

Prevalence of food allergy and intolerance in the adult Dutch population

Jeannette J. Niestijl Jansen, MD,^a Alwine F. M. Kardinaal, MSc,^a

Geertje Huijbers, RD,^a Berber J. Vlieg-Boerstra, RD,^b

Ben P. M. Martens, MD,^b and Theo Ockhuizen, PhD^a

Zeist and Utrecht, The Netherlands

The prevalence of food allergy and intolerance (FA/FI) was studied in a random sample (n = 1483) of the Dutch adult population. First, the self-reported FA/FI reactions were investigated by questionnaire. Subsequently, in a clinical follow-up study, it was determined in how many cases this self-reported FA/FI could be objectively confirmed by double-blind placebo-controlled food challenge. More than 10% of the population (12.4%) reported FA/FI to specific food(s). Of the 144 subjects potentially available for the clinical follow-up study, 73 completed the whole protocol. In 12 subjects FA/FI could be confirmed by double-blind placebo-controlled food challenge. This indicates a minimum prevalence of FA/FI in the population of 0.8% (12 of 1483). Assuming that FA/FI is equal among participants, nonparticipants, and dropouts, the prevalence of FA/FI in the Dutch adult population is estimated to be 2.4%. The food (ingredients) involved included pork, white wine, and menthol. Two persons reacted to additives. In three persons glucose intolerance was observed. However, these specific intolerances probably do not reflect the distribution in the general population because the study population formed an extremely heterogeneous group, both with regard to the offending foods and the symptoms. The majority of the subjects had no serious complaints that required medical advice. We conclude that there is a gap between self-reported FA/FI and FA/FI that can be objectively confirmed by double-blind placebo-controlled food challenge. (J ALLERGY CLIN IMMUNOL 1994;93:446-56.)

Key words: Prevalence, food allergy or intolerance, double-blind placebo-controlled food challenge

In the past decade food allergy (FA) and food intolerance (FI) have attracted more public attention than ever before, not only in the Netherlands, but also in other industrialized countries such as Great Britain and the United States. However, the extent of FA/FI in an open population has scarcely been studied.¹ This lack of prevalence data makes it difficult to decide on health policy

Abbreviations used

DBPCFC:	Double-blind placebo-controlled food challenge
FA:	Food allergy
FI:	Food intolerance
p-GTT:	Prolonged glucose tolerance test

From ^athe Department of Human Nutrition, Netherlands Organization for Applied Scientific Research Toxicology and Nutrition Institute, Zeist; and ^bClinical Division, Allergy Centre Utrecht.

Supported by grants from the Netherlands Prevention Fund and the Ministry of Welfare, Health and Cultural Affairs. Received for publication Sept. 22, 1992; revised July 15, 1993; accepted for publication July 20, 1993.

Reprint requests: Alwine F. M. Kardinaal, MSc, Department of Human Nutrition, TNO Toxicology and Nutrition Institute, P.O. Box 360, 3700 AJ Zeist, The Netherlands.

Copyright © 1994 by Mosby-Year Book, Inc.
0091-6749/94 \$3.00 + 0 1/1/50231

measures and to reliably determine a possible increase of the problem.

A small number of studies have been conducted on the population level.²⁻⁶ Subjects were asked if they had ever experienced adverse reactions to foods. The number of persons who responded positively varied from 4.9%⁴ to 33%.² In the study by Cohen et al.⁴ among American blood donors, an attempt was made for an objective assessment of FA or FI: in 23% of the subjects a self-reported adverse reaction to food could be confirmed by double-blind food challenge, which indicates a

real prevalence of 1%. In a survey population in the United Kingdom, Young et al.⁵ could confirm an adverse reaction to food additives in only 0.026%, whereas 7.4% had claimed such a reaction. In a recent study by Young⁶ the self-reported FI to additives in the United Kingdom had decreased to 5.3%. Estimates of the prevalence of FA/FI for the total population, based on studies among selected patient populations, are in the range of 0.1% to 2%.⁷⁻⁹ The prevalence of FA/FI among children has been studied more often.¹⁰⁻¹⁵ In a prospective study in the Netherlands¹⁵ in a random population of infants, followed from birth until the age of 6 months, 5.3% showed symptoms that might have been due to food allergy. This diagnosis was confirmed by positive results of elimination and rechallenge in 1.7%. Recently, a study on alleged FA/FI among Dutch children, aged 0 to 5 years, has been published. According to 11.4% of the parents interviewed, their child was allergic or intolerant to food or food ingredients.¹⁶ The prevalence of FA/FI in the adult Dutch population was not known. Therefore we restricted our study population to subjects over the age of 18. The aim of our study was to assess the prevalence of FA/FI that can be objectively confirmed by double-blind placebo-controlled food challenge (DBPCFC).

METHODS

Study design

In the fall of 1989, about 1500 persons, aged 18 to 70 years, completed a questionnaire on adverse food reactions in a door-to-door survey.¹⁷ Hereto, a random sample was drawn from the complete housing register of Utrecht and five smaller municipalities (encompassing about 150,000 inhabitants). Each interviewer received one address from which to proceed in obtaining five interviews. Excluded were persons outside the age range, and persons of nonnative ethnic origin. The sample obtained was representative of the Dutch adult population with regard to age, education, and socioeconomic class, as well as prevalence of self-reported food intolerance; this was assessed by comparing the results of the regional sample with those of a national sample of more than 6500 persons, obtained by the same procedure. For practical reasons, the follow-up study described here was limited to the regional survey. The interview was introduced as a study on food and nutrition, intended to minimize selective response. The central question was: "Do you have allergic or intolerance reactions after eating or drinking specific foods; or are there any foods you don't use any more because they give you trouble?" Other relevant background information was gathered such as age, education, and occupation, type of food, type and severity of reaction,

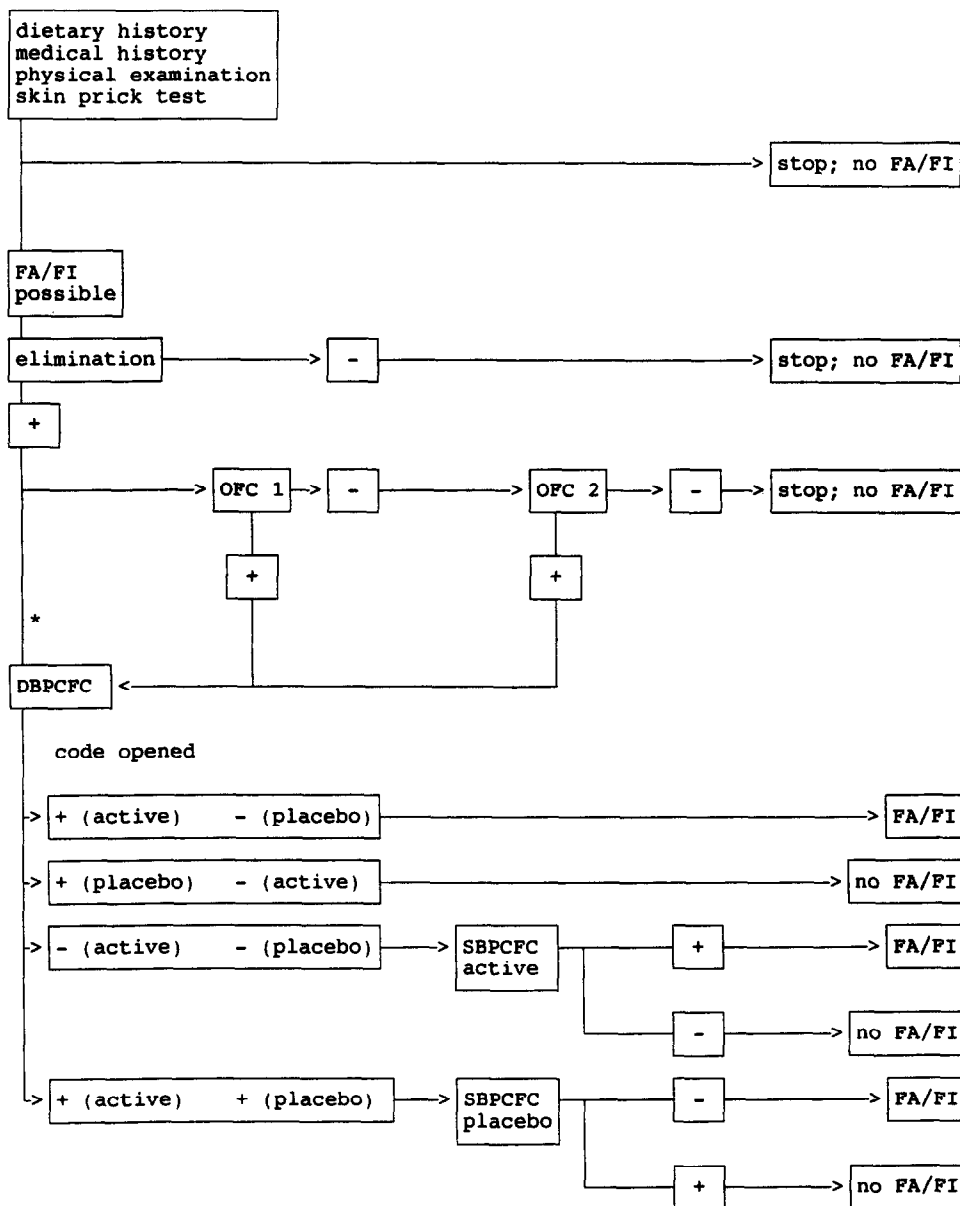
diagnosis by a physician, and allergic reactions to non-food agents. Name and address was acquired from those who answered positively to the central question. These subjects were contacted in the period from October 1990 to March 1992 to participate in a clinical follow-up study. The study was approved by the Institute's medical-ethical review board.

A range of consecutive diagnostic procedures^{18, 19} was followed to objectively assess a reproducible adverse reaction after ingestion of the offending food or food ingredient (Fig. 1). After each diagnostic phase the probability of FA/FI was evaluated by the research team, which consisted of a research physician, an experienced dietitian, a research dietitian, and a consulting dermatologist/allergist. The outcome of the evaluations determined whether a subject was excluded or included for further investigations. Only confirmation by DBPCFC was accepted as definitive evidence of food allergy or intolerance.

It should be stressed that subjects in this study were not patients who had been invited to participate because of clinical symptoms but representatives of a healthy population who had self-defined food allergy as the cause of minor or major health disorders.

Diagnostic procedures

The first diagnostic phase consisted of a medical and dietary history and a skin prick test. The medical history included questions on family history, atopic constitution, offending food(s), reproducibility, time between intake and onset of the symptoms, use of medication, role of alcohol intake, and physical exertion. A physical examination was performed and a differential diagnosis was made to evaluate other causes of the presented symptoms. Subsequently, a detailed dietary history was taken, with specific attention paid to intake of known triggers of intolerance reactions and the (time) relationship between the intake of specific foods and symptoms.²⁰ On the same day a skin prick test was performed with a standard range of extracts of foods and food ingredients (apple, banana, beef, butter bean, cocoa, carrot, cayenne pepper, celery, milk, cucumber, codfish, coriander, egg white, egg yolk, grape, hazelnut, kiwi, onion, orange, paprika, pea, peanut, pork, potato, shrimp, soybean, spinach, tomato, walnut, wheat, white cabbage, yeast [ARTU Biologicals, Lelystad, Netherlands]) and inhalant allergens (Allergolisk Laboratories, Copenhagen, Denmark); the range was completed with other offending food(s) mentioned in the history. A positive skin prick test result was defined as a wheal of 2 mm or greater in diameter (after subtracting the diameter of any wheal produced by the diluent control). Controls for skin testing were the phosphate-buffered diluent and histamine, 1 mg/ml, applied by the same technique. Blood samples were drawn and stored at -20° C. In case of confirmation of FA/FI by DBPCFC, the respective blood samples were tested in the Central Laboratory of the Netherlands Red Cross Blood Trans-



* additives or biogenic amines suspected; open provocation not feasible;

FIG. 1. Diagnostic flow chart. OFC, Open food challenge; SBPCFC, single-blind placebo-controlled food challenge.

fusion Service (Amsterdam, Netherlands) for corresponding IgE-specific antibodies.

Excluded in this stage were only subjects for whom the previously self-reported adverse reactions were clearly refuted by the history. All other subjects proceeded to the next phase, elimination of the suspected food substance from the diet. All subjects were individually instructed by the dietitian. The dietary prescription was followed until the subject completed his or her participation in the study. The purpose of this elimination was to reduce the symptoms before the provocation procedure was applied. The elimination strategy

aimed at the best chance for eliminating all symptoms at the lowest cost to the subject, as concerns acceptance of the diet. The interval before provocation was 2 weeks for foods and food ingredients, 3 weeks for biogenic amine-rich foods, and 4 weeks for food additives. These intervals were considered to be the minimum period necessary for a clear reduction of symptoms on the basis of the authors' experience. During this period the severity of symptoms was registered in a diary by the subjects. On the basis of this symptom score and self-estimated improvement, the effect of the elimination was calculated. A 50% reduction of symptoms was

required for proceeding to the challenge procedure; in case of less improvement, the suspected food was to be excluded as a main cause of symptoms.

The foods selected for challenge were those most likely to provoke symptoms, according to history. Consistency of reported relationship between intake and symptoms was taken into account, as well as measurability and severity of symptoms. For example, a food reported to cause reproducible, immediate swelling of the face was preferred for challenge to a food said to elicit mild pruritus after 24 hours. If the food chosen did not elicit any reaction, a second food, if reported to cause symptoms, was to be administered. All provocations took place under strict medical observation for at least 2 hours. During the observation time blood pressure, pulse rate, forced expiratory volume in 1 second and peak expiratory flow were measured every half hour with a Mini Wright Ventilometer VM1 (Clement Clarke International, Harlow, Essex, U.K.). Also, all objectively observable symptoms and complaints noted by the subject were registered. After each provocation, any late symptoms were recorded in a diary by the subject for 2 to 4 days, and verified by the physician as much as possible. Subjects with a history of life-threatening reactions were to be excluded from challenge. If possible, the suspected food was reintroduced in an open challenge. Provocation took place with the amount usually consumed, unless the history indicated a definite reaction to smaller amounts or a very severe reaction. If no symptoms evolved, the open provocation was repeated with a higher dose after at least 2 to 7 days. Subjects showing a positive reaction on open provocation were subsequently challenged in double-blind fashion. If additives or biogenic amines were suspected, open provocation was not feasible, and the subjects were directly challenged in double-blind fashion with capsules. Whenever possible, the double-blind provocation was performed with the food substance in freeze-dried form, packed in opaque, titanium dioxide-coated gelatin capsules. However, if the food was not available in dried form, if the indicated test dose was too large, or if the symptoms were mainly oropharyngeal in nature, the suspected food was masked in another vehicle to make it indistinguishable from the placebo.²¹ Subjects were challenged first randomly with either food or placebo, and the interval before the second part of the DBPCFC was at least 1 week. Confirmation by DBPCFC was accepted if the subject had clear symptoms after provocation with the active substance and no symptoms after the placebo challenge. If the result of the DBPCFC was equivocal, a third single-blind challenge according to the protocol (Fig. 1) was performed to exclude or confirm the reaction. Subjects suspected of intolerance to mono- and disaccharides were subjected to a prolonged glucose tolerance test (p-GGT) with 75 gm glucose given orally. Blood glucose levels were measured every 30 minutes until 3.5 hours after the test dose with an Exactech Companion blood glucose sensor (Medisense,

Cambridge, Mass.). A positive result was defined as a nadir blood glucose concentration of 2.8 mmol/L or less in combination with clinical symptoms of hypoglycemia.

Data analysis

Descriptive statistics were calculated to assess the frequency of self-reported and confirmed food allergy and intolerance in both the study and source populations. To assess possible selection bias, nonparticipants and dropouts were compared with the subjects who completed the study. Subjects from higher occupational groups and subjects who had other allergies were significantly more willing to participate in the clinical follow-up study (Table I). Subjects who dropped out during the follow-up study had an atopic constitution (defined as manifesting allergy symptoms in combination with at least two positive skin prick test results of which at least one was caused by an inhalant allergen) more often than subjects who completed all the necessary procedures. Although other allergies were more prevalent in the study population as compared with the general population, this factor was not predictive of the confirmation of self-reported FA/FI, nor was atopy or any other factor (age, sex, occupation, reported symptoms). This means that nonparticipation or dropout did not give rise to measurable selection bias.

Statistical analyses were performed with the chi square test and Fisher's exact test, with the use of the BMDP statistical software package (BMDP Statistical Software, Inc., Los Angeles, Calif.).²²

RESULTS

Response

Of the 1483 persons who responded to the questionnaire (86% of the contacted sample), 198 claimed allergy or intolerance reactions to specific foods. Of these 198 persons, 144 (73%) gave their names and addresses and therefore were potentially available for the clinical follow-up study. The final population in the follow-up study consisted of 90 subjects who agreed to participate; 54 persons refused (Table II). After the first diagnostic phase, there was a reasonable indication for FA/FI in 54 subjects. Of those, 17 subjects dropped out for several reasons (Table II). The remaining 37 subjects all completed the necessary procedures (Fig. 2).

Self-reported food allergy or intolerance

The survey population comprised more women than men (65% and 35%, respectively). Women more often reported adverse reactions to food than men (15% and 9%, respectively). Adjusted for sex, 12.4% of the population reported food allergy or intolerance reactions to specific foods.

TABLE I. Survey-derived characteristics of participants and nonparticipants in the clinical follow-up study

Characteristics	Participants (%) (n = 90)	Nonparticipants (%) (n = 108)	p Value
Sex			
Men	28	22	NS
Women	72	78	
Age (yr)			
18-24	9	16	
25-34	24	29	
35-44	27	16	NS
45-54	10	13	
55-64	19	11	
65-69	11	16	
Occupational group			
High	70	51	
Low	13	27	<0.05
Housewives	17	22	
Other allergies, total	77	54	<0.01
Pollen allergy	14	11	NS
House dust allergy	31	17	<0.05
Allergy to domestic animals	21	9	<0.05
Symptoms related to food intake*			
Skin	41	46	NS
Oral	6	7	NS
Gastrointestinal	34	28	NS
Respiratory	9	15	NS
Headache	7	4	NS
Neurologic	1	5	NS
Miscellaneous	8	7	NS
No symptoms mentioned	17	14	NS
Severity of the symptoms			
Very severe	15	15	
Moderately severe	29	18	NS
Uncomfortable	56	67	

NS, Not significant.

*More than one item could be scored; percentages do not add up to 100%.

TABLE II. Reasons for nonparticipation in and dropout during the clinical follow-up study

Reasons	Nonparticipation (n = 54)	Dropout (n = 17)
Lack of time	17	6
Fear of severe reactions	2	6
Interfering medical problems	—	2
No interest	7	—
No FA/FI any more	4	—
Other reasons	16	3
Not contacted	8	—

Food groups mentioned most frequently were fruit, chocolate, and vegetables. Only 1.6% of the population said that they were intolerant to additives (Table III). FA/FI was reported more often by women ($p < 0.005$), persons with other allergies ($p < 0.001$), and persons with allergic family members ($p < 0.0001$). Age, education, and occupational group were not associated with reporting FA/FI.

Confirmed food allergy or intolerance

In 36 of the 90 subjects who started the clinical follow-up study, a relationship between symptoms and food intake was excluded after the first diagnostic phase. Their personal suspicion of FA/FI could not be substantiated in any way. Almost

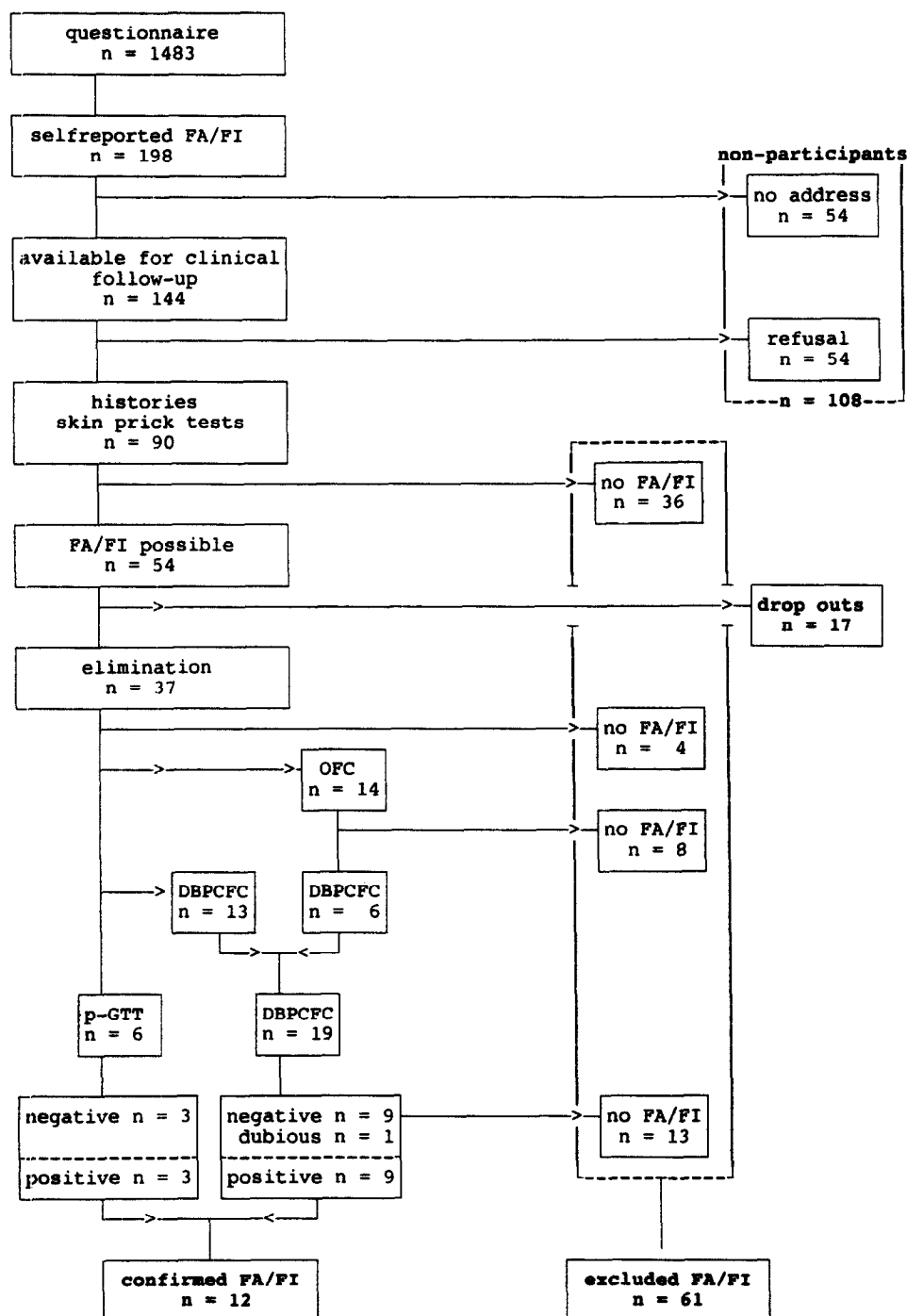


FIG. 2. Flow diagram of the results. OFC, Open food challenge.

half of these persons reported indigestion after a heavy, fatty meal and did not mention specific foods (apart from "fat" or "cholesterol"). Examples of other supposed relationships that were excluded from further study were those between cocoa and multiple sclerosis and between choco-

late and acne. Also excluded were subjects who reported only nonfood or contact allergies, who could not mention any food that caused an adverse reaction, or who were clearly alcoholic.

On the basis of history and skin prick test results, FA/FI was identified as a possible cause of

TABLE III. Foods and ingredients mentioned in the survey as causes of FA/FI

Food/ingredient	Percent of the total population
Chocolate	2.2
Vegetables	2.2
Fruit	1.6
Animal fat	1.6
Additives*	1.6
Pork	1.1
Herbs and condiments	0.9
Milk products	0.7
Alcoholic beverages	0.7

*Sum of food colorings, food preservatives, monosodium glutamate, fragrances, and flavorings.

the symptoms in 54 subjects. Of those, 37 subjects were willing to undergo provocation with the suspected food or food ingredient. In 14 subjects an open provocation could be performed. A positive reaction occurred in only six subjects; the remaining eight persons were excluded from the study when no symptoms occurred after two subsequently performed open provocations with the suspected food. Open provocation was not feasible in 17 subjects; these were considered for direct DBPCFC. Four subjects were excluded before provocation because there was far less than 50% improvement of their symptoms after the elimination period. For six subjects, who were suspected of having intolerance to mono- and disaccharides, a p-GTT was performed. Positive results were found in three of these subjects, including both a nadir glucose concentration below 2.8 mmol/L and symptoms such as visual complaints, transpiration, dizziness, and weakness.

FA/FI could be confirmed by DBPCFC in 12 subjects. Table IV shows the most important characteristics of these subjects. Intolerance to additives could be confirmed in two subjects, glucose intolerance in three subjects, and intolerance to histamine in another two subjects. In the remaining subjects, symptoms were caused by kiwi, white wine, trassi, pork, and menthol, respectively.

The young man who suspected allergy to kiwi reported an itching throat immediately after consuming a small amount. Double-blind challenge was performed with a blended fruit mix in which the kiwi pips were imitated, in both active and placebo food, by blackberry jam. The kiwi-con-

taining mix caused itching and coughing 5 minutes after consumption of 3 to 4 teaspoons, containing 3 to 4 gm of kiwi. The placebo mix did not elicit any reaction. A 39-year-old woman had reacted twice to a convenience food (salad, dried vegetables) with angioedema and swollen lips within 20 minutes after consumption; symptoms disappeared after administration of an antihistamine medication. Double-blind challenge was performed with capsules; because the history did not identify the most likely agent, a consecutive challenge with different additives was chosen: first 10 mg of tartrazine, then, and with 30-minute intervals, 500 mg of monosodium glutamate, 50 and 100 mg of sodium benzoate, and 100 mg of sodium sorbate. The observed swelling of face and hands subsided after 3 hours.

Subject E (Table IV) suspected that grapes, shrimp, and cocoa caused urticaria and pruritus; however, elimination of these foods from the diet did not decrease her symptoms. Reevaluation resulted in elimination of biogenic amines and histamine liberators and subsequent decrease in symptoms and use of medication. Challenge with the active capsules (105 mg histamine) elicited urticaria within 1 hour. Subject B reported flushing after consumption of two sips of an alcoholic drink. Open challenge with 80 ml of white wine showed swelling of eyelids and flushing after 10 minutes; double-blind challenge with 40 ml of white wine also caused flushing. Subject F was challenged with vanillin and sodium benzoate (first dose 10 mg and 50 mg, respectively; second dose, after 1 hour, 25 mg and 250 mg). Although complaints were only subjective in the first active challenge (dizziness, headache, coldness, difficulty with reading), a consecutive single-blind challenge (with 10 mg of vanillin and 250 gm of benzoate, repeated after 1 hour) showed a visible response in a greying and one-sided distortion of the face.

Other positive challenges included a skin reaction and diarrhea 2 hours after consumption of a few grams of trassi (a condiment containing dried shrimp); extreme transpiration several hours after consumption of a relatively large (200 gm) portion of pork, accompanied by an alcoholic drink (alcohol alone did not elicit any reaction, neither did the combination of beef and alcohol); aggravation of aphthae within 1 hour after challenge with menthol; tachycardia and hypertension after oral challenge with 50 mg of histamine.

In most of these cases, DBPCFC had to be performed with masked foods, either because the

TABLE IV. Self-reported food allergy or intolerance confirmed by DBPCFC

Subject	Age (yr)	Sex	Symptoms	Food (substance)	Interval
A	63	M	Perspiration	Pork + alcohol	> 12 hr
B	51	F	Flush	White wine	30 min
C	58	F	Aphthae	Menthol	1 hr
D	27	M	Itching of throat	Kiwi fruit	Immediate
E	62	F	Urticaria	Histamine	1 hr
F	40	F	Migraine, neurologic symptoms	Vanillin + benzoic acid	1 hr
G	62	M	Dizziness, blurred vision, transpiration	Glucose	2.5 hr
H	32	F	Tremor, visual disorders	Glucose	3.5 hr
I	58	F	Tremor, blurred vision, transpiration	Glucose	2.5 hr
J	39	F	Angioedema	Tartrazine, MSG + benzoic acid + sorbic acid	1 hr
K	58	F	Palpitations, hypertension	Histamine	1.5 hr
L	38	M	Rash, prurigo	Trassi*	ca 12 hr

MSG, Monosodium glutamate.

*Indonesian condiment prepared from pulverized dried fish and shrimp.

challenge dose was too large for capsule challenge or because the suspected food was not available in capsules. In each case, ample attention was given to the development of an active and a placebo food, which looked and tasted equal and were tested by a volunteer panel before being used for challenge.

Only the reaction to kiwi could be confirmed as FA by positive skin prick test (+ + + +) and RAST (+). Four persons (subjects E, H, J, and K) in whom FA/FI was confirmed had consulted a doctor for their complaints. The majority of the subjects we saw during the clinical follow-up study had no serious complaints that required medical advice.

Prevalence

In conclusion, in 16% (12 of 73) of the subjects with self-reported FA/FI who completed all necessary procedures, FA/FI could be objectively confirmed by DBPCFC. This means a prevalence of food allergy and intolerance in the source population of 0.8% (12 of 1483). Although selection bias cannot be ruled out completely, it was not expressed in the distribution of background variables in participants ($n = 90$) and nonparticipants ($n = 108$). Therefore assuming that the prevalence of FA/FI is equal among participants and nonparticipants (i.e., assuming that 16% of all self-reported FA/FI may be confirmed by

DBFC), the prevalence of food allergy or intolerance in the adult Dutch population is estimated to be 2.4% (1.8% in men and 2.9% in women, the difference being nonsignificant).

DISCUSSION

The results of the present study indicate a prevalence of about 12% for self-reported FA/FI, the prevalence being higher in women (15%) than men (9%). Higher prevalences, but a comparable difference between women and men, were found by Burr and Merrett³ (26% and 19%, respectively) and also by Bender and Matthews² (39% and 26%). Young et al.⁵ reported that 17% of the British population perceive problems with foods or food additives. A much lower prevalence has been found by Cohen et al.⁴ This large variation in prevalence figures can be explained by the subjective nature of the relationship between complaints and food consumption, the varying ways in which the survey questions were formulated, and the amount of media publicity devoted to adverse food reactions at the time of the study. The prevalence of objectively confirmed reactions has been shown or estimated to be much lower.^{4, 5, 7} In our study the proportion of self-reported reactions that could be confirmed is equal in men and women. This means that because more women reported reactions, the prevalence of adverse reactions to foods in our population is higher in

women (2.9%) than in men (1.8%). However, this difference is not statistically significant.

Clinical studies have demonstrated the general unreliability of patient history, skin tests, RAST, and various other methods in accurately predicting the presence of FA/FI, compared with DBPCFC.^{8, 23-26} The ideal prevalence study design would be to challenge all subjects in a representative sample of the population with DBPCFC, and a highly standardized procedure.¹⁹ However, a prerequisite for use of DBPCFC is that a specific relationship between food consumption and symptoms is suspected by either the subject or the physician. If no such relationship can be demonstrated, DBPCFC is not possible. A preselection of subjects for DBPCFC is necessary. Therefore in our study we chose to preselect persons for DBPCFC by subsequent steps: questionnaire, medical and dietary history, skin test, elimination diet, and open provocation. Evaluations were made on the basis of objectively observed evidence, as much as possible. In case of equivocal results, the person was given the benefit of the doubt, until in another phase the possibility of FA/FI could be firmly rejected. However, in each diagnostic step, misclassification cannot be completely excluded. Persons may have been diagnosed as having no FA/FI before reaching the phase of the "gold standard." Moreover, the DBPCFC was performed only once, sometimes followed by a single-blind challenge. In the Workshop on Experimental Methodology for Clinical Studies of Adverse Reactions to Foods and Food Additives,¹⁸ it was advised to perform a second or even third DBPCFC in case of mild or equivocal symptoms. When objective symptoms are being evaluated, a single DBPCFC is generally deemed sufficient to establish a diagnosis.^{8, 23, 26} The Dutch Consensus Meeting²⁷ also agreed on a single DBPCFC to confirm adverse reactions in clinical practice. We believe that repeated challenges, implicating more visits to our Institute, could have seriously reduced the number of participants.

In subjects in whom glucose intolerance was suspected, a p-GTT was performed. We realize that this method of diagnosis is liable to be criticized because its sensitivity and specificity are not exactly known. However, there is no consensus on the use of any other method either.^{28, 29} It has been suggested that the p-GTT be abandoned as a diagnostic test and that hypoglycemia be documented after ordinary meals³⁰ or that blood glucose levels be measured during spontaneously occurring symptomatic episodes.^{31, 32} In a preva-

lence type of study in which the biologic mechanism is not the object of study, it may indeed be preferred to perform a DBPCFC with sugar or sugar-rich food and observe any objective symptoms.

The first, and maybe most important, selection has been to invite for further clinical investigation only those persons who reported an adverse reaction to foods in the questionnaire. Those with a genuine FA/FI who did not relate their symptoms to food intake have been missed. We could possibly have improved on the study design by inviting for medical and dietary history skin tests a subsample of those who answered negatively in the questionnaire. In spite of this, we believe that the study design chosen allowed us to obtain a fair estimate of FA/FI in the general population.

The prevalence of 0.8% of the adult Dutch population with FA/FI, confirmed by DBPCFC, is the minimum estimate. Because only 37% (73 of 198) of the potential population for clinical follow-up completed the study, assumptions for nonparticipants need to be made. On the assumption that the prevalence of FA/FI is equal in participants, nonparticipants, and dropouts, a best estimate of 2.4% is reached. In only one of 12 subjects with confirmed FA/FI could an IgE-mediated reaction be demonstrated. This would be 0.2%, which is also the prevalence of FA in adults, as estimated by Chandra.³³ Of course, these small numbers do not allow us to draw firm conclusions about the exact proportions in the total population. There are arguments supporting a higher prevalence and other arguments supporting a lower real prevalence of FA/FI than the estimate based on equal proportions among participants and nonparticipants (including dropouts). First, subjects with FA/FI causing severe symptoms may have refused participation because of fear of adverse reactions by provocation. Second, we may have failed to identify the right food; provocation with the wrong food would not have elicited any reaction and thus the subject would have been wrongly diagnosed as having no FA/FI. Finally, inherent in food challenge is the possibility that the doses chosen may have been too low, possibly because the reaction threshold has increased after a period of elimination diet. In these cases real prevalence may be higher than our estimate. On the other hand, especially those subjects who had reproducible symptoms clearly related to food may have been more eager to participate, whereas subjects who saw no benefit

in participation were those who did not really have adverse reactions to food. The direction in which these factors will influence real prevalence cannot be measured, but they will partly counterbalance each other.

Possible selective recruitment of subjects was evaluated by comparing participants with nonparticipants on the basis of population characteristics (Table I). On average, participants belonged to a higher occupational category and reported allergy to other environmental factors more often than nonparticipants. However, these factors did not appear to influence the actual assessment of FA/FI. Therefore these comparisons support our best estimate of FA/FI of 2.4% in the whole adult population. None of the variables measured was associated with the presence of confirmed FA/FI. This means that in clinical practice it will be impossible to predict the chances of actual FA/FI on the basis of age, sex, atopy, or symptoms. Our results, once again, show that a patient's history is not enough to warrant the diagnosis of FA/FI and subsequent food elimination: appropriate testing procedures are necessary.

Adverse reactions to food do not seem to be a major health problem in the Netherlands. Our study population formed an extremely heterogeneous group. The majority of subjects had mild symptoms, which in many cases will not result in use of the health care system. Therefore studies based on allergy clinic populations may present a very different view. The foods or food ingredients involved varied, as did the symptoms. Their relative importance cannot be assessed from the results of our study. This heterogeneity makes it very difficult to suggest any coordinated action for direct support to persons with more severe forms of FA/FI. Because FA/FI, not only in our study, but in the whole population, is expressed by various symptoms caused by various foods, diagnosis will often be difficult. This may lead to an overestimation of the role of food and unjustified dietary restrictions in some cases, especially if no other cause of symptoms can be found. However, it can also result in chronic complaints, which can easily be cured if the diagnosis of FA/FI has been made. In our opinion, the large gap between self-reported and clinically confirmed FA/FI constitutes a challenge for health educators. A realistic appraisal of FA/FI may also be supported by making information available to the public, as the Dutch government has done by installing a national information bureau on FA/FI. The need for information is conceivably better reflected in the

self-reported prevalence of FA/FI than in the actual prevalence.

In conclusion, food allergy and intolerance do occur among adults, but not to the extent that is indicated by results of questionnaire surveys. In 0.8% to 2.4% of the adult population, the relationship between adverse reactions and foods can be objectively confirmed. In the majority of cases relatively mild symptoms, for which no medical help is required, are experienced. Nonimmunologically mediated reactions seem to occur far more often than true allergic reactions. The prevalence of FA/FI was not associated with age, occupational category, atopic status, previous gastrointestinal disorders, or reported symptoms; there is a nonsignificant tendency for a higher prevalence among women. To gain insight into possible risk factors, a study of more specifically defined intolerances is needed.

We thank Ann Colen for technical assistance in preparing the challenge foods.

REFERENCES

1. Nichaman MZ, McPherson RS. Estimating prevalence of adverse reactions to foods: principles and constraints. *J ALLERGY CLIN IMMUNOL* 1986;78:148-54.
2. Bender AE, Matthews DR. Adverse reactions to foods. *Br J Nutr* 1981;46:403-7.
3. Burr ML, Merrett TG. Food intolerance: a community survey. *Br J Nutr* 1983;49:217-9.
4. Cohen M, Splansky GL, Gallagher J, Bernstein DI, Bernstein IL. Epidemiologic survey and validation of adverse food reactions (AFR) in adult populations [Abstract]. *J ALLERGY CLIN IMMUNOL* 1985;75:206.
5. Young E, Patel S, Stoneham M. The prevalence of reaction to food additives in a survey population. *J R Coll Physicians Lond* 1987;21:241-7.
6. Young E. Atopy, allergy and the alimentary canal. *Proc Nutr Soc* 1991;50:299-303.
7. Commission of the European Communities. Report of a working group on adverse reactions to ingested additives. III/556/81-EN. Brussels: Commission of the European Communities, 1981.
8. Sampson HA. Immunologically mediated food allergy: the importance of food challenge procedures. *Ann Allergy* 1988;60:262-9.
9. Juhlin L. Incidence of intolerance to food additives. *Int J Dermatol* 1980;19:548-51.
10. Kajosaari M. Food allergy in Finnish children aged 1 to 6 years. *Acta Paediatr Scand* 1982;71:815-9.
11. Jakobsson I, Lindberg T. A prospective study of cow's milk protein intolerance in Swedish infants. *Acta Paediatr Scand* 1979;68:853-9.
12. Bahna SL. Control of milk allergy: a challenge for physicians, mothers and industry. *Ann Allergy* 1978;41:1-12.
13. Wood CBS. How common is food allergy? *Acta Paediatr Scand* 1986;323:76-83.
14. Host A, Husby S, Osterballe O. A prospective study of

- cow's milk allergy in exclusively breast-fed infants. *Acta Paediatr Scand* 1988;77:663-70.
15. Douwes AC, Van Weert-Waltman ML, Folkertsma K, Fagel IFM, Verboom WSW. Prevalentie van voedselallergie bij Amsterdamse zuigelingen. *Ned Tijdschr Geneesk* 1988;132:1392-6.
 16. Van Bockel-Geelkerken M, Meulmeester JF. Prevalentie van vermeende voedsel-overgevoeligheid bij kleuters. *Ned Tijdschr Geneesk* 1992;136:1351-6.
 17. Kardinaal AFM. Epidemiology of food allergy and food intolerance. In: Somogyi JC, Müller HR, Ockhuizen TH, eds. Food allergy and food intolerance. Nutritional aspects and developments. *Bibliotheca Nutritio et Dieta* 48. Basel: Karger, 1991:105-15.
 18. Metcalfe DD, Sampson HA. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J ALLERGY CLIN IMMUNOL* 1990; 86(suppl):421-42.
 19. Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. *J ALLERGY CLIN IMMUNOL* 1988;82: 986-97.
 20. Vlieg-Boerstra BJ, Martens BPM, Huijbers GB, Kardinaal AFM, Niestijl Jansen JJ. Dietary assessment as a dietitian's tool in diagnosing food allergy and food intolerance 1992 (submitted for publication).
 21. Huijbers GB, Colen AAB, Niestijl Jansen JJ, et al. Masking foods for food challenge. Practical aspects of masking foods for double-blind placebo-controlled food challenge. *J Am Diet Assoc* (accepted for publication).
 22. Dixon WJ, ed. *BMDP Statistical Software Manual*. Berkeley: University of California Press, 1988.
 23. Leinhas JL, McCaskill CC, Sampson HA. Food allergy challenges: guidelines and implications. *J Am Diet Assoc* 1987;87:604-8.
 24. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients. II. A detailed analysis of reaction patterns during oral food challenge. *J ALLERGY CLIN IMMUNOL* 1985;75:356-63.
 25. Bernstein M, Day JH, Welsh A. Double-blind food challenge in the diagnosis of food sensitivity in the adult. *J ALLERGY CLIN IMMUNOL* 1982;70:205-10.
 26. Pastorello EA, Stocchi L, Pravettoni V, et al. Role of the elimination diet in adults with food allergy. *J ALLERGY CLIN IMMUNOL* 1989;84:475-83.
 27. Working Committee Consensusbijeenkomst voedselovergevoeligheid (Consensus Meeting on Adverse Reactions to Food). Resultaat van een consensusbijeenkomst (Results of a consensus meeting). Utrecht: National Organization for Quality Assurance in Hospitals, 1991.
 28. Lefèbvre PJ, Andreani D, Marks V, Creutzfeldt W. Statement on post-prandial or reactive hypoglycaemia [Letter]. *Diabet Med* 1988;5:200.
 29. Johnson DD, Dorr KE, Swenson WM, Service FJ. Reactive hypoglycemia. *JAMA* 1980;243:1151-5.
 30. Betteridge DJ. Reactive hypoglycemia. *Br Med J* 1987; 295:286-7.
 31. Gale E. Causes of hypoglycaemia. *Br J Hosp Med* 1985; 28:159-62.
 32. Palardy J, Havrankova J, Lepage R, et al. Blood glucose measurements during symptomatic episodes in patients with suspected postprandial hypoglycemia. *New Engl J Med* 1989;321:1421-5.
 33. Chandra RK. Food allergy: 1992 and beyond. *Nutr Res* 1992;12:93-9.
 34. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients. I. Correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenge. *J ALLERGY CLIN IMMUNOL* 1985;75:348-55.