10

The epidemiology of adverse food reactions

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10.1 Introduction

Epidemiology is the study of the distribution of disease within populations. In collecting data about patterns of disease in a population, researchers are able not only to describe the scope of the problem in quantitative terms but also to further our understanding of the disease and its pathogenesis. Important clues may be uncovered about possible risk factors which may lead to the development of novel preventative or therapeutic strategies. An example of this in allergy is the high association between early exposure to bacterial infections and the absence of allergy in later childhood (Matricardi *et al*. 2000). This raises the question of whether we will be able to prevent allergies developing in children by alteration of the gastrointestinal flora and has stimulated research into DNA vaccines that use common bacterial DNA sequences to modulate the infant's immune system.

10.2 Methodological issues

10.2.1 Defining adverse food reactions

There are internationally agreed definitions for adverse food reactions, as have been discussed in Chapter 1. Unfortunately, terms such as 'food intolerance' are still used inconsistently. Thus the term 'intolerance' according to internationally agreed definitions is taken to mean physiological reactions to foods that do not have an immunological mechanism. However the term 'cows' milk protein intolerance' is often used to describe an immunological reaction to cows' milk that is non IgE-mediated (Host *et al*. 1997). It is not uncommon for authors to

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use several definitions of food allergy or food intolerance within a single publication. Any critical analysis of epidemiological studies must begin with a detailed understanding of the definitions used (for example, Table IV in Zeiger *et al*. 1999). This is of critical importance in comparative studies where like must be compared with like.

The international definitions of adverse food reactions exclude food aversion. Such aversions have a psychological origin and cannot be reproduced under objective conditions when the patient and observer are blinded to the identity of the food consumed. In population studies, up to a third of adults may report symptoms of adverse food reactions; however, double-blinded, placebo-controlled studies (Young *et al*. 1994) show that the majority of these are not reproducible. This discrepancy between real and perceived adverse food reactions is likely to be accounted for by the large number of subjects who have food aversion. The failure to differentiate between food aversion and reproducible adverse food reactions in studies relying on self-reporting (Bjornsson *et al*. 1996) or open challenges (Crespo *et al*. 1995) must be considered when prevalence data is assessed.

In this chapter we will focus on food allergies as this form of adverse food reaction is the best studied and associated with the highest morbidity. Additionally, we will describe adverse reactions to food additives. Although any food can cause allergic reactions, most reactions are caused by a limited range of foods. In infants and young children, the commonly implicated foods are cows' milk, egg, soy, wheat and peanuts. For older children, teenagers and adults, foods such as fish and shellfish are also a significant problem.

10.2.2 Diagnosing adverse food reactions

Different studies vary considerably in their working diagnostic criteria for food allergy. This has an important influence on the resultant measurement of prevalence and incidence in a population. In looking at IgE-mediated allergic problems, there are three levels of diagnostic criteria: (1) questionnaire-based histories, (2) specific IgE and/or skinprick testing and (3) food challenges (see Chapter 3). If, for example, we compare two population studies defining the prevalence of cows' milk allergy, one using skin testing and the other questionnaire-derived data, a higher prevalence will emerge in the latter study design. Double-blinded, placebo-controlled food challenges represent the gold standard but can not be practically used in large population-based studies where a combination of skinprick testing and questionnaire-based histories is more applicable.

10.2.3 Measuring the frequency of adverse food reactions and relating this to the natural history

There are a number of ways of measuring the degree to which a population is affected by a disease process such as food allergy. The best approach depends on

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the question being asked. Investigators usually measure either the incidence or the prevalence. The incidence is the number of new cases of adverse food reactions developing over a specified time. This is a useful measure when studying causality and possible preventative strategies but it gives little idea of the proportion of the population affected by the problem. The prevalence is the proportion of a specified population who suffer from adverse food reactions at a particular time. This figure is useful for gauging the health burden imposed by the problem in a population. Prevalence rates reflect two dynamic processes: the acquisition of new cases of allergy in a population (incidence) and the simultaneous loss of allergy in that population (either due to death or clinical remission). Therefore a static prevalence between two time points may fail to reveal high incidence and resolution rates that negate each other.

Many studies quote cumulative incidence which does not reflect the resolution of the adverse food reactions. While this indicates the proportion of the population who will have suffered allergy over a defined time period, it tends to overestimate the magnitude of the problem at a given time point which is better reflected by the point or period prevalence. The natural history of food allergy must be taken into account if we are sensibly to interpret incidence and prevalence rates in a population. For example, cows' milk allergy mainly presents in the first year of life and is almost entirely outgrown over the following four years (Figure 10.1). Therefore its incidence peaks by one year of age decreasing to almost zero at five years. The prevalence of cows' milk allergy will increase until a year of age after which it also starts to decrease as the remission rate exceeds the incidence rate. Cumulative incidence meanwhile will increase to a plateau at one to two years of age (Dean 1997).

If prevalence or incidence rates are being compared across two populations, it is important that the two populations have similar demographics. Thus the two populations may need to be standardised with respect to male–female ratio and the age structure of the populations, as both these variables significantly affect incidence and prevalence rates for food allergy. Care is also required when

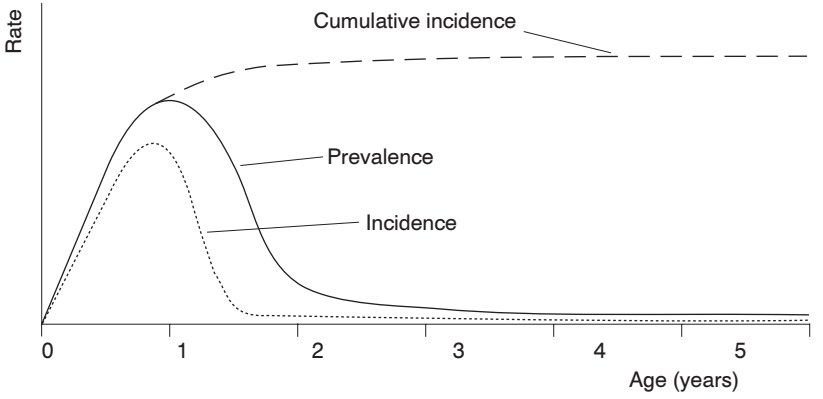

Figure 10.1 Natural history of cows' milk allergy.

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prevalence rates are compared over time between different age groups in a population because of the cohort effect. If a higher rate of food allergy is found in infancy than adults, there are two potential explanations: firstly, this may reflect high remission rates of the problem or secondly it may be explained by a cohort effect in that the cohort of infants born in the 1990s may have a higher incidence of food allergy compared to the cohort of infants born several decades ago.

10.2.4 Implications of study design

In deciding on which study to use to estimate the prevalence of food allergy statistical, practical and financial constraints must be considered. The ideal sample would include all the individuals in the population but this is clearly impossible and our studies must be conducted on a subset of the total population. It is this down-sizing that leads to important methodological problems due to the selection procedures. The different types of study described below represent different selection procedures and give rise to different problems. It is impossible to obtain a subset that completely represents the entire population from which it is derived.

Case series

Many reports about food allergy have been based on personal series derived from general clinics or tertiary clinics. Such series are unable to provide any information about incidence and prevalence in a population as there is no known denominator associated with the data. Nevertheless, such series provide useful qualitative information about food allergies in different populations. Thus the fact that allergy to royal jelly is the most common cause of food allergy diagnosed in tertiary clinics in Hong Kong, but is never seen in European tertiary clinics is highly relevant (Leung *et al.* 1997). Furthermore, case series are useful in identifying novel problems. The fact that sesame seed allergy was rarely seen in European allergy clinics several decades ago but today represents an important component of the clinical case load suggests that this problem is increasing (Kanny *et al.* 1996).

Case series, however, are fraught with methodological problems, most notably bias. A bias is any error in the design or conduct of a study that results in a result other than the true one, due to systematic (though unintentional) skewing of the data. Bias may be introduced either in the selection of subjects or in the collection of information (Sackett 1979). A study looking at the association of soy allergy with cows' milk allergy (Zeiger *et al*. 1999) provides a good example of selection bias in a case series. The prevalence of soy allergy in one clinic was more than ten times greater than in the other three centres. This particular centre was a tertiary paediatric allergy clinic that saw a highly selected population, more likely to include children with multiple food allergies.

There is also a potential for information bias in case series because data are often collected retrospectively either directly from subjects or from their clinical

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notes. Patients often do not have a good recall of events, leading to a form of information bias called recall bias. A good example of recall bias is a birth cohort study in which mothers were asked about the duration of breast feeding at 11 and 47 months of age (Huttly *et al*. 1990). At 47 months there was only 70% agreement with data obtained from the same mothers at 11 months. Although case series do not provide robust epidemiological data, they provide a window through which current clinical experience may be viewed. They often form the initial basis of many hypotheses that can subsequently be tested in more definitive studies where cases and control subjects are compared.

Case-control studies

Case-control studies are a natural extension of case series having the added advantage that they provide control subjects with which the cases can be compared. Similar to case series, they provide no data on incidence and prevalence as here again the denominator remains unknown. They are, however, useful in the early testing of hypotheses that relate to associations and risk factors for food allergy. However, they make the assumption that all the differences between subjects and controls represent risk factors for the disease being investigated. In practice measured differences may be brought about by important biases in selection and information. Furthermore, confounding factors may occur where an apparent association between an exposure and an outcome is partially or entirely due to another associated exposure.

An example of a case-control study, is one looking at the aetiology of peanut allergy. It was concluded that children sensitised to peanut had a higher level of peanut exposure *in utero* due to higher maternal consumption (Frank *et al*. 1999). This result, which has not been confirmed in cohort studies, probably occurred because of recall bias as the mothers of infants with peanut allergy, are likely to have spent more time considering their consumption of peanuts during pregnancy prior to filling in the study questionnaire. Despite these potential problems, case-control studies represent a rapid way of providing important evidence about a hypothesis that can be later tested using a more definitive approach.

Cross-sectional studies

Cross-sectional studies are population-based studies within a defined geographical region. This approach considerably reduces the potential for selection bias. Furthermore they allow the point prevalence of the condition studied to be estimated. However, such studies by their nature afford a single glimpse of the population at one specific time point. Therefore no data can be derived about changes in incidence and natural history of the condition over time. Such studies allow us to identify risk factors for food allergies as the population contains both cases and control subjects. Cross-sectional studies involve large numbers of subjects and require considerable resources. They may also be affected by bias and confounding factors.

Mailed questionnaires are often used in cross-sectional studies but response rates can be very low, even after reminders are sent. In the High Wycombe

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population study of food intolerance (Young *et al*. 1994), replies were received from only 52.7% of subjects. It can be argued that responders are likely to differ substantially from the non-responders, introducing an important selection bias. Such problems may be reduced with door-to-door interviews but other problems emerge, for example, subjects out at work may escape interview. Telephone-based interviews are becoming increasingly common (Munoz-Furlong *et al*. 1989) but these exclude subjects without a telephone and those who choose to be ex-directory, which will bias the sample. Evidence from cross-sectional studies also provides useful data on the prevalence of disease in a population and highlights potential causal factors. Evidence collected using this approach must eventually be substantiated by the results of cohort studies to decide if it has been affected by selection or information bias.

Cohort studies

Cohort studies are less affected by the problems inherent in other approaches for the single reason that subjects are included and exposures recorded before the outcome has occurred. This eliminates a major source of bias. Cohort studies, unlike cross-sectional studies, are not subject to the cohort effect as all the participants are born over a specified narrow time period. Furthermore, one is able to estimate the incidence and remission rates as well as prevalence and thus obtain a more complete picture of the natural history of a disease. Such studies provide the best quantitative and qualitative description of food allergy within a population but make the highest demands on time and resources. Nevertheless, cohort studies are not completely immune to methodological problems. Selection bias may operate slowly over a longer period of time. At the start of the study, there is likely to be a loss of participants due to failure to enrol while others may become lost to follow-up during the study. The loss of potential subjects at enrolment and during follow-up is likely to introduce important selection bias.

Cohort studies are important in identifying risk factors for food allergy. This risk is usually quantified using odds ratios or relative risks. Confounding can still occur where a third factor may account for a perceived association between a particular exposure and an allergic outcome. Where such confounding variables are suspected and identified, their effects can be eliminated by the application of statistical methods such as logistic regression analysis. An example is the association seen between prolonged breast feeding and food allergy. This is not a real association as it is confounded by eczema; infants with eczema are deliberately breast fed for longer periods and eczema is a known risk factor for food allergy.

Although cohort studies have their limitations, they generally provide the best form of evidence concerning the prevalence and natural history of a disease within a population. They are well suited to the study of the natural history of food allergy. They also provide pointers to potential causal factors which can be subsequently tested within the context of a randomised interventional study

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where allocation of the exposure is random and not subject to known or unknown confounders.

Interventional studies
In many ways interventional studies are very similar to cohort studies except that the investigator is able to allocate the exposure artificially, preferably at random. The randomised, double-blinded, placebo-controlled study (RDBPC study), where exposure allocation is random and known to neither subject nor investigator, is the gold standard for generating evidence. Unfortunately, although the data generated by a good study are invaluable, these studies are difficult to set up for financial, practical and ethical reasons. It is only ethical to randomise subjects between two or more interventions if there is no evidence to suggest that one is more beneficial than the other. It may be difficult to recruit a sufficiently large and representative study population to have sufficient power to be able to arrive at definitive conclusions. Even once a study population has been recruited problems may occur with loss to follow-up because of a perceived failure of the active or control intervention.

Most interventional studies in food allergy have focused on maternal dietary exclusion during pregnancy and/or lactation as well as modification of the infant diet. In general they have been unsuccessful. A problem that pervades all such studies is that elimination of a food from the diet may not be achieved to a sufficient degree or at an early enough time point to ensure a successful intervention. These 'no difference found' studies become very difficult to interpret, leading to 'newer and better' interventional studies.

10.3 Commonly reported food allergies

10.3.1 Cows' milk

Introduction
Cows' milk is an important weaning food in many countries. In recent years it has become practically ubiquitous, being found in an increasing range of commercially produced foods (Sampson 1998). There is extensive cross-reactivity between milks of different species (Businco *et al*. 1995, Carroccio *et al*. 1999). Cows' milk is one of the first foods to enter an infant's diet and therefore is often the first to cause problems. Adverse reactions to cows' milk can be divided into two main groups, immunological (IgE or non-IgE mediated) or non-immunological (Host *et al*. 1997, Host and Halken 1998). This latter group is mainly due to lactase deficiency and may be difficult to differentiate clinically from non-IgE mediated cows' milk allergy (Host *et al.* 1997, Bruinjzeel-Koomen *et al*. 1995). Cows' milk allergy gives rise to a spectrum of disease from immediate symptoms ranging from urticaria to anaphylaxis (Goldman *et al*. 1963, Sampson *et al*. 1992) and late symptoms which may not develop for 24 to 48 hours. Most early reactors have specific IgE to cows' milk (Hill *et al*. 1988, Host and Halken 1990).

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Prevalence and natural history

Adverse reactions to milk presents early, median age 4–8 weeks with a range of 1–52 weeks (Jakobson and Lindberg 1979, Host 1990, Schrander *et al*. 1993). In general, infants do not develop symptoms on their first exposure to cows' milk (Host 1990). Half react within a week of first exposure and three-quarters within four weeks (Host 1990, Jakobson and Lindberg 1979). Of note, a quarter of the children have their first symptoms while being exclusively breast fed (Host 1990).

Symptoms suggestive of cows' milk allergy or intolerance are relatively common and are seen in 2–15% of infants (Table 10.1). This variability is probably due to different diagnostic criteria, study design, geographical differences and different ages. Where subjects have been prospectively recruited and diagnosis is based on food challenge, the cumulative incidence has been found to be remarkably similar at 1.9–2.3% in the first three years of life (Table 10.1). Unfortunately few of these studies differentiate between the different types of adverse reactions or whether specific IgE is present. Where they do, 25–50% of infants develop symptoms within 1–3 hours (Schrander *et al.* 1993, Jakobson and Lindberg 1979, Host 1990).

The peak prevalence of cows' milk allergy is seen at 1–2 years of age. After this age, children start to lose their reactivity (Table 10.1). The remission rate in one study was 56% at 1 year, 77% at 2 years, 87% at 3 years and 92% at 5 and 10 years (Host 1990, Host 1997). The majority of children with persistent cows' milk allergy beyond 5 years of age have IgE to cows' milk (Host 1990, Host *et al.* 1997).

Within the adult population, adverse reactions to cows' milk are reported by 0.7% of the population but only 10% of these have specific IgE to cows' milk. The prevalence of IgE-mediated cows' milk allergy in adults is therefore extremely low at 0.07% and is probably due largely to persistent allergy from childhood (Bjornsson *et al*. 1996, Niestijl *et al*. 1994) (Table 10.1). Lactase deficiency is probably responsible for most adverse reactions to cows' milk in adults (Bruinjzeel-Koomen *et al.* 1995).

10.3.2 Soy

Introduction

Soy is a fairly recent addition to the Western diet although soybeans have been eaten for centuries in the Far East. The most commonly reported adverse reactions to soy are gastrointestinal symptoms, often as an enterocolitis syndrome or colitis (Powell 1978). Specific IgE to soy is not thought to be involved (Zeiger *et al*. 1999). Skin lesions are occasionally seen but IgE-mediated symptoms or anaphylaxis are extremely rare (Cantani and Lucenti 1997).

It had been thought that most cows' milk allergic children also reacted to soy (Cantani and Lucenti 1997). However, the early studies relied on the history, RAST tests or skinprick tests to make the diagnosis. When open or blinded challenges are used to diagnose both the cows' milk and soy allergy, 11–32% of

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children are found to react to both (Table 10.2). This variation in results between studies probably stems from the fact that they each enrolled different populations with different proportions of children with IgE and non-IgE mediated cows' milk allergy.

Prevalence and natural history

In general, adverse reactions to soy are first seen in the later part of infancy although when infants are exposed to soy at a young age, reactions can occur (Bruno *et al*. 1997). The prevalence of self-reporting of soy allergy is very low unless a selected, atopic population is studied (Table 10.3). In atopic children presenting to allergy clinics the prevalence is 1.2–3% when diagnosed by open challenge. In unselected childhood population, the prevalence is only 0–0.3%. Most of these children have positive specific IgE to soy and react within four hours. Where soy allergic children have been followed up, all have been found to outgrow their allergy within seven years (Bock 1982). This correlates with adult studies where the prevalence of soy allergy has been estimated as zero (Table 10.3). Soy may behave as an aeroallergen in both adults and children; in Barcelona, aerosolised soy from the port has been linked to epidemics of asthma (Navarro *et al*. 1993).

10.3.3 Peanuts and tree nuts

Introduction

Over the last few decades, peanuts have become a ubiquitous part of the Western diet as they are a versatile form of easily digested protein (Lucas 1979). In a study looking at the use of dietary manipulation to prevent the development of food allergy, all infants in the control group were exposed to whole peanuts by their second birthday (Zeiger *et al*. 1989); occult exposure probably occurs even earlier. Adverse reactions to peanuts and tree nuts are generally IgE mediated, occurring rapidly with subjects presenting with dermatological, respiratory and gastrointestinal manifestations (Hourihane *et al*. 1997). Peanuts and tree nuts are responsible for a third of all admissions with anaphylaxis (Bock 1992). Peanuts are part of the legume family, they are more closely related to peas, beans, soy and lentils than the tree nuts. It has been suggested that there is extensive cross-reactivity between peanut and tree nuts in terms of sensitisation but not clinical reactivity (Sampson and McCaskill 1985, Bernhisel-Broadbent and Sampson 1989). However a recent British survey suggested that 50% of people with peanut allergy have symptoms with other nuts (Loza and Brostoff 1995). For the legume family, most subjects show sensitisation to at least two members of the family but very few subjects are clinically allergic to more than one (Bernhisel-Broadbent and Sampson 1989).

Prevalence and natural history

Peanut and tree nut allergy generally presents in childhood (Sampson 1990, Kivity *et al*. 1994). The majority of children react to peanut on their first

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Table 10.1 Epidemiology of adverse food reactions to cows' milk – key studies

Author, date	Type of study	Country	No. of subjects	Point prevalence	Cumulative incidence	Definition
Halpern *et al*. 1973	Prospective series	USA	1084	1.8%		History
Dean 1997	Population based, birth cohort	UK	1218	4.4% at 1y; 1.9% at 2y; 0.4% at 4y	5.1% to 4y	History
Arshad *et al.*1993	Population based, birth cohort	UK	1174	1.8% at 2y		History
Burr and Merrett 1983	Population based, cross-sectional	UK	475	1% in adults		History
Young *et al.*1994	Population based, cross-sectional	UK	18 880	2.7%, all age groups		History
Niestijl Jansen *et al*. 1994	Population based, cross-sectional	Holland	1483	0.7%, 18–70y		History
Bjornsson *et al*. 1996	Population based, cross-sectional	Sweden	1812	1% (sp IgE) 0.07% (sp IgE and symptoms) aged 20–44y		Sp IgE ± history
Kajosaari 1982	Population based, cross-sectional	Finland	802	2% at 1y 5% at 2y 2% at 3y 0% at 6y		Open challenge at home

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Kivity *et al.* 1994	Retrospective series	Israel, recent onset symptoms to food	112	0%, 10–48y		Open or double-blinded challenges
Gerrard *et al.* 1973	Prospective series	Canada	787		7.5%	Open challenge at home
Schrander *et al.* 1993	Population based, birth cohort	Netherlands	1158		2.3% to 1y	Open challenge
Jakobson and Lindberg 1979	Population based, birth cohort	Sweden	1079		1.9% to 1y	Open challenge
Bock 1987	Population based, birth cohort	USA	480		15% to 3y (history) 2.2% to 3y (challenge)	History ± open/ double-blinded challenge
Host and Halken 1990	Population based, birth cohort	Denmark	1749		2.2% to 3y	Open or double-blinded challenges

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Table 10.2 Combined cows' milk and soy allergy – key studies

Author, date	Country	Number of subjects	Basis of diagnosis of cows' milk allergy	Basis of diagnosis of soy allergy	Prevalence of soy allergy in children with proven cows' milk allergy	Comments
Kuitunen *et al*. 1975	UK	35	Open challenge	Open challenge	11%	Non-IgE, mean age 5m
Perkkio *et al*. 1981	Italy	103	Open challenge	Open challenge	11%	Non-IgE
Bardare *et al*. 1988	France	29	Open challenge	Open challenge	17%	Mixed
Paganus *et al*. 1992	Finland	19	Open challenge	Open challenge	32%	Mixed, mean age 11m
Zeiger *et al*. 1999	USA	93	Open or blinded food challenge	Open or blinded challenge	14%	Mainly IgE, mean age 19m

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Table 10.3 Epidemiology of adverse food reactions to soy – key studies

Author, date	Type of study	Country	No. of subjects	Point prevalence	Cumulative incidence	Definition
Dean 1997	Population based, birth cohort	UK, unselected	1218	0% at 1y; 0% at 2y; 0% at 4y	0% to 4y	History
Young *et al*. 1994	Population based, cross-sectional	UK	18 880	0.3%, all age groups		History
Niestijl Jansen *et al*. 1994	Population based, cross-sectional	Holland	1483	0%, 18–70y		History
Bjornsson *et al*. 1996	Population based, cross-sectional	Sweden	1812	2% (sp IgE) 0% (sp IgE and symptoms) aged 20–44y		Sp IgE ± history
Giampietro *et al*. 1992	Prospective series	Italy, atopic children	317	3%, 1m to 10y		Open challenge
Kivity *et al*. 1994	Retrospective series	Israel, recent onset symptoms to foods	112	0%, 10–48y		Open or double-blinded challenges
Magnolfi *et al*. 1996	Prospective series	Italy, atopic children	704	21% by SPT, 1.1% by DBPCFC 1m to 18y		SPT± Double-blinded challenge
Sampson 1988	Prospective series of children with eczema	USA	204	5%		Double-blinded challenges
Bruno *et al*. 1997	Prospective series, multi-centre	Italy – infants with history suggestive of food allergy	505	1.2% at 6m to 14y		Double-blinded challenge
Bock 1987	Population based, birth cohort	USA (middle-class community)	480		2.2% to 3y (history) 0.4% to 3y (challenge)	History ± open/ double-blinded challenge

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Table 10.4 Epidemiology of adverse food reactions to peanut and tree nuts – key studies

Author, date	Type of study	Country	No of subjects	Point prevalence	Cumulative incidence	Definition
Burr and Merrett 1983	Population based, cross-sectional	UK	475	0% adults		History
Foucard 1991	Cross-sectional medical students	Sweden	1050	9%		History
Young *et al*. 1994	Population based, cross-sectional	UK	18 880	1.7% (all nuts) in all ages		History
Niestijl Jansen *et al*. 1994	Population based, cross-sectional	Holland	1483	0% adults		History
Emmett *et al*. 1999	Population based, cross-sectional	UK	46 252	0.61% (0–4y) 0.53% (15–44y) 0.30% (>44y)		History
Tariq *et al*. 1996	Population based, birth cohort	UK	1456	1.3% (SPT) at 4y 1.1% (history and SPT) at 4y		See left
Kajosaari 1982	Population based, cross-sectional	Finland	802	2% at 1y 1% at 2y 2% at 3y 0% at 6y		Open challenge at home

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Munoz-Furlong *et al*. 1989	Population based, cross-sectional	USA	12 032	0.4% (0–17y) 0.7% (>17y)		History via telephone interview
Bjornsson *et al*. 1996	Population based, cross-sectional	Sweden	1812	3% (sp IgE) 0% (sp IgE and symptoms) aged 20–44y		Sp IgE ± history
Kivity *et al*. 1994	Retrospective series	Israel, recent onset symptoms with food	112	20%, 10–48y		Open or double-blinded challenges
Golding *et al*. 1998	Population based, birth cohort	UK	14 000		0.21% to 2y 0.31% to 4y 0.67% to 5y	Double-blinded food challenge
Bock 1987	Population based, birth cohort	USA	480		1.3% to 3y (history) 0.6% to 3y (challenge)	History ± open/ double-blinded challenge

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known exposure. Sensitisation must therefore be due to occult exposure (Hourihane *et al.* 1997). Reactions to peanuts and tree nuts are relatively common. Up to 2% of infants have histories of adverse reactions to peanuts with the highest prevalence figures being seen around four years of age (Table 10.4). Rates in adults appear to be lower unless a highly selected atypical population is studied (Foucard 1991). Where challenges are used to confirm the diagnosis, the prevalence figures drop to under 0.7% (Table 10.4). Historically, peanut and tree nut allergies have been considered to be lifelong problems (Sampson and Scanlon 1989, Bock and Atkin 1989). However, recently, evidence has been presented to suggest that at least some children outgrow their allergy by five years of age (Golding *et al*. 1998, Hourihane *et al*. 1998). This is supported by the evidence that the prevalence of peanut allergy is lower in adults (Table 10.4).

10.3.4 Fish and shellfish

Introduction

Fish is usually introduced relatively late into the infant diet and is therefore one of the less common infant food allergies. Shellfish usual enter the diet even later and adverse reactions to these are usually not seen until the teenage years or adulthood. Both fish and shell allergy are generally IgE mediated with a rapid onset of symptoms. Both have been implicated in anaphylaxis (Kemp *et al*. 1995, Yunginger *et al*. 1988, Bock 1992).

There is cross-reactivity between different species of fish – more at the immunological level than the clinical level. Sera from subjects with codfish allergy cross-reacts with proteins from other species but not with shrimp or milk (Hansen *et al*. 1997, de Martino *et al*. 1990, Helbling *et al*. 1999). Cross-reactivity at the immunological and clinical levels is also seen with shellfish (Castillo *et al*. 1994). It is unclear, though, to what extent there is clinical cross-reactivity between fish and shellfish.

Prevalence and natural history

Adverse reactions to fish are reported in less than 0.5% of young children (Table 10.5). An exception is one Finnish birth cohort study where 5% of infants reacted to fish on an open challenge at home (Kajosaari 1982). Fish allergy seems to increase with increasing age with up to 1.5% of adults having adverse reactions to fish by history (Table 10.5). However, in one study only 0.1% adults had both symptoms and specific IgE to fish (Bjornsson *et al*. 1996). Up to 2.1% of the adult population report adverse reactions to shellfish; no paediatric studies report significant shellfish allergy in children (Table 10.5). The natural history of fish allergy is unclear but there is one study that suggests that most children do not outgrow this problem (Bock 1982).

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Table 10.5 Epidemiology of adverse reactions to fish and shellfish – key studies

Author, date	Type of study	Country	No. of subjects	Point prevalence	Cumulative incidence	Definition
Burr and Merrett 1983	Population based, cross-sectional	UK	475	1.5% (fish) 2.1% (shellfish) In adults		History
Bock 1987	Population based, birth cohort	USA	480		None to 3y	History
Young *et al*. 1994	Population based, cross-sectional	UK	18 880	2.9% (fish and shellfish) all ages		History
Niestijl Jansen *et al*. 1994	Population based, cross-sectional	Holland	1483	0% in adults		History
Dean 1997	Population based, birth cohort	UK	1218	0.2% at 2y 0.1% at 4y	0.2% to 4y	History
Bjornsson *et al*. 1996	Population based, cross-sectional	Sweden	1812	0.3% (sp IgE) 0.1% (sp IgE and symptoms) aged 20–44y		Sp IgE ± history
Rance *et al*. 1999	Prospective series, children with food allergy	France	703	0% <1y 3.3% 1–3y 8.5% 3–6y 17.5% 6–15y		Open or blinded food challenge
Kajosaari 1982	Population based, cross-sectional	Finland	802	5% at 1y 2% at 2y 3% at 3y 1% at 6y		Open challenge at home
Kivity *et al*. 1994	Retrospective series	Israel, subjects with recent onset allergic symptoms to food	112	None, 10–48y		Open or double-blinded challenges

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10.3.5 Egg

Introduction

Egg is an early weaning food in diets worldwide. Although chicken egg is the predominant form in the developed world, in other countries eggs from other animals are commonly eaten, but epidemiology for these is lacking. Adverse food reactions to egg are acute and IgE mediated, implicated in cardiorespiratory, gastro-intestinal and skin (including exacerbation of eczema) reactions (Burks *et al*. 1998). Egg proteins may cause IgE-mediated occupational asthma in egg-processing workers (Bernstein *et al*. 1987). The most allergenic part is the egg white, but allergens also reside in the yolk. The eggs from other birds such as turkey, duck and goose contain the same major allergens as are found in chicken egg (Langeland 1983). Egg allergy is a marker for peanut allergy (Dean 1997), and appears to be the food most associated with later onset asthma/allergic rhinitis with up to one in three children developing skin test reactivity to aeroallergens by the age of four years (Dean 1997, Nickel *et al*. 1997). Key epidemiological studies are shown in Table 10.6.

Prevalence and natural history

There is no evidence of sensitisation to egg at birth (Kulig *et al*. 1999), and the majority (85–90%) of clinical reactions occur in the first 2–3 years of life while 55–88% of reactions occur on the first known exposure to egg (Ford and Taylor 1982, Langeland 1983). The incidence of clinical egg allergy varies with the definition used. It ranges from 2.4% in children up to four years old if the definition is based on history of a clinical reaction (Dean 1997) to 0.6% in children up to three years old if the more rigorous definition based on DBPCFC is used (Bock 1987). However, a study using open egg challenge at home as an endpoint suggests a peak prevalence of egg allergy of 9% at three years of age (Kajosaari 1982). No new case of egg allergy after the age of ten years was found in a study of 112 patients with food allergy presenting to an allergy clinic, supporting the notion that egg causes allergy only in the early years (Kivity *et al*. 1994). The rate of positive skinprick or specific IgE to egg is 1.5–4 times greater than clinical reactivity (Kjellmann *et al.* 1988, Dean 1997). In the atopic population the risk of egg allergy is increased by up to 3–5 times (Ratner and Uuntract 1952, Hill *et al*. 1997).

Up to 75% of children with egg allergy can tolerate egg by seven years of age (Kjellmann *et al.* 1988) and in one birth cohort study the mean age of developing tolerance was 19 months (range 12–42 months) (Kjellmann *et al.* 1988). Resolution is less likely to occur in those children with cardiorespiratory reactions to egg (Ford and Taylor 1982).

10.3.6 Wheat

Introduction

Wheat is another food consumed worldwide. However, there are geographical variations in consumption patterns and age of introduction into the diet; for

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Table 10.6 Epidemiology of adverse food reactions to eggs – key studies

Author, date	Type of study	Country	No. of subjects	Point prevalence	Cumulative incidence	Definition
Young *et al*. 1994	Population based, cross-sectional	UK	18 880	2.3% at > 6 months old		History
Dean 1997	Population based, birth cohort	UK	1218	1.6% at 1y 1.4% at 2 y 0.6% at 4y	2.4% to 4y	History
Varjonen *et al*. 1992	Atopic population, cross-sectional	Finland	434	0.5% at 15–16y		History and SPT
Dean 1997	Population based, birth cohort	UK	981	0.8% at 4y		SPT
Hill *et al*. 1997	Population based, birth cohort	Australia	332		3.2% to 2y	SPT
Hill *et al*. 1997	Atopic population, birth cohort	Australia	620		16.4% to 2y	SPT
Bjornsson *et al*. 1996	Population-based, cross-sectional	Sweden	1397	0.8% (sp IgE); 0.2% (sp IgE and history) at 20–44y		History ± sp IgE
Kulig *et al*. 1999	Population based, birth cohort	Germany	4082	0% at birth 6.3% at 1y 4.5% at 3y 4.5% at 6y	13.4% to 6y	Sp IgE
Kajosaari 1982	Population based, cross-sectional	Finland	802	6% at 1y 7% at 2y 9% at 3y 1% at 6y		Open challenge at home
Bock 1987	Population based, birth cohort	USA	480		2.3% to 3y (history);0.6% to 3y (challenge)	Open history ± double-blinded food challenges

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example in some Asian countries such as Japan it is consumed earlier and in larger amounts (Hill *et al*. 1997). Wheat causes a range of allergies, either IgE-mediated causing acute hypersensitivity and delayed eczema reactions seen mainly in infants, or a cell-mediated immunological inflammation of the small bowel, coeliac disease, seen in children and adults. Key epidemiological studies are shown in Table 10.7.

Prevalence and natural history

IgE-mediated wheat allergy is uncommon with a cumulative incidence of 1–2% in the first six years of life. IgE-mediated wheat allergy may occur less commonly in later childhood or adulthood (Kivity *et al*. 1994), and in the latter is also responsible for the occupational disease, baker's asthma. In young children, IgE-mediated wheat allergy causes predominantly mild reactions, but in adults wheat may be responsible for up to 63% of cases of exercise-induced food-related anaphylaxis (Guinnepain *et al*. 1996). Specific IgE data probably overestimate clinical reactivity by 2–3 times (Kulig *et al*. 1999).

The true prevalence of coeliac disease is unknown. The conventional view has been that prevalence in the UK is around 1:1500, but more recent data from the UK (Hins *et al*. 1999) and Italy (Catassi *et al*. 1994) suggests that 1:300 of the population in Europe may have some form of gluten sensitivity. In older studies coeliac disease was more common in the first two years of life, but the average age of diagnosis in childhood is now increasing, being five years of age in Finland (Ferguson 1999). This may be due to the later introduction of gluten into infant diet which delays the onset of clinical disease (Anderson 1992), and presentation in later childhood and adults who have previously clinically tolerated wheat is becoming more common.

Patients with coeliac disease need to pursue a lifelong gluten-free diet, and they also need to avoid rye, barley and possibly oats. There is not much good epidemiological data on the natural history of IgE-mediated wheat allergy, although in a select population of subjects aged 3–18 years with eczema and wheat allergy, 33% became tolerant within 1–2 years (Sampson and Scanlon 1989).

10.3.7 Fruits and vegetables

Introduction

Vegetables and fruits are staple foods in diets worldwide although the types of vegetables and fruits consumed vary widely. It is therefore not surprising that considerable geographical variations exist in respect of adverse reactions to specific fruits and vegetables. Vegetables, and more particularly fruit, may cause adverse reactions that are either IgE-mediated which most often have their onset after the first few years of life (in contrast to many other foods), or occur via other mechanisms, typically in early childhood. Key epidemiological studies are shown in Table 10.8.

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Table 10.7 Epidemiology of adverse food reactions to wheat – key studies

Author, date	Type of study	Country	No. of subjects	Point prevalence	Cumulative incidence	Definition
Young *et al.* 1994	Population based, cross-sectional	UK	18 880	0.9% at > 6 months old		History
Dean 1997	Population based, birth cohort	UK	1218	0.5% at 1y 0.5% at 2y 0.2% at 4y	0.9% to 4y	History
Bjornsson *et al.* 1996	Population-based, cross-sectional	Sweden	1397	3% (sp IgE); 0% (sp IgE and history) at 20–44y		Sp IgE ± history
Kulig *et al.* 1999	Population based, birth cohort	Germany	4082	0% at birth 0.8% at 1y 2% at 3y 4% at 6y	5% to 6y	Sp IgE
Kajosaari 1982	Population based, cross-sectional	Finland	802	1% at 1y 1% at 2y 0% at 3y 0% at 6y		Open challenge at home
Bock 1987	Population based, birth cohort	USA	480		0.8% to 3y (history); 0.2% to 3y (challenge)	Open history ± double-blinded food challenges

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Table 10.8 Epidemiology of adverse food reactions to fruit and vegetables – key studies

Author, date	Type of study	Country	No. of subjects	Point prevalence	Cumulative incidence	Comments
Foucard 1991	Cross-sectional, medical students	Sweden	1050	7% apple/related fruits		History
Young *et al*. 1994	Population based, cross-sectional	UK	18 880	3.5% citrus 1.2–1.3% tomatoes 1.0% non-citrus 0.5% vegetables at > 6 months old		History
Niestijl Jansen *et al*. 1994	Population based, cross-sectional	Holland	1483	2.2% vegetables 1.6% fruit at 18–70y		History
Saarinen and Kajosaari 1980	Population based, birth cohort	Finland	145		Citrus fruits 13.1% to 3y	History
Varjonen *et al*. 1992	Atopic population, cross-sectional	Finland	416	6.9% apple 3.8% carrot 1.4% celery 1.2% paprika 0.2% orange at 15–16y		History and SPT
Saarinen and Kajosaari 1980	Population based, birth cohort	Finland	145		Citrus fruits 3.4% to 3y	Open challenge at home
Kajosaari 1982	Population based, cross-sectional	Finland	802	Citrus fruits 5% at 1y 2% at 6y		Open challenge at home
Bock 1987	Population based, birth cohort	USA	480		Fruits and fruit juices 12% to 3y	Open history ± double-blinded food challenges

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Prevalence and natural history

In the young child, fruits and fruit juices may cause minor gastro-intestinal reactions. Fruits and vegetables, particularly tomatoes, strawberry and citrus fruits also cause perioral rashes, usually eczema and urticaria, in early childhood. If one includes these minor non-IgE mediated skin and gastro-intestinal symptoms, fruits and fruit juices were the foods most commonly causing adverse reactions in one study with a cumulative incidence of 12% in children less than three years of age, with 58% of reactions occurring to orange juice, tomato juice and apple (Bock 1987). Other studies suggest a cumulative incidence of adverse reactions to citrus fruits of around 3–5% in the first three years of life (Saarinen and Kajosaari 1980, Kajosaari 1982), with a higher rate of 13% if the definition is based on history rather than food challenge (Saarinen and Kajosaari 1980).

In contrast to the minor reactions of early childhood, IgE-mediated reactions occur later, so that up to 75% of IgE reactions to fruits and vegetables have their onset after two years of age (Crespo *et al.* 1995). In an allergy clinic based study, fruits and vegetables were responsible for the vast majority of IgE-mediated food allergy presenting after the age of ten years (Kivity *et al*. 1994). Many of these later childhood reactions occur in a subgroup of children with pollen sensitisation resulting in cross-reactivity to a range of fruits. This food allergy presents as a contact allergy with oral symptoms, known as the oral allergy syndrome, and occurs mainly with raw fruit or vegetables. The prevalence of allergy to different fruits and vegetables varies with the type and amount of pollen present, which determines the cross-reacting fruits and vegetables. Thus in Scandinavia, with its high levels of birch pollen, there is a high prevalence of apple allergy (Foucard 1991), whereas in Japan where there is more Japanese cedar, the allergy is mainly to melon and kiwi (Arai *et al*. 1998).

Regarding the natural history of adverse reactions to fruits and vegetables, clinical reactivity is short-lived in those children with onset in early childhood. In one study, tolerance to fruits and fruit juices was achieved after a mean of 15 months (range 3–34 months, median 13 months) (Bock 1987). The natural history data for the later onset predominantly IgE-mediated reactions are not well defined, but are certainly of longer duration.

10.3.8 Chocolate

Chocolate

A 2.2–6.6% self-reporting of reactions to chocolate are reported in two questionnaire surveys (Niestijl Jansen *et al*. 1994, Young *et al*. 1994). In an American population-based birth cohort study of 480 children followed up to three years old, 1.7% complained of adverse reactions to chocolate, but none was confirmed on food challenge (Bock 1987), and chocolate is rarely a cause of positive food challenge in allergy clinics (Bock *et al*. 1988, Crespo *et al*. 1995). It is likely that the majority of the reported reactions are to other components in the chocolate, for example cows' milk and nuts.

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10.3.9 Food additives

The commonest food additives thought to cause adverse reactions are tartrazine (E102), sunset yellow (E110), annatto, aspartame, benzoic acid and sulphites (Fuglsang *et al*. 1993). Key epidemiological studies are shown in Table 10.9. Adverse reactions to food additives can occur at any age. A UK study showed a higher reporting of adverse reactions to food additives in the first ten years of life, and more often occurring in females (Young *et al.* 1987). The mechanism of the reaction is often unknown, and IgE-mediated reactions are rare. Questionnaire-based studies give a high 6.6–7.4% prevalence of self-reported adverse reactions to food additives in the general population. However, when food challenges are used to make the diagnosis, the prevalence falls to about 0.23%. One study shows the risk to be greatest in the atopic population, with no reactions observed in non-atopic individuals (Fuglsang *et al.* 1994). Virtually all reactions are minor and limited to the skin (worsening of eczema/urticaria) with serious systemic reactions rarely reported. Regarding the natural history, there are no good epidemiological data.

10.3.10 Interpreting data on the natural history of food allergy

Food allergies can be divided into groups with similar natural histories (Figure 10.2). Cohort studies have been very successful in delineating the natural history of allergies to foods such as cows' milk and egg because they are almost completely outgrown within a few years. For longer lived allergies, such as fish, shellfish, peanut and tree nuts, the natural history is less clear because of the difficulties in interpreting the available data. This is illustrated by results from an interview survey investigating the prevalence of peanut allergy (Emmett *et al*. 1999). The data (Figure 10.3) suggest that more males are affected in childhood whereas in adulthood peanut allergy is more prevalent in females. There are a number of possible explanations for these results. Firstly, peanut allergy may be outgrown at an earlier age in males. Secondly, peanut allergy may be acquired later in females. Thirdly, there may be a combination of both of the above. Fourthly, the data may be explained by a cohort effect: the adult generation surveyed may have a lower inherent risk of peanut allergy than the childhood generation such that if the survey was repeated in 15 years' time, a greater adult prevalence would be seen as these children become adults. And lastly, the results may have also been subjected to information bias as a house-to-house survey will primarily sample adult females who may not be aware that adult male co-habitants have an allergy to peanuts thereby reducing the apparent prevalence in adult males. Even if these issues can be resolved, we are left only knowing the prevalence of peanut allergy which is a summation of existing cases, new cases and remissions. In order to overcome these problems, prospective cohort studies are needed where the point prevalence is established longitudinally together with the incidence and remission rates.

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Table 10.9 Epidemiology of adverse food reactions to food additives – key studies

Author, date	Type of study	Country	No. of subjects	Point prevalence	Definition
Young *et al*. 1987	Population based, cross-sectional	UK	18 582	7.4% at > 6 months old	History
Fuglsang *et al*. 1994	Population based, cross-sectional	Denmark	4274	6.6% at 5–16y	History
Fuglsang *et al*. 1994	Non-atopic population, cross-sectional	Denmark	4274	0% at 5–16y	Open challenge
Fuglsang *et al*. 1994	Atopic population, cross-sectional	Denmark	4274	9.8% at 5–16y	Open challenge
Young *et al*. 1987	Population based, cross-sectional	UK	649	0.23% at > 4 y	History and DBPCFC

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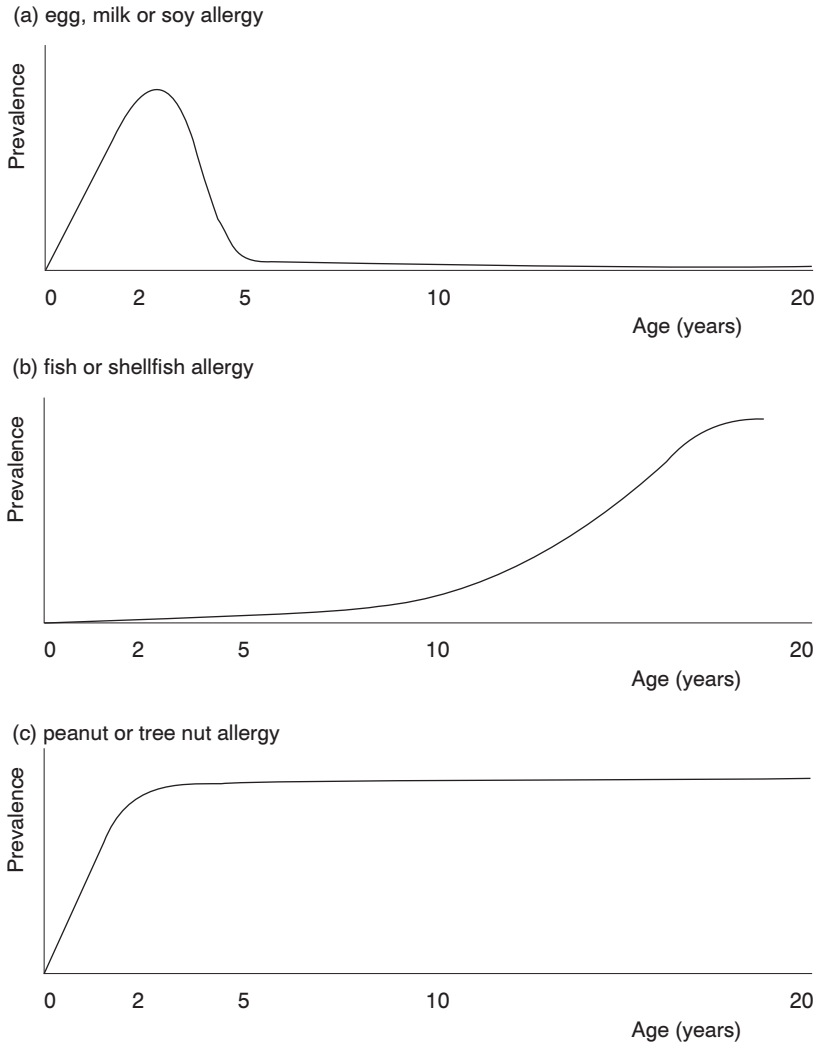

Figure 10.2 Natural histories of different food allergies.

10.4 Geographical variations

Data concerning the incidence of adverse food reactions from different countries may shed some light on factors that might be important in the development of adverse food reactions. These factors include genetic, cultural, dietary and other environmental differences. Unfortunately all the cohort studies are from Europe, Australia and the USA, with no comparable data from other countries. However, there are case series from these other countries that allow comparisons to be made between foods that are important in causing adverse reactions in different countries.

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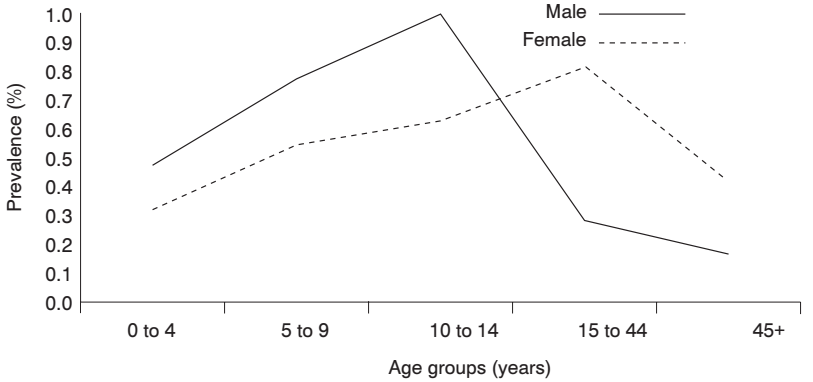

Figure 10.3 Prevalence of peanut allergy in males and females (Emmett *et al*. 1999).

10.4.1 Common food allergies

Table 10.10 compares clinical reactions to foods, and Table 10.11 compares skinprick/specific IgE reactions to foods, between allergy clinic populations from different countries. As such they deal with a selected population and some studies involve small numbers. They show that cows' milk and egg are among the 2–3 commonest foods causing allergy in most countries. Peanut, fish, soy, wheat and shellfish are among the next most common groups of foods causing allergy, although significant variations occur between countries. Thus, for example, shellfish allergy appears to be more common in countries such as the Philippines, Thailand and Singapore where it is a part of the staple diet from early infancy, than in many other countries where it is consumed later and less commonly. In contrast, clinical peanut allergy which is a big problem in Western countries appears to be less common in most Asian countries, and also in Spain (Crespo *et al*. 1995). Thus in Japan it is very rare (Hill *et al.* 1997), and in one study from Singapore no cases of nut allergy were seen in 124 consecutive admissions with anaphylaxis (Goh *et al*. 1999). Positive skinprick test to peanut appears to be less common in many Asian countries, especially in Japan, although it accounted for 10% of positive skin tests in a Singapore allergy clinic (Shek and Lee 1999).

Table 10.10 also shows variations in fruit and vegetable allergy with higher rates in Mediterranean countries. Thus peach allergy is common in a Spanish study (Crespo *et al*. 1995, Cuesta-Herranz *et al*. 1998) and accounts for 44% of 112 positive food challenges in patients between 10 and 48 years of age in an Israel allergy clinic (Kivity *et al*. 1994). In both countries, peach consumption is high.

Coeliac disease also has geographical variations. Although formerly thought to be a disease associated with north-west Europeans, including the countries of their migration, chiefly the USA, an equivalent prevalence is being reported in other European countries (Greco *et al*. 1989). It appears to be uncommon

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Table 10.10 Foods causing clinical allergic reactions in allergy clinics from different countries. (Data presented as percentage of total reactions.)

Spain Crespo *et al.* 1995	France Rance *et al.* 1999	USA Bock *et al.* 1988	Japan Hill *et al.* 1997	Philippines Hill *et al.* 1997
608 foodstuffs, SPT & sp IgE & history, children	813 foodstuffs, SPT/sp IgE & FC, children	481 DBPCFCs in 323 children	79 FCs, mean age 5.2y	46 FCs, mean age 2.0y
Egg 20.1%	Egg 35.7%	Egg 33.1%	Egg 59.4%	Cows' milk 32.6%
Fish 17.8%	Peanut 23.6%	Peanut 18.7%	Cows' milk 22.8%	Shellfish 26.1%
Cows' milk 14.3%	Cows' milk 8.3%	Cows' milk 18.1%	Wheat 12.6%	Egg 21.7%
Lentils 5.9%	Mustard 6%	Soy 6.7%	Soy 5.1%	Fish 10.9%
Peaches 5.1%	Cod 4.3%	Nuts 4.8%		Wheat 4.3%
Peanut 3.9%	Hazelnut 1.8%	Shellfish 4.4%		Peanut 2.2%
Chick peas 3.9%	Kiwi 1.5%	Fish 4.0%		Soy 2.2%
Crustaceans 3.8%	Wheat 1.5%	Wheat 3.3%		

FC: food challenge

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Table 10.11 Foods causing sensitisation (positive skin prick/specific IgE tests) in paediatric allergy clinics in Australia and Asia. (Modified from Hill *et al*. 1997. Data presented as percentage of total reactions.)

Australia	Hong Kong	China	Thailand	Japan	Philippines	Singapore	Taiwan
Egg 37%	Cows' milk 41%	Egg 64%	Shellfish 22%	Egg 48%	Fish 25%	Shellfish 36%	Egg 30%
Cows' milk 23%	Egg 29%	Cows' milk 14%	Peanut 21%	Cows' milk 18%	Shellfish 22%	Cows' milk 16%	Cows' milk 21%
Peanut 22%	Wheat 10%	Peanut 9%	Soy 16%	Wheat 12%	Wheat 15%	Egg 16%	Peanut 19%
Sesame 5%	Fish 10%	Soy 9%	Rice 16%	Fish 9%	Egg 12%	Wheat 14%	Soy 12%
Cashew 4%	Soy 9%	Wheat 4%	Egg 15%	Soy 8%	Cows' milk 12%	Peanut 10%	Shellfish 9%
Hazelnut 2%	Peanut 4%		Cows' milk 10%	Rice 4%	Peanut 8%	Soy 8%	Wheat 7%
Walnut 2%				Peanut 1%	Soy 6%		

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elsewhere, and seems not to occur in Afro-Caribbeans or Chinese (Ferguson 1999).

10.4.2 Novel and uncommon food allergies

There are a number of foods that are eaten in geographically or culturally quite specific populations and adverse food reactions are limited to these groups. However, with diversification of cultures and diets across the globe, particularly in developed countries, adverse reactions to these foods may be seen in many other countries. A good example is sesame seed, to which allergy in Western countries was rarely reported (Rance *et al*. 1999). However, there are reports of an increasing number of cases of sesame seed allergy in France coincident with the increase in Middle Eastern food and fast food bread (Kolopp-Sarda *et al*. 1997). Sesame seed often causes severe clinical allergy hence its importance. In France sesame seed was responsible for 0.6% of IgE-mediated food allergies seen in recent years in an allergy clinic population (Rance *et al*. 1999).

Table 10.12 makes the point that uncommon food allergens are important causes of food allergy in specific countries. In an Israel allergy clinic population, sunflower seed was responsible for 22.3% of 112 positive food challenges in subjects between 10 and 48 years of age (Kivity *et al*. 1994). In Singapore, out of 124 consecutive admissions with anaphylaxis, the commonest cause was bird's nest soup (Goh *et al*. 1999), a food not implicated in allergy elsewhere in the world. In Japan rice appears to be a relatively common cause of allergy causing atopic eczema, although more severe acute reactions to rice are rare (Ikezawa *et al*. 1992). Rice is also a common cause of food allergy in Thailand (Hill *et al*. 1997). Adverse reaction to buckwheat is a common problem in Japan. In a population of 92,680 schoolchildren in Japan, the incidence of adverse reaction to buckwheat on questionnaire was 0.22% (Takahashi *et al*. 1998). The risk of anaphylaxis to buckwheat was higher than for egg and milk. In Hong Kong, royal jelly consumption is common with 31.3% of 461 hospital employees surveyed in one study consuming it (Leung *et al*. 1997); 7.4% of the subjects had a positive skinprick test to pure royal jelly, 0.6% had a history of clinical allergy, and nearly all employees with a positive skinprick test also had other atopic features. Pineapple allergy is responsible for a reported 23.5% of food allergy in Indonesia (Hill *et al*. 1997).

Table 10.12 Some uncommon foods causing allergy in specific countries

France	Japan	Hong	Singa-Kong	Spain pore	Israel	Indonesia	Poland
Lentil Mustard Snail	Rice Buck-wheat	Royal jelly	Bird's nest soup	Lentil	Sun-flower seed	Pineapple Chicken	Beef

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In Spain, with its Mediterranean diet, lentils are the legumes most commonly implicated in allergy (Pascual *et al*. 1999), and a common cause of anaphylaxis. Chick peas, peas, and green beans are also not uncommonly seen as causes of food allergy in Spain, with lentils, chick peas and beans forming 4.9% of the protein diet in Spain. In France, lentil is responsible for 0.8% of clinical food allergy seen in an allergy clinic, having not been seen in previous years (Rance *et al*. 1999). Lentils do not appear in the list of the 481 positive food challenges in a large USA allergy clinic based study (Bock *et al*. 1988). Mustard is an important cause of allergy in France, accounting for 6% of all food allergies seen in an allergy clinic (Rance *et al.* 1999), but does not appear to be a problem in other countries.

Beef allergy is a problem in Poland where it ranks among the six foods most likely to cause allergy (Czaja-Bulsa and Bachorska 1998), and is also a problem in China (Hill *et al*. 1997). Chicken is a common reported cause of allergy in Indonesia (Hill *et al.* 1997). In other countries, meats are often reported by subjects as causes of adverse reactions, but rarely confirmed by food challenge. Thus, in UK and Dutch questionnaire studies, 1.6–2.7% of respondents from random populations reported adverse reactions to meat and meat products (Young *et al*. 1994, Niestijl Jansen *et al*. 1994). However, this high figure has not been substantiated by studies involving food challenges in which adverse reactions to meats were found to be rare (Bock 1987, Crespo *et al*. 1995). Snail allergy is reported only from France, Spain and Portugal where it is eaten as a delicacy (de la Cuesta *et al*. 1989). Many of the allergic reactions are severe, involving respiratory compromise.

10.5 Cross-reactions between foods

Cross-reactivity is due to a reaction to identical or similar protein allergens that occur in more than one food, or in a food and an inhalant pollen. This is different from associated reactivity where two or more food allergens may be seen to be associated epidemiologically. A good example of the latter is the high rate of association between egg and peanut allergy although the allergens are not related. Establishing a cross-reaction requires the demonstration of at least a positive correlation between the magnitude of specific IgE to both foods, and RAST inhibition studies are needed for confirmation. Cross-reactivity is seen at an immunological level when a subject is sensitised to both foods on the basis of positive skinprick or specific IgE testing to both foods. However, often only a smaller proportion will demonstrate clinical cross-reactivity, that is a reaction to both foods on clinical exposure.

Table 10.13 lists the common cross-reactions involving foods. For fish and legumes, there are good data regarding cross-reactivity at immunological (skin prick/specific IgE) and clinical levels. One study demonstrated 73% immunological cross-reactivity for ten different fish species, but only 28% clinical cross-reactivity to two or more of the same ten species (Bernhisel-Broadbent *et al.* 1992). In the case of legumes, the same authors demonstrated immunological

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Table 10.13 Common cross-reactions involving foods

Index food or pollen	Cows' milk	Chicken egg	Cod	Shrimp	Peanut	Latex
Cross-reacting foods	Soy 11–35% clinical cross-reaction Sheep and goat milk 50–75% clinical cross-reaction	Duck, geese & turkey egg	Other fish 28% clinical cross-reaction 73% skinprick/ IgE cross-reaction	Crustaceans, molluscs	Other legumes e.g. soya bean, garden pea, chick pea, lentil, guar, liquorice, carob, gum arabic and other beans 5–60% clinical cross-reaction 75% skinprick/ IgE cross-reaction	Fruits and vegetables e.g. banana, pear, avocado, chestnut, papaya, potato, tomato
References	Juntunen and Ali-Yrkko 1983 Bardare *et al*. 1988 Zeiger *et al*. 1999	Langeland 1983	Bernhisel-Broadbent *et al*. 1992	Musmand *et al*. 1993	Bernhisel-Broadbent and Sampson 1989 Crespo *et al*. 1995	Lavaud *et al*. 1992 Beezold *et al*. 1996

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Table 10.13 continued

Index food or pollen	Birch pollen	Ragweed pollen	Mugwort pollen	Grass pollen
Cross-reacting foods	Fruits and vegetables e.g. apple, celery, carrot, potato, kiwi, hazelnut, cherry 5–60% clinical cross-reaction 10–75% skinprick/IgE cross-reaction	Fruits and vegetables e.g. watermelon, melon, cucumber, banana	Legumes (see peanut) Also celery, carrot, nuts, mustard	Tomato, potato, green pea, peanut, watermelon, melon, apple, orange, kiwi
References	Dreborg and Foucard 1983 Foucard 1991 Caballero *et al.* 1994	Ortolani *et al.* 1998	Caballero and Martin-Esteban 1998	Caballero and Martin-Esteban 1998

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cross-reactivity between legumes in 49 out of 69 patients (71%) with atopic eczema, but only 2 out of 41 patients (5%) evaluated showed clinical cross-reactivity (Berhisel-Broadbent and Sampson 1989). By way of contrast, another study showed considerable clinical cross-reactivity between the legumes in the context of acute reactions (Crespo *et al*. 1995). In the latter study, out of 67 patients seen in an allergy clinic, 43 (64%) showed clinical allergic reactions to more than one legume (mainly lentil, peanut, chick pea, pea and bean).

In Scandanavian countries there is a high prevalence of birch pollen sensitisation, reaching up to 10–15% in teenagers and young adults (Eriksson 1978). Between 30% and 75% report clinical reactivity to fruits and vegetables, occurring chiefly as the oral allergy syndrome in adolescents and adults, with apple being the food most commonly implicated (Dreborg and Foucard 1983, Pastorella *et al*. 1995). Clinical cross-reactivity can be confirmed in around 60–75% of birch pollen allergic patients with immunological cross-reactivity to foods (Foucard 1991). These data are from patient history and food challenges done at home, and a lower reaction rate is likely with more rigorous food challenge procedures (Caballero *et al*. 1994).

10.6 Occupational food allergy

There are a number of subjects who are at increased risk of developing food allergy related to occupational exposure, virtually all mediated by an IgE reaction. The most common and best studied foods are listed below.

10.6.1 Shellfish

A number of shellfish can cause occupational asthma and rhinoconjunctivitis primarily from inhalation of particles during food processing. The reactions have been demonstrated to occur with shrimp, crab and oyster handlers. Workers affected include those involved in seafood processing, cooks and fishermen (Malo and Cartier 1993). Up to 10–40% of workers exhibit respiratory symptoms, and in studies where skin testing has been done up to 60% are found to be positive, with a close correlation between skin test reactivity and clinical reactivity (Orford and Wilson 1985, Cartier *et al*. 1986).

10.6.2 Flour

Baker's asthma is due to sensitisation to cereal proteins. The majority of cases are reported to wheat, rye and barley, and it has been one of the most common occupational diseases in the UK (Block *et al*. 1984). One study found 7–9% of bakers to be affected (Thiel and Ulmer 1980), and there may be a long latent period of up to 10–15 years before symptoms occur. Again, atopic individuals appear to be at increased risk (Prichard *et al*. 1985).

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10.6.3 Legumes and seeds

Various legumes and seeds can cause occupational asthma. The most common and best studied is the coffee bean, caused by the green (unroasted) coffee bean, which produces a positive skin test in up to 82%, and a clinical reaction in up to 10%, of exposed workers (Osterman *et al*. 1985). Cotton seed, linseed and tea dust can all cause occupational asthma (Cartier and Malo 1990).

10.6.4 Eggs

Egg proteins may cause occupational asthma in 5–20% of workers involved in egg processing, and atopy again appears to be a risk factor (Bernstein *et al*. 1987, Smith 1990).

10.7 Risk factors for the development of adverse food reactions

For all the risk factors that may be involved in the development of adverse food reactions, much of the epidemiology has concentrated on asthma, eczema or total allergy. Few studies look specifically at risk factors for adverse food reactions. This section concentrates on the literature concerning adverse food reactions, and more specifically IgE-mediated food allergy.

10.7.1 Associated morbidity

Markers of atopy as a whole are associated with an increased risk of developing adverse food reactions. Thus asthma, eczema and rhinitis are increased in children with food allergy compared to the general population (Zeiger and Heller 1995, Hide *et al*. 1996). The strongest association is between eczema and food allergy, and the risk appears to be greatest in infancy and in those with moderate to severe eczema (Burks *et al*. 1998, Sampson 1996). The literature appears to be best for peanut allergy. One study found that in peanut-allergic children atopy in some other form was present in up to 96% of subjects (Ewan 1996). In the Isle of Wight birth cohort study half of the children with peanut allergy had asthma and two-thirds had eczema, considerably higher than the rates in the cohort as a whole (Tariq *et al*. 1996).

10.7.2 Immunological markers

The role of cord blood total IgE as a marker for the development of food allergy is not clear. Studies do not consistently show a positive association (Dean 1997, Kjellmann *et al*. 1988, Kulig *et al*. 1999). Furthermore, in the recent German multicentre allergy study where an association between cord blood total IgE and sensitisation to foods at one year of age was found, the authors comment on the poor predictive performance of cord blood IgE (Kulig *et al*. 1999). This study

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puzzlingly also showed that an elevated cord blood total IgE was a significant protective factor for early-onset atopic eczema (Edenharter *et al*. 1998). Thus, cord blood total IgE is an unhelpful marker in predicting the development of food allergy and in planning appropriate prevention strategies.

Prenatal sensitisation with antigen-specific IgE has been reported but seems to be uncommon, and limited to cows' milk (Businco *et al*. 1983, Host *et al*. 1992). It is therefore unlikely to play a role in the vast majority of food allergy. None of the large birth cohort studies have demonstrated any specific IgE to foods in cord blood, including cows' milk, even in children who subsequently developed clinical or immunological sensitisation (Kjellmann *et al*. 1988, Hide *et al*. 1996, Kulig *et al*. 1999). It is therefore not surprising to find that dietary intervention in pregnancy has shown no benefit in modifying the natural history of IgE-mediated food allergy. Food sensitisation as measured by allergen-specific T-cell responses have been demonstrated in cord and fetal blood (Jones *et al*. 1998). However, none of these responses have been assessed to be risk factors in the development of food allergy. It is unclear whether these responses are derived from a memory T-cell population or from a naive population.

10.7.3 Genetic factors

Family history of atopy

If either parent has a history of an allergic disease then siblings are at increased risk of developing allergic disease, which includes eczema, asthma, allergic rhinitis and food allergy (Zeiger and Heller 1995). The risk is greater if either parent is atopic, and increases if both parents are atopic. In children with cows' milk allergy, a family history of atopy in first-degree relatives has been found in 23–80% of cases (Goldman 1963, Ventura 1988, Host 1990). Findings from a Danish study looking at skin reactions to foods are presented in Table 10.14, confirming the association of food allergy and family history of atopy (Kjellman 1983).

A family history of food allergy in a first-degree relative increases the risk of food allergy approximately fourfold in other family members (Dean 1997). In families with at least two food allergic individuals, the same food is frequently implicated. The best-studied food is peanut whereby if one sibling has peanut allergy then the risk of another sibling having peanut allergy is 7%. This represents a tenfold increased risk compared with the general population in whom the risk is 0.6% (Tariq *et al*. 1996). However, there is a lack of good literature looking at the risk for other foods and in general there are no studies, such as twin studies, that separate the role of genetic and environmental factors in the development of food allergy.

Associated food allergy

In view of the association between food allergy and atopy, it is not surprising to find an individual with food allergy having allergy to one or more foods, even in

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the absence of cross-reactivity. This associated reactivity is seen for egg and peanuts (Dean 1997), and is best studied with cows' milk. Children with cows' milk allergy have a 7–58% chance of developing egg allergy, 0–16% chance of developing cereal allergy and a 0–35% chance of developing allergy to orange (Host 1995). Associated reactivity in cows' milk allergic subjects is also seen to tomato and banana (Host 1995). The Melbourne Atopy Cohort Study which prospectively followed an atopic birth cohort of 100 children who developed cows' milk allergy found evidence of allergy to one or more other foods in up to 75% of subjects in the five years of follow-up (Hill *et al.* 1999). These associated food allergies are more likely to reflect the underlying atopic tendency of the individual rather than constituting an additional and specific risk factor for the development of food allergy.

HLA studies

A number of different HLA genotypes have been shown to be associated with different types of food allergy. The data are best for peanut allergy and coeliac disease (Howell *et al*. 1998, Howdle and Blair 1992).

Gene linkage studies

Linkage of genes on a number of chromosomes with various atopic markers such as asthma and eczema has been demonstrated (Cookson *et al*. 1989, Nickel *et al*. 1999). However, no specific markers for food allergy have been established and none of the candidate genes has shown clinical application in terms of predicting or preventing the development of food allergy.

Environmental factors

The following have been shown to be statistically significant risk factors, after multivariate analysis, for the development of food allergy in the first 1–7 years of life: a history of both parents smoking, male gender, 4-month IgE $\geq$ 1 SD, and nasal eosinophils at one year of age (Arshad *et al*. 1992, Zeiger and Heller 1995). Many other factors have been shown to be associated with the development of aeroallergen sensitisation, asthma or total allergy, but not specifically food allergy. These include prematurity, season of birth, pets, maternal asthma, either parent smoking, defects in lymphocyte regulation, immune response genes, specific and early infections with viruses, and exposure to products of pollution (Dean 1997, Lucas *et al*. 1990, Zeiger and Heller 1995).

Table 10.14 History of food allergy before seven years of age in comparison with a family history of atopy. (Adapted from Kjellmann 1983.)

Atopic parents	Total % of children with food allergy
2	58
1	29
0	13

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10.8 Intervention strategies aimed at preventing adverse food reactions

Most of the work in this area has been directed at preventing allergic sensitisation (primary prevention), rather than the prevention or suppression of clinical disease once sensitisation has occurred (secondary and tertiary prevention respectively). Up to now, no therapy has been shown to be of value in secondary or tertiary prevention of adverse food reactions. Furthermore, whilst some studies show that pharmacological intervention may alter the incidence and natural history of asthma, there are no comparable data regarding adverse food reactions (Bustos *et al*. 1995, Warner 1997). This section therefore concentrates on the dietary intervention studies set up with the aim of preventing or reducing the occurrence of adverse food reactions. Some of the studies look at children with a high risk of atopy (usually defined as those children with at least one first-degree relative with documented atopic disease), others at unselected children from the general population. Most do not focus specifically on reaction to food as an endpoint, and this section concentrates on the few studies that use immunological (skinprick or specific IgE) testing to foods or clinical reactivity using food challenge as endpoints for the preventative strategies. Some of the well-conducted intervention studies using eczema as an end-point are also mentioned, in view of the association of eczema with adverse food reactions in the early years of life.

10.8.1 Maternal intervention

Intervention in pregnancy

The potential for *in utero* sensitisation to food allergens via the placenta or swallowing of amniotic fluid has led to a number of investigators restricting possible antigens in the maternal diet during pregnancy.

Intervention during lactation

The potential for sensitisation during lactation also exists as small amounts of food allergens have been found in breast milk. Beta-lactoglobulin is found in the breast milk of 95% of mothers consuming cows' milk during lactation (Host *et al*. 1988). Peanut and other proteins have also been found in breast milk (Bock 1982). Such observations have led investigators to assess the allergy prevention effects of a restricted maternal diet during lactation.

There are other studies where the maternal dietary intervention occurred during pregnancy and lactation.

Using the endpoints of clinical food reactions and immunological sensitisation, there is no evidence from the available studies (Table 10.15) to suggest that dietary restriction in pregnancy reduces the risk of the infant developing adverse food reactions, in either normal or high-risk subjects. One study has suggested a possible protective effect of maternal peanut avoidance in pregnancy and lactation in an atopic population (Hourihane and Kilburn 1997). This study was

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Table 10.15 Prospective randomised studies assessing the effect of maternal dietary intervention in pregnancy and lactation on the development of adverse food reactions

Study (reference)	No. and type of subjects	Maternal diet	Follow-up period (yrs)	Definition of adverse food reaction	Outcome
Kjellman *et al*. 1988	210, atopic population, birth cohort	No egg, no cows' milk in 3rd trimester vs. no restriction	1.5	SPTs to egg and cows' milk in 1/3 of subjects	No difference
Lilja *et al*. 1991	162, atopic population, birth cohort	Reduced egg and cows' milk in 3rd trimester and 1st 2 months of lactation vs. no restriction	1.5	SPTs and sp IgE to ovalbumin, ovomucoid and beta-lactoglobulin Total IgE	No difference
Falth-Magnusson and Kjellman 1992	197, atopic population, birth cohort	No egg, no cows' milk in 3rd trimester vs. no restriction	5	SPTs and sp IgE	No difference
Sigurs *et al*. 1992 Hattevig *et al*. 1996	115, atopic population, birth cohort, groups assigned by hospital rather than true randomisation	No egg, no cows' milk, no fish in 1st 3 months of lactation vs. no restrictions	10	History of intolerance to cows' milk/egg SPT/sp IgE to egg, cows' milk, hazelnut, peanut, fish, wheat Eczema	No difference in history and SPT/sp IgE Less eczema in prophylaxis group at 4y but not at 10y

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retrospective and uncontrolled, but suggested that in an atopic population the consumption of peanuts by mothers during pregnancy and lactation was associated with an earlier onset of peanut allergy in the children. There was no difference in the cumulative incidence of peanut allergy, and timing of immunological sensitisation to peanut was not assessed. An alternative explanation of the data is that the children of mothers consuming peanuts during pregnancy and lactation had the opportunity to consume peanuts earlier in life than those whose mothers did not eat peanuts. Furthermore, the findings of this study are not supported by a study based on the Isle of Wight birth cohort (Tariq *et al*. 1996). This study showed no effect of reduced/no maternal nut ingestion in pregnancy on the development of immunological or clinical reaction to nuts in a non-randomised population followed up until four years of age.

Using eczema as the endpoint, which of course may or may not be associated with adverse food reactions, a number of studies in atopic populations using maternal dietary restriction during lactation alone (Chandra *et al*. 1989, Lovegrove *et al*. 1994, Hattevig *et al*. 1996) or during the last trimester of pregnancy and lactation (Chandra *et al*. 1986) have shown a reduction in eczema. The protective effect lasts for between 18 months and four years, with no effect being seen on ten-year follow-up (Hattevig *et al.* 1996). Not all the studies are randomised, and two of the studies have an unusually high prevalence of eczema in the control (no dietary restriction) population (Chandra *et al.* 1986, Lovegrove *et al.* 1994).

In conclusion there is no consistent evidence to support maternal pregnancy dietary restriction in an attempt to reduce the risk of adverse food reactions. This is not surprising given the studies showing an absence of specific IgE to foods in cord blood (Kjellmann *et al*. 1988, Hide *et al*. 1996, Kulig *et al*. 1999). Although in infants from an atopic population the risk of eczema in the short to medium term may be reduced by dietary restriction during lactation, there is no long-term benefit and no association with reduced adverse food reactions.

10.8.2 Infant intervention

Breast feeding vs. cows' milk vs. other milks

There are large variations between the studies comparing the different milks, namely breast milk, soya, hypoallergenic formulae (partially or extensively hydrolysed cows' milk), and cows' milk formulae given to the infant and the development of allergy. Many of the studies have looked for effects of the type of infant milk feeding on the development of allergic respiratory or skin disease, rather than on food or immunological (skinprick/specific IgE) reactions. A number of the early studies attempting to look at the impact of the infant milk formula on the risk of developing adverse food reactions showed a marginal reduction in skin test reactions and clinical adverse reactions to cows' milk (Hamburger 1984, Host *et al*. 1988, Saarinen and Kajosaari 1995). However,

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many were not randomised or prospective in their design. The more recent studies which attempt to look at the impact on adverse food reactions are randomised (Table 10.16) and use food challenge and skinprick/specific IgE endpoints, and occasionally eczema, as markers for adverse food reactions.

Of the studies listed in Table 10.16 only one shows a reduced specific IgE and clinical reactivity to milk in the intervention group with a partially hydrolysed formula, an effect that disappeared after 6 months of age (Vandenplas *et al*. 1995). The one other study that did suggest a reduction in reactions to cows' milk in breast/hydrolysate-fed babies versus unmodified cows' milk using open food challenge is flawed by the intervention group having a different year of recruitment for the control (cows' milk) group (Halken *et al*. 1993). The other studies do not consistently support any link between the type of infant milk feed and the development of adverse food reactions if skinprick/specific IgE and food challenge criteria are applied.

A number of studies in Table 10.16 use eczema, which in the early years may be associated with food intolerance, as the endpoint. The studies consistently show a protective effect of breast milk or cows' milk based hydrolysates versus unmodified cows' milk based formula on the development of eczema in the first 12–48 months of life in an atopic population (Chandra and Hamed 1991, Mallet and Henocq 1992, Vandenplas *et al*. 1995, Oldaeus *et al*. 1997). Only one small study looking at a normal population suggests a benefit of breast milk over cows' milk in reducing the risk of eczema, but with only short-term follow-up (Lucas *et al*. 1990). The data do not consistently support any benefit of breast feeding over a hydrolysed formula, nor do they favour an extensively hydroysed formula over a partially hydrolysed one. Soy-based formulas confer no protective benefit, and no evidence supports the use of goat or sheep milk which immunologically cross-react with cows' milk (Miskelly *et al*. 1988, Chandra *et al*. 1989, Chandra and Hamed 1991).

In conclusion, international studies do not suggest the view that different infant formulae or prolonged breast feeding reduce the risk of IgE mediated milk or other food allergies. However, there is a consistent view from a number of studies, particularly in regard to the atopic population, that breast milk and milk hydrolysates do reduce the risk of developing eczema in early childhood, an effect that disappears after 4–5 years of age.

Introduction of solids

There are no good prospective randomised studies looking specifically at the effect of delaying the introduction of solids on the risk of adverse food reactions. Prospective, non-randomised studies from a normal population (Fergusson *et al*. 1990) and an atopic population (Kajosaari 1991) have shown that delayed introduction of solid foods for 4–6 months reduced the risk of eczema. The study using a normal population showed a risk of chronic/recurrent eczema 2.9 times greater in those infants fed four or more solid foods before the age of four months compared with infants receiving no solid foods before four months of age. This difference was maintained until ten years of age (Fergusson *et al.*

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Table 10.16 Prospective, randomised trials assessing the effect of infant milk feeding on the development of adverse food reactions

Study (reference)	No and type of subjects	Infant milk	Follow-up period (yrs)	Definition of adverse food reaction	Outcome
Lucas *et al*. 1990	75, preterm, population based	Breast milk vs. preterm cows' milk for 1.5 months	1.5	Eczema	Reduced eczema in breast-fed group up to 18 months
Chandra and Hamed 1991	288, atopic population, birth cohort	Whey hydrolysate vs. cows' milk vs. soya vs. breast fed > 4 months	1.5	Sp IgE/SPT to cows' milk and soya Eczema	No difference in sp IgE/SPTs Increased eczema in cows' milk and soya groups
Schmitz *et al*. 1992	256, population based, birth cohort	Cows' milk vs. partially hydrolysed casein for first few days in breast-fed babies	1	History Sp IgE to cows' milk Eczema	No difference
Mallet and Henocq 1992	165, atopic population, birth cohort	Casein hydrolysate vs. cows' milk for 4 months	4	Sp IgE to cows' milk Eczema	No difference in sp IgE Reduced eczema up to 4y
Vandenplas *et al*. 1995	58, atopic population, birth cohort	Partially hydrolysed whey vs. cows' milk for 6 months	7	Open FC Sp IgE to cows' milk at 6 months Eczema	At 6 months 33% of control group had intolerance to cows' milk vs. 4% in intervention group (p=0.006). No difference at 1y. Reduced cows' milk IgE in intervention group at 6 months Reduced eczema in intervention group up to 1y

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Oldaeus *et al*. 1997	155, atopic population, birth cohort	Partially hydrolysed (PH) vs. extensively hydrolysed (EH) vs. cows' milk (CM) vs. breast fed (BF) for 9 months	1.5	Open or DBPC food challenges in 20% SPT & sp IgE to egg & cows' milk Eczema	No difference in positive FC Increased SPT to egg in PH group at 9 months but not at 18 months Increased eczema in CM and PH up to 9 months and in CM at 18 months, compared with BF & EH groups
De Jong *et al*. 1998	1533, population based, birth cohort	Cows' milk vs. protein-free formula for first 3 days in breast-fed babies	2	History Sp IgE to egg & cows' milk Eczema	No difference

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1990). In the study of an atopic population, eczema and a history of food allergy were reduced at the age of one year in the group fed solids after six months of age compared with those with solids introduced at three months. No food challenges or skinprick/IgE testing were performed in the first year, but at five years there was no difference between skin testing to fish, milk and wheat, history of food allergy and eczema between the two groups (Kajosaari 1991). A randomised, population-based study in Finland showed no difference in the cumulative incidence of fish and citrus allergy at three years old between children with fish introduced early or late (after one year old) into the diet, although the children with earlier introduction reacted earlier in life (Saarinen and Kajosaari 1980). Similar observations have been reported with coeliac disease. The later introduction of gluten into the infant diet has altered the age of onset and type of clinical presentation of coeliac disease in countries such as the UK and Scandanavia, but does not seem ultimately to stop the development of the disease, a view supported by the increase in serological population screening studies (Logan 1992, Ascher 1996, Hallert 1998).

Various guidelines exist in the UK recommending delayed introduction of solids in infants at increased risk of atopy, and in the same at-risk group delaying the ingestion of peanut products until after three years of age (Committee on Toxicity of Chemicals in Food 1998). On the basis of the studies presented, these guidelines do not appear to be evidence-based. Furthermore, the observation that 88% of egg reactions and 80% of peanut reactions occur after the first known exposure (Ford and Taylor 1982, Hourihane and Kilburn 1997) suggests that allergen avoidance is not straightforward and sensitisation may occur earlier in life and by other means, such as food contamination or inhaled sensitisation (Witteman 1995).

In conclusion, the evidence to date suggests that delaying the introduction of a solid food will perhaps postpone rather than prevent the development of clinical food allergy. There are no data suggesting that immunological (skin test or specific IgE) reactivity is affected. Thus, at the age of five years no difference in sensitisation to foods between those with solids introduced early or late into the diet can be found (Kajosaari 1991). These observations are probably not surprising as a delay in the age at which clinical reactivity develops may simply reflect the timing of the food being introduced into the diet, thereby giving the individual the first opportunity to clinically react to the food. Although there is some evidence that delaying the introduction of solids to 4–6 months reduces the risk of eczema in the medium term, the data come from non-randomised studies, and thus have to be interpreted with caution.

Combined maternal and infant measures

Two of the best trials in the field of dietary avoidance involve combined maternal and infant interventions (Zeiger and Heller 1995, Hide *et al.* 1996). Both are prospective and randomised with assessments by physicians blinded to the randomisation group in an atopic population. Both used skin test/specific IgE and food challenge criteria as endpoints for adverse food reactions, as well as other

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Table 10.17 Prospective, randomised trials assessing the effect of mixed maternal and infant dietary measures on the development of adverse food reactions

Study (reference)	No. and type of subjects	Maternal and infant diet	Follow-up period (yrs)	Definition of AFR	Outcome
Zeiger *et al*. 1989 Zeiger and Heller 1995	288, atopic population, birth cohort, randomised, physician blinded	Maternal egg, cows' milk and peanut avoidance in 3rd trimester and lactation + infant breast or casein hydrolysate (6 months), cows' milk and solids delayed > 6 months (later for some solids) vs. American Academy of Pediatrics guidelines	7	DBPCFC (50% of subjects) Sp IgE/SPT to cows' milk, egg, wheat, corn, soy, peanut, cod, chicken/beef	Reduced food intolerance at 1y and reduced cows' milk IgE/SPT at 1y and 2y in intervention group Reduced eczema at 1y in intervention group
Arshad *et al*. 1992 Hide *et al*. 1996	120, atopic population, birth cohort, randomised, physician blinded	Maternal egg, cows' milk, fish and nuts exclusion during lactation + infant breast +/− soy hydrolysate, solids delayed >11 months vs. no restrictions	4	Open challenge SPT to cows' milk, egg, wheat, fish, peanut Eczema	Differences in prevalence of cows' milk/egg intolerance and food SPTs did not reach statistical significance Reduced eczema until 4y in intervention group

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atopic diseases including eczema (Table 10.17). One study involved maternal dietary restriction in pregnancy and lactation, infant breast or casein hydrolysate feeding for six months, and delayed introduction of solids until at least six months into the infant diet (Zeiger and Heller 1995). There was a reduction in adverse food reactions in the intervention group at one year of age using a combination of clinical history and DBPCFC for diagnosis. These differences were almost entirely due to cows' milk allergy. The effect had disappeared by two years of age. The intervention group also showed a significant reduction in cows' milk specific IgE and cows' milk skinprick test at one and two years of age, but not thereafter. There were equal numbers sensitised to peanut at all ages including seven years when this was the commonest positive food allergen. Eczema was reduced at one year in the intervention group but not thereafter. The second study from the Isle of Wight cohort (Hide *et al.* 1996) involved maternal food avoidance during breast feeding and infant cows' milk avoidance until nine months with breast or soya hydrolysate used until then and egg introduced as the first solid at 11 months. There were reduced numbers of subjects with positive food challenges and food skin tests, mostly at one year old but never reaching statistical significance. Eczema was reduced until the four-year follow-up.

The conclusions from combined maternal and infant dietary exclusions are of a reduction in cows' milk allergy until 1–2 years of age, and a reduction in eczema in the first 1–4 years of life. As the natural history of cows' milk allergy is one of natural resolution by the age of two years in the vast majority, it is not surprising that the effect of dietary avoidance on food allergy disappears by two years of age. These studies on combined exclusion diets show no long-term benefit in preventing egg, peanut and other persistent food allergies.

10.9 Conclusions

The measured incidence and prevalence of adverse food reactions in a population depend largely on the precise definition and diagnostic criteria. The gold standard for diagnosing adverse food reactions is the DBPCFC but this is not suited to large epidemiological studies for practical reasons. In such studies, specific IgE alone will measure allergic sensitisation rather than clinical allergy and overestimate the true incidence and prevalence of food allergy. In such large population studies, the combination of a specific clinical history for food allergy together with specific IgE determination or SPT provides a more accurate measure of food allergy in the population.

The measurement of incidence and prevalence in birth cohort studies provides the most reliable epidemiological data; the bias inherent in other study designs is considerably reduced and problems of interpretation due to cohort effects are diminished. Such prospective studies also allow accurate description of the natural history of adverse food reactions.

Regrettably, there are few such studies and those that have been performed have been in European or other developed countries. Nevertheless, comparative

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data on the relative importance of adverse food reactions in different populations can be derived from case series that rank the relative importance of different food allergies seen in specialist allergy clinics. Important observations emerge from such comparative data. Firstly, egg and milk allergies are the most common food allergies world-wide. Secondly, certain food allergies that are common in Western countries, such as peanut allergy, may be uncommon in Asian countries such as Japan. Thirdly, certain food allergies that are never seen or are extremely rare in Western countries are important causes of allergy in other countries. This forces us to rethink our concept of 'common' and 'uncommon' allergenic foods. Different food allergens are clinically important in different countries: mustard allergy in France; sunflower seed allergy in Israel; lentil allergy in Spain; royal jelly allergy in Hong Kong; and bird's nest allergy in Singapore. Fourthly, it emerges that foods described as 'hypoallergenic' may be important allergens in countries outside Western Europe and North America. Thus beef allergy is important in Poland, chicken allergy is important in Hong Kong and rice allergy is a significant problem in Japan.

The erosion in the distinction between common and uncommon food allergens and between allergenic and hypoallergenic foods has important implications for the food industry. The 'globalisation' of eating habits and introduction of new foods into different cultures, e.g. kiwi fruit, sesame and mango, is likely to lead to changes in the pattern of food allergies seen across the world, with new, previously rare, allergies occurring with increasing frequency in different countries. Additionally, there are considerations to be taken into account in the development of novel foods, especially when derived from genetically modified organisms (GMOs). Existing proposals to evaluate the safety of GMOs with respect to food allergy depend on whether the transgenic protein is derived from a common or uncommon allergenic source. In the light of the above, such a distinction seems artificial at best and is likely to be misleading. We are not justified in dismissing the risk posed by a transgenic protein derived from an 'uncommon' food allergen.

It is an interesting fact that the frequency of adverse food reactions in a population is clearly related to its presence in the local diet and its early introduction in infancy, as demonstrated by the previously cited examples of common and uncommon food allergens. It is therefore surprising that dietary intervention aimed at delaying the introduction of a food into a child's diet fails to reduce the prevalence of food allergies. Although dietary intervention during pregnancy and lactation is clearly able to reduce infantile eczema and delay its onset, there is no convincing evidence that it significantly prevents the development of food allergies, with the exception of cows' milk. Importantly, several studies fail to demonstrate the presence of specific IgE to most food allergens in cord blood. This argues strongly against allergic sensitisation being completed *in utero* and suggests that the transplacental passage of allergen may not play an important role. Cows' milk allergy is the exception since specific IgE to beta lactoglobulin and other cows' milk proteins have been detected in cord blood. This perhaps explains why combined dietary intervention during

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pregnancy and lactation prevents the development of cows' milk allergy. However, as far as other food allergens are concerned, maternal dietary exclusion and delayed introduction into the infant's diet merely delays the manifestation of food allergy but does not appear to inhibit the development of allergic sensitisation and subsequent clinical allergy.

In summary, important epidemiological work needs to be done with respect to food allergy. An international effort, similar to the International Study of Asthma and Allergies in Childhood (ISAAC), would be a useful approach. This would ideally employ concurrent birth cohort studies in different parts of the globe. Such studies would yield important data on the world-wide prevalence of different food allergies and provide important clues to the pathogenesis of food allergy with the discovery of novel interventional strategies.

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