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

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

20

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37 **Contributors**

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

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

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

45 Jocelyne Just: involvement in the analysis and interpretation of the data and substantial  
46 involvement in revising the manuscript prior to submission.

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

50 Antoine Deschildre: involvement in the acquisition, analysis and interpretation of the data, and  
51 substantial involvement in writing the manuscript.

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

53 **Abstract**

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

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

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

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

76 of peanut, with beta coefficients associated to the risk and 95% credible intervals of 0.05 [0.02;  
77 0.08] and 0.01 [0.01; 0.02] respectively.

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

84

#### 85 **Keywords**

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

#### 88 **Abbreviations and definitions**

89 BIC: Bayesian Information Criterion

90 ED<sub>p</sub>: Eliciting Dose producing a reaction in a proportion  $p$  of the allergic population

91 IQR: Interquartile range

92 LOAEL: Lowest Observed Adverse Effect Level

93 NOAEL: No Observed Adverse Effect Level

94 OFC: Oral Food Challenge

95 RMSE: Root Mean Square Error

96 SPT: Skin Prick Test

97

98 **Capsule summary**

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

103

104 **Key messages (highlights box)**

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

114

115        **Introduction**

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

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

140 8]. Thus, the threshold of the allergic population is often described using only one threshold  
141 distribution curve whatever distinctive features may be observed between the patients in the  
142 study population.

143 The MIRABEL project was conducted by the French Agency for Food, Environmental and  
144 Occupational Health & Safety (ANSES) in partnership with the French National Institute for  
145 Agricultural Research (INRA) and the Allergy Vigilance Network ([www.allergyvigilance.org](http://www.allergyvigilance.org)).  
146 The objectives and the methods of the MIRABEL survey have been previously published [15,  
147 16], as well as the characteristics of the population, mainly children (< 16 years: 86%) and  
148 primary peanut allergic patients [17, 18]. One of the objectives was to accurately define the  
149 population threshold distribution for peanut in order to assess allergic risk and to improve food  
150 labeling. This study presents an original approach to estimate threshold doses using predictive  
151 factors. The model is based on routinely collected medical data. It could be a tool for allergists  
152 to identify high-risk patients who are susceptible to react to small amounts of peanut and to  
153 improve peanut allergy management with a personalized approach integrating the risk of  
154 allergic reaction.

## 155 **Materials and methods**

### 156 **Study design and population**

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

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

### 173 **Data collection**

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

### 183 **Threshold dose from oral food challenge**

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

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

### 195 **Statistical methods for threshold dose distribution modeling**

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

211 the complexity of the models compared with the AIC), and the Root Mean Square Error  
212 (RMSE, commonly used to measure of the difference between values predicted by a model and  
213 the values observed). Inferences were performed using the Bayesian approach and were  
214 implemented in the OpenBUGS software version [23] via the BRugs package of R version  
215 3.0.1. Simulations of the ED values from parameter estimates were done using second order  
216 Monte-Carlo simulations to separate variability and uncertainty [6] (details are provided in the  
217 Online Repository Online Repository).

## 218 **Results**

### 219 **Study population**

220 Overall, 785 patients were included in the MIRABEL survey [15, 17, 18]. Out of these, 280  
221 patients underwent an OFC (open OFC: 55%) and were considered for inclusion in the present  
222 analysis. One patient who did not react during a complete OFC, 14 sensitized patients with  
223 incomplete OFC, and 27 patients with missing data were not retained. The study population  
224 thus comprised 238 patients. The allergy was confirmed by a positive OFC in 86% of cases.  
225 From the 238 patients, 29 initially considered as sensitized patients had a positive OFC (12.2%)  
226 and 34 allergic patients did not react during incomplete OFC (14.3%). The patients were mainly  
227 children (mean age at the date of the OFC: 9 years (6-11) and 87% under 16 years), and males  
228 (62%) (Table 1). The median threshold dose was of 67 mg (16-244) of peanut protein. . The  
229 minimum and the maximum threshold doses were 0.03 and 2404 mg of peanut protein,  
230 respectively.

### 231 **Predictive factors of threshold doses**

232 In univariate analysis, the level of Ara h 2 sIgE, the size of the SPT and presence of atopic  
233 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 (ED<sub>p</sub>)**

254 The ED<sub>01</sub> 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<sub>01</sub> and the

258 highest credible interval: 1.33 [0.15; 3.93] mg of peanut protein. The Loglogistic model with  
259 predictive factors produced intermediate results: 0.89 [0.08; 3.46] mg of peanut protein. The  
260 basic Weibull, Lognormal and Loglogistic distributions produced lower values for the ED<sub>01</sub> and  
261 lower credible intervals than the ones with predictive factors: respectively 0.08 [0.03; 0.17],  
262 0.72 [0.42; 1.14] and 0.40 [0.20; 0.74] mg of peanut protein. Similar tendencies were observed  
263 for the other ED<sub>p</sub> values. Figure 3 shows that the threshold distribution curve estimated with  
264 the Cox model was the closest to the Kaplan-Meier estimates and that all values from Kaplan-  
265 Meier were comprised in the Cox model 95% credible interval. It can also be seen that the  
266 Weibull model with predictive factors, which produced the higher probabilities of reaction and  
267 the higher credible interval, is more conservative than the Lognormal and Loglogistic models  
268 with predictive factors. The Cox model with the highest credible interval integrates the highest  
269 part of variability. Table 3 also shows that whatever the model used, females had lower EDs  
270 than males.

### 271 **Prediction of threshold dose for a given patient in clinical practice**

272 Figure 4 shows how the threshold dose range related to a given allergic risk can be predicted  
273 for a patient from the SPT size and level of Ara h 2 sIgE using the Cox model. For example,  
274 with an SPT size of 10 mm and a level of Ara h 2 sIgE of 42 kU/L, the threshold doses triggering  
275 a reaction in 1% of the allergic females range between 0.04 and 0.89 with a median value of  
276 0.17 mg of peanut protein. For similar values of SPT size and Ara h 2 sIgE level, the threshold  
277 doses triggering a reaction in 10% and 50% of allergic females range between [2.36, 16.1] with  
278 a median of 6.33 and [18.3, 136] with a median of 67.3 mg of peanut protein, respectively.

279 **Discussion**

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

287 **Factors influencing the threshold dose**

288 Univariate analysis identified four variables which significantly influence the threshold dose.  
289 In fact, the female gender, a diagnosis of peanut allergy without the presence of atopic  
290 dermatitis, a high level of Ara h 2 sIgE and a large SPT size all lead to a lower threshold dose  
291 of reaction. Similarly, van der Zee et al. [14] also reported that the level of peanut sIgE and the  
292 absence of atopic dermatitis were closely associated to lower threshold doses from a study of  
293 126 OFCs in peanut allergic children modeled by a Cox model. In contrast to our results, they  
294 also observed an age effect, with lower threshold doses for teenagers, but not a gender effect.  
295 The reason why atopic dermatitis may affect the threshold dose is not clearly understood. One  
296 hypothesis, by van der Zee, Dubois [14], is that the presence of atopic dermatitis may mask  
297 early, mild cutaneous symptoms in the setting of an OFC. Blumchen, Beder [9] used a  
298 lognormal distribution to model individual peanut thresholds from a population of 63 peanut  
299 allergic children explored with a modified OFC protocol (dose increment every 2 hours). They  
300 observed that the threshold dose was significantly and inversely correlated with peanut and Ara  
301 h 2 sIgE levels, SPT size, basophil activation, and TH2 cytokine production by peripheral blood  
302 mononuclear cells. However, symptom severity did not correlate with the threshold or any of

303 these markers. Finally, Santos, Du Toit [24] assessed the basophil activation test (BAT) as a  
304 means of predicting the severity and threshold of reactivity to peanut during OFCs in 124  
305 children, including 52 with a positive OFC. They concluded that BAT can be used not only to  
306 estimate the threshold of allergic reactions during OFCs, but also the severity of the reaction.  
307 However, this result was not confirmed by Reier-Nilsen, Michelsen [25], who evaluated the  
308 accuracy of clinical and/or immunological characteristics to predict OFC reactivity threshold  
309 and the severity of the reaction in a population of 96 children (5 to 15 years old) with a history  
310 of severe allergic reactions to peanut and/or sensitization to peanut. They observed that BAT  
311 had the best accuracy to predict reactivity threshold as well as LOAEL, but not the severity of  
312 the reaction. ED was also associated to the gender, with a lowest dose in females. We have  
313 previously shown that severe peanut-allergic phenotypes were more frequent in girls [18].  
314 McWilliam, Koplin [26] found that female adolescents of the Australian “SchoolNuts” cohort  
315 were more likely to report experiencing any adverse food reaction in the past 12 months but  
316 found no significant sex difference associated with anaphylaxis and did not show data on ED  
317 [26]. The impact of gender on ED and FA severity are lacking and our finding has to be  
318 confirmed in prospective studies.

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

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

### 328 **The ED<sub>01</sub> value**

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

### 344 **Variability and uncertainty**

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

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

358 However, our study has some limitations. As repeated measures of threshold dose for each  
359 patient were not available, we could not account for intra-individual variability. Moreover,  
360 patients selected to be tested by OFC might have specific characteristics and thus did not reflect  
361 general peanut allergic patients. Regarding MIRABEL patients, we did not observe any  
362 discrepancies between patients with and without OFCs, except for asthma comorbidity and age  
363 at diagnosis [17]. Due to the recruitment process, allergic individuals who did not consult  
364 allergists could not have been included in our survey and lead to selection bias. Moreover,  
365 allergists who performed the OFC were aware of the peanut sIgE or prick test results and the  
366 assessment of the reaction occurring during the OFC was not standardized. Data on individual  
367 NOAELs were not available. Therefore, it was not possible to use the method proposed by  
368 Taylor, Crevel [32] to account for the fact that the reacting dose ranges between the NOAEL  
369 and the LOAEL and not necessarily equals the LOAEL value. This could lead to an  
370 underestimation of the frequency of lower threshold doses. Finally, it is important to mention  
371 that threshold doses in this work are related to reaction by ingestion and are not appropriate to  
372 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<sup>1</sup>, 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 <sup>(2)</sup>	95% CI <sup>(2)</sup>	95% CI <sup>(2)</sup>	95% CI <sup>(2)</sup>
Oral food challenges					
- Positive, n (%)					
- Threshold dose mg of peanut protein					
Median (IQR) <sup>(1)</sup>	204 (86)84 (16 - 244)				
[0; 5[, n (%)	19 (8)				
[5; 50[, n (%)	71 (30)				
[50; 100[, n (%)	35 (15)				
[100; 1000[ n (%)	92 (38)				
≥1000, n (%)	21 (9)				
Age at OFC (year)					
Median (IQR)					
Min -, Max	8 (6 - 11)	[-0.04; 0.03]	[-0.09; 0.04]	[-0.08; 0.03]	[-0.04; 0.03]
	2 - 27				
Gender (males), n (%)	147 (62)	[-0.02; 0.55]	[-0.95; 0.15]	[-0.98; 0.07]	<b>[0.01; 0.57]</b>
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)	<b>[-0.62; -0.04]</b>	<b>[0.02; 1.18]</b>	<b>[0.08; 1.18]</b>	<b>[-0.63; -0.05]</b>
- 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)	8 (1 - 55)	<b>[0.01; 0.02]</b>	<b>[-0.03; -0.01]</b>	<b>[-0.03; -0.01]</b>	<b>[0.01; 0.02]</b>
Min - Max	0.01 - 101				
Skin prick tests size (mm)					
Median (IQR)	10 (7 - 13)	<b>[0.04; 0.09]</b>	<b>[-0.15; -0.05]</b>	<b>[-0.14; -0.06]</b>	<b>[0.04; 0.10]</b>

Min - Max	0.01 - 30				
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<sup>(1)</sup> sIgE: specific IgE, IQR = Interquartile range.

<sup>(2)</sup> 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 <sup>(1)</sup>	BIC <sup>(4)</sup>	RMSE <sup>(5)</sup>
<b>Weibull with covariables</b> $d \sim Weibull(a, b_i)$ $F(d; a, b_i) = 1 - \exp(-b_i d^a)$	$a$	$\log(b_i) =$	0.65	[0.58; 0.72]	2687 [2667; 2713]	528 [515; 564]
		$\beta_0$ (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]		
<b>Lognormal with covariables</b> <sup>(2)</sup> $d \sim Lognormal(\mu_i, \sigma)$ $F(d; \mu, \sigma) = \Phi\left(\frac{\ln(d) - \mu_i}{\sigma}\right)$	$\mu_i =$	$\beta_0$ (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]		
		$\sigma$	1.92	[1.74; 2.12]		
<b>Loglogistic with covariables</b> $\ln(d) \sim Logistic(\mu_i, \sigma)$ $F(d; \mu, \sigma) = \frac{1}{1 + \exp\left(\frac{d - \mu_i}{\sigma}\right)}$	$\mu_i =$	$\beta_0$ (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]		
		$\sigma$	1.07	[0.96; 1.2]		
<b>Cox model</b> <sup>(3)</sup> $F(d) = 1 - \exp\left(\int_0^d h_0(u) \exp(\beta_1 Z_1 + \dots + \beta_4 Z_4) du\right)$	$h(d) =$	$h_0(d)$	0.44	[0.04; 0.77]	1619 [1604; 1633]	519 [509; 541]
		$\beta_1$ (Gender)	0.05	[0.02; 0.08]		
		$\beta_2$ (SPT)	0.01	[0.01; 0.02]		
		$\beta_3$ (Ara h 2)	-0.01	[-0.01; -3 e-04]		
		$\beta_4$ (Gender * Ara h 2)				
<b>Basic Weibull</b> $d \sim Weibull(a, b) \text{ — } F(d; a, b) = 1 - \exp(-bd^a)$	$a$		0.57	[0.52; 0.63]	2720 [2699; 2746]	547 [542; 575]
		$b$		0.04		
<b>Basic Lognormal</b> <sup>(2)</sup> $d \sim Lognormal(\mu, \sigma) \text{ — } F(d; \mu, \sigma) = \Phi\left(\frac{\ln(d) - \mu}{\sigma}\right)$	$\mu$		4.51	[4.23; 4.79]	2721 [2700; 2746]	732 [575; 1195]
		$\sigma$		2.08		
<b>Basic Loglogistic</b> $\ln(d) \sim Logistic(\mu, \sigma) \text{ — } F(d; \mu, \sigma) = \frac{1}{1 + \exp\left(\frac{d - \mu}{\sigma}\right)}$	$\mu$		4.56	[4.29; 4.83]	2646 [2621; 2680]	606 [586; 611]
		$\sigma$		1.19		

$d$ : Threshold dose

<sup>(1)</sup> 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.

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

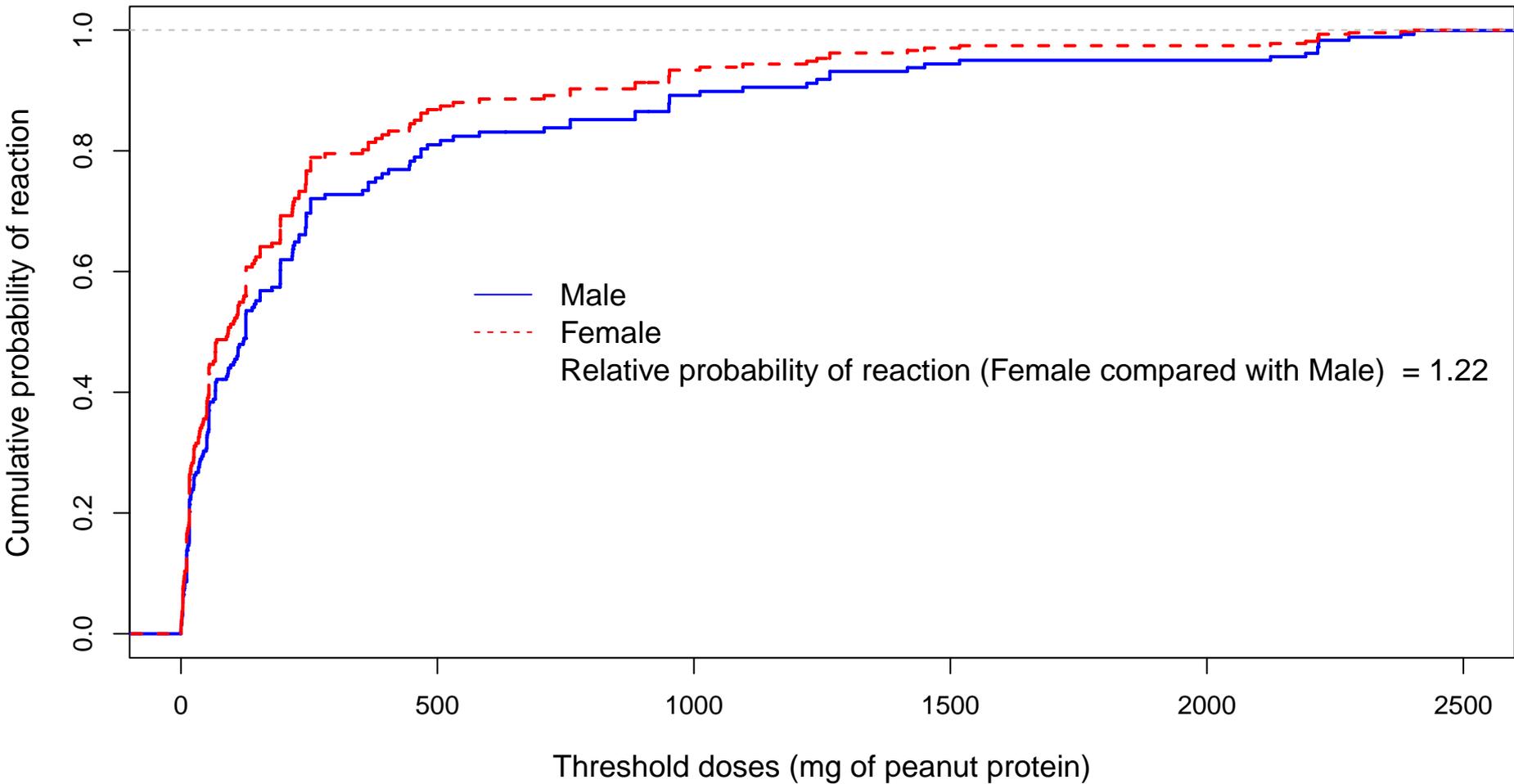
**Table 3: Eliciting doses (ED<sub>p</sub> in mg of peanut protein) triggering an allergic reaction for p% of the population. The ED<sub>p</sub> are described by their median and the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles. These percentiles define a 95% credible interval around the median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

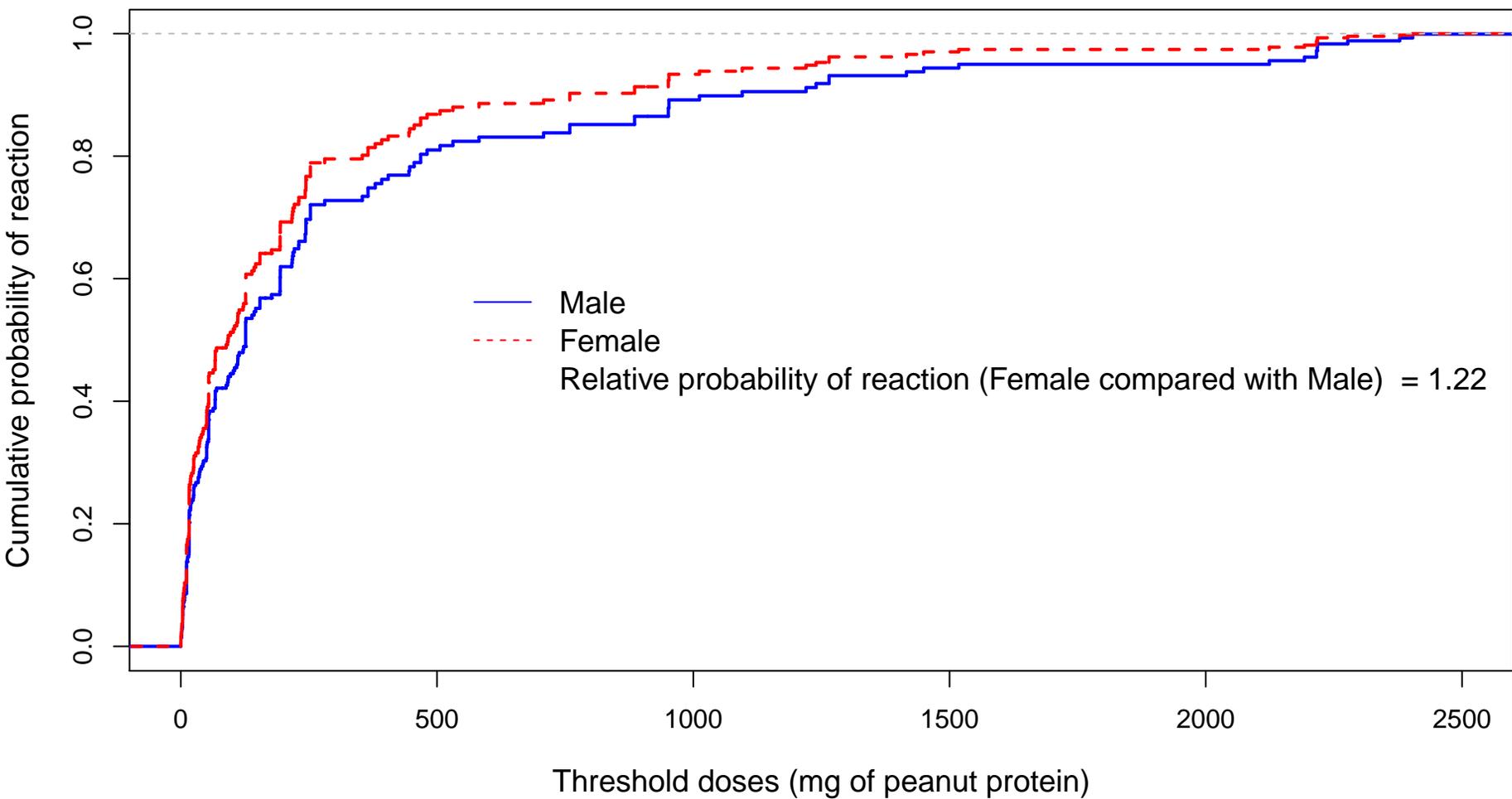
	Models	Estimator	ED <sub>p</sub>						
			1	5	10	50	90	95	99
Entire population	Kaplan Meier	Median	0.19	3.62	8.13	126	1455	2218	2392
		2.5 <sup>th</sup> percentile	0.03	1.81	4.00	89.8	1055	2143	2321
		97.5 <sup>th</sup> percentile	2.25	5.97	11.1	177	2218	NA	NA
	Weibull with covariables	Median	0.20	2.58	7.94	149	962	1448	2830
		2.5 <sup>th</sup> percentile	0.02	0.32	1.03	20.7	136	204	393
		97.5 <sup>th</sup> 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
		2.5 <sup>th</sup> percentile	0.15	0.58	1.20	15.3	188	382	1426
		97.5 <sup>th</sup> 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
		2.5 <sup>th</sup> percentile	0.08	0.51	1.15	12.7	136	302	1737
		97.5 <sup>th</sup> percentile	3.46	18.9	42.1	441	5014	11731	76115
	Cox model	Median	0.26	3.9	11.1	127	1244	2191	2218
		2.5 <sup>th</sup> percentile	0.03	0.94	2.93	16.4	126	194	251
		97.5 <sup>th</sup> percentile	2.24	11.1	25.0	676	2389	2400	2403
	Basic Weibull	Median	0.08	1.38	4.94	137	1144	1817	3896
		2.5 <sup>th</sup> percentile	0.03	0.74	2.96	105	891	1377	2789
		97.5 <sup>th</sup> percentile	0.17	2.39	7.77	176	1526	2479	5556
	Basic Lognormal	Median	0.72	3.08	6.74	104	1597	3472	14841
		2.5 <sup>th</sup> percentile	0.42	1.99	4.53	78.8	1079	2224	8457
		97.5 <sup>th</sup> percentile	1.14	4.46	9.23	135	2510	5863	28724
	Basic Loglogistic	Median	0.40	2.98	7.47	108	1576	3890	28998
		2.5 <sup>th</sup> percentile	0.20	1.84	4.96	83.1	1069	2461	15442
		97.5 <sup>th</sup> percentile	0.74	4.68	10.88	145	2534	6880	62987

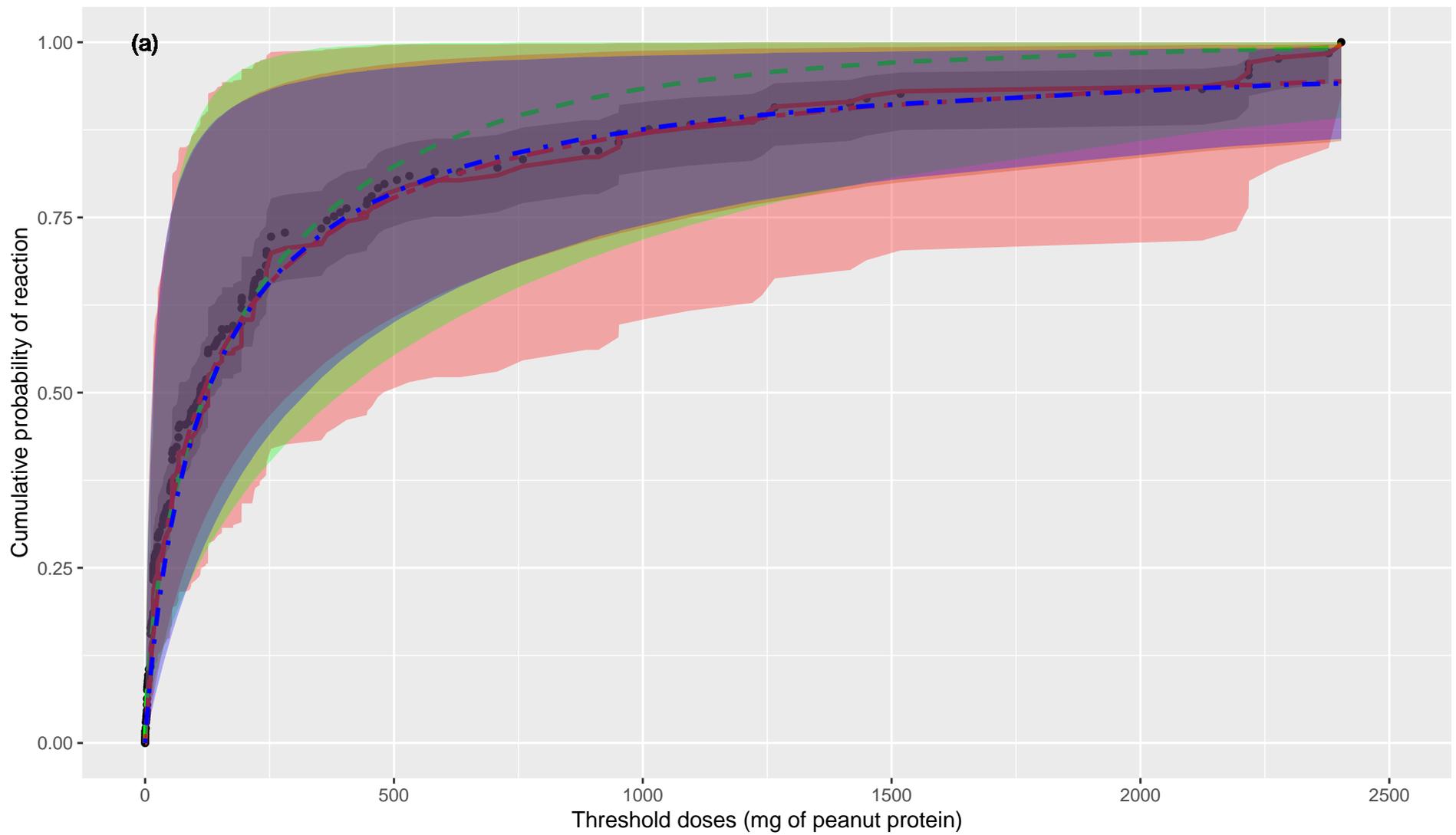
According to gender	<b>Kaplan Meier (Female)</b>	Median	0.03	3.22	6.32	64.7	752	1444	2218
		2.5 <sup>th</sup> percentile	0.01	0.24	3.65	49.1	457	739	2011
		97.5 <sup>th</sup> percentile	3.74	10.68	14.9	125	NA	NA	NA
	<b>Kaplan Meier (Male)</b>	Median	0.22	3.54	7.96	153	2198	2276.	2396
		2.5 <sup>th</sup>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

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

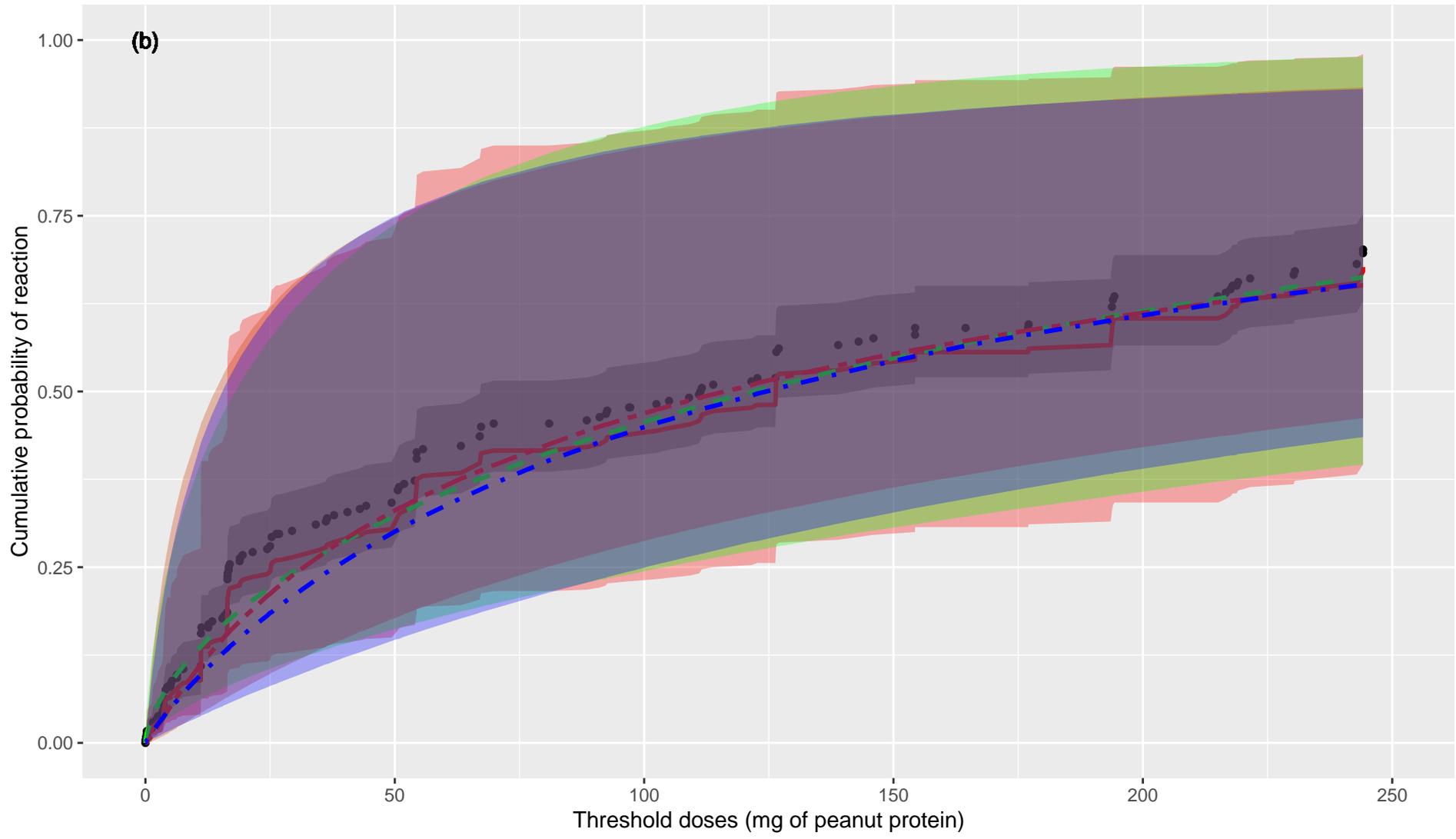
NA = Not Available. Sometimes, the bound of confidence interval for the Kaplan Meier approach cannot be estimated as Greenwood's formula, used to construct the bound of the confidence interval, does not work when the cumulative probability of reaction is close to 1.







(b)



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

