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70th Anniversary Conference on 'Nutrition and health: from conception to adolescence'

Symposium II: Infant and childhood nutrition and disease Breast-feeding and later risk of CVD and obesity: evidence from randomised trials

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The relationship between breast-feeding and later cardiovascular health has been investigated in randomised trials and observational studies. This review focuses on randomised control trials, regarded as the 'gold standard' in establishing causal relationships between interventions and outcomes. Since it is not ethical to randomise healthy term infants to be breast- or formula-fed, only two randomised control trials have examined effects of breast-feeding on later health. In one randomised control trial, preterm infants randomised to receive banked donor breast milk had significantly lower blood pressure (BP), more favourable plasma lipid profile and reduced leptin resistance at age of 13–15 years compared with those who were fed preterm formula; with a dose–response relationship between the proportion of human milk and later outcomes. In contrast, a cluster-randomised control trial of a breast-feeding promotion intervention in healthy term infants (Promotion of Breast-feeding Intervention Trial study) found no effect of the intervention on adiposity or BP at 6 years, despite increased incidence, duration and exclusivity of breast-feeding. Potential explanations for the discrepancy between the two studies include: (i) beneficial effects of breast milk on cardiovascular health might be confined to preterm infants; (ii) effects on cardiovascular outcomes may not manifest until adolescence, a concept supported by other studies; (iii) if the underlying mechanism for the effect of breast-feeding on later cardiovascular outcome is slower early growth; a concept supported by data from animal models, human observational studies and now experimental studies in human subjects; it is plausible that differences in early growth between groups in the Promotion of Breast-feeding Intervention Trial were insufficient to produce a detectable effect on these outcomes.

Breast-feeding: Randomised trial: Blood pressure: Plasma lipids: Obesity

Breast-feeding has several short-term benefits for morbidity and mortality, particularly in situations where there is inadequate access to clean water, and for infants born preterm[1,2]. However, in recent years, there has been increasing focus on the possibility that breast-feeding, or breast milk feeding, could have beneficial effects for later health outcomes, including the risk of obesity and CVD[1–3]. Evidence from human subjects relating to this concept comes from two sources: observational studies and randomised trials. This paper focuses on data from experimental or randomised trials, while an accompanying paper by Christopher Owen reviews data from observational studies.

Breast-feeding and later health: observational studies *v.* randomised trials

Both types of study can provide data relevant to the question of whether breast-feeding influences later health outcomes, and both approaches have strengths and weaknesses[4]. Observational studies, such as birth cohorts, have

Abbreviations: BP, blood pressure; PROBIT, Promotion of Breastfeeding Intervention Trial; RCT, randomised control trial.

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the advantage that sample sizes are often large, final disease end-points may be available and hence results can often be rapidly obtained. Their main disadvantage lies in the fact that causality cannot be demonstrated because the mode of infant feeding is not randomly assigned; hence, these studies can show associations between infant feeding and later health but cannot alone be used as a basis for policy. Furthermore, as many of these cohorts were not established specifically to examine later effects of infant feeding, the available data on early nutritional exposures may be sub-optimal. In contrast, the main advantage of randomised trials lies in the fact that they can demonstrate causal relationships between intervention and outcome, provided studies are well designed and executed. Hence, they are regarded as the 'gold-standard' in terms of providing evidence that can be used to underpin public health practice. The main disadvantage of prospective studies (whether randomised or observational) in the context of investigating later health effects is the time-scale required to study later health outcomes such as CVD, which do not manifest until decades after the intervention. Consequently, studies generally use proxy measures of these later outcomes; for example, plasma lipids or blood pressure (BP) as markers of CVD risk. There is then the question of the extent to which these proxy markers measured in childhood or adolescence predict the eventual disease risk. While certain parameters such as BP or plasma cholesterol concentration have been shown to track with age[5], this is not the case for other measures such as plasma insulin or bone mass.

Methodological issues in studies comparing breast-feeding with not breast-feeding

There are specific difficulties when comparing outcomes in infants who are breast-fed *v.* those who are not, in particular that it is unethical and unfeasible to randomly assign healthy term infants to their mode of feeding. This precludes the use of the 'gold-standard' randomised trial approach for the majority of the population. In both randomised trials and observational studies, there is the additional problem that neither 'breast-feeding' nor the alternative ('not breast-feeding') are precise or constant entities; breast-feeding varies in duration and exclusivity, and nutrient intakes vary even within the same infant over the course of a day, while the alternative, 'not breast-feeding', can also vary in terms of the type of milk or infant formula used. Thus, in contrast to the situation in a pharmaceutical trial that compares fixed doses of drug and placebo for a fixed time period, there is much more variability or 'noise' in any comparison of breast-feeding *v.* not breast-feeding.

Other issues that are important when comparing the findings of the many different studies in this field include the classification and definition of infant feeding and the source of data on infant feeding. At one extreme, some studies use a crude measure such as 'ever' *v.* 'never' breast-fed, whereas at the other extreme, studies include much more detailed data on breast-feeding duration and exclusivity. Some studies obtain infant feeding data prospectively from the mother or medical records, whereas others rely on maternal recall, sometimes years after the event. It is well recognised that the apparent incidence of breast-feeding is influenced by the method used to obtain the information[6]. This problem could be addressed by adopting more standardised methods for collecting and classifying infant feeding behaviour in prospective studies. However, so far this has not been achieved.

The type of data collected on potential confounding variables also varies in quantity and quality between studies, and this is recognised to be a significant problem when performing systematic reviews and meta-analyses[1,3]. It is particularly relevant in studies examining the relationship between breast-feeding and later cognitive outcome, where studies that adjust for maternal IQ are less likely to report a significant beneficial effect of breast-feeding on cognitive outcome than those adjusting for more proxy measures such as maternal educational level or social status[3]. However, this issue is also important for studies examining effects on later fatness or obesity risk, where parental BMI is a significant, but inconsistently measured, confounder[3]. Although confounding is a major issue for observational studies, it is also relevant for randomised trials where later follow-up is incomplete[4].

Specific difficulties in conducting long-term follow-up studies

In order to examine effects of infant nutrition on later health outcomes, long-term follow-up is required. A major problem experienced to some degree by all studies in this field is that of attrition or loss-to-follow-up. The degree of attrition varies depending on the length of follow-up, nature of the investigations proposed and the inconvenience involved for the subject. The problem of attrition in long-term follow-up studies was recently discussed in detail in a paper that addressed the statistical implications of attrition for the interpretation of data[4]. Attrition can lead to selection bias, since subjects who are lost to follow-up are rarely identical to those who agree to participate, and also to a loss of power to detect a hypothesised effect. It may also affect the generalisability of the findings. Rather than imposing arbitrary figures for what constitutes an 'acceptable' follow-up rate, for example, 80% as used to separate 'high'- and 'low'-quality randomised control trials (RCT) in evidence-based medicine[7,8], it has been suggested that investigators should explicitly address the potential effects of attrition when analysing and reporting follow-up studies, so that readers are able to consider the likely impact when interpreting findings[4].

Experimental studies in breast-feeding research

Given the inherent difficulties discussed earlier, it is perhaps not surprising that there have been only two randomised trials comparing health outcomes in relation to breast-feeding or breast milk feeding in human subjects. The design of these two studies is described in the next section, followed by a discussion on the results of follow-up data on BP, plasma lipids and obesity.

Randomised trial of infant feeding in preterm infants[9]

This randomised trial was initiated in 1982, at a time when there was considerable uncertainty about the best way to

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feed preterm infants. The diets commonly used to feed preterm infants at the time included unsupplemented banked donor breast milk and infant formulae designed to meet the nutritional requirements for healthy term infants. It was therefore considered both acceptable and feasible to randomise these vulnerable infants to their diet during the neonatal period to test the hypothesis that improving their nutrition would have benefits for both short- and long-term health outcomes. A total of 926 preterm infants (birthweight <1850 g and gestational age <37 weeks) were recruited from five UK neonatal units, and randomised to the milk received for, on average, the first month of life. In three of the hospitals, where there was a breast milk bank, the assignment was either to unsupplemented banked donor breast milk or to a newly developed nutrient-enriched preterm infant formula. In the remaining two centres, which did not have a breast milk bank, the assignment was to standard term infant formula or to preterm infant formula. In all cases, the randomised assignment could be fed as the infant's sole diet if the mother chose not to express any of her own breast milk, or given as a supplement to maternal breast milk if the latter was available. The comparison of donor breast milk *v.* preterm infant formula represents the only trial in which human infants have been randomised to breast milk *v.* infant formula without confounding by the mother's decision to breast-feed.

Infants enrolled in this trial were intensively monitored while they were in the neonatal unit, with daily records of nutritional intake, regular anthropometry and blood sampling. They were subsequently followed-up at intervals throughout childhood and into early adult life to examine effects of infant diet on a variety of later health outcomes, including neurodevelopment, bone health and cardiovascular health. It is important to note that many of the preterm infants in the study were never actually breast-fed; human milk was typically fed via a naso-gastric tube during the period of hospitalisation and many infants did not breast-feed after discharge. This is therefore primarily a study of 'breast milk feeding' rather than 'breast-feeding'.

Randomised trial of a breast-feeding promotion intervention in healthy term infants (the Promotion of Breast-feeding Intervention Trial trial[10])

This cluster-randomised trial, conducted in the Republic of Belarus, compared outcomes in healthy term infants born in clinics that were randomly assigned either to a breast-feeding promotion intervention (modelled on the UNICEF 'Ten steps to successful breast-feeding'[11]) *v.* standard management. The study enrolled 17 046 mother–infant pairs from thirty-one clinics (the unit of randomisation). The intervention resulted in a significant increase in both the incidence and duration of breast-feeding and exclusive breast-feeding up to 1 year of age. For example, rates of 'any breast-feeding' for the intervention and control groups were 72·7 % *v.* 60 % at 3 months, 36·1 % *v.* 24·4 % at 6 months and 19·7 % *v.* 11·4 % at 12 months, respectively. Rates of exclusive breast-feeding were also significantly higher in the intervention group (43·3 % *v.* 6·4 % at 3 months and 7·9 % *v.* 0·6 % at 6 months).

This was not a trial of breast-feeding *v.* formula-feeding, but rather compared groups of infants who received 'some' breast-feeding' *v.* those receiving 'more' and 'more exclusive' breast-feeding. Children from this study are being followed up throughout childhood, with 6-year follow-up data already published (see later).

Breast milk feeding and later cardiovascular health outcomes

Blood pressure

Two hundred and sixteen subjects (of 926 subjects originally enrolled and 831 survivors) from the preterm RCT were studied at 13–15 years of age. Those who had been randomised to receive human milk, either as sole diet or as a supplement to maternal breast milk, during the neonatal period had significantly lower mean and diastolic BP, with a mean difference of 4·1 and 3·2 mmHg, respectively, between groups ($P<0·05$ for both). This difference remained after adjusting for sex, neonatal Na intake and current BMI[12]. Furthermore, there was a 'dose–response' effect, with decreasing BP as the proportion of human milk received in the neonatal period increased ($P = 0·02$ for trend). Although the observed effect size is small in terms of the effect at an individual level, it would be expected to have a significant impact at a population level in terms of reducing morbidity and mortality from CVD. For example, lowering population-wide diastolic BP by only 2 mmHg would be expected to prevent approximately 100 000 myocardial and cerebrovascular events per year in the United States alone[13].

In contrast to these findings of an apparent beneficial effect of breast milk on later BP in subjects born preterm, at 6-year follow-up of the Promotion of Breastfeeding Intervention Trial (PROBIT) cohort, no significant effect of the intervention on BP was found[14]. One interpretation of this finding is that breast milk does not affect later BP in healthy term infants and that the results from previous observational studies suggesting a beneficial effect of breast milk on later BP in this population reflect residual confounding. However, interestingly, other studies in animal models (including baboons) and human subjects have found that effects of early nutrition and growth on later BP, plasma lipids and fatness may not 'emerge' until adolescence[15–17], and an earlier follow-up of the preterm RCT cohort found no effect of early nutrition on BP at 8 years of age[18]. A third possibility, since the PROBIT study was essentially a trial of 'some' *v.* 'more' breast-feeding, is that the separation between the intervention groups in this study in terms of breast-feeding behaviour was insufficient to demonstrate an effect. This possibility is discussed further later in this paper.

Plasma lipid profile

Plasma lipids were measured at 13–15-year follow-up of the preterm RCT[19]. The group randomised to human milk either as sole diet or as a supplement to maternal breast milk during the neonatal period had significantly lower concentrations of LDL-cholesterol, apo-B, and a lower

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LDL:HDL ratio during adolescence, all likely to be favourable changes in terms of later cardiovascular risk. These subjects also had significantly lower levels of the inflammatory marker, C-reactive protein CRP. Once again, there was a dose–response effect with more favourable plasma lipid concentrations in those with the highest neonatal intakes of human milk ($P = 0{\cdot}04$ for trend for LDL:HDL). Plasma cholesterol is known to track with age[5]. The effect size of about a 10% reduction in plasma cholesterol found in this study is very similar to that reported from a meta-analysis of breast-feeding in term infants[17]. In terms of the likely impact on later health, systematic reviews in adults have estimated that a 10% reduction in the concentration of plasma cholesterol in plasma would reduce the incidence of CVD by 25%[20,21] and mortality by 13–14%[22].

No plasma lipid results are yet available from the PROBIT cohort, although the 10-year follow-up study (currently underway) includes measurement of blood lipids.

Fatness and obesity

Follow-up of the preterm RCT cohort at ages 10[23], 13–15 years[12,19] and 20 years of age[24] found no significant impact of neonatal diet, including human milk, on body composition. The latter was measured using the *in vivo* gold standard 'four component' model at the 10- and 20-year follow-ups. The 6-year follow-up of the PROBIT cohort also reported no significant differences in weight, BMI, waist or hip circumference and skinfold thicknesses between intervention and control groups[14]. However, at 13–15-year follow-up of the preterm trial, subjects randomised to standard diets (donor breast milk or term infant formula) had a significantly lower leptin:fat mass ratio (a measure of leptin resistance) compared with those randomised to the 'enriched' diet (preterm infant formula; $P<0{\cdot}05$), with an inverse dose–response relationship between neonatal human milk intake and later leptin resistance[25]. This finding raises the hypothesis that a lower nutrient diet during the neonatal period, of which human milk is an example, may result in lower leptin resistance that could potentially influence later fatness and obesity risk. However, this requires further investigation with longer follow-up.

How could breast milk feeding reduce the risk of CVD or obesity?

It is relevant to consider potential mechanism(s) for an effect of breast-feeding or breast milk feeding on later cardiovascular health or obesity risk. One possibility is that the effect relates to a specific factor or factors in human milk; for example, one of the many growth factors or hormones present in breast milk but not in infant formulae. However, an alternative explanation that has received considerable research focus is that these effects are mediated by differences in the early growth patterns of breast-fed compared with formula-fed infants with, on average, slower early growth in breast-fed infants. The growth acceleration hypothesis, proposed by Singhal and Lucas[26], proposes that more rapid infant growth (shown by upward centile crossing for weight and/or length) results in an increased risk of later CVD and obesity. In support of their hypothesis, they point out that this phenomenon is observed in a wide variety of animal species, in whom rapid early growth confers short-term benefits for growth and survival but at a cost to the individual's later health or longevity[27]. It also explains why the early post-natal period and infant nutrition should be influential, since early nutrition is the main modifiable influence on infant growth, and the first months of life are the period when most catch-up or catch-down growth occurs as the infant adjusts its growth pattern.

This hypothesis is now supported by data from many observational studies. For example, data from more than twenty-seven studies (much of it summarised in systematic reviews[28–30]) suggest that faster weight gain (upward centile crossing for weight) in infancy is associated with a greater risk of long-term obesity. This association has been reported for obesity in adults and children, in both high- and low-income countries, and is consistent for cohorts over the past 80 years. The effect size of infant growth rate on later obesity risk may be substantial, and it has been estimated that up to 20% of the risk of being overweight later in childhood can be attributed to weight gain in the highest quintile in infancy[30]. Data from a smaller number of studies suggest rapid infant growth is associated with higher BP (reviewed in[31,32]), insulin resistance[33–35], endothelial function[36] and carotid intima-media thickness[37].

The growth acceleration hypothesis is also now supported by data from randomised trials of early nutrition in healthy term infants[38,39]. Infants randomised to receive growth-promoting, nutrient-enriched formulae (thought at the time the studies were initiated to be beneficial) were found to have higher BP[31] and greater fat mass[40] at age 5–8 years. Furthermore, in non-randomised analyses, adverse effects on these later health outcomes were clearly related to a faster early growth pattern. Importantly, this association between more rapid infant growth and adverse later outcome was seen in breast-fed infants as well as those fed formulae. Breast-fed infants showed a 25% increase in later fat mass for each one SD increase in weight between birth and 9 months of age[40]. In a randomised trial of high- *v.* low-protein infant formulae in healthy term infants with normal birthweights, those who received a higher-protein formula showed faster early growth and had significantly higher BMI, with the effect persisting at age 2 years. Infants randomised to receive the lower protein formula had a growth pattern more similar to that of a breast-fed reference group[39].

Data from both observational studies and randomised trials are thus consistent with the hypothesis that more rapid early growth, which can be the result of a higher plane of infant nutrition, is causally related to adverse effects on later cardiovascular and obesity risk. As yet, the underlying mechanism for the apparent 'coupling' between early growth and later health outcomes is unclear, but suggested mechanisms include effects of early growth on epigenetic 'marking', on the set-points of hormonal axes underpinning appetite, satiety and growth, or on fundamental processes relating to ageing (reviewed in[41]). Much of the mechanistic research in this field has been conducted

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in animal models although some human data are now available to support all three concepts.

Conclusion

Although regarded as the 'gold standard' in terms of demonstrating causality, due to ethical and practical difficulties only two randomised trials have examined the effect of breast-feeding on later cardiovascular health and obesity. One study, in preterm infants, suggests that breast milk has beneficial effects on cardiovascular risk factors measured during adolescence, while the other study, in healthy term infants, has found no such effect up to 6 years of age. There are a number of potential explanations for the discrepancy between the two studies. Firstly, beneficial effects of breast milk on cardiovascular health might be confined to more vulnerable preterm infants. Secondly, effects on cardiovascular outcomes may not manifest until adolescence, a concept supported to some extent by other studies in animals and human subjects. Thirdly, if, as supported by a significant body of literature from animal models, human observational studies and now experimental studies in human infants, the underlying mechanism for the effect of breast milk on later cardiovascular outcome is a slower early growth pattern, it is plausible that the difference in early growth pattern between groups in the PROBIT trial, which essentially compared 'some' breast-feeding with 'more' breast-feeding, was insufficient to produce a detectable effect on these outcomes.

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