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META-ANALYSIS

Breastfeeding in Infancy and Blood Pressure in Later Life: Systematic Review and Meta-Analysis

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The influence of breastfeeding on blood pressure in later life is uncertain. The authors conducted a systematic review of published studies from which estimates of a mean difference (standard error) in blood pressure between breastfed and bottle-fed subjects could be derived. They searched MEDLINE and Excerpta Medica (EMBASE) bibliographic databases, which was supplemented by manual searches of reference lists. Fifteen studies (17 observations) including 17,503 subjects were summarized. Systolic blood pressure was lower in breastfed compared with bottle-fed infants (pooled difference: –1.4 mmHg, 95% confidence interval (CI): –2.2, –0.6), but evidence of heterogeneity between study estimates was evident (χ^2_{16} = 42.0, $p < 0.001$). A lesser effect of breastfeeding on systolic blood pressure was observed in larger ($n \geq 1{,}000$) studies (–0.6 mmHg, 95% CI: –1.2, 0.02) compared with smaller ($n < 1{,}000$) studies (–2.3 mmHg, 95% CI: –3.7, –0.9) (p for difference in pooled estimates = 0.02). A small reduction in diastolic blood pressure was associated with breastfeeding (pooled difference: –0.5 mmHg, 95% CI: –0.9, –0.04), which was independent of study size. If causal, the small reduction in blood pressure associated with breastfeeding could confer important benefits on cardiovascular health at a population level. Understanding the mechanism underlying this association may provide insights into pathways linking early life exposures with health in adulthood.

blood pressure; bottle feeding; breast feeding; cardiovascular system; hypertension; infant nutrition; milk, human; review literature

Abbreviation: CI, confidence interval.

Evidence is growing that blood pressure levels in both childhood and young adulthood are influenced by factors operating early in life (1–4) and are associated with later cardiovascular disease (5). Specifically, several cohort studies suggest that blood pressure may be determined by early nutritional exposures, including sodium intake in infancy (6), consumption of formula feed (7), and breastfeeding (8). Detection, treatment, and control of hypertension in adulthood does not reduce cardiovascular disease risk to normotensive levels (9), supporting efforts to identify primary prevention interventions that could be started in early life. Any long-term effect of breastfeeding on blood pressure levels may have implications for policies promoting breastfeeding, particularly among the least affluent families with the lowest breastfeeding rates (10) and the highest risks of premature cardiovascular disease (11), and it may increase understanding of cardiovascular disease mechanisms operating through early life exposures.

Interpreting individual studies of the association between breastfeeding and blood pressure in isolation is complicated. Firstly, cohort studies include infants born in different decades during the 20th century (8, 12, 13). The composition of bottle (artificial) feeds has changed during this time, and associations with particular components of these feeds may explain differences in results. Secondly, different definitions of breastfeeding have been used (13, 14). Thirdly, the strength of the relation may depend on the age at outcome measurement (15, 16). Finally, control for confounding

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factors may have been inadequate (17). We conducted a systematic review and meta-analysis of studies reporting on blood pressure levels in breast- and bottle-fed subjects and explored possible sources of heterogeneity using meta-regression (18).

MATERIALS AND METHODS

Included studies

Articles were included if they fulfilled the following criteria: 1) having been breastfed in infancy was compared with bottle (artificial) feeding, 2) systolic or diastolic blood pressure had been measured as an outcome, and 3) an estimate of the mean difference in blood pressure between breast- and bottle-fed groups could be extracted from the article. Our review was restricted to human subjects.

Data sources

We systematically searched all published papers, letters, abstracts, and review articles on infant feeding and cardiovascular disease, cardiovascular disease risk factors, and growth by using the MEDLINE and Excerpta Medica (EMBASE) bibliographic databases from their inception to April 2003. We used a combined text word and MESH heading search strategy (refer to the Appendix), and we manually searched reference lists of all studies that fulfilled our eligibility criteria. Using the "saved searches" and "auto alerts" automated facilities incorporated within the MEDLINE and EMBASE databases, we reran the search every week until May 2004. No restriction was made regarding language of publication. Two papers then in press but not yet published (19, 20) were also considered for inclusion. When clarifications were required, we corresponded with the authors, but no additional data were supplied. One of the authors (R. M. M.) assessed study eligibility and extracted data by using a prepiloted, standardized form.

We did not use a simple quality score, which might be arbitrary. Instead, we conducted meta-regression analyses to assess specific aspects of quality, including control of confounding, loss to follow-up, recall bias, definition of breastfeeding, and sample size (refer to the information below).

Statistical analysis

A meta-analysis of the mean differences, and their standard errors, in systolic and diastolic blood pressures between breastfed and bottle-fed infants was conducted. The fully adjusted estimates from individual studies were used in the meta-analysis where available; otherwise, the crude estimates were used. Heterogeneity was assessed by using the Q test (18). Because heterogeneity was marked, random-effects models were computed. One paper followed up subjects at ages 13–16 years (15), some of whom were included in an analysis based on follow-up at ages 7.5–8 years (16). Because the two studies cannot be considered independent in a meta-analysis, we performed a meta-analysis with and without including this later follow-up study to determine its impact on the overall pooled mean difference.

Selected study characteristics, chosen a priori, were entered as indicator variables in separate meta-regression analyses (18) to assess their impact on between-study variation (heterogeneity), as follows: study size (<1,000/ ≥1,000); reliance on maternal recall of breastfeeding beyond infancy (yes/no); whether breastfeeding occurred for at least 2 months (yes/no); whether breastfeeding was exclusive for at least 2 months (yes/no); age at measurement of blood pressure (<10 years/11–45 years/>45 years); decade of birth (before 1980/after 1980); proportion of target population included in the main analysis (<30 percent/31–60 percent, >61 percent); method of blood pressure measurement (automated/manual); and whether effect estimates in the final models controlled for social factors in childhood or adulthood (yes/no), maternal factors in pregnancy (yes/no), or current weight (yes/no). Papers that assessed blood pressure in infancy only (age <1 year) were investigated separately because the focus of our inquiry was on the long-term, rather than acute, effects of breastfeeding. Funnel plots, the Egger (weighted regression) test, and the Begg and Mazumdar (rank correlation) tests for funnel plot asymmetry were conducted to examine the relation between sample size and observed mean differences in blood pressure by infant feeding group (21).

Sensitivity analysis

We examined the likely impact on the overall pooled relation between breastfeeding and blood pressure of also including the five potentially eligible studies that did not provide quantitative estimates (table 1). In all five studies, null results were reported, and a mean difference in systolic blood pressure of 0.0 mmHg between breast- and bottle-fed subjects was assigned. The meta-analysis was then repeated to estimate the pooled mean difference when all studies were included (i.e., both those with published estimates and the five studies without published estimates). For the five studies without quantitative data, an estimate of the standard error was based on the sample size and assumed a standard deviation of 10 mmHg where this parameter was not reported (22–24).

RESULTS

Description of studies

The electronic search yielded 3,403 references. Abstract review suggested that 17 were potentially relevant to the analysis relating breastfeeding with blood pressure beyond 12 months (8, 12–16, 23–33). Ten other papers were identified from a manual search of reference lists (22, 34–42). Of the 27 studies, 12 published studies were included in the meta-analysis (8, 12–16, 25–27, 34–36) (Web table 1; this information is described in the supplementary table referred to as "Web table 1" in the text, which is posted on the *Journal*'s website (http://aje.oupjournals.org/)). Reasons for exclusion (n = 15) are given in figure 1. Together with the three additional studies identified after April 2003 (which

TABLE 1. Studies reporting on associations between method of infant feeding and blood pressure beyond 12 months of age that were not included in the current meta-analysis

First author, source (year of publication) (reference no.)	No. breastfed*; no. bottle fed (sex)	Infant feeding comparison	Infant year of birth	Age at which infant feeding was assessed	Age at which outcome measurement occurred	Description of results
Baranowski, families from an ethnically diverse population in Texas (1992) (22)	245 total (M† + F†)	Duration of any breastfeeding	Not stated	Interviewer administered questions to mother 3–4 years after infant's birth	3–4 years	No significant correlations between duration of breastfeeding and SBP† or DBP† observed; quantitative estimates not reported
Cobaleda Rodrigo, Madrid, Spain (1989) (23)	1,893 total (M + F)	Ever vs. never breastfed	1965–1983	0–18 years; method unclear	0–18 years	No significant differences between duration of breastfeeding and SBP or DBP observed; no quantitative estimates given
Simpson, births in Dunedin maternity hospital, New Zealand (1981) (37)	692 total (M + F)	Ever vs. never breastfed	1972–1973	3 years; method unclear	7 years	No significant difference in breastfeeding rates or duration of breastfeeding when comparing children with high, medium, and low blood pressure; no quantitative estimates given
Marmot, subsample of 238 eligible subjects living in London and Bristol, United Kingdom who were part of the 1946 national birth cohort (*n* = 5,362), England (1980) (24)	95; 47 (M + F)	Exclusively breastfed for 5 months vs. exclusively bottle fed	1946	First and third year of life; methods not stated	31–32 years	"There were no consistent differences [in blood pressure levels] between those who had been breastfed and those who had been bottle fed"; no quantitative estimates given
Fall, 297 women born and still living in East Hertfordshire (total births = 5,585), England (1995) (41)	279; 11 (F)	Breastfed, bottle fed, breast- and bottle fed	1923–1930	During infancy; infant feeding mode recorded by health visitors	60–71 years	"No differences occurred between the three feeding groups in any of the risk factors measured" (included systolic and diastolic blood pressures); no quantitative estimates given

* Includes partially breastfed.

involved 10,062 subjects) (19, 20, 43), 15 studies with 17,503 participants were included in the meta-analysis relating breastfeeding with blood pressure beyond 12 months (Web table 1).

Two of these 15 studies were based on a follow-up of a randomized controlled trial in preterm infants (15, 16), eight were prospective cohorts (8, 14, 20, 25–27, 36, 43), and one was a historical cohort (13); in four cross-sectional surveys of blood pressure, infant feeding history was based on retrospective recall by the mother (12, 19, 34, 35). These studies included populations from the United Kingdom, Finland, Holland, Belgium, Italy, Czech Republic, Croatia, South Africa, and Australia. Individual studies were relatively homogeneous with respect to ethnicity. The year of birth of the subjects ranged from 1918 to 1994. The proportion of the target population included in the main analysis was unstated in one paper (35), less than 30 percent in four studies (12, 13, 15, 36), 30–60 percent in four studies (8, 20, 27, 43), and more than 60 percent in six studies (14, 16, 19, 25, 26, 34).

From these 15 studies, 17 estimates of systolic blood pressure differences were derived, of which 12 included males and females combined and five were sex specific. Eleven systolic blood pressure observations (nine studies) were of children (aged 1–16 years), and six observations (five studies) occurred in later adulthood (age ≥17 years). One study reported results for diastolic blood pressure only (25). From the 15 studies, 13 estimates of diastolic blood pressure differences were derived, 12 of which included males and females combined and one of which was for males only. Nine diastolic blood pressure observations (eight studies) were of children aged 1–16 years, and four observations (four studies) occurred in adulthood (age ≥17 years).

Definitions of breastfeeding

The 15 studies used different definitions of breastfeeding. In a randomized controlled trial with follow-up at ages 7.5–8 years (16) and ages 13–16 years (15), preterm infants were randomly assigned to donated, banked breast milk or

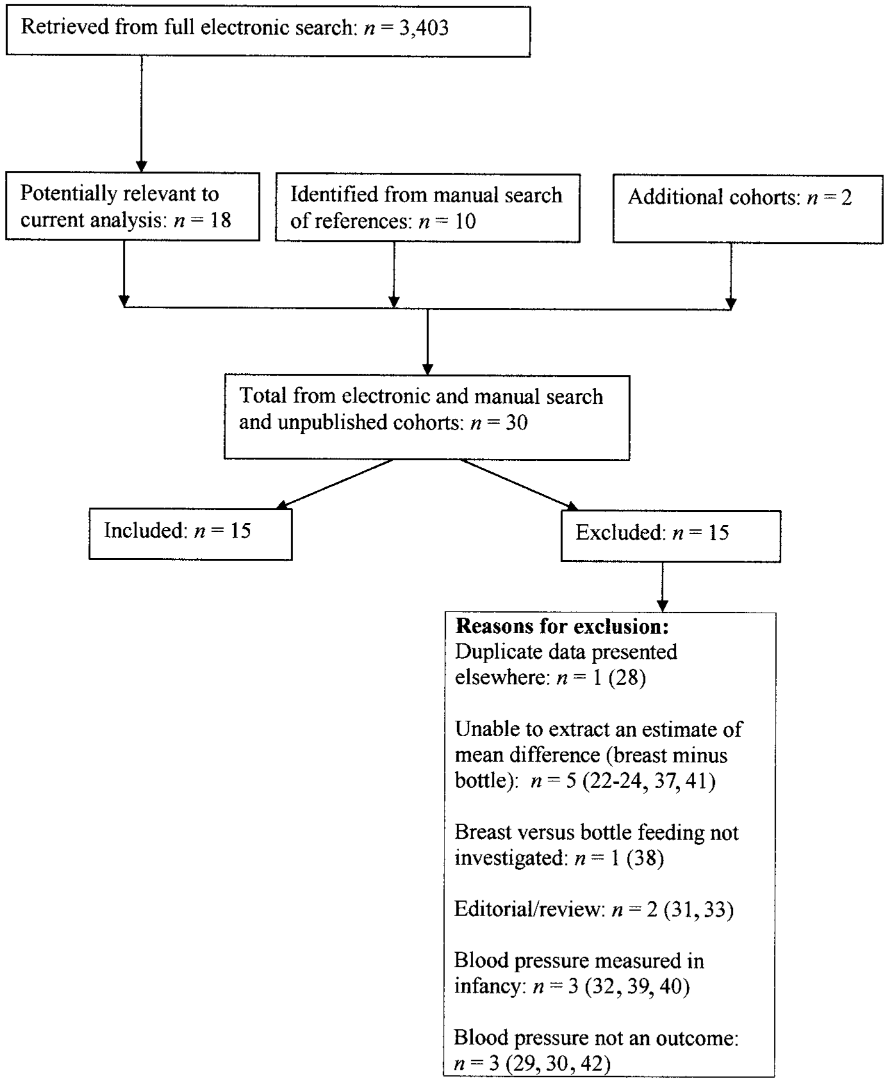

FIGURE 1. Summary of outcomes of studies retrieved for analysis, 1966–2004.

preterm formula (either as the sole diet or a supplement to mother's milk) until they weighed 2,000 g or were discharged to home. In the other studies, the exposure was defined as 1) any breastfeeding in five studies (12, 19, 25, 26, 35); 2) exclusive breastfeeding in five studies (exclusive for the first 10 days only (13), for at least 3 months (27, 34), for at least 15 weeks (8), or for at least 12 months (36)); 3) both any breastfeeding and exclusive breastfeeding for at least 2 months in one study (43); and 4) any breastfeeding for at least 3 months in one study (14) and at least 6 months in another (20). In all studies except the randomized controlled trial (15, 16), the comparator group was exclusive bottle feeding. Five of the studies (providing six observations) relied on maternal recall beyond infancy, ranging from 3–18 years (14), to 3 years (27), to 5–7 years (34), to 20–28 years (12), and to 44–60 years (19).

Breastfeeding and systolic blood pressure

The results for systolic blood pressure, shown in figure 2, are based on 14 studies with 17 observations. Mean systolic blood pressure was lower in breastfed infants compared with bottle-fed infants according to 10 observations from eight studies (8, 14, 15, 20, 26, 35, 36, 43). Seven observations (from six studies) showed no or little difference in systolic blood pressure among breastfed versus formula-fed infants (12, 13, 16, 19, 27, 34). Two of these seven observations were from the randomized controlled trial in preterm infants with follow-up at ages 7–8 years (16). When the original study was followed up into adolescence (ages 13–16 years), having received breast milk was associated with a 2.7-mmHg reduction in blood pressure (15).

In a random-effects model, mean systolic blood pressure was lower among breastfed infants (mean difference: –1.4

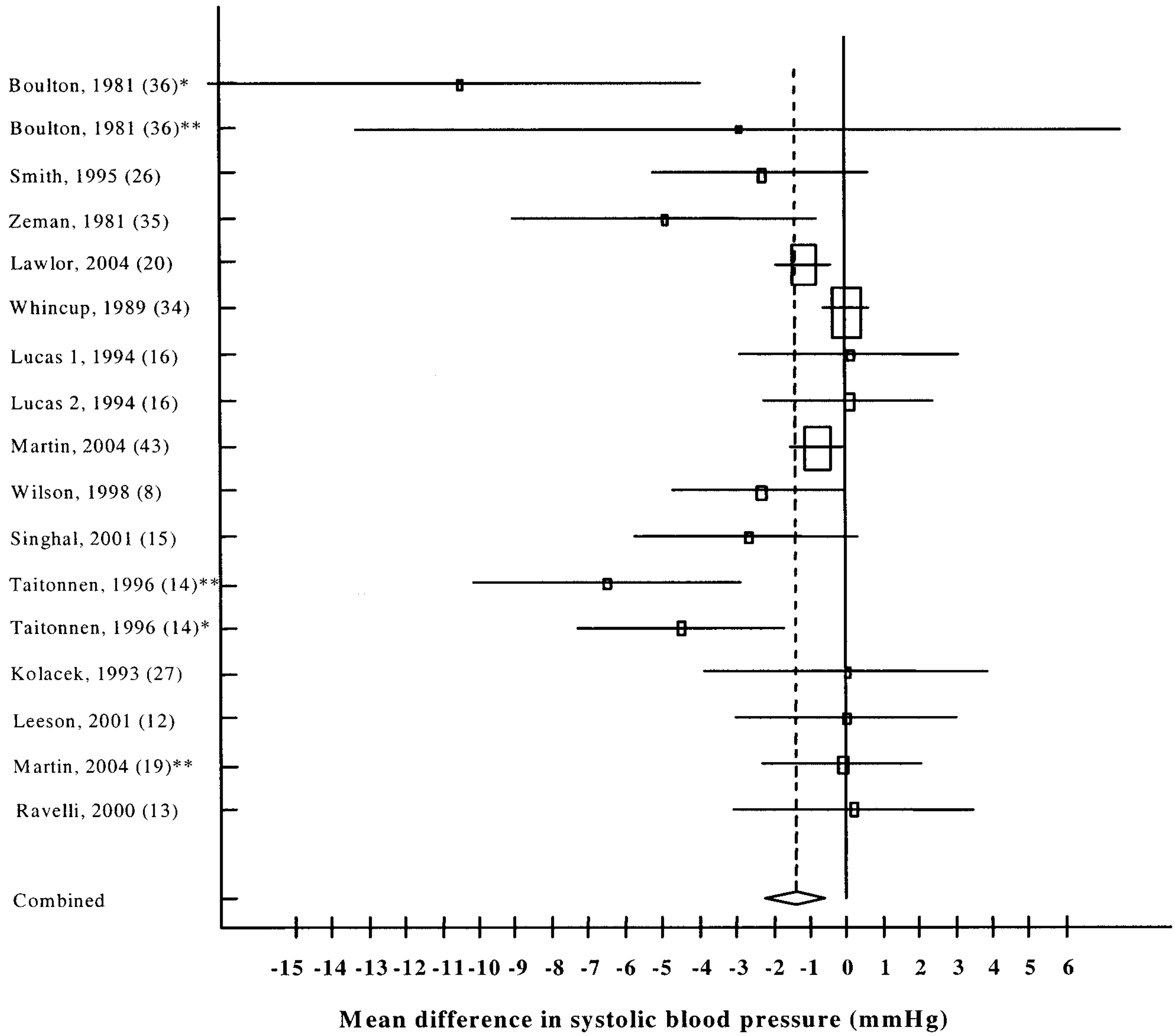

FIGURE 2. Mean difference (95% confidence interval) in systolic blood pressure (mmHg) for infants who were breastfed minus infants who were bottle fed: studies reporting on the association between breastfeeding and systolic blood pressure, 1966–2004. The first author, the year of publication, and the reference number (in parentheses) are indicated on the *y*-axis. These studies are arranged in descending order of mean age at which blood pressure was measured. The box corresponding to each study is proportional to the inverse of the variance, with horizontal lines showing the 95% confidence intervals of the mean difference in systolic blood pressure (mmHg). The combined estimate is based on a random-effects model shown by the dashed vertical line and diamond (95% confidence interval). The solid vertical line represents the null result, that is, zero mean difference in blood pressure. Lucas 1 or 2 denotes estimates using different comparator groups (Web table 1). * Female-specific estimates; ** male-specific estimates.

mmHg, 95 percent confidence interval (CI): –2.2, –0.6; p = 0.001) (figure 2). There was also evidence of marked heterogeneity between studies (χ^2_{16} = 42.0, p < 0.001). Exclusion of the study by Singhal et al. (15) (because of lack of independence from Lucas et al.'s study (16)) had little impact on the pooled difference (–1.3, 95 percent CI: –2.2, –0.5). Controlling for study size in a meta-regression analysis lowered the τ^2 estimate of between-study variation from 1.69 when study size was not included in the model to 0.47 when study size was included, suggesting that some of the observed heterogeneity was explained by study size. In a stratified meta-analysis, a smaller effect of breastfeeding on later systolic blood pressure was observed in the larger studies ($n \geq$ 1,000) (difference: –0.6 mmHg, 95 percent CI: –1.2, 0.02; p = 0.06) compared with the smaller studies (n < 1,000) (difference: –2.3 mmHg, 95 percent CI: –3.7, –0.9; p = 0.001). This difference was unlikely to be due to chance (p = 0.02). There was evidence of heterogeneity in models restricted to small studies (χ^2_{12} = 27.1, p = 0.007) but less evidence among the four larger studies (χ^2_3 = 6.1, p = 0.1).

In studies where the duration of breastfeeding was at least 2 months, the pooled blood pressure difference between breast- and bottle-fed groups (–2.0 mmHg) was on average 1.6 mmHg larger (95 percent CI: –0.4, 3.5; $p = 0.1$) than in studies with a shorter duration of breastfeeding (pooled difference: –0.6 mmHg). Similarly, the difference in blood pressure between breast- and bottle-fed groups was 1.4 mmHg greater (95 percent CI: –0.4, 3.2; $p = 0.1$) in those born up to 1980 (pooled difference: –2.7 mmHg) compared with those born after 1980 (pooled difference: –0.8 mmHg).

Only four of the 17 observations on systolic blood pressure controlled for potential socioeconomic (19, 20, 43) or maternal antenatal factors (such as body mass index, smoking in pregnancy, education, parity, marital status) (8, 20, 43) or current body size (8, 20, 43). Controlling for confounding produced a greater than 30 percent reduction in crude effect estimates in two (19, 43) of three studies in which comparison with crude estimates was possible. In meta-regression analysis, there was weak evidence that studies not controlling for socioeconomic factors (pooled difference: –2.0 mmHg) had mean differences in blood pressure 1.4 mmHg higher (95 percent CI: –0.6, 3.3; $p = 0.17$) than in studies controlling for socioeconomic factors (pooled difference: –0.9 mmHg). In one study, a large reduction in blood pressure associated with having been breastfed for at least 3 months (Web table 1) was reported to have been somewhat attenuated after controlling for current weight, age, birth weight, time of birth, birth order, mother's age, and history of high antenatal maternal blood pressure (14), but quantitative estimates suitable for inclusion in the meta-analyses were not available. Several studies controlled for current weight (14) or body mass index (8, 15) or ponderal index (20) in their final model, which may have had the effect of overcontrolling for a factor on the causal pathway if breastfeeding lowers blood pressure by reducing later adiposity (44).

In meta-regression analyses, there was little evidence that heterogeneity was explained by reliance on maternal recall of breastfeeding ($p = 0.9$), age at measurement of blood pressure ($p = 0.8$), whether breastfeeding was exclusive for at least 2 months ($p = 0.6$), method of blood pressure measurement ($p = 0.2$), or proportion of the target population included in the main analysis ($p = 0.9$).

Breastfeeding and diastolic blood pressure

The results for 13 observations (12 studies) relating to diastolic blood pressure are shown in figure 3. Mean diastolic blood pressure was lower among breastfed infants according to nine observations from eight studies (8, 12, 15, 16, 19, 20, 25, 43). In a random-effects model, the pooled mean diastolic blood pressure was lower among breastfed infants (difference: –0.5 mmHg, 95 percent CI: –0.9, –0.04; $p = 0.03$). There was less evidence of heterogeneity between estimates ($\chi^2_{12} = 20.2$; $p = 0.06$) than in the analysis of breastfeeding and systolic blood pressure. Exclusion of the study by Singhal et al. (15) had little impact on the pooled difference (–0.4, 95 percent CI: –0.8, –0.01). The effect of breastfeeding on later diastolic blood pressure was similar in the four larger studies ($n \geq 1,000$) (difference: –0.4 mmHg, 95 percent CI: –0.9, 0.1; $p = 0.10$) compared with the seven smaller studies ($n < 1,000$) (difference: –0.6 mmHg, 95 percent CI: –1.5, 0.2; $p = 0.15$). Studies that relied on maternal recall of breastfeeding beyond infancy showed pooled differences in mean diastolic blood pressure (0.0 mmHg) that were 0.6 mmHg smaller (95 percent CI: 0.2, 1.1; $p = 0.004$) than in studies that did not rely on recall (pooled difference: –0.7 mmHg).

We found little evidence that between-study heterogeneity in estimates was explained by age at measurement of blood pressure ($p = 0.5$), decade of birth ($p = 0.2$), stipulation of a minimum duration of breastfeeding ($p = 0.5$), proportion of the target population in the main analysis ($p = 0.2$), whether breastfeeding was exclusive for at least 2 months ($p = 0.2$), method of blood pressure measurement ($p = 0.4$), or whether effect estimates controlled for socioeconomic factors ($p = 0.9$), maternal factors in pregnancy ($p = 0.9$), or current weight ($p = 0.9$).

Studies that formally tested for interaction found little evidence of sex differences in the association between breastfeeding and systolic or diastolic blood pressure (20, 43). Repeating analyses after excluding the first published (in 1981) of the included studies (35, 36), which could be regarded as hypothesis-generating reports, made little difference to the pooled-effect estimates for systolic (mean difference: –1.1 mmHg, 95 percent CI: –1.8, –0.4; $p = 0.003$) or diastolic (mean difference: –0.5 mmHg, 95 percent CI: –1.0, –0.06; $p = 0.03$) blood pressure.

Small study effects

For systolic blood pressure, there was evidence of differential small study effects on inspection of funnel plots (figure 4) and the Begg ($p = 0.09$) test for funnel plot asymmetry, but there was no such evidence for diastolic blood pressure (Begg test: $p = 0.3$). That is, we found some evidence that small studies (i.e., those with higher standard errors, located to the right of the figure), compared with larger studies, reported larger mean differences in systolic blood pressure between infant feeding groups.

Excluded studies

Table 1 summarizes the results from the five studies not included in the meta-analysis because a mean difference in blood pressure could not be obtained (22–24, 37, 41). All reported no "statistically significant" association between breastfeeding and either systolic or diastolic blood pressure. These studies were relatively small—only 3,262 subjects in total compared with 17,503 included in the meta-analysis. In a sensitivity analysis, inclusion in the meta-analysis of the assumed zero estimates from the five studies (table 1) with no published mean differences attenuated the overall summary estimate for systolic blood pressure (mean difference: –1.0 mmHg, 95 percent CI: –1.6; –0.4; p = 0.002), but there was still strong evidence of an inverse association.

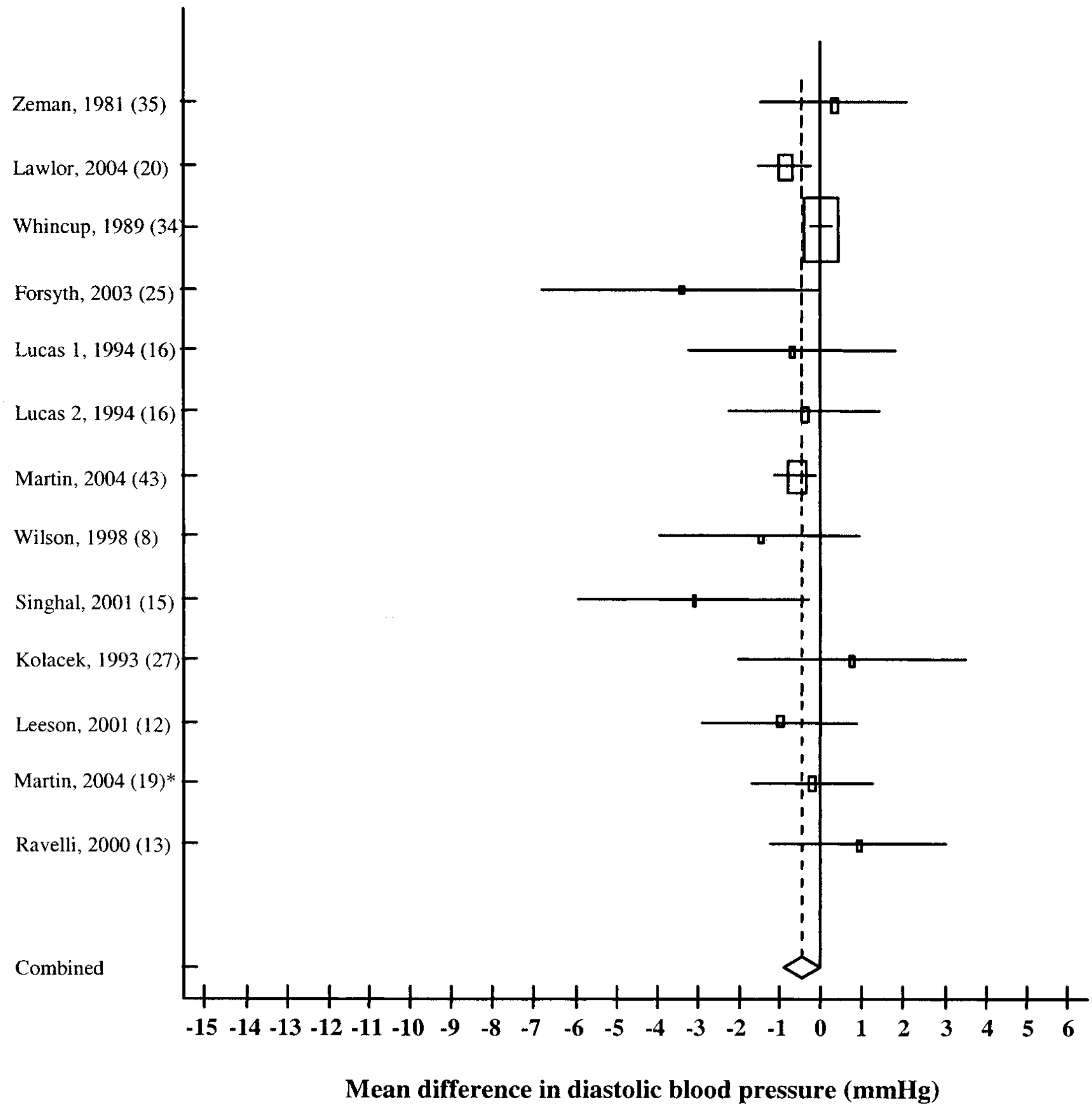

FIGURE 3. Mean difference (95% confidence interval) in diastolic blood pressure (mmHg) for infants who were breastfed minus infants who were bottle fed: studies reporting on the association between breastfeeding and diastolic blood pressure, 1966–2004. The first author, the year of publication, and the reference number (in parentheses) are indicated on the *y*-axis. These studies are arranged in descending order of mean age at which blood pressure was measured. The box corresponding to each study is proportional to the inverse of the variance, with horizontal lines showing the 95% confidence intervals of the mean difference in diastolic blood pressure (mmHg). The combined estimate is based on a random-effects model shown by the dashed vertical line and diamond (95% confidence interval). The solid vertical line represents the null result, that is, zero mean difference in blood pressure. Lucas 1 or 2 denotes estimates using different comparator groups (Web table 1). * Male-specific estimate.

Blood pressure in infancy

Overall, six studies were identified that examined the relation between infant feeding mode and blood pressure measured before 12 months of age (32, 39, 40, 45–47) (table 2). The mean difference in blood pressure by feeding mode, and the associated standard error, could be estimated from four of these studies (six observations) (32, 40, 45, 46). In random-effects models, the pooled systolic blood pressure difference in infancy associated with breastfeeding was –1.7 mmHg (95 percent CI: –4.0, 0.6; $p = 0.15$), although there was some evidence of heterogeneity ($\chi^2_5 = 11.8$; $p = 0.04$). The pooled diastolic blood pressure difference in infancy associated with breastfeeding was –1.1 (95 percent CI: –4.0, 1.8; p = 0.4; $\chi^2_3 = 8.2$, $p = 0.04$).

DISCUSSION

Breastfeeding was associated with a 1.4- and 0.5-mmHg reduction in systolic and diastolic blood pressure, respec-

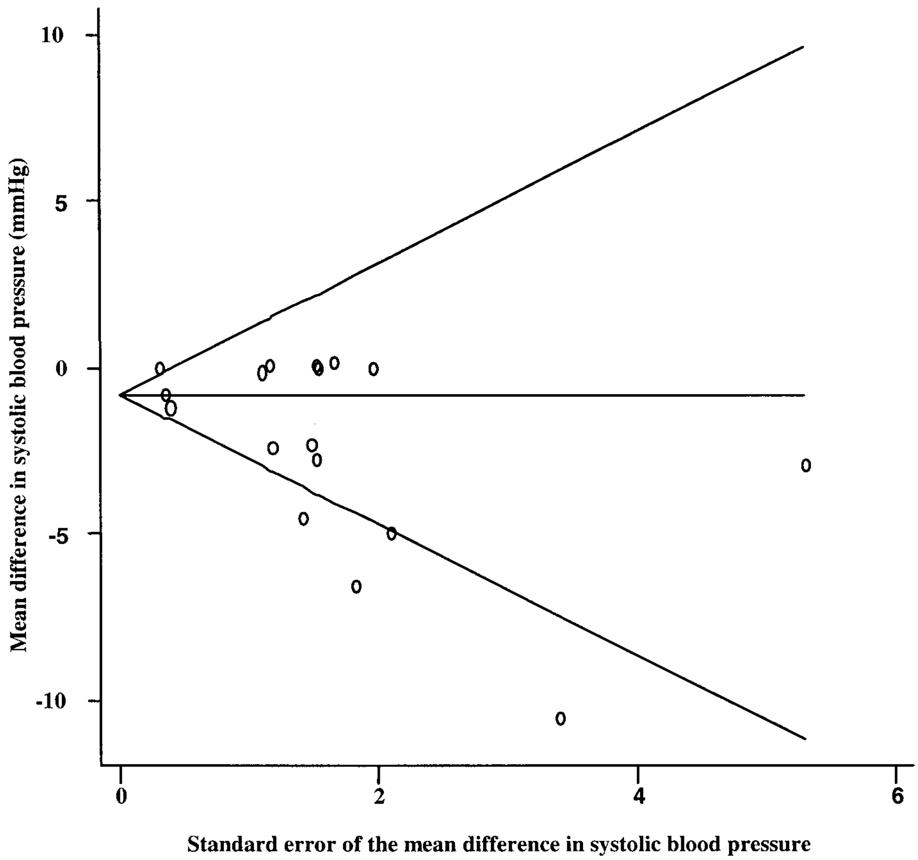

FIGURE 4. Begg's funnel plot (with pseudo 95% confidence limits) for studies reporting on the association between breastfeeding and systolic blood pressure, 1966–2004.

tively, although differences in systolic blood pressure between feeding groups were reduced in large (difference: –0.6 mmHg) compared with smaller (difference: –2.3 mmHg) studies. These pooled estimates are similar to those found by Owen et al. (48) in a recent review, even though the current report includes recently published data on an extra 10,062 subjects from three studies that included more than 1,500 participants each.

Chance, bias, and confounding

A number of studies reported inverse associations between breastfeeding and blood pressure, including two (of three) with more than 3,500 subjects each (20, 43), suggesting that these findings are unlikely to be due to type 1 error alone. Selection bias would arise if excluded subjects had a different breastfeeding–blood pressure association compared with those who were included. In one study, a protective effect of breast milk on blood pressure was observed when 26 percent of the original cohort were followed up at ages 13–16 years (15), but not when 81 percent were examined at ages 7.5–8 years (16), suggesting either the possibility of selection bias in the later follow-up or an amplification of the breastfeeding–blood pressure association (49). When all the studies were considered, we found similar effect estimates in studies with more than 60 percent follow-up and in those with less than 30 percent follow-up, suggesting that the association between breastfeeding and blood pressure did not systematically vary between studies according to follow-up rates.

Although reporting of ever having been breastfed after up to 20 years is highly correlated with obstetric records (50), breastfeeding duration may be remembered less accurately (51). Three cross-sectional studies relied on retrospective reporting of exclusive (34) or any breastfeeding 7 years (34), 28 years (12), and 60 years (19) after birth, and these studies showed little evidence of an association between breastfeeding and blood pressure. In meta-regression analysis, reliance on maternal recall was associated with an attenuation of the difference in diastolic (but not systolic) blood pressure between breast- and bottle-fed groups. Publication bias is a concern because most studies in this review were small, and mean blood pressure differences were greater in the smaller compared with the larger studies.

Relatively few studies controlled for potential confounding factors, although adjusted effect estimates were attenuated by at least 30 percent in two studies (19, 43). In the meta-regression analyses, studies controlling for socio-

TABLE 2. Studies relating breastfeeding to blood pressure levels in infancy (before 12 months of age), by year of publication

First author, source (year of publication) (reference no.)	No. breastfed; no. bottle fed (sex)	Infant feeding comparison	Infant year of birth	Age at which infant feeding was assessed	Age at which outcome measurement occurred	Mean difference (breast-bottle) in mmHg (standard error): Unadjusted or simple model	Mean difference (breast-bottle) in mmHg (standard error): Fully adjusted model	Covariates in multiply-adjusted models
Studies included in the meta-analysis								
Pomeranz, infants born in a single hospital, Israel (2002) (45)	7; 31 (M* + F*)	Ever breastfed vs. milk formula made with either mineral water (low sodium) or tap water (high sodium)	Not stated	Birth	6 months	SBP*: –6.1 (2.0); DBP*: –7.3 (3.1)	Not given	None
Bernstein, term infants born in Johannesburg Hospital, South Africa (1990) (46)	43; 81 (M + F)	Exclusively breastfed (*n* = 43) vs. low-sodium formula (*n* = 42) or high-sodium formula (*n* = 39)	1988	6 weeks	6 weeks	Breastfed vs. low-sodium formula: –1.6 (2.2); breastfed vs. high-sodium formula: –4.1 (2.0)	Not given	None
Zinner, about 4% of infants born in hospitals in Boston, Massachusetts, and Rhode Island (1980) (32)	154; 264 (M + F)	Breastfed vs. bottle fed	Not stated	Infancy	1–6 days	SBP: 0.0 (0.95); DBP: –0.7 (0.92)	Not given	None
Schachter, hospital births, Pittsburgh, Pennsylvania (1979) (40)	30; 141 (M + F)	Breastfed vs. bottle fed	Not stated	Infancy	6 months	White ethnicity: SBP: –0.5 (1.8); DBP: –1.5 (1.3). Black ethnicity: SBP: 3.3 (3.3); DBP: 5.8 (3.5)	Not given	Results stratified by ethnicity
Studies excluded from the meta-analysis								
Cohen, neonates born at two hospitals, United States (1992) (47)	7; 11 (M + F)	Breastfed, bottle fed	Not stated	Infancy	24–94 hours (mean: 55 hours)	During a feed; blood pressure of breastfed babies approximately 15 mmHg higher than those bottle fed but about 2 mmHg higher (derived from figure 2) before and 30–60 minutes after a feed		
de Swiet, 500 infants born in a hospital in Kent, England (1977) (39)	Not stated (M + F)	Breastfed, bottle fed	1975	Infancy	4 days and 6 weeks	No differences in blood pressure levels between infants breastfed vs. bottle fed		

* M, male; F, female; SBP, systolic blood pressure; DBP, diastolic blood pressure.

economic factors showed smaller systolic blood pressure differences between breast- and bottle-fed subjects. The distribution of breastfeeding was less socially determined before World War II (52) compared with now (10), and results from prewar cohorts may be free from confounding by social class (53). The two prewar studies reviewed showed little evidence of any association between breastfeeding and blood pressure (13, 19), although nondifferential misclassification is a possibility in the Caerphilly cohort that relied on recall of breastfeeding status 44–60 years after infancy (19), and the Dutch famine cohort may not be generalizable (13). Accelerated postnatal weight gain is a potential confounding factor because it is associated with raised blood pressure (54) and may influence infant feeding practices (55). In the only study to examine this issue (43), the association of breastfeeding with blood pressure was not altered by postnatal growth.

Relevance to contemporary cohorts

Modern formula feeds, which more closely resemble the nutrient content of breast milk, were not developed until the mid-1970s (56). Previously, bottle-fed infants were given unmodified cow's milk preparations and other alternatives such as condensed milk (52, 57). Several studies of infants born since 1980, however, show a blood-pressure-lowering effect of breastfeeding (8, 15, 20, 25, 26, 43), suggesting that if the results are causal, they are relevant to modern cohorts.

Population health implications

Reductions in population mean blood pressure levels of as little as 2 mmHg could reduce the prevalence of hypertension by up to 17 percent, the number of coronary heart disease events by 6 percent, and strokes and transient ischemic attacks by 15 percent (9, 58). This reduction equates to preventing 3,000 coronary heart disease events and 2,000 strokes annually among those under age 75 years in the United Kingdom (59). The effect estimates from our meta-analysis could therefore translate into the prevention of a substantial number of deaths annually.

Mechanisms

Breastfeeding could influence blood pressure via a variety of mechanisms, including 1) reducing sodium intake in infancy (60); 2) increasing intake of long-chain polyunsaturated fatty acids, important structural components of tissue membrane systems, including the vascular endothelium (25); and 3) protecting against hyperinsulinemia in infancy (61–63) and insulin resistance in early life (64), adolescence (65), and adulthood (13), processes that may in turn raise blood pressure via a number of mechanisms (66).

The concomitant association of breastfeeding with both taller stature (particularly leg length) (67, 68) and lower blood pressure is in line with previously reported inverse relations between stature (particularly leg length) and blood pressure in adulthood (64, 69). Height and leg length may reflect the dynamic properties of the arterial tree, with short height increasing the systolic peak because of the early return of reflected arterial pulse waves (64). Two studies that controlled for current height found that this made very little difference to effect estimates (34, 43), suggesting that height may not be on the causal pathway between breastfeeding and blood pressure. Alternatively, breastfeeding may program both growth rate and the formation of blood pressure control mechanisms (70).

Conclusions

Breastfeeding is inversely associated with blood pressure, but the possibility of publication bias and residual confounding cannot be excluded. If causal, the observed reduction in blood pressure associated with breastfeeding may have a small, but important effect on public health, especially in populations where early bottle feeding is common.

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All three authors developed the hypothesis. R. M. M. acquired the data, performed the analysis, wrote the first draft of the paper, and coordinated its completion under the supervision of G. D. S. and D. G. The first draft was significantly revised after comments from these two authors. All authors contributed to and approved the final version.

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REFERENCES

1. Stary HC. Lipid and macrophage accumulations in arteries of children and the development of atherosclerosis. Am J Clin Nutr 2000;72:1297S–306S.
2. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998;338:1650–6.
3. Zinner SH, Martin LF, Sacks F, et al. A longitudinal study of blood pressure in childhood. Am J Epidemiol 1974;100:437–42.
4. Barker DJP. Mothers, babies and health in later life. London, United Kingdom: Churchill Livingstone, 1998.
5. McCarron P, Davey Smith G, Okasha M, et al. Blood pressure in young adulthood and mortality from cardiovascular disease. Lancet 2000;355:1430–1.
6. Geleijnse JM, Hofman A, Witteman JCM, et al. Long-term effects of neonatal sodium restriction on blood pressure. Hypertension 1997;29:913–17.
7. Martin RM, McCarthy A, Davies DP, et al. Association between infant nutrition and blood pressure in early adulthood: the Barry Caerphilly Growth cohort study. Am J Clin Nutr 2003;77:1489–97.
8. Wilson AC, Forsyth JS, Greene SA, et al. Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study. BMJ 1998;316:21–5.
9. Cook NR, Cohen J, Hebert PR, et al. Implications of small reductions in diastolic blood pressure for primary prevention. Arch Intern Med 1995;155:701–9.
10. Foster K, Lader D, Cheesborough S. Infant feeding 1995: a survey of infant feeding practices in the United Kingdom carried out by the Social Survey Division of ONS on behalf of the Department of Health, the Scottish Office Department of Health, the Welsh Office and the Department of Health and Social Services in Northern Ireland. London, United Kingdom: The Stationary Office, 1997.
11. Frankel S, Davey Smith G, Gunnell D. Childhood socioeconomic position and adult cardiovascular mortality: the Boyd Orr Cohort. Am J Epidemiol 1999;150:1081–4.
12. Leeson CP, Kattenhorn M, Deanfield JE, et al. Duration of breast feeding and arterial distensibility in early adult life: population based study. BMJ 2001;322:643–7.
13. Ravelli ACJ, van der Meulen JH, Osmond C, et al. Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. Arch Dis Child 2000;82:248–52.
14. Taittonen L, Nuutinen M, Turtinen J, et al. Prenatal and postnatal factors in predicting later blood pressure among children: cardiovascular risk in young Finns. Pediatr Res 1996;40:627–32.
15. Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. Lancet 2001;357:413–19.
16. Lucas A, Morley R. Does early nutrition in infants born before term programme later blood pressure? BMJ 1994;309:304–8.

17. Simmons D. NIDDM and breastfeeding. Lancet 1997;350:157–8.
18. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, eds. Systematic reviews in health care: meta-analysis in context. London, United Kingdom: BMJ Publishing Group, 2003:285–312.
19. Martin RM, Ben-Shlomo Y, Gunnell D, et al. Breastfeeding and cardiovascular disease risk factors, incidence and mortality: the Caerphilly Study. J Epidemiol Community Health (in press).
20. Lawlor DA, Najman JM, Sterne J, et al. 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 2004;110:2417–23.
21. Sterne JAC, Egger M, Davey Smith G. Investigating and dealing with publication and other biases. In: Egger M, Davey Smith G, Altman DG, eds. Systematic reviews in health care: meta-analysis in context. London, United Kingdom: BMJ Publishing Group, 2001:189–208.
22. Baranowski T, Bryan GT, Harrison JA, et al. Height, infant-feeding practices and cardiovascular functioning among 3 or 4 year old children in three ethnic groups. J Clin Epidemiol 1992; 45:513–18.
23. Cobaleda Rodrigo A, Hidalgo Vicario MI, Plaza Perez I, et al. Prevalence of breast feeding and its relation to cardiovascular risk factors in the pediatric population of Fuenlabrada. (In Spanish). An Esp Pediatr 1989;31:350–5.
24. Marmot MG, Page CM, Atkins E, et al. Effect of breast feeding on plasma cholesterol and weight in young adults. J Epidemiol Community Health 1980;34:164–71.
25. Forsyth JS, Willatts P, Agostoni C, et al. Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood. BMJ 2003;326:953–5.
26. Smith RE, Kok A, Rothberg AD, et al. Determinants of blood pressure in Sowetan infants. S Afr Med J 1995;85:1339–42.
27. Kolacek S, Kapetanovic T, Luzar V. Early determinants of cardiovascular risk in adults. B. Blood pressure. Acta Paediatr 1993;82:377–82.
28. Kolacek S, Kapetanovic T, Zimolo A, et al. Influence of early infant nutrition on cardiovascular risk factors in adults. (In Croatian). Arhiv Za Zastitu Majke i Djeteta 1990;34:215–26.
29. Strbak V, Hromadova M, Kostalova L, et al. Search for optimal age for weaning. Ten year prospective study. Endocr Regul 1993;27:215–21.
30. Strbak V, Skultetyova M, Hromadova M, et al. Late effects of breast-feeding and early weaning: seven year prospective study in children. Endocr Regul 1991;25:53–7.
31. Roberts SB. Prevention of hypertension in adulthood by breast-feeding? Lancet 2001;357:406–7.
32. Zinner SH, Lee YH, Rosner B, et al. Factors affecting blood pressures in newborn infants. Hypertension 1980;2:99–101.
33. Fall C. Nutrition in early life and later outcome. Eur J Clin Nutr 1992;46:S57–S63.
34. Whincup PH, Cook DG, Shaper AG. Early influences on blood pressure: a study of children aged 5–7 years. BMJ 1989;299: 587–91.
35. Zeman J, Simkova M. Blood pressure values in infants and young children in relation to the duration of breast feeding. (In Czech). Ceska Slov Pediatr 1981;36:593–4.
36. Boulton J. Nutrition in childhood and its relationships to early somatic growth, body fat, blood pressure, and physical fitness. Acta Paediatr Scand Suppl 1981;284:1–85.
37. Simpson A, Mortimer JG, Silva PA, et al. Correlates of blood pressure in a cohort of Dunedin seven year old children. In: Onesti G, Kim KE, eds. Hypertension in the young and the old. New York, NY: Grune and Stratton, 1981:155–63.
38. Lucas A, Morley R, Hudson GJ, et al. Early sodium intake and later blood pressure in preterm infants. Arch Dis Child 1988;63: 656–7.
39. de Swiet M, Shinebourne EA. Blood pressure in infancy. Am Heart J 1977;94:399–401.
40. Schachter J, Kuller LH, Perkins JM, et al. Infant blood pressure and heart rate: relation to ethnic group (black or white), nutrition and electrolyte intake. Am J Epidemiol 1979;110:205–18.
41. Fall CHD, Osmond C, Barker DJP, et al. Fetal and infant growth and cardiovascular risk factors in women. BMJ 1995; 310:428–32.
42. Viikari J, Akerblom HK, Rasanen L, et al. Cardiovascular risk in young Finns. Experiences from the Finnish Multicentre Study regarding the prevention of coronary heart disease. Acta Paediatr Scand Suppl 1990;365:13–19.
43. Martin RM, Ness AR, Gunnell D, et al. Does breastfeeding in infancy protect against obesity in childhood? The Avon Longitudinal Study of Parents and Children. Circulation 2004;109: 1259–66.
44. Von Kries R, Koletzko B, Sauerwald T, et al. Breast feeding and obesity: cross sectional study. BMJ 1999;319:147–50.
45. Pomeranz A, Dolfin T, Korzets Z, et al. Increased sodium concentrations in drinking water increase blood pressure in neonates. J Hypertens 2002;20:203–7.
46. Bernstein HM, Cooper PA, Turner MJ. Dynamic skinfold thickness measurement in infants fed breast-milk, low- or high-sodium formula. S Afr Med J 1990;78:644–8.
47. Cohen M, Witherspoon M, Brown DR, et al. Blood pressure increases in response to feeding in the term neonate. Dev Psychobiol 1992;25:291–8.
48. Owen CG, Whincup PH, Gilg JA, et al. Effect of breast feeding in infancy on blood pressure in later life: systematic review and meta-analysis. BMJ 2003;327:1189–95.
49. Law CM, de Swiet M, Osmond C, et al. Initiation of hypertension in utero and its amplification throughout life. BMJ 1993; 306:24–7.
50. Kark JD, Troya G, Friedlander Y, et al. Validity of maternal reporting history and the association with blood lipids in 17 year olds in Jerusalem. J Epidemiol Community Health 1984; 38:218–25.
51. Vobecky JS, Vobecky J, Froda S. The reliability of the maternal memory in a retrospective assessment of nutritional status. J Clin Epidemiol 1988;41:261–5.
52. Fildes V. Infant feeding practices and infant mortality in England, 1900–1919. Continuity Change 1998;13:251–80.
53. Wadsworth M, Marshall S, Hardy R, et al. Breast feeding and obesity: relation may be accounted for by social factors. (Letter). BMJ 1999;319:1576.
54. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens 2000;18: 815–31.
55. Ounsted M, Sleigh G. The infant's self-regulation of food intake and weight gain. Difference in metabolic balance after growth constraint or acceleration in utero. Lancet 1975;1:1393–7.
56. Department of Health. Guidelines on the nutritional assessment of infant formulas. Report of the Working Group on the Nutritional Assessment of Infant Formulas of the Committee on Medical Aspects of Food and Nutrition Policy. London, United Kingdom: The Stationary Office, 1996.
57. Department of Health and Social Security. Present day practice in infant feeding. London, United Kingdom: HMSO, 1974.
58. Stamler R. Implications of the INTERSALT study.

Hypertension 1991;17:I16–I20.
59. Petersen S, Rayner M, Press V. Coronary heart disease statistics: 2000 edition. London, United Kingdom: British Heart Foundation, 2001.
60. Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. JAMA 1983;250:370–3.
61. Lucas A, Sarson DL, Blackburn AM, et al. Breast vs. bottle: endocrine responses are different with formula feeding. Lancet 1980;1:1267–9.
62. Salmenpera L, Perheentupa J, Siimes MA. Exclusively breast-fed healthy infants grow slower than reference infants. Pediatr Res 1985;19:307–12.
63. Axelsson IE, Ivarsson SA, Raiha NC. Protein intake in early infancy: effects on plasma amino acid concentrations, insulin metabolism, and growth. Pediatr Res 1989;26:614–17.
64. Langenberg C, Hardy R, Kuh D, et al. Influence of height, leg and trunk length on pulse pressure, systolic and diastolic blood pressure. J Hypertens 2003;21:537–43.
65. Singhal A, Fewtrell M, Cole TJ, et al. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089–97.
66. Reaven G, Hoffman BB. A role for insulin in the aetiology and course of hypertension? Lancet 1987;2:435–7.
67. Martin RM, Davey Smith G, Mangtani P, et al. Association between breast feeding and growth: The Boyd-Orr cohort study. Arch Dis Child Fetal Neonatal Ed 2002;87:F193–F201.
68. Wadsworth ME, Hardy RJ, Paul AA, et al. Leg and trunk length at 43 years in relation to childhood health, diet and family circumstances; evidence from the 1946 national birth cohort. Int J Epidemiol 2002;31:383–90.
69. Gunnell D, Whitley E, Upton MN, et al. Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. J Epidemiol Community Health 2003;57:141–6.
70. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? Lancet 2004;363:1642–5.

APPENDIX

MEDLINE Search Strategy for Systematic Review

1 exp Infant Nutrition/
2 (breast adj3 (feeding or fed)).tw.
3 infant diet$.tw.
4 Bottle Feeding/
5 (bottle adj3 (feeding or fed)).tw.
6 (artificial adj3 (feeding or fed)).tw.
7 weaning.tw.
8 Milk, Human/
9 breast milk.tw.
10 dried milk.tw.
11 (infant adj3 nutrition).tw.
12 infant diet$.tw.
13 infant feeding.tw.
14 early nutrition.tw.
15 infant food.tw.
16 breastfeeding.tw.
17 breastfed.tw.
18 breastmilk.tw.
19 or/1–18
20 exp “Body Weights and Measures”/
21 body mass index.tw.
22 bmi.tw.
23 exp Obesity/
24 overweight.tw.
25 (obese or obesity).tw.
26 leg length.tw.
27 sitting height.tw.
28 weight.tw.
29 height.tw.
30 exp Growth/
31 child$ growth.tw.
32 Cardiovascular Diseases/
33 exp Myocardial Ischemia/
34 exp Vascular Diseases/
35 exp Cholesterol/
36 exp Lipids/
37 lipid$.tw.
38 cholesterol.tw.
39 triglyceride$.tw.
40 cardiovascular.tw.
41 (coronary adj3 disease$).tw.
42 ldl.tw.
43 lipoprotein$.tw.
44 hdl.tw.
45 hypertension.tw.
46 blood pressure.tw.
47 (systolic or diastolic).tw.
48 exp Diabetes Mellitus/
49 diabetes.tw.
50 (niddm or iddm).tw.
51 insulin resistan$.tw.
52 glucose intolerance.tw.
53 or/20–52
54 animal/ not human/
55 53 not 54
56 55 and 19
57 exp Epidemiologic Studies/