Risks of Formula Feeding

A BRIEF ANNOTATED BIBLIOGRAPHY
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A Brief Annotated Bibliography

When breastfeeding is not exclusively practised, infant formulas are generally used. The World Health Organization International Code of Marketing of Breast-Milk Substitutes requires that parents be fully informed about the health hazards of unnecessary or improper use of infant formula. This brief annotated bibliography gives some examples from the extensive body of research documenting the importance of breastfeeding and in turn the associated risks of formula feeding.

The World Health Organization Recommends

The World Health Organization recommends exclusive breastfeeding for the first six months of life, the introduction of local, nutrient rich complementary foods thereafter with continued breastfeeding to two years of age or beyond.

(World Health Assembly Resolution 54.2, 2001)

For Infants and Children

1 Increased risk of asthma
2 Increased risk of allergy
3 Reduced cognitive development
4 Increased risk of acute respiratory disease
5 Increased altered occlusion
6 Increased risk for infection from contaminated formula
7 Increased risk of nutrient deficiencies
8 Increased risk of childhood cancers
9 Increased risk of chronic diseases
10 Increased risk of diabetes
11 Increased risk of cardiovascular disease
12 Increased risk of obesity
13 Increased risk of gastrointestinal infections
14 Increased risk of mortality
15 Increased risk of otitis media and ear infections
16 Increased risk of side effects of environmental contaminants

For Mothers

1 Increased risk of breast cancer
2 Increased risk of overweight
3 Increased risk of ovarian cancer and endometrial cancer
4 Increased risk of osteoporosis
5 Reduced natural child spacing
6 Increased risk of rheumatoid arthritis
7 Increased stress and anxiety
8 Increased risk of maternal diabetes
**RISKS OF FORMULA FEEDING**

**For Infants and Children**

### 1 Increased risk of asthma

- A longitudinal prospective study of 1246 healthy infants in Arizona, USA, aimed to determine the relationship between breastfeeding and recurrent wheeze. The results showed that non-atopic children at the age of six years, who had not been breastfed, were three times more likely to have recurrent wheezing.


- A study of 2184 children done by the Hospital for Sick Children in Toronto determined that the risk of asthma and wheeze was approximately 50 per cent higher when infants were formula-fed compared to infants who were breastfed for nine months or longer.


- Researchers in West Australia studied 2602 children to determine the development of asthma and wheeze at six years of age. Not breastfeeding increased the risk of asthma and wheeze by 40 per cent compared to infants who were exclusively breastfed for four months. The authors recommend exclusive breastfeeding for at least four months to reduce the risk of asthma.


- The reviewers looked at 29 studies to evaluate the protective effect of breastfeeding on asthma and atopy. After applying strict criteria for assessment, 15 studies remained in the review. All 15 showed a protective effect of breastfeeding. They concluded that the evidence is clear and consistent that not breastfeeding puts infants at risk for asthma and atopy.


### 2 Increased risk of allergy

- Children in Finland who had been breastfed the longest had the lowest incidence of atopy, eczema, food allergy and respiratory allergy. At 17 years of age, the incidence of respiratory allergy for those who had little breastfeeding was 65 per cent and for those who were breastfed the longest 42 per cent.

  [Saarinen UM, Kajosarri M. Breastfeeding as a prophylactic against atopic disease: Prospective follow-up study until 17 years old. Lancet 346: 1065-1069, 1995]

- Infants with a maternal history of respiratory allergy or asthma were assessed for atop dermatitis during the first year of life. Exclusive breastfeeding for the first three months of life was found to have a protective effect against dermatitis.


- The effects of maternal dietary vitamins C and E on breastmilk antioxidant composition to protect against the development of atopy in infants were assessed. Mothers with atopic disease kept four-day food records and breastmilk samples were collected at the infants’ age of one month.

  [Results showed that maternal intake of vitamin C in her diet but not as a supplement determined the concentration of vitamin C in breastmilk. A higher concentration of vitamin C in breastmilk was associated with a reduced risk of atopy in the infant. Vitamin E had no consistent relationship with atopy. Thus a maternal diet rich in natural food sources of vitamin C during breastfeeding can reduce the risk of atopy in high-risk infants.


### 3 Reduced cognitive development

- To determine the impact of exclusive breastfeeding on cognitive development for infants born small for gestational age, this US-based study evaluated 220 infants, using the Bayley Scale of Infant Development at 13 months and the Wechler Preschool and Primary Scales of Intelligence at five years. The researchers concluded that exclusively breastfed (without supplements) small for gestational age infants had a significant advantage in cognitive development without compromising growth.


- Breastfeeding has potentially long-term beneficial effects on a person’s life through its influence on childhood cognitive and educational development, concludes this UK study. Regression analysis was used to determine that breastfeeding was significantly and positively associated with educational levels obtained by age 26 as well as cognitive abilities at age 53 years.


- USA school-aged children (439) born between 1991 and 1993 and who weighed less than 1,500 g at birth were given a variety of cognitive tests. The very low-birth weight infants who had never been breastfed were found to have lower test scores in overall intellectual function, verbal ability, visual-spatial and motor skills than those who had been breastfed.


- Children of socioeconomic disadvantaged Filipino mothers were followed from birth through to middle childhood and assessed for cognitive ability at 8.5 and 11.5 years of age. After controlling for confounding variables, children who had been breastfed for 12 to 18 months had higher scores on the Philippines Nonverbal Intelligence Test. The effects were even greater for low-birth weight infants (1.6 and 9.8 points respectively). The authors conclude that long-term breastfeeding is important after the introduction of complementary foods, and even more so for low-birth weight infants.

4 Increased risk of acute respiratory disease

- Brazilian children not breastfed were 16.7 times more likely to be diagnosed with pneumonia than children who had received only breastmilk as infants.
  

- To determine the modifiable risk factors for acute lower respiratory infection in young children, this Indian hospital-based study compared 201 cases to 311 controls. Breastfeeding was one of the key modifiable risk factors for lower respiratory infection in children under five years of age.
  

- A number of sources were used to examine the relationship between breastfeeding and risk of hospitalization for lower respiratory tract disease in healthy full-term infants with access to adequate health facilities. Analysis of the data concluded that in developed countries, infants who were formula-fed experienced more than three times the severity of respiratory tract illness and required more frequent hospitalization compared to infants who had been breastfed exclusively for four months or more.
  

5 Increased altered occlusion

- Breastfeed for straight teeth is the message from this research on feeding, sucking and dentition. This retrospective study of 1130 preschool children (three to five years of age) looked at the impact of the type of feeding and non-nutritive sucking activity on occlusion in deciduous dentition. Detailed infant feeding and non-nutritive sucking activity history was collected by questionnaire in addition to an oral examination by a dentist.
  

6 Increased risk for infection from contaminated formula

- A Belgian-based outbreak of necrotizing enterocolitis (NEC) is traced back to infant formula contaminated with Enterobacter sakazakii. A total of 12 infants developed NEC during the outbreak and two infants (twin brothers) died.
  

- A case report from a recent US based outbreak of Enterobacter sakazakii in a neonatal intensive care unit documents the death of a 20-day-old infant who developed fever, tachycardia, decreased vascular profusions and seizures at 11 days. The infant died at day 20. E. sakazakii cultures were identified from the spinal fluid and trace to contaminated powdered infant formula used in the NICU.
  
  Weir E. Powdered infant formula and fatal infection with Enterobacter sakazakii. CMAJ 166, 2002

7 Increased risk of nutrient deficiencies

- Infants fed the same soy-based infant formula brand in Israel during 2003 were hospitalized in intensive care units with severe encephalopathy. Two died of cardiomyopathy. Analysis showed that the thiamine level of the formula was undetectable. The soy-based formula-fed infants admitted with symptoms indicating thiamine deficiency experienced a rapid improvement when treated with thiamine.
  

8 Increased risk of childhood cancers

- The UK Childhood Cancer Study analyzed 3500 childhood cancer cases and the relationship to breastfeeding. Results showed a small reduction for leukemia and for all cancers combined when infants had “ever been breastfed.”
  

- A case controlled study in the United Arab Emirates looked at 117 cases of acute lymphocytic leukemia and 117 controls. They found that the breastfeeding duration of those with leukemia was significantly shorter than the breastfeeding duration of the controls. They concluded that breastfeeding duration of six months or longer may protect against childhood acute leukemia and lymphomas.
  

- Lack of breastfeeding is known to increase the risk of cancer. This novel study found a significant level of genetic damage in infants aged nine to 12 months who were not breastfed. The authors speculate that the genetic damage may play a role in the development of cancer in childhood or later life.
  
This systematic review to look at the evidence for the effect of breastfeeding on the risk of developing childhood leukemia examined 111 studies from which they identified 32 eligible articles. Of these they reviewed 10 and found that four had quality evidence regarding the association between breastfeeding and leukemia. In the two largest and highest-quality studies breastfeeding was associated with a significant risk reduction and in one of these studies, greater durations reflected greater protection. They note that in the US approximately 1.4 billion dollars are spent annually to treat childhood leukemia.


9 Increased risk of chronic diseases

Celiac disease may be triggered by an autoimmune response when an infant is exposed to a food containing gluten proteins. Ivarsson and her team of researchers looked at the breastfeeding patterns of 627 children with celiac disease and at 1254 healthy children to determine the effect of breastfeeding during the time of introduction of gluten-containing foods on the outcome of the development of celiac disease.

An astounding 40 per cent risk reduction was reported for the development of celiac disease in children at two years of age or younger for those who were breastfed when dietary gluten was introduced. The effect was even more pronounced in infants who continued to be breastfed after dietary gluten was introduced, the authors noted.


Inflammatory bowel disease and Crohn’s disease are chronic gastrointestinal conditions that are more frequent for those who are formula-fed. A meta-analysis on 17 relevant studies supports the hypothesis that breastfeeding is associated with lower risks of Crohn’s disease and ulcerative colitis.


To determine the effect of early infant feeding practices (i.e. the impact of breastfeeding versus no breastfeeding; the duration of breastfeeding; and the effect of breastfeeding while introducing gluten-containing foods) on the development of celiac disease (CD), the authors reviewed the literature available on breastfeeding and CD.

They found that children with CD were breastfed for a significantly shorter period of time. Children being breastfed at the time of gluten reduction had a 52 per cent reduction of risk for developing CD compared with children who were not breastfeeding at the time of introduction.

The authors pose two potential mechanisms for the protective effect. First, that continued breastfeeding limits the actual amounts of gluten received. Secondly, that breastfeeding protects against intestinal infections. Infections can increase the permeability of the infant's gut and therefore allow the passage of gluten into the lamina propria.

Others have suggested that breastmilk IgA may reduce the immune response to ingested gluten or immune modulation may occur through specific T-cell suppressive effects.


10 Increased risk of diabetes

To determine the link between cow’s milk (and cow’s milk-based infant formula) consumption and the development of antibody response to cow’s milk protein, Italian researchers measured the antibody response of 16 breastfed and 12 cow’s milk-fed infants under four months of age. Cow’s milk-fed infants had elevated levels of beta-casein antibodies when compared to breastfed infants. They concluded that breastfeeding for the first four months prevented the production of antibodies and could have a preventive effect on the development of Type 1 diabetes.


In this case-controlled study, 46 native Canadian Type II diabetes patients were matched with 92 controls. Pre- and postnatal risk factors were compared. Breastfeeding was found to reduce the risk of Type II diabetes.


Early introduction of infant formula, solids and cow’s milk are factors shown to increase the incidence of Type I diabetes later in life. Swedish (517) and Lithuanian (286) children aged 0 to 15 years who were diagnosed with Type I diabetes were compared to non-diabetic controls. The results showed that exclusive breastfeeding for five months and total breastfeeding for longer than seven or nine months are protective against diabetes.


Data was collected via questionnaires in this case-controlled study consisting of 868 diabetic Czech children and 1,466 controls. This study too confirms that the risk for type I diabetes decreases with increased duration of breastfeeding. Not breastfeeding was associated with an increased risk – OR of 1.93. Breastfeeding for 12 months or longer reduced the risk significantly – OR of 0.42.

Malove H et al. Absence of breast-feeding is associated with the risk of type 1 diabetes: a case-control study in a population with rapidly increasing incidence. Eur J Pediatr 165: 114-119, 2005

11 Increased risk of cardiovascular disease

To confirm links between infant nutrition and health risks in later life, British researchers measured blood pressure at 13 to 16 years of age in 216 children who had been born prematurely. For those who had received preterm infant formula or routine infant formula, blood pressure was higher than for those who had received breastmilk during infancy. The authors concluded that for children born prematurely, breastfeeding lowers blood pressure in later life and that this conclusion can be extended to term infants as well.


This UK study looked at the cholesterol levels of 1500 children aged 13 to 16 years and determined that breastfeeding may have long term benefits for cardiovascular disease by reducing levels of total cholesterol and low-density lipid cholesterol. The research

(continued on page 7)
1 Increased risk of breast cancer

Breast-feeding decreases the risk of breast cancer in mothers and infection, allergy, and autoimmunity in infants. The presence of mediators of the innate immune system in human milk, including defensins, cathelicidins, and toll-like receptors (TLRs), were extracted and analysed from the whey fractions of colostrum and transitional and mature milk (n = 40) from normal mothers (n = 18) and from mothers with autoimmune or allergic diseases.

The authors suggest that the innate immune system in breast milk is complex and likely provides protection for maternal breast tissue and the developing digestive tract of newborns.


Researchers from England evaluated a possible association between cancer incidence and breastfeeding during infancy. This study included nearly 4000 adults who were originally surveyed from 1937-1939. The data included on meta-analysis showed that the rates of breast cancer diagnosed in premenopausal women were approximately 12 per cent lower among women who had been breastfed as infants.


2 Increased risk of overweight

A Brazilian cohort of 405 women were followed at six and nine months postpartum to determine the association between weight retention and breastfeeding practices. When women who had 22 per cent body fat and breastfed for 180 days were compared with those who had breastfed for only 30 days, each month of breastfeeding brought an average reduction of 0.44 kg in weight. In conclusion the authors confirm the association between breastfeeding and postpartum weight and that the promotion of longer breastfeeding brings an average reduction of 0.44 kg in weight. In this study included nearly 4000 adults who were originally surveyed from 1937-1939. The data included on meta-analysis showed that the rates of breast cancer diagnosed in premenopausal women were approximately 12 per cent lower among women who had been breastfed as infants.


3 Increased risk of ovarian cancer and endometrial cancer

Not breastfeeding has been associated with increased risk of ovarian cancer. A large case-control Italian study of 1031 women with epithelial ovarian cancer were compared to 2411 women admitted to the same network of hospitals for a wide spectrum of acute non-neoplastic conditions, unrelated to known risk factors for ovarian cancer. Results showed inverse trends in risk with increasing duration of breastfeeding and the number of children breastfed. Additional analyses by histologic subtypes suggested that the protective role of breastfeeding would be larger for serious neoplasms.


To determine the link between breastfeeding and endometrial cancer, this Japanese hospital-based case-control study compared cases of women with endometrial cancer (155) with controls (96) selected from women attending the outpatient clinic for cervical cancer screening. The women were interviewed to determine breastfeeding practices, contraceptive usage, as well as potential risk factors for endometrial cancer. The authors observed a greater risk of endometrial cancer for parous women who had never breastfed, and concluded that breastfeeding reduces the risk of endometrial cancer in Japanese women.


4 Increased risk of osteoporosis

Longitudinal studies have suggested that both pregnancy and lactation are associated with a bone mineral density loss of up to five per cent, and that the loss recovers after weaning. Cross-sectional studies have indicated that women with many children and a long total period of lactation have similar or higher bone mineral density and similar or lower fracture risk than their peers who have not given birth and breastfed. This trend has been observational and found in cross-sectional case-control studies. The causal relationships have yet to be determined.


5 Reduced natural child spacing

A questionnaire was used to obtain data from Nigerian breastfeeding mothers to determine the impact of breastfeeding practices on lactational amenorrhoea. Exclusive breastfeeding was practised by 100 per cent of the mothers on discharge. This went down to 3.9 per cent at six months. Feeding on cue was practised by 98.9 per cent of the mothers. By six weeks 33.8 per cent of mothers resumed mensus and this rose to 70.2 per cent at six months. The duration of lactational amenorrhoea was longer in exclusively breast-feeding mothers than in those who were not. None of the 178 mothers who participated in the survey became pregnant.


6 Increased risk of rheumatoid arthritis

Female reproductive and hormonal risks factors were studied in a cohort of 121,700 women enrolled in the Nurses’ Health Study. Breastfeeding for more than 12 months was inversely related to the development of rheumatoid arthritis. The effect was found to be dose related. Those who breastfed shorter had a higher risk.

Karlson E W et al. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis?: Results from the Nurses Health Study. Arthritis & Rheumatism 50: 3458-3467, 2004
7 Increased stress and anxiety

To find out if there is a relationship between feeding practices, stress, and mood and levels of serum cortisol, prolactin and ACTH (adrenocorticotropic hormone) in mothers, the author compared the emotional responses of 84 exclusively breastfeeding, 99 exclusively formula-feeding and 33 non-postpartum healthy control women. The mothers’ responses were studied at four to six weeks post-partum.

Overall the breastfeeding mothers had more positive moods, reported more positive events, and perceived less stress than formula-feeders. Breastfeeders had less depression and anger than formula-feeders and serum prolactin levels were inversely related to stress and mood in formula-feeders.


A prospective study followed 7276 term UK infants for 7.5 years. Full data was available for 4763 children. At seven years of age those not breastfed had both systolic and diastolic pressures higher than those who had been breastfed. There was a 0.2mm Hg reduction for each three months of breastfeeding. The authors suggest there may be significant benefits during adulthood as a one per cent reduction in population systolic blood pressure is associated with a 1.5 per cent reduction in overall mortality.


(continued from page 5)

suggests that early exposure to breastmilk may program fat metabolism in later life, resulting in lower blood cholesterol levels and therefore a lower risk of cardiovascular disease.


12 Increased risk of obesity

To determine the impact of infant feeding on childhood obesity, this large Scottish study looked at body-mass index of 32,200 children aged 39 to 42 months. After elimination of confounding factors, socioeconomic status, birthweight and sex, the prevalence of obesity was significantly higher in the formula-fed children, leading to the conclusion that formula feeding is associated with an increase in childhood obesity risk.


In order to determine factors associated with the development of overweight and obesity, 6650 German school-aged children between the ages five to 14 years of age were examined. Breastfeeding was found to be protective against obesity. The protective effect was greater when the infants were exclusively breastfed.


Active follow-up of 855 German mother and baby pairs was used to determine the relationship between not breastfeeding and increased risk of overweight and obesity. After a two year follow-up 8.4 per cent of children were overweight and 2.8 per cent severely overweight: 8.9 per cent were never breastfed, while 62.3 per cent were breastfed for at least six months.

Children who were exclusively breastfed more than three months and less than six months had a 20 per cent reduction risk, while those who had breastfed exclusively for at least six months had a 60 per cent risk reduction for becoming overweight compared to those who were formula-fed.

Weyermann M et al. Duration of breastfeeding and risk of overweight in childhood: a prospective birth cohort study from Germany. Int J Obes advance online publication February 28, 2006

13 Increased risk of gastrointestinal infections

Seven hundred and seventy-six infants from New Brunswick, Canada, were assessed for the relationship between respiratory and gastrointestinal illnesses and breastfeeding during the first six months of life. Although the rates of exclusive breastfeeding were low, the results showed a significant protective effect against total illness during the first six months of life. For those breastfed, the incidence of gastrointestinal infections was 47 per cent lower; the rate of respiratory disease was 34 per cent lower than those who were not breastfed.


A comparison between infants who received primarily breastmilk during the first 12 months of life and infants who were exclusively formula-fed or who were breastfed for three months or less, found that diarrheal disease was twice as high for the formula-fed infants as for those who were breastfed.


Breastfeeding promotion in Belarus significantly reduced the incidence of gastrointestinal infections by 40 per cent.


14 Increased risk of mortality

Compared with exclusive breastfeeding, children who were partially breastfed had a 4.2 times increased risk of death due to diarrheal disease. Not breastfeeding was associated with a 14.2 times increased risk for death due to diarrheal disease in Brazilian children.


8 Increased risk of maternal diabetes

Breastfeeding also reduces the mother’s risk of type II diabetes later in life. The longer the duration of breastfeeding, the lower the incidence of diabetes, according to this Harvard based study. The researchers studied 83,585 mothers in the Nurses’ Health Study (NHS) and 73,418 mothers in the Nurses’ Health Study II (NHS II), and determined that each year of breastfeeding reduced the mother’s risk of diabetes by 15 per cent.


(continued from page 5)
Infants in Bangladesh who were partially breastfed or not breastfed had a risk of acute respiratory infection death 2.4 times greater than exclusively breastfed infants. If children were predominantly breastfed the risk of death due to acute respiratory infection was similar to that of exclusively breastfed children.


The researchers examined 1204 infants who died between 28 days and one year from causes other than congenital anomaly or malignant tumor and 7740 children who were still alive at one year to calculate mortality and whether or not the infant was breastfed as well as the duration–response effects.

Children who were never breastfed had a 21 per cent greater risk of dying in the postneonatal period than those who were breastfed. Longer breastfeeding was associated with lower risk. Promoting breastfeeding has the potential to save about 720 postneonatal deaths in the United States each year. In Canada this would be about 72 deaths.


This important study from Ghana was designed to evaluate whether the timing of breastfeeding initiation and the type of breastfeeding practiced are associated with risk of neonatal mortality. The study included 10,947 infants who survived day two and whose mothers were visited during the neonatal period.

Breastfeeding was initiated during the first day in 71 per cent of infants and in 98.7 per cent by day three. Breastfeeding was exclusive for 70 per cent during the neonatal period. The risk of neonatal death was fourfold higher in infants given milk-based fluids or solids in addition to breastmilk. There was a marked dose-response of increasing risk of neonatal mortality with delayed breastfeeding initiation from hour one to day seven. Initiation after day one was associated with a 2.4-fold increase in mortality risk. The authors conclude that 16 per cent of neonatal deaths can be prevented if all infants are breastfed from day one and 22 per cent can be prevented if breastfeeding is initiated during the first hour.


15 Increased risk of otitis media and ear infections

The number of episodes of acute otitis media increased significantly with decreased duration and exclusivity of breastfeeding. US infants who were exclusively breastfed for four months or more had a 50 per cent reduction of episodes compared to infants who were not breastfed. A 40 per cent reduction of episodes was reported for breastfeeding infants who were supplemented before four months of age.


Between six and 12 months of age the incidence of first episodes of otitis media is greater for formula-fed infants than for exclusively breastfed infants. For exclusively breastfed infants the incidence increased from 25 per cent to 51 per cent compared to a rise from 54 per cent to 76 per cent for exclusively formula fed infants. The authors concluded that breastfeeding even for a short period (three months) would significantly reduce the episodes of otitis media during infancy.


16 Increased risk of side effects of environmental contaminants

A Dutch study showed that at six years of age, cognitive development is affected by prenatal exposure to polychlorinated biphenyls (PCBs) and dioxins. An adverse effect of prenatal exposure on neurological outcome was also demonstrated in the formula-fed group but not in the breastfed group. Despite higher PCB exposures from breast milk, the study found at 18 months, 42 months of age, and at six years of age a beneficial effect of breastfeeding on the quality of movements, in terms of fluency, and in cognitive development tests.

The data gives evidence that prenatal exposure to PCBs does have subtle negative effects on neurological and cognitive development of the child up to school age. The study also gives evidence that breastfeeding counteracts the adverse developmental effects of PCBs and dioxins.


Another Dutch study to determine the perinatal effects of exposure to polychlorinated biphenyls (PCBs), assessed breastfed and formula-fed infants at nine years of age. By measuring auditory P300 latencies (the reaction time to incoming stimuli, which are known to be negatively impacted by PCBs) they found that those who were formula-fed or breastfed for less than six to 16 weeks, experienced greater latency and delayed mechanisms in the central nervous system that evaluate and process relevant stimuli. On the other hand breastfeeding accelerates these mechanisms.


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