*, 27(3), 397-404.

Lack of breastfeeding in infancy was associated with an increased risk of ulcerative colitis (chronic inflammatory disorder of the colon) and Crohn's disease (chronic inflammatory disorder affecting any part of the gut, aggravated by food intolerance).

Rigas, A., Rigas, B., Glassman, M., Yen, Y. Y., Lan, S. J., Petridou, E., ... & Trichopoulos, D. (1993). Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. *Annals of epidemiology*, 3(4), 387-392.

Medical records concerning pediatric or adolescent patients first diagnosed with Crohn's disease or ulcerative colitis in two New York hospitals during a 5-year period (1986 to 1990) were abstracted, and information concerning sex, age, race, birthplace, sibship size, birth order, maternal age at birth, month of birth, duration of breast-feeding, and maternal smoking was

recorded. Data concerning 68 patients with Crohn's disease, 39 patients with ulcerative colitis, and 202 control patients were Page 39 of 63 analyzed through multiple logistic regression. Breast-feeding was negatively associated with Crohn's disease (P 0.04) and ulcerative colitis (P 0.07), with relative risk point estimates around 0.5 and with evidence of duration-dependent trends in both instances. There was no evidence of association of either disease with maternal age at birth, birth order, maternal smoking, or season of birth.

Koletzko, S., Sherman, P., Corey, M., Griffiths, A., & Smith, C. (1989). Role of infant feeding practices in development of Crohn's disease in childhood. *BMJ: British Medical Journal*, 298(6688), 1617.

Lack of breastfeeding was a risk factor associated with later development of Crohn's disease.

Juvenile Rheumatoid Arthritis (JRA) and other rheumatic diseases

Montoya, J., Matta, N. B., Suchon, P., Guzman, M. C., Lambert, N. C., Mattei, J. P., ... & Balandraud, N. (2016). Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case–control retrospective study. *Annals of the rheumatic diseases*, 75(5), 879-882.

Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting the spine and pelvis of young adults. On the HLA-B27 genetic background, the occurrence of AS is influenced by the intestinal microbiota. The goal of our study was to test whether breast feeding, which influences microbiota, can prevent the development of AS. First, 203 patients with HLA-B27-positive AS fulfilling the modified New York criteria were recruited in the Department of Rheumatology, Ste Marguerite hospital in Marseilles. A total of 293 healthy siblings were also recruited to make up a control group within the same families. Second, 280 healthy controls, and 100 patients with rheumatoid arthritis and their siblings were recruited. The data collected were age, gender, number of brothers and sisters, age at disease onset, type and duration of feeding (breast or bottle). Patients with AS had been breast fed less often than healthy controls. In families where children were breastfed, the patients with AS were less often breastfed than their healthy siblings (57% vs 72%), giving an OR for AS onset of 0.53 (95% CI (0.36 to 0.77), p value=0.0009). Breastfeeding reduced familial prevalence of AS. The frequency of breastfeeding was similar in the AS siblings and in the 280 unrelated controls. However, patients with AS were less often breast fed compared with the 280 unrelated controls (OR 0.6, 95% CI (0.42 to 0.89), p <0.01). Our study suggests a breastfeeding-induced protective effect on the occurrence of AS. To our knowledge, this is the first study of breastfeeding history in patients with AS.

Mason, T., Rabinovich, C. E., Fredrickson, D. D., Amoroso, K., Reed, A. M., Stein, L. D., & Kredich, D. W. (1995). Breastfeeding and the development of juvenile rheumatoid arthritis. *The Journal of rheumatology*, 22(6), 1166-1170.

Children who have had JRA, especially pauciarticular JRA, are less likely to have been breastfed than controls, suggesting that breast feeding may have a protective effect on the development of JRA. Lower odds ratio were noted for increased durations of breast feeding.

Mental Health

Liu, J., Leung, P., & Yang, A. (2014). Breastfeeding and active bonding protects against children's internalizing behavior problems. *Nutrients*, 6(1), 76-89.

Breastfeeding is associated with numerous health benefits to offspring and mothers and may improve maternal-infant bonding. Ample evidence suggests breastfeeding can improve child neurodevelopment, but more research is needed to establish whether breastfeeding is linked to the development of child psychopathology. This paper aims to explore the effects of both breastfeeding and mother-child interactions on child behavioral outcomes at a later age. Children from the China Jintan Child Cohort Study (N = 1267), at age six years old were assessed, along with their parents. Children who were breastfed exclusively for a period of time in the presence of active bonding were compared to those who were breastfed in the absence of active bonding as well as to children who were not exclusively breastfed, with or without active bonding. Results from ANOVA and GLM, using SPSS20, indicate that children who were breastfed and whose mothers actively engaged with them displayed the lowest risk of internalizing problems (mean = 10.01, SD = 7.21), while those who were neither exclusively breastfed nor exposed to active bonding had the least protection against later internalizing problems (mean = 12.79, SD = 8.14). The effect of breastfeeding on internalizing pathology likely represents a biosocial and holistic effect of physiological, and nutritive, and maternal-infant bonding benefits.

Julvez, J., Guxens, M., Carsin, A. E., Forns, J., Mendez, M., Turner, M. C., & Sunyer, J. (2014). A cohort study on full breastfeeding and child neuropsychological development: the role of maternal social, psychological, and nutritional factors. *Developmental Medicine & Child Neurology*, 56(2), 148-156.

This study investigated whether duration of full breastfeeding is associated with child neuropsychological development and whether this association is explained by social, psychological, and nutritional factors within families. Participants in this study were a population-based birth cohort in the city of Sabadell (Catalonia, Spain). Females were recruited during the first trimester of pregnancy between July 2004 and July 2006. Information about parental characteristics and breastfeeding was obtained through questionnaires. Full breastfeeding was categorized as never, short term (≤ 4 mo), long term (4–6mo), or very long term (> 6 mo). A trained psychologist assessed the neuropsychological development of children at 4 years of age (n=434) using the McCarthy Scales of Children's Abilities (MSCA). Full breastfeeding showed an independent association with child general MSCA scores after adjusting for a range of social, psychological, and nutritional factors (> 6 mo, coefficient=7.4 [95% confidence interval=2.8–12.0], $p=0.011$). Maternal social class, education level, and IQ were also associated with child neuropsychological scores, but did not explain breastfeeding associations. Omega-3 (n3) fatty acid levels were not associated with child neuropsychological scores. Very long-term full breastfeeding was independently associated with neuropsychological functions of children at 4 years of age. Maternal indicators of intelligence, psychopathology, and colostrum n3 fatty acids did not explain this association.

Oddy, W. H., Kendall, G. E., Li, J., Jacoby, P., Robinson, M., De Klerk, N. H., ... & Stanley, F. J. (2010). The long-term effects of breastfeeding on child and adolescent mental health: a pregnancy cohort study followed for 14 years. *The Journal of pediatrics*, 156(4), 568-574. Breastfeeding for less than 6 months compared with 6 months or longer was an independent predictor of mental health problems through childhood and into adolescence. This relationship was supported by the random effects models (increase in total CBCL score: 1.45; 95% confidence interval 0.59, 2.30) and generalized estimating equation models (odds ratio for CBCL morbidity: 1.33; 95% confidence interval 1.09, 1.62) showing increased behavioral problems with shorter breastfeeding duration.

Menopause (timing of)

Hardy, R., & Kuh, D. (2002). Does early growth influence timing of the menopause? Evidence from a British birth cohort. *Human reproduction*, 17(9), 2474-2479.

Few adult environmental or behavioral factors have been consistently associated with age at menopause. The peak number of follicles obtained in utero or lost before ovulation begins may be more important. This study investigates whether birthweight, childhood body size, having been breastfed and early socioeconomic circumstances are associated with age at menopause. 1572 British women were followed up since their birth in 1946, so far until 53 years. Age at menopause varied by duration of breastfeeding, weight at age 2 years, childhood socioeconomic status, but not birthweight. In a multiple regression model, women of low weight at 2 years had an earlier menopause and those who had been breastfed had a later menopause than others. Early life influences may influence ovarian ageing, highlighting the importance of investigating factors from across the life course.

Multiple Sclerosis

Brenton, J. N., Engel, C. E., Sohn, M. W., & Goldman, M. D. (2017). Breastfeeding during infancy is associated with a lower future risk of pediatric multiple sclerosis. *Pediatric neurology*, 77, 67-72.

Risk of multiple sclerosis (MS) is influenced by environment and genetics. Infant breastfeeding appears protective against some childhood autoimmune disorders, but its impact on risk of MS in childhood is unknown. The objective of this study is to analyze the association of breastfeeding in infancy on future risk of pediatric-onset MS. Biological mothers of 36 consecutive pediatric-onset MS patients completed a questionnaire on history of breastfeeding and various birth and demographic factors. The control group consisted of 72 otherwise healthy patients with a diagnosis of migraine and normal brain magnetic resonance imaging obtained less than 12 months before enrollment. Inverse probability of treatment weighting was used to reduce selection bias and balance the covariates between breastfed and non-breastfed children. Demographics (with the exception of body mass index) and birth factors were not significantly different between groups. Whereas 36% of cases were breastfed, 71% of controls were breastfed ($P = 0.001$). The median duration of breastfeeding was 0 weeks (range: 0 to 40 weeks) for cases and 16 weeks (range: 0 to 216 weeks) for controls. Lack of infant

breastfeeding was associated with future diagnosis of pediatric-onset MS (odds ratio = 4.43; 95% confidence interval, 1.68 to 11.71; $P = 0.003$). This association remained significant after correcting for covariates, such as body mass index and age at diagnosis. These data demonstrate that absence of infant breastfeeding has an association with an increased risk of pediatric-onset MS diagnosis.

Tarrats, R., Ordonez, G., Rios, C., & Sotelo, J. (2002). Varicella, ephemeral breastfeeding and eczema as risk factors for multiple sclerosis in Mexicans. *Acta neurologica scandinavica*, 105(2), 88-94.

The incidence of multiple sclerosis (MS) in Mexico and other countries of Latin America has increased steadily for the last two decades. Breastfeeding has been abandoned in large segments of society and the incidence of varicella and childhood eczema keeps a north south gradient similar to that described for MS. A case-control study was conducted using a questionnaire that included demographic, nutritional, infectious and personal antecedents previously identified in other reports as possible risk factors for MS. The frequency of varicella, lack of breastfeeding, and eczema in the medical history of MS patients were significant when compared with controls. These factors may participate in the sharp increase of MS in countries like Mexico traditionally considered as an area of very low incidence.

Pisacane, A., Impagliazzo, N., Russon, M., Valiani, R., Mandarini, A., Florio, C., & Vivo, P. (1994). Breastfeeding and multiple sclerosis. *BMJ*, 308(6941), 1411-1412.

Researchers concluded that prolonged breast feeding was associated with a decreased risk of multiple sclerosis.

Dick, G. (1976). The etiology of multiple sclerosis.

Although thought to be multifactorial in origin, and without a clearly defined etiology, lack of breastfeeding does appear to be associated with an increased incidence of multiple sclerosis.

Obesity, body composition and self-regulations of intake

van Strien, T., Beijers, R., Smeekens, S., & Winkens, L. H. (2019). Duration of breastfeeding is associated with emotional eating through its effect on alexithymia in boys, but not girls. *Appetite*, 132, 97-105.

Emotional eating (EE), or eating in response to negative emotions, was earlier shown to be associated with difficulty in identifying emotions (alexithymia). To improve our understanding of possible causes of alexithymia and EE, we assessed possible associations with duration of breastfeeding in infancy. The aim of the present study was to examine in a prospective, longitudinal study whether duration of breastfeeding is associated with EE in adolescence, through its effect on alexithymia difficulty identifying emotions, and whether this mediation effect is contingent on gender. Our hypothesis was that longer duration of breastfeeding would be associated with lower EE in adolescence through its effect on lower alexithymia difficulty identifying feelings in boys but not in girls (Moderated mediation). The sample included 129 children and their families (67 boys and 62 girls). Duration of breastfeeding was reported by the mother when the infant was 15 months old. Alexithymia difficulty identifying feelings (Toronto

Alexithymia Scale) and EE (Dutch Eating Behavior Questionnaire) were reported by the child at 12 years of age. EE was also reported by the child at 16 years of age. Moderated mediation was significant for EE at 12 years, and borderline significant for EE at 16 years. As hypothesized, for boys but not for girls, longer duration of breastfeeding was related to less difficulties in identifying feelings, resulting in lower degrees of EE in adolescence. It is concluded that breastfeeding in infancy may protect boys against EE through its positive association with better ability to identify feelings.

Bell, L. K., Jansen, E., Mallan, K., Magarey, A. M., & Daniels, L. (2018). Poor dietary patterns at 1–5 years of age are related to food neophobia and breastfeeding duration but not age of introduction to solids in a relatively advantaged sample. *Eating Behaviors*.

Previous studies have investigated associations between individual foods or food group intake, and breastfeeding duration, age of solid introduction and food neophobia. This study aimed to investigate associations between whole dietary patterns in young children, and breastfeeding duration, age of solid introduction and food neophobia. Parents of children (N = 234) aged 1-5 years completed an online questionnaire. Dietary risk scores were calculated using the Toddler (1-3 years) or Preschool (>3-<5 years) Dietary Questionnaires which evaluates the previous week's food-group intake (scored 0-100; higher score = higher risk of poor dietary quality). Neophobia was measured using the Child Food Neophobia scale (1.0-4.0; higher score = more neophobic). Associations were investigated using multivariable linear regression, adjusting for covariates. Children (54% female, 3.0 ± 1.4 years) were from advantaged families and were breastfed until 11.8 (5.0 - 16.0) months, started solids at 5.6 ± 1.4 months of age, moderately neophobic (2.1 ± 0.7) and at moderate dietary risk (29.2 ± 9.2). Shorter breastfeeding duration ($\beta = -0.21$; $p = 0.001$) and poorer child food neophobia scores ($\beta = 0.36$; $p < 0.001$) were associated with higher dietary risk scores. Age of introduction to solids showed no association with dietary risk ($p = 0.744$). These findings suggest that in addition to breastfeeding promotion, supporting parents to manage neophobic behaviour may be important in promoting healthy eating patterns in early childhood.

Bell, S., Yew, S. S. Y., Devenish, G., Ha, D., Do, L., & Scott, J. (2018). Duration of Breastfeeding, but Not Timing of Solid Food, Reduces the Risk of Overweight and Obesity in Children Aged 24 to 36 Months: Findings from an Australian Cohort Study. *International journal of environmental research and public health*, 15(4), 599.

This study aimed to determine whether breastfeeding duration and the timing of solid food were independently associated with being overweight or obese in early childhood. Subjects were 953 children participating in the Study of Mothers and Infants Life Events Affecting Oral Health (SMILE) birth cohort study, based in Adelaide, Australia. Socio-demographic information and data on breastfeeding duration and age of introduction of solid food were collected at birth, 3, 4, 6, 12, and 24 months via mailed or online questionnaires completed by mothers. The weight and height of children were measured at a dental examination when children were aged between 24 and 36 months. Body mass index was calculated, and children were categorised into weight groups according to the World Health Organization growth standards. Multivariable logistic regression analysis was conducted, adjusting for maternal age at birth, education, socio-economic status, pre-pregnancy weight, smoking in pregnancy, method of delivery, and child's

birthweight. Risk of overweight/obesity was independently associated with maternal pre-pregnancy BMI, smoking in pregnancy, and birthweight. Children that were breastfed for 12 months or more had a significantly lower risk of being overweight/obese than those breastfed for less than 17 weeks (AOR 0.49; 95%CI 0.27, 0.90; p for trend =0.009). Age of introduction of solid food, however, was not associated with the risk of being overweight/obese at 24 to 36 months. This study provides further evidence of an inverse relationship between breastfeeding and risk of overweight/obesity, however, no association with the timing of solid food was detected.

Byrne, M. L., Schwartz, O. S., Simmons, J. G., Sheeber, L., Whittle, S., & Allen, N. B. (2018). Duration of Breastfeeding and Subsequent Adolescent Obesity: Effects of Maternal Behavior and Socioeconomic Status. *Journal of Adolescent Health*, 62(4), 471-479.

Previous research has shown that longer duration of breastfeeding is associated with less risk of obesity in childhood and adolescence. However, although putative physiological mechanisms have been proposed, less work has focused on psychosocial or environmental factors, including socioeconomic status (SES) and stressful family environments. The current study examined the role of observed maternal emotional behavior and SES (parental education) in the association between duration of breastfeeding and adolescent body mass index (BMI). One hundred fifteen mothers and adolescents participated in interaction tasks when adolescents were approximately 12 years of age. We measured adolescent BMI at approximately 15 years of age and, at one point over the course of the study, mothers retrospectively reported on the duration of breastfeeding. Controlling for adolescent gender, age, physical activity, number of perinatal complications, SES, birth weight, and mother's depressive symptoms, longer duration of breastfeeding was associated with lower adolescent BMI ($p = .019$), and this association was moderated by the mother's observed behavior during interactions with her adolescent, such that greater frequency of dysphoric behavior was associated with a stronger association between breastfeeding and adolescent BMI ($p = .002$). Longer duration of breastfeeding mediated the association between higher family SES and lower adolescent BMI. This study is the first to show that observed parental behavior during adolescence may be an important moderator of the association between breastfeeding and obesity. The findings provide justification for future intervention research examining family environment factors in improving adolescent health.

Patel, N., Dalrymple, K. V., Briley, A. L., Pasupathy, D., Seed, P. T., Flynn, A. C., & Poston, L. (2018). Mode of infant feeding, eating behaviour and anthropometry in infants at 6-months of age born to obese women—a secondary analysis of the UPBEAT trial. *BMC pregnancy and childbirth*, 18(1), 355.

Maternal obesity and rapid infant weight gain have been associated with increased risk of obesity in childhood. Breastfeeding is suggested to be protective against childhood obesity, but no previous study has addressed the potential benefit of breastfeeding as a preventive method of childhood obesity amongst obese women. The primary aim of this study was to assess the relationship between mode of feeding and body composition, growth and eating behaviours in 6-month-old infants of obese women who participated in UPBEAT; a multi-centre randomised controlled trial comparing a lifestyle intervention of diet and physical activity to standard care during pregnancy. Three hundred and fifty-three mother and infant pairs attended a 6-months

postpartum follow-up visit, during which they completed the Baby-Eating Behaviour Questionnaire, a parent-reported psychometric measure of appetite traits. Measures of infant body composition were also undertaken. As there was no effect of the antenatal intervention on infant feeding and appetite the study was treated as a cohort. Using regression analyses, we examined relationships between: 1) mode of feeding and body composition and growth; 2) mode of feeding and eating behaviour and 3) eating behaviour and body composition. Formula fed infants of obese women in comparison to those exclusively breastfed, demonstrated higher weight z-scores (mean difference 0.26; 95% confidence interval 0.01 to 0.52), higher rate of weight gain (0.04; 0.00 to 0.07) and greater catch-up growth (2.48; 1.31 to 4.71). There was also a lower enjoyment of food ($p = 0.002$) amongst formula fed infants, following adjustment for confounders. Independent of the mode of feeding, a measure of infant appetite was associated with sum of skinfold thicknesses (β 0.66; 95% CI 0.12 to 1.21), calculated body fat percentage (0.83; 0.15 to 1.52), weight z-scores (0.21; 0.06 to 0.36) and catch-up growth (odds ratio 1.98; 1.21 to 3.21). In obese women, exclusive breastfeeding was protective against increasing weight z-scores and trajectories of weight gain in their 6-month old infants. Measures of general appetite in early infancy were associated with measures of adiposity, weight and catch up growth independent of cord blood leptin concentrations and mode of early feeding.

Modrek, S., Basu, S., Harding, M., White, J. S., Bartick, M. C., Rodriguez, E., & Rosenberg, K. D. (2017). Does breastfeeding duration decrease child obesity? An instrumental variables analysis. *Pediatric obesity*, 12(4), 304-311.

Many studies have documented that breastfeeding is associated with a significant reduction in child obesity risk. However, a persistent problem in this literature is that unobservable confounders may drive the correlations between breastfeeding behaviors and child weight outcomes. This study examines the effect of breastfeeding practices on child weight outcomes at age 2. This study relied on population-based data for all births in Oregon in 2009 followed for two years. We used instrumental variables methods to exploit variations in breastfeeding by mothers immediately after delivery and the degree to which hospitals encouraged mothers to breastfeed in order to isolate the effect of breastfeeding practices on child weight outcomes. We found that for every extra week that the child was breastfed, the likelihood of the child being obese at age 2 declined by 0.82% [95% CI -1.8% to 0.1%]. Likewise, for every extra week that the child was exclusively breastfed, the likelihood of being obese declined by 0.66% [95% CI -1.4 to 0.06%]. While the magnitudes of effects were modest and marginally significant, the results were robust in a variety of specifications. The results suggest that hospital practices that support breastfeeding may influence childhood weight outcomes.

Paolella, G., & Vajro, P. (2016). Childhood obesity, breastfeeding, intestinal microbiota, and early exposure to antibiotics: what is the link?. *JAMA pediatrics*, 170(8), 735-737.

Prevention of obesity is among the well-recognized beneficial effects that breastfeeding exerts on a variety of organs and systems. This effect seems to occur via various mechanisms: (1) a low content of proteins in human milk as opposed to the high content found in formula and cow's milk that leads to obesogenic concentrations of insulin and insulin-like growth factor 1 in blood; (2) a good balance of other hormonal molecules that regulate the fat to lean body mass ratio or favor better recognition of satiety; (3) an optimal intestinal microbiota (IM) composition;

and (4) food preferences later in life. However, the breastfeeding-obesity link has been questioned because of several confounding factors,¹ including maternal habits during gestation and breastfeeding as well as the mother's metabolic health status (obesity and diabetes), race, and ethnicity. The duration of breastfeeding is also an issue that should be considered in studies of breastfeeding and obesity. Indeed, a long duration of breastfeeding (>7 months) has been associated with a reduced risk of overweight and obesity,² while a short duration (≤ 4 months) may not be sufficient to obtain the beneficial effects of breastfeeding.³ Another confounding factor is early exposure to antibiotics, which is increasing even for minor infections. Antibiotics were found to induce a growth-promoting effect in prepubertal children, possibly by altering their IM.⁴ The neonatal IM composition is influenced by prenatal and postnatal antibiotic exposure⁵ and other age-specific modifiers such as mode of delivery (natural birth vs cesarean delivery) and mother-to-infant transfer of bacterial strains and human milk oligosaccharides via breastfeeding. The latter are structurally diverse unconjugated glycans that are highly abundant in and unique to human milk; they can stimulate the growth and/or activity of healthy intestinal bacteria.

Gibbs, B. G., & Forste, R. (2014). Socioeconomic status, infant feeding practices and early childhood obesity. *Pediatric obesity*, 9(2), 135-146.

Children from low socioeconomic households are at greater risk of obesity. As breastfeeding can protect against child obesity, disadvantaged infants are less likely to breastfeed relative to more advantaged children. Whether infant feeding patterns, as well as other maternal characteristics mediate the association between social class and obesity has not been established in available research. Examine the impact of infant feeding practices on child obesity and identify the mechanisms that link socioeconomic status (SES) with child obesity. Based on a nationally representative longitudinal survey (ECLS-B) of early childhood (n = 8030), we examine how breastfeeding practices, the early introduction of solid foods and putting an infant to bed with a bottle mediate the relationship between social class and early childhood obesity relative to the mediating influence of other maternal characteristics (BMI, age at birth, smoking, depression and daycare use). Infants predominantly fed formula for the first 6 months were about 2.5 times more likely to be obese at 24 months of age relative to infants predominantly fed breast milk. The early introduction of solid foods (< 4 months) and putting the child to bed with a bottle also increased the likelihood of obesity. Unhealthy infant feeding practices were the primary mechanism mediating the relationship between SES and early childhood obesity. Results are consistent across measures of child obesity although the effect size of infant feeding practices varies. The encouragement and support of breastfeeding and other healthy feeding practices are especially important for low socioeconomic children who are at increased risk of early childhood obesity. Targeting socioeconomically disadvantaged mothers for breastfeeding support and for infant-led feeding strategies may reduce the negative association between SES and child obesity. The implications are discussed in terms of policy and practice.

Moss, B. G., & Yeaton, W. H. (2014). Early childhood healthy and obese weight status: potentially protective benefits of breastfeeding and delaying solid foods. *Maternal and child health journal*, 18(5), 1224-1232.

The aim of this study was to assess the relationship between breastfeeding and postponing introduction to solid food (SF) on children's obesity and healthy weight status (WS), at 2 and 4 years. Drawing upon a nationally representative sample of children from the Early Childhood Longitudinal Study-Birth Cohort, we estimated the magnitude of the relationship between children's WS and early feeding practices. Contingency tables and multinomial logistic regression were used to analyze obese and healthy WS for breastfed and never breastfed children and examine three timing categories for SF introduction. With both percentages and odds, breastfeeding and delaying introduction to SF until 4 months were associated with lower obesity rates and higher, healthy WS rates (typically 5–10 %). Analyses of feeding practice combinations revealed that when children were not breastfed, obesity odds decreased when SF introduction was postponed until 4 months. Obesity odds were further reduced when SF delay was combined with breastfeeding. Consistent increases in healthy WS were also observed. Benefits were stable across both follow-up periods. Breastfeeding and delaying complementary foods yielded consistently and substantially lower likelihood of obesity and greater probability of healthy WS. Health policies targeting early feeding practices represent promising interventions to decrease preschool obesity and promote healthy WS.

Robinson, S. M., Crozier, S. R., Harvey, N. C., Barton, B. D., Law, C. M., Godfrey, K. M., ... & Inskip, H. M. (2014). Modifiable early-life risk factors for childhood adiposity and overweight: an analysis of their combined impact and potential for prevention—. *The American journal of clinical nutrition*, 101(2), 368-375.

The objective was to examine the relation between the number of early-life risk factors and obesity outcomes among children in a prospective birth cohort (Southampton Women's Survey). Five risk factors were defined: maternal obesity [prepregnant body mass index (BMI; in kg/m(2)) >30], excess gestational weight gain (Institute of Medicine, 2009), smoking during pregnancy, low maternal vitamin D status (<64 nmol/L), and short duration of breastfeeding (none or <1 mo). Obesity outcomes examined when the children were aged 4 and 6 y were BMI, dual-energy X-ray absorptiometry-assessed fat mass, overweight, or obesity (International Obesity Task Force). Data were available for 991 mother-child pairs, with children born between 1998 and 2003. Of the children, 148 (15%) had no early-life risk factors, 330 (33%) had 1, 296 (30%) had 2, 160 (16%) had 3, and 57 (6%) had 4 or 5. At both 4 and 6 y, there were positive graded associations between number of early-life risk factors and each obesity outcome (all $P < 0.001$). After taking account of confounders, the relative risk of being overweight or obese for children who had 4 or 5 risk factors was 3.99 (95% CI: 1.83, 8.67) at 4 y and 4.65 (95% CI: 2.29, 9.43) at 6 y compared with children who had none (both $P < 0.001$). Having a greater number of early-life risk factors was associated with large differences in adiposity and risk of overweight and obesity in later childhood. These findings suggest that early intervention to change these modifiable risk factors could make a significant contribution to the prevention of childhood obesity.

Yan, J., Liu, L., Zhu, Y., Huang, G., & Wang, P. P. (2014). The association between breastfeeding and childhood obesity: a meta-analysis. *BMC public health*, 14(1), 1267.

The increase in childhood obesity is a serious public health concern. Several studies have indicated that breastfed children have a lower risk of childhood obesity than those who were not

breastfed, while other studies have provided conflicting evidence. The objective of this meta-analysis was to investigate the association between breastfeeding and the risk of childhood obesity. The PubMed, EMBASE and CINAHL Plus with Full Text databases were systematically searched from start date to 1st August 2014. Based on the meta-analysis, pooled adjusted odds ratio (AOR) and 95% confidence interval (CI) were calculated. I² statistic was used to evaluate the between-study heterogeneity. Funnel plots and Fail-safe N were used to assess publication bias and reliability of results, and results from both Egger test and Begg test were reported. Twenty-five studies with a total of 226,508 participants were included in this meta-analysis. The studies' publication dates ranged from 1997 to 2014, and they examined the population of 12 countries. Results showed that breastfeeding was associated with a significantly reduced risk of obesity in children (AOR = 0.78; 95% CI: 0.74, 0.81). Categorical analysis of 17 studies revealed a dose-response effect between breastfeeding duration and reduced risk of childhood obesity. Results of our meta-analysis suggest that breastfeeding is a significant protective factor against obesity in children.

Gale, C., Logan, K. M., Santhakumaran, S., Parkinson, J. R., Hyde, M. J., & Modi, N. (2012). Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis—. *The American journal of clinical nutrition*, 95(3), 656-669.

Early-life nutrition may influence later body composition. The effect of breastfeeding and formula feeding on infant body composition is uncertain. PubMed was searched for human studies that reported the outcomes fat-free mass, fat mass, or the Page 40 of 63 percentage of fat mass in breastfed and formula-fed infants. Bibliographies were hand searched, and authors were contacted for additional data. The quality of studies was assessed. Differences in outcomes between feeding groups were compared at prespecified ages by using fixed-effects analyses except when heterogeneity indicated the use of random-effects analyses. RESULTS: We identified 15 studies for inclusion in the systematic review and 11 studies for inclusion in the meta-analysis. In formula-fed infants, fat-free mass was higher at 3-4 mo [mean difference (95% CI): 0.13 kg (0.03, 0.23 kg)], 8-9 mo [0.29 kg (0.09, 0.49 kg)], and 12 mo [0.30 kg (0.13, 0.48 kg)], and fat mass was lower at 3-4 mo [-0.09 kg (-0.18, -0.01 kg)] and 6 mo [- 0.18 kg (-0.34, - 0.01 kg)] than in breastfed infants. Conversely, at 12 mo, fat mass was higher in formula-fed infants [0.29 kg (- 0.03, 0.61 kg)] than in breastfed infants. CONCLUSION: Compared with breastfeeding, formula feeding is associated with altered body composition in infancy.

McCorry, C., & Layte, R. (2012). Breastfeeding and risk of overweight and obesity at nine-years of age. *Social science & medicine*, 75(2), 323-330.

Whether breastfeeding is protective against the development of childhood overweight and obesity remains the subject of considerable debate. Although a number of meta-analyses and syntheses of the literature have concluded that the greater preponderance of evidence indicates that breastfeeding reduces the risk of obesity, these findings are by no means conclusive. The present study used data from the Growing Up in Ireland study to examine the relationship between retrospectively recalled breastfeeding data and contemporaneously measured weight status for 7798 children at nine-years of age controlling for a wide range of variables including; socio-demographic factors, the child's own lifestyle-related behaviours, and parental BMI. The results of the multivariable analysis indicated that being breastfed for between 13 and 25 weeks

was associated with a 38 percent ($p < 0.05$) reduction in the risk of obesity at nine-years of age, while being breastfed for 26 weeks or more was associated with a 51 percent ($p < 0.01$) reduction in the risk of obesity at nine-years of age. Moreover, results pointed towards a dose–response patterning in the data for those breastfed in excess of 4 weeks. Possible mechanisms conveying this health benefit include slower patterns of growth among breastfed children, which it is believed, are largely attributable to differences in the composition of human breast milk compared with synthesised formula. The suggestion that the choice of infant feeding method has important implications for health and development is tantalising as it identifies a modifiable health behaviour that is amenable to intervention in primary health care settings and has the potential to improve the health of the population.

Crume, T. L., Bahr, T. M., Mayer-Davis, E. J., Hamman, R. F., Scherzinger, A. L., Stamm, E., & Dabelea, D. (2012). Selective protection against extremes in childhood body size, abdominal fat deposition, and fat patterning in breastfed children. *Archives of pediatrics & adolescent medicine*, 166(5), 437-443.

To determine whether the effect of breastfeeding on childhood measures of adiposity differs across percentiles of childhood body mass index (BMI), subcutaneous (SAT) and visceral (VAT) adipose tissue deposition, ratio of subcutaneous to triceps skinfold (STR), and intramyocellular lipid accumulation (IMCL). Four hundred forty-two children and adolescents aged 6 to 13 years participating in the Exploring Perinatal Outcomes Among Children study (EPOCH) with material recall of infant diet. RESULTS: No significant differences in mean levels of childhood adiposity levels between adequate and low breastfeeding status were detected using linear regression models. However, in quantile regression models, adequate breastfeeding was associated with lower levels of adiposity levels for those in the upper percentiles (>60th percentile for VAT, 85th and 95th percentiles for BMI, and 95th percentiles for SAT and STR) and a null effect for those at the 50th percentile or lower. These effects were independent of sociodemographic, perinatal, and current lifestyle factors. We found no relationship between breastfeeding and IMCL at any percentile of the distribution. CONCLUSIONS: Rather than shifting the entire distribution of adiposity-related measures in childhood, breastfeeding selectively protects against extremes in body size and fat deposition, reinforcing the American Academy of Pediatrics recommendation for 6 months of exclusive breastfeeding as the optimal infant diet.

Li, R., Fein, S. B., & Grummer-Strawn, L. M. (2008). Association of Breastfeeding Intensity and Bottle-Emptying Behaviors at Early Infancy With Infants' Risk for Excess Weight at Late Infancy. *Pediatrics*, 122(Supplement 2), S77-S84.

Our goal was to test the hypothesis that infants who were breastfed more intensively during early infancy ($< \text{or} = 6$ months) will be less likely to have excess weight during late infancy (> 6 months) and to examine the independent impact of infant-initiated bottle emptying and mothers' encouragement of bottle emptying on infants' risk for excess weight. The sample consisted of 1896 mothers who participated in postpartum surveys of the Infant Feeding Practice Study II and who provided at least 1 weight measurement of their infants during the second half of infancy. We used multiple logistic regression models to assess the association between infants' risks for excess weight during the second half of infancy and 3 self-reported feeding practices during the first half of infancy after adjusting for a series of sociodemographic characteristics.

The early feeding practices examined included the percentage of all milk feedings in which infants consumed breast milk (breastfeeding intensity), the frequency of bottle feedings in which infants initiated bottle emptying, and the frequency of bottle feedings in which mothers encouraged bottle emptying. Infants fed with low (< 20% of milk feeds being breast milk) and medium (20%- 80%) breastfeeding intensity in the first half of infancy were at least 2 times more likely to have excess weight during the second half of infancy than those breastfed at high intensity (> 80%). Infants who often emptied bottles in early infancy were 69% more likely than those who rarely emptied bottles to have excess weight during late infancy. However, mothers' encouragement of bottle emptying was negatively associated with their infants' risk for excess weight during the second half of Page 41 of 63 infancy. Infants' risk for excess weight during late infancy was negatively associated with breastfeeding intensity but positively associated with infant-initiated bottle emptying during early infancy. These findings not only provide evidence for the potential risk of not breastfeeding or breastfeeding at a low intensity in development of childhood obesity, but they also suggest that infant-initiated bottle emptying may be an independent risk factor as well.

Kramer, M. S., Matush, L., Vanilovich, I., Platt, R. W., Bogdanovich, N., Sevkovskaya, Z., ... & Davey Smith, G. (2007). Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6.5 y: evidence from a large randomized trial—. *The American Journal of Clinical Nutrition*, 86(6), 1717-1721.

The evidence that breastfeeding protects against obesity and a variety of chronic diseases comes almost entirely from observational studies, which have a potential for bias due to confounding, selection bias, and selective publication. Objective: We assessed whether an intervention designed to promote exclusive and prolonged breastfeeding affects children's height, weight, adiposity, and blood pressure at age 6.5 y. Design: The Promotion of Breastfeeding Intervention Trial (PROBIT) is a cluster-randomized trial of a breastfeeding promotion intervention based on the WHO/UNICEF Baby-Friendly Hospital Initiative. A total of 17 046 healthy breastfed infants were enrolled from 31 Belarussian maternity hospitals and their affiliated clinics; of those infants, 13 889 (81.5%) were followed up at 6.5 y with duplicate measurements of anthropometric variables and blood pressure. Analysis was based on intention to treat, with statistical adjustment for clustering within hospitals or clinics to permit inferences at the individual level. Results: The experimental intervention led to a much greater prevalence of exclusive breastfeeding at 3 mo in the experimental than in the control group (43.3% and 6.4%, respectively; $P < 0.001$) and a higher prevalence of any breastfeeding throughout infancy. No significant intervention effects were observed on height, body mass index, waist or hip circumference, triceps or subscapular skinfold thickness, or systolic or diastolic blood pressure. Conclusions: The breastfeeding promotion intervention resulted in substantial increases in the duration and exclusivity of breastfeeding, yet it did not reduce the measures of adiposity, increase stature, or reduce blood pressure at age 6.5 y in the experimental group. Previously reported beneficial effects on these outcomes may be the result of uncontrolled confounding and selection bias.

Weyermann, M., Rothenbacher, D., & Brenner, H. (2006). Duration of breastfeeding and risk of overweight in childhood: a prospective birth cohort study from Germany. *International journal of obesity*, 30(8), 1281.

Whereas a recently published meta-analysis showed that ever breastfeeding reduces the risk of obesity in childhood significantly, the recent literature describing the relationship between duration of breastfeeding and risk of overweight or obesity in childhood remains inconclusive. Between November 2000 and November 2001, all mothers and their newborns were recruited after delivery at the Department of Gynecology and Obstetrics at the University of Ulm, Germany. Active follow-up was performed at the age of 12 months and 24 months. Of the 1066 children included in the baseline examination, information on body mass index was available for 855 (80%) at the 2-year follow-up. At this age 72 children (8.4%) were overweight and 24 (2.8%) were severely overweight. Whereas 76 children (8.9%) were never breastfed, 533 children (62.3%) were breastfed for at least 6 months, and 322 children (37.7%) were exclusively breastfed for at least 6 months. Compared to children who were breastfed for less than 3 months, the adjusted odds ratio (OR) for overweight was 0.4 in children who were breastfed for at least 6 months. When considering the time of exclusive breastfeeding, the adjusted OR for overweight was 0.8 in children who were exclusively breastfed for at least 3 but less than 6 months and 0.4 in children who were exclusively breastfed for at least 6 months compared to children who were exclusively breastfed less than 3 months. These results highlight the importance of prolonged breastfeeding for the prevention of overweight in children.

Nelson, M. C., Gordon-Larsen, P., & Adair, L. S. (2005). Are adolescents who were breast-fed less likely to be overweight? Analyses of sibling pairs to reduce confounding. *Epidemiology*, 247-253.

Cohort analyses suggesting that breastfeeding protects against being overweight have been criticized for inadequately controlling for confounding associated with the self-selection of feeding practices. Using nationally representative U.S. data from the National Longitudinal Study of Adolescent Health (1994-1996), we performed traditional cohort analyses ($n = 11,998$) using logistic regression to estimate the relation between breast-feeding and adolescent overweight (body mass index \geq 85 percentile, based on year 2000 CDC growth charts), controlling for known potential confounders. Breastfeeding also was assessed in a subsample of 850 sibling pairs to account for unmeasured genetic and environmental factors. Among girls in the full cohort, the odds of being overweight declined among those who had been breastfed at least 9 months; odds ratios ranged from 0.90 for ≥ 9 months. A similar effect was seen in boys, although these trends were less consistent. In contrast, an analysis of sibling pairs provided no evidence of breast-feeding effects on weight within discordant trends.

CONCLUSION: Cohort data indicate that odds of being overweight decrease as breast-feeding duration increases, at least among girls. However, sibling analyses suggest that this relationship may not be causal but rather attributable to unmeasured confounding related to mothers' choice to breast-feed, or to other childhood risk factors for overweight. Our results illustrate the utility of sibling analyses in understanding the true effect of early life exposures (such as breast-feeding) on health outcomes over time, independent of confounding factors that may not be satisfactorily controlled using traditional prospective cohort methods.

Harder, T., Bergmann, R., Kallischnigg, G., & Plagemann, A. (2005). Duration of breastfeeding and risk of overweight: a meta-analysis. *American journal of epidemiology*, 162(5), 397-403. Observational studies suggest a longer duration of breastfeeding to be associated dose dependently with a decrease in risk of overweight in later life. The authors performed a comprehensive meta-analysis of the existing studies on duration of breastfeeding and risk of overweight. Studies were included that reported the odds ratio and 95% confidence interval (or the data to calculate them) of overweight associated with breastfeeding and that reported the duration of breastfeeding and used exclusively formula-fed subjects as the referent. Seventeen studies met the inclusion criteria. By meta-regression, the duration of breastfeeding was inversely associated with the risk of overweight (regression coefficient=0.94, 95% confidence interval (CI): 0.89, 0.98). Categorical analysis confirmed this dose-response association (9 months: OR=0.68, 95% CI: 0.50, 0.91). One month of breastfeeding was associated with a 4% decrease in risk (OR=0.96/month of breastfeeding, 95% CI: 0.94, 0.98). The definitions of overweight and age had no influence. These findings strongly support a dose-dependent association between longer duration of breastfeeding and decrease in risk of overweight.

Owen, C. G., Martin, R. M., Whincup, P. H., Smith, G. D., & Cook, D. G. (2005). Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. *Pediatrics*, 115(5), 1367-1377.

A systematic review of published studies investigating the association between infant feeding and a measure of obesity was performed with Medline (1966 onward) and Embase (1980 onward) databases, supplemented with manual searches. Data extraction was conducted by 2 authors. Sixty-one studies reported on the relationship of infant feeding to a measure of obesity in later life; of these, 28 (298900 subjects) provided odds ratio estimates. In these studies, breastfeeding was associated with a reduced risk of obesity, compared with formula feeding (odds ratio: 0.87; 95% confidence interval [CI]: 0.85-0.89). The inverse association between breastfeeding and obesity was particularly strong in 11 small studies of or =500 subjects (odds ratio: 0.88; 95% CI: 0.85-0.90). In 6 studies that adjusted for all 3 major potential confounding factors (parental obesity, maternal smoking, and social class), the inverse association was reduced markedly (from an odds ratio of 0.86 to 0.93) but not abolished. A sensitivity analysis examining the potential impact of the results of 33 published studies (12505 subjects) that did not provide odds ratios (mostly reporting no relationship between breastfeeding and obesity) showed little effect on the results. CONCLUSIONS: Initial breastfeeding protects against obesity in later life.

Arenz, S., Rückerl, R., Koletzko, B., & von Kries, R. (2004). Breast-feeding and childhood obesity—a systematic review. *International journal of obesity*, 28(10), 1247.

To investigate the relationship between breast-feeding and obesity in childhood. DESIGN: Systematic review and metaanalysis of published epidemiological studies (cohort, case-control or cross-sectional studies) comparing early feeding-mode and adjusting for potential confounding factors. Electronic databases were searched and reference lists of relevant articles were checked. Calculations of pooled estimates were conducted in fixed- and random-effects models. Heterogeneity was tested by Q-test. Publication bias was assessed from funnel plots and by a linear regression method. OUTCOME MEASURES: Odds ratio (OR) for obesity in

childhood defined as body mass index (BMI) percentiles. RESULTS: Nine studies with more than 69,000 participants met the inclusion criteria. The meta-analysis showed that breast-feeding reduced the risk of obesity in childhood significantly. The adjusted odds ratio was 0.78, 95% CI (0.71, 0.85) in the fixed model. The assumption of homogeneity of results of the included studies could not be refuted (Q-test for heterogeneity, $P > 0.3$), stratified analyses showed no differences regarding different study types, age groups, definition of breast-feeding or obesity and number of confounding factors adjusted for. A dose-dependent effect of breast-feeding duration on the prevalence of obesity was reported in four studies. Funnel plot regression gave no indication of publication bias. CONCLUSION: Breast-feeding seems to have a small but consistent protective effect against obesity in children.

Bogen, D. L., Hanusa, B. H., & Whitaker, R. C. (2004). The effect of breast-feeding with and without formula use on the risk of obesity at 4 years of age. *Obesity research*, 12(9), 1527-1535. This was a retrospective cohort study. Participants were 73,458 white and black low-income children followed from birth through 4 years of age. Obesity at age 4 years was defined as measured BMI \geq 95th percentile. Feeding exposure was based on breastfeeding duration and the age of formula initiation. At age 4 years, the prevalence of obesity was 11.5%. Only 16% of children were breastfed 8 weeks or longer. Breastfeeding was associated with a reduced risk of obesity only in white children whose mothers had not smoked in pregnancy. In this subgroup, the reduction in obesity risk, compared with those never breastfed, occurred only for children who were breast-fed at least 16 weeks without formula (adjusted odds ratio 0.71) or at least 26 weeks with concurrent formula (0.70). Among whites whose mothers smoked in pregnancy and among blacks, breastfeeding was not associated with a reduced risk of obesity at age 4 years. In a population of low-income children, breastfeeding was associated with a reduced risk of obesity at age 4 years only among whites whose mothers did not smoke in pregnancy and only when breast-feeding continued for at least 16 weeks without formula or at least 26 weeks with formula.

Grummer-Strawn, L. M., & Mei, Z. (2004). Does breastfeeding protect against pediatric overweight? Analysis of longitudinal data from the Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System. *Pediatrics*, 113(2), e81-e86.

To examine whether increasing duration of breastfeeding is associated with a lower risk of overweight in a low-income population of 4-year-olds in the United States, 177,304 children up to 60 months of age were included in the final pediatric-only analysis, and 12,587 were included in the pregnancy-pediatric linked analysis. The duration of breastfeeding showed a dose-response, protective relationship with the risk of overweight only among non-Hispanic whites; no significant association was found among non-Hispanic blacks or Hispanics. Among non-Hispanic whites, the adjusted odds ratio of overweight by breastfeeding for 6 to 12 months versus never breastfeeding was 0.70 and for > 12 months versus never was 0.49.

Breastfeeding for any duration was also protective against underweight (BMI-for-age below the 5th percentile). Prolonged breastfeeding is associated with a reduced risk of overweight among non-Hispanic white children. Breastfeeding longer than 6 months provides health benefits to children well beyond the period of breastfeeding.

Toschke, A. M., Vignerova, J., Lhotska, L., Osancova, K., Koletzko, B., & Von Kries, R. (2002). Overweight and obesity in 6-to 14-year-old Czech children in 1991: protective effect of breast-feeding. *The Journal of pediatrics*, 141(6), 764-769.

Cross-sectional survey data collected in 1991 on 33,768 school-children aged 6 to 14 years in the Czech Republic. Overall prevalence of overweight (obesity) was lower in breast-fed children: ever breast-fed (9.3%) compared with never breast-fed (12.4%). The effect of breast-feeding on overweight/obesity did not diminish with age in children 6 to 14 years old and could not be explained by parental education, parental obesity, maternal smoking, high birth weight, watching television, number of siblings, and physical activity. Adjusted odds ratios for breast-feeding were for overweight 0.80 (95% CI, 0.71-0.90) and for obesity 0.80 (95% CI, 0.66-0.96). A reduced prevalence of overweight/obesity was associated with breast-feeding in a setting where socioeconomic status was homogeneous. This suggests that the effect of breast-feeding on the prevalence of obesity is not confounded by socioeconomic status.

Armstrong, J., & Reilly, J. J. (2002). Breastfeeding and lowering the risk of childhood obesity. *The Lancet*, 359(9322), 2003-2004.

Population-based sample of 32,200 Scottish children studied at age 39-42 months. The prevalence of obesity was significantly lower in breastfed children, and the association persisted after adjustment for socioeconomic status, birthweight, and sex. The adjusted odds ratio for obesity (body-mass index greater than or equal to 98th percentile) was 0.70. Results suggest that breastfeeding is associated with a reduction in childhood obesity risk.

Gillman, M. W., Rifas-Shiman, S. L., Camargo Jr, C. A., Berkey, C. S., Frazier, A. L., Rockett, H. R., ... & Colditz, G. A. (2001). Risk of overweight among adolescents who were breastfed as infants. *Jama*, 285(19), 2461-2467.

In this Harvard survey of 8186 girls and 7155 boys, aged 9 to 14 years, overweight status was defined as body mass index exceeding the 95th percentile for age and sex from US national data. In the first 6 months of life, 9553 subjects (62%) were only or mostly fed breast milk, and 4744 (31%) were only or mostly fed infant formula. A total of 7186 subjects (48%) were breastfed for at least 7 months while 4613 (31%) were breastfed for 3 months or less. At ages 9 to 14 years, 404 girls (5%) and 635 boys (9%) were overweight. Among subjects who had been only or mostly fed breast milk, compared with those only or mostly fed formula, the odds ratio (OR) for being overweight was 0.78, after adjustment for age, sex, sexual maturity, energy intake, time watching television, physical activity, mother's body mass index, and other variables reflecting social, economic, and lifestyle factors. Compared with subjects who had been breastfed for 3 months or less, those who had been breastfed for at least 7 months had an adjusted OR for being overweight of 0.80. Timing of introduction of solid foods, infant formula, or cow's milk was not related to risk of being overweight. Infants who were fed breast milk more than infant formula, or who were breastfed for longer periods, had a lower risk of being overweight during older childhood and adolescence.

Von Kries, R., Koletzko, B., Sauerwald, T., Von Mutius, E., Barnert, D., Grunert, V., & Von Voss, H. (1999). Breastfeeding and obesity: cross sectional study. *Bmj*, 319(7203), 147-150.

A German study of 9357 children aged 5-6 years of age found that infants fed only breastmilk until 3-5 months were more than a third less likely to be obese than infants fed formula from the start. Infants breastfed exclusively for 6-12 months were 43% less likely to be obese. Breastfeeding beyond 12 months was better still, giving infants a 72% lower chance of becoming obese children. After adjusting for potential confounding factors, breastfeeding remained a significant protective factor against the development of obesity. v

Tulldahl, J., Pettersson, K., Andersson, S. W., & Hulthén, L. (1999). Mode of infant feeding and achieved growth in adolescence: early feeding patterns in relation to growth and body composition in adolescence. *Obesity Research*, 7(5), 431-437.

This Swedish study examined the relations between length of breast-feeding, growth, and body composition in a group of 781 adolescents. Data on feeding pattern in infancy and on weight and height from birth up to 18 years were collected. Both boys and girls who were exclusively breast-fed for more than 3 months were leaner and showed a trend towards lower skinfold values.

Oral and Dental Health

Avila, W. M., Pordeus, I. A., Paiva, S. M., & Martins, C. C. (2015). Breast and bottle feeding as risk factors for dental caries: a systematic review and meta-analysis. *PloS one*, 10(11), e0142922.

Understanding the role that breastfeeding and bottle feeding play in the development of dental caries during childhood is essential in helping dentists and parents and care providers prevent the disease, and also for the development of effective public health policies. However, the issue is not yet fully understood. The aim of this systematic review and meta-analysis was to search for scientific evidence in response to the question: Do bottle fed children have more dental caries in primary dentition than breastfed children? Seven electronic databases and grey literature were used in the search. The protocol number of the study is PROSPERO CRD 42014006534. Two independent reviewers selected the studies, extracted data and evaluated risk of bias by quality assessment. A random effect model was used for meta-analysis, and the summary effect measure were calculated by odds ratio (OR) and 95% CI. Seven studies were included: five cross-sectional, one case-control and one cohort study. A meta-analysis of cross-sectional studies showed that breastfed children were less affected by dental caries than bottle fed children (OR: 0.43; 95%CI: 0.23–0.80). Four studies showed that bottle fed children had more dental caries ($p < 0.05$), while three studies found no such association ($p > 0.05$). The scientific evidence therefore indicated that breastfeeding can protect against dental caries in early childhood. The benefits of breastfeeding until age two is recommended by WHO/UNICEF guidelines. Further prospective observational cohort studies are needed to strengthen the evidence.

Kato, T., Yorifuji, T., Yamakawa, M., Inoue, S., Saito, K., Doi, H., & Kawachi, I. (2015). Association of breast feeding with early childhood dental caries: Japanese population-based study. *BMJ open*, 5(3), e006982.

We investigated the association between breastfeeding duration during the first half year of life and the risk of early childhood caries from the age of 30 to 66 months in Japan. Early childhood caries-defined as a child's visit to a dentist for treatment of dental caries during the past 12 months-was ascertained from the caregiver from the age of 30 months in the survey. We estimated the risk of dental caries each year according to duration of breast feeding using logistic regression analyses. We controlled for a set of biological factors (birth weight, sex, parity and maternal age at delivery) and socioeconomic factors (maternal educational attainment and smoking status, marital status at delivery, family income and region of birth and residence). We found that infants who had been breast fed for at least 6 or 7 months, both exclusively and partially, were at elevated risk of dental caries at the age of 30 months compared with those who had been exclusively formula fed. Adjusted ORs were 1.78 (95% CI, (1.45 to 2.17)) for the exclusively breastfed group and 1.39 (1.14 to 1.70) for the partially breastfed group. However, the associations became attenuated through the follow-up period and were no longer statistically significant beyond the age of 42 months for the partially breastfed group and beyond the age of 54 months for the exclusively breastfed group.

Tham, R., Bowatte, G., Dharmage, S. C., Tan, D. J., Lau, M. X. Z., Dai, X., ... & Lodge, C. J. (2015). Breastfeeding and the risk of dental caries: a systematic review and meta-analysis. *Acta Paediatrica*, 104, 62-84.

The objective of this study was to synthesise the current evidence for the associations between breastfeeding and dental caries, with respect to specific windows of early childhood caries risk. Sixty-three papers included. Children exposed to longer versus shorter duration of breastfeeding up to age 12 months (more versus less breastfeeding), had a reduced risk of caries (OR 0.50; 95%CI 0.25, 0.99, I² 86.8%). Children breastfed >12 months had an increased risk of caries when compared with children breastfed <12 months (seven studies (OR 1.99; 1.35, 2.95, I² 69.3%). Amongst children breastfed >12 months, those fed nocturnally or more frequently had a further increased caries risk (five studies, OR 7.14; 3.14, 16.23, I² 77.1%). There was a lack of studies on children aged >12 months simultaneously assessing caries risk in breastfed, bottle-fed and children not bottle or breastfed, alongside specific breastfeeding practices, consuming sweet drinks and foods, and oral hygiene practices limiting our ability to tease out the risks attributable to each. Breastfeeding in infancy may protect against dental caries. Further research needed to understand the increased risk of caries in children breastfed after 12 months.

Tanaka, K., Miyake, Y., Sasaki, S., & Hirota, Y. (2013). Infant feeding practices and risk of dental caries in Japan: the Osaka Maternal And Child Health Study. *Pediatric dentistry*, 35(3), 267-271.

Subjects were 315 children. Information about the variables under study and potential confounding factors were obtained by questionnaire during pregnancy and when the children were two to nine, 16 to 24, 29 to 39, and 41 to 49 months old. Outcome data were collected at 41 to 50 months old. Children were classified as having ECC if one or more primary teeth had decayed or been filled. RESULTS: Compared with breast-feeding for six months or fewer, breast-feeding for 18 months or longer tended to be positively associated with a risk of ECC, and a U-shaped relationship was observed. Use of a bottle to drink sweetened liquids other than

milk and the introduction of solid foods at six months old or later were positively associated with a risk of ECC. There was no significant association between bottle-feeding while falling asleep at night and the risk of ECC. CONCLUSION: Prolonged breast-feeding, bottle use for sweetened liquids other than milk, and the introduction of solid foods at six months old or later might be risk factors for the development of dental caries.

Nunes, A. M. M., Alves, C. M. C., Borba de Araújo, F., Ortiz, T. M. L., Ribeiro, M. R. C., Silva, A. A. M. D., & Ribeiro, C. C. C. (2012). Association between prolonged breast-feeding and early childhood caries: a hierarchical approach. *Community dentistry and oral epidemiology*, 40(6), 542-549.

This study was conducted to investigate the association between prolonged breastfeeding and early childhood caries (ECC) with adjustment for important confounders, using hierarchical approach. Methods: This retrospective cohort study involved 260 low income children (18-42 months). The number of decayed teeth was used as a measure of caries. Following a theoretical framework, the hierarchical model was built in a forward fashion, by adding the following levels in succession: level 1: age; level 2: social variables; level 3: health variables; level 4: behavioral variables; level 5: oral hygiene-related variables; level 6: oral hygiene quality measured by visible plaque; and level 7: contamination by mutans streptococci. Sequential forward multiple Poisson regression analysis was employed. Results Breast-feeding was not a risk factor for ECC after adjustment for some confounders (incidence density ratio, 1.15; 95% confidence interval, 0.84-1.59, $P = 0.363$). Conclusion Prolonged breast-feeding was not a risk factor for ECC while age, high sucrose consumption between main meals and the quality of oral hygiene were associated with disease in children.

Salone, L. R., Vann Jr, W. F., & Dee, D. L. (2013). Breastfeeding: an overview of oral and general health benefits. *The Journal of the American Dental Association*, 144(2), 143-151. Breastfeeding is the reference against which alternative infant feeding models must be measured with regard to growth, development and other health outcomes. Although not a systematic review, this report provides an update for dental professionals, including an overview of general and oral health-related benefits associated with breastfeeding. The authors examined the literature regarding general health protections that breastfeeding confers to infants and mothers and explored associations between breastfeeding, occlusion in the primary dentition and early childhood caries. To accomplish these goals, they reviewed systematic reviews when available and supplemented them with comparative studies and with statements and reports from major nongovernmental and governmental organizations. When compared with health outcomes among formula fed children, the health advantages associated with breastfeeding include a lower risk of acute otitis media, gastroenteritis and diarrhea, severe lower respiratory infections, asthma, sudden infant death syndrome, obesity and other childhood diseases and conditions. Evidence also suggests that breastfed children may develop a more favorable occlusion in the primary dentition. The results of a systematic review in which researchers examined the relationship between breastfeeding and early childhood caries were inconclusive. CONCLUSIONS: The American Academy of Pediatric Dentistry, Chicago, suggests that parents gently clean infants' gums and teeth after breastfeeding. The American Academy of Pediatrics recommends that breastfeeding should be exclusive for about the first six months of life and

should continue, with the introduction of appropriate complementary foods, to at least age 12 months or beyond, as desired by mother and child. Dentists and staff members can take steps to ensure they are familiar with the evidence and guidelines pertaining to breastfeeding and to oral health. They are encouraged to follow the surgeon general's recommendations to promote and support optimal breastfeeding and oral health practices among their patients. S

Romero, C. C., Scavone-Junior, H., Garib, D. G., Cotrim-Ferreira, F. A., & Ferreira, R. I. (2011). Breastfeeding and non-nutritive sucking patterns related to the prevalence of anterior open bite in primary dentition. *Journal of Applied Oral Science*, 19(2), 161-168.

Infant feeding and non-nutritive sucking were investigated in a 3-6 year-old sample of 1,377 children, from Sao Paulo. Children were grouped according to breastfeeding duration: non-breastfed, shorter than 6 months, interruption between 6 and 12 months, and longer than 12 months. Three calibrated dentists performed clinical examinations and classified overbite into 3 categories: normal, anterior open bite and deep bite. Results showed children who were non-breastfed had significantly more chances of having anterior open bite compared with both children who were breastfed, and in the subgroup without history of non-nutritive sucking, with the children that breastfed longest associated with a 3.7 times lower chance of having anterior open bite than non-breastfed children.

Sánchez-Molins, M., Grau, J. C., Lischeid, C. G., & Ustrell, J. T. (2010). Comparative study of the craniofacial growth depending on the type of lactation received. *European journal of paediatric dentistry: official journal of European Academy of Paediatric Dentistry*, 11(2), 87-92. The study of cases and controls (observational, analytical and retrospective) and lateral telerradiographs of the cranium of 197 patients (106 breast-fed and 91 bottle-fed) were compared. First, the upper incisors were found to be protruded in the bottle-fed group. Second, subjects belonging to the breast-fed group displayed a brachycephalic mandible arch, while those fed with bottle had a dolichocephalic Steiner mandibular plane. Third, both facial depth and distance of the pogonion to the perpendicular nasion presented a certain tendency to a retruded mandibular bone in the bottle-fed group. And fourth, the frequency of use of dummy and thumb suction were greater in the bottle feed group, without statistical significance. In addition to the multiple advantages that mother's milk offers to newborns, breastfeeding also helps correct orofacial development (not only for the incisors position, but also for the vertical and sagittal relations of the mandible with upper maxillary and cranial basis).

Kobayashi, H. M., Scavone Jr, H., Ferreira, R. I., & Garib, D. G. (2010). Relationship between breastfeeding duration and prevalence of posterior crossbite in the deciduous dentition. *American Journal of Orthodontics and Dentofacial Orthopedics*, 137(1), 54-58.

This cross-sectional retrospective epidemiologic study assessed the relationship between exclusive breastfeeding duration and the prevalence of posterior crossbite in the deciduous dentition. METHODS: Clinical examinations were performed in 1377 Brazilian children (690 boys, 687 girls), 3 to 6 years old, from 11 public schools in São Paulo, Brazil. Based on questionnaires answered by the parents, the children were classified into 4 groups according to the duration of exclusive breastfeeding: G1, never (119 subjects); G2, less than 6 months (720 subjects); G3, 6 to 12 months (312 subjects); and G4, more than 12 months (226 subjects). The

statistical analyses included the chi-square test ($P < 0.05$) and the odds ratio. RESULTS: The posterior crossbite was observed in 31.1%, 22.4%, 8.3%, and 2.2% of the children, in groups G1, G2, G3, and G4, respectively. The results showed a statistically significant relationship between exclusive breastfeeding duration and the prevalence of posterior crossbite.

CONCLUSIONS: Children who were breastfed for more than 12 months had a 20-fold lower risk for the development of posterior crossbite compared with children who were never breastfed and a 5-fold lower risk compared with those breastfed between 6 and 12 months.

Kramer, M. S., Vanilovich, I., Matush, L., Bogdanovich, N., Zhang, X., Shishko, G., ... & Platt, R. W. (2007). The effect of prolonged and exclusive breast-feeding on dental caries in early school-age children. *Caries Research*, 41(6), 484-488.

To study the effects of prolonged and exclusive breast-feeding on dental caries, we followed up children participating in the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster-randomized trial of a breast-feeding promotion intervention based on the WHO/UNICEF Baby-Friendly Hospital Initiative. A total of 17,046 healthy, mother-infant breast-feeding pairs were enrolled from 31 Belarussian maternity hospitals and affiliated polyclinics, of whom 13,889 (81.5%) were followed up at 6.5 years. At follow-up, polyclinic pediatricians transcribed the reports of a standard dental examination performed by public health dentists at age 6 years and recorded in the children's polyclinic charts. Analysis was based on intention to treat, with a statistical model that accounts for clustering within hospitals/clinics to permit inferences at the individual level. The experimental intervention led to a large increase in exclusive breast-feeding at 3 months (43.3 vs. 6.4%, $p < 0.001$) and a significantly higher prevalence of any breast-feeding at all ages up to and including 12 months. No significant intervention effects were observed on dental caries. Our results, based on the largest randomized trial ever conducted in the area of human lactation, provide no evidence of beneficial or harmful effects of prolonged and exclusive breast-feeding on dental caries at early school age.

Iida, H., Auinger, P., Billings, R. J., & Weitzman, M. (2007). Association between infant breastfeeding and early childhood caries in the United States. *Pediatrics*, 120(4), e944-e952. Despite limited epidemiologic evidence, concern has been raised that breastfeeding and its duration may increase the risk of early childhood caries. The objective of this study was to assess the potential association of breastfeeding and other factors with the risk for early childhood caries among young children in the United States. METHODS: Data about oral health, infant feeding, and other child and family characteristics among children 2 to 5 years of age ($N = 1576$) were extracted from the 1999-2002 National Health and Nutrition Examination Survey. The association of breastfeeding and its duration, as well as other factors that previous research has found associated with early childhood caries, was examined in bivariate analyses and by multivariable logistic and Poisson regression analyses. RESULTS: After adjusting for potential confounders significant in bivariate analyses, breastfeeding and its duration were not associated with the risk for early childhood caries. Independent associations with increased risk for early childhood caries were older child age, poverty, being Mexican American, a dental visit within the last year, and maternal prenatal smoking. Poverty and being Mexican American also were independently associated with severe early childhood caries, whereas characteristics that were independently associated with greater decayed and filled surfaces on primary teeth

surfaces were poverty, a dental visit within the last year, 5 years of age, and maternal smoking.

CONCLUSIONS: These data provide no evidence to suggest that breastfeeding or its duration are independent risk factors for early childhood caries, severe early childhood caries, or decayed and filled surfaces on primary teeth. In contrast, they identify poverty, Mexican American ethnic status, and maternal smoking as independent risk factors for early childhood caries, which highlights the need to target poor and Mexican American children and those whose mothers smoke for early preventive dental visits.

Peres, K. G., Barros, A. J., Peres, M. A., & Victora, C. G. (2007). Effects of breastfeeding and sucking habits on malocclusion in a birth cohort study. *Revista de saude Publica*, 41(3), 343-350.

A sample of 359 children was dentally examined and their mothers interviewed. Anterior open bite and posterior cross bite were recorded. Information regarding breastfeeding and non-nutritive sucking habits was collected at birth, in the first, third, sixth and twelfth months of life, and at six years of age. Control variables included maternal schooling and child's birthweight, cephalic perimeter, and sex. Prevalence of anterior open bite was 46.2%, and that of posterior cross bite was 18.2%. Nonnutritive sucking habits between 12 months and four years of age and digital sucking at age six years were the main risk factors for anterior open bite. Breastfeeding for less than nine months and regular use of pacifier between age 12 months and four years were risk factors for posterior cross bite.

Wondwossen, F., Åstrøm, A. N., Bjorvatn, K., & Bårdsen, A. (2006). Sociodemographic and behavioural correlates of severe dental fluorosis. *International Journal of Paediatric Dentistry*, 16(2), 95-103.

Three hundred and six adolescents (12-15 years) and 233 mothers participated in the study. The children were examined for dental fluorosis. The prevalence of severe dental fluorosis was 24.1 % and 75.9% in the moderate- and high-fluoride areas, respectively. The odds for having severe fluorosis varied according to the fluoride concentration of the drinking water, age, consumption of tea, length of breastfeeding and method of storing water. Breastfeeding for > 18 months and the use of clay pots for storing drinking water helped protect against severe dental fluorosis. Being male and consuming fish might be associated with higher fluorosis scores. In order to avoid dental fluorosis, low-fluoride drinking water should be provided in the relevant villages. A prolonged period of breastfeeding, the use of clay pots for storing water, and possibly a reduced intake of tea and whole fish in infants might also help to avoid severe fluorosis in children growing up in traditionally fluoride endemic areas.

Trawitzki, L. V. V., Anselmo-Lima, W. T., Melchior, M. O., Grechi, T. H., & Valera, F. C. (2005). Breast-feeding and deleterious oral habits in mouth and nose breathers. *Revista Brasileira de Otorrinolaringologia*, 71(6), 747-751.

Breast-feeding promotes several benefits in childhood, among them favoring the nasal breathing. The study population consisted of 62 children ranging in age from 3 years and 3 months to 6 years and 11 months who were submitted to Page 46 of 63 otorhinolaryngologic evaluation to determine nasal and mouth breathers and to a speech language pathologic interview. The otorhinolaryngologic evaluation involved the following exams: anterior

rhinoscopy, oroscopy and radiologic examination. The parents of the children were questioned about the form of feeding (natural and/or artificial), the duration of breast-feeding and the presence of deleterious oral habits (suction and biting). The breast-feeding period was longer among nasal breathers and was concentrated in the period between 3 and 6 months of age. Regarding the use of bottle, the results showed that most of the children in both groups used this type of feeding during the first years of life, with no significant difference between groups ($p=0.58$). There was a marked presence of deleterious oral habits among mouth breathers, with a statistically significant difference between groups regarding suction and biting habits. Mouth-breathing children were breast-fed for a shorter period of time and had a history of deleterious oral habits compared to nose breathers.

Holman, D. J., & Yamaguchi, K. (2005). Longitudinal analysis of deciduous tooth emergence: IV. Covariate effects in Japanese children. *American Journal of Physical Anthropology: The Official Publication of the American Association of Physical Anthropologists*, 126(3), 352-358. Sample of 114 Japanese children born in Tokyo in 1914 and 1924. Parametric survival analysis was used to quantify the effects of nutritional status, breastfeeding behavior, and sex on the hazard of deciduous tooth emergence. Children of poor nutritional status exhibited significantly delayed emergence of all deciduous teeth, with effects that ranged from 14-29% increases in mean emergence times. Children of medium nutritional status exhibited increases in mean emergence times of 5- 9% for the canines and lower molars, and 13-17% for the incisors. Partial breastfeeding had no effect on tooth emergence, but children who were not breastfed at all showed delayed emergence of the upper incisors. No significant sex differences in emergence were found. The findings contradict the idea that moderate malnutrition has little effect on deciduous tooth emergence. Furthermore, nutritional differences may account for some of the observed differences among populations in the timing of tooth emergence.

Viggiano, D., Fasano, D., Monaco, G., & Strohmenger, L. (2004). Breast feeding, bottle feeding, and non-nutritive sucking; effects on occlusion in deciduous dentition. *Archives of disease in childhood*, 89(12), 1121-1123.

A retrospective study from Italy among of 1130 preschool children has found that non-nutritive sucking and bottle feeding can have a substantial effect on dental occlusion. Open bite was associated with non-nutritive sucking while posterior cross-bite was associated with both bottle feeding and non-nutritive sucking.

Charchut, S. W., Allred, E. N., & Needleman, H. L. (2003). The effects of infant feeding patterns on the occlusion of the primary dentition. *Journal of dentistry for children*, 70(3), 197-203. Study included 126 children. Parents completed questionnaires regarding feeding and health history, and the primary dental occlusion was recorded for each child. The authors found that: (1) predominant bottle-feeding between 0 and 6 months of age was associated with the development of a pacifier habit; (2) children who used a pacifier were more likely to develop a nonmesial step occlusion, an overjet >3 mm, and an open bite; (3) children who sucked their thumb were more likely to develop an overjet >3 mm; and (4) in the absence of nonnutritive oral habits, children who were predominantly bottle-fed between 0 and 6 months of age were more likely to develop an overbite >75%, although just shy of nominal statistical significance.

Valaitis, R., Hesch, R., Passarelli, C., Sheehan, D., & Sinton, J. (2000). A systematic review of the relationship between breastfeeding and early childhood caries. *Can J Public Health*, 91(6), 411-17.

This systematic review investigated the relationship between early childhood caries and breastfeeding. A lack of methodological consistency, related to the study of the association of breastfeeding and ECC, and inconsistent definitions of ECC and breastfeeding, make it difficult to draw conclusions. Due to conflicting findings in less rigorous research studies, no definitive time at which an infant should be weaned was determined, and parents should begin an early and consistent mouth care regime.

Oulis, C. J., Berdouses, E. D., Vadiakas, G., & Lygidakis, N. A. (1999). Feeding practices of Greek children with and without nursing caries. *Pediatric dentistry*, 21(7), 409-416.

In this study of 260 children ages 3-5, the authors concluded that breastfeeding for more than 40 days may act preventively and inhibit the development of nursing caries in children.

Ramos-Gomez, F. J., Tomar, S. L., Ellison, J., Artiga, N., Sintes, J., & Vicuna, G. (1999).

Assessment of early childhood caries and dietary habits in a population of migrant Hispanic children in Stockton, California. *ASDC journal of dentistry for children*, 66(6), 395-403.

This study estimated the prevalence of early childhood caries and related behavioral risk factors in a population of low-income, Mexican-American children in Stockton, California. Data was collected on 220 children ages six years or less using a parent-completed questionnaire and clinical dental examinations. Mean age at weaning from breast-or bottle-feeding and patterns of bottle use during sleep did not differ significantly between children with caries and those without.

Erickson, P. R., & Mazhari, E. (1999). Investigation of the role of human breast milk in caries development. *Pediatric Dentistry*, 21, 86-90.

This in-vivo and in-vitro study showed that human breast milk is not cariogenic.

Mattos-Graner, R. D. O., Zelante, F., Line, R. C. S. R., & Mayer, M. P. A. (1998). Association between caries prevalence and clinical, microbiological and dietary variables in 1.0 to 2.5-year-old Brazilian children. *Caries Research*, 32(5), 319-323.

Children who were either never breast-fed or only until 3 months exhibited a significantly higher caries prevalence than those breast-fed for a longer time.

Davis, D. W., & Bell, P. A. (1991). Infant feeding practices and occlusal outcomes: a longitudinal study. *Journal (Canadian Dental Association)*, 57(7), 593-594.

A strong association was found between exclusive bottle-feeding and anteroposterior malocclusion.

Labbok, M. H., & Hendershot, G. E. (1987). Does breast-feeding protect against malocclusion?

An analysis of the 1981 Child Health Supplement to the National Health Interview Survey.

American journal of preventive medicine, 3(4), 227-232.

Data from the Child Health Supplement to the 1981 National Health Interview Survey were analyzed to assess the association between breast-feeding and malocclusion. Increased durations of breast-feeding were associated with a decline in the proportion of children with malocclusion, an association that remains when controlled for known associated variables.

Parent-child relationships

Schwarze, C. E., Hellhammer, D. H., Stroehle, V., Lieb, K., & Mobascher, A. (2015). Lack of breastfeeding: A potential risk factor in the multifactorial genesis of borderline personality disorder and impaired maternal bonding. *Journal of personality disorders*, 29(5), 610-626. Borderline personality disorder (BPD) is characterized by a pattern of intense but unstable interpersonal relationships. These interpersonal dysfunctions may originate from impaired bonding and attachment that is determined during early life. Remarkably, it has been reported that the quality of mother-infant relationship is influenced by the feeding mode. Thus, bottle feeding instead of breastfeeding and possible lack of maternal bonding-related behavior may increase the risk for later psychopathology and attachment problems as seen in BPD. A total of 100 BPD patients and 100 matched healthy controls underwent semi-structured interviews, based on retrospective information about early risk factors and breastfeeding during infancy. The authors' analyses revealed that BPD patients were significantly less breastfed compared to healthy controls (no breastfeeding in BPD: 42.4%; no breastfeeding in controls: 18.2%; $p < .001$). The BPD diagnosis was significantly predicted by the variable "no breastfeeding" ($p < .001$; odds ratio [OR] = 3.32; confidence interval [CI] [1.74, 6.34]), even after adjustment for childhood trauma and several confounding factors ($p = .001$). The variable "no breastfeeding" accounts for 9.1% of the variance of the BPD diagnosis and is associated with low perceived maternal bonding ($p = .006$). Breastfeeding may act as an early indicator of the mother-infant relationship that seems to be relevant for bonding and attachment later in life.

Liu, J., Leung, P., & Yang, A. (2014). Breastfeeding and active bonding protects against children's internalizing behavior problems. *Nutrients*, 6(1), 76-89. Breastfeeding is associated with numerous health benefits to offspring and mothers and may improve maternal-infant bonding. Ample evidence suggests breastfeeding can improve child neurodevelopment, but more research is needed to establish whether breastfeeding is linked to the development of child psychopathology. This paper aims to explore the effects of both breastfeeding and mother-child interactions on child behavioral outcomes at a later age. Children from the China Jintan Child Cohort Study (N=1267), at age six years old were assessed, along with their parents. Children who were breastfed exclusively for a period of time in the presence of active bonding were compared to those who were breastfed in the absence of active bonding as well as to children who were not exclusively breastfed, with or without active bonding. Results from ANOVA and GLM, using SPSS20, indicate that children who were breastfed and whose mothers actively engaged with them displayed the lowest risk of internalizing problems (mean=10.01, SD=7.21), while those who were neither exclusively breastfed nor exposed to active bonding had the least protection against later internalizing problems (mean=12.79, SD=8.14). The effect of breastfeeding on internalizing pathology likely

represents a biosocial and holistic effect of physiological, and nutritive, and maternal-infant bonding benefits.

Papp, L. M. (2014). Longitudinal associations between breastfeeding and observed mother–child interaction qualities in early childhood. *Child: care, health and development*, 40(5), 740-746.

Longitudinal associations between breastfeeding and observed mother–child interaction qualities in early childhood. *Child: care, health and development*, 40(5), 740-746.

Despite extensive literature on the role of breastfeeding in maternal and child health and cognitive development, few studies have systematically tested whether breastfeeding predicts children's socio-emotional outcomes. The present study examined associations between trajectories of breastfeeding and observed parent–child interaction qualities of maternal sensitivity, child positivity, and child negativity from 6 months to 3 years of age. Data were drawn from the NICHD Study of Early Child Care and Youth Development (n = 1306 US families). Hierarchical linear modelling accounted for demographic and early characteristics, including home environment, maternal depression, and observed global relationship quality. Breastfeeding was associated with increases in observed maternal sensitivity over time, even after the effects of demographic and early characteristics were controlled. Accounting for the covariates, breastfeeding was not associated with child behaviour (i.e. positivity, negativity) in mother–child interaction across early childhood. Improved relationship quality, specifically through changes in maternal behaviour, may be another advantage experienced by breastfeeding mothers and children.

McKee, M. D., Zayas, L. H., & Jankowski, K. R. B. (2004). Breastfeeding intention and practice in an urban minority population: relationship to maternal depressive symptoms and mother–infant closeness. *Journal of reproductive and infant psychology*, 22(3), 167-181.

In a sample of low-income African American and Hispanic women in the urban Northeast, mothers' perception of closeness to their infants was greater among breastfeeders compared to bottle-feeders.

Fergusson, D. M., & Woodward, L. J. (1999). Breastfeeding and later psychosocial adjustment. *Paediatric and perinatal epidemiology*, 13(2), 144-157.

Children who were breastfed for a longer duration were more likely, at age 15-18 years, to report higher levels of parental attachment and tended to perceive their mothers as being more caring and less overprotective towards them compared with bottle-fed children. After adjustment for maternal and perinatal factors, the duration of breastfeeding remained significantly associated with adolescent perceptions of maternal care, with increasing duration of breast feeding being associated with higher levels of perceived maternal care during childhood.

Protection against toxins (environmental contaminants, chemicals, heavy metals)

Jacobson, J. L., & Jacobson, S. W. (2003). Prenatal exposure to polychlorinated biphenyls and attention at school age. *The Journal of pediatrics*, 143(6), 780-788.

To examine the relation of prenatal polychlorinated biphenyl (PCB) exposure to child performance on neuropsychological tests of attention and information processing. Study design In this prospective, longitudinal study, assessment of prenatal PCB exposure was based on umbilical cord serum and maternal serum and milk concentrations. The children were tested in their homes at age 11 years. Multiple regression was used to examine the relation of this exposure to performance on 15 neuropsychological tests after controlling for a broad range of potential confounding variables. RESULTS: Adverse effects were seen primarily in children who had not been breastfed. Among these children, prenatal PCB exposure was associated with greater impulsivity, poorer concentration, and poorer verbal, pictorial, and auditory working memory. There was no evidence of visual-spatial deficit or increased hyperactivity. CONCLUSIONS: These findings are consistent with earlier reports of greater vulnerability to prenatal PCB exposure in children who were not breastfed. It is not clear whether the protection offered by breast-feeding is caused by nutrients in breast milk or better quality of intellectual stimulation often provided by breast-feeding mothers.

Schizophrenia

Sørensen, H. J., Mortensen, E. L., Reinisch, J. M., & Mednick, S. A. (2005). Breastfeeding and risk of schizophrenia in the Copenhagen Perinatal Cohort. *Acta Psychiatrica Scandinavica*, 112(1), 26-29.

The current sample comprises 6841 individuals from the Copenhagen Perinatal Cohort of whom 1671 (24%) had been breastfed for 2 weeks or less (early weaning) and 5170 (76%) had been breastfed longer. Maternal schizophrenia, parental social status, single mother status and gender were included as covariates in a multiple regression analysis of the effect of early weaning on the risk of hospitalization with schizophrenia. The sample comprised 93 cases of schizophrenia (1.4%). Maternal schizophrenia was the strongest risk factor and a significant association between single mother status and elevated offspring risk of schizophrenia was also observed. Early weaning was significantly related to later schizophrenia in both unadjusted and adjusted analyses (adjusted odds ratio 1.73). No or <2 weeks of breastfeeding was associated with elevated risk of schizophrenia.

Stress Resilience

Montgomery, S. M., Ehlin, A., & Sacker, A. (2006). Breastfeeding and resilience against psychosocial stress. *Archives of disease in childhood*, 91(12), 990-994.

Some early life exposures may result in a well controlled stress response, which can reduce stress-related anxiety. Breastfeeding may be a marker of some relevant exposures, so we assessed whether it was associated with modification of the relationship between parental divorce and anxiety. The 1970 British Cohort Study is following the lives of those born in one week in 1970 and living in Great Britain. This study uses information collected at birth and at ages 5 and ten years for 8958 subjects. Class teachers answered a question on anxiety among 10-year olds using an analogue scale (range 0-50) that was log transformed to minimise skewness. Among 5672 non-breast-fed subjects, parental divorce/separation was associated

with a Page 48 of 63 statistically significantly raised risk of anxiety, with a regression coefficient of 9.4. Among the breastfed group this association was much lower: 2.2. Interaction testing confirmed statistically significant effect modification by breastfeeding, independent of simultaneous adjustment for multiple potential confounding factors, producing an interaction coefficient of -7.0 indicating a 7% reduction in anxiety after adjustment. Breastfeeding is associated with resilience against the psychosocial stress linked with parental divorce/separation. This could be because breastfeeding is a marker of exposures related to maternal characteristics and parent-child interaction.

Tonsillitis

Wardhana, H., Kharisman, I., & Stella, P. (2018). Association Between Exclusive Breastfeeding and the Risk of Tonsillitis in Children Under Five in Demak, Central Java. *Indonesian Journal of Medicine*, 3(2), 71-76.

Upper respiratory infection (URI) remains one of the primary causes of child mortality in Indonesia. Some studies have shown that exclusive breastfeeding can prevent various infectious diseases including URI. However, in some places the incidence of tonsillitis is still high although the target of exclusive breastfeeding coverage has been met. This study aimed to determine the association between exclusive breastfeeding and the risk of tonsillitis in children under five in Demak, Central Java. This was a cross sectional study conducted at 3 Community Health Centers, Demak, Central Java, from March to April 2017. A sample of 35 children under five years old were selected for this study. The dependent variable was the incidence of tonsillitis. The independent variable was history of exclusive breastfeeding. The data were collected by questionnaire. Tonsillitis was determined by history taking and physical examination. The data were analyzed by Fisher exact test. Children without history of exclusive breastfeeding had an increased risk of contracting tonsillitis (OR= 9.58; p= 0.015) compared to those with history of exclusive breastfeeding. Provision of exclusive breastfeeding is associated with lower risk of tonsillitis in children under five.

Pisacane A, et al. Breastfeeding and tonsillectomy. *BMJ*. 1996 Mar 23;312(7033):746-7.

Transplant recipients

Kois, W. E., Campbell, D. A., Lorber, M. I., Sweeton, J. C., & Dafoe, D. C. (1984). Influence of breast feeding on subsequent reactivity to a related renal allograft. *Journal of Surgical Research*, 37(2), 89-93.

A history of breastfeeding was associated with dramatic improvements in graft function rates after sibling donor as well as maternal donor transplantation.

Campbell, J. D., Lorber, M. I., Sweeton, J. C., Turcotte, J. G., Niederhuber, J. E., & Beer, A. E. (1984). Breastfeeding and maternal-donor renal allografts. Possibly the original donor-specific transfusion. *Transplantation*, 37(4), 340-344.

The posttransplant course of 55 patients who had received a primary maternal-donor transplant was studied. A history of breast feeding was associated with a more favorable posttransplant course as measured by the percentage of patients who had no rejection episodes during the first post-transplant year. The one-year graft function rate for breast-fed recipients was 82%; this was statistically significantly better than the 57% measured for non-breast-fed recipients. \

Vaccine Response

Silfverdal, S. A., Ekholm, L., & Bodin, L. (2007). Breastfeeding enhances the antibody response to Hib and Pneumococcal serotype 6B and 14 after vaccination with conjugate vaccines. *Vaccine*, 25(8), 1497-1502.

This was an open non-randomised multi-centre study enrolling 101 healthy Swedish infants. Vaccine against pneumococcal diseases was administered concomitantly with DTaP/IPV/Hib at 3, 5, and 12 months. Duration of breastfeeding was calculated for days of almost exclusive as well as of total (any form of) breastfeeding. At 13 months of age, 6 out of 83 children did not reach 0.2µg/ml against serotype 6B, and five of these were breastfed less than 90 days. Four children did not reach 1µg/ml against Hib and all those were breastfed less than 90 days. One month after the second dose, at 6 months of age, children breastfed 90 days or more showed significantly higher GMC against serotype 14. This study indicates that children exclusively breastfed 90 days or more might get a better serological protection against Hib, and the pneumococcal serotypes 6B and 14 after vaccination, compared to children less breastfed.

Schaller, J. P., Kuchan, M. J., Thomas, D. L., Cordle, C. T., Winship, T. R., Buck, R. H., ... & Wheeler, J. G. (2004). Effect of dietary ribonucleotides on infant immune status. Part 1: Humoral responses. *Pediatric research*, 56(6), 883.

The objective of this study was to explore effects of ribonucleotides on infant immune status as measured by antibody responses to routine infant immunizations. Infants were randomized to a milk-based formula with or without ribonucleotides. A cohort of human milk-fed infants was also followed. Infants were given Haemophilus influenzae type b (Hib), diphtheria, tetanus, acellular pertussis, and oral poliovirus vaccinations at 2, 4, and 6 mo of age, and specific antibody responses were assessed at 2, 6, 7, and 12 mo. Human-milk-fed infant responses to the polio vaccine were significantly higher than formula-fed infants.

Pabst, H. F., Spady, D. W., Pilarski, L. M., Carson, M. M., Beeler, J. A., & Krezolek, M. P. (1997). Differential modulation of the immune response by breast-or formula-feeding of infants. *Acta Paediatrica*, 86(12), 1291-1297.

Spontaneous integrin expression on CD4+, CD8+ and CD19+ lymphocytes at 6 months was significantly lower in breastfed than formula-fed infants ($p < 0.05$). In another study of 59 formula-fed and 64 breastfed 12-month-old children blast transformation and cytokine production by lymphocytes, and T cell changes were measured before and after measles-mumps-rubella vaccination (MMR). Before vaccination, lymphocytes of breastfed children had lower levels of blast transformation without antigen ($p < 0.001$), with tetanus toxoid ($p < 0.02$) or Candida ($p < 0.04$), and lower interferon-gamma production ($p < 0.03$). Fourteen days after the live viral vaccination, only the breastfed children had increased production of interferon-gamma

($p < 0.02$) and increased percentages of CD56+ ($p < 0.022$) and CD8+ cells ($p < 0.004$). These findings are consistent with a Th1 type response by breastfed children, not evident in formula-fed children. Feeding mode has an important long-term immunomodulating effect on infants beyond weaning.

Pabst, H. F., & Spady, D. W. (1990). Effect of breast-feeding on antibody response to conjugate vaccine. *The Lancet*, 336(8710), 269-270.

The antibody levels of immunized infants were significantly higher in the breastfed than the formula-fed group. These findings are strong evidence that breastfeeding enhances the active humoral immune response in the first year of life.

Hahn-Zoric, M., Fulconis, F., Minoli, I., Moro, G., Carlsson, B., Böttiger, M., ... & Hanson, L. Å. (1990). Antibody responses to parenteral and oral vaccines are impaired by conventional and low protein formulas as compared to breast-feeding. *Acta Paediatrica*, 79(12), 1137-1142.

The breastfed group had significantly higher antibody levels than two formula-fed groups together. Breastfed infants thus showed better serum and secretory responses to perioral and parenteral vaccines than the formula fed, whether with a conventional or low-protein content.

Effects on Lactating Parent

CANCER

Breast Cancer

Islami, F., Liu, Y., Jemal, A., Zhou, J., Weiderpass, E., Colditz, G., ... & Weiss, M. (2015). Breastfeeding and breast cancer risk by receptor status—a systematic review and meta-analysis. *Annals of Oncology*, 26(12), 2398-2407.

Breastfeeding is inversely associated with overall risk of breast cancer. This association may differ in breast cancer subtypes defined by receptor status, as they may reflect different mechanisms of carcinogenesis. We conducted a systematic review and meta-analysis of case-control and prospective cohort studies to investigate the association between breastfeeding and breast cancer by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. This meta-analysis represents 27 distinct studies (8 cohort and 19 case-control), with a total of 36 881 breast cancer cases. Among parous women, the risk estimates for the association between ever (versus never) breastfeeding and the breast cancers negative for both ER and PR were similar in three cohort and three case-control studies when results were adjusted for several factors, including the number of full-term pregnancies (combined OR 0.90; 95% CI 0.82–0.99), with little heterogeneity and no indication of publication bias. In a subset of three adjusted studies that included ER, PR, and HER2 status, ever breastfeeding showed a stronger inverse association with triple-negative breast cancer (OR 0.78; 95% CI 0.66–0.91) among parous women. Overall, cohort studies showed no significant association between breastfeeding and ER+/PR+ or ER+ and/or PR+ breast cancers, although one and two studies (out of four and seven studies, respectively) showed an inverse

association. This meta-analysis showed a protective effect of ever-breastfeeding against hormone receptor-negative breast cancers, which are more common in younger women and generally have a poorer prognosis than other subtypes of breast cancer. The association between breastfeeding and receptor-positive breast cancers needs more investigation.

Zhou, Y., Chen, J., Li, Q., Huang, W., Lan, H., & Jiang, H. (2015). Association between breastfeeding and breast cancer risk: evidence from a meta-analysis. *Breastfeeding medicine*, 10(3), 175-182.

Quantification of the association between breastfeeding and breast cancer risk is still conflicting. Therefore, we conducted a meta-analysis to summarize the evidence from epidemiological studies of breastfeeding with the risk of breast cancer. Pertinent studies were identified by a search of PubMed between January 1, 2008 and July 31, 2014. The random-effect model was used. Sensitivity analysis, subgroups analysis, and publication bias were conducted. Twenty-four articles with 27 studies involving 13,907 breast cancer cases were included in this meta-analysis. Pooled results suggested that breastfeeding was inversely associated with the risk of breast cancer. The summary relative risk (RR) of breast cancer for the ever compared with never categories of breastfeeding was 0.613 (95% confidence interval [CI], 0.442–0.850). An inverse association was also found for the longest compared with the shortest categories of breastfeeding with the risk of breast cancer (RR=0.471; 95% CI, 0.368–0.602). No evidence of publication bias was found. Findings from this meta-analysis suggest that breastfeeding, particularly a longer duration of breastfeeding, was inversely associated with risk of breast cancer.

Stuebe, A. M., Willett, W. C., Xue, F., & Michels, K. B. (2009). Lactation and incidence of premenopausal breast cancer: a longitudinal study. *Archives of internal medicine*, 169(15), 1364-1371.

Findings from observational studies suggest an inverse association between lactation and premenopausal breast cancer risk, but results are inconsistent, and data from large prospective cohort studies are lacking. METHODS: We used information from 60,075 parous women participating in the prospective cohort study of the Nurses' Health Study II from 1997 to 2005. Our primary outcome was incident premenopausal breast cancer. RESULTS: We ascertained 608 incident cases of premenopausal breast cancer during 357,556 person-years of follow-up. Women who had ever breastfed had a covariate-adjusted hazard ratio (HR) of 0.75 (95% confidence interval [CI], 0.56-1.00) for premenopausal breast cancer compared with women who had never breastfed. No linear trend was found with duration of total lactation ($P = .95$), exclusive lactation ($P = .74$), or lactation amenorrhea ($P = .88$). The association between lactation and premenopausal breast cancer was modified by family history of breast cancer (P value for interaction = .03). Among women with a first-degree relative with breast cancer, those who had ever breastfed had a covariate-adjusted HR of 0.41 (95% CI, 0.22-0.75) for premenopausal breast cancer compared with women who had never breastfed, whereas no association was observed among women without a family history of breast cancer. CONCLUSION: In this large, prospective cohort study of parous premenopausal women, having ever breastfed was inversely associated with incidence of breast cancer among women with a family history of breast cancer.

Clarke, C. A., Purdie, D. M., & Glaser, S. L. (2006). Population attributable risk of breast cancer in white women associated with immediately modifiable risk factors. *BMC cancer*, 6(1), 170.

Estrogen/progestin replacement therapy (EPRT), alcohol consumption, physical activity, and breast-feeding duration differ from other factors associated with breast cancer in being immediately modifiable by the individual, thereby representing attractive targets for future breast cancer prevention efforts. To justify such efforts, it is vital to quantify the potential population-level impacts on breast cancer considering population variations in behavior prevalence, risk estimate, and baseline incidence. For each of these four factors, we calculated population attributable risk percents (PARs) using population-based survey (2001) and cancer registry data (1998-2002) for 41 subpopulations of white, non-Hispanic California women aged 40-79 years, and ranges of relative risk (RR) estimates from the literature. Using a single RR estimate, subpopulation PARs ranged from 2.5% to 5.6% for hormone use, from 0.0% to 6.1% for recent consumption of ≥ 2 alcoholic drinks daily, and 4.6% to 11.0% for physical inactivity. Using a range of RR estimates, PARs were 2-11% for EPRT use, 1-20% for alcohol consumption and 2-15% for physical inactivity. Subpopulation data were unavailable for breastfeeding, but PARs using published RR estimates ranged from 2% to 11% for lifetime breastfeeding ≥ 31 months. Thus, of 13,019 breast cancers diagnosed annually in California, as many as 1,432 attributable to EPRT use, 2,604 attributable to alcohol consumption, 1,953 attributable to physical inactivity, and 1,432 attributable to never breastfeeding might be avoidable. Conclusion: The relatively feasible lifestyle changes of discontinuing EPRT use, reducing alcohol consumption, increasing physical activity, and lengthening breastfeeding duration could lower population breast cancer incidence substantially.

Becher, H., Schmidt, S., & Chang-Claude, J. (2003). Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene-environment interaction. *International journal of epidemiology*, 32(1), 38-48.

Case-control-family study performed in Germany including 706 cases by age 50 years, 1381 population, and 252 sister controls, investigated main effects for environmental/lifestyle factors and genetic susceptibility and gene-environment. Familial predisposition showed the strongest main effect and the estimated gene carrier probability gave the best fit. High parity and longer duration of breastfeeding reduced breast cancer risk significantly, a history of abortions increased risk and age at menarche showed no significant effect. These findings corroborate results from other studies.

Gammon, M. D., Neugut, A. I., Santella, R. M., Teitelbaum, S. L., Britton, J. A., Terry, M. B., ... & Levin, B. (2002). The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast cancer research and treatment*, 74(3), 235-254.

Established risk factors for breast cancer that were found to increase risk among Long Island women include lower parity, late age at first birth, little or no breastfeeding, and family history of breast cancer.

Collaborative Group on Hormonal Factors in Breast Cancer. (2002). Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. *The Lancet*, 360(9328), 187-195. Data from 47 epidemiological studies in 30 countries that included information on breastfeeding patterns and other aspects of childbearing were collected, checked, and analysed centrally, for

50 302 women with invasive breast cancer and 96 973 controls. Fewer parous women with cancer than parous controls had ever breastfed (71% vs 79%), and their average lifetime duration of breastfeeding was shorter (9.8 vs 15.6 months). The relative risk of breast cancer decreased by 4.3% for every 12 months of breastfeeding in addition to a decrease of 7.0% (5.0-9.0; $p < 0.0001$) for each birth. It is estimated that the cumulative incidence of breast cancer in developed countries would be reduced by more than half, from 6.3 to 2.7 per 100 women by age 70, if women had the average number of births and lifetime duration of breastfeeding that had been prevalent in developing countries until recently. Breastfeeding could account for almost two-thirds of this estimated reduction in breast cancer incidence. The longer women breast-feed the more they are protected against breast cancer. The lack of or short lifetime duration of breastfeeding typical of women in developed countries makes a major contribution to the high incidence of breast cancer in these countries.

Zeng T et al. (2001). Long-term Breastfeeding Lowers Mother's Breast Cancer Risk. *Am J Epidemiol* 2001; 152:1129-1135.

Women who breastfed a child for more than 24 months had a 54% reduced risk of developing breast cancer compared with women who breastfed for no more than 6 months. Women who breastfed for at least 73 months over the course of their lives had a much lower risk of breast cancer. The investigators found that the protective effect of breastfeeding applied to a woman's risk of developing breast cancer both before and after menopause. Also confirmed that the later age of menarche and first pregnancy at a younger age lowers breast cancer risk. Women who went through menopause later and those with a family history of breast cancer were at increased risk.

Marcus, P. M., Baird, D. D., Millikan, R. C., Moorman, P. G., Qaqish, B., & Newman, B. (1999). Adolescent reproductive events and subsequent breast cancer risk. *American Journal of Public Health*, 89(8), 1244-1247.

This study compared rates of breast cancer between 751 mothers who had breastfed at least once and 743 mothers who had not. Breastfeeding reduced the risk of breast cancer by 20% in women age 20 to 49 years and by 30% in women ages 50 to 74 years. Moreover, breastfeeding seemed to protect against breast cancer regardless of the number of children breastfed, mother's age at first and last lactation, and menstrual history. R. Millikan et al. *International Journal of Epidemiology* 1999; 28:396- 402. This study investigated the relationship between reproductive events during adolescence and subsequent breast cancer risk. in 862 case patients and 790 controls in the Carolina Breast Cancer Study. Miscarriage, induced abortion, and full-term pregnancy before 20 years of age were not associated with breast cancer. Among premenopausal women, breast-feeding before 20 years of age was inversely associated with disease. Oral contraceptive use before 18 years of age was positively associated with disease risk among African American women only.

Newcomb, P. A., Egan, K. M., Titus-Ernstoff, L., Trentham-Dietz, A., Greenberg, E. R., Baron, J. A., ... & Stampfer, M. J. (1999). Lactation in relation to postmenopausal breast cancer. *American journal of epidemiology*, 150(2), 174-182.

As part of a multicenter population-based case-control study, the authors examined postmenopausal breast cancer risk according to breastfeeding characteristics. This analysis

included only data on parous postmenopausal women (3,633 cases and 3,790 controls). After adjustment for age, parity, age at first birth, and other breast cancer risk factors, breastfeeding for at least 2 weeks was associated with a slightly reduced risk of breast cancer in comparison with women who had never lactated (relative risk = 0.87). There was only a modest suggestion that increasing cumulative duration of lactation was inversely associated with breast cancer risk; the relative risk for women who had breastfed for $>$ or $=24$ months was 0.73. Age at first lactation was not consistently associated with risk. Modest inverse associations appeared to persist even up to 50 years since first lactation. Use of hormones to suppress lactation was not associated with postmenopausal breast cancer, nor was inability to breastfeed related to risk. These results suggest that lactation may have a slight and perhaps long-lasting protective effect on postmenopausal breast cancer risk.

Newcomb, P. A., Storer, B. E., Longnecker, M. P., Mittendorf, R., Greenberg, E. R., Clapp, R. W., ... & MacMahon, B. (1994). Lactation and a reduced risk of premenopausal breast cancer. *New England Journal of Medicine*, 330(2), 81-87.

If women who do not breastfeed or who breastfed for less than 3 months were to do so for 4 to 12 months, breast cancer among parous premenopausal women could be reduced by 11%. If all women with children lactated for 24 months or longer, the incidence might be reduced by nearly 25%.

Layde, P. M., Webster, L. A., Baughman, A. L., Wingo, P. A., Rubin, G. L., Ory, H. W., & Cancer and Steroid Hormone Study Group. (1989). The independent associations of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. *Journal of clinical epidemiology*, 42(10), 963-973.

After controlling for age at first full term pregnancy and other potentially compounding factors, parity and duration of breastfeeding also had a strong influence on the risk of breast cancer. Compared with parous women who never breastfed, women who had breastfed for 25 months or more had a lower relative risk.

McTIERNAN, A. N. N. E., & Thomas, D. B. (1986). Evidence for a protective effect of lactation on risk of breast cancer in young women: results from a case-control study. *American Journal of Epidemiology*, 124(3), 353-358.

Among both premenopausal and postmenopausal women, risk of breast cancer decreases with increasing duration of lifetime lactation experience although the effect was consistently stronger for premenopausal women.

Endometrial Cancer

Jordan, S. J., Na, R., Johnatty, S. E., Wise, L. A., Adami, H. O., Brinton, L. A., ... & Freudenheim, J. L. (2017). Breastfeeding and endometrial cancer risk: An analysis from the Epidemiology of Endometrial Cancer Consortium. *Obstetrics and gynecology*, 129(6), 1059. The objective of this study was to investigate the association between breastfeeding and endometrial cancer risk using pooled data from 17 studies participating in the Epidemiology of Endometrial Cancer Consortium. We conducted a meta-analysis with individual-level data from three cohort and 14 case-control studies. Study-specific odds ratios (ORs) and 95% confidence

intervals (CI) were estimated for the association between breastfeeding and risk of endometrial cancer using multivariable logistic regression, and pooled using random-effects meta-analysis. We investigated between-study heterogeneity with I^2 and Q statistics and meta-regression. After excluding nulliparous women, the analyses included 8981 women with endometrial cancer and 17241 control women. Ever breastfeeding was associated with an 11% reduction in risk of endometrial cancer (pooled OR=0.89, 95% CI 0.81–0.98). Longer average duration of breastfeeding per child was associated with lower risk of endometrial cancer, although there appeared to be some levelling of this effect beyond 6–9 months. The association with ever breastfeeding was not explained by greater parity and did not vary notably by body mass index or histological subtype (grouped as endometrioid and mucinous versus serous and clear cell). Our findings suggest that reducing endometrial cancer risk can be added to the list of maternal benefits associated with breastfeeding. Ongoing promotion, support and facilitation of this safe and beneficial behavior might therefore contribute to the prevention of this increasingly common cancer.

Wang, L., Li, J., & Shi, Z. (2015). Association between breastfeeding and endometrial cancer risk: evidence from a systematic review and meta-analysis. *Nutrients*, 7(7), 5697-5711. Quantification of the association between breastfeeding and risk of endometrial cancer is still conflicting. We therefore conducted a meta-analysis to assess the association between breastfeeding and endometrial cancer risk. Pertinent studies were identified by a search of PubMed and Web of Knowledge through April 2015. A random effect model was used to combine the data for analysis. Sensitivity analysis and publication bias were conducted. Dose-response relationships were assessed by restricted cubic spline and variance-weighted least squares regression analysis. Fourteen articles involving 5158 endometrial cancer cases and 706,946 participants were included in this meta-analysis. Pooled results suggested that breastfeeding significantly reduced the risk of endometrial cancer (summary relative risk (RR): 0.77, 95% CI: 0.62–0.96, I^2 : 63.0%), especially in North America (summary RR: 0.87, 95% CI: 0.79–0.95). A linear dose-response relationship was found, with the risk of endometrial cancer decreased by 2% for every one-month increase in the duration of breastfeeding (summary RR: 0.98, 95% CI: 0.97–0.99). Our analysis suggested that breastfeeding, particularly a longer duration of breastfeeding, was inversely associated with the risk of endometrial cancer, especially in North America, but not in Europe and Asia, probably due to the small number of cases included. Due to this limitation, further studies originating in other countries are required to assess the association between breastfeeding and endometrial cancer risk.

Pettersson, B., Adami, H. O., Bergström, R., & Johansson, E. D. (1986). Menstruation span—a time-limited risk factor for endometrial carcinoma. *Acta obstetrica et gynecologica Scandinavica*, 65(3), 247-255.

Lactation provides a hypoestrogenic effect with less stimulation of the endometrial lining. This event may offer a protective effect from endometrial cancer.

Esophageal Cancer

Cheng, K. K., Sharp, L., McKinney, P. A., Logan, R. F. A., Chilvers, C. E. D., Cook-Mozaffari, P., ... & Day, N. E. (2000). A case-control study of oesophageal adenocarcinoma in women: a preventable disease. *British journal of cancer*, 83(1), 127.

Breastfeeding was associated with reduced risk of subsequently developing this cancer (OR = 0.41) and there was a significant dose-response effect.

Hodgkin's Disease

Glaser, S. L., Clarke, C. A., Nugent, R. A., Stearns, C. B., & Dorfman, R. F. (2003).

Reproductive factors in Hodgkin's disease in women. *American journal of epidemiology*, 158(6), 553-563.

Breastfeeding was associated with a lower unadjusted risk of Hodgkin's disease, apparently irrespective of parity (for one birth, odds ratio (OR) = 0.6, for two births, OR = 0.8, for three or more births, OR = 0.6) and duration (among nursers, the unadjusted odds ratio for each additional month of lactation was 1.0).

Ovarian Cancer

Wallack, D., Bunker, C. H., Edwards, R. P., Kelley, J. L., Odunsi, K., Moysich, K., ... & Modugno, F. (2018). Abstract PR10: Breastfeeding protects against epithelial ovarian cancer: Results of the HOPE Study.

The objective of this study was to examine the association between breastfeeding patterns and risk of epithelial ovarian cancer. We examined duration, age, and timing factors related to breastfeeding episodes among parous women in a population-based case-control study conducted in western PA, eastern OH, and southwestern NY from 2003-2008 (the HOPE Study). We compared 689 incident cases of epithelial ovarian cancer (EOC) to 1572 community controls frequency-matched to cases by age and three-digit telephone exchange. Multivariable unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for EOC associated with breastfeeding patterns adjusting for age, race, parity, duration of oral contraceptive use, education, tubal ligation, hysterectomy, talc use, and family history of breast or ovarian cancer. Compared to never breastfeeding, breastfeeding any offspring was associated with a significant 28% reduction in EOC risk (OR=0.72; 95% CI=0.58-0.90). That protection appeared to last more than 30 years (OR=0.70, 95%CI=0.54-0.92), although the magnitude of the protection decreased over time (OR=0.54, 0.74, 0.83 and 0.70 for <10, 10-19, 20-19, and 30+ years since last breastfeeding episode, trend p=0.013). Greater number of offspring nursed provided increased protection (OR=0.75, 95%CI=0.60-0.93 and OR=0.44, 95%CI=0.28-0.63 for nursing 1-2 and 3+ offspring, respectively, compared to never breastfed, trend p<0.001). Longer total breastfeeding duration also provided increased protection (OR=0.74 and 0.58 for less than and greater than 1 year total duration, respectively, compared to never breastfed, trend p=0.002). Although there did not appear to be any benefit from longer average duration per episode (OR=0.73 and OR=0.70 for 1-3 and 4 or more months average per episode, respectively), longer duration for both the first (OR=0.75 and OR=0.67 for 1-3 and 4 or more months, respectively, trend p=0.004) and last (OR=0.76 and OR=0.65 for 1-3

and 4 or more months, respectively, trend $p=0.003$) breastfeeding episode provided greater protection. Earlier age at first breastfeeding episode appeared more protective than a later age of first breastfeeding (OR=0.65, 0.73, 0.94, for first episode at age <25, 25-29, and 30+, respectively). Age at last breastfeeding episode did not appear to have a substantial impact on risk (OR=0.67, 0.78, 0.74, for last episode at age <25, 25-29, and 30+, respectively). Breastfeeding is protective against EOC. Although this protection decreases over time, it persists for more than 30 years. Longer total duration and increasing number of offspring nursed increase the protective effect, as does an earlier age at first breastfeeding episode.

Sung, H. K., Ma, S. H., Choi, J. Y., Hwang, Y., Ahn, C., Kim, B. G., ... & Kim, T. J. (2016). The effect of breastfeeding duration and parity on the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *Journal of preventive medicine and public health*, 49(6), 349.

We conducted a systematic review and meta-analysis to summarize current evidence regarding the association of parity and duration of breastfeeding with the risk of epithelial ovarian cancer (EOC). A systematic search of relevant studies published by December 31, 2015 was performed in PubMed and EMBASE. A random-effect model was used to obtain the summary relative risks (RRs) and 95% confidence intervals (CIs). Thirty-two studies had parity categories of 1, 2, and ≥ 3 . The summary RRs for EOC were 0.72 (95% CI, 0.65 to 0.79), 0.57 (95% CI, 0.49 to 0.65), and 0.46 (95% CI, 0.41 to 0.52), respectively. Small to moderate heterogeneity was observed for one birth ($p<0.01$; $Q=59.46$; $I^2=47.9\%$). Fifteen studies had breastfeeding categories of <6 months, 6-12 months, and >13 months. The summary RRs were 0.79 (95% CI, 0.72 to 0.87), 0.72 (95% CI, 0.64 to 0.81), and 0.67 (95% CI, 0.56 to 0.79), respectively. Only small heterogeneity was observed for <6 months of breastfeeding ($p=0.17$; $Q=18.79$, $I^2=25.5\%$). Compared to nulliparous women with no history of breastfeeding, the joint effects of two births and <6 months of breastfeeding resulted in a 0.5-fold reduced risk for EOC. The first birth and breastfeeding for <6 months were associated with significant reductions in EOC risk.

Feng, L. P., Chen, H. L., & Shen, M. Y. (2014). Breastfeeding and the Risk of Ovarian Cancer: A Meta-Analysis. *Journal of midwifery & women's health*, 59(4), 428-437.

The aim of this meta-analysis was to assess the association between breastfeeding and risk of ovarian cancer. Relevant observational studies were identified by a search of the MEDLINE and EMBASE databases through December 2012. Summary odds ratios (ORs) for ovarian cancer, comparing women who had breastfed with women who had not, were calculated using a random-effects model. A dose-response meta-analysis assessed the risk of ovarian cancer by breastfeeding duration. A total of 19 studies were included in the meta-analysis. Compared with women who had not breastfed, women who had breastfed had a significantly decreased risk of ovarian cancer, with an OR of 0.66 (95% CI, 0.57-0.76; $P < .001$). We observed an inverse linear relationship with breastfeeding duration: for every one-month increase in breastfeeding, the OR was 0.98 (95% CI, 0.97-0.99; $P < .001$). A nonlinear association was also apparent, with a sharp decrease in the OR when breastfeeding duration was 8 to 10 months. There was evidence of heterogeneity ($I^2 = 83.9\%$). No publication bias was found (Begg test, $P = 0.89$; Egger test, $P = 0.89$). Breastfeeding reduces the risk of ovarian cancer proportional to duration. Breastfeeding for 8 to 10 months may be most effective for reducing the risk of ovarian cancer.

Li, D. P., Du, C., Zhang, Z. M., Li, G. X., Yu, Z. F., Wang, X., ... & Zhao, Y. S. (2014). Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. *Asian Pac J Cancer Prev*, 15(12), 4829-4837.

The present systematic review and meta-analysis was conducted to assess any association between breastfeeding and the risk of ovarian cancer. A systematic search of published studies was performed in PUBMED and EMBASE and by reviewing reference lists from retrieved articles through March 2013. Data extraction was conducted independently by two authors. Pooled relative risk ratios were calculated using random-effect models. Totals of 5 cohort studies and 35 case-control studies including 17,139 women with ovarian cancer showed a 30% reduced risk of ovarian cancer when comparing the women who had breastfed with those who had never breastfed (pooled RR = 0.70, 95% CI: 0.64-0.76; $p = 0.00$), with significant heterogeneity in the studies ($p = 0.00$; $I^2 = 76.29\%$). A significant decrease in risk of epithelial ovarian cancer was also observed (pooled RR = 0.68, 95% CI: 0.61-0.76). When the participants were restricted to only parous women, there was a slightly attenuated but still significant risk reduction of ovarian cancer (pooled RR = 0.76, 95% CI: 0.69-0.83). For total breastfeeding duration, the pooled RRs in the < 6 months, 6-12 months and > 12 months of breastfeeding subgroups were 0.85 (95% CI: 0.77-0.93), 0.73 (95% CI: 0.65-0.82) and 0.64 (95%CI: 0.56-0.73), respectively. Meta-regression of total breastfeeding duration indicated an increasing linear trend of risk reduction of ovarian cancer with the increasing total breastfeeding duration ($p = 0.00$). Breastfeeding was inversely associated with the risk of ovarian cancer, especially long-term breastfeeding duration that demonstrated a stronger protective effect.

Luan, N. N., Wu, Q. J., Gong, T. T., Vogtmann, E., Wang, Y. L., & Lin, B. (2013). Breastfeeding and ovarian cancer risk: a meta-analysis of epidemiologic studies—. *The American journal of clinical nutrition*, 98(4), 1020-1031.

We performed a meta-analysis to summarize available evidence of the association between breastfeeding and breastfeeding duration and EOC risk from published cohort and case-control studies. Relevant published studies were identified by a search of MEDLINE through December 2012. Two authors (T-TG and Q-JW) independently performed the eligibility evaluation and data abstraction. Study-specific RRs from individual studies were pooled by using a random-effects model, and heterogeneity and publication-bias analyses were conducted. Five prospective and 30 case-control studies were included in this analysis. The pooled RR for ever compared with never breastfeeding was 0.76 (95% CI: 0.69, 0.83), with moderate heterogeneity ($Q = 69.4$, $P < 0.001$, $I^2 = 55.3\%$). Risk of EOC decreased by 8% for every 5-mo increase in the duration of breastfeeding (RR: 0.92; 95% CI: 0.90, 0.95). The risk reduction was similar for borderline and invasive EOC and was consistent within case-control and cohort studies. Results of this meta-analysis support the hypothesis that ever-breastfeeding and a longer duration of breastfeeding are associated with lower risks of EOC. Additional research is warranted to focus on the association with cancer grade and histologic subtypes of EOC.

Jordan, S. J., Cushing-Haugen, K. L., Wicklund, K. G., Doherty, J. A., & Rossing, M. A. (2012). Breast-feeding and risk of epithelial ovarian cancer. *Cancer Causes & Control*, 23(6), 919-927. Data from participants in a population-based study of ovarian cancer in western Washington State, USA (2002-2007) who had had at least one birth (881 cases and 1,345 controls) were

used to assess relations between patterns of breast-feeding and ovarian cancer. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Women who ever breast-fed had a 22 % reduction in risk of ovarian cancer compared with those who never breast-fed (OR = 0.78, 95% CI 0.64-0.96) and risk reduction appeared greater with longer durations of feeding per child breast-fed (OR = 0.56, 95% CI 0.32- 0.98 for 18 months average duration breast-feeding versus none). Introduction of supplementary feeds did not substantially alter these effects. The overall risk reduction appeared greatest for the endometrioid and clear cell subtypes (OR per month of average breast-feeding per child breast-fed = 0.944, 95% CI 0.903-0.987). Among women who have had the opportunity to breast-feed, ever breast-feeding and increasing durations of episodes of breast-feeding for each breast-fed child are associated with a decrease in the risk of ovarian cancer independent of numbers of births, which may be strongest for the endometrioid subtype.

Zhang, M., Xie, X., Lee, A. H., & Binns, C. W. (2004). Prolonged lactation reduces ovarian cancer risk in Chinese women. *European journal of cancer prevention*, 13(6), 499-502. To investigate the effect of lactation on the risk of ovarian cancer for Chinese women, a case-control study was conducted. Cases were 275 patients with histologically confirmed epithelial ovarian cancer. Controls were 623 women without neoplasm. Multivariate logistic regression models were used to assess the association between ovarian cancer risk and lactation variables, accounting for age, locality, full-term pregnancy, oral contraceptive use and family history of the cancer. The adjusted odds ratios were 0.51 and 0.44 respectively for women with over 12 months of lactation and at least three children breastfed, compared with those with 4 months or less lactation and one child breastfed. The corresponding dose-response relationships were also significant ($P < 0.05$). Therefore, prolonged lactation could reduce the risk of ovarian cancer for Chinese women.

Zhang, M., Lee, A. H., & Binns, C. W. (2004). Reproductive and dietary risk factors for epithelial ovarian cancer in China. *Gynecologic oncology*, 92(1), 320-326. A case-control study was conducted to investigate the effects of reproductive and dietary risk factors on ovarian cancer risk in China. Cases were 254 patients with histologically confirmed epithelial ovarian cancer. Controls were 652 women without neoplasm and long-term dietary modifications. The adjusted odds ratios (OR) for women having at least two full-term pregnancies, two or more incomplete pregnancies, and first full-term pregnancy at 21-25 years of age were 0.45, 0.56, and 0.40, respectively, compared with nulliparity. The OR of ever lactation was 0.50 and oral contraceptive was 0.48, while postmenopausal women appeared to have an increased risk with OR 1.48. For the highest versus the lowest quartile intakes of nutrients, the OR were 2.17 for fat, 0.36 for fibre, 0.26 for carotene, 1.59 for retinol, 0.31 for vitamin C, and 0.41 for vitamin E, with significant dose-response relationships. Conclusion. It is evident that full-term and incomplete pregnancies, lactation, and oral contraceptive use can reduce the ovarian cancer risk. Moreover, consumption of foods low in fat but high in fibre, carotene and vitamins appears to be protective against ovarian cancer in Chinese women.

Tung, K. H., Goodman, M. T., Wu, A. H., McDuffie, K., Wilkens, L. R., Kolonel, L. N., ... & Sobin, L. H. (2003). Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study. *American Journal of Epidemiology*, 158(7), 629-638.

In this multiethnic, population-based, case-control study, conducted in Hawaii and Los Angeles, California, a structured questionnaire was given to 558 histologically confirmed epithelial ovarian cancer cases and 607 population controls. Duration of breastfeeding (odds ratio = 0.4 for the highest vs. the lowest quartile) was significantly and inversely related to non-mucinous tumors but not to mucinous tumors.

Greggi, S., Parazzini, F., Paratore, M. P., Chatenoud, L., Legge, F., Mancuso, S., & La Vecchia, C. (2000). Risk factors for ovarian cancer in central Italy. *Gynecologic oncology*, 79(1), 50-54.

This case-control study analyzed risk factors for ovarian cancer. Cases included 440 women (age range 13-80 years) with a histologically confirmed diagnosis of epithelial ovarian cancer. Breastfeeding for more than 1 year was associated with an OR of 0.5.

Titus-Ernstoff, L., Perez, K., Cramer, D. W., Harlow, B. L., Baron, J. A., & Greenberg, E. R. (2001). Menstrual and reproductive factors in relation to ovarian cancer risk. *British journal of cancer*, 84(5), 714.

563 cases in Massachusetts and New Hampshire were ascertained from hospitals and statewide tumour registries; control women (n = 523) were selected randomly and matched to case women. Ovarian cancer risk was reduced among parous women, relative to nulliparous women (OR = 0.4). Among parous women, higher parity (P = 0.0006), increased age at first (P = 0.03) or last (P = 0.05) birth, and time since last birth (P = 0.04) were associated with reduced risk. Early pregnancy losses, abortions, and stillbirths were unrelated to risk, but preterm, term, and twin births were protective. Risk was lower among women who had breast-fed. relative to those who had not (OR = 0.7), but the average duration of breast-feeding per child was unrelated to risk. Age at menarche and age at menopause were unrelated to risk overall, although increasing menarcheal age was protective among premenopausal women (P = 0.02). Menstrual cycle characteristics and symptoms were generally unrelated to risk, although cycle-related insomnia was associated with decreased risk (OR = 0.5). No association was found between the type of sanitary product used during menstruation and ovarian cancer risk. In analyses by histologic subtype, reproductive and menstrual factors had most effect on risk of endometrioid/clear cell tumours, and least influential with regard to risk of mucinous tumours.

Siskind, V., Green, A., Bain, C., & Purdie, D. (1997). Breastfeeding, menopause, and epithelial ovarian cancer. *Epidemiology*, 188-191.

Cases 20-69 years of age with a recent diagnosis of epithelial ovarian cancer (767) were compared with community controls (1367). A number of reproductive and contraceptive factors that suppress ovulation, including gravidity, breastfeeding, and oral contraception, reduced the risk of ovarian cancer. Environmental factors and medical conditions that increased risk included talc use, endometriosis, ovarian cysts, and hyperthyroidism. Gynecologic surgery including hysterectomy and tubal ligation were protective. Ness-RB et al. "Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer." *Epidemiology*-. Mar 2000; 11

(2) : 111-117 Breastfeeding seems to be somewhat protective against ovarian cancer, but only before menopause.

John, E. M., Whittemore, A. S., Harris, R., Itnyre, J., & Collaborative Ovarian Cancer Group. (1993). Characteristics relating to ovarian cancer risk: collaborative analysis of seven US case-control studies. Epithelial ovarian cancer in black women. *JNCI: Journal of the National Cancer Institute*, 85(2), 142-147.

Decreased risks of epithelial ovarian cancer in black women were associated with parity of four or higher, breast-feeding for 6 months or longer, and use of oral contraceptives for 6 years or longer.

Gwinn, M. L., Lee, N. C., Rhodes, P. H., Layde, P. M., & Rubin, G. L. (1990). Pregnancy, breast feeding, and oral contraceptives and the risk of epithelial ovarian cancer. *Journal of clinical epidemiology*, 43(6), 559-568.

A marked reduction in risk was associated with ever having breast fed.

Schneider 2nd, A. P. (1987). Risk factor for ovarian cancer. *The New England journal of medicine*, 317(8), 508.

Breastfeeding should be added to the list of factors that decrease ovulatory age and thereby decrease the risk of ovarian cancer.

Thyroid Cancer

Yi, X., Zhu, J., Zhu, X., Liu, G. J., & Wu, L. (2016). Breastfeeding and thyroid cancer risk in women: A dose-response meta-analysis of epidemiological studies. *Clinical Nutrition*, 35(5), 1039-1046.

The association between breastfeeding and thyroid cancer risk is not consistent from epidemiological studies. To better clarify the association including assessing a potential dose-response relationship, we conducted a comprehensive meta-analysis. We searched PubMed (MEDLINE) up to November 2015 for prospective studies or case-control studies that evaluated the association between breastfeeding and risk of thyroid cancer. Effect estimates were pooled using a fixed-effects model. Nine reports (2 prospective studies, 6 case-control studies and 1 pooled analysis of 14 case-control studies) involving 2423 cases and 350,081 non-cases were identified. After pooling relevant studies, there was a significant inverse association between ever breastfeeding and risk of thyroid cancer (RR = 0.91, 95% CI 0.83–0.99), with minor heterogeneity ($I^2 = 10.1\%$). The dose-response analysis revealed a significant linear relationship between the duration of breastfeeding and risk of thyroid cancer. The summary RR for an increment of 1 month of breastfeeding with risk of thyroid cancer was 0.983 (95% CI 0.98–0.99). When focusing on cohort studies, a more prominent linear dose-response relationship was detected, with the combined RR for every increment of 1 month of breastfeeding to be 0.965 (95% CI 0.96–0.97). This meta-analysis suggests that breastfeeding is potentially inversely associated with thyroid cancer risk. Also longer duration of breastfeeding may further decrease thyroid cancer risk. If validated in large-scale prospective studies, our findings may have implications for impacting women's decision in breastfeeding.

Cao, Y., Wang, Z., Gu, J., Hu, F., Qi, Y., Yin, Q., ... & Quan, B. (2015). Reproductive factors but not hormonal factors associated with thyroid cancer risk: a systematic review and meta-analysis. *BioMed research international*, 2015.

Many studies have investigated the association between hormonal and reproductive factors and thyroid cancer risk but provided contradictory and inconclusive findings. This review was aimed at precisely estimating this association by pooling all available epidemiological studies. 25 independent studies were retrieved after a comprehensive literature search in databases of PubMed and Embase. Overall, common hormonal factors including oral contraceptive and hormone replacement therapy did not alter the risk of thyroid cancer. Older age at menopause was associated with weakly increased risk of thyroid cancer in overall analysis (RR = 1.24, 95% CI 1.00–1.53,); however, longer duration of breast feeding was related to moderately reduced risk of thyroid cancer, suggested by pooled analysis in all cohort studies (RR = 0.7, 95% CI 0.51–0.95,). The pooled RR in hospital-based case-control studies implicated that parous women were more susceptible to thyroid cancer than nulliparous women (RR = 2.30, 95% CI 1.31–4.04,). The present meta-analysis suggests that older age at menopause and parity are risk factors for thyroid cancer, while longer duration of breast feeding plays a protective role against this cancer. Nevertheless, more relevant epidemiological studies are warranted to investigate roles of hormonal and reproductive factors in thyroid carcinogenesis.

Mack, W. J., Preston-Martin, S., Bernstein, L., Qian, D., & Xiang, M. (1999). Reproductive and hormonal risk factors for thyroid cancer in Los Angeles County females. *Cancer Epidemiology and Prevention Biomarkers*, 8(11), 991-997.

Individually matched case-control study (292 pairs) of female thyroid cancer patients found that risk increased with number of pregnancies in women using lactation suppressants and decreased with duration of breastfeeding.

Uterine Cancer

Brock, K. E., Berry, G., Brinton, L. A., Kerr, C., MacLennan, R., Mock, P. A., & Shearman, R. P. (1989). Sexual, reproductive and contraceptive risk factors for carcinoma-in-situ of the uterine cervix in Sydney. *The Medical Journal of Australia*, 150(3), 125-130.

A protective effect against uterine cancer was found for women who breastfeed.

CARDIOVASCULAR HEALTH

Tschiderer, L., Seekircher, L., Kunutsor, S. K., Peters, S. A., O'Keeffe, L. M., & Willeit, P. (2022). Breastfeeding Is Associated With a Reduced Maternal Cardiovascular Risk: Systematic Review and Meta-Analysis Involving Data From 8 Studies and 1 192 700 Parous Women. *Journal of the American Heart Association*, 11(2), e022746.

Breastfeeding has been robustly linked to reduced maternal risk of breast cancer, ovarian cancer, and type 2 diabetes. We herein systematically reviewed the published evidence on the association of breastfeeding with maternal risk of cardiovascular disease (CVD) outcomes. METHODS AND RESULTS:

Our systematic search of PubMed and Web of Science of articles published up to April 16, 2021, identified 8 relevant prospective studies involving 1 192 700 parous women (weighted mean age: 51.3 years at study entry, 24.6 years at first birth; weighted mean number of births: 2.3). A total of 982 566 women (82%) reported having ever breastfed (weighted mean lifetime duration of breastfeeding: 15.6 months). During a weighted median follow-up of 10.3 years, 54 226 CVD, 26 913 coronary heart disease, 30 843 stroke, and 10 766 fatal CVD events were recorded. In a random-effects metaanalysis, the pooled multivariable-adjusted hazard ratios comparing parous women who ever breastfed to those who never breastfed were 0.89 for CVD (95% CI, 0.83–0.95; I²=79.4%), 0.86 for coronary heart disease (95% CI, 0.78–0.95; I²=79.7%), 0.88 for stroke (95% CI, 0.79–0.99; I²=79.6%), and 0.83 for fatal CVD (95% CI, 0.76–0.92; I²=47.7%). The quality of the evidence assessed with the Grading of Recommendations Assessment, Development, and Evaluation tool ranged from very low to moderate, which was mainly driven by high between-studies heterogeneity. Strengths of associations did not differ by mean age at study entry, median follow-up duration, mean parity, level of adjustment, study quality, or geographical region. A progressive risk reduction of all CVD outcomes with lifetime durations of breastfeeding from 0 up to 12 months was found, with some uncertainty about shapes of associations for longer durations. CONCLUSIONS: Breastfeeding was associated with reduced maternal risk of CVD outcomes.

Kirkegaard, H., Bliddal, M., Støvring, H., Rasmussen, K. M., Gunderson, E. P., Køber, L., ... & Nohr, E. A. (2018). Breastfeeding and later maternal risk of hypertension and cardiovascular disease—The role of overall and abdominal obesity. *Preventive medicine*, 114, 140-148.

In this study, we examined how any, full, and partial breastfeeding durations were associated with maternal risk of hypertension and cardiovascular disease (CVD), and how prepregnancy body mass index (BMI) and waist circumference 7 years postpartum influenced these associations. A total of 63,260 women with live-born singleton infants in the Danish National Birth Cohort (1996–2002) were included. Interviews during pregnancy and 6 and 18 months postpartum provided information on prepregnancy weight, height, and the duration of full and partial breastfeeding. Waist circumference was self-reported 7 years postpartum. Cox regression models were used to estimate hazard ratios of incident hypertension and CVD, registered in the National Patient Register from either 18 months or 7 years postpartum through 15 years postpartum. Any breastfeeding ≥ 4 months was associated with 20–30% lower risks of hypertension and CVD compared to < 4 months in both normal/underweight and overweight/obese women. At follow-up starting 7 years postpartum, similar risk reductions were observed after accounting for waist circumference adjusted for BMI. Partial breastfeeding > 2 months compared to ≤ 2 months, following up to 6 months of full breastfeeding, was associated with 10–25% lower risk of hypertension and CVD. Compared with short breastfeeding duration, additional partial breastfeeding was as important as additional full breastfeeding in reducing risk of hypertension and CVD. Altogether, longer duration of breastfeeding was associated with lower maternal risk of hypertension and CVD irrespective of prepregnancy BMI and abdominal adiposity 7 years after delivery. Both full and partial breastfeeding contributed to an improved cardiovascular health in mothers.

Nguyen, B., Gale, J., Nassar, N., Bauman, A., Joshy, G., & Ding, M. (2018). Breastfeedings and cardiovascular disease hospitalisation and mortality in mothers from a large Australian cohort study. *Revue d'Épidémiologie et de Santé Publique*, 66, S310.

There is growing evidence that breastfeeding has short- and long-term maternal cardiovascular health benefits. However, few studies have investigated the longitudinal association between

breastfeeding and maternal cardiovascular disease (CVD) outcomes. This study aimed to examine the association between breastfeeding and (1) CVD hospitalisation, and (2) CVD mortality in a large Australian cohort. Baseline questionnaire data (2006–2008) from a sample of 100,864 parous women aged ≥ 45 years from New South Wales, Australia, were linked to hospitalisation and death data until June 2014 and December 2013, respectively. CVD hospitalisation was based on the first CVD-related hospitalisation since baseline in women without self-reported medically diagnosed CVD at baseline or without prior CVD hospitalisation in the six years prior to study entry. Self-reported lifetime breastfeeding duration was categorised as: never breastfed, > 0 –6 months, > 6 –12 months, > 12 –24 months and ≥ 24 months. Ever versus never breastfeeding was also compared. Cox proportional hazard models were used to explore the association between breastfeeding and CVD outcomes. Covariates included sociodemographic characteristics, lifestyle risk factors, and medical and reproductive history. There were 3,428 (3.4%) first CVD-related hospital admissions and 418 (0.4%) deaths during a mean follow-up time of 6.1 years for CVD hospitalisation, and 5.7 years for CVD mortality. In the unadjusted and fully-adjusted models, ever breastfeeding was associated with lower risks of CVD hospitalisation and CVD mortality compared to never breastfeeding (all $P < 0.01$). Longer duration of lifetime breastfeeding was associated with lower risk of CVD hospitalisation and mortality in the unadjusted model only (P for trend < 0.05) with no significant linear trend in the fully-adjusted models. There was no evidence of effect modification by age, parity, time since last birth or smoking (P for interaction > 0.1). Ever-breastfeeding, and to some extent lifetime breastfeeding duration, are associated with lower maternal risk of CVD hospitalisation and mortality in this large cohort of middle-aged and older Australian women. Breastfeeding may offer long-term maternal cardiovascular health benefits.

Qu, G., Wang, L., Tang, X., Wu, W., & Sun, Y. (2018). Association between duration of breastfeeding and maternal hypertension: a systematic review and meta-analysis. *Breastfeeding Medicine*, 13(5), 318–326. Recently, an increasing number of studies have implied that breastfeeding has a protective effect on maternal hypertension, but it remains controversial. The aim of this study is to evaluate the effect of breastfeeding on maternal hypertension through meta-analysis. Eligible studies were searched and identified in various databases. Meta-analysis was conducted to assess the association between the duration of breastfeeding and maternal hypertension. Seven eligible studies that contained 444,759 participants were included in our study. Meta-analysis of these seven studies showed a significant protective effect of breastfeeding on maternal hypertension. Specifically, pooled odds ratios (ORs) of hypertension for >0 –6, >6 –12, and >12 months of breastfeeding were 0.92 (95% confidence interval [CI]: 0.88–0.96, $I^2 = 67.5\%$), 0.89 (95% CI: 0.86–0.92, $I^2 = 0$), and 0.88 (95% CI: 0.84–0.93, $I^2 = 43.9\%$), respectively, compared with non-breastfeeding mothers, and the pooled OR of hypertension was 0.93 (95% CI: 0.91–0.95, $I^2 = 40.8\%$) for women who breastfed compared with women who had not. Furthermore, the pooled hazard ratio of hypertension was 1.34 (95% CI: 1.17–1.52, $I^2 = 58.7\%$) for women who did not breastfeed compared with women who breastfed for more than 12 months for their first child. Different durations of breastfeeding have different protective effects against the development of maternal hypertension, and breastfeeding for >12 months has a better effect than <12 months.

Nguyen, B., Jin, K., & Ding, D. (2017). Breastfeeding and maternal cardiovascular risk factors and outcomes: A systematic review. *PloS one*, 12(11), e0187923.

There is growing evidence that breastfeeding has short- and long-term cardiovascular health benefits for mothers. The objectives of this systematic review were to examine the association between breastfeeding and maternal cardiovascular risk factors and outcomes that have not previously been synthesized systematically, including metabolic syndrome, hypertension and cardiovascular disease. This systematic review meets PRISMA guidelines. The MEDLINE, EMBASE and CINAHL databases were systematically searched for relevant publications of any study design from the earliest publication date to March 2016. The reference lists from selected articles were reviewed, and forward and backward referencing were conducted. The methodological quality of reviewed articles was appraised using validated checklists. Twenty-one studies meeting the inclusion criteria examined the association between self-reported breastfeeding and one or more of the following outcomes: metabolic syndrome/metabolic risk factors (n = 10), inflammatory markers/adipokines (n = 2), hypertension (n = 7), subclinical cardiovascular disease (n = 2), prevalence/incidence of cardiovascular disease (n = 3) and cardiovascular disease mortality (n = 2). Overall, 19 studies (10 cross-sectional/retrospective, 9 prospective) reported significant protective effects of breastfeeding, nine studies (3 cross-sectional/retrospective, 5 prospective, 1 cluster randomized controlled trial) reported non-significant findings and none reported detrimental effects of breastfeeding. In most studies reporting significant associations, breastfeeding remained associated with both short- and long-term maternal cardiovascular health risk factors/outcomes, even after covariate adjustment. Findings from several studies suggested that the effects of breastfeeding may diminish with age and a dose-response association between breastfeeding and several metabolic risk factors. However, further longitudinal studies, including studies that measure exclusive breastfeeding, are needed to confirm these findings. The evidence from this review suggests that breastfeeding is associated with cardiovascular health benefits. However, results should be interpreted with caution as the evidence gathered for each individual outcome was limited by the small number of observational studies. Additional prospective studies are needed.

Peters, S. A., Yang, L., Guo, Y., Chen, Y., Bian, Z., Du, J., ... & Chen, Z. (2017). Breastfeeding and the risk of maternal cardiovascular disease: a prospective study of 300 000 Chinese women. *Journal of the American Heart Association*, 6(6), e006081.

Breastfeeding confers substantial benefits to child health and has also been associated with lower risk of maternal cardiovascular diseases (CVDs) in later life. However, the evidence on the effects of CVD is still inconsistent, especially in East Asians, in whom the frequency and duration of breastfeeding significantly differ from those in the West. In 2004–2008, the nationwide China Kadoorie Biobank recruited 0.5 million individuals aged 30 to 79 years from 10 diverse regions across China. During 8 years of follow-up, 16 671 incident cases of coronary heart disease and 23 983 cases of stroke were recorded among 289 573 women without prior CVD at baseline. Cox regression yielded adjusted hazard ratios (HRs) and 95% CIs for incident CVD by breastfeeding. Overall, ≈99% of women had given birth, among whom 97% reported a history of breastfeeding, with a median duration of 12 months per child. Compared with parous women who had never breastfed, ever breastfeeding was associated with a significantly lower risk of CVD, with adjusted HRs of 0.91 (95% CI, 0.84–0.99) for coronary heart disease and 0.92

(95% CI, 0.85–0.99) for stroke. Women who had breastfed for ≥ 24 months had an 18% (HR, 0.82; 0.77–0.87) lower risk of coronary heart disease and a 17% (HR, 0.83; 0.79–0.87) lower risk of stroke compared with women who had never breastfed. Among women who ever breastfed, each additional 6 months of breastfeeding per child was associated with an adjusted HR of 0.96 (95% CI, 0.94–0.98) for coronary heart disease and 0.97 (95% CI, 0.96–0.98) for stroke. Among Chinese women, a history of breastfeeding was associated with an $\approx 10\%$ lower risk of CVD in later life and the magnitude of the inverse association was stronger among those with a longer duration of breastfeeding.

Wiklund, P., Xu, L., Lyytikäinen, A., Saltevo, J., Wang, Q., Völgyi, E., ... & Cheng, S. (2012). Prolonged breast-feeding protects mothers from later-life obesity and related cardio-metabolic disorders. *Public health nutrition*, 15(1), 67-74.

Retrospective study in Finland of 212 women (mean age 48, range 36–60 years) to investigate the long-term effects of duration of postpartum lactation on maternal body composition and risk for cardio-metabolic disorders in later life. Body composition was measured using dual-energy X-ray absorptiometry and serum glucose, insulin and lipids were analyzed using enzymatic photometric methods 16–20 years after the last pregnancy. Medical history and lifestyle factors were collected via a self-administered questionnaire. Detailed information regarding weight change patterns during each pregnancy was obtained from personal maternity tracking records. At 16–20 years after their last pregnancy, women who had breast-fed for less than 6 months had higher total body fat mass and fat mass percentage, particularly in the android region (46.5 (sd 8.2) %) than mothers who had breast-fed for longer than 6 months (39.0 (sd 10.2) %) or for longer than 10 months (38.4 (sd 10.9) %, $P < 0.01$). These differences were independent of pre-pregnancy weight and BMI, menopausal status, smoking status, level of education, participation in past and present leisure-time physical activity, and current dietary energy intake. Higher body fat mass was also associated with higher fasting serum glucose concentration and insulin resistance, TAG, LDL cholesterol and total cholesterol concentrations, as well as higher systolic and diastolic blood pressure ($P < 0.05$ for all). Conclusions Short duration of breast-feeding may induce weight retention and fat mass accumulation, resulting in increased risk of cardiometabolic disorders in later life.

Stuebe, A. M., Schwarz, E. B., Grewen, K., Rich-Edwards, J. W., Michels, K. B., Foster, E. M., ... & Forman, J. (2011). Duration of lactation and incidence of maternal hypertension: a longitudinal cohort study. *American journal of epidemiology*, 174(10), 1147-1158.

Never or curtailed lactation has been associated with an increased risk for incident hypertension, but the effect of exclusive breastfeeding is unknown. The authors conducted an observational cohort study of 55,636 parous women in the US Nurses' Health Study II. From 1991 to 2005, participants reported 8,861 cases of incident hypertension during 660,880 person-years of follow-up. Never or curtailed lactation was associated with an increased risk of incident hypertension. Compared with women who breastfed their first child for ≥ 12 months, women who did not breastfeed were more likely to develop hypertension (hazard ratio (HR) = 1.27, 95% confidence interval (CI): 1.18, 1.36), adjusting for family history and lifestyle covariates. Women who never breastfed were more likely to develop hypertension than women who exclusively breastfed their first child for ≥ 6 months (HR = 1.29, 95% CI: 1.20, 1.40). The

authors found similar results for women who had never breastfed compared with those who had breastfed each child for an average of ≥ 12 months (HR = 1.22, 95% CI: 1.13, 1.32). In conclusion, never or curtailed lactation was associated with an increased risk of incident maternal hypertension, compared with the recommended ≥ 6 months of exclusive or ≥ 12 months of total lactation per child, in a large cohort of parous women.

Schwarz, E. B., Ray, R. M., Stuebe, A. M., Allison, M. A., Ness, R. B., Freiberg, M. S., & Cauley, J. A. (2009). Duration of lactation and risk factors for maternal cardiovascular disease. *Obstetrics and gynecology*, 113(5), 974.

To examine dose-response relationships between the cumulative number of months women lactated and postmenopausal risk factors for cardiovascular disease. METHODS: We examined data from 139,681 postmenopausal women (median age 63 years) who reported at least one live birth on enrolling in the Women's Health Initiative observational study or controlled trials. Multivariable models were used to control for sociodemographic (age, parity, race, education, income, age at menopause), lifestyle, and family history variables when examining the effect of duration of lactation on risk factors for cardiovascular disease, including obesity (body mass index [BMI] at or above 30), hypertension, self-reported diabetes, hyperlipidemia, and prevalent and incident cardiovascular disease. RESULTS: Dose-response relationships were seen; in fully adjusted models, women who reported a lifetime history of more than 12 months of lactation were less likely to have hypertension (odds ratio [OR] 0.88, $P < 0.001$), diabetes (OR 0.80, $P < 0.001$), hyperlipidemia (OR 0.81, $P < 0.001$), or cardiovascular disease (OR 0.91, $P = 0.008$) than women who never breast-fed, but they were not less likely to be obese. In models adjusted for all above variables and BMI, similar relationships were seen. Using multivariate adjusted prevalence ratios from generalized linear models, we estimate that among parous women who did not breast-feed compared with those who breast-fed for more than 12 months, 42.1% versus 38.6% would have hypertension, 5.3% versus 4.3% would have diabetes, 14.8% versus 12.3% would have hyperlipidemia, and 9.9% versus 9.1% would have developed cardiovascular disease when postmenopausal. Over an average of 7.9 years of postmenopausal participation in the Women's Health Initiative, women with a single live birth who breast-fed for 7-12 months were significantly less likely to develop cardiovascular disease (hazard ratio 0.72, 95% confidence interval 0.53-0.97) than women who never breast-fed. CONCLUSION: Among postmenopausal women, increased duration of lactation was associated with a lower prevalence of hypertension, diabetes, hyperlipidemia, and cardiovascular disease.

Stuebe, A. M., Michels, K. B., Willett, W. C., Manson, J. E., Rexrode, K., & Rich-Edwards, J. W. (2009). Duration of lactation and incidence of myocardial infarction in middle to late adulthood. *American journal of obstetrics and gynecology*, 200(2), 138-e1.

We assessed the relation between duration of lactation and maternal incident myocardial infarction. STUDY DESIGN: This was a prospective cohort study of 89,326 parous women in the Nurses' Health Study. RESULTS: During 1,350,965 person-years of follow-up, 2540 cases of coronary heart disease were diagnosed. Compared with parous women who had never breastfed, women who had breastfed for a lifetime total of 2 years or longer had 37% lower risk of coronary heart disease (95% confidence interval, 23-49%; P for trend $< .001$), adjusting for age, parity, and stillbirth history. With additional adjustment for early-adult adiposity, parental

history, and lifestyle factors, women who had breastfed for a lifetime total of 2 years or longer had a 23% lower risk of coronary heart disease (95% confidence interval, 6-38%; P for trend = .02) than women who had never breastfed. CONCLUSION: In a large, prospective cohort, long duration of lactation was associated with a reduced risk of coronary heart disease.

Lee, S. Y., Kim, M. T., Jee, S. H., & Yang, H. P. (2005). Does long-term lactation protect premenopausal women against hypertension risk? A Korean women's cohort study. *Preventive medicine*, 41(2), 433-438.

Little is known about the long-term effect of lactation on maternal cardiovascular health except for a few animal or human experimental studies. The objective of this study was to examine the effects of lactation on the incidence of hypertension in premenopausal women. METHODS: The data were derived from a cohort study with 6 years follow-up (1995-2000). The cohort was composed of 177,749 Korean premenopausal women, aged 20-59, who had medical evaluations in 1992 and 1994. During the follow-up, blood pressure was measured as part of the 1996, 1998, and 2000 periodic examinations. RESULTS: In multivariate Cox proportional hazard models, lactation decreased the risk of hypertension (risk ratio, 0.92; 95% confidence interval, 0.90-0.96). Compared with women who with no history of lactation, 1-6 months of lactation decreased the risk of hypertension (RR, 0.90; 95% CI, 0.87-0.93), as did 7-12 months (RR, 0.92; 95% CI, 0.87-0.98) or 13-18 months (RR, 0.93; 95% CI, 0.86-0.99). In particular, the coexistence of obesity and no lactation increased the risk of hypertension (P for interaction = 0.028). CONCLUSION: This finding suggests that lactation may be a protective factor against hypertension among premenopausal women.

Mezzacappa, E. S., Kelsey, R. M., Myers, M. M., & Katkin, E. S. (2001). Breast-feeding and maternal cardiovascular function. *Psychophysiology*, 38(6), 988-997.

Groups of breastfeeding and bottle-feeding women were compared on pre-ejection period (PEP), heart rate (HR), cardiac output (CO), and total peripheral resistance (TPR) recorded for 1-minute periods before and during standard laboratory stressors. Compared with bottle-feeders, breastfeeders had higher CO throughout the session, and greater decreases in CO and increases in TPR during cold pressor. In a second experiment, HR and blood pressure (BP) were compared before and after one breastfeeding and one bottle-feeding session in a within-subjects design. Both studies support the notion that breast-feeding alters maternal cardiovascular function, possibly through the actions of oxytocin.

DIABETES AND METABOLIC DISEASE

Corrado, F., Giunta, L., Granese, R., Corrado, S., Micali, M., Santamaria, A., ... & Di Benedetto, A. (2019). Metabolic effects of breastfeeding in women with previous gestational diabetes diagnosed according to the IADPSG criteria. *The Journal of Maternal-Fetal & Neonatal Medicine*, 32(2), 225-228.

The aim of our study is to confirm whether the positive effects reported are maintained in the larger cohorts of patients with mild form of gestational diabetes mellitus (GDM) because recently diagnosed according to IADPSG criteria. This retrospective study includes 97 evaluable

consecutive women with prior GDM who have the follow-up oral glucose tolerance test at least 3 months after delivery. Fasting and 2-h plasma glucose values, homeostasis model assessment (HOMA-IR), total cholesterol, and triglycerides were obtained in pregnancy and during the postpartum control. These patients were divided in 81 (83.5%) who lactate until 3 months and 16 (16.5%) who did not lactate. During pregnancy, there are no significant differences between the two groups for age, BMI, fasting and 2-h plasma glucose values, HOMA-IR, total cholesterol and triglycerides. At the postpartum control, we have at univariate analysis significant differences for all these parameters except total cholesterol. After adjustment for confounders we still have, in the breastfeeding group, HOMA-IR reduction (OR 0.370; 95% CI 0.170–0.805; $p < .01$) as significant independent variable, whose improvement is the most acknowledged important factor for the prevention of abnormal glucose tolerance later in life. These encouraging results confirm our determination to warmly advice the women affected by GDM to breastfeeding at least for 3 months.

Chowdhury, R., Sinha, B., Sankar, M. J., Taneja, S., Bhandari, N., Rollins, N., ... & Martines, J. (2015). Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. *Acta Paediatrica*, 104, 96-113.

A systematic literature search was conducted in PubMed, Cochrane Library and CABI databases. Outcome estimates of odds ratios or relative risks or standardised mean differences were pooled. In cases of heterogeneity, subgroup analysis and meta-regression were explored. Breastfeeding >12 months was associated with reduced risk of breast and ovarian carcinoma by 26% and 37%, respectively. No conclusive evidence of an association between breastfeeding and bone mineral density was found. Breastfeeding was associated with 32% lower risk of type 2 diabetes. Exclusive breastfeeding and predominant breastfeeding were associated with longer duration of amenorrhoea. Shorter duration of breastfeeding was associated with higher risk of postpartum depression. Evidence suggesting an association of breastfeeding with postpartum weight change was lacking. This review supports the hypothesis that breastfeeding is protective against breast and ovarian carcinoma, and exclusive breastfeeding and predominant breastfeeding increase the duration of lactational amenorrhoea. There is evidence that breastfeeding reduces the risk of type 2 diabetes. However, an association between breastfeeding and bone mineral density or maternal depression or postpartum weight change was not evident.

Aune, D., Norat, T., Romundstad, P., & Vatten, L. J. (2014). Breastfeeding and the maternal risk of type 2 diabetes: A systematic review and dose–response meta-analysis of cohort studies. *Nutrition, Metabolism and Cardiovascular Diseases*, 24(2), 107-115.

Breastfeeding has been associated with reduced risk of maternal type 2 diabetes in some cohort studies, but the evidence from published studies have differed with regard to the strength of the association. To clarify this association we conducted a systematic review and dose–response meta-analysis of breastfeeding and maternal risk of type 2 diabetes. We conducted a systematic review and dose–response meta-analysis of prospective studies of breastfeeding and maternal risk of type 2 diabetes. We searched the PubMed, Embase and Ovid databases up to September 19th 2013. Summary relative risks were estimated using a random effects model. Six cohort studies including 10,842 cases among 273,961 participants were included in

the meta-analysis. The summary RR for the highest duration of breastfeeding vs. the lowest was 0.68 (95% CI: 0.57–0.82, I² = 75%, heterogeneity = 0.001, n = 6). The summary RR for a three month increase in the duration of breastfeeding per child was 0.89 (95% CI: 0.77–1.04, I² = 93%, heterogeneity < 0.0001, n = 3) and the summary RR for a one year increase in the total duration of breastfeeding was 0.91 (95% CI: 0.86–0.96, I² = 81%, heterogeneity = 0.001, n = 4). There was little difference in the summary estimates whether or not BMI had been adjusted for. The inverse associations appeared to be nonlinear, nonlinearity < 0.0001 for both analyses, and in both analyses the reduction in risk was steeper when increasing breastfeeding from low levels. This meta-analysis suggests that there is a statistically significant inverse association between breastfeeding and maternal risk of type 2 diabetes.

Gunderson, E. P. (2014). Impact of breastfeeding on maternal metabolism: implications for women with gestational diabetes. *Current diabetes reports*, 14(2), 460.

Lactating women compared with nonlactating women display more favorable metabolic parameters, including less atherogenic blood lipids, lower fasting and postprandial blood glucose as well as insulin, and greater insulin sensitivity in the first 4 months postpartum. However, direct evidence demonstrating that these metabolic changes persist from delivery to postweaning is much less available. Studies have reported that longer lactation duration may reduce long-term risk of cardiometabolic disease, including type 2 diabetes, but findings from most studies are limited by self-report of disease outcomes, absence of longitudinal biochemical data, or no assessment of maternal lifestyle behaviors. Studies of women with a history of gestational diabetes mellitus (GDM) also reported associations between lactation duration and lower the incidence of type 2 diabetes and the metabolic syndrome. The mechanisms are not understood, but hormonal regulation of pancreatic β -cell proliferation and function or other metabolic pathways may mediate the lactation association with cardiometabolic disease in women.

Gunderson, E. P., Crites, Y., Chiang, V., Walton, D., Azevedo, R. A., Fox, G., ... & Hedderson, M. M. (2012). Influence of breastfeeding during the postpartum oral glucose tolerance test on plasma glucose and insulin. *Obstetrics and gynecology*, 120(1), 136.

Participants were enrolled in the Study of Women, Infant Feeding, and Type 2 Diabetes, a prospective observational cohort study of 1,035 Kaiser Permanente Northern California members who had been diagnosed with GDM and subsequently underwent a 2-hour 75-g OGTT at 6-9 weeks postpartum for the study enrollment examinations from 2008 to 2011. For this analysis, we selected 835 study participants who reported any intensity of lactation and were observed either breastfeeding their infants (ie, putting the infant to the breast) or not breastfeeding during the OGTT. Of 835 lactating women, 205 (25%) breastfed their infants during the 2-hour 75-g OGTT at 6-9 weeks postpartum. Mean (standard deviation) duration of breastfeeding during the OGTT was 15.3 (8.1) minutes. Compared with not having breastfed during the OGTT, having breastfed during the test was associated with lower adjusted mean (95% confidence interval) 2-hour glucose (mg/dL) by -6.2 (- 11.5 to -1.0; P=.02), 2-hour insulin (microunits/mL) by -15.1 (-26.8 to -3.5; P=.01), and natural log 2-hour insulin by -0.15 (- 0.25 to -0.06; P<0.01), and with higher insulin sensitivity index_{0,120} by 0.08 (0.02-0.15; P=.02), but no differences in plasma fasting glucose or insulin concentrations. CONCLUSION: Among

postpartum women with recent gestational diabetes mellitus, breastfeeding an infant during the 2-hour 75-g OGTT may modestly lower plasma 2-hour glucose (5% lower on average) as well as insulin concentrations in response to ingestion of glucose.

Stuebe, A. M., & Rich-Edwards, J. W. (2009). The reset hypothesis: lactation and maternal metabolism. *American journal of perinatology*, 26(1), 81.

For maternal metabolism, pregnancy ends not with delivery, but with weaning. In several recent epidemiological studies, authors have reported an association between duration of breastfeeding and reduced maternal risk of metabolic disease. These findings parallel data from animal models showing favorable changes in metabolism associated with lactation. During gestation, visceral fat accumulates, and insulin resistance and lipid and triglyceride levels increase. These changes appear to reverse more quickly, and more completely, with lactation. In this article, we review animal and human studies regarding the effects of lactation on adiposity, lipid, and glucose homeostasis. We hypothesize that lactation plays an important role in "resetting" maternal metabolism after pregnancy.

Stuebe, A. M., Rich-Edwards, J. W., Willett, W. C., Manson, J. E., & Michels, K. B. (2005). Duration of lactation and incidence of type 2 diabetes. *Jama*, 294(20), 2601-2610.

Lactation is associated with improved glucose and insulin homeostasis, independent of weight change. Prospective observational cohort study of 83,585 parous women in the Nurses' Health Study (NHS) and retrospective observational cohort study of 73,418 parous women in the Nurses' Health Study II (NHS II). Among parous women, increasing duration of lactation was associated with a reduced risk of type 2 diabetes. For each additional year of lactation, women with a birth in the prior 15 years had a decrease in the risk of diabetes of 15% (95% confidence interval, 1%-27%) among NHS participants and of 14% (95% confidence interval, 7%-21%) among NHS II participants, controlling for current body mass index and other relevant risk factors for type 2 diabetes. Longer duration of breastfeeding was associated with reduced incidence of type 2 diabetes in 2 large US cohorts of women. Lactation may reduce risk of type 2 diabetes in young and middle-aged women by improving glucose homeostasis.

McManus, R. M., Cunningham, I., Watson, A., Harker, L., & Finegood, D. T. (2001). Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. *Metabolism-Clinical and Experimental*, 50(6), 715-719.

Lactation has been recommended as beneficial for the maternal metabolic abnormalities associated with glucose intolerance and diabetes risk, although associations between breastfeeding (BF), glucose tolerance, and adipose tissue distribution are unknown. Therefore, a population of women with recent gestational diabetes (GDM) was evaluated with comparison of results for lactating versus nonlactating women. A total of 26 women participated (14 BF and 12 nonbreastfeeding [nonBF]) with a singleton vaginal delivery after 36 weeks gestation. At 3 months postpartum, each woman completed a 75-g oral glucose tolerance test (OGTT), a frequently sampled intravenous glucose tolerance test (FSIGT), and computed tomography (CT) scanning for adipose distribution and mass. Insulin sensitivity was not significantly different between BF and nonBF groups (4.97 ± 0.78 v 3.44 ± 1.0 [$\times 10^{-4}$ min⁻¹(μ U/mL) nor was glucose effectiveness (1.92 ± 0.22 v $1.56 \pm$

0.19 [times] 10[minus]2 min[minus]1). However, the disposition index (DI) (insulin sensitivity [SI] [times] acute insulin response to glucose [AIRg]) was higher in the BF group (129.9 [plusmn] 26.0 v 53.4 [plusmn] 18.0 [times] 10[minus]4 min[minus]1; P = .03). Visceral fat (103 [plusmn] 14 v 97 [plusmn] 15 cm²) and subcutaneous fat (362 [plusmn] 36 v 460 [plusmn] 68 cm²) were similar between the groups. We conclude that 3 months of BF in a population with previous GDM was associated with improved pancreatic [beta]-cell function, but not with any difference in measures of adiposity.

Davies, H. A., Clark, J. D., Dalton, K. J., & Edwards, O. M. (1989). Insulin requirements of diabetic women who breastfeed. *BMJ: British Medical Journal*, 298(6684), 1357.
Breastfeeding decreased insulin requirements in diabetic women. Reduction in insulin dose postpartum was significantly greater in those who were breastfeeding than those who were bottle feeding.

EMOTIONAL HEALTH

Hamdan, A., & Tamim, H. (2012). The relationship between postpartum depression and breastfeeding. *The International Journal of Psychiatry in Medicine*, 43(3), 243-259.
The purpose was to investigate the possible correlation or predictive relationship between breastfeeding and Postpartum Depression (PPD). Method: We conducted a prospective study in which 137 Arab women were assessed during pregnancy and postpartum. Current breastfeeding was correlated with postpartum outcomes (EPDS and MINI), employment, and use of formula at 2 and 4 months postpartum, as well as with other variables. Results: Women who were breastfeeding at 2 and 4 months had lower scores on EPDS ($p < 0.0037$ and $p < 0.0001$, respectively) and were less likely to be diagnosed with PPD at 4 months ($p < 0.0025$). Higher scores on EPDS and diagnosis of PPD at 2 months were predictive of lower rates of breastfeeding at 4 months ($p < 0.0001$ and $p < 0.005$, respectively). Women who were employed and using formula at 2 months were less likely to breastfeed at 4 months ($p < 0.003$) and were less likely to be diagnosed with PPD ($p < 0.05$) at 4 months. Discussion: The results indicate that women who breastfeed their infants reduced their risk of developing PPD, with effects being maintained over the first 4 months postpartum. PPD may also decrease the rate of breastfeeding, suggesting a reciprocal relationship between these variables.

Groër, M. W. (2005). Differences between exclusive breastfeeders, formula-feeders, and controls: a study of stress, mood, and endocrine variables. *Biological research for nursing*, 7(2), 106-117.

The purpose of this study was to examine relationships among lactational status, naturalistic stress, mood, and levels of serum cortisol and prolactin and plasma adrenocorticotrophic hormone (ACTH). Eighty-four exclusively breastfeeding, 99 exclusively formula-feeding, and 33 non-postpartum healthy control women were studied. The postpartum mothers were studied cross-sectionally once between 4 and 6 weeks after the birth. Stress was measured using the Perceived Stress Scale, the Tennessee Postpartum Stress Scale, and the Inventory of Small Life Events. Mood was measured using the Profile of Mood States. Serum prolactin, plasma

ACTH, and serum cortisol levels were measured by commercial ELISA (enzyme-linked immunosorbent assay) kits. Results indicate that breastfeeding mothers had more positive moods, reported more positive events, and perceived less stress than formula-feeders. Reports of stressful life events were generally equivalent in the two groups. Serum prolactin was inversely related to stress and mood in formula-feeders. When breast and formula-feeders were compared to controls, they had higher serum cortisol, lower stress, and lower anxiety. Breastfeeders had lower perceived stress than controls. Breastfeeders had lower depression and anger and more positive life events reported than formula-feeders. However, there were few correlations among stress, mood, and the hormones in postpartum mothers, and those only in formula-feeders, whereas strong relationships were found between serum ACTH and a number of stress and mood variables in controls. Postpartum mothers reported a range of stress and negative moods at 4 to 6 weeks, and in formula-feeders, serum prolactin was related to some of the stress and mood variables. Breastfeeding appears to be somewhat protective of negative moods and stress.

McKee, M. D., Zayas, L. H., & Jankowski, K. R. B. (2004). Breastfeeding intention and practice in an urban minority population: relationship to maternal depressive symptoms and mother–infant closeness. *Journal of reproductive and infant psychology*, 22(3), 167-181.

This study examines predictors of planning to breastfeeding and of successful breastfeeding initiation and persistence, including the relationship to maternal depressive symptoms, social support, and mothers' perception of closeness to their infants, in a sample of low-income African American and Hispanic women in the urban Northeast. Detailed interviews were conducted in the early third trimester, at 2 weeks following delivery, and 3 months postpartum. Rates of intention to breastfeed were similar for Hispanic and African American women. A smaller proportion of Hispanic women persisted, especially among those women who supplemented with formula. For all women, we found no relationship between breastfeeding practice and either social support or depressive symptoms. Mothers' perception of closeness to their infants was greater among breastfeeders compared to bottle-feeders.

Harlow, B. L., Cohen, L. S., Otto, M. W., Spiegelman, D., & Cramer, D. W. (2004). Early life menstrual characteristics and pregnancy experiences among women with and without major depression: the Harvard study of moods and cycles. *Journal of Affective Disorders*, 79(1-3), 167-176.

From a population-based sample of 4161 premenopausal women 36-45 years of age, we identified 332 women who met criteria for past or current major depression and a sample of 644 women with no such history. In person interviews included a detailed assessment of menstrual cycle characteristics from age at menarche through study enrollment as well as other reproductive landmarks. Risk of depression increased significantly with decreasing age at menarche ($P < 0.001$). The risk of depression was also higher in women with heavier menstrual flow and cycle irregularity during the first 5 years of menstruation. Women with a history of multiple abortions were 2-3-times more likely to develop major depression (95% CI 1.6-4.1). Increasing months of breastfeeding was associated with a decreased risk of depression after adjustment for education, marital status, and number of livebirths (P -value, test of trend = 0.012). This association was largely confined to depression during the postpartum period. Menstrual

and pregnancy history exposures were self-reported and retrospectively assessed. However, women with and without a history of depression were subject to similar recall requirements that likely resulted in an underestimate of most risk estimates. Clinicians involved in routine obstetrical and gynecological care of women need to recognize that menstrual and pregnancy history events may serve as potential markers for subsequent psychiatric sequelae.

Sjögren, B., Widström, A. M., Edman, G., & Uvnaus-Moberg, K. (2000). Changes in personality pattern during the first pregnancy and lactation. *Journal of Psychosomatic Obstetrics & Gynecology*, 21(1), 31-38.

Significant changes occur in women's personality during pregnancy and lactation. The trend is toward a lifestyle interpreted as more relaxed and tolerant to monotony. In this study of 161 women during pregnancy and 3-6 months after delivery, women who had breastfed for at least 8 weeks differed significantly from those who had not. They had lower scores on the Somatic Anxiety, Muscular Tension, Monotony Avoidance, Suspicion, Social Desirability and the Impulsiveness scale and higher scores on the Socialization scale.

Nissen, E., Gustavsson, P., Widström, A. M., & Uvnäs-Moberg, K. (1998). Oxytocin, prolactin, milk production and their relationship with personality traits in women after vaginal delivery or Cesarean section. *Journal of Psychosomatic Obstetrics & Gynecology*, 19(1), 49-58.

Personality profiles reflecting anxiety and social interaction showed that anxiety was inversely related with basal levels of oxytocin and prolactin in the cesarean section mothers, whereas the pulsatility of oxytocin was related to social desirability in both groups. Social desirability and oxytocin pulsatility were also correlated with the amount of milk transferred from the mother to the baby. The correlations indicate that central oxytocin may be involved in behavioral adaptations to the maternal role.

Uvnäs-Moberg, K. (1998). OXYTOCIN MAY MEDIATE THE BENEFITS OF POSITIVE SOCIAL INTERACTION AND EMOTIONS¹. *Psychoneuroendocrinology*, 23(8), 819-835.

In both male and female rats, oxytocin exerts potent physiological antistress effects. If daily oxytocin injections are repeated over a 5-day period, blood pressure is decreased by 10-20 mmHg, the withdrawal latency to heat stimuli is prolonged, cortisol levels are decreased and insulin and cholecystokinin levels are increased. These effects last from 1 to several weeks after the last injection. After repeated oxytocin treatment weight gain may be promoted and the healing rate of wounds increased. Oxytocin released in response to social stimuli may be part of a neuroendocrine substrate which underlies the benefits of positive social experiences.

Virden, S. F. (1988). The relationship between infant feeding method and maternal role adjustment. *Journal of Nurse-Midwifery*, 33(1), 31-35.

At one month postpartum, women who breastfeed their infants had scores indicating less anxiety and more mutuality than the women bottle feeding their infants.

FERTILITY

Vekemans, M. (1997). Postpartum contraception: the lactational amenorrhea method. *The European Journal of Contraception & Reproductive Health Care*, 2(2), 105-111.

During lactation, menses before 6 months are mostly anovulatory, and fertility remains low. The lactational amenorrhea method is based on three simultaneous conditions: (1) the baby is under 6 months; (2) the mother is still amenorrheic; and (3) she practices exclusive or quasi-exclusive breastfeeding on demand, day and night. Experiments with LAM extended to 9-12 months are ongoing. The lactational amenorrhea method is at least 98% effective.

MACULAR DEGENERATION

Erke, M. G., Bertelsen, G., Peto, T., Sjølie, A. K., Lindekleiv, H., & Njølstad, I. (2013). Lactation, female hormones and age-related macular degeneration: the Tromsø Study. *British Journal of Ophthalmology*, 97(8), 1036-1039.

Some risk factors for age-related macular degeneration (AMD) have been shown to act differently in women and men. The present study aims to investigate this disparity by examining associations between female hormones, reproductive history and AMD. Women aged 65-87 years were invited to this cross-sectional, population-based study in Norway. Participants underwent physical examination, retinal photography, answered questionnaires and had blood samples taken. The sample included 1512 women, of whom 48 (3.2%) had late AMD and 378 (25%) had large drusen >125 µm phenotype. Length of breast feeding per child was significantly associated with late AMD (OR per month 0.80, 95% CI 0.68 to 0.94) in multivariable regression analysis. We observed no associations between late AMD or drusen >125 µm and contraceptives, oral hormonal replacement therapy, parity, age at first childbirth, age of menarche, age of menopause, number of menstruating years or the reason for menopause. Longer duration of lactation was associated with lower frequency of maternal late AMD when controlled for confounders. Other reproductive factors and hormone replacement therapy were not significantly associated with AMD.

MENOPAUSAL

Sievert, L. L., Freedman, R. R., Garcia, J. Z., Foster, J. W., Soriano, M. D. C. R., Longcope, C., & Franz, C. (2002). Measurement of hot flashes by sternal skin conductance and subjective hot flash report in Puebla, Mexico. *Menopause*, 9(5), 367-376.

Symptoms 67 perimenopausal women aged 40 to 65 years participated in interviews, anthropometric measures, and a 2-hour recording of sternal skin conductance. Women who subjectively reported hot flashes were measured in a warmer room, were more likely to be postmenopausal, reported more frequent consumption of coffee, and spent fewer months breast-feeding their last child compared with women who did not report the experience of hot flashes during the testing period.

MORBIDITY AND MORTALITY

Munguía, M. U., Esparza, S. L., Stern, D., Posadas, M. M., Ridaura, R. L., & Lajous, M. (2018). Breastfeeding Duration and the Risk of All-Cause and Breast Cancer Mortality Among Parous Women From the Mexican Teachers' Cohort.

Women who have breastfed have a lower risk of breast and ovarian cancer and other chronic diseases. Currently, breast cancer has become the leading cause of death from cancer in Mexican women. In Mexico, exclusive breastfeeding rates have declined one third in the last decade, and only 35% of women breastfed at least 1 year, which provides a unique scenario in which to analyze breastfeeding and mortality. The aim of the current study was to estimate the impact of lifetime breastfeeding duration on the risk of all-cause and breast cancer mortality in Mexican women. We analyzed parous women who were enrolled in a Mexican Teachers' Cohort since 2006 and observed over 10 years. Months of breastfeeding per pregnancy were self-reported at baseline. We categorized participants according to the accumulated duration of any mode of breastfeeding (never, < 6 months, 6 to 11 months, 12 to 23 months, and ≥ 24 months). Deaths were identified using the employer's database and next of kin reports, and the date and cause of death were obtained from national mortality databases. We used Cox proportional hazards regression models adjusted for baseline age, parity (one, two, three, and four or more children), age at first birth (< 20, 20 to 24, 25 to 29, and ≥ 30 years), BMI at age 18 years (≤ 25 or > 25), socioeconomic level (tertiles), and smoking (current, past, and never) to estimate hazard ratios (HRs). Mean age at baseline was 43 ± 7 years. Over 767,600 person-years of follow-up, 952 all-cause deaths and 92 breast cancer deaths occurred among 92,794 parous women. Mean age at death was 57 ± 7 years. The incidence rate per 1,000 person-years of all-cause mortality was 1.8 for women who did not breastfeed, 1.18 (< 6 months), 1.21 (6 to 11 months), 1.01 (12 to 23 months), and 1.26 (≥ 24 months). HRs for all-cause mortality among parous women with lifetime breastfeeding of < 6 months was 0.79 (95% CI, 0.63 to 0.97), 0.85 (95% CI, 0.70 to 1.05) for 6 to 11 months, 0.78 (95% CI, 0.64 to 0.94) for 12-23 months, and 0.88 (95% CI, 0.69 to 1.10) for > 24 months compared with parous women who never breastfed. No dose-response relationship was found when comparing HRs of the different categories of breastfeeding. HR for breast cancer mortality for women who ever breastfed compared with parous women who never breastfed was 0.75 (95% CI, 0.45 to 1.33). Breastfeeding among parous Mexican women was associated with lower all-cause mortality. Breastfeeding could potentially reduce premature deaths in women.

MULTIPLE SCLEROSIS

Krysko, K. M., Rutatangwa, A., Graves, J., Lazar, A., & Waubant, E. (2020). Association between breastfeeding and postpartum multiple sclerosis relapses: a systematic review and meta-analysis. *JAMA Neurology*, 77(3), 327-338.

In this systematic review and meta-analysis of 24 studies that include 2974 women, there was a reduced rate of postpartum multiple sclerosis relapses in women who were breastfeeding compared with those who were not breastfeeding, with a stronger benefit of exclusive rather than nonexclusive breastfeeding. Compared with nonbreastfeeding, breastfeeding was associated with a 43% lower rate of postpartum relapse, although it is not possible to exclude residual confounding.

Portaccio, E., & Amato, M. P. (2019). Breastfeeding and post-partum relapses in multiple sclerosis patients. *Multiple Sclerosis Journal*, 25(9), 1211-1216.

While it is acknowledged that exclusive breastfeeding has well-established benefits for both infant/child and mother health, evidence on the relationships between breastfeeding and disease course in women with multiple sclerosis (MS) is still controversial. On one hand, in the postpartum period, a disease worsening is possible, particularly in women with more active MS. On the other hand, the use of disease modifying drugs is currently contraindicated during lactation. In this topical review, we describe available evidence on the relationship between breastfeeding and disease activity in MS. In some studies, a possible protective role for exclusive breastfeeding against the risk of postpartum relapse has been suggested, while, in others, its impact was neutral. Waiting for definitive evidence on this topic, we propose a pragmatic approach to breastfeeding choice, on a case-by-case basis, considering the disease characteristics before and during pregnancy and the patient's therapeutic history.

Langer-Gould, A., Smith, J. B., Hellwig, K., Gonzales, E., Haraszti, S., Koebnick, C., & Xiang, A. (2017). Breastfeeding, ovulatory years, and risk of multiple sclerosis. *Neurology*, 89(6), 563-569. Methods: We recruited women with newly diagnosed MS or its precursor, clinically isolated syndrome (CIS) (n = 397), and matched controls (n = 433) into the MS Sunshine Study from the membership of Kaiser Permanente Southern California. A structured in-person questionnaire was administered to collect the behavioral (pregnancies, breastfeeding, hormonal contraceptive use) and biological (age at menarche and menopause, amenorrhea) factors to make up ovulatory years. Results: Among women who had live births, a cumulative duration of breastfeeding for ≥ 15 months was associated with a reduced risk of MS/CIS (adjusted odds ratio [OR] 0.47, 95% confidence interval [CI] 0.28–0.77; $p = 0.003$ compared to 0–4 months of breastfeeding). Being ≥ 15 years of age at menarche was also associated with a lower risk of MS/CIS (adjusted OR 0.56, 95% CI 0.33–0.96; $p = 0.035$). Total ovulatory years and the remaining factors that determine it, including gravidity, parity, episodes of amenorrhea, and hormonal contraceptive use, as well as age at first birth, showed no significant association with the risk of MS/CIS. Conclusions: Mothers who breastfeed longer may be at lower subsequent risk of developing multiple sclerosis. This is consistent with the other known maternal health benefits of breastfeeding and with our previous observation that women with MS who breastfeed exclusively are at lower risk of postpartum relapses.

OSTEOARTHRITIS

Cooley, H. M., Stankovich, J., & Jones, G. (2003). The association between hormonal and reproductive factors and hand osteoarthritis. *Maturitas*, 45(4), 257-265.

Cross-sectional study of 348 women from 76 families in Tasmania. Parity, increasing age at menopause and years of menstruation were associated with both symptomatic hand osteoarthritis and a more severe distal interphalangeal score while both current and ever use of hormone replacement therapy were significantly associated with increased prevalence of Heberden's nodes and severity of Heberden's nodes and distal interphalangeal osteoarthritis. Hormone replacement therapy usage less than 5 years was associated with increased severity of both distal interphalangeal disease and Heberden's nodes. No factors were associated with carpometacarpal disease apart from ever breast-feeding which was protective (OR 0.37). These results require confirmation in clinical trials or carefully controlled longitudinal studies but suggest that estrogen exposure around the time of disease onset (either endogenous or

exogenous) may have a "priming" effect on the severity of distal interphalangeal osteoarthritis while breast-feeding in earlier life may be protective for carpometacarpal osteoarthritis.

OSTEOPOROSIS

Duan, X., Wang, J., & Jiang, X. (2017). A meta-analysis of breastfeeding and osteoporotic fracture risk in the females. *Osteoporosis International*, 28(2), 495-503.

Our meta-analysis included 12 studies from PubMed, Embase, and Web of Science. Finding indicated breastfeeding may well reduce the risk of osteoporotic fracture. Several epidemiologic studies have investigated that breastfeeding is associated with short-term bone loss in the women, but the long-term effect on osteoporotic fracture risk remains unclear. Thus, we conducted this meta-analysis to explore the potential association between breastfeeding and osteoporotic fracture risk in the females and possible dose-response relationship between them. Twelve articles including 14,954 participants were identified. The pooled RRs of osteoporotic hip and forearm fracture for the highest vs lowest duration of breastfeeding were 0.84 (95 % CI 0.67–1.05), 0.72 (95 % CI 0.52–0.99), and 0.82 (95 % CI 0.56–1.19), respectively. In subgroup analysis, breastfeeding was associated with a decreased risk of osteoporotic fracture in case-control study (RR = 0.70, 95 % CI 0.49–0.99) and postmenopausal women (RR = 0.66, 95 % CI 0.47–0.93). In dose-response analysis, osteoporotic and hip fracture risk decreased by 0.9 and 1.2 % for each month increment of breastfeeding, respectively. Our meta-analysis revealed that breastfeeding may well reduce the risk of osteoporotic fracture. More cohort studies with large sample sizes are needed to confirm the conclusion.

Jimenez-Arreola, J., & Aguilera, L. B. M. (2015). Breastfeeding as preventive factor for osteoporosis in adult women. *Nutricion hospitalaria*, 32(6), 2600-2605.

Breastfeeding is considered protective of osteoporosis, by endocrine changes, such as the rise of intestinal absorption of calcium and the renal conservation of the same, however, other studies demonstrate that with more one child they present a loss of bone mineral density (BMD) (2-9%).to determine if breastfeeding is a protective factor or a risk in osteoporosis in Queretaro's women.retrospective study of cases and controls. 114 women from 35 to 60 years divided in control group (without breastfeeding) and women those that breastfeed. Diagnostic of BMD by bone densitometry of two regions: Hip (femur) and lumbar. Clinical history applies. Criteria of inclusion: age 35-60 years. Criteria of exclusion: consumption: calcium, hormonal replacement therapy, treatment for osteoporosis: breastfeeding or pregnant. It will provide evidence of a central trend, T couplet, correlations, Chi2 y profitable reasons.breastfeeding was found to have a protection factor con 0.903 OR (0.768-1.006). Inverse correlation of BMI/BMD in hip and lumbar regions, in women that did not breast contrary to those that did breastfeed. In both groups it was determined a greater age of pregnancy with greater BMD in the hips and greater size of the child, only in women that breastfeed. Being the obesity factor of the women that breastfeed. However, a inverse correlation was found among Age/BMD in three regions from women that breaststed, contrary to those that did not breastfeed specifically in the BMD lumbar.breastfeeding is beneficial for the mother as it is a protective factor against osteoporosis, as long as it holds the first 6 months and for newborn optimal linear growth.

Canal-Macias, M. L., Roncero-Martin, R., Moran, J. M., Lavado-Garcia, J. M., del Carmen Costa-Fernandez, M., & Pedrera-Zamorano, J. D. (2013). Increased bone mineral density is associated with breastfeeding history in premenopausal Spanish women. *Archives of medical science: AMS*, 9(4), 703.

During lactation abundant calcium is lost from the mother as a result of the amount of breast milk produced. Lactation leads to transient fragility, with some women experiencing even fragility fractures, but nearly all of these women subsequently undergo a large increase in bone mineral density (BMD), confirming that the BMD must have declined during lactation but it increases after weaning. We have retrospectively examined the relationship between the duration of breastfeeding and bone properties in Spanish premenopausal healthy women, to identify the site-specific changes in BMD. Four hundred and thirty-three premenopausal healthy women, 295 with a mean of 7.82 ± 6.68 months of exclusive breastfeeding and 138 control women, were studied. We examined total, trabecular and cortical volumetric BMD (mg/mm^3) at the distal radius using peripheral quantitative computed tomography. Areal BMD (g/cm^2) was measured using dual energy X-ray absorptiometry at the femoral neck, lumbar spine, trochanter and Ward's triangle. Phalangeal bone ultrasound was measured by amplitude-dependent speed of sound. Areal BMD analysis at L2–L4 revealed significant intergroup differences ($p < 0.05$). There were significant intergroup differences in the volumetric BMD in both total and cortical bone ($p < 0.05$). The observed BMD of breast-feeders was higher than the BMD in non-breast-feeding women. Additionally, the lactation subgroup analysis revealed significant differences in the areal BMD at trochanter and L2–L4 ($p < 0.05$) and in the cortical volumetric BMD ($p < 0.05$). This study adds to the growing evidence that breastfeeding has no deleterious effects and may confer an additional advantage for BMD in premenopausal women.

Akkus, Z., Camdeviren, H., Celik, F., Gur, A., & Nas, K. (2005). Determination of osteoporosis risk factors using a multiple logistic regression model in postmenopausal Turkish women. *Saudi medical journal*, 26(9), 1351-1359.

To determine the risk factors of osteoporosis using a multiple binary logistic regression method and to assess the risk variables for osteoporosis, which is a major and growing health problem in many countries. METHODS: We presented a case-control study, consisting of 126 postmenopausal healthy women as control group and 225 postmenopausal osteoporotic women as the case group. The study was carried out in the Department of Physical Medicine and Rehabilitation, Dicle University, Diyarbakir, Turkey between 1999-2002. The data from the 351 participants were collected using a standard questionnaire that contains 43 variables. A multiple logistic regression model was then used to evaluate the data and to find the best regression model. RESULTS: We classified 80.1% (281/351) of the participants using the regression model. Furthermore, the specificity value of the model was 67% (84/126) of the control group while the sensitivity value was 88% (197/225) of the case group. We found the distribution of residual values standardized for final model to be exponential using the Kolmogorow-Smirnow test ($p=0.193$). The receiver operating characteristic curve was found successful to predict patients with risk for osteoporosis. This study suggests that low levels of dietary calcium intake, physical activity, education, and longer duration of menopause are independent predictors of the risk of low bone density in our population. CONCLUSION: Adequate dietary calcium intake

in combination with maintaining a daily physical activity, increasing educational level, decreasing birth rate, and duration of breast-feeding may contribute to healthy bones and play a role in practical prevention of osteoporosis in Southeast Anatolia. In addition, the findings of the present study indicate that the use of multivariate statistical method as a multiple logistic regression in osteoporosis, which may be influenced by many variables, is better than univariate statistical evaluation.

Chantry, C. J., Auinger, P., & Byrd, R. S. (2004). Lactation among adolescent mothers and subsequent bone mineral density. *Archives of pediatrics & adolescent medicine*, 158(7), 650-656.

The bone mineral density (BMD) for 5 regions of the proximal femur as measured by dual energy x-ray absorptiometry were compared for 5 groups of women aged 20 to 25 years (n = 819); the groups included those who had been: (1) adolescent mothers and had breastfed (n = 94), (2) adolescent mothers and had not breastfed (n = 151), (3) mothers who first gave birth as adults and breastfed (n = 67), (4) mothers who first gave birth as adults and had not breastfed (n = 89), and (5) nulliparous (n = 418). During young adulthood, women who breastfed during adolescence had higher adjusted BMDs, which was statistically significant in 4 of the 5 regions, than those who had not breastfed and BMDs equivalent to nulliparous women. Adjusting also for obstetric variables, women who breastfed during adolescence had higher BMDs in all 5 regions compared with their peers who had not breastfed (total proximal femur area difference, 0.053 gm/cm²). In this nationally representative sample, breastfeeding by adolescent mothers was associated with greater BMD in the proximal femur during young adulthood. Lactation was not found to be detrimental and may be protective to the bone health of adolescent mothers.

Huo, D., Lauderdale, D. S., & Li, L. (2003). Influence of reproductive factors on hip fracture risk in Chinese women. *Osteoporosis international*, 14(8), 694-700.

To assess the relationships between reproductive factors and the risk of hip fractures in postmenopausal Chinese women, the authors analyzed data from a matched case-control study conducted in the Beijing metropolitan area among women aged 50 years and older. One hundred and fifty-six cases who sustained a hip fracture after minor trauma between January 1994 and May 1996 were identified from hospital records, of whom 121 could be located (78%). All cases agreed to be interviewed: Two controls were selected from the neighbors of each hip fracture case and matched to the cases by age within a 5-year range. Information on reproductive factors and potential confounders was obtained through personal interviews. Although univariate analyses revealed that later age at menopause, parity and breastfeeding were protective factors, only breastfeeding was statistically associated with risk of hip fracture after adjusting for potential confounding in multivariable logistic models. As compared with women with average duration of breastfeeding per child less than or equal to 6 months, women with average duration of breastfeeding per child 7-12 months, 13-23 months; and greater than or equal to 24 months had odds ratios of 1.14, 0.28, and 0.34 respectively. Among parous women, 13% reduced risk was associated with every 6 months increase in breastfeeding per child. The authors conclude that extended breastfeeding is associated with a reduced hip fracture risk among Chinese women in Beijing.

Melton, L. J., Bryant, S. C., Wahner, H. W., O'Fallon, W. M., Malkasian, G. D., Judd, H. L., & Riggs, B. L. (1993). Influence of breastfeeding and other reproductive factors on bone mass later in life. *Osteoporosis International*, 3(2), 76-83.

The odds ratio that a woman with osteoporosis did not breastfeed her baby was 4 times higher than for a control woman. Blaauw, R. et al. "Risk factors for development of osteoporosis in a South African population." SAMJ 1994; 84:328-32. Page 58 of 63 Whether or not women had ever breastfed, total duration of breastfeeding and duration of breastfeeding per child were not associated with reduced bone mineral, but breastfeeding for more than 8 months was associated with greater bone mineral at some sites. Melton L et al. "Influence of breastfeeding and other reproductive factors on bone mass later in life." Osteoporos Int 1993 Mar;3(2):76-83

SMOKING REDUCTION

Carswell, A. L., Ward, K. D., Vander Weg, M. W., Scarinci, I. C., Girsch, L., Read, M., ... & Chen, W. (2018). Prospective associations of breastfeeding and smoking cessation among low-income pregnant women. *Maternal & Child Nutrition*, e12622.

Although low-income pregnant women have high rates of smoking and low rates of breastfeeding, few studies have examined prospective associations between these risk factors in community samples. Doing so may help improve breast-feeding support programs in this population. We used a secondary analysis of 247 low-income pregnant smokers in Memphis, Tennessee, who were interviewed up to 4 times (twice during pregnancy and twice through 6 months postpartum). Smoking cessation during prepartum and postpartum was defined as a self-report of not smoking for ≥ 1 week and an expired carbon monoxide level of < 10 ppm. Multivariable logistic regression analyses were used to determine whether intent to breastfeed was associated with smoking cessation and whether smoking cessation was associated with actual breastfeeding. Models were adjusted for sociodemographic, pregnancy-related, and smoking-related confounders. Thirty-nine percent of participants intended to breastfeed, and 38% did so. Women who intended to breastfeed were 2 times more likely to quit smoking prepartum (adjusted OR = 1.99, 95% CI [1.06, 3.74]), but not postpartum (adjusted OR = 1.27, 95% CI [0.57, 2.84]). Quitting smoking at baseline and during pregnancy was associated with subsequent breastfeeding (adjusted OR 2.27, 95% CI [1.05, 4.94] and adjusted OR = 2.49, 95% CI [1.21, 5.11]). Low-income women who intended to breastfeed were more likely to quit smoking during pregnancy and those who quit smoking at baseline and prepartum were more likely to breastfeed. Simultaneously supporting breastfeeding and smoking cessation may be very useful to change these important health behaviours among this high-risk population.

Lauria, L., Lamberti, A., & Grandolfo, M. (2012). Smoking behaviour before, during, and after pregnancy: the effect of breastfeeding. *The Scientific World Journal*, 2012.

Data for this study were obtained from a population-based follow-up study in 25 Italian Local Health Units (LHUs) to evaluate pregnancy, delivery, and postpartum care in Italy. A sample of 3534 women was recruited and interviewed within a few days of their giving birth and at 3, 6, and 12 months after delivery, by trained interviewers using questionnaires. The objective of the study was to evaluate changes in smoking behaviour from one interview to the next. Of 2546 women who completed the follow-up, smoking prevalences before and during pregnancy were

21.6% and 6.7%; smoking prevalences and smoking relapse at 3, 6, and 12 months were 8.1% and 18.5%, 10.3% and 30.3%, and 10.9% and 32.3%, respectively. Smoking during and after pregnancy was more likely among women who were less educated, single, not attending antenatal classes, employed, and not breastfeeding. The results show that women who are breastfeeding smoke less than not breastfeeding women, even after controlling for other predictors (i.e., smoking relapse at 12 months: OR = 0.43, 95% CI: 0.19, 0.94). A low maternal mood increases the risk of smoking relapse within 6 months of about 73%. This study also suggests that prolonged breastfeeding reduces the risk of smoking relapse and that this reduction may be persistent in time. Interventions targeting breastfeeding promotion may also indirectly support smoking cessation, even in absence of specific interventions.

POSTPARTUM WEIGHT LOSS

Armenta, R. F., Kritz-Silverstein, D., Wingard, D., Laughlin, G. A., Wooten, W., Barrett-Connor, E., & Araneta, M. R. (2015). Association of breastfeeding with postmenopausal visceral adiposity among three racial/ethnic groups. *Obesity*, 23(2), 475-480.

We examined the association between breastfeeding and postmenopausal visceral adiposity. Participants were community-dwelling women aged 55-80 from the Caucasian Rancho Bernardo Study, the Filipino Women's Health Study, and the Health Assessment Study of African-American Women who had visceral adipose tissue (VAT) measurements by computed tomography between 2000 and 2002. Linear regression was used to determine the association between average breastfeeding duration per child and VAT. In Caucasian, Filipino, and African-American women, average number of live births was 3, 4, and 3; average breastfeeding duration was 4.3, 1.8, and 5.1 months, respectively. Filipino women had more live births, were more likely to breastfeed, and breastfed shorter durations. African-American women had lower VAT, despite higher subcutaneous adipose tissue (SAT), BMI, and waist girth. Women who breastfed >3 months on average had 8.8 cm(3) lower VAT than women who breastfed ≤3 months, independent of covariates. Women who initiated breastfeeding had lower BMI and waist girth than those who did not, but they did not differ by VAT unless they breastfed >3 months. Associations were independent of race/ethnicity. Results suggest breastfeeding initiation is associated with reduced BMI and smaller waist girth, and breastfeeding >3 months is associated with lower postmenopausal VAT.

Zhu, Y., Hernandez, L. M., Dong, Y., Himes, J. H., Hirschfeld, S., & Forman, M. R. (2015). Longer breastfeeding duration reduces the positive relationships among gestational weight gain, birth weight and childhood anthropometrics. *J Epidemiol Community Health*, 69(7), 632-638. The relationship between gestational weight gain (GWG) and childhood growth remains controversial. An examination on whether infant feeding practices mediate this relationship may improve our understanding of it. We investigated whether the relationships among GWG, birth weight and childhood anthropometrics were mediated through infant feeding practices (breastfeeding duration and age at introduction of solid foods) in a cross-sectional multiethnic study of 1387 mothers and their children aged 0-5.9 years in the USA (2011-2012). Child anthropometrics included age-specific and sex-specific z-scores for weight-for-age (WAZ),

height/length-for-age (HAZ), weight-for-height/length (WHZ) and body mass index-for-age (BMIZ); and ulnar length, a marker for limb growth. We used structural equation modelling to calculate standardised path coefficients and total, direct and indirect associations of GWG, birth weight and infant feeding practices with child anthropometrics. Maternal GWG had a positive indirect association with all anthropometrics mediated via birth weight, whereas longer breastfeeding duration reduced the positive associations of GWG and birth weight with WAZ, WHZ and BMIZ in non-Hispanics ($\beta=-0.077$, -0.064 and -0.106 , respectively). Longer breastfeeding duration and introducing solid foods at a later age were positively associated with ulnar length ($\beta=0.023$ and 0.030 , respectively) but not HAZ, suggesting a distinct association, for the first time, with limb growth. Findings suggest that promoting longer breastfeeding duration among women with excessive GWG who had high birthweight newborns may mitigate the potential for their offspring to develop obesity. In addition, findings reinforce the importance of promoting appropriate GWG and preventing high birth weight, which are positively associated with childhood anthropometrics.

Jarlenski, M. P., Bennett, W. L., Bleich, S. N., Barry, C. L., & Stuart, E. A. (2014). Effects of breastfeeding on postpartum weight loss among US women. *Preventive medicine*, 69, 146-150. The aim of this study is to evaluate the effects of breastfeeding on maternal weight loss in the 12 months postpartum among U.S. women. Using data from a national cohort of U.S. women conducted in 2005–2007 (N = 2102), we employed propensity scores to match women who breastfed exclusively and non-exclusive for at least three months to comparison women who had not breastfed or breastfed for less than three months. Outcomes included postpartum weight loss at 3, 6, 9, and 12 months postpartum; and the probability of returning to pre-pregnancy body mass index (BMI) category and the probability of returning to pre-pregnancy weight. Compared to women who did not breastfeed or breastfed non-exclusively, exclusive breastfeeding for at least 3 months resulted in 3.2 pound (95% CI: 1.4,4.7) greater weight loss at 12 months postpartum, a 6.0-percentage-point increase (95% CI: 2.3,9.7) in the probability of returning to the same or lower BMI category postpartum; and a 6.1-percentage-point increase (95% CI: 1.0,11.3) in the probability of returning to pre-pregnancy weight or lower postpartum. Non-exclusive breastfeeding did not significantly affect any outcomes. Our study provides evidence that exclusive breastfeeding for at least three months has a small effect on postpartum weight loss among U.S. women.

Oken, E., Patel, R., Guthrie, L. B., Vilchuck, K., Bogdanovich, N., Sergeichick, N., ... & Martin, R. M. (2013). Effects of an intervention to promote breastfeeding on maternal adiposity and blood pressure at 11.5 y postpartum: results from the Promotion of Breastfeeding Intervention Trial, a cluster-randomized controlled trial-. *The American journal of clinical nutrition*, 98(4), 1048-1056.

Differences between mothers who do and do not succeed in breastfeeding are likely to confound associations of lactation with later maternal adiposity. OBJECTIVE: We compared adiposity and blood pressure (BP) in women randomly assigned to an intervention to promote prolonged and exclusive breastfeeding or usual care. DESIGN: We performed a cluster-randomized trial at 31 hospitals in Belarus in 1996-1997. RESULTS: Of 17,046 women enrolled at delivery, we assessed 11,867 women (69.6%) at 11.5 y postpartum. The prevalence of

exclusive breastfeeding ≥ 3 mo was 44.5% in 6321 women in the intervention group and 7.1% in 5546 women in the control group. At 11.5 y postpartum, mean (\pm SD) body mass index (BMI; in kg/m²) was 26.5 ± 5.5 , the percentage of body fat was $33.6\% \pm 8.3\%$, and systolic BP was 124.6 ± 14.6 mm Hg. On intention-to-treat analysis (without imputation) with adjustment for clustering by hospital, mean outcomes were lower in intervention compared with control mothers for BMI (mean difference: -0.27; 95% CI: -0.91, 0.37), body fat (-0.49%; 95% CI: -1.25%, 0.27%), and systolic BP (-0.81 mm Hg; 95% CI: -3.33, 1.71 mm Hg), but effect sizes were small, CIs were wide, and results were attenuated further toward the null after adjustment for baseline characteristics. Results were similar in sensitivity analyses [ie, by using conventional observational analyses disregarding treatment assignment, instrumental variable analyses to estimate the causal effect of breastfeeding, and multiple imputation to account for missing outcome measures ($n = 17,046$)]. **CONCLUSION:** In women who initiated breastfeeding, an intervention to promote longer breastfeeding duration did not result in an important lowering of adiposity or BP.

Sámano, R., Martínez-Rojano, H., Martínez, E. G., Jiménez, B. S., Rodríguez, G. P. V., Zamora, J. P., & Casanueva, E. (2013). Effects of breastfeeding on weight loss and recovery of pregestational weight in adolescent and adult mothers. *Food and nutrition bulletin*, 34(2), 123-130.

Exclusive breastfeeding (EBF) in adolescent mothers has been associated with greater postpartum maternal weight loss. **OBJECTIVE:** To assess the associations between EBF and weight loss in adolescent and adult mothers and between EBF and weight and length gain of their children. **METHODS:** A cohort of 68 adolescent mothers (15 to 19 years), 64 adult mothers (20 to 29 years), and their infants were studied. Anthropometric measurements were performed at 15, 90, 180, and 365 days postpartum in the mothers and children. EBF was defined as consumption of human milk without supplementation of any type (water, juice, nonhuman milk, or food) for 4 months. **RESULTS:** Sixty-five percent of mothers sustained EBF for 4 months. There were no significant differences in the weight or length of the infants of adolescent and adult mothers at 365 days postpartum. Among infants of adult mothers, there was a significant difference between the weight gain of those who were exclusively breastfed and those who were not exclusively breastfed ($6,498 \pm 1,060$ vs $6,096 \pm 1,035$ g, $p < .050$) at 365 days postpartum, according to the parameters for weight gain and length established by the World Health Organization (WHO). Among both adult and adolescent mothers, those who practiced EBF lost more weight than those who did not practice EBF (-2.9 kg, 95% interquartile range, -5.7 to 0.8 kg, vs -1.8 kg 95% interquartile range -2.8 to 2.2 kg; $p = .004$). Gestational weight gain, duration of EBF, and recovery menstruation explained 21% of the variance ($F = 28.184$, $p = .001$) in change in postpartum maternal weight (in kilograms) from 0 to 365 days postpartum in all mothers. Pregestational weight, duration of EBF, and maternal age were factors that explained 14% ($F = 22.759$, $p = .001$) of the change in the weight and length of the infants from 0 to 365 days of life. **CONCLUSIONS:** EBF in adolescent and adult mothers influences postpartum weight loss and provides adequate infant growth in accordance with the WHO 2006 standards.

Østbye, T., Peterson, B. L., Krause, K. M., Swamy, G. K., & Lovelady, C. A. (2012). Predictors of postpartum weight change among overweight and obese women: results from the Active Mothers Postpartum study. *Journal of women's health, 21*(2), 215-222.

Data from Active Mothers Postpartum (AMP), a study of overweight and obese postpartum women (n=450), were analyzed to determine the effect of baseline characteristics, breastfeeding, diet, physical activity, and contraception on weight change from 6 weeks to 12, 18, and 24 months postpartum. The repeated measures mixed model was used to test the association of these effects with weight change. RESULTS: Although mean weight loss was modest (0.49 kg by 24 months), the range of weight change was striking (+21.5 kg to -24.5 kg, standard deviation [SD] 7.4). Controlling only for baseline weight, weight loss was associated with breastfeeding, hormonal contraception, lower junk food and greater healthy food intake, and greater physical activity. Only junk food intake and physical activity were significant after controlling for all other predictors. CONCLUSIONS: Eating less healthy foods and being less physically active put overweight and obese women at risk of gaining more weight after a pregnancy.

Baker, J. L., Gamborg, M., Heitmann, B. L., Lissner, L., Sørensen, T. I., & Rasmussen, K. M. (2008). Breastfeeding reduces postpartum weight retention. *The American journal of clinical nutrition, 88*(6), 1543-1551.

We selected women from the Danish National Birth Cohort who ever breastfed (>98%), and we conducted the interviews at 6 (n = 36 030) and 18 (n = 26 846) mo postpartum. We used regression analyses to investigate whether breastfeeding (scored to account for duration and intensity) reduced PPWR at 6 and 18 mo after adjustment for maternal prepregnancy body mass index (BMI) and gestational weight gain (GWG). RESULTS: GWG was positively ($P < 0.0001$) associated with PPWR at both 6 and 18 mo postpartum. Breastfeeding was negatively associated with PPWR in all women but those in the heaviest category of prepregnancy BMI at 6 ($P < 0.0001$) and 18 ($P < 0.05$) mo postpartum. When modeled together with adjustment for possible confounding, these associations were marginally attenuated. We calculated that, if women exclusively breastfed for 6 mo as recommended, PPWR could be eliminated by that time in women with GWG values of approximately 12 kg, and that the possibility of major weight gain (≥ 5 kg) could be reduced in all but the heaviest women. CONCLUSION: Breastfeeding was associated with lower PPWR in all categories of prepregnancy BMI. These results suggest that, when combined with GWG values of approximately 12 kg, breastfeeding as recommended could eliminate weight retention by 6 mo postpartum in many women.

Kac, G., Benício, M. H., Velásquez-Meléndez, G., Valente, J. G., & Struchiner, C. J. (2004). Breastfeeding and postpartum weight retention in a cohort of Brazilian women. *The American journal of clinical nutrition, 79*(3), 487-493.

The relation between postpartum weight retention and breastfeeding practices is controversial. 405 women aged 18-45 y were assessed at 0.5, 2, 6, and 9 mo postpartum. The outcome variable, postpartum weight retention, was expressed as the difference between the observed weight at each follow-up and the reported prepregnancy weight. Mean postpartum weight retention at the end of the study was 3.1 kg. Single women aged greater than or equal to 30 y retained more weight than did younger single women or married women. The combined effect of

breastfeeding duration and percentage of body fat at baseline was significant only for women with < 30% body fat. According to the model's prediction, when women who had 22% body fat and breastfed for 180 d were compared with those who had 22% body fat and breastfed for only 30 d, each month of breastfeeding contributed -0.44 kg to postpartum weight retention. When only the percentage of body fat was varied, the total effect was 3.0, 1.7, 1.2, and 0.04 kg in women with 18%, 25%, 28%, and 35% body fat, respectively. These results support the hypothesis of an association between breastfeeding and postpartum weight retention and suggest that encouraging prolonged breastfeeding might contribute to decreases in postpartum weight retention.

Dewey, K. G., Cohen, R. J., Brown, K. H., & Rivera, L. L. (2001). Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. *The Journal of nutrition*, 131(2), 262-267.

Infants were exclusively breastfed for 4 months and then randomly assigned to continue exclusive breastfeeding until 6 months or to receive solid foods in addition to breast milk between 4 and 6 months. Maternal weight loss between 4 and 6 months was significantly greater in the exclusive breastfeeding group than in the group given solid foods. The estimated average additional nutritional burden of continuing to exclusively breastfeed until 6 months was small, representing only 0.1 to 6% of the recommended dietary allowance for energy, vitamin A, calcium and iron. Women in the exclusive breastfeeding group were more likely to be amenorrheic at 6 mo than women in the SF group, which conserves nutrients such as iron.

Kramer, F. M., Stunkard, A. J., Marshall, K. A., McKinney, S., & Liebschutz, J. (1993). Breast-feeding reduces maternal lower-body fat. *Journal of the American Dietetic Association*, 93(4), 429-433.

Mothers who breastfed exclusively or partially had significantly larger reductions in hip circumference and were less above their prepregnancy weights at 1 month postpartum than mothers who fed formula exclusively.

RELATIONSHIP (maternal-infant)

Kent, K., Wilkins, G., & Peterson, H. (2018). Attachment in Breastfeeding Versus Formula Feeding.

According to John Bowlby, infants are born with an innate need to maintain a close proximity to a primary caregiver “to protect an individual against physical and psychological threats and alleviate distress” (Bowlby, 2008, as cited in Amani, 2016, p. 510). Bowlby defines attachment as “the emotional bond between infant and caregiver, who is typically the mother” (Bowlby, 2008, as cited in Amani, 2016, p. 506). One way infants foster attachment to their caregiver is through their feeding process, such as breastfeeding or formula feeding. According to Hockenberry and Wilson (2015), “the most outstanding psychological benefit of breastfeeding is the close maternal-child relationship” (p. 277). Whereas, formula feeding “denies the infant the important component of close human contact” (Hockenberry & Wilson, 2015, p. 280). The

purpose of this Evidence-Based Practice Brief is to compare mother-infant bonding when exclusively breastfeeding as compared to formula feeding. With information gathered, nurses will be able to effectively educate patients on breastfeeding and formula feeding as related to mother-infant bonding through the assessment and implementation phase of the nursing process.

Papp, L. M. (2014). Longitudinal associations between breastfeeding and observed mother–child interaction qualities in early childhood. *Child: care, health and development*, 40(5), 740-746.

Despite extensive literature on the role of breastfeeding in maternal and child health and cognitive development, few studies have systematically tested whether breastfeeding predicts children's socio-emotional outcomes. The present study examined associations between trajectories of breastfeeding and observed parent–child interaction qualities of maternal sensitivity, child positivity, and child negativity from 6 months to 3 years of age. Data were drawn from the NICHD Study of Early Child Care and Youth Development (n = 1306 US families). Hierarchical linear modelling accounted for demographic and early characteristics, including home environment, maternal depression, and observed global relationship quality. Breastfeeding was associated with increases in observed maternal sensitivity over time, even after the effects of demographic and early characteristics were controlled. Accounting for the covariates, breastfeeding was not associated with child behaviour (i.e. positivity, negativity) in mother–child interaction across early childhood. Improved relationship quality, specifically through changes in maternal behaviour, may be another advantage experienced by breastfeeding mothers and children.

Kim, P., Feldman, R., Mayes, L. C., Eicher, V., Thompson, N., Leckman, J. F., & Swain, J. E. (2011). Breastfeeding, brain activation to own infant cry, and maternal sensitivity. *Journal of child psychology and psychiatry*, 52(8), 907-915.

Research points to the importance of breastfeeding for promoting close mother–infant contact and social-emotional development. Recent functional magnetic resonance imaging (fMRI) studies have identified brain regions related to maternal behaviors. However, little research has addressed the neurobiological mechanisms underlying the relationship between breastfeeding and maternal behavior in human mothers. We investigated the associations between breastfeeding, maternal brain response to own infant stimuli, and maternal sensitivity in the early postpartum. Methods: Seventeen biological mothers of healthy infants participated in two matched groups according to feeding method – exclusive breastfeeding and exclusive formula-feeding at 2–4 weeks postpartum. fMRI scanning was conducted in the first postpartum month to examine maternal brain activation in response to her own baby's cry versus control baby-cry. Dyadic interactions between mothers and infants at 3–4 months postpartum were videotaped in the home and blindly coded for maternal sensitivity. Results: In the first postpartum month, breastfeeding mothers showed greater activations in the superior frontal gyrus, insula, precuneus, striatum, and amygdala while listening to their own baby-cry as compared to formula-feeding mothers. For both breastfeeding and formula-feeding mothers, greater activations in the right superior frontal gyrus and amygdala were associated with higher maternal sensitivity at 3–4 months postpartum. Conclusions: Results suggest links between

breastfeeding and greater response to infant cues in brain regions implicated in maternal–infant bonding and empathy during the early postpartum. Such brain activations may facilitate greater maternal sensitivity as infants enter their social world.

RHEUMATOID ARTHRITIS

Chen, H., Wang, J., Zhou, W., Yin, H., & Wang, M. (2015). Breastfeeding and risk of rheumatoid arthritis: a systematic review and metaanalysis. *The Journal of rheumatology*, jrheum-150195. Previous studies have examined the association between breastfeeding and rheumatoid arthritis (RA), but their results were inconsistent. The aim of this study was to perform a metaanalysis to clarify the effect of breastfeeding on RA risk. The PubMed, EMBASE, Chinese National Knowledge Infrastructure, and Wanfang databases were searched for relevant studies published up to September 10, 2014. Data were extracted, and multivariable-adjusted OR with 95% CI were pooled in the random-effects model. A total of 6 studies were included in the metaanalysis (RA cases: 1672, sample size: 143,670). Overall, an inverse association between breastfeeding and RA was observed (OR 0.675, 95% CI 0.493–0.924, $p = 0.014$). In the subgroup analysis, decreased RA risk was also found in both breastfeeding 1–12 months (OR 0.783, 95% CI 0.641–0.957, $p = 0.015$) and breastfeeding > 12 months (OR 0.579, 95% CI 0.462–0.726, $p < 0.0005$). Sensitivity analysis and cumulative analysis further strengthened the validity of the results. No publication bias was found in this metaanalysis. This metaanalysis suggests that breastfeeding is associated with a lower risk of RA, no matter if breastfeeding time is longer or shorter than 12 months.

Adab, P., Jiang, C. Q., Rankin, E., Tsang, Y. W., Lam, T. H., Barlow, J., ... & Cheng, K. K. (2014). Breastfeeding practice, oral contraceptive use and risk of rheumatoid arthritis among Chinese women: the Guangzhou Biobank Cohort Study. *Rheumatology*, 53(5), 860-866. Hormonal and reproductive factors are implicated in the aetiology of RA, but results of previous studies have been mixed. The aim of this cross-sectional study was to assess the relationships between RA, use of oral contraceptives (OCs) and history of breastfeeding in a population of older women from South China. We used baseline data from 7349 women ≥ 50 years of age in the Guangzhou Biobank Cohort. Questionnaires were used to obtain socio-demographic, lifestyle and obstetric history data, including parity, OC use and breastfeeding practices. The main outcome was RA. Women were asked about history of RA and were examined to assess joint swelling. RF levels were measured. The presence of RA was defined in two ways: (i) as reporting physician–diagnosed RA or pain and swelling in at least three joints (including the wrist), and (ii) also having at least one of the following: positive RF, morning stiffness or objective swelling of the small joints of the hands. Compared with those who had never breastfed, breastfeeding was associated with half the risk of RA. The risk was lower with increasing duration of breastfeeding [adjusted odds ratio (OR) 0.54 (95% CI 0.29, 1.01) for breastfeeding at least 36 months; P for trend = 0.04]. OC use had no relationship with RA. Breastfeeding (especially longer duration) but not OC use is associated with a lower risk of RA. This has potentially important implications for future RA disease burden, given the declining

rates of breastfeeding and the one-child policy in China. Further research is needed to explain the biological mechanism.

Orellana, C., Klareskog, L., Alfredsson, L., & Bengtsson, C. (2015). SAT0335 Breastfeeding is Associated with a Decreased Risk of Acpa-Positive Rheumatoid Arthritis: Results from the Swedish EIRA Study. *Annals of Rheumatic Diseases*, 74, 780.

Breastfeeding has been associated with both a decreased [1,2] and an increased [3] risk of developing RA. To our knowledge no previous study has investigated the impact of breastfeeding on the two subgroups of RA, characterized by presence/absence of antibodies to citrullinated peptides (ACPA). To study the association between breastfeeding and the risk of ACPA-positive and ACPA-negative RA among women aged 18-70. Data from the population-based EIRA (Epidemiological Investigation of RA) case-control study was analyzed. In total, 938 incident cases and 1917 controls participated between 2006-2011. An extensive questionnaire was answered by the participants, including questions regarding duration of breastfeeding for each delivered child and potential confounders (education, smoking, BMI, oral contraceptive use, postmenopausal hormone therapy, reproductive factors). Total history of breastfeeding was categorized into 0-3, 4-7, 8-12, 13-19 and ≥ 20 months, using the lowest category as the reference group. We calculated odds ratios (ORs) with 95% confidence intervals (CI) by means of unconditional logistic regression, adjusting for age, residential area and number of children. A longer duration of breastfeeding was associated with a decreased risk of ACPA-positive RA (OR 4-7 months=1.0, 95% CI 0.7-1.4; OR 8-12 months=0.8, 95% CI 0.6-1.2; OR 13-19 months=0.6, 95% CI 0.4-0.9; OR ≥ 20 months=0.7, 95% CI 0.4-1.0) compared to parous women who breastfed less than 3 months. No association between breastfeeding and ACPA-negative RA was found. Conclusions: Our results indicate that a longer duration of breastfeeding reduces the risk of ACPA-positive RA among parous women, but has no association with the risk of ACPA-negative RA. Further research is needed to explore the biological mechanisms behind our findings but our study contributes to the knowledge of environmental risk factors such as breastfeeding and its different impact on the subgroups of RA.

Karlson, E. W., Mandl, L. A., Hankinson, S. E., & Grodstein, F. (2004). Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis?: Results from the Nurses' Health Study. *Arthritis & Rheumatism*, 50(11), 3458-3467.

We studied female reproductive and hormonal risk factors for rheumatoid arthritis (RA) in a cohort of 121,700 women enrolled in the longitudinal Nurses' Health Study. The diagnosis of incident RA in 674 women was confirmed. Using a multivariate model that adjusted for age, body mass index, smoking, parity, and other hormonal factors, we observed a strong trend for decreasing risk of RA with increasing duration of breast-feeding ($P = 0.001$). For women who breast-fed (compared with parous women who did not breast-feed), the risk ratios (RRs) were as follows: breast-feeding for ≤ 3 total months, RR 1.0; for 4-11 total months, RR 0.9; for 12-23 total months, RR 0.8; and for ≥ 24 total months, RR 0.5. Very irregular menstrual cycles were associated with an increased risk of RA (RR 1.4). Age at menarche ≤ 10 years was

associated with an increased risk of seropositive RA (RR 1.6) but not significantly associated with risk of RA. Parity, total number of children, age at first birth, and OC use were not associated with an increased risk of RA in this cohort. CONCLUSION: In this large cohort, breast-feeding for >12 months was inversely related to the development of RA. This apparent effect was dose dependent, with a significant trend toward lower risk with longer duration of breast-feeding.

SLEEP

Montgomery-Downs, H. E., Clawges, H. M., & Santy, E. E. (2010). Infant feeding methods and maternal sleep and daytime functioning. *Pediatrics*, 126(6), e1562-e1568.

We did not find differences between women who were exclusively breastfeeding, exclusively formula feeding, or using a combination of the 2 methods, with respect to the assessed parameters.

CONCLUSIONS: Efforts to encourage women to breastfeed should include information about sleep.

Specifically, women should be told that choosing to formula feed does not equate with improved sleep.

The risks of not breastfeeding should be weighed against the cumulative lack of evidence indicating any benefit of formula feeding on maternal sleep.

Hughes O, Mohamad MM, Doyle P, Burke G. The significance of breastfeeding on sleep patterns during the first 48 hours postpartum for first time mothers. *J Obstet Gynaecol*. 2018 Apr;38(3):316-320. doi: 10.1080/01443615.2017.1353594. Epub 2017 Oct 12. PMID: 29022404.

Breastfeeding women (still in hospital) slept on average 2.6 hours longer than women who bottle-fed. Environmental factors such as background noise, shared rooms, type of delivery, sleep patterns and reasons for wakefulness of first-time mothers immediately following delivery while still in the hospital. Feeding and worrying about the neonate did not influence the total sleep time.

Doan, T., Gay, C. L., Kennedy, H. P., Newman, J., & Lee, K. A. (2014). Nighttime breastfeeding behavior is associated with more nocturnal sleep among first-time mothers at one month postpartum. *Journal of Clinical Sleep Medicine*, 10(03), 313-319.

To describe sleep duration and quality in the first month postpartum and compare the sleep of women who exclusively breastfed at night to those who used formula. We conducted a longitudinal study in a predominantly low-income and ethnically diverse sample of 120 first-time mothers. Both objective and subjective measures of sleep were obtained using actigraphy, diary, and self-report data. Measures were collected in the last month of pregnancy and at one month postpartum. Infant feeding diaries were used to group mothers by nighttime breastfeeding behavior. Mothers who used at least some formula at night ($n = 54$) and those who breastfed exclusively ($n = 66$) had similar sleep patterns in late pregnancy. However, there was a significant group difference in nocturnal sleep at one month postpartum as measured by actigraphy. Total nighttime sleep was 386 ± 66 minutes for the exclusive breastfeeding group and 356 ± 67 minutes for the formula group. The groups did not differ with respect to daytime sleep, wake after sleep onset (sleep fragmentation), or subjective sleep disturbance at one month postpartum. Women who breastfed exclusively averaged 30 minutes more nocturnal sleep than women who used formula at night, but measures of sleep fragmentation did not differ. New mothers should be encouraged to breastfeed exclusively since breastfeeding may promote sleep during postpartum recovery. Further research is needed to better understand how infant feeding method affects maternal sleep duration and fragmentation.

Doan, T., Gardiner, A., Gay, C. L., & Lee, K. A. (2007). Breast-feeding increases sleep duration of new parents. *The Journal of perinatal & neonatal nursing*, 21(3), 200-206.

As part of a randomized clinical trial, the study utilized infant feeding and sleep data at 3 months postpartum from 133 new mothers and fathers. Infant feeding type (breast milk or formula) was determined from parent diaries. Sleep was measured objectively using wrist actigraphy and subjectively using diaries. Lee's General Sleep Disturbance Scale was used to estimate perceived sleep disturbance. RESULTS: Parents of infants who were breastfed in the evening and/or at night slept an average of 40-45 minutes more than parents of infants given formula. Parents of infants given formula at night also self-reported more sleep disturbance than parents of infants who were exclusively breast-fed at night. CONCLUSIONS: Parents who supplement their infant feeding with formula under the impression that they will get more sleep should be encouraged to continue breastfeeding.

SYSTEMIC LUPUS ERYTHEMATOSUS

Cooper, G. S., Dooley, M. A., Treadwell, E. L., St. Clair, E. W., & Gilkeson, G. S. (2002). Hormonal and reproductive risk factors for development of systemic lupus erythematosus: results of a population-based, case-control study. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, 46(7), 1830-1839.

In humans, 85% of systemic lupus erythematosus (SLE) patients are women, which suggests the importance of hormonal factors in disease pathogenesis. The purpose of this study was to examine hormonal and reproductive risk factors for lupus among women. This population-based, case-control study included 240 female SLE and 321 controls. Breastfeeding was associated with a decreased risk of developing SLE (OR 0.6), with a statistically significant trend for number of babies breastfed and total weeks of breast-feeding. There were no associations with number of pregnancies or live births. Natural menopause occurred earlier in women with subsequent development of SLE compared with controls ($P < 0.001$). There was little association between SLE and current use or duration of hormone replacement therapy or oral contraceptives, and no association with previous use of fertility drugs.

URINARY TRACT INFECTIONS

Coppa, G. V., Gabrielli, O., Giorgi, P., Catassi, C., Montanari, M. P., Varaldo, P. E., & Nichols, B. L. (1990). Preliminary study of breastfeeding and bacterial adhesion to uroepithelial cells. *The Lancet*, 335(8689), 569-571.

The oligosaccharide content of breast-milk and urine from nursing mothers is very similar, and the pattern of oligosaccharides excreted by infants is also strongly correlated with that of breastmilk. The oligosaccharides cause inhibition of bacterial adhesion, suggesting that breastfeeding may have a preventive effect on urinary tract infection in both mother and infant.

Societal Effects

CHILD ABUSE AND PARENTING SENSITIVITY

Weaver, J. M., Schofield, T. J., & Papp, L. M. (2018). Breastfeeding duration predicts greater maternal sensitivity over the next decade. *Developmental psychology*, 54(2), 220.

The current study represents the first longitudinal investigation of the potential effects of breastfeeding duration on maternal sensitivity over the following decade. This study also examined whether infant attachment security at 24 months would mediate longitudinal relations between breastfeeding duration and changes in maternal sensitivity over time. Using data from 1,272 families from the National Institute of Child Health and Human Development's Study of Early Child Care and Youth Development, we found that longer breastfeeding duration (assessed up to age 3) predicted increases in observed maternal sensitivity up to child age 11, after accounting for maternal neuroticism, parenting attitudes, ethnicity, maternal years of education, and presence of a romantic partner. Additionally, secure attachment at 24 months was predicted by breastfeeding duration, but it did not act as a mediator of the link from breastfeeding duration to maternal sensitivity in this study. Generating a more specific understanding of how breastfeeding impacts the mother-child dyad beyond infancy will inform recommendations for best practices regarding breastfeeding. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

Pearson, R. M., Lightman, S. L., & Evans, J. (2011). The impact of breastfeeding on mothers' attentional sensitivity towards infant distress. *Infant Behavior and Development*, 34(1), 200-205. Maternal response towards infant distress has an important impact on infant development. In animals it is established that lactation and pup suckling plays an important role in maintaining maternal responses. Previous research suggests that breastfeeding is associated with sensitive maternal responses in human mothers. However, this may be because women who are more sensitive to their infant choose to breastfeed. The current study investigated the attentional sensitivity towards infant distress in women who went on to breast or formula feed during pregnancy as well as after birth. We hypothesised that differences in breast and formula feeding mothers would only emerge after birth once feeding had commenced. METHOD: 51 women were seen during late pregnancy and between 3 and 6 months after birth (27 were breast and 24 were formula feeding). Sensitivity to infant distress was measured as the extent of women's attentional bias towards infant distress stimuli. RESULTS: After birth, we found that our index of attentional bias towards infant distress was 37ms (0.5 S.D.s) (CI; 6-69, $p=0.021$) higher in breastfeeding compared to formula feeding mothers. However, mothers who went on to breastfeed did not show greater attentional bias towards infant distress already during late pregnancy. CONCLUSIONS: Our results suggest that the act of breastfeeding may influence mothers' attentional sensitivity towards infant distress. Previous research suggests breastfeeding is indicative of sensitive parenting. The current findings may suggest a mechanism by which breastfeeding and/or associated infant interaction could contribute to this sensitivity

Strathearn, L., Mamun, A. A., Najman, J. M., & O'Callaghan, M. J. (2009). Does breastfeeding protect against substantiated child abuse and neglect? A 15-year cohort study. *Pediatrics*, 123(2), 483-493.

A total of 7223 Australian mother-infant pairs were monitored prospectively over 15 years. In 6621 (91.7%) cases, the duration of breastfeeding was analyzed with respect to child maltreatment (including neglect, physical abuse, and emotional abuse), on the basis of substantiated child protection agency reports. Multinomial logistic regression was used to compare no maltreatment with nonmaternal and maternally perpetrated maltreatment and to adjust for confounding in 5890 cases with complete data (81.5%). Potential confounders included sociodemographic factors, pregnancy wantedness, substance abuse during pregnancy, postpartum employment, attitudes regarding infant caregiving, and symptoms of anxiety or depression. RESULTS: Of 512 children with substantiated maltreatment reports, >60% experienced > or =1 episode of maternally perpetrated abuse or neglect (4.3% of the cohort). The odds ratio for maternal maltreatment increased as breastfeeding duration decreased, with the odds of maternal maltreatment for nonbreastfed children being 4.8 times the odds for children breastfed for > or =4 months. After adjustment for confounding, the odds for nonbreastfed infants remained 2.6 times higher, with no association seen between breastfeeding and nonmaternal maltreatment. Maternal neglect was the only maltreatment subtype associated independently with breastfeeding duration. CONCLUSION: Among other factors, breastfeeding may help to protect against maternally perpetrated child maltreatment, particularly child neglect.

Lvoff, N. M., Lvoff, V., & Klaus, M. H. (2000). Effect of the baby-friendly initiative on infant abandonment in a Russian hospital. *Archives of pediatrics & adolescent medicine*, 154(5), 474-477.

Encouraging early mother-infant contact with suckling and rooming-in may provide a simple, low-cost method for reducing infant abandonment. The mean infant abandonment rate decreased from 50.3 per 10,000 births in the first 6 years to 27.8 per 10,000 births in the next 6 years following implementation of the Baby-Friendly Hospital Initiative at a Russian hospital. A retrospective review of 800 pregnancies at one family practice revealed an association between lack of breastfeeding and physical and sexual abuse of the mother and/or her children. This anecdotal association has not been previously reported, and is worth further study using more rigorous methods. Acheson, L., "Family Violence and Breast-feeding" *Arch Fam Med* July 1995; Vol 4, pp 650-652.

Buranasin, B. (1991). The effects of rooming-in on the success of breastfeeding and the decline in abandonment of children. *Asia Pacific Journal of Public Health*, 5(3), 217-220.

This study analyzed the effect of management of rooming-in, conducted in one of the regional hospitals in Thailand, on the success of breastfeeding. Data based on 2,000 infants born in 1987 and 1990 showed a significant improvement on separation time of infant and mother after delivery and predominant breastfeeding. Separation time was reduced from 6.3 to 1.62 hours and predominant breastfeeding was significantly increased from 85 to 99 percent. Data obtained from the community related to the initiation and predominant breastfeedings showed a

significant increase (p less than 0.05). The findings showed a progressive reduction of deserted children after management of rooming-in.

CHILD SPACING

Singh, R., Tripathi, V., Singh, K., Ahuja, R. K., Vani, M. K., & Dwivedi, S. N. (2012).

Breastfeeding as a time-varying-time-dependent factor for birth spacing: multivariate models with validations and predictions. *World health & population*, 13(3), 28-51.

Data used in the present study are from the National Family Health Survey 1992-93 (International Institute for Population Sciences 1995), India. Our study has developed Cox model analyses to see the effect of breastfeeding as a time-varying and time-dependent factor on birth spacing. While it is acknowledged that breastfeeding has a protective effect on birth spacing, such analysis of breastfeeding allows for a more nuanced understanding of that effect. Multivariate analysis revealed that breastfeeding, ever experience of fetal loss, education of women, employment status of women, education of husband, media exposure, survival status of index child and place of residence played an important part in extending birth space in at least one of the birth-spacing intervals (first to fifth). However, the variables varied from the first birth spacing to the fifth birth spacing. Breastfeeding is the only covariate found to be a significant protective factor associated with each birth spacing. Furthermore, this study validates the developed models with their prediction utilities for birth spacing.

Defo, B. K. (1997). Effects of infant feeding practices and birth spacing on infant and child survival: a reassessment from retrospective and prospective data. *Journal of Biosocial Science*, 29(3), 303-326.

Retrospective and prospective data show that: (a) a short preceding birth interval is detrimental for child survival in the first 4 months of life; (b) full and partial breast-feeding have direct protective effects on child survival in the first 4-6 months of life, with the effects of the former stronger than those of the latter; (c) early subsequent conception significantly increases mortality risks in the first 16 months of life of the index child. These findings are robust to various controls, e.g. study design, data defects, child's health conditions at/around birth, postnatal maternal and child recurrent illnesses, patterns of utilization of health care services, and immunization status of the child.

Thapa, S., Short, R. V., & Potts, M. (1988). Breast feeding, birth spacing and their effects on child survival. *Nature*, 335(6192), 679.

Sufficient birth spacing helps with the survival of the older sibling and the new infant. Prolonged lactation helps to promote the spacing of children.

ENVIRONMENT

There is less use of natural resources (glass, plastic, metal, and paper used in bottles, bags, nipples, and formula cans) and also less waste for landfills. The breastfed infant is not exposed to chemicals in nipples and bottles.

FINANCIAL COST TO GOVERNMENT AND FAMILIES

Economic Expense

Rollins, N. C., Bhandari, N., Hajeighbhoy, N., Horton, S., Lutter, C. K., Martines, J. C., ... & Group, T. L. B. S. (2016). Why invest, and what it will take to improve breastfeeding practices?. *The Lancet*, 387(10017), 491-504.

Despite its established benefits, breastfeeding is no longer a norm in many communities. Multifactorial determinants of breastfeeding need supportive measures at many levels, from legal and policy directives to social attitudes and values, women's work and employment conditions, and health-care services to enable women to breastfeed. When relevant interventions are delivered adequately, breastfeeding practices are responsive and can improve rapidly. The best outcomes are achieved when interventions are implemented concurrently through several channels. The marketing of breastmilk substitutes negatively affects breastfeeding: global sales in 2014 of US\$44.8 billion show the industry's large, competitive claim on infant feeding. Not breastfeeding is associated with lower intelligence and economic losses of about \$302 billion annually or 0.49% of world gross national income. Breastfeeding provides short-term and long-term health and economic and environmental advantages to children, women, and society. To realise these gains, political support and financial investment are needed to protect, promote, and support breastfeeding.

Pokhrel, S., Quigley, M. A., Fox-Rushby, J., McCormick, F., Williams, A., Trueman, P., ... & Renfrew, M. J. (2015). Potential economic impacts from improving breastfeeding rates in the UK. *Archives of disease in childhood*, 100(4), 334-340.

To calculate potential cost savings attributable to increases in breastfeeding rates from the National Health Service perspective. Cost savings focussed on where evidence of health benefit is strongest: reductions in gastrointestinal and lower respiratory tract infections, acute otitis media in infants, necrotising enterocolitis in preterm babies and breast cancer (BC) in women. Savings were estimated using a seven-step framework in which an incidence-based disease model determined the number of cases that could have been avoided if breastfeeding rates were increased. Point estimates of cost savings were subject to a deterministic sensitivity analysis. Treating the four acute diseases in children costs the UK at least £89 million annually. The 2009–2010 value of lifetime costs of treating maternal BC is estimated at £959 million. Supporting mothers who are exclusively breast feeding at 1 week to continue breast feeding until 4 months can be expected to reduce the incidence of three childhood infectious diseases and save at least £11 million annually. Doubling the proportion of mothers currently breast feeding for 7–18 months in their lifetime is likely to reduce the incidence of maternal BC and save at least £31 million at 2009–2010 value. The economic impact of low breastfeeding rates is

substantial. Investing in services that support women who want to breastfeed for longer is potentially cost saving.

Food Expense

The cost to supply artificial baby milk (ABM) to one child is between \$1,160 and \$3,915 per year depending on the brand. Even mothers on WIC need to buy approximately 200 cans of concentrate to feed her infant in the first year. Breastfeeding Support Consultants, Information on Infant Feeding Costs, April 1998 (based on Illinois and North Carolina suburban supermarket prices).

Medical Expenses

Bartick, M. C., Schwarz, E. B., Green, B. D., Jegier, B. J., Reinhold, A. G., Colaizy, T. T., ... & Stuebe, A. M. (2017). Suboptimal breastfeeding in the United States: Maternal and pediatric health outcomes and costs. *Maternal & child nutrition*, 13(1), e12366.

The aim of this study was to quantify the excess cases of pediatric and maternal disease, death, and costs attributable to suboptimal breastfeeding rates in the United States. Using the current literature on the associations between breastfeeding and health outcomes for nine pediatric and five maternal diseases, we created Monte Carlo simulations modeling a hypothetical cohort of U.S. women followed from age 15 to age 70 years and their children from birth to age 20 years. We examined disease outcomes using (a) 2012 breastfeeding rates and (b) assuming that 90% of infants were breastfed according to medical recommendations. We measured annual excess cases, deaths, and associated costs, in 2014 dollars, using a 2% discount rate. Annual excess deaths attributable to suboptimal breastfeeding total 3,340 (95% confidence interval [1,886 to 4,785]), 78% of which are maternal due to myocardial infarction (n = 986), breast cancer (n = 838), and diabetes (n = 473). Excess pediatric deaths total 721, mostly due to Sudden Infant Death Syndrome (n = 492) and necrotizing enterocolitis (n = 190). Medical costs total \$3.0 billion, 79% of which are maternal. Costs of premature death total \$14.2 billion. The number of women needed to breastfeed as medically recommended to prevent an infant gastrointestinal infection is 0.8; acute otitis media, 3; hospitalization for lower respiratory tract infection, 95; maternal hypertension, 55; diabetes, 162; and myocardial infarction, 235. For every 597 women who optimally breastfeed, one maternal or child death is prevented. Policies to increase optimal breastfeeding could result in substantial public health gains. Breastfeeding has a larger impact on women's health than previously appreciated.

Unar-Munguía, M., Meza, R., Colchero, M. A., Torres-Mejía, G., & de Cosío, T. G. (2017). Economic and disease burden of breast cancer associated with suboptimal breastfeeding practices in Mexico. *Cancer Causes & Control*, 28(12), 1381-1391.

Exclusive breastfeeding and longer breastfeeding reduce women's breast cancer risk but Mexico has one of the lowest breastfeeding rates worldwide. We estimated the lifetime economic and disease burden of breast cancer in Mexico if 95% of parous women breastfeed each child exclusively for 6 months and continue breastfeeding for over a year. We used a static

microsimulation model with a cost-of-illness approach to simulate a cohort of Mexican women. We estimated breast cancer incidence, premature mortality, disability-adjusted life years (DALYs), medical costs, and income losses due to breast cancer and extrapolated the results to 1.116 million Mexican women of age 15 in 2012. Costs were expressed in 2015 US dollars and discounted at a 3% annual rate. We estimated that 2,186 premature deaths (95% CI 2,123–2,248), 9,936 breast cancer cases (95% CI 9,651–10,220), 45,109 DALYs (95% CI 43,000–47,217), and \$245 million USD (95% CI 234–256) in medical costs and income losses owing to breast cancer could be saved over a cohort's lifetime. Medical costs account for 80% of the economic burden; income losses and opportunity costs for caregivers account for 15 and 5%, respectively. In Mexico, the burden of breast cancer due to suboptimal breastfeeding in women is high in terms of morbidity, premature mortality, and the economic costs for the health sector and society.

Walters, D., Horton, S., Siregar, A. Y. M., Pitriyan, P., Hajeerhoy, N., Mathisen, R., ... & Rudert, C. (2016). The cost of not breastfeeding in Southeast Asia. *Health policy and planning*, 31(8), 1107-1116.

Rates of exclusive breastfeeding are slowly increasing, but remain suboptimal globally despite the health and economic benefits. This study estimates the costs of not breastfeeding across seven countries in Southeast Asia and presents a cost-benefit analysis of a modeled comprehensive breastfeeding strategy in Viet Nam, based on a large programme. There have been very few such studies previously for low- and middle-income countries. The estimates used published data on disease prevalence and breastfeeding patterns for the seven countries, supplemented by information on healthcare costs from representative institutions. Modelling of costs of not breastfeeding used estimated effects obtained from systematic reviews and meta-analyses. Modelling of cost-benefit for Viet Nam used programme data on costs combined with effects from a large-scale cluster randomized breastfeeding promotion intervention with controls. This study found that over 12 400 preventable child and maternal deaths per year in the seven countries could be attributed to inadequate breastfeeding. The economic benefits associated with potential improvements in cognition alone, through higher IQ and earnings, total \$1.6 billion annually. The loss exceeds 0.5% of Gross National Income in the country with the lowest exclusive breastfeeding rate (Thailand). The potential savings in health care treatment costs (\$0.3 billion annually) from reducing the incidence of diarrhoea and pneumonia could help offset the cost of breastfeeding promotion. Based on the data available and authors' assumptions, investing in a national breastfeeding promotion strategy in Viet Nam could result in preventing 200 child deaths per year and generate monetary benefits of US\$2.39 for every US\$1, or a 139% return on investment. These encouraging results suggest that there are feasible and affordable opportunities to accelerate progress towards achieving the Global Nutrition Target for exclusive breastfeeding by 2025.

Colchero, M. A., Contreras-Loya, D., Lopez-Gatell, H., & González de Cosío, T. (2015). The costs of inadequate breastfeeding of infants in Mexico—. *The American journal of clinical nutrition*, 101(3), 579-586.

The objective of the article was to estimate the pediatric costs of inadequate breastfeeding in Mexico associated with the following acute health conditions: respiratory infections, otitis media,

gastroenteritis, necrotizing enterocolitis (NEC), and sudden infant death syndrome (SIDS). The authors estimated the economic costs of inadequate breastfeeding as follows: the sum of direct health care costs for diseases whose risk increases when infants are non-exclusively breastfed <6 mo or are not breastfed from ages 6 to <11 mo, lost future earnings due to premature infant death, and the costs of purchasing infant formula. Incidence cases were retrieved from national surveillance systems, except for NEC and SIDS, which were estimated from the literature. A sensitivity analysis was carried out to provide a range of costs based on different assumptions of the number of incident cases of all infant health outcomes examined. The model applied to the cohort of 1-y-old children born in 2012. The total annual costs of inadequate breastfeeding in Mexico for the studied cohort ranged from \$745.6 million to \$2416.5 million, where the costs of infant formula accounted for 11–38% of total costs. A range of 1.1–3.8 million reported cases of disease and from 933 to 5796 infant deaths per year for the diseases under study are attributed to inadequate infant breastfeeding practices; altogether these represent nearly 27% of the absolute number of episodes of such diseases. This study provides costs of inadequate breastfeeding that had not been quantified in Mexico. The costs presented in this article provide the minimum amount that the country should invest to achieve better breastfeeding practices.

Bartick, M. C., Stuebe, A. M., Schwarz, E. B., Luongo, C., Reinhold, A. G., & Foster, E. M. (2013). Cost analysis of maternal disease associated with suboptimal breastfeeding. *Obstetrics & Gynecology*, 122(1), 111-119.

Using literature on associations between lactation and maternal health, we modeled the health outcomes and costs expected for a U.S. cohort of 15-year-old females followed to age 70 years. In 2002, this cohort included 1.88 million individuals. Using Monte Carlo simulations, we compared the outcomes expected if 90% of mothers were able to breastfeed for at least 1 year after each birth with outcomes under the current 1-year breastfeeding rate of 23%. We modeled cases of breast cancer, premenopausal ovarian cancer, hypertension, type 2 diabetes mellitus, and myocardial infarction considering direct costs, indirect costs, and cost of premature death (before age 70 years) expressed in 2011 dollars. RESULTS: If observed associations between breastfeeding duration and maternal health are causal, we estimate that current breastfeeding rates result in 4,981 excess cases of breast cancer, 53,847 cases of hypertension, and 13,946 cases of myocardial infarction compared with a cohort of 1.88 million U.S. women who optimally breastfed. Using a 3% discount rate, suboptimal breastfeeding incurs a total of \$17.4 billion in cost to society resulting from premature death (95% confidence interval [CI] \$4.38-24.68 billion), \$733.7 million in direct costs (95% CI \$612.9-859.7 million), and \$126.1 million indirect morbidity costs (95% CI \$99.00- 153.22 million). We found a nonsignificant difference in number of deaths before age 70 years under current breastfeeding rates (4,396 additional premature deaths, 95% CI -810-7,918). CONCLUSIONS: Suboptimal breastfeeding may increase U.S. maternal morbidity and health care costs. Thus, investigating whether the observed associations between suboptimal breastfeeding and adverse maternal health outcomes are causal should be a research priority.

Roberts, T. J., Carnahan, E., & Gakidou, E. (2013). Can breastfeeding promote child health equity? A comprehensive analysis of breastfeeding patterns across the developing world and what we can learn from them. *BMC medicine*, 11(1), 254.

In 2010 more than 7.7 million children died before their fifth birthday. Over 98% of these deaths occurred in developing countries, and recent estimates have attributed hundreds of thousands of these deaths to suboptimal breastfeeding. **METHODS:** This study estimated prevalence of suboptimal breastfeeding for 137 developing countries from 1990 to 2010. These estimates were compared against WHO infant feeding recommendations and combined with effect sizes from existing literature to estimate associated disease burden using a standard comparative risk assessment approach. These prevalence estimates were disaggregated by wealth quintile and linked with child mortality rates to assess how improved rates of breastfeeding may affect child health inequalities. **RESULTS:** In 2010, the prevalence of exclusive breastfeeding ranged from 3.5% in Djibouti to 77.3% in Rwanda. The proportion of child Disability Adjusted Life Years (DALYs) attributable to suboptimal breastfeeding is 7.6% at the global level and as high as 20.2% in Swaziland. Suboptimal breastfeeding is a leading childhood risk factor in all developing countries and consistently ranks higher than water and sanitation. Within most countries, breastfeeding prevalence rates do not vary considerably across wealth quintiles. **CONCLUSIONS:** Breastfeeding is an effective child health intervention that does not require extensive health system infrastructure. Improvements in rates of exclusive and continued breastfeeding can contribute to the reduction of child mortality inequalities in developing countries.

Bartick, M., & Reinhold, A. (2010). The burden of suboptimal breastfeeding in the United States: a pediatric cost analysis. *Pediatrics*, peds-2009.

A 2001 study revealed that \$3.6 billion could be saved if breastfeeding rates were increased to levels of the Healthy People objectives. It studied 3 diseases and totaled direct and indirect costs of premature death. The 2001 study can be updated by using current breastfeeding rates and adding additional diseases analyzed in the 2007 breastfeeding report from the Agency for Healthcare Research and Quality. Using methods similar to those in the 2001 study, we computed current costs and compared them to the projected costs if 80% and 90% of US families could comply with the recommendation to exclusively breastfeed for 6 months. Excluding type 2 diabetes (because of insufficient data), we conducted a cost analysis for all pediatric diseases for which the Agency for Healthcare Research and Quality reported risk ratios that favored breastfeeding: necrotizing enterocolitis, otitis media, gastroenteritis, hospitalization for lower respiratory tract infections, atopic dermatitis, sudden infant death syndrome, childhood asthma, childhood leukemia, type 1 diabetes mellitus, and childhood obesity. We used 2005 Centers for Disease Control and Prevention breastfeeding rates and 2007 dollars. If 90% of US families could comply with medical recommendations to breastfeed exclusively for 6 months, the United States would save \$13 billion per year and prevent an excess 911 deaths, nearly all of which would be in infants (\$10.5 billion and 741 deaths at 80% compliance). Current US breastfeeding rates are suboptimal and result in significant excess costs and preventable infant deaths. Investment in strategies to promote longer breastfeeding duration and exclusivity may be cost-effective.

Pugh, L. C., Milligan, R. A., Frick, K. D., Spatz, D., & Bronner, Y. (2002). Breastfeeding duration, costs, and benefits of a support program for low-income breastfeeding women. *Birth*, 29(2), 95-100.

This community-based randomized clinical trial involving low-income mothers compared usual care with an intervention comprising hospital and home visits, and telephone support by a community health nurse/peer counselor team for 6 months after delivery. Forty-one women were recruited after delivery of a full-term singleton infant and randomly assigned to intervention or usual care groups. Women receiving the community health intervention breastfed longer than the women receiving usual care. The infants in the intervention group had fewer sick visits and reported use of fewer medications than infants in the usual care group. The intervention cost (\$301/mother) was partially offset by cost savings on formula and health care. Community health nurse and peer counselor support can increase breastfeeding duration in low-income women, and has the potential to reduce total costs including the cost of support.

Weimer, J. P. (2001). *The economic benefits of breastfeeding: A review and analysis* (No. 33813). United States Department of Agriculture, Economic Research Service.

A minimum of \$3.6 billion would be saved if breastfeeding were increased from current levels (64 percent in-hospital, 29 percent at 6 months) to those recommended by the U.S. Surgeon General (75 and 50 percent). This figure is likely an underestimation of the total savings because it represents cost savings from the treatment of only three childhood illnesses: otitis media, gastroenteritis, and necrotizing enterocolitis. This report reviews breastfeeding trends and previous studies that assessed the economic benefits of breastfeeding.

Ball, T. M., & Wright, A. L. (1999). Health care costs of formula-feeding in the first year of life. *Pediatrics*, 103(Supplement 1), 870-876.

In the first year of life, after adjusting for confounders, there were 2033 excess office visits, 212 excess days of hospitalization, and 609 excess prescriptions for these three illnesses per 1000 never-breastfed infants compared with 1000 infants exclusively breastfed for at least 3 months. These additional health care services cost the managed care health system between \$331 and Page 63 of 63 \$475 per never-breastfed infant during the first year of life.

Montgomery, D. L., & Splett, P. L. (1997). Economic benefit of breast-feeding infants enrolled in WIC. *Journal of the American Dietetic Association*, 97(4), 379-385.

Compared with formula-feeding, breast-feeding each infant enrolled in WIC saved \$478 in WIC costs and Medicaid expenditures during the first 6 months of the infant's life.

Tuttle, C. R., & Dewey, K. G. (1996). Potential cost savings for Medi-Cal, AFDC, food stamps, and WIC programs associated with increasing breast-feeding among low-income Hmong women in California. *Journal of the American Dietetic Association*, 96(9), 885-890.

If women breast-fed each child for at least 6 months, the total projected savings over a 7.5-year period ranges from \$3,442 to \$6,096 per family. This translates into an estimated yearly savings of between \$459 and \$808 per family. Savings were calculated based on estimates of the resulting decrease in infant morbidity, maternal fertility, and formula purchases.

A pre-publication study by the Wisconsin State Breastfeeding Coalition estimated the following health care savings in Wisconsin if Breastfeeding rates were at 75% at discharge-50% at six months:

\$4,645,250/yr Acute Otitis Media
\$437,120/yr Bronchitis
\$6,699,600/yr Gastroenteritis
\$262,440/yr Allergies
\$758,934/yr Asthma
\$578,500/yr Type I Diabetes (birth - 18 yrs)
\$17,070,000/yr Breast Cancer
\$30,984,432/yr TOTAL HEALTH COST SAVINGS

VACCINE EFFECTIVENESS (see also “Vaccine Response”)

Haque, R., Snider, C., Liu, Y., Ma, J. Z., Liu, L., Nayak, U., ... & Alam, M. (2014). Oral polio vaccine response in breast fed infants with malnutrition and diarrhea. *Vaccine*, 32(4), 478-482. Oral vaccines for polio (OPV) and rotavirus are less effective in children in the developing world. The reasons for this are not well understood. We tested for risk factors for poor response to OPV in infants from an urban slum of Dhaka, Bangladesh. Diminished serum neutralizing response to OPV, but not failure of intramuscularly administered vaccines, was associated with malnutrition, diarrhea, and shorter breastfeeding duration. Children with malnutrition (WAZ <-2) had significantly lower OPV 3 titers ($p = 0.029$). Children who had 2 or more diarrhea episodes during the 1st months of life were more than twice as likely to experience OPV failure as those who had 1 diarrhea episode or no diarrhea ($p = 0.0245$). In contrast, each additional month in exclusive breastfeeding was associated with an increase in OPV 3 titer by 0.41 ($p = 0.0072$) and 0.16 ($p = 0.0065$) at the 25th and 50th percentiles of OPV 3 titers respectively. These data are consistent with a defect in induction of immunity in the gut for OPV but not parenteral vaccines, a defect that may be amenable to intervention in part via promotion of exclusive breastfeeding.

Hahn-Zoric, M., Fulconis, F., Minoli, I., Moro, G., Carlsson, B., Böttiger, M., ... & Hanson, L. Å. (1990). Antibody responses to parenteral and oral vaccines are impaired by conventional and low protein formulas as compared to breast-feeding. *Acta Paediatrica*, 79(12), 1137-1142. Breastfed infants showed a better serum and secretory responses to oral and parenteral vaccines than the formula-fed, whether with a conventional or low protein content.