

A population study of food intolerance

Elspeth Young, Michael D Stoneham, Anne Petruckevitch, Jeremy Barton, Roberto Rona

Summary

We did a population study to identify the prevalence of reactions to eight foods commonly perceived to cause sensitivity in the UK. A cross-sectional survey of 7500 households in the Wycombe Health Authority area and the same number of randomly-selected households nationwide was followed up by interviews of positive respondents from the Wycombe Health Authority area. Those who agreed entered a double-blind, placebo-controlled food challenge study to confirm food intolerance.

20·4% of the nationwide sample and 19·9% of the High Wycombe sample complained of food intolerance. Of the 93 subjects who entered the double-blind, placebo-controlled food challenge, 19·4% (95% confidence interval 11·4%–27·4%) had a positive reaction. The estimated prevalence of reactions to the eight foods tested in the population varied from 1·4% to 1·8% according to the definition used. Women perceived food intolerance more frequently and showed a higher rate of positive results to food challenge.

There is a discrepancy between perception of food intolerance and the results of the double-blind placebo-controlled food challenges. The consequences of mistaken perception of food intolerance may be considerable in financial, nutritional, and health terms.

Lancet 1994; 343: 1127–30

Introduction

Food intolerance was recognised in ancient Greece but it is recently, with the recognition of atopy and reaginic antibody IgE, that immunological food intolerance has been described.¹ Food reactions in childhood are common, often transient,² and previous studies indicate that less than half perceived food intolerance is confirmed by double-blind placebo-controlled challenge.³ Investigation is difficult because of the lack of any simple specific in-vitro or in-vivo test. Many mechanisms of food intolerance have been identified⁴ and only a few are immunological. The best way to establish food intolerance is dietary exclusion and controlled challenge repeated on several occasions.⁵

As a result of a review by the UK Royal College of Physicians and the British Nutrition Foundation,⁴ the UK Ministry of Agriculture, Fisheries, and Food commissioned a study of the prevalence of reactions to food additives⁶ and subsequently the present study of reactions to foods. Ethical committee consent was granted for all stages of the study.

Subjects and methods

A questionnaire was designed with a separate sheet for each member of the household. Questions were about perceived connection between food ingestion and itching, eczema, urticaria, angio-oedema, asthma, rhinitis, intestinal symptoms, joint symptoms, behavioural or mood changes, and headaches.

Amersham Hospital, Department of Dermatology, Amersham, Bucks MP7 0JD, UK (E Young MRCP, M D Stoneham MRCP), Division of Community Health, Guy's and St Thomas's Hospitals, London (A Petruckevitch MSc, J Barton BSc, R Rona FFPHM)

Correspondence to: Dr Elspeth Young.

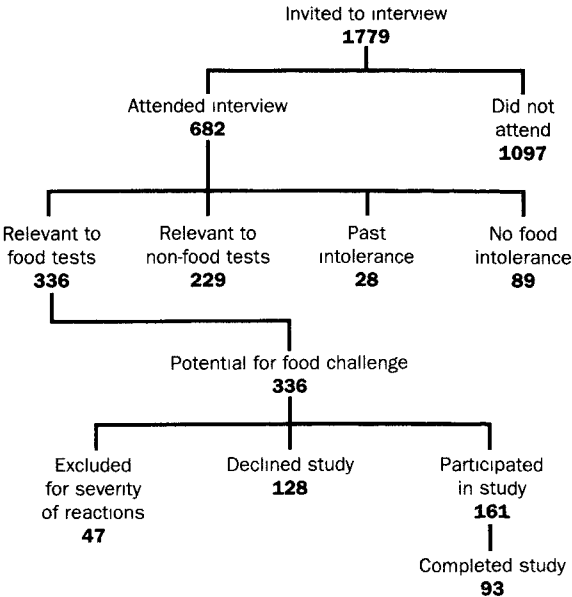


Figure 1: Flow chart of participants

Two random samples of households—7500 from the Wycombe Health Authority population and another of 7500 households nationwide—were taken from electoral registers. The number selected was calculated to contact approximately 20 000 individuals (the average household size in the High Wycombe area was estimated to be 2·66). A reminder questionnaire was sent to all non-respondents after three weeks and, at a later date, an abbreviated questionnaire was circulated to all non-respondents.

Those from the High Wycombe area who claimed food intolerance in the questionnaire and indicated willingness to help were asked standard questions directed to symptoms related to food ingestion, foods involved, personal and family history of atopic disease, and past medical history. A decision was made, following an algorithm, as to whether food challenge would be offered. Exclusion criteria were: age less than 6 months, pregnancy, mental illness or disability, a severe or anaphylactic reaction to foods, and reported reactions to foods not included in the challenge study.

Eight foods were selected for challenge:⁷ cow's milk, hen's egg, wheat, soya, citrus fruit (as orange), fish/shellfish (as prawn), prepared in cans with corn flour and rice flour as placebo challenges, with herbs to mask the flavour in savoury cans, and

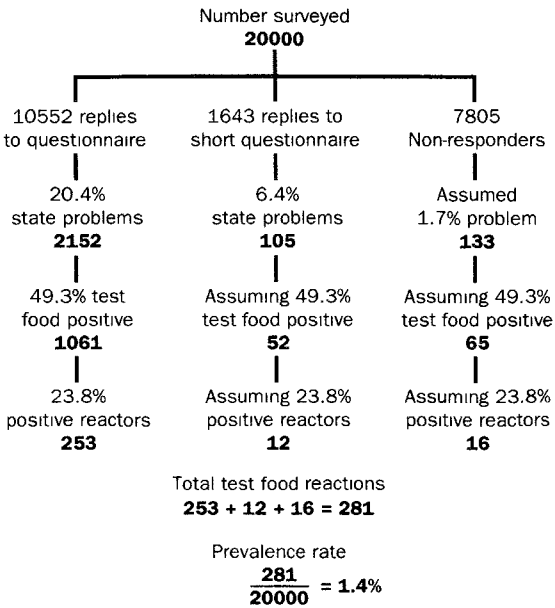


Figure 2: Method used to calculate prevalence

	Wycombe health authority (n = 10 552)		Nationwide (n = 8328)	
	No	Reported reaction (%)	No	Reported reaction (%)
Chocolate	696	6.6	571	6.9
Additives	517	4.9	483	5.8
Citrus	367	3.5	290	3.5
Fish/shellfish	308	2.9	236	2.8
Cow's milk	303	2.9	210	2.5
Cheese	245	2.3	225	2.7
Hen's eggs	218	2.1	214	2.6
Nuts	182	1.7	132	1.6
Alcohol	176	1.7	89	1.1
Meat	172	1.6	183	2.2
Caffeine	146	1.4	98	1.2
Tomatoes	124	1.2	111	1.3
Non-citrus fruit	107	1.0	83	1.0
Wheat	99	0.9	75	0.9
Vegetables	49	0.5	43	0.5
Soya	35	0.3	27	0.3

Table 1: Questionnaire responses: foods reported as causing symptoms

orange oil in sweet cans; and nuts (peanut, brazil, walnut, and hazel), and chocolate prepared as a bar with carob as placebo and peppermint oil as a disguising flavour. Blinding was confirmed by tasting panels.

Those selected for study were required to exclude the eight test foods from their diet for three weeks (five weeks if they suffered from eczema or behavioural symptoms). A baseline period of 7 days was followed by two 7-day periods consisting of an initial 3-day challenge followed by a 4-day rest period (those with eczema or behavioural symptoms had a baseline period of 7 days followed by two 14 day periods—a 7-day challenge and a 7-day rest). Subjects were randomly allocated to the order in which active and placebo challenge was administered; all were challenged with the eight foods selected for study as a sweet and savoury can, and a bar taken at the same time daily. One three-day period (or seven day period for eczema or behavioural symptoms) was active challenge and the other was placebo. Daily diary cards were completed during the test, a separate card for asthma, intestinal problems, urticaria, headache, rhinitis, joint symptoms, behavioural and mood problems, and eczema. The cards recorded severity and frequency of each symptom on a scale of 0–3 (no symptoms, mild, moderate, or severe symptoms). Objective scores such as measurement of peak flow in asthma were also marked on diary cards. Subjects who reported severe symptoms were observed in clinic for two hours after the first food challenge. Control patients were recruited from questionnaire respondents reporting one of the eight diary-card conditions which were not perceived as related to food.

Decision as to whether an individual had a positive reaction was by a computerised algorithm. Total diary-card scores were calculated for each condition for the active and placebo periods separately. Assessment of a subject's overall food intolerance was calculated as the difference between active and placebo scores. The simple difference was preferred as providing a more straightforward description of the subject's reactivity than a ratio of responses because the latter would have exaggerated the response of individuals with lower scores for the active and placebo period. Cut off points for the differences of 5 or 3 were chosen

	Wycombe health authority (n = 10 552)		Nationwide (n = 8328)	
	No	(%)	No	(%)
Itching	1707	16.2	1232	14.9
Eczema	1889	17.9	1220	14.7
Urticaria	825	7.8	514	6.2
Angioedema	848	8.0	526	6.3
Asthma	1570	14.9	1202	14.4
Hayfever	3020	28.6	2070	24.8
Stomach	814	7.7	762	9.2
Joints	1584	15.0	1359	16.3
Behaviour	1380	13.0	1178	14.2
Migraine	2167	20.5	1676	20.1

Table 2: Questionnaire responses: symptoms

arbitrarily to incorporate definite cases or definite/probable cases, respectively. Prevalence figures were calculated on this basis. As it is impossible to assess sensitivity and specificity of any cut-off point, the chance of misclassification cannot be excluded.

Those excluded from challenge because of the severity of symptoms and who had confirmatory evidence of history by skin prick testing or RAST results were included as positive reactors; the remainder were arbitrarily allocated a frequency of 25% of that of the positive reactors. We also calculated prevalence, assuming a frequency of 50% and 100% of positive reactions.

Results

There were questionnaire replies from 10 552 individuals (52.7%) in the Wycombe Health Authority population and 8328 (41.6%) nationwide. Perceptions of the effect of food on health were similar in both groups (table 1). In the Wycombe Health Authority population, 2152 of 10 552 subjects (19.9%) perceived an intolerance to foods. The abbreviated questionnaire sent to all non-respondents resulted in a 17.4% response rate with 6.4% of those claiming a reaction. Table 2 shows the symptoms reported; atopic conditions were slightly more frequent in the Wycombe Health Authority.

Atopic symptoms (hayfever, asthma, or eczema) were reported in 27% of the overall respondents. Food reactions were more commonly reported in those with atopic symptoms, 28% of people with atopy as compared to 15% of those without. With the exception of children, positive respondents showed a female predominance with women between the ages of 21 and 50 reporting the highest frequency of reactions. Figure 1 is a flow chart of participants. Potential subjects for study were lost at all stages. Of those attending interview, 89 were excluded on the basis that their history was not compatible with food intolerance. Those with symptoms related to foods which had occurred more than five years ago but who were now tolerant were also excluded. 47 were excluded because of the severity of their symptoms, including 25 patients with urticaria and angio-oedema (10 related to shellfish and 15 related to nuts). Anaphylaxis had occurred in 4 of these patients; a further 19 suffered severe migraine headaches and 3 were excluded because of severe gut reactions. Many declined the study because of the complexity of the trial procedure. Those who withdrew during the challenge period gave their reasons as difficulty in complying with the protocol, social inconvenience, intercurrent illness, or dislike of the test-challenge foods.

Analysis was based on the difference between diary-card scores while on active and placebo challenges. There was no effect of the order in which challenges were taken, as tested with a 5% significance level in the *t* test.⁸ The method of calculating prevalence is shown in figure 2. Those whose

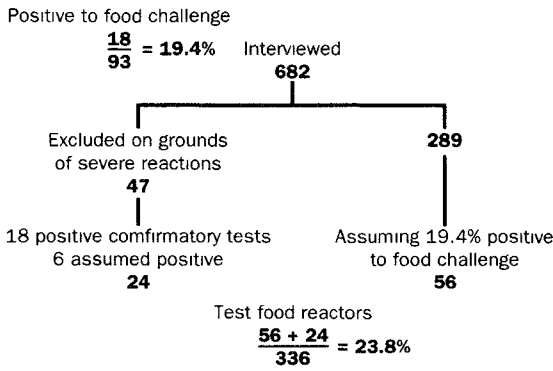


Figure 3: Prevalance of food intolerance

diary cards showed a difference of five or more between active and placebo challenge were considered positive to challenge. 93 subjects (62 female, 31 male) completed the study and 18 (3 male, 15 female) had positive results—a 19.4% (95% confidence interval [CI] 11.4%–27.4%) positive challenge rate (intestinal symptoms in 5, headache in 3, behavioural symptoms in 2, urticaria in 2, joint symptoms in 7, asthma in 1, and multiple symptoms in 4). 3 of 5 (60%) less than 10 yrs old were positive, 0 of 10 (0%) 11–30, 7 of 49 (14.3%) 31–50, and 8 of 29 (27.6%) over the age of 50. Of the 47 excluded because of severe symptoms, 18 of 25 with severe urticaria/angioedema had confirmatory evidence by skin prick test or RAST and were considered positive reactors; we estimated that 25% of the remaining 22 of these should be considered to be positive reactors, ie, 5.5 (approximated to 6).

Calculation of the prevalence of intolerance based on 49.3% of those interviewed who gave a positive history to the eight test foods is shown in figure 2. A positive challenge rate of 23.8% was calculated for these subjects. A similar rate of positive challenge in a similar proportion of cases was assumed for all positive respondents to the original questionnaire. The potential number of cases in those responding to the abbreviated questionnaire was calculated, assuming a similar proportion of positive results in the 6.4% claiming intolerance. Assuming proportionally a lesser perceived intolerance rate of 1.7% in those not responding to the original or abbreviated questionnaire, the potential number of cases in the non-respondent population indicated a prevalence rate in the population of 1.4%. Assuming a 50% and 100% positive reaction rate of those with a history of severe reaction, the prevalence would have been 1.5% and 1.7%, respectively. With less stringent criteria, a prevalence rate was calculated based on the number of cases considered positive to challenge if there was a difference in diary-card scores greater than 3 between active and placebo challenge. Positive reactions in 26 of 93 subjects were found by this criterion ie, 28% (95% CI 18.9%–37.1%) and the prevalence rate in the population was calculated as 1.8%. Assuming a 50% and 100% positive reaction rate of those with a history of severe reactions, prevalence would have been 1.9% and 2.1% respectively.

45 control patients with similar symptoms to those studied but who did not perceive a problem with foods were interviewed and 24 agreed to food challenge. Thirteen of these completed the challenge and 1 was positive (7.7%) (95% confidence interval 0–22).

Discussion

To our knowledge, this is the first study of its kind to assess the prevalence of food intolerance in the community. Previous studies have involved selected populations, most often atopic, in a hospital setting.^{9,10} There have, however, been three population studies on cow's milk allergy in infants.^{11–13} Our results give prevalence of intolerance for eight test foods studied of 1.4% with stringent criteria and 1.8% with less-stringent criteria. These eight foods accounted for 49.3% of reported reactions but we also identified other foods causing symptoms. Our prevalences are, therefore, an underestimate. It is difficult to estimate by how much, as our study gives indicative figures only and misclassification could have led to error in either direction.

The use of double-blind placebo-controlled challenge study is necessary for objective assessment of food allergy and for comparisons.¹⁴ Previous studies have shown less than 50% of reported reactions being confirmed when

controlled challenges are used.³ The discrepancy between perception and prevalence is less than in our previous study of food additive intolerance where 7.4% of the population perceived a problem but only 0.01% by stringent criteria and 0.23% by less stringent criteria could be proven.⁶

We were surprised at the number of severe reactions reported, many of which had been self-managed without seeking medical advice, particularly in instances of angioedema to shellfish and nuts where the subject decided to avoid the offending food which may result in falsely low estimates of such reactions. Migraine accounted for most reported reactions with chocolate as the major cause. We enquired specifically for reactions to cheese to identify migraine reactions and differentiate them from those with cow's milk allergy. A recent study showed food-induced migraine confirmed by double-blind placebo-controlled food challenge in 15% of migraine sufferers.¹⁵ Intestinal symptoms, particularly irritable bowel, were recorded to the widest range of food substances and account for a large number of reported cases of food-induced disease.¹⁶

Our prevalence figures are in keeping with other studies.¹⁷ There are difficulties in conducting a double blind placebo controlled challenge study of this nature. The allergenicity of many of the foods, particularly cow's milk, may be diminished by canning, resulting in falsely low positives to challenge. Many patients, mostly men, were lost to the study because of the inconvenience of the trial procedure. Nevertheless, we did achieve positive challenge results in 19.4% to 28% (according to definition) of those submitted to controlled challenge. Compliance in completing the diary cards in this study was high as the patients were counselled about the importance of this to the study and at the end of the study period the diary cards were checked by the clinician who went over them in detail with the patient. As a final check, one of us (AP) double-checked all diary cards for completeness in statistical analysis.

Food intolerance is perceived as a problem by 20.4% of the UK population who responded to the questionnaire, but with controlled challenge to eight foods the actual prevalence is 1.4% when a strict criterion was applied (that is a difference of at least five points in the scores between active and placebo) and 1.8% when the less stringent criterion of three points was applied. Contrary to the lay and media perception of the problem, food intolerance exists in the population to a greater extent than food additive intolerance based on our results of this and a previous study.

This work was supported by the Ministry of Agriculture, Fisheries, and Food. We thank the British Market Research Bureau, Cadbury Schweppes Limited, and H J Heinz Company for their provision of challenge materials, and Professor John Warner for advice and encouragement.

References

- 1 Sampson HA. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol* 1988; **81**: 635–45.
- 2 Bock SA. Prospective appraisal of complaints of adverse reactions to food in children during the first three years of life. *Paediatrics* 1987; **79**: 683–88.
- 3 Sampson HA. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann Allergy* 1988; **60**: 262–69.
- 4 Joint Report: food intolerance and food aversion. *Proc R Coll Phys* 1984; **18**: 83–123.
- 5 Bock SA. A critical evaluation of clinical trials in adverse reactions to foods in children. *J Allergy Clin Immunol* 1986; **78**: 165–72.
- 6 Young E, Patel S, Stoneham MD, Rona R, Wilkinson JD. The prevalence of reactions to food additives in a survey population. *J R Coll Physicians Lond* 1987; **21**: 241–71.
- 7 Price CE, Rona RJ, Chinn S. Height of primary school children and parents' perceptions of food intolerance. *BMJ* 1988; **296**: 1696–99.

- 8 Pocock SJ. Clinical trials: a diagnostic practical approach. Chichester: John Wiley & Sons, 1991: 110–22.
- 9 Buckley RH, Metcalfe D. Food allergy. *JAMA* 1982; **1248**: 2627–31.
- 10 Metcalfe DD. Food hypersensitivity. *J Allergy Clin Immunol* 1984; **73**: 749–62.
- 11 Hide DW, Guyer BM. Cows milk intolerance in Isle of Wight infants. *Br J Clin Pract* 1983; **37**: 285–87.
- 12 Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. *Allergy* 1990; **45**: 587–96.
- 13 Schrandt JJP, van den Bogart JPH, Forget PP, Schrandt-Strumpel CTRM, Kulijten RH, Kester ADM. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993; **152**: 640–44.
- 14 May CD. Defined versus ill-defined syndromes associated with food sensitivity. *J Allergy Clin Immunol* 1986; **78**: 144–46.
- 15 Webber RW, Vaughan TR. Food and migraine headache. *Immunol & Allergy Clin NA* 1991; **11**: 831–41.
- 16 Nanda R, James R, Smith H, Dudley CRK, Jewell DP. Food intolerance and the irritable bowel syndrome. *Gut* 1989; **30**: 1099–104.
- 17 Anderson JA. The clinical spectrum of food allergy in adults. *Clin Exp Allergy* 1991; **21**: 304–15.

Origin of adult male mediastinal germ-cell tumours

R S K Chaganti, E Rodríguez, S Mathew

Summary

The origin of primary extragonadal germ-cell tumours, especially mediastinal and pineal germ-cell tumours in adult males remains uncertain, although the predominant view is that they originate in misplaced primordial germ cells retained in extra-gonadal sites, in contrast to gonadal germ-cell tumours which are considered to arise in premeiotic spermatocytes.

We hypothesised that if mediastinal germ-cell tumours and gonadal germ-cell tumours were derived from precursor cells in different developmental states and in different cellular environments, non-random genetic changes in the two groups would be significantly different. To test this hypothesis, we compared non-random chromosomal abnormalities in mediastinal germ-cell tumours with those in gonadal germ-cell tumours. Our results show that although the two groups differed in the composition of histological subsets, their non-random chromosomal changes were essentially the same.

These data suggest gonadal origin of all germ-cell tumours with occasional migration of precursors early in development to extragonadal sites to become established as primary extragonadal germ-cell tumours. Based on a review of cytogenetic data on carcinoma in situ, primary mediastinal and gonadal germ-cell tumours, embryonal migration of primordial germ-cells, and meiotic behaviour of spermatocytes, a model of origin of all germ-cell tumours in males is suggested.

Lancet 1994; **343**: 1130–32

Introduction

The majority of male germ-cell tumours (GCTs) are gonadal while a minority occur in extragonadal sites,¹ most commonly in the thymus.² Retroperitoneal GCTs are generally considered to be metastases of primary gonadal lesions, while the origin of primary mediastinal GCTs and pineal GCTs has been a matter for speculation. Although mediastinal GCTs were once thought to be metastases from occult gonadal primaries, they are now thought^{3,4} to be of local origin, derived from primordial germ cells (PGCs) misplaced during embryogenesis.⁵ According to this

view, extragonadal GCTs originate from malignant transformation of dormant PGCs under selective local conditions and at a different developmental stage than gonadal GCTs which arise from PGCs or meiocytes before anaphase I of meiosis.^{5,6}

Recent genetic information on GCTs suggest another origin for mediastinal GCTs. The concepts of specificity of genetic change, (recognised as non-random chromosome changes), which underlies malignant transformation of target stem cells during developmental regulation, has become established in defining pathways of tumorigenesis.⁷ If primary extragonadal GCTs were to be derived from misplaced PGCs, patterns of non-random genetic changes shown by extragonadal mediastinal GCTs and GCTs would reflect their origins

Materials and methods

Between Jan 1988 and June 1992, we attempted karyotypic analysis of more than 200 GCTs biopsied at the Memorial Sloan-Kettering Cancer Center, and successfully analysed the karyotype of 58%.^{8,9} We compared the types and incidence of non-random chromosome abnormalities in mediastinal GCTs with those in gonadal GCTs.

Histological diagnosis was on formalin-fixed and haematoxylin-eosin-stained sections of biopsy specimens obtained within 1–2 hours of resection. Tumours were histologically classified according to World Health Authority GCT classification. Diagnosis of primary mediastinal GCT was made after occult testicular lesions were ruled out by sonography.⁵ 30 specimens from 23 patients were diagnosed as mediastinal GCTs; 19 primary and 13 metastatic. 172 specimens from 153 patients were diagnosed as gonadal; 70 primary and 102 metastatic. Short-term culture and cytogenetic analysis was attempted on each biopsy specimen as described previously.⁸ In the case of specimens with successful karyotypic analysis, clonal chromosome abnormalities were defined and described according to ISCN (1991).¹⁰

Results

Yolk-sac and undifferentiated carcinomas were more frequent in mediastinal GCTs compared with gonadal GCTs, while seminomas and embryonal carcinomas were more frequent in gonadal GCTs (table). Karyotyping was successful in 25 of 30 mediastinal GCTs (14 primary, 13 metastatic) and 92 of 172 gonadal GCTs (33 primary, 59 metastatic). The modal chromosome number in both groups was 64. However, mediastinal GCTs had a higher proportion of near-diploid tumours (58%) and a lower proportion of near-triploid tumours (27%) compared to gonadal GCTs (32% and 57%, respectively). This

Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA (Prof R S K Chaganti PhD, E Rodríguez PhD, S Mathew PhD)

Correspondence to: Prof R S K Chaganti