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Association of diarrhoea in childhood with blood pressure and coronary heart disease in older age: analyses of two UK cohort studies

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Abstract

Background—There is a suggestion that acute dehydration in childhood may lead to elevated blood pressure. We examined if episodes of diarrhoea in childhood, a recognized proxy for acute dehydration, were related to measured blood pressure and coronary heart disease in older adults.

Methods—Data were pooled from two prospective UK cohort studies (participants born 1920–39) in which episodes of diarrhoea were ascertained from health visitor records from birth until 5 years of age. Blood pressure and coronary heart disease were assessed during medical examination in men and women over 64 years of age. In total, 5203 men and women had data on diarrhoea in early life, adult blood pressure and a range of covariates; 4181 of these also had data on coronary heart disease status.

Results—The prevalence of diarrhoea in infancy (3.3%) and between 1 and 5 years (1.1%) was low. There was no relation of diarrhoea from either period (age- and sex-adjusted results for diarrhoea in infancy presented here) with measured blood pressure [coefficient for systolic; 95% CI (confidence interval): 0.44; −2.88–3.76] or coronary heart disease (Odds ratio, OR; 95% CI: 0.91; 0.54–1.54) in adulthood. There was a similar lack of association when hypertension was the outcome of interest. These observations were unchanged after adjustment for a range of covariates.

Conclusions—In the largest study to date to examine the relation, there was no evidence that diarrhoea in early life had an influence on measured blood pressure, hypertension or coronary heart disease in older adults.

Keywords

blood pressure; children; diarrhoea; hypertension; coronary heart disease

The concept of predictive adaptive response posits that prevailing environmental conditions during sensitive periods in early life lead to permanent phenotypic change.[1,2] For example, the human baby reacts to sub-optimal pre- or post-natal nutrition by slowing physical

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growth. Similarly, a bout of severe dehydration in infancy could ‘programme’ increased water, and hence salt, retention in response to an environmental forecast of a high risk of future life-threatening dehydration.[3] While such a response would have immediate survival advantages if subsequent episodes of dehydration were to occur, because salt retention also gives rise to elevated blood pressure[4], there could be deleterious effects in the longer term, particularly adult life.

This line of argument has been used to formulate the recently advanced hypothesis that diarrhoea in infancy, which is often accompanied by dehydration,[5] will predict raised blood pressure.[6] If shown to be correct, this hypothesis has considerable implications for the prevention of hypertension and cardiovascular disease by control of infant diarrhoea and concomitant dehydration, most obviously in low-income countries where diarrhoea is common.

There is some indirect support for a link between diarrhoea and raised blood pressure or coronary heart disease. First, in an ecological study, adult coronary heart disease, an established risk factor for which is raised blood pressure, was positively correlated with infant mortality rates ascribed to diarrhoea and enteritis some 50 years earlier.[7] However, somewhat counter to this finding, in the Interheart study in which blood pressure was the outcome of interest, a negative rather than positive association with infant mortality rates was apparent.[8] Second, in population-based studies at the level of the individual, infant or perinatal death in one or more siblings[9] and a higher number of siblings[10]—both correlates of diarrhoea—have been shown to predict both total cerebrovascular disease and haemorrhagic stroke in adulthood. The latter is the health end point most strongly associated with blood pressure. Third, in a randomized control trial, sodium restriction in the first six months of life—the physiological converse of dehydration—was associated with lower mean blood pressure at 15 years of age.[11] Fourth, a recent study has shown that women who experienced climatic conditions in the first year of life that were most likely to result in dehydration (summers with higher temperature, lower rainfall) had increased levels of systolic blood pressure in older age.[12] Fifth, in a large cohort of UK children, raised levels of diastolic but not systolic blood pressure at 7 years of age were seen in the very small number (6/7840) who experienced hospital admission for dehydration in the first 6 months of life.[6] Finally, in the same study, salt consumption from carer-completed food and drink diaries at 4, but not 8, months of age was positively associated with systolic, but not diastolic, blood pressure at 7 years of age.[13]

Given that blood pressure in middle- and older age is likely to have a greater influence on subsequent cardiovascular disease risk than blood pressure measured earlier in life,[14] it is important to directly examine the relation, if any, of dehydration in early life, as proxied by diarrhoea, with blood pressure in older age groups. However, to date, no such study exists. In the English county of Hertfordshire in the first half of the 20th century, health visitors kept records of childhood illness, including diarrhoea, from birth up until 5 years of age. In mid- to older age, these persons, representing two retrospective cohort studies, were invited for medical examination. These data give us the opportunity of exploring critical periods of childhood diarrhoea, if any, in relation to not only adult blood pressure but also coronary heart disease.

Subjects and methods

In Hertfordshire between 1911 and 1948, each birth was notified by the attending midwife and the birthweight recorded. Periodically, health visitors examined the baby at home during infancy and up to the age of 5 years. When the children were one year old, the health visitors recorded their weight, feeding method (classified as breast-fed, bottle-fed or a combination thereof in the first year of life), and whether they had experienced diarrhoea in the preceding year, amongst other health conditions. Subsequently, the health visitors also recorded diarrhoeal episodes between the ages of 1 and 5 years. In the present analyses, we used diarrhoea as a proxy for dehydration, a common complication of the illness.[5]

We utilized the National Health Service Central Register (Southport) to trace men and women who were singleton births, had both birthweight and infant weight recorded, and were still resident in the county of Hertfordshire. These persons were represented by two birth cohorts, details of which were given in Table 1. Between 1989 and 1995, individuals born 1920–30 in three areas of Hertfordshire and still residing there were invited to take part in follow-up health surveys to examine the relations between early environment and susceptibility to disease in later life.[15–18] Between 1998 and 2004, we also traced and surveyed men and women who were born in 1931–39 (known as the ‘Hertfordshire Cohort Study’).[19]

In both cohorts, participants were interviewed at home by research nurses who obtained information on medical and social history. Father’s occupation was used to define social class at birth, and current social class was derived from the participant’s own occupation or, in the case of housewives, their husband’s. After the interview, participants were invited to attend a clinic for further detailed clinical investigations. Blood pressure was measured during the home visit (in the case of studies conducted prior to 1998) or during the clinic visit (in the case of the Hertfordshire Cohort Study) with an automated recorder (Dinamap) while the participant was seated. Two readings were taken (three in the Hertfordshire Cohort Study) on the left arm using the cuff size recommended for the arm circumference; the average reading was used in the present analyses. Height was measured with a portable stadiometer and weight with a Seca scale. Hypertension was defined as blood pressure ≥160/≥100 mmHg[20] and/or self-reported treatment with anti-hypertensive medication.

The Rose/WHO chest pain questionnaire[21] was utilized and standard 12 lead electrocardiography administered according to the 1982 Minnesota protocol.[22] Electrocardiograms were Minnesota-coded independently and in duplicate by two trained coders who were blind to all other data. In the current analyses, coronary heart disease was defined as the presence of one or more of the following: angina according to the questionnaire on chest pain (stage I or II); electrocardiography Minnesota codes 1-1, 1-2 (Q and QS codes) or a history of surgery for coronary revascularization, either coronary artery bypass graft or coronary angioplasty. In keeping with previous analyses, our criteria did not include a history of heart attack because of possible error of recall or diagnosis.[16,17]

Statistical analysis

We used ANOVA and χ^2 test to examine the characteristics of the participants. Multiple linear regression was used to explore the relation between diarrhoea in early life and adult blood pressure, controlling for potential confounding factors. The recorded blood pressures of individuals treated for hypertension is likely to be lower than their inherent, untreated levels. Without appropriate correction, this could result in underestimates of the effect of potential determinants and reduced statistical power.[23] For the purposes of the linear regression analyses, we therefore adjusted the recorded blood pressures of treated individuals, based on known treatment effects,[24] by adding 10 mmHg to systolic blood pressure and 5 mmHg to diastolic blood pressure. This simple method of adjustment has been shown to be effective at reducing the potentially distorting influence of anti-hypertensive therapy in quantitative studies of blood pressure.[25] The association between diarrhoea in early life and the prevalence of coronary heart disease was assessed using multiple logistic regression. Estimates were calculated for each cohort separately and combined using a standard inverse variance weighting.

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Results

Details of the two Hertfordshire cohorts featured in the present analyses and the response to the follow-up surveys are given in Table 1. Table 2 shows the characteristics of the 5618 participants in the two cohorts who had their blood pressure measured; values are shown for all participants combined and for the two birth cohorts separately. There were marked differences between the cohorts as regards most of the characteristics shown. Compared with the cohort born between 1920 and 1930, the cohort born in 1931–39 (the Hertfordshire Cohort Study) was slightly older at interview, with a higher mean body mass index, but lower mean systolic and diastolic blood pressure. A higher proportion of the cohort born in 1931–39 was taking anti-hypertensive medication and a smaller proportion was classified as hypertensive. There were no differences between the cohorts in the proportion of participants who had a recorded case of diarrhoea in infancy but there were fewer episodes of diarrhoea between the ages of 1 and 5 years among the later-born cohort. In the combined dataset, information on diarrhoea in infancy and between the ages of 1 and 5 years was available for 5146 (92%) and 5203 (93%) participants, respectively. The prevalence of diarrhoea in infancy (3.3%) and between 1 and 5 years (1.1%) was low.

Table 3 shows the distribution of potential confounding factors in the two cohorts according to whether the participants had a history of diarrhoea either in infancy or between the ages of 1 and 5 years. There were no associations between diarrhoea at either age and social class (in childhood or currently), birthweight, sex, height or adult body mass index. There was a suggestion that infants and children with diarrhoea were less likely to have been exclusively breast-fed in the 1920–30 cohort, although the reverse was true in the 1931–39 cohort. There were slight differences in age at interview according to a history of diarrhoea in infancy in the 1920–30 cohort and according to a history of diarrhoea aged one to five in the 1931–39 cohort, although the direction of these associations was not consistent.

In linear regression analyses, adjusting for age and sex, and correcting for the effect of antihypertensive therapy, there were no significant associations in either cohort between diarrhoea in infancy or subsequently and either systolic or diastolic blood pressure in adulthood (Table 4). Further adjustment for potential confounding factors (social class at birth and currently, birthweight, method of feeding in infancy, height and current body mass index) had little effect on these relations. When estimates from the individual cohorts were combined using standard inverse of variance weighting, results were essentially unchanged. We also examined the associations between diarrhoea in infancy or subsequently and risk of hypertension. Out of the 5146 people with data on diarrhoea in infancy, 2496 had hypertension; there were 2539 cases of hypertension in 5203 individuals with data on diarrhoea aged 1–5. In each of these analyses, there was no strong evidence of a link between diarrhoea and hypertension. For example, relative to the diarrhoea-free groups, the combined estimate (odds ratio) from the individual cohorts, adjusted for age and sex, was 1.16 (95% CI (confidence interval) 0.86 to 1.57) for diarrhoea in infancy, and 1.03 (95% CI 0.61 to 1.74) for diarrhoea aged 1–5.

In total, of the 4351 men and women who were examined in clinic, 558 (12.8%) had coronary heart disease. The prevalence did not differ significantly between the individual cohorts: there were 174 (12.5%) cases in the 1920–30 cohort and 384 (13%) in the 1931–39 cohort. Of the men and women who were examined for the presence of coronary heart disease, 4146 (95.3%) had data on diarrhoea in infancy and 4181(96.1%) had data on diarrhoea between the ages of 1 and 5 years. There were no pronounced or statistically robust associations between records of diarrhoea at any stage in early life and later development of coronary heart disease (Table 5). Fully adjusted models also revealed null results.

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Discussion

In the present study, we tested the recently advanced hypothesis that via dehydration diarrhoea in early life leads to elevated blood pressure in adulthood and therefore an increased prevalence of coronary heart disease. In the largest dataset to date to directly examine this relation we found no support for any such associations. We explored the influence of sensitive periods by stratifying according to whether diarrhoea had occurred during infancy or between the ages of 1 and 5 years; again, there were also no associations.

A plausible explanation for these null results is misclassification of diarrhoea cases, data for which were extracted from health visitor records. The same records have been used to show that lower respiratory tract infection in childhood is associated with adult chronic obstructive pulmonary disease[26] and impaired lung function;[27] breast-feeding is related to lower adult cholesterol concentration;[16] birthweight and weight at one year interact in their association with increased rates of circulatory disease mortality;[15,28] and children who were exclusively breast-fed in infancy had a lower risk of diarrhoea than those who received bottle feeds.[29] That these findings have been replicated in a series of other studies[30–34] provides some support for the validity of the health visitor records. However, importantly, we did not find a relation between socioeconomic position and diarrhoea in the present analyses, and, while children who were breast-fed seemed to be at lower risk of diarrhoea, the effect was modest and not consistent across the cohorts. This may be because the earlier study[29] that found an association between feeding method and diarrhoea was based on 15 726 individuals traced from the health visitor records for 1911–1930, in part for a study of mortality, while the group utilized in the present analyses comprised only those surviving individuals who were still resident in Hertfordshire and therefore able to take part in a medical exam. It is plausible that the most severe cases of infant diarrhoea resulted in death in early life and were therefore not included in this dataset, so excluding potentially important effects. In keeping with this suggestion, there was no association between diarrhoeal disease and height in the present cohort; it is known that severe diarrhoeal disease —especially if repetitive—leads to stunted growth.

In the only study to examine the influence on later blood pressure of childhood dehydration severe enough to warrant hospitalization in the first six months of life, increased levels of diastolic but not systolic blood pressure were found at 7 years of age in children based in the south west of England (the ALSPAC study).[6] In our analyses, the cases of diarrhoea may have not led to the same degree of dehydration. It may be that only severe diarrhoea elicits salt retention and leads to raised blood pressure levels; however, we were unable to assess the severity of our diarrhoea cases. An alternative explanation is that the apparent impact of diarrhoea in early life on childhood blood pressure may be lost by older age. It is also plausible that, in the ALSPAC study, the statistical imprecision resulting from a very low number of dehydration cases (only 6 in a cohort of 7840) led to a spurious result. In the present study, the number of persons ‘exposed’ to diarrhoea was also not considerable; studies with higher numbers will produce more precise estimates of risk.

In conclusion, despite the absence of support for an association between childhood diarrhoea and adult blood pressure in the present analyses, given the paucity of data, and the possibility that potentially important effects could not be excluded, further investigation is required. A range of approaches could be utilized, including, in humans, replication of the present study design, randomized trials of improved hygiene practices that reduce diarrhoea among infants (particularly in low- and middle-income countries), and, in animals, trials of severe dehydration in early life on later blood pressure.

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KEY MESSAGES

- Findings from studies using a diverse range of designs provide largely circumstantial support for the recently advanced hypothesis that dehydration in infancy leads to raised blood pressure levels.
- We found that medical records of diarrhoea (a proxy for dehydration) in infancy and between years 1 and 5 showed no relation with either blood pressure or coronary heart disease assessed in older adults.
- Further examination of this relation is warranted, using randomized trials of improved hygiene practices that reduce diarrhoea among infants (particularly in low- and middle-income countries), and, in animals, trials of severe dehydration in early life on later blood pressure.

Table 1

Details of the two Hertfordshire birth cohorts, data collection and participants

Cohort	Data collection	Number invited	Number interviewed (% of invited)	Number (% of invited) with blood pressure data	Number (% of invited) with CHD data
Hertfordshire cohort born 1920–30[a]	1989–91 (East Herts)	1722	1233 (72)	1231 (71)	–
	1992–93 (East Herts)	655	515 (79)	–	502 (77)
	1993–94 (North West Herts)	1015	586 (58)	585 (58)	586 (58)
	1994–95 (North Herts)	1428	824 (58)	819 (57)	306 (47)
Hertfordshire cohort born 1931–39 (‘Hertfordshire Cohort Study’)	1998–2004	6099	3225 (53)	2986 (49)	2957 (48)

[a]In contrast to the Hertfordshire Cohort Study, data collection on the first Hertfordshire birth cohort was conducted as a series of studies. We therefore describe these component studies separately. Two studies were carried out in East Herts; blood pressure data from the initial study is used in these analyses. In the repeat study, only those men and women who had complete measurements on all blood samples taken in the initial study were invited to attend clinic for assessment of coronary heart disease. In the North Herts study, while data on blood pressure are available for both men and women, only women had full assessment of coronary heart disease at clinic; number (% invited) with CHD data therefore refers to women only.

Table 2

Characteristics of the study participants with data on blood pressure

Characteristic	1920–30 birth cohort (n = 2682)	1931–39 birth cohort (n = 2986)
Age at interview, years	65.7 (3.10)	66.1 (2.85)
Systolic blood pressure, mmHg	159.2 (23.7)	133.3 (19.3)
Diastolic blood pressure, mmHg	85.3 (12.6)	70.7 (11.3)
Height, m	1.67 (0.09)	1.68 (0.09)
BMI, kg/m^2	26.9 (4.01)	27.4 (4.34)
Birthweight, kg	3.50 (0.55)	3.43 (0.53)
Sex		
Male	1653 (62.8)	1574 (52.7)
Female	9977 (37.2)	1412 (47.3)
Father’s social class		
Non-manual	372 (14.1)	452 (15.4)
Manual	2105 (80.03)	2350 (78.7)
Unclassified	155 (5.89)	184 (6.16)
Current social class		
Non-manual	990 (37.6)	1207 (40.4)
Manual	1615 (61.42)	1730 (57.9)
Unclassified	27 (1.03)	49 (1.64)
Anti-hypertensive drugs		
Yes	776 (29.5)	1083 (36.3)
No	1856 (70.5)	1903 (63.7)
Hypertensive		
Yes	1609 (61.1)	1203 (40.3)
No	1023 (38.9)	1783 (59.7)
Diarrhoea in infancy		
Yes	64 (2.96)	107 (3.58)
No	2096 (97.0)	2879 (96.4)
Diarrhoea aged 1–5 years		
Yes	32 (1.44)	23 (0.77)
No	2185 (98.6)	2963 (99.2)
Method of infant feeding		
Breast	1793 (68.1)	1786 (59.8)
Bottle	146 (5.35)	274 (9.18)
Breast and bottle	693 (26.3)	926 (31.0)

Percentages do not always add up to 100 due to rounding.

Table 3

Covariates according to diarrhoea in infancy and between 1 and 5 years of age

	1920–30 cohort				1931–39 cohort			
	Diarrhoea in infancy		Diarrhoea aged 1–5 yrs		Diarrhoea in infancy		Diarrhoea aged 1–5 years	
	Yes (*n* = 64)	**No (*n* = 2096)**	**Yes (*n* = 32)**	**No (*n* = 2185)**	**Yes (*n* = 107)**	**No (*n* = 2879)**	**Yes (*n* = 23)**	**No (*n* = 2963)**
	Mean (SD)							
Age at interview (years)	64.1 (2.62)	65.2 (2.91)	65.0 (2.92)	65.4 (3.01)	66.4 (3.01)	66.1 (2.84)	67.4 (2.67)	66.1 (2.85)
BMI (kg/m^2)	27.4 (5.00)	26.9 (4.04)	26.1 (3.76)	26.9 (4.05)	27.7 (4.76)	27.3 (4.32)	28.1 (4.29)	27.4 (4.34)
Height (m)	1.67 (0.09)	1.67 (0.09)	1.68 (0.08)	1.67 (0.09)	1.67 (0.10)	1.68 (0.09)	1.67 (0.09)	1.68 (0.90)
Birthweight (kg)	3.46 (0.53)	3.50 (0.55)	3.59 (0.57)	3.51 (0.54)	3.37 (0.52)	3.43 (0.53)	3.45 (0.56)	3.43 (0.53)
	Number (%)							
Sex								
Male	32 (50.0)	1262 (60.21)	16 (50.0)	1315 (60.2)	57 (53.3)	1517 (52.7)	11 (47.8)	1563 (52.8)
Female	32 (50.0)	834 (39.8)	16 (50.0)	870 (39.8)	50 (46.7)	1362 (47.3)	12 (52.2)	1400 (47.3)
Father's social class								
Non-manual	10 (15.6)	291 (13.9)	5 (15.6)	296 (13.6)	18 (16.8)	434 (15.1)	2 (8.70)	450 (15.2)
Manual	52 (81.3)	1684 (80.3)	25 (78.1)	1761 (80.6)	83 (77.6)	2267 (78.7)	21 (91.3)	2329 (78.6)
Unclassified	2 (3.13)	121 (5.77)	2 (6.25)	128 (5.86)	6 (5.61)	178 (6.18)	0 (0)	184 (6.21)
Current social class								
Non-manual	26 (40.6)	814 (38.8)	14 (43.8)	849 (38.9)	46 (43.0)	1161 (40.3)	13 (56.5)	1194 (40.3)
Manual	38 (59.4)	1261 (60.2)	18 (56.3)	1315 (60.2)	60 (56.1)	1670 (58.0)	9 (39.1)	1721 (58.0)
Unclassified	0 (0)	21 (1.00)	0 (0)	21 (0.96)	1 (0.93)	48 (1.67)	1 (4.35)	48 (1.62)
Method of infant feeding								
Breast	34 (53.1)	1399 (66.7)	21 (65.6)	1481 (67.8)	69 (64.5)	1717 (59.6)	15 (65.2)	1771 (59.8)
Bottle	4 (6.25)	117 (5.58)	3 (9.38)	118 (5.40)	6 (5.61)	268 (9.31)	3 (13.0)	271 (9.15)
Breast and bottle	26 (40.6)	580 (27.7)	8 (25.0)	586 (26.8)	32 (29.9)	894 (31.1)	5 (21.7)	921 (31.8)

Percentages do not always total 100 due to rounding.

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Table 4

Relation (regression coefficient, 95% CI) of diarrhoea in infancy (n = 5146) and between 1 and 5 years of age (n = 5203) with adult blood pressure (individual cohorts and combined)

	Systolic blood pressure (mmHg)		Diastolic blood pressure (mm Hg)	
	Adjusted for age and sex	**Multivariate-adjusted**[a]	**Adjusted for age and sex**	**Multivariate-adjusted**[a]
Diarrhoea in infancy				
1920–30 cohort	−1.99 (−8.00 to 4.02)	−2.08 (−8.17 to 4.02)	−0.57 (−3.70 to 2.56)	−0.05 (−3.36 to 3.05)
1931–39 cohort	1.51 (−2.48 to 5.50)	0.83 (−3.06 to 4.72)	0.24 (−1.87 to 2.34)	0.03 (−2.07 to 2.12)
Combined estimate	0.44 (−2.88 to 3.76)	0.04 (−3.24 to 3.32)	−0.15 (−1.77 to 1.75)	−0.03 (−1.79 to 1.72)
Diarrhoea aged 1–5 years				
1920–30 cohort	1.20 (−7.18 to 9.58)	2.40 (−5.87 to 10.68)	0.75 (−3.64 to 5.14)	1.13 (−3.26 to 5.51)
1931–39 cohort	1.31 (−7.18 to 9.80)	0.85 (−7.43 to 9.13)	−1.53 (−6.02 to 2.97)	−1.75 (−6.22 to 2.71)
Combined estimate	1.26 (−4.71 to 7.22)	1.64 (−4.20 to 7.49)	−0.36 (−3.50 to 2.78)	−0.24 (−3.36 to 2.89)

[a]Adjusted for age, sex, social class at birth and currently, method of infant feeding, birthweight, and current BMI and height.

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Table 5

Relation (odds ratios, 95% CI) of diarrhoea in infancy (*n*=4146) and between 1 and 5 years of age (*n*=4181) with adult coronary heart disease (individual cohorts and combined)

	Odds ratios	
	Adjusted for age, sex	**Multivariate-adjusted**[a]
Diarrhoea in infancy		
1920–30 cohort	0.74 (0.22 to 2.45)	0.68 (0.20 to 2.26)
1931–39 cohort	0.96 (0.54 to 1.70)	0.86 (0.46 to 1.59)
Combined estimate	0.91 (0.54 to 1.54)	0.82 (0.47 to 1.42)
Diarrhoea aged 1–5 years		
1920–30 cohort	0.44 (0.06 to 3.31)	0.47 (0.06 to 3.66)
1931–39 cohort	0.96 (0.28 to 3.24)	1.02 (0.30 to 3.49)
Combined estimate	0.77 (0.27 to 2.21)	0.84 (0.29 to 2.41)

[a]Adjusted for age, sex, social class at birth and currently, method of infant feeding, birthweight and current BMI and height.