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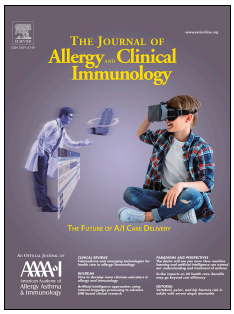

Global patterns in anaphylaxis due to specific foods: a systematic review

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Systematic review to identify the predominant causes of food anaphylaxis

Global patterns in anaphylaxis due to specific foods: a systematic review

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Declaration of interests

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ABSTRACT:

Background: There are increasing global data relating to prevalence of food allergy and food-induced anaphylaxis, however this is often based on surrogate measures of sensitization rather than objective symptoms at food challenge. In terms of protecting food-allergic consumers from reactions, there has been no global survey assessing geographical differences in the proportion of anaphylaxis triggered by specific foods.

Objective: To identify common triggers for food-induced anaphylaxis, and how these vary from country to country.

Methods: Systematic review of relevant reports published between January 2010 and November 2020. Results were reported following PRISMA guidelines. Publications were screened and data extracted by two independent reviewers, and risk of bias assessed.

Results: Sixty-five studies (encompassing 41 countries and all 6 regions as defined by the Food & Agriculture Organization of the United Nations) were included. Significant regional variations in the most common triggers of food-anaphylaxis were seen, however, in general there was good agreement between local legislative requirements for allergen disclosure and the commonest allergens for each region/nation.

Conclusions: Local legislation for allergen disclosure generally reflect those allergens commonly responsible for food-anaphylaxis. Cow's milk and crustacea appear to be cause a higher proportion of anaphylaxis compared to peanut in some regions.

Clinical Implication: In addition to peanut and tree nuts, cow's milk and shellfish/crustacea are important causes of anaphylaxis globally.

Capsule Summary

This systematic review provides the first global snap-shot of regional differences in patterns of anaphylaxis due to specific foods.

Key words

Allergen labelling, Anaphylaxis, Codex, Epidemiology, Food allergy, Prevalence.

Abbreviations:

95%CI	95% confidence interval
ED	Emergency Department
FAO	Food and Agricultural Organization of the United Nations
ICU	Intensive care
LTP	Lipid transfer protein
NASWP	North America and Southwest Pacific Region
WHO	World Health Organization

INTRODUCTION

Food supply increasingly involves supply chains across multiple countries. The Codex Alimentarius (often abbreviated to Codex) is a set of international food standards, guidelines and codes of practice established by the Food and Agricultural Organization of the United Nations (FAO) and World Health Organization (WHO) to facilitate the safety of global trade in food supply. Currently, Codex requires disclosure for ingredients relating to 8 food groups: cereals containing gluten, crustacea, egg, fish, peanut and soybean, milk, tree nuts; sulphites (where present at concentrations of ≥10 mg/kg) must also be declared.[1]

The Codex list includes food allergens which are generally considered to cause over 90% of food-induced allergic reactions in most regions. However, anaphylaxis has been reported to almost all foods, and there are significant geographical differences in the prevalence of allergen-specific food allergies worldwide,[2] presumably due to differences in dietary consumption and/or exposure. Some countries/regions therefore include additional allergens which must be declared on food labels.[3]

There are increasing data globally relating to the relative prevalence of food allergy due to specific foods, however these epidemiological data may not correspond to the list of foods which commonly cause anaphylaxis.[4] Prevalence data should ideally be derived from unselected populations, but this often results in very small numbers of individuals allergic to a specific food and thus a high level of uncertainty over the resulting estimated prevalence data generated. More information relating to specific food triggers can be obtained from less rigorous methodologies (for example, diagnosis based on self-report, or the presence of sensitization with or without

clinical history). However, this may not correspond to real-world data relating to the occurrence of food-induced allergic reactions due to accidental exposure. This may be because some food allergies resolve over time (for example, the majority of younger children allergic to cow's milk and hen's egg), or because some allergens (such as those implicated in pollen food allergy syndrome) are not generally considered to cause systemic reactions in most affected individuals.[5] In terms of assessing the risk posed to food-allergic consumers, there has been no global survey assessing geographical differences in the relative proportions of anaphylaxis due to specific foods. We therefore undertook a systematic review to address this evidence gap.

METHODS

We undertook a systematic review of the literature to identify studies reporting proportions of anaphylaxis in different countries/regions due to specific food triggers. This was undertaken and reported in accordance with the PRISMA Statement.[6]

Search strategy

We used the search strategy from a systematic review of global anaphylaxis epidemiology[4] (but limited to food allergens as the trigger for anaphylaxis) to perform a systematic search on the following electronic databases: MEDLINE (Ovid), PubMed and EMBASE (Ovid). There was no registered protocol for this review, but the methods and analyses were planned *a priori*. No language restrictions were made, and we planned to include non-English papers if they met our inclusion criteria. Abstracts were independently screened by two authors, and disagreements were resolved by discussion. We also reviewed reference lists of included studies and review articles to identify other relevant studies.

Study selection

We included all studies which provided details as to specific triggers for food anaphylaxis, either presenting to a medical facility or reported to a central registry. We also included case series recording more than 10 fatalities due to food anaphylaxis. Risk of bias was assessed according to Hoy et al.[7] Studies at high risk of bias were excluded unless there were no other datasets to inform for that specific country. Where multiple publications were identified for the same dataset with overlapping time periods, we included the report with the largest number of individuals where we could be certain that no duplication was present.

Data extraction and analyses

Data were extracted in duplicate, and any discrepancies identified were resolved by discussion and/or by contacting authors for clarifications. The different definitions used for anaphylaxis in individual studies were noted accordingly, along with an indication of the completeness of the data (proportion of cases where a specific food trigger was identified). Data were expressed as the proportion of anaphylaxis cases due to a specified food trigger compared to all cases of food-anaphylaxis reported in that case series. Heat-maps were used to identify the most common food allergens in each data series, and to facilitate between-country comparisons.

In order to compare the proportion of anaphylaxis to reported prevalence for that allergen by region, both prevalence rates and anaphylaxis frequencies for individual allergens were pooled across studies using a generalized linear mixed model in R (metaprop function, metafor package, logit transformation with a random intercept logistic regression model for the summary estimate,) (R project, version 4.0.3). This approach avoids many of the issues surrounding the use of transformations when undertaking meta-analyses of proportions.[8,9] We conducted meta-analyses even if significant heterogeneity was seen between study estimates, as is the norm when conducting meta-analysis of proportions. Additional information regarding the datasets used to determine prevalence is available in the Online Repository and Table E1.

RESULTS

Sixty-five studies (encompassing 41 countries and all 6 regions as defined by the Food & Agriculture Organization of the United Nations) were identified for inclusion (Figure 1). Details of the individual studies appear in Figure E1 and 2, along with the definition of anaphylaxis used and an indication of data completeness and risk of bias assessment.

In total, six studies reported food anaphylaxis fatalities (covering Australia,[10] United Kingdom,[11,12] USA (New York City),[13] Canada (Ontario),[14] France[15]) while an additional two studies reported intensive care admissions due to food-induced anaphylaxis.[16,17] These studies are reported in Figure E1. Fifty-seven other studies were included: 10 reports from anaphylaxis registries, 21 reporting visits to Emergency Departments and 4 reporting hospitalizations due to food-anaphylaxis, 4 surveys, one report of emergency medical services usage and 17 describing clinic referrals for food-anaphylaxis. All but two studies provided details as to specific triggers for food anaphylaxis; two (one from Chile, another from Morocco) included non-anaphylaxis reactions, but were included in this analysis due to an absence of alternative data for these countries. These studies are reported in Figure 2.

Major causes of food-induced anaphylaxis by CODEX region

To further assess geographical variations in the most common food allergens reported to cause anaphylaxis, the data from the Figure 2 were tabulated by Codex region (Figure 3) and plotted on a global map (Figure 4). These data demonstrated that while there are some allergens that are a common cause of anaphylaxis in multiple regions, there are also some foods which seem to be limited as a common

trigger to just one or two regions. Of note, soya was not a major cause of food-anaphylaxis in any region.

Common food triggers for anaphylaxis compared to prevalence

Finally, prevalence data were obtained for Europe, North America/Southwest Pacific (NASWP) and Asia from the literature, and the estimated pooled prevalence (derived from meta-analysis, and reported in Table E1) for a specified food trigger plotted against the proportion of reported anaphylaxis reactions caused by that food (Figure 5). For Europe, crustacea and cow's milk appeared to cause a higher proportion of anaphylaxis in adults compared to peanut given the reported prevalence of allergy to those triggers. Hazelnut and some fruits caused a lower proportion of anaphylaxis for their reported prevalence, compared to peanut; this could be due to their role as triggers for pollen-food allergy syndrome. Fish and crustacea were common causes of anaphylaxis in adults in Asia, although this may be exaggerated by the relatively lower proportion of peanut anaphylaxis in this region.

Discussion

As food supply becomes increasingly globalized, there is a need to identify which foods should be singled out on food labels for disclosure in order to help protect food-allergic consumers. Epidemiological data relating to prevalence and incidence of food allergy are limited by the impracticality of conducting food challenges in those with suspected allergy, to distinguish between non-allergic adverse reactions to food, IgE-sensitization without clinical reactivity and true IgE-mediated food allergy with associated risk of anaphylaxis. For example, pollen-food allergy syndrome is thought to affect up to 35% of individuals in some regions,[75] but such patients are considered to be at lower risk of anaphylaxis compared to those with primary food sensitization.[5] In addition, Codex requirements for allergen disclosure are for the scenario where the presence of the allergen may not be obvious (e.g. in processed foods), rather than for fresh foods – since fruits and vegetables are generally visible and typically not consumed as highly-processed foods, they do not currently feature as specified allergens in Codex (although this may change in the future with the increased use of "vegetable protein concentrates") . To our knowledge, this analysis is the first in the literature to report a global assessment of the most common food triggers for anaphylaxis, using a systematic approach. Rather than rely of reports of prevalence to specific food allergens which are limited by a lack of robust data,[4] we instead used real-world data as to the most common causes of anaphylaxis presenting to medical facilities, as a surrogate measure to inform the choice of "priority" allergens for inclusion in legislation.

We found significant inter-regional and intra-regional differences in the most common triggers for food-anaphylaxis. Significant variations in the prevalence of

allergy to different food triggers have been reported in Europe;[76,77] it is therefore perhaps not surprising that similar differences were also evident for anaphylaxis, both within and between Codex regions. Peanut and tree nuts are a common cause of anaphylaxis in the European and NASWP regions, but less so in Asia. Wheat is generally less common as a cause of anaphylaxis, but accounts for a disproportionate number of anaphylaxis presentations in China. These differences can potentially present a challenge for the regulation of food allergens within the supply change, as food products produced and packaged in one country are often consumed in another, while tourism can also significantly impact the specific food allergies that consumers might present with. In this respect, it is reassuring that in general, there was good agreement between local legislative requirements for allergen disclosure and the most common allergens causing anaphylaxis in that locality.

It was also revealing to compare the relative frequencies of food triggers causing anaphylaxis compared to their reported prevalence in causing food allergy. Data were available for this comparison for Europe, NASWP and Asia. Using peanut as a reference allergen, our data indicate Crustacea appear to cause a disproportionate number of anaphylaxis reactions in all 3 regions in adults. Interestingly, cow's milk allergy also appears to cause a greater-than-expected proportion of anaphylaxis in children in Europe and Asia. Cow's milk allergy may be considered to be a less "serious" food allergy, as it is commonly outgrown in early childhood. However, there are increasing data that in older children with persisting allergy to cow's milk, it is a common cause of not just anaphylaxis but near-fatal and fatal anaphylaxis.[11,12,16] For example, in Greece, cow's milk allergy is relatively uncommon compared to the rest

of Europe,[76,77] and yet still accounts for around one quarter of anaphylaxis presentations.[18] This may be due to a lower awareness of cow's milk as a potential cause of severe reactions, and its ubiquitous use in Western-style diets, particularly in processed foods.

Conversely, at least in Europe, some fruits and tree nuts appeared to be less likely to cause anaphylaxis, presumably because these data do not distinguish between allergy due to primary food sensitization (with higher risk of anaphylaxis) and pollen-food allergy syndrome. Fruit as a food group was a common cause of anaphylaxis globally. However, the likely impact of differences in patterns of cross-sensitization and cross-reactivity are not obvious from these data. In Northern Europe, allergy to fruit is commonly associated with birch pollen sensitization; in Mediterranean regions, LTP (particularly to peach LTP) is also a common cause, which appears to be independent of pollen sensitization.[76] However, in China, peach is also a relatively common cause of anaphylaxis, but this is usually associated with cross-reactivity to mugwort pollen; in contrast to European LTP allergy, LTP-related anaphylaxis in China is often due to primary sensitization to mugwort.[78] More research is needed to better understand the clinical implications of geographical differences in sensitization patterns between different plant-derived allergens.

Strengths and Limitations of this study

The inclusion of global datasets identified through a systematic search of the literature is a key strength of this analysis. However, it is important to note the limitations of this analysis: different definitions were used to assign both "anaphylaxis" and the causative trigger, including ICD-9/-10 codes which are subject

to miscoding.[79] However, we believe that even with this limitation, the data would still represent the more severe end of the spectrum of allergic symptoms. The proportion of anaphylaxis due to any given specific food trigger is dependent on multiple factors, including underlying prevalence of allergy to that trigger within the population, consumption patterns, inherent ability of that allergen to cause more severe reactions and host factors such as IgE-sensitization. While these factors are all potential confounders, the use of real-world data provides an additional dimension to better understand which allergens are more likely to cause anaphylaxis than others. It is therefore not surprising that there is a clear correlation between prevalence of allergy to a specific food and the proportion of anaphylaxis cases it causes (as shown in Figure 3). This comparison was limited by the high uncertainty in data relating to food allergy prevalence, and the very limited data from some regions. This is particularly a concern for North America, where challenge-based epidemiological data is lacking; despite using systematic methodologies to estimate prevalence using household sampling approaches, allergy to cow's milk in adults is apparently more common than peanut allergy (perhaps due to lack of distinction between lactose intolerance rather than IgE-mediated allergy).[80] The use of real-world anaphylaxis data may therefore provide less uncertainty as to the major causes of food-anaphylaxis compared to relying on estimates of food allergy prevalence alone.

Conclusions

Using a systematic approach, we identified important and often region-specific differences in the most common food allergens causing anaphylaxis across the globe. However, legislative requirements for food allergen disclosure generally

mirrored the local allergens most commonly responsible for food-anaphylaxis events. Cow's milk and shellfish/crustacea are important causes of anaphylaxis globally, in addition to peanut and tree nuts. These data support the use of location-specific epidemiology to guide both public health policy and research with respect to food allergy.

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Author Contributions:

P.J. Turner conceived the study design, led the data analysis and drafting of the manuscript. All authors contributed data to the analysis and were involved in data interpretation. All authors reviewed the manuscript and amended or approved the final version.

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FIGURE LEGENDS

Figure 1: PRISMA flow diagram

Figure 2: Studies reporting food anaphylaxis events presenting to medical facilities (Emergency Department (ED) visits, hospitalizations, clinics). Data are presented as the proportion of all reported cases of food-anaphylaxis due to the specified food trigger. Heat-map colors indicate *relative* (rather than *absolute*) prevalence of specific foods within each case series.

Figure 3: Common food allergens reported to cause anaphylaxis, by Codex region and country. 'X' indicates local legislation requiring disclosure for that allergen; (X) indicates more limited or voluntary disclosure recommended.[3] Heat-map colors indicate *relative* (rather than *absolute*) prevalence of that allergen (group) as a common cause of food-anaphylaxis in that region.

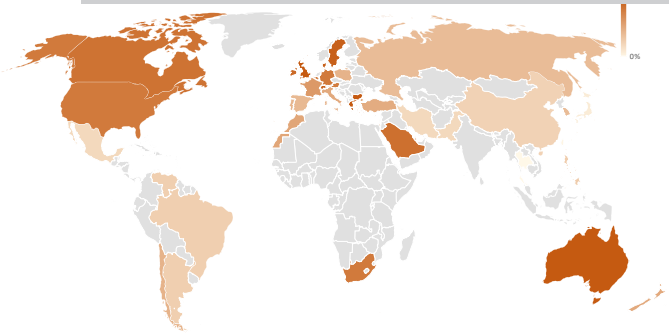
Figure 4: Global maps showing variations in the relative proportion of reported food-anaphylaxis cases due to a specific food trigger **(**peanut and tree nuts (combined), seafood, cow's milk, wheat, egg, soybean, fruit (combined) and sesame), by country.

Figure 5: Comparison of the proportion of total food-anaphylaxis caused by a specific food trigger in any given region, compared to its prevalence as a cause of food allergy. Dotted lines represent 95%CI. 95%CI for prevalence estimates are reported in Table E1. For Europe and North America / SW Pacific (NASWP), the bubble size represents the relative number of fatalities reported due to food

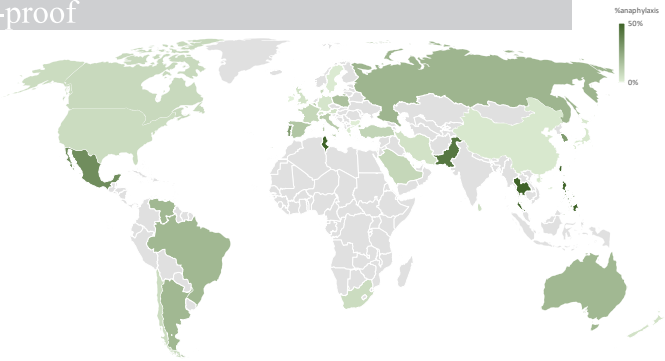
anaphylaxis for the specific food trigger (these data were not available for the Asia region). The blue dashed line is included to facilitate comparisons of these data to peanut.

	FATALITIES					ICU admissions	
	Australia	**UK**		**USA: NY City**	**Canada: Ontario**	**France**	**USA/Canana**	**France**
	National Database	National Fatality registry		Regional Database	Fatality data Database	Fatality data Database	Multicentre Database	Multicentre Database
	Care review	Case review		ICD-9 & ICD-10	Case review	Case review	ICU admission	ICU admission
	1997-2013	**1992-2018**		**2000-14**	**1986-2011**	**2002-18**	**2010-15**	**2003-13**
Risk of bias	Low	Low		Low	Low	Moderate	Low	Low
% identified food trigger	91%	74%	71%	75%	85%	89%	74%	95%
Reference	10	11,12		13	14	15	16	17
	All ages (n=22)	Adults (n=121)	<16y (n=66)	All ages (n=24)	All ages (n=40)	All ages (n=18)	<18y (n=705)	<18y (n=62)
All nuts (incl unspecified)	36%	52%	35%	25%	55%	56%		44%
Peanut	18%	20%	14%	17%	40%	39%	33%	27%
Tree nuts (combined)	9%	9%	9%	8%	15%	17%		16%
Cashew						6%		11%
Pistachio								2%
Hazelnut						6%		
Walnut	5%					6%		3%
Almond							14%	
Brazil nut								
Pecan								
Macadamia								
Other tree nuts								
Sesame		0.8%	3%					
Spices/seeds (excl. sesame)								
Mustard								
Pine nut								
Wheat	5%							2%
Other grains								
Buckwheat	5%							
Hen's egg		0.5%	0%				3%	5%
Cow's milk	5%	5.0%	26%	4%	2.5%	11%	7%	31%
Other mammalian milks						11%		3%
Celery								
Shrimp/Crustacea	45%	6.6%	6.1%	29%	10%		2%	
Fish	5%			8%			5%	3%
Molluscs		0.5%				6%		
Soybean						6%		
Legumes (excl. peanut, soya)		0.5%	1.5%					
(of which pea)								
Lupine								
Fruits (all)		1%	1.5%				1%	2%
Peach								
Kiwi								
Banana								
Fig								
Apple								2%
Mango								
Avocado								
Carrot								
Chicken								
Other animal products						11%		3%

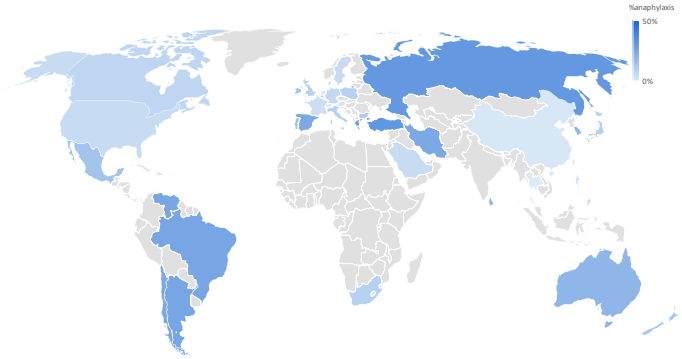
PEANUT + TREE NUTS



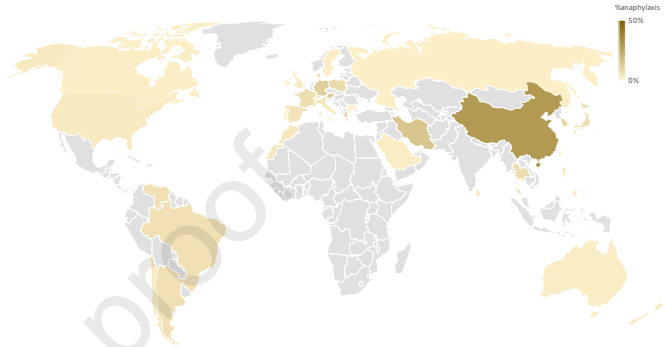
SEAFOOD incl. FISH, SHELLFISH



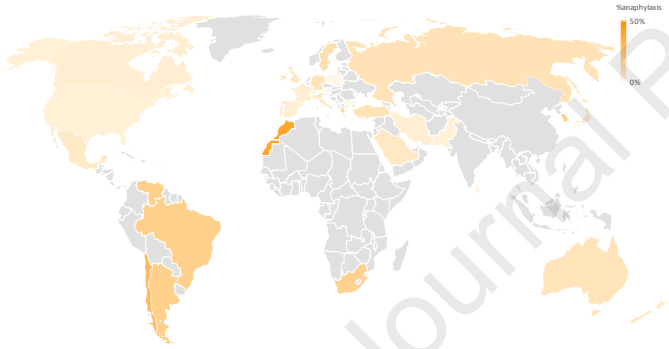
COW'S MILK / DAIRY



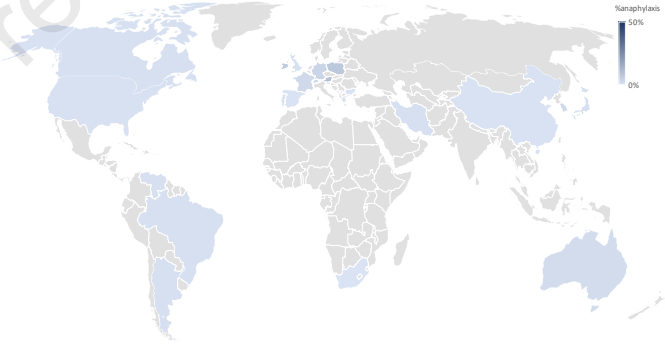
WHEAT



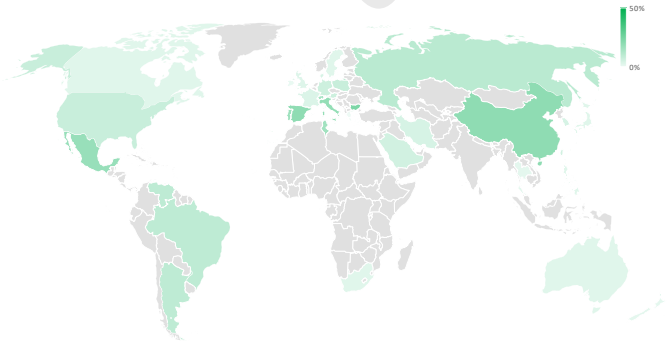
HEN's EGG



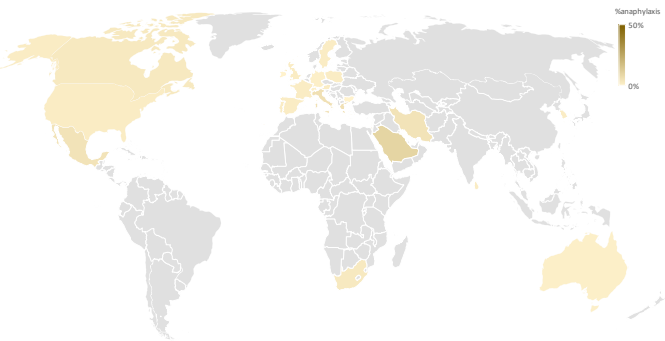
SOYBEAN



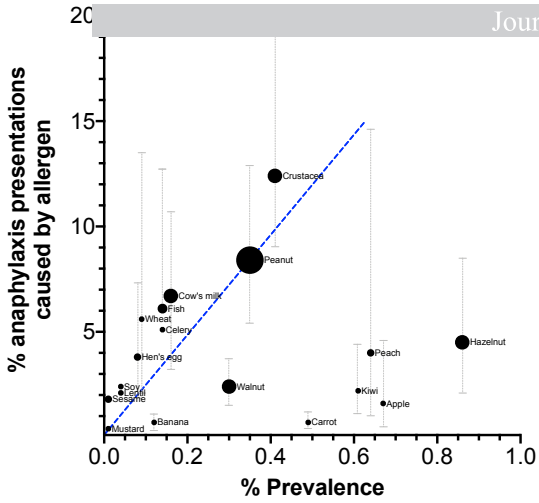
FRUIT



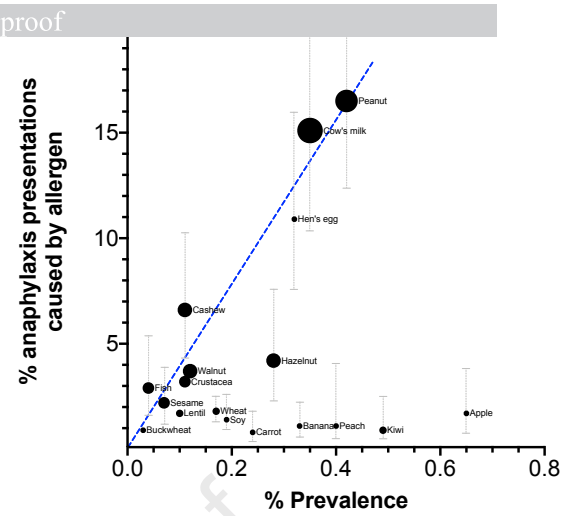
SESAME



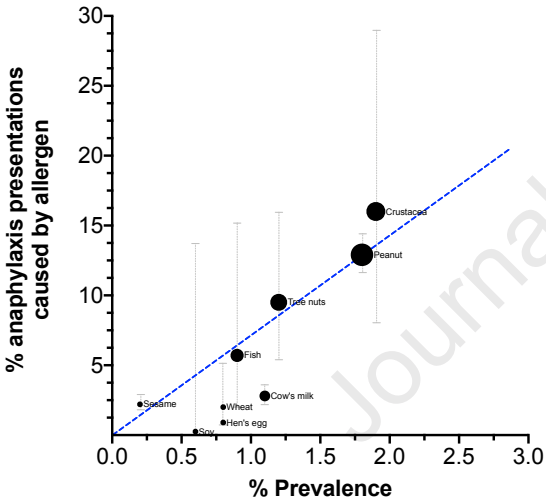
EUROPE: adults



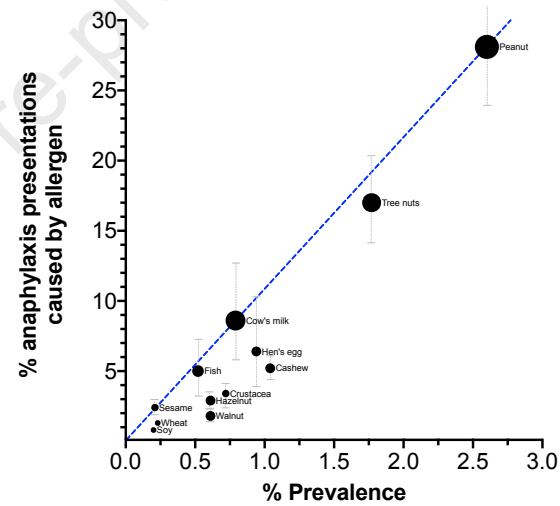
EUROPE: children



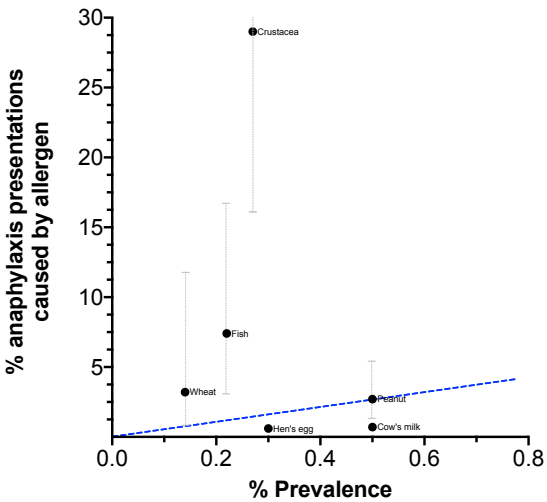
NASWP: adults



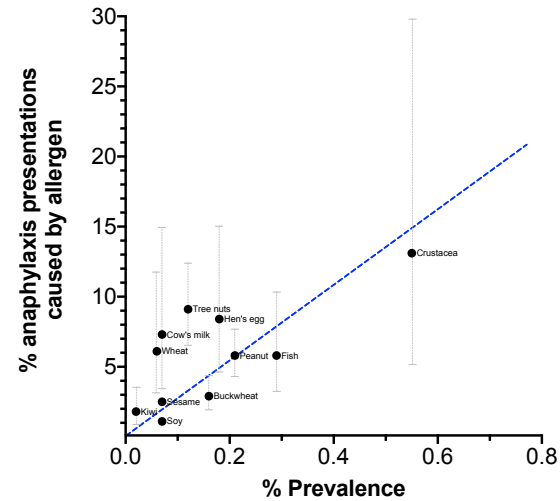
NASWP: children

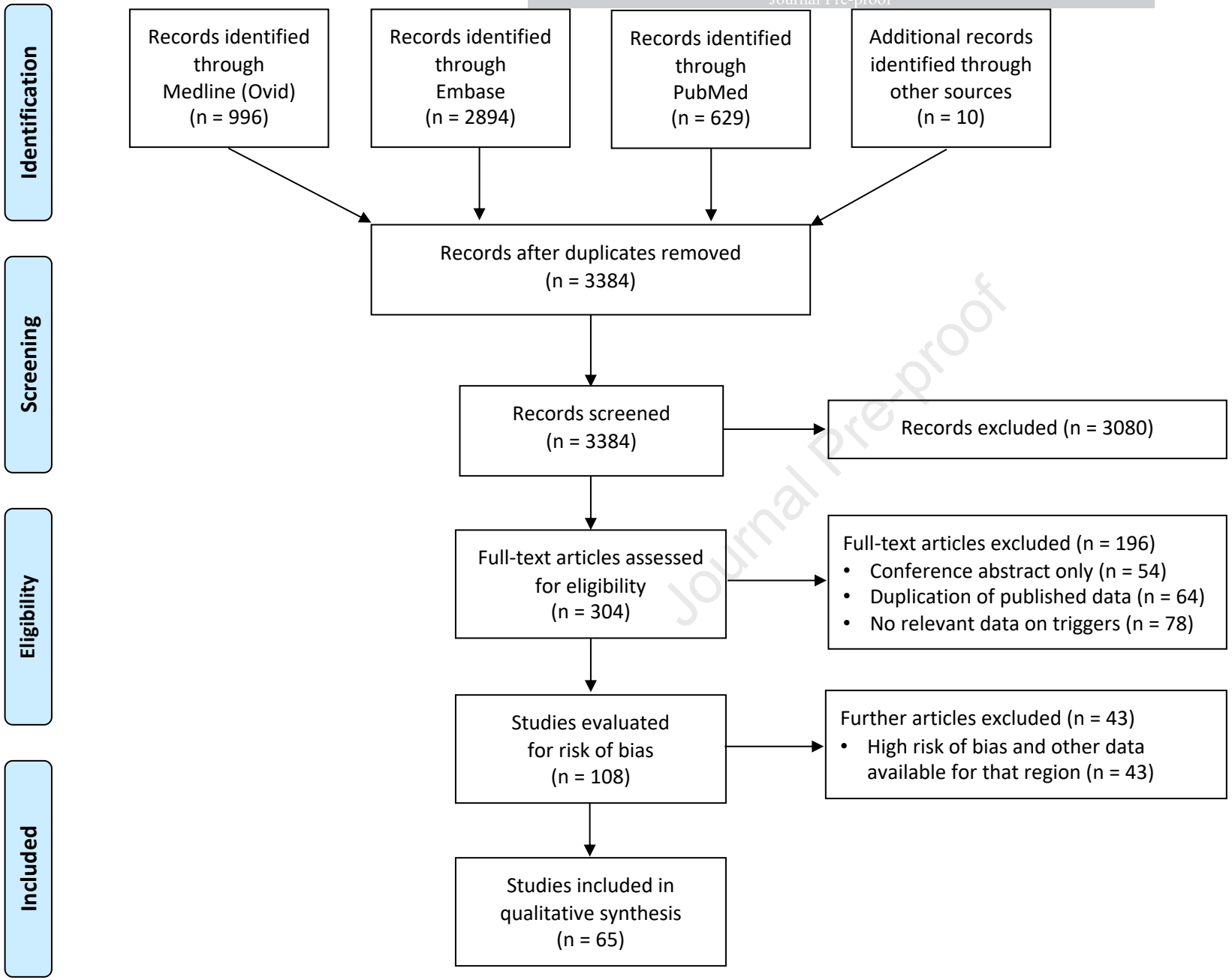


ASIA: adults



ASIA: children





Assignment of anaphylaxis	European Anaphylaxis Register (NORA) Multinational Registry Clinician				Multicentre ED Visits NIAID	Australia National Survey ASCIA	Regional EMS use n/a	Austria Mulicentre Registry Clinician	Belgium Local ED Visits Clinician	Bulgaria Mulicentre Registry Clinician	Canada Local ED Visits ICD-10	Canada Multicenter ED Visits ICD-10	Chile Local Referrals	China Regional Referrals NIAID	Denmark Local Referrals NIAID	France Multicentre Registry NIAID		Mulicentre Registry Clinician	Germany Mulicentre Registry Clinician	Greece Mulicentre Registry Clinician	Hong Kong Regional Database NIAID	Iran Local Referrals		Mulicentre Referrals Clinician
	2011-2014	**2007-2015**	**2007-2017**		**2006-9**	**2006-16**	**2008-16**	**2011-2014**	**2008-2012**	**2011-2014**	**2011/12**	**2011-17**	**2006-16**	**2000-14**	**2013/14**	**2015**		**2002-17**	**2011-2014**	**2011-2014**	**2009-19**	**2005-09**	**2006-16**	**2012-15**
Risk of bias	Low	Low	Low		Low	Moderate	Low	Moderate	Moderate	Moderate	Low	Low	High	Low	Moderate	Low		Low	Low	Moderate	Low	High	High	Moderate
% identified food trigger	92%	87%	94%	94%	87%	100%	75%	94%	100%	100%	86%	90%	Not stated	89%	89%	58%	61%	83%	94%	100%	Not stated	100%	90%	88%
Reference	18	19	20		21	22	23	18	24	18	25	26	27	28	29	30		31	18	18	32	33	34	35
	All ages (n=1070)	<18y (n=1291)	18-64y (n=1254)	65+y (n=122)	All ages (n=112)	10-14y (n=53)	<16y (n=1394)	All ages (n=31)	<15y (n=153)	All ages (n=17)	Adults (n=62)	All ages (n=2769)	All ages (n=282)	All ages (n=907)	All ages (n=40)	Adults (n=55)	<18y (n=82)	All ages (n=1951)	All ages (n-459)	All ages (n=34)	<18y (n=133)	<14y (n=63)	All ages (n-70)	All ages (n=69)
All nuts (incl unspecified)	39%	47%			23%	66%	52%	39%	40%	59%	24.3%	41.9%	22%		48%	16%	35%	28%	40%	67%	26%			13%
Peanut	17%	25%	5%	1%	18%	34%	52%	16%	20%	18%	8.1%	20.8%	17%	5.0%	10%	16%	35%	13.3%	19%	5.9%	12%	3%	8.6%	4%
Tree nuts (combined)	21%	22%			5%	23%		23%	20%	41%	6.5%	14.5%	5%	7.1%	38%			14.8%	20%	18%	14%		18.6%	9%
Cashew	4.7%	6.7%			1%	9%		0%		0%		5.1%		1%				6.4%	1.1%	11.8%				
Pistachio		1.8%				2%						1.3%						1.0%						
Hazelnut	8.1%	6.7%	7%	13%		1%		6.5%		17.6%		2.9%						3.3%	12.0%	0%			2.9%	7%
Walnut	3.5%	3.8%				6%		9.7%		11.8%		1.7%	5%					1.7%	3.3%	5.9%			12.9%	
Almond	1.6%				2%	2%		3.2%		5.9%		1.3%						0.8%	1.1%	0%			2.9%	1%
Brazil nut	3.5%	3.3%										0.1%						0.8%						
Pecan												0.7%						0.1%						
Macadamia												0.3%						0.2%						
Other tree nuts					2%	2%		3.2%		5.9%		1.1%						0.5%	2.8%	0%				
Sesame	1.4%	1.5%				1%		0%		0%		2.5%						2.6%	0.9%	5.9%			2.9%	10%
Spices/seeds (excl. sesame)		1.2%												1.7%	3%			0.3%				2%	7.1%	
Mustard												0.2%						0.3%						
Pine nut		1.0%			2%	2%						0.5%						1.4%						
Wheat	8.9%	2.4%	14%	14%	1%	1%		13%		0%		1.5%	3%	37%	8%			7.1%	12%	8.8%		33%	1.4%	16%
Other grains		1.6%												4.3%	2.5%								1.4%	
Buckwheat					1%							0.2%		3.4%				3.0%			2%			
Hen's egg	6.9%	10%			1%	4%	14%	0%	16%	0%	1.6%	7.4%	33%			1.8%	7%	2.5%	10%	15%	7%	6%	7.1%	22%
Cow's milk	6.5%	11%			1%	8%	23%	3%	17%	12%	1.6%	8.1%	25%	1.5%	2.5%	0%	11%	4.2%	7.4%	29%	5%	57%	1.4%	32%
Other mammalian milks		1%										0.1%						3.1%						
Celery	3.3%	0.9%	6%	6%				3%		0%		0%			2.5%			3.7%	3.3%	15%				
Shrimp/Crustacea	4.7%	1.9%	10%	12%	22%	8%	6%	3%	5%	0%	12.9%	3.8%	5%	3.1%	8%	31%	2.0%	6.9%	2.8%	0%	19%		1.4%	
Fish		1.5%			5%			2%	6%	1%	1.6%	3.1%	2%					1.7%	1.0%	2.0%	17%		4.3%	
Molluscs		1.0%			1%							0.1%						2.9%						
Soybean	3.7%	1.5%	6%	5%		2%		10%		0%		0.9%		0.3%				2.9%	4.4%	0%			1.4%	
Legumes (excl. peanut, soya)		3.8%											2%	3.8%				0.9%						
(of which pea)		0.9%																0.4%						
Lupine		1.0%			2%							0%						2.6%						
Fruits (all)	9.0%	3.2%			4%	1%	4%	7%		24%		2.8%		21%	5%			3.5%	7.0%	0%			7.1%	4%
Peach												0.1%		2.6%				0.7%						3%
Kiwi					2%	1%					3.2%	1.1%		3.2%				1.7%					1.4%	1%
Banana												0.8%						0.8%						
Fig												0.1%						0.7%						
Apple												0.2%						0.6%						
Mango												0.5%						0.7%						
Avocado																		0.6%						
Carrot												0.1%			2.5%			0.7%						
Chicken	8.7%	4.1%										0.3%						1.7%						
Other animal products					3%		6%	16%		6%				3.4%		9.1%	4.0%	3%	6.8%	6%			1.4%	2%

	Ireland	Israel	Italy		Japan			R. Korea			Latin America	Mexico		Morocco	New Zealand		Pakistan	Philippines	Poland		Portugal	Qatar	Russia
	Mulicentre	Local	Multicentre		Multicentre		National	Multicentre			Regional	Local		Local	National		Local	Local	Local	Mulicentre	National	Local	Local
	Registry	ED visits	Registry		Hospitalization		Survey	Referrals	ED Visits	Registry	Registry	Survey		Referrals	Hospitalisations		Hospitalisations	ED Visits	Referrals	Registry	Registry	Referrals	Referrals
	Clinician	NIAID	NIAID		ICD-10 coding		self-report	NIAID	NIAID	NIAID	Clinician	Clinician		All reactions	ICD-10		NIAID	NIAID	Clinician	Clinician	NIAID	NIAID	NIAID
	2013-15	**2013-18**	**2010**		**2014-17**		**2004**	**2009-13**	**2012-16**	**2016-18**	**2008-10**	**2013**	**2014/5**	**2008**	**2002-11**	**2006-15**	**1998-2012**	**1998-2012**	**2006-15**	**2011-14**	**2007-17**	**2012-16**	**2011-15**
Risk of bias	Low	Moderate	Low		Moderate		Moderate	Low	Low	Low	Moderate	Moderate	Moderate	High	High	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate	Moderate
% identified food trigger	90%	91%	88%	97%	21%		92%	93%	89%	95%	Not stated	100%	100%	100%	21%	68%	89%	62%	96%	100%	96%	Not stated	Not stated
Reference	36	37	38		39		40	56	57		41	42	43	44	45	46	47	48	49	18	50	51	52
	<16y (n=144)	<16y (n-317)	Adults (n=361)	<18y (n=221)	Adults (n=3587)	<19y (n=5491)	All ages (n=319)	<18y (n-740)	Adults (n=196)	<20y (n=21)	Adults (n=63)	<18y (n=284)	<18y (n=69)	Adults (n=15)	5-13y (n=13)	Adults (n=27)	Adults (n=1598)	<15y (n=1441)	All ages (n=21)	All ages (n=36)	All ages (n=51)	All ages (n=12)	All ages (n=859)	All ages (n=316)	<18y (n=80)
All nuts (incl unspecified)	49%	30%	21%	32%				17%	3.1%	19%	6%	18%					6.3%	32.5%	10%		22%	22%	21.3%		
Peanut	24%	8.2%	6.7%	8.6%	1.1%	4.4%	3.4%	6.2%	3.1%	19%	3.2%	4.9%	7%	9%	0%	26.0%	6.3%	17.5%	10%	14%	11%	0%	6.5%	11%	6%
Tree nuts (combined)	25%	28%	15.0%	23.0%				10.9%			3.2%	13%	6%	0%	7%			15%			11%	22%	12.9%	26%	13%
Cashew	15%							0.8%				1.4%										16.7%	2.4%		
Pistachio								0.3%				0.7%											0.8%		
Hazelnut	4.9%		10.3%	14.5%				0.2%				0.7%										8.3%	1.9%		
Walnut	1.4%		2.2%	4.5%			1.1%	8.0%				8.1%										0%	5.0%		
Almond	1.4%		1.1%	3.2%				0.5%			1.6%	0.7%										0%	1.9%		
Brazil nut																							0%		
Pecan								0.2%															0%		
Macadamia								0.2%			1.6%	0.3%											0%		
Other tree nuts	1%		0.8%	0.9%								1.1%										0%	0.9%		
Sesame	3.5%	6.9%					3.2%	0.9%				1.8%		5%						3%		0%	1.5%	7.4%	
Spices/seeds (excl. sesame)																							1.5%		
Mustard																							0.2%		
Pine nut			0.6%	0.0%				2.3%				3.9%											1.9%		
Wheat	2.8%	0.3%	4.2%	3.2%	4.8%	4.8%	12%	7.2%	3.1%	5%	19%	8.1%	6%			4%	0.6%	1.7%		3%		8.3%	0.8%	5.2%	1.3%
Other grains								0.9%					3%										0.7%		
Buckwheat					2.5%	2.1%	1.4%	6.5%	3.1%	14%	1.6%	3.2%													1%
Hen's egg	24%	4.4%	1.1%	15%	0.6%	11%	18%	13.6%				25.4%	20%		8%	44%	1.1%	9.2%	5%		6%	0%	7.0%	13%	11%
Cow's milk	14%	24%	3.9%	15%	0.3%	7.5%	28%	28.4%			1.6%	18.0%	26%		15%			14%		3%	10%	17%	15.8%	9%	31%
Other mammalian milks								0.1%															0.6%		2%
Celery	0%																				11%	8.3%			
Shrimp/Crustacea	1%	3.2%	9.7%	2.3%			1.1%	3.5%	39%	14%	30%	2.5%	20%	36%	31%		6.6%	4.1%	43%	44%	6%	17%	20.2%	11%	21%
Fish	1%		5.5%	7.7%			2.3%	3.0%				1.1%		9%	0%					17%	6%		7.6%		
Molluscs	0%							0.8%			1.6%			9%									6.6%		
Soybean	1%						1.7%	1.4%			3.2%	1.8%	1%									8.3%	0.5%		
Legumes (excl. peanut, soya)	1%	1.6%	4.4%	1.4%																			0.6%		
(of which pea)																							0.1%		
Lupine	0%																						0.5%		
Fruits (all)	1.4%	1.0%	19.9%	10.4%			2.8%	2.1%	5%	14%	4.8%	8.1%	10%	18%	15%		1%	2%		3%	8%	8.3%	16.9%		11%
Peach		0.3%	9.1%	4.5%				0.7%				0.7%		5%									4.8%		
Kiwi	1%	0.6%	1.1%	0%			1.7%	0.8%			0%	4.2%											4.4%		
Banana			0.6%	0.5%			1.1%					0.4%											1.4%		
Fig			0.6%	0%																					
Apple			5.3%	3.2%				0.2%				0.7%											2.4%		
Mango			0%	0%							1.6%	0.7%											0.1%		
Avocado			0.6%	0%																			0.1%		
Carrot																									
Chicken																				4%			0.5%		1.3%
Other animal products								3.1%	15%	14%	6.4%								19%	7%	6%	8.3%	1.2%		3%

	Saudi Arabia	**Singapore**		**South Africa**	**Spain**				**Sri Lanka**	**Sweden**	**Switzerland**	**Taiwan**	**Thailand**		**Tunisia**	**Turkey**		**UK**			**USA**				
	Local ED Visits CVS/RS **2015-17**	Multicentre ED Visits NIAID **2014/15**		Local ED Visits Clinician **2014-16**	Local ED Visits NIAID **2004/5**	Mulicentre Registry Clinician **2011-14**	Local ED Visits NIAID **2012-14**	Local ED Visits NIAID **2013-15**	Local Referrals NIAID **2012-17**	Multicentre ED Visits 2+ organs **2007**	Mulicentre Registry Clinician **2011-14**	Local ED Visits NIAID **2009-11**	Local Referrals NIAID **2004-13**	Local ED Visits NIAID **2007-16**		Local ED Visits NIAID **1997-2007**	National AAI prescription NIAID **2008-11**	Local Referrals Clinician **2010-12**	Multicentre Referrals Clinician **2009/10**	Local ED Visits NIAID **2004-08**	National ED Visits ICD-9 **2005-14**	Local Referrals NIAID **2002-13**		Regional ED Visits ICD-9 **2008-12**	Local ED Visits ICD-9 **2005-14**	
Risk of bias	Moderate	Low		Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate		Moderate	Moderate	Not stated	Low	Moderate	Low	Moderate		Moderate	Low	
% identified food trigger	Not stated	86%	84%	98%	92%	73%	92%	100%	87%	77%	94%	81%	97%	93%	96%	92%	Not stated	Not stated	94%	56%	71%	100%	100%	86%	86%	83%
Reference	53	54		55	59	18	60	61	62	63	18	64	65	66		67	68	69	70	71	72	73		74	13	
	All ages (n=63)	Adults (n=99)	<18y (n=137)	<15y (n=78)	All ages (n=61)	All ages (n=64)	<15y (n=106)	All ages (n=48)	All ages (n=90)	<18y (n=129)	All ages (n=137)	All ages (n=53)	<18y (n=60)	Adult (n=171)	<18y (n=38)	All ages (n=53)	All ages (n=211)	<18y (n=30)	<18y (n=235)	<18y (n=152)	<18y (n=7310)	Adults (n=90)	<18y (n=128)	<19y (n=1893)	Adults (n=1970)	<18y (n=2043)
All nuts (incl unspecified)	43%	6%	21%	46%		20%	24%	21%		48%	47%						24%	27%	66%	40%		32%	55%	51%	23%	39%
Peanut	43%	4%	10%	33%		4.7%	17%	8%		19%	20%	0%					24%	27%	30%	20%	32%	12%	32%	34%	12.8%	27.4%
Tree nuts (combined)			7%	13%	5%	16%	7%	12.5%		19%	27%								36%			20%	23%	17%	10.1%	11.2%
Cashew		1%	2%	9%		1.6%				8%	6.6%															
Pistachio			1%	1%						2%																
Hazelnut			1%	1%	2%	1.6%				2%	8.8%															
Walnut			3%		2%	7.8%				2%	2.2%															
Almond					2%	4.7%				2%	1.5%									20%						
Brazil nut																					19.6%					
Pecan																										
Macadamia																										
Other tree nuts				1%		0%				2%	8.0%															
Sesame	10%			3%		1.6%			2%	2%	0.7%											2.2%	0.8%			
Spices/seeds (excl. sesame)	6%				2%				2%	0.8%									2.1%			2.2%	0%			
Mustard								4%																		
Pine nut																										
Wheat	2%	2%	2%			4.7%			3%	2%	2.9%	0%	18%	0%	3%				2.6%	5%		3.3%	1.6%			
Other grains		1%			2%																					
Buckwheat																			1%			1.1%				
Hen's egg	8%	1%	4%	19%	13%	7.8%	24%		2%	12%	4.4%	0%	12%				11%	20%	9.8%	5%	3.3%	1.1%	16%		0.9%	3.4%
Cow's milk	6%	0%	7%	10%	23%	0%	42%	4%	26%	6%	1.5%	0%	2%				32%	23%	8.9%	7%	6.0%	0.0%	17%	5.4%	3.0%	5.2%
Other mammalian milks																										
Celery						0%					5.1%															
Shrimp/Crustacea	6%	32%	17%	3%	5%	13%		29%	4%	0.8%	3.6%	62%	53%	49%	53%	67%		10%	5%	26%	5.1%	34%	3.1%		6.3%	2.5%
Fish	3%	1%	6%	4%	25%		4%		2%	0.8%		13%		8%	11%		9%					3.3%	3.1%	6.5%	19.8%	7.4%
Molluscs		2%	1%						1%					5%	5%											
Soybean						0%					4.4%								0.9%	1%		2.2%	0%			
Legumes (excl. peanut, soya)	3%			1%	2%												5%	10%	0.9%							
(of which pea)				0%																		0%	0.8%			
Lupine																										
Fruits (all)	6%	0%	2%	3%	12%	20%	7%	33%		3%	15%	6%		2%	0%	16%			3.4%	10%		7.8%	0.8%		8.7%	4.7%
Peach																										
Kiwi	1.6%	0%	2%							0.8%												2.2%	0%			
Banana										0.8%												1.0%				
Fig																										
Apple										0.8%																
Mango	1.6%																									
Avocado																										
Carrot																										
Chicken					2%																					
Other animal products						6.3%	0%		44%		10%	0%								4%		1.1%	1.6%			

	Peanut	Tree Nuts	Sesame	Wheat	Hen's egg	Cow's milk	Celery	Crustacea	Mollusca	Fish	Soybean	Lupine	Other legumes	Fruit	Buckwheat
CODEX	X	X		X	X	X		X		X	X				
AFRICA															
Morocco	X	X	X	X	X	X	X	X	X	X	X	X			
South Africa	X	X		X	X	X		X	X	X	X				
ASIA															
China	X	X		X	X	X		X		X	X				
Hong Kong	X	X		X	X	X		X		X	X				
Japan	X	(X)		X	X	X		X		(X)	(X)			(X)	X
R. Korea	X	(X)		X	X	X		X	(X)	(X)	X				X
Pakistan															
Phillipines	X	X		X	X	X		X		X	X				
Singapore	X	X		X	X	X		X		X	X				
Sri Lanka															
Taiwan	X	X	X	X	X	X		X		X	X				
Thailand	X	X		X	X	X		X		X	X				
EUROPE															
EU	X	X	X	X	X	X	X	X	X	X	X	X			
Israel															
Russia															
Switzerland	X	X	X	X	X	X	X	X	X	X	X	X			
Turkey	X	X	X	X	X	X	X	X	X	X	X	X			
United Kingdom	X	X	X	X	X	X	X	X	X	X	X	X			
LATIN AMERICA / CARIBBEAN (LAC)															
Argentina	X	X		X	X	X		X		X	X				
Brazil	X	X		X	X	X		X		X	X				
Chile	X	X		X	X	X		X		X	X				
Mexico	X	X		X	X	X		X		X	X				
Venezuela	X	X		X	X	X		X		X	X				
NEAR EAST															
Iran															
Qatar	X	X	X	X	X	X		X		X	X	X			
Saudi Arabia	X	X	X	X	X	X		X		X	X	X			
Tunisia															
NORTH AMERICA / SW PACIFIC (NASWP)															
Australia	X	X	X	X	X	X		X	X	X	X	X			
Canada	X	X	X	X	X	X		X	X	X	X				
New Zealand	X	X	X	X	X	X		X	X	X	X	X			
USA	X	X	(X)	X	X	X		X		X	X				

ONLINE REPOSITORY

Global patterns in anaphylaxis due to specific foods: a systematic review

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SUPPLEMENTARY METHODS

Estimated prevalence of allergy to specific foods

Prevalence rates for individual allergens were pooled across included studies using a generalized linear mixed model in R (metaprop function, metafor package, logit transformation with a random intercept logistic regression model for the summary estimate, with a continuity correction of 0.5) (R project, version 4.0.3). This approach avoids many of the issues surrounding the use of transformations when undertaking meta-analyses of proportions.[8,9] We conducted meta-analysis even if significant heterogeneity was seen between study estimates, as is the norm when conducting meta-analysis of proportions. Normal approximation was used for calculating confidence intervals.

For Europe, prevalence was estimated on the basis of reported rates of challenge-positive food allergy reported in a systematic review[E1] and also generated by the Europrevall studies (on the basis of study-defined probable food allergy).[E2,E3]

For North America and Southwest Pacific (NASWP), there are no prevalence data for adults based on food challenges in unselected populations. Instead, adult prevalence data was extracted from Gupta et al[E4] and compared to equivalent data for Canada.[E5] As outlined in the discussion, due to concerns that the reported prevalence of cow's milk allergy in adults by Gupta et al is likely to be an overestimate, the equivalent figure for Canada was used instead. For prevalence of food allergy in children in the NASWP region, rates were pooled from studies reporting prevalence for USA,[E6] Canada[E5] and Australia[E7] (only the latter incorporated food challenges to assess prevalence).

Limited data exists for the prevalence of food allergy in the Asia region.[E8] For adults, data were pooled from a study conducted in Taiwan[E9] and India[E10]. For children, data for China and India were extracted from the EuroPrevall-INCO Surveys[E11] and 2 studies from Thailand[E12,E13] (all of which included food challenges to confirm food allergy), as well as published data for Japan[E14] and Korea[E15] which did not rely on challenge-positive outcomes.

The pooled estimates for reported prevalence to specific food allergens are shown in Table E1.

	Europe		N. America/SW Pacific		Asia	
	Adults	**Children**	**Adults**	**Children**	**Adults**	**Children**
references	E1, E2	E1, E3	E4, E5	E5 – E7	E9, E10	E11 – E15
Peanut	0.35 (0.20-0.60)	0.42 (0.25-0.70)	1.8 (0.6-1.9)	2.60 (2.17-3.11)	0.46 (0.36-0.58)	0.21 (0.17-0.27)
Tree nuts (combined)			1.2 (1.1-1.3)	1.77 (1.26-2.47)		0.12 (0-6.63)
Cashew		0.11 (0-0.62)	0.5 (0.5-0.6)	1.04 (0.59-1.84)		
Hazelnut	0.86 (0.39-1.90)	0.28 (0.10-0.77)	0.6 (0.5-0.7)	0.61 (0.54-0.69)		
Walnut	0.30 (0.14-0.66)	0.12 (0.04-0.41)	0.6 (0.6-0.7)	0.61 (0.54-0.69)		
Sesame	0.01 (0-1.35)	0.07 (0.01-0.88)	0.2 (0.2-0.3)	0.21 (0.17-0.25)		0.07 (0.05-0.10)
Mustard	0.00 (0-2.29)					
Wheat	0.09 (0.03-0.29)	0.16 (0.09-0.29)	0.8 (0.7-0.9)	0.23 (0.10-0.53)	0.14 (0.04-0.53)	0.06 (0.02-0.23)
Buckwheat		0.03 (0-0.37)				0.16 (0.13-0.21)
Hen's egg	0.08 (0.03-0.25)	0.32 (0.17-0.60)	0.8 (0.7-0.9)	0.94 (0.53-1.67)	0.30 (0.22-0.40)	0.18 (0.04-0.80)
Cow's milk	0.16 (0.07-0.35)	0.35 (0.20-0.63)	1.1* (0.9-2.1)	0.79 (0.26-2.33)	0.48 (0.38-0.61)	0.07 (0.01-0.82)
Celery	0.14 (0.04-0.45)	0.04 (0-1.50)				
Shrimp/ Crustacea	0.41 (0.21-0.80)	0.11 (0.04-0.29)	1.9 (1.8-2.1)	0.72 (0.36-1.45)	0.27 (0-7.5)	0.55 (0.36-0.84)
Fish	0.14 (0.06-0.33)	0.04 (0.01-0.18)	0.9 (0.8-1.0)	0.52 (0.24-1.12)	0.22 (0.01-1.4)	0.29 (0.26-0.32)
Soybean	0.04 (0.01-0.19)	0.19 (0.07-0.57)	0.6 (0.5-0.7)	0.20 (0.06-0.66)		0.07 (0.06-0.09)
Lentil	0.04 (0.01-0.35)	0.10 (0.01-0.79)				
Peach	0.64 (0.24-1.67)	0.40 (0.20-0.80)				
Kiwi	0.61 (0.32-1.17)	0.49 (0.28-0.83)				0.02 (0-0.70)
Banana	0.12 (0.02-0.71)	0.33 (0.13-0.85)				
Apple	0.67 (0.30-1.51)	0.65 (0.31-1.36)				
Carrot	0.49 (0.27-0.91)	0.24 (0.11-0.51)				

Table E1: Estimated prevalence of allergy to specific foods. See supplementary methods for further details. *Prevalence based on Canadian data

SUPPLEMENTARY FIGURE LEGENDS

Figure E1: Studies reporting fatalities and ICU admissions for food anaphylaxis. Figures represent the percentage of all cases attributed to a food allergen, caused by a specified food trigger. Heat-map colors indicate *relative* (rather than *absolute*) prevalence of specific foods within each case series.

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