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I, Megan P Syck, hereby submit this original work as part of the requirements for the degree of Master of Science in Industrial Hygiene (Environmental Health).

It is entitled:

Sensitivity to Oral Food Allergies in Subjects with Allergic Rhinitis and Eczema

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Sensitivity to Oral Food Allergies in Subjects with Allergic Rhinitis and Eczema

By

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Abstract

Oral food allergies for the worldwide general population have been on the rise within the past three decades and are becoming a prevalent issue among pediatric patients (Foong et al., 2017; Zhu et al., 2015). Allergic rhinitis and atopic dermatitis (eczema), along with oral food allergies and sensitivities, are all classified as allergic diseases (Foong et al., 2017). Since these diseases are classified as allergic-type diseases, they likely have a higher chance of comorbidity (Foong et al., 2017). If the diseases are truly comorbid, as suggested by Foong et al. (2017), then it may be possible to use documented clinical histories of allergic hypersensitivities as predictors of increased sensitivity to food allergens. This study's objective was to determine if a history of allergic rhinitis or eczema are associated with an increase in severity or sensitivity to specific oral food allergies. Our hypothesis was that study subjects with a history of eczema or allergic rhinitis would have increased sensitivity to oral food allergens compared to participants without a history of eczema or allergic rhinitis. This hypothesis was tested using a data set of 435 total participants enrolled in an oral food allergen desensitization study with positive allergy screening tests for one or more tested foods. Reaction probability to the allergens was calculated based on the allergic responses during the oral challenge phase as the cumulative dose was incrementally increased. The severity of the reaction was determined using a 3-category (1=mild, 3=severe) scale based upon the participants' clinical responses during the challenge. Non-parametric Kaplan Meier event estimates were used to evaluate the dose-response relationship using a censored univariate model, and parametric survival analysis was used to for regression modeling. The severity of reactions was evaluated for participants with and without allergic rhinitis and eczema. A slightly statistically significant relationship was found in participants with cashew allergies and a history of eczema. All other allergens had a p-value greater than 0.05 and were not statistically significant regardless of either disease's history. The results of the statistical analyses did not fully support the

hypothesis. Future direction and research should be done to determine if additional factors would impact oral food allergies' sensitivity.

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Acknowledgements

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Finally, I am extending a thank you to the National Institute for Occupational Safety and Health (NIOSH) for allowing me to further my education through the Education and Research Training Grant Stipend. This funding was used to support me during my time at the University of Cincinnati and I am forever grateful for their support.

Introduction

Allergic reactions (hypersensitivities) are abnormal responses to outside sources (allergens), which cause the immune system to react by producing antibodies for a specific allergen (CDC, 2020). There are four different types of hypersensitivity reactions (allergic reactions). The most acute hypersensitivity reaction (type I hypersensitivity) is an IgE-mediated response that is immediate and is the primary cause anaphylaxis and/or angioedema.

The severity of an allergic reaction following exposure to an allergen varies depending on the type of allergic response, the route of exposure, and/or the amount of the allergen exposure. Allergies can take on various forms from acute reactions (e.g. hay fever, anaphylaxis) to delayed responses (e.g. allergic asthma, atopic dermatitis), and range in severity from mild nuisance to lethal. Allergic rhinitis is classified as a type I hypersensitivity impacting the sinus cavities. A stuffy nose, watery swollen eyes, and sneezing are classic symptoms of this disease. Atopic dermatitis, a type IV hypersensitivity commonly known as eczema, is another allergic disease that impacts the skin and causes the affected skin to turn red, itch, and sometimes peel or flake.

Comorbidity is a term generally used to define when more than one disease is present simultaneously in a patient and is often associated with worse health outcomes than the presence of one disease alone (Valderas et al., 2009). If the diseases are truly comorbid, as suggested by Foong et al. (2017), it may be possible to use data regarding sensitivities to food allergens, eczema, and allergic rhinitis to predict certain outcomes regarding various levels of hypersensitivities. Due to allergic diseases' comorbidity as the prevalence increases, research is needed to find predictors for the dose-response relationship and its severity.

Our hypothesis is that study subjects with a history of eczema, or allergic rhinitis would increase sensitivity to oral food allergens compared to participants without a history of eczema or allergic rhinitis. To test this hypothesis, we evaluated whether subjects with reported histories of allergic rhinitis or eczema had reactions to four food allergens at lower doses than those without a history. We used non-parametric Kaplan-Meier survival analysis to evaluate the relationship between cumulative allergen dose and allergic reaction events. Full parametric survival analysis was used to test whether allergic hazards (based on hazard curve models) were significantly different for subjects with histories of eczema and allergic rhinitis, relative to subject without. Finally, an evaluation of reaction severity was completed to determine if participants with a history of either allergic disease had more severe reactions compared to those without a history of either allergic disease.

Methods

Dataset:

The dataset used for this study was data collected from Stanford University. The collection process was completed via a placebo-controlled dose-response model used for testing food allergies. The dataset included 435 participants at 7 sites as an Investigational New Drug (IND) using double-blind placebo-controlled oral food challenge (DBPCFC) testing, DBPCFC testing for food allergies is the current gold standard method for characterization (Grabenhenrich et al. 2017). The participants were recruited between September 2010 and March 2016 at the Stanford Food Allergy Clinic. Three different tests (skin prick tests, total IgE, & specific IgE) were completed as inclusion criteria during the initial screening to confirm suspected food allergies. Skin prick tests comprised of three main contents: allergen extracts,

histamine, which served as a positive control, and saline serving as a negative control. The skin prick tests were completed for each participant on the back or inside the forearm and measured for the mean wheal diameter 20 minutes after being administered. An ImmunoCAP fluorescence enzyme immunoassay was used to measure IgE levels for the specific allergens (Sindher, 2018). IgE levels and skin prick tests were used to determine qualification for participants in the DBPCFC study. Participants in the initial visit were considered to have an allergy if serum levels were IgE >0.35 kU/L and/or have a positive SPT (>3 mm above the negative control).

Participants were excluded from this study if they had a medical history of hypotension and/or required intubation from a food allergy. Participants with a history of asthma having a forced expiratory volume of less than 80 percent in the first second of forced breathe (FEV1), severe or moderate asthma or other significant nonallergic medical conditions were excluded from this study. Monitoring for oral food allergy challenges was completed using a standardized method and scoring system (described in summary below) and was performed while the suspected allergen dose was being incrementally increased to reach a final cumulative dose of at least 500 mg. The challenge was terminated when at a least one *observable* challenge-terminating reaction was identified, or after the maximum cumulative dose was completed. It is noteworthy that unobservable subjective *symptoms* were not a basis for challenge termination. The no observed adverse effect level (NOAEL) was recorded as the dose before the terminating dose and is the "successfully consumed dose" (SCD); the lowest observed adverse effect level (LOAEL) is the dose at which the first allergic reaction was observed and is the "challenge terminating dose". This classification means that the true dose at which an allergic reaction

occurs within the interval between the NOAEL and the LOAEL (NOAEL < reaction dose ≤ LOAEL). Reactions occurring at the lowest administered dose have a NOAEL that is greater than 0 but less than the LOAEL (0 < NOAEL < lowest administered dose [LOAEL]) and are therefore considered to be left-censored. In contrast, subjects that have no reaction at any administered dose up to the highest tested cumulative dose have an unbounded LOAEL and are considered to be right-censored data (NOAEL > highest administered dose and no observed LOAEL).

This Stanford study's oral food challenges included testing of eleven different food allergens; however, only the four allergens with the highest number of participants were used in this thesis: cashew, walnut, peanuts, and hazelnut (described below). The oral food challenge dose in the form protein powder was incrementally increased every 15 minutes if tolerated. Vital signs were monitored, and a physical exam was conducted by a clinician every 15 minutes during the course of the challenge. Bock's criteria were used to characterize the dose-related adverse effects based on severity and type of reaction from the oral food challenge. The Bock criteria are an accepted framework for classifying allergic reaction severity to one of three levels: mild (1), moderate (2), or severe (3); specific objective clinical criteria for each reaction type, based on affected organ system, are used as a basis for classification (Grabenhenrich et al., 2017). A negative challenge result for the participant was determined if the cumulative tolerated dose (CTD) was equal to or greater than 500mg of food protein. The total cumulative protein amount is the amount of ingested protein with no observed dose-related adverse effects (Sindher, 2018).

Statistical Analysis:

Data analysis was conducted using R Studios Version 1.2.1335 with supporting statistical packages including survival, survminer, icenReg, and other supporting packages for organizing

the dataset and run various statistical analyses. The data on participant's history of allergic rhinitis and eczema are binomial (1=yes, 0=no). Based on our proposed hypothesis, the corresponding null hypothesis is that there is no difference in food allergy sensitivity for subjects with and without histories of food allergies. The null hypothesis is rejected if subjects with histories of allergic rhinitis or eczema are more (or less) sensitive to food allergens, either in terms of reaction dose or response severity, relative to subjects without histories of rhinitis or eczema. Like the Bock criteria used in classifying subject reaction severity, a scale used here also has three categories (1=mild, 2 =moderate, 3=severe) but is a modification of the Bock criteria in that it is an overall aggregate severity score that assigns an increased severity score when allergic reactions occur amongst one or more organs system (Zhu et al., 2015). The scale was determined based on the level of clinical evaluations, the number of organ systems impact, and whether the reaction involved the respiratory or cardiovascular system. With this scale, a reaction labeled with a mild severity level (1) involved symptoms from one organ system (i.e., skin) as long as the clinical observation was low in severity. A reaction labeled with a moderate severity level (2) involved two different organ systems (i.e., skin and gastrointestinal) and/or a moderate clinical observation severity. The final reaction severity level is a severe level (3) which consists of any observation with the cardiovascular system and/or lower respiratory system, impacting three or more organ systems (i.e., skin, gastrointestinal and upper respiratory) or a severe clinical observation. All severity level data are recorded in Table 5 and Table 6 depending on the disease being evaluated.

The no observed adverse effect level (NOAEL) was used for each allergen (cashew, walnut, peanut, and hazelnut) in all statistical analyses. Data frames were created to remove

any unknown histories of either disease. This reduced the number of participants to 306 participants for the peanut allergen when evaluating allergic rhinitis and 309 participants for eczema. The analysis for Cashew included 123 participants for allergic rhinitis and 121 participants for eczema. The analysis for walnut included 98 participants for allergic rhinitis and 100 participants for eczema. Hazelnut had the least number of participants being analyzed at 58 participants for allergic rhinitis and 57 participants for eczema. This data is summarized in table 1 and 2.

The allergen reaction doses used for statistical analysis were recorded in milligrams (mg) of purified protein. Due to the skewed distribution of the cumulative dose data, modeling was performed with log-transformed data. Prior to transformation, doses were converted to micrograms of protein to avoid negative log values (1 mg = 1000 μg). Box plots were created to allow for a visual comparison of each allergen's medians in participants with or without a history of eczema in Figure 3 and allergic rhinitis in Figure 4.

Kaplan-Meier (KM) survival analysis models were used to check the dose-response potency among the two diseases (allergic rhinitis and eczema) independently. KM analysis was performed using the R survival and survminer packages and plotted using ggplot2 and ggfortify. The KM models were modified to use the cumulative dose as the independent variable for the x-axis instead of the usual variable time.

The R package IcenReg was used for parametric survival modeling of the associations between the dose-related sensitivity to food allergens and disease (allergic rhinitis or eczema). We adopted a previously described dose-distribution modeling approach, as described by Crevel et al. (2007) together with interval censoring survival analysis, as previously described

(Taylor et al. 2010), which is a widely accepted as one that uses the available data most effectively. Interval censoring survival analysis permits the use of data points from first-dose reactors (left-censored observations), as well as those not reacting at the highest dose (in cases where allergy is nonetheless independently proved [right-censored observations]) (Taylor et al. 2009; Allen et al. 2014, Haber et al., 2021). Dose administration data were analyzed as the cumulative doses successfully given on the day of the challenge. Responses were adjusted for any responses observed during the matching placebo treatment performed on a separate day +/- 2 weeks from the initial challenge date. Appropriate parametric model distributions were selected based on goodness of fit for each parametric fit (as determined by the log likelihood), as well as visual examination of diagnostic plots of the fitted probability dose-distribution curves to standard exponential, Weibull, loglogistic, gamma, log-normal and general gamma distributions. Statistical significance of model parameters (eczema and allergic rhinitis) were evaluated from summaries of the model fits.

Results

All participants provided medical history and demographic data for this study. Medical history included eczema and allergic rhinitis history and was answered by the participants with yes/no questions. Participants were given options to select triggers relating to eczema and/or allergic rhinitis, which included: dust, exercise, food allergies, grass, molds, pets, viral illness, weeds, and/or others. Table 1 provides a summary of the study participants with and without allergic rhinitis by allergen, and Table 2 provides a summary of the study participants with and without eczema by the allergen. Here, we evaluate the four allergens with the largest datasets (cashew (n =157), walnut (n=140), peanut (n=391), and hazelnut (n=110)).

Table 1. Number of subjects with and without a history of allergic rhinitis by allergen.

Allergic Rhinitis	Peanut	Cashew	Walnut	Hazelnut
Yes	227	90	73	45
No	79	33	25	13
Total	306	123	98	58

Table 2. Number of subjects with and without a history of eczema by allergen.

Eczema	Peanut	Cashew	Walnut	Hazelnut
Yes	219	90	77	44
No	90	31	23	13
Total	309	121	100	57

Table 3 shows the severity of reactions among the different allergens in participants with and without allergic rhinitis. As previously mentioned, severity is graded using a three-category scale and is based on clinical results from the oral food allergy challenge. When evaluating the table, two of the allergens (peanut and cashew) had the highest percentage of participants in the moderate severity (category 2) regardless of allergic rhinitis history. In contrast, two allergens (hazelnut and walnut) did not have a higher percentage of moderate severity than the other two categories except for participants with a walnut allergy and a history of allergic rhinitis. Overall, the percentage of severe reactions (category 3) are lower than the mild and moderate severity categories except for those with a peanut allergy and a history of allergic rhinitis.

Table 3. The percentage of subjects with reaction severities (ranked by 1 = mild and 3 = severe) among participants with and without allergic rhinitis by allergen (peanut, cashew, walnut and hazelnut).

Table 3. The percentage of subjects with reaction severities (ranked by 1 = mild and 3 = severe) among **Severity Categories** participants with and without allergic rhinitis by allergen.				
Allergen	**Allergic history**	**Severity Categories (1=mild, 3=severe)**		
		1	**2**	**3**
Peanut	**History**	25%	49%	26%
	No History	30%	51%	19%
Cashew	**History**	29%	56%	16%
	No History	36%	48%	15%
Walnut	**History**	40%	52%	8%
	No History	60%	32%	8%
Hazelnut	**History**	58%	40%	2%
	No History	62%	31%	8%

A few similar trends were observed in this table (Table 4) as they were in Table 3. The first trend is a higher percentage of moderate severity cases in those with a history of eczema than the group without a history of eczema. The allergen hazelnut did not fit this trend in either group (history or no history of eczema), and this was also noticed in those with a cashew allergy and no history of eczema. The final trend was that the third severity level had the lowest percentage of reactions except for those with a cashew allergy (no eczema history) and those with a peanut allergy (eczema history).

Table 4. The severity of reaction (ranked by 1 = mild and 3 = severe) among participants with and without eczema by allergen (peanut, cashew, walnut and hazelnut).

Table 4. The severity of reaction (ranked by 1 = mild and 3 = severe) among participants with and without eczema by allergen (peanut, cashew, walnut and hazelnut).

Allergen	Allergic history	Severity Categories (1=mild, 3=severe)		
		1	2	3
Peanut	**History**	30%	43%	27%
	No History	20%	63%	17%
Cashew	**History**	38%	51%	11%
	No History	13%	61%	26%
Walnut	**History**	45%	47%	8%
	No History	43%	43%	13%
Hazelnut	**History**	59%	36%	5%
	No History	62%	38%	0%

To get a sense of the cumulative NOAEL dose-response data for individuals with and without allergic histories, a series of boxplots were generated for each allergen. Boxplots are useful for summarizing the quartile range of continuous data. Figure 1 presents boxplot analyses of NOAEL doses for participants with (light blue) and without (green) histories of eczema for each of the four allergens (cashew, hazelnut, walnut, and peanut). This figure is used to visualize the spread of the data and compare the medians and quartile ranges amongst subjects with a history of eczema compared to those without. Participants with an unknown eczema history are excluded from the plot. Two of the allergens (cashew and hazelnut) have higher medians for the participants with a history of eczema than those with no history. The medians for the peanut allergen are relatively equal regardless of eczema history. The final allergen (walnut) has a higher median in participants without eczema history compared to those with eczema. Three out of the four allergens (walnut, hazelnut and peanut) had an interquartile range (IQR) (the difference between the 3rd and 1st quartile) of 3.2 log ug (24.53 ug

or 0.24 mg) in participants without eczema and an IQR of 2.8 log ug (16.44 ug or 0.16 mg) (in those participants with eczema. A lower IQR shows that fifty percent of the data is closer together in those with eczema than those without eczema. One allergen (Hazelnut) had an IQR of 2.4 log ug (11.02 ug or 0.01 mg) for those without a history of eczema compared to an IQR of 3.2 log ug (24.53 ug or 0.24 mg) for those with a history of eczema. This indicates that fifty percent of those with a hazelnut allergy and no history of eczema have a spread of data closer together than those with a hazelnut allergy and eczema.

Figure 2, as in Figure 1, contains boxplots for the participants with (orange) and without (green) a history of allergic rhinitis for each of the four allergens, and is also used for visual comparison. The medians for two of the allergens (peanut and hazelnut) are relatively similar regardless of allergic rhinitis history. The median for the allergen cashew was slightly higher in the group with a history of allergic rhinitis than those without a history. In contrast, the median for the allergen walnut is higher in the population of participants without allergic rhinitis than in those with a history of allergic rhinitis. Three out of four of the allergens (walnut, peanut and cashew) had an IQR of 2.4 log ug (11.02 ug or 0.01 mg) for those without a history of allergic rhinitis and an IQR of 3.6 log ug (36.60 ug or 0.36 mg) for those with a history of allergic rhinitis. This means that fifty percent of those participants without a history of allergic rhinitis have a spread of data closer together than those with allergic rhinitis. The other allergen (hazelnut) had an IQR of 2.8 log ug (16.44 ug or 0.16 mg) for those without a history of allergic rhinitis and an IQR of 3.2 log ug (24.53 ug or 0.24 mg) for those with a history of the disease. This allergen had a smaller spread in data between the fifty percent of participants who had no history of allergic rhinitis than those participants with the disease.

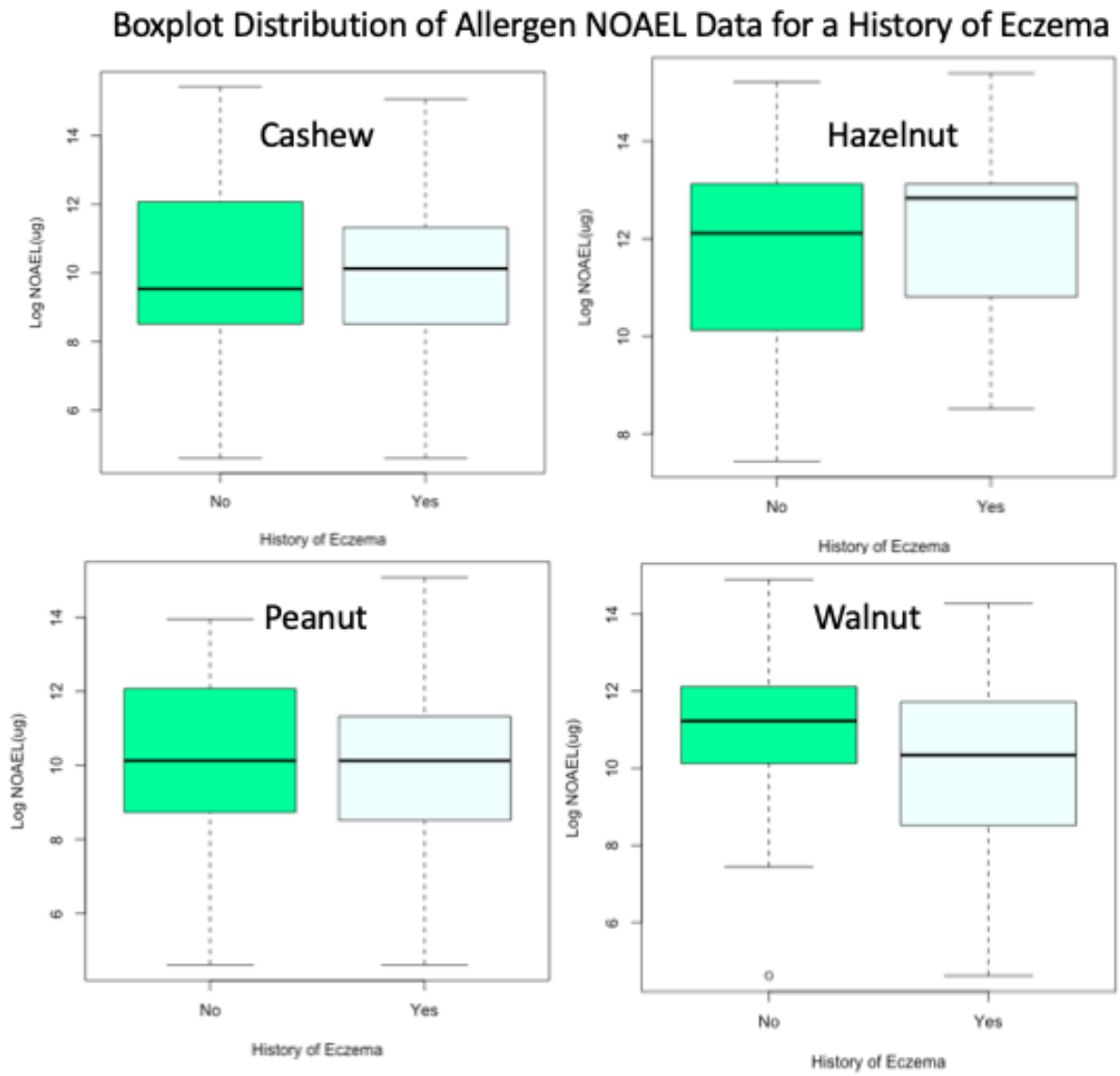

Figure 1. Boxplot distribution data of the log-transformed data for the NOAEL (in micrograms) means for participants with (blue) and without (green) a history of eczema for the four different allergens (Cashew, Hazelnut, Peanut and Walnut).

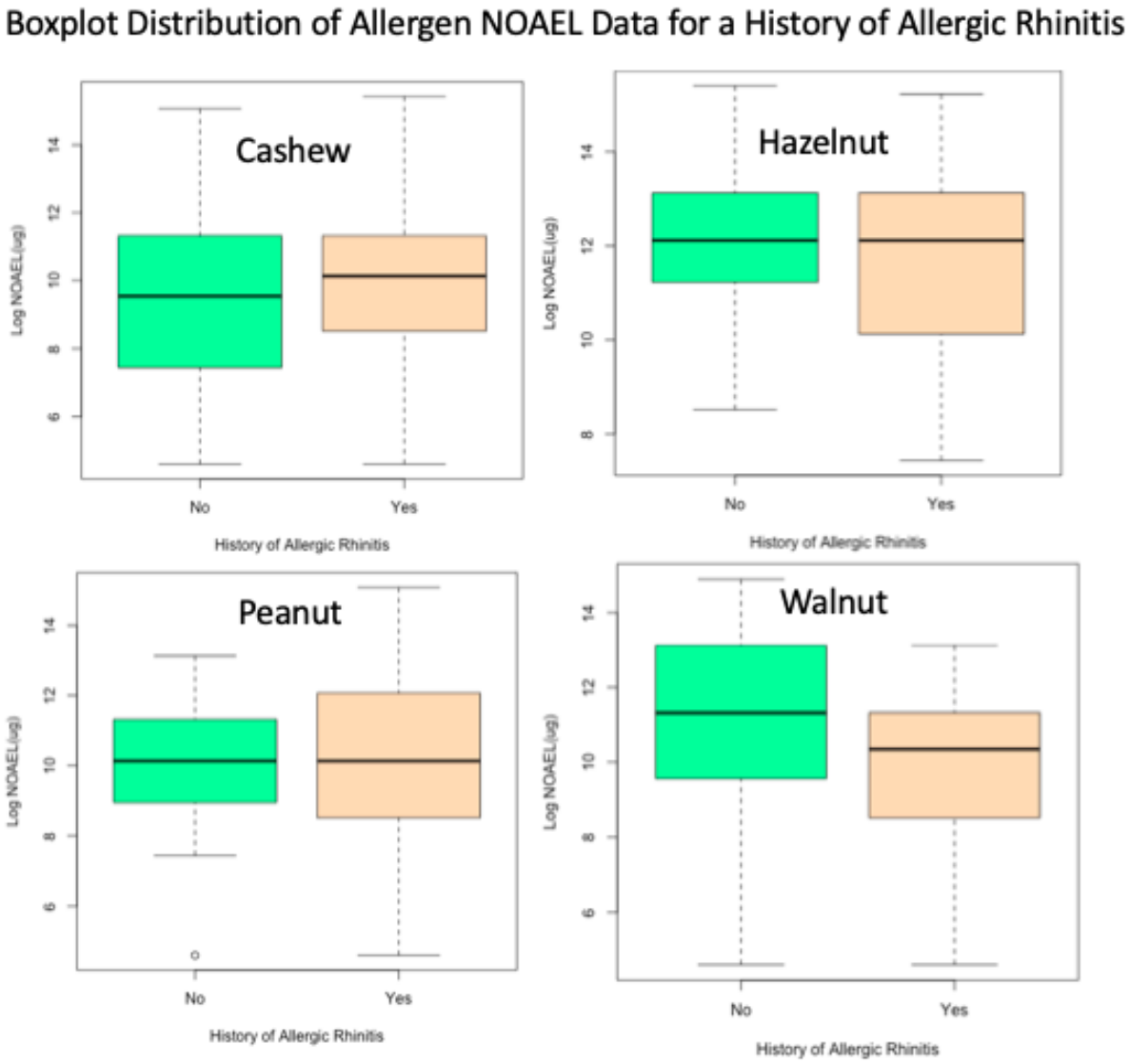

Figure 2. Boxplot distribution of the log-transformed data for the NOAEL (in micrograms) means for participants with (orange) and without (green) a history of allergic rhinitis for the four different allergens (Cashew, Hazelnut, Peanut and Walnut).

A Kaplan-Meier approach was used to visualize reaction events for each subject as a function of cumulative allergen dose (Figure 3), based on the participant's history of eczema. When evaluating the plot, it appears that those participants with eczema (blue line) at low doses may have a slightly higher rate of a reaction when compared to those without eczema

(red line) for cashew and walnut. The same potential trend is noted when evaluating the Kaplan-Meier models (Figure 4) for participants with and without allergic rhinitis.

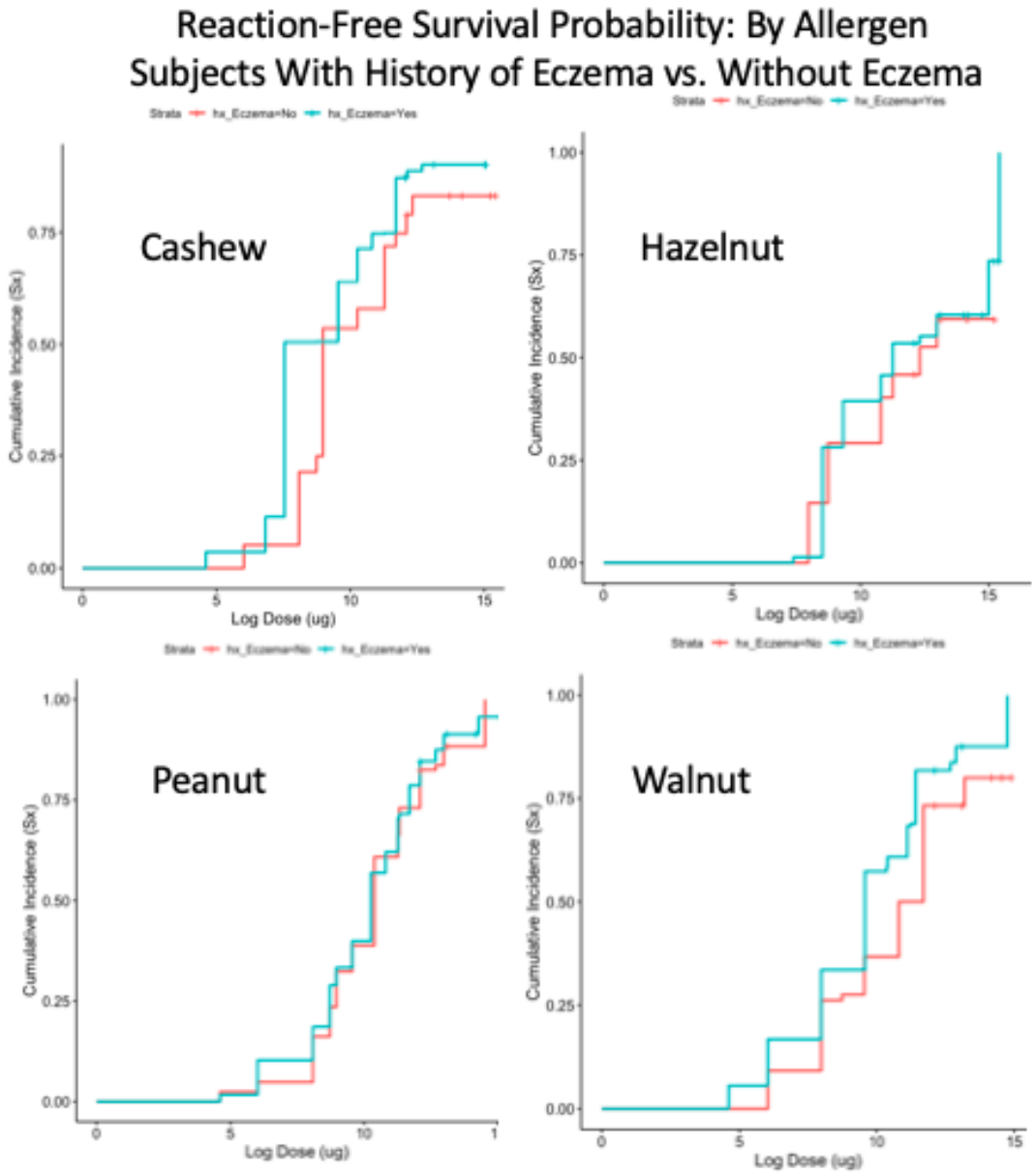

Figure 3. Reaction-Free (NOAEL) Probability in participants with (blue) and without (red) eczema among the four allergens (cashew, hazelnut, peanut and walnut). Vertical tics on each plot indicate a censoring event

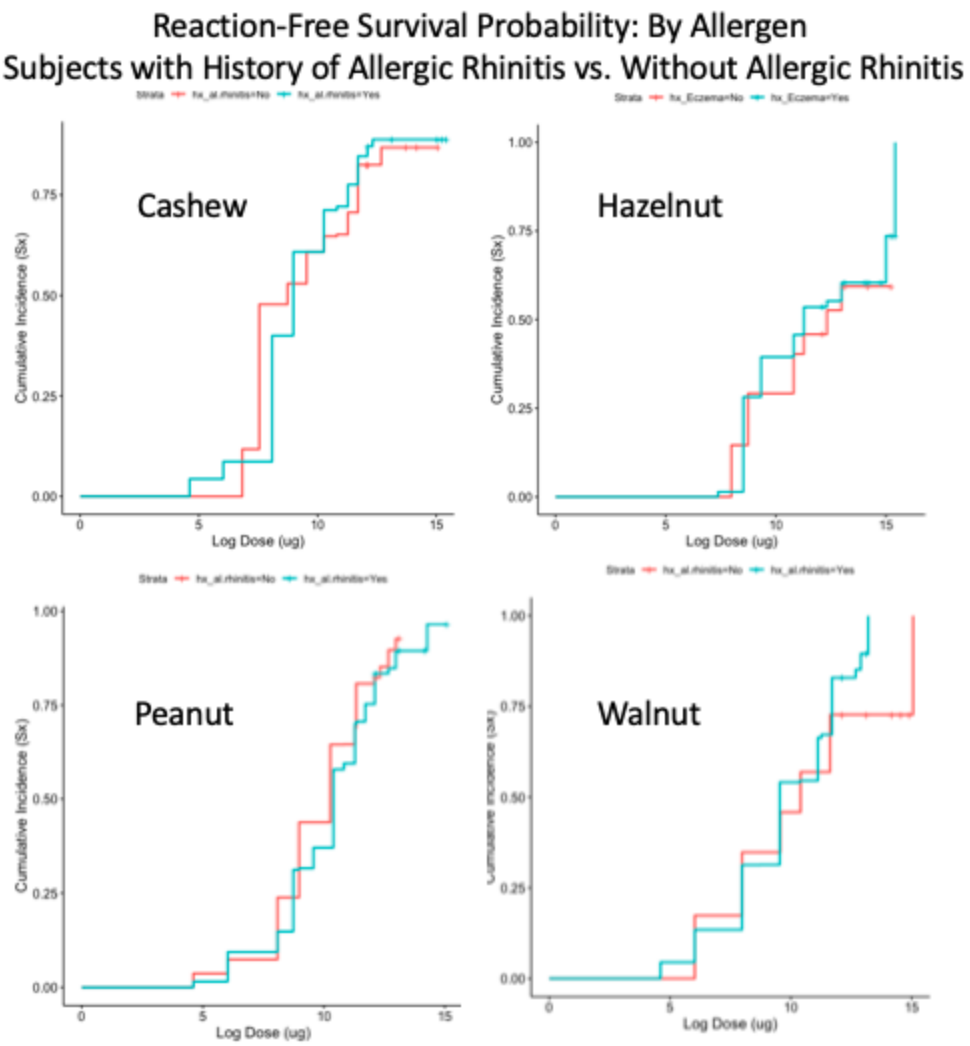

Figure 4. Reaction-Free Survival Probability in participants with (blue) and without (red) allergic rhinitis among the four allergens (cashew, hazelnut, peanut and walnut). Vertical tics on each plot indicate a censoring event.

The next step was to determine whether subjects with a history of eczema or rhinitis were statistically more sensitive (in terms of dose) to oral food allergens than subjects without these allergic histories. This was tested by analyzing dose-response event data with parametric survival models. Although semi-parametric models are commonly used for survival analysis, these models can be difficult to implement with censored data, and parametric models have been shown to provide better predictions in the tails of the data when the correct distribution

is selected for the model (Allen et al., 2014). The first step in preparing parametric models is identifying a suitable distribution as a basis of the model. Figure 5 shows the fit of different choices of parametric baseline models to the semiparametric plots. From these plots, log-logistic, gamma and log-normal models fit the data similarly well across all allergens and for both allergic groups. Figure 5 displays the parametric model fits for each allergen overlaid by the semiparametric plot for both eczema (Left panels) and allergic rhinitis (right panel). For all four allergens (cashew, peanut, walnut and hazelnut), the loglogistic, gamma logistic, and log-normal models all fit close together and follow the Kaplan-Meier overlay when evaluating the eczema and rhinitis; the other less well-fitting models are discarded. Based on this plot and supported by log-likelihood values, the log logistic distribution was selected for modeling.

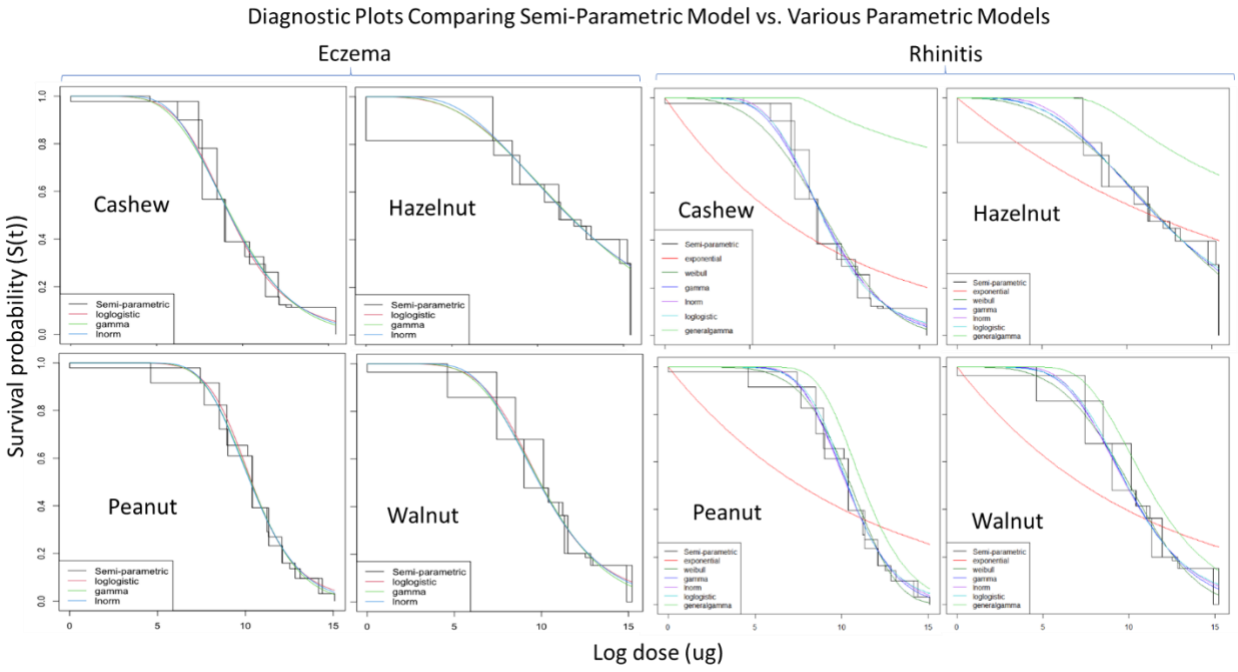

Figure 5. Diagnostic plots for various parametric models

Using the Log-logistic distribution, we next plotted the overall reaction probabilities for each of the evaluated food allergens regardless of allergic history (Figure 6). The median log reaction doses (probability = 50%) are 9.6, 11.9, 10.1 and 10.2 ug for Cashew, Hazelnut, Peanut and Walnut, respectively. These doses convert to doses of 14.3, 153.9, 24.7, and 26.5 mg of protein. The allergen with the highest potency was cashew as it had the lowest median reaction dose at 50%. The allergen with the lowest potency was hazelnut as it had the highest median reaction dose while both peanut and walnut had similar potencies around 24-26 mg of allergen.

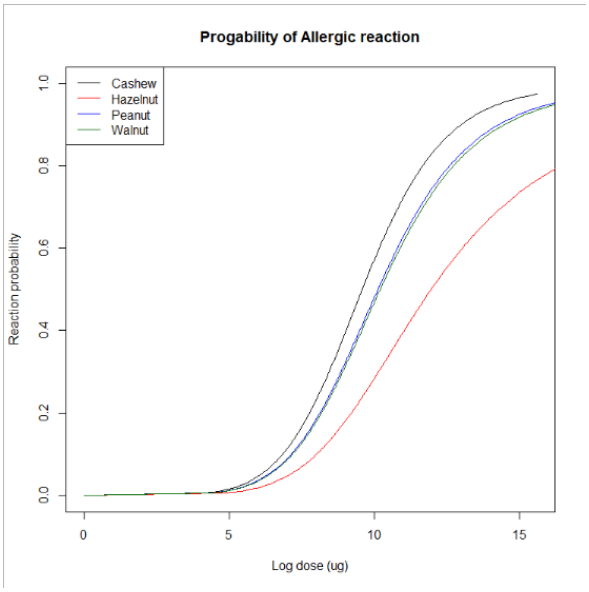

Figure 6: Dose response for each allergen.

As previously mentioned, this study used the log-transformed NOAEL data (µg protein) to complete all statistical analyses and modeling. The oral food allergens were analyzed using the parametric-Hazards Model for both diseases (allergic rhinitis and eczema). The parametric models for subjects with (black) and without (red) histories to asthma are shown in for subjects with a history of eczema (Figure 7) and allergic rhinitis (Figure 8). It is interesting that there seems to be a greater difference in the sensitivity of subjects with/without eczema for cashew

and walnut, and almost no difference for peanut. Hazelnut group was the smallest group and hence has the largest confidence interval and no clear difference in response between the two groups. Among the subjects with/without allergic rhinitis, only walnut appeared so show an apparent separation between the two groups.

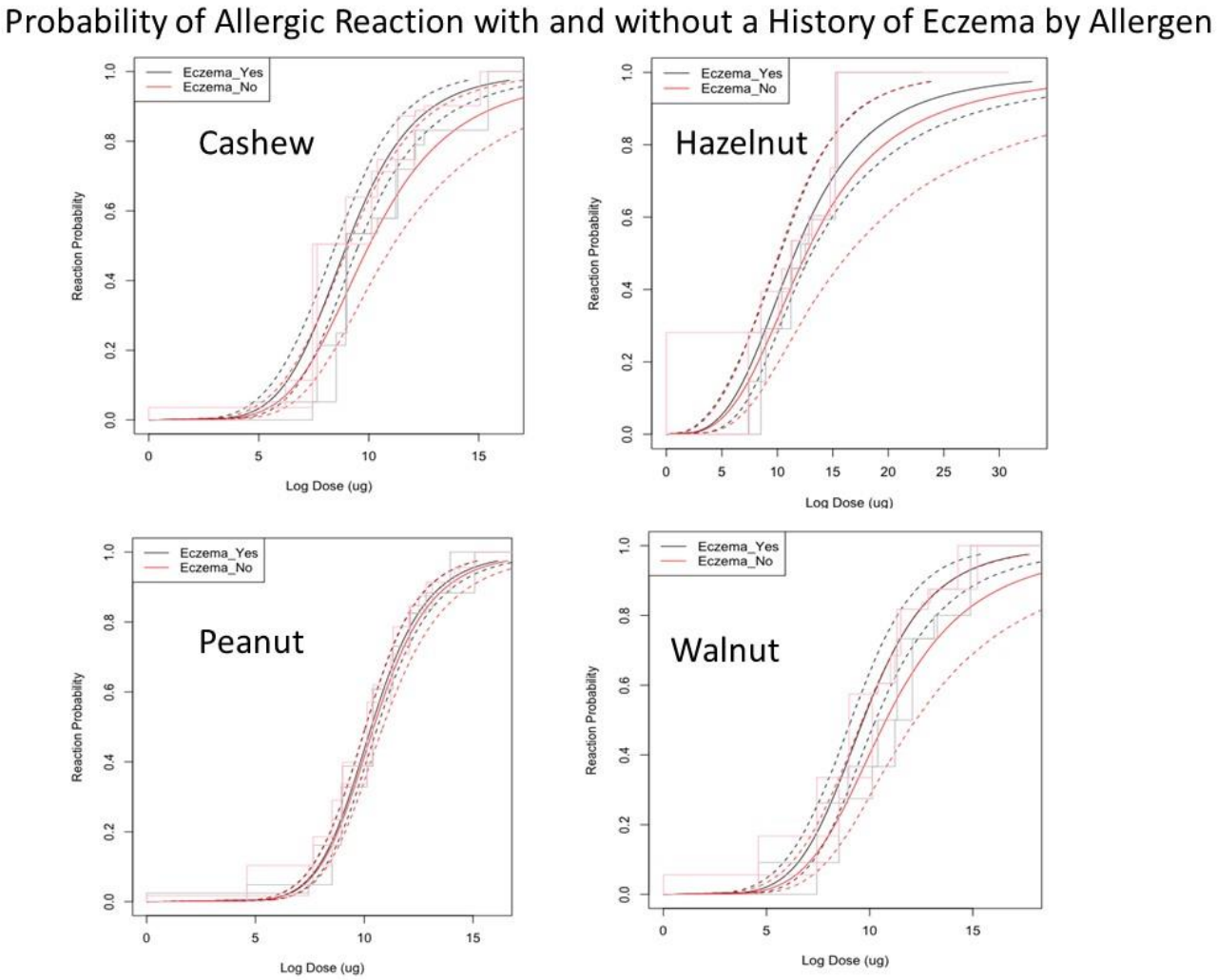

Figure 7. Parametric Model with a Kaplan Meier Overlay for Eczema for the four different allergens (cashew, hazelnut, peanut, and walnut). The black line represents semi-parametric line, the red line represents the logistic model, the green line represents the gamma logistic model and the blue line represents the log normal model.

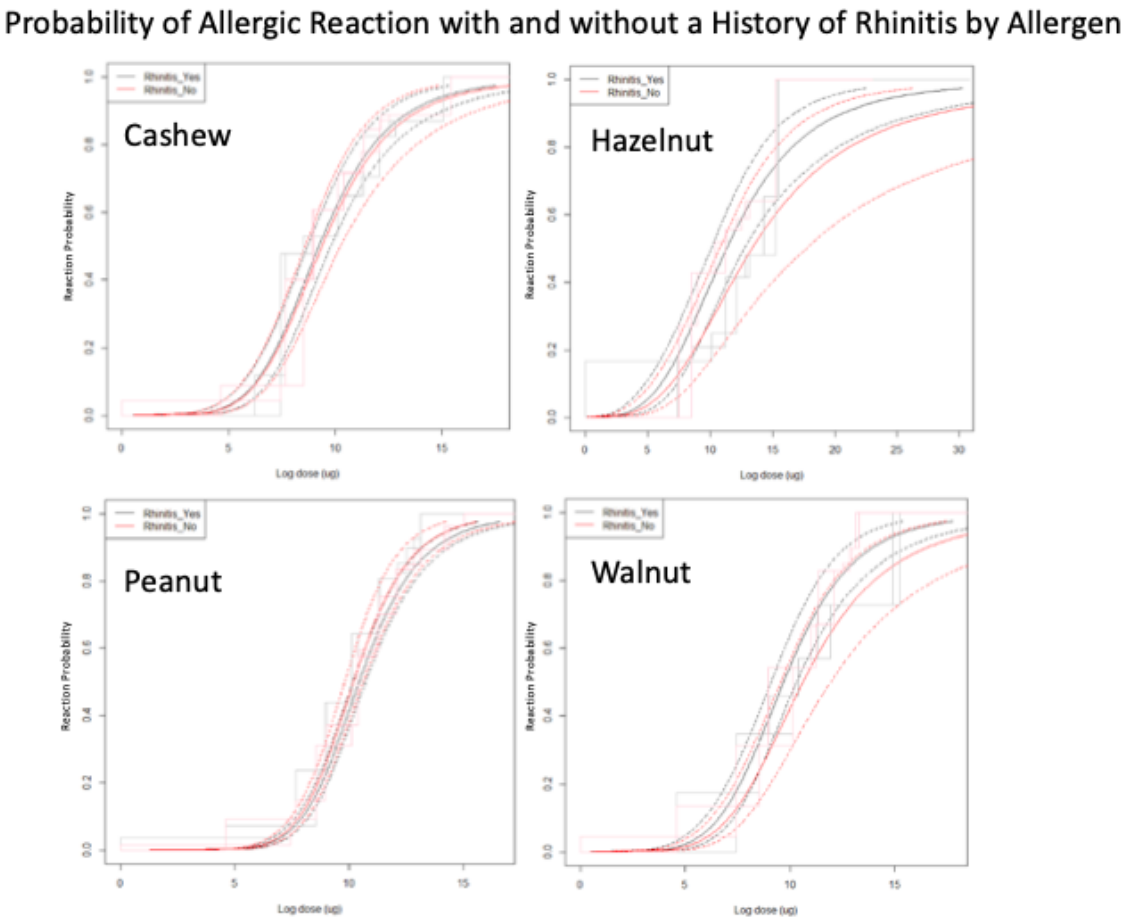

Figure 8. Parametric model with a Kaplan-Meier overlay by allergen (cashew, hazelnut, peanut, and walnut) for allergic rhinitis. The black line represents semi-parametric line, the red line represents the logistic model, the green line represents the gamma model and the blue line represents the log normal model.

The statistical results from the parametric analysis are given in Table 5 (eczema) and Table 6 (allergic rhinitis). When evaluating Table 5, note that the p-value for one allergen (cashew) is statically significant, and Walnut is nearly significant at the 5% threshold for statistical significance for eczema history. All other allergens in Tables 5 and 6 for both diseases (allergic rhinitis and eczema) have p-value much greater than 0.05, making the p-values not statically significant.

Table 5. Parametric model p-values for the four allergens for participants with eczema

Eczema	
Allergen	**p-value**
Cashew	0.042*
Walnut	0.076
Peanut	0.646
Hazelnut	0.512
* = Statistically Significant ($p \leq 0.05$)	

Table 6. Parametric model p-values for the four allergens for participants with allergic Rhinitis

Allergic Rhinitis	
Allergen	P-value
Cashew	0.779
Walnut	0.129
Peanut	0.287
Hazelnut	0.197

Discussion

According to the Centers for Disease Control and Prevention, eight percent of children have been diagnosed with at least one oral food allergy (CDC, 2020). Currently, oral food allergies do not have a cure, and avoiding the allergen is the main way to prevent an adverse immune reaction (CDC, 2020). Since oral food allergies are becoming more prevalent among children and have been continuing to rise over the past three decades, it has become increasingly important to understand potential predictors for allergies (Foong et al., 2017; Zhu et al., 2015). The increase in allergies and the lack of treatment options give rise to the need for studies of this nature to provide potential answers to dose-response relationships and predictors for oral food allergies. This study evaluated four common food allergens (cashew, hazelnut, peanut, and walnut) for severity levels and used various statistical analyses to determine if a relationship was present between the allergen and allergic rhinitis or eczema.

Our hypothesis was that study subjects with a history of eczema or allergic rhinitis would have increased sensitivity to oral food allergens than participants without a history of eczema or allergic rhinitis. It was thought that those with either disease, when exposed to an oral food allergen, may trigger a similar immune response which would contribute to eczema or allergic rhinitis. This hypothesis was first tested by examining box plots comparing the median NOAEL dose in those with or without a history of one of the diseases. When the medians were visually compared for each of the four allergens and two diseases, the medians of those with a history of the evaluated disease were higher or relatively equal to those without history. Some exceptions did occur where those without the disease had visually higher medians than those with the disease.

To further investigate the relationships between the allergens and allergic rhinitis or eczema, Kaplan-Meier survival models were used to visualize the cumulative occurrence of the allergic event. These plots showed a potential increase in the likeliness of a reaction with both diseases at low dose levels. Parametric models were used to determine the p-values among the four allergens and the participants with a history of one disease. Only one outcome (cashew and a history of eczema) was found to have a slightly statistically significant p-value; Walnut just missed being significant. Finally, nonparametric regression analyses were completed, which showed the regression data generally fit the Kaplan-Meier curve overlays but did not appear to support the hypothesis fully.

Of the allergens tested here, cashews, walnuts and hazelnuts are all tree nuts. Peanuts are in fact not a nut at all but are legumes. Although peanuts do share some protein similarities with tree nuts, evolutionary distance makes peanuts distinct form the other foods we

evaluated. The cooccurrence of allergies in individual subjects, particularly some tree nut allergies, has been systematically described (Purington et al. 2018)

Eczema is a type IV cell-mediated immunity. In a study by Kivistö et al. 2019 of 80 twin pairs, a history of eczema (atopic dermatitis) was demonstrate as a significant factor for oral food allergies (Kivistö et al.,2019). No such relationship has been described for allergic dermatitis.

Limitations did occur within this study. The first limitation was due to the use of the NOAEL for all statistical analyses. Since the NOAEL was used, the actual dose which caused a reaction is unknown. The dose would be somewhere between the NOAEL and lowest-observed-adverse effect level (LOAEL). However, this issue would have also arisen if the LOAEL data had been used in place of the NOAEL since we still would not know the "true" dose that caused the reaction. Another limitation of this study would be the grading of severity levels as the grading depended on the clinical observations determined by a medical professional. Another limitation is that more patients had mild to moderate reactions than severe reactions, which could be due to terminating at the first reaction in the challenge. If the dose was greater, the severity of the reaction might also increase, especially in those who reacted at the lowest dose. It is important to understand that participants with a history of asthma having a FEV1 of less than 80 percent, severe or moderate asthma or other significant nonallergic medical conditions were excluded from this study. These participants were excluded due to a high risk of death; however, these participants could have a higher level of severity to the allergens but are not included within the study. The final limitation is the potential for misclassification bias within the study. Since the participant's guardians provided the history for allergies, allergic rhinitis, and eczema, the

results are likely impacted by self-reporting bias. If participant history were misclassified, it would skew the results in various ways depending on if the diseases and allergies were truly present or absent in the participant.

Conclusion

Oral food allergies are increasing globally and have continuously trended up in the last three decades (Foong et al., 2017; Zhu et al., 2015). Due to the concerning increase in oral food allergies, research is needed to determine if there are any predictors for these allergies and understand the dose-response relationships for the allergies. Our study tests the hypothesis that participants with allergic rhinitis or eczema have increased sensitivity to oral food allergens than those without a history of the disease. Upon investigation, statistical analyses only partially supported this hypothesis.

The null hypothesis of this study is that subjects with and without a history of allergic diseases (allergic rhinitis or eczema) have similarly distributed NOAEL doses. In contrast, the alternative hypothesis for this study would suggest that participants with a history of allergic diseases (allergic rhinitis or eczema) are likely to have a lower NOAEL doses compared to this without a history, and if the reactions are related may be predisposed to food allergen hypersensitivity. The dose response distribution appears to be similar across the different allergens with an exception of cashew and walnuts.

However, an important consideration exists in regard to the interpretations of boxplots. While boxplots may be used to find the IQR of the allergen data they are not useful to for visualizing the occurrence of reaction events over the range of doses. Therefore, Kaplan-Meier

plots were utilized as a visual tool to evaluate reaction rates as a result of the cumulative dose of the allergens. This study had a few limitations, with the most impactful being misclassification bias due to data self-reporting. Additional studies should be completed to determine if the additional variables combined with allergic rhinitis and eczema could impact oral food allergies' sensitivity.

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