Fig 1—Median weights for infants in Newcastle upon Tyne, birth to 15 months (points), compared with median curves of 1990 national data (continuous lines)

Results

The mean standard deviation score for weight of boys was 0.42 higher than that for girls after the age of 3 months (table 1), and twice as many girls as boys fell below the 3rd weight centile during the first year. There was an equivalent excess of boys above the 97th centile (table 2).

The boys' weight curves rose slightly above the British median while those for girls fell substantially below the median (fig 1). Comparing the means for boys and girls in Newcastle with the Tanner and Whitehouse standards showed mean differences in standard deviation scores of 0.34–0.37 after the age of 3 months.

Discussion

The differences observed in this study are not trivial, being equivalent to over half an intercentile space and resulting in major imbalances in the number of boys and girls who fall outside the normal range for weight.

Although the new standards present problems, these were present to a similar order in the standard they have replaced.

Although it is puzzling to find that children in Newcastle show such striking discrepancies with the two growth standards, it should be remembered that these standards are based, in infancy, on small numbers of children (160 children for the Tanner and Whitehouse standard; 252 for the 1990 standard). The Newcastle dataset comprises 3418 children, with 60–90% of the birth cohort represented in each 3 month age band. This observation thus cannot be easily explained by sampling error or bias. A smaller cohort of children studied in Glasgow showed similar differences.⁷ These findings imply that there is either a substantial and previously unrecognised regional variation or a more general problem with the standards.

It is a matter of urgency to discover whether similar sex differences are observable in southern Britain. If they are, the current weight curves are not representative and require modification. In the meantime, researchers using weight centiles or standard deviation scores as selection criteria should investigate the possibility of sex differences in their study populations so that they avoid inadvertently recruiting a study sample with a major sex imbalance.

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Cohort study of peanut and tree nut sensitisation by age of 4 years

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Abstract

Objective—To determine the prevalence of sensitisation to peanuts and tree nuts in all children born during one year in one geographical area.

Design—Birth cohort study with structured review at ages 1, 2, and 4 years.

Setting—All children born on the Isle of Wight between January 1989 and February 1990.

Subjects—Of 1456 children originally included, 1218 were reviewed at age 4 years. Of these, 981 had skin prick tests.

Main outcome measures—Positive skin test results, clinical atopic disease, and risk factors for the development of atopy.

Results—15 of 1218 (1.2%) children were sensitised to peanuts or tree nuts (13 to peanuts). Six had had allergic reactions to peanuts (0.5% of the population), one to hazelnuts, and one to cashew nuts; three had had anaphylactic reactions. Seven children had positive skin test results or detectable IgE to peanuts without clinical symptoms. Two children

who reacted to peanut in infancy had lost their sensitivity by 4 years. Family history of atopy, allergy to egg (odds ratio 9.9, 95% confidence interval 2.1 to 47.9, and eczema (7.3, 2.1 to 26.1) were important predictors for peanut allergy.

Conclusions—IgE mediated allergy to peanuts is common in early childhood. In many the allergy persists but a minority may develop tolerance.

Introduction

Peanuts cause a potentially serious form of food allergy,¹ and some people with no physical reaction to peanuts have been found to have specific IgE antibody in the serum on radioallergosorbent testing (RAST) or a positive skin prick test result. Sensitisation to peanuts may occur when very young and is usually life long.^{2,3} Although parents are advised that young children should not eat whole nuts, peanut butter and nuts mixed in food are allowed. There is concern about hidden nuts in processed foods and improved labelling is

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needed. The prevalence of allergy to peanut and tree nuts is not known. This whole population study estimates the prevalence of allergy to edible nuts in early childhood and looks at the possible routes of sensitisation.

Subjects and methods

We approached the mothers of all children born on the Isle of Wight ($n = 1536$) between January 1989 and February 1990 prenatally. After exclusion of perinatal deaths, adopted children, and those who refused to participate, 1456 children were included in the study. Most had cord serum IgE titre measured at birth. Findings at age 1 and 2 years have been published.^{4,5}

We took data on feeding, atopic disease, family history, parental smoking, exposure to pets, housing conditions, and intercurrent illness from records at birth, 1, and 2 years and updated them. Questions about eating nuts were asked only at age 4 years. Some families had moved away leaving 1218 (83.6%) children for review after their fourth birthday. The proportion of atopic children among the 169 children lost to follow up was similar to that estimated for the whole cohort at age 2 years (23% *v* 23.4%). No reactions to nuts had been reported in those lost to follow up. Skin prick tests for peanuts were not done at ages 1 and 2 years.

SKIN PRICK TESTS

At 4 every child was offered a skin prick test with a battery of air and food allergens including peanut extract. Children who had suffered reactions to peanuts or tree nuts and those with a positive skin test reaction to peanuts were recalled to elucidate the possible routes of sensitisation and for repeat skin tests with soya, pea, peanut, and tree nut extracts (peanut ALK, Horsholm, Denmark; others Allergopharm, Reinbek, Germany). Histamine (0.1%) and physiological saline were used as positive and negative controls. A mean weal diameter at least 3 mm bigger than that seen with saline after 15 minutes was taken as a positive result.

BIOCHEMICAL ANALYSIS

We took 4.3 ml of blood from each child and spun it at 3000 rpm for 15 minutes. The total IgE titre in the resulting serum was measured with IgE total enzyme linked immunoassay (EIA) kits on a Roche Cobas core analyser (Roche, Germany).⁶ This is a one step solid phase sandwich method in which serum, standards, and controls were incubated with beads coated with monoclonal antibody to IgE together with a monoclonal anti-IgE labelled with horseradish peroxidase. After washing, the beads were incubated with substrate [3,3',5,5'-tetramethylbenzidine]. The intensity of colour produced was proportional to the IgE concentration. A correlation of 0.99 was found compared with the Pharmacia EIA kit. Specific IgE to nuts, pea, and soya was measured by Phadezym enzyme linked immunoassay testing (Pharmacia, Sweden). Briefly, 50 µl of serum was incubated with the antigen bound paper discs for three hours at room temperature. After washing, the discs were incubated with enzyme labelled anti-IgE overnight. The discs were washed again and reincubated with substrate at 37°C for two hours. The absorbances were measured at 420 nm and compared with a standard curve prepared as above.

STATISTICAL ANALYSIS

Data were analysed with SPSS/PC+, version 4 (Chicago, USA). We analysed differences in proportions by Fisher's exact test. Logistic regression was used to calculate adjusted odds ratios and 95% confidence intervals for an independent effect of various risk factors. Related variables were studied separately by entering them into the regression model one by one.

Table 1—Number (percentage) of children with sensitivity to peanuts and atopic disease at age 4 years

	Peanut sensitive† (n = 13)	Not peanut sensitive (n = 1205)
Asthma (n = 181)	6 (46)*	175 (14.5)
Eczema (n = 145)	8 (62)**	137 (11.4)
Rhinitis (n = 65)	4 (31)***	61 (5.1)

Fisher's exact test: *P<0.01, **P<0.005, ***P<0.001.

†Allergy and non-clinical sensitisation.

Table 2—Reactions to peanuts and tree nuts

Case No	Nut	Symptoms	Age at first reaction (months)
1	Peanut	Facial rash	30
2	Peanut	Facial rash	10
3	Peanut	Generalised urticaria, angio-oedema, asthma*	9
4	Peanut	Angio-oedema	7
5	Peanut	Generalised urticaria, angio-oedema, asthma*	12
6	Peanut	Exacerbation of eczema†	24
7	Hazelnut	Angio-oedema, asthma*	25
8	Cashew	Generalised urticaria, angio-oedema	48

*Anaphylactic reaction (more than one system affected).

†Symptoms occurred 30 minutes after ingestion.

Results

Of the 1218 children studied at age 4 years, 981 (80.5%) had skin prick tests. Eight children allergic to peanuts and tree nuts were identified by history and skin tests, and seven had non-clinical sensitisation to peanuts based on a positive skin test result alone, giving an overall cumulative prevalence of sensitivity to peanuts and to all nuts of 1.1% (95% confidence interval 0.5% to 1.6%) and 1.2% (0.7% to 1.9%) respectively. All children sensitive to nuts had atopic disorders, and peanut sensitisation was associated with asthma, eczema, and rhinitis (table 1). Three children had recurrent urticaria, three had IgE mediated allergy to egg (positive skin test results at previous follow ups), and one had intolerance (negative skin test result) to strawberry. Two of the children with egg allergy had lost it by age 4 years. Fourteen of the allergic children were breast fed for between 5 and 72 weeks and one was given formula milk from birth.

Ten mothers recalled eating nuts during pregnancy (peanuts, nine; tree nuts, five) and seven during lactation (peanuts, six; tree nuts, six). Thirteen children had eaten peanuts (10 peanut butter) and nine had had tree nuts by age 4 years. The mean age at first recorded exposure to peanuts was 12.6 (range 7 to 36) months. Six children (0.5% of the study population, 95% confidence interval 0.1% to 0.8%) had reacted to peanuts, five immediately and one within half an hour of ingestion (table 2). One child reacted to hazelnuts and one to cashew nuts. The mean age at first reaction was 20.6 months. Three children had anaphylactic reactions (two to peanuts, one to hazelnuts).

Fourteen (93%) of the children with nut allergies had a family history of atopic disease. A family history of atopy was associated with peanut sensitisation (table 3). One mother had peanut allergy, and five out of six children who had had an allergic reaction to peanuts had atopic mothers. All 14 children who had skin prick tests had positive reactions to at least one allergen other than nuts. Aeroallergen sensitisation was more common among children sensitised to peanuts than among other

Table 3—Number (percentage) of children with genetic and early life predictors for peanut sensitisation

	Peanut sensitive† (n = 13)	Not peanut sensitive (n = 1205)
Family history of atopy (n = 713)	12 (92)*	701 (58.2)
Male sex (n = 624)	10 (77)	614 (51)
Infantile eczema (n = 122)	5 (38)**	117 (9.7)
Infantile wheeze (n = 106)	2 (15)	104 (8.6)
Milk allergy‡ (n = 62)	1 (8)	61 (5.1)
Egg allergy‡ (n = 29)	3 (23)***	26 (2.2)

Fisher's exact test: *P<0.05, **P<0.01, ***P<0.005.

†Allergy plus non-clinical sensitisation.

‡Recorded at age 1 or 2 years, or both.

children (10/12 (83%) v 179/ 969 (18.5%), P<0.001). One of the children allergic to peanuts had a positive skin test reaction to soya.

The total serum IgE titre in 14 of the sensitive children was higher than the age adjusted normal. Total IgE was significantly higher in children with a positive enzyme linked immunoassay result for peanuts (2081.7 v 440.6 ku/l, P<0.05) and there was a trend for the titre to parallel the degree of test positivity. Cord serum IgE titre at birth did not correlate with the results of skin prick or enzyme linked immunoassays for peanuts. Skin prick tests with peanuts gave positive results in 11 children but none reacted to garden peas. Five children had positive enzyme linked immunoassay results for peas, four of whom also had positive reactions to peanuts. In some the enzyme linked immunoassay results correlated poorly with skin test responses (table 4).

Allergy to egg (confirmed by skin test) was associated with peanut sensitisation (table 3). Logistic regression (n = 1086) showed that egg allergy during the first two years of life was a significant risk factor (odds ratio 9.9, 95% confidence interval 2.1 to 47.9; P<0.01). The influence of family history did not reach significance (7.4, 1.0 to 60.9; P<0.07), but eczema at 4 years was a significant predictor of peanut sensitivity (7.3, 2.1 to 26.1; P<0.01). Other factors studied included asthma or rhinitis at age 4 years, infantile eczema, infantile wheeze, male sex, low birth weight (<2.5 kg), high cord IgE titre (>0.5 ku/l), introduction to formula milk before age 3 months, breast feeding for less than three months, parental (maternal) smoking, exposure to cat

or dog, and low socioeconomic group (social classes IV and V according to the registrar general's classification).

The mean duration of breast feeding and the age at introduction to formula milk were similar for children with and without nut sensitivity (16 v 14.8 weeks and 11.4 v 10.5 weeks respectively). Maternal nut ingestion during pregnancy or lactation or both did not increase nut sensitisation in the children (table 4). One mother denied eating nuts while pregnant or breast feeding and yet her child suffered angio-oedema immediately after the first recorded ingestion of peanut butter at age 7 months (case 4). More surprisingly, a child who suffered anaphylaxis at 9 months and had a positive skin test reaction to peanuts at 1 year had negative skin and enzyme linked immunoassay results at 4 years (case 3). Peanuts were excluded from his diet. An open food challenge was not performed because of parental refusal. One child had repeated exacerbations of eczema after eating peanut butter (case 6), and this improved after avoiding peanuts. He had negative results to peanuts and tree nuts on enzyme linked immunoassay at 4 years. Though food challenges were not performed, one peanut sensitive child from a vegetarian family regularly ate nuts in her diet without any untoward effects (case 10).

Table 5 gives the specificity and sensitivity for the factors linked to peanut sensitisation. Family history of atopy was sensitive but not specific whereas infantile eczema, egg allergy, and atopic disease at age 4 years had greater specificity and low sensitivity. All the factors had a poor positive predictive value for the development of peanut allergy.

Table 5—Sensitivity, specificity, and predictive value (as percentages) of risk factors for allergy and non-clinical sensitisation to peanuts

	Sensitivity	Specificity	Predictive value
Family history	92.3	41.8	1.7
Asthma*	46.1	85.5	3.3
Eczema*	61.5	88.6	5.5
Rhinitis*	30.8	94.9	6.1
Infantile eczema	38.5	90.3	4.1
Allergy to egg†	23.1	97.8	10.3

*At age 4 years.

†Recorded at age 1 or 2 years, or both.

Table 4—Total IgE, results of enzyme linked immunoassay and skin prick test, and maternal ingestion of nuts in 15 children with nut sensitivity

Case No*	Total IgE (ku/l)†	Enzyme linked immunoassay‡ (skin prick test)						Maternal ingestion§	
		Peanut	Almond	Brazil nut	Walnut	Hazelnut	Cashew nut¶	Peanut	Tree nut
1	306	0(+)	0(-)	0(-)	0(-)	0(+)	0	P+L	P+L
2	408	1(+)	0(+)	0(-)	1(-)	1(-)	0	P+L	P or L
3	198	0(-)	0(-)	0(-)	0(-)	0(-)	0	P+L	P+L
4	5	2(+)	1(-)	0(-)	0(-)	0(-)	0	None	None
5	2809	2(+)	2(+)	0(-)	0(+)	0(-)	0	None	None
6	157	0	0	0	0	0	0	None	P+L
7	246	0(+)	0(+)	0(-)	0(-)	0(-)	2	None	None
8	1296	0(-)	0(+)	3(+)	0(-)	1(+)	2	P or L	None
9	2130	1(+)	0(+)	0(-)	0(-)	0(-)	0	None	None
10	1148	2(+)	0(-)	0(-)	0(-)	0(-)	0	P+L	P+L
11	3526	2(+)	2(-)	1(-)	2(-)	1(-)	0	None	None
12	7387	3(+)	2(-)	0(-)	0(-)	0(-)	0	P or L	None
13	1997	3(-)	1(-)	1(-)	0(-)	2(-)	0	P+L	None
14	469	3(+)	0(+)	0(-)	2(-)	1(-)	0	P+L	P+L
15	938	4(+)	3(-)	1(-)	0(-)	1(-)	0	P or L	None

*First eight correspond to the cases in table 2 in same order.

† Normal range 5-55 ku/l.

‡Grades 0 = <0.35 PRU/Phadebas RAST units/ml, 1 = 0.35-0.69 PRU/ml, 2 = 0.7-3.49 PRU/ml, 3 = 3.5-17.5 PRU/ml, and 4 = >17.5 PRU/ml.

§P = pregnancy, L = lactation.

¶Skin prick test not performed.

Radioallergosorbent inhibition was performed in five children who had large discrepancies between the results of skin and enzyme linked immunoassays (cases 8, 12, 13, 14, and 15). Sera were incubated with peanut protein extract (4 g/l) in a 1:1 ratio at 4°C overnight. The mixture was centrifuged and 0.1 ml aliquots of the supernatant reincubated with tree nut extracts. There was 88% inhibition of radioallergosorbent tests to walnut in case 14. All other inhibition values were below 40% (data not shown).

Discussion

Up to 10% of people with allergic disease may be sensitive to peanuts.⁷ In our cohort the cumulative prevalence of nut allergy at 4 years was 1.2%. Only 238 (16.3%) of the original cohort could not be reviewed, and there is no reason that they would have significantly biased the results. All children with a history of a reaction to peanuts or tree nuts were seen and tested. It is possible that a few with asymptomatic sensitisation were missed among the 237 not given skin tests. Seven of 13 children allergic to peanuts had non-clinical sensitisation. Extrapolating this information to the whole cohort gives an estimated prevalence of sensitisation to peanut of 1.3%. We may, therefore, have underestimated the prevalence of peanut sensitisation. The prevalence of non-clinical tree nut sensitisation remains unknown as tree nuts were not included in the skin test battery for the whole cohort.

Nut allergy in our cohort could increase with further exposure, and those with non-clinical sensitisation may develop symptoms. Two children who apparently lost their peanut sensitivity raise the hope that some children could become tolerant as is the case with allergies to cows' milk or eggs. Studies suggest that nut allergy usually persists even in those who develop it early.^{3,8} One study noted an association between peanut and tree nut sensitisation.⁸ In our study radioallergosorbent test inhibition revealed a likely cross-reactivity between peanut and walnut in only one of five children. Cross reactivity between peanut and tree nuts needs research.

Studies list a range of symptoms resulting from nut allergy. The symptoms recorded in this study were limited as they were primarily described by parents. The pattern, however, followed that reported previously, with skin reactions most common followed by respiratory symptoms.^{2,4}

Transplacental sensitisation before birth or sensitisation through breast milk is possible.⁹ In this study maternal nut ingestion did not increase nut sensitisation in the children. Furthermore, duration of breast feeding and age at introduction to formula milk were similar for children with and without nut sensitisation. Despite a low sensitivity and predictive value, infantile eczema and eczema at 4 years were significant for peanut sensitisation. It is thus likely that babies of atopic families who develop eczema carry an increased risk of peanut allergy. Likewise, allergy to egg early in life could precede peanut allergy. A positive skin test reaction to egg at 1 year has been reported to increase allergic disease by age 7 years.¹⁰

Information on nut ingestion by mothers during pregnancy and lactation and by the children may be unreliable as it was gathered after their fourth birthday. One child sensitive to peanuts who had not eaten peanuts and may not have been sensitised through the mother was given a formula milk. Sensitisation through

Key messages

- Sensitisation to peanuts or tree nuts can develop early in life in children from atopic families and is likely to be life long
- This study suggests that 1 in 200 children could have reactions to peanuts and tree nuts by the age of 4 years and a similar number could have asymptomatic sensitisation
- Children with allergy to peanuts invariably have another atopic disorder such as asthma, eczema, or rhinitis
- Sensitisation to peanuts and tree nuts may coexist

formula milk containing peanut extract or oil has been reported. Reactions to peanut may occur on first ever exposure.¹¹ In such cases, especially in those with high degree of atopy, sensitisation may follow inadvertent ingestion of hidden peanuts or minute amounts of peanut protein contaminating other foods.

A study showed that highly atopic children (total IgE titre over 10 times normal plus multiple positive radioallergosorbent test results) are more likely to be sensitised to peanuts.² Most children allergic to nuts in this cohort had high total IgE titres, with the levels being more or less parallel to the results of enzyme linked immunoassay for peanuts. However, cord IgE at birth was a poor predictor of nut allergy.

Peanut and tree nut allergy is increasingly recognised as a potentially serious health problem. This study estimates the prevalence of nut allergy in early childhood. It raises questions of cross reactivity between peanuts and tree nuts and the possible routes of sensitisation. The predictive value of eczema and allergy to egg early in life requires confirmation.

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