Later Effects of Breastfeeding Practice: The Evidence

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Abstract

Breastfeeding plays a key role in the programming process during early life but, due to confounding factors, it is difficult to draw conclusions on long-term health benefits. The magnitude of the beneficial effect of breastfeeding on blood pressure (−2 mm Hg) and total cholesterol (−0.2 mmol/l) is likely to have public health implications. However, it is unknown whether breastfeeding reduces the risk of cardiovascular mortality. Breastfeeding may protect against the development of celiac disease. The protective role of breastfeeding against type 1 diabetes seems likely, but the mechanisms involved are still under discussion. There is no convincing evidence that breastfeeding reduces the risk of leukemia and cancer. Breastfeeding is associated with a better cognitive development (+3 points) that is present as early as at 6 months of age and sustained throughout childhood and adolescence. The benefits of breast milk may be related to its high content in docosahexaenoic acid which plays an important role in brain development. Increasing the duration of breastfeeding is correlated with an increase in cognitive development.

Introduction

‘Programming’ describes the finding that, during critical windows in early life, hormones, metabolites and neurotransmitters are able to have a long-term influence on health. Breastfeeding plays a key role in the programming process during early life.

It is difficult to draw firm conclusions on the causal relationship between breastfeeding and long-term health benefits [1]. For obvious reasons, it is unethical to perform randomized experimental studies involving breastfeeding. Available information is limited to observational studies, and confounding is therefore a concern: educational, socioeconomic, and lifestyle factors associated
with the mother’s decision to breastfeed; recall bias on the nature and duration of breastfeeding, etc. Even in studies controlling for known confounding variables, residual confounding is still an issue.

The aim of the present article is to review the long-term consequences of breastfeeding on health, with the exception of allergy and obesity.

**Effects of Early Growth**

Singhal [2] has proposed the postnatal growth acceleration hypothesis, suggesting that faster growth (upward centile crossing), particularly in infancy, adversely programs the metabolic syndrome. Faster neonatal weight gain was shown to program insulin resistance in preterm infants randomly assigned to a nutrient-enriched diet (preterm formula) that promoted faster growth compared with the standard diet (banked breast milk or preterm formula). Several studies have found that breastfed infants are shorter at the age of 12 months compared with formula-fed infants. Investigators recently found in the Avon cohort that children presented at age 7–8 years with a trend toward higher serum insulin-like growth factor-1 (IGF-1) in exclusively breastfed infants as compared with partially breastfed infants and never breastfed infants. The IGF-1 axis would be programmed during infancy, with low IGF-1 values during breastfeeding, and higher IGF-1 levels and, as a consequence, higher growth velocity later in childhood [3].

**Cardiovascular Health**

**Blood Pressure**

In the early 1980s a randomized trial comparing the use of banked human milk with preterm formula for feeding premature infants gave the opportunity to measure blood pressure at age 13–16 years [4]. The mean diastolic blood pressure was higher when assigned preterm formula than banked human milk: 65.0 vs. 61.9 mm Hg (95% CI for difference −5.8 to −0.6; p = 0.016). No difference was found for systolic blood pressure.

A first meta-analysis was aimed at determining whether breastfeeding in infancy was associated with lower blood pressure at later age [5]. The pooled mean difference in systolic blood pressure was −1.10 mm Hg in participants breastfed as infants. No difference was found for diastolic blood pressure. Another meta-analysis, including an extra ~10,000 subjects from 3 studies with more than 1,500 participants each, showed that breastfeeding was associated with a 1.4 and 0.5 mm Hg reduction in systolic and diastolic blood pressure, respectively [6]. In these 2 publications, the difference was independent of age at measurement of blood pressure and year of birth, and was reduced in large studies (n ≥ 1,000) compared with smaller ones.
The magnitude of the effect of breastfeeding on blood pressure is similar to the effect of salt restriction (−1.3 mm Hg) and weight loss (−2.8 mm Hg) in normotensive subjects, and is likely to have substantial public health implications [7]. A lowering of population-wide diastolic blood pressure by only 2 mm Hg would reduce the prevalence of hypertension by 17%, and the risk of coronary heart disease and that of stroke and transient ischemic attacks by 6 and 15%, respectively.

The lower sodium content of breast milk may play a role in the reduction of blood pressure, as well as the high content of LCPUFA in breast milk, which are incorporated into cell membranes of the vascular endothelium. A randomized controlled trial showed that dietary supplementation with LCPUFA in infant formula from birth to 6 months was associated with a significant reduction in mean and diastolic blood pressure at 6 years of age [8] (table 1).

### Lipid Metabolism

The randomized trial on premature infants previously described [4] made it possible to study lipoprotein profile in 13- to 16-year-old adolescents born preterm [9]. Adolescents fed human milk at birth had a lower LDL to HDL ratio than those given preterm formula. There was a dose-response effect supporting a causal link between breast milk feeding and the lipoprotein profile in later life. A meta-analysis of 37 studies showed that blood total cholesterol (TC) differed with age. TC levels were higher in breastfed than in formula-fed infants (<1 year), due to the very high content of cholesterol in breast milk and to the absence or very low content of cholesterol in most infant formulae (mean TC difference 0.64; 95% CI 0.50 to 0.79 mmol/l) [10]. The mean TC in childhood or adolescence (1–16 years) was not related to feeding patterns in infancy. A recent study from Brazil also showed no influence of breastfeeding on TC among male adolescents [11]. However, the meta-analysis showed that TC in adults was lower among those breastfed in infancy (mean TC difference −0.18; 95% CI −0.30 to −0.06 mmol/l). Patterns for LDL cholesterol were

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**Table 1.** Blood pressure (mm Hg) at age 6 years in children who as infants had been randomized to be fed with formula supplemented with long-chain polyunsaturated fatty acids or with formula without supplementation

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Supplemented formula (n = 65)</th>
<th>Formula without supplementation (n = 71)</th>
<th>Mean difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>74.8</td>
<td>77.8</td>
<td>−3.0 (−5.4 to −0.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diastolic</td>
<td>57.3</td>
<td>60.9</td>
<td>−3.6 (−6.5 to −0.6)</td>
<td>0.018</td>
</tr>
<tr>
<td>Systolic</td>
<td>92.4</td>
<td>94.7</td>
<td>−2.3 (5.3 to 0.7)</td>
<td>0.132</td>
</tr>
</tbody>
</table>

From Forsyth et al. [8].

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Later Effects of Breastfeeding Practice
similar to those for TC throughout. Whatever the underlying programming stimulus, long-term modifications in cholesterol metabolism are likely to occur, either by regulation of HMG-CoA reductase activity or LDL-receptor activity. Even if the difference in adult TC of 0.2 mmol/l is modest, a reduction in mean TC of this magnitude in adult life would be associated with a reduction in coronary heart disease incidence of approximately 10%.

**Cardiovascular Disease**

An important question is to determine whether the effects of breastfeeding in infancy on lipid metabolism and blood pressure lead to a reduction in cardiovascular risk in adulthood. The potentially beneficial effects on lipid metabolism and blood pressure could be reduced by a negative effect on arterial function. Two studies showed that arterial distensibility in 10-year-old children and in adults was related to the duration of breastfeeding [12, 13]. A longer duration of breastfeeding was associated with stiffer arteries. However, the study performed in adults showed no difference in distensibility between participants who had been bottle fed and those breastfed for less than 4 months. Further studies are necessary before drawing any conclusions.

The British Boyd-Orr cohort consists of subjects who were originally surveyed in 1937–1939, when they were 0–19 years of age. The follow-up of this cohort made it possible to show in 63- to 82-year-old participants that breastfeeding was inversely associated with ultrasound measured intima-media thickness of the common carotid and bifurcation as well as carotid and femoral plaques, compared with bottle feeding [14]. These results may suggest a beneficial effect of breastfeeding on atherosclerosis. However, there was no clear evidence of a duration-response relationship between breastfeeding and intima-media thickness. The study of the same cohort based on a larger number of subjects and a systematic review with meta-analysis of 4 studies failed to show any beneficial effect of breastfeeding on cardiovascular disease mortality [15]. The study of the cohort of Caerphilly, Wales, surprisingly showed a positive association between breastfeeding and coronary heart disease mortality. There was however no duration-response effect, which might be expected if an adverse effect of breastfeeding was causal [16]. In contrast, the study of the participants of the Nurses' Health Study showed an 8% reduced risk of coronary heart disease [17].

There is still no convincing evidence that breastfeeding reduces the risk of cardiovascular mortality.

**Disorders of the Immune System**

**Celiac Disease**

A recent review of 6 observational studies suggested that breastfeeding may protect against the development of celiac disease (CD) [18]. With the
exception of a small study, an association was found between a increasing duration of breastfeeding and reduced risk of developing CD. The meta-analysis showed that the risk of CD was markedly reduced in infants who were breastfeeding at the time of gluten introduction as compared with non-breastfed infants (OR 0.48, 95% CI 0.40 to 0.59). However, breastfeeding may not provide permanent protection against CD but only delay the onset of symptoms.

**Inflammatory Bowel Disease**

Perinatal events may play a role in the etiology of inflammatory bowel disease (IBD). A meta-analysis from 2004 showed a protective effect of breastfeeding on the risk of IBD: the risk of Crohn's disease (CD) and ulcerative colitis (UC) decreased by 33 and 23%, respectively [19]. However, of a total of 17 studies, only 4 studies of Crohn's disease and 4 studies of UC were of high methodological quality. A pediatric, population-based, case-control study was recently performed in northern France to examine the environmental risk factors associated with IBD [20]. In a multivariate model adjusted for the mother's education level, breastfeeding (partial or exclusive) was a risk factor for Crohn's disease (odds ratio 2.1; 95% CI 1.3 to 3.4; \( p = 0.003 \)), but not for UC. Children with Crohn's disease were breastfed (exclusively or not) for an average of 2 weeks more than the controls, but the difference was not significant. Further studies are needed to fully understand the relation between breastfeeding and IBD.

**Diabetes Mellitus**

The protective role of breastfeeding against type 1 diabetes seems likely even if the mechanisms involved are still under discussion. A European multi-center study showed that breastfeeding of any duration was associated with a 25% reduction in risk of type 1 diabetes [21]. The early introduction of cow's milk may in fact be the main contributory factor [1]. It has been suggested that immunization against cow's milk proteins would trigger an autoimmune reaction against pancreatic \( \beta \) cells due to a structural similarity between one or several cow's milk proteins and antigens located on \( \beta \) cells. This hypothesis is further supported by experimental studies in animals showing that feeding with hydrolyzed cow's milk proteins is associated with a lower risk of diabetes. More information will come from the TRIGR study in Finland, randomizing high-risk infants to different supplemental formulae, either a hydrolyzed formula or a regular cow's milk-based formula, after breastfeeding for 6–8 months of life.

**Malignant Disease**

Breast milk may play a role in the prevention of childhood leukemia and cancer by stimulating or modulating the immune response and promoting its
development in early life. Only 2 of the 4 studies considered to be of good methodological quality in the recent review by Guise et al. [22] found a risk reduction of acute lymphocytic leukemia (odds ratios 0.80 and 0.67) associated with breastfeeding. A meta-analysis of 26 studies on breastfeeding and childhood cancer showed that having ever been breastfed was associated with a lower risk of 9% for acute lymphocytic leukemia, 24% for Hodgkin’s disease, and 41% for neuroblastoma [23]. However, methodological limitations were pointed out.

In the British Boyd-Orr cohort, as compared with never having breastfed, ever having breastfed was not associated with the incidence of all cancers or of any individual cancer type. However, a meta-analysis of 11 studies, including that of the Boyd-Orr cohort, showed that breastfed women had a slightly reduced risk of premenopausal breast cancer (RR = 0.88; 95% CI 0.79 to 0.98) but not of postmenopausal breast cancer [24].

**Cognitive Development**

Most studies have shown that breastfeeding is associated with enhanced neurodevelopment. The meta-analysis of Anderson et al. [25] showed an increment in cognitive function of 3.14 points for breastfed infants compared with formula-fed infants. Better cognitive development was present as early as 6 months of age and was sustained throughout childhood and adolescence. Low birth weight infants derived larger benefits (5.18 points) than did normal weight infants (2.66 points), an increasing duration of breastfeeding was accompanied by an increase in cognitive development. A specific role of breast milk is suggested by the randomized controlled trial of Lucas et al. [26], who demonstrated a higher IQ in 7.5- to 8-year-old children born preterm who had received breast milk via a nasogastric tube. The benefits of breast milk may be related to its high content in docosahexaenoic acid (DHA, 22:6(n-3)) that plays an important role in brain development. Breastfed infants undergoing postmortem examination because of sudden death had a greater proportion of DHA in their brain cortex relative to those fed formula (fig. 1) [27]. The role of DHA is further suggested by the fact that DHA supplementation of breastfeeding mothers for 4 months after delivery resulted in a higher Bayley psychomotor development index in infants at 30 months of age [28].

The most important residual confounding factor is the influence of maternal socioeconomic status on the child’s cognitive development. A study from the Philippines evaluated the relation between breastfeeding and cognitive development in a population in which breastfeeding was inversely correlated with socioeconomic advantages, as opposed to industrialized countries [29]. Scores at 8.5 and 11.5 years were higher for infants breastfed longer (1.6 and 9.8 points higher among normal birth weight and low birth weight infants, respectively; infants breastfed for 12–18 vs. <6 months).
Little is known about the effects of breastfeeding in adulthood. A positive association between the duration of breastfeeding and cognitive function was observed in 2 samples of young Danish adults, assessed with 2 different IQ tests [30]. In men aged 60–74 years from the Caerphilly cohort, having been artificially fed was associated with a lower cognitive function only in those with a birth weight below the median [31].

A very recent study involving >5,000 US children used sibling comparison analysis. Any confounding factor that is the same for both members of a pair of siblings was automatically controlled for [32]. Breastfeeding was associated with an increase of around 4 points that was mostly accounted for by maternal intelligence. When fully adjusted for confounding factors, the benefit in breastfed infants was small and not significant (0.52; CI −0.19 to 1.23).

**Conclusion**

Breastfeeding is an unequalled way of providing ideal food for the healthy growth and development of infants. The main advantages on later health associated with breastfeeding are an enhanced cognitive development, as well as lower blood pressure and plasma total cholesterol, although no effect could be demonstrated on the cardiovascular risk.
References

Discussion

Dr. Giovannini: A very interesting lecture and I perfectly agree with every point. Breastfeeding is much better in the dietary treatment of inborn metabolic disorders. In the Journal of Pediatrics we published a paper regarding the best behavior in phenylketonuria children breastfed for at least the first months of life [1]. This is very important because human milk is lower in phenylalanine and rich in DHA. The second very important point, in Acta Paediatrica [2] we showed that women who had been breastfed were breastfeeding more easily. I greatly appreciate the problem of cholesterol; it is an economical and social problem, because breastfed adults have 6.9 mg/dl lower cholesterol than non-breastfed adults.

Dr. Turck: I could not more agree with you. I have to apologize for forgetting to say that breastfeeding can be used in metabolic disorders. In my unit, where we also deal with metabolic disorders, it was after your publication that we started to think about using breastfeeding more than we used to. It is obviously a question of social interaction. In my country the situation of breastfeeding is not very good, with 60% of children being breastfed after leaving the maternity ward. Even if the situation is getting better, the duration of breastfeeding is very low. I think that, from the individual point of view, all the aspects that I showed you are not very interesting, but from a public health perspective, if we want to have some interest from the politicians, points such as cholesterolemia and perhaps cardiovascular risk are important to raise.

Dr. Agostoni: If I can add just a few words regarding amino acid disorders. Two months ago there was a publication showing the positive effects of human milk in children suffering from propionic acidemia and other amino acid disorders [3]. In your review did you have the opportunity to look at the results? It seems to me that the clearest advantage of breastfeeding was shown in children with mental handicaps or at risk of mental handicaps.

Dr. Turck: There was a paper related to the British millennium cohort where previously breastfed children had fewer handicaps than previously non-breastfed children.

Dr. Ziegler: In one of the studies you mentioned you showed that there was no association between breastfeeding and dyslipidemia in 60- to 82-year-olds. There is a similar study showing a lack of association between breastfeeding and, in this case, obesity when the subjects were older. I wish to point out that there is a fundamental difference in breastfeeding as practiced today and probably for the last 50 years where the mother and perhaps the father make the decision to breastfeed, which is influenced...
by their health beliefs. In contrast, 80 years ago breastfeeding was more or less universally practiced and formula was fed only when there were certain circumstances that necessitated it. The formulas used then were fundamentally different from the formulas that were developed later. So breastfeeding meant something different 80 years ago compared to today.

Dr. Turck: Again it is a combination of an effect on development and also of environment, but of course the formulas in the 1930s have nothing to do with what they are now.

Dr. Seidman: I was intrigued with your data regarding the increased risk of Crohn's disease in children in France. We carried out a very similar case-control study in Montreal. As you know most French Canadian families have a founder effect with genetic origins from the north of France but living in a different environment in Quebec. We studied close to 200 cases of pediatric-onset Crohn's disease and 200 controls who were pair-matched for timing of diagnosis and area of residence [4]. We didn't find that a history of breastfeeding in the first 6 months of life affected risk. I would appreciate your comments. I should emphasize that the rate of breastfeeding in Quebec is extremely low amongst the developed countries of the world, and that might be one consideration. If a family has a history of Crohn's disease, which is by far the leading risk factor for developing Crohn's disease with an odds ratio of 4.6 in our study, it may be that the parents would try breastfeeding more often than the control family with the idea that it would be protective.

Dr. Turck: The results came from a multivariate analysis and we controlled for family history which is, I completely agree with you, by far the most important risk factor for inflammatory bowel disease (IBD) in children.

Dr. Guandalini: My question is actually speculative about the protective role of breastfeeding on IBD. I am sure you have given some thought to why this may be. Has it to do with the microflora that is different between breastfed and formula-fed infants; has it to do with the lower antigenic load from other solids that are taken, or has it to do with the later introduction of complementary feeding?

Dr. Turck: One explanation, which is just speculation, is that because of breastfeeding the infections happen later in life in breastfed children, so there might be a window during which any infection might have some deleterious effect on the immune system, but it is really just speculation. We are more interested by the pollution story because the region is very highly polluted and high particle levels have been found in breast milk and also in tissues from patients with IBD. So we are trying to find out if this could be an explanation. But if the risk is doubled, Crohn's disease is still a rare disease. Even if its incidence is increasing, I think this should not lead us to modify our policy which, of course, is pushing breastfeeding in industrialized countries.

Dr. Barclay: Concerning cognitive development, in the review by Der et al. [5] I think their own study was the only one that had controlled for maternal IQ. In the other studies, maternal IQ was not taken into account. So is it correct that if you control for maternal IQ, the effect of breastfeeding on cognitive development disappears?

Dr. Turck: Other studies controlled for maternal education but this study controlled especially for maternal IQ. I think using the siblings allows you to take into account most confounding factors. In their discussion Der et al. speak of another study with siblings giving the same results, i.e. there is no benefit from breastfeeding. I think that it is a very difficult issue and even if there is an effect, it is really a small one.

Dr. Ziegler: There is one other study by Jacobson et al. [6] where the mother's IQ was actually measured, and when the child's IQ was corrected for the mother's IQ there was no significant effect of breastfeeding on the child's IQ.

Dr. Brunser: I think your observations on Crohn's disease are very interesting. There is work by Hollander [7] who measured intestinal permeability in the relatives of
patients with Crohn's disease, and he demonstrated that the parents of children who have Crohn's disease also have disturbances in intestinal permeability. So he thought that if you develop Crohn's disease because your family is prone to Crohn's disease, there must be some kind of disturbance in intestinal permeability.

Dr. Turck: But the risk of Crohn's disease in our study was 5 times higher in cases with a family history of IBD, which was the strongest risk factor.

Dr. Ferreira: I am a pediatric gastroenterologist, not an investigator, so I don't know all the studies as you do. I am wondering if we are not trying to compare something that is not comparable, because even with the power of meta-analysis we cannot reach a conclusion. Is there a study comparing siblings? Sometimes a mother can breastfeed one infant and cannot breastfeed another. Is there a study comparing the two?

Dr. Turck: That was the case in the study by Der et al. [5]. They had 334 pairs of siblings who were breastfed and perhaps 450 pairs with one breastfed and the other not. They could not find any difference in cognitive development between these two.

Dr. Ferreira: And cardiovascular disease in adult life?

Dr. Turck: I have to say that I don't remember. I don't think so, but I am not 100% sure.

Dr. Ferreira: I have another question. Is it possible to think about the gut, not about food but about the gut, because we also see obesity in breastfed infants. Is it possible that babies have a more absorptive gut capacity which in infancy gives them a higher rate of growth and later in life they are more prone to absorb more cholesterol and lipid substances, and more prone to cardiovascular disease, metabolic syndrome and truncal obesity? Is it possible that the problem is in the gut and not in the feeding?

Dr. Turck: I don't think there is a clear answer to your question. At least I can't answer it. To me the main reason for promoting breastfeeding is the pleasure of the child and the pleasure of the mother while she is breastfeeding. This is a scientific issue and a health policy issue, so I can't answer the question.

Dr. Ferreira: All the pediatricians agree that breastfeeding is better but we must try to prove that advantage.

Dr. Turck: There are obviously limits to the meta-analyses and all the studies that have been published.

Dr. Michaelsen: I agree with your conclusion on the studies on IQ. It has remained quite consistent up to the last BMJ study [5] which showed a small (half an IQ point) but non-significant effect. Another US sibling study showed a significant effect of breastfeeding. There are two other pieces of information. One is that there is a DHA mechanism that could explain this and is supported by the results of preterm infants. The other piece of information is the PROBIT study from Belarus by Kramer et al. [8]. I have been at two meetings where some new results from the 6-year follow-up were given. It was a randomized study, where they randomized hospitals to promote breastfeeding or not. So apart from the randomized studies by Lucas and Singhal, this is another kind of randomized study. They underlined that they saw an effect on IQ in that study, not on obesity and allergies. This is some information that might again support that there is a small effect in IQ, which is consistent in many studies.

Dr. Turck: Thank you, this is an important point.

Dr. Solomons: You showed a picture of Dr. Burrill Crohn, and my question has to do with Crohn's disease. How could someone in the 1930s discover a 'new' disease? Where was Crohn's disease before Dr. Crohn discovered it? Was it in fact a new disease of the 20th century or a missed diagnosed disease of antiquity? Dr. Ziegler pointed out the difference between the formulas – then and now. Are there any studies that detail whether the complementary feeding patterns of breastfeeding mothers and artificial-feeding mothers are different? I wonder if anyone knows of any studies on complementary feeding patterns or differential early feeding patterns?
Dr. Turck: To answer your first question, it seems that in the old British medical literature descriptions of what we now call Crohn’s disease were made at the end of the 18th century, so that may be part of the answer. The increase in incidence, of course, might be due to a better recognition of the disease. In our region we have a registry that started in 1988 with a system of interviews that allows us to be sure that we haven’t missed a diagnosis from 1988 on. In this period we observed a 25% increase in Crohn’s disease but at the same time a 25% decrease in ulcerative colitis. I have no answer to your second question.

Dr. Haschke: A very short and nonscientific comment on your historical persons, as to whether they were breastfed or not. There is a comprehensive review on the history of breastfeeding by Fomon published in 1983 and it is clear that animal milk started to be extensively used not earlier than in the mid 19th century, so all your historical persons can be considered to have been breastfed.

Dr. Turck: I am not very anxious about that.

Dr. Agostoni: We cannot exclude that women from higher social classes, whose children presumably have a higher IQ due to positive environmental stimulation, have dietary habits that result in milk with higher DHA levels. Again, we do not know the start and the end of this ‘virtuous’ circle: what is the cause and what is the effect.

References