

Disproportionate fetal growth and raised IgE concentration in adult life

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Summary

A follow-up study was carried out to determine whether either impaired or disproportionate fetal growth are associated with a raised total serum IgE concentration in men and women aged 50 years. The serum IgE concentration was measured in 146 men and 134 women born in Preston (Lancashire, UK) between 1935 and 1943, whose size at birth had been measured in detail.

Sixty-two subjects were found to have an IgE concentration above 80 IU/ml. Compared with subjects with a normal IgE on average they had a 0.30 inch larger head circumference at birth ($P=0.004$) and weighed 5.6 ounces more at birth ($P=0.04$). People with a raised and with a normal IgE were of similar crown–heel length at birth, indicating that *in utero* those with a raised IgE had had disproportionate growth of the head in relation to the trunk and limbs. The prevalence of a raised IgE rose from 14% in subjects whose head circumference at birth was 13 inches or less to 37% in those whose head circumference was more than 14 inches. This association was independent of gestational age at birth and of the mother's pelvic size and parity. It was also independent of adult physique, social class and smoking, and was similar in men and women. In multiple logistic regression analyses odds ratios of a raised IgE rose progressively to more than 4 as head circumference at birth increased from 13 inches or less to more than 14 inches.

One possibility is that these associations reflect the long-term effects of sustaining fetal brain growth at the expense of the trunk, in particular the thymus. This may be a consequence of fetal under-nutrition in late gestation.

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Introduction

There is now a considerable body of evidence in both experimental animals and humans that fetal under-nutrition during critical periods in early development can have life-long effects on structure, physiology and metabolism [1]. This phenomenon is known as programming. Different organs and tissues have periods of rapid cell division at different times during fetal development, and fetal under-nutrition has differing effects according to the stage of gestation. In humans programming at different stages in gestation is thought to underlie relations between specific patterns of impaired and disproportio-

nate fetal growth and diabetes, ischaemic heart disease and obstructive lung disease [2]. In experimental animals the thymus has consistently been shown to be one of the organs most sensitive to fetal and neonatal under-nutrition. Its size and DNA content are permanently reduced by transient maternal under-nutrition during pregnancy and early lactation [3,4].

Atopy is associated with a persistent IgE response to common environmental antigens and has been linked to an imbalance in thymus derived lymphocytes [5]. We hypothesize that this imbalance may be the result of impaired thymic maturation during a critical period in fetal development. To determine whether a long-term alteration in immune function and atopy may be associated with either impaired or disproportionate fetal growth we have studied the serum IgE concentration in a

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population of 50-year-old men and women for whom we have detailed records of anthropometric measurements at birth.

Subjects and methods

A standardized record form was kept for each woman admitted to the maternity ward at Sharoe Green Hospital, Preston (Lancashire, UK) between 1935 and 1943. The record included the mother's parity, external conjugate diameter of the pelvis (distance between the symphysis pubis and the tip of the spine of the fifth lumbar vertebra) and date of her last menstrual period, and the baby's birth weight, placental weight, length from crown to heel, and head circumference. The weight was measured in pounds (1 pound = 0.45 kg) and the length and head circumference in inches (1 inch = 2.54 cm). Measurements had often been rounded and we therefore preserved the original units.

As described in a previous publication [6] we used the National Health Service central register to trace all babies born in the hospital between 1935 and 1943. The total sample came from 1298 singleton infants who were born to married mothers during 1935–1943 and had complete records. We traced 1122 (86%), of whom 503 were still living in the county of Lancashire. A total of 449 of these took part in our first study of blood pressure. They agreed to be interviewed at home and were visited by a field-worker who had not seen the birth data recorded for that person. Height was measured with a portable stadiometer and weight with a portable Seca scale. The waist circumference and hip girth were measured. The father's occupation was used to define social class at birth, and current social class was derived from the subject's or husband's occupation. Alcohol consumption was converted to the total number of grams consumed each week (1 unit = 8 g), and categorized according to criteria in general use as low (men ≤ 168 g, women ≤ 112 g), moderate (169–280 g, 113–168 g), and high (> 280 g, > 168 g) [7].

After the interview, the 393 subjects who lived in or close to Preston were asked to come to Sharoe Green Hospital to have a blood sample taken [8]. Of those asked, 281 complied and an aliquot was available for measurement of the IgE concentration in 280. The average birth weight of the 280 subjects studied was 0.1 pounds more than the 1018 not studied, and the head circumference 0.3 inches less.

The serum IgE concentration was measured by an ELISA technique. A purified mouse monoclonal antibody, HB121 (concentration 2 $\mu\text{m}/\text{ml}$ in coating buffer at pH 9.5), was bound to the wells of a microtitre plate. Serum samples were diluted in PBS/0.1% Tween 20 and added to the plates. After incubation at 37°C for 1½ h,

plates were washed in PBS/0.1% Tween 20 and bound IgE was detected by horseradish peroxidase labelled rabbit antihuman IgE (Dako Ltd, 16 Manor Courtyard, Hughenden, High Wycombe, Bucks, UK), diluted to 1:1000, using orthophenylene diamine as substrate. Standard curves were constructed using reference sera, which were calibrated against a WHO international standard.

Statistical analysis

The serum IgE concentration was below the limit of detection of the assay (5 IU/ml) in 58 subjects (21%). As in a previous study of IgE concentration in relation to airflow obstruction [9] we classified the subjects into those with a serum IgE below the upper limit of the reference range of the laboratory that carried out the assays (≤ 80 IU/ml—the geometric mean for adults plus 1 SD) and those with a serum IgE above this level. If subjects whose IgE was less than 5 IU/ml were assigned a value midway between this and zero (i.e. 2.5 IU/ml), transformation of the IgE concentrations using logarithms produced an approximately normal distribution. Multiple logistic and linear regression were used to analyse the data treating the IgE concentration as both a dichotomous and a continuous variable. These gave similar results. In view of the group of subjects whose IgE concentration was below the limit of detection of the assay we present results treating a raised serum IgE as a dichotomous variable. The divisions of birth weight, head circumference and length at birth used in the logistic regression analyses were those that gave the least discrepant numbers of subjects in each grouping given the rounding of the measurements. The logistic regression analyses produced estimates of odds ratios, which are a measure of the strength of associations between disease and a putative exposure.

Results

The age of the 280 men and women ranged from 47 to 55 years, with a mean of 51 years. The geometric mean IgE was 31.0 IU/ml in the 146 men and 18.9 IU/ml in the 134 women. Forty-one men and 21 women had a serum IgE concentration above 80 IU/ml. There was no significant relationship between serum IgE and current age within the narrow age range of people studied.

Table 1 shows the mean body size, at birth and currently, and adult life-style influences in men and women, and the differences between those with and without an IgE concentration above 80 IU/ml. Compared with those with a normal IgE, men and women with a raised IgE were significantly heavier at birth and had a larger head circum-

Table 1. Mean differences between men and women with and without an IgE concentration above 80 IU/ml

	Difference (raised IgE-normal)					P value*
	Mean		Men (41 raised IgE 105 normal)	Women (21 raised IgE 113 normal)	Total* (95% CI)* (62 raised IgE 218 normal)	
	Men	Women				
<i>Body size at birth</i>						
Birth weight (oz)	111.3	113.0	4.2	8.0	5.6 (0.3-10.9)	0.04
Head circumference at birth (inches)	13.6	13.6	0.33	0.25	0.30 (0.10-0.50)	0.004
Length at birth ^a (inches)	20.4	20.3	0.12	0.15	0.13 (-0.17-0.44)	0.4
Ponderal index at birth ^a (oz/in ³ × 1000)	13.1	13.4	0.19	0.63	0.36 (-0.15-0.87)	0.2
Ratio of head circumference to length at birth (× 100) ^a	66.9	66.9	1.1	0.7	1.0 (-0.1-2.0)	0.07
Placental weight (oz)	21.8	20.8	-1.1	2.7	0.3 (-1.1-1.8)	0.6
<i>Current body size</i>						
Height ^b (m)	1.74	1.60	0.027	0.014	0.022 (0.004-0.040)	0.02
Weight ^b (kg)	79.2	66.0	2.1	3.6	2.7 (-0.8-6.2)	0.1
Body mass index ^b (kg/m ²)	26.2	25.7	-0.1	0.9	0.3 (-0.9-1.4)	0.7
Waist to hip ratio ^b (%)	92.7	82.2	1.6	0.5	0.8 (-1.2-2.8)	0.4
<i>Adult life style</i>						
% smoker	38	29	9	11	9 (-4-23)	0.2
% social class IV, V ^c	21	32	-9	2	-5 (-17-8)	0.5
% with moderate or high alcohol intake	27	7	10	-3	5 (-5-16)	0.3

*Adjusted for sex.

^aLength at birth not recorded for 1 subject.^bNot recorded for 1 subject.^cSocial class could not be classified for 6 subjects.

Table 2. Prevalence and odds ratios of a serum IgE concentration greater than 80 IU/ml in 280 men and women aged 47-55 years

	Sex	Number of subjects	Percentage with IgE > 80 IU/ml	Univariate odds ratios (95% confidence interval)	Multivariate odds ratios (95% confidence interval)
Birth weight (pounds)	Male	146	28	1.0 (baseline)	1.0 (baseline)
	Female	134	16	0.5 (0.3-0.9)	0.9 (0.4-2.3)
Head circumference at birth (inches)	≤ 5.5	68	23	0.8 (0.3-2.0)	2.0 (0.6-7.2)
	6.5	101	14	0.4 (0.2-1.0)	0.8 (0.3-2.1)
	7.5	79	22	0.7 (0.4-1.4)	1.0 (0.5-2.2)
	> 7.5	31	27	1.0 (baseline)	1.0 (baseline)
Height* (m)	≤ 13.0	84	14	1.0 (baseline)	1.0 (baseline)
	13.5	57	21	1.6 (0.7-3.9)	2.1 (0.8-5.9)
	14.0	93	23	1.8 (0.8-3.8)	2.2 (0.9-5.8)
	> 14.0	46	37	3.5 (1.5-8.3)	4.5 (1.5-13.6)
Current smoking (number of cigarettes per day)	≤ 1.60	31	12	1.0 (baseline)	1.0 (baseline)
	1.70	58	18	1.6 (0.7-4.0)	1.5 (0.6-4.1)
	1.80	100	33	3.7 (1.5-8.8)	3.4 (1.0-11.4)
	> 1.80	91	32	3.6 (1.2-10.3)	3.1 (0.8-12.5)
	0	186	19	1.0 (baseline)	1.0 (baseline)
	14	41	22	1.2 (0.5-2.7)	1.4 (0.6-3.3)
	≥ 15	53	32	2.0 (1.0-3.9)	2.2 (1.1-4.5)

*Not recorded for 1 subject.

Table 3. Percentages of men and women aged 47–55 years with a serum IgE concentration greater than 80 IU/ml according to head circumference and gestational age at birth. Numbers of subjects in parentheses

Gestational age (weeks)	Head circumference at birth (inches)		
	≤14.0	>14.0	All
<37.0	33 (15)	— (0)	33 (15)
37, 38	9 (35)	0 (4)	8 (39)
39, 40	23 (80)	33 (18)	24 (98)
≥41.0	18 (61)	53 (19)	26 (80)
All	19 (191)	39 (41)	23 (232)

ference at birth. Their mean birth weight was 5.6 ounces more ($P=0.04$) and their mean head circumference at birth 0.30 inches more ($P=0.004$). There were, however, no significant differences in mean length and as a result those with a raised IgE had a higher ratio of head circumference to length at birth ($P=0.07$). Their mean ponderal index (weight/length³) and placental weight were both similar. As expected higher birth weight babies tended to have a larger head circumference. In a simultaneous analysis, when head circumference was taken into account there was no independent relationship between birth weight and a raised IgE.

Men and women with a raised IgE were taller than those with a normal IgE, by 0.027 m in men and 0.014 m in women ($P=0.02$). They were on average 2.7 kg heavier ($P=0.1$) and had a similar mean body mass index and waist to hip ratio. Men and women with a raised IgE were more likely to be current smokers, although the difference was not statistically significant. There were no statistically significant differences in the percentage of men and women in social class IV and V both currently and at birth (data not shown), or the percentage with a moderate or high alcohol intake.

The mother's external conjugate diameter was recorded for 278 subjects. Larger external conjugate diameter in the mother was strongly associated with larger head circumference at birth in the infant ($P=0.0004$). There was, however, no association between external conjugate diameter and a raised IgE, and the association between large head circumference at birth and a raised IgE was independent of maternal pelvic size. The mother's parity was recorded for 275 of the men and women, with 217 of the subjects being a firstborn. There was no association between parity and a raised IgE.

Table 2 shows the prevalence and odds ratios of a serum IgE concentration greater than 80 IU/ml according to sex, current height, head circumference at birth, birth weight and current smoking. Odds ratios are presented for univariate analysis, and for multivariate analysis simultaneously taking account of the other variables in the table. The subjects were divided into four groups for current height, head circumference at birth and birth weight. The percentage of subjects with a raised IgE was highest in men, tall subjects, those with a large head circumference and weight at birth, and in heavy smokers. As head circumference at birth increased from 13 or less to more than 14 inches, the prevalence of a raised IgE rose from 14% to 37%.

In univariate logistic regression analyses odds ratios of a raised IgE were significantly higher in men, in subjects with a large head circumference at birth and in tall subjects. The decreased odds ratio associated with birth weight between 5.5 and 6.5 pounds, and the increased odds ratio associated with smoking 15 or more cigarettes per day were of borderline statistical significance.

In multiple logistic regression analyses of the simultaneous effects of sex, height, head circumference at birth, birth weight and current smoking the odds ratios of a raised IgE rose progressively with increasing head circumference at birth from 1.0 to 4.5, the highest odds ratio being in people whose head circumference at birth had been greater than 14 inches. The association between odds ratios and head circumference at birth was similar in each social class, both currently and at birth. When the head circumference was taken into account there was no significant association between higher birth weight and a raised IgE, and odds ratios were highest in those whose birth weight was 5.5 pounds or less. Inclusion of gestational age in the logistic regression model made little difference to the odds ratios of a raised IgE associated with the different birth weight groupings. Tall stature and smoking 15 or more cigarettes per day were associated with significantly increased odds ratios. When adult height was taken into account there was no longer an association between male sex and a raised IgE. In each height group the prevalence of a raised IgE was similar in men and women, although there were few men in the shortest group and few women in the tallest group.

Recording of the date of the mother's last menstrual period allowed estimation of the gestational age at birth for 232 subjects. Thirty-three per cent of subjects born prematurely at less than 37 weeks gestation had a raised IgE (Table 3). However, this was based on only 15 subjects and was not significantly higher than in all other subjects. As might be expected increasing gestational age at delivery was associated with a larger head circumfer-

ence at birth ($P < 0.0001$). Multiple regression analysis showed that the relation between a larger head circumference at birth and a raised IgE was independent of duration of gestation, and was, if anything, stronger among people born full-term (37 or more weeks gestation). Among these men and women, born full-term, the prevalence of a raised IgE rose with increasing gestational age at birth, although this did not achieve statistical significance ($P = 0.06$). The highest prevalence of a raised IgE in adult life, 53%, occurred in the 19 men and women born at 41 or more weeks gestation with a head circumference at birth greater than 14 inches (Table 3).

Discussion

We have shown that a raised serum IgE concentration in adult men and women was strongly related to a large head circumference at birth (Table 1). In multiple regression analyses men and women with a head circumference at birth greater than 14 inches had a risk of developing a raised IgE more than 4 times greater than those with a head circumference of 13 inches or less (Table 2).

The study sample comprised men and women who were born in Sharoe Green Hospital and still living in or close to the town who had survived into middle-age. However, our analyses were based on internal comparisons and selection of the sample would bias the risk estimates up or down only if the relations between early growth and a raised IgE concentration differed in those selected and not selected. This seems an unlikely explanation of our findings, especially as the relationship between head circumference at birth and a raised IgE was independent of possible confounding factors including social class, current smoking and adult body size, and was similar in both sexes. It was also independent of gestational age at birth and of the mother's pelvic size and parity. Furthermore, the strength and graded nature of the relationship make it less likely that it depends on some unknown confounding variable.

Tall adult stature, male sex and heavy smoking were also associated with a raised IgE. Multiple regression analysis suggested that the association with the male sex could be the result of men being on average taller than women. The association between heavy smoking and a raised IgE is in accordance with previous studies [9].

Subjects born before 37 weeks gestation had a high prevalence of a raised IgE, but the number of subjects was small and the difference not statistically significant. Among subjects born full-term increasing gestational age at birth was associated with a rising prevalence of a raised IgE and more than half of the men and women born at 41 or more weeks gestation with a head circum-

ference of 14 or more inches had a raised IgE concentration (Table 3). A U-shaped association between gestational age at birth and atopy has not, to our knowledge, been proposed before and, like the association with a large head circumference at birth, must await confirmation in other studies currently in progress. It may, however, in part explain the inconsistent results of studies addressing whether prematurity is associated with atopy [10,11].

The processes underlying the association of a raised IgE in adult life with a large head circumference at birth are at present a matter for speculation. The tendency to persisting high levels of IgE production associated with atopy is thought to result from a diminished TH-1 lymphocyte γ interferon response to common environmental antigens, and by dominant secretion of interleukin-4 and interleukin-5 by the TH-2 lymphocyte subtype, leading to IgE production by B-lymphocytes [5]. Little is known about why atopic individuals react in this manner.

One possible explanation for our findings is that increased growth factor levels associated with nutrient surplus and accelerated fetal growth preferentially increase the TH-2 lymphocyte population. We are not aware of any experimental data to support this explanation. Alternatively, in mice lymphoid irradiation leads to a dominant TH-2 response as the result of a diminished TH-1 cell population [12]. This suggests that TH-2 dominance may also result from a greater sensitivity of TH-1 cells to adverse environmental stimuli.

Impaired fetal nutrition throughout gestation results in low birth weight growth retarded infants and is associated with global impairment of thymic development and increased susceptibility to infection [13]. The effects of under-nutrition in the later stages of pregnancy depend on the growth rate of the fetus. The most rapidly growing fetuses, indicated by larger head size, experience impaired growth if exposed to under-nutrition, while those growing more slowly may be unaffected [14]. In those growing faster a 'brain-sparing' reflex [15] redistributes blood and nutrients to the brain at the expense of the trunk and limbs, resulting in a disproportionate fetus. In such circumstances the thymus is severely reduced in weight [16,17]. The functional significance of this is unknown. Furthermore, in the post-term fetus, while most organs simply experience a deceleration in growth there is marked wasting of the thymus [18]. The reduced thymic weight found in both disproportionate and post-mature fetuses parallels our observations of a higher prevalence of a raised IgE in these groups. We suggest that disproportionate fetal growth and post-maturity may be associated with a raised IgE in adult life as the result of a diminished population of TH-1 lymphocytes, itself a

result of impaired thymic maturation during a critical period late in fetal development.

In a recent study of 1586 men born at the Jessop Hospital in Sheffield during 1907–1924 adult death-rates from non-cardiovascular disease were markedly elevated among men born at 41 or more weeks gestation with a head circumference at birth of 14 inches or more [19]. Deaths from cancer were over-represented in this subgroup of the Sheffield men and one possibility is that this may have been the result of defective immune surveillance as a result of impaired early thymic development.

Although family and twin studies have been interpreted as indicating that atopy is largely genetic in origin the classical twin study may be an unreliable method of estimating the genetic component in most of the common diseases of adult life [20]. The sharing of a common placenta by most monozygotic twins and the intergenerational transmission of fetal growth patterns [21] suggest that the high concordance for atopy in monozygotic twins could in part reflect a similar intrauterine environment. Ecological evidence points to a strong environmental component in the aetiology of atopic diseases, and our finding of an association between accelerated fetal growth and a raised IgE is compatible with the higher prevalence of atopy in more affluent geographical areas [22]. The incidence of atopy has risen over recent decades and the known increase in head circumference at birth over the same period [23] is consistent with this. There is insufficient ecological evidence to distinguish whether or not there is a superimposed adverse stimulus late in gestation as suggested by our observations.

Our findings suggest that research directed towards the causes of atopy should examine the development of the different thymic derived lymphocyte populations in late fetal life and the nutritional and other influences that regulate them.

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