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Symposium II: Infant and childhood nutrition and disease
Breast-feeding and cardiovascular risk factors and outcomes in later life: evidence from epidemiological studies

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This paper considers the body of observational evidence examining the association of being breast-fed to cardiovascular risk factors and outcomes in later life, and whether any potentially advantageous findings are causal. Early cardiovascular consequences/correlates of breast-feeding, compared to being formula fed, include markedly higher levels of total blood cholesterol, lower levels of pre-prandial blood glucose and insulin and lower levels of adiposity. However, a key issue is whether these early differences at a period of rapid development programme/influence cardiovascular risk factors and outcomes in later life. Evidence of long-term effects of early feeding, largely from observational studies, has shown that those breast-fed have lower levels of blood total cholesterol, lower risk of type-2 diabetes and marginally lower levels of adiposity and blood pressure in adult life. There is no strong evidence to suggest effects of early feeding on adult levels of blood glucose, blood insulin and CHD outcomes, although further data are needed. However, the influence of confounding factors, such as maternal body size, maternal smoking and socio-demographic factors, and exclusivity of early feeding on these potentially beneficial associations needs to be considered before inferring any causal effects. Moreover, fewer studies have examined whether duration of exclusive breast-feeding has a graded influence on these risk factors and outcomes; such data would help further in deciding upon causal associations. While strong observational evidence suggests nutritional programming of adult cholesterol levels, associations with other markers of cardiometabolic risk and their consequences in later life need to be confirmed in well-conducted observational and experimental studies.

Infant nutrition: Breast-feeding: Cardiovascular risk factors: Cardiovascular outcomes

Some studies have suggested that weight at 1 year may show stronger associations with cardiovascular risk and CHD, independent of birth weight[1–3]. If true, this would suggest that postnatal nutrition, including initial infant feeding may be an important determinant of cardiovascular outcome[4]. However, studying the effects of infant feeding on cardiovascular risk is complicated by several factors. Firstly, it is possible that the effects of infant feeding may change with age[5,6], although most studies have examined only short-term outcomes. Secondly, infant feeding practice, including the content of bottle feeds and social economic status of mothers who choose to breast-feed, has changed markedly during the twentieth century[7], as have other aspects of the early life environment[8,9]. Thus, the relevance of infant feeding to cardiovascular risk may be different for historical and contemporary children.

An important limitation of the evidence presented here is that it is based on observational studies; experimental studies are generally impracticable in this context, except in highly specific circumstances of preterm birth or randomised controlled trials of breast-feeding promotion[10,11]. Hence, when considering the association between infant feeding and cardiovascular outcome, confounding is an important possibility, and maternal factors, such as social-economic status and increasing adiposity levels, are of particular potential importance. In addition, it is important to acknowledge the exclusivity of initial feeding practices. Exclusive breast-feeding as defined by the World Health Organization (breast-feeding while giving no other food or liquid, not even water, with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines)[12] is rarely sustained, and often supplemented with other formula or other complementary foods (especially when there are concerns that an infant is underweight). Hence, potential benefits of early feeding on health outcomes in later life may be diluted if those ever or partly breast-fed are compared with those formula-fed. Alternatively, considering the fewer number exclusively breast-fed may reduce statistical power to detect potentially beneficial associations. This is particularly relevant in high-income countries, such as the UK, where prevalence of exclusive feeding is low, with only 20 % of infants being exclusively fed at 6 weeks, 7 % at 4 months and very few (<1 %) achieving 6 months[13].

The aim of this paper is to examine systematic reviews of the evidence examining the association of infant feeding to short- and long-term cardiovascular risk factors (including BMI, obesity, blood cholesterol, glucose and insulin) and outcomes in later life (including CHD and type-2 diabetes). Systematic reviews allow the strength and consistency of associations across individual studies to be quantified, and the extent of publication bias and the role of confounding factors to be gauged.

Breast-feeding *v.* bottle-feeding and CHD

Observational studies of men and women born in Hertfordshire in the early part of the twentieth century, have shown that those who were 'weaned' before 1 year (assumed to refer to the substitution of breast milk for other foods) have lower rates of CHD in adult life, compared with those breast-fed beyond 1 year[14,15]. However, these findings have not been replicated in other studies[16], and no experimental studies have examined this issue. A systematic review and meta-analysis of four observational studies involving 25 166 adults, carried out in developed countries (three UK studies and one USA) found little association between infant feeding and CVD mortality in later life[17]. One study suggested that breast-feeding was cardio-protective compared to those formula fed, while three studies suggested that formula feeding was protective. However, all studies and the pooled estimate (rate ratio 1·06, 95 % CI 0·94, 1·20) had 95 % CI that included a rate ratio of 1 (i.e. a value of no effect)[18]. The association between infant feeding and IHD was equally inconclusive[18]. Data from national cohorts, or historical cohorts,
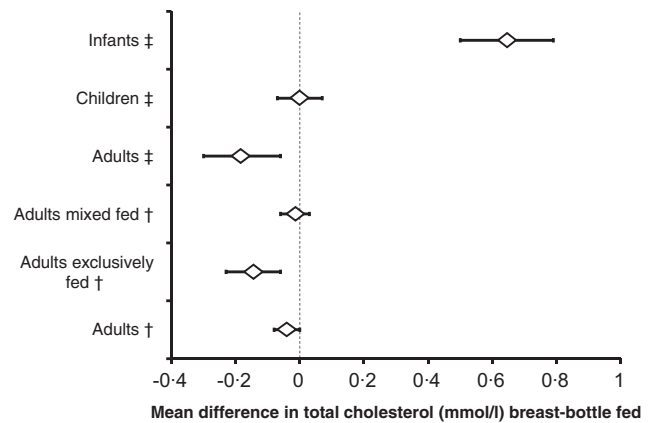
Fig. 1. Pooled mean difference (diamond with 95 % CI) in blood cholesterol between breast-fed and bottle-fed participants, in different age groups (infants aged <1 years, children aged 1–16 years, adults aged >16 years), exclusive and non-exclusive feeders (as defined in the individual studies), from †Owen *et al.*[22] and ‡Owen *et al.*[21].

may throw further light on the presence (or absence) of any relationship. However, at present there is insufficient evidence to suggest that breast-feeding directly influences subsequent cardiovascular mortality.

Breast-feeding *v.* bottle-feeding and cholesterol

Reports from historical cohort studies suggest that blood cholesterol in adulthood may be influenced by infant feeding, with bottle-feeding and prolonged breast-feeding having been related to higher levels of adult serum cholesterol[19,20]. A systematic review that examined the life-course relationship between infant feeding and blood cholesterol identified thirty-seven published papers, with fifty-two estimates (including 10 681 individuals) of total cholesterol in those breast-fed compared with those formula-fed[21]. These estimates were obtained from observational studies, carried out in mostly high-income populations. Twenty-six observations were in infants, seventeen were in children or adolescents, and nine were in adults. A meta-analysis revealed that infants (<1 year of age) initially breast-fed had far higher total cholesterol (0·64 mmol/l, 95 % CI 0·50, 0·79 mmol/l) than those formula-fed (Fig. 1). This finding is likely to be a direct consequence of nutritional differences between breast and formula milk, with breast milk being higher in cholesterol compared to standard formula feeds. Of interest was whether these differences in serum cholesterol persist in later life. Mean total cholesterol in childhood and adolescence showed no consistent difference between those breast-fed and formula-fed in early life (Fig. 1). However, in adults, mean total cholesterol was lower in those who were breast-fed. Although the overall difference was modest (0·18 mmol/l, 95 % CI 0·06, 0·30 mmol/l, Fig. 1), it was remarkably consistent between studies including subjects of different ages (from 17 to 64 years) and years of birth (from 1920 to 1975); similar effects were observed for LDL throughout. However, the number of adult studies

was small, the role of confounding factors, particularly by socio-economic factors, could not be systematically examined, and the influence of exclusive feeding could not be gauged. Hence, a further review of adult studies was carried out to address these issues, using data provided by study authors to complement data previously published. In total, seventeen studies were identified (including 17 498 individuals)[22]. Overall, the mean difference in adult levels of blood cholesterol was small (0·04 mmol/l lower in those breast-fed compared with formula-fed), but larger differences were observed (0·15 mmol/l, 95 % CI 0·06, 0·23 mmol/l) in seven studies that reported 'exclusive' feeding patterns (Fig. 1). Adjustment for adult socio-economic position, BMI and smoking status had little impact on these differences, although the possibility that other potential confounders might partially explain these differences remains[22]. These findings suggest nutritional programming of cholesterol synthesis by exposure to breast milk in early life, although, the biological mechanism for this process remains unclear[23–26]. The long-term cholesterol lowering effect associated with breast-feeding has been replicated in a limited follow-up (25 %) of adolescents, who were preterm at birth and randomised to breast or formula milk[10]. However, further studies in adults are needed to establish the effect of infant feeding on cholesterol levels in later life. If these findings are corroborated in further studies (both observational and experimental), this may show that promotion of breast-feeding in early life may be one population strategy to reduce cholesterol in later life. Although the reduction in cholesterol in adulthood associated with breast-feeding is modest (approximately 0·2 mmol/l), this could result in a reduction in CHD incidence of the order of 5 %.

Breast-feeding *v.* bottle-feeding and blood pressure

Several small observational studies have suggested that initial breast-feeding may be related to markedly lower blood pressure levels in childhood, compared with those formula-fed[27–29]. Whether these effects persist into adulthood is of particular interest, especially as the Na content of formula feed, particularly in the UK, has been substantially reduced to the level found in breast milk since the 1980s[30,31]. Reduced Na intake in early life has been related to lower levels of blood pressure in infancy and adult life[32,33]. A study of children fed different infant formulae concluded that feeds supplemented with long-chain PUFA may result in lower blood pressures, comparable to those fed breast milk[34]. However, further data from experimental studies are needed to confirm these findings.

A systematic review of the association between infant feeding and blood pressure in later life published in 2003 identified twenty-eight observational studies and one randomised-controlled trial of children who were premature at birth[35,36]. Mean differences in systolic blood pressure (SBP) and diastolic blood pressure between breast- and bottle-fed subjects (representing 19 763 individuals) were obtained from these studies and used in a meta-analysis[36]. Eight observations of SBP were in infants, twelve in
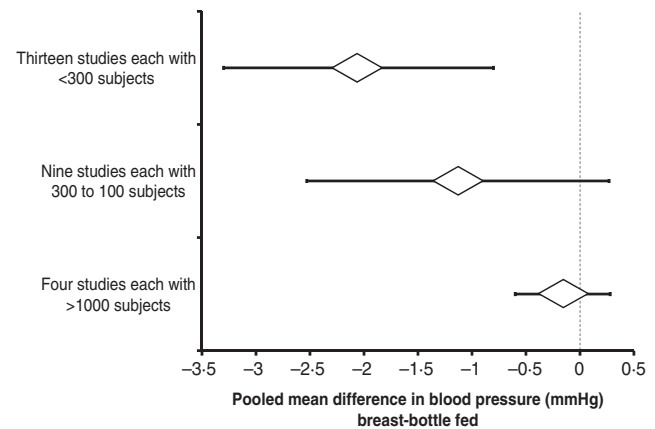
Fig. 2. Mean difference (diamond with 95 % CI) in blood pressure between breast-fed and bottle-fed participants, pooled from studies with less than 300 subjects, 300–1000 subjects, greater than 1000 subjects, from Owen *et al.*[36].

children and six in adults. Overall, the pooled mean difference in SBP was 1·1 mmHg (95 % CI 0·4, 1·8 mmHg) lower in those breast-fed compared with those formula-fed; effects on diastolic blood pressure were much smaller. However, there was considerable heterogeneity between estimates ($P < 0·001$). In an attempt to explain the source of heterogeneity the analysis was repeated by age group at outcome (infants ≤1 year, children >1–16 years, adults >16 years), date of birth (before and after 1980) and by size of the study (<300 participants, 300–1000 and >1000). Little difference in the overall protective effect of breast-feeding over formula feeding on SBP was observed by age or date of birth. However, the effect size decreased appreciably with increasing study size, with a difference of 2·1 mmHg in studies with less than 300 participants, 1·1 mmHg with 300–1000 participants and 0·2 mmHg with more than 1000 participants (Fig. 2). In addition, the difference in SBP was larger in sixteen studies that reported on the association between initial feeding and blood pressure in later life, compared with the difference in ten studies that did not report on the association, but where estimates were obtained from data requests. These findings raise the possibility of publication bias.

Another meta-analysis of the association between breast-feeding and blood pressure in later life published in 2005[37], included information from fourteen studies (17 503 subjects), including data from three studies not available at the time of the earlier review (two studies with follow-up in childhood and one in adulthood). The review excluded studies in infancy and previously unpublished estimates used in the earlier meta-analysis[36]. A similar pooled difference in SBP was obtained (1·4 mmHg, 95 % CI 0·6, 2·2 mmHg)[37]. However, as with the earlier review, there was evidence of publication bias. While the role of residual confounding by socio-economic and parental factors in these reviews remains uncertain, some studies have shown that the association between breast-feeding in infancy and blood pressure in later life is independent of important confounding factors, including socio-economic, maternal and anthropometric markers[18,36,38]. However, even if the potential role of publication bias were to be

ignored, the overall difference in SBP from these reviews (just over 1 mmHg) is modest[36,37] and will have little impact on cardiovascular outcomes in later life (although other reviews have not reached the same conclusion). Despite this review effectively excluding any important overall lowering effect of initial breast-feeding on blood pressure, it does not exclude the possibility that an extended duration of breast-feeding has a protective effect. Unfortunately, more data are needed to establish the role of duration of feeding on blood pressure further[21,29], but any effect may be modest given the overall difference between those breast-fed and formula-fed.

Breast-feeding *v.* bottle-feeding, type-2 diabetes and risk factors for diabetes

Studies on Pima Indians and adults born around the time of the Dutch Famine (1943–1947), which collected data on infant feeding from contemporary records, have shown that those initially breast-fed have less insulin resistance and glucose intolerance in later life compared with those formula-fed[20,39]. A case–control study of Native Canadians (with only forty-six cases and ninety-two age-matched controls) showed that children breast-fed were at lower risk of type-2 diabetes[40]. However, recall bias in the ascertainment of infant feeding practices (by parental or caregiver interview) in this latter study cannot be excluded[40]. The consistency and relevance of these findings to populations in higher income countries remain unclear. To date there has only been one systematic review and meta-analysis examining the association of infant feeding to insulin-glucose levels and type-2 diabetes[41]. Seven observational studies were identified, which examined the association between infant feeding and type-2 diabetes (with 76 744 individuals), nineteen studies the association with blood glucose (including twelve studies with 560 infants, seven studies with 5261 adults and children without diabetes), thirteen studies with insulin (seven studies with 291 infants, six studies with 4800 adults and children without diabetes). Insulin was used as a proxy for insulin resistance[42], where higher levels often led to diabetes in later life[43]. Overall, those breast-fed had a lower risk of diabetes compared to those formula-fed (OR 0·61, 95 % CI 0·44, 0·85), with remarkably similar effects across studies from very different populations[20,39]. In three of these studies, the effect was similar after adjustment for birth weight, parental diabetes and body size. However, it was not possible to systematically adjust for potential confounders in all these published studies. While preprandial blood glucose levels (as well as postprandial levels) were lower in infants breast-fed compared with formula-fed (0·17 mmol/l, 95 % CI 0·05, 0·28 mmol//l), there was no evidence of a difference in fasting blood glucose levels in later life. For insulin, preprandial levels were lower in infancy among those breast-fed (more so 60 min postprandially, and especially in five studies that reported exclusive feeding). There was some evidence to suggest that these effects persisted into later life, with fasting insulin levels being 3 % lower among those breast-fed (95 % CI −8 %, 1 %). The explanation for these beneficial effects of early breast-feeding on diabetes risk in later life remains unclear. As the studies are largely observational the possibility of confounding or intermediaries (such as birth weight, maternal socio-economic factors, maternal or individual obesity) explaining the association cannot be excluded. However, plausible biological mechanisms by which early feeding might influence diabetes risk have been proposed[44–46]. These findings suggest that one in twenty cases of type-2 diabetes in Westernised populations might be attributable to breast-feeding[41]. Hence, if further evidence lends support to a causal association (especially from other ethnic populations and in terms of the optimal duration of feeding), breast-feeding promotion may offer scope for diabetes prevention. However, it must be acknowledged that reductions in levels of obesity in later life are likely to result in a greater yield.

Breast-feeding *v.* bottle-feeding and obesity

Any potential effects of initial feeding on levels of obesity in later life are of considerable public health interest as these are likely to impact on markers of diabetes, such as glucose tolerance and insulin resistance. While there is good evidence to suggest immediate effects of infant feeding on body size and early growth, where breast-fed infants are smaller and grow less quickly than those mixed/formula-fed (where mixed fed are those breast-fed and formula-fed), the degree to which these differences persist into adulthood remains a topic of debate. A number of systematic reviews of largely observational evidence have been published examining the association between infant feeding and obesity in later life[47–50]. While all these studies suggest lower levels of obesity among those breast-fed[47,48,50] or those breast-fed for longer durations[49], it is unclear as to whether publication bias and/or confounding factors may explain all or some of the association. A review of nine studies with more than 69 000 individuals[47], which adjusted for at least three potential confounders (including birthweight parental overweight–smoking–education, dietary markers, physical activity and/or socio-economic factors) showed that those breast-fed had a 22 % lower risk of obesity compared to those formula fed (pooled OR 0·78, 95 % CI 0·71, 0·85). Effects were similar across studies of different size, and there was some evidence in a smaller number of studies that longer durations of breast-feeding were more protective. Another more inclusive review of twenty-eight studies (with 298 900 individuals) also showed that breast-feeding was associated with a reduced risk of obesity compared with formula feeding (OR 0·87, 95 % CI 0·85, 0·89), but that the inverse association was stronger in smaller studies, raising the possibility of small study/publication bias[48]. In six studies that adjusted simultaneously for potential confounding factors (including parental obesity, parental smoking and social class) the inverse association was reduced markedly (from an OR of 0·86 to 0·93) but not abolished. A sensitivity analysis examining the potential impact of the results of thirty-three published studies (12 505 subjects) that did not provide OR (mostly reporting no relation between breast-feeding and obesity) had little
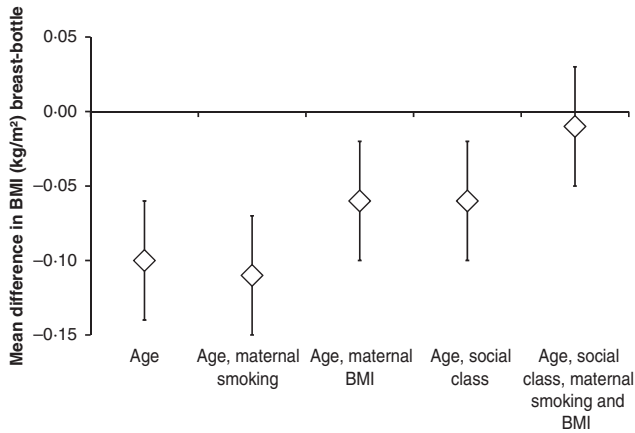
Fig. 3. Mean difference (diamond with 95 % CI) in BMI between breast-fed and bottle-fed participants, pooled from eleven studies with different levels of adjustment, from Owen *et al.*[51].

effect on the results. A recent update on these reviews (including thirty-three studies) confirmed these earlier associations (pooled OR 0·78, 95 % CI 0·72, 0·84) and the presence of publication bias, but showed no marked effect of confounding factors (including socio-economic status and parental anthropometry)[50].

To examine the role of publication/small study bias further another review was carried out, examining the difference in BMI in later life between those breast-fed and formula fed, using data provided by study investigators as opposed to using published data[51]. A request for data was made for mean differences in BMI with different levels of adjustment; including (i) socio-economic status, (ii) maternal smoking in pregnancy, (iii) maternal BMI and (iv) (i)–(iii). The effect of adjustment is shown in Figure 3, and shows that the small difference in BMI between those breast-fed and formula-fed is effectively abolished after combined adjustment.

Further evidence that the association between infant feeding and obesity may not be entirely causal comes from sibling pair analysis[52] and experimental studies of breast-feeding promotion[53], which showed little difference in body size between sibling pairs, and those breast-fed for shorter and longer durations. However, not all studies have reached similar conclusions[54]. It has been argued that BMI may not be an adequate measure of body fatness to detect differences in body size between infant feeding groups, although other more sophisticated measures have also shown no or little association[55,56]. While fewer studies have examined the effect of duration of breast-feeding, some reviews have suggested a graded inverse relationship with levels of obesity/adiposity, but again the role of exclusive feeding and adjustment for potential confounders needs to be considered further[49,51]. While there is no dispute over the association between early breast-feeding and lower levels of adiposity/overweight/obesity in later life, and plausible biological explanations have been proposed[57], the debate over whether this association is causally related, and to what degree, will continue. Further follow-up of experimental studies of breast-feeding promotion[53], and more recent studies examining

the specific content of formula feeds may assist in answering this further[57]. However, it is noteworthy that any potential effect sizes of early feeding on obesity are much smaller than the impact of other lifestyle determinants, such as parental obesity[58].

Summary

The case for breast-feeding rests on a number of health benefits, including protection against infection (of particular importance in the developing world)[59–62], allergic outcomes[63], improved neural and psychosocial development[64,65], as well as potentially beneficial effects on maternal health (which are reviewed elsewhere)[62]. From a cardiovascular perspective, the case for breast-feeding, and for making the nutritional content of formula feeds similar to breast milk, rests on a combination of both short- and long-term benefits. Observational studies examining long-term benefits provide strong evidence of reduced blood cholesterol levels[21,22], raising the possibility that moves to reduce cholesterol levels in early life may not be beneficial for long-term cholesterol metabolism[66–68]. Those breast-fed have also been shown to have lower risk of diabetes and marginally lower insulin levels in later life, although further studies examining these latter associations with follow-up in adult life are needed[41]. Effects of early feeding on blood pressure and adiposity have been observed, but evidence suggests that small study/publication bias and confounding factors may largely account for these associations[36,37,48]. From an epidemiological perspective breast-feeding is a difficult exposure to work with, in terms of defining exclusivity, duration and whether feeding practices are ascertained from contemporary records or recalled after the event (raising the possibility of measurement error). Fewer studies have examined the optimal duration of breast-feeding and timing of weaning (defined as the introduction of liquid and solid foods other than breast or formula milk) for optimal health[69] and there is much debate over whether current recommendations of 6 months in the UK might be reduced[70]. Moreover, the different circumstances that lead a mother to breast-feed as opposed to formula/mix feed (which may differ overtime and in different populations) are important[71]. While adjusting associations between early feeding and later health outcomes for maternal factors such as education, adiposity and smoking, as well as individual/familial socio-economic markers is appropriate, this does not rule out that other factors known or as yet unknown may partly/wholly account for associations observed. In addition, over-adjustment for markers of body size at different stages of the life-course may lead to spurious associations[72]. Only evidence from well-conducted observational studies (which collect data on exclusivity and duration of feeding, as well as potential confounding factors), breast-feeding promotion trials[11,53], and trials of infant formulae *v.* breast milk with adequate follow-up rates in adult life, will be able to establish whether beneficial associations between breast-feeding and cardiovascular risk factors and outcomes are truly causal, and if so, of public health importance.

Acknowledgements

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