Chapter 13

# BREAST-FEEDING INFLUENCES ON LATER LIFE - CARDIOVASCULAR DISEASE

D.A. LEON and G. RONALDS
*Department of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel St, London, WC1E 7HT, UK. David.Leon@lshtm.ac.uk*

## 1. INTRODUCTION

Cardiovascular disease represents a major challenge to public health globally. While there is now a clear downward trend in mortality from coronary heart disease (CHD) and stroke in many Western high income countries,[1-2] it is projected that in many other parts of the world mortality will increase steeply in the next 20 years. In an authoritative review, Yusuf *et al* have estimated that by 2020 the annual number of deaths worldwide from CHD will be double the level seen in 1990.[3] These increases will affect low as well as middle income countries. In part the trend is a consequence of population aging. However, it is believed that, in many areas of the world, the increase in cardiovascular disease is also being driven by profound shifts in behaviour and diet. These changes are occurring as part of a process that includes the wide-spread migration of people from rural areas to cities, which is happening in almost all low and middle income countries.

In some areas of the world communicable diseases remain the top priority for public health. However, even in sub-Saharan Africa, circulatory diseases are rapidly becoming major contributors to mortality: here, in 1990 it was estimated that the number of deaths from cardiovascular disease was only slightly lower than those from infectious and parasitic diseases.[3] In all other global regions the numbers of CHD deaths appreciably outnumbered those from infectious and parasitic diseases.

*G. R. Goldberg et al. (eds.), Breast-Feeding: Early Influences on Later Health,*

The increasing global importance of cardiovascular disease justifies a continual review and appraisal of our current understanding of the aetiology of these conditions and the prospects for both primary and secondary prevention. The 52 country INTERHEART study,[4] which includes many low and middle-income countries, has recently made an assessment of risk factors. It concluded that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of coronary heart disease events (myocardial infarctions) worldwide in both sexes and at all ages in all regions.

Interventions in adult life have been shown to be effective in primary and secondary prevention of cardiovascular disease. Smoking, diet and exercise are clear priority areas. Where available and affordable, pharmaceutical treatments for hypertension and adverse lipid profiles have been shown to be highly effective in reducing morbidity and mortality. However, in addition to these later-life risk factors, there is intriguing evidence that cardiovascular risk may also be related to circumstances in early life.

The possibility that experiences in infancy and childhood could contribute to cardiovascular disease in adult life has been discussed for decades.[5] However, in recent years this debate has focussed on the possible links between impaired fetal growth and later disease risk, encapsulated in the so-called "fetal origins hypothesis".[6] As reviewed elsewhere,[7] historical prospective cohort studies from a number of countries (including Britain,[8-9] Sweden,[10] Finland,[11] USA[12] and India[13]) have found that the risk of coronary heart disease events declines as size at birth increases. This inverse association has been found in all published studies with the exception of one small investigation from Gothenburg, Sweden.[14] Most of these studies are restricted to mortality as an endpoint, although a number also include non-fatal myocardial infarction and other indicators of CHD such as angina. This inverse association is little affected by adjustment for socio-economic factors and is evident without adjustment for adult body size. A smaller number of studies have also been able to look at the association of size at birth with risk of stroke.[15-18] These have also found the existence of an inverse association.

One interpretation of the link between size at birth and later cardiovascular disease is that it reflects the long-term consequences of impaired nutrition *in utero*. These could include effects on final cell number or organ structure and function that in turn could result in differences in risk in later life. Size at birth is thus simply a proxy measure of *in utero* nutrition. It has been argued, however, that it may be difficult to differentiate between the effects of impaired fetal growth and accelerated (or catch-up) growth in the post-natal period.[19] Indeed, it has recently been argued that it is nutrition in infancy rather than *in utero* that is the important early-life influence on

later cardiovascular risk.[20] Clearly one crucial aspect of nutrition in infancy is breast-feeding. Over the past few years there has been increasing interest in whether breast-feeding is indeed associated with cardiovascular disease risk in later life.

This chapter will review the current evidence for an association between breast-feeding and cardiovascular disease risk in later life. The evidence relating breast-feeding with cardiovascular events will be examined first. Following this, the association of breast-feeding with cardiovascular risk factors such as blood pressure and serum lipids will be reviewed. As detailed below, systematic reviews and meta-analyses of each of these areas have been published. We have not attempted to replicate this very detailed work. Instead we aim to bring all this evidence together in one place. This will involve summarising the key findings of these meta-analyses and any additional later studies that have been published. However, we also aim to identify some of the broader issues in the interpretation of the evidence and to assess its significance. Finally we consider important evidence from one of the few randomised trials that has contributed to this topic.

## 2. METHODOLOGICAL ISSUES

Before preceding to outline the substantive results found in the literature it is necessary to reiterate some methodological cautions made elsewhere, which should be borne in mind when assessing the evidence.[21-22]

### 2.1 Defining the exposure "breast-feeding"

It is important to make one obvious point at the outset. Investigations of the effect of breast-feeding on outcomes in later life are complicated by the difficultly of being precise and consistent in defining what constitutes the exposure "breast-feeding". First, do we define a breast-fed infant as one who is exclusively breast-fed, or simply as an infant who is predominantly breast-fed before weaning? Moreover, is there a minimum qualifying period of breast-feeding required? Second, the nature of the 'unexposed' group is unusual in the case of infant feeding. In contrast to an exposure such as tobacco smoking, where we can compare smokers with never smokers, in the case of breast-feeding those not breast-fed actually receive some other food in infancy. Thus the comparison is implicitly between breast-feeding and an alternative food. This creates a central difficulty in interpretation: is any difference in later disease outcome due to the biological effect of breast-feeding or to the effect of the alternative food ? Third, the alternative food can vary: the composition of artificial bottle feeds has changed dramatically

over time. This is of particular importance when considering the evidence linking breast-feeding with cardiovascular events, such as myocardial infarctions or deaths from coronary heart disease. The study populations required to investigate this will generally have been born in the first 50 years of the 20th century if they are to be old enough to have developed cardiovascular disease. The composition of infant feeds in, for example, Caerphilly, Wales in the 1930s were very different to feeds given to neonates in hospital settings in the 1990s. [23]

## 2.2 Confounding and reverse causality

Finally, although common to all observational studies and in no way unique to the long-term effects of breast-feeding, there is concern about whether all potential alternative explanations for an association (confounders) have been adequately accounted for. Moreover, there is the question of whether or not breast-feeding in infancy may have itself been influenced by illness or behavioural characteristics that are predictive of, for example, cardiovascular disease. This is the problem of reverse causality (see also Chapter 11 by Kramer).

The potential problems of confounding and reverse causality mean that there is often uncertainty about whether any statistical association between breast-feeding and later outcomes really represents an effect of breast-feeding *per se*. For this reason, properly conducted randomised trials of breast-feeding should provide a much more persuasive level of evidence. However, as we discuss at the end of this chapter, the main randomised trial evidence available about the association of breast-feeding with later cardiovascular risk factors is not as persuasive as it first appears.

# 3. BREAST-FEEDING AND CARDIOVASCULAR EVENTS

A meta-analysis of 4 studies that presented data on breast-feeding in relation to subsequent cardiovascular mortality was published by Martin *et al* in 2004.[24] It included a total of 3093 cardiovascular deaths among subjects born between 1904 and 1939. Three of the studies were from the UK and one from California, USA.[25] Of the UK studies, the results of one (from the Boyd-Orr cohort) were published as part of the meta-analysis for the first time, a second was in press although subsequently published [23], while the third (the Hertfordshire cohort) contributed data that had been updated from the original publication.[26] The information on breast-feeding in infancy was

collected prospectively in one study, was from maternal recall during the subject's childhood in two studies and was based on subject's self-report in middle age in the fourth study.

The meta-analysis compared infants who were exclusively or partially breast-fed with those who were never breast-fed, i.e. were bottle-fed. With adjustments for a range of factors, which varied across studies (including age, birthweight, socio-economic position in childhood and adult life), the meta-analysis produced a pooled rate ratio for all causes of death of 1.01 (95% CI 0.91 – 1.13) among those who were ever breast-fed relative to those who were never breast-fed. For cardiovascular disease deaths (including coronary heart disease and stroke) the equivalent rate ratio was 1.06 (0.94 – 1.20). Thus, from these four studies there was no evidence that people who were ever breast-fed had a different risk of death from all causes or cardiovascular disease than those who were never breast-fed in infancy. An analysis looking at the effect of prolonged breast-feeding on cardiovascular mortality in three of the studies also failed to find any statistically significant association.

Subsequent to this meta-analysis an additional study looking at breast-feeding in relation to cardiovascular events was published from the US Nurses Health Study.[27] This was based on 2039 incident fatal and non-fatal myocardial infarctions, strokes and deaths from coronary heart disease occurring between 1992-2000 among 87252 US nurses born between 1921-46. Whether subjects were breast-fed in infancy was based on self-report in 1992. A validation of these data was made by asking the surviving mothers of 3515 nurses about breast-feeding. This found self-report to have a specificity of 71% and a sensitivity of 90%. The study found that the rate ratio for any cardiovascular event was 0.91 (95% CI 0.83 – 1.01) among those who were ever breast-fed compared to those never breast-fed. This rate ratio was adjusted for age, subject's cigarette smoking in adult life and birthweight. The direction of the effect seen in this study is opposite to that produced by Martin *et al's* meta-analysis.

Without conducting a further formal meta-analysis it is thus clear that the evidence published to date suggests that there is no association between risk of cardiovascular events and ever having been breast-fed in infancy. However, data are limited, most notably by the absence of prospectively gathered information on breast-feeding of a consistent type. It is therefore possible that a small real association between breast-feeding and cardiovascular events does exist.

# 4. BREAST-FEEDING AND CARDIOVASCULAR RISK FACTORS

The number of studies able to investigate the link between breast-feeding and cardiovascular disease is inevitably limited, as this requires information on breast-feeding in very large cohorts of people who are already well into middle age. Nevertheless, we can gain further insights by examining whether breast-feeding is linked to cardiovascular disease risk factors such as blood pressure and serum lipid profiles. These can be examined in much younger cohorts than are required for looking at cardiovascular events *per se*, opening up many more possibilities for *ad hoc* studies of contemporary populations of children and adolescents as well as adults.

In the following two sub-sections we review the evidence for an association between breast-feeding and both blood pressure and serum lipids. Equally relevant in this context would be to examine the link between breast-feeding and insulin-mediated glucose uptake and type 2 diabetes, and obesity. These outcomes are dealt with in Chapters 11 and 12.

## 4.1 Blood pressure

There have been two meta-analyses of the association between breast-feeding in infancy and blood pressure in later life, one published in 2003 by Owen *et al*[28], the second in 2005 by Martin *et al*. [21] Both found that, compared to people who were exclusively or predominantly bottle-fed, those who were breast-fed had a slightly lower systolic blood pressure (SBP). They both also found some evidence of publication bias, with the size of the effect declining as study size increased. Neither study found any evidence of a different effect of infant feeding by the age at which blood pressure was measured. The later meta-analysis, unlike the earlier one, also found a small statistically significant reduction in diastolic blood pressure (DBP) associated with breast-feeding.

The meta-analysis by Owen *et al*[28] included 24 studies. These covered 8 analyses of systolic blood pressure as an outcome in infancy, 12 in childhood and in 6 in adult life. Half the studies included subjects born before 1980, the other half being born later. The total number of subjects who were classified as breast-fed was slightly less than 8,500 while those who were bottle-fed numbered just under 11,300. One of the studies included was a randomised controlled trial, the others being observational studies.

Overall, this meta-analysis[28] found that the difference in SBP between breast-fed and bottle-fed infants was -1.10 mmHg (95% CI -1.79, -0.42) i.e. the breast-fed had lower SBP. The equivalent estimate for DBP was -0.36

mm Hg (-0.79, +0.08). Formal tests showed that the largest effects were observed for the 13 estimates based on less than 300 subjects while the smallest in the 4 studies with more than 1000 subjects (p=0.046).

The most recent meta-analysis by Martin *et al* [21] only included information from 14 studies, in contrast to the 24 included by Owen *et al*. How is this discrepancy to be explained? Firstly, Martin *et al* excluded the studies of blood pressure in infancy. However, it appears that a number of the other studies not included by Martin *et al*, but included in the earlier meta-analysis, were those where Owen *et al* had admirably obtained results directly from researchers that went beyond those available in published papers – a procedure that would be intended to minimise publication bias.

On the plus side Martin *et al* included three studies [23, 29-30] on this issue that had not been published at the time Owen *et al* had produced their meta-analysis, two of which were very large.[29-30] Overall, Martin *et al* included just over 17,500 subjects, although the breakdown by category of infant feeding was not given.

Despite the fact that the two meta-analyses only shared 11 studies in common, the summary result produced by Martin *et al* is very similar to that produced by Owen *et al*. Their pooled difference in SBP among the breast-fed compared to bottle-fed was -1.4 mmHg (95% CI -2.2, -0.6) i.e. the breast-fed had lower SBP. The equivalent estimate for DBP was -0.5 mm Hg (-0.9, -0.04). As found in the earlier meta-analysis there was also statistically significant evidence of publication bias, with the size of effect being inversely proportional to study size.

In summary there is evidence that individuals who were classified as having been breast-fed in infancy had lower blood pressure in childhood and adult life. The difference in blood pressure is relatively small, however, at just over 1 mmHg SBP. Interestingly, Owen *et al* describe this as being of "limited clinical or public health importance." In contrast, Martin *et al* suggest that, if causal, this small difference "could confer important benefits on cardiovascular risk at the population level."

This takes us to the key issue of whether this association is indeed a real effect: the evidence for publication bias is strong, with the smaller effects seen in the larger studies being of marginal statistical significance. The second important caveat concerns the great heterogeneity in definitions of infant feeding seen across the different studies. One could argue that a more consistent definition that encapsulated the key aspects of infant feeding might yield larger effects than observed, although this is pure speculation. Finally, it is notable that neither of the meta-analyses were able to consistently include estimates adjusted for a broad range of confounders. The potential importance of this omission is illustrated by the ALSPAC study,[29] in which adjustment for social, economic, maternal and

anthropometric variables reduced the effect of breast- vs. bottle-feeding by a third from -1.2 mmHg to -0.8 mmHg SBP.

## 4.2 Lipid profiles

The first systematic review and meta-analysis of infant feeding in relation to cardiovascular risk factors looked at blood cholesterol in infancy, childhood and adult life. This was published in 2002 by Owen *et al*[31], the group that subsequently undertook the meta-analysis of blood pressure discussed in the previous section. It included 37 studies with 52 observations on total serum cholesterol : 26 in infancy, 17 in childhood or adolescence, and 9 in adulthood. With serum low-density lipoprotein (LDL) as the outcome there were 7 observations in infancy, 4 in childhood or adolescence and 6 in adulthood. Most of the studies were of subjects born in the late 1960s or later, with the exception of the 3 oldest cohorts of people born between 1920 and 1946. All the studies were observational, the majority being cohort studies.

As in the case of the other meta-analyses reviewed above, there was considerable variation across studies in the criteria used to categorise individuals as having been breast-fed or bottle-fed. Studies were included in the meta-analysis even if it was not possible to identify groups that had either been exclusively breast or bottle-fed before they were weaned. The vast majority of studies obtained information on breast-feeding during infancy either directly from clinical records or from a parental questionnaire.

The authors of the meta-analysis decided *a priori* to look at the association of infant feeding with serum lipids in three pre-defined age groups (<1 year, 1-16 years, 17+ years). The results confirmed their view that the strength and direction of the association did indeed vary across the three age groups ($p<0.001$). In infancy, breast-fed babies had higher total cholesterol concentrations than bottle-fed (+0.64 mmol/L; 95% CI +0.49, +0.79). In children and adolescents there was no difference in total cholesterol between those who were breast and those who were bottle-fed (0.00 mml/L; 95% CI -0.07, +0.07). In adults, those who were breast-fed had lower total cholesterol than those who were bottle-fed (-0.18 mmol/L; -0.06, -0.30). The patterns observed for LDL cholesterol were similar those seen for total cholesterol throughout.

Since this meta-analysis was undertaken several new studies have been published that have also looked at the association of infant feeding with serum lipids. The Caerphilly cohort study [23] reported on total cholesterol and LDL cholesterol levels in middle age (45-59 years), in relation to infant feeding. It found no evidence of a statistically significant difference. However, it is striking that contrary to the results of the meta-analysis, this

study suggested, if anything, that in adults total cholesterol was higher in breast compared to bottle-fed (+0.05 mmol/L; 95% CI -0.09, +0.18). The Caerphilly study is in fact relatively large compared to the other adult studies in the meta-analysis. It included 1159 breast and 421 bottle-fed infants, while the meta-analysis as a whole included 1519 breast and 495 bottle-fed infants. Given this, it is plausible that if formally combined into a new single meta-analysis, there would no longer be a statistically significant difference in total cholesterol in adult life by whether people were breast or bottle-fed in infancy.

The second paper of relevance that was published after Owen's 2002 meta-analysis was based on the follow-up of a randomised controlled trial of infant feeding in pre-term babies.[32] Out of a total of 926 infants recruited into two parallel infant feeding trials, this paper reported the results concerning serum lipoprotein profile in 216 participants followed up to age 13-16 years. The authors found that the LDL/HDL ratio was lower (a good thing for cardiovascular risk) among people who were assigned to banked breast-milk compared to those who were not (p=0.04). However, they found no statistically significant differences in total cholesterol or LDL cholesterol per se. They concluded that their data provided evidence "for the long-term benefits of breast-feeding". There are, however, a number of issues concerning the interpretation of results from this trial (which also reported on blood pressure in relation to infant feeding) that are best dealt with separately in the next section.

## 5. RANDOMISED TRIALS OF BREAST-FEEDING

Many of the limitations of the observational data that have been summarised above would be overcome if it were possible to follow-up people who had been randomised in infancy to well-characterised feeding regimes. However, the view that breast-milk provides, in most situations, optimal infant nutrition creates an almost insuperable ethical barrier to randomisation of infant feeding. However, in special situations trials are justifiable. An excellent example is the trail of pre-term feeding established by Lucas et al in 1982.[33] This was established to look at the effects of different feeds on post-natal growth in pre-term infants weighing less than 1850g at birth.

Members of this trial were followed-up in childhood, at ages 7.5-8 years, and in adolescence, at ages 13-16 years. A series of papers have emerged looking at infant feeding in relation to a range of outcomes, including blood pressure[34-35], lipid profiles[32] and insulin resistance.[36] Two parallel randomised trials were conducted. The first trial allocated 502 babies to

either banked breast (N=253) or to pre-term formula (N=249). The second trial allocated babies to either normal term formula or pre-term formula feed. As breast-milk was not a component of the randomisation further details of this second trial are not discussed here.

Within the first trial the feed received by each infant was not solely determined by the randomisation. Some infants received the allocated feed as a supplement. The numbers of subjects in each arm of the trial and the actual feed they received is shown in Table 13-1 together with the numbers followed up into childhood and adolescence.

What is immediately apparent is that the follow-up to adolescence was very far from complete. However, on the reasonable assumption that equal efforts were made to trace all subjects in the trial regardless of feeding regime, *a priori* there is little reason to think that the groups should be biased other than by chance due to the relatively small numbers included. This is confirmed by analyses presented in one of the papers, [35] which suggests that there were minimal differences between those who were followed up and those who were not. Table 13-2 shows mean blood pressures at first follow-up, aged 7.5-8 years of age, according to trial arm.[34]

The differences in SBP and DBP are very small between the various groups, although no formal statistical test between the two arms of the trial was conducted in the paper.[34] Table 13-3 shows mean blood pressures, this time by allocated arm of the trial for the even smaller number of subjects followed-up to age 13-16 years.[35]

Thus it appears that while in childhood there are minimal differences in blood pressure according to infant feeding, by adolescence there is evidence of a difference. With respect to serum lipids, Table 13-4 shows mean levels at age 13-16 years.[32]

*Table 13-1.* Numbers of subjects at recruitment and follow-up of a randomised trial of pre-term feeding by assignment (see reference 33)

| | Actual feeding regime | | Follow-up at ages | |
|---|---|---|---|---|
| | | | 7.5 – 8 years | 13 – 16 years |
| Arm 1 | Banked breast-milk | N=83 | N=66 | N=13 |
| | Banked breast-milk + mother's milk | N=170 | N=133 | N=53 |
| Arm 2 | Pre-term formula | N=76 | N=60 | N=17 |
| | Pre-term formula + mother's milk | N=173 | N=146 | N=47 |

*Table 13-2.* Mean blood pressures at age 7.5 – 8 years of age by trial arm (see reference 34) and feeding received (mmHg)

| Initial randomisation | | | SBP | DBP |
|---|---|---|---|---|
| Arm 1 | Banked breast-milk | N=66 | 98.7 | 61.0 |
| | Banked breast-milk + mother's milk | N=133 | 99.3 | 61.4 |
| Arm 2 | Pre-term formula | N=60 | 98.6 | 61.7 |
| | Pre-term formula + mother's milk | N=146 | 99.2 | 61.8 |

*Table 13-3.* Mean blood pressures at age 13 – 16 years of age by trial arm (mmHg) (see reference 35)

| | Banked breast-milk (n=66) | Pre-term formula (n=64) | p-value for difference |
|---|---|---|---|
| Diastolic BP | 61.9 | 65.0 | 0.016 |
| Systolic BP | 113.6 | 116.3 | 0.075 |
| Mean arterial pressure | 81.9 | 86.1 | 0.001 |

*Table 13-4.* Mean serum lipid levels at age 13 – 16 years of age by trial arm (see reference 32)

| | Banked breast-milk (n=66) | Pre-term formula (n=64) | p-value for difference |
|---|---|---|---|
| LDL/HDL ratio | 2.2 | 2.5 | 0.04 |
| Mean total cholesterol (mmol/L) | 3.8 | 4.1 | 0.06 |

These results, plus others not shown in this chapter, led the investigators to conclude that "Together with other epidemiological data and our experimental observations … our findings suggest that breast-milk has a major beneficial effect on cardiovascular health".[32] The strength of this conclusion – at least in terms of results from this particular trial – may be questioned. As can be seen from Table 13-1, two thirds of infants randomised to receive pre-term formula actually received this as a supplement to breast-milk. In total, only 76 (15%) out of 502 infants randomised in this trial received no breast-milk at all (either from the mother or a milk bank). Of the 130 subjects followed-up at 13-16 years, only 17 (13%) had not been fed breast-milk of one sort or another. It is therefore difficult to interpret the differences shown in Tables 13-3 and 13-4.

The trial was essentially a pragmatic one, not designed to look at the effects of breast-feeding *per se*. The fact that most of the subjects also received breast-milk was simply how it turned out. The real distinction between the two arms of the trial is that no one in arm 1 received pre-term formula, while everyone in arm 2 did (see Table 13-1). So, the key conclusion one might draw here is that at age 13-16 years, those who were given pre-term formula are more likely to display markers of cardiovascular

disease risk. One could not really claim that the trial provides strong evidence for the beneficial effects of breast-milk *per se*. Thus, despite the advantage of experimental design, unfortunately this trial at least has relatively little to contribute to the evidence base concerning breast-milk or breast-feeding and their relationship to cardiovascular risk factors or events.

## 6. SUMMARY AND CONCLUSIONS

Current evidence, almost exclusively from observational studies, provides a rather mixed picture. From the few studies that have been able to look at fatal or non-fatal cardiovascular events, there is little indication that breast-feeding is associated with either an increased or decreased risk. With respect to blood pressure, the meta-analyses suggest a small but statistically significant lowering of around 1mmHg SBP associated with having been breast-fed in infancy. However, there is a strong indication from the meta-analyses that even this small effect may partly be accounted for by publication bias. The strongest evidence for an effect of breast-feeding reviewed in this chapter is for serum lipids, where there is good evidence that being breast-fed is associated with an increase in serum total cholesterol in infancy. In childhood there appears to be no association, while in adults there is some indication of breast-feeding being associated with a small decline in total cholesterol levels.

As already outlined at the start of the chapter, this whole area of research is made particularly difficult by the fact that breast-feeding can be defined in many different ways. Some studies use definitions that are equivalent to exclusive breast-feeding prior to weaning, while others define it as having ever been breast-fed. This problem of classification is likely to dilute any real associations that may exist. The other major problem is one of interpretation. A result implying that breast-feeding is a "good thing" for cardiovascular health could equally be construed as evidence for a "bad" effect of bottle-feeding. From these data alone, we cannot convincingly determine which conclusion is correct. This is not simply a philosophical debating point. As discussed above in relation to the interpretation of results from the randomised trial of infant feeding, the issue has implications for all research on this topic.

Some progress in this area will be made if studies are conducted which define breast-feeding in a more precise and comparable way, and take account of the composition of alternative infant feeds. This will be most easily done by following up more recent study populations that were originally recruited to look at shorter-term effects of infant feeding on outcomes such as growth. With respect to randomised trial evidence, looking

at the cardiovascular disease risk profiles of children (and later adults) who were part of the PROBIT trial in Belarus (see Chapters 5 and 10) is likely to prove fruitful.

## REFERENCES

1. Levi F, Lucchini F, Negri E, La Vecchia C (2002) Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. *Heart* 88:119-124.
2. Arciero TJ, Jacobsen SJ, Reeder GS *et al* (2004) Temporal trends in the incidence of coronary disease. *Am J Med* 117:228-233.
3. Yusuf S, Reddy S, Ounpuu S, Anand S (2001) Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 104:2746-2753.
4. Yusuf S, Hawken S, Ounpuu S *et al* (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 364:937-952.
5. Forsdahl A (1977) Are poor living conditions in childhood and adolescence an important risk factor for arteiosclerotic heart disease ? *Br J Prev Soc Med* 31**:**91-95.
6. Barker DJP (1995) Fetal origins of coronary heart disease. *BMJ* 311:171-174.
7. Lawlor DA, Ben-Shlomo Y, Leon DA (2004) Pre-adult influences on cardiovascular disease. In: Kuh D, Ben-Shlomo Y, eds. *Life Course Influences on Adult Disease*, Oxford: Oxford University Press.
8. Barker DJP, Winter PD, Osmond C, Margetts B (1989) Weight in infancy and death from ischaemic heart disease. *Lancet* ii:577-580.
9. Frankel S, Elwood P, Sweetnam P, Yarnell J, Davey-Smith G (1996) Birthweight, adult risk factors and incident coronary heart disease: the Caerphilly study. *Public Health* 110:139-143.
10. Leon DA, Lithell HO, Vågerö D *et al* (1998) Reduced fetal growth rate and increased risk of ischaemic heart disease mortality in 15 thousand Swedish men and women born 1915-29. *BMJ* 317:241-245.
11. Forsen T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJ (1999) Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. *BMJ* 319:1403-1407.
12. Rich-Edwards J, Stampfer M, Manson J *et al* (1995) Birthweight, breastfeeding and the risk of coronary heart disease in the Nurses' Health Study. *Am J Epidemiol* 141:S78.
13. Stein CE, Fall CHD, Kumaran K, Osmond C, Cox V, Barker DJP (1996) Fetal growth and coronary heart disease in South India. *Lancet* 348:1269-1273.
14. Eriksson M, Tibblin G, Cnattingius S (1994) Low birthweight and ischaemic heart disease. *Lancet* 343:731.
15. Hypponen E, Leon DA, Kenward MG, Lithell H (2001) Prenatal growth and risk of occlusive and haemorrhagic stroke in Swedish men and women born 1915-29: historical cohort study. *BMJ* 323:1033-1034.
16. Martyn CN, Barker DJ, Osmond C (1996) Mothers' pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. *Lancet* 348:1264-1268.
17. Rich-Edwards JW, Stampfer MJ, Manson JE *et al* (1997) Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ* 315:396-400.

18. Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ (2000) Early growth, adult income, and risk of stroke. *Stroke* 31:869-874.
19. Lucas A, Fewtrell MS, Cole TJ (1999) Fetal origins of adult disease-the hypothesis revisited. *BMJ* 319:245-249.
20. Singhal A, Lucas A (2004) Early origins of cardiovascular disease: is there a unifying hypothesis? *Lancet* 363:1642-1645.
21. Martin RM, Gunnell D, Smith GD (2005) Breastfeeding in infancy and blood pressure in later life: systematic review and meta-analysis. *Am J Epidemiol* 161:15-26.
22. Kramer MS, Guo T, Platt RW *et al* (2002) Breastfeeding and infant growth: biology or bias? *Pediatr* 110:343-347.
23. Martin RM, Ben Shlomo Y, Gunnell D, Elwood P, Yarnell JW, Davey SG (2005) Breast-feeding and cardiovascular disease risk factors, incidence, and mortality: the Caerphilly study. *J Epidemiol Community Health* 59:121-129.
24. Martin RM, Davey-Smith G, Mangtani P, Tilling K, Frankel S, Gunnell D (2004) Breastfeeding and cardiovascular mortality: the Boyd Orr cohort and a systematic review with meta-analysis. *Eur Heart J* 25:778-786.
25. Wingard DL, Criqui MH, Edelstein SL *et al* (1994) Is breast-feeding in infancy associated with adult longevity? *Am J Public Health* 84:1458-1462.
26. Fall CHD, Barker DJP, Osmond C, Winter PD, Clark PMS, Hales CN (1992) The relation of infant feeding to adult serum cholesterol and death from ischaemic heart disease. *BMJ* 304:801-805.
27. Rich-Edwards JW, Stampfer MJ, Manson JE *et al* (2004) Breastfeeding during infancy and the risk of cardiovascular disease in adulthood. *Epidemiology* 15:550-556.
28. Owen CG, Whincup PH, Gilg JA, Cook DG (2003) Effect of breast-feeding in infancy on blood pressure in later life: systematic review and meta-analysis. *BMJ* 327:1189-1195.
29. Martin RM, Ness AR, Gunnell D, Emmett P, Davey-Smith G (2004) Does breast-feeding in infancy lower blood pressure in childhood? The Avon Longitudinal Study of Parents and Children (ALSPAC). *Circulation* 109:1259-1266.
30. Lawlor DA, Najman JM, Sterne J, Williams GM, Ebrahim S, Davey SG (2004) Associations of parental, birth, and early life characteristics with systolic blood pressure at 5 years of age: findings from the Mater-University study of pregnancy and its outcomes. *Circulation* 110:2417-2423.
31. Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG (2002) Infant feeding and blood cholesterol: a study in adolescents and a systematic review. *Pediatrics* 110:597-608.
32. Singhal A, Cole TJ, Fewtrell M, Lucas A (2004) Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. *Lancet* 363:1571-1578.
33. Lucas A, Gore SM, Cole TJ *et al* (1984) Multicentre trial on feeding low birthweight infants: effects of diet on early growth. *Arch Dis Child* 59:722-730.
34. Lucas A, Morley R (1994) Does early nutrition in infants born before term programme later blood pressure ? *BMJ* 309:304-308.
35. Singhal A, Cole TJ, Lucas A (2001) Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet* 357:413-419.
36. Singhal A, Fewtrell M, Cole TJ, Lucas A (2003) Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet* 361:1089-1097.