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Breastfeeding and cardiovascular mortality: the Boyd Orr cohort and a systematic review with meta-analysis

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Aims To investigate the association of breastfeeding with all-cause, cardiovascular, and ischaemic heart disease mortality.
Methods and results A long-term follow-up of 4999 children originally surveyed from 1937 to 1939 was undertaken (Boyd Orr cohort). Four thousand three hundred and seventy-nine subjects (88%) were traced in adulthood and 3555 (71%) had complete data on all covariates. The results were combined with a meta-analysis of the published literature. In the Boyd Orr study, there was little evidence that breastfeeding was associated with all-cause (hazard ratio: 1.04 [95% CI: 0.90–1.20]), cardiovascular (1.04 [0.83–1.30]), or ischaemic heart disease (1.02 [0.77–1.36]) mortality, compared with bottle-feeding. Meta-analyses of observational studies showed little evidence of an association of breastfeeding with all-cause (pooled rate ratio: 1.01 [95% CI: 0.91–1.13]) or cardiovascular (1.06 [0.94–1.20]) mortality. There was a moderate-to-high degree of between-study heterogeneity for the association between breastfeeding and ischaemic heart disease mortality (I^2 value–indicating the degree of between-study variation attributable to heterogeneity–66%), and estimates were consistent with both an important beneficial or adverse effect of breastfeeding.
Conclusion There is little consistent evidence that breastfeeding influences subsequent all-cause or cardiovascular disease mortality. Results from other well-designed cohorts may clarify residual uncertainty.

Introduction

There is increased interest in the association between nutritional exposures in early life and future risk of cardiovascular disease.[1] Having been breastfed as an infant is associated with lower levels of adiposity and insulin resistance in infancy,[2] and with increased stature.[3] Breastfeeding may, therefore, be an early-life exposure that influences future health. Some support for this idea comes from epidemiological studies linking breastfeeding with lower levels of cholesterol,[4] blood pressure,[5] insulin resistance[6,7] and atherosclerosis.[8] Results are mixed,[9] and in the yellow baboon breastfeeding is associated with atherosclerosis.[10]

We investigated the association of breastfeeding with all-cause and cardiovascular mortality in a 65-year

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follow-up of the Boyd Orr cohort, and conducted a systematic review of studies of cardiovascular mortality in breastfed and formula-fed infants. The Boyd Orr cohort involved subjects born between 1918 and 1939, an era when social and educational factors played little part in a mother's decision to breast or bottle-feed.[11] Therefore, confounding by social, educational and economic factors is likely to be less of an issue than in more recent cohorts.[12]

Methods

The Boyd Orr cohort

The methods used in the Boyd Orr cohort have been described previously.[13] Briefly, the cohort comprises 4999 children from 1352 families living in 16 urban and rural districts in Britain who underwent a one-week assessment of family diet and health in 1937–1939.[14] Using the National Health Service Central Register (NHSCR), we traced 4379 (88%) of the original study members. The trace rate has increased slightly since earlier publications, as a result of further searches of archived records, contacts with surviving study members, and additional notifications from the NHSCR.

The method of infant feeding, age, sex, per-capita weekly income and household food expenditure, number of siblings, and survey district were obtained from the original survey material.[14] The method of infant feeding was coded as ever breastfed or never breastfed. The duration of breastfeeding was coded as: $\leqslant$5 months; 6–11 months; $\geqslant$12 months; and unknown. Birth-order was based on the child's position amongst the children living in the household at the time of the survey.[13] The social class of the head of the household was assigned using the Registrar General's 1931 classification.[13] The Townsend score, an ecological measure of socioeconomic deprivation, was based on levels of unemployment, car ownership, housing tenure, and overcrowding at the time of the 1991 census in the Health Authority area of residence of each subject in 1998 or at the time of the subject's emigration or death.

Cause of death was defined by the International Classification of Diseases, Ninth (ICD-9) or Tenth (ICD-10) Revision. Cause-specific categories of death investigated were cardiovascular disease (ICD-9: 390–459; ICD-10: I00–I99); ischaemic heart disease (ICD-9: 410–414; ICD-10: I20–I25); and cerebrovascular disease (ICD-9: 430–438; ICD-10: I60–I69).

Systematic review

We conducted a systematic search of all published papers, letters, abstracts, and review articles on infant feeding and cardiovascular disease in the MEDLINE and Excerpta Medica (EMBASE) bibliographic databases from their inception up to April 2003. We employed a combined text word and MeSH heading search strategy, including terms for infant nutrition, bottle-feeding, human milk, breastfeeding, weaning, infant-feeding, early nutrition, cardiovascular disease, myocardial ischaemia, vascular disease, and coronary disease (Appendix). We manually searched reference lists of all retrieved studies. Articles were considered eligible for inclusion in the current review if infants who had been breastfed were compared with those who had been bottle (artificially) fed, if the outcome was cardiovascular disease or ischaemic heart disease mortality, and if estimates of the association between having been breastfed in infancy and cardiovascular disease or ischaemic heart disease mortality could be obtained from the paper or after correspondence with the authors. We also included results from an analysis of the Caerphilly cohort, which is in press.[15]

Statistical analysis

Boyd Orr cohort

Associations of breastfeeding with potential confounding variables were investigated using the χ^2 test, t test, two-sample Wilcoxon rank-sum (Mann–Whitney) test, and logistic regression as appropriate. The relation of breastfeeding with mortality was investigated using Cox's proportional hazards models. Subjects who were never breastfed formed the reference group. For this analysis, follow-up was censored on 28 February 2003. Subjects who had been traced but with whom contact via the NHS central register had been lost after 1948 (for example, if the subject is not currently registered with a Health Authority doctor), or who emigrated or died are included in the survival analysis up to the date of death, emigration, or their last contact. Since age is a strong determinant of mortality risk and individuals entered the study at different ages and over a two-year period (1937–1939), we controlled for current age in all models using age as the follow-up time scale.

As both the prevalence of breastfeeding[3] and mortality rates differed substantially between survey areas, all models were stratified by survey district. Since clustering effects may have arisen because several cohort members belonged to the same families and, therefore, shared childhood conditions and possible genetic effects on mortality, we calculated robust standard errors to allow for a between-family component of variation. The analysis controlling for age, sex, survey district, and within-family clustering forms the simple model presented in the results.

Multivariable models were developed which controlled additionally for the social class of the child's father, the Townsend score for area of residence in adulthood, and the child's birth order. We then investigated whether controlling additionally for family income, household food expenditure, the number of children in the household, or year-of-birth group (four-level categorical variable split at 1 January 1925, 1930, and 1935) influenced associations of breastfeeding with the mortality outcomes. Survival analyses were based on the 3555 subjects (1739 males and 1816 females) with complete data on all covariates.

The proportional hazards assumption was investigated by testing the constancy over time of the log hazard ratio for each model.[16] We assessed whether the effect of breastfeeding on total and cause-specific mortality differed according to sex using the likelihood ratio test (fully adjusted models). Since baboon studies suggest that breastfeeding may interact with post-weaning diet to influence the development of atherosclerosis,[10] we tested for interaction by childhood body mass index (dichotomised at the median). Finally, changes in feeding patterns, for example, with respect to the exclusivity of breastfeeding or alternatives to breastfeeding, may have occurred over the range of years of birth of the subjects (1918–1939). Therefore, we also tested for interaction by year-of-birth category.

Systematic review

A meta-analysis comparing any or exclusive breastfeeding with exclusive bottle-feeding in relation to total, cardiovascular, and ischaemic heart disease mortality was conducted. If results for both any or exclusive breastfeeding were presented in the paper, the exclusive breastfeeding association was used in the meta-analysis. The rate ratio and standard error of the rate ratio

were analysed. To assess the impact of prolonged breastfeeding, separate meta-analyses comparing any or exclusive breastfeeding >1 year with bottle-feeding were undertaken.

Additional unpublished data from the Hertfordshire cohort[17,18] were obtained, with follow-up to 31 December 1999 and including results for both men and women for mortality due to cardiovascular disease (ICD-9: 390–459) and ischaemic heart disease (ICD-9: 410–414) (Syddall H, MRC Environmental Epidemiology Unit, personal communication 2003). These data are therefore an update of results previously published in 1992[17] and 1993.[18] The paper in 1992[17] was based on only part ($n = 5718$) of the cohort of men that were ultimately traced ($n = 10,374$), and the 1993 paper was only for mortality follow-up to the end of 1992.[18] The updated results based on a fuller follow-up of the whole Hertfordshire cohort are used in this meta-analysis, with written permission.

Unlike randomised controlled trials, no generally accepted lists of appropriate quality criteria for observational studies are available. We chose a priori not to use a simple quality score, which might be arbitrary, but assessed specific aspects of the quality of each study, including control of confounding, loss to follow-up, recall bias, definition of breastfeeding, and sample size.

Cochran's Q statistic was used to test for between-study heterogeneity in estimates.[19] Since this test has a low power for detecting heterogeneity when the number of studies is small, we also calculated the I^2 test (Q statistic minus degrees of freedom, divided by Q statistic) as a quantitative measure of the degree of inconsistency across studies that is not dependent on the number of studies.[20] An I^2 value of 0% indicates no observed heterogeneity and larger values reflect increasing heterogeneity. Since it is feasible that any true effect of breastfeeding differs according to its duration or exclusivity, the population studied, or the era in which subjects were born (aspects of generalisability), we pooled estimates using random effects models.

We used two-sided tests of significance and the precision of our estimates was based on 95% confidence limits throughout. No formal statistical approaches to account for multiple hypothesis testing were used, but we have quoted exact rather than threshold p-values. All analyses were performed using Stata 8.0[19].

Results

Boyd Orr cohort

The 4379 survey participants traced (2163 men; 2216 women) and included in this analysis contributed 213,471 person-years of observation between 1 January 1948 and 28 February 2003. A total of 3861 (88%) cohort subjects had a record of the method of infant feeding. Of these, 2717 (70%) were breastfed. The mean age of subjects at the time of the survey and, hence, the age at which the infant feeding method was recorded, was 7.1 years (SD: 4.1 years; range: from 24 days to 19.6 years), and did not differ by whether subjects were breastfed (6.9 years) or bottle-fed (7.1 years) ($p = 0.2$). The prevalence of breastfeeding initiation and duration did not differ by sex (Table 1) and was similar amongst infants born in the 1920s or earlier (71%) and 1930s (70%) ($p = 0.2$). The median duration of breastfeeding was 9 months (range: up to 24 months for males and 25 months for females) (Table 1). As reported in a previous publication,[3] the prevalence of breastfeeding varied according to geographical location (range: 50–80%) and was associated with a greater weekly per capita household income and expenditure on food, but not with childhood social class.

By 28 February 2003, 760 of the men (35%) and 511 of the women (23%) had died. Amongst males, 355 (47%) had died from cardiovascular disease, 260 of them from ischaemic heart disease and 55 from cerebrovascular disease. Amongst females, 182 (36%) had died from cardiovascular disease, 88 of them from ischaemic heart disease and 48 from cerebrovascular disease.

We found no evidence that either breastfeeding initiation or duration were associated with total or cardiovascular disease mortality in simple or fully adjusted models (Table 2). Additional adjustments for year-of-birth category, number of children in the household, weekly household income, or weekly expenditure on food made little difference to hazard ratios relating breastfeeding to total and cause-specific mortality (data not shown). Sex-specific hazard ratios for associations of ever having been breastfed with mortality were calculated for comparison with studies included in the meta-analysis. Amongst males, the fully adjusted hazard ratio for all-cause mortality was 1.09 (95% CI: 0.90–1.32) and for females was 0.93 (0.75–1.16). The hazard ratio for cardiovascular disease mortality amongst males was 1.02 (0.77–1.36) and for females was 1.07 (0.75–1.53). Finally, the hazard ratio for ischaemic heart disease mortality amongst males was 0.90 (0.65–1.24) and for females was 1.40 (0.82–2.39). There was little statistical evidence, however, of sex differences in associations

Table 1 Percentage distribution of breastfeeding initiation and duration

Breastfeeding duration	Male ($n = 1891$)	Female ($n = 1970$)	p-value
Never breastfed	30	29	
Any breastfeeding	70	71	0.5[a]
Total months breastfed			
⩽5	16	16	
6–11	25	25	
⩾12	5	6	
Duration not stated	24	23	0.5[a]
Median duration (IQR)[b] in months	9 (3–9)	9 (4–9)	0.5[c]

[a] p-value for differences in breastfeeding between males and females calculated using χ^2 test.
[b] IQR: interquartile range.
[c] Two-sample Wilcoxon rank-sum (Mann–Whitney) test.

Table 2 Hazard ratios (95% CIs[a]) for the association of breastfeeding initiation and duration with total and cause-specific mortality (up to 28 February 2003) amongst 3555 subjects with full data

Duration of breastfeeding	All causes ($n = 944$)	Cardiovascular disease ($n = 393$)	Ischaemic heart disease ($n = 258$)	Stroke ($n = 73$)
Simple model[b]				
Never breastfed	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever breastfed	1.03 (0.89–1.19)	1.04 (0.83–1.29)	1.01 (0.77–1.34)	1.17 (0.72–1.90)
⩽5 months	1.07 (0.86–1.33)	0.94 (0.66–1.33)	0.86 (0.55–1.36)	1.51 (0.78–2.90)
6–11 months	0.96 (0.79–1.16)	0.89 (0.66–1.21)	0.88 (0.60–1.28)	0.88 (0.44–1.73)
⩾12 months	0.95 (0.70–1.28)	1.02 (0.65–1.60)	1.05 (0.60–1.83)	1.16 (0.41–3.34)
Duration not stated	1.08 (0.91–1.28)	1.22 (0.93–1.59)	1.23 (0.88–1.71)	1.23 (0.69–2.20)
Trend[d]	0.98 (0.91–1.06)	0.97 (0.86–1.10)	0.97 (0.83–1.13)	0.98 (0.76–1.28)
Fully adjusted model[c]				
Never breastfed	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Ever breastfed	1.04 (0.90–1.20)	1.04 (0.83–1.30)	1.02 (0.77–1.36)	1.16 (0.71–1.90)
⩽5 months	1.09 (0.88–1.36)	0.96 (0.67–1.35)	0.89 (0.56–1.41)	1.56 (0.81–3.00)
6–11 months	0.97 (0.80–1.18)	0.91 (0.67–1.22)	0.90 (0.62–1.31)	0.85 (0.42–1.69)
⩾12 months	0.95 (0.71–1.27)	1.04 (0.66–1.62)	1.07 (0.61–1.87)	1.14 (0.40–3.26)
Duration not stated	1.08 (0.91–1.28)	1.20 (0.92–1.57)	1.20 (0.86–1.68)	1.24 (0.67–2.27)
Trend[d]	0.98 (0.91–1.06)	0.97 (0.85–1.10)	0.98 (0.84–1.15)	0.94 (0.72–1.23)

[a] Standard errors are adjusted for possible within-family clustering of exposures and mortality.
[b] Simple models control for current age and sex and are stratified by survey district.
[c] Fully adjusted models control additionally for social class in childhood, Townsend score for area of residence in 1998, and birth order, and are stratified by survey district.
[d] Change in hazard ratio per unit increase in category of breastfeeding (excluding duration not stated).

between ever having been breastfed and all-cause (p for interaction: 0.3), cardiovascular disease ($p = 0.9$), ischaemic heart disease ($p = 0.2$), and cerebrovascular disease ($p = 0.2$) mortality (fully adjusted models).

There was little evidence that associations between breastfeeding and all-cause (p for interaction: 0.9), cardiovascular disease ($p = 0.4$), ischaemic heart disease ($p = 0.9$), and cerebrovascular disease ($p = 0.3$) mortality differed according to childhood BMI (fully adjusted models). Associations were similar when stratified by year-of-birth category and there was no evidence of interaction ($p \geqslant 0.25$ for all mortality outcomes).

Systematic review

The search strategy identified two studies from three publications with data that could be included in the meta-analysis.[17,18,21] In addition to the results from the Boyd Orr and Caerphilly cohorts,[15] there was a total of four studies for the meta-analysis (Table 3). These four studies provided four observations on ever having been breastfed and all-cause mortality, six on cardiovascular disease mortality, and four on ischaemic heart disease mortality. All four studies were historical cohorts born between 1904 and 1939.

Random effects models showed little difference in all-cause mortality between breast and bottle-fed subjects (Fig. 1), and there was little evidence of heterogeneity (Q statistic: $\chi^2_3 = 3.0$, $p = 0.4$; I^2 value for the percentage of variation attributable to heterogeneity:[20] 1%).

Five observations from three studies suggested little or no association between breastfeeding and cardiovascular disease mortality in both males and females[17,18,21] and one suggested a possible adverse effect (Caerphilly cohort). In random effects meta-analysis, cardiovascular disease mortality was similar in breastfed versus bottle-fed subjects (pooled rate ratio: 1.06; 95% CI: 0.94–1.20). There was no statistical evidence of between-study heterogeneity (Q statistic: $\chi^2_5 = 1.8$, $p = 0.9$; I^2 value: 0%).

Ischaemic heart disease mortality was 6% lower amongst males who had been breastfed in the Hertfordshire cohort, but 56% higher amongst breastfed females. This result is in line with point estimates from the Boyd Orr cohort suggesting that ischaemic heart disease mortality was 10% lower amongst males who had been breastfed, but 40% higher amongst breastfed females (although there was little statistical evidence of interaction: $p = 0.2$). In Caerphilly, however, ischaemic heart disease mortality was 73% higher amongst breastfed males. In a random effects meta-analysis, there was evidence of heterogeneity (Q statistic: $\chi^2_3 = 8.7$, $p = 0.03$; I^2 value: 66%). The confidence limits around the pooled rate ratio (1.19; 95% CI: 0.89–1.58) are consistent with either an 11% reduction or a 58% increase in ischaemic heart disease deaths associated with breastfeeding.

There was little evidence that prolonged breastfeeding was associated with all-cause mortality (pooled rate ratio: 0.94; 95% CI: 0.71–1.24), although there was moderate statistical evidence of heterogeneity (Q statistic: $\chi^2_2 = 3.1$, $p = 0.2$; I^2: 35%) (Fig. 2).

There was weak evidence that prolonged breastfeeding was associated with a 16% increase (95% CI: 0.99–1.36; $p = 0.06$) in cardiovascular disease mortality, and no evidence of inconsistency in estimates (Q statistic: $\chi^2_4 = 0.7$, $p = 0.9$; I^2 value: 0%). There was little evidence that prolonged breastfeeding was associated

Table 3 Studies included in the meta-analysis in ascending order of year of birth

Author (year)	Source	Year born	Age infant feeding assessed	Definitions of infant feeding	Length of follow-up (yrs) and percentage of target followed-up in parenthesis	Sex	Mortality outcomes (number of deaths)	Estimated rate ratios (95% CI)[a]		Variables adjusted for
								Any or exclusively breastfed vs. bottle-fed	Prolonged (>1 yr) breastfed vs. bottle-fed	
Wingard[21] (1994)	1373 bright children, California	1904–1915	11 yr	No breastfeeding: any breastfeeding	71–82 (85%)	M	All-cause (284)	0.77 (0.55–1.09)[b]	0.74 (0.50–1.09)[b]	Age, birth weight, infant health, socioeconomic status
							CVD (90)	1.04 (0.53–2.04)[b]	1.13 (0.55–2.33)[b]	
						F	All-cause (165)	1.20 (0.71–2.04)[b]	1.36 (0.77–2.40)[b]	
							CVD (37)	1.07 (0.33–3.49)[b]	0.87 (0.24–3.15)[b]	
Hertfordshire cohort (follow-up updated to 1999[e])[17,18]	5908 women and 10,374 men born in 11 of 12 districts in Hertfordshire	1911–1930[f]	Infancy	Exclusively breastfed; breast and bottle-fed; exclusively bottle-fed	71 (43%[g])	M	IHD (1365)	0.94 (0.77–1.15)[c,e] 0.87 (0.70–1.08)[d,e]	1.07 (0.86–1.33)[e]	Age
							CVD (1940)	1.01 (0.85–1.21)[c,e] 0.97 (0.80–1.16)[d,e]	1.21 (1.00–1.46)[e]	
						F	IHD (197)	1.56 (0.79–3.07)[c,e] 1.26 (0.62–2.56)[d,e]	1.14 (0.54–2.44)[e]	
							CVD (388)	1.07 (0.70–1.64)[c,e] 0.89 (0.57–1.39)[d,e]	1.07 (0.67–1.71)[e]	
Boyd Orr (2003)	4999 men and women from a survey of diet and health in pre-war Britain	1918–1939	0–19 yr (mean 7 yr)	No breastfeeding: any breastfeeding	64–66 (71%)	All	All-cause (944)	1.04 (0.90–1.20)	0.95 (0.71–1.27)	Age, survey area, childhood social class, Townsend score in adulthood; birth order
							CVD (393)	1.04 (0.83–1.30)	1.04 (0.66–1.62)	
							IHD (258)	1.02 (0.77–1.36)	1.07 (0.61–1.87)	
Caerphilly (2003)[15]	2512 middle-aged men living in Caerphilly, South Wales	1918–1939	45–59	Never breastfed: any breastfeeding	17–21 (63%)	M	All-cause (512)	1.03 (0.84–1.26)		Age, birth order, father's social class, social class in adulthood
							CVD (245)	1.29 (0.94–1.76)		
							IHD (184)	1.73 (1.17–2.55)		

CVD is cardiovascular disease. IHD is ischaemic heart disease.

[a] From fully adjusted models.

[b] Standard errors for calculation of CIs derived from number of deaths given in Table 3 of the paper[21] and assuming a Poisson distribution.

[c] Rate ratios are for exclusively breastfed and weaned at one year versus exclusively bottle-fed.

[d] Rate ratios are for breast and bottle-fed versus exclusively bottle-fed.

[e] Data are from the follow-up of the Hertfordshire cohort to the end of 1999 and are an update of data published in 1992[17] and 1993.[18]

[f] Females traced from 1923 onwards.

[g] Taking as denominator all births in Hertfordshire in relevant districts. The tracing rate as the percentage relative to births that were sent for tracing was 60–74%.

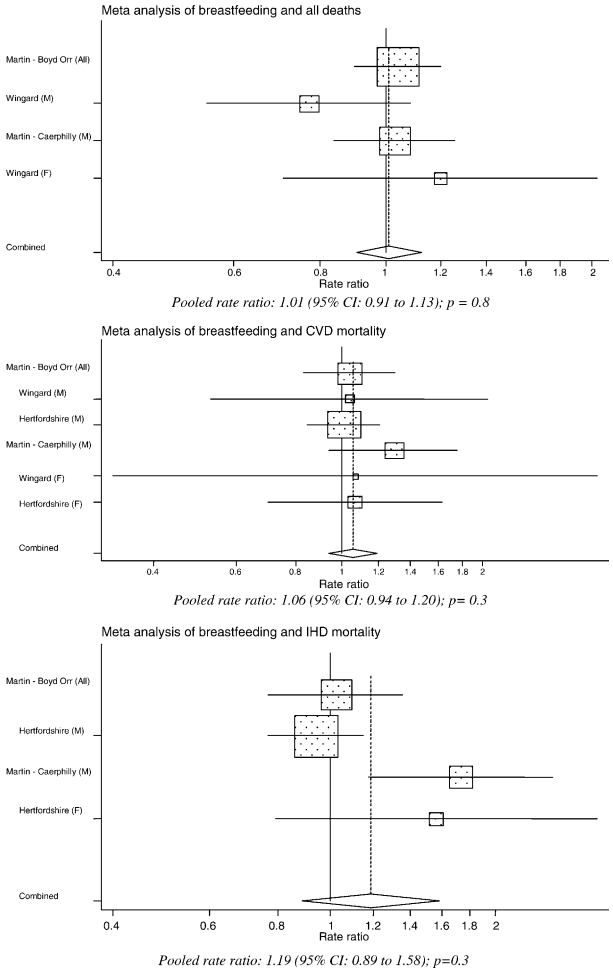

Fig. 1 Rate ratios and 95% confidence intervals (CI) for all-cause, cardiovascular, and ischaemic heart disease mortality in breastfed compared with bottle-fed infants. (The study author is indicated on the *y*-axis. The sex of the participants (male [M], female [F], or all [A]) is indicated in parenthesis. The box for each study is proportional to the inverse of the variance; horizontal lines show 95% CIs of the rate ratios. The pooled estimate is based on a random effects model shown by a dashed vertical line and diamond (95% CI).)

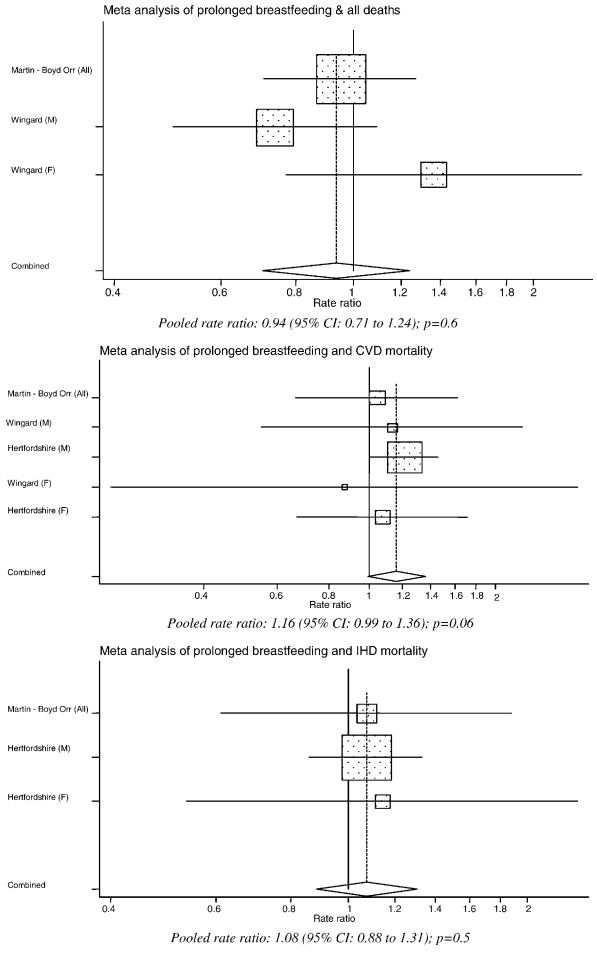

Fig. 2 Rate ratios and 95% confidence intervals (CI) for all-cause, cardiovascular, and ischaemic heart disease mortality in prolonged breastfeeding compared with bottle-feeding. (The study author is indicated on the *y*-axis. The sex of the participants (male [M], female [F], or all [A]) is indicated in parenthesis. The box for each study is proportional to the inverse of the variance; horizontal lines show 95% CIs of the rate ratios. The pooled estimate is based on a random effects model shown by a dashed vertical line and diamond (95% CI).)

with ischaemic heart disease mortality (rate ratio: 1.08; 95% CI: 0.88—1.31; $p = 0.5$) and there was no heterogeneity (Q statistic: $\chi^2_1 = 0.03$, $p = 0.9$; I^2: 0%).

Discussion

Our analyses (based on 1905 all-cause deaths, 3093 cardiovascular disease deaths, and 2004 ischaemic heart disease deaths) do not support the hypothesis that breastfeeding in infancy influences patterns of all-cause mortality. Ever having been breastfed was not associated with cardiovascular disease mortality overall, but the possibility that prolonged breastfeeding is associated with a 16% increase in cardiovascular disease deaths was suggested by the data. The available observational evidence for the association between ever having been breastfed and ischaemic heart disease mortality was inconsistent, and an important protective or adverse effect of breastfeeding could not be excluded.

Other evidence on this issue comes from two postmortem studies linking breastfeeding with atheroma formation,[8,22] and one case-control study[23] with nonfatal myocardial infarction as an outcome. These data, however, are limited and conflicting. In one postmortem study ($n = 160$), children and young adults (range: 2—30 years-old) who had been breastfed for at least four weeks showed more coronary artery plaques (16%) than bottle-fed children (5%),[22] although breastfed subjects were slightly older and interpretation is hampered by failure to adjust for age. In contrast, an earlier postmortem study in young adults found lower rates of coronary atheroma amongst those breastfed (25%) compared with those bottle-fed (60%) in infancy.[8] A small case-control study ($n = 71$) found no association between breastfeeding and nonfatal myocardial infarction.[23]

Limitations

There are at least three possible sources of bias in the studies reviewed here. First, selection bias is a potential problem as the studies were based on at least 70% of the target population in only two cohorts (the Boyd Orr study and Wingard et al.[21]). Selection bias is only an issue, however, if subjects who are lost to follow-up have a different breastfeeding-mortality association compared with those who are included.

Second, information bias could occur if there were systematic differences in the accurate recall of breastfeeding exposure in relation to future risk of cardiovascular disease mortality. Recall bias is unlikely in the Hertfordshire cohort[17,18] as breastfeeding was prospectively ascertained. Recall of the infant feeding method up to 20 years earlier is highly correlated with obstetric records,[24] suggesting that the short periods of retrospective recall in the studies of Wingard et al.[21] and Boyd Orr did not distort the results. The Caerphilly cohort relied on recall of 45–59 years.[15] It is feasible that differential recall of breastfeeding due to some third factor related to future mortality outcome (such as social position) may explain the positive association observed between breastfeeding and ischaemic heart disease mortality. Such a possibility is suggested by a small study showing differences in recall of breastfeeding by social position.[24] Finally, publication bias is possible, but the studies were relatively large (each based on over 100 deaths), we obtained unpublished estimates from the Caerphilly cohort and there was no suggestion that the results of smaller studies differed systematically from larger studies.

Since the mother's choice to breastfeed may be related to other factors influencing the future health of the child, the possibility of confounding, particularly by social position, needs to be considered. In the Boyd Orr and Caerphilly cohorts and the Wingard et al.[21] study, controlling for the potential confounding effects of socioeconomic position in childhood or adulthood made little difference to effect estimates. All the cohorts in this review were based on pre-World War II births, an era when breastfeeding was not as strongly related to social position and education as it is now.[11] Therefore, our results are of interest as they are less likely than studies based on more recent infant feeding experience to be confounded by social position.[12]

Generalisability

The results of this analysis may not be generalisable to the future pattern of cardiovascular disease mortality of infants breastfed today. First, the alternatives to breastfeeding at the inception of the cohorts analysed in this report included packaged preparations of cereals, wheat and flour designed to be made up with milk at home, condensed milk, and fresh cow milk.[11] These preparations differ substantially from modern formulae.[25] The increasing modification of infant formulae to more closely resemble breastmilk may make any slight differences in cardiovascular outcomes by infant feeding groups less relevant to modern birth cohorts.

Second, the influence of breastfeeding in humans may depend on subsequent childhood dietary patterns, which are now very different from those in the early twentieth century. In the Boyd Orr and Caerphilly cohorts, there was no evidence of interaction by BMI on breastfeeding-ischaemic heart disease associations, which may have been observed if an effect of breastfeeding depended on later diet.

Conclusion

As confounding and bias may have distorted results from individual studies, the statistical combination of estimates into a combined rate ratio needs to be interpreted with caution. Our new analysis, together with evidence from published and unpublished literature, does not provide strong evidence that breastfeeding is related to all-cause or cardiovascular disease mortality. The confidence limits around our point estimates and the observed between-study heterogeneity for associations between breastfeeding and ischaemic heart disease, however, do not rule out important beneficial or adverse cardiovascular effects of breastfeeding. Given that experimental data from baboon models has previously linked breastfeeding with atherogenic patterns of cholesterol metabolism and atherosclerosis,[10] and a longer duration of breastfeeding has been associated in one epidemiological study with increased arterial stiffness,[9] further evidence on the breastfeeding-cardiovascular disease mortality association is required to help to resolve remaining uncertainty.

Although we found little evidence to support a cardioprotective effect of breastfeeding extending into old age, its beneficial influence on infant and child health and cognitive development supports the idea that it should be promoted as the infant feeding method of choice.[25]

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Contributors

G.D.S. and S.F. established the adult follow-up phase of the Carnegie Survey of Diet and Health in pre-war Britain using original records loaned by the Rowett Research Institute. R.M.M. and D.G. currently maintain the Boyd Orr cohort database. R.M.M., G.D.S., and D.G. developed the hypothesis. R.M.M. did the analysis, wrote the first draft of the paper and coordinated completion. K.T. gave statistical advice. All authors contributed to, and approved, the final version.

Appendix. MEDLINE search strategy for systematic review

Infant feeding
MeSH headings:
exp Infant Nutrition/
Bottle Feeding/
Milk, Human/

Text word terms:
(breast adj3 (feeding or fed)).tw
infant diet$.tw
(bottle adj3 (feeding or fed)).tw
(artificial adj3 (feeding or fed)).tw
weaning.tw
breast milk.tw
dried milk.tw
(infant adj3 nutrition).tw
infant diet$.tw
infant feeding.tw
early nutrition.tw
infant food.tw
breastfeeding.tw
breastfed.tw
breastmilk.tw

Cardiovascular disease and risk factors
MeSH headings:
Cardiovascular Diseases/
exp Myocardial Ischemia/
exp Vascular Diseases/
exp Cholesterol/
exp Lipids/
exp Diabetes Mellitus/

Text word terms:
lipid$.tw
cholesterol.tw
triglyceride$.tw
cardiovascular.tw
(coronary adj3 disease$).tw
ldl.tw
lipoprotein$.tw
hdl.tw
hypertension.tw
blood pressure.tw
(systolic or diastolic).tw
diabetes.tw
(niddm or iddm).tw
insulin resistan$.tw
glucose intolerance.tw

Growth
MeSH headings:
"Body Weights and Measures"/
exp Obesity/
exp Growth/

Text word terms:
body mass index.tw
bmi.tw
overweight.tw
(obese or obesity).tw
leg length.tw
sitting height.tw
weight.tw
height.tw
child$ growth.tw

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