Wheezing and eczema in relation to infant anthropometry: evidence of developmental programming of disease in childhood

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Abstract

Early life factors and, in particular, the fetal environment have been suggested to programme risk of allergic disease in later life. Diversion of nutrients away from immune organs towards the brain, a process termed brain sparing, has been proposed as a mechanism underpinning this association. The study population was a group of 256 seven-year old children from the UK recruited from two general practitioner surgeries. Historical anthropometric data from birth to age three and current anthropometry were assessed as predictors of parent-reported wheeze and eczema. Eczema at seven years was not related to any anthropometric indices at birth or during infancy. A smaller head circumference at 10–15 days of age was noted in children with current wheeze at age 7 years ($P = 0.018$) and this relationship persisted after adjustment for current anthropometry and confounders. Comparison of children with head circumference over 36.5 cm at 10–15 days with those with head circumference under 35.5 cm, showed reduced odds for wheeze at 7 years (OR 0.12, 95% CI 0.03–0.44, $P_{\text{trend}} = 0.009$). These data suggest that factors that determine fetal growth may be associated with wheeze in childhood and support the developmental origins of health and disease hypothesis. Brain sparing does not appear to play a role in this early life programming.

Keywords: wheeze, eczema, fetal programming, anthropometry.

Introduction

A range of large-scale cohort studies has suggested that there are robust relationships between nutri-

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tional status in pregnancy, fetal development and disease in later life (Curhan *et al.*, 1996; Barker, 2003; Eriksson *et al.*, 2003a). Associations have been reported between weight at birth and risk of hypertension (Barker *et al.*, 1990), type 2 diabetes (Eriksson *et al.*, 2003b) and coronary heart disease (Forsen *et al.*, 2004) in adulthood. These associations are strengthened when evidence of disproportion at

birth (small or large head circumference in relation to truncal length, thinness at birth) is considered instead of birthweight, and when the influences of post-natal growth are also assessed (Barker *et al.*, 1992; Phillips *et al.*, 1994; Eriksson *et al.*, 2003a). On this basis it is suggested that fetal growth retardation followed by rapid catch-up in infancy and in childhood are strong predictors of non-communicable diseases in adult life (developmental origins of health and disease hypothesis) (Barker, 2003).

Low weight and disproportion at birth may to some extent reflect the nutritional environment encountered *in utero* (Godfrey & Robinson, 1998). Whilst only a few studies have demonstrated associations between nutrition in human pregnancy and later disease outcomes (Campbell *et al.*, 1996; Godfrey *et al.*, 1994a), a large number of animal studies have demonstrated the biological plausibility of disease programming through exposure to poor nutrition during fetal development (Langley-Evans, 2004). Several studies of mice and rats have identified the immune system as being a target for programming and have shown that the development of the thymus may be particularly vulnerable to the effects of nutritional perturbation (Beach *et al.*, 1982; Calder & Yaqoob, 2000; Langley-Evans *et al.*, 2002).

The development of the human immune system may also be vulnerable to adverse programming effects of undernutrition. Moore (1998) has shown that the capacity to resist infection may be impaired in those subject to fetal undernutrition, whilst a number of other studies have focused upon the possibility that susceptibility to atopic disease may be determined by fetal environment. Several studies have shown increased prevalence of atopic conditions in individuals of lower weight at birth and in particular in those born with a large head circumference (Godfrey *et al.*, 1994b; Fergusson *et al.*, 1997; Gregory *et al.*, 1999; Shaheen *et al.*, 1999). There is evidence that thymic function is associated with infant anthropometry (McDade *et al.*, 2001). Godfrey *et al.* (1994b) have suggested that the association of atopy with a disproportionately large head at birth provides evidence of a brain sparing response in which the fetus subject to nutrient restraint prioritizes the flow of blood and nutrients away from the truncal organs,

including the thymus, to favour more critical brain development. Benn *et al.* (2001) however, noted that thymus size was not related to allergic disease at age 5, and also that thymus size and head circumference are positively related, which appears to negate the brain sparing hypothesis. Most recently Bolte *et al.* (2004) have reported that both disproportionately small and large head circumference at birth, indicative of both over- and undernutrition are related to atopic sensitization and elevated serum IgE at age 5–7. The evidence in this area is therefore complex and contradictory and in general has not considered the possible interaction of fetal growth with growth in infancy as an influence upon development of atopy. The aim of the present study was to assess the relationship between wheezing or eczema and birth and infant anthropometry.

Methods

Study participants

The study population comprised 7-year-old children registered with two General Practitioner (GP) practices in Northampton, UK. The practices were in the same locality and shared a similar mix of cultural and social groups. Children eligible to participate in the study were identified from a database compiled by the GP practices. The parents of a total of 547 children were contacted by letter around the time of the child's 7th birthday with an invitation to participate in the study. 256 children (46.8% of those contacted) took part in the study. All multiple births and children of non-Caucasian origin were excluded from the study, as these children were more likely to be of low birthweight. Table 1 shows the social class distribution and other demographic characteristics of the children in the study. Ethical approval for this study was obtained from the Northampton Medical Research Ethics Committee.

Protocol for assessment of atopy in children

Each child and their parents received a letter inviting participation in the study, once the child reached their 7th birthday, along with an information leaflet, reply

Table 1. Characteristics of study cohort

Characteristic	<i>n</i> (percentage of cohort)
Preterm gestation*	11 (4.3)
Full term gestation*	245 (95.7)
Social class at birth	
I	9 (3.7)
II	24 (9.8)
IIIM, NM	151 (61.9)
IV	38 (15.6)
V	22 (9.0)
Social class at 7 year	
I	12 (4.9)
II	25 (10.5)
III	137 (55.9)
IV	51 (20.6)
V	20 (8.1)
Exposure to smoking	
<i>In utero</i>	40 (16.3)
At age 7	75 (30.6)
Breastfed	176 (71.8)
Formula fed	69 (28.2)
Wheeze	64 (26.1)
Eczema	81 (33.1)
Family history asthma	140 (57.1)
Family history eczema	131 (53.4)

Percentage data are based on only the 245 full term births within the study cohort, except for * where percentage is based on *n* = 256.

slip and stamped addressed envelope. The reply slip gave an opportunity for parents to choose the venue (either the surgery or their home) and the time of day for a structured interview. At the interview a further written and verbal explanation of the study was given to both parent and child, and an opportunity provided for questions, followed by informed verbal and written consent. A three-part questionnaire was used to collect demographic data, history of illness and anthropometry, both current and historical. Demographic data included occupation, the number of people living in the house, pet ownership, smoking history and immunization history. Social class was assigned to each child on the basis of parental occupation using the Registrar Generals classification (OPCS, 1990). Where both parents were working the higher occupational class was applied to the analysis.

Data on wheezing and eczema were collected using questions based on The International Study of Asthma and Allergies in Childhood (ISAAC) criteria

(Asher & Weiland, 1998) to explore the prevalence of wheezing and eczema in the study population. The ISAAC programme used common criteria to evaluate the worldwide prevalence of atopic disease and the criteria were originally developed to children aged 6–7 or 13–14. The current study therefore considered children at an age for which the ISAAC approach had been previously validated. Children were defined as having ‘current wheeze’ when a parent reported at least one episode of wheezing in the past 12 months. Eczema was recorded if parents reported an itchy rash coming and going for at least 6 months.

The anthropometric data were obtained by reference to the Personal Child Record Book (PCRB). This parent-held health record is routinely maintained for all UK children by midwives and health visitors from birth to 5 years. The PCRB recorded weight, length (height) and head circumference at 6-time points encompassing the record from the delivery of the infant and five checks at home or at GP clinics by health visitors. Pilot studies had shown that when several health professionals had made these measurements on the same group of children under field conditions, variation for head circumference and weight was less than 0.5% and variation between measurements for length was 0.77%. PCRB records were incomplete for some of the children, with the records for the 5th check at 36 months being particularly depleted. Where the PCRB was not available, historical information was gained from one of three sources. Firstly, the mother’s discharge report from the midwifery department, stored in the medical records, provided information detailing type of birth (normal, forceps, ventouse or caesarean) and infant birthweight, length and head circumference. This also allowed distinction to be made between full-term birth and preterm birth. Where the infant was identified as being born before 36 weeks gestation the child was excluded from all further analyses (11 children were excluded on this basis). The Health Authority electronic database was accessed as a second source of data, to obtain a record of measurements made by the midwife or health visitor, such as weight, length and head size recorded at birth, 6 weeks and 7–8 months. Finally, health visitor records provided measurements at these, and other key stages, such as

10–15 days after birth. These other sources were used to obtain less than 10% of the records.

For all of the 7-year olds (106 boys and 139 girls), the researcher recorded questionnaire responses and carried out measurements of current weight, height and head circumference that were determined by a single researcher using standardized methods. Children were weighed using Tanita scales. The scales were preset and the child asked to stand on the scales clothed, but with outdoor clothing and shoes removed. Height was measured using a Portable Raven Minimetre. The measuring arm was at right angles to the back and then placed on the floor with the back resting against an upright surface. The child was placed under the measuring arm and asked to stand upright, with heels flat to the floor, shoulders, buttocks and head touching the tape and looking forwards (Tanner, 1989). Head circumference was measured using a Lasso tape placed around the maximum circumference of the supra-orbital ridge and the occipital protuberance (Bax *et al.*, 1990). All 245 eligible subjects recruited had current measurements of weight, length and head size recorded at interview.

Statistical analysis

Data were analysed using the Statistics Package for Social Sciences version 9. Initial analyses used a case-control approach to compare birth and infant characteristics using an independent samples *T*-test, grouping the children as either unaffected controls, or as suffering wheeze or eczema. To further these initial analyses and allow for covariates and confounders the data were analysed using stepwise binary logistic regression analysis (backward conditional method, using $P > 0.10$ as the criterion for elimination of a variable from the model). In all case-control analyses and in the final iterations of the binary logistic regression models probability of 5% or less was accepted as statistically significant.

Results

As shown in Table 1, 11 of the children were born prior to 36 weeks gestation and these were excluded from all further analyses of the data. The majority of

the children were born into families in social class III and remained in the same socio-economic class up to their 7th birthday and recruitment to the study. Only a small proportion of women reported having smoked when pregnant, but the vast majority of children were passive smokers, with 84% exposed to at least one smoker in the household. 70% of mothers reported having breastfed their infants at least in the initial few days after delivery. Data on duration of breastfeeding was incomplete. Uptake of childhood immunizations (MMR, diphtheria, whooping cough, tetanus) was nearly universal (data not shown).

Wheezing or whistling in the chest within the last 12 months (interpreted as asthma) was reported for a quarter of the study population (Table 1). A greater proportion reported an itchy rash coming and going for at least 6 months (interpreted as eczema). Ponderal index (weight/length³) has often been used as a measure of relative thinness or fatness at birth (Phillips *et al.*, 1994). In this study we have applied the same measure at all the ages studied to provide a consistent comparison. Between birth and 7 years ponderal index fell in all children, in keeping with the reduction in adiposity that generally accompanies the transition from infancy to the early school years.

In comparing children with wheeze to those who did not, it was apparent that current anthropometry was a significant factor. Children with wheeze were heavier and fatter (greater PI) at 7 years of age and tended to have a smaller head circumference (Table 2). There were no differences in anthropometric measures at birth between cases and controls and in infancy the only apparent difference was that head circumference at 10–15 days of age (check 1) was significantly smaller in the children who later developed wheeze.

Eczema symptoms were reported for 32.9% of the children. The comparison of children with eczema and those who were free of persistent rash, revealed that there were no significant differences in birth or infant anthropometry (Table 3). However, the children with eczema tended to be shorter ($P = 0.026$) at 7 years of age, and to be thinner children ($P = 0.050$) at check 3 (7–9 months).

Binary logistic regression analysis confirmed the finding of the preliminary analysis for wheezing

Table 2. Case-control comparison of children with wheeze at age 7 years and wheeze-free children

Anthropometric measure	<i>n</i>	Controls	<i>n</i>	Cases	<i>P</i>
Birthweight (kg)	178	3.38 ± 0.48	62	3.37 ± 0.42	0.650
Birth Length (cm)	165	51.22 ± 2.67	58	51.39 ± 0.30	0.548
HC at birth (cm)	168	34.55 ± 1.40	56	34.63 ± 1.43	0.855
PI at birth (kg/m ³)	165	25.19 ± 2.93	58	24.93 ± 2.90	0.307
Weight check 1 (kg)	136	3.59 ± 0.52	45	3.47 ± 0.42	0.159
Length check 1 (cm)	100	51.75 ± 2.54	30	51.65 ± 1.66	0.950
HC check 1 (cm)	99	36.01 ± 1.38	30	35.35 ± 1.21	0.021
PI check 1 (kg/m ³)	100	25.81 ± 2.49	30	25.11 ± 1.76	0.103
Weight check 2 (kg)	145	4.71 ± 0.58	42	4.60 ± 0.54	0.252
Length check 2 (cm)	131	55.95 ± 2.73	42	55.24 ± 2.08	0.172
HC check 2 (cm)	129	38.32 ± 1.75	42	38.59 ± 1.95	0.638
PI check 2 (kg/m ³)	130	26.92 ± 2.96	42	27.24 ± 2.31	0.592
Weight check 3 (kg)	146	8.44 ± 1.06	49	8.45 ± 0.92	0.752
Length check 3 (cm)	142	70.16 ± 3.23	48	69.82 ± 2.80	0.586
HC check 3 (cm)	137	44.88 ± 1.53	43	44.83 ± 1.43	0.547
PI check 3 (kg/m ³)	142	24.50 ± 2.88	48	24.86 ± 2.67	0.854
Weight check 4 (kg)	128	11.54 ± 1.25	39	11.63 ± 1.19	0.671
Length check 4 (cm)	126	81.17 ± 4.35	38	80.87 ± 2.97	0.804
HC check 4 (cm)	49	47.65 ± 2.02	15	47.59 ± 1.20	0.757
PI check 4 (kg/m ³)	124	21.65 ± 2.83	37	21.96 ± 2.45	0.681
Weight check 5 (kg)	123	15.01 ± 1.95	33	15.39 ± 2.02	0.299
Length check 5 (cm)	118	96.23 ± 4.70	33	95.84 ± 3.32	0.717
HC check 5 (cm)	8	50.72 ± 1.72	4	51.75 ± 0.95	0.299
PI check 5 (kg/m ³)	116	17.01 ± 2.18	31	17.42 ± 2.24	0.357
Weight age 7 (kg)	182	24.71 ± 3.99	62	26.09 ± 6.01	0.046
Height age 7 (cm)	182	122.49 ± 5.66	62	122.01 ± 5.50	0.665
HC age 7 (cm)	182	53.86 ± 1.43	62	53.06 ± 1.59	0.685
PI age 7 (kg/m ³)	182	13.41 ± 1.46	62	14.31 ± 2.70	0.002

HC, head circumference; PI, ponderal index. All data are shown as mean ± standard deviation for *n* observations in each group. *P*-values are adjusted for multiple comparisons using the Bonferroni correction.

children compared to non-wheezing children and indicated that a smaller head circumference at age 10–15 days was a strong predictor of wheeze at age 7. A number of regression models were constructed, initially including all birth and infant anthropometry, anthropometry at age 7 and all of the available variables relating to social class (current and social class at birth), smoking exposures and gestational age at birth. The final model shown in Table 4 represents the first significant model generated by the backward conditional method that included both infant anthropometric characteristics and potential confounders. Table 4 shows that in comparing children in the lowest tertile for head circumference to the highest tertile risk fell by 88% with an increase of 1 cm. This was significant after adjustment for gender, gestational

age, social factors and smoking exposure at birth and age 7, infant feeding method and family history of asthma. Binary logistic regression analysis confirmed that there were no significant associations between eczema and infant anthropometry. The only significant risk factor for childhood eczema identified in the current data set was a family history of eczema ($P = 0.013$).

Discussion

The aim of this study was to explore the possibility that anthropometric indices at birth and during infancy may predict risk of wheezing and atopic disease in childhood. An important objective of the study was to test the brain-sparing hypothesis

Table 3. Case-control comparison of children with eczema at age 7 years and eczema-free children

Anthropometric measure	<i>n</i>	Controls	<i>n</i>	Cases	<i>P</i>
Birthweight (kg)	161	3.37 ± 0.47	79	3.40 ± 0.44	0.816
Birth Length (cm)	149	51.29 ± 2.56	74	51.21 ± 2.62	0.570
HC at birth (cm)	151	34.56 ± 1.45	73	34.58 ± 1.32	0.783
PI at birth (kg/m ³)	149	24.98 ± 2.77	74	25.43 ± 3.19	0.419
Weight check 1 (kg)	117	3.55 ± 0.50	64	3.58 ± 0.50	0.796
Length check 1 (cm)	89	51.58 ± 2.20	41	52.05 ± 2.68	0.291
HC check 1 (cm)	85	35.77 ± 1.41	44	36.01 ± 1.27	0.374
PI check 1 (kg/m ³)	89	25.78 ± 2.46	41	25.33 ± 2.09	0.128
Weight check 2 (kg)	126	4.68 ± 0.59	61	4.68 ± 0.54	0.602
Length check 2 (cm)	115	55.61 ± 2.06	58	56.09 ± 3.46	0.380
HC check 2 (cm)	112	38.37 ± 1.94	59	38.41 ± 1.51	0.830
PI check 2 (kg/m ³)	114	27.17 ± 2.39	58	26.63 ± 3.51	0.250
Weight check 3 (kg)	130	8.50 ± 0.97	65	8.33 ± 1.14	0.105
Length check 3 (cm)	127	69.98 ± 3.12	63	70.27 ± 3.12	0.775
HC check 3 (cm)	120	45.44 ± 1.34	60	44.73 ± 1.50	0.620
PI check 3 (kg/m ³)	127	24.85 ± 2.58	63	24.05 ± 3.23	0.050
Weight check 4 (kg)	112	11.60 ± 1.23	55	11.48 ± 1.24	0.321
Length check 4 (cm)	110	81.22 ± 1.77	54	80.84 ± 4.90	0.740
HC check 4 (cm)	47	47.83 ± 1.77	17	47.08 ± 2.00	0.402
PI check 4 (kg/m ³)	108	21.67 ± 2.62	53	21.82 ± 3.01	0.757
Weight check 5 (kg)	105	15.27 ± 1.99	51	14.71 ± 1.91	0.095
Length check 5 (cm)	101	96.28 ± 3.89	50	95.87 ± 5.38	0.695
HC check 5 (cm)	7	50.69 ± 1.23	5	50.20 ± 1.64	0.117
PI check 5 (kg/m ³)	99	17.17 ± 2.16	48	16.95 ± 2.28	0.311
Weight age 7 (kg)	164	25.15 ± 4.78	80	24.83 ± 4.24	0.438
Height age 7 (cm)	164	122.77 ± 5.71	80	121.48 ± 5.28	0.026
HC age 7 (cm)	164	52.81 ± 1.52	80	52.67 ± 1.45	0.441
PI age 7 (kg/m ³)	164	13.54 ± 1.89	80	13.82 ± 1.90	0.244

HC, head circumference; PI, ponderal index. All data are shown as mean ± standard deviation for *n* observations in each group. *P*-values are adjusted for multiple comparisons using the Bonferroni correction.

advanced by Godfrey *et al.* (1994b). This suggests that exposure of the fetus to a poor nutritional environment triggers responses that divert the flow of nutrients away from organs that have functions that are non-critical for fetal viability, for example the thymus, towards other organs such as brain or cardiovascular for which optimal development is a prerequisite for survival. This hypothesis is in part supported by observations that thymic function is related to markers of intrauterine growth retardation (McDade *et al.*, 2001).

The main finding of the study was that whilst the prevalence of eczema at age 7 was largely unrelated to birth or infant anthropometry, wheezing at this age was predicted by a smaller head circumference at 10–15 days of age. Birthweight or thinness at birth did

not predict wheezing at age 7. We did identify increased weight and relative fatness with a smaller head circumference as characteristics at age 7 that are associated with wheezing. This supports other data that identifies obesity as a risk factor for wheeze and atopic asthma (Schachter *et al.*, 2003). For both conditions studied in this cohort the strongest predictors were a family history of asthma or eczema.

Larger head circumference at birth has been previously reported to be associated with both elevated IgE in adulthood (Godfrey *et al.*, 1994b; Gregory *et al.*, 1999; Leadbitter *et al.*, 1999) and with risk of asthma in adolescence (Fergusson *et al.*, 1997). Head circumference at birth is, however, often poorly measured and may not represent the true size of the brain owing to moulding during delivery (Sorbe &

Table 4. Binary logistic regression model- contributory factors for childhood wheezing

	Odds Ratio	95% CI
Head circumference at 10–15 days (cm)		
<35.50	1.00	
35.51–36.50	0.18	0.05–0.67
>36.51	0.12	0.03–0.44
Current social class		
I	1.00	
II	1.53	0.01–150.30
III	2.42	0.07–86.39
IV	3.35	0.20–55.30
V	1.87	0.15–22.51
Smoking in pregnancy		
No exposure	1.00	
Exposed	1.94	0.32–11.55
Passive smoking at 7 year		
Not exposed	1.00	
Exposed	2.93	0.92–11.42
Sex		
Male	1.00	
Female	0.921	0.29–2.90
Breastfeeding		
Breastfed	1.00	
Never breastfed	0.683	0.21–2.25
Family History of wheeze		
Yes	1.00	
No	0.40	0.14–1.18
Ponderal Index at 7 year		
<12.77 kg m ⁻³	1.00	
12.77–13.98 kg m ⁻³	0.98	0.31–3.12
>13.98 kg m ⁻³	4.42	1.22–16.07

Data were analysed using stepwise binary logistic regression (backward conditional model, $P = 0.0141$). The criteria for removal of a variable from the model was $P > 0.10$ at each iteration.

Dahlgren, 1983). In this study we found no significant association between wheezing at age 7 and head circumference at birth. However, by 10–15 days a small head circumference appeared to be a significant predictor of later wheezing. Head circumferences in the middle and upper tertile reduced odds of wheezing at 7 by 82 and 88%, respectively, and this finding was robust after adjustment for family history, current anthropometry, gestation at birth and other confounders. Head circumference at 10–15 days is likely to provide a better index of brain growth *in utero* than

the same measurement taken at birth, as by the time of this measurement all moulding is likely to have resolved and yet insufficient time will have elapsed for significant growth. Our main conclusion from the study is, therefore, that factors that impede brain growth *in utero* also programme the development of childhood wheeze. Whether this occurs through effects on the developing immune system or through other mechanisms is not clear.

Head circumference *per se* does not provide an indicator of disproportionate growth, which Barker and colleagues argue is a key step in programming long-term disease risk (Barker, 2003). Bolte *et al.* (2004) have recently considered head circumference in relation to birthweight as a predictor of allergic sensitization. This is not a useful measure of disproportion however, as weight reflects relative body fatness as well as skeletal mass and length. Other workers have used head circumference/length ratio as a better marker of disproportion (Barker *et al.*, 1992). We have applied the latter criterion to our analysis and found that the difference in head circumference between wheezing and non-wheezing children persisted (Head/length ratio: non-wheezing 0.696 ± 0.021 , current wheezing 0.686 ± 0.017 , $P = 0.021$).

In this study we used the questions used in the ISAAC study to define wheezing in children. Wheezing in childhood has many causes and may be attributable to allergic asthma, exercise-induced asthma or symptoms of viral or other respiratory infections. The term wheezing is also often misinterpreted by parents participating in studies of this nature (Cane *et al.*, 2000) and this may produce an over-estimate of symptoms. In the light of this it is important to exercise caution in interpreting our findings as indicative of programming of the immune system. Aspects of adult lung function have been related to birth anthropometry, suggesting that pulmonary development may also be constrained by a poor intrauterine environment (Barker *et al.*, 1991). Indeed in an Indian population small head circumference at birth predicted reduced adult lung function (Stein *et al.*, 1997). Studies of the long-term effects of intrauterine exposure to famine show increased risk of chronic obstructive pulmonary disease in adults (Lopuhaa *et al.*, 2000). Animal studies also suggest that prenatal undernutri-

tion produces increased vulnerability to lung injury in adult animals (Langley-Evans *et al.*, 1997). None of these issues has yet been explored in children. Wheezing in childhood may be determined before birth via more than one route, in keeping with its multiple manifestations and immediate causes.

The present study agrees with several others in this area in that the finding that birthweight does not appear to predict risk of wheezing or eczema in childhood. Whilst Shaheen *et al.* (1999) reported that among adults of the 1970 British birth cohort low birthweight was associated with diagnosed asthma and with wheezing, most other studies find no association with wheeze, atopy and weight at birth (Demissie *et al.*, 1997; Gregory *et al.*, 1999; Bolte *et al.*, 2004). Indeed Bolte *et al.* (2004) found that among 5–7 years old children there was no relationship between weight at birth and wheeze, although birthweight was positively related to atopic sensitization. Greater head circumference has generally been reported to be the main fetal indicator of asthma risk and elevated serum IgE. However, only Fergusson *et al.* (1997) have reported the association with asthma and the study of Godfrey *et al.* (1994b) is weak in that it did not truly report an association of head circumference and IgE concentration, as it arbitrarily grouped the participants into low and high IgE groups. 80 IU mL⁻¹ was taken as the cut-off for 'raised' IgE concentrations, although many laboratories would regard this as within normal ranges.

In the present study we note the opposite relationship between head circumference and childhood wheeze and in this regard our findings contradict the brain-sparing hypothesis. In this we support the findings of Benn *et al.* (2001) who reported that thymus size and head circumference were positively associated. Our data and the published data from Benn *et al.* (2001) and McDade *et al.* (2001) suggest that undernutrition or other adverse stimuli in fetal life limit growth of both brain and thymus and hence impair long-term thymic function. This may programme the immune system towards an allergic Th2 phenotype. This hypothesis merits further exploration through detailed analysis of CD4+ T lymphocytes and other markers of a predominant Th2 phenotype in appropriate cohorts.

The principle finding of the present paper is that head circumference at 10–15 days post-natally predicts risk of wheezing in childhood. This is a very isolated finding, in that head circumference at birth and at later points in infancy are not associated with later wheeze. This may reflect issues such as the size of the cohort studied and the missing values within the data set. As stated previously head circumference at this age, a routine measurement for all infants, is a more reliable indicator of prenatal brain growth as moulding of the head associated with delivery is likely to have recovered. Whilst the finding of this relationship may provide an important indicator of the critical window in time during which early life events may programme risk of wheeze, we cannot exclude the possibility that the observation is an artefactual, 'false-positive' result. Further work with larger cohorts of children would be necessary to explore this more effectively.

The general lack of agreement between studies in this area may reflect the complexity of modelling interactions between pre- and post-natal growth, the occurrence of unidentified and hence uncontrolled for confounders and the fact that the most likely programming stimulus and maternal nutritional status is only crudely defined by birth anthropometry. We have recently shown that maternal nutrient intakes are poor predictors of birth anthropometry (Langley-Evans & Langley-Evans, 2003) and this complements an extensive literature showing that in well-nourished women, diet is less important than smoking and social class in determining fetal growth patterns (Doyle *et al.*, 1992; Godfrey *et al.*, 1996; Mathews *et al.*, 1999). Animal studies very clearly show that controlled manipulations of diet in pregnancy alone can produce gross changes in size of the thymus, spleen and mesenteric node (Langley-Evans *et al.*, 2002) and can also induce impairments of immune function that are persistent both within (Calder & Yaqoob, 2000) and between generations (Beach *et al.*, 1982). Further studies are needed to explore the relationships between human nutritional status in pregnancy and atopic outcomes in children.

It is important to acknowledge several limitations within our study that may impact on the interpretation of the findings. Firstly only 47% of subjects

approached agreed to participate. We have no data on the non-participants and therefore cannot exclude the possibility of selection bias. Whilst the level of self-reported wheeze and was comparable to the UK averages reported by the ISAAC Study Group (Austin *et al.*, 1999), we found a greater prevalence of eczema. Other studies have shown that the families with one or several family members with atopic diseases are more prone to participate, and this form of selection bias may explain the high noted prevalence figures in our study. Reliance on parental report of wheezing and eczema is of course another potential source of error, but by following the ISAAC questionnaire we have followed a standard methodology for the field. Serology and skin-prick testing is generally considered unnecessary to confirm wheezing and eczema. Within this study, as with other work in this area (Bolte *et al.*, 2004), we have assumed that parental misclassification would be independent of the birth and infant characteristics that we have assessed. Any parental bias would be likely to have masked the effects that we have noted.

The sample size for the study was low compared to many in this area, and this may have reduced statistical power. This coupled with the missing data points for many of the anthropometric measures undermines the main findings of the study. However, this cohort was of comparable size to those reported by Godfrey *et al.* (1994b) and by Gregory *et al.* (1999) and considerably larger than the population studied by McDade *et al.* (2001). Missing data from medical records also impacted on some of the analyses and in particular head circumference was often not measured between check 4 (18–24 months) and interview at age 7. However, none of the anthropometric characteristics identified as significantly related to wheeze were strongly undermined by missing data and the confirmation of the association between smaller head circumference at check 1 and current wheeze using binary logistic regression analysis suggests that this observation is robust despite there only being 129 valid cases in the analysis. Missing values occurred to an equal extent in children with and without wheeze and so did not contribute a source of bias. This analysis also discounted the potential confounding effect of passive smoking, which was experienced by a high

proportion of the 7-year-olds that were studied. There is an inherent danger in our 'case-control' approach to analysis in that this considers the outcome of multiple statistical tests in an independent manner. The production of regression models that consider all of the independent and interdependent measures together has been a vital step ensuring the robustness of our final conclusions.

Our data suggest that patterns of growth *in utero* and during childhood interact to predict the occurrence of wheezing at age 7. Children, both boys and girls, with a smaller head just after birth and who are heavier for their height at age 7 have increased risk of wheeze but no increased risk of eczema. With the exception of head circumference at 10–15 days, birth and infant anthropometry were generally poor predictors of childhood wheeze and eczema. Whilst smaller head circumference around the time of birth may be predictive of childhood wheezing, the limitations of this study mean that further work is required to investigate the importance of this finding. These data support the broad concept that wheezing and eczema may be subject to intrauterine programming influences, but suggest that the brain sparing response previously invoked by other researchers does not underpin this programming.

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