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Gender, prick test size and rAra h 2 sIgE level may predict the eliciting dose in patients with peanut allergy: evidence from the Mirabel survey

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Running title: Predictive factors to determine eliciting dose in patients with peanut allergy

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Contributors

Amélie Crépet: leader in the development and design of the MIRABEL project, involvement in the formulation of hypotheses, and in the acquisition, statistical analysis and interpretation of the data and in writing the manuscript.

Chabi Fabrice Elégbédé: involvement in statistical analysis and interpretation of the data, and writing the manuscript.

Alexandra Papadopoulos: involvement in developing the MIRABEL project, and substantial involvement in revising the manuscript prior to submission.

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Denise-Anne Moneret-Vautrin: involvement in developing the MIRABEL project, in the formulation of hypotheses, in the acquisition, analysis and interpretation of the data, and substantial involvement in revising the manuscript prior to submission.

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All the authors have approved the final version of the article.

Abstract

Background: Peanut allergy management is based on active avoidance and access to emergency treatment including self-injectable adrenaline. Knowing the dose at which a patient is likely to react is crucial for risk assessment and could significantly improve management by integrating a personalized approach.

Objective: To develop a threshold dose distribution curve model from routinely collected data.

Methods: The MIRABEL survey is an observational study of 785 patients with peanut allergy/sensitization conducted in France, Belgium and Luxemburg. The current analysis included the 238 participants for whom medical and oral food challenge data were available. Several statistical models (Kaplan-Meier, Cox model, Weibull and Lognormal with predictive factors, basic Weibull and Lognormal) were compared to select the best model and predictive factor combination associated with the threshold doses. Inferences were made with a Bayesian approach.

Results: Patients were mainly children (mean age: 9 years [IQR: 6-11]; 87% < 16 years) and males (62%). Median Ara h2 s IgE was of 8kUA/L [IQR: 1-55] and median skin prick test size of 10 mm [IQR: 7-13]. OFC was positive in 204 patients (86%). The median threshold dose was of 67 mg of peanut protein [IQR: 16-244]. The dose at which 1% of the patients are likely to react with objective symptoms was 0.26 [0.03; 2.24] mg of peanut protein. Gender, size of the skin prick test (SPT) and Ara h 2 specific IgE level had a significant impact on the threshold dose distribution curve. The Cox model was the most effective to predict threshold doses with this combination of factors. Girls react to lower doses than boys with a beta coefficient associated to the risk and a 95% credible interval of 0.44 [0.04; 0.77]. The higher the size of the SPT and the Ara h 2 specific IgE level are, the higher the risk of reacting to a small amount

of peanut, with beta coefficients associated to the risk and 95% credible intervals of 0.05 [0.02; 0.08] and 0.01 [0.01; 0.02] respectively.

Conclusion and clinical relevance: according to the model, routinely collected data could be used to estimate the threshold dose. The consequences could be the identification of high-risk patients who are susceptible to react to small amounts of peanut and a personalized management of peanut allergy integrating the risk of allergic reaction. Limitations of this study are that assessors of OFC outcome were aware of SPT and Arah2 results, and a further validation study is required to confirm the predictive value of these parameters.

Keywords

Threshold dose modeling, Eliciting dose, Peanut allergy, Predictive factors, Cox model, Risk assessment.

Abbreviations and definitions

BIC: Bayesian Information Criterion

ED_p: Eliciting Dose producing a reaction in a proportion p of the allergic population

IQR: Interquartile range

LOAEL: Lowest Observed Adverse Effect Level

NOAEL: No Observed Adverse Effect Level

OFC: Oral Food Challenge

RMSE: Root Mean Square Error

SPT: Skin Prick Test

Capsule summary

A dose distribution model including significant predictive factors improves threshold dose assessment in peanut allergic patients. Routinely collected data (gender, level of Ara h 2 sIgE and size of skin prick test) can be used by clinicians to estimate the allergic risk and consequently to personalize management.

Key messages (highlights box)

- The threshold of the allergic population is often described using only one threshold distribution curve whatever distinctive features which may be observed between the patients in the study population.
- Significant predictive factors impacting OFC threshold dose were identified and the Cox model (integrating these factors) produces the best fit of the OFC threshold distribution curve.
- Physicians could use routinely collected data to identify patients with a higher risk of reaction at low doses (high-risk patients). This approach could result in a more personalized management integrating the risk of allergic reaction.

Introduction

Patients with food allergy react to a wide range of amounts of food. The dose of food below which no reaction is observed is known as the "threshold" dose [1]. Individual thresholds can be estimated from oral food challenges (OFC), a time consuming and expensive procedure which can also cause severe reactions. Clinical threshold doses lie between the highest dose observed not to produce any adverse effect (NOAEL) and the lowest dose to produce an adverse effect (LOAEL). In practice, the threshold dose is often estimated as being the LOAEL. Thresholds can also be defined at a population level. Thus, thresholds are defined as the minimum eliciting dose (ED) which designates the amount of allergenic food to produce a reaction in a determined proportion p of the allergic population (EDp). Population thresholds are characterized by fitting threshold distribution curves to individual thresholds determined by OFC. Accurately estimating a threshold at individual and population levels is crucial as it plays an important role in food allergy risk assessment and management [2, 3]. Indeed, threshold doses combined with consumed quantities and allergen concentrations in food are used by risk assessors to estimate the risk of the allergic population. [4], [5], [6] Threshold doses can also be used by risk managers to establish safe limits, i.e. a maximum amount of unintended allergen in food to protect the majority of the allergic population [7, 8]. Finally, threshold doses are essential for the allergist to make diet recommendations to their patients.

Many individual factors - such as age, gender, comorbidities, stress, effort- could impact the threshold doses and thus the associated population threshold dose distribution [9-13]. This explains why individual variability should be taken into account when modeling threshold dose distribution curves. There are only a few published studies which focus on how factors related to allergy can be combined to predict individual threshold doses and the threshold distribution curve [14]. Indeed, methods are generally based on considering the best fitting of individual thresholds by several parametric probability distributions without using predictive factors [2,

8]. Thus, the threshold of the allergic population is often described using only one threshold distribution curve whatever distinctive features may be observed between the patients in the study population.

The MIRABEL project was conducted by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) in partnership with the French National Institute for Agricultural Research (INRA) and the Allergy Vigilance Network (www.allergyvigilance.org). The objectives and the methods of the MIRABEL survey have been previously published [15, 16], as well as the characteristics of the population, mainly children (< 16 years: 86%) and primary peanut allergic patients [17, 18]. One of the objectives was to accurately define the population threshold distribution for peanut in order to assess allergic risk and to improve food labeling. This study presents an original approach to estimate threshold doses using predictive factors. The model is based on routinely collected medical data. It could be a tool for allergists to identify high-risk patients who are susceptible to react to small amounts of peanut and to improve peanut allergy management with a personalized approach integrating the risk of allergic reaction.

Materials and methods

Study design and population

The MIRABEL study is an observational multicenter survey based on the voluntary participation of patients from Metropolitan France, Belgium and Luxembourg, recruited from April 2012 to December 2013 during visits to their allergists. The 70 allergists who participated in the recruitment were affiliated to the Allergy Vigilance Network and were representative of the medical practice of all the members of the network (76% office-based and 24% hospital-based). Details have previously been described [15-18]. All the recruited patients were sensitized to

peanut (wheal diameter of skin prick test (SPT) ≥ 3 mm and/or peanut specific IgE ≥ 0.35 kUA/L). Allergic patients were those who reported an allergic reaction to peanut at their first visit to the allergist. Severe or potentially severe reactions were: anaphylactic shock, laryngeal angioedema, acute asthma, and serious systemic reaction (involving two or more organs). Non-severe reactions were: rash/dermatitis, urticarial or subcutaneous angioedema, gastro-intestinal symptoms, others. Patients without any previous clinical reaction in real life at the time of the first visit and before the OFC (if done) were considered to be sensitized rather than allergic. The study population for this analysis was the subgroup of patients for whom a peanut OFC was performed. The study was approved by the French Data Protection Authority (CNIL) (Authorization no. DE-2011-048). All patients or parents signed an informed consent.

Data collection

An anonymized standard medical questionnaire was completed by the allergists. All the collected data are described elsewhere [15-18]. The variables selected for the statistical analysis were those which could impact the threshold dose, in line with previous studies [17, 18] gender, diagnosis by the allergist at the first visit (allergy, sensitization), the age at which the OFC was performed, allergic comorbidities (atopic dermatitis, asthma, allergic rhinitis, other food allergy), and the results of the following allergic tests: wheal diameter of the SPT for peanut expressed in mm and the level of Ara h 2 sIgE expressed in kUA/L (immunoCAP system, Thermofisher, Uppsala, Sweden). Composite variables were used to distinguish patients according to the number of allergic comorbidities.

Threshold dose from oral food challenge

In this observational survey, threshold doses of peanut were obtained by single-blinded, double-blinded placebo-controlled or open OFCs, according to the French guidelines [19, 20]. The threshold dose was defined as the lowest cumulative dose of roasted crushed peanuts causing

an objective reaction, converted into mg of peanut protein (LOAEL). The OFC was considered negative in the absence of an objective reaction for a cumulative dose ≥ 7 g of peanut (1.75 g of peanut protein). The threshold dose of patients diagnosed as allergic but who did not react during an incomplete OFC were considered above the highest cumulative dose in the challenge trial, and treated as right-censored [14] in the analysis. The allergic or sensitized patients who did not react during a complete OFC and sensitized patients who did not react during an OFC which was stopped before the last incremental dose were excluded from the study to focus only on patients with confirmed allergy.

Statistical methods for threshold dose distribution modeling

Parametric Weibull, Lognormal, and Loglogistic distributions were used to model the threshold dose distribution [2]. In order to study the association of the predictive variables with the threshold doses, an approach integrating the predictive factors as covariables in the Weibull and Lognormal models was developed (Online Repository). The Cox regression model generally used in epidemiology to estimate the association between a disease and predictive factors during time [21, 22] was adapted to the allergy topic. The occurrence of the allergic reaction was considered as the disease and the threshold dose was used instead of the time(details are provided in the Online Repository). All the models were adapted to account for right censored data. First, each variable was introduced singly in the different models to test their influence on the threshold dose. Variables with a 95% confidence interval of their estimated coefficient that does not contain 0 were considered as significant. These variables were then introduced together in the models and their interactions were tested. Basic modeling of the threshold dose distribution by Weibull, Lognormal and Loglogistic distributions was also conducted in order to compare our results with literature. The models were compared using two criteria: the Bayesian Information Criterion (BIC, commonly used for model selection and which penalizes

the complexity of the models compared with the AIC), and the Root Mean Square Error (RMSE, commonly used to measure of the difference between values predicted by a model and the values observed). Inferences were performed using the Bayesian approach and were implemented in the OpenBUGS software version [23] via the BRugs package of R version 3.0.1. Simulations of the ED values from parameter estimates were done using second order Monte-Carlo simulations to separate variability and uncertainty [6] (details are provided in the Online Repository Online Repository).

Results

Study population

Overall, 785 patients were included in the MIRABEL survey [15, 17, 18]. Out of these, 280 patients underwent an OFC (open OFC: 55%) and were considered for inclusion in the present analysis. One patient who did not react during a complete OFC, 14 sensitized patients with incomplete OFC, and 27 patients with missing data were not retained. The study population thus comprised 238 patients. The allergy was confirmed by a positive OFC in 86% of cases. From the 238 patients, 29 initially considered as sensitized patients had a positive OFC (12.2%) and 34 allergic patients did not react during incomplete OFC (14.3%). The patients were mainly children (mean age at the date of the OFC: 9 years (6-11) and 87% under 16 years), and males (62%) (Table 1). The median threshold dose was of 67 mg (16-244) of peanut protein. . The minimum and the maximum threshold doses were 0.03 and 2404 mg of peanut protein, respectively.

Predictive factors of threshold doses

In univariate analysis, the level of Ara h 2 sIgE, the size of the SPT and presence of atopic dermatitis were significantly associated with the ED, whatever the model (Table 1): the greater

234 the SPT size and level of Ara h 2 and the absence of atopic dermatitis, the lower the ED. Gender
235 was also significantly associated with the threshold dose for the Cox model. Table 2 presents
236 the combination of significant predictive variables for each model. Using the Weibull and Cox
237 models, the combination of the variables significantly influencing the threshold dose were:
238 gender, SPT size, level of Ara h 2 sIgE and the interaction between gender and the level of Ara
239 h 2 sIgE. The Lognormal and Loglogistic models were composed of the combination of the
240 SPT size and the level of Ara h 2 sIgE. Figure 1 depicts that girls react to lower doses than
241 boys for identical SPT size and level of Ara h 2 sIgE (Cox model). For a given amount of peanut
242 protein, SPT size and level of Ara h 2 sIgE, the risk of reaction for girls is 1.22-fold higher than
243 for boys. Figure 2(a, b) shows that the larger the SPT, the higher the risk of reacting to a small
244 amount of peanut. Figure 2(c, d) also shows the same risk increase according to the level of Ara
245 h 2 sIgE.

246 **Comparison of models**

247 Table 2 shows comparison results of the Bayesian Information Criterion (BIC) and the Root
248 Mean Square Error (RMSE). Both clearly demonstrated that the Cox model was the best model.
249 The BIC identified the Loglogistic models with and without predictive factors as giving the
250 second best results, followed by the Weibull with predictive factors. In contrast, the Weibull
251 model with and without predictive factors scored second best with the RMSE criterion followed
252 by the Loglogistic models with predictive factors.

253 **Predicted eliciting doses (EDp)**

254 The ED_{01} calculated from the Weibull with predictive factors and Cox models were close to the
255 Kaplan Meier estimates: respectively 0.20 [0.02; 0.99] and 0.26 [0.03; 2.24] versus 0.19 [0.03;
256 2.25] mg of peanut protein (Table 3), with a smaller 95% credible interval for the Weibull
257 model. The Lognormal model with predictive factors gave a higher value for the ED_{01} and the

highest credible interval: 1.33 [0.15; 3.93] mg of peanut protein. The Loglogistic model with predictive factors produced intermediate results: 0.89 [0.08; 3.46] mg of peanut protein. The basic Weibull, Lognormal and Loglogistic distributions produced lower values for the ED_{01} and lower credible intervals than the ones with predictive factors: respectively 0.08 [0.03; 0.17], 0.72 [0.42; 1.14] and 0.40 [0.20; 0.74] mg of peanut protein. Similar tendencies were observed for the other EDp values. Figure 3 shows that the threshold distribution curve estimated with the Cox model was the closest to the Kaplan-Meier estimates and that all values from Kaplan-Meier were comprised in the Cox model 95% credible interval. It can also be seen that the Weibull model with predictive factors, which produced the higher probabilities of reaction and the higher credible interval, is more conservative than the Lognormal and Loglogistic models with predictive factors. The Cox model with the highest credible interval integrates the highest part of variability. Table 3 also shows that whatever the model used, females had lower EDs than males.

Prediction of threshold dose for a given patient in clinical practice

Figure 4 shows how the threshold dose range related to a given allergic risk can be predicted for a patient from the SPT size and level of Ara h 2 sIgE using the Cox model. For example, with an SPT size of 10 mm and a level of Ara h 2 sIgE of 42 kU/L, the threshold doses triggering a reaction in 1% of the allergic females range between 0.04 and 0.89 with a median value of 0.17 mg of peanut protein. For similar values of SPT size and Ara h 2 sIgE level, the threshold doses triggering a reaction in 10% and 50% of allergic females range between [2.36, 16.1] with a median of 6.33 and [18.3, 136] with a median of 67.3 mg of peanut protein, respectively.

Discussion

Our analysis shows that the Cox model results in the best predictions of EDp, close to the known EDs reported in the literature. The modeling we describe identifies significant predictive factors of the threshold dose in a large population, mainly children (86%: < 16 years of age), with primary peanut allergy. It is based on routinely collected medical data. This modeling could be a tool for allergists to approach allergic risk from routinely collected medical data, and consequently to better manage high-risk patients (identification of the risk to react at low doses, advices on the consumption of products with PAL, indication and procedure of OFC).

Factors influencing the threshold dose

Univariate analysis identified four variables which significantly influence the threshold dose. In fact, the female gender, a diagnosis of peanut allergy without the presence of atopic dermatitis, a high level of Ara h 2 sIgE and a large SPT size all lead to a lower threshold dose of reaction. Similarly, van der Zee et al. [14] also reported that the level of peanut sIgE and the absence of atopic dermatitis were closely associated to lower threshold doses from a study of 126 OFCs in peanut allergic children modeled by a Cox model. In contrast to our results, they also observed an age effect, with lower threshold doses for teenagers, but not a gender effect. The reason why atopic dermatitis may affect the threshold dose is not clearly understood. One hypothesis, by van der Zee, Dubois [14], is that the presence of atopic dermatitis may mask early, mild cutaneous symptoms in the setting of an OFC. Blumchen, Beder [9] used a lognormal distribution to model individual peanut thresholds from a population of 63 peanut allergic children explored with a modified OFC protocol (dose increment every 2 hours). They observed that the threshold dose was significantly and inversely correlated with peanut and Ara h 2 sIgE levels, SPT size, basophil activation, and TH2 cytokine production by peripheral blood mononuclear cells. However, symptom severity did not correlate with the threshold or any of

these markers. Finally, Santos, Du Toit [24] assessed the basophil activation test (BAT) as a means of predicting the severity and threshold of reactivity to peanut during OFCs in 124 children, including 52 with a positive OFC. They concluded that BAT can be used not only to estimate the threshold of allergic reactions during OFCs, but also the severity of the reaction. However, this result was not confirmed by Reier-Nilsen, Michelsen [25], who evaluated the accuracy of clinical and/or immunological characteristics to predict OFC reactivity threshold and the severity of the reaction in a population of 96 children (5 to 15 years old) with a history of severe allergic reactions to peanut and/or sensitization to peanut. They observed that BAT had the best accuracy to predict reactivity threshold as well as LOAEL, but not the severity of the reaction. ED was also associated to the gender, with a lowest dose in females. We have previously shown that severe peanut-allergic phenotypes were more frequent in girls [18]. McWilliam, Koplin [26] found that female adolescents of the Australian "SchoolNuts" cohort were more likely to report experiencing any adverse food reaction in the past 12 months but found no significant sex difference associated with anaphylaxis and did not show data on ED [26]. The impact of gender on ED and FA severity are lacking and our finding has to be confirmed in prospective studies.

In our study, the best model was the Cox model composed of gender, SPT size, the level of Ara h 2 sIgE and the interaction between gender and the Ara h 2 sIgE level. This interaction implies that the association between the Ara h 2 sIgE and the threshold dose is different between girls and boys. The presence of atopic dermatitis disappeared with adjustment for other variables. The fact that the combination of SPT size and Ara h 2 sIgE level is the best predictor of the threshold dose is a new concept. Several studies have been conducted to define predictive factors to diagnose peanut allergy [27-31]. Our analysis contributes to improving the prediction

of the threshold dose using a combination of routinely available data of allergic diagnosis such as Ara h 2 sIgE and SPT. These results have to be confirmed with further data and analyses.

The ED_{01} value

The criteria used to test the goodness-of-fit concluded that the Cox model followed by the Weibull model with predictive factors is the most appropriate one to model threshold data. Taylor, Baumert [8] consented to a reference dose of 0.2 mg of peanut protein which is a consensus of ED_{01} values estimated from 16 published studies using basic Loglogistic and Lognormal distributions. This value is close to the one obtained with the Cox model and the Weibull model and comprised in their credible intervals, which reinforce our results. The basic Weibull proposed lower ED values and the basic Lognormal and Loglogistic higher ED values. The fact that Weibull distribution produced lower values than other models has already been observed in previous studies [2, 32]. Blumchen, Beder [9] found a ED_{05} value of 1.95 mg of peanut protein which is lower than the ones obtained with our models (around 3 mg of peanut protein except for the Weibull one at 1.4 mg peanut protein). Blom, Vlieg-Boerstra [33] reported a ED_{05} value of 1.6 mg in a population of 135 peanut allergic children. These differences can largely be explained by the characteristics of the populations, and the differences in the OFC protocol including subjective versus objective stopping criteria, as discussed by Taylor, Houben [34].

Variability and uncertainty

Our study was multicenter and patients were recruited by both office- and hospital-based allergists. This made it possible to integrate inter-individual variability. Bayesian modeling coupled with second order Monte-Carlo simulations makes it possible to account for both inter-individual variability and model uncertainty [6]. With the basic model, the credible interval of the threshold distribution curves reflects only uncertainty, whereas with the models integrating

predictive factors, they also reflect inter-individual variability. Indeed, for fixed values of model parameters randomly selected in their distribution, a cumulative distribution function can be calculated reflecting the differences between individual threshold doses in the MIRABEL population. If this process is repeated for different values of the model parameters, a credible interval reflecting model parameter uncertainty can be estimated. When the predictive factors are taken into account, a cumulative distribution function is obtained not only for a fixed value of model parameters but also for fixed values of the factors. Therefore, the credible interval accounts both for model parameter uncertainty and inter-individual variability.

However, our study has some limitations. As repeated measures of threshold dose for each patient were not available, we could not account for intra-individual variability. Moreover, patients selected to be tested by OFC might have specific characteristics and thus did not reflect general peanut allergic patients. Regarding MIRABEL patients, we did not observe any discrepancies between patients with and without OFCs, except for asthma comorbidity and age at diagnosis [17]. Due to the recruitment process, allergic individuals who did not consult allergists could not have been included in our survey and lead to selection bias. Moreover, allergists who performed the OFC were aware of the peanut sIgE or prick test results and the assessment of the reaction occurring during the OFC was not standardized. Data on individual NOAELs were not available. Therefore, it was not possible to use the method proposed by Taylor, Crevel [32] to account for the fact that the reacting dose ranges between the NOAEL and the LOAEL and not necessarily equals the LOAEL value. This could lead to an underestimation of the frequency of lower threshold doses. Finally, it is important to mention that threshold doses in this work are related to reaction by ingestion and are not appropriate to other exposure routes such as inhalation.

373 **Consequences for medical practices and risk management**

374 Our findings could have implications for risk assessment (threshold dose modeling), for patient
375 management (identification of the most sensitive patients, “low threshold reactors”) and diet
376 advice (products with precautionary labeling), OFC indications and procedure (low-dose
377 challenge protocol, single dose protocol) and for policy makers (food labeling, precautionary
378 allergen labeling) [35].

379 Integrating predictive factors by routinely collected data make it possible to integrate inter-
380 individual variability. This is particularly significant when threshold dose modeling is used to
381 perform risk assessment. To be conservative, it is important to consider the lower bound of the
382 threshold dose confidence interval integrating differences between individuals instead of a
383 median value. In the same way, this type of modeling produces a threshold dose distribution
384 per group of allergic individuals presenting similar predictive factors as opposed to the basic
385 modeling which only takes into account one distribution for a whole population. This is
386 particularly relevant for clinicians giving dietary advice or to choose the OFC procedure or to
387 modulate the dose escalation of the OFC [36, 37]. Thus, while the prediction of a threshold
388 level with the proposed model provides additional information, it should be interpreted in the
389 light of the patient’s clinical history and presence of other risk factors. Furthermore, it does not
390 give information about the severity of the reaction but can be used to identify patients who are
391 at risk of reacting to small amounts of the allergen. It is consequently a step forward to a more
392 personalized approach, integrating allergic reaction risk [38]. Finally, our study is also
393 important for manufacturers and public health agencies as they could use threshold doses for
394 improving labeling practices in the food industry and developing standardized policies, and
395 consequently increasing food safety and peanut allergic consumer confidence.

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Table 1: OFC results, patients characteristics and allergy tests (sIgE[1], skin prick test) : associations with the threshold dose

OFC results, patients characteristics and allergy tests	Values	Association with the threshold dose			
		Weibull	Lognormal	Loglogistic	Cox
		95% CI[(2)]	95% CI[(2)]	95% CI[(2)]	95% CI[(2)]
Oral food challenges - Positive, n (%) - Threshold dose mg of peanut protein Median (IQR)[(1)] [0; 5[, n (%) [5; 50[, n (%) [50; 100[, n (%) [100, 1000[n (%) ≥1000, n (%)	204 (86)84 (16 - 244) 19 (8) 71 (30) 35 (15) 92 (38) 21 (9)				
Age at OFC (year) Median (IQR) Min -, Max	8 (6 - 11) 2 - 27	[-0.04; 0.03]	[-0.09; 0.04]	[-0.08; 0.03]	[-0.04; 0.03]
Gender (males), n (%)	147 (62)	[-0.02; 0.55]	[-0.95; 0.15]	[-0.98; 0.07]	**[0.01; 0.57]**
Confirmed diagnosis of peanut allergy, n (%)	209 (88)	[-0.46; 0.31]	[-1.02; 0.60]	[-0.94; 0.55]	[-0.4; 0.38]
Allergic comorbidities					
- Atopic dermatitis, n (%)	162 (68)	**[-0.62; -0.04]**	**[0.02; 1.18]**	**[0.08; 1.18]**	**[-0.63; -0.05]**
- Asthma, n (%)	155 (65)	[-0.30; 0.26]	[-0.47; 0.64]	[-0.53; 0.54]	[-0.33; 0.25]
- Rhinitis, n (%)	130 (55)	[-0.45; 0.08]	[-0.34; 0.76]	[-0.26; 0.80]	[-0.47; 0.08]
- Other food allergy, n (%)	148 (62)	[-0.46; 0.07]	[-0.41; 0.74]	[-0.25; 0.86]	[-0.5; 0.06]
- Atopic dermatitis + Asthma, n (%)	107 (45)	[-0.47; 0.11]	[-0.23; 0.87]	[-0.26; 0.88]	[-0.47; 0.08]
- Atopic dermatitis + Asthma + Other food allergy, n (%)	77 (32)	[-0.47; 0.11]	[-0.36; 0.87]	[-0.24; 0.87]	[-0.49; 0.10]
Specific IgE to Ara h 2 (kUA/L), Median (IQR) Min - Max	8 (1 - 55) 0.01 - 101	**[0.01; 0.02]**	**[-0.03; -0.01]**	**[-0.03; -0.01]**	**[0.01; 0.02]**
Skin prick tests size (mm) Median (IQR)	10 (7 - 13)	**[0.04; 0.09]**	**[-0.15; -0.05]**	**[-0.14; -0.06]**	**[0.04; 0.10]**

Min - Max	0.01 - 30				

(1) sIgE: specific IgE, IQR = Interquartile range.
(2) 95% CI: the credible interval defined by the 2.5th and the 97.5th percentiles of the parameter distribution associated with each predictive variable. Boldfaced text indicates statistical significance. The variable is significantly associated with threshold dose if the 95% CI does not contain 0. For the Weibull and Cox models, a positive confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk. For the Lognormal and Loglogistic models, a negative confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk.

Table 2: Significant predictive variables, model parameter estimates and criteria to compare models

	Model parameters		Mean	95% CI(1)	BIC(4)	RMSE(5)
Weibull with covariables $d \sim Weibull(a, b_i)$ $F(d; a, b_i) = 1 - exp(-b_i d^a)$	a		0.65	[0.58; 0.72]	2687 [2667; 2713]	528 [515; 564]
	$\log(b_i) =$	$\beta_0\ (Intercept)$	-4.45	[-5.04; -3.87]		
		$\beta_1\ (Gender)$	0.42	[0.04; 0.78]		
		$\beta_2\ (SPT)$	0.05	[0.02; 0.07]		
		$\beta_3\ (Ara\ h\ 2)$	0.01	[0.01; 0.02]		
		$\beta_4\ (Gender * Ara\ h\ 2)$	-0.01	[-0.01; -1 e-04]		
Lognormal with covariables (2) $d \sim Lognormal(\mu_i, \sigma)$ $F(d; \mu, \sigma) = \Phi\left(\frac{ln(d) - \mu_i}{\sigma}\right)$	$\mu_i =$	$\beta_0\ (Intercept)$	5.74	[5.17; 6.3]	2701 [2680; 2726]	731 [554; 1249]
		$\beta_1\ (SPT)$	-0.07	[-0.11; -0.02]		
		$\beta_2\ (Ara\ h\ 2)$	-0.02	[-0.02; -0.01]		
	σ		1.92	[1.74; 2.12]		
Loglogistic with covariables $ln(d) \sim Logistic(\mu_i, \sigma)$ $F(d; \mu, \sigma) = \frac{1}{1 + exp\left(\frac{d - \mu_i}{\sigma}\right)}$	$\mu_i =$	$\beta_0\ (Intercept)$	5.86	[5.33; 6.39]	2592 [2579; 2615]	595 [532; 2047]
		$\beta_1\ (SPT)$	-0.07	[-0.12; -0.03]		
		$\beta_2\ (Ara\ h\ 2)$	-0.02	[-0.02; -0.01]		
	σ		1.07	[0.96; 1.2]		
Cox model (3) $F(d) = 1 - exp\left(\int_0^d h_0(u)\ exp(\beta_1 Z_1 + \ ... + \ \beta_4 Z_4) du\right)$	$h(d) =$	$h_0(d)$			1619 [1604; 1633]	519 [509; 541]
		$\beta_1\ (Gender)$	0.44	[0.04; 0.77]		
		$\beta_2\ (SPT)$	0.05	[0.02; 0.08]		
		$\beta_3\ (Ara\ h\ 2)$	0.01	[0.01; 0.02]		
		$\beta_4\ (Gender * Ara\ h\ 2)$	-0.01	[-0.01; -3 e-04]		
Basic Weibull $d \sim Weibull(a, b)$ — $F(d; a, b) = 1 - exp(-b d^a)$	a		0.57	[0.52; 0.63]	2720 [2699; 2746]	547 [542; 575]
	b		0.04	[0.03; 0.06]		
Basic Lognormal (2) $d \sim Lognormal(\mu, \sigma)$ — $F(d; \mu, \sigma) = \Phi\left(\frac{ln(d) - \mu}{\sigma}\right)$	μ		4.51	[4.23; 4.79]	2721 [2700; 2746]	732 [575; 1195]
	σ		2.08	[1.89; 2.3]		
Basic Loglogistic $ln(d) \sim Logistic(\mu_i, \sigma)$ — $F(d; \mu, \sigma) = \frac{1}{1 + exp\left(\frac{d - \mu}{\sigma}\right)}$	μ		4.56	[4.29; 4.83]	2646 [2621; 2680]	606 [586; 611]
	σ		1.19	[1.06; 1.33]		

d: Threshold dose
(1) 95% CI: the credible interval defined by the 2.5th and the 97.5th percentiles of the parameter distribution associated with each predictive variable. The variable is significantly associated with the threshold dose if the 95% CI does not contain 0. For the Weibull and Cox models, a positive confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk. For the Lognormal and Loglogistic models, a negative confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk.

(2) Φ: the cumulative distribution function of the standard normal distribution.
(3) $h_0(d)$: the baseline hazard, as defined in the repository material.
(4)BIC: Bayesian Information Criteria, the lower the BIC value, the best the model
(5)RMSE: Root Mean Square Error, the lower the RMSE value, the best the model

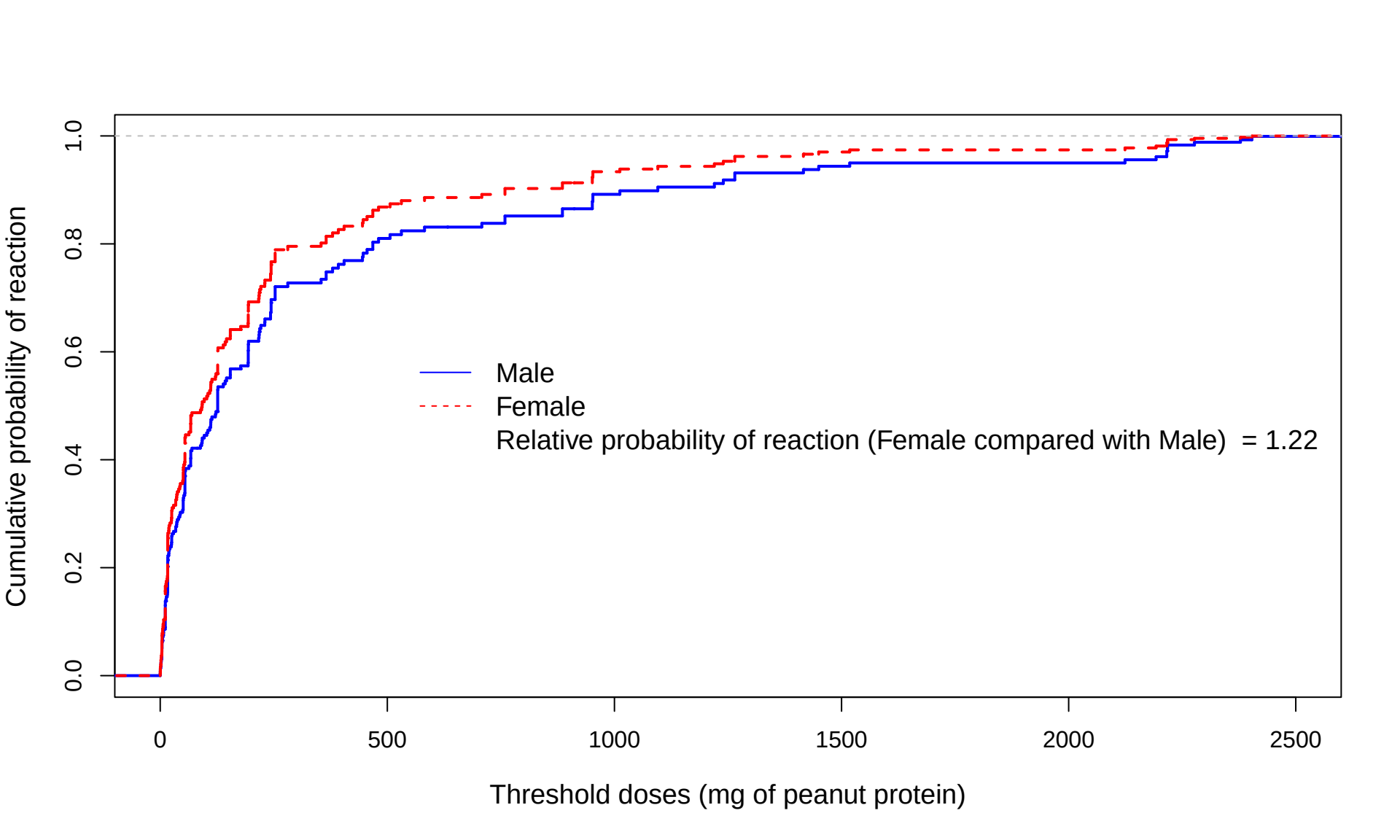
Table 3: Eliciting doses (ED_p in mg of peanut protein) triggering an allergic reaction for p% of the population. The EDp are described by their median and the 2.5th and 97.5th percentiles. These percentiles define a 95% credible interval around the median estimate. The interval integrates all values for predictive variables and for model parameters.

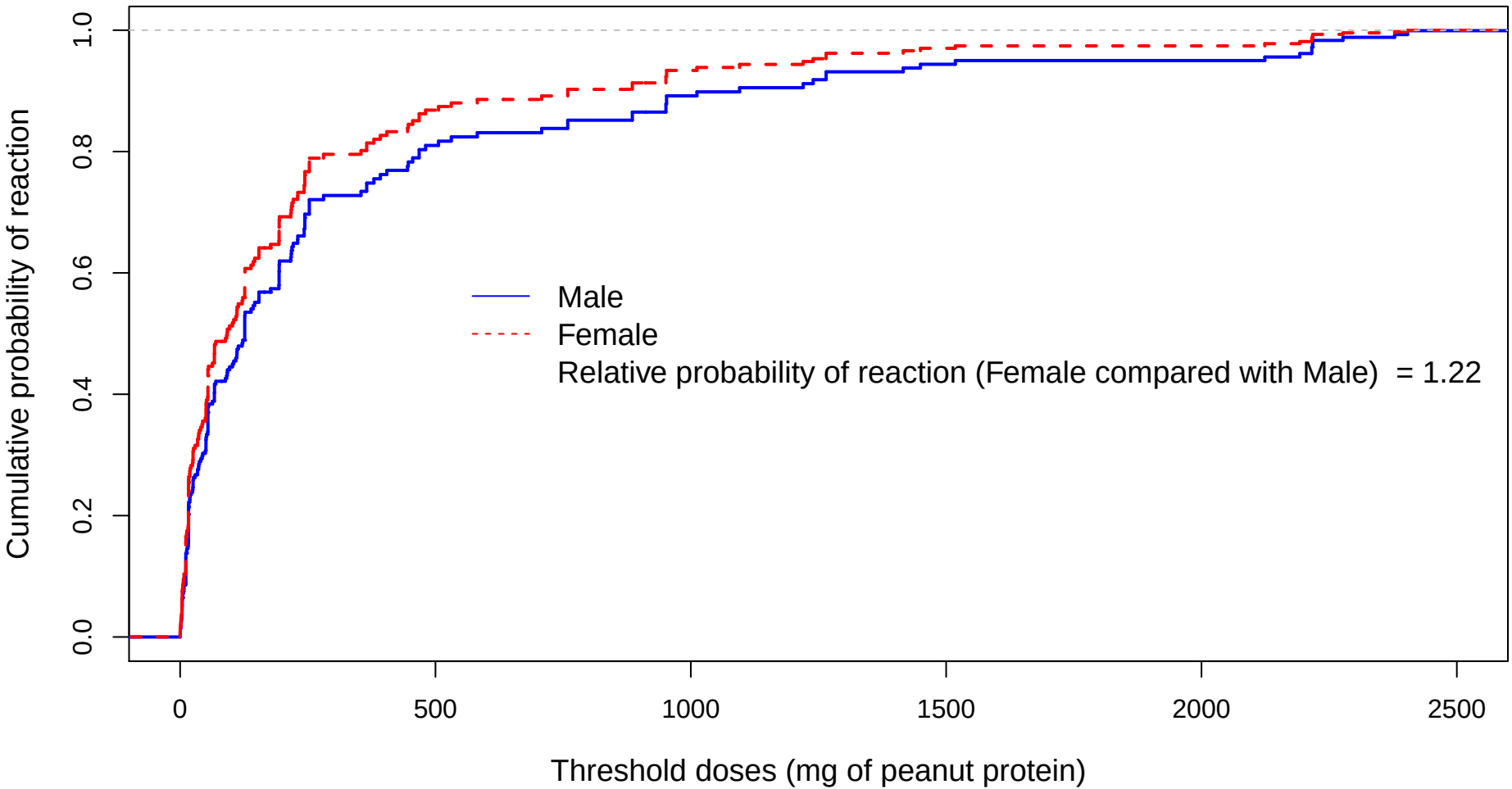
	Models	Estimator	ED_p						
			1	5	10	50	90	95	99
Entire population	**Kaplan Meier**	Median	0.19	3.62	8.13	126	1455	2218	2392
		2.5th percentile	0.03	1.81	4.00	89.8	1055	2143	2321
		97.5th percentile	2.25	5.97	11.1	177	2218	NA	NA
	Weibull with covariables	Median	0.20	2.58	7.94	149	962	1448	2830
		2.5th percentile	0.02	0.32	1.03	20.7	136	204	393
		97.5th percentile	0.99	11.0	32.3	567	3692	5612	11056
	Lognormal with covariables	Median	1.33	5.17	10.7	135	1653	3349	12562
		2.5th percentile	0.15	0.58	1.20	15.3	188	382	1426
		97.5th percentile	3.93	14.2	28.5	343	4454	9352	38011
	Log-logistic with covariables	Median	0.89	5.37	12.1	132	1422	3165	18770
		2.5th percentile	0.08	0.51	1.15	12.7	136	302	1737
		97.5th percentile	3.46	18.9	42.1	441	5014	11731	76115
	Cox model	Median	0.26	3.9	11.1	127	1244	2191	2218
		2.5th percentile	0.03	0.94	2.93	16.4	126	194	251
		97.5th percentile	2.24	11.1	25.0	676	2389	2400	2403
	Basic Weibull	Median	0.08	1.38	4.94	137	1144	1817	3896
		2.5th percentile	0.03	0.74	2.96	105	891	1377	2789
		97.5th percentile	0.17	2.39	7.77	176	1526	2479	5556
	Basic Lognormal	Median	0.72	3.08	6.74	104	1597	3472	14841
		2.5th percentile	0.42	1.99	4.53	78.8	1079	2224	8457
		97.5th percentile	1.14	4.46	9.23	135	2510	5863	28724
	Basic Loglogistic	Median	0.40	2.98	7.47	108	1576	3890	28998
		2.5th percentile	0.20	1.84	4.96	83.1	1069	2461	15442
		97.5th percentile	0.74	4.68	10.88	145	2534	6880	62987

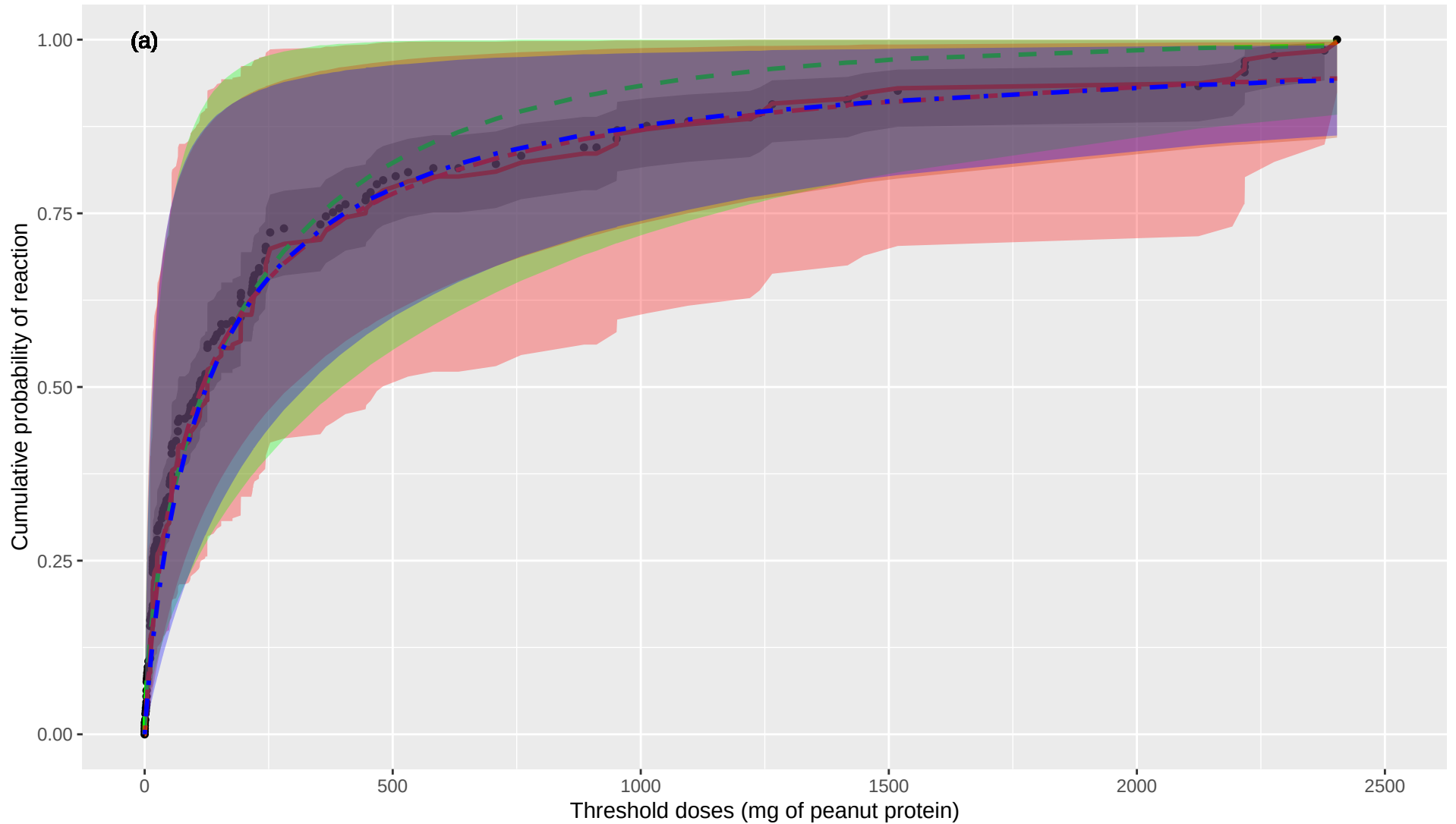
According to gender	**Kaplan Meier (Female)**	Median	0.03	3.22	6.32	64.7	752	1444	2218
		2.5th percentile	0.01	0.24	3.65	49.1	457	739	2011
		97.5th percentile	3.74	10.68	14.9	125	NA	NA	NA
	Kaplan Meier (Male)	Median	0.22	3.54	7.96	153	2198	2276.	2396
		2.5th percentile	0.07	1.61	3.81	113	1238	2204	2372
		97.5th percentile	2.99	7.78	12.3	218	NA	NA	NA
	Weibull with covariables (Female)	Median	0.14	1.75	5.44	104	674	1015	1980
		2.5th percentile	0.03	0.39	1.26	25.6	169	254	494
		97.5th percentile	0.50	5.35	15.4	264	1708	2592	5152
	Weibull with covariables (Male)	Median	0.29	3.90	12.2	237	1534	2300	4464
		2.5th percentile	0.02	0.30	0.94	18.2	117	177	339
		97.5th percentile	1.10	11.9	34.6	608	4011	6083	12072
	Lognormal with covariables (Female)	Median	1.26	4.85	9.95	124	1491	3014	11264
		2.5th percentile	0.15	0.59	1.22	15.4	184	369	1354
		97.5th percentile	3.63	13.2	26.2	315	4064	8600	35195
	Lognormal with covariables (Male)	Median	1.44	5.61	11.6	145	1752	3534	13148
		2.5th percentile	0.15	0.59	1.22	15.6	192	387	1441
		97.5th percentile	4.01	14.4	28.7	342	4463	9396	38538
	Loglogistic with covariables (Female)	Median	0.59	3.60	8.09	88.2	944	2101	12210
		2.5th percentile	0.07	0.44	1.00	11.0	116	252	1408
		97.5th percentile	2.20	11.9	26.1	268	3011	6974	46166
	Loglogistic with covariables (Male)	Median	1.16	7.17	16.3	179	1920	4316	25084
		2.5th percentile	0.12	0.77	1.75	19	202	446	2566
		97.5th percentile	3.78	21.33	46.5	483	5378	12457	80017
	Cox model (Female)	Median	0.19	3.63	8.29	98.5	828	1250	2218
		2.5th percentile	0.03	1.26	3.36	16.4	127	217	446
		97.5th percentile	0.96	6.33	15.8	230	2217	2318	2400
	Cox model (Male)	Median	0.68	6.10	13.5	220	2210	2270	2218
		2.5th percentile	0.03	0.50	2.41	16.4	111	149	194
		97.5th percentile	2.40	12.6	25.5	755	2392	2401	2403
	Basic Weibull (Female)	Median	0.07	1.11	3.82	95.3	735	1149	2383
		2.5th percentile	0.02	0.41	1.65	62.1	508	760	1519
		97.5th percentile	0.24	2.70	7.83	142	1176	1956	4374
	Basic Weibull (Male)	Median	0.10	1.82	6.36	173	1423	2257	4826
		2.5th percentile	0.03	0.77	3.24	123	1059	1632	3260
		97.5th percentile	0.28	3.68	11.5	243	2127	3493	8045
	Basic Lognormal (Female)	Median	0.63	2.49	5.23	71.1	951	1981	7871
		2.5th percentile	0.25	1.22	2.83	47.3	569	1104	3824

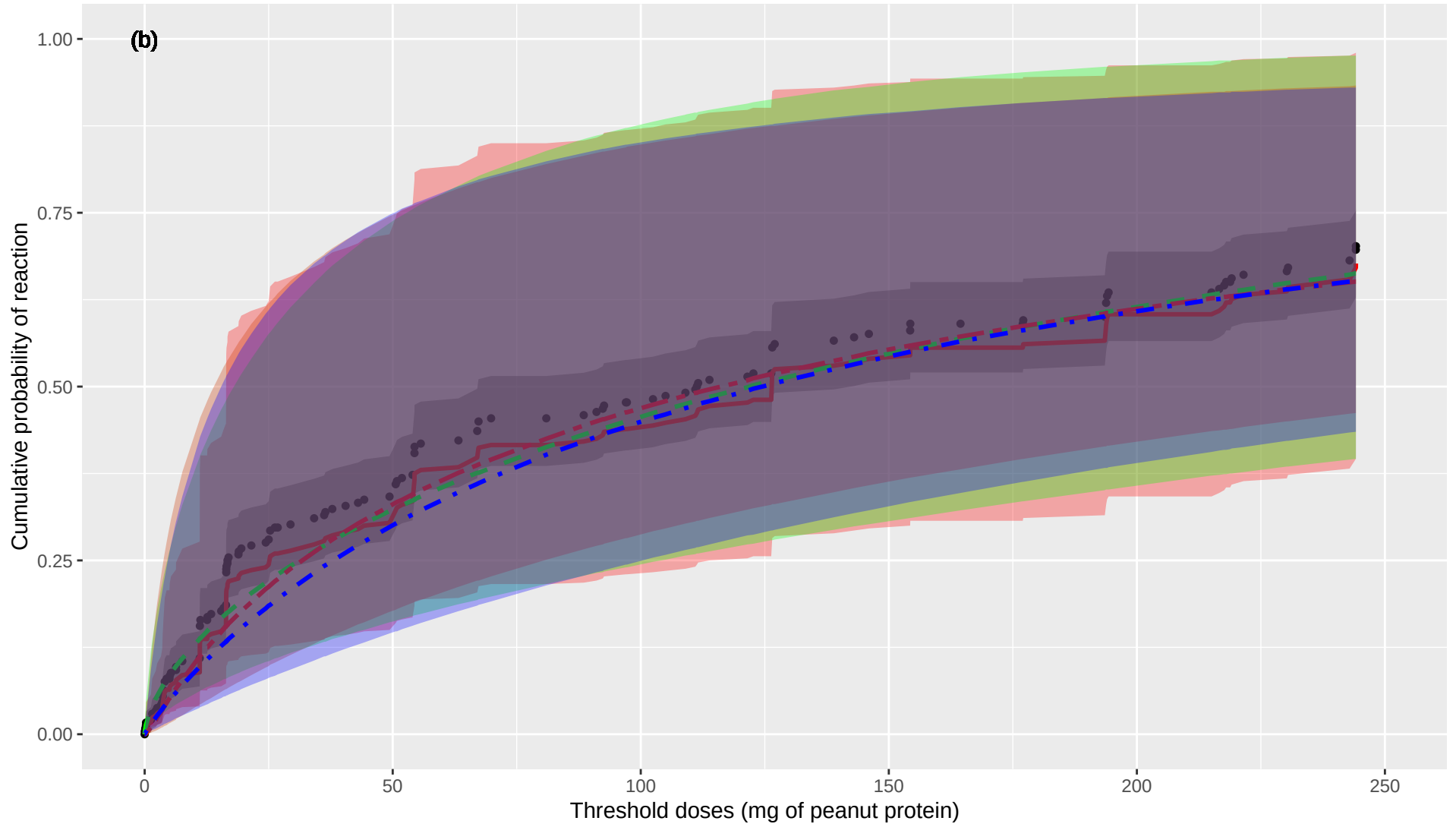
		97.5th percentile	1.34	4.57	8.77	110.4	1834	4209	21174
	Basic Loglogistic (Male)	Median	0.81	3.60	7.93	130	2086	4575	20105
		2.5th percentile	0.41	2.15	5.06	90.6	1281	2665	10198
		97.5th percentile	1.54	5.87	12.1	183	3887	9396	50095
	Basic Loglogistic (Female)	Median	0.43	2.72	6.18	72.7	846	1938	12285
		2.5th percentile	0.14	1.25	3.24	48.0	478	993	4733
		97.5th percentile	1.06	5.20	11.0	111	1626	4253	39265
	Basic Lognormal (Male)	Median	0.40	3.24	8.38	137	2232	5712	46572
		2.5th percentile	0.15	1.58	4.70	93.4	1335	3067	19498
		97.5th percentile	0.91	5.73	13.6	195	4169	12061	126298

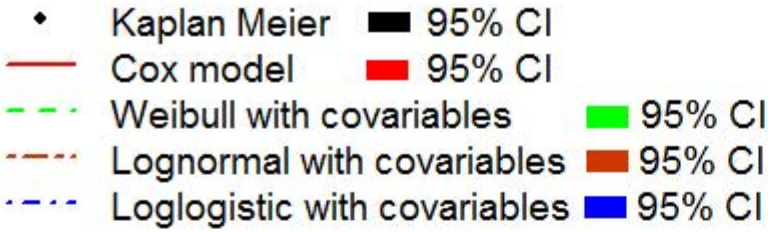
NA = Not Available. Sometimes, the bound of confidence interval for the Kaplan Meier approach cannot be estimated as Greenwood's formula, used to construct the bound of the confidence interval, does not work when the cumulative probability of reaction is close to 1.

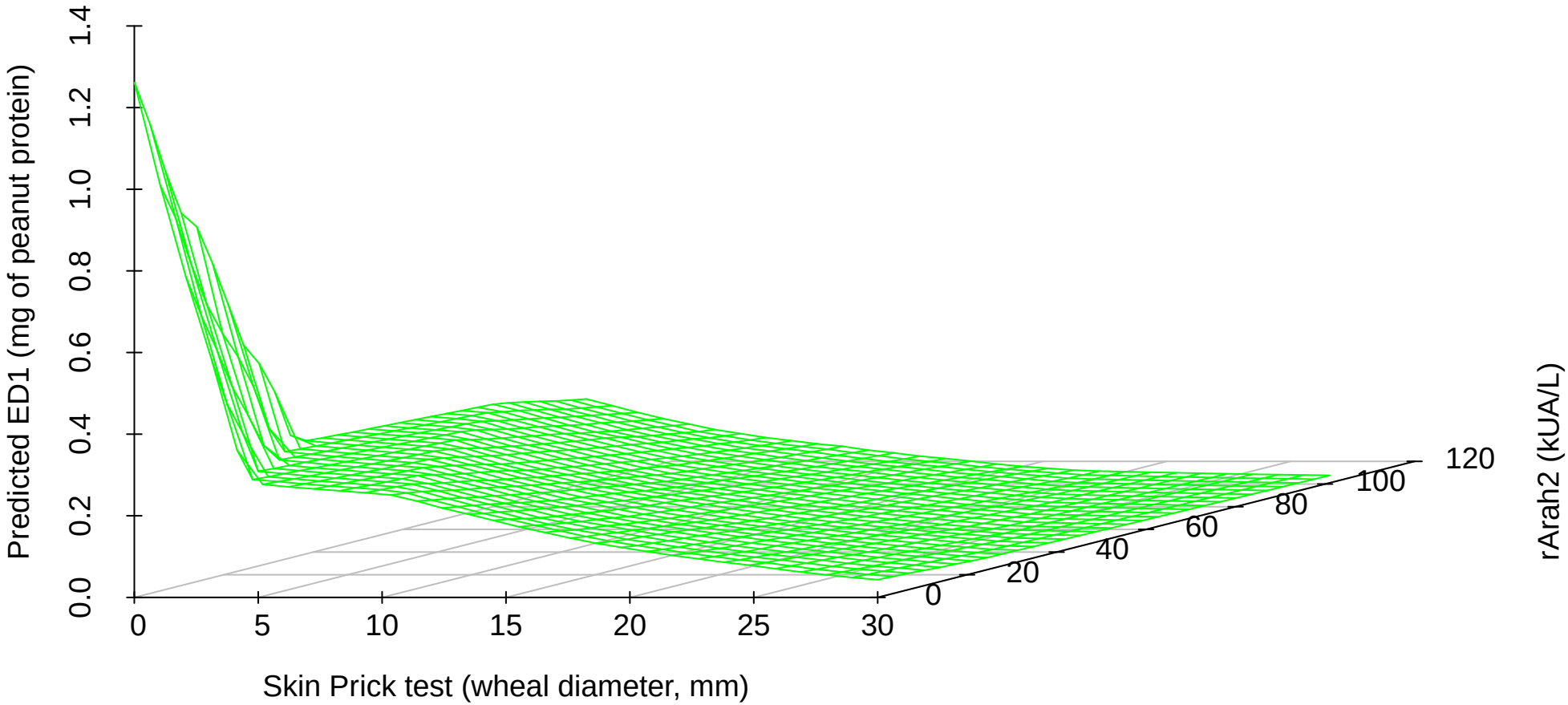

Cumulative probability of reaction
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
2000
2500
Threshold doses (mg of peanut protein)
Male
Female
Relative probability of reaction (Female compared with Male) = 1.22

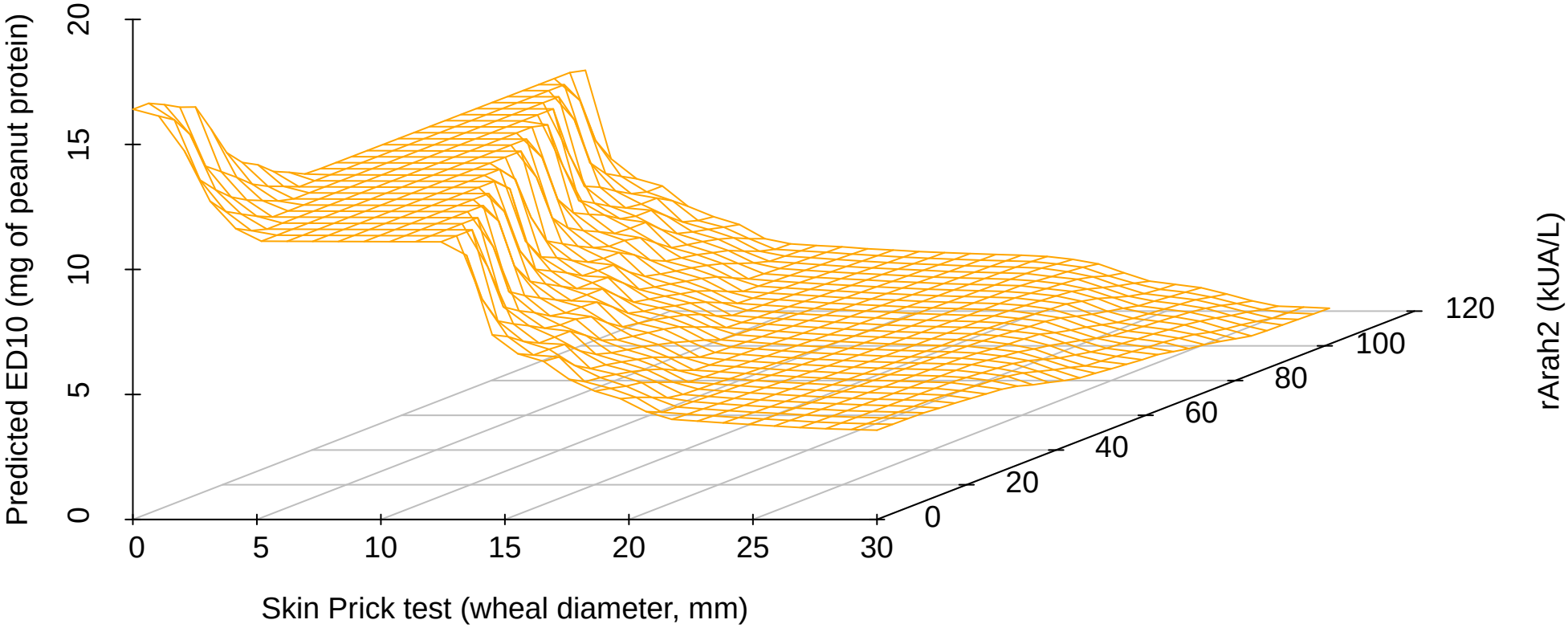

Cumulative probability of reaction
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
2000
2500
Threshold doses (mg of peanut protein)
Male
Female
Relative probability of reaction (Female compared with Male) = 1.22

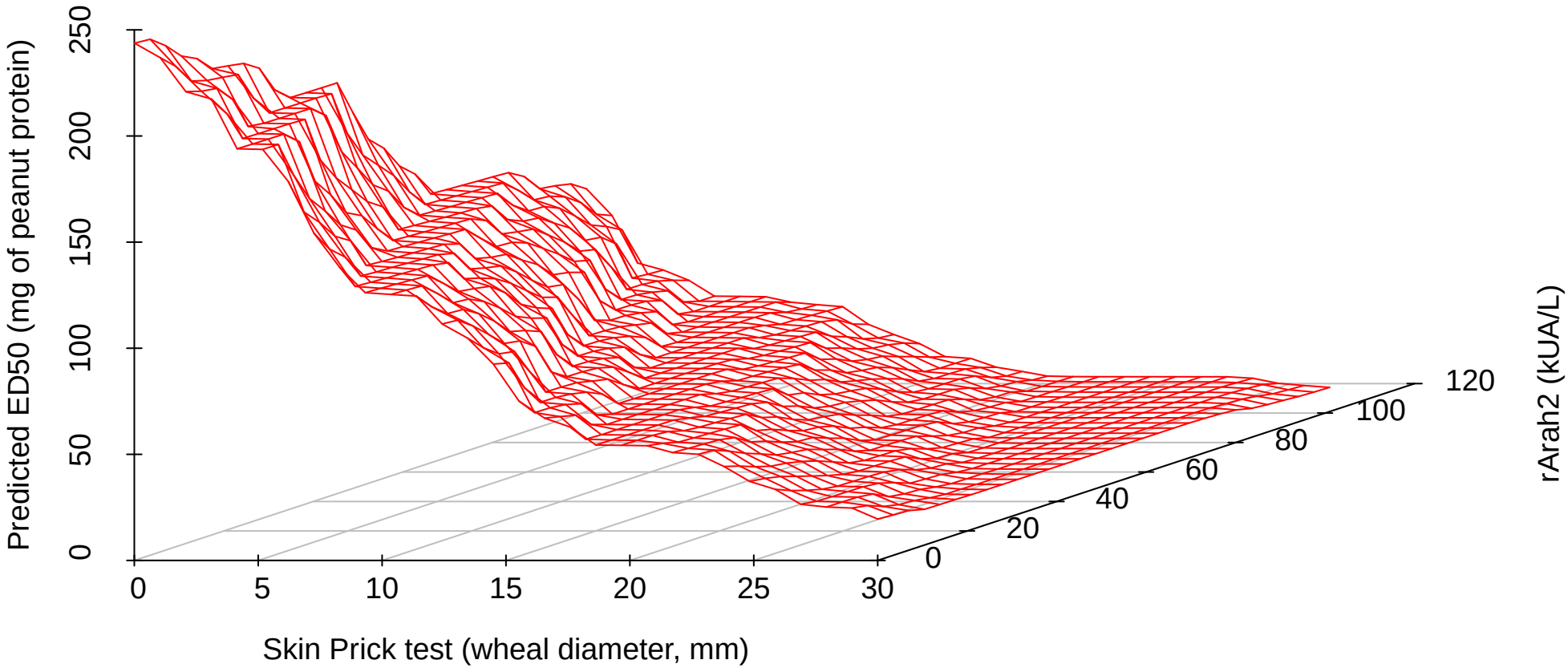

(a)
1.00
0.75
0.50
0.25
0.00
Cumulative probability of reaction
0
500
1000
1500
2000
2500
Threshold doses (mg of peanut protein)


(b)
1.00
0.75
0.50
0.25
0.00
Cumulative probability of reaction
0
50
100
150
200
250
Threshold doses (mg of peanut protein)


Kaplan Meier
95% CI
Cox model
95% CI
Weibull with covariables
95% CI
Lognormal with covariables
95% CI
Loglogistic with covariables
95% CI


Predicted ED1 (mg of peanut protein)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0
5
10
15
20
25
30
Skin Prick test (wheal diameter, mm)
0
20
40
60
80
100
120
rArah2 (kUA/L)


Predicted ED10 (mg of peanut protein)
0
5
10
15
20
0
5
10
15
20
25
30
Skin Prick test (wheal diameter, mm)
0
20
40
60
80
100
120
rArah2 (kUA/L)


Predicted ED50 (mg of peanut protein)
0
50
100
150
200
250
0
5
10
15
20
25
30
Skin Prick test (wheal diameter, mm)
0
20
40
60
80
100
120
rArah2 (kUA/L)