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Published in:
Clinical and Experimental Allergy

DOI:
10.1111/cea.13753

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Remington, B. C., Westerhout, J., Dubois, A. E. J., Blom, W. M., Kruizinga, A. G., Taylor, S. L., Houben, G. F., & Baumert, J. L. (2021). Suitability of low-dose, open food challenge data to supplement double-blind, placebo-controlled data in generation of food allergen threshold dose distributions. *Clinical and Experimental Allergy*, *51*(1), 151-154. https://doi.org/10.1111/cea.13753

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Received: 25 June 2020 | Revised: 21 September 2020 | Accepted: 1 October 2020

DOI: 10.1111/cea.13753

RESEARCH LETTER

WILEY

Suitability of low-dose, open food challenge data to supplement double-blind, placebo-controlled data in generation of food allergen threshold dose distributions

To the Editor,

Food allergen threshold dose distributions are used in food allergen risk assessment to determine the level of risk within a food-allergic population to a defined exposure amount of allergenic food protein and to help inform allergen risk management decisions. There has been a long-standing interest in determining threshold dose distributions for different food allergens from a research and a risk management perspective.[1-3] More recently, allergen risk management programmes utilizing population threshold dose distributions to inform the decision-making process have been endorsed by multiple international stakeholder groups and national agencies.[4-7] The interest shown by all stakeholders regarding this area of research had placed an emphasis on gathering as many data points, from as many foods, as possible to better inform allergen risk assessments and risk management.

The estimation of the threshold dose-distribution for a specific food typically involves the utilization of data from clinical dose-response tests using double-blind, placebo-controlled food challenges (DBPCFC).[8] Distribution modelling already becomes possible with the availability of several tens of data points, but simulation studies have shown that a sample size of 60 patients or more is preferred for the most stable estimates of population-based eliciting doses (ED05, ED10, etc).[9] However, in practice it is problematic to obtain 60 data points from DBPCFCs for several foods due to a scarcity of allergic patients which leads to food challenge data scarcity. Even for regulated allergens, the DBPCFC data available may not be sufficient to reach 60 individuals in all cases. Remington et al[3] (2020) have recently updated a long-established database of food challenge results used to create allergen dose distributions, and a number of regulated allergens are missing data or did not have more than 60 data points available. For example, limited or no data were available for certain tree nuts (almond, pecan, pistachio), some crustacean shellfish (crab, lobster), or any molluscan shellfish, and less than 60 data points were available for sesame, mustard and lupin.[3] This raises the question of the possibility for using other or Supplementary information sources to arrive at an estimate for the dose-distribution, that is the use of open food challenge data in addition to DBPCFC data to increase the amount of data available for analysis.

To date, no study has compared the threshold dose distributions resulting from open food challenges to those resulting from DBPCFCs in a controlled manner. The current study aims to compare dose distributions from open food challenges and DBPCFCs in a single clinic to investigate whether open challenge data can help to supplement the dose-distribution analysis when few data from DBPCFC are available. Risk assessment strategies thus may benefit from additional open food challenge data sources when DBPCFC data are scarce. The paper concludes with a discussion of the implications for risk management.

Data of all positive open food challenges and DBPCFCs in children (Jan 2002-April 2015) were retrospectively extracted from the tertiary care paediatric allergy department at Beatrix Children's Hospital, University Medical Center Groningen (UMCG). Children were referred to the UMCG from primary and secondary care centres because of suspected food allergy. Medical ethical approval was not required for this study as all procedures were performed as part of routine clinical care. The study population consisted of children with suspected food allergy undergoing either an open or DBPC food challenge. In general, dosing protocols for both open and DBPC food challenges began in the low mg range (0.6-1.8 mg food protein) and increased over 6 doses to a final dose in the range of 1400-2200 mg protein. In some individual cases, dosing schemes could be modified to start or finish with a higher amount of protein. Similar matrices were available for both DBPC and open food challenges. However, in a few cases an open challenge could have included no matrix. If individuals had multiple positive DBPCFCs to the same food, or multiple positive open challenges to the same food, only the first positive challenge for each protocol was utilized for analysis. Children with a history of previous anaphylactic reactions were not excluded from challenges. In cases where individuals had positive results from both food challenge methods, the open challenge data point was excluded from the analysis.

A stacked model averaging interval-censored survival analysis was used to fit 5 dose-distribution functions (Weibull, Log-Gaussian [Log-Normal], Log-Logistic, Generalized Pareto and Log-Laplace [Log-Double-Exponential]) to the data for analyses and combined the weighted results into a single, averaged dose-dose distribution for each data set.[10] R software (https://www.r-project.org/) and the publicly available Stackedsurv package (https://doi.org/10.5281/zenodo.3401470) were used for all analyses. No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs) for objective symptoms were derived from the cumulative dosing scheme using previously

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established consensus criteria and utilized to represent the interval at which the objective reaction occurred.[8] Objective symptoms were deemed to be any symptom that was externally observable. Exceptions included abdominal pain, which was considered an objective symptom provided it was observed in children less than 3 years old and subjective if observed in older children.[8] Subjects showing an objective reaction at the first dose were included (left-censored observations), as well as subjects demonstrating subjective symptoms but not reacting to the highest dose given with objective symptoms (right-censored observations). Data were analysed for each food separately. The fitted threshold dose distributions for open and DBPCFC data were compared for potential significant differences by inspecting the overlap, or lack thereof, in the 95% confidence intervals (CI).

A total of 756 DBPCFC and 304 open food challenge results were available from 23 different foods. However, only 4 foods (egg, hazelnut, milk and peanut) contained sufficient data for further analysis with a total of 199 positive open food challenges and 575 positive DBPCFCs from 527 patients. In total, 96 of these individuals had positive results from both food challenge methods and the open challenge data point was excluded from the analysis. After curation of the data, only peanut (n = 45 open; 267 DBPCFC) and hazelnut (n = 38 open; 78 DBPCFC) contained sufficient data for further analysis (Table 1).

The threshold dose distributions of peanut and hazelnut for open challenges and DBPCFCs were not deemed significantly different from each other due to similar distributions for both challenge methods with broadly overlapping 95% confidence intervals (Figure 1A,B). Additionally, the Kaplan-Meier distributions for the peanut and hazelnut open challenge data sets were well within the observed study-to-study variations of DBPCFC data sets from different clinics with differing clinical protocols, as previously reported from 27 peanut studies and 10 hazelnut studies (Figure 1C,D).

The analysis was carried out using data from a single tertiary care paediatric allergy department in an effort to limit several important external factors (different dosing protocols, different food matrices, different nurses' and doctors' interpretations of allergic symptoms, different protocol stopping criteria, etc) that can introduce study-to-study heterogeneity and complicate the relatively simple comparison of the resulting threshold dose distributions. Additionally, the stacked model averaging analysis incorporates random effects into the threshold dose-distribution modelling, so any differences in the resulting distributions for open food challenges and DBPCFCs should contain limited confounding factors. The dose distributions for peanut and hazelnut do differ slightly depending on the food challenge methodology utilized, as seen in Figure 1. However, these small differences could be in small part due to the relatively limited data for the open challenges and more data could result in a slight shift in the open distributions. Additionally, the small variations between the open food challenge distribution and the DBPCFC distribution within this single allergy clinic are limited in comparison with study-to-study variations from different clinics and different clinical protocols (Figure 1C,D). The small variations observed in this study would not warrant the exclusion of open food challenge data in future analyses.

Additional analysis was carried out (Figures S1-S3) within the study population to compare threshold dose distributions from open food challenges to DBPCFCs for egg, hazelnut, milk, and peanut in 1) all positive food challenges, 2) only in individuals with both a positive DBPCFC and a positive open food challenge and 3) utilizing only the first positive food challenge regardless of challenge method. In these three additional analyses, similar results were observed to those presented here in detail, further indicating that open food challenge data could be used to strengthen data sets where DBPCFC data are limited. From the results of our study, potential differences or preferences for choosing between an open or DBPC food challenge seem to be pertinent for diagnostic purposes but not for the determination of food allergen dose distributions,

TABLE 1 Number of children with positive open food challenges and DBPCFCs at tertiary care paediatric allergy department at Beatrix Children's Hospital, University Medical Center Groningen (UMCG), (2002-April 2015)

		Open food challenge					DBPC food challenge			
				Censored					Censored	
Allergen	Total n	n[a]	Age [years] range (mean)	Right-censored	Left-censored	Excluded[b]	n	Age [years] range (mean)	Right-censored	Left-censored
Milk	140	9[c]	0.9-14.1 (4.1)	2	1	36	131	0.3-17.6 (3.5)	20	9
Peanut	312	45	0.8-17.6 (6.7)	14	2	27	267	0.9-17.8 (8.4)	132	13
Egg	110	11[c]	0.8-12 (3.2)	2	1	27	99	0.8-17.8 (4.5)	27	8
Hazelnut	116	38	1.4-15.4 (7.6)	14	4	6	78	1.3-18 (8.5)	47	7

[a]The number of subjects included for analysis after exclusion of open challenges from individuals who completed both an open food challenge and a DBPC food challenge.

[b]The number of open challenge data points excluded from analysis because individuals had both a positive open challenge result and a positive DBPC food challenge result.

[c]Not enough data for dose-distribution analysis.

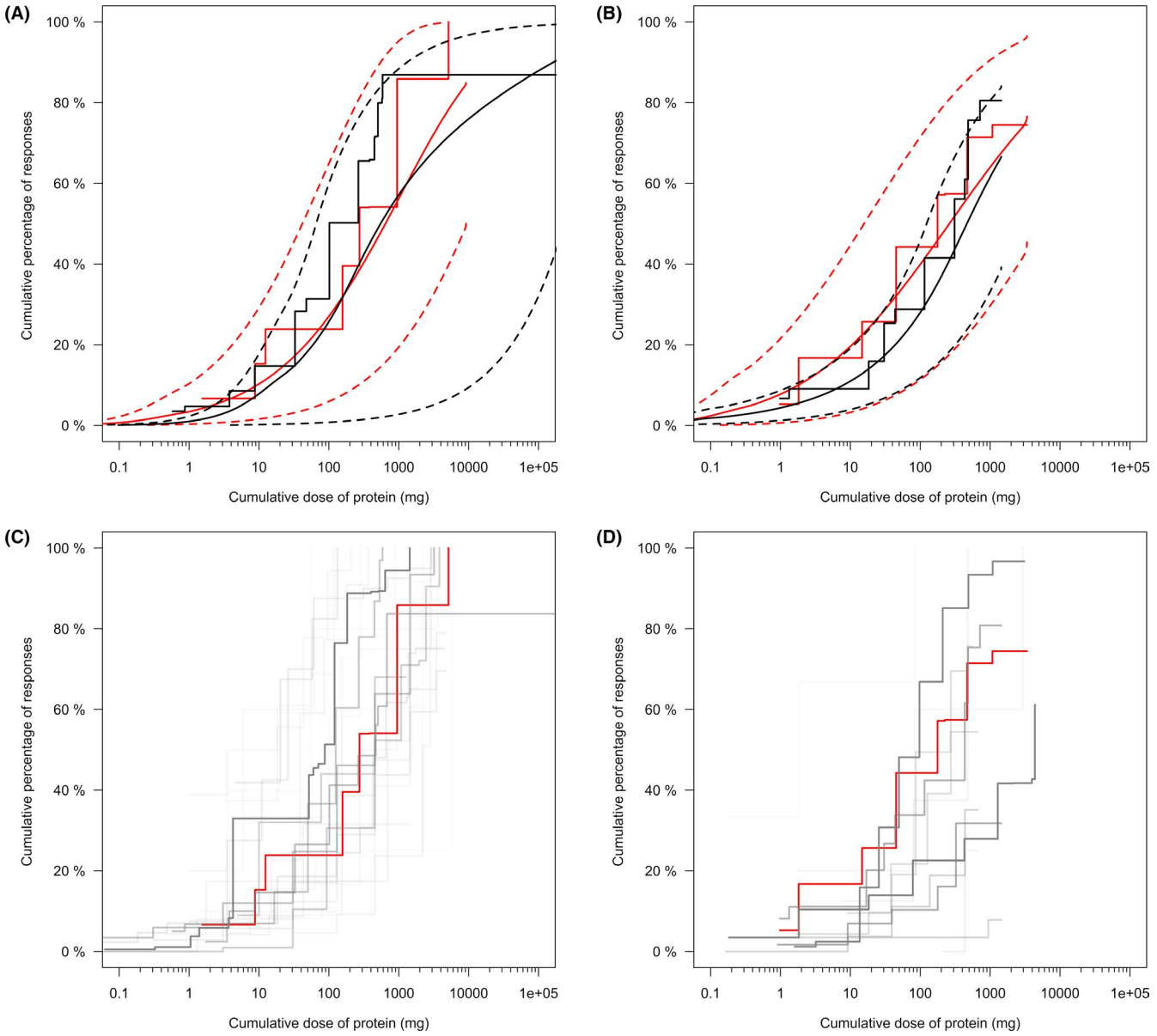

FIGURE 1 (A) Peanut-allergic and (B) hazelnut-allergic dose distributions for open food challenges (red) and DBPCFCs (black), with 95% confidence intervals. (C) Peanut-allergic and (D) hazelnut-allergic Kaplan-Meier distributions for UMCG open food challenges (red) in comparison to DBPCFC study-specific Kaplan-Meier distributions (black, darker indicates a study with more observations) from 27 peanut studies and 10 hazelnut studies as previously summarized by Remington et al (2020).[3] If an individual at the UMCG reported positive food challenges for both open and double-blind food challenge methods then, the open challenge data point was excluded from the analysis

provided that similar challenge protocols (protein form, matrices, dose schemes) are used.

In conclusion, this study provides support for the use of open food challenge data to supplement DBPCFC data for the generation of food-allergic population threshold dose distributions when there is limited or no data from DBPCFCs available for certain foods. This could be particularly interesting to fill data gaps for several foods existing on regulatory priority lists including certain tree nuts (almond, pecan, pistachio), crustacean shellfish (crab, lobster), or any molluscan shellfish. Additionally, the use of open food challenge data could be utilized to fill data gaps for geographic regions that do not routinely perform DBPCFCs and to provide data on less commonly allergenic foods (corn, rice, pea, lentil, etc).

ACKNOWLEDGEMENTS

The authors wish to thank C. Dorien van Ginkel, MD, PhD, Vicky Sideridou, MD, and Faisal Bakhsh, MSc, from the University Medical Centre Groningen (Groningen, the Netherlands) for their help with the food challenge data extraction.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

BCR contributed to study design, data generation, data analysis, data interpretation, figures and writing. JW, WMB and AEJD contributed to study design, data generation, data analysis, data interpretation, figures and critically revising the manuscript. AGK, SLT, GFH and JLB contributed to study design, data analysis, data interpretation, figures and critically revising the manuscript.

FUNDING INFORMATION

This research was party financially supported through Dutch Governmental TNO Research Cooperation Funds, as well as through funding from the Food Allergy Research & Resource Program (FARRP) at the University of Nebraska. FARRP a food industry-funded consortium with more than 100 member food companies.

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