Breastfeeding and Atherosclerosis

Intima-Media Thickness and Plaques at 65-Year Follow-Up of the Boyd Orr Cohort

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Objectives—The impact of breastfeeding in infancy on cardiovascular disease risk is uncertain. We related breastfeeding in infancy to atherosclerosis in adulthood.

Methods and Results—A historic cohort study based on a 65-year follow-up of the Carnegie (Boyd Orr) survey of diet and health in prewar Britain, 1937 to 1939. A total of 732 eligible cohort members living in or around Aberdeen, Bristol, Dundee, Wisbech, and London were invited for follow-up examinations in 2002, and 405 (55%) participated. In models controlling for age and sex, breastfeeding was inversely associated with common carotid intima-media thickness (IMT; difference −0.03 mm; 95% CI, −0.07 to 0.01), bifurcation IMT (difference −0.19 mm; 95% CI, −0.37 to −0.01), carotid plaque (odds ratio [OR], 0.52; 95% CI, 0.29 to 0.92), and femoral plaque (OR, 0.54; 95% CI, 0.26 to 1.12), compared with bottle-feeding. Controlling for socioeconomic variables in childhood and adulthood, smoking and alcohol made little difference to effect estimates. Controlling for factors potentially on the causal pathway (blood pressure, adiposity, cholesterol, insulin resistance, and C-reactive protein) made little difference to observed associations.

Conclusions—Breastfeeding may be associated with a reduced risk of atherosclerosis in later life. Measurement error and power considerations limit the extent to which conclusions about the mechanisms underlying this relationship can be made. (Arterioscler Thromb Vasc Biol. 2005;25:1-7.)

Key Words: infant nutrition
• breastfeeding
• cardiovascular disease risk factors
• intima-media thickness
• atherosclerosis
• historical cohort

Breastfeeding in infancy is a possible determinant of later coronary heart disease and its risk factors. A postmortem study found fewer coronary plaques among breastfed versus bottle-fed young accident victims, and breastfeeding was inversely associated with coronary heart disease mortality, except when prolonged. Several mechanisms could underpin these observations. In meta-analyses, breastfeeding was associated with a 0.18 mmol/L reduction in total cholesterol in adults and a 1.10 mm Hg reduction in systolic blood pressure. Bottle-feeding, in contrast, is positively associated with blood pressure and insulin resistance.

Others show no relationship of breastfeeding with coronary heart disease, and prolonged breastfeeding may adversely affect arterial distensibility (a suggested predictor of coronary heart disease). In yellow baboons, prolonged breastfeeding followed by a high-fat diet was positively associated with atherosclerosis, although generalizing to humans is problematic.

Common carotid and bifurcation intima-media thickness (IMT), and the presence of coronary and femoral plaques, are established measures of preclinical atherosclerosis and predict incident stroke and ischemic heart disease. We investigated the association between breastfeeding and atherosclerosis measured by arterial ultrasound in 63- to 82-year-old participants in the Boyd Orr cohort.

Methods

The Boyd Orr cohort comprises 4999 participants from 1343 families in 16 centers in England and Scotland who participated in a 1-week survey of diet and health when aged 0 to 19 years between 1937 and 1939. The National Health Service Central Register (NHSCR) was used to trace 4379 (88%) individuals. Between 1997 and 1998, all 3182 traced survivors were sent questionnaires. Of the 1648 responses, 1378 (84%) consented to further follow-up. In February 2002, 2563 of the original cohort were alive and living in Britain, and 1295 (51%) participants who had consented to further follow-up were known to be still alive and contactable. We contacted all 732 (29%) participants living near clinics in Bristol, London, Wisbech, Aberdeen, and Dundee, and 85% (n = 619) responded, of whom 405 (16% of total; 55% of those contacted) underwent clinical examination; and 339 (13% of total; 46% of those contacted) returned for arterial ultrasound scans (Figure I, available online at http://atvb.ahajournals.org).
Arterial Ultrasound Scan

The right and left carotid and common femoral arterial bifurcations were studied with an Advanced Technology Laboratories HDI (high-definition imaging) 3000 triplex system using a high-resolution broadband-width linear array transducer 7-4 MHz (Phillips Medical Systems). Measurements were made of IMT and plaques, where present, by 1 vascular technologist, blind to infant feeding mode.\(^{14}\) (For full details please see http://atvb.ahajournals.org.)

The common carotid IMT was measured at its thickest point, 1.5- to 2-cm proximal to the flow divider, on the distal wall of the common carotid artery. Bifurcation IMT was defined as described previously.\(^{14}\) In the presence of a plaque, its maximum thickness was measured, and this was taken as the bifurcation IMT. In the absence of a plaque, the IMT measured at the bulb origin was defined as the bifurcation IMT. Plaques were defined at the time of ultrasound measurement as described previously.\(^{14}\)

Statistical Analysis

Associations of breastfeeding with continuously distributed variables were investigated with random-effects linear regression modeling because clustering effects (shared genetic influences on atherosclerosis and propensity to being breastfed) may have arisen because several cohort members belonged to the same families (the 339 subjects were from 261 families). Associations between breastfeeding and the prevalence of plaques were investigated using logistic regression and robust SEs computed to account for clustering. (Please see http://atvb.ahajournals.org for a detailed modeling strategy.) To assess the sensitivity of our conclusions to possible selection bias, we repeated the analyses using inverse probability weighting\(^{19}\) (for details, please see http://atvb.ahajournals.org).

Results

Overall, 182 (45%) men and 223 (55%) women were followed up in clinic, and 155 (46%) men and 184 (54%) women were scanned (Figure 1). Their mean age was 71 years (range 63 to 82) with no sex difference (\(P=0.5\)). Method of infant feeding was available for 362 participants, of whom 272 (75%) were breastfed with no sex difference (\(P=0.7\)). The median duration of breastfeeding was 9 months (IQR, 5 to 9) in both sexes (\(P=0.7\)). This is similar to the prevalence (70%) and median duration (9 months; IQR, 4 to 9) of breastfeeding in the full cohort.\(^{20}\) Breastfed subjects were 284 g (95% CI, 65 to 503) heavier at birth, but there was little difference in infant feeding mode by age, year born, sex, childhood social class, food expenditure, nutrient intake, adult social class, smoking, or alcohol use (Table I, available online at http://atvb.ahajournals.org).

Representativeness

Compared with the remaining surviving survey members (n=2563), clinic participants were 10 months younger at baseline (95% CI, 4 to 14 months), taller (difference in height z score, 0.19; 95% CI, 0.07 to 0.32), more likely to have been breastfed (75% versus 69%), and when they were children, the family per-capita weekly food expenditure was >5 shillings (ie, 25 pence, equivalent to £12.16 at current prices) among 55% of participants versus 41% of nonparticipants. Birth year, sex, birth weight, father’s social class, and childhood body mass index (BMI) were similar whether subjects were followed up or not.

Cardiovascular Disease Risk Factors

In general, there was little evidence of differences in risk factors (adiposity, blood pressure, lipids, or insulin resistance) between breastfed and bottle-fed participants (Table 1). There was some evidence that breastfeeding was associated with lower average glycemia measured by hemoglobin A1c (HbA1c) in those without diabetes (difference −0.07%; 95% CI, −0.17 to 0.02). In models controlling for age, sex, socioeconomic, and behavioral factors and BMI, the difference in HbA1c between breastfed and bottle-fed subjects was −0.12% (95% CI, −0.26 to 0.02; \(P=0.1\)) in all subjects and −0.10% (95% CI, −0.19 to 0.00; \(P=0.05\)) in subjects without diabetes. There was no evidence of an association of breastfeeding with type 2 diabetes (odds ratio [OR], 0.97; 95% CI, 0.41 to 2.30; \(P=0.9\)). There was some evidence of a reduction in odds of being on an antihypertensive drug associated with breastfeeding (OR, 0.67; 0.40 to 1.12; \(P=0.1\)).

Atherosclerosis

In line with other population-based studies,\(^{14}\) the common carotid IMT was normally distributed with means (SD) of 0.79 (0.18) and 0.72 (0.13) mm for men and women, respectively; the mean (SD) bifurcation IMT was 1.82 (0.78) and 1.63 (0.69) mm for men and women, respectively. In age- and sex-adjusted models, breastfeeding was associated with reductions in bifurcation IMT (difference, −0.19; 95% CI, −0.37 to −0.01) and odds of carotid plaque (OR, 0.52; 95% CI, 0.29 to 0.92; Table II, available online at http://atvb.ahajournals.org).

In models controlling for age, sex, and socioeconomic and behavioral factors, breastfeeding was associated with reductions in common carotid (difference −0.03 mm; 95% CI, −0.07 to 0.01) and bifurcation (−0.23 mm; 95% CI, −0.40 to −0.06) IMT compared with bottle-feeding (Table 2). Breastfeeding was also associated with reductions in odds of carotid (OR, 0.45; 0.24 to 0.86) and femoral (0.46; 95% CI, 0.21 to 1.01) plaques (Table 3). Further adjustment for cardiovascular disease risk factors hardly altered the effect estimates, except HbA1c, which attenuated the association between breastfeeding and bifurcation IMT by 13%.

Neither birth weight (a marker for fetal growth), childhood leg length (a marker for childhood growth and adverse exposures during growth),\(^{21}\) nor specific nutrient intakes in childhood confounded the breastfeeding–atherosclerosis associations. There was little evidence of interaction by sex, age at examination, year of birth category, childhood BMI, energy, fat, or saturated fat intake. There was little evidence of a duration-response relationship between breastfeeding and atherosclerosis (Table III, available online at http://atvb.ahajournals.org). The mean difference in bifurcation IMT was 0.12 mm (95% CI, −0.04 to 0.28; \(P=0.16\)) and the OR for carotid plaques was 2.05 (95% CI, 1.03 to 4.08; \(P=0.04\)) per category of increasing breastfeeding duration.
Breastfeeding was inversely associated with atherosclerosis, measured by IMT and plaque prevalence. We also observed a 0.12% reduction in HbA1c in breastfed versus bottle-fed subjects. However, of borderline statistical significance, the findings are of interest for at least 2 reasons. First, the differences in IMT and plaque prevalence associated with breastfeeding were of a similar magnitude to differences seen in smokers versus never-smokers and those with and without evidence of coronary heart disease. Second, the decision to breastfeed in the pre–World War II era was less conscious than mothers who bottle-feed, and the influence of possible confounding factors in recent studies of the socioeconomic confounding at the design stage of this study. In contrast, breastfeeding mothers of children born during the last 30 to 40 years are more educated and more health-conscious than mothers who bottle-feed, and the influence of possible confounding factors in recent studies of the long-term effects of breastfeeding is probably impossible to completely control for. The breastfeeding–atherosclerosis associations were independent of other early life factors, such as birth weight, nutrition, and socioeconomic conditions in childhood, of socioeconomic environment in adulthood, and of factors (smoking and alcohol) operating in later life that

### TABLE 1. Distribution of Cardiovascular Disease Risk Factors by Infant Feeding Mode

<table>
<thead>
<tr>
<th>CHD Risk Factor</th>
<th>Mean (SD)</th>
<th>Mean Difference† (95% CI; breastfed−bottle-fed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adiposity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.45 (4.34)</td>
<td>27.47 (4.69)</td>
</tr>
<tr>
<td>Fat mass index (kg/m²)</td>
<td>9.37 (3.40)</td>
<td>9.42 (3.16)</td>
</tr>
<tr>
<td>Lean mass index (kg/m²)</td>
<td>18.09 (2.13)</td>
<td>18.05 (2.58)</td>
</tr>
<tr>
<td>Fat mass percent</td>
<td>33.27 (7.93)</td>
<td>33.67 (7.18)</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.90 (0.092)</td>
<td>0.91 (0.097)</td>
</tr>
<tr>
<td>Waist/thigh ratio</td>
<td>1.815 (0.218)</td>
<td>1.842 (0.214)</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>147.78 (21.79)</td>
<td>149.02 (23.60)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>82.78 (10.29)</td>
<td>83.24 (9.60)</td>
</tr>
<tr>
<td><strong>Lipid profile</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.75 (1.21)</td>
<td>5.68 (1.16)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.57 (0.42)</td>
<td>1.60 (0.45)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.52 (1.08)</td>
<td>3.40 (0.94)</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)‡</td>
<td>1.32 (0.42)</td>
<td>1.36 (0.45)</td>
</tr>
<tr>
<td>hs-CRP (mg/L)†</td>
<td>2.04 (1.01)</td>
<td>2.17 (1.14)</td>
</tr>
<tr>
<td><strong>Glycemia/insulin resistance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/L)‡†</td>
<td>8.00 (0.59)</td>
<td>8.08 (0.60)</td>
</tr>
<tr>
<td>Insulin resistance (HOMA)‡†</td>
<td>1.90 (0.62)</td>
<td>1.94 (0.63)</td>
</tr>
<tr>
<td>HbA1c (%) all participants†</td>
<td>5.74 (0.58)</td>
<td>5.82 (0.67)</td>
</tr>
<tr>
<td>HbA1c (%) participants not receiving antidiabetic treatment†</td>
<td>5.63 (0.38)</td>
<td>5.70 (0.45)</td>
</tr>
</tbody>
</table>

hs-CRP indicates high-sensitivity C-reactive protein; HOMA, homeostasis model assessment.

*The cluster unit was the family.
†All models for mean differences based on random-effects linear regression and control for sex and age; all models except biochemistry also control for the hour of the examination and field observer; all models with blood pressures as outcomes control, in addition, for arm circumference, room temperature, and the Omron machine used.
‡Values were log transformed; geometric means and logged regression coefficients are presented.
††Two subjects with outlying HbA1c values were omitted.
may be related to healthy upbringing among children of mothers who breastfed.

We were unable to establish a mechanism by which breastfeeding may influence atherosclerosis. We had hypothesized that any association may operate via blood pressure,29 cholesterol levels,1 glycemia, or insulin resistance,3,4 but effect estimates were only altered a little after controlling for glycosylated hemoglobin. However, measurement error may account for this apparent lack of any substantial effect of controlling for these factors. Furthermore, we cannot exclude the possibility that lifelong exposure (as opposed to concurrent risk factor levels) to increased blood pressure, cholesterol levels, or insulin resistance may be underlying mechanisms. Breastfeeding has been associated with a reduced prevalence of arterial plaques in children,8 and cardiovascular disease risk factors measured in childhood are prospectively associated with IMT in adulthood, independently of contemporaneous risk factors.26 Breastfeeding may be more strongly associated with blood pressure, cholesterol levels, glycemia, or insulin resistance much earlier in life, perhaps during the infant feeding period,27,28 protecting against early arterial damage.

Acute and chronic viral/bacterial infections have been associated with atherosclerosis, although the evidence is inconclusive.20 We could not investigate whether breastfeeding protects against atherosclerosis by reducing exposure to persistent infections in infancy.23,30

**Limitations**

First, selection bias is possible because the study was based on a proportion of the original cohort, but it requires that breastfeeding–atherosclerosis associations differ among clinic participants versus nonparticipants. This seems unlikely for the following reasons. Effect sizes were little altered when analyses were reweighted to account for missing values, although models assume data were missing at random. Inverse breastfeeding–ischemic heart disease associations observed during clinic follow-up (OR, 0.88) were also observed among 418 nonclinic participants who returned

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**TABLE 2. Association of Breastfeeding With Carotid and Bifurcation IMT Controlling for Potential Confounding Variables and Risk Factors for Coronary Heart Disease**

<table>
<thead>
<tr>
<th>Cumulative Adjustment</th>
<th>Common Carotid IMT (n=306)</th>
<th>Bifurcation IMT (n=306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.19 (−0.37 to −0.01); P=0.04</td>
</tr>
<tr>
<td>Age, sex, and socioeconomic‡ factors</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.24 (−0.41 to −0.06); P=0.009</td>
</tr>
<tr>
<td>Age, sex, socioeconomic‡ and behavioral¶ factors</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.23 (−0.40 to −0.06); P=0.009</td>
</tr>
<tr>
<td>+ Systolic blood pressure</td>
<td>−0.03 (−0.06 to 0.01); P=0.2</td>
<td>−0.23 (−0.40 to −0.06); P=0.009</td>
</tr>
<tr>
<td>+ BMI</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.23 (−0.40 to −0.06); P=0.008</td>
</tr>
<tr>
<td>+ Waist/hip ratio</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.22 (−0.39 to −0.05); P=0.01</td>
</tr>
<tr>
<td>+ Total cholesterol</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.22 (−0.39 to −0.05); P=0.01</td>
</tr>
<tr>
<td>+ High-sensitivity C-reactive protein§</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.23 (−0.40 to −0.06); P=0.009</td>
</tr>
<tr>
<td>+ HOMA insulin resistance§</td>
<td>−0.03 (−0.07 to 0.01); P=0.1</td>
<td>−0.22 (−0.39 to −0.05); P=0.01</td>
</tr>
<tr>
<td>+ HbA1c</td>
<td>−0.02 (−0.06 to 0.01); P=0.2</td>
<td>−0.20 (−0.37 to −0.03); P=0.02</td>
</tr>
</tbody>
</table>

Regression Coefficients From the Above Models (95% CI; breastfed–bottle-fed)

| Smoking (current or past vs never)                         | 0.02 (−0.02 to 0.05); P=0.4 | 0.27 (0.11 to 0.43); P=0.001 |
| Systolic blood pressure (per 10 mm Hg)                     | 0.02 (0.01 to 0.03); P=0.001 | 0.03 (−0.01 to 0.07); P=0.1 |
| BMI (per quintile)                                         | 0.01 (0.00 to 0.02); P=0.05 | 0.04 (−0.02 to 0.09); P=0.2 |
| Waist/hip ratio (per quintile)                             | 0.00 (−0.01 to 0.01); P=0.9 | 0.06 (0.00 to 0.13); P=0.07 |
| Total cholesterol (per mmol/L)                              | 0.01 (−0.01 to 0.02); P=0.3 | −0.05 (−0.12 to 0.02); P=0.2 |
| High-sensitivity C-reactive protein (per quintile)          | 0.01 (0.00 to 0.02); P=0.2 | 0.06 (0.01 to 0.11); P=0.03 |
| HOMA (per quintile)                                        | 0.00 (−0.01 to 0.02); P=0.6 | 0.03 (−0.02 to 0.09); P=0.3 |
| HbA1c (per %)                                               | 0.03 (0.01 to 0.05); P=0.008 | 0.14 (0.04 to 0.24); P=0.004 |

†Based on random-effects linear regression models.
‡Father’s social class, birth order, household food expenditure in childhood, social class in adulthood, and area where the clinic survey was undertaken.
¶Smoking and alcohol consumption in adulthood (models with alcohol and smoking were based on 304 subjects because of missing data).
+Extra variable in model in addition to age, sex, and socioeconomic and behavioral factors.
§Entered as logged variables.
*Regression coefficients are change in IMT (mm) per unit increase in risk factor. HOMA indicates homeostasis model assessment.
questionnaires (OR, 0.84). Breastfeeding–atherosclerosis associations were similar in those with and without ischemic heart disease, suggesting selection by disease status does not explain the results. Survival bias was an unlikely explanation for the absence of associations with blood pressure, adiposity, or cholesterol levels because there was little evidence of interaction by age. Second, method of infant feeding was obtained when the children were a mean age of 6.3 years, suggesting the possibility of misclassification. However, long-term recall appears to be a valid method of obtaining infant-feeding information up to 20 years earlier.31 Recall bias seems implausible because atherosclerosis was measured prospectively. Third, in line with other historic cohorts, breastfed babies were heavier than bottle babies at birth, suggesting a size-based influence on choice to breastfeed.32 Birth weight has been inversely related to the degree of subclinical atherosclerosis in adulthood,33 pointing to the potential importance of genetic or in utero factors. Although we found little evidence that controlling for birth weight attenuated associations between breastfeeding and atherosclerosis, birth weight was self-reported in a subsample (59%) of the cohort, and residual confounding is possible. The finding that rapid weight gain in the first 2 weeks postnatally is positively associated with insulin resistance,34 and endothelial dysfunction,35 independent of birth weight, supports the suggestion that factors promoting early postnatal growth (eg, formula feeding compared with breastfeeding) might adversely affect later cardiovascular health.7 Finally, the findings may have arisen by chance because we conducted a number of statistical tests. However, an inverse breastfeeding–atherosclerosis relationship was a prespecified, end point–specific hypothesis.

**Generalizability**

Baboon studies suggest that infant feeding method may interact with a diet high in saturated fat in childhood to influence the development of atherosclerosis.3,13 Given subspecies differences in the apolipoprotein A genetic variants

**TABLE 3. Association of Breastfeeding With Carotid and Femoral Plaques Controlling for Potential Confounding Variables and Risk Factors for Coronary Heart Disease**

<table>
<thead>
<tr>
<th>Cumulative Adjustment</th>
<th>OR (95% CI) Carotid Plaques (n=306)</th>
<th>OR (95% CI) Femoral Plaques (n=306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>0.52 (0.29 to 0.92); P=0.03</td>
<td>0.54 (0.26 to 1.12); P=0.1</td>
</tr>
<tr>
<td>Age, sex, and socioeconomic factors</td>
<td>0.47 (0.25 to 0.88); P=0.02</td>
<td>0.47 (0.22 to 1.04); P=0.06</td>
</tr>
<tr>
<td>Age, sex, and socioeconomic and behavioral factors</td>
<td>0.45 (0.24 to 0.86); P=0.02</td>
<td>0.46 (0.21 to 1.01); P=0.05</td>
</tr>
<tr>
<td>+Systolic blood pressure</td>
<td>0.44 (0.23 to 0.84); P=0.01</td>
<td>0.46 (0.21 to 1.00); P=0.05</td>
</tr>
<tr>
<td>+BMI</td>
<td>0.44 (0.23 to 0.84); P=0.01</td>
<td>0.45 (0.20 to 0.99); P=0.05</td>
</tr>
<tr>
<td>+Waist/hip ratio</td>
<td>0.45 (0.24 to 0.86); P=0.02</td>
<td>0.45 (0.20 to 1.00); P=0.05</td>
</tr>
<tr>
<td>+Total cholesterol</td>
<td>0.46 (0.24 to 0.87); P=0.02</td>
<td>0.46 (0.20 to 1.02); P=0.06</td>
</tr>
<tr>
<td>+High-sensitivity C-reactive protein§</td>
<td>0.45 (0.24 to 0.86); P=0.02</td>
<td>0.42 (0.18 to 0.99); P=0.05</td>
</tr>
<tr>
<td>+HOMA insulin resistance§</td>
<td>0.45 (0.24 to 0.86); P=0.02</td>
<td>0.46 (0.21 to 1.01); P=0.05</td>
</tr>
<tr>
<td>+HbA1c</td>
<td>0.50 (0.26 to 0.96); P=0.04</td>
<td>0.45 (0.20 to 1.00); P=0.05</td>
</tr>
</tbody>
</table>

| Smoking (current or past vs never)                                                   | 1.54 (0.87 to 2.73); P=0.1          | 1.67 (0.95 to 2.94); P=0.08          |
| Systolic blood pressure (per 10 mm Hg)                                              | 1.24 (1.08 to 1.42); P=0.003        | 1.07 (0.92 to 1.24); P=0.4           |
| BMI (per quintile)                                                                   | 1.13 (0.93 to 1.37); P=0.2          | 1.08 (0.86 to 1.36); P=0.5           |
| Waist/hip ratio (per quintile)                                                       | 1.36 (1.08 to 1.69); P=0.008        | 1.03 (0.79 to 1.33); P=0.9           |
| Total cholesterol (per mmol/L)                                                       | 0.81 (0.63 to 1.05); P=0.1          | 0.99 (0.77 to 1.27); P=0.9           |
| High-sensitivity C-reactive protein (per quintile)                                   | 1.33 (1.10 to 1.61); P=0.003        | 1.30 (1.05 to 1.61); P=0.02          |
| HOMA (per quintile)                                                                  | 1.31 (1.06 to 1.62); P=0.01         | 0.93 (0.73 to 1.18); P=0.6           |
| HbA1c (per %)                                                                         | 1.71 (1.18 to 2.48); P=0.005        | 0.93 (0.65 to 1.34); P=0.7           |

†Based on robust standard errors.
‡Father’s social class, birth order, household food expenditure in childhood, social class in adulthood, and area where the clinic survey was undertaken.
¶Smoking and alcohol consumption in adulthood (models with alcohol and smoking were based on 304 subjects because of missing data).
§Extra variable in model in addition to age, sex, and socioeconomic and behavioral factors.
"Entered as logged variables.
*ORs are change in odds of plaque per unit increase in risk factor.
HOMA indicates homeostasis model assessment.
and levels of lipoprotein A, and a lack of data from other primates, it is possible that these findings are specific for this particular subspecies of baboon and thus have little relevance to humans. However, an influence of breastfeeding in humans may depend on later dietary patterns, which are now very different from those in the early 20th century. We found no interactions by childhood BMI, energy, fat, or saturated fat intake on breastfeeding–atherosclerosis associations, although power to detect these was limited.

Artificial feeds in the 1920s to 1930s were largely based on unmodified cow’s milk. Unlike formula milks of today (low in cholesterol, saturated fatty acid, and sodium), unmodified cow’s milk (unless it was diluted) had a high sodium concentration (low in breastmilk) but more closely resembled the cholesterol and saturated fatty acid content of mature breastmilk. Distinct associations with particular components of artificial feeds (such as differences in salt content) may produce different results in contemporary versus historic cohorts. Other differences between the composition of breast milk and cow’s milk and modern formula feeds in hormones (eg, leptin and thyroxine), immunoglobulins, and nucleotides might be important. Altered hormonal responses to breast and formula feeds, for example, different insulin and growth factor effects may explain variations in outcomes in later life. We had no information on breastfeeding exclusivity and do not know whether results differ among infants who were exclusively or partially breastfed.

Comparison With Other Studies

In line with our findings, a postmortem study in young adults found lower rates of coronary atheroma among those breastfed (25%) compared with those artificially fed (60%). In Hertfordshire, men who had been partially or exclusively breastfed <1 year had lower standardized mortality ratios (SMRs; 73 and 79, respectively) compared with those who had been exclusively breastfed for >1 year (SMR, 97) or exclusively bottle-fed (SMR, 95). The results are in line with data from a recently published study on 87 252 participants in the Nurses Health Study, born between 1921 and 1946. Ever having been breastfed was associated with an 8% to 10% reduction in risk of coronary heart disease and stroke; the reduction in risk of coronary heart disease was 16% for women breastfed >9 months. However, other studies have found no association between breastfeeding and coronary artery plaques among young accident victims at postmortem, nonfatal myocardial infarction, and cardiovascular or coronary heart disease mortality. Small sample size and selection bias are a concern with these studies. We have shown recently no association of breastfeeding with ischemic heart disease mortality (hazard ratio, 1.02) in the Boyd Orr cohort. Although breastfeeding may influence subclinical atherosclerosis, other factors may be important for survival among those with disease.

The inverse relationship between breastfeeding and HbA1c, a measure of average glycaemia, concurs with 2 studies showing lower levels of impaired glucose tolerance and type 2 diabetes in adult life among breastfed subjects. We observed differences in systolic and diastolic blood pressure of −1.62 mm Hg and −0.74 mm Hg, respectively, between breastfed and bottle-fed subjects, in line with a recent meta-analysis. However, the current study was only powered to detect differences of 6.5 mm Hg systolic and 3.2 mm Hg diastolic blood pressure. Despite recent interest in the relationship between breastfeeding and obesity, our findings indicate no evidence of any such association.

Breastfeeding is associated with a reduction in atherosclerosis, but the mechanism is unclear. Prospective investigations of the association between breastfeeding and ischemic heart disease are lacking. Furthermore, such studies would have to be prohibitively large and long term to detect small but (on a population level) important reductions in ischemic heart disease. Approximately 40% of infants are never breastfed in the United Kingdom. In the absence of prospective evidence, this study suggests the possibility that the promotion of breastfeeding could be a potential component of the public health strategy to reduce future levels of ischemic cardiovascular disease. However, further studies in large adult populations are needed to confirm these findings. In particular, the hypothesis that breastfeeding influences later cardiovascular disease risk factors could ethically and feasibly be tested on an intention-to-treat basis in large controlled trials of successful breastfeeding promotion interventions with long-term follow-up.

Acknowledgments

The Wellcome Trust funded R.M.M. to undertake the clinical follow-up as part of a research training fellowship in clinical epidemiology (grant GR063779/FR). The arterial ultrasound scans were performed and analyzed with funding by the British Heart Foundation (BHF: project grant PG/02/125). We are very grateful to the cohort members who participated so willingly in the follow-up study. We also acknowledge all the research workers in the original survey in 1937-9. Susie Potts is thanked for all her hard work in providing secretarial and administrative support to the study. The hypothesis was developed by D.G., G.D.S., R.M.M., S.E., and S.E. The fieldwork was conducted by R.M.M., N.G., M.G., and S.W. under the direction of a steering group (S.E., G.D.S., D.G., and J.H.). A.N. provided expert advice on the conduct and analysis of the arterial scans. N.G., M.G., and A.N. analyzed the ultrasound scan data. R.M.M. did the statistical analysis, wrote the first draft and coordinated completion of the article. R.M.M. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically commented on and edited earlier drafts and approved the final version of this article.

References

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Breastfeeding and atherosclerosis: intima-media thickness and plaques at 65 year follow up of the Boyd Orr Cohort

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Methods

The Boyd Orr cohort has been described in detail. Briefly, it comprises 4,999 participants from 1,343 families in 16 centres in England and Scotland who participated in a one week survey of diet and health when aged 0-19 years between 1937-1939. The National Health Service Central Register (NHSCR) was used to trace 4,379 (88%) individuals. The trace rate has increased slightly since earlier publications, following further searches of archived records, contacts with study members and additional notifications from the NHSCR.

Between 1997-8 all 3,182 traced survivors were sent health and lifestyle questionnaires. Of the 1,648 responses, 1,378 (84%) consented to further follow-up. In February 2002, 2,563 of the original cohort were alive and living in Britain. 1295 (51%) participants who had consented to further follow-up were known to be still alive and contactable. We contacted all 732 (29%) participants living near clinics in Bristol, London, Wisbech, Aberdeen and Dundee and 85% (n=619) responded, of whom 405 (16% of total, 55% of those contacted) underwent clinical examination and 339 (13% of total, 46% of those contacted) returned for arterial ultrasound scans (Figure 1). Ethical approval was obtained from MREC Scotland. All participants gave informed consent.

VARIABLES AT BASELINE

Method of infant feeding (any breastfeeding and its duration, or exclusively bottle fed) was obtained by direct questioning of mothers at the time of the original survey. Age at baseline, sex, per-capita weekly household food expenditure, number of children in the house, and survey district were obtained
Birth order was based on the child’s position amongst the children living in the household during the survey. Social class of the head of the household was assigned using the Registrar General’s 1931 classification. Internally age and sex standardised z-scores for measured childhood height, leg-length and body mass index (BMI) were available. Childhood nutrient intake was derived from 7 day household diet diaries. Measured birth weights were obtained from original maternity records for 56 of the current study members. Data on self-reported birthweight from the 1997-1998 questionnaire was also available (n = 210), and overall 237 (59%) of the 405 study participants had data on measured or self reported birthweight.

CLINIC MEASUREMENTS

*Anthropometry:* Weight and body composition (body fat, fat mass, fat free mass) were measured by leg-to-leg bioimpedence using the Tanita TBF 300 body-fat analyser (Tanita Corp, Tokyo, Japan). Height and sitting height, and waist (midway between lower ribs and iliac crests in relaxed exhalation), hip (point of maximum circumference) and right mid-thigh (midway between lateral inguinal fold and mid-patella) circumferences were measured. Circumference values used in the analyses were based on the mean of two measurements. Body mass, fat mass and lean (fat-free) mass indices were defined as weight (kg)/height (m^2), fat mass (kg)/height (m^2) and lean mass (kg)/height (m^2), respectively. Waist-hip and waist-thigh ratios were defined as the mean waist circumference divided by the mean hip/thigh circumference, respectively.
Risk factors for cardiovascular disease and type 2 diabetes: A history of diabetes, hypertension and ischaemic heart disease, use of diabetes and anti-hypertensive medication, cigarette smoking and alcohol consumption were determined by questionnaire. Social class in adulthood was based on the subject’s (for men and unmarried women) or spouse’s (women) main employment, classified using the 1966 Classification of Occupations. Supine blood pressure was measured twice after 5 minutes rest using an automated oscillometric monitor (OMRON HEM-705CP; Omron, Matsusaka Co, Japan). Values of systolic, diastolic and ankle systolic blood pressures were based on the mean of two measurements. After a minimum 6-hour fast, bloods were taken for insulin (using an insulin-specific assay that does not cross-react with proinsulin and split forms of proinsulin), glycosylated haemoglobin (HbA1c), glucose, total cholesterol, HDL-cholesterol, triglycerides and high sensitivity C-reactive protein (a marker of the low grade inflammatory response associated with atherosclerosis); we calculated LDL-cholesterol using the Friedewald-Fredrickson formula.7

Diabetes was defined as self-reported diabetes and/or a fasting glucose concentration ≥ 7 mmol/l. Insulin resistance was estimated by homeostasis model assessment (HOMA) as the product of fasting glucose (mmol/l) and insulin (µU/ml) divided by 22.5.8 HOMA scores were not calculated for those with fasting glucose ≥ 7 mmol/l or with diagnosed diabetes as the results are inaccurate in these groups.8

ARTERIAL ULTRASOUND SCAN
The right and left carotid and common femoral arterial bifurcations were studied with an Advanced Technology Laboratories HDI (high-definition imaging) 3000 triplex
system using a high-resolution broadband width linear array transducer 7-4 MHz (Phillips Medical Systems, Reigate, UK). Measurements were made of IMT and plaques, where present, of the carotid and femoral arteries by one vascular technologist, blind to infant feeding mode, as previously described. After the carotid and common femoral artery bifurcations were localized by a transverse scan, the probe was rotated 90° to obtain and record a longitudinal image of both the anterior and posterior artery walls. The carotid bifurcation was examined over a length of 3 cm (1.5 cm proximal and distal to the flow divider) for plaques. The common carotid IMT was measured at its thickest point 1.5-2 cm proximal to the flow divider, on the distal (far) wall of the common carotid artery (i.e. if the thickest point was at 1.6 cm, this point was measured). IMT was also measured at the origin of the bulb, which was defined as the point at which the arterial wall diverges to form the bulb. Bifurcation IMT was defined for each individual as in a previous report. In the presence of a plaque, its maximum thickness was measured, and this was taken as the bifurcation IMT; in the absence of a plaque, the IMT measured at the bulb origin was the thickest part of the intima-media complex and was defined as the bifurcation IMT. The common femoral artery was examined at the femoral bifurcation and scanned for a length of about 3 cm (1.5 cm proximal and distal to the flow divider). The common femoral IMT was measured at its thickest point just above the bifurcation on both left and right sides.

For each participant the mean of the specified measurements made of the left and right common carotid IMT and the mean bifurcation IMT of both left and right carotid bulb origin measurements, including plaque, were used in analyses. An artery was classified as affected by plaque if there was a localized thickening in excess of 1.2
mm and increased density involving all ultrasonic layers, with or without flow
disturbance. Plaques were identified at the time of ultrasound measurements. In the
analysis, patients were classed as having a carotid plaque if one was identified on one
or both carotid arteries and a femoral plaque if on one or both femoral arteries.

In 24 subjects repeat arterial ultrasound measures were taken 1-3 months apart. The
intra-observer absolute mean difference between repeat measures of carotid IMT
(bias) was 0.02 mm, the within-subject standard deviation was 0.08 mm and the intra-
class correlation coefficient was 0.846. For bifurcation IMT the corresponding values
were 0.31 mm, 0.34 mm and 0.722. The levels of bias are similar to intra-observer
mean differences in carotid (0.06–0.13 mm) and bifurcation IMT (0.15-0.66 mm)
found in other reproducibility studies. The within-subject standard deviation and
intra-class correlation coefficient for carotid IMT compares favourably with other
studies (standard deviations: 0.08 mm and 0.12 mm; intra-class correlation
coefficient: 0.74).

STATISTICAL ANALYSIS
Associations of breastfeeding with baseline variables were investigated using $\chi^2$ tests,
t-tests and the two-sample Wilcoxon rank-sum test as appropriate. Insulin,
triglyceride, C-reactive protein, and HOMA scores were log transformed because of
their skewed distribution. Clustering effects may have arisen because several cohort
members belonged to the same families (the 339 subjects were from 261 families).
Associations of breastfeeding with continuously distributed variables were therefore
investigated with random effects linear regression modelling using the maximum
likelihood estimator. This allows for a between family component of variation in
mean values (e.g. of IMT) which may arise as a result of shared genetic influences on atherosclerosis and propensity to being breastfed. Associations between breastfeeding and the prevalence of carotid and femoral plaques were investigated using logistic regression, and robust standard errors computed to account for clustering.

All basic regression models control for sex and age at clinical examination. To standardise conditions of measurement, all adiposity and blood pressure models control for the time of the examination and the field observer; all models involving brachial or ankle blood pressure control in addition for arm circumference, room temperature, and the Omron machine used. Multivariable models controlled additionally for social class, birth order, and household food expenditure in childhood; social class, smoking and alcohol in adulthood; and clinic location. To assess possible mechanisms underlying associations of breastfeeding with atherosclerosis, separate models controlled – in addition to the above variables – for the following factors: systolic blood pressure, total cholesterol, HOMA insulin resistance, HbA1c, body mass index, waist-hip ratio and C-reactive protein.

There was little evidence of sex differences in breastfeeding-atherosclerosis associations and results are presented for men and women combined. Since baboon studies suggest that infant-feeding method may interact with a diet high in saturated fat in childhood to influence the development of atherosclerosis, the possibility of effect-modification by childhood BMI, energy, fat and saturated fat intake (dichotomised at the median) was examined using likelihood ratio tests. Since changes in the social environment or alternatives to breastfeeding may have occurred between 1918-1939, interaction by year of birth (binary variable split at the median,
1932) was assessed. To assess possible selection and survival biases, we tested for interaction by presence/absence of clinical ischaemic heart disease (those with disease may have been less likely to attend clinics) and by quartiles of age at examination.

SENSITIVITY ANALYSIS
To assess the sensitivity of our conclusions to possible selection bias we repeated the analyses using inverse probability weighting. Observations are weighted by the inverse of the probability of observing a response, giving greater weight to subjects with an increased probability of missing observations. The weighted analysis was implemented by creating a binary response that was 1 if the subjects were followed-up in the clinic (n = 405) and 0 if a potentially eligible surviving survey member was not followed up (n = 2563). A logistic regression model was used to identify predictors of clinic follow-up, using as covariates variables collected during the original survey (age, father’s social class, per capita family food expenditure, whether ever breastfed, survey district, birth order and number of children in the house). This model calculates the probability of an observation being present. Subject-specific weights were calculated as the inverse of the fitted probabilities from the logistic regression model, normalised to sum to one. The analytical models were then refitted with the observed data weighted using these inverse probability weights. To assess whether possible selection bias related to non-response per-se rather than place of residence, we repeated this analysis using study area non-respondents (n = 327). Analyses were carried out using Stata.
Original cohort alive & living in Britain in 2002
n = 2563

Consented to follow-up, alive & contactable
n = 1295 (51%)

Living near clinics in Bristol, London, Wisbech, Aberdeen and Dundee
n = 732 (29%)

No. of respondents: n = 619

Did not wish to participate: n = 165
Agreed to discuss possible participation: n = 454

Seen in clinical follow up study: n = 405 (16% of total, 55% of those contacted)

No. who underwent arterial ultrasound scan: n = 339 (13% of total, 46% of those contacted)

No. scanned with data on method of infant feeding: n = 306
## Table I: Distribution of breastfeeding in clinic study sample (n=362)

<table>
<thead>
<tr>
<th></th>
<th>Breastfed (n=272)</th>
<th>Bottle fed (n=90)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age at clinic follow up (yrs)</td>
<td>70.7 (4.15)</td>
<td>70.4 (4.14)</td>
<td>0.6†</td>
</tr>
<tr>
<td>Year of birth (median, IQR)</td>
<td>1932 (1928 to 1935)</td>
<td>1932 (1930 to 1935)</td>
<td>0.6‡</td>
</tr>
<tr>
<td>Female</td>
<td>56%</td>
<td>58%</td>
<td>0.7§</td>
</tr>
<tr>
<td>Birthweight* (kg)</td>
<td>3.51 (0.62)</td>
<td>3.23 (0.93)</td>
<td>0.01†</td>
</tr>
</tbody>
</table>

Mean (SD) daily per capita nutrient intake in childhood

- **Energy (MJ)**: 9.60 (2.39) vs. 9.76 (2.46), p-value 0.6†
- **Protein (g/MJ)**: 6.89 (0.69) vs. 6.76 (0.62), p-value 0.1†
- **Fat (g/MJ)**: 8.91 (1.55) vs. 8.78 (1.89), p-value 0.5†
- **Saturated fat (g/MJ)**: 3.74 (0.92) vs. 3.65 (1.06), p-value 0.4†
- **Carbohydrate (g/MJ)**: 34.66 (3.63) vs. 35.12 (4.42), p-value 0.3†
- **Vitamin C (mg/MJ)**: 4.00 (1.98) vs. 3.57 (1.86), p-value 0.07†
- **Vitamin E (mg/MJ)**: 0.42 (0.17) vs. 0.40 (0.19), p-value 0.3†

Clinic site

- **London & Bristol**: 53 vs. 39
- **Scotland**: 36 vs. 49
- **Wisbech**: 11 vs. 12, p-value 0.07§

Father’s social class

- **I/II**: 5 vs. 9
- **III**: 23 vs. 31
- **IV**: 25 vs. 19
- **V**: 20 vs. 13
- **Unemployed**: 21 vs. 23
- **Unclassifiable**: 7 vs. 4, p-value 0.2§

Per capita weekly household food expenditure (shillings & pence)

- **< 3s**: 4 vs. 11
- **3s-4s 11.75d**: 40 vs. 34
- **5s-6s 11.75d**: 32 vs. 30
- **> 7s**: 25 vs. 24, p-value 0.06§
<table>
<thead>
<tr>
<th></th>
<th>Breastfed (n=272)</th>
<th>Bottle fed (n=90)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Social class in adulthood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>35</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>44</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>IV/V/armed forces/unclassified*</td>
<td>21</td>
<td>20</td>
<td>0.9†</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or past smoker</td>
<td>54</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>46</td>
<td>44</td>
<td>0.9†</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumes weekly</td>
<td>49</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Consumes occasionally or never</td>
<td>51</td>
<td>52</td>
<td>0.9†</td>
</tr>
</tbody>
</table>

*Unpaired t-test. †Wilcoxon ranksum test. ‡χ² test for heterogeneity using appropriate degrees of freedom. *Based on combining self-report and measured birthweights. †No. in Bristol was 7. ‡Armed forces: n=6; unclassifiable: n = 6. **Two people had missing data on alcohol and smoking.
Table II: Distribution of sub-clinical atherosclerosis by infant feeding mode.

<table>
<thead>
<tr>
<th></th>
<th>Mean (standard deviation)</th>
<th>Mean difference† (95% CI) (breastfed minus bottle fed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (clusters*)</td>
<td>Breastfed</td>
</tr>
<tr>
<td>Common carotid IMT (mm)</td>
<td>306 (237)</td>
<td>0.74 (0.15)</td>
</tr>
<tr>
<td>Bifurcation IMT (mm)</td>
<td>306 (237)</td>
<td>1.68 (0.72)</td>
</tr>
</tbody>
</table>

Number (%)

<table>
<thead>
<tr>
<th></th>
<th>Breastfed</th>
<th>Bottle fed</th>
<th>Odds ratio (95% CI)† (breastfed vs bottle fed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid plaque</td>
<td>306</td>
<td>136/226 (60)</td>
<td>58/80 (73)</td>
</tr>
<tr>
<td>Femoral plaque</td>
<td>306</td>
<td>168/226 (74)</td>
<td>66/80 (83)</td>
</tr>
</tbody>
</table>

*The cluster unit was the family. †All models for mean differences based on random effects linear regression and control for sex and age; ‡Logistic regression models control for age at examination and sex and confidence intervals are based on robust standard errors to control for clustering.
Table III: Associations of duration of breastfeeding with atherosclerosis

<table>
<thead>
<tr>
<th>CHD risk factor</th>
<th>Bottle-fed</th>
<th>&lt; 6 months</th>
<th>6-11 months</th>
<th>≥ 12 months</th>
<th>P for trend‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=80</td>
<td>n=44</td>
<td>n=100</td>
<td>n=15</td>
<td></td>
</tr>
<tr>
<td>Carotid IMT (mm)</td>
<td>ref</td>
<td>-0.03 (0.03)</td>
<td>-0.03 (0.02)</td>
<td>-0.05 (0.04)</td>
<td>0.5</td>
</tr>
<tr>
<td>Bifurcation IMT (mm)</td>
<td>ref</td>
<td>-0.36 (0.12)</td>
<td>-0.19 (0.10)</td>
<td>-0.12 (0.18)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Odds ratio† (SE§)(breastfed vs bottle-fed)

<table>
<thead>
<tr>
<th>CHD risk factor</th>
<th>Bottle-fed</th>
<th>&lt; 6 months</th>
<th>6-11 months</th>
<th>≥ 12 months</th>
<th>P for trend‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=80</td>
<td>n=44</td>
<td>n=100</td>
<td>n=15</td>
<td></td>
</tr>
<tr>
<td>Carotid plaques</td>
<td>ref</td>
<td>0.22 (0.10)</td>
<td>0.60 (0.23)</td>
<td>0.65 (0.38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Femoral plaques</td>
<td>ref</td>
<td>0.47 (0.27)</td>
<td>0.45 (0.21)</td>
<td>0.12 (0.09)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Numbers in this analysis are reduced as unknown duration of breastfeeding is excluded. †Controlling for father’s social class, birth order, household food expenditure in childhood, social class in adulthood, area where the clinic survey was undertaken, smoking and alcohol intake in adulthood. ‡Compares subjects who were breastfed for 6+ months vs those breastfed but for < 6 months. §Robust standard errors.


