Patterns and prevalence of adult food allergy (PAFA)

Final Report

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University of Manchester, Manchester University NHS Foundation Trust, Amsterdam University Medical Centre, University of Southampton, Isle of Wight NHS Trust.

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Abbreviations

ARC - Allergic rhinoconjunctivitis

BMI - Body mass index

DBPCFC - Double-blind, placebo-controlled food challenge

ECRHSII - European Community Respiratory Health Survey II

FIR - Food information regulations

FSA - Food Standards Agency

GDPR - General Data Protection Regulation

GP - General Practitioner

HDM - House dust mite

IBS - Irritable Bowel Syndrome

IgE - Immunoglobulin E

IMD - Index of Multiple Deprivation

IoW - Isle of Wight

IoW 1989 - Isle of Wight 1989 birth cohort

IRAS - Integrated Research Application System

ISAAC - International Study of Asthma and Allergies in Childhood

LTP - Lipid transfer protein

MAAS - Manchester Asthma and Allergy Study birth cohort

N/A - Not applicable

NHS - National Health Service

ONS - Office for National Statistics

PAFA - Patterns and Prevalence of Adult Food Allergy

PFAS - Pollen-food allergy syndrome

REC - Research Ethics Committee

SPSS - Statistical Package for the Social Sciences

SPT - Skin prick test

STELAR - Study Team for Early Life Asthma Research

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1. Lay Summary

There are many types of adverse reactions people can have to food. These range from toxic reactions (like food poisoning) to intolerance (like lactose intolerance), to food allergy. Food allergy, also known as hypersensitivity, is caused by a type of antibody molecule called Immunoglobulin E (IgE) which is usually developed to help the body fight parasitic infections like malaria. In some individuals, the body starts to produce IgE to environmental agents, like pollen, dust, and food, causing allergies. A cure is currently lacking for most types of food allergy, and allergic individuals must avoid the causative food for life to prevent allergic reactions. Unfortunately, many allergic individuals experience accidental reactions due to inadvertently being exposed to an allergen.

Although in many patients an allergy is mild (and often associated with pollen allergy) some experience more severe reactions which may result in hospital admission and, in rare instances, can be fatal. The burden of food allergy in the UK adult population is not well described in the literature and for this reason the Food Standards Agency (FSA) commissioned the Patterns and Prevalence of Adult Food Allergy (PAFA) study to investigate this further.

The PAFA study investigated how many adults have an IgE-mediated food allergy in the UK. The community survey in Greater Manchester found that more than 30% of adults report having some type of adverse reaction to food, with cow's milk and cereals containing gluten being the most frequently reported foods. However, only around 6% of the UK adult population were estimated to have a clinically confirmed IgE-mediated food allergy with a spectrum of severity of reaction from mild (like oral itching) to anaphylaxis. This equates to around 2.4 million people in the UK. Important foods were peanut, and tree nuts like hazelnut, walnut, and almond. Many individuals also had IgE-mediated allergies to fresh fruits like apple and peach, which are associated with allergies to birch tree pollen. These types of allergies are often called pollen-food allergy syndrome or oral allergy syndrome. Allergies to foods like milk, fish, shrimp, and mussels were uncommon, as was IgE-mediated food allergy to wheat. Many of the individuals were found to have food allergies that were caused by several different foods, and only around half reported having had a food allergy that was formally diagnosed by a doctor. Around 7% of the population had other types of adverse reactions to food not caused by IgE, such as irritable bowel syndrome (IBS) and conditions like coeliac disease.

Two longitudinal birth cohort studies, one based on the Isle of Wight (IoW) and another based in South Manchester, have been studying the development of food allergies from infancy to adulthood by following the participants since birth. In PAFA it was found that the young adults in these studies who had developed food allergies as children retained their food allergies as they grew up. However, seven out of ten of the older adults in the community study reported that their food allergies developed in adulthood. This suggests that the burden of food allergy increases in adulthood.

The evidence the PAFA study has collected helps us understand how many people are affected by IgE-mediated food allergy, and that the considerable burden of childhood food allergy transitions into adulthood and then continues to further evolve. Exposure to environmental allergens, such as birch and related tree pollens, and their relationship with food allergy (spanning different severities) deserve further investigation. There is also a need to undertake clinical confirmation of non-IgE-mediated adverse reactions in the community survey participants to provide a stronger evidence base as to the burden of other types of adverse food reaction in the UK.

2. Executive Summary

One of the main types of immune-mediated adverse reactions to food is known as an IgE- mediated immediate hypersensitivity reaction. Although this type of reaction can be mild, some individuals experience more severe symptoms resulting in hospitalisation and, rarely, such reactions can be fatal. A robust, evidence-based approach regarding the prevalence of adverse reactions is required to underpin the development of effective policies seeking to manage, prevent, and treat such conditions. However, the best quality data available on adverse reactions to foods in adults in the UK are more than 20 years old. In order to obtain more current data, a community survey was undertaken in Greater Manchester using quota sampling to ensure respondents were representative of the UK population with regards to age, gender, ethnicity, and deciles of deprivation. This was complemented by an adult follow-up of the IoW (IoW) 1989 birth cohort and Manchester Asthma and Allergy Study birth cohort (MAAS) to provide data on risk factors of IgE-mediated food allergy and identify what proportion of food allergy in adults was persistent childhood allergy.

The diagnosis of IgE-mediated food allergy is complex. Therefore, the approach taken in the study was to use a screening questionnaire to capture as many individuals as possible who had adverse reactions to food as possible. Patients with a possible IgE-mediated food allergy or a possible non-IgE-mediated food allergy were then identified through their reported symptoms and time of onset of reaction. Everyone who reported an adverse reaction to a clearly defined food was invited to have tests and complete a questionnaire about their reactions. Using test results and questionnaire responses patients with a probable IgE-mediated food allergy were then identified. As the tests for IgE-mediated food allergy are limited and can often provide false positive or negative results, these individuals were then invited to a clinical interview and had additional tests performed if deemed necessary. All this information was then collated and discussed with an expert panel to confirm whether they truly had a confirmed IgE-mediated food allergy. These data were then used to estimate the crude prevalence rate of adult food allergy.

Prevalence of self-reported adverse reactions and possible IgE-mediated food allergy: the crude prevalence of self-reported adverse reactions to foods in the community survey was estimated to be 36.4% (35.0-37.7, 95%CI). The prevalence of those with symptoms consistent with a possible IgE-mediated adverse reaction to food and a time of onset of <2h to a panel of 43 priority foods was estimated at 18.35% (17.27-19.47, 95%CI), with the two most important foods being reported as being cow's

milk and cereals containing gluten. Overall, 6.4% (5.7-7.1, 95%CI) of the population sample reported having a doctor-diagnosed food allergy.

Prevalence of probable IgE-mediated food allergy: the crude prevalence of probable IgE-mediated food allergy (reported symptoms and time of onset consistent with an IgE-mediated and evidence of IgE-sensitisation to the same food) was estimated as being 7.44% (6.24-8.79, 95%CI). More than 50% of individuals reported that they experienced allergic reactions to more than one food. There was a very low prevalence of probable IgE-mediated allergy to cow's milk, fish and cereals containing gluten, with tree nuts, peanut and fresh fruits, such as apple and kiwi, dominating.

Prevalence of confirmed IgE-mediated food allergy: Almost 70% of individuals with a probable IgE-mediated food allergy who were clinically assessed had their allergy confirmed, giving a crude estimate of the prevalence of confirmed IgE-mediated food allergy of 5.73% (4.29-7.49, 95%CI). Participants had a spectrum of severity of reaction from mild to severe, including anaphylaxis. Many were allergic to multiple foods which was often associated with an allergy to tree pollen such as birch.

Prevalence of possible non-IgE-mediated adverse reactions to food: the prevalence of possible non-IgE-mediated adverse reaction to food was estimated at 6.85% (5.7-8.16, 95%CI).

The crude estimates of prevalence are consistent between the community survey and the PAFA adult follow up of the MAAS cohort. Whilst the majority of IgE-mediated food allergy in young adults from the cohort studies was persistent childhood allergy, 70% of participants in the community survey reported their allergies developed in adulthood.

The PAFA study has helped us understand the prevalence, patterns and trajectories of IgE-mediated food allergy. It has demonstrated that the considerable burden of childhood food allergy transitions into adulthood and then continues to evolve. Further evidence is required to understand how environmental factors (such as pollution, climate change and highly urbanised environments) and exposure to birch and related tree pollens leads to adult-onset food allergies. There is also a need to undertake clinical confirmation of non-IgE-mediated adverse reactions in the community survey participants.

3. Introduction

Food allergy is characterised by a reproducible, immune-mediated adverse reaction to specific foods (Johansson et al., 2001) (highlighted in red in Figure 1), and should be distinguished from other reproducible adverse reactions to food (e.g. pharmacological reactions to compounds found in foods, such as histamine and tyramine), and conditions such as lactose intolerance.

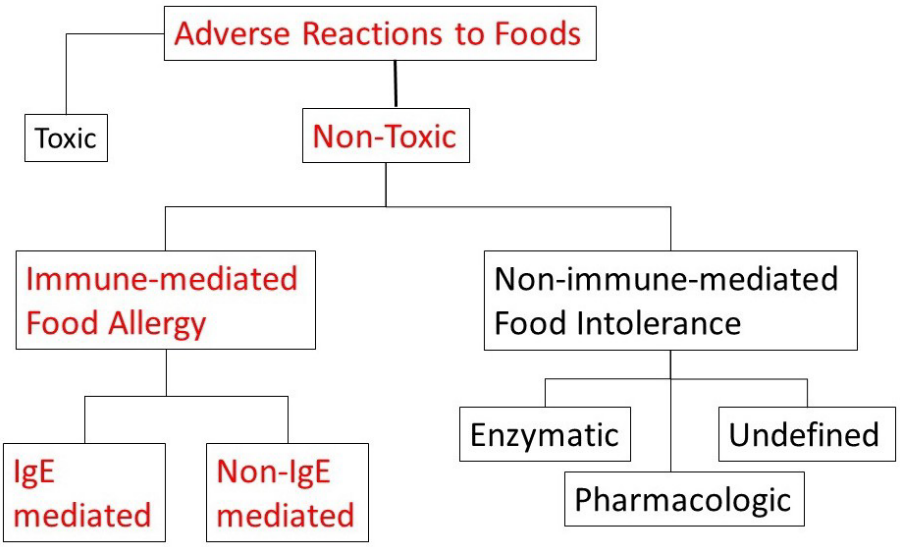


Figure 1. Classification of adverse reactions to food (Johansson et al., 2001)

There are two main types of immune-mediated adverse reactions to food with well-defined pathologies:

- IgE-mediated immediate hypersensitivity reactions in which sensitised subjects typically present with symptoms within two hours of consuming a food and can cause severe and, at times, life threatening allergic reactions such as anaphylaxis (Johansson et al., 2001); and
- T-cell mediated reactions such as the gluten intolerance syndrome known as coeliac disease where symptoms develop over a longer period of time (Al-Toma et al., 2019).

Food allergic individuals experience reactions ranging from mild to severe and even life-threatening reactions. They experience considerable morbidity, with all aspects of their lives being affected by a restricted diet and the risk of accidental allergic reactions (DunnGalvin et al., 2015). IgE-mediated food hypersensitivity is responsible for 65% of hospitalisations due to adverse reactions to food and has caused 86% of fatal reactions in the UK from 1992-2012 with young adults being particularly vulnerable (Turner et al.,

2015). Another type of immune-mediated adverse reactions to food includes gastrointestinal tract disorders, in particular those experienced by young infants and children, which in some cases (such as eosinophilic oesophagitis) involve both IgE- and non-IgE-mediated mechanisms and often present with overlapping features.

Other types of adverse reaction to food lack clear pathology and established diagnostic criteria. These include non-coeliac gluten sensitivity (Potter et al., 2018) and conditions such as IBS. Such conditions can be confused with lactose intolerance and coeliac disease and may be triggered by dietary fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (Borghini et al., 2017, De Giorgio et al., 2016). Individuals suffering from such conditions (often termed “food intolerance”) can contribute significantly to perceived rates of food allergy in adults. They were estimated to affect up to 7% of the European population in a recent meta-analysis although such figures are confounded by significant variations in study design (Sperber et al., 2017). These conditions are often poorly diagnosed and individuals perhaps follow unnecessarily restricted diets. This, in turn, may impact their nutritional wellbeing, especially those committed to gluten-free diets due to the comparatively lower nutritional value of gluten-free foods (Fry et al., 2018, Wu et al., 2015, Catassi et al., 2017). Consequently, helping adults with adverse food reactions to better understand and manage their condition, including making safe and healthy food choices, is a major public health objective.

A robust evidence base regarding the prevalence of adverse food reactions, their patterns and risk factors for their development is required to underpin the development of effective policies to manage, prevent and treat them. This dataset can also inform allergenicity risk assessments and associated management decisions such as foods included on allergen labelling priority lists, such as Annex II of the Food Information Regulations. Such evidence will also support approvals of novel foods and processes (including foods from Genetically Modified Organisms).

Some of the best quality data available on adverse food reactions in adults in the UK come from a community survey undertaken more than 30 years ago (Young et al., 1994). The study showed that whilst around 20% of the population complained of experiencing some form of food intolerance, only approximately 1.4% had confirmed allergic reactions assessed via oral food challenges to cow’s milk, hen’s egg, wheat, soya, citrus fruit (as orange), fish/shellfish (as prawn). Since that time, it is expected that IgE-mediated reactions to food may have become more common in adults, for example, as a consequence of the increase in the number of children with persistent food allergies

reaching adulthood. The European Community Respiratory Health Survey II (ECRHSII) study reported a wide range in prevalence of sensitisation (i.e. production of specific IgE) to food allergens from 7.7% in Iceland to 24.6% in the USA, with 14.5% for the UK population. The main sensitising food commodities were shrimp (6.2%), hazelnut (4.9%) and wheat (3.9%) while a strong link was found between food and pollen sensitisation (Burney et al., 2010). The pan-European community assessment in the EuroPrevall study also showed that the prevalence of probable IgE-mediated food allergy (i.e. reported reactions to a food consistent with an IgE-mediated food allergy and evidence of sensitisation to that same food), varied widely across Europe, ranging from 0.3% in Athens up to 5.6% in Zurich (Lyons et al., 2019). The most common sensitising foods were hazelnut and fruits such as peach and apple. Sensitisation to these foods was closely associated with tree pollen sensitisation, particularly the major birch pollen allergen Bet v 1 (Burney et al., 2014).

Adult food allergy has not been studied systematically in England in recent times. Consequently, it is not known whether the patterns, prevalence, and phenotypes of adverse food reactions in adults have changed over the last 20 years, particularly in relation to IgE-mediated reactions. In order to describe the trajectories of food allergies across the life course and identify risk factors for each trajectory and the major foods involved, two birth cohorts whose members have now reached adulthood were followed-up. The two longitudinal cohorts included in the PAFA study were the IoW 1989 cohort (Arshad et al., 2020) and MAAS (Clark et al., 2019) (Clark 2019). The cohorts were recruited at birth. The IoW 1989 cohort was assessed regularly up to 26 years of age while the MAAS cohort was assessed regularly up to 18+ years of age. Data on food allergy outcomes, as defined on the basis of history and IgE-sensitisation tests were available at 26 and 18+ years of age respectively in the two cohorts.

The follow-up data provided us with information on IgE-mediated food allergy in young adults aged between 18-32 years (Table 1). Their ethnicity reflected that of England and Wales in the 1990’s when they were originally sampled, and the cohort participants are primarily of white ethnic origin.

Table 1. Description of MAAS and IoW cohorts

Cohort	IoW	MAAS
Study region	Isle of Wight	Manchester
Recruitment	1989-1990	1995-1997
Age at recruitment	Birth	Birth
Number of participants recruited	1,456	1,084
Number of participants at last follow-up	1,033	595
Age at last follow-up (mean)	25-27 (26) years	18-22 (19) years
Age in 2022	32-33 years	25-27 years

Existing data from these cohorts are vast and include sensitisation to inhalant and food allergens from 1 year of age, parentally reported symptoms from standardised questionnaires and, only in MAAS, extracts of diagnoses and healthcare utilisation from primary care records.

The PAFA project sought to fill the gaps in our knowledge about IgE-mediated food allergies by collecting population-level data on patterns and prevalence of adverse food reactions in adults in the UK, including possible non-IgE adverse reaction to food and IgE-mediated food allergies. It was undertaken by capitalising on the two birth cohorts, together with a community survey in Greater Manchester. The study was conducted between 2018 and 2023, through the COVID-19 pandemic which caused considerable disruption to the set up and delivery of the study.

3.1 PAFA Project Objectives

Objective 1: To determine the prevalence of IgE-mediated food allergy in adulthood. The prevalence of adult food allergy will be defined in the UK population using a community–based survey of adults aged 18-70 years in Greater Manchester (community survey) and follow-up data from the MAAS and IoW 1989 population-based cohorts (Cohorts). Clinical assessment of the symptomatic population (clinical history, evidence of IgE-mediated sensitisation to the culprit food and, where possible, by oral food challenge) was used to

facilitate estimates of prevalence of both adult onset and persistent childhood food allergy.

Objective 2: To describe the different trajectories of food allergy across the life course. We will harmonise, and where possible integrate, prospectively collected data available in MAAS and IoW 1989 population-based cohorts to enable the trajectories of food allergies to be described from birth to early adulthood. Risk factors for each trajectory will be identified and mapped to data obtained from the community survey.

Objective 3: To describe adverse reactions to foods that are not mediated by IgE in adults. Data collected in the community survey and Cohorts will allow the estimation of the prevalence of self-reported adverse reactions to food which may also be non-IgE-mediated. In addition, a repository of data and biological samples will be formed for future investigation (e.g. biomarker analysis [serological and/or genetic]) to provide an indication of the extent to which these reactions relate to lactose intolerance and coeliac disease.

4. Materials and Methods

4.1 Study populations

4.1.1 Community Survey

A community-based survey design was adopted in order to recruit an unselected population group representative of the UK population, in terms of age, gender, index of deprivation and ethnicity (Lyons et al., 2019, Kummeling et al., 2009). Five GP practices were identified in Greater Manchester with catchment areas covering neighbourhoods spanning across all deciles of deprivation and ethnic diversity of the UK based on ethnicity data from the 2011 census (ONS, 2013). It was undertaken in Greater Manchester in three stages as follows:

PAFA Stage 1: The PAFA Stage 1 study was approved through ethics submission IRAS number: 260430; REC reference: 19/NW/0749. Inclusion criteria were adults aged 18-70 years registered with a chosen GP practice. Exclusion criteria were individuals either receiving palliative care or suffering from dementia. A stratified sampling approach was taken to achieve a balanced demographic. Specifically, random sampling of patients registered with participating GP practices was undertaken against quotas of age and gender based on the UK population as described in the 2011 census data (ONS, 2013). Subjects received a pack with a letter explaining the study and inviting them to take part. The pack also contained a paper copy of the screening questionnaire which was designed to capture data on adverse reactions to a list of priority foods together with free text fields to declare up to three further foods (Table 2). The questionnaire could have either been completed and posted back in a prepaid envelope, or electronically, for those who preferred to do so, through the unique identifier provided to enable online submission. Alternatively, they were provided with a telephone number to call the study team and complete it over the phone. Subjects with mobile phone numbers registered to the GP also received up to two reminder text messages containing a personalised link to complete the questionnaire online. The study recruitment ran from March 2021- February 2022.

Table 2. PAFA priority foods

¶including milk products such as butter, cheese, yoghurt, crème fraiche and fromage frais

*including shrimp, lobster, and crab

†including mussels, clams, oysters, squid, and octopus.

Food category	Food commodity
Dairy	Milk
Dairy	Eggs
Meat	Chicken and beef (Stage 2 only)
Seafood	Fish
Seafood	Crustacean shellfish*
Seafood	Molluscan shellfish†
Cereals and pseudocereals	Buckwheat
Cereals and pseudocereals	Corn (maize)
Cereals and pseudocereals	Rice
Cereals and pseudocereals	Wheat, gluten
Fruit	Apple
Fruit	Avocado
Fruit	Banana
Fruit	Kiwi fruit
Fruit	Melon
Fruit	Orange
Fruit	Peach
Fruit	Strawberry
Fruit	Tomato

Legumes	Chickpea
Legumes	Lentil
Legumes	Lupin
Legumes	Pea
Legumes	Peanut
Legumes	Soybean
Other seeds	Mustard
Other seeds	Poppy
Other seeds	Sesame
Other seeds	Sunflower
Tree Nuts and nut-like seeds	Almond
Tree Nuts and nut-like seeds	Brazil nut
Tree Nuts and nut-like seeds	Cashew
Tree Nuts and nut-like seeds	Coconut
Tree Nuts and nut-like seeds	Hazelnut
Tree Nuts and nut-like seeds	Macadamia
Tree Nuts and nut-like seeds	Pecan
Tree Nuts and nut-like seeds	Pistachio
Tree Nuts and nut-like seeds	Walnut
Vegetables	Bell pepper (Stage 2 only)
Vegetables	Carrot

Vegetables	Celery, celery seeds and celeriac
Vegetables	Potato
Vegetables	Pumpkin

PAFA Stage 2: The PAFA Stage 2 study was approved through ethics submission IRAS number: 295890; REC reference:21/YH/0262 by the Yorkshire and The Humber - South Yorkshire Research Ethics Committee. Exclusion criteria were individuals either receiving palliative care or suffering from dementia. Respondents from Stage 1 were also omitted in the Stage 2 follow-up study if they had moved away from the GP practice or had a GPDPR opt-out and did not wish to participate in the research study.

The inclusion criterion was being a PAFA Stage 1 respondent who agreed to be recontacted for PAFA Stage 2. Participants who reported adverse reactions to Stage 1 priority foods (cases) and those who reported no adverse reactions to any food (controls) were invited to take part. The free text responses of cases who only reported reactions to “other” foods (i.e. in the free text fields) were analysed and categorised as priority food, specific food, composite food or poorly defined food (Figure 2). Participants with incomplete responses were removed.

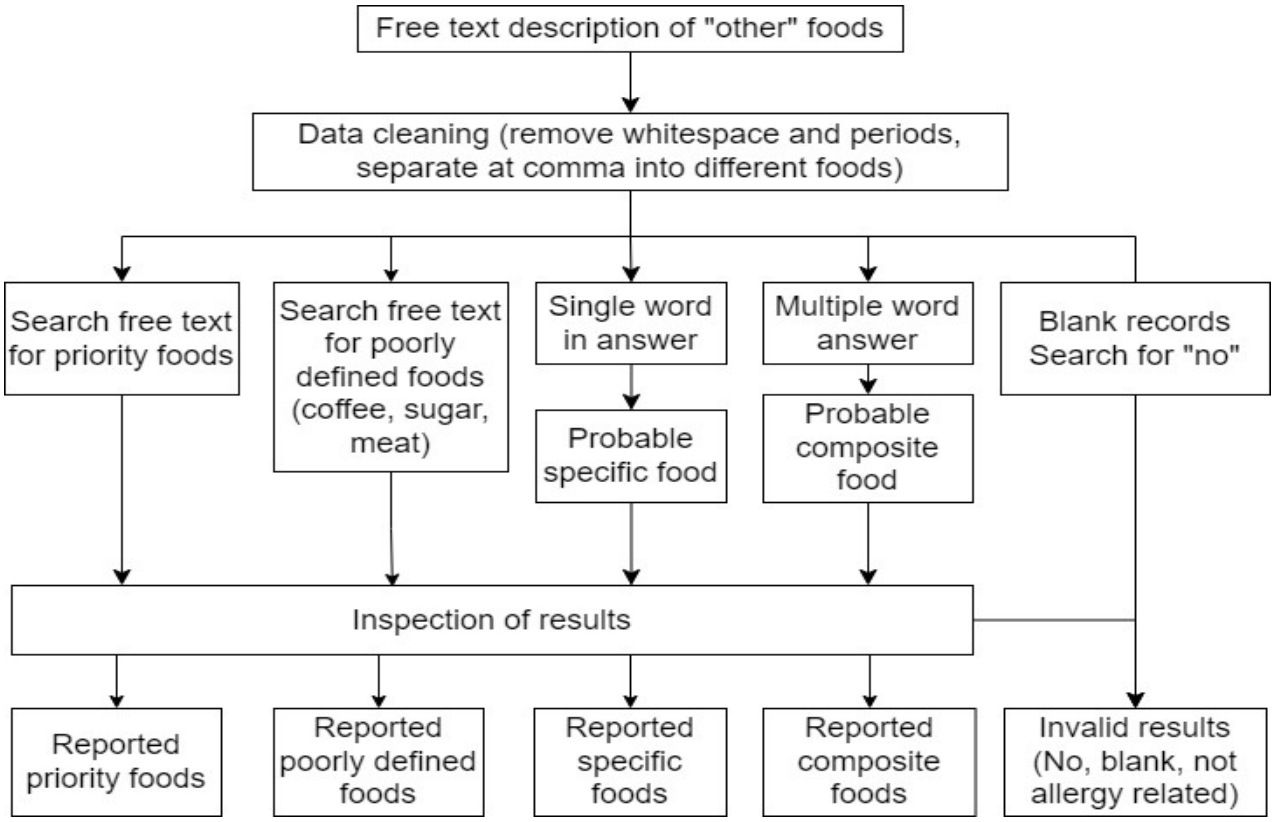


Figure 2. Data cleaning strategy for Stage 1 participants reporting reactions to "other" foods.

Different types of "other" food terms included fresh foods (aubergine, beetroot, raw carrot, onion, garlic, pineapple, radish) and spices, such as cinnamon. In relation to composite foods, terms such as curry, spicy foods, pastry, fatty and fried foods as well as sweets (pear drops and love hearts) frequently appeared. The final category of "poorly defined/ unknown" foods included individuals reporting reactions to coffee, sugar, vinegar and "meats" (Figure 3). Based on this analysis, individuals who reported reactions to "other" foods were invited only if a well-defined food was reported.

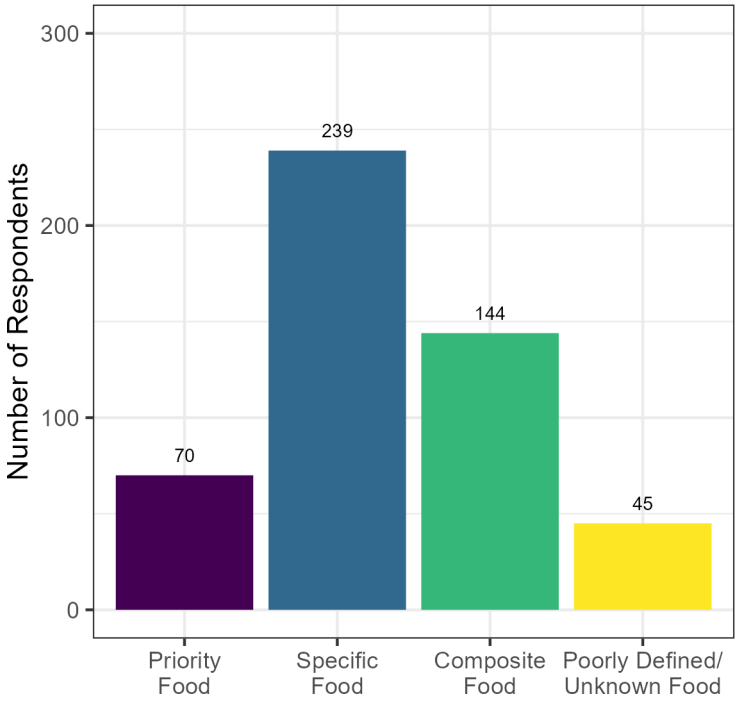


Figure 3. Frequencies of different types of food category reported by participants reporting reactions to "other" foods.

Eligible cases and controls were invited for a face-to-face appointment, usually at the GP practice. An additional, longer questionnaire was administered, and a blood sample was taken for serum analysis of total and specific IgE (see section 5.3) between March 2022 and May 2023. Participants were also invited to have skin prick tests (SPT) to a panel of food and inhalant allergens (peanut, hazelnut, Brazil nut, cashew nut, walnut, almond, hen's egg, cow's milk, sesame, cod, blue mussel, shrimp, kiwi, peach, wheat, sesame, house dust mite (HDM), grass pollen, birch pollen). A positive result was defined as a wheal ≥3 mm diameter compared to the negative control (saline). Participants who had uncontrolled asthma (Codreanu et al., 2006) did not undergo SPT at the GP surgery.

PAFA Stage 3: The PAFA Stage 3 study was approved through ethics submission IRAS no 305963; REC 22/YH/0160 and subsequent amendments were approved through the Yorkshire and The Humber - South Yorkshire Research Ethics Committee. In Stage 3 clinical confirmation of food allergy was undertaken in individuals with either a probable IgE-mediated food allergy or those in whom further clinical evaluation was deemed necessary to exclude such a food allergy. Community survey invitees to PAFA Stage 3 were identified based on data collected in PAFA Stage 2 and their consent to be contacted for PAFA Stage 3 (Figure 4). Cohort invitees with probable IgE-mediated food

allergy were identified on the basis of analysis of historic data and samples. Participants were excluded if they were either receiving palliative care or suffering from dementia.

PAFA Stage 3 involved a clinical assessment (visit 3-1) which was undertaken either by telephone or in person by completing a clinical history form developed for the EuroPrevall outpatient clinic study (Fernández-Rivas et al., 2015) (Figure 4) and took approximately one hour to complete. Following the consultation, subjects could be invited to have further tests or blood samples taken for additional IgE testing (visit 3-2). Following visit 3-1 (and, where undertaken, visit 3-2) a panel evaluated the patient's history and test results to either confirm a diagnostic outcome (see section 4.4.1) or identify the need and eligibility of a participant for an oral food challenge to confirm their food allergy. Participants identified as eligible were initially invited to a clinical appointment for pre-food challenge checks (visit 3-3) which were then followed-up by the challenge itself performed over two days with at least a week apart (Visits 3-4 and 3-5). The clinical diagnosis and food challenges were performed as previously described (Grabenhenrich et al., 2017, Fernández-Rivas et al., 2015, Cochrane et al., 2012) and included double-blind, placebo-controlled food challenges (DBPCFC) followed by open food challenges. In a DBPCFC the patient is given the sensitising food in incremental doses and any symptoms of an allergic reaction are recorded at each dose. The taste, texture and colour of the food under test is hidden in a matrix and for PAFA this was either a smoothie (for fruit challenges) or a chocolate dessert matrix (for tree nuts and seeds). The challenge took place on two days; on one day the participant received only the matrix and on another day the matrix containing the food under test. The participant and the clinical team are "blinded" as to whether the challenge day is active (contains the sensitising food) or placebo (vehicle only). After both days the supervising clinician decides whether the test is positive, negative or inconclusive. The top dose given equated to a daily serving of the food. If a participant did not react on either day, they were usually given an open challenge with a larger dose of the food itself. All final outcomes were reviewed by the expert panel (see section 4.4.1). Stage 3 started in November 2022 with clinical assessments completed by November 2023.

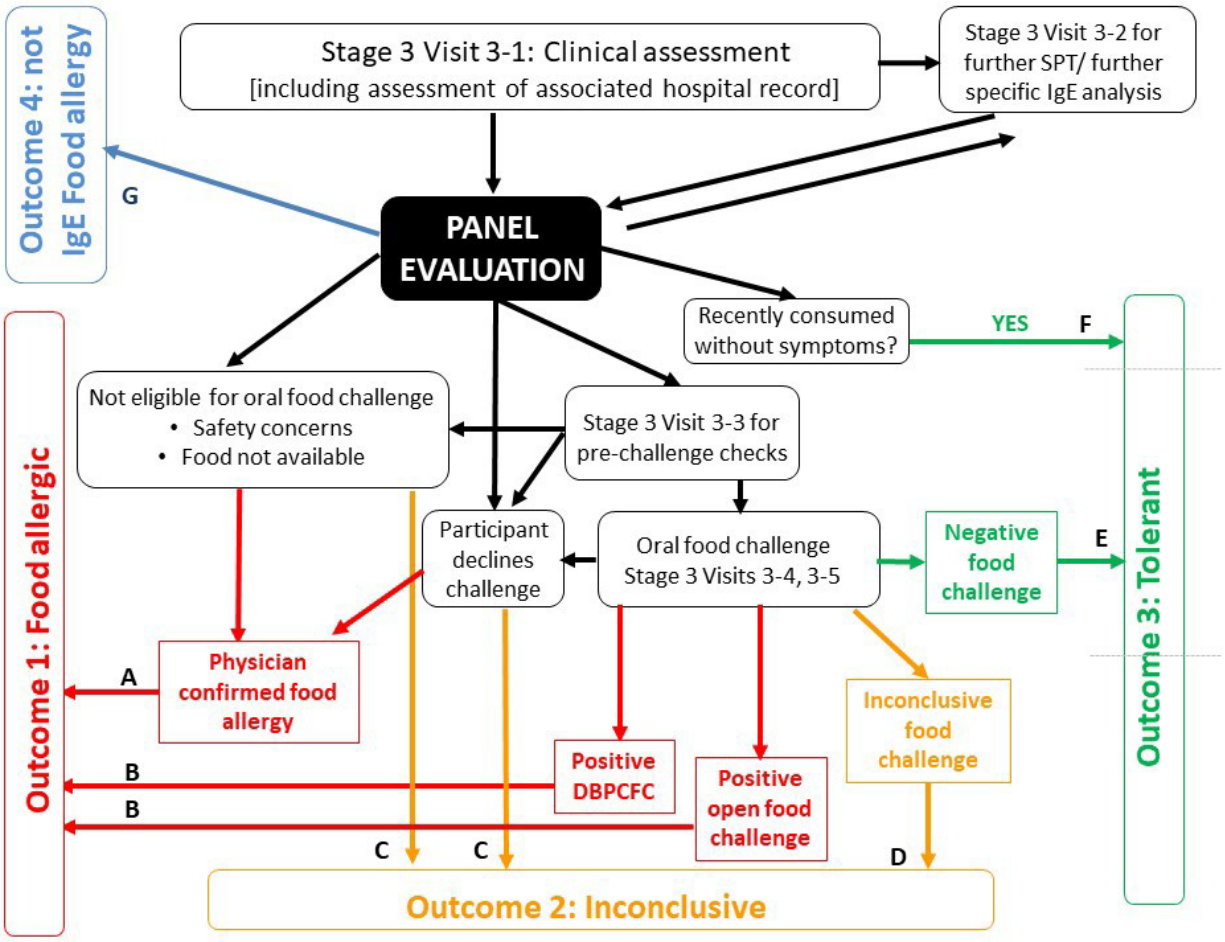


Figure 4. Flow chart summarising the connectivity between different study visits and expert panel evaluation

Pathways are denoted by letters A-G together with the outcomes from clinical diagnoses in PAFA Stage 3 which are described more fully in section 4.4.1.

4.1.2 Cohorts

All children born in the IoW between January 1989 and February 1990 were eligible for inclusion in the initial 1989 IoW cohort. A total of 1509 pregnant mothers were recruited and consented to complete questionnaires soon after the birth of their children. Parental consent was obtained from the parents of 1456 out of 1536 children born for inclusion into a longitudinal study of asthma and allergic disease. Participants were followed up at six time points over the course of 26 years – at age 1, 2, 4, 10, 18 and the latest at 26 years of age. A total of 1033 participants were seen at 26 years of age (Arshad et al., 2020).

The MAAS cohort was formed in 1995 when women were recruited during pregnancy from south Manchester. A total of 1,084 participants were initially recruited and then

followed up at seven timepoints – at 1, 3, 5, 8, 11, 13-16 and 18+ years of age. A total of 595 participants were assessed at 18+ years (Clark et al., 2019).

The wealth of data already available in the IoW 1989 and MAAS birth cohort studies has been used to describe the life course trajectories of food allergy (Clark et al., 2019; Arshad et al., 2020) and includes:

- 4.1.1.1 historic data on food allergy collected in the IoW 1989 and MAAS studies to understand trajectories
- 4.1.1.2 data on asthma, allergic rhinitis and eczema collected for the IoW 1989 cohort at the 26-year follow-up and similar data from the MAAS 18+ year assessment
- 4.1.1.3 selected allergic rhinitis, asthma and eczema data when available at different follow- ups from IoW and MAAS extracted from the Study Team for Early Life Asthma Research (STELAR) consortium (Custovic et al., 2015) and
- 4.1.1.4 data on potential risk factors for food allergy from previous IoW 1989 and MAAS assessments

Cohort members with a probable IgE-mediated food allergy (defined in section 4.4.1) were invited for further clinical assessment (PAFA Stage 3). This was undertaken by the clinical teams from either the IoW NHS Trust (for the IoW 1989 cohort), or Manchester University Foundation Trust (for the MAAS cohort). The new dataset collected in PAFA Stage 3 has been used in conjunction with previously collected data to define the trajectories of food allergy and their risk factors.

4.2 Data assessment

4.2.1 Cohort data harmonisation

The historic cohort data for MAAS and IoW 1989 were uploaded to the PAFA Cohort REDCap database (Harris et al., 2019a, Harris et al., 2009a). These cohorts were led by different teams and, as a result, different questionnaires were administered to participants in the two separate studies. However, most of the questions were based on the International Study of Asthma and Allergies in Childhood (ISAAC) assessments (Asher and Weiland, 1998) and, therefore, structured in a similar manner. The first steps involved harmonising the data from the two cohorts at the final age of assessment (18+ years in MAAS and 26 years of age in IoW 1989). The variables from both cohorts were reviewed with regard to their potential for harmonisation, taking into consideration

multiple features across the datasets, the question asked/response options, and the data structure.

Examples are provided in Table 3. This process was then repeated for each of the earlier cohort assessments and paired based on the age of assessment (Table 4). Some variables could not be matched as there was no equivalent or had not been asked at the timepoint being harmonised.

Table 3. Examples of data harmonisation for MAAS and IoW cohorts

Study variable	IOW follow-up at 26 years	MAAS follow-up at 18+ years
Food associated with worst reaction – mapped to PAFA classification	"Have you had a food allergy since you were 18?" Participant able to provide up to 3 problem foods, worst reaction identified from reported symptoms	“Which of all these foods gave you the worst problems?” Presented after list of foods.
Food reaction time coded as less than 2 hours or more than 2 hours	“How quickly does the reaction occur after contact with the food?”	“How long after eating the food did your child start with the first symptom?” Response given in minutes, hours, days
Any history of hay fever	“Do you have any nasal allergies, including hay fever?”	“Have you ever had hay fever?”

A codebook was developed to record the harmonisation of variables. The STELAR consortium database (Custovic et al., 2015) was used to extract further variables including additional risk factors for development of food allergy which had been collected at earlier assessments for these cohorts (Table 4).

Table 4. Correspondence of assessment age in the MAAS and IoW 1989 cohorts

At several time points there was no assessment in one cohort that could be paired with an assessment at a similar age in the other cohort; X: no equivalent time point.

MAAS assessment age (years)	IoW 1989 assessment age (years)
1	1
3	2
5	4
8	X
11	10
13-16	X
X	18
18+	26

Historical cohort data were collated using the PAFA REDCap and STELAR databases and downloaded into Statistical Package for the Social Sciences (SPSS). Data were checked, refined and aligned so that any participant reporting an issue after eating a food was identified. The food identified was harmonised to the PAFA priority foods where possible and coded as ‘other’ if it could not be matched. In the IoW 1989 cohort questionnaire, participants were able to self-report the details of up to three foods (Table 3). In MAAS, participants were presented with a list of foods and asked to identify if they ever had adverse reactions after eating each food asked to identify the food causing the worst problems (Table 3).

Some participants provided additional information about the food they reported as a problem, including symptoms and reaction times. These were screened to assess whether the information provided matched a profile consistent with either a possible IgE or possible non-IgE-mediated adverse reaction to food. Participants reporting a positive SPT or serum specific IgE that matched the reported food were categorised as having a probable IgE-mediated adverse reaction to food.

The remaining participants with either a possible IgE- or possible non-IgE-mediated adverse reaction to food were reviewed on a case-by-case basis. Where serum samples were available from participants, further analysis was carried out to confirm whether an individual had a specific IgE response to the reported food, together with other PAFA priority foods included in the core serological testing panel (section 4.3). Participants were classified according to the definitions in section 4.4.1.

4.2.2 New data collection

For the community survey questionnaire data were collected in a pseudonymised form using REDCap (Harris et al., 2019a, Harris et al., 2009a). The questionnaires used in PAFA Stage 1 and Stage 2 were developed based on those used in the EuroPrevall community survey in adults (Lyons et al., 2019). A list of 43 priority allergenic foods was available to choose from in addition to allowing free-text reporting of foods. The list comprised of foods for which allergen labelling is mandatory in the UK through the Food Information Regulation (SI 1855 2014) and other foods associated with inhalant allergies to pollen (birch pollen in particular), such as apples, kiwi and legumes. Foods associated with non-IgE-mediated food allergies, such as chicken, were also included (Table 2). Data on the type of symptoms and time of onset of a reaction were collected for each reported food in PAFA Stage 2.

4.3 Serological analysis

Total and specific serum IgE were determined using Phadia -Thermo Fisher ImmunoCAP by the Academic Medical Center in Amsterdam. Specific IgE binding to a standard panel of food extracts and individual food allergen molecules was determined, complemented with IgE to the major birch pollen allergen Bet v 1, grass pollen profilin (Phl p 12), grass pollen extract and HDM extract. The panel was designed to cover the most relevant food allergies and dissect the molecular basis of sensitisation (see Table 5) focussing on the following:

- foods listed on Annex II of FIR: egg (as hen's egg), milk (as cow's milk), fish, shrimp (as an exemplar crustacean shellfish), mussels (as an exemplar molluscan shellfish), peanut, the tree nuts - hazelnut, walnut, cashew nut, Brazil nut and almond -, sesame seed and wheat
- other foods identified as causing severe reactions: peach, kiwi, and red meat

The core panel was used for serological analysis of community survey participants in Stage 2 and for additional testing of cohort participants. It was supplemented with total serum IgE analysis and additional testing for specific IgE to food extracts and components such as parvalbumin for fish (Gad c 1 from cod; also a pan-allergen for cross-reactivity to other fish species), β-lactoglobulin (Bos d 5) and casein (Bos d 6) for milk, ovomucoid for egg (Gal d 1) as required to further support effective diagnosis. A borderline test result was classified as being ≥ 0.1-0.34 kU specific IgE/L and a positive test result was ≥ 0.35 kU specific IgE /L.

The core panel was designed to cover all the foods listed above, accounting for the following: confirming/ rejecting probable food allergy and establishing the origin of sensitisation. The rationale behind the composition of the core panel for serological analysis is described below.

In food sensitisation, there are essentially three routes: primary sensitisation to the food, primary sensitisation to pollen with cross-reactivity to food, and primary sensitisation to food with cross-reactivity to other foods. The two molecules most prominently involved in pollen food cross-reactivity (clinically linked to the so-called pollen-food allergy syndrome, PFAS) are Bet v 1 in birch pollen and profilin in grass pollen (Phl p 12). These were both included in the panel to get insight in the source of sensitisation, but also as a surrogate marker for sensitisation to many plant foods in PFAS (e.g., apple, celery, and carrot) that were not tested in the panel. The most important molecule implicated in food-food cross-reactivity is lipid transfer protein (LTP). There is consensus that in most cases sensitisation to LTP starts with peach LTP, Pru p 3. This molecule was added to the panel as surrogate for LTP cross-sensitisation for foods beyond peach such as fruits (e.g. apple), tree nuts (e.g. hazelnut) and vegetables (e.g. carrot). The rest of the molecules in the panel were marker allergens for primary sensitisation to foods. For peanut, tree nuts and sesame seed, their respective 2S albumins were chosen (Ara h 2, Ber e 1, Cor a 14, Jug r 1, Ana o 3, Ses i 1) because they are accepted as the most relevant allergens for establishing clinical allergy. For kiwi, its cysteine protease Act d 1 is considered as its major allergen for primary sensitisation. For wheat, Tri a 19, the ω-5 gliadin, was included because of its role in cofactor-dependent food allergy. If sensitised to wheat but negative to Tri a 19, a positive test for grass pollen was considered to be most likely at the basis of wheat sensitisation. Finally, for foods of animal origin the following marker proteins that are recognised as the most relevant major allergens were tested: tropomyosin for shrimp (Pen a 1; also a marker protein for cross-reactivity to other crustaceans and to molluscs),

parvalbumin for fish (Gad c 1 from cod; also a pan-allergen for cross-reactivity to other fish species), β-lactoglobulin (Bos d 5) and casein (Bos d 6) for milk, ovomucoid for egg (Gal d 1) and the sugar moiety galactose-α-1,3-galactose for red meat. All sera from subjects enrolled in PAFA Stage 2 were tested for this complete panel.

The scientific justification above was not the only reason for working with this panel. The more comprehensive alternative option of a microarray with 114 allergen molecules was also considered but not chosen due to high cost and much poorer sensitivity compared to the singleplex ImmunoCAPs.

Overall, the panel worked very well but not fully providing all information needed to establish whether a patient had a probable IgE-mediated food allergy or not. For that reason, additional tests were performed where warranted after consultation with the clinical investigators. For example, if patients reported symptoms to apple but had a negative test to allergens associated with fruit allergy (Bet v 1, profilin [Phl p 12] and Pru p 3), an extra test with apple extract was performed to confirm or reject probable food allergy. In cases where such a patient tested positive, IgE to the food extract and/or the apple homologue of Bet v 1 in apple (Mal d 1) was tested to make sure that this led to a cross-reactive food allergy. Similar approaches were followed for other foods. When patients reported allergy to foods beyond the PAFA priority foods, such as banana, avocado, pine nuts, lentils, chickpeas, green peas, or fig, then IgE was measured against extracts of these foods to ascertain probable food allergy or reject it.

Table 5. ImmunoCAP selection used for serology

N/A = not applicable

Sample type	Species	Extract used (Yes/No)	Corresponding selected component	Allergen type/Protein family
Legumes	Peanut	Yes	Ara h 2	2S albumin
Tree nuts	Brazil nut	Yes	Ber e 1	2S albumin
Tree nuts	Hazelnut	Yes	Cor a 14	2S albumin
Tree nuts	Walnut	Yes	Jug r 1	2S albumin
Tree nuts	Cashew	Yes	Ana o 3	2S albumin
Tree nuts	Almond	Yes	None available	N/A
Other Seeds	Sesame	Yes	Ses i 1	2S albumin
Other Seeds	Wheat	No	Tri a 19	Seed storage prolamin: ω-5 Gliadin
Shellfish	Shrimp	Yes	Pen a 1	Tropomyosin
Shellfish	Blue mussel	Yes	None available	N/A
Fish	Cod	Yes	Gad c 1	Parvalbumin
Red meat	Bovine (beef)	No	Bovine thyroglobulin	Galactose-alpha-1,3-galactose
Fruit	Peach	Yes	Pru p 3	LTP

Fruit	Kiwi	Yes	Act d 1	Cysteine protease
Milk	Cow's milk	Yes	None included	N/A
Environmental (outdoor)	Birch pollen	No	Bet v 1	PR10
Environmental (outdoor)	Grass pollen	Yes	Phl p 12	Profilin
Environmental (indoor)	House dust mite	Yes	None included	N/A

4.4 Data analysis

4.4.1 Outcomes

The classification of IgE and non-IgE-mediated adverse food reactions was based on the type of symptoms and time of onset of the allergic reaction as follows:

Self-reported adverse reaction to food: any type of adverse reaction to food reported by a participant.

Possible IgE-mediated food allergy: defined as self-reported symptoms that occur within 2 hours of consumption of a particular food and are typical of an IgE-mediated food allergy. Symptoms include itching, tingling or swelling in the mouth, lips, or throat; nettle sting like rash or itchy skin, or red rash; diarrhoea or vomiting (other than food poisoning); stomach cramps; runny, stuffy nose, or sneezing; red, sore, or running eyes; breathlessness; fainting or dizziness.

Possible non-IgE-mediated adverse reactions to food: defined as self-reported symptoms manifested more than two hours after consumption of a particular food. Symptoms include difficulty swallowing, fainting or dizziness; headaches; stomach cramps; diarrhoea or vomiting (other than food poisoning); other digestive problems (e.g. bloating, wind).

Probable IgE-mediated food allergy: defined as self-reported symptoms associated with consumption of a particular food and occur within 2 hours of consumption, together with evidence of sensitisation to food in the form of a positive skin prick test (SPT; ≥3mm wheal diameter) and/or positive serum specific IgE (≥0.35kU/L) to a food and/or food component.

Confirmed IgE-mediated food allergy: In PAFA Stage 3 IgE-mediated food allergies were confirmed based on patient assessment and tests as described previously (section 4.1.2 and Figure 4) with four different outcomes:

Outcome 1 - Confirmed IgE-mediated food allergy comprising:

A) Clinician confirmed IgE-mediated food allergy (Figure 4, pathway A) which was defined as all of the following:

- Self-reported symptoms associated with consumption of a particular food which are typical of an IgE-mediated food allergy
- Symptom onset within 2 hours of contact with food
- Evidence of sensitisation in the form of a positive SPT (a mean wheal diameter ≥3mm compared to the negative control) or positive serum specific IgE (≥0.35kU/L) test to the same food

B) Oral food challenge confirmed food allergy (Figure 4, pathway B) attributed if symptoms (either objective or severely persistent (>45 min) subjective symptoms) were experienced on the active arm of the challenge and either:

- Not on the placebo day; or
- Are less severe on the placebo day compared to verum day; or
- Clear symptoms were observed on the verum day but placebo challenge was not performed (e.g. the participant did not accept the second challenge day)

The same pre- and post-challenge assessments and criteria for positivity as described for DBPCFC were applied following an open food challenge (see section 4.1.1).

Outcome 2 - Inconclusive regarding IgE-mediated food allergy as:

- the reported signs/symptoms are not clearly attributable to an IgE-mediated food allergy and an oral food challenge was not performed (Figure 4, pathway C)
- the reported signs/symptoms during an oral food challenge could not be clearly attributed to an IgE-mediated food allergy, or if a challenge day was stopped before reaching the final dose without ingestion-related signs/symptoms, or the patient reacted on the placebo arm of the DBPCFC (Figure 4, pathway D)

Outcome 3 - Tolerant regarding IgE-mediated food allergy where:

- each challenge day (placebo and serum separately and follow-up open food challenge) was reported as negative with no clinical signs/ symptoms, or observed signs/symptoms were not thought to be caused by the test food (Figure 4, pathway E)
- an individual consumes the food towards which probable food allergy was indicated in Stage 2 within the last three months without symptoms; or if the food has not been eaten recently but the study participant never had symptoms and is not sensitised towards that food (Figure 4, pathway F)

Outcome 4 - patients who had symptoms which were consistent with an adverse reaction to food not mediated by IgE (Figure 4, pathway G). This was added later as a 'catch-all' for those with symptoms which are not IgE related but are persistent and troublesome and are not adequately covered by the word 'tolerant'.

4.4.2 Target population size

The target community survey population size was based on previous studies as follows:

Stage 1: In the ECRHSII/EuroPrevall study over all seven centres employing the same sampling frame (patients registered with GPs) 54.9% of an initial sample of 28,269 subjects responded (Burney et al., 2014) similar to that obtained in a previous study of food intolerance undertaken in 1994 (Young et al., 1994). Of these 20% reported an adverse reaction to food and 9.2% to one of the group of 24 priority allergenic foods. It was, therefore, estimated that for the community survey, a sample size of up to 35,000 adults would provide around 4,000-5,000 respondents representative of the UK population. An estimated 1,000-1,500 of those would report some type of adverse reaction to food and 50% of these individuals (~500-750 subjects) were anticipated to report an adverse reaction typical of an IgE-mediated food allergy (i.e. within two hours)

to a food from the list of priority allergenic foods (Burney et al., 2014, Young et al., 1994, Lyons et al., 2019). This would provide estimates of the prevalence of possible IgE-mediated food allergy with 95% CI of 9.4 to 10.6%.

Stage 2: Based on previous studies it was expected that 50% of Stage 1 participants would report adverse reactions with characteristic IgE-mediated symptoms (i.e. possible IgE-mediated food allergy). Considering an anticipated response rate of at least 50% (Burney et al., 2014) it was estimated that 500-750 participants with possible food allergy would respond to invitations to have their adverse food reactions further evaluated in Stage 2. Up to 1,000 age-matched control subjects would also be invited to Stage 2.

Assuming the prevalence of probable food allergy to be 1-2% (Lyons et al., 2019, Nwaru et al., 2014), this was estimated to provide 100-200 cases of probable IgE-mediated food allergy.

Stage 3: Based on a response rate of at least 60% it was estimated that 60-120 Stage 2 participants with probable food allergy would attend for a full Stage 3 clinical evaluation, including food challenge if appropriate. It was also estimated that 70% of participants would have an IgE-mediated food allergy confirmed by clinical evaluation alone, the remainder having IgE-mediated food allergy confirmed by DBPCFC. On this basis it was estimated that between 42-84 individuals with confirmed food allergy would be identified.

For the cohorts there were 1,033 participants at the age 26 years follow-up of IoW 1989 and 595 at the age 18+ years follow-up of MAAS. Based on a 4% rate of probable food allergy seen in the IoW 1989 cohort at 18 years and the approximate 2% of participants in the MAAS cohort with peanut allergy at 8 years of age (Nicolaou et al., 2010), it was estimated that at least 40 cases of probable food allergy would be identified across both the cohorts. As with the community survey participants it was anticipated that 60% of these participants would accept an invitation to a Stage 3 clinical evaluation of whom 70% would have a confirmed IgE mediated food allergy giving at least 17 participants.

4.4.3 Cohort primary analysis: trajectories of food allergy

The prevalence of probable or confirmed IgE-mediated food allergy at age 18+ to 26 years was estimated in the joint IoW 1989 and MAAS datasets. Participants from the population cohorts with probable or confirmed food allergy were divided into childhood (≤ 18 years) and adulthood (18+ or 26 years) onset. The proportions with childhood and adulthood onset were calculated. If more than 26 cases of a particular food allergy were

identified, it was planned that the prevalence would be computed for that allergy. There were not sufficient cases for individual food allergens to undertake this analysis.

Additionally, we calculated the prevalence of possible, probable or confirmed IgE-mediated food allergy and the prevalence of possible non-IgE mediated adverse reaction to food at 18+ to 26 years in the joint IoW 1989 and MAAS dataset.

4.4.4 Cohort secondary analysis: identification of risk factors

The similarities and differences in the relationship between plausible risk factors for confirmed and probable food allergy were assessed in the confirmed and reported childhood and adulthood onset participants.

Two control groups were included:

- 4.4.1.1 Primary control group – all other cohort participants with no self-reported symptoms associated with consumption of food at any time point
- 4.4.1.2 Atopic control group – all other cohort participants with no self-reported symptoms associated with food consumption at any time point and positive SPTs to any of the aeroallergens (e.g. HDM, grass, tree, cat, dog, Alternaria or Aspergillus)

The atopic control group was included to identify risk factors for food allergy rather than just atopy.

From this nested case-control study, for each potential risk factor, we fitted a logistic regression model in which the outcome variables had three categories - control and case: childhood onset, and case: adulthood onset. This approach was prespecified in the data analysis plan to maximise the data in the model and therefore the precision of the estimates. Given the low numbers of adult-onset cases those data are not presented.

The analyses were performed by using the statistical analysis software Stata 18 (StataCorp LLC, Texas, USA).

4.4.5. Community survey data analysis

For the Community survey data cleaning, engineering and analysis were undertaken using a REDCap database (Harris et al., 2019b, Harris et al., 2009b) and R Studio. Deciles of deprivation were assigned to Stage 1 respondents' postcodes using the Ministry of Housing, Communities & Local Government English Indices of Deprivation

2019 Postcode Lookup tool. Prevalence and its CI were calculated using an online calculator (Kohn and Senyak 2019).

5. Results

5.1 Community Survey

The study was designed to sample up to 35,000 residents of Greater Manchester to achieve a population of respondents of between 4,000-5,000 of whom it had been anticipated that about 1,000-1,500 would report an adverse reaction to food. This was based on response rates achieved in the EuroPrevall Community Survey in adults (Lyons et al., 2019, Burney et al., 2014). Against this plan, the implementation of a stratified sample structured on the ONS 2011 census data with regard to age and gender provided a population of 4,828 respondents with complete responses from a total of 29,726 invitees (Figure 5).

The population sample obtained had a balanced demographic profile in terms of age and gender (Figure 6; Table 6) with 53.9% and 45.2% of respondents being female and male, respectively, similar to the gender distribution in the 2011 census (51% females and 49% males). The quotas for age and gender were largely met with oversampling, which was especially marked in the age group 18-29 years old and particularly for males (Figure 6A). Thus, in the final sample, the response rate was 5.5% with only 60% of the quota filled for males aged 18-29 and 8.8% with 81% of the quota filled for males aged 30-39.

To ensure participants had a broad socioeconomic profile, sampling was undertaken in GP practices with catchment areas spanning across low, mid-range and high deciles of deprivation and different degrees of ethnic diversity. Higher response rates were obtained from participants belonging to the most affluent deciles, and consequently these were slightly over-represented with 35% of respondents. The middle deciles were represented by 35% of the population sample with only 30% of respondents coming from deciles 1-3 (Figure 6B). The respondents in PAFA Stage 1 were ethnically diverse and of those respondents who provided data on their ethnicity 77.2% were white (Table 6). This was lower than the 2011 and 2023 census data, with a greater proportion of those of other and mixed ethnicities (Table 6). The majority of respondents agreed to be contacted again, although this rate was higher for those reporting adverse reactions compared to those reporting no adverse reactions (94.2% compared to 86.4%).

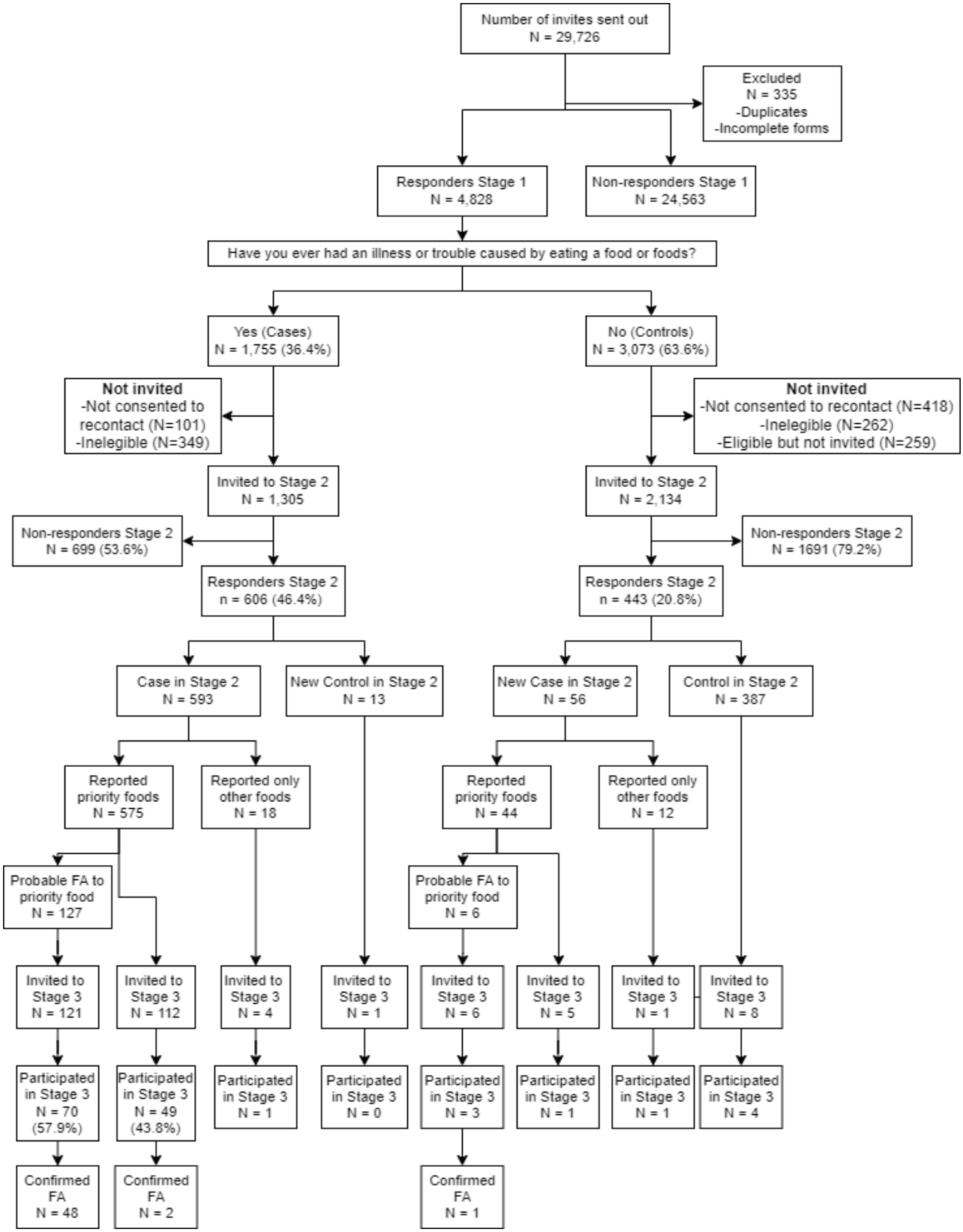


Figure 5. Consort diagram for PAFA Community Survey respondents.

Response rates are given to one decimal place for simplicity.

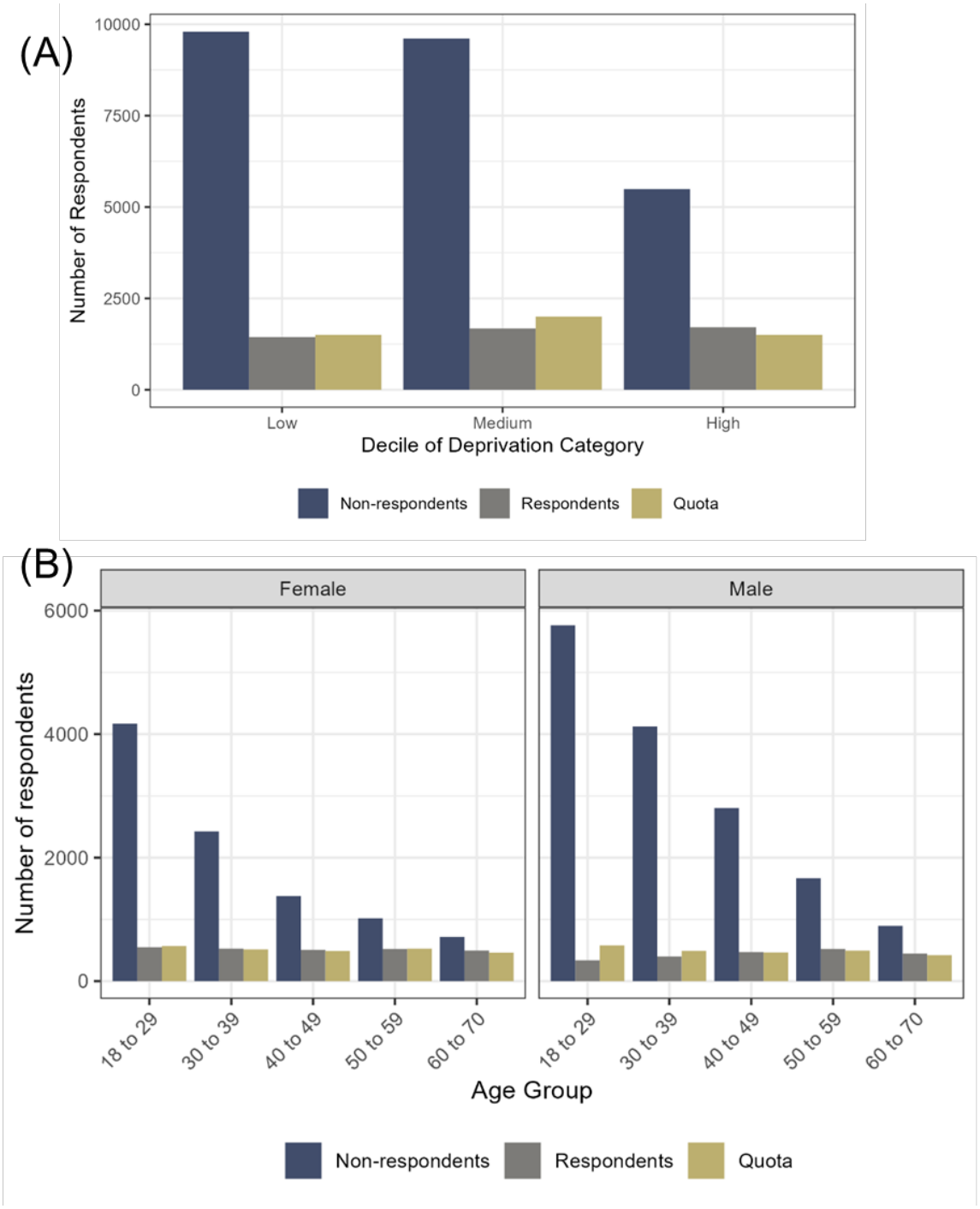


Figure 6. PAFA Stage 1 study responses by decile of deprivation (A) and age and gender (B).

Table 6. Demographics of PAFA Stage 1 respondents

Demographic factor	PAFA Stage 1 Number (%)
Gender - Female	2603 (53.91)
Gender - Male	2180 (45.15)
Gender - Others	18 (0.37)
Gender - Missing	27 (0.56)
Ethnicity – White	3729 (77.24)
Ethnicity – Asian	412 (8.53)
Ethnicity – Black	128 (2.65)
Ethnicity – Mixed	154 (3.19)
Ethnicity – Other	139 (2.88)
Ethnicity – Missing	266 (5.51)
Age – 18-29	903 (18.70)
Age – 30-39	926 (19.18)
Age – 40-49	981 (20.32)
Age – 50-59	1056 (21.87)
Age – 60-70	950 (19.68)
Age – Missing	12 (0.25)
Decile of deprivation – low deciles (1-3)	1438 (29.78)
Decile of deprivation – medium deciles (4-7)	1678 (34.76)
Decile of deprivation – high deciles (8-10)	1712 (35.46)

Quotas are based on data from the ONS 2011 Census for England and Wales were taken from ONS 2012 bulletin. No quota was used for ethnicity or decile of deprivation. ONS2011/2023 census data for ethnicity were as follows: White - 86/81.7%; Asian - 7.5/9.3%; Black- 3/4%; Mixed - 2/2.9%; other - 1/2.1%.

Using the sample frame from Stage 1, participants reporting adverse reactions to food (cases) and those who did not report adverse reactions (controls), were invited to take part in PAFA Stage 2 (Figure 5). After eligibility checks were completed, a total of 1,306 case and 2,134 control participants were invited to Stage 2, of whom 606 (46.4%) and 443 (20.8%), respectively, accepted to participate. The difference in response rates between cases and controls was in part due to differences in the mode of contact since all of the cases were contacted by phone as well as text message, while the majority of the control subjects only received text messages. This difference was a reflection of the capacity of the study team which was only geared for around 1000 participants in Stage 2.

In PAFA Stage 2 certain subjects had their status altered from cases to controls and vice versa, with 13 cases becoming “new” controls and 56 control participants becoming “new” cases. Neither of these “new” groups of respondents were included in the calculations for estimating prevalence since the contact method was different and the control arm respondents had a different and lower response rate and a different demographic profile (Table 7). These participants were included in PAFA Stage 3, where appropriate, as consistent with the commitment to participants to evaluate their potential food allergies but not included in the prevalence calculations (Figure 5).

The majority of cases who participated in PAFA Stage 2 were women (66.50%), consistent with the bias towards females reporting adverse reactions to food observed in PAFA Stage 1 (62.62%). In contrast the gender balance of the control participants reflected that of the PAFA Stage 1 population (Figure 7A). Younger age groups were underrepresented, especially in the control arm, as were those coming from lower deciles of deprivation (Figure 7A, B). Both case and control participants had similar distributions for ethnic diversity, but the numbers for some groups, such as the Asian participants were lower at 5.45-5.64% for Stage 2 participants compared to 8.53% of the Stage 1 population.

Table 7. Demographics of PAFA Stage 1 participants reporting adverse reactions to a priority allergenic food who participated in PAFA Stage 2.

Demographic factor	Cases group (%)	Control group (%)
Gender - Female	403 (66.50)	224 (50.56)
Gender - Male	202 (33.33)	213 (48.08)
Gender - Others	0 (0)	4 (0.90)
Gender - Missing	1 (0.17)	2 (0.45)
Ethnicity – White	502 (82.84)	370 (83.52)
Ethnicity – Asian	33 (5.45)	25 (5.64)
Ethnicity – Black	12 (1.98)	8 (1.81)
Ethnicity – Mixed	25 (4.13)	12 (2.71)
Ethnicity – Other	17 (2.81)	7(1.58)
Ethnicity – Missing	17 (2.81)	21 (4.74)
Age – 18-29	87 (14.36)	30 (6.77)
Age – 30-39	128 (21.12)	57 (12.86)
Age – 40-49	127 (20.96)	102 (23.02)
Age – 50-59	144 (23.76)	112 (25.28)
Age – 60-70	119 (19.64)	142 (32.05)
Age – Missing	1 (0.17)	0 (0)
Decile of deprivation – low deciles (1-3)	137 (22.61)	99 (22.35)
Decile of deprivation – medium deciles (4-7)	228 (37.62)	138 (31.15)
Decile of deprivation – high deciles (8-10)	241 (39.77)	206 (46.50)

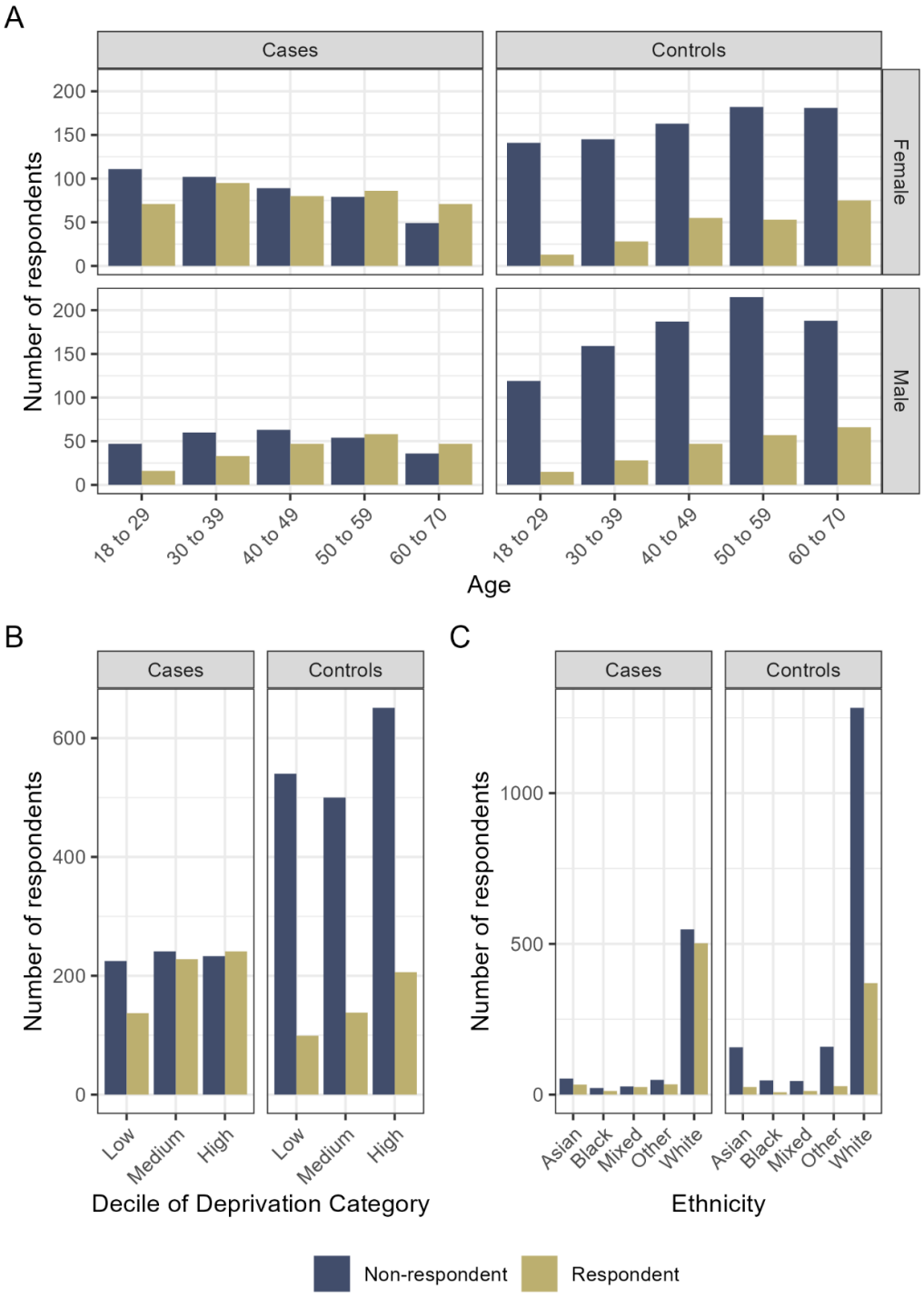


Figure 7. Demographic characteristics of responders and non-responders in PAFA Stage 2 cases and control subjects

Distributions are as follows: A - Age and gender; B – Decile of deprivation (low - deciles 1-3; medium – deciles 4-7; high – deciles 8-10); C - Ethnicity

Overall, 258 community survey Stage 2 participants were invited to Stage 3, of whom 129 attended a clinical assessment (50.00% response rate overall) with 51 Stage 3 participants having their IgE-mediated food allergy clinically confirmed (Figure 5, Figure

8, Table 8). Of those invited 121 were cases with a probable food allergy to a priority food representing all but six of the participants with a probable IgE-mediated food allergy from Stage 2. Amongst these cases there were 70 who attended for a clinical assessment (57.85% response rate) with 48 having their food allergy confirmed. Stage 3 also included 116 Stage 2 cases who had reported a reaction only to a non-priority food, or those in whom further clinical evaluation was deemed necessary to exclude a food allergy. For example, SPT was only performed to shrimp and serum specific IgE testing was only performed to an allergen from one shrimp species (Penaeus aztecus, Pen a 1) - where a participant reported reacting to crustacean shellfish – therefore participants were invited to a clinical assessment and further testing to exclude allergy to other crustaceans. The last category of participants did not meet the definition of having a probable food allergy but were either sensitised to a food they do not eat or required further confirmatory testing, such as prick to prick testing with fresh foods. Of the 50 “case” participants who attended for clinical assessment (43.10% response rate), a further two individuals had a food allergy confirmed.

The Stage 3 population was still dominated by females, although less so than for cases in Stage 1 and was still ethnically diverse. There was further underrepresentation of those aged 18-29 and those coming from low deciles of deprivation (Table 8).

Table 8. Demographics of participants in PAFA Stage 3

Demographic factor	Number of participants (%)
Gender - Female	82 (63.57)
Gender - Male	47 (36.43)
Gender - Others	0 (0)
Gender - Missing	0 (0)
Ethnicity – White	104 (80.62)
Ethnicity – Asian	10 (7.75)
Ethnicity – Black	4 (3.10)
Ethnicity – Mixed	3 (2.33)
Ethnicity – Other	3 (2.33)
Ethnicity – Missing	5 (3.88)
Age – 18-29	17 (13.18)
Age – 30-39	24 (18.60)
Age – 40-49	30 (23.25)
Age – 50-59	31 (24.03)
Age – 60-70	26 (20.16)
Age – Missing	1 (0.78)
Decile of deprivation – low deciles (1-3)	22 (17.05)
Decile of deprivation – medium deciles (4-7)	49 (37.98)
Decile of deprivation – high deciles (8-10)	58 (44.96)

From Stage 2 control participants 20 were invited for a Stage 3 assessment of whom: 6 were “new” cases identified in Stage 2 as having a probable IgE-mediated food allergy; 5 were “new” cases who had been invited to exclude food allergy; and 1 was a “new” case who reported only non-priority foods. A further 8 control participants were also invited to Stage 3 to exclude food allergy based on the results of serological testing. There were also 9 control subjects who attended for a Stage 3 assessment (response rate of 45%) of whom only 1 individual with a probable food allergy had their allergy confirmed.

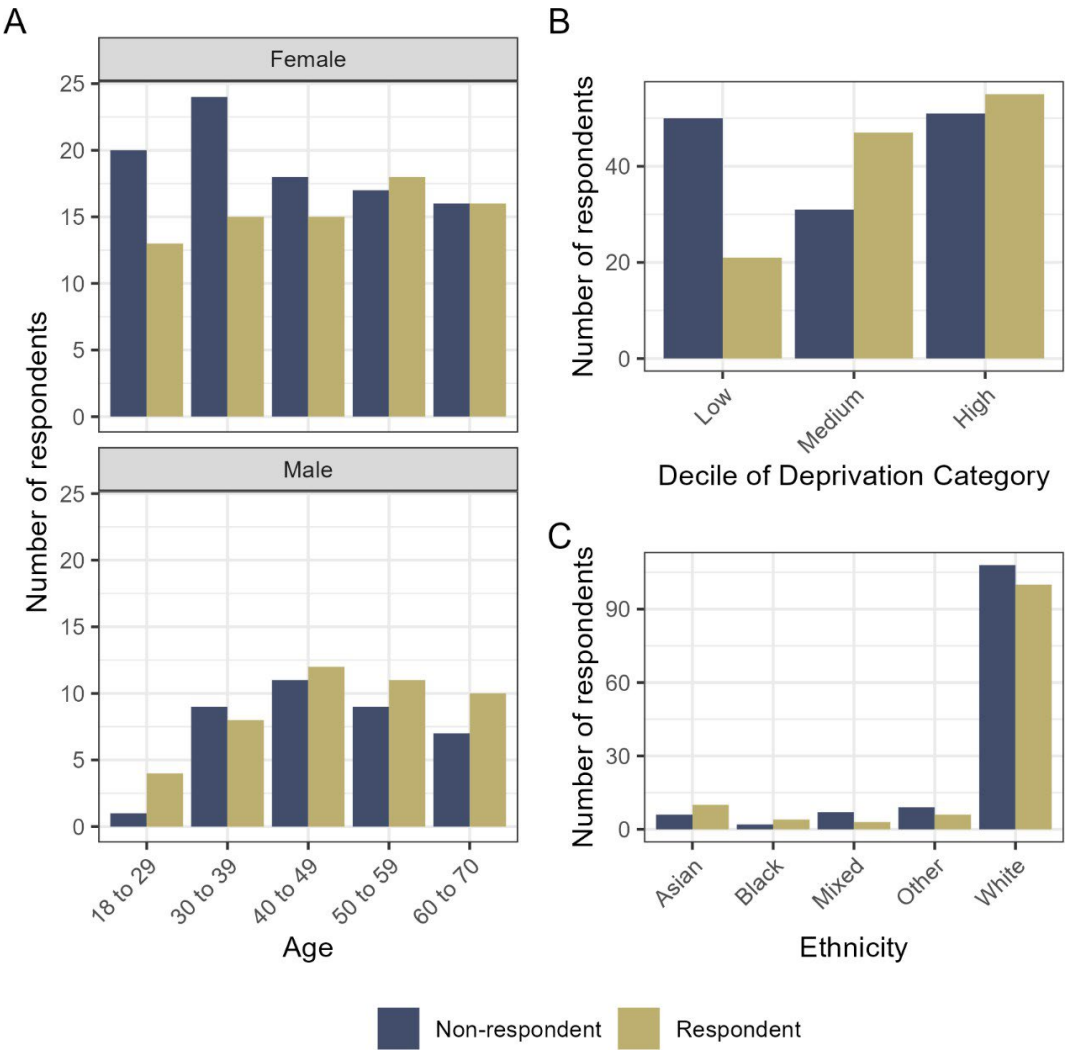


Figure 8. Demographic characteristics of responders and non-responders in PAFA Stage 3.

Distributions are as follows: A - Age and gender; B – Decile of deprivation (low - deciles 1-3; medium – deciles 4-7; high – deciles 8-10); C – Ethnicity

5.1.1. Characteristics of the population reporting adverse reactions to foods

Of the 4,828 participants in Stage 1, 1,755 reported an adverse reaction to food giving an estimated prevalence of 36.35% (35.00-37.71, 95% CI) (Figure 9A) with the majority

reporting a reaction onset of less than 2 hours (Figure 9B). The majority (66%) of these participants were female and 6.4% (5.74 – 7.13, 95% CI) reported having had a doctor diagnosed food allergy. The majority reported adverse reactions to PAFA priority foods (n= 1,425, 81.20%), giving an estimated prevalence of 29.51% (28.25-30.82 95%CI) (Figure 9). Reactions to foods that are included in Annex II of the UK mandatory food allergen labelling list (UK Food Information for Consumers regulation 2014) were reported by 1,253 participants. Of the participants reporting an adverse reaction to a priority food, 42.53% reported a reaction to only one food, with 45.47% reporting reactions to between 2-5 foods and the remaining 12.00% reporting reactions to more than five foods.

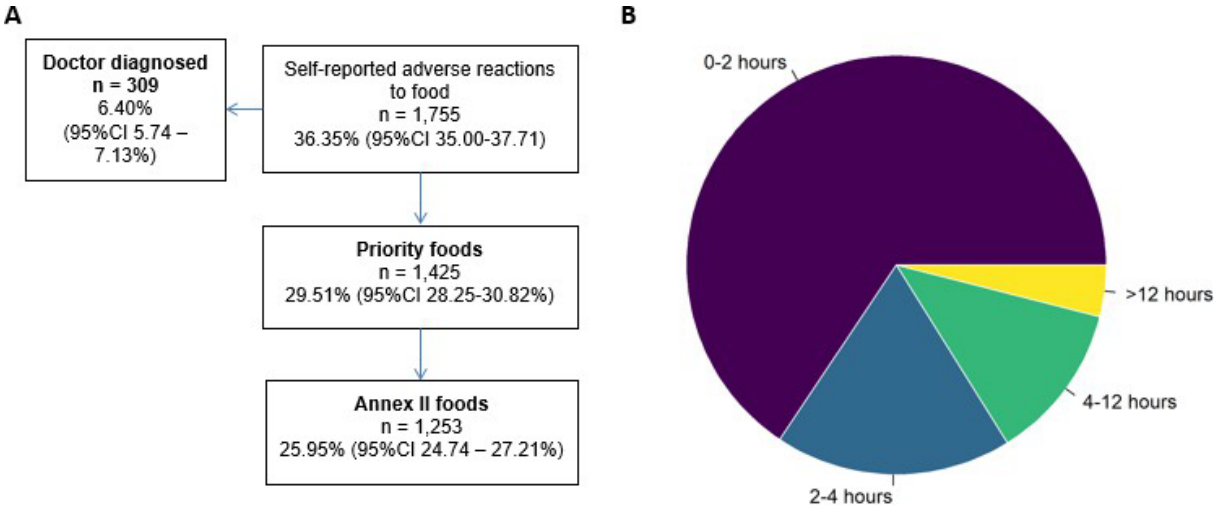


Figure 9. Characteristics of the PAFA Stage 1 population reporting adverse reactions regarding (A) types of foods reported and (B) time of onset of reaction.

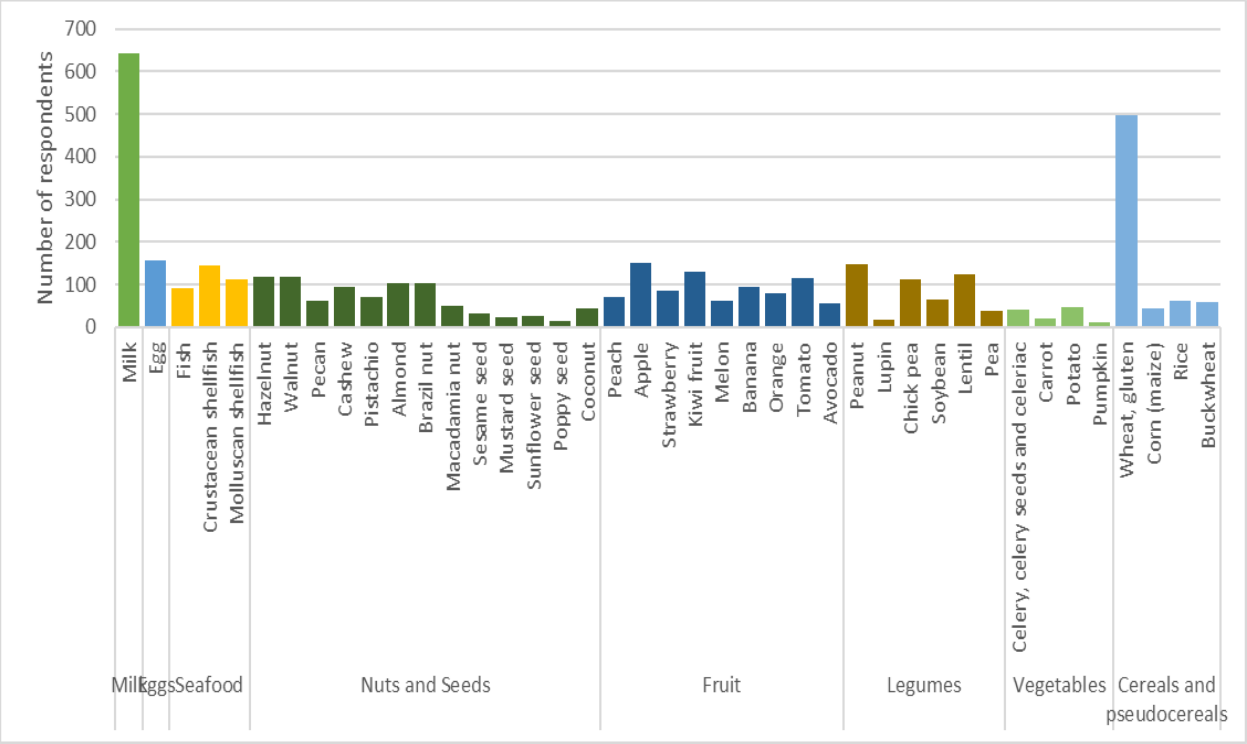


Figure 10. PAFA Stage 1 Patterns of self-reported reactions to priority food

The majority of Stage 1 participants with adverse reactions to food reported they were triggered after consumption of milk and cereals containing gluten, equating to 13.28% and 10.27% respectively of the entire Stage 1 population of 4,828 participants (Figure 10). Of those reporting reactions to other priority foods, 3.21% were to egg, 2.32-2.98% to molluscan and crustacean shellfish, and 1.91% to fish. Of plant derived foods the second most commonly reported food was peanut (3.04%) and tree nuts which ranged from 2.42% for both hazelnut and walnut, to only 1.06% for macadamia nut. Reactions to fresh fruit were more common with 2.36% of individuals reporting reactions to apple and 2.15% to kiwi. The least frequently reported foods were pumpkin and poppy seed (0.10 and 0.17%, respectively), whilst only about 0.29% of the reported reactions were to foods such as mustard, sunflower seed and as well as lupin (Figure 10).

The data from Stage 2 cases were then used to calculate the prevalence of adverse reactions to foods. Since the gender and age profile of case respondents in Stage 2 was broadly similar to the profile of those reporting adverse reactions to food in Stage 1, the attrition between Stage 1 and Stage 2 together with the 45.44 % response rate for cases (593 respondents of 1,305 invitees) were taken into account to calculate the crude prevalence. In Stage 2, 575 of the 1,253 Stage 1 participants who reported a reaction to a priority food giving a crude estimated prevalence of adverse reactions to a priority food in this group of 33.68% (31.48-35.96, 95% CI; 575 out of 1707), higher than that

observed in Stage 1 (estimated prevalence of 29.51% (28.25-30.82, 95% CI). The prevalence of self-reported adverse reactions to Annex II foods was also higher than that in Stage 1 (31.05 % for Stage 2 versus 29.51% in Stage 1).

Of the 606 cases who participated in Stage 2, 10.23% reported having a doctor diagnosed food allergy, giving a crude estimated prevalence of a doctor diagnosed food allergy of 3.63% (2.84–4.63, 95% CI) almost half of that observed in Stage 1. The differences in the crude prevalence of adverse reactions to PAFA priority foods between Stage 1 and Stage 2 may reflect either a selection bias in the Stage 2 case respondents and/or the different way in which the question was posed in Stage 2, providing many more options than the Stage 1 screening questionnaire. The most commonly reported diagnosis was for IBS (11.60%) with around 1% reporting they had been told by a doctor they had coeliac disease. These results are similar to the ones reported in a mass screening project for the UK (Mustalahti et al., 2010) (Figure 12).

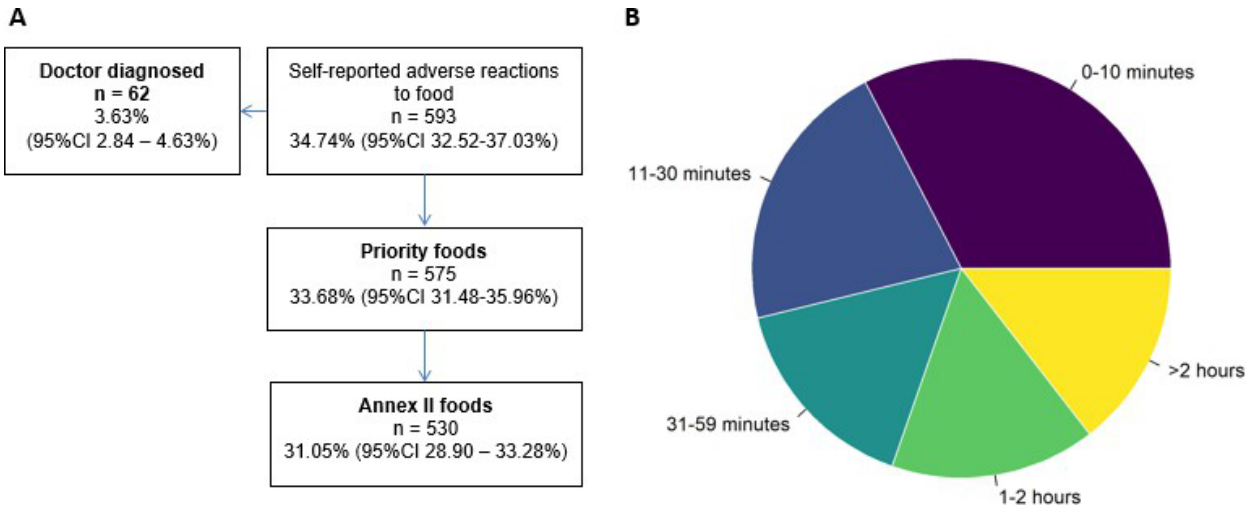


Figure 11. Prevalence of self-reported adverse reactions to food in the PAFA Stage 2 case population

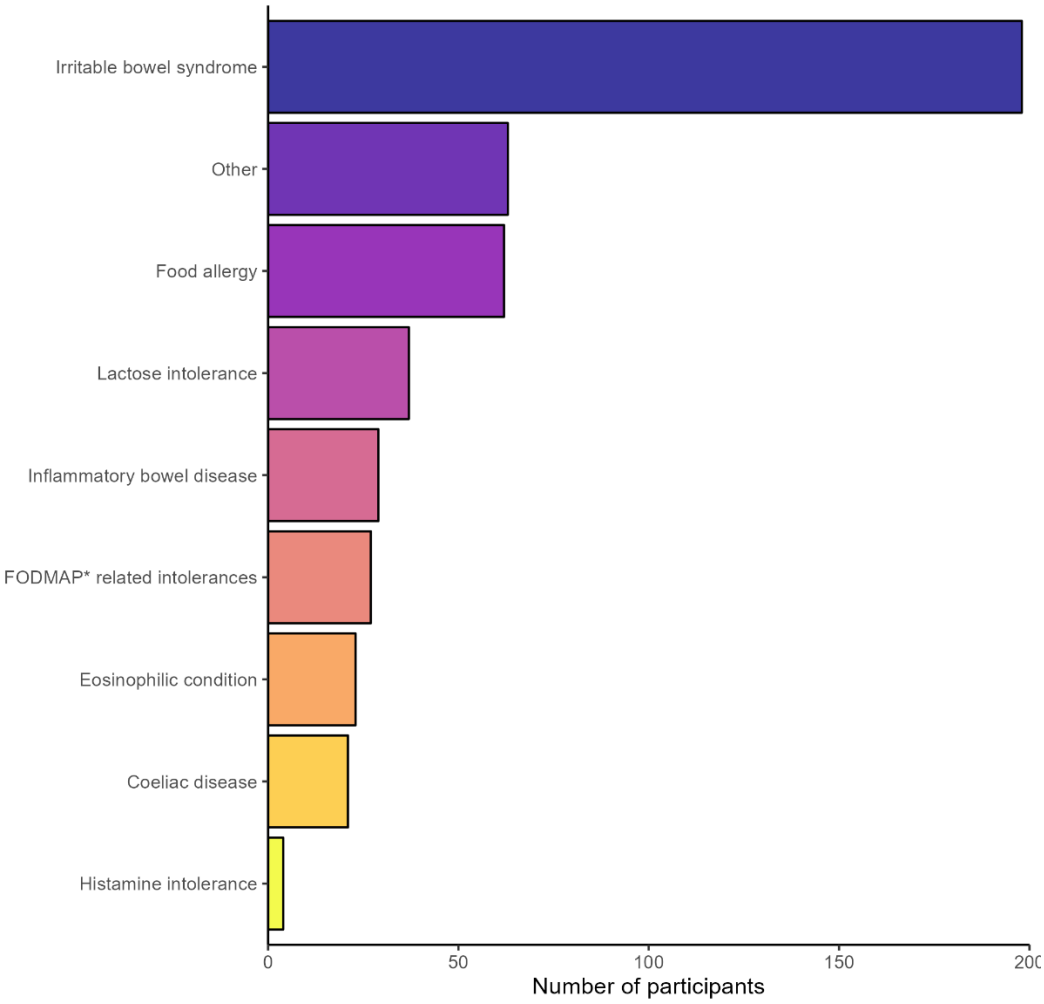


Figure 12. Self-reported doctor diagnosed adverse reactions to foods in PAFA Stage 2

5.1.2 Possible and probable, IgE- mediated adverse reactions to food

Individuals reporting reactions to a priority allergenic food in Stage 1 were classified as either having a possible IgE-mediated adverse reaction or a possible non-IgE-mediated adverse reaction to food (Figure 13) using the definitions provided in section 5.5.

In Stage 1, a total of 886 individuals reported a reaction to a priority food which could be classified as a possible IgE-mediated food allergy giving a crude estimated prevalence of 18.35% (17.27-19.47, 95%CI; 886 out of 4828). The food-by-food prevalence cannot be calculated since the time of onset of reaction was not reported for each food at Stage 1. The majority of those reporting a reaction were female (66%), 51.50% of whom were aged 18-39. The gender difference in reporting adverse reactions was smaller in older age groups. The overall ethnicity was well balanced and represented the UK population, although the proportion of those of white and mixed ethnicity were slightly increased compared to those of Asian, black and other ethnicity (Figure 14).

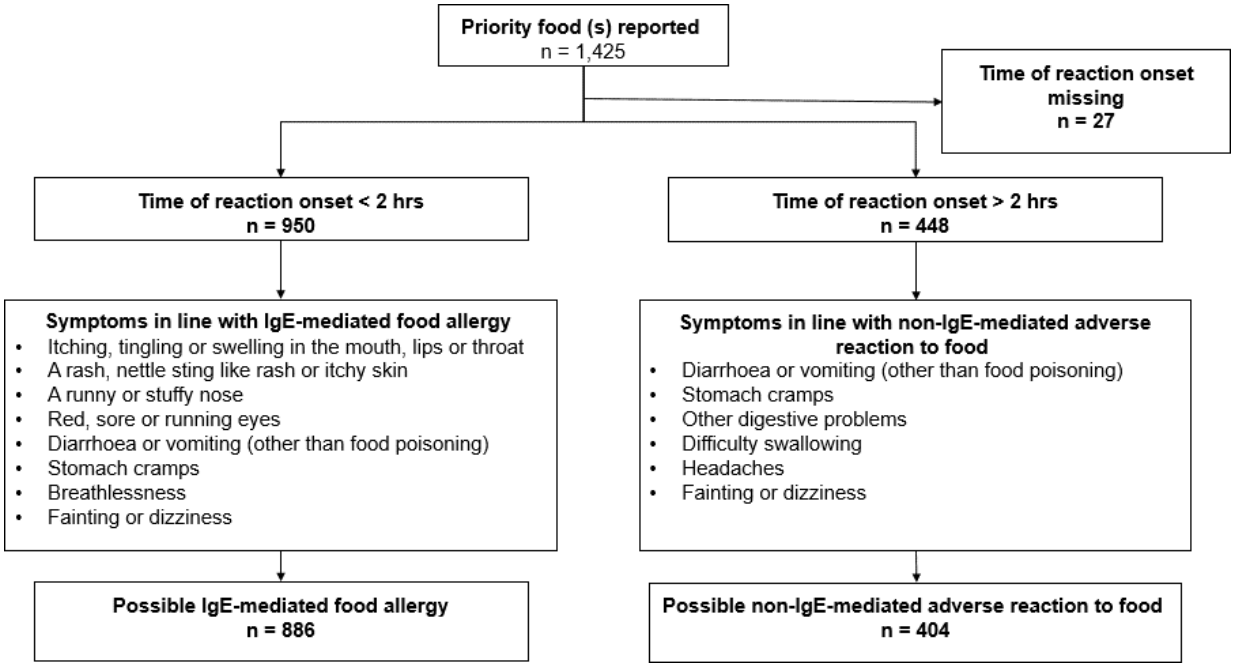


Figure 13. Stratification of PAFA Stage 1 participants into those with possible IgE and possible non-IgE mediated adverse reactions to any priority food.

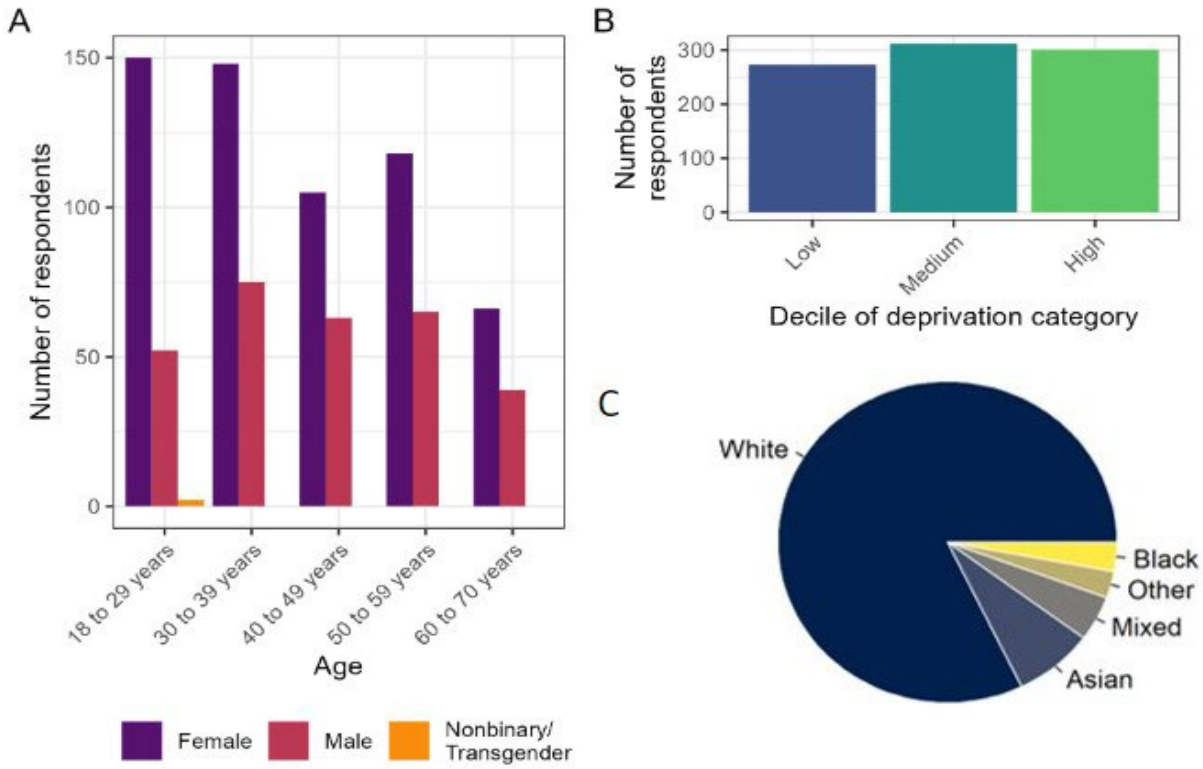


Figure 14. Demographic characteristics of the population reporting a possible IgE mediated adverse reactions to at least one priority food in PAFA Stage 1.

Responses were analysed by: A – gender and age; B – deciles of deprivation and C – ethnicity.

Of all the reactions reported by participants with a possible IgE-mediated food allergy, the majority were to milk and cereals containing gluten (44.69% and 31.71%, respectively, of all reported reactions) (Figure 15). Reactions to animal food ranged from almost 11.5% of participants reporting reactions to egg, and between 7.7-10.2% to molluscan and crustacean with 6% reporting a reaction to fish. Of plant derived foods the second most frequently reported food was peanut (13.5%) and tree nuts (which ranged from 11.7 - 11.4% for hazelnut and walnut to only 5% for macadamia nut). Reactions to fresh fruit were more common with 12.8% of individuals reporting reactions to apple and 11.7% to kiwi. The least reported foods were poppy seed and pumpkin (~0.5-1%) whilst only 1.5% reported reactions to mustard and sunflower seed as well as lupin (Figure 15). Many individuals reported reactions to multiple foods, with 25% reporting two foods and 14% reporting reactions to more than five foods.

Taking into account the Stage 2 response rate for cases (see section 5.1.1), the prevalence of self-reported possible IgE-mediated food allergy to each of the priority foods in Stage 2 was then estimated (Table 9). Using these data the crude estimated prevalence of a possible IgE-mediated reaction to at least one priority food was 29.00% (26.85-31.21, 95% CI). This rate is higher than that estimated from the Stage 1 data because Stage 2 participants reported the symptoms they experienced and time of onset of reaction for each of the priority foods. This contrasts with Stage 1 where symptoms and time of onset were only reported once and not on a food-by-food basis. In addition, the list of priority foods was extended in Stage 2 to include chicken and beef together with bell pepper. The difference in response rates may also reflect a bias in the Stage 2 population of respondents. The crude estimated prevalence of possible IgE-mediated reactions to cow's milk was 13.53 % (11.94-15.25, 95% CI) and 10.54% to cereals containing gluten (9.13-12.1, 95% CI) (Table 9). Other important food groups were tree nuts, fresh fruits (especially apple, kiwi and tomato) and legumes such as peanut, chickpeas and lentils. The least reported foods were mustard, pumpkin and poppy seeds with other seeds, such as sunflower and lupin being very low.

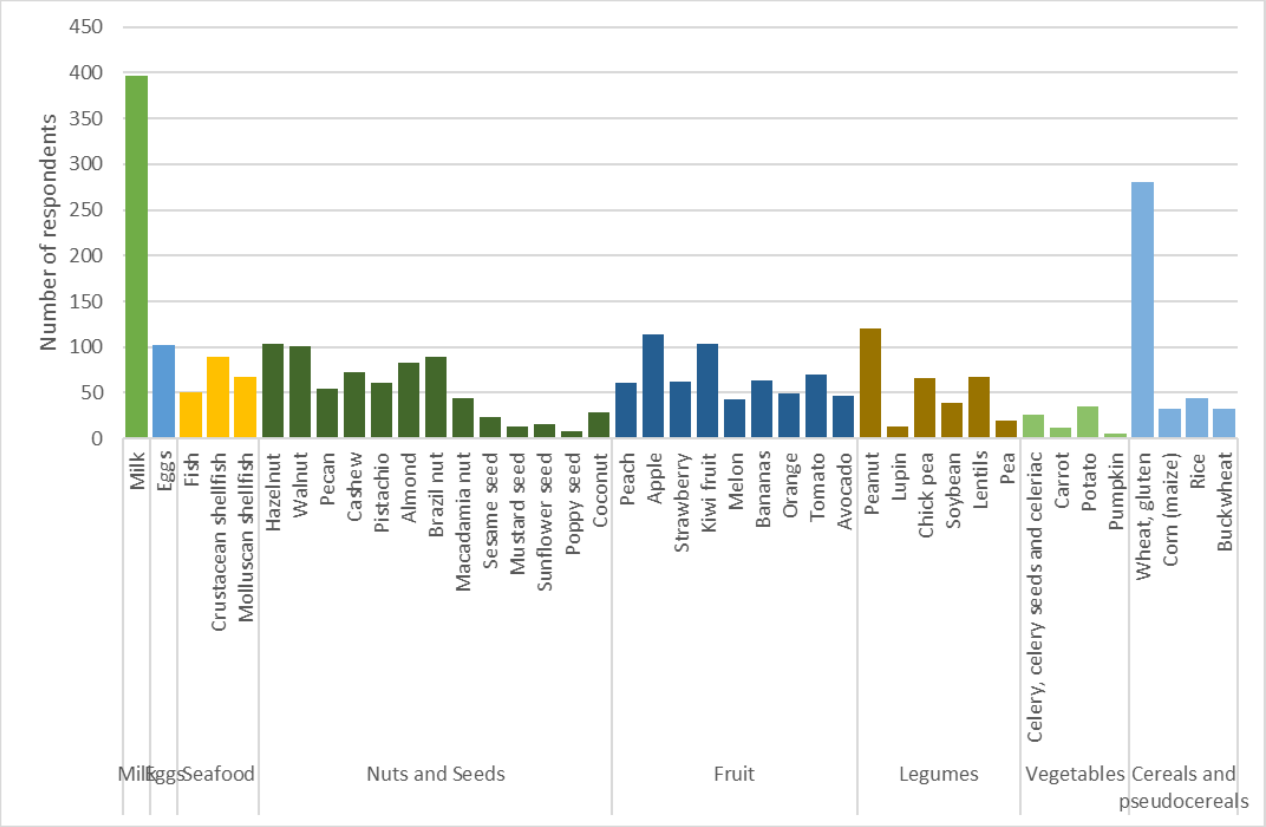


Figure 15. Self-reported possible IgE-mediated reactions to priority foods in PAFA Stage 1

The prevalence of probable IgE-mediated food allergy was then estimated based on the symptom profile, time of onset of a reaction and sensitisation to the same food (Table 9). Sensitisation was established using serum specific IgE to either the food itself or a component, together with SPT results where available. The demographic profile of this population is presented in Figure 16 and reflects that of the participants with a possible IgE-mediated food allergy, with a greater proportion of female compared to male participants aged 18-39 and maintaining ethnic diversity.

Table 9. Crude estimated prevalence of adverse reactions to priority foods.

Figures are given as a percentage with (95% CI). No surrogate available - for certain foods no serum specific IgE analysis or SPT testing was performed and no relevant surrogate marker or SPT test was available.

Food type	Stage 2 - Possible IgE-mediated food allergy	Stage 2 - Possible non- IgE adverse reaction to food	Stage 2 - Probable IgE-mediated food allergy
At least one priority food	29.00 [26.85-31.21]	6.85 [5.7-8.16]	7.44 [6.24-8.79]
Beef	0.64 [0.32-1.15]	0.29 [0.1-0.68]	0 [0-0.22]
Chicken	0.35 [0.13-0.76]	0.35 [0.13-0.76]	No surrogate available
Crustacean Shellfish	2.75 [2.03-3.64]	0.53 [0.24-1.00]	0.53 [0.24-1.00]
Egg	3.57 [2.74-4.57]	0.47 [0.20-0.92]	0.23 [0.06-0.60]
Fish	1.41 [0.90-2.08]	0.12 [0.01-0.42]	0.29 [0.10-0.68]
Milk	13.53 [11.94-15.25]	1.99 [1.38-2.77]	0.64 [0.32-1.15]
Molluscan Shellfish	2.69 [1.98-3.58]	0.53 [0.24-1.00]	0.06 [0.00 -0.33]
Wheat and cereals containing gluten	10.54 [9.13-12.1]	2.4 [1.73-3.24]	0.00 [0.00-0.22]
Rice	1.46 [0.95-2.15]	0.12 [0.01-0.42]	No surrogate available
Buckwheat	0.88 [0.49-1.45]	0.00 [0.00 -0.22]	No surrogate available
Corn	1.05 [0.63-1.66]	0.00 [0.00 -0.22]	No surrogate available
Apple	4.10 [3.21-5.15]	0.41 [0.17-0.84]	2.23 [1.58-3.04]

Avocado	1.11 [0.67-1.73]	0.06 [0.00-0.33]	0.23 [0.06-0.6]
Bananas	2.23 [1.58-3.04]	0.23 [0.06-0.60]	0.41 [0.17-0.84]
Kiwi	4.10 [3.21-5.15]	0.18 [0.04-0.51]	1.82 [1.24-2.57]
Melon	1.35 [0.86-2.01]	0.12 [0.01-0.42]	0.23 [0.06-0.6]
Orange	2.05 [1.43-2.84]	0.35 [0.13-0.76]	0.12 [0.01-0.42]
Peach	2.23 [1.58-3.04]	0.06 [0.00-0.33]	1.41 [0.9-2.08]
Strawberry	1.99 [1.38-2.77]	0.12 [0.01-0.42]	0.70 [0.36-1.22]
Tomato	3.34 [2.54-4.30]	0.12 [0.01-0.42]	1.00 [0.58-1.59]
Chickpea	2.17 [1.53-2.98]	0.53 [0.24-1.00]	0.12 [0.01-0.42]
Lentils	1.87 [1.29-2.64]	0.64 [0.32-1.15]	No surrogate available
Lupin	0.35 [0.13-0.76]	0.00 [0.00 -0.22]	0.00 [0.00-0.22]
Pea	0.82 [0.45-1.37]	0.35 [0.13-0.76]	No surrogate available
Peanut	3.40 [2.59-4.37]	0.29 [0.10-0.68]	1.76 [1.19-2.50]
Soybean	1.58 [1.04-2.29]	0.35 [0.13-0.76]	0.23 [0.06-0.60]
Almond	2.17 [1.53-2.98]	0.29 [0.10-0.68]	1.29 [0.81-1.94]
Brazil Nut	2.34 [1.68-3.18]	0.23 [0.06-0.60]	1.52 [1.00-2.22]
Cashew	2.34 [1.68-3.18]	0.41 [0.17-0.84]	1.17 [0.72-1.80]
Coconut	0.94 [0.54-1.52]	0.12 [0.01-0.42]	0.06 [0.00-0.33]
Hazelnut	2.81 [2.08-3.71]	0.18 [0.04-0.51]	2.05 [1.43-2.84]
Macadamia Nut	1.05 [0.63-1.66]	0.12 [0.01-0.42]	0.47 [0.20-0.92]
Mustard Seed	0.82 [0.45-1.37]	0.18 [0.04-0.51]	No surrogate available
Pecan	1.46 [0.95-2.15]	0.23 [0.06-0.6]	0.88 [0.49-1.45]

Pistachio	1.35 [0.86-2.01]	0.29 [0.1-0.68]	0.64 [0.32-1.15]
Poppy Seed	0.18 [0.04-0.51]	0.12 [0.01-0.42]	0.06 [0.00-0.33]
Sesame Seed	1.17 [0.72-1.8]	0.23 [0.06-0.6]	0.53 [0.24-1.00]
Sunflower Seed	0.18 [0.04-0.51]	0.18 [0.04-0.51]	0.00 [0.00-0.22]
Walnut	3.28 [2.49-4.24]	0.35 [0.13-0.76]	2.11 [1.48-2.91]
Bell pepper	1.93 [1.33-2.7]	0.12 [0.01-0.42]	0.00 [0.00 -0.22]
Carrot	0.47 [0.2-0.92]	0.00 [0.00 -0.22]	0.18 [0.04-0.51]
Celery	0.82 [0.45-1.37]	0.12 [0.01-0.42]	0.23 [0.06-0.60]
Potato	0.88 [0.49-1.45]	0.12 [0.01-0.42]	0.00 [0.00 -0.22]
Pumpkin	0.23 [0.06-0.6]	0.06 [0-0.33]	No surrogate available

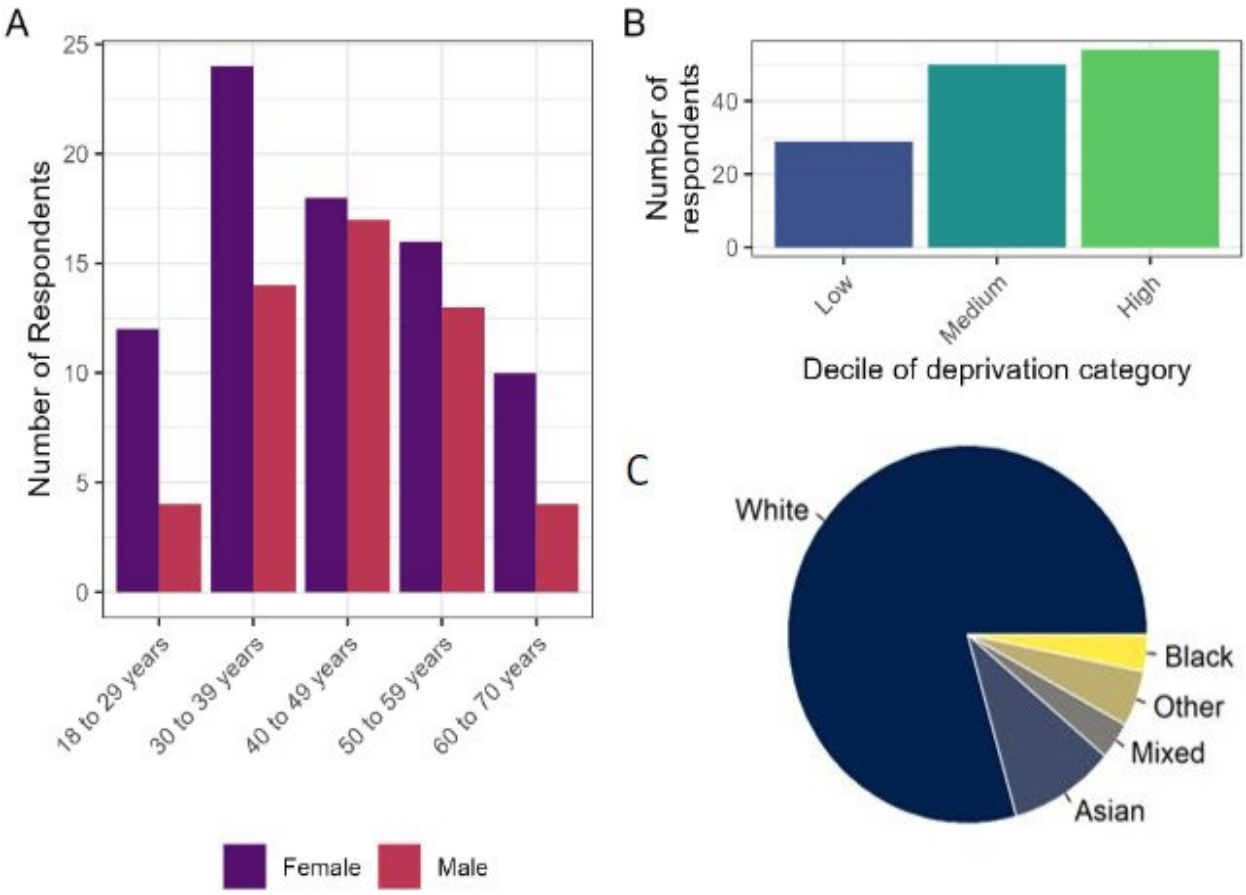


Figure 16. Demographic characteristics of the population who reported a probable IgE-mediated adverse reaction to at least one priority food in PAFA Stage 2.

Responses were analysed by: A – gender and age; B – deciles of deprivation; C- ethnicity.

The prevalence of probable IgE-mediated food allergy was much lower than that of possible IgE-mediated food allergy. Due to either incomplete food specific IgE testing or a lack of effective surrogate markers, the prevalence of probable food allergy could not be estimated for certain foods (Table 9). Using this approach and adjusting for response rates (see section 5.1.1) the crude estimated prevalence of probable IgE-mediated food allergy to at least one priority food was 7.44% (6.24-8.79, 95% CI). Prominent foods were tree nuts for which the crude estimated prevalence ranged from 2.11% (1.7- 2.91, 95% CI) for walnut and 2.05% (1.43-2.84, 95% CI) for hazelnut to 0.47% (0.20-0.92, 95% CI) for macadamia nut. The prevalence of probable allergy to peanut was also high at 1.76 % (1.19-2.50, 95% CI). Fruit was an important food category in giving rise to probable IgE food allergy with the prevalence of probable kiwi fruit allergy estimated at 1.82% (1.24-2.57, 95% CI). Surrogate markers together with supplementary testing indicated that the prevalence of apple and peach probable IgE-mediated allergy was higher at 2.23% (1.58-

3.04, 95% CI) and 1.41% (0.9-2.08, 95% CI), respectively. The prevalence of probable IgE-mediated food allergy to animal-derived foods was much lower than that to plant-derived foods as milk was estimated at 0.64% (0.32-1.15, 95% CI), crustacean shellfish at 0.53% (0.24-1.00, 95% CI) and hen's egg at 0.23% (0.06-0.60, 95% CI). Uncommon probable allergies to foods for which allergen labelling is required included celery and soybean as both showed a prevalence of probable IgE-mediated food allergy at 0.23% (0.06-0.60 95%CI), whilst molluscan shellfish estimated at 0.06% (0.00-0.33, 95% CI) and for cereals containing gluten at 0.00% (0.00-0.22, 95% CI).

More than half of those with either possible or a probable food allergy had allergies to more than one food (Figure 17). Almost one third (27.82%) of those with a probable food allergy reported that their allergy developed in childhood, with 47.37% reporting adult-onset food allergy and a remaining 24.81% of participants reporting they had both childhood and adult-onset food allergies.

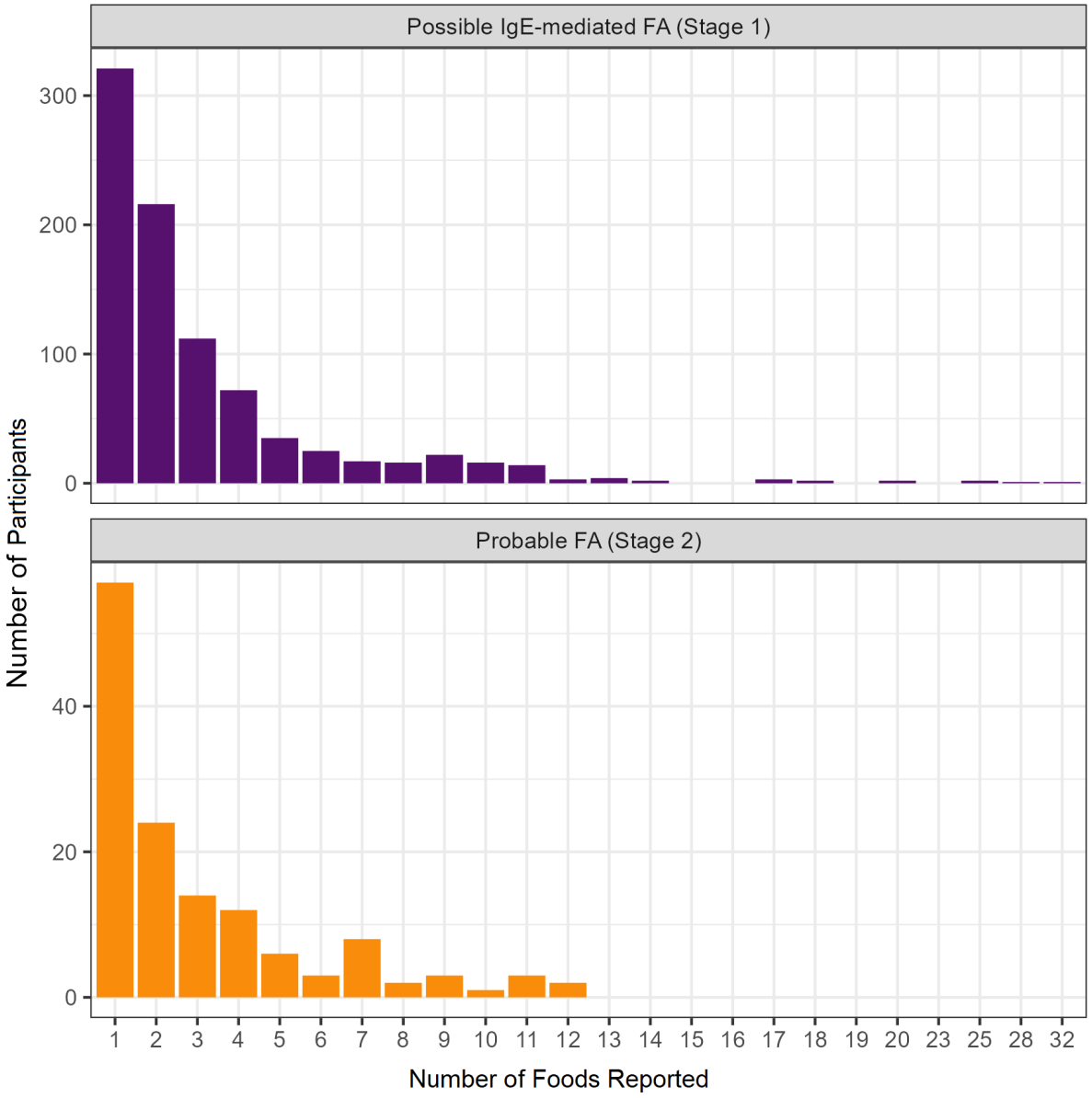


Figure 17. Number of foods reported by PAFA participants with either possible IgE mediated allergy to a priority food from Stage 1 or probable IgE-mediated allergy to a priority food in Stage 2.

5.1.3 Patterns of sensitisation to food

As explained in section 4.3, all sera of cases and controls enrolled in stage 2 were tested for specific IgE using a core panel of foods, components and inhalant allergens. The panel was designed to pick up the most important food sensitisations and establish their likely origin of (primary) sensitisation (designated “core” panel in Figure 18). In addition, when warranted, sera were tested on additional foods and/or components to confirm or reject probable food allergy and/or to establish the likely source of primary sensitisation (designated “extended” in Figure 18). In total, 69 extra foods and 17 additional components were included in the extended panel. The left panels in Figure 18 show the

distribution of negative (<0.1 U/L), borderline (≥ 0.1 and < 0.35 kU/L) and positive (≥ 0,35 kU/L) for cases (Figure 18A) and controls (Figure 18C). Figure 18B shows the distribution of negative, borderline and positive results of the extended panel for cases.

There are a few observations to be highlighted with respect to the data collected. The most common sensitisations are against HDM and grass pollen, with their ranking being opposite for cases and controls. The slightly higher importance of grass pollen for cases can most likely be - at least partially - explained by the cross-reactivity between the grass pollen profilin and closely related profilin homologues in plant foods. The third most important sensitisation is to Bet v 1, used as surrogate for birch pollen sensitisation, and for its dominant role in PFS. Within the core panel there are several foods that are well-established for their potential cross- reactivity to pollen due to Bet v 1 sensitisation such as hazelnut, walnut, kiwi and peanut. It is striking that Bet v 1 sensitization and hazelnut sensitisation go together almost without exception: of participants sensitised to Bet v 1, 86.73% of cases and 91.18% of controls were also sensitised to hazelnut. For the other foods, the concordance is far less obvious. This difference can be explained by the fact that the hazelnut ImmunoCAP is spiked with Cor a 1, the hazelnut homologue of Bet v 1, to increase the test sensitivity for specific IgE. This strategy was not implemented in the ImmunoCAP system for the other foods tested. Another observation is that 15.65% of Stage 2 participants with Bet v 1 sensitisation do not report food allergy (controls), although their serum IgE does cross- react to foods. This is indicated by their positive IgE test results against the typical Bet v 1- associated foods meaning that not all cross-reactive antibodies translate into clinical PFS.

Amongst those sensitised to Bet v 1-associated foods, sensitisation to the marker proteins for primary sensitisation to these foods (hazelnut: Cor a 14; walnut: Jug r 1; sesame seed: Ses i 1; kiwi: Act d 1; peanut: Ara h 2) is much less common. Exceptions are Brazil nut and cashew nut, where Bet v 1 cross-reactivity seems to play a minor role, with the majority being sensitised to their 2S albumin components Ber e 1 and Ana o 3, respectively, pointing to the fact that patients are directly sensitised by these tree nuts.

Sensitisation to profilin (grass pollen Phl p 12), also implicated in pollen-food cross-reactivity, is much rarer, although overall sensitisation to grass pollen is more common than birch pollen. The most likely explanation is that sensitisation to pollen profilin only occurs in highly grass pollen sensitised patients, suggesting that profilin is a minor protein in pollen, whereas Bet v 1 is a very dominant protein (up to 20% of total protein) facilitating sensitisation more easily.

Another cross-reactive allergen, albeit mainly between plant foods (and to a much lesser extent with pollen), is Pru p 3, i.e. the lipid transfer protein from peach. This allergen is associated with more severe symptoms, and sensitisation was originally thought to be found only in the Mediterranean area. In fact, in this survey, sensitisation to Pru p 3 is more common than to tree nuts, sesame seed and peanut 2S albumins.

Very little sensitisation was detected towards certain foods that are on the labelling directive, i.e., fish, molluscs (using blue mussel as representative species), mustard seed, wheat, lupin, and soybean. On the other hand, sensitisation to milk and egg were quite common, but mostly seen in those who were regularly eating the food without symptoms, often in the setting of a very high total IgE. Sensitisation to shrimp was quite common, among both cases and controls, and most commonly seen in those with sensitisation to HDM but not associated with symptoms on ingestion of the food.

Sensitisation to apple was very common within the extended panel, most likely due to primary sensitisation to Bet v 1. Also, sensitisation to peach is likely explained by this. A few tree nuts that were not in the core panel were also found to be quite frequently positive, i.e., pistachio, pecan and macadamia. Finally, IgE against banana and cherry was also detected in a considerable number of patients.

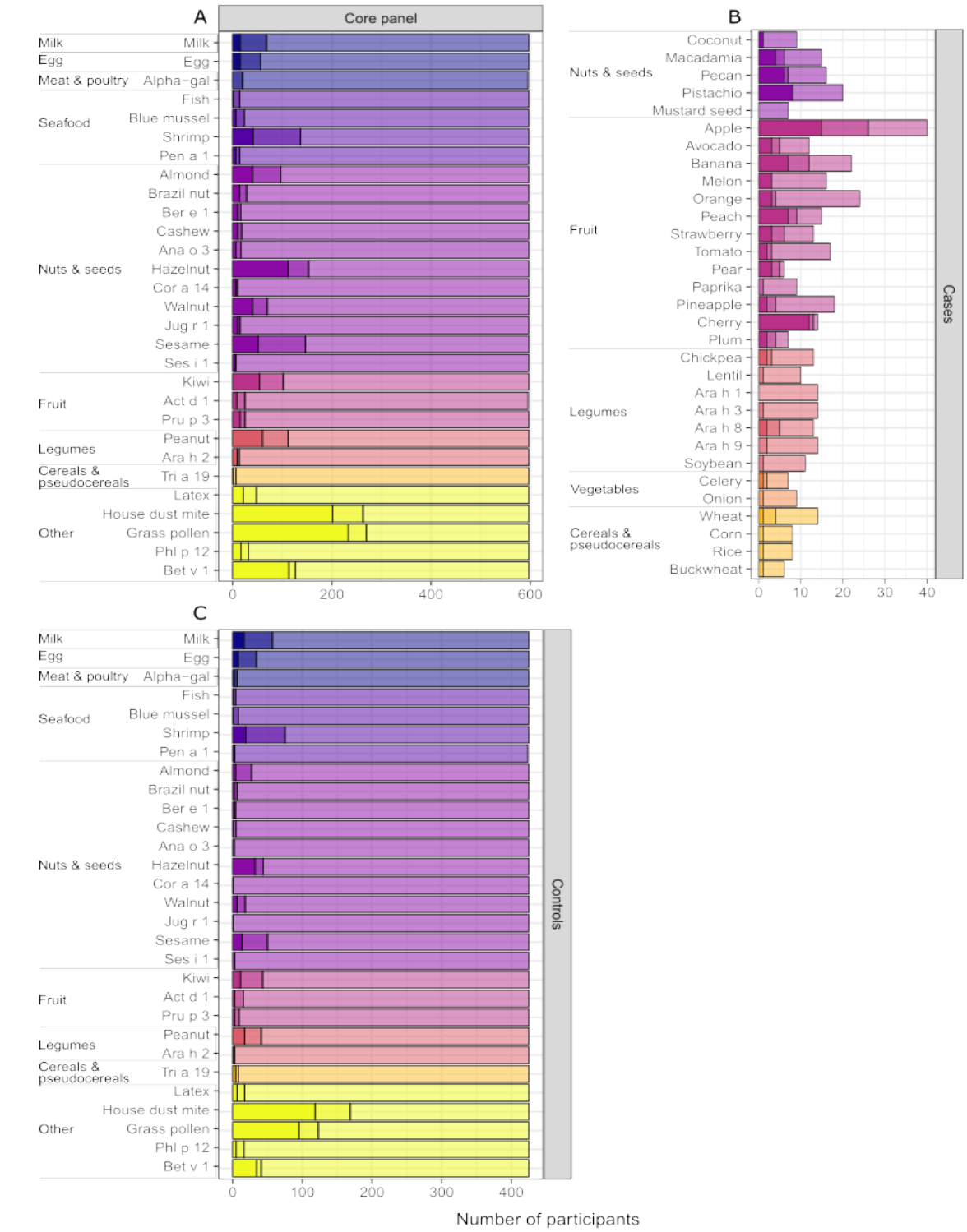


Figure 18. Serum specific IgE testing in the PAFA community survey participants.

A – core panel for cases; B – extended panel for cases; C – core panel for controls. The darkest colour in each bar represents a positive result, the second darkest colour a borderline result, and the lightest colour a negative result. Where five or fewer participants were tested for a food or component, this has been excluded for clarity. The

extended panel for controls was not included as less than five controls per food underwent additional testing.

5.1.4 Confirmation of food allergy

A total of 51 participants had their IgE-mediated food allergy confirmed in Stage 3 (Figure 5), the majority of diagnoses being made following a full clinical assessment and an expert panel review. As observed for those with a probable IgE-mediated food allergy, the majority (58.2%) reported their food allergy commenced when they were adults.

Many study subjects were considered ineligible for food challenge based on the history of previous severe reactions, current medication usage (such as antidepressants or beta-blockers) or pre-existing medical conditions (such as a recent myocardial infarction or were under investigation for cancer). Of those who were invited many declined the challenge due to personal circumstances, such as the need to take time off from work as annual leave, as well as anxiety about the procedure. A total of five subjects had a food challenge. Only one was partially completed as the participant, who was having a DBPCFC to kiwi, reacted on the placebo arm with objective signs of an allergic reaction. The severity of the reaction necessitated unblinding the challenge. Investigations have indicated that the participant had a previously undiagnosed IgE-mediated food allergy to oatmeal, an ingredient in the challenge meal which was responsible for causing the reaction. Further investigation is ongoing through the NHS Allergy Clinic. The remaining four challenges were completed of which, one was negative to pistachio, two had positive DBPCFC to apple and one to kiwi fruit.

Taking into account the overall 50.07% response rate for cases reporting reactions to priority foods in Stage 3, the raw estimated prevalence of confirmed IgE-mediated food allergy was 5.73 (4.29-7.49, 95% CI, 50 out of 872). As observed in Stage 2 (Figure 17) the majority of subjects experienced multiple types of IgE-mediated food allergy and many presented a complex clinical picture with participants having a confirmed IgE-mediated allergy to certain foods and an adverse reaction which was not mediated by IgE to other foods. For example, one participant was diagnosed as having a pollen-associated allergy to hazelnut, was diagnosed as tolerant to walnut and had an adverse reaction not mediated by IgE to milk. The severity of reactions ranged from mild to severe and not all of those with a confirmed food allergy were at risk of a severe, or generalised, reaction.

Participants frequently changed the reported foods during their Stage 3 assessment visit. For example, one participant did not report symptoms to Brazil nut at Stage 2 but was assessed in Stage 3 since they had a positive IgE test of 0.4 kU of specific IgE /L to the component Ber e 1. Following clinical assessment, it transpired that the participant did experience symptoms and consequently went on to have an allergy to Brazil nut confirmed. Another participant did not report symptoms to peach at Stage 2 but developed allergy to peach (as nectarine) in the time interval between the Stage 2 and Stage 3 study visits. Yet another participant reported symptoms at Stage 2, had negative serological or skin test results but was undergoing immunotherapy which likely compromised the test results. Following the Stage 3 clinical assessment they were diagnosed as having a pollen associated food allergy.

Confirmed food allergies were dominated by plant derived foods and, in particular, tree nuts with the most prominent ones being hazelnut and walnut followed by Brazil nut and almond. Cashew, pistachio, pecan and macadamia nuts affected fewer study subjects than other types of tree nuts or peanut. Many individuals reported reactions to all tree nuts included in the PAFA list of priority foods in Stage 2 but following Stage 3 consultation it was often found that they had a confirmed food allergy to only certain tree nuts. There were also instances when reactions to tree nuts, such as hazelnut, were not accompanied by a positive food specific IgE-test but participants did have a positive SPT to that food showing the value of using both types of diagnostic test. In addition, there were instances where individuals were highly sensitised to certain tree nuts but did not report symptoms to those foods as they had never eaten them before.

Pollen-associated food allergies, especially sensitisation to Bet v 1 or birch pollen were frequently encountered as would have been expected since 18.89% of the PAFA Stage 2 cases were sensitised to Bet v 1. Multiple allergies to fresh fruits, especially those from the Rosaceae family (apple, peach, strawberry) were also very prominent as well as some unusual fruits such as fig. Many of these participants expanded the list of foods they reacted to during the Stage 3 assessment to foods not included in the PAFA priority foods list such as cherry, plum and pear. Although in many of these participants the reactions were mild, there were instances where more severe reactions were encountered which precluded subjects having an oral food challenge. Several participants reported symptoms to a variety of fruit such as kiwi, melon, strawberry, peach, tomato and bell pepper at Stage 2, which were consistent with pollen-associated food allergy, but had a negative serological test to Bet v 1. However, their SPT test to

birch pollen was positive together with certain food extracts. On occasion the food extract also gave a negative serological test result and where available, retesting was done to the Bet v 1 homologue which would confirm reactivity. However, this was not always possible due to either the extract or component reagents not being available for certain foods. For example, a number of individuals with pollen-associated food allergy also reported reactions to orange but it was not possible to confirm if this was IgE-mediated since no birch pollen homologue has been identified for orange to date.

Of the confirmed allergies, very few were to animal foods, in particular fish, and crustacean shellfish. Diagnosis of reactions to egg were complex due to the impact of cooking procedures with some individuals experiencing reactions to only raw or lightly cooked egg as might be experienced to mousse-style desserts made with raw egg white or lightly scrambled eggs. Although IgE-mediated reactions to milk were not confirmed, a few patients experienced adverse reactions not mediated by IgE which would have required further follow up to confirm if it was, for example, persistent or transient lactose intolerance.

5.1.5 Possible non-IgE-mediated adverse reactions to food

A smaller number of Stage 1 participants (405) reported reactions consistent with possible non-IgE-mediated adverse reactions to foods giving a prevalence of possible non-IgE-mediated adverse reactions of 6.85% (5.7-8.16, 95%CI). The majority of the population reporting possible non IgE-mediated adverse reactions were female (64.6%), 47% of whom were 18-39 years of age. The gender difference in reporting was smaller for those over 50 years of age (Figure 19A). The ethnicity of the population reporting possible non-IgE-mediated reactions generally reflected that of the overall respondents.

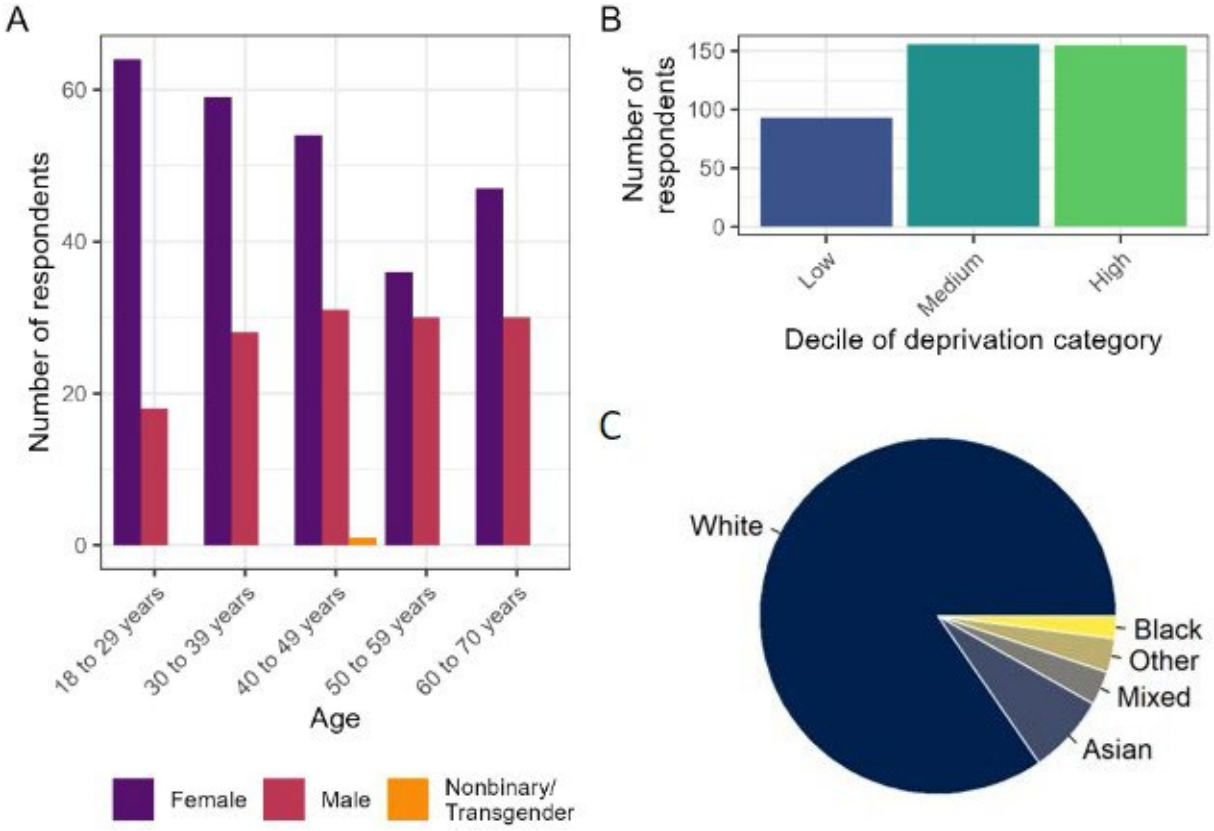


Figure 19. Demographic characteristic of the population reporting a possible non-IgE-mediated adverse reactions to food in PAFA Stage 1.

Responses were analysed by: A – gender and age; B – decile of deprivation; C - ethnicity).

Reported reactions to milk and cereals containing gluten dominated the Stage 1 population with possible non-IgE-mediated food allergy accounting for 47% and 40% respectively of all the reactions reported (Figure 20). It was notable that the number of reactions to foods such as peanut, tree nuts and fresh fruits were lower and ranging from 1.2-7.0%. Interestingly, 9.6-10.6% of reported reactions were to lentils and chickpeas (Figure 20). As observed in those reporting possible IgE-mediated reactions, most participants reported 2 or more foods causing an adverse reaction with one individual reporting 28 foods.

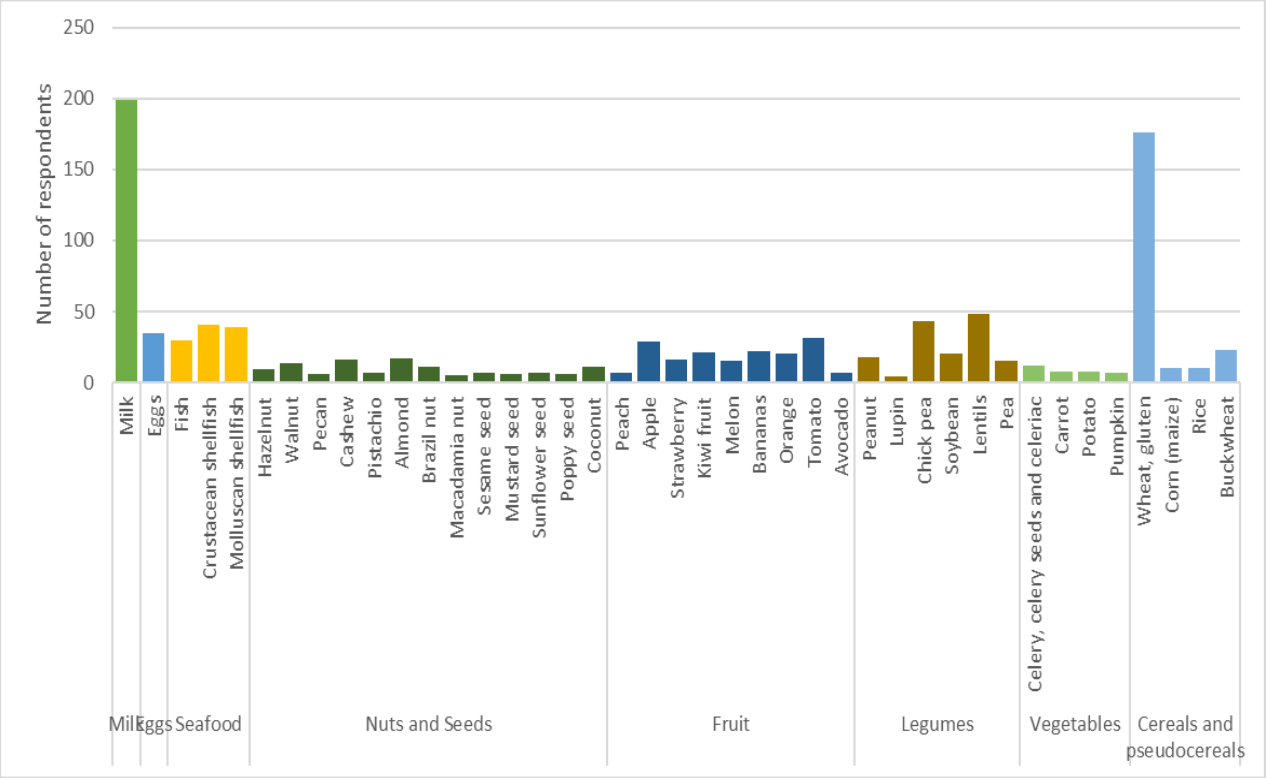


Figure 20. PAFA Stage 1 self-reported possible non-IgE-mediated reactions to priority foods

In PAFA Stage 2, 6.85% (5.70-8.16, 95% CI) of participants were identified as having possible non-IgE-mediated food allergy. The difference with Stage 1 is likely to be in part due to the fact that symptoms and time of onset were reported on a food-by-food basis in Stage 2. Other differences may relate to bias in Stage 2 respondents arising from the lower response rate. As in Stage 1, reactions were again dominated by reported reactions to cow's milk and cereals containing gluten, with other important foods being chickpeas and lentils with a prevalence of 0.53% (0.24-1.00, 95% CI) and 0.64% (0.32-1.15, 95% CI) respectively.

Although the individuals with possible non-IgE food adverse reactions to food were not explicitly followed up in PAFA Stage 3, many individuals were invited in Stage 3 to confirm they did not have an IgE-mediated food allergy. Following that visit it became evident that many of them were experiencing adverse reactions to foods, mainly gastrointestinal symptoms, which were not consistent with IgE-mediated food allergies. In addition, some individuals with confirmed IgE-mediated food allergies to one or more foods also had other types of non-IgE-mediated adverse reaction to foods such as IBS.

5.2 Cohorts

5.2.1 Participants included in the study

The two cohorts consisted of 1,628 participants. Of these 1,033 were assessed at a mean age of 26 years in IoW and 595 assessed at a mean age of 19 years in the 18+ MAAS assessment. Of the total participants, 47% were male and 98% were of white ethnicity. 30% of the study population suffered or have suffered from asthma and 46% having or have had hay fever. Of note, 6% were sensitised to birch pollen on skin prick testing at 26 years in the IoW 1989 cohort compared to 24% at the 18+ year MAAS assessment (Table 10).

Table 10. Demographic characteristics of all cohort participants

Figures represent counts (%). N/A – not available.

Parameter	IoW 1989	MAAS	Combined
Number seen at last complete assessment	1033	595	1628
Age: mean (range) at last complete assessment	26 (26, 27)	19 (19, 20)	26 (19, 27)
Male sex	472 (46%)	297 (50%)	(47%)
Ethnicity - Caucasian	1046 (99%)	570 (96%)	(98%)
Ethnicity - Asian/Chinese	0 (0%)	4 (1%)	(0.2%)
Ethnicity - Black (African)	0 (0%)	1 (0.2%)	(0.06%)
Ethnicity - Other	9 (1%)	20 (3%)	29 (1%)
Current asthma	145 (14%)	96 (16%)	241 (15%)
ARC (current)	318 (31%)	228 (38%)	(34%)
ARC (January)	89 (28%)	10 (4%)	(18%)
ARC (February)	99 (31%)	14 (6%)	(21%)

ARC (March)	114 (36%)	35 (15%)	(27%)
ARC (April)	156 (49%)	89 (39%)	(45%)
ARC (May)	210 (66%)	155 (68%)	(67%)
ARC (June)	244 (77%)	189 (83%)	433 (79%)
ARC (July)	233 (73%)	184 (81%)	417 (76%)
ARC (August)	183 (58%)	133 (58%)	316 (58%)
ARC (September)	130 (41%)	48 (21%)	178 (33%)
ARC (October)	89 (28%)	19 (8%)	108 (20%)
ARC (November)	85 (27%)	11 (5%)	96 (18%)
ARC (December)	85 (27%)	11 (5%)	96 (18%)
Current eczema	105 (10%)	86 (14%)	191 (12%)
Mother asthma (current)	Not asked	101/552 (18%)	N/A
Mother eczema (current)	Not asked	65/552 (12%)	N/A
Mother ARC (current)	Not asked	198/552 (36%)	N/A
Father asthma (current)	Not asked	71/552 (13%)	N/A
Father eczema (current)	Not asked	50/552 (9%)	N/A
Father ARC (current)	Not asked	185/552 (34%)	N/A
Mother asthma (ever had)	154/952 (16%)	Not asked	N/A
Mother eczema (ever had)	123/951 (13%)	Not asked	N/A
Mother ARC (ever had)	234/951 (25%)	Not asked	N/A
Mother food allergy (ever had)	82/951 (9%)	Not asked	N/A
Father asthma (ever had)	121/941 (13%)	Not asked	N/A

Father eczema (ever had)	54/939 (6%)	Not asked	N/A
Father ARC (ever had)	182/938 (19%)	Not asked	N/A
Father food allergy (ever had)	28/936 (6%)	Not asked	N/A
BMI <18.5	54 (5%)	Not measured	N/A
BMI 18.5-24.9	527 (51%)	Not measured	N/A
BMI 25-29.9	122 (12%)	Not measured	N/A
BMI >30	65 (6%)	Not measured	N/A
BMI Missing	265 (26%)	Not measured	N/A
Units of alcohol per week - 0	289 (28%)	Not asked	N/A
Units of alcohol per week – 1-14	469 (45%)	Not asked	N/A
Units of alcohol per week - >14	95% (9%)	Not asked	N/A
Units of alcohol per week - Missing	180 (17%)	Not asked	N/A
Current pet ownership - cat	257/1031 (25%)	115/594 (19%)	372/1625 (23%)
Current pet ownership - dog	263/1031 (26%)	189/594 (32%)	452/1625 (28%)
Current smoker	322 (31%)	80 (13%)	402 (25%)
Current vaper	Not asked	32 (5%)	N/A
Either smoker or vaper	Not asked	98 (16%)	N/A
Birch pollen sensitisation - SPT positive at 18 years	49/851 (6%)	121/507 (24%)	170/1358 (13%)
Birch pollen sensitisation - SPT positive at 26 years	29/556 (5%)	Not determined	N/A
Birch pollen sensitisation - Bet v 1 positive at 18 years	Not determined	75/362 (21%)	N/A

5.2.2 Cohort participants reporting adverse reactions to food in 26 or 18+ years assessments

The number of participants reporting an adverse reaction to food was 146 (Figure 21). In the IoW 1989 cohort, 5.91% reported adverse reactions at 26 years of age. In the MAAS cohort, 14.29% reported adverse reactions at the 18+ year assessment (Figure 21). The crude estimated prevalence of self-reported adverse reactions for the combined cohorts was 8.97% (7.62-10.46, 95% CI).

Following the review process, 9 probable IgE cases and 41 possible IgE cases were identified for progression to Stage 3 from the 1,033 IoW 1989 cohort participants assessed at age 26 years (Figure 21). From MAAS, 31 probable IgE cases, 26 possible IgE cases and 3 unclear cases were identified for progression to Stage 3 from the 595 assessed at the 18+ year assessment (Figure 21).

Based on historical assessment data, the prevalence of probable food allergy is 2.46% (1.76-3.33, 95% CI, 40 out of 1,628). For the IoW 1989 cohort it is 0.87% (0.40-1.65,

95% CI, 9 out of 1,033) and for the MAAS cohort it is 5.21% (3.57-7.31, 95% CI, 31 out of 595). Considering possible or probable food allergy, the overall prevalence is 6.57% (5.42-7.89, 95% CI, 107 out of 1,628). For IoW 1989 cohort it is 4.8% (0.3.6-6.33, 95%CI, 50 out of 1,033) and for the MAAS cohort it is 9.58% (7.34-12.23, 95% CI, 57 out of 595).

Of those invited, 16 individuals from the IoW 1989 cohort and 22 from the MAAS cohort participated in the Stage 3 assessment (response rates of 32 and 37%, respectively). For 18 participants, this included an in-person visit for further specific serological testing and SPT to assess for food allergy.

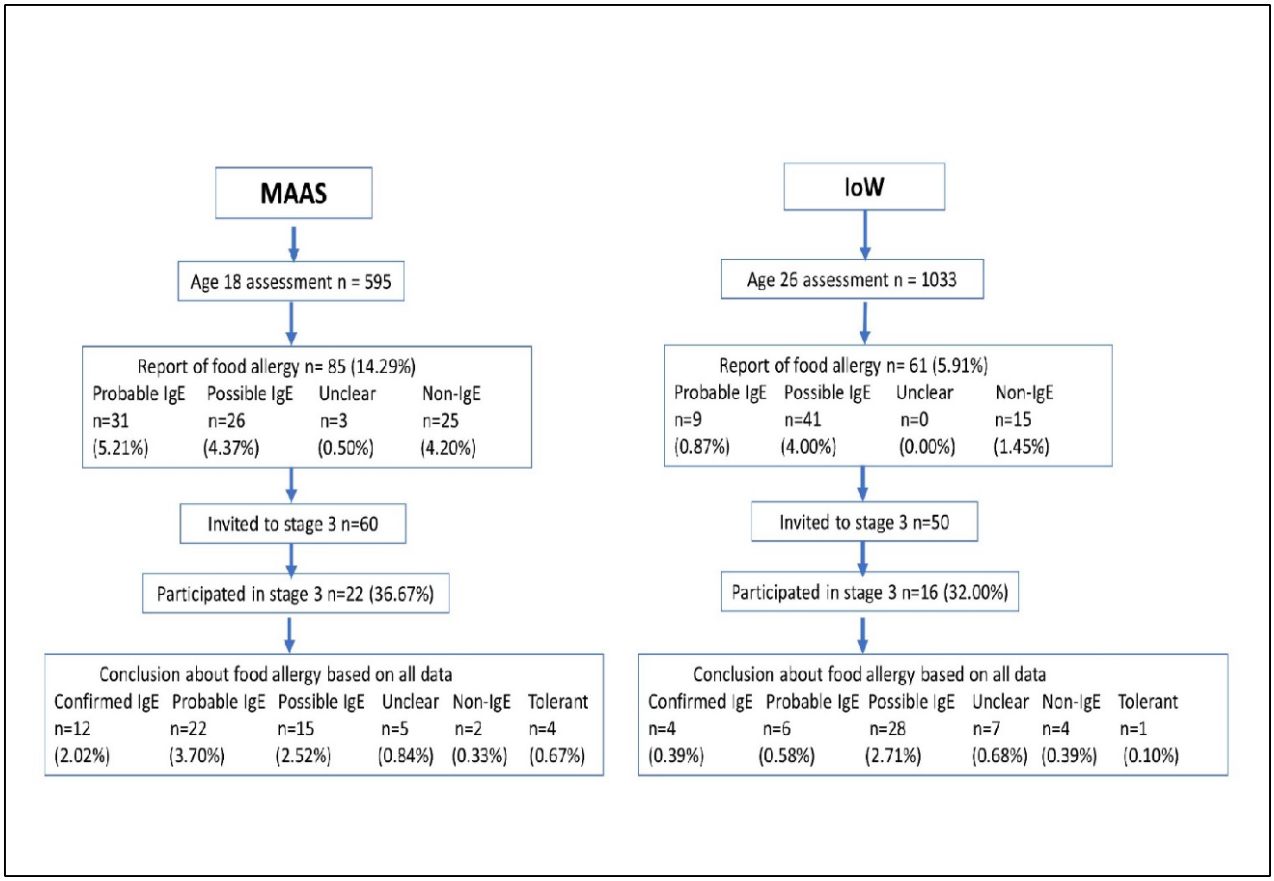


Figure 21. Flow diagram of participants in the IoW and MAAS cohorts

Figures in boxes represent number of participants. Final conclusion for each participant based on all data from historical and Stage 3 assessments.

5.2.3 Cohort participants with possible, probable or confirmed food allergy based on PAFA assessment

The demographics of the participants with possible, probable and confirmed food allergy, as defined in Stage 3, are described in Table 11. These were similar to all IoW 1989 and MAAS participants assessed at 26 or 18+ year assessments. Specifically, the age mean were 26 and 19 years in the IoW 1989 and MAAS cohorts, respectively, and there were similar numbers of males and females and white ethnicity was predominant (Table 11).

As expected when selected on the basis of reported food allergy, those invited to Stage 3 were more likely to have asthma (31% vs 15%), allergic rhinoconjunctivitis (53% vs 34%) and eczema (30% vs 12%) (Tables 10 and 11). Additionally, those invited to Stage 3 were more likely to be sensitised to birch pollen (e.g., SPT positive at 18 years in 38% vs 13%).

Table 12 shows the characteristics of the reactions to foods in the participants with possible, probable and confirmed food allergy, as defined in Stage 3. MAAS reported the

characteristics of the “worse food allergy” at the 18+ year assessment so these characteristics are described for that food in each cohort. Almost all reactions were reported as occurring within 2 hours of exposure to the food with 41% and 9% of reactions were respiratory or cardiovascular, respectively, 68% having multiple reactions and 7% needed treatment with adrenaline (Table 12).

The most common food allergen categories (focusing on confirmed and probable food allergy) were tree nuts (25 participants) followed by legumes including peanuts (19 participants), fruit (15 participants), seafood and fish (3 participants), hen’s egg, cow’s milk and oilseed (1 participant each) (Table 13). There were no cases of confirmed or probable vegetable nor cereal grain allergen.

Table 11. Demographic characteristics of cohort participants with possible, probable or confirmed IgE-mediated food allergy.

Food allergy outcome as per Stage 3 assessment in section 4.4.1. Figures are counts (%) unless stated otherwise. N/A – not available.

Parameter	IoW 1989	MAAS	Combined
Number seen at last complete assessment	38	50	88
Median age (25th, 75, centiles) at last complete assessment	26.34 (26.13, 26.92)	19.27 (18.99, 19.64)	20.46 (19.21, 26.26)
Male sex	16 (42.11%)	24 (48.00%)	(45.45%)
Ethnicity - White (Caucasian)	38 (100.00%)	46 (92.00%)	(95.45%)
Ethnicity - Asian/Chinese	0 (0.00%)	0 (0.00%)	(0.00%)

Ethnicity - Black (African)	0 (0.00%)	0 (0.00%)	(0.00%)
Ethnicity - Other	0 (0.00%)	4 (8.00%)	4 (4.55%)
Current asthma	12 (31.58%)	15 (30.00%)	27 (30.68%)
Current ARC	17 (44.74%)	29 (58.00%)	46 (52.27%)
ARC (current)	6 (35.29%)	1 (3.45%)	7 (15.22%)
ARC (January)	6 (35.29%)	1 (3.45%)	7 (15.22%)
ARC (February)	8 (47.06%)	2 (6.90%)	10 (21.74%)
ARC (March)	10 (58.82%)	8 (27.59%)	18 (39.13%)
ARC (April)	14 (82.35%)	22 (75.86%)	36 (78.26%)
ARC (May)	15 (88.24%)	25 (86.21%)	40 (86.96%)
ARC (June)	15 (88.24%)	24 (82.76%)	39 (84.78%)
ARC (July)	14 (82.35%)	17 (58.62%)	31 (67.39%)
ARC (August)	9 (52.94%)	6 (20.69%)	15 (32.61%)
ARC (September)	7 (41.18%)	2 (6.90%)	9 (19.57%)
ARC (October)	6 (35.29%)	1 (3.45%)	7 (15.22%)
ARC (November)	6 (35.29%)	1 (3.45%)	7 (15.22%)
Current eczema	12 (31.58%)	14 (28.00%)	26 (29.55%)
Mother asthma (current)	Not asked	12/48 (25.00%)	N/A
Mother eczema (current)	Not asked	6/48 (12.50%)	N/A
Mother ARC (current)	Not asked	23/48 (47.92%)	N/A

Father asthma (current)	Not asked	11/48 (22.92%)	N/A
Father eczema (current)	Not asked	7/48 (14.58%)	N/A
Father ARC (current)	Not asked	23/48 (47.92%)	N/A
Mother asthma (ever had)	7/35 (20.00%)	Not asked	N/A
Mother eczema (ever had)	5/35 (14.29%)	Not asked	N/A
Mother ARC (ever had)	10/35 (28.57%)	Not asked	N/A
Mother food allergy (ever had)	5/34 (14.71%)	Not asked	N/A
Father asthma (ever had)	3/31 (9.68%)	Not asked	N/A
Father eczema (ever had)	1/32 (3.13%)	Not asked	N/A
Father ARC (ever had)	7/30 (23.33%)	Not asked	N/A
Father food allergy (ever had)	2/33 (6.06%)	Not asked	N/A
BMI <18.5	5 (13.16%)	Not measured	N/A
BMI 18.5-24.9	15 (39.47%)	Not measured	N/A
BMI 25-29.9	1 (2.63%)	Not measured	N/A
BMI >30	7 (18.42%)	Not measured	N/A
BMI Missing	10 (26.32%)	Not measured	N/A
Units of alcohol per week - 0	9 (23.68%)	Not asked	N/A

Units of alcohol per week – 1-14	20 (52.63%)	Not asked	N/A
Units of alcohol per week - >14	2 (5.26%)	Not asked	N/A
Units of alcohol per week - Missing	7 (18.42%)	Not asked	N/A
Current pet ownership - cat	13 (34.21%)	8 (16.00%)	21 (23.86%)
Current pet ownership - dog	12 (31.58%)	13 (26.00%)	25 (28.41%)
Current smoker	13 (34.21%)	6 (12.00%)	19 (21.59%)
Current vaper	Not asked	3 (6.00%)	N/A
Either smoker or vaper	Not asked	7 (14.00%)	N/A
Birch pollen sensitisation - SPT positive at 18 years	3/23 (13%)	22/43 (51%)	25/66 (38%)
Birch pollen sensitisation - SPT positive at 26 years	2/20 (10%)	Not determined	N/A
Birch pollen sensitisation - Bet v 1 positive at 18 years	Not determined	12/27 (44%)	N/A

Table 12. Characteristics of worst food allergy reported by cohort participants with confirmed, probable or possible IgE-mediated food allergy.

MAAS reported the characteristics of the “worse food allergy” at the 18+ year assessment as so these characteristics are described for that food in each cohort. In IoW 1989 cohort, the worst food allergy was selected on the basis of reactions reported for up to 3 food allergens. Figures are counts (%).

Parameter	IoW 1989 (N=38)	MAAS (N=50)	Combined (N=88)
Time to symptoms onset: <30 min	25 (65.79%)	45(95.74%)	70 (82.35%)
Time to symptoms onset: 30min-2 hours	11 (28.95%)	1 (2.13%)	(14.11%)
Time to symptoms onset: 2-12 hours	1 (2.63%)	1 (2.13%)	(2.35%)
Time to symptoms onset: >12 hours	1 (2.63%)	0 (0.00%)	(1.14%)
Reaction: Cutaneous	8 (21.05%)	19 (38.00%)	(30.68%)
Reaction: Respiratory	12 (31.58%)	24 (48.00%)	(40.91%)
Reaction: Cardiovascular	0 (0.00%)	8 (16.00%)	(9.09%)
Reaction: Digestive	20 (52.63%)	14 (28.00%)	(38.64%)
Reaction: Oral	18 (47.37%)	43 (86.00%)	(69.32%)
Reaction: Eyes, nose	0 (0.00%)	13 (26.00%)	(14.77%)
Reaction: Other	5 (13.16%)	1 (2.00%)	6 (6.82%)

Number of self-reported previous adverse reactions to food: Only once	11(28.95%)	11 (22.00%)	22 (25.00%)
Number of self-reported previous adverse reactions to food: 2-4 times	6 (15.79%)	20 (40.00%)	26 (29.55%)
Number of self-reported previous adverse reactions to food: >4 times	17 (44.74%)	17 (34.00%)	34 (38.64%)
Number of self-reported previous adverse reactions to food: Missing	4 (10.53%)	2 (4.00%)	6 (6.82%)
Treatment: Antihistamines	12 (35.29%)	16 (32.00%)	28 (33.33%)
Treatment: Adrenaline	3 (9.38%)	3 (6.00%)	6 (7.32%)
Last reaction: last year	22 (57.89%)	18 (36.00%)	40 (45.45%)
Last reaction: 2-5 years	5 (13.16%)	12 (24.00%)	17 (19.32%)
Last reaction: 5-10 years	5 (13.16%)	6 (12.00%)	11 (12.50%)
Last reaction: >10 years	3 (7.89%)	11 (22.00%)	14 (15.91%)
Last reaction: Missing	3 (7.89%)	3 (6.00%)	6 (6.82%)

Table 13. Number of participants with confirmed, probable or possible food allergy to different food groups by age of onset of any food allergy

Age of onset of a food allergy was classified as either being during childhood or adulthood. Figures are counts (%). Percentages are rounded to the nearest integer.

PAFA food category	Age of onset	No. of confirmed food allergy (%)	No. of probable food allergy (%)	No. of possible food allergy (%)	No. of any adverse reaction to food (%)
Milk	Adult	0	0	2 (10)	2 (7)
Milk	Child	0	1 (3)	3 (11)	4 (5)
Egg	Adult	0	0	0	0
Egg	Child	0	1 (3)	2 (7)	3 (4)
Seafood (including fish)	Adult	0	1 (20)	2 (10)	3 (10)
Seafood (including fish)	Child	0	2 (6)	5 (18)	7 (25)
Nuts and seeds	Adult	3 (60)	1 (20)	0	4 (13)
Nuts and seeds	Child	12 (48)	9 (29)	4 (14)	25 (30)
Legumes (including peanut)	Adult	0	2 (40)	0	2 (7)
Legumes (including peanut)	Child	6 (24)	11 (35)	5 (18)	22 (26)
Fruit	Adult	2 (40)	1 (20)	6 (30)	9 (30)
Fruit	Child	7 (28)	5 (16)	4 (14)	16 (19)
Vegetables	Adult	0	0	4 (20)	4 (13)

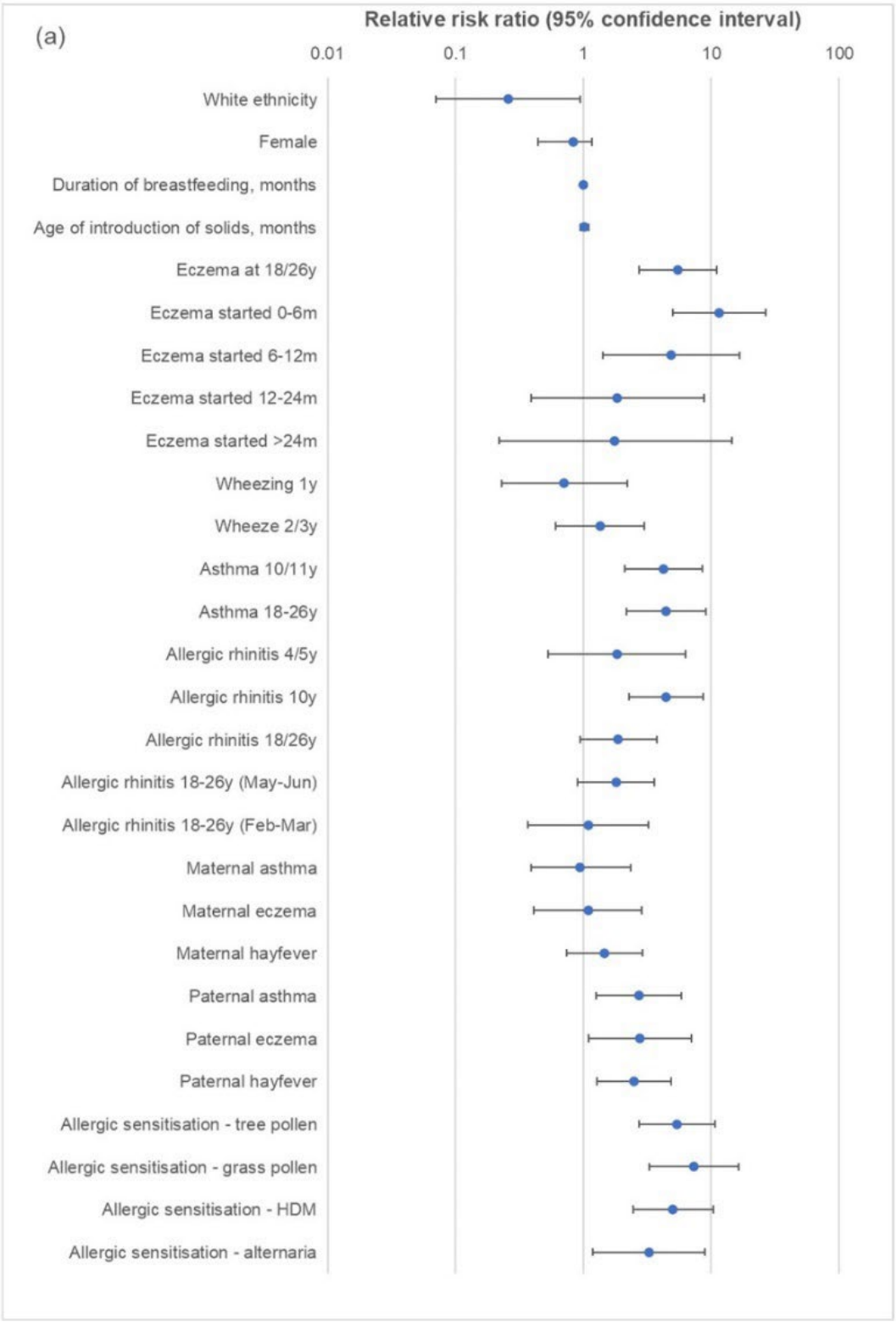
Vegetables	Child	0	0	3 (11)	3 (4)
Cereals and pseudocereals	Adult	0	0	2 (10)	2 (7)
Cereals and pseudocereals	Child	0	0	0	0
Other	Adult	0	0	4 (20)	4 (13)
Other	Child	0	2 (6)	2 (7)	4 (5)
Total	Adult	5	5	20	30
Total	Child	25	31	28	84

5.2.4 Potential risk factors food allergy

The next stage of the analysis involved an assessment of the risk factors for food allergy. This risk factor analysis is limited to childhood onset food allergy as there were only a few cases of adult onset.

Cases of childhood onset food allergy were significantly less likely to be of white ethnicity compared to all controls but the magnitude of this associated was reduced with atopic controls and the statistical evidence decreased. Eczema at 26 or 18+ years was significantly associated with food allergy compared to both all controls and atopic controls. This association was driven by eczema with an onset in the first year of life.

Asthma at 26 or 18+ years was significantly associated with food allergy compared to all controls and atopic controls. A similar association was observed for asthma at 10 or 11 years of age. Allergic rhinitis at 10 years was significantly associated with food allergy compared to all controls and topic controls. Lastly, tree pollen sensitisation was significantly associated with food allergy compared to all controls and atopic controls. No significant associations were seen with grass pollen, HDM or mould sensitisation for the atopic controls.



Odds Ratio calculated from the logistic regression model.

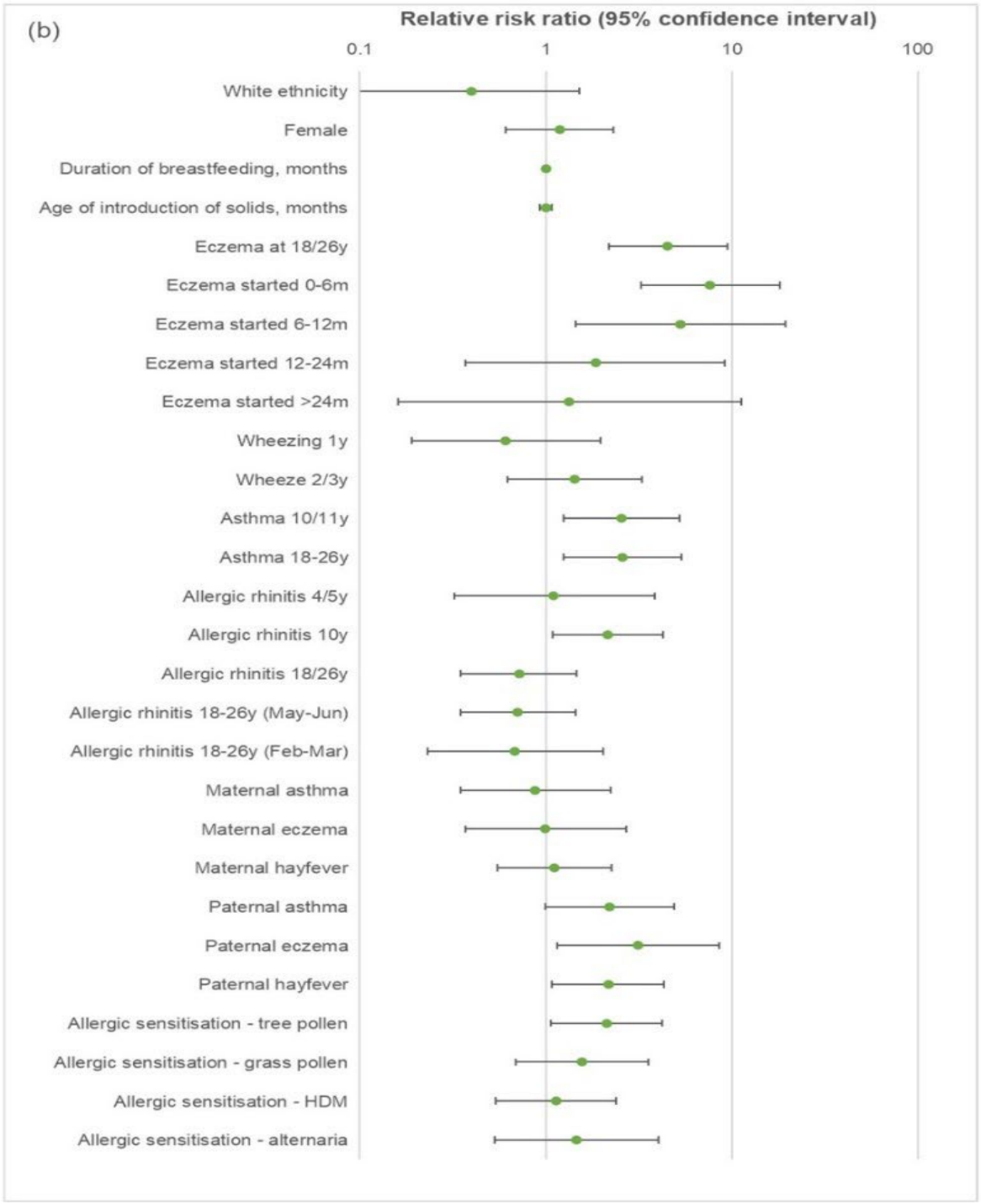


Figure 22. Risk factors for confirmed and probable childhood onset food allergy versus (a) all controls and (b) atopic controls

6. Discussion

6.1 PAFA study populations

The community population sample and the cohort studies provided complementary data on the prevalence of adult IgE-mediated food allergy. The community survey provided a population from the Greater Manchester area which represents the type of built-up area where 94.9% of the population in England and 88% of the population Wales live, according to the 2021 census (ONS, 2023). A population of almost 30,000 adults were surveyed (against a target population of 35,000) giving 4,828 respondents against a target of between 4,000-5,000. The population sample was well balanced with regard to age and gender and had good representation from lower and upper deciles of deprivation and ethnicity (including those of Asian and Black ethnicities) against the ONS 2011 and 2023 census data for England and Wales. Despite using a stratified sampling strategy, the poor response rate in males aged 18-29 meant they were underrepresented in the PAFA Stage 1 population, as has been observed in many other epidemiological surveys (Harrison et al., 2020, Lallukka et al., 2020). This shortcoming was addressed by the assessment of food allergy in young adults in the IoW 1989 and MAAS cohorts with a total of 1628 participants seen at their final assessments of age 26 (IoW) and 18+ (MAAS), although the cohorts are almost all of white ethnicity.

The data collected across the different ages for the IoW 1989 and MAAS cohorts are vast and different questions have been used to assess the study variables and risk factors.

Harmonising these data proved challenging because data for a number of variables was collected by asking similar but slightly different questions in each of the cohorts. For example, the key study variable to assess self-reported adverse reactions was posed quite differently. In MAAS, participants were asked if they had ever had a problem or illness from eating certain foods using a pre-populated list. They were then asked in detail about their worst reacting food. In the IoW 1989 cohort, previous food allergy was not taken into account at the 26-year assessment as participants were simply asked if they had had food allergy since they were 18 years of age. In addition, although the IoW participants were asked about adverse reactions to foods at different ages, they were only asked to identify three key foods. The difference in the final age of assessment for the two cohorts also has the potential to introduce some heterogeneity into the data although adult populations are regularly described in terms of 10-year age groups minimising this as a potential issue. Additionally, the MAAS cohort had more 18+ year

sensitisation data than the IoW cohort at 26 years as they had all been assessed with the ImmunoCAP Immuno-Solid phase Allergy Chip which covers 112 allergens. However, participants in both cohorts had similar sensitisation patterns when tested using the PAFA serological screening panel.

6.2 The prevalence of IgE-mediated food allergy in adulthood

In the community survey more than 36% of respondents (1,755) reported an adverse reaction to food of whom 1,425 reported a reaction to at least one of the PAFA priority foods. This meets the original target of ~1,000-1,500 respondents reporting an adverse reaction to food and gave an estimated prevalence of self-reported adverse reactions to food of 36.35% (35.00-37.71, 95% CI) in adults of 18-70 years old. The younger adults in the cohorts had a lower prevalence of self-reported adverse reactions to foods in adulthood which was estimated to be 12.04% (10.50-13.72, 95% CI). The prevalence of adverse reactions to food in the community survey was similar to that in the EuroPrevall community survey in adults in Zurich where 37.3% of subjects reported an adverse reaction to food (Lyons et al., 2020b, Burney et al., 2014) whilst in a Swedish study in adults the prevalence was 32.5% (29.6–35.4, 95%CI) (Rentzos et al., 2019). It is much higher than the prevalence of self-reported adverse reactions to foods in a telephone survey from the USA where 19% of respondents reported an adverse reaction to food (Gupta et al., 2019). The majority (66%) of those reporting a reaction in our study were female, as was found in both the US (Gupta et al., 2019), EuroPrevall (Lyons et al., 2019) and Swedish (Rentzos et al., 2019) studies. The US study was stratified by age and showed a similar skewing of reporting of adverse food reactions to the younger population although it was not as marked as in the PAFA study. In the USA, a higher case-rate was observed in the population aged over 60 years.

A response rate of 46.4% was achieved for cases invited to take part in the nested case-control in Stage 2 of the community survey, higher than the 43.3% response rate achieved in the EuroPrevall adult survey (Lyons et al., 2019) and slightly lower than the anticipated response rate of 50%. Nevertheless, a total of 606 individuals reporting adverse reactions to food attended a Stage 2 study visit against the 500-750 participants originally anticipated. They had a broadly similar demographic compared to those who did not take part.

The estimated prevalence of possible IgE-mediated allergy in PAFA Stage 2 in the community survey in adults aged 18-70 was 29% (26.85-31.21, 95% CI). This was higher

than that originally anticipated in the study design which sought to provide estimates of the prevalence of possible IgE-mediated food allergy with 95% CI of 9.4 to 10.6%. There were sufficient study subjects in the community survey to estimate the prevalence of possible IgE-mediated food allergy on a food-by-food basis which showed that the most prevalent foods were milk and cereals containing gluten. This is in contrast to the USA study where the most commonly reported food was shellfish (2.9% of reactions) (Gupta et al., 2019).

As in the EuroPrevall study, symptom patterns and time of onset of a reaction of less than 2 hours (characteristics of an IgE-mediated food allergy) were coupled with evidence of sensitisation to calculate the prevalence of probable IgE-mediated food allergy. Thus, the crude estimated prevalence of probable IgE-mediated food allergy was 7.44% (6.24-8.79, 95% CI), higher than that observed in the EuroPrevall Zurich centre which was 5.46% (3.94-7.66, 95% CI) (Lyons et al., 2019) and in Sweden which was 5.9% (4.5–7.4 95% CI). Despite being widely reported in the community survey, adverse reactions to cow's milk and cereals containing gluten were not found to be IgE-mediated, the crude estimate prevalence of probable IgE-mediated food allergy to these foods being low. These data are similar to the EuroPrevall adult survey in Zurich where milk was also the most common food reported, with a self-reported prevalence of 7.85% (Burney et al 2014), which translated into prevalence of probable IgE-mediated milk allergy of only 0.24% (0.00-1.02, 95% CI) (Lyons et al 2019). However, self-reported adverse reactions to wheat were much lower in Zurich than in PAFA (2.2%) (Burney et al 2014) but had a higher prevalence of probable IgE-mediated allergy of 0.9% (0.00-0.73 95% CI) (Lyons et al., 2019). Instead, the most important foods causing probable IgE-mediated food allergy in the PAFA study were tree nuts, such as hazelnut and walnut, peanut and fruits such as apple and kiwi. Similarly, probable IgE-mediated food allergy to animal foods, such as fish, were uncommon in both PAFA (0.29%; 0.1-0.68, 95%CI) and the EuroPrevall study (0.02%; 0.00-0.35, 95%CI) (Lyons et al., 2019) with none of the individuals reporting symptoms to fish being sensitised in a Swedish food hypersensitivity community study (Rentzos et al., 2019). Importantly the crude estimates of probable IgE-mediated food allergy to priority foods clearly indicate that the tree nut species (including Brazil nut) listed in Annex II of the labelling regulation are significant causes of food allergy in UK adults. However, animal-derived foods, and especially milk, egg and molluscan shellfish have a very low prevalence in the UK adult population, as do foods such as celery, mustard, and lupin.

The original study design anticipated that PAFA Stage 2 would identify between 100-150 cases of probable IgE-mediated food allergy and 127 were identified, of whom 121 were invited to a Stage 3 clinical assessment. An additional 137 Stage 2 participants who were, for example, sensitised to a food they did not eat, were also invited for a clinical assessment. A total of 129 attended and although the overall response rate was below 60%, that of those with a probable IgE-mediated food allergy was higher at 57.85%. A total of 51 participants had their food allergy confirmed against the original target of at least 62 individuals. Most (68.57%) of the cases with probable IgE-mediated food allergy who came to a PAFA Stage 3 assessment had their allergy confirmed, and although confirmatory food challenges had been planned, many of the participants were not eligible due to other health conditions and medication. Of those who were eligible many declined. Nevertheless, thorough clinical assessment was undertaken by an expert panel who reviewed the records and arrived at a consensus as for the outcome of the clinical assessment.

The number of participants who were cases in Stage 2 and had their food allergy confirmed in Stage 3 gave a crude estimated prevalence of confirmed IgE-mediated food allergy of 5.73% (4.29-7.49, 95% CI). Not all those participants with a confirmed IgE-mediated food allergy were at risk of a severe or generalised reaction. Further detailed analysis of subtypes and severity will improve our understanding of these important aspects of food allergic disease. Following the clinical interview, the causative foods changed from those reported in Stage 1 or Stage 2 with some participants adding more, whilst for others certain foods were no longer reported. More than 80% of the adults assessed had complex, multiple food allergies, especially those associated with sensitisation to the major birch pollen allergen, Bet v 1. This is also similar to the observations in the EuroPrevall study where sensitisation to the birch pollen allergens Bet v 1 and the birch profilin allergen Bet v 2 was associated with food sensitisation (Burney et al., 2014) which can result in individuals reacting to multiple fresh foods. Similarly in Sweden, where 14.6% of the study participants were IgE-sensitised to birch pollen, it was associated with allergies to foods such as almond, apple, Brazil nut, hazelnut, kiwi, pear and walnut (Rentzos et al., 2019).

During the community survey a small number of individuals (n=13) who had reported adverse reactions to foods changed to reporting no adverse reactions in Stage 2, whilst a further 56 individuals who did not report reactions in Stage 1 - and were invited to Stage 2 as controls - changed their status and reported adverse reactions to foods, becoming

“new” cases. This was expected as it is part of the study design to ensure that as many as possible of those individuals reporting adverse reactions are identified and was observed in the EuroPrevall adult survey too (Lyons et al., 2019). However, the different mode of contact for controls, the low response rate of 20.8% and a different demographic profile mean that a more sophisticated approach needs to be adopted. This can be planned by using analysis techniques, such as random forest, to build a model using concatenated Stage 1 and Stage 2 data to impute missing data for both the cases and controls (Hong and Lynn, 2020, Shah et al., 2014). However, the effective application of such approaches requires in-depth analysis of the interrelationships of the study variables linked to a clear understanding of the mechanisms underlying the missing data. This will also be linked to the application of numerical severity scoring algorithms to symptom profiles which has been developed for large population studies (Fernández-Rivas et al., 2022).

Similar to the community survey participants, MAAS cohort participants were highly sensitised to Bet v 1 and had associated food allergies to fruit. Sensitisation to birch pollen was much lower in the IoW1989 cohort and fruit allergy is less common.

Geographic variations in the patterns and prevalence of pollen-associated IgE-mediated food allergy have been observed before, both in the multi-centre EuroPrevall study in adults (Lyons et al., 2019), but also in Sweden (Rentzos et al., 2019) and Japan (Kiguchi et al., 2021). Maps of important allergenic pollen-producing trees in the UK show that birch is widely found in the Northwest and the Isle of Wight with a density of between 59-2,501 trees per km2. However, the density of alder - another closely-related species of trees belonging to the Fagales - is much higher in the Northwest with a density of 37-789 trees per km2 compared to the Isle of Wight where such trees are uncommon ranging from 3-22 trees per km2 (McInnes et al., 2017). These differences are borne out in pollen count data where the alder and hazel pollen season in the Northwest of England starts in late January and lasts until the end of March with the birch pollen season then starting in early April and continuing until early May (Adams-Groom et al., 2020). In contrast there is no alder or hazel pollen in Southcentral or Southeast of England, where the birch pollen season again lasts from early April until early May (Adams-Groom et al., 2020). Alder pollen has been shown to be an important factor in PFAS in Japan (Kato et al., 2023).

The hypothesis that birch, and related alder and hazelnut nut pollen allergy, drives the development of many IgE-mediated food allergies in UK adults would indicate that certain regions of the UK, such as the IoW, Lincolnshire and the Wash - where such trees are

uncommon - might be expected to have lower rates of pollen-associated IgE-mediated food allergy.

Air pollution might also act as a driver in urban areas since it has been linked to increases in levels of expression of Bet v 1 in birch pollen (Ziemianin et al., 2021). There is also evidence that air pollution can have acute effects on those with food allergies having been associated with allergic exacerbations in China (Hou et al., 2021).

6.3 The trajectories of food allergy across the life course

The combination of the community survey and cohort follow up also allowed the PAFA study to demonstrate that childhood onset food allergy dominated in young adults.

However, around 70% of the older community survey participants (aged 18-70) reported that at least one of their allergies developed in adulthood. Key risk factors for childhood onset food allergy (compared to any other participant) were early onset eczema (remained even in comparison with atopic controls), co-existing asthma or allergic rhinitis (also compared to atopic controls), paternal asthma or hay fever or tree pollen sensitisation.

6.4 Adverse reactions to foods that are not mediated by IgE

Based on data from the community survey it is clear that a smaller number of individuals experienced possible non-IgE-mediated food allergies that had a time of onset greater than 4 hours with a crude estimated prevalence of 8.37% (7.6-9.18, 95% CI). However, during the clinical evaluations in PAFA Stage 3 it became evident that a significant number of the cases reporting symptom onset of less than 2 hours were also experiencing adverse reactions to food which were not consistent with an IgE-mediated food allergy. Indeed, the majority of doctor diagnoses that community survey participants reported in Stage 2 were associated with IBS. Causative foods include milk and cereals containing gluten, together with legumes such as chickpeas and lentils.

7. Conclusion

Prevalence of IgE-mediated food allergy in adulthood

The assessment of the community survey and follow-up data from the IoW and MAAS cohorts revealed that more than one third of the adult population report some type of adverse reaction to food, with cow's milk and cereals containing gluten being the major reported foods. A much smaller proportion of these adverse reactions are caused by IgE with around 7% of the adult population having a probable IgE-mediated food allergy and around 6% having a confirmed food allergy. It is clear that diagnosis of adult food allergy is complex and individuals often experience several different types of adverse reaction to food.

Major causative foods are plant-based and include peanut, tree nuts, fresh fruits (notably apple, peach and kiwi fruit). Other foods currently on Annex II of the food information for consumers regulation, such as soybean, celery, mustard and lupin, rarely caused IgE-mediated food allergy. Many of the plant-based food allergies are associated with sensitisation to birch pollen which results in individuals often having multiple food allergies. Allergies to animal derived foods are much less common and many, such as fish and molluscan shellfish allergies, are rare too.

The trajectories of food allergy across the life course

The PAFA project demonstrated that childhood food allergies persist into early adulthood and then further increase with around half of food allergies developing in later adulthood.

Adverse reactions to foods that are not mediated by IgE

There is a significant burden of adverse reactions to foods affecting around 8% of the adult population that are not mediated by IgE. However, this area is poorly described as diagnostic biomarkers are currently lacking.

8. Recommendations

- Further evidence is required to understand how new onset sensitisation to tree pollens, such as birch, alder and hazel contribute to a considerable number of new cases of food allergies later on in adulthood. It is also important to understand how the interactions with other environmental factors, such as pollution, climatic conditions and the impact of highly urbanised environments may further modify the numbers of adults with food allergy.
- Should the relationship between pollen exposure and adult food allergy be borne out this may be useful to predict areas of the country where food allergy rates might be higher and also understand how climate change and changing diets might affect the patterns and prevalence of food allergy in adults in future. The transition of the food system towards plant-based diets and alternative proteins poses poorly understood risks regarding food allergy, especially when coupled with drives to reduce food processing which may have both beneficial and detrimental effects on the allergenicity of foods but which is not well understood. There is a potential that exposure to novel food ingredients, which may contain higher levels of the allergens involved in pollen associated food allergies, could further increase the prevalence and burden of adult food allergy in the future.
- Some allergies are relatively rare in adulthood, such as milk and fish. Conducting an outpatient clinic survey may provide valuable confirmation as for the relative proportions of the different types of food allergy in the population.
- Around half of those with a probable IgE-mediated food allergy reported having been diagnosed with a food allergy in the past. It will be important to confirm this observation through interrogation of GP records whilst current ethical approvals are in place to verify this and gauge existing unmet health needs in terms of diagnosis.
- Indications from this study are that adverse reactions not consistent with an IgE-mediated food allergy are common and pose a significant health burden. There is the opportunity to follow up this study's subjects for a full clinical evaluation to provide confirmation of these adverse reactions. The PAFA study has also developed a biobank of serum/plasma and DNA samples to help support diagnosis of other conditions such as coeliac disease and persistent lactose intolerance. Diagnosis of many of these conditions is difficult and the case control

study structure of PAFA lends itself to supporting efforts to identify novel biomarkers based on multi-omic technology.

- Linking data on prevalence and severity with research on quality of life and economic cost will help define the impact that adult food allergy has on food allergic consumers.

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