

**PREVALENCE OF FOOD SENSITIZATION AND PROBABLE
FOOD ALLERGY AMONG ADULTS IN INDIA: THE
EUROPREVALL-INCO STUDY**

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1 **Abstract**

2 Background: Data is lacking regarding the prevalence of food sensitization and probable food allergy
3 among general population in India. We report the prevalence of sensitization and prevalence of
4 probable food allergy to 24 common foods among adults from general population in Karnataka,
5 South India.

6 Methodology: The study was conducted in two stages; a screening study and a case-control study.
7 11,791 adults in age group 20-54 were randomly sampled from general population in South India
8 and answered a screening questionnaire. 588 subjects (236 cases and 352 controls) participated in
9 the case control study involving a detailed questionnaire and specific IgE estimation for 24 common
10 foods.

11 Results: A high level of sensitization (26.5%) was observed to most of the foods in the general
12 population, higher than that observed among adults in Europe, except for those foods that cross
13 react with birch pollen. Most of the sensitization was observed in subjects who had total IgE above
14 the median IgE level. A high level of cross reactivity was observed among different pollens and foods
15 and among foods. The prevalence of probable food allergy (self-reports of adverse symptoms after
16 consumption of food and specific IgE to the same food) was 1.2%, which was mainly accounted for
17 cow's milk (0.5%) and apple (0.5%).

18 Conclusion: Very high levels of sensitization was observed for most foods, including those not
19 commonly consumed in the general population. For the levels of sensitization, the prevalence of
20 probable food allergy was low. This disassociation needs to be further explored in future studies.

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Background:

There are few data regarding prevalence of sensitization to different foods and probable food allergies among adults, especially in Asia(1). In a meta-analysis of prevalence of food allergies(2) to plant foods, of 36 studies, food sensitization utilizing specific IgE was measured in 11, food specific IgE for vegetables and legumes in 1, wheat specific IgE in 6 and soy specific IgE in 4. ECRHS and NHANES confirmed high prevalence of food sensitization among adults in Europe(3) and USA(3, 4). Among European countries, overall prevalence of sensitization to one or more foods was 16.2%, with highest prevalence of sensitization to any food observed in Italy (21.9%) and lowest in Iceland (7.7%). The NHANES study in US, estimated overall prevalence of sensitization to any out of the four foods, milk, egg, shrimp and peanut to be between 13 to 15.9% depending on age(4). Prevalence of sensitization to any of 24 foods from Europrevall analysis revealed high prevalence of 24.6%(3). In a recent meta-analysis of prevalence of food allergy in Europe(5) the pooled life-time and point prevalence of self-reported food allergy were 17.3% and 5.9% respectively. Sensitization to one or more foods by specific IgE was 10.1%, skin prick test was 2.7% and positive food challenge was 0.9%. Prevalence estimates show great heterogeneity between different studies and in different countries(2, 5-13), which could in part be due to lack of application of comparable protocols between studies.

There are no studies on prevalence of sensitization to foods in general population from India. The EU-funded integrated project on prevalence, basis and costs of food allergy was initiated in 2005(14). This multi-centre study, using the same standardized methodology, was extended to emerging economies transitioning from traditional to modern life styles. Of these only Karnataka in India collected information on adults. The study evaluated the prevalence of food related symptoms, sensitization to 24 common foods and the prevalence of probable food allergy in a randomly selected general population (15). We report the prevalence of sensitization and prevalence of probable food allergy to 24 common foods (Fish, Cow's milk, Egg, Mustard seed, Soybean, Peanut, Lentil, Wheat, Buckwheat, Walnut, Poppy seed, Melon, Sunflower, Corn, Banana, Sesame, Shrimp, Tomato, Kiwi, Carrot, Celery, Apple, Peach and Hazelnut) among adults from general population in Karnataka, South India and characterize common food related symptoms in this Indian population. We also compare the seroprevalence rates for these foods in 6 European countries participating in the adult Europrevall study(16).

Methods:

Sampling area and sample size: Europrevall study was part of the multicenter cross-sectional surveys of the general population funded by European Commission to study prevalence and factors associated with food sensitization and food allergy(17). In the first phase the study included both adults (20-54 years) and children (7-10 years) in 8 European countries(17). The second phase involved the international co-operation (INCO) group comprising centres in Hong Kong, India and Russia (15). The adult study was successfully completed in 6 European countries and in India. The study was undertaken in two cities in Karnataka, South India. Bangalore, the capital of Karnataka State, is a metropolitan city, a major cultural and economic hub and is the third most populous city in India with a total population of 4.5 million. Mysore is the second most populous city in Karnataka State with a total population of nearly 1 million. Bangalore is in transition to a modern western style of living from the traditional, while Mysore retains a more traditional lifestyle including habits of

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76 food consumption and preparation. The sampling frame included the whole of the cities of
77 Bangalore and Mysore. The population in Bangalore is distributed within 100 administrative units
78 and Mysore within 65 administrative units. Thirty administrative units and 100 houses were
79 randomly selected in each administrative unit in both Bangalore and Mysore and all adults aged 20-
80 54 years living in those households were included. A central co-ordinating centre selected the cases
81 and controls for the nested case-control study. The detailed methodology for sample size estimation
82 in the Europrevall study is published elsewhere(15, 17). There were no previous studies on the
83 prevalence of food allergy from general population in India on which to base sample size
84 estimations. Sample size estimation for the case-control study to have 90% power to detect an odds
85 ratio of 2 to an exposure that 15% of the population were exposed to needed 240 cases and 240
86 controls(17). As per Europrevall protocol at least 4000 adult subjects were to be screened during the
87 first phase of the study with the aim of identifying at least 240 potential cases of food allergy. This
88 assumed a prevalence of at least 6% of the general adult population with probable food allergy.

89 Instrument: The Europrevall questionnaire was standardized throughout all participating countries
90 and was developed from relevant pre-existing questionnaires(18). Two questionnaires were used for
91 the Europrevall study in all the participating countries including India(15, 17). A brief screening
92 questionnaire was first administered to all participants and included information on demography
93 and adverse reaction to foods. The case control questionnaire was administered to all cases and
94 randomly selected controls from the rest of the general population and included additional
95 questions regarding food consumption, details of adverse reactions to foods of interest, various risk
96 factors and exposures associated with food allergy and a detailed occupational history. All
97 questionnaires used in the study were translated to regional languages and translated back to
98 english according to the standard protocol of the Europrevall study(15, 17). The questionnaires were
99 then pilot tested in the population before the start of the study. A food frequency questionnaire was
100 administered to all the participants. The study was cleared by the Institutional Ethics Committee of
101 Allergy Asthma Associates and informed consent was obtained from the study participants.

102 Data Collection: The investigators participating in the Europrevall INCO study underwent training
103 regarding all procedures of the Europrevall study from the co-ordinating centre. The same training
104 was then imparted to all field workers and medical officers in the participating INCO centres. In
105 India, data collection was performed by a house to house survey by trained field workers both
106 during the screening and the case-control studies. Before the field work was initiated, after
107 adequate training, consistency of data collection from the field workers was demonstrated by
108 comparison with the principal investigator and the kappa coefficient (inter-rater agreement)
109 calculated. Sera were collected from the participants for case-control study for estimation of total
110 and specific IgE to priority Europrevall foods and common environmental allergens. The priority
111 Europrevall foods tested were uniform in all the countries and included 24 common foods
112 (Europrevall priority foods); Fish, Cow's milk, Egg, Mustard seed, Soybean, Peanut, Lentil, Wheat,
113 Buckwheat, Walnut, Poppy seed, Melon, Sunflower, Corn, Banana, Sesame, Shrimp, Tomato, Kiwi,
114 Carrot, Celery, Apple, Peach and Hazelnut. The levels of serum specific IgE to twenty-four foods were
115 measured using an ImmunoCAP 250 system (Thermofisher Scientific, Uppsala, Sweden) at a single
116 central laboratory, (Amsterdam Medical Centre, Amsterdam, the Netherlands). The testing followed
117 a two stage strategy; five food mixes (2 commercial and 3 custom made) were tested first and when
118 positive (≥ 0.35 kU_A/l), each individual food in that mix was tested separately. The various mixes used
119 in the first stage were as follows; CAP mix 1 (commercial, fx5): hen's egg, cow's milk, soy, peanut,
120 wheat, fish, CAP mix 2 (commercial, fx6): sesame seed, wheat, buckwheat, corn, rice, CAP mix 3
121 (custom made): hazelnut, tomato, walnut, carrot, celery, CAP mix 4 (custom made): shrimp, poppy

seed, lentil, mustard, sunflower, CAP mix 5 (custom made): apple, kiwi, melon, banana, peach. Along with these 24 foods, specific IgE was also tested for these inhalant allergens; house dust mite, mugwort (artemisia), grass, birch, parietaria and cat.

Data quality monitoring: An extensive quality control procedure was adopted during the study to maintain good data quality and uniformity across all Europrevall centres(17). Data were entered into a centralised database maintained by the co-ordinating centre in UK. Weekly quality checks on data entries and monthly monitoring of the study progress was conducted by the study co-ordinator. Site visit by the central study co-ordinator to assess data quality was conducted across all Europrevall centres. This was followed by a 'Good Clinical Practice Audit' and 'Ethical Audit' by an independent auditor to confirm that the study satisfied ethical requirements in all the participating centres.

Definition of food sensitization, probable food allergy: The definition of sensitization to foods was specific IgE ≥ 0.35 kU_A/l and probable food allergy was defined as self-reports of adverse symptoms after consumption of food and specific IgE to the same food of ≥ 0.35 kU_A/l.

Data analysis and statistical methods: Stata was used for the analysis. Descriptive statistics were calculated for demographic variables and symptoms related to adverse food reactions. Weighted population prevalence of sensitivity, clinical complaints and probable symptoms related to allergy were estimated. Rates of serum sensitivities to 24 Europrevall priority foods were compared with the rates from other European centres taking part in the adult Europrevall study; Zurich (Switzerland), Madrid (Spain), Utrecht (Netherlands), Lodz (Poland), Sofia (Bulgaria) and Reykjavik (Iceland).

Results:

A total of 10,916 subjects aged 18-54 completed the screening questionnaire during the first phase of the study, 6546 from Bangalore and 4370 from Mysore. Before the field study, kappa coefficient (inter-rater agreement) was calculated for field workers after their training and was found to be 89.7% in Bangalore and 92.9% in Mysore. The response rate for the screening phase in both Bangalore and Mysore was greater than 95%. Demographic characteristics of the study population enrolled in the screening and case control study are presented in Table 1. The prevalence of self-reported reaction to foods among study subjects from screening questionnaire among males and females from Bangalore and Mysore are presented in Table 2. The most common manifestation of self-reported reactions to foods were itching and urticaria and females in both Mysore and Bangalore had higher prevalence of itching and urticaria than males.

The second phase involved administering a more detailed case control questionnaire and blood sampling for serology for 24 Europrevall priority foods (Fig 1). Nine hundred and ten subjects were invited to participate and 588 subjects consented to participate with a response rate of 64.6%. The response rate was slightly higher for cases (67.4%) compared to controls (62.8%). There was no significant difference in demographic variables between subjects in case control study who participated in serology and those who did not (Supplement Table 1). Weighted population prevalence of sensitization to any food, prevalence of clinical symptoms and prevalence of probable food allergy to any food is presented in Table 3a. Just over a quarter of the population were sensitized but the prevalence of probable food allergy to any allergen was 1.2%. Participants in Bangalore had higher rates of sensitization than subjects in Mysore. Weighted prevalence of

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probable food allergy was very low, with men in Bangalore having a higher prevalence than men in Mysore but women in Mysore having a higher prevalence than women in Bangalore. Weighted population prevalence of sensitization to individual foods, clinical complaints related to individual foods and prevalence of probable allergy to each of these foods is presented in Table 3b. Shrimp and sesame were the most common sensitizers whereas foods most commonly associated with clinical symptoms were fish, banana, cow's milk and melon. Moderate correlation was observed between sensitization to house dust mites and shrimp (0.51). The prevalence of probable food allergy was very low in this region of India with highest prevalence observed for cow's milk and apple.

Seroprevalence rates for the 24 Europrevall priority foods between India and 6 other centres participating in the adult Europrevall study are compared (Fig 2). We observed that the highest seroprevalence to 'any food' was in subjects from India. The highest seroprevalence for 'any food' among European centres was in subjects from Zurich (Switzerland) followed by Madrid (Spain) and the lowest seroprevalence was seen in subjects from Reykjavik (Iceland). Among the individual Europrevall priority foods, subjects from India were found to have the highest rates of sensitization to most of the foods in comparison to centres from the 6 European countries except for fish, walnut, kiwi, carrot, celery, apple, peach and hazelnut. A high correlation was observed between birch pollen sensitization in the Indian population and foods commonly known to cross react with birch pollen such as kiwi, peach and celery (Supplement Table 2 a) and similarly between artemisia and apple, kiwi, peach and celery (Supplement Table 2 b) (19). Similarly, high correlations were observed with sesame sensitization and sensitization to hazelnuts ($r=0.71$) and walnuts ($r=0.62$). Grass pollen sensitization had high correlation with celery ($r=0.82$), tomato ($r=0.82$), melon ($r=0.80$), carrot ($r=0.80$), wheat ($r=0.78$), buckwheat ($r=0.75$), corn ($r=0.75$), peach ($r=0.71$), kiwi ($r=0.71$), and poppy ($r=0.71$). Mean total IgE levels were similar between Bangalore and Mysore and between cases and controls and were higher than those observed in Europe(20) and America(21). Mean IgE levels in adults from Europe in Europrevall study (personal communication/unpublished) showed a difference between cases (98.03; SD 232.5) and controls (150.12; SD 393.24) and was much lower than the levels in the Indian population (Table 1). Sub-group analysis comparing sensitization among subjects with total IgE levels greater and lower than median total IgE levels (237 IU/ml) showed that subjects with higher than median levels of IgE had very high levels of sensitization for both food and aeroallergens (Table 4).

There was similarity in frequency of consumption of milk, eggs, soybean, wheat and poppy seed in subjects in this study from India and Europe. Fish, Shrimp, other shellfish, chocolate, apple, melon, orange and corn were consumed in Europe much more commonly than in India. Some of the foods were not consumed by a majority of the Indian population; More than 95% had never consumed hazelnut, walnut, peach, kiwi, celery, and more than 80% had never consumed strawberries, avocado and buckwheat. Peanut, banana, tomato, carrots, chickpeas, lentils, rice, sesame, mustard and sunflower were consumed in India much more commonly than in Europe.

Among the various participating European Centers, there was similarity in frequency of consumption of milk, eggs, hazelnut, walnut, apple, banana, orange, tomato, carrot, wheat, rice, corn, shrimp, other shellfish (except Lodz, Poland, where 63% of subjects had never consumed other shellfish), peanut (except Utrecht, Netherlands, where >50% of the subjects consumed peanuts and >40% consumed poppy seedson most days or most weeks). Fish was most commonly consumed in Reykjavik and Madrid. The least consumption of peach and kiwi was in Reykjavik and the least

consumption of melon was in Lodz, Poland, which also had the highest strawberry, celery and mustard seed consumption. Athens had the least consumption of avocado, buckwheat, sunflower seed and soybean and the highest consumption of sesame seed and melon. Vilnius had the highest consumption of avocado. Madrid had the highest consumption of chickpea and lentils and Lodz, the lowest.

Discussion

Prevalence of sensitization to 'any' of 24 Europrevall priority foods in adults from Karnataka was 26.5% and higher among subjects from Bangalore compared to subjects from Mysore. Both men (34.0%) and women (29.5%) from Bangalore had a higher sensitization rates as compared to men (19.0%) and women (18.6%) from Mysore. In contrast to the high rates of sensitization, the prevalence of probable food allergy was very low (1.2%). The highest prevalence of probable food allergy was observed among women from Mysore (1.6%) which accounted for all the cases. There were no probable food allergy cases among men from Mysore and very few among women in Bangalore (0.30%). The weighted population prevalence of food related symptoms to 'any' food including foods other than the Europrevall priority foods were observed to be 19.2% overall and the highest prevalence was observed among men in Mysore and the lowest among men from Bangalore. Most common food related symptoms were itching and urticaria and women from both Bangalore and Mysore had a higher prevalence of itching and urticaria compared to men. The highest prevalence of sensitization to individual foods was observed for shrimp and sesame and was above 13%. The lowest prevalence of sensitization was observed for fish at 0.5%. The prevalence of probable food allergy to individual foods was observed almost exclusively for cow's milk and apple (0.50% each) with very few cases with probable food allergy to egg and banana (0.05% each) and to sesame, wheat and tomato (0.02% each).

The highest prevalence of sensitization to 'any' of the 24 Europrevall priority foods was observed in India, followed by Switzerland, Spain, Netherlands, Poland, Bulgaria and Iceland in descending order. Among individual foods, highest prevalence of sensitization was observed in subjects from India compared to other countries from Europe for all foods except fish, walnut, kiwi, carrot, celery, apple, peach and hazelnut. Cross reactivity among different foods and pollens and foods could explain the high levels of sensitization to plant foods in the general population. Cross reactive carbohydrate determinants (CCD's) are commonly present in many plant foods and account for a high rate of false positives when serum specific IgE are measured(22, 23). This could explain the high sensitization rates observed in our population. A high correlation between birch and artemisia pollen sensitization and sensitization to apple and celery, kiwi and peach was observed in India. However, the clinical relevance of these are yet to be demonstrated. Artemisia is the third most common sensitizing pollen among atopic patients in India(24) and one of the clinically important weeds in South India(25). Though nearly 8% of the general population in India are sensitized to birch, there are no birch trees in South India. This could again be possibly be related to the anti-CCD IgE, which has been identified a cross-reactive IgE-binding structure in pollen, including birch pollen (26).

Though shrimp is not commonly consumed in this region of Karnataka, it was one of the most common sensitizers with sensitization rates around 15%. A moderate correlation between house dust mite and shrimp sensitization was observed in this study ($r=0.51$). We observed a higher symptom rates for fish as compared to sensitization rates unlike all the other foods tested which

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249 showed higher sensitization rates as compared to clinical reactivity. The reasons for this are not clear
250 and could include scombroidosis, anisakis allergy or other type of reactivity not related to ‘true fish
251 allergy’. This needs further investigation.

252 Sesame is a common food consumed in India and was the second most common sensitizer. Sesame
253 oil is used for cooking as well as applied to the skin as a massage oil. Peanut, mustard and lentils are
254 routinely consumed in India and have shown sensitization rates between 5-10%. Sesame can cross
255 react to foods like peanut, mustard, soybean, lentils, sunflower seeds and tree nuts (walnut and
256 hazelnut (27) (28) (29) which may explain sensitization rates for foods uncommonly consumed in
257 India like hazelnut, walnut and soybean, though there is probably an increase in soybean
258 consumption in recent years. Though there is low consumption of hazelnuts in India, the high
259 sensitization rates (7.3%) could be due to anti-CCD IgE recognizing CCD-bearing allergens such as
260 Cora 11 (30) or to cross reactivity to pollen (mugwort) (19) or food (sesame) (27) (31). Sunflower
261 seeds are not commonly consumed, but sunflower oil is the most common cooking oil used in this
262 region of India. It was interesting to observe that though the subjects in India had a very high total
263 IgE levels and specific IgE levels for most foods, the prevalence of sensitization to foods such as fish,
264 cow’s milk and egg were the lowest, similar to other parts of the world(3). Data from an earlier
265 Europrevall study on adults confirmed that the high rates of sensitization to foods was mainly
266 related to sensitization to pollens(16). A detailed component resolved diagnostics is necessary to
267 unravel the prevalence and extent of cross reactivity among different foods in the Indian population.

268 Factors controlling both the development of sensitization and conversion from an asymptomatic
269 sensitization to clinical disease are thus far not clearly elucidated. Dissociation between sensitization
270 and clinical disease in African and South East Asian children have been observed earlier(23, 32, 33).
271 While large number of studies have evaluated development of sensitization to aeroallergens and still
272 have failed to elucidate the pathways and pathogenesis to satisfactorily explain sensitization and
273 progression to clinical disease, very few have been published on sensitization to foods. The role of
274 exposure to the food allergen as one of the factors associated with sensitization remains to be
275 determined as we observed high rates of sensitization to foods uncommonly consumed and low
276 rates of sensitization to foods consumed frequently such as milk and egg. There is also evidence that
277 factors that determine sensitization to foods may be different from those that are associated to
278 sensitization to aeroallergens(3, 20) and a detailed evaluation is warranted to understand these
279 differences. We observed very high levels of total IgE and specific IgE to both foods and inhalants in
280 general population in this study. These observations are similar to other studies in Africa and Asia.
281 What could be the reasons for non-specific increase in levels of specific IgE and high levels of total
282 IgE in these populations? Previous studies have shown that populations residing in endemic regions
283 of tuberculosis and malaria show non-specific elevation of IgE, the reasons for which are unclear(34-
284 36). There is also an interesting hypothesis put forward that the host response via IgE is an important
285 defense mechanism for neutralising venoms from various insect bites, noxious xenobiotics, irritants
286 such as diesel exhaust particles along with offering protection against helminths(37). If this were
287 indeed true, it could perhaps explain why populations in Asia and Africa that are commonly bitten by
288 mosquitoes and ants regularly and exposed to high levels of air pollution have high levels of IgE.

289 There was a clear disassociation observed between rates of sensitization and prevalence of probable
290 food allergy in our study. The most common foods associated with probable food allergy among
291 adults in India were apple and cow’s milk (0.50% each) accounting to 1% of the total of 1.2% of

observed probable food allergy in adults. Apple is commonly consumed in India and a sensitization rate of 7.3% in the general population was observed. A moderate correlation between sensitization to artemesia and apple was observed and component resolved diagnostics may be needed in future studies to confirm whether it is due to true apple allergy or cross reactivity to artemesia. Cow's milk is one of the most commonly consumed food in India, with most people consuming it on a daily basis, directly as milk or in its myriad processed forms such as butter, ghee, yoghurt, buttermilk or cheese, but sensitization rates were low and it was the third last food in the order of sensitization (2.7%). No probable food allergy was observed for many foods associated with high rates of sensitization above 10% such as shrimp, buckwheat and corn whereas very few cases (0.02-0.05% weighted prevalence) were observed for sesame, wheat, tomato and banana. The reasons for the Indian population with higher levels of food specific IgE than most western countries but lower prevalence of probable food allergy remain unclear. Further studies on the immunological profile and environmental influences including dietary customs are necessary to unravel this paradox.

In western world and in Asian countries like China(38), prevalence of food allergy is increasing and is possibly the most common cause of anaphylaxis(39). In developed countries, asthma pandemic preceded increasing prevalence of food allergy(1). Many countries in Asia with lower prevalence of respiratory allergies, show an increasing prevalence of respiratory allergies, almost matching the prevalence in western countries(1). Respiratory allergies are increasing in India and with increasing urbanization and affluence, food allergies could become a major problem(1, 40). High prevalence of sensitization to specific foods are cause for concern and unless the reasons for the present disassociation of sensitization and clinical disease are ascertained and sustained in the general population, India could be heading for a major epidemic of food allergy which it is ill equipped to handle.

In summary, prevalence of sensitization to common EuroPrevall priority foods in general population in Karnataka in India is very high and a quarter of the population is sensitized. The weighted population prevalence of probable food allergy is very low, compared to the high degree of sensitization. Nearly half of the population has total IgE >300 and the high total IgE and specific IgE levels in this population are unlikely to be related to parasitic infestation and needs to be further investigated.

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Tables

Table 1. Demographic characteristics of the adult Europrevall INCO study subjects

Variable	Screening	Case	Control
	N=10,931	N= 241	N=346
	N (%)	N (%)	N (%)

Age (years)	20-29	4295 (39.34)	74 (30.83)	103 (29.94)
	30-39	3255 (29.81)	78 (32.50)	111 (32.27)
	>39	3369 (30.85)	88 (36.67)	130 (37.79)
Mean Age (SD)		34.30 (9.54)	36.34 (9.29)	36.60 (9.51)
Gender	Male	5540 (50.75)	86 (35.68)	158 (45.66)
	Female	5376 (49.25)	155 (64.32)	188 (54.34)
Bangalore	Male	3340 (51.02)	49 (45.37)	103 (56.91)
	Female	3206 (48.98)	59 (54.63)	78 (43.09)
Mysore	Male	2200 (50.34)	36 (28.13)	52 (32.10)
	Female	2170 (49.66)	92 (71.88)	110 (67.90)
Education	High School or less	n/a	183 (75.93)	222 (64.53)
	Vocational education diploma	n/a	20 (8.30)	49 (14.24)
	University degree	n/a	38 (15.77)	73 (21.22)
Dietary habits	Vegetarian	n/a	36 (14.94)	46 (13.37)
	Non-vegetarian	n/a	205 (85.06)	298 (86.63)
Current Smoker	Yes	n/a	28 (11.62)	34 (9.88)
	No	n/a	213 (88.38)	310 (90.12)
Alcohol consumption	Yes	n/a	15 (6.22)	27 (7.85)
	No	n/a	226 (93.78)	317 (92.15)
Concomitant allergies	Allergic rhinitis	n/a	34 (14.11)	11 (3.02)
	Asthma	n/a	13 (5.39)	8 (2.33)
	Skin allergies	n/a	94 (39.00)	28 (8.14)
	Drug allergies	n/a	27 (11.20)	18 (5.23)
Total IgE	Mean (SD)	n/a	529.39 (700.59)	522.19 (793.81)
	< 300	n/a	66 (55.46)	109 (57.67)
	301-1000	n/a	32 (26.89)	48 (25.40)
	>1000	n/a	21 (17.65)	32 (16.93)
Parasitic infestations*	Yes	n/a	10 (17.86)	16 (16.84)

	No	n/a	46 (82.14)	79 (83.16)

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427 **Table 2. Prevalence of Self-reported reaction to foods among study subjects from the screening**
 428 **questionnaire**

Symptoms	Bangalore (N= 6536)		Mysore (N= 4368)		Total (N=10,904)
	Male (N= 3336)	Female (N= 3200)	Male (N= 2199)	Female (N= 2169)	
	n (%)	n (%)	n (%)	n (%)	n (%)
Itching and urticaria	53 (1.59)	67 (2.09)	24 (1.09)	45 (2.07)	189 (1.73)
Breathlessness	8 (0.24)	10 (0.31)	11 (0.50)	21 (0.97)	50 (0.46)
Runny stuffy nose	12 (0.36)	10 (0.31)	17 (0.77)	28 (1.29)	67 (0.61)
Diarrhoea or vomiting (not food poisoning)	23 (0.69)	26 (0.81)	12 (0.55)	16 (0.74)	77 (0.71)
Headache	9 (0.27)	12 (0.38)	14 (0.64)	27 (1.24)	62 (0.57)
Fainting or dizziness	4 (0.12)	1 (0.03)	12 (0.55)	21 (0.97)	38 (0.35)

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430 **Table 3 a. Weighted population prevalence of sensitization for any allergen, clinical complaints**
 431 **among all subjects and in those with serology and prevalence of probable allergy to any allergen.**

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	Weighted population prevalence (%)			
Any Food	Serology	Clinical Complaint (among those with serology)	Clinical Complaint (all subjects)	"Probable" Allergy
Bangalore Men	34.0	8.6	12.1	1.5
Bangalore Women	29.5	19.7	21.3	0.3
Mysore Men	19.0	26.8	25.8	0.0
Mysore Women	18.6	17.9	21.2	1.6
WHOLE POPULATION	26.5	15.8	19.2	1.2

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433 **Table 3 b. Weighted population prevalence of sensitization to Europrevall priority foods, clinical**
434 **complaints among all subjects related to individual Europrevall priority foods and prevalence of**
435 **probable allergy to each of these individual Europrevall priority foods.**

	Weighted population prevalence (%)			
Any Food	Serology	Clinical Complaint (among those with serology)	Clinical Complaint (all subjects)	“Probable” Allergy
Shrimp	15.53	0.07	0.68	0.00
Sesame	13.97	0.07	0.67	0.02
Wheat	11.93	0.58	0.64	0.02
Buckwheat	12.41	0.50	0.28	0.00
Tomato	9.84	0.12	0.41	0.02
Corn	10.77	0.00	0.03	0.00
Banana	9.29	1.25	2.62	0.05
Celery	8.78	0.00	0.00	0.00
Lentil	8.78	0.05	0.32	0.00
Soy Bean	9.24	0.02	0.01	0.00
Melon	8.28	1.08	0.98	0.00
Peanut	8.73	0.67	2.22	0.00
Carrot	8.25	0.00	0.01	0.00
Apple	7.27	0.55	0.35	0.50
Poppy Seed	8.71	0.00	0.01	0.00
Sunflower	8.20	0.55	0.36	0.00
Kiwi	8.23	0.00	0.00	0.00
Peach	7.24	0.00	0.00	0.00
Hazelnut	7.27	0.00	0.00	0.00
Walnut	6.21	0.00	0.00	0.00
Mustard Seed	4.68	0.00	0.01	0.00
Cow’s Milk	2.71	1.11	2.39	0.50

Egg	2.56	0.70	1.14	0.05
Fish	0.50	2.83	3.50	0.00

Table 4. Weighted population prevalence of sensitization to Europrevall priority foods and aeroallergens by level of total IgE (median total IgE=237 IU/ml)

	Overall weighted population prevalence (%)	Weighted population prevalence if total IgE<median	Weighted population prevalence if total IgE>median
Any Food	26.49	4.46	46.29
Shrimp	15.53	3.24	26.56
Sesame	13.97	2.13	24.60
Wheat	11.93	2.13	20.73
Buckwheat	12.41	3.19	20.69
Tomato	9.84	3.19	15.81
Corn	10.77	2.13	18.54
Banana	9.29	1.06	16.67
Celery	8.78	2.13	14.76
Lentil	8.78	1.06	15.72
Soy Bean	9.24	1.06	16.58
Melon	8.28	1.06	14.76
Peanut	8.73	1.06	15.62
Carrot	8.25	2.13	13.76
Apple	7.27	1.12	12.80
Poppy Seed	8.71	2.13	14.62
Sunflower	8.20	1.06	14.62
Kiwi	8.23	2.13	13.71
Peach	7.24	1.06	12.80
Hazelnut	7.27	1.06	12.85
Walnut	6.21	0.00	11.80
Mustard Seed	4.68	0.00	8.89
Cow's Milk	2.71	0.05	5.12
Egg	2.56	0.05	4.83
Fish	0.50	0.00	0.95
Any aeroallergen	33.12	7.60	56.04
House Dust Mite	26.06	6.44	44.03
Mugwort	14.03	3.19	23.97
Grass	11.06	2.18	19.19
Birch	7.93	1.06	14.22
Parietaria	11.57	3.24	19.19
Cat	2.69	0.05	5.11

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1 **Abstract**

2 Background: Data is lacking regarding the prevalence of food sensitization and probable food allergy
3 among general population in India. We report the prevalence of sensitization and prevalence of
4 probable food allergy to 24 common foods among adults from general population in Karnataka,
5 South India.

6 Methodology: The study was conducted in two stages; a screening study and a case-control study.
7 11,791 adults in age group 20-54 were randomly sampled from general population in South India
8 and answered a screening questionnaire. 588 subjects (236 cases and 352 controls) participated in
9 the case control study involving a detailed questionnaire and specific IgE estimation for 24 common
10 foods.

11 Results: A high level of sensitization (26.5%) was observed to most of the foods in the general
12 population, higher than that observed among adults in Europe, except for those foods that cross
13 react with birch pollen. Most of the sensitization was observed in subjects who had total IgE above
14 the median IgE level. A high level of cross reactivity was observed among different pollens and foods
15 and among foods. The prevalence of probable food allergy (self-reports of adverse symptoms after
16 consumption of food and specific IgE to the same food) was 1.2%, which was mainly accounted for
17 cow's milk (0.5%) and apple (0.5%).

18 Conclusion: Very high levels of sensitization was observed for most foods, including those not
19 commonly consumed in the general population. For the levels of sensitization, the prevalence of
20 probable food allergy was low. This disassociation needs to be further explored in future studies.

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Background:

There are few data regarding prevalence of sensitization to different foods and probable food allergies among adults, especially in Asia(1). In a meta-analysis of prevalence of food allergies(2) to plant foods, of 36 studies, food sensitization utilizing specific IgE was measured in 11, food specific IgE for vegetables and legumes in 1, wheat specific IgE in 6 and soy specific IgE in 4. ECRHS and NHANES confirmed high prevalence of food sensitization among adults in Europe(3) and USA(3, 4). Among European countries, overall prevalence of sensitization to one or more foods was 16.2%, with highest prevalence of sensitization to any food observed in Italy (21.9%) and lowest in Iceland (7.7%). The NHANES study in US, estimated overall prevalence of sensitization to any out of the four foods, milk, egg, shrimp and peanut to be between 13 to 15.9% depending on age(4). Prevalence of sensitization to any of 24 foods from Europrevall analysis revealed high prevalence of 24.6%(3). In a recent meta-analysis of prevalence of food allergy in Europe(5) the pooled life-time and point prevalence of self-reported food allergy were 17.3% and 5.9% respectively. Sensitization to one or more foods by specific IgE was 10.1%, skin prick test was 2.7% and positive food challenge was 0.9%. Prevalence estimates show great heterogeneity between different studies and in different countries(2, 5-13), which could in part be due to lack of application of comparable protocols between studies.

There are no studies on prevalence of sensitization to foods in general population from India. The EU-funded integrated project on prevalence, basis and costs of food allergy was initiated in 2005(14). This multi-centre study, using the same standardized methodology, was extended to emerging economies transitioning from traditional to modern life styles. Of these only Karnataka in India collected information on adults. The study evaluated the prevalence of food related symptoms, sensitization to 24 common foods and the prevalence of probable food allergy in a randomly selected general population (15). We report the prevalence of sensitization and prevalence of probable food allergy to 24 common foods (Fish, Cow's milk, Egg, Mustard seed, Soybean, Peanut, Lentil, Wheat, Buckwheat, Walnut, Poppy seed, Melon, Sunflower, Corn, Banana, Sesame, Shrimp, Tomato, Kiwi, Carrot, Celery, Apple, Peach and Hazelnut) among adults from general population in Karnataka, South India and characterize common food related symptoms in this Indian population. We also compare the seroprevalence rates for these foods in 6 European countries participating in the adult Europrevall study(16).

Methods:

Sampling area and sample size: Europrevall study was part of the multicenter cross-sectional surveys of the general population funded by European Commission to study prevalence and factors associated with food sensitization and food allergy(17). In the first phase the study included both adults (20-54 years) and children (7-10 years) in 8 European countries(17). The second phase involved the international co-operation (INCO) group comprising centres in Hong Kong, India and Russia (15). The adult study was successfully completed in 6 European countries and in India. The study was undertaken in two cities in Karnataka, South India. Bangalore, the capital of Karnataka State, is a metropolitan city, a major cultural and economic hub and is the third most populous city in India with a total population of 4.5 million. Mysore is the second most populous city in Karnataka State with a total population of nearly 1 million. Bangalore is in transition to a modern western style of living from the traditional, while Mysore retains a more traditional lifestyle including habits of

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76 food consumption and preparation. The sampling frame included the whole of the cities of
77 Bangalore and Mysore. The population in Bangalore is distributed within 100 administrative units
78 and Mysore within 65 administrative units. Thirty administrative units and 100 houses were
79 randomly selected in each administrative unit in both Bangalore and Mysore and all adults aged 20-
80 54 years living in those households were included. A central co-ordinating centre selected the cases
81 and controls for the nested case-control study. The detailed methodology for sample size estimation
82 in the Europrevall study is published elsewhere(15, 17). There were no previous studies on the
83 prevalence of food allergy from general population in India on which to base sample size
84 estimations. Sample size estimation for the case-control study to have 90% power to detect an odds
85 ratio of 2 to an exposure that 15% of the population were exposed to needed 240 cases and 240
86 controls(17). As per Europrevall protocol at least 4000 adult subjects were to be screened during the
87 first phase of the study with the aim of identifying at least 240 potential cases of food allergy. This
88 assumed a prevalence of at least 6% of the general adult population with probable food allergy.

89 Instrument: The Europrevall questionnaire was standardized throughout all participating countries
90 and was developed from relevant pre-existing questionnaires(18). Two questionnaires were used for
91 the Europrevall study in all the participating countries including India(15, 17). A brief screening
92 questionnaire was first administered to all participants and included information on demography
93 and adverse reaction to foods. The case control questionnaire was administered to all cases and
94 randomly selected controls from the rest of the general population and included additional
95 questions regarding food consumption, details of adverse reactions to foods of interest, various risk
96 factors and exposures associated with food allergy and a detailed occupational history. All
97 questionnaires used in the study were translated to regional languages and translated back to
98 english according to the standard protocol of the Europrevall study(15, 17). The questionnaires were
99 then pilot tested in the population before the start of the study. A food frequency questionnaire was
100 administered to all the participants. The study was cleared by the Institutional Ethics Committee of
101 Allergy Asthma Associates and informed consent was obtained from the study participants.

102 Data Collection: The investigators participating in the Europrevall INCO study underwent training
103 regarding all procedures of the Europrevall study from the co-ordinating centre. The same training
104 was then imparted to all field workers and medical officers in the participating INCO centres. In
105 India, data collection was performed by a house to house survey by trained field workers both
106 during the screening and the case-control studies. Before the field work was initiated, after
107 adequate training, consistency of data collection from the field workers was demonstrated by
108 comparison with the principal investigator and the kappa coefficient (inter-rater agreement)
109 calculated. Sera were collected from the participants for case-control study for estimation of total
110 and specific IgE to priority Europrevall foods and common environmental allergens. The priority
111 Europrevall foods tested were uniform in all the countries and included 24 common foods
112 (Europrevall priority foods); Fish, Cow's milk, Egg, Mustard seed, Soybean, Peanut, Lentil, Wheat,
113 Buckwheat, Walnut, Poppy seed, Melon, Sunflower, Corn, Banana, Sesame, Shrimp, Tomato, Kiwi,
114 Carrot, Celery, Apple, Peach and Hazelnut. The levels of serum specific IgE to twenty-four foods were
115 measured using an ImmunoCAP 250 system (Thermofisher Scientific, Uppsala, Sweden) at a single
116 central laboratory, (Amsterdam Medical Centre, Amsterdam, the Netherlands). The testing followed
117 a two stage strategy; five food mixes (2 commercial and 3 custom made) were tested first and when
118 positive (≥ 0.35 kU_A/l), each individual food in that mix was tested separately. The various mixes used
119 in the first stage were as follows; CAP mix 1 (commercial, fx5): hen's egg, cow's milk, soy, peanut,
120 wheat, fish, CAP mix 2 (commercial, fx6): sesame seed, wheat, buckwheat, corn, rice, CAP mix 3
121 (custom made): hazelnut, tomato, walnut, carrot, celery, CAP mix 4 (custom made): shrimp, poppy

seed, lentil, mustard, sunflower, CAP mix 5 (custom made): apple, kiwi, melon, banana, peach. Along with these 24 foods, specific IgE was also tested for these inhalant allergens; house dust mite, mugwort (artemisia), grass, birch, parietaria and cat.

Data quality monitoring: An extensive quality control procedure was adopted during the study to maintain good data quality and uniformity across all Europrevall centres(17). Data were entered into a centralised database maintained by the co-ordinating centre in UK. Weekly quality checks on data entries and monthly monitoring of the study progress was conducted by the study co-ordinator. Site visit by the central study co-ordinator to assess data quality was conducted across all Europrevall centres. This was followed by a 'Good Clinical Practice Audit' and 'Ethical Audit' by an independent auditor to confirm that the study satisfied ethical requirements in all the participating centres.

Definition of food sensitization, probable food allergy: The definition of sensitization to foods was specific IgE ≥ 0.35 kU_A/l and probable food allergy was defined as self-reports of adverse symptoms after consumption of food and specific IgE to the same food of ≥ 0.35 kU_A/l.

Data analysis and statistical methods: Stata was used for the analysis. Descriptive statistics were calculated for demographic variables and symptoms related to adverse food reactions. Weighted population prevalence of sensitivity, clinical complaints and probable symptoms related to allergy were estimated. Rates of serum sensitivities to 24 Europrevall priority foods were compared with the rates from other European centres taking part in the adult Europrevall study; Zurich (Switzerland), Madrid (Spain), Utrecht (Netherlands), Lodz (Poland), Sofia (Bulgaria) and Reykjavik (Iceland).

Results:

A total of 10,916 subjects aged 18-54 completed the screening questionnaire during the first phase of the study, 6546 from Bangalore and 4370 from Mysore. Before the field study, kappa coefficient (inter-rater agreement) was calculated for field workers after their training and was found to be 89.7% in Bangalore and 92.9% in Mysore. The response rate for the screening phase in both Bangalore and Mysore was greater than 95%. Demographic characteristics of the study population enrolled in the screening and case control study are presented in Table 1. The prevalence of self-reported reaction to foods among study subjects from screening questionnaire among males and females from Bangalore and Mysore are presented in Table 2. The most common manifestation of self-reported reactions to foods were itching and urticaria and females in both Mysore and Bangalore had higher prevalence of itching and urticaria than males.

The second phase involved administering a more detailed case control questionnaire and blood sampling for serology for 24 Europrevall priority foods (Fig 1). Nine hundred and ten subjects were invited to participate and 588 subjects consented to participate with a response rate of 64.6%. The response rate was slightly higher for cases (67.4%) compared to controls (62.8%). There was no significant difference in demographic variables between subjects in case control study who participated in serology and those who did not (Supplement Table 1). Weighted population prevalence of sensitization to any food, prevalence of clinical symptoms and prevalence of probable food allergy to any food is presented in Table 3a. Just over a quarter of the population were sensitized but the prevalence of probable food allergy to any allergen was 1.2%. Participants in Bangalore had higher rates of sensitization than subjects in Mysore. Weighted prevalence of

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probable food allergy was very low, with men in Bangalore having a higher prevalence than men in Mysore but women in Mysore having a higher prevalence than women in Bangalore. Weighted population prevalence of sensitization to individual foods, clinical complaints related to individual foods and prevalence of probable allergy to each of these foods is presented in Table 3b. Shrimp and sesame were the most common sensitizers whereas foods most commonly associated with clinical symptoms were fish, banana, cow's milk and melon. Moderate correlation was observed between sensitization to house dust mites and shrimp (0.51). The prevalence of probable food allergy was very low in this region of India with highest prevalence observed for cow's milk and apple.

Seroprevalence rates for the 24 Europrevall priority foods between India and 6 other centres participating in the adult Europrevall study are compared (Fig 2). We observed that the highest seroprevalence to 'any food' was in subjects from India. The highest seroprevalence for 'any food' among European centres was in subjects from Zurich (Switzerland) followed by Madrid (Spain) and the lowest seroprevalence was seen in subjects from Reykjavik (Iceland). Among the individual Europrevall priority foods, subjects from India were found to have the highest rates of sensitization to most of the foods in comparison to centres from the 6 European countries except for fish, walnut, kiwi, carrot, celery, apple, peach and hazelnut. A high correlation was observed between birch pollen sensitization in the Indian population and foods commonly known to cross react with birch pollen such as kiwi, peach and celery (Supplement Table 2 a) and similarly between artemesia and apple, kiwi, peach and celery (Supplement Table 2 b) (19). Similarly, high correlations were observed with sesame sensitization and sensitization to hazelnuts ($r=0.71$) and walnuts ($r= 0.62$). Grass pollen sensitization had high correlation with celery ($r=0.82$), tomato ($r=0.82$), melon ($r=0.80$), carrot ($r=0.80$), wheat ($r=0.78$), buckwheat ($r=0.75$), corn ($r=0.75$), peach ($r=0.71$), kiwi ($r=0.71$), and poppy ($r=0.71$). Mean total IgE levels were similar between Bangalore and Mysore and between cases and controls and were higher than those observed in Europe(20) and America(21). Mean IgE levels in adults from Europe in Europrevall study (personal communication/unpublished) showed a difference between cases (98.03; SD 232.5) and controls (150.12; SD 393.24) and was much lower than the levels in the Indian population (Table 1). Sub-group analysis comparing sensitization among subjects with total IgE levels greater and lower than median total IgE levels (237 IU/ml) showed that subjects with higher than median levels of IgE had very high levels of sensitization for both food and aeroallergens (Table 4).

There was similarity in frequency of consumption of milk, eggs, soybean, wheat and poppy seed in subjects in this study from India and Europe. Fish, Shrimp, other shellfish, chocolate, apple, melon, orange and corn were consumed in Europe much more commonly than in India. Some of the foods were not consumed by a majority of the Indian population; More than 95% had never consumed hazelnut, walnut, peach, kiwi, celery, and more than 80% had never consumed strawberries, avocado and buckwheat. Peanut, banana, tomato, carrots, chickpeas, lentils, rice, sesame, mustard and sunflower were consumed in India much more commonly than in Europe.

Among the various participating European Centers, there was similarity in frequency of consumption of milk, eggs, hazelnut, walnut, apple, banana, orange, tomato, carrot, wheat, rice, corn, shrimp, other shellfish (except Lodz, Poland, where 63% of subjects had never consumed other shellfish), peanut (except Utrecht, Netherlands, where >50% of the subjects consumed peanuts and >40% consumed poppy seedson most days or most weeks). Fish was most commonly consumed in Reykjavik and Madrid. The least consumption of peach and kiwi was in Reykjavik and the least

consumption of melon was in Lodz, Poland, which also had the highest strawberry, celery and mustard seed consumption. Athens had the least consumption of avocado, buckwheat, sunflower seed and soybean and the highest consumption of sesame seed and melon. Vilnius had the highest consumption of avocado. Madrid had the highest consumption of chickpea and lentils and Lodz, the lowest.

Discussion

Prevalence of sensitization to 'any' of 24 Europrevall priority foods in adults from Karnataka was 26.5% and higher among subjects from Bangalore compared to subjects from Mysore. Both men (34.0%) and women (29.5%) from Bangalore had a higher sensitization rates as compared to men (19.0%) and women (18.6%) from Mysore. In contrast to the high rates of sensitization, the prevalence of probable food allergy was very low (1.2%). The highest prevalence of probable food allergy was observed among women from Mysore (1.6%) which accounted for all the cases. There were no probable food allergy cases among men from Mysore and very few among women in Bangalore (0.30%). The weighted population prevalence of food related symptoms to 'any' food including foods other than the Europrevall priority foods were observed to be 19.2% overall and the highest prevalence was observed among men in Mysore and the lowest among men from Bangalore. Most common food related symptoms were itching and urticaria and women from both Bangalore and Mysore had a higher prevalence of itching and urticaria compared to men. The highest prevalence of sensitization to individual foods was observed for shrimp and sesame and was above 13%. The lowest prevalence of sensitization was observed for fish at 0.5%. The prevalence of probable food allergy to individual foods was observed almost exclusively for cow's milk and apple (0.50% each) with very few cases with probable food allergy to egg and banana (0.05% each) and to sesame, wheat and tomato (0.02% each).

The highest prevalence of sensitization to 'any' of the 24 Europrevall priority foods was observed in India, followed by Switzerland, Spain, Netherlands, Poland, Bulgaria and Iceland in descending order. Among individual foods, highest prevalence of sensitization was observed in subjects from India compared to other countries from Europe for all foods except fish, walnut, kiwi, carrot, celery, apple, peach and hazelnut. Cross reactivity among different foods and pollens and foods could explain the high levels of sensitization to plant foods in the general population. Cross reactive carbohydrate determinants (CCD's) are commonly present in many plant foods and account for a high rate of false positives when serum specific IgE are measured(22, 23). This could explain the high sensitization rates observed in our population. A high correlation between birch and artemisia pollen sensitization and sensitization to apple and celery, kiwi and peach was observed in India. However, the clinical relevance of these are yet to be demonstrated. Artemisia is the third most common sensitizing pollen among atopic patients in India(24) and one of the clinically important weeds in South India(25). Though nearly 8% of the general population in India are sensitized to birch, there are no birch trees in South India. This could again be possibly be related to the anti-CCD IgE, which has been identified a cross-reactive IgE-binding structure in pollen, including birch pollen (26).

Though shrimp is not commonly consumed in this region of Karnataka, it was one of the most common sensitizers with sensitization rates around 15%. A moderate correlation between house dust mite and shrimp sensitization was observed in this study ($r=0.51$). We observed a higher symptom rates for fish as compared to sensitization rates unlike all the other foods tested which

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249 showed higher sensitization rates as compared to clinical reactivity. The reasons for this are not clear
250 and could include scombroidosis, anisakis allergy or other type of reactivity not related to ‘true fish
251 allergy’. This needs further investigation.

252 Sesame is a common food consumed in India and was the second most common sensitizer. Sesame
253 oil is used for cooking as well as applied to the skin as a massage oil. Peanut, mustard and lentils are
254 routinely consumed in India and have shown sensitization rates between 5-10%. Sesame can cross
255 react to foods like peanut, mustard, soybean, lentils, sunflower seeds and tree nuts (walnut and
256 hazelnut (27) (28) (29) which may explain sensitization rates for foods uncommonly consumed in
257 India like hazelnut, walnut and soybean, though there is probably an increase in soybean
258 consumption in recent years. Though there is low consumption of hazelnuts in India, the high
259 sensitization rates (7.3%) could be due to anti-CCD IgE recognizing CCD-bearing allergens such as
260 Cora 11 (30) or to cross reactivity to pollen (mugwort) (19) or food (sesame) (27) (31). Sunflower
261 seeds are not commonly consumed, but sunflower oil is the most common cooking oil used in this
262 region of India. It was interesting to observe that though the subjects in India had a very high total
263 IgE levels and specific IgE levels for most foods, the prevalence of sensitization to foods such as fish,
264 cow’s milk and egg were the lowest, similar to other parts of the world(3). Data from an earlier
265 Europrevall study on adults confirmed that the high rates of sensitization to foods was mainly
266 related to sensitization to pollens(16). A detailed component resolved diagnostics is necessary to
267 unravel the prevalence and extent of cross reactivity among different foods in the Indian population.

268 Factors controlling both the development of sensitization and conversion from an asymptomatic
269 sensitization to clinical disease are thus far not clearly elucidated. Dissociation between sensitization
270 and clinical disease in African and South East Asian children have been observed earlier(23, 32, 33).
271 While large number of studies have evaluated development of sensitization to aeroallergens and still
272 have failed to elucidate the pathways and pathogenesis to satisfactorily explain sensitization and
273 progression to clinical disease, very few have been published on sensitization to foods. The role of
274 exposure to the food allergen as one of the factors associated with sensitization remains to be
275 determined as we observed high rates of sensitization to foods uncommonly consumed and low
276 rates of sensitization to foods consumed frequently such as milk and egg. There is also evidence that
277 factors that determine sensitization to foods may be different from those that are associated to
278 sensitization to aeroallergens(3, 20) and a detailed evaluation is warranted to understand these
279 differences. We observed very high levels of total IgE and specific IgE to both foods and inhalants in
280 general population in this study. These observations are similar to other studies in Africa and Asia.
281 What could be the reasons for non-specific increase in levels of specific IgE and high levels of total
282 IgE in these populations? Previous studies have shown that populations residing in endemic regions
283 of tuberculosis and malaria show non-specific elevation of IgE, the reasons for which are unclear(34-
284 36). There is also an interesting hypothesis put forward that the host response via IgE is an important
285 defense mechanism for neutralising venoms from various insect bites, noxious xenobiotics, irritants
286 such as diesel exhaust particles along with offering protection against helminths(37). If this were
287 indeed true, it could perhaps explain why populations in Asia and Africa that are commonly bitten by
288 mosquitoes and ants regularly and exposed to high levels of air pollution have high levels of IgE.

289 There was a clear disassociation observed between rates of sensitization and prevalence of probable
290 food allergy in our study. The most common foods associated with probable food allergy among
291 adults in India were apple and cow’s milk (0.50% each) accounting to 1% of the total of 1.2% of

observed probable food allergy in adults. Apple is commonly consumed in India and a sensitization rate of 7.3% in the general population was observed. A moderate correlation between sensitization to artemesia and apple was observed and component resolved diagnostics may be needed in future studies to confirm whether it is due to true apple allergy or cross reactivity to artemesia. Cow's milk is one of the most commonly consumed food in India, with most people consuming it on a daily basis, directly as milk or in its myriad processed forms such as butter, ghee, yoghurt, buttermilk or cheese, but sensitization rates were low and it was the third last food in the order of sensitization (2.7%). No probable food allergy was observed for many foods associated with high rates of sensitization above 10% such as shrimp, buckwheat and corn whereas very few cases (0.02-0.05% weighted prevalence) were observed for sesame, wheat, tomato and banana. The reasons for the Indian population with higher levels of food specific IgE than most western countries but lower prevalence of probable food allergy remain unclear. Further studies on the immunological profile and environmental influences including dietary customs are necessary to unravel this paradox.

In western world and in Asian countries like China(38), prevalence of food allergy is increasing and is possibly the most common cause of anaphylaxis(39). In developed countries, asthma pandemic preceded increasing prevalence of food allergy(1). Many countries in Asia with lower prevalence of respiratory allergies, show an increasing prevalence of respiratory allergies, almost matching the prevalence in western countries(1). Respiratory allergies are increasing in India and with increasing urbanization and affluence, food allergies could become a major problem(1, 40). High prevalence of sensitization to specific foods are cause for concern and unless the reasons for the present disassociation of sensitization and clinical disease are ascertained and sustained in the general population, India could be heading for a major epidemic of food allergy which it is ill equipped to handle.

In summary, prevalence of sensitization to common Europrevall priority foods in general population in Karnataka in India is very high and a quarter of the population is sensitized. The weighted population prevalence of probable food allergy is very low, compared to the high degree of sensitization. Nearly half of the population has total IgE >300 and the high total IgE and specific IgE levels in this population are unlikely to be related to parasitic infestation and needs to be further investigated.

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Tables

Table 1. Demographic characteristics of the adult Europrevall INCO study subjects

Variable		Screening	Case	Control
		N=10,931	N= 241	N=346
		N (%)	N (%)	N (%)

Age (years)	20-29	4295 (39.34)	74 (30.83)	103 (29.94)
	30-39	3255 (29.81)	78 (32.50)	111 (32.27)
	>39	3369 (30.85)	88 (36.67)	130 (37.79)
Mean Age (SD)		34.30 (9.54)	36.34 (9.29)	36.60 (9.51)
Gender	Male	5540 (50.75)	86 (35.68)	158 (45.66)
	Female	5376 (49.25)	155 (64.32)	188 (54.34)
Bangalore	Male	3340 (51.02)	49 (45.37)	103 (56.91)
	Female	3206 (48.98)	59 (54.63)	78 (43.09)
Mysore	Male	2200 (50.34)	36 (28.13)	52 (32.10)
	Female	2170 (49.66)	92 (71.88)	110 (67.90)
Education	High School or less	n/a	183 (75.93)	222 (64.53)
	Vocational education diploma	n/a	20 (8.30)	49 (14.24)
	University degree	n/a	38 (15.77)	73 (21.22)
Dietary habits	Vegetarian	n/a	36 (14.94)	46 (13.37)
	Non-vegetarian	n/a	205 (85.06)	298 (86.63)
Current Smoker	Yes	n/a	28 (11.62)	34 (9.88)
	No	n/a	213 (88.38)	310 (90.12)
Alcohol consumption	Yes	n/a	15 (6.22)	27 (7.85)
	No	n/a	226 (93.78)	317 (92.15)
Concomitant allergies	Allergic rhinitis	n/a	34 (14.11)	11 (3.02)
	Asthma	n/a	13 (5.39)	8 (2.33)
	Skin allergies	n/a	94 (39.00)	28 (8.14)
	Drug allergies	n/a	27 (11.20)	18 (5.23)
Total IgE	Mean (SD)	n/a	529.39 (700.59)	522.19 (793.81)
	< 300	n/a	66 (55.46)	109 (57.67)
	301-1000	n/a	32 (26.89)	48 (25.40)
	>1000	n/a	21 (17.65)	32 (16.93)
Parasitic infestations*	Yes	n/a	10 (17.86)	16 (16.84)

	No	n/a	46 (82.14)	79 (83.16)

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427 **Table 2. Prevalence of Self-reported reaction to foods among study subjects from the screening**
 428 **questionnaire**

Symptoms	Bangalore (N= 6536)		Mysore (N= 4368)		Total (N=10,904)
	Male (N= 3336)	Female (N= 3200)	Male (N= 2199)	Female (N= 2169)	
	n (%)	n (%)	n (%)	n (%)	n (%)
Itching and urticaria	53 (1.59)	67 (2.09)	24 (1.09)	45 (2.07)	189 (1.73)
Breathlessness	8 (0.24)	10 (0.31)	11 (0.50)	21 (0.97)	50 (0.46)
Runny stuffy nose	12 (0.36)	10 (0.31)	17 (0.77)	28 (1.29)	67 (0.61)
Diarrhoea or vomiting (not food poisoning)	23 (0.69)	26 (0.81)	12 (0.55)	16 (0.74)	77 (0.71)
Headache	9 (0.27)	12 (0.38)	14 (0.64)	27 (1.24)	62 (0.57)
Fainting or dizziness	4 (0.12)	1 (0.03)	12 (0.55)	21 (0.97)	38 (0.35)

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430 **Table 3 a. Weighted population prevalence of sensitization for any allergen, clinical complaints**
 431 **among all subjects and in those with serology and prevalence of probable allergy to any allergen.**

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	Weighted population prevalence (%)			
Any Food	Serology	Clinical Complaint (among those with serology)	Clinical Complaint (all subjects)	"Probable" Allergy
Bangalore Men	34.0	8.6	12.1	1.5
Bangalore Women	29.5	19.7	21.3	0.3
Mysore Men	19.0	26.8	25.8	0.0
Mysore Women	18.6	17.9	21.2	1.6
WHOLE POPULATION	26.5	15.8	19.2	1.2

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433 **Table 3 b. Weighted population prevalence of sensitization to Europrevall priority foods, clinical**
434 **complaints among all subjects related to individual Europrevall priority foods and prevalence of**
435 **probable allergy to each of these individual Europrevall priority foods.**

	Weighted population prevalence (%)			
Any Food	Serology	Clinical Complaint (among those with serology)	Clinical Complaint (all subjects)	“Probable” Allergy
Shrimp	15.53	0.07	0.68	0.00
Sesame	13.97	0.07	0.67	0.02
Wheat	11.93	0.58	0.64	0.02
Buckwheat	12.41	0.50	0.28	0.00
Tomato	9.84	0.12	0.41	0.02
Corn	10.77	0.00	0.03	0.00
Banana	9.29	1.25	2.62	0.05
Celery	8.78	0.00	0.00	0.00
Lentil	8.78	0.05	0.32	0.00
Soy Bean	9.24	0.02	0.01	0.00
Melon	8.28	1.08	0.98	0.00
Peanut	8.73	0.67	2.22	0.00
Carrot	8.25	0.00	0.01	0.00
Apple	7.27	0.55	0.35	0.50
Poppy Seed	8.71	0.00	0.01	0.00
Sunflower	8.20	0.55	0.36	0.00
Kiwi	8.23	0.00	0.00	0.00
Peach	7.24	0.00	0.00	0.00
Hazelnut	7.27	0.00	0.00	0.00
Walnut	6.21	0.00	0.00	0.00
Mustard Seed	4.68	0.00	0.01	0.00
Cow’s Milk	2.71	1.11	2.39	0.50

Egg	2.56	0.70	1.14	0.05
Fish	0.50	2.83	3.50	0.00

Table 4. Weighted population prevalence of sensitization to Europrevall priority foods and aeroallergens by level of total IgE (median total IgE=237 IU/ml)

	Overall weighted population prevalence (%)	Weighted population prevalence if total IgE<median	Weighted population prevalence if total IgE>median
Any Food	26.49	4.46	46.29
Shrimp	15.53	3.24	26.56
Sesame	13.97	2.13	24.60
Wheat	11.93	2.13	20.73
Buckwheat	12.41	3.19	20.69
Tomato	9.84	3.19	15.81
Corn	10.77	2.13	18.54
Banana	9.29	1.06	16.67
Celery	8.78	2.13	14.76
Lentil	8.78	1.06	15.72
Soy Bean	9.24	1.06	16.58
Melon	8.28	1.06	14.76
Peanut	8.73	1.06	15.62
Carrot	8.25	2.13	13.76
Apple	7.27	1.12	12.80
Poppy Seed	8.71	2.13	14.62
Sunflower	8.20	1.06	14.62
Kiwi	8.23	2.13	13.71
Peach	7.24	1.06	12.80
Hazelnut	7.27	1.06	12.85
Walnut	6.21	0.00	11.80
Mustard Seed	4.68	0.00	8.89
Cow's Milk	2.71	0.05	5.12
Egg	2.56	0.05	4.83
Fish	0.50	0.00	0.95
Any aeroallergen	33.12	7.60	56.04
House Dust Mite	26.06	6.44	44.03
Mugwort	14.03	3.19	23.97
Grass	11.06	2.18	19.19
Birch	7.93	1.06	14.22
Parietaria	11.57	3.24	19.19
Cat	2.69	0.05	5.11