Abstract

Blood pressure in adulthood has a strong influence on risk of coronary heart disease and stroke. It has been postulated that factors operating in early life (in utero and in infancy and childhood), influence the development of blood pressure in adulthood, and that nutrition early in life may programme subsequent blood pressure.

Small observational studies suggest that breast feeding may be related to noticeably lower blood pressure in childhood. Similar conclusions were reached by a follow up study of participants in a randomised controlled trial of feeding in preterm infants. Not all published studies have reported an association. We performed a systematic review to examine whether there are consistent mean differences in blood pressure between adults who were initially breast fed or bottle fed with formula milk.

Methods

We searched Embase, Medline, and Web of Science databases for published papers, letters, abstracts, and review articles on the effects of feeding in infancy on blood pressure. Relevant references were identified using a combined text word and MESH or subject heading (for Medline and Embase only) search strategy of infant feeding (breast fed, feed{s/ing}, milk; milk, human; bottle fed, feed{s/ing}; infant feed{s/ing}, nutrition; formula fed, feed{s/ing}) and blood pressure (blood pressure, or hypertension). We restricted our review to studies in humans.

The electronic search (completed March 2003) identified 339 references; a review of the abstracts showed that 35 were potentially relevant and an additional 10 were likely to have relevant data. We excluded 16 of these 45 papers after further review. Thus 29 papers were considered relevant because either the abstract indicated that blood pressure had been measured in different infant feeding groups or the data were provided. For all studies we sought the difference in systolic and diastolic blood pressure between those exclusively breast fed and those exclusively bottle fed, adjusted for current age and sex (if appropriate) and for height and body mass index. In studies including different ethnic groups, we sought additional adjustment for ethnicity. Information was obtained from 14 of the 29 studies directly (with various levels of adjustment), and we approached the investigators of the other studies for further results. Results were obtained for 11 of these studies; we had direct access to two, and we obtained data from the archives of the 1970 British cohort study (10 year olds). No responses were elicited for four studies; two were large, well conducted, observational studies, and the others were small ( < 100 participants) and in infants and children (aged 1 and 6, respec-

Introduction

Blood pressure in adulthood has a strong influence on risk of coronary heart disease and stroke. It has been postulated that factors operating in early life (in utero and in infancy and childhood), influence the development of blood pressure in adulthood, and that nutrition early in life may programme subsequent blood pressure.

The influence of breast feeding on blood pressure is of interest because of the differing composition of breast milk and formula milk, particularly the sodium and fatty acid content. Until the 1980s the sodium content of breast milk in Western countries was much lower than that of formula milk. Low sodium intake in infancy has been related to lower levels of blood pressure both in the short term and in the long term. Long chain polyunsaturated fatty acids are present in breast milk but not in formula milk. These play an important part in the vascular endothelium and, when given as nutritional supplements, seem to reduce blood pressure in adults and children.

Similar conclusions were reached by a follow up study of participants in a randomised controlled trial of feeding in preterm infants. Not all published studies have reported an association. We performed a systematic review to examine whether there are consistent mean differences in blood pressure between adults who were initially breast fed or bottle fed with formula milk.
One reviewer (CGO) completed the search and extracted data from the studies on two occasions. The 25 studies for which data were obtained had information on systolic blood pressure and 22 also had data on diastolic blood pressure. One study gave three estimates, providing 27 estimates of systolic blood pressure and 24 estimates of diastolic blood pressure.

Differences in blood pressure between infant feeding groups were collected on more than one occasion in three studies from the same cohort. In these studies data from the earliest age was used for overall estimates. In one of these studies, with high response rates (at 7 years and 18 years), both estimates were used in the age specific analysis. Overall, there were 26 estimates of systolic blood pressure and 23 estimates of diastolic blood pressure.

In most studies the feeding groups were separate; in one study the breastfed infants were partly bottle fed and in another study the bottle fed infants were partly breast fed. In 10 additional studies we were unable to verify the exclusiveness of infant feeding. Bottle fed infants receiving standard formulas were included in preference to those receiving specially supplemented formulas. Except for one study, we were able to systematically exclude these from the analysis.

Statistical analysis

In the meta-analysis we used the mean difference in systolic blood pressure between infant feeding groups (breast fed and bottle fed) and the standard error of the difference from individual studies. The META command in STATA was used across studies to test for heterogeneity of the differences in systolic blood pressure between infant feeding groups. Because heterogeneity was noticeable, we produced pooled estimates of the difference in systolic blood pressure using random effects models. Publication bias was assessed with funnel plots. Begg and Egger tests were also performed. Analyses were carried out after stratifying by study size in three groups chosen a priori: less than 300 participants; 300 to 1000 participants; and more than 1000 participants. The METAREG command was used to explore whether there were differences between age groups based on the mean age of the sample (infants ≤ 1 year, children > 1 to 16 years, adolescents and adults > 16 years), dates of birth (including whether born before or after 1980), the impact of ascertaining infant feeding status in infancy or by parental questionnaire at least three years after birth, and the difference in effect size between studies that reported on the association between infant feeding and blood pressure and those that did not. The effect of adjustment for current body size (height and body mass index) was also examined in 10 studies (12 observations), with data before and after adjustment.

Assessment of study quality

Methods for defining study quality in observational studies are less clearly defined than those for experimental studies. We used sensitivity analyses to examine the effects of different methods of ascertaining exposure (particularly contemporary ascertainment or recalled ascertainment) and to examine the effects of excluding groups that used mixed feeding methods. It

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Fig 1 Mean differences in systolic blood pressure (95% confidence intervals) between breastfed and bottle fed participants. Box area proportional to inverse of variance, with horizontal lines showing 95% confidence intervals. Y axis in ascending order of mean age (years) at which blood pressure was measured. Dashed vertical line and diamond (95% confidence interval) is pooled estimate based on a random effects model.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Source</th>
<th>Year born</th>
<th>Age at blood pressure measurement</th>
<th>No breast fed, No bottle fed</th>
<th>Formula type, comments</th>
<th>Exclusive feeding groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen**</td>
<td>CS</td>
<td>Born at North Central Bronx Hospital or Newark Israel Medical Center, USA</td>
<td>In infancy</td>
<td>NS</td>
<td>55 hours</td>
<td>7, 11</td>
<td>NS</td>
</tr>
<tr>
<td>Zinner**</td>
<td>CS</td>
<td>Born at Boston City Hospital or Women's &amp; Infants Hospital, Rhode Island, USA</td>
<td>In infancy</td>
<td>NS</td>
<td>1-6 days</td>
<td>154, 264</td>
<td>NS</td>
</tr>
<tr>
<td>Dillon†</td>
<td>CS</td>
<td>Born at Queen Charlotte's Maternity Hospital, London, UK</td>
<td>In infancy</td>
<td>NS</td>
<td>6 days</td>
<td>14, 8</td>
<td>Standard formula including Baby Milk Plus, Cow and Gate</td>
</tr>
<tr>
<td>Bernstein</td>
<td>CS</td>
<td>Born in Johannesburg Hospital, South Africa</td>
<td>In infancy</td>
<td>1987-8</td>
<td>6 weeks</td>
<td>43, 39</td>
<td>Yes, exclusively breast fed or formula fed</td>
</tr>
<tr>
<td>Schachter**</td>
<td>C</td>
<td>Born at a large obstetric and gynaecological hospital, USA</td>
<td>Maternal records in infancy</td>
<td>NS</td>
<td>6 months</td>
<td>30, 141</td>
<td>Not known</td>
</tr>
<tr>
<td>Pomerantz**</td>
<td>C</td>
<td>Born in Meer General Hospital, Israel</td>
<td>In infancy</td>
<td>1987-8</td>
<td>6 weeks</td>
<td>43, 39</td>
<td>Standard formula diluted with mineral water or tap water</td>
</tr>
<tr>
<td>Boulton**</td>
<td>CS</td>
<td>Born in Queen Victoria's Hospital, seen at Adelaide Children's Hospital, Australia</td>
<td>In infancy</td>
<td>1976-9</td>
<td>1 year</td>
<td>14, 47</td>
<td>Formula fed including cow milk, lactogen, proprietary simulated breast milk.</td>
</tr>
<tr>
<td>Zeman**</td>
<td>CS</td>
<td>Born at Czech Children's Hospital, Prague, Czech Republic</td>
<td>In infancy</td>
<td>NS</td>
<td>8-26 months</td>
<td>42, 13</td>
<td>Formula fed dried cows' milk</td>
</tr>
<tr>
<td>Baranowski†‡</td>
<td>CS</td>
<td>Studies of Children Activity and Nutrition in Texas, USA</td>
<td>Parental interview</td>
<td>1981-3</td>
<td>3-4 years</td>
<td>60, 185</td>
<td>Standard formula including Enfamil, Similac, SMA</td>
</tr>
<tr>
<td>Whincup†</td>
<td>CS</td>
<td>Subjects recruited from 9 of 24 towns involved in the British Regional Heart Study, UK</td>
<td>Parental questionnaire at 5-8 years</td>
<td>1979-83</td>
<td>5-8 years</td>
<td>1221, 1787</td>
<td>Standard formula</td>
</tr>
<tr>
<td>Forsyth†</td>
<td>CS</td>
<td>Recruited from four European centres (Dundee, Birmingham, UK; Leuven, Belgium; Milan, Italy)</td>
<td>In infancy</td>
<td>1992</td>
<td>5.8 years</td>
<td>83, 71</td>
<td>Standard formula</td>
</tr>
<tr>
<td>Williams**‡</td>
<td>C</td>
<td>Dundon Multidisciplinary; Health and Development Study</td>
<td>Parental questionnaire at 3 years</td>
<td>1972-3</td>
<td>7 and follow up at 18</td>
<td>192, 327; 197, 319</td>
<td>NS</td>
</tr>
<tr>
<td>Wilson†</td>
<td>C</td>
<td>Dundee infant feeding study, Scotland</td>
<td>In infancy</td>
<td>1985-6</td>
<td>6-10 years</td>
<td>73, 99</td>
<td>Bottle fed</td>
</tr>
<tr>
<td>Lucas†</td>
<td>RCT</td>
<td>Born at Norwegian, Cambridge, Sheffield, Ipswich, and King's Lynn neonatal units, UK &lt;1.85 kg birth weight</td>
<td>In infancy</td>
<td>1982-85</td>
<td>7.5-8 Years</td>
<td>66, 60</td>
<td>Standard formula (Farley's Ostermilk)</td>
</tr>
<tr>
<td>Runa**‡</td>
<td>CS</td>
<td>National Study of Health and Growth England 1993 sample; England 1984 sample; Scotland 1994 sample</td>
<td>All parental questionnaire at 9 years</td>
<td>1983-5; 1984-1985</td>
<td>All 8-9 years</td>
<td>157, 308; 213, 318; 124, 273</td>
<td>All not known</td>
</tr>
<tr>
<td>Esposito-Di Piuente**</td>
<td>CS</td>
<td>Children from a primary school in Naples, Italy</td>
<td>Parental questionnaire at 9-11 years</td>
<td>1980-2</td>
<td>9-11 years</td>
<td>43,17</td>
<td>Standard formula</td>
</tr>
<tr>
<td>BCS70**†</td>
<td>C</td>
<td>National Child Development Study and British Cohort Study 1970</td>
<td>Parental questionnaire at 5 years</td>
<td>1970</td>
<td>10 years</td>
<td>951, 5133</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ten Towns Heart Health Study**</td>
<td>Mixed C</td>
<td>Ten Towns Heart Health Study, UK</td>
<td>Parental questionnaire at 5-7 years</td>
<td>1982-6</td>
<td>13-16 (mean 15) years</td>
<td>980, 951</td>
<td>Standard formula</td>
</tr>
<tr>
<td>Taittonen†</td>
<td>C</td>
<td>Part of Cardiovascular Risk Study in Finns</td>
<td>Parental questionnaire</td>
<td>1962-74</td>
<td>17 years</td>
<td>760, 150</td>
<td>NS</td>
</tr>
<tr>
<td>Kolacek**</td>
<td>C</td>
<td>Born in three locations in Croatia</td>
<td>In infancy</td>
<td>1968-9</td>
<td>18-23 years</td>
<td>199, 78</td>
<td>27% bottle fed, 73% fed diluted cows' milk</td>
</tr>
</tbody>
</table>

Continued on next page
was not possible to distinguish formally on quality of blood pressure measurement (nearly all studies used automated machines) or on response rates, which were not provided for many studies.

**Results**

From 24 studies we obtained 26 mean differences in systolic blood pressure and 25 in diastolic blood pressure (table 1). All
were observational studies, except for one randomised controlled trial in preterm infants.14 Non-randomised comparisons of breastfed and bottle fed infants were obtained from another randomised controlled trial.15 Eight observations on systolic blood pressure were in infants, 12 were in children, and six were in adults (fig 1). In a random effects model including all studies, mean systolic blood pressure was lower in breastfed participants than in bottle fed participants (−1.10 mm Hg, 95% confidence interval −1.78 to −0.42 mm Hg). We found noticeable heterogeneity between studies ($\chi^2 = 59.4, df = 25, P < 0.001$). No consistent difference was, however, found between the three age groups (P = 0.601) or between studies in participants born before and after 1980 (P = 0.832, table 2).

Studies that reported noticeable and statistically significant differences in blood pressure between feeding groups were mostly small, raising the possibility of publication bias (see fig 1). Even studies with such bias was provided by a funnel plot (fig 2). The Egger test was significant (P = 0.033) for publication bias but not the Begg test (P = 0.186). The estimate of effect size decreased with increasing study size: −2.05 mm Hg in the 13 studies with fewer than 300 participants, −1.13 mm Hg in the seven studies (nine observations) with 300 to 1000 participants, and −0.16 mm Hg in the four studies with more than 1000 participants (test for trend between groups P = 0.046). However, a test for trend with study size treated as a continuous variable, was not significant (P = 0.209). In 10 studies (12 observations) in which we were able to examine the effect of adjustment for current body size, the difference was similar both before and after adjustment. The effect size seemed greatest in 16 studies that had reported on the association between infant feeding method and systolic blood pressure (−1.67 mm Hg, −2.80 to −0.53 mm Hg) than in 10 studies that did not (−0.54 mm Hg, −1.36 to 0.28 mm Hg). This difference was not, however, significant (P = 0.194).

Mean diastolic blood pressure showed no noticeable difference between breastfed and bottle fed groups (fig 3 and table 2). In a random effects model, breastfed participants had similar mean diastolic blood pressure to bottle fed participants (−0.36 mm Hg, −0.79 to 0.08 mm Hg). Significant heterogeneity was found between studies ($\chi^2 = 38.9, df = 22, P = 0.014$), although there was no consistent difference between age groups (P = 0.96) and no difference between participants born before and after 1980 (P = 0.80). This difference was unaltered when the analysis was restricted to studies that adjusted for current body size. We found no evidence of publication or inclusion bias, and the results were similar for studies of different sizes.

The difference in blood pressure between feeding groups was unaltered by infant feeding status being recorded in infancy (n = 15) or by parent administered questionnaire (n = 11) at least three years after birth (P = 0.595).16,17 No important effects were found on the results for either systolic or diastolic blood pressure after the exclusion of 12 studies where feeding was not exclusive or could not be confirmed.18,19 We did not adjust for sex in our analysis.

**Discussion**

Our systematic review found that publication bias may partly explain the lower mean systolic blood pressure observed in participants that had been breast fed in infancy, with large studies showing little difference. Studies with more than 1000 participants, which are less subject to publication bias, reliably excluded a mean difference greater than 0.6 mm Hg, suggesting an effect of little clinical or public health importance. Feeding in infancy was not significantly associated with diastolic blood pressure.

Even if publication bias is discounted, the overall difference in systolic blood pressure of 1.1 mm Hg is modest. The relatively weak association between infant feeding and systolic blood pressure is not likely to reflect imprecise ascertainment of early feeding practices, as most were documented either during infancy from health records or from questionnaires administered to parents, the accuracy of which has shown to be valid up to 20 years after birth.20 In addition, the difference in blood pressure between feeding groups was similar in studies that recorded infant feeding status in infancy to those based on a parental questionnaire later in life.

Random allocation of infants to breast feeding or bottle feeding has been regarded as inappropriate, except in the special

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**Table 2** Random effects meta-analyses by subgroup (study size, age group, and of those born before and after 1980)

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>No of estimates of blood pressure</th>
<th>Mean (95% CI) difference in blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>By study size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300 participants</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>300-1000 participants</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>&gt;1000 participants</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>By age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants (&lt;1 years)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Children (&gt;1 to 16 years)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Adults (&gt;17 years)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>By year of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born before 1980</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Born after 1980</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

**Fig 2** Begg’s funnel plot (pseudo 95% confidence limits) showing mean difference in systolic blood pressure by standard error of mean difference.
circumstances of preterm birth, in which one randomised trial has been carried out.\(^1\) That trial showed no marked difference in blood pressure between 8 year old children who were breast fed or bottle fed as infants.\(^1\) A follow up examination showing noticeably higher mean blood pressures among bottle fed infants was based on only a quarter of the study population; at such low follow up rates the validity of the comparisons cannot be assumed, and the degree of control for the original study centre has been questioned.\(^2\) The other studies in this review were observational, so that there is a possibility of confounding, particularly by social factors, current body size, and diet in later life. However, since bottle feeding tends to be related to lower social class, a greater tendency to obesity, and a less healthy diet in later life, all of which are likely to be related to higher mean blood pressure, any confounding effects are likely to have exaggerated, rather than reduced, the extent to which mean blood pressure levels are higher among participants that were bottle fed.\(^3\)\(^4\)

Although our review effectively excludes any important overall lowering effect of breast feeding on blood pressure, it is possible that prolonged breast feeding has a protective effect.\(^5\) This issue requires further systematic examination.

We were unable to examine whether infants fed formula milk supplemented with long chain polyunsaturated fatty acids had lower blood pressure in childhood compared with infants fed standard formulas.\(^6\) The results do not, however, suggest that naturally occurring long chain polyunsaturated fatty acids in breast milk have an appreciable effect on blood pressure. The results from large studies effectively exclude the effect size observed in the recently reported small trial of supplementation with long chain polyunsaturated fatty acids, although the confidence intervals around that estimate were wide.\(^7\) The absence of marked differences in blood pressure between infant feeding groups (either before or after 1980) are also of interest because of the higher sodium content of formula milk up to 1980.\(^8\) In the 1970s, the average sodium intake of formula fed infants at one month of age in most of the populations studied here would have been around 20 mmol a day higher than that of infants who were breast fed.\(^9\) However, the interpretation of the results depends on the strength of association between sodium intake and blood pressure assumed. Using the large effect estimates derived from a randomised controlled trial of salt restriction in neonates, a 20 mmol a day difference might be expected to produce a difference in systolic blood pressure in the order of 5-6 mm Hg between infants that were breast fed or bottle fed—a difference that is easy to exclude among the infants in four studies before 1980 (data not presented).\(^1\) However, the more conservative effect estimates from systematic reviews of sodium reduction trials in adults would be consistent with differences between bottle fed and breastfed infants of 1-2 mm Hg, which would be considerably more difficult to exclude with confidence.\(^1\)\(^2\) The absence of any appreciable change in the size of this difference between the 1970s and 1990s, particularly in the largest studies, suggests that the effects of changing sodium intake in infancy on subsequent blood pressure have been modest.

**Conclusions**

The lower levels of systolic blood pressure associated with breast feeding in infancy identified in our review were observed mainly
What is already known on this topic

Early studies suggested that breast feeding in infancy may protect against high blood pressure in later life.

Many studies examining this effect have been small, raising the possibility of publication bias.

What this study adds

Selective publication of small studies shows that breast feeding reduces blood pressure in later life.

The effect in larger studies seems to be small and of limited clinical or public health importance.

in small studies; with little difference shown in studies of 1000 participants or more. The association of breast feeding and lower blood pressure may well be partly explained by publication bias. Hence the results of small studies showing large differences in blood pressure should be treated cautiously. Our analysis suggests that any effect of breast feeding on blood pressure is modest and of limited clinical or public health importance. However, blood pressure is not the only relevant outcome; the case for breast feeding rests on a combination of short and long term benefits, including improved neural and psychosocial development, potential protection against obesity and allergic disease, and lower blood cholesterol levels in later life. 19-26

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Contributors: CGO, PHW, and DGC had the idea for this paper: CGO extracted the data and carried out the statistical analysis with the support of JAG. CGO drafted the paper to which all authors contributed; he will act as guarantor for the paper.

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Ethical approval: Not required.

References


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