



Evergreen Perinatal Education
WHERE EXCELLENCE IN HEALTHCARE BEGINS

OUTCOMES OF BREASTFEEDING

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I. Effects on the Infant

A. Infection

1. Candidiasis

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

2. Diarrhea

Breast-fed children, compared with the bottle-fed ones, have a lower incidence of acute gastroenteritis due to the presence of several antiinfective 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 ftyris*) 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. ftyris*; the neutral low-molecular-weight fraction was effective toward *E. coli* O119 and *S. ftyris* 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. ftyris*. Consequently, oligosaccharides are one of the important defensive factors contained in human milk against acute diarrheal infections of breast-fed infants. Coppa GV, et al. Human milk oligosaccharides inhibit the adhesion to Caco-2 cells of diarrheal pathogens: *Escherichia coli*, *Vibrio cholerae*, and *Salmonella ftyris*. *Pediatr Res*. 2006 Mar;59(3):377-82.

Case-control study of diarrhoeal disease cases presenting to 34 general practices in England. Data were available on 304 infants (167 cases and 137 controls). After adjustment for confounders, breast feeding was associated with significantly less diarrhoeal 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 diarrhoeal disease in those not sterilising bottles/teats with steam or chemicals. The protective effect of breast feeding did not persist beyond two months after breast feeding had stopped. Breast feeding protects against diarrhoeal disease in infants in England although the degree of protection may vary across infants and wear off after breast feeding cessation. Education about the benefits of breast feeding and the risks of inadequate sterilisation should be targeted at carers in deprived areas or households. Quigley MA et al. How protective is breast feeding against diarrhoeal disease in infants in 1990s England? A case-control study. *Arch Dis Child*. 2006 Mar;91(3):245-50

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 alpha1,3- or alpha1,4-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 alpha1,2-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. Newburg-DS et al. "Innate protection conferred by fucosylated oligosaccharides of human milk against diarrhea in breastfed infants." *Glycobiology*. Mar 2004; 14(3): 253-263.

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. Baker D et al. "Inequality in infant morbidity: causes and consequences in England in the 1990s." *J Epidemiol Community Health* 1998 Jul;52(7):451-8

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. Scariati PD et al. "A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States." *Pediatrics* 1997 Jun;99(6):E5

The type of milk consumed before start of diarrhea 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. Fuchs SC et al. "Case-control study of risk of dehydrating diarrhoea in infants in vulnerable period after full weaning." *BMJ* 1996 Aug 17;313(7054):391-4

In the first year of life the incidence of diarrheal illness among breastfed infants was half that of formula-fed infants. Dewey KG et al. "Differences in morbidity between breast-fed and formula-fed infants." *J Pediatr* 1995 May;126(5 Pt 1):696-702

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. Lerman, Y. et al. "Epidemiology of acute diarrheal diseases in children in a high standard of living settlement in Israel". *Pediatr Infect Dis J* 1994; 13(2):116-22.

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. Long KZ et al. Proportional hazards analysis of diarrhea due to enterotoxigenic *Escherichia coli* and breastfeeding in a cohort of urban Mexican children. *Am J Epidemiol*. 1994 Jan 15;139(2):193-205.

In this study of 500 Brazilian infants \leq 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). Blake PA, et al. "Pathogen-specific risk factors and protective factors for acute diarrheal disease in urban Brazilian infants." *J Infect Dis* 1993 Mar;167(3):627-32

The addition to the breast-milk diet of even water, teas, and other nonnutritive liquids doubled or tripled the likelihood of diarrhea. Supplementation of breast-feeding with additional nutritive foods or liquids further increased significantly the risk of diarrhea. Popkin BM et al. "Breast-feeding and diarrheal morbidity." *Pediatrics* 1990 Dec;86(6):874-82.

3. Enteroviruses

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 \leq 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. Sadeharju K et al. "Maternal antibodies in breast milk protect the child from enterovirus infections." *Pediatrics*. 2007 May;119(5):941-6.

4. Gastroenteritis

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 \geq 2500 g. We compared 475 infants breastfed exclusively for \geq 6 months (group A), 870 infants breastfed fully/exclusively \geq 4 months, but not exclusively \geq 6 months (group B) and 619 infants not breastfed/breastfed $<$ 4 months (group C). RESULTS: In multivariate analysis \geq 6 months of exclusive breastfeeding reduced significantly the risk for \geq 1 episode of gastrointestinal infection(s) during months 1-9 compared to no/ $<$ 4 months breastfeeding (adjusted odds ratio [OR]: 0.60; 95% confidence interval [CI]: 0.44-0.82). The application of the World Health Organization (WHO)-child growth standards showed lower weight-for-length z-scores in first days of life in group C versus groups A and B, whereas in months 6/7 group C showed the highest scores. CONCLUSION: Differences in child growth depending on breastfeeding duration should be investigated further. Concerning health outcomes our findings support the recommendation for \geq 6 months of exclusive breastfeeding. Rebhan B, Kohlhuber M, Schwegler U, Fromme H, Abou-Dakn M, Koletzko BV. "Breastfeeding duration and exclusivity associated with infants' health and growth: data from a prospective cohort study in Bavaria, Germany." *Acta Paediatr.* 2009 Jun;98(6):974-80.

Sixty-seven children aged 18 days to 18 months were admitted with hypernatraemic dehydration caused by acute gastro-enteritis. 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. Abu-Ekteish-F; Zahraa-J. "Hypernatraemic dehydration and acute gastro-enteritis in children." *Annals-Of-Tropical-Paediatrics.* Sep 2002; 22 (3) : 245-249.

5. Giardia

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.

6. Haemophilus Influenza

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-SA et al. „Long term enhancement of the IgG2 antibody response to *Haemophilus influenzae* type b by breast-feeding." *Pediatric Infectious Disease Journal.* Sep 2002; 21 (9): 816-821.

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. Harabuchi Y et al. "Human milk secretory IgA antibody to nontypeable *Haemophilus influenzae*: possible protective effects against nasopharyngeal colonization. *J Pediatr* 1994 Feb;124(2):193-8

The adjusted odds ratio for exposure to breastfeeding was 0.5. Arnold C, et al. "Day care attendance and other risk factors for invasive *Haemophilus influenzae* type b disease." *Am J Epidemiol* 1993 Sep 1;138(5):333-40

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). Petersen GM. "Effects of age, breast feeding, and household structure on *Haemophilus influenzae* type b disease risk and antibody acquisition in Alaskan Eskimos. *Am J Epidemiol* 1991 Nov 15;134(10):1212-21

In a population-based case-control study of risk factors for primary invasion of haemophilus influenza, type B disease, breastfeeding was protective of infants less than 6 months of age. Cochi, S.L. "Primary Invasive Haemophilus Influenza Type B Disease, A Population Based Assessment of Risk Factors". Journal of Pediatrics 1986 Jun;108(6):887-96.

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

OBJECTIVE: To examine the associations of duration of exclusivebreastfeeding 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. Duijts L, Jaddoe VW, Hofman A, Moll HA. "Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy." Pediatrics 2010; 126:1e18-e25.

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. **RESULTS:** 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.**CONCLUSIONS:** 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. Ladomenou F, Moschandreas J, Kafatos A, Tselentis Y, Galanakis E. Protective effect of exclusive breastfeeding against infections during infancy: a prospective study. Arch Dis Child. 2010 Dec;95(12):1004-8.

8. Meningitis in Preterm Infants

The incidence of any infection and sepsis/meningitis are significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants. Hylander MA et al. "Human milk feedings and infection among very low birth weight infants." Pediatrics 1998 Sep;102(3):E38

9. Necrotizing Enterocolitis

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. McGuire W; Anthony MY. "Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review." Archives of Disease in Childhood. Jan 2003; 88 (1) Special Iss. SI : 11-14.

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. Schanler RJ, et al. "Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula." Pediatrics 1999 Jun;103(6 Pt 1):1150-7

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. Caplan MS, et al. "Necrotizing enterocolitis: a review of pathogenetic mechanisms and implications for prevention."(review) *Pediatr Pathol* 1993 May-Jun;13(3):357-69

Based on both laboratory and clinical studies, human milk feeding appears to have protective effects against development of necrotizing enterocolitis. Buescher ES. "Host defense mechanisms of human milk and their relations to enteric infections and necrotizing enterocolitis."(review) *Clin Perinatol* 1994 Jun;21(2):247-62

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

10. Otitis Media (ear infection)

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. Scariati PD et al. "A longitudinal analysis of infant morbidity and the extent of breastfeeding in the United States." *Pediatrics* 1997 Jun;99(6):E5

In infants who were breast fed 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). Dewey KG et al. "Differences in morbidity between breast-fed and formula-fed infants." *J Pediatr* 1995 May;126(5 Pt 1):696-702

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. Duncan B et al. "Exclusive breast-feeding for at least 4 months protects against otitis media." *Pediatrics* 1993 May;91(5):867-72

Short duration of breastfeeding involved another significant risk of recurrent respiratory infections and otitis media. Alho, O., "Risk Factors for Recurrent Acute Otitis Media and Respiratory Infection in Infancy". *INT J PED OTORHINOLARYNGOLOGY* 1990; 19:151-61

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. Teele, D.W., *Epidemiology of Otitis Media During the First Seven Years of Life in Greater Boston: A prospective, Cohort Study*". *J of INFEC DIS*.1989.

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

11. Pneumococcal Disease

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. Levine OS et al. "Risk factors for invasive pneumococcal disease in children: a population-based case-control study in North America." *Pediatrics* 1999 Mar;103(3):E28

12. Respiratory Infections (general)

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 > or = 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 > or = 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. CONCLUSIONS: 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. Chantry CJ, Howard CR, Auinger P. "Full breastfeeding duration and associated decrease in respiratory tract infection in US children." *Pediatrics*. 2006 Feb;117(2):425-32.

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. Oddy WH et al. "Breast feeding and a birth cohort study respiratory morbidity in infancy: a birth cohort study." *Archives of Disease in Childhood*. Mar 2003; 88 (3) : 224-228.

Data from 33 studies indicated 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. Bachrach V, Schwarz E, Bachrach L. "Breastfeeding and the Risk of Hospitalization for Respiratory Disease in Infancy: A Meta-analysis." *Arch Pediatr Adolesc Med*. 2003;157:237-243.

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. Cesar JA et al. "Impact of breast feeding on admission for pneumonia during postneonatal period in Brazil: nested case-control study. *BMJ* 1999 May 15;318(7194):1316-1320

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. Cushing AH, et al. "Breastfeeding reduces risk of respiratory illness in infants." *Am J Epidemiol* 1998 May 1;147(9):863-70

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. deDuran, C.M. "Cytologic Diagnosis of Milk Micro Aspiration". *Imm Allergy Practice* 1991; xiii (10);402-5

13. Respiratory Syncytial Virus

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. Somech, R et al. "Epidemiologic, socioeconomic, and clinical factors associated with severity of respiratory syncytial virus infection in previously healthy infants." *Clinical Pediatrics*, 45 (7): 621-627 Sep 2006.

Breastfeeding was associated with a lower risk of RSV hospitalization (odds ratio: 0.34). Bulkow LR et al. Risk factors for severe respiratory syncytial virus infection among Alaska native children. *Pediatrics* 2002 Feb;109(2):210-6

Breastfeeding was associated with a lower incidence of RSV infection during the first year of life. Holberg,C.J., "Risk Factors for RSV Associated Lower Respiratory Illnesses in the First Year of Life". *AM J Epidemiol* 1991; 133 (135-51)

14. Salmonellosis

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. Rowe SY et al. "Breast-feeding decreases the risk of sporadic salmonellosis among infants in FoodNet sites." *Clin Infect Dis*. 2004 Apr 15;38 Suppl 3:S262-70.

15. Sepsis in Preterm Infants

The incidence of any infection and sepsis/meningitis are significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants. Hylander MA et al. "Human milk feedings and infection among very low birth weight infants." *Pediatrics* 1998 Sep;102(3):E38

16. Tobacco smoke (protective effect against exposure to)

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 $>$ or $=$ 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. Karmaus W, Dobai AL, Ogbuanu I, et al. Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. *J Asthma*. 2008 Oct;45(8):688-95.

Toxic substances in tobacco smoke are known to have negative effects on the antioxidant capacity of 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 breast feeding ($p < 0.05$). Conclusion: Tobacco smoke exposure of infants significantly decreases their serum antioxidant vitamin A, C and E levels. However, breast feeding may help to prevent the decrement of antioxidant vitamin levels of passive smoking infants. Yilmaz G, Isik Agras P, Hizli S, Yurdakok K, Coskun T. The effect of passive smoking and breast feeding on serum antioxidant vitamin (a, c, e) levels in infants. *Acta Paediatr*. 2008 Oct 29

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 $>$ or $=$ 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. Karmaus W, Dobai AL, Ogbuanu I, Arshard SH, Matthews S, Ewart S. "Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children." *J Asthma*. 2008 Oct;45(8):688-95.

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. Chatzimichael A et al. "The role of breastfeeding and passive smoking on the development of severe bronchiolitis in infants." *Minerva Pediatr*. 2007 Jun;59(3):199-206.

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. Jin C, Rossignol AM. "Effects of passive smoking on respiratory illness from birth to age eighteen months, in Shanghai, People's Republic of China." *J Pediatr* 1993 Oct;123(4):553-8

Odds of respiratory illness with maternal smoking were 7 times higher among children who were never breastfed than among those who were breastfed. Woodward A et al. "Acute Respiratory Illness in Adelaide Children: BreastFeeding Modifies the Effect of Passive Smoking". *J Epidemiol Community Health* 1990 Sep;44(3):224-30

17. Urinary Tract Infections

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. Marild-S et al. "Protective effect of breastfeeding against urinary tract infection." *Acta Paediatrica*. Feb 2004; 93(2):164-168

Breastfed infants have a relative risk of developing a UTI of 0.38 compared to formula-fed infants. Pisacane A et al. "Breast-feeding and urinary tract infection." *J Pediatr* 1992 Jan;120(1):87-9

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. Coppa GV et al. "Preliminary study of breastfeeding and bacterial adhesion to uroepithelial cells." *Lancet* 1990 Mar 10;335(8689):569-71

B. Infant and Childhood Illnesses

1. Anemia and Iron Deficiency

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. Assis A et al. "Hemoglobin concentration, breastfeeding and complementary feeding in the first year of life." *Revista-De-Saude-Publica*. Aug 2004; 38 (4) : 543-551[Portuguese]

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 ($Hb <105$ 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. Thorsdottir I et al. "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*. Apr 2003; 57 (4) : 505-513.

2. Autoimmune Thyroid Disease

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%). Fort P, et al. Breast and soy-formula feedings in early infancy and the prevalence of autoimmune thyroid disease in children. *J Am Coll Nutr*. 1990 Apr;9(2):164-7.

3. Constipation and Anal Fissures

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. Andiran F et al. "Cows milk consumption in constipation and anal fissure in infants and young children." *Journal of Paediatrics and Child Health*. Jul 2003; 39 (5): 329-331.

4. Cryptorchidism (undescended testicle)

This case-controlled study showed a significant association of cryptorchidism and lack of breastfeeding. Mori, M. "Maternal and other factors of cryptorchidism: a case-control study in Japan" *Kurume Med J*, 1992;39:53-60

5. Esophageal and Gastric Lesions

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 PH et al. "Risk factors for severe esophageal and gastric lesions in term neonates: A case-control study." *Journal of Pediatric Gastroenterology and Nutrition*. Oct 2000; 31 (4): 377-380.

6. Gastroesophageal Reflex

Breastfed neonates demonstrate gastroesophageal reflux episodes of significantly shorter duration than formula fed neonates. Heacock, H.J., "Influence of Breast vs. Formula Milk in Physiologic Gastroesophageal Reflux in Healthy Newborn Infants". *J. Pediatr Gastroenterol Nutr*, 1992 January; 14(1): 41-6

7. Inguinal Hernia

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. Pisacane, A. "Breast-feeding and inguinal hernia" *Journal of Pediatrics* 1995;Vol 127, No. 1, pp 109-111

8. Lactose Malabsorption

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. Rudzeviciene O et al. "Lactose malabsorption in young Lithuanian children with atopic dermatitis." *Acta Paediatrica*. Apr 2004; 93 (4) : 482-486.

9. Morbidity and Mortality

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 breast-feeding. 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 breast-feeding 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. Conclusions: 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. Lauer, JA; Betran, AP; Barros, AJD; de Onis, M. "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 SEP 2006

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. Edmond KM, Zandoh C, Quigley MA, et al. "Delayed breastfeeding initiation increases risk of neonatal mortality." *Pediatrics*. 2006 Mar;117(3):e380-6.

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. Bahl, R; Frost, C; Kirkwood, et al. "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 (6): 418-426 Jun 2005.

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. Chen, AM et al. "Breastfeeding and the Risk of Postneonatal Death in the United States." *Pediatrics* 2004 May 113(5):e435-e439

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. Raisler J et al. "Breast-feeding and infant illness: a dose-response relationship?" *J Public Health* 1999 Jan;89(1):25-30

The incidence of any infection and sepsis/meningitis are significantly reduced in human milk-fed VLBW infants compared with exclusively formula-fed VLBW infants. Hylander MA et al. "Human milk feedings and infection among very low birth weight infants." *Pediatrics* 1998 Sep;102(3):E38

During the first 6 months of life, breastfeeding has a protective effect of 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

Jones EG et al. "Relationship between infant feeding and exclusion rate from child care because of illness." *J Am Diet Assoc* 1993 Jul;93(7):809-11

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. Van Den Bogaard, C. "Relationship Between Breast Feeding in Early Childhood and Morbidity in a General Population". *Fan Med*, 1991; 23:510-515

There is 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. Habicht, J.P., "Does Breast Feeding Really Save Lives, or Are Apparent Benefits due to Biases?" *Am J Epidemiology*, 1986

10. 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.

11. Pyloric Stenosis

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. CONCLUSIONS: 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. Krogh C, Biggar RJ, Fischer TK et al. Bottle-feeding and the Risk of Pyloric Stenosis. *Pediatrics* 2012;130:1-7

Infants with pyloric stenosis were less likely to have been breastfed during the first week of life. Pisacane A, et al. Breast feeding and hypertrophic pyloric stenosis: population based case-control study. *BMJ*. 1996 Mar 23;312(7033):745-6.

12. Sudden Infant Death Syndrome

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. Fern R. et al. Breastfeeding and Reduced Risk of Sudden Infant Death Syndrome: A Meta-analysis. *Pediatrics*. June 2011, 10:1542.

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. Vennemann MM et al. "Does breastfeeding reduce the risk of sudden infant death syndrome?" *Pediatrics*. 2009 Mar;123(3):e406-10.

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. Hauck FR et al. "Sleep environment and the risk of sudden infant death syndrome in an urban population: The Chicago infant mortality study." *Pediatrics*. May 2003; 111 (5) Suppl. S: 1207-1214.

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 breast feeding over 16 weeks as the reference. Mixed feeding in the first week post partum did not increase the risk. Alm-B et al. "Breast feeding and the sudden infant death syndrome in Scandinavia, 1992-95." *Archives-Of-Disease-In-Childhood*. Jun 2002; 86 (6): 400-402.

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. McVea KL et al. The role of breastfeeding in sudden infant death syndrome. *J Hum Lact* 2000 Feb;16(1):13-20.

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. L'Hoar MP et al. "Sudden unexpected death in infancy: epidemiologically determined risk factors related to pathological classification." *Acta Paediatr* 1998 Dec;87(12):1279-87

Not breastfeeding at discharge from an obstetric hospital at any stage of the infant's life was associated with an increased risk of SIDS. Mitchell, A. "Results from the First Year of The New Zealand Count Death Study". *N.Z. Med A*, 1991; 104:71-76

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., "Risk Factors for SIDS: Results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiologic Study". *Ann NY ACAD Sci*, 1988.

13. Toddler Illnesses

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. Gulick, E.E. "The Effects of Breastfeeding on the Toddler Health." *Pediatric Nursing*, 1986 Jan-Feb;12(1):51-4.

14. Wheezing

Soto-Ramirez N, Karmaus W, Zhang H et al "Modes of Infant Feeding and the Occurrence of Coughing/Wheezing in the First Year of Life." *J Hum Lact* 2012.

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. Garcia-Marcos L, Mallol J, Solé D, Brand PL; EISL Study Group. "International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life." *Pediatr Allergy Immunol*. 2010 Aug;21(5):878-88.

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. Eneli, IU; Karmaus, W; Davis, S; Kuehr, J. "Airway hyperresponsiveness and body mass index: The Child Health and Environment Cohort Study in Hesse, Germany." *Pediatric Pulmonology*, 41 (6): 530-537 Jun 2006

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. Baker D et al. "Inequality in infant morbidity: causes and consequences in England in the 1990s." *J Epidemiol Community Health* 1998 Jul;52(7):451-8

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. Burr ML, et al. "Infant feeding, wheezing, and allergy: a prospective study." *Arch Dis Child* 1993 Jun;68(6):724-8

Within the group who had had early wheezing, infants who had been breastfed for at least one month subsequently had less severe wheezing. Porro E, et al. "Early wheezing and breast feeding." *J Asthma* 1993;30(1):23-8

Breastfeeding seems to protect against wheezing respiratory tract illnesses in the first 4 months of life, particularly when other risk factors are present. Wright, A.L., "breastfeeding and lower respiratory tract illnesses in the first year of life." *British Medical Journal*, 1989.

C. Allergies

1. Allergies in general

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. Friedman NJ, Zeiger RS. "The role of breast-feeding in the development of allergies and asthma." *J Allergy Clin Immunol*. 2005 Jun;115(6):1238-48.

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. Stoney-RM et al. "Maternal breast milk long-chain n-3 fatty acids are associated with increased risk of atopy in breastfed infants." *Clinical and Experimental Allergy*. Feb 2004; 34(2): 194-200.

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. van-Odijk J et al. "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*. Sep 2003; 58 (9): 833-843

2187 children were followed to age 6 years to study the association between duration of exclusive breast feeding 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. Oddy WH et al. "Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study." *BMJ* 1999 Sep 25;319(7213):815-9

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). Tariq SM, et al. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol.* 1998 May;101(5):587-93.

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 risk babies in comparison with those not receiving these interventions. Marini A et al. "Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. *Acta Paediatr Suppl* 1996 May;414:1-21

Breastfeeding, even for short periods was clearly associated with lower incidence of wheezing, prolonged colds, diarrhea, and vomiting. Merrett, T.G., "Infant Feeding & Allergy: 12 Month Prospective Study of 500 Babies Born into Allergic Families". American Allergies, 1988.

2. Allergic Rhinitis

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. Bloch AM et al. "Does breastfeeding protect against allergic rhinitis during childhood? – A meta-analysis of prospective studies." *Acta-Paediatrica.* 2002; 91 (3):275-279

3. Asthma (see also "Wheezing")

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. Kuiper S et al. "Interactive effect of family history and environmental factors on respiratory tract-related morbidity in infancy. *J Allergy Clin Immunol.* 2007 May 9

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). Oddy WH; Peat JK; de Klerk NH. "Maternal asthma, infant feeding, and the risk of asthma in childhood." *Journal of Allergy and Clinical Immunology.* Jul 2002; 110 (1) : 65-67.

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. Dell S, To T. "Breastfeeding and asthma in young children - Findings from a population-based study." *Archives-Of-Pediatrics-And-Adolescent-Medicine.* Nov 2001; 155 (11):1261-1265

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. Gdalevich M, Mimouni D, Mimouni M. Breast-feeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001 Aug;139(2):261-6

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. Haby-MM et al. Asthma in preschool children: prevalence and risk factors. *Thorax*, Aug 2001; 56 (8) : 589-595

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. Oddy W et al. *British Medical Journal* Sep 1999;319:815-819.

4. Eczema

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. C Benn, J Wohlfahrt, P Aaby et al. Breastfeeding and Risk of Atopic Dermatitis, by Parental History of Allergy, during the First 18 Months of Life *American Journal of Epidemiology* 2004 160(3):217-223

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. Gdalevich M, et al. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001 Oct;45(4):520-7.

D. Development and Intelligence

1. Bedwetting

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 did not make a difference in the rate of enuresis. Barone JG et al. "Breastfeeding during infancy may protect against bed-wetting during childhood." *Pediatrics*. 2006 Jul;118(1):254-9

2. Brain Activity in Infants of Depressed Mothers

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. Jones NA, McFall BA, Diego MA. "Patterns of brain electrical activity in infants of depressed mothers who breastfeed and bottle feed: the mediating role of infant temperament." *Biol Psychol*. 2004 Oct;67(1-2):103-24

3. Brainstem, Cognitive, and Motor Development in Preterm Infants

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 non-breast 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 <1 year), only the values for the >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. Vohr BR, Poindexter BB, Dusick AM, et al. 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*. 2006 Jul;118(1):e115-23

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 , $P < .05$) and higher cognitive scores at 12 months corrected age (101 ± 11 vs 90 ± 9 , $P < .05$). HMG infants had higher scores (motor $R^2 = 0.2$, cognitive $R^2 = 0.3$; $P < .05$) 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. Bier J-AB, et al. "Human Milk Improves Cognitive and Motor Development of Premature Infants During Infancy." *Journal of Human Lactation* November 2002, 18 (4) 361-367

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. Amin SB et al. "Brainstem maturation in premature infants as a function of enteral feeding type." *Pediatrics* Aug 2000; 106 (2): 318-322.

4. Cognitive Development, Intelligence, and IQ

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. Iacovou M, Sevilla A. Infant feeding: the effects of scheduled vs. on-demand feeding on mothers' wellbeing and children's cognitive development. *Eur J Public Health*. 2012 Mar 14

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. Guxens M,

Mendez MA, Moltó-Puigmartí C, et al. Breastfeeding, long-chain polyunsaturated fatty acids in colostrum, and infant mental development. *Pediatrics*. 2011 Oct;128(4):e880-9. Epub 2011 Sep 19.

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 confounding 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. C McCrory and R Layte. "The effect of breastfeeding on children's educational test scores at nine years of age: Results of an Irish cohort study." *Soc Sci Med* 21 Mar 2011.

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 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. Kramer M, Aboud F, Mironova E, et al. Breastfeeding and Child Cognitive Development: New Evidence From a Large Randomized Trial. *Arch Gen Psychiatry*. 2008;65(5):578-584

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, breast feeding 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 breast feeding, 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. Lawlor, DA et al. "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 Mar 2006.

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. Victora CG, et al. Breastfeeding and school achievement in Brazilian adolescents. *Acta Paediatr*. 2005 Nov;94(11):1656-60.

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. Smith MM et al. "Influence of breastfeeding on cognitive outcomes at age 6-8 years: Follow-up of very low birth weight infants." *American-Journal-Of-Epidemiology*. Dec 1 2003; 158 (11): 1075-1082.

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 <4 months, 4-6 months and >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 breast fed 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 breast fed 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. Oddy-WH et al. "Breast feeding and cognitive development in childhood: a prospective birth cohort study." *Paediatric and Perinatal Epidemiology*. Jan 2003; 17 (1) : 81-90

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. Jacobson-JL; Jacobson-SW. "Association of prenatal exposure to an environmental contaminant with intellectual function in childhood." *Journal of Toxicology Clinical Toxicology*. 2002; 40 (4) : 467-475

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. Fewtrell MS; et al. "Double-blind, randomized trial of long-chain polyunsaturated fatty acid supplementation in formula fed to preterm infants." *Pediatrics*, Jul 2002; 110 (1): 73-82

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 Mortensen EL; et al. "The association between duration of breastfeeding and adult intelligence." *JAMA-Journal-of-the-American-Medical-Association*. May 8 2002; 287 (18):2365-2371

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. Rao MR et al. "Effect of breastfeeding on cognitive development of infants born small for gestational age." *Acta-Paediatrica*. 2002; 91 (3):267-274.

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. Quinn-PJ et al. "The effect of breastfeeding on child development at 5 years: A cohort study." *Journal-Of-Paediatrics-And-Child-Health*. Oct 2001; 37 (5): 465-469.

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 3months 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 (Raven score), maternal education, and smoking in pregnancy. Angelsen-NK et al. Breast feeding and cognitive development at age 1 and 5 years. *Archives-Of-Disease-In-Childhood*. Sep 2001; 85 (3) : 183-188

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. Anderson JW et al. *American Journal of Clinical Nutrition*, Oct 1999, 70.

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 breast-feeding did not predict psychomotor development scores. Paine BJ, Makrides M, Gibson RA. "Duration of breast-feeding and Bayley's Mental Developmental Index at 1 year of age." *J Paediatr Child Health* 1999 Feb;35(1):82-5.

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. . Horwood LJ, Fergusson DM. "Breastfeeding and later cognitive and academic outcomes." *Pediatrics* 1998 Jan;101(1):E9

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. Riva E et al. "Early breastfeeding is linked to higher intelligence quotient scores in dietary treated phenylketonuric children. *Acta Paediatr* 1996 Jan;85(1):56-8

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. Lucas, A., "Breast Milk and Subsequent Intelligence Quotient in Children Born Preterm". *Lancet* 1992;339:261-62

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. Morrow-Tlucak, M. "Breast Feeding and Cognitive Development During the First 2 years of Life." *Soc Sci Med*, 1988, 26(6):635-9.

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. Morley, R., "Mothers Choice to provide Breast Milk and Developmental Outcome". *Arch Dis Child*, 1988

5. Gastrointestinal and Immune Development (see also "Vaccine Response")

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. Penders, J et al. 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 Feb 1 2005

Review: 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 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 anti-microbial 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. Kelly D and Coutts AG. *Proceedings of the-Nutrition Society*, May 2000; 59(2): 177-185.

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. Orrhage K and Nord CE. "Factors controlling the bacterial colonization of the intestine in breastfed infants." *Acta Paediatr Suppl* 1999 Aug;88(430):47-57

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. Carver JD. "Dietary nucleotides: effects on the immune and gastrointestinal systems." *Acta Paediatr Suppl* 1999 Aug;88(430):83-8

Review article: 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. Hanson LA. "Breastfeeding provides passive and likely long-lasting active immunity. *Ann Allergy Asthma Immunol* 1998 Dec;81(6):523-33; quiz 533-4, 537

Secretory IgA concentration increased more rapidly during the first 6 months after birth in infants exclusively breastfed than in those exclusively bottle fed. Fitzsimmons SP, et al. "Immunoglobulin A subclasses in infants' saliva and in saliva and milk from their mothers." *J Pediatr* 1994 Apr;124(4):566-73

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. Koutras, A.K., "Fecal Secretory Immunoglobulin A in Breast Milk vs. Formula Feeding in Early Infancy". *J Ped Gastro Nutr*, 1989.

6. Hormones

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 lactoferrin have been shown to influence gastrointestinal development and host defense. Bernt KM and Walker WA. "Human milk as a carrier of biochemical messages." *Acta Paediatr Suppl* 1999 Aug;88(430):27-41.

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. Murphy MS. "Growth factors and the gastrointestinal tract." *Nutrition* 1998 Oct;14(10):771-4

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. Kling PJ et al. "Human milk as a potential enteral source of erythropoietin." *Pediatr Res* 1998 Feb;43(2):216-21

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. Lucas A et al. "Plasma prolactin and clinical outcome in preterm infants." *Archives of Disease in Childhood*, 1990, 65:977-983.

7. Neurological, Psychomotor and Social Development

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. Sacker A, Quigley M, Kelly Y. "Breastfeeding and Developmental Delay: Findings From the Millennium Cohort Study." *Pediatrics* Vol. 118 No. 3 September 2006, pp. e682-e689

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. Khedr E et al. "Neural maturation of breastfed and formula-fed infants." *Acta Paediatrica*. Jun 2004; 93 (6) : 734-738

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 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. Morley-R et al. "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*. Mar 1 2004; 113 (3):515-521.

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. Hart S et al. Brief report: breast-fed one-week-olds demonstrate superior neurobehavioral organization. *J Pediatr Psychol*. 2003 Dec;28(8):529-34.

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. Bouwstra H et al. "Exclusive breastfeeding of healthy term infants for at least 6 weeks improves neurological condition." *Journal of Nutrition*. Dec 2003; 133 (12) : 4243-4245

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. Dewey KG et al. Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. *J Nutr* 2001 Feb;131(2):262-7

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. Agostoni C. "Breastfeeding duration, milk fat composition and developmental indices at 1 year of life among breastfed infants." *Prostaglandins Leukotrienes and Essential Fatty Acids*. Feb 2001; 64 (2) : 105-109.

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. Gerrish CJ and Mennella JA. "Short-term influence of breastfeeding on the infants' interaction with the environment. *Dev Psychobiol* 2000 Jan;36(1):40-48.

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. Vestergaard M et al. Duration of breastfeeding and developmental milestones during the latter half of infancy. *Acta Paediatr* 1999 Dec;88(12):1327-32

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%). Barros FC. "Breast feeding, pacifier use and infant development at 12 months of age: a birth cohort study in Brazil." *Paediatr Perinat Epidemiol* 1997 Oct;11(4):441-50

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. Temboury MC et al. "Influence of breast-feeding on the infant's intellectual development." *J Pediatr Gastroenterol Nutr* 1994 Jan;18(1):32-6

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. Baumgartner, C., "Psychomotor and Social Development of Breast Fed and Bottle Fed babies During their First year of Life". *Acta Paediatrica Hungarica*, 1984 25(4):409-17.

8. Sleep Cycles and Arousal

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 the formula fed infants. Cubero J et al. The circadian rhythm of tryptophan in breast milk affects the rhythms of 6-sulfatoxymelatonin and sleep in newborn. *Neuro Endocrinol Lett*. 2005 Dec 28;26(6)

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. Horne RS et al. Comparison of evoked arousability in breast and formula fed infants. *Arch Dis Child*. 2004 Jan;89(1):22-5.

9. Speech and Language Development

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. Dee DL et al. "Associations between breastfeeding practices and young children's language and motor skill development." *Pediatrics*. 2007 Feb;119 Suppl 1:S92-8

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. Vestergaard M et al. "Duration of breastfeeding and developmental milestones during the latter half of infancy." *Acta Paediatr*. 1999 Dec;88(12):1327-32

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 breast fed for less than 4 months this risk was even higher (OR = 2.7). Obel C et al. "Smoking during pregnancy and babbling abilities of the 8-month-old infant." *Paediatr Perinat Epidemiol*. 1998 Jan;12(1):37-48.

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 first-born, 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 FE, Duganzich DM. "The effects of infant feeding, birth order, occupation and socio-economic status on speech in six-year-old children." *N Z Med J*. 1983 Jun 22;96(734):483-6.

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. Broad FE. "Further studies on the effects of infant feeding on speech quality." *N Z Med J*. 1975 Dec 10;82(553):373-6.

10. Thymus Development

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. Jeppesen DL et al. "T-lymphocyte subsets, thymic size and breastfeeding in infancy." *Pediatric Allergy and Immunology* 15(2):127 April 2004

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 et al, "Breast-feeding influences thymic size in late infancy." *Eur J Pediatr* 1999 Dec;158(12):964-7

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 et al. Thymus size evaluated by sonography. A longitudinal study on infants during the first year of life. *Acta Radiol* 1997 Mar;38(2):222-7

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 mean 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. Hasselbalch H et al. Decreased thymus size in formula-fed infants compared with breastfed infants. *Acta Paediatr* 1996 Sep;85(9):1029-32

11. Visual Acuity

Breastfeeding has been reported to benefit visual development in children. A higher concentration of docosahexanoic 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 formula-fed 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. Singhal A et al. "Infant nutrition and stereoacuity at age 4-6 y." *Am J Clin Nutr*. 2007 Jan;85(1):152-9.

Observational studies suggested that breastfeeding benefits the visual development of preterm children, which has been attributed to the presence of docosahexanoic 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. Williams C, et al. 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. *American-Journal-Of-Clinical-Nutrition*. Feb 2001; 73 (2) : 316-322

E. Pain and Physiologic Response During Feedings

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. Efe E, Ozer ZC. "The use of breast-feeding for pain relief during neonatal immunization injections." *Appl Nurs Res*. 2007 Feb;20(1):10-6.

Clinical studies have shown reduction in the changes in physiological parameters and pain score measurements following pre-emptive 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. Shah, PS; Aliwalas, LL; Shah, V. *Cochrane Database Of Systematic Reviews*, (3): 4950-4950 2006

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. Breast-feeding and maternal holding should be considered as pain-control measures for the neonate during heel-stick procedures. Phillips RM, Chantry CJ, Gallagher MP. Analgesic effects of breast-feeding or pacifier use with maternal holding in term infants. *Ambul Pediatr*. 2005 Nov-Dec;5(6):359-64

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. Blaymore Bier JA et al. "Breastfeeding infants who were extremely low birth weight. *Pediatrics* 1997 Dec;100(6):E3

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. Marino BL et al. "Oxygen saturations during breast and bottle feedings in infants with congenital heart disease." *J Pediatr Nurs* 1995 Dec;10(6):360-4

Supine bottle feeding has a significant effect on middle-ear pressure dynamics, probably caused by the aspiration of milk into the ear. Tully SB et al. "Abnormal tympanography after supine bottle feeding." *J Pediatr* 1995 Jun;126(6):S105-11

F. Long Term Effects

1. Autism

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. Al-Farsi YM, Al-Sharbati MM, Waly MI, et al. Richard C.; Effect of suboptimal breast-feeding on occurrence of autism: A case-control study." *Nutrition*, 2012 Jul; 28 (7/8): e27-32

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. Schultz ST et al. Breastfeeding, infant formula supplementation, and Autistic Disorder: the results of a parent survey. *Int Breastfeed J.* 2006 Sep 15;1:16

Comparing the weaning times of 145 autistic infants a control group of 224 normal children, the children in the control group breastfed significantly longer than the autistic infants. Tanoue Y, Oda S. Weaning time of children with infantile autism. *J Autism Dev Disord* 1989;19:425–34

2. Appendicitis

Breast feeding 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 suggesting that breast feeding may possibly give protection against the development of appendicitis. Alves JG, Figueiroa JN, Barros I. Does breast feeding provide protection against acute appendicitis? A case-control study. *Trop Doct.* 2008 Oct;38(4):235-6.

Pisacane A, et al. Breast feeding and acute appendicitis. *BMJ.* 1995 Apr 1;310(6983):836-7.

3. Bone mass

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. Jones G, Riley M, Dwyer T. Breastfeeding in early life and bone mass in prepubertal children: a longitudinal study. *Osteoporos Int* 2000;11(2):146-52

4. Cancer

a) Breast Cancer in Adulthood

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

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. Freudenheim, J. "Exposure to breast milk in infancy and the risk of breast cancer." *Epidemiology* 1994 5:324-331

b) Childhood Cancer

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. Smulevich VB, Solionova LG, Belyakova SV. "Parental occupation and other factors and cancer risk in children: I. Study methodology and non-occupational factors." *Int J Cancer* 1999 Dec 10;83(6):712-7.

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. Davis, M.K. "Infant Feeding and Childhood Cancer." *Lancet* 1988 13;2(8607):365-8.

c) DNA Damage

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. Dundaroz R et al. "Analysis of DNA damage using the comet assay in infants fed cow's milk." *Biology-Of-The-Neonate*. 2003; 84 (2) : 135-141.

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 breast-fed compared to those who were breast-fed. Dundaroz-R. "Preliminary study on DNA damage in non breast-fed infants." *Pediatrics-International*, Apr 2002; 44 (2) : 127-130.

d) Hodgkin's Disease

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. Davis MK. "Review of the evidence for an association between infant feeding and childhood cancer." *Int J Cancer Suppl* 1998;11:29-33

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. Schwartzbaum, J. "An Exploratory Study of Environmental and Medical Factors Potentially Related to Childhood Cancer." *Medical & Pediatric Oncology*, 1991; 19 (2):115-21.

e) Leukemia and Lymphoma

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. Flores-Lujano J, Perez-Saldivar ML, Fuentes-Pananá EM, et al. Breastfeeding and early infection in the aetiology of childhood leukaemia in down syndrome. *Br J Cancer*. 2009 Sep 1;101(5):860-4.

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 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. Kwan-Mlet al. Breastfeeding and the risk of childhood leukemia: A meta-analysis. Public-Health-Reports. Nov-Dec 2004; 119 (6) : 521-535

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. Perrillat-F. "Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study." British-Journal-Of-Cancer. Apr 8 2002; 86 (7): 1064-1069.

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. European Journal of Cancer 2001 January;37:234-238.

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 associations were stronger with longer duration of breast-feeding. Shu XO et al, "Breast-feeding and risk of childhood acute leukemia. J Natl Cancer Inst 1999 Oct 20;91(20):1765-72

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. Robison L et al. Journal of the National Cancer Institute 1999;91:1765-1772.

f) Neuroblastoma

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. Daniels-JL et al. "Breast-feeding and neuroblastoma, USA and Canada" Cancer-Causes-And-Control. June 2002; 13 (5):401-405.

g) Testicular Cancer

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. Coupland CAC et al. "Maternal risk factors for testicular cancer: a population-based case-control study." *Cancer Causes and Control*. Apr 2004; 15(3):277-283.

h) Tumor growth

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. Wolf JS. "Lactoferrin inhibits growth of malignant tumors of the head and neck." *Orl Journal for Oto-Rhino-Laryngology and its Related Specialties*. 2003; 65(5): 245-249.

5. Cardiovascular Disease (Atherosclerosis, Cholesterol Concentration)

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 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 <3, 3-6, or >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. Labayen I, Ruiz JR, Ortega FB, Loit HM, Harro J, Villa I, Veidebaum T, Sjostrom M. "Exclusive breastfeeding duration and cardiorespiratory fitness in children and adolescents." *Am J Clin Nutr*. 2012 Feb;95(2):498-505.

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 <3 or >6 mo and formula-fed children. The choice of infant feeding appears to have an effect on the vascular system already in early childhood. [Evelein AM](#), et al. "[The association between breastfeeding and the cardiovascular system in early childhood](#)." *Am J Clin Nutr*. 2011 Apr;93(4):712-8. Epub 2011 Feb 10.

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 ageing 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. Singhal A. "The early origins of atherosclerosis." *Adv Exp Med Biol*. 2009;646:51-8.

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. Owen CG, Whincup PH, Kaye SJ, Does initial breastfeeding lead to lower blood cholesterol in adult life? A quantitative review of the evidence. *Am J Clin Nutr*. 2008 Aug;88(2):305-14.

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, or breastfed 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. Rudnicka AR, Owen CG, Strachan DP. "The effect of breastfeeding on cardiorespiratory risk factors in adult life." *Pediatrics*. 2007 May;119(5):e1107-15.

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, RM; Ebrahim, S; Griffin, M et al. "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 Jul 2005

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. Martin RM et al. "Breastfeeding in infancy and blood pressure in later life: systematic review and meta-analysis. *Am J Epidemiology* 2005, 161:15-26.

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 breast fed 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. Lawlor DA et al. "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*. 2004 Oct 19;110(16):2417-23.

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.

Singhal A et al. "Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study." *Lancet*. May 15 2004; 363(9421): 1571-1578.

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. Martin RM et al. "Does breast-feeding in infancy lower blood pressure in childhood? The Avon Longitudinal Study of Parents and Children (ALSPAC)." *Circulation*. 2004 Mar 16;109(10):1259-66

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 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. Owen-CG et al. "Infant feeding and blood cholesterol: A study in adolescents and a systematic review." *Pediatrics*. Sep 2002; 110 (3) : 597-608.

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 provide experimental evidence of programming of a cardiovascular risk factor by early diet and further support the long-term beneficial effects of breastmilk. Singhal A, Cole TJ, Lucas A. "Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials." *Lancet* 2001 Feb 10;357(9254):413-9

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. Ravelli-ACJ et al. "Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity." *Archives-Of-Disease-In-Childhood*. Mar 2000; 82 (3) : 248-252.

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. Plancoulaine-S et al. "Infant-feeding patterns are related to blood cholesterol concentration in prepubertal children aged 5-11y." *European Journal of Clinical Nutrition*. Feb 2000; 54 (2) : 114-119.

6. Celiac Disease

Henriksson C, Bostrom A, Wiklund IE. "What effect does breastfeeding have on coeliac disease? A systematic review update." *Evid. Based Med*. published 4 August 2012, 10.1136

Coeliac disease (CD) is a disorder that may depend on genetic, immunological, and environmental factors. Recent observational studies suggest that breast feeding may prevent the development of CD. AIM: To evaluate articles that compared effects of breast feeding 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 breast feeding and decreased risk of developing CD. Meta-analysis showed that the risk of CD was significantly reduced in infants who were breast feeding at the time of gluten introduction (pooled odds ratio 0.48, 95% CI 0.40 to 0.59) compared with infants who were not breast feeding 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 breast feeding 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 breast feeding and CD. Akobeng AK, et al. "Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies." *Arch Dis Child*. 2006 Jan;91(1):39-43.

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. Ivarsson A et al. "Breast-feeding protects against celiac disease." *American-Journal-Of-Clinical-Nutrition*. May 2002; 75 (5):914-921/

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 breast-feeding). 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. Peters U et al. "A case-control study of the effect of infant feeding on celiac disease." *Annals-Of-Nutrition-And-Metabolism*. Jul-Aug 2001; 45 (4) : 135-142.

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. Auricchio S et al. "Does breast feeding protect against the development of clinical symptoms of celiac disease in children?" *J Pediatr Gastroenterol Nutr* 1983;2(3):428-33.

7. Conduct Disorders

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. Shelton K, Collishaw S, Rice F et al. "Using a genetically informative design to examine the relationship between breastfeeding and childhood conduct problems." *European Child & Adolescent Psychiatry*, 2011 Dec; 20 (11/12): 571-9.

8. Diabetes Mellitus

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. Owen CG et al. "Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence." *Am J Clin Nutr.* 2006 Nov;84(5):1043-54.

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 for other factors. Conclusions; Longer exclusive and total breastfeeding appears as an independent protective factor against type 1 diabetes. Kuehne-VS et al. "Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood." *Diabetes Metabolism Research and Reviews.* Mar-Apr 2004; 20(2):150-157.

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. Young-TK et al. "Type 2 diabetes mellitus in children - Prenatal and early infancy risk factors among native Canadians." *Archives-Of-Pediatrics-And-Adolescent-Medicine.* Jul 2002; 156 (7):651-655

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 <beta>-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. Monetini L. "Bovine beta-casein antibodies in breast- and bottle-fed infants: their relevance in Type 1 diabetes." *Diabetes-Metabolism-Research-And-Reviews.* Jan-Feb 2001; 17 (1) : 51-54

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. Kimpimaki-T, et al. "Short-term exclusive breastfeeding predisposes young children with increased genetic risk of Type I diabetes to progressive beta-cell autoimmunity." *Diabetologia*. Jan 2001; 44 (1) : 63-69

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 breast feeding as the initial feeding method was significantly protective (OR 0.65).

McKinney et al. "Perinatal and neonatal determinants of childhood type 1 diabetes. A case-control study in Yorkshire, U.K." *Diabetes Care* 1999 Jun;22(6):928-32

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). Pettitt DJ, Knowler WC. "Long-term effects of the intrauterine environment, birth weight, and breast-feeding in Pima Indians." *Diabetes Care* 1998 Aug;21 Suppl 2:B138-41

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.

9. *Helicobacter pylori* infection

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. 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

10. *Haemophilus influenzae* Meningitis

A strong negative correlation between breastfeeding and incidence of *Haemophilus influenzae* infection 5 to 10 years later. Silfverdal SA et al. "Protective effect of breastfeeding: an ecologic study of *Haemophilus influenzae* meningitis and breastfeeding in a Swedish population." *Int J Epidemiol* 1999 Feb;28(1):152-6

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

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 breast-fed (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. Geary RB, Richardson AK, Frampton CM, et al. "Population-based cases control study of inflammatory bowel disease risk factors." *J Gastroenterol Hepatol*. 2010 Jan 14.

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). Barclay A et al. "Systematic Review: The Role of Breastfeeding in the Development of Pediatric Inflammatory Bowel Disease" *J Peds* Volume 155, Issue 3, Pages 421-426 (September 2009)

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. Thompson-NP; Montgomery-SM; Wadsworth-MEJ; Pounder-RE; Wakefield-AJ. "Early determinants of inflammatory bowel disease: use of two national longitudinal birth cohorts. *European Journal of Gastroenterology and Hepatology*. Jan 2000; 12 (1):25-30

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). Corrao G et al. "Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study." *Int J Epidemiol* 1998 Jun;27(3):397-404.

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 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. Rigas A et al. Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood." *Ann Epidemiol*. 1993 Jul;3(4):387-92.

Koletzko S, Griffiths A, Corey M, Smith C, Sherman P. "Infant feeding practices and ulcerative colitis in childhood." *BMJ*. 1991 Jun 29;302(6792):1580-1.

Lack of breastfeeding was a risk factor associated with later development of Crohn's disease. Koletzko, S., "Role of Infant Feeding Practices in Development of Crohn's Disease in Childhood". *Br Med J*, 1989 Jun 17;298(6688):1617-8.

12. Juvenile Rheumatoid Arthritis (JRA)

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. Mason T et al. "Breast feeding and the development of juvenile rheumatoid arthritis." *J Rheumatol* 1995 Jun;22(6):1166-70

13. Mental Health

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. Oddy W et al. "The Long-Term Effects of Breastfeeding on Child and Adolescent Mental Health: A Pregnancy Cohort Study Followed for 14 Years." *J Peds* Dec 2009.

14. Menopause (timing of)

Few adult environmental or behavioral factors have been consistently associated with age at menopause. The peak number of follicles attained 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. Hardy-R; Kuh-D. "Does early growth influence timing of the menopause? Evidence from a British birth cohort." *Human Reproduction*. Sep 2002; 17 (9) : 2474-2479

15. Multiple Sclerosis

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

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. Dick, G. "The Etiology of Multiple Sclerosis." *Proc Roy Soc Med* 1976;69:611-5

Pisacane A, et al. Breast feeding and multiple sclerosis. *BMJ* 1994 May 28;308(6941):1411-2.

16. Obesity and self-regulations of intake

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. McCrory C, Layte R. "Breastfeeding and risk of overweight and obesity at nine-years of age." *Social Science & Medicine*, 2012 Jul; 75 (2): 323-30.

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. Crume TL, Bahr TM, Mayer-Davis EJ et al. Selective protection against extremes in childhood body size, abdominal fat deposition, and fat patterning in breastfed children. *Arch Pediatr Adolesc Med*. 2012 May;166(5):437-43.

Our goal was to test the hypothesis that infants who were breastfed more intensively during early infancy (< 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 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. Li R, Fein SB, Grummer-Strawn LM. Association of breastfeeding intensity and bottle-emptying behaviors at early infancy with infants' risk for excess weight at late infancy. *Pediatrics*. 2008 Oct;122 Suppl 2:S77-84.

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. **Kramer M, Matush L, Vanilovich I, et al.** "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." *American Journal of Clinical Nutrition*, Vol. 86, No. 6, 1717-1721, December 2007.

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. Weyermann M, Rothenbacher D, Brenner H. "Duration of breastfeeding and risk of overweight in childhood: a prospective birth cohort study from Germany." *Int J Obes*. 2006 Aug;30(8):1281-7.

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 ≥ 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 <3 months of breast-feeding to 0.78 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. Nelson MC, Gordon-Larsen P, Adair LS. "Are adolescents who were breast-fed less likely to be overweight? Analyses of sibling pairs to reduce confounding." *Epidemiology*. 2005 Mar;16(2):247-53.

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 (<1 month of breastfeeding: odds ratio (OR)=1.0, 95% CI: 0.65, 1.55; 1-3 months: OR=0.81, 95% CI: 0.74, 0.88; 4-6 months: OR=0.76, 95% CI: 0.67, 0.86; 7-9 months: OR=0.67, 95% CI: 0.55, 0.82; >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. Harder T, et al. "Duration of breastfeeding and risk of overweight: a meta-analysis." *Am J Epidemiol* 2005;162:397-403.

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 <500 subjects (odds ratio: 0.43; 95% CI: 0.33-0.55) but was still apparent in larger studies of ≥ 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. Owen, C. G., R. M. Martin, P. H. Whincup et al. Effect of infant feeding on the risk of obesity across the life course: A quantitative review of published evidence. *Pediatrics* 2005; 115(5):1367-77.

To investigate the relationship between breast-feeding and obesity in childhood. DESIGN: Systematic review and meta-analysis 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. Arenz S, et al. "Breast-feeding and childhood obesity--a systematic review." *Int J Obes Relat Metab Disord*. 2004 Oct;28(10):1247-56.

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. Bogen DL, Hanusa BH, Whitaker RC. "The effect of breast-feeding with and without formula use on the risk of obesity at 4 years of age." *Obes Res.* 2004 Sep;12(9):1527-35

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 12587 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. Grummer-Strawn LM; Mei Z. "Does Breastfeeding protect against pediatric overweight? Analysis of longitudinal data from the Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System." *Pediatrics*-. Feb 1 2004; 113 (2):81-86

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. Toschke AM et al "Overweight and obesity in 6- to 14-year-old Czech children in 1991: Protective effect of breast-feeding." *J Pediatr* 2002;141:764-9 December 2002.

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. Armstrong-J; Reilly-JJ. "Breastfeeding and lowering the risk of childhood obesity." *Lancet.* Jun 8 2002; 359 (9322): 2003-2004.

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. Gillman MW et al. Risk of Overweight Among Adolescents Who Were Breastfed as Infants. *JAMA* 2001 May 16;285(19):2461-2467.

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. von Kries, R. "Breast feeding and obesity: cross sectional study." *BMJ* 1999; 319: 147-150.

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. Tulldahl J, Pettersson K, Andersson SW, Hulthen L. "Mode of infant feeding and achieved growth in adolescence: early feeding patterns in relation to growth and body composition in adolescence." *Obes Res* 1999 Sep;7(5):431-7.

17. Oral and Dental Health

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. CC Romero, H Scavone-Junior, DG Garib, FA Cotrim-Ferreira, and RI Ferreira. "Breastfeeding and non-nutritive sucking patterns related to the prevalence of anterior open bite in primary dentition." *J Appl Oral Sci*, April 1, 2011; 19(2): 161-8.

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). Sánchez-Molins M, Grau Carbó J, Lischeid Gaig C, Ustrell Torrent JM. Comparative study of the craniofacial growth depending on the type of lactation received. *Eur J Paediatr Dent*. 2010 Jun;11(2):87-92.

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. Kobayashi HM, Scavone H Jr, Ferreira RI, Garib DG. Relationship between breastfeeding duration and prevalence of posterior crossbite in the deciduous dentition. *Am J Orthod Dentofacial Orthop*. 2010 Jan;137(1):54-8.

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. Kramer MS, Vanilovich I, Matush L, Bogdanovich N, Zhang X, Shishko G, Muller-Bolla M, Platt RW. The

effect of prolonged and exclusive breast-feeding on dental caries in early school-age children. New evidence from a large randomized trial. *Caries Res.* 2007;41(6):484-8. Epub 2007 Sep 18

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. Iida H, Auinger P, Billings RJ et al (2007) "Association between infant breastfeeding and early childhood caries in the United States." *Pediatrics*;120(4): e944-52.

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%. Non-nutritive 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. Peres KG et al. "Effects of breastfeeding and sucking habits on malocclusion in a birth cohort study." *Rev Saude Publica.* 2007 Jun;41(3):343-350.

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. Wondwossen, F et al. "Sociodemographic and behavioural correlates of severe dental fluorosis." *International Journal Of Paediatric Dentistry*, 16 (2): 95-103 Mar 2006

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 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. Trawitzki LV et al. "Breast-feeding and deleterious oral habits in mouth and nose breathers." *Rev Bras Otorrinolaringol (Engl Ed).* 2005 Nov-Dec;71(6):747-51.

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. Holman, DJ; Yamaguchi, K. Longitudinal analysis of deciduous tooth emergence: IV. Covariate effects in Japanese children. *American Journal Of Physical Anthropology*, 126 (3): 352-358 Mar 2005.

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. Viggiano D et al (2004). Breast feeding, bottle feeding, and non-nutritive sucking; effects on occlusion in deciduous dentition. *Arch Dis Child* 89: 1121-1123.

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. Charchut SW, Allred EN, Needleman HL. The effects of infant feeding patterns on the occlusion of the primary dentition. *J Dent Child (Chic)*. 2003 Sep-Dec;70(3):197-203.

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. Valaitis R, et al. A systematic review of the relationship between breastfeeding and early childhood caries. *Canadian-Journal-Of-Public-Health-Revue-Canadienne-De-Sante-Publique*. Nov-Dec 2000; 91(6) : 411-417.

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. Oulis CJ et al. "Feeding practices of Greek children with and without nursing caries." *Pediatr Dent* 1999 Nov-Dec;21(7):409-16.

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. Ramos-Gomez-FJ et al. "Assessment of early childhood caries and dietary habits in a population of migrant Hispanic children in Stockton, California." *Journal-Of-Dentistry-For-Children* 1999; 66 (6): 395-403, 366

This in-vivo and in-vitro study showed that human breast milk is not cariogenic. Erickson PR, Mazhari E. "Investigation of the role of human breast milk in caries development." *Pediatr Dent* 1999 Mar-Apr;21(2):86-90.

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. Mattos-Graner RO et al. "Association between caries prevalence and clinical, microbiological and dietary variables in 1.0 to 2.5-year-old Brazilian children. *Caries Res* 1998;32(5):319-23.

A strong association was found between exclusive bottle-feeding and anteroposterior malocclusion. Davis DW, Bell PA. "Infant feeding practices and occlusal outcomes: a longitudinal study." *J Can Dent Assoc* 1991 Jul;57(7):593-4.

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. Labbok MH, Hendershot GE. "Does breast-feeding protect against malocclusion? An analysis of the 1981 Child Health Supplement to the National Health Interview Survey." *Am J Prev Med*. 1987 Jul-Aug;3(4):227-32.

18. Parent-child relationships

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 bottlefeeders. McKee MD; Zayas LH; Jankowski KRB. "Breastfeeding intention and practice in an urban minority population: relationship to maternal depressive symptoms and mother infant closeness." *Journal of Reproductive and Infant Psychology*. Aug 2004; 22 (3) : 167-181.

Children who were breast fed 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. Fergusson DM, Woodward LJ. "Breast feeding and later psychosocial adjustment." *Paediatr Perinat Epidemiol* 1999 Apr;13(2):144-57

19. Protection against toxins (environmental contaminants, chemicals, heavy metals)

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 breast fed. 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 breast fed. 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. Jacobson JL, Jacobson SW. "Prenatal exposure to polychlorinated biphenyls and attention at school age." *J Pediatr*. 2003 Dec;143(6):780-8.

20. Schizophrenia

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. Sorensen HJ et al. "Breastfeeding and risk of schizophrenia in the Copenhagen Perinatal Cohort." *Acta Psychiatr Scand*. 2005 Jul;112(1):26-9.

21. Stress Resilience

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 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. Breast feeding 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. Montgomery, SM; Ehlin, A; Sacker, A. "Breast feeding and resilience against psychosocial stress." *Archives Of Disease In Childhood*, Efirst Date: 3 Aug 2006

22. Tonsillitis

Pisacane A, et al. Breast feeding and tonsillectomy. *BMJ*. 1996 Mar 23;312(7033):746-7.

23. Transplant recipients

A history of breastfeeding was associated with dramatic improvements in graft function rates after sibling donor as well as maternal donor transplantation. Kois WE et al. Influence of breast feeding on subsequent reactivity to a related renal allograft. *J Surg Res.* 1984 Aug;37(2):89-93.

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 posttransplant 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. Campbell DA et al. Breast feeding and maternal-donor renal allografts. *Transplantation* 1984 Apr;37(4):340-4.

24. Vaccine Response

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. Silfverdal SA, Ekholm L, Bodin L. "Breastfeeding enhances the antibody response to Hib and Pneumococcal serotype 6B and 14 after vaccination with conjugate vaccines." *Vaccine.* 2007 Feb 9;25(8):1497-502. Epub 2006 Oct 30.

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. Schaller JP et al. "Effect of dietary ribonucleotides on infant immune status. Part 1: Humoral responses." *Pediatric-Research.* Dec 2004; 56 (6) : 883-890

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 HF, Spady DW, Pilarski LM, et al. "Differential modulation of the immune response by breast- or formula-feeding of infants." *Acta Paediatr.* 1997 Dec;86(12):1291-7.

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. Papst, H.F. , Spady, D.W. "Effect of Breast Feeding on Antibody Response to Conjugate Vaccine". *Lancet*, 1990 Aug 4; 336(8710): 2609-70.

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. Hahn-Zoric M et al. Antibody responses to parenteral and oral vaccines are impaired by conventional and low protein formulas as compared to breast-feeding. *Acta Paediatr Scand* 1990; 79:1137-1142.

II. Maternal Effects

A. Cancer

1. Breast Cancer

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. Stuebe AM, Willett WC, Xue F, Michels KB. Lactation and incidence of premenopausal breast cancer: a longitudinal study. *Arch Intern Med.* 2009 Aug 10;169(15):1364-71.

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. Clarke, CA; Purdie, DM; Glaser, SL. "Population attributable risk of breast cancer in white women associated with immediately modifiable risk factors." *BMC CANCER*, 6: 170-170 JUN 27 2006

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. Becher H; Schmidt S; Chang-Claude J. "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.* Feb 2003; 32 (1): 38-48.

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. Gammon MD. "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*, Aug 2002; 74 (3): 235-254.

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. Beral V et al. "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." *Lancet*, Jul 20 2002; 360 (9328): 187-195

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. Zeng T et al. Long-term Breastfeeding Lowers Mother's Breast Cancer Risk. *Am J Epidemiol* 2001; 152:1129-1135.

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. Marcus PM, Baird DD, Millikan RC, Moorman PG, Qaqish B, Newman B. Adolescent reproductive events and subsequent breast cancer risk. *Am J Public Health* 1999 Aug;89(8):1244-7

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 PA et al. "Lactation in relation to postmenopausal breast cancer." *Am J Epidemiol* 1999 Jul 15;150(2):174-82

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%. Newcomb, P. et al. "Lactation and reduced risk of premenopausal breast cancer." *N Engl J Med* 1994; 330(2):81-87.

After controlling for age at first full term pregnancy and other potentially compounding factors, parity and duration of breast feeding 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. Layde, P.M., "The Independent Associations of Parity Age at First full Term Pregnancy, and Duration of Breast Feeding with the Risk of Breast Cancer." *Journal of Clinical Epidemiol*, 1989.

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. McTieman, A., Evidence of Protective Effect of Lactation on Risk of Breast Cancer in Young Women." *American Journal of Epidemiology*, 1986

2. Endometrial Cancer

Lactation provides a hypoestrogenic effect with less stimulation of the endometrial lining. This event may offer a protective effect from endometrial cancer. Petterson B, et al. "Menstruation span- a time limited risk factor for endometrial carcinoma". *Acta Obstet Gynecol Scand* 1986;65:247-55

3. Esophageal Cancer

Breastfeeding was associated with reduced risk of subsequently developing this cancer (OR = 0.41) and there was a significant dose-response effect. Cheng-KK et al. "A case-control study of oesophageal adenocarcinoma in women: a preventable disease." *British-Journal-Of-Cancer*. Jul 2000; 83 (1) : 127-132

4. Hodgkin's Disease

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). Glaser SL et al. "Reproductive factors in Hodgkin's disease in women." *Am J Epidemiol*. 2003 Sep 15;158(6):553-63.

5. Ovarian Cancer

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; Xie-X; Lee-AH; Binns-CW. "Prolonged lactation reduces ovarian cancer risk in Chinese women." *European-Journal-Of-Cancer-Prevention*. Dec 2004; 13(6): 499-502

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. Zhang-M; Lee-AH; Binns-CW. "Reproductive and dietary risk factors for epithelial ovarian cancer in China." *Gynecologic Oncology*. Jan 2004; 92(1): 320-326.

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 nonmucinous tumors but not to mucinous tumors. Tung KH et al. "Reproductive factors and epithelial ovarian cancer risk by histologic type: a multiethnic case-control study." *Am J Epidemiol*. 2003 Oct 1;158(7):629-38.

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. Greggi S et al. "Risk factors for ovarian cancer in central Italy." *Gynecologic-Oncology*. Oct 2000; 79 (1): 50-54.

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. Titus-Ernstoff L. "Menstrual and reproductive factors in relation to ovarian cancer risk." *British-Journal-Of-Cancer*. Mar 2 2001; 84 (5) : 714-721

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. Siskind V et al. "Breastfeeding, menopause, and epithelial ovarian cancer. *Epidemiology* 1997 Mar;8(2):188-91

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. John EM et al. "Characteristics relating to ovarian cancer risk: collaborative analysis of seven U.S. case-control studies. *Epithelial ovarian cancer in black women. J Natl Cancer Inst* 1993 Jan 20;85(2):142-7

A marked reduction in risk was associated with ever having breast fed. Gwinn ML et al. "Pregnancy, breast feeding, and oral contraceptives and the risk of epithelial ovarian cancer. *J Clin Epidemiol* 1990;43(6):559-68

Breastfeeding should be added to the list of factors that decrease ovulatory age and thereby decrease the risk of ovarian cancer. Schneider, A.P. "Risk Factor for Ovarian Cancer." *New England Journal of Medicine*, 1987

6. Thyroid Cancer

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. Mack WJ et al, "Reproductive and hormonal risk factors for thyroid cancer in Los Angeles County females." *Cancer Epidemiol Biomarkers Prev* 1999 Nov;8(11):991-7

7. Uterine Cancer

A protective effect against uterine cancer was found for women who breastfeed. Brock, K.E., "Sexual, Reproductive, and Contraceptive Risk Factors for Carcinoma-in-Situ of the Uterine Cervix in Sidney." *Medical Journal of Australia*, 1989.

B. Cardiovascular Health

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. Stuebe AM, Schwarz EB, Grewen K, et al. "Duration of lactation and incidence of maternal hypertension: a longitudinal cohort study." *Am J Epidemiol*. 2011 Nov 15;174(10):1147-58. Epub 2011 Oct 12.

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, $P < .001$), diabetes (OR 0.80, $P < .001$), hyperlipidemia (OR 0.81, $P < .001$), or cardiovascular disease (OR 0.91,

P=.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. Schwarz EB et al. "Duration of lactation and risk factors for maternal cardiovascular disease." *Obstet Gynecol.* 2009 May; 113(5):974-82.

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. Stuebe AM, Michels KB, Willett WC, et al. "Duration of lactation and incidence of myocardial infarction in middle to late adulthood." *Am J Obstet Gynecol.* 2009 Feb;209 (2):138.e1-8.

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. Lee SY, et al. "Does long-term lactation protect premenopausal women against hypertension risk? A Korean women's cohort study." *Prev Med.* 2005 Aug;41(2):433-8

Groups of breastfeeding and bottle-feeding women were compared on preejection 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. Mezzacappa-ES et al. "Breast-feeding and maternal cardiovascular function." *Psychophysiology*, Nov 2001; 38 (6) : 988-997

C. Diabetes and Metabolic Disease

For maternal metabolism, pregnancy ends not with delivery, but with weaning. In several recent epidemiological studies, authors have reported an association between duration of breast-feeding 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 AM, Rich-Edwards JW. The reset hypothesis: lactation and maternal metabolism. *Am J Perinatol.* 2008 Nov 21;

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. Stuebe AM et al. Duration of lactation and incidence of type 2 diabetes. *JAMA*. 2005 Nov 23;294(20):2601-10.

McManus RM, Cunningham I, Watson A, Harker L, Finegood DT. Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. *Metabolism*. 2001 Jun;50(6):715-9.

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. Davies, H.A., "Insulin Requirements of Diabetic Women who Breast Feed." *British Medical Journal*, 1989 May 20;298(6684):1357-8.

D. Emotional Health

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 ($p < 0.0001$). Breastfeeding women at 2 months had lower scores on EPDS ($p < 0.003$) 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. Hamdan A; Tamim H. "The Relationship Between Postpartum Depression And Breastfeeding." *International Journal of Psychiatry in Medicine*, 2012; 43 (3): 243-59.

The purpose of this study was to examine relationships among lactational status, naturalistic stress, mood, and levels of serum cortisol and prolactin and plasma adrenocorticotropic hormone (ACTH). Eighty-four exclusively breastfeeding, 99 exclusively formula-feeding, and 33 nonpostpartum 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. Groer MW. Differences between exclusive breastfeeders, formula-feeders, and controls: a study of stress, mood, and endocrine variables *Biol Res Nurs*. 2005 Oct;7(2):106-17.

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 bottlefeeders. McKee MD; Zayas LH; Jankowski KRB. "Breastfeeding intention and practice in an urban minority population: relationship to maternal depressive symptoms and mother infant closeness." *Journal of Reproductive and Infant Psychology*. Aug 2004; 22 (3) : 167-181.

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. Harlow-BL et al. "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*. Apr 2004; 79(1-3): 167-176.

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. Sjogren-B et al. "Changes in personality pattern during the first pregnancy and lactation." *Journal-Of-Psychosomatic-Obstetrics-And-Gynecology*. Mar 2000; 21 (1):31-38.

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. Nissen E, Gustavsson P, Widstrom AM, Uvnas-Moberg K. "Oxytocin, prolactin, milk production and their relationship with personality traits in women after vaginal delivery or Cesarean section." *J Psychosom Obstet Gynaecol* 1998 Mar;19(1):49-58

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. Uvnas-Moberg K. "Oxytocin may mediate the benefits of positive social interaction and emotions." *Psychoneuroendocrinology* 1998 Nov;23(8):819-35

At one month postpartum, women who breast fed their infants had scores indicating less anxiety and more mutuality than the women bottle feeding their infants. Virden, S.F., "The Relationship Between Infant Feeding Method and Maternal Role Adjustment." *Journal of Nurse Midwives*, 1988 Jan-Feb;33(1):31-5.

E. Fertility

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. Vekemans M. "Postpartum contraception: the lactational amenorrhea method." *Eur J Contracept Reprod Health Care* 1997 Jun;2(2):105-11

F. Menopausal 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. Sievert LL et al.

“Measurement of hot flashes by sternal skin conductance and subjective hot flash report in Puebla, Mexico.” *Menopause the Journal of the North American Menopause Society*. Sep-Oct 2002; 9 (5): 367-376.

G. Osteoarthritis

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. Cooley-HM; Stankovich-J; Jones-G. “The association between hormonal and reproductive factors and hand osteoarthritis.” *Maturitas*. Aug 20 2003; 45 (4) : 257-265

H. Osteoporosis

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 maybe influenced by many variables, is better than univariate statistical evaluation. Akkus Z, et al. Determination of osteoporosis risk factors using a multiple logistic regression model in postmenopausal Turkish women.” *Saudi Med J*. 2005 Sep;26(9):1351-9

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. Chantry CJ, Auinger P, Byrd RS. “Lactation among adolescent mothers and subsequent bone mineral density.” *Arch Pediatr Adolesc Med*. 2004 Jul;158(7):650-6.

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. Huo-DZ; Lauderdale-DS; Li-LM. "Influence of reproductive factors on hip fracture risk in Chinese women." *Osteoporosis International*. Aug 2003; 14 (8) : 694-700

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.

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." *Osteoporosis International* 1993 Mar;3(2):76-83

I. Smoking Reduction

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. Lauria L, Lamberti A, Grandolfo M. "Smoking behaviour before, during, and after pregnancy: the effect of breastfeeding." *Scientific World Journal*. 2012;2012:154910. Epub 2012 Mar 12.

J. Postpartum Weight Loss

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. Baker JL, Gamborg M, Heitmann BL, Lissner L, Sørensen TI, Rasmussen KM. "Breastfeeding reduces postpartum weight retention." *Am J Clin Nutr*. 2008 Dec;88(6):1543-51.

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. Kac-G et al. "Breastfeeding and postpartum weight retention in a cohort of Brazilian women." *American-Journal-Of-Clinical-Nutrition*. Mar 2004; 79 (3) : 487-493

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.

Dewey KG et al. Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. *J Nutr* 2001 Feb;131(2):262-7

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. Kramer, F., "Breastfeeding reduces maternal lower body fat." *J Am Diet Assoc* 1993;93(4):429-33

K. Relationship (maternal-infant)

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. Kim, P., Feldman, R., Mayes, L. C., Eicher, V., Thompson, N., Leckman, J. F. and Swain, J. E. (2011), Breastfeeding, brain activation to own infant cry, and maternal sensitivity. *Journal of Child Psychology and Psychiatry*, 52: 907–915. doi: 10.1111/j.1469-7610.2011.02406.x

L. Rheumatoid Arthritis

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. Karlson EW et al. "Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the Nurses' Health Study." *Arthritis Rheum*. 2004 Nov;50(11):3458-67.

M. Sleep

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 breast-feeding. Doan et al. "Breast-feeding Increases Sleep Duration of New Parents." J Perinat Neonatal Nurs. 2007 Jul-Sep;21(3):200-6

N. Systemic Lupus Erythematosus

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 breast-fed 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. Cooper-GS et al. "Hormonal and reproductive risk factors for development of systemic lupus erythematosus - Results of a population-based, case-control study." Arthritis-And-Rheumatism. Jul 2002; 46 (7) : 1830-1839.

O. Urinary Tract Infections

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. Coppa GV et al. "Preliminary study of breastfeeding and bacterial adhesion to uroepithelial cells." Lancet 1990 Mar 10;335(8689):569-71

III. Societal Effects

A. Child Abuse and Parenting Sensitivity

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 hypothesized 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. Pearson RM, Lightman SL, Evans J. "The impact of breastfeeding on mothers' attentional sensitivity towards infant distress." Infant Behav Dev. 2010 Dec 23

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 ≥ 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. Strathearn L, Mamun AA, Najman JM, O'Callaghan MJ. "Does breastfeeding protect against substantiated child abuse and neglect? A 15-year cohort study." *Pediatrics*. 2009 Feb;123(2):483-93.

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. Lvoff-NM et al. Effect of the baby-friendly initiative on infant abandonment in a Russian hospital. *Archives-Of-Pediatrics-And-Adolescent-Medicine*. MAY 2000; 154(5):474-477.

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, 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.

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. Buranasin B. "The effects of rooming-in on the success of breastfeeding and the decline in abandonment of children." *Asia Pac J Public Health*. 1991;5(3):217-20.

B. Child Spacing

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. Singh R, Tripathi V, Singh K, et al. Breastfeeding as a time-varying-time-dependent factor for birth spacing: multivariate models with validations and predictions. *World Health Popul*. 2012;13(3):28-51.

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. Kuate D. "Effects of infant feeding practices and birth spacing on infant and child survival: a reassessment from retrospective and prospective data." *J Biosoc Sci* 1997 Jul;29(3):303-26

Sufficient birth spacing helps with the survival of the older sibling and the new infant. Prolonged lactation helps to promote the spacing of children. Thapa, S., "Breastfeeding, birth spacing and their effects on child survival." *Nature* 1988;335:679-82

C. 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.

D. Financial Cost to Government and Families

1. 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).

2. Medical Expenses

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 and cost 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. Bartick, M., & Reinhold, A. "The burden of suboptimal breastfeeding in the United States: a pediatric cost analysis. *Pediatrics*, Jan 2010, 125, 5, 1048-56.

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. Pugh LC et al. "Breastfeeding duration, costs, and benefits of a support program for low-income breastfeeding women." *Birth* 2002 Jun;29(2):95-100.

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. Weimer, D. *The Economic Benefits of Breastfeeding: A Review and Analysis*. Economic Research Service, US Department of Agriculture, Food Assistance and Nutrition Research Report No. 13. 20 pp, March 2001, <http://www.ers.usda.gov/publications/fanrr13/>

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 \$475 per never-breastfed infant during the first year of life. Ball TM, Wright AL. "Health care costs of formula-feeding in the first year of life." *Pediatrics* 1999 Apr;103(4 Pt 2):870-6

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. Montgomery DL, Splett PL. "Economic benefit of breast-feeding infants enrolled in WIC." *J Am Diet Assoc* 1997 Apr;97(4):379-85

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. Tuttle CR, Dewey KG. "Potential cost savings for Medi-Cal, AFDC, food stamps, and WIC programs associated with increasing breast-feeding among low-income Hmong women in California. *J Am Diet Assoc* 1996 Sep;96(9):885-90

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

E. Vaccine Effectiveness (see also “Vaccine Response”)

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. Hahn-Zoric, M., "Antibody responses to parenteral and oral vaccines are impaired by conventional and low protein formulas as compared to breastfeeding." *Acta Paediatr Scand* 1990; 79:1137-42