Original Research Article

A First-Order Mathematical Model of Peanut Tolerance Progression during Oral Immunotherapy

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ABSTRACT

Peanut allergy is potentially a life-threatening condition that places significant clinical and psychological burden on affected children and their families. In spite of the strong efficacy of peanut oral immunotherapy (OIT) shown in increasing tolerance thresholds, the time-dependent progression of desensitization has not been much expressed through a simple quantitative framework. In this study, a first-order dynamic quantitative model has been developed to describe the progression of peanut tolerance during OIT using published aggregate clinical outcomes from the U.S. Food and Drug Administration (FDA) statistical review of Phase 3 Study ARC005. In the referenced trial, 73.5% of AR101-treated participants tolerated at least 600mg of peanut protein at the exit double-blind, placebo-controlled food challenge, where only 6.3% in the placebo group reported it after approximately 12 months of therapy. Assuming that the rate of improvement was proportional to the remaining proportion of participants who had not yet achieved the tolerance endpoint, a first-order differential equation was used to represent the increase in tolerance probability over time. With the fitted model, a desensitization rate constant of approximately 0.111 $month^{-1}$ and a tolerance half-time of about 6.26 months were produced. The results suggest that a simple first-order mathematical model can provide an interpretable representation of peanut desensitization dynamics during OIT in a population level and also serve as a useful conceptual framework for future modeling studies.

Keywords: Peanut allergy; oral immunotherapy; mathematical modeling; desensitization dynamics; differential equation; food allergy simulation

INTRODUCTION

Peanut allergy has become one of the major public health concerns especially among children and their families as it poses a risk of severe anaphylaxis and growing burden on the treatment from its persistence. More specifically, peanut allergy, unlike milk or egg allergies, is more likely to suffer from lack of spontaneous resolution, along with a possibility of more serious reactions caused by trace exposure. This creates a continuing need for strict avoidance, emergency preparedness, and psychosocial vigilance in daily life that may impair well-being and increase family stress (1, 2).

In response to the aforementioned challenges, peanut oral immunotherapy (OIT) has been developed as one of the most significant active treatment approaches for immunoglobulin E (IgE)-mediated food allergy. OIT applies administration of gradually increasing doses of peanut protein followed by a maintenance period

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Accepted June 15, 2026
https://doi.org/10.70251/HYJR2348.43611618

of dosing to increase the threshold of reactivity to accidental exposure. Early randomized studies have reported that clinically meaningful desensitization may be induced by peanut OIT, while altering immune responses related to allergy (3). Larger multicenter trials later confirmed that the proportion of participants who were able to tolerate predefined peanut protein challenge doses increased substantially by peanut OIT when compared with placebo. This supports the role of peanut OIT as an effective therapeutic strategy in selected patients (4, 5). More trials conducted to younger children have suggested that earlier intervention may improve the outcomes of desensitization (5).

Although peanut OIT has demonstrated strong clinical promise, it is not the only immunotherapeutic strategy researched for peanut allergy. Studies of peanut sublingual immunotherapy and epicutaneous immunotherapy have suggested that these approaches may offer different safety and efficacy tradeoffs compared with oral immunotherapy (6, 7). However, these modalities have generally produced more modest desensitization outcomes than OIT, which remains the most intensively studied and clinically influenced immunotherapy approach for peanut allergy (8, 9). As a result, OIT has become the most intensively researched and clinically influential approach for food immunotherapy after regulatory approval of peanut allergen powder-dnfp in the United States (4, 9). In addition, there have been ongoing questions about durability, adverse events, and optimal treatment duration of OIT from expert reviews, leaving treatment responses to remain heterogeneous across patients (9-11).

The desensitization-oriented biological mechanisms during OIT are complex by its nature, involving multiple interacting immune pathways. Prior studies have explained changes in allergen-specific IgE, IgG4, basophil activation, mast-cell responsiveness, and T-cell regulation during treatment (12-14). However, these immunologic findings do not always lead to clinical challenge outcomes. In practice, discrete end points, including the maximum tolerated peanut dose during a double-blind and placebo-controlled food challenge, define treatment success rather than a continuous biological marker. Because of this issue, an important interpretative gap has been generated. The clinical literature demonstrates that tolerance tends to increase over time during treatment, yet the shape of that time-dependent progression is not usually expressed in a simple quantitative framework.

In a perspective that a quantitative framework can provide a useful bridge between observed clinical outcomes and theoretical understanding of treatment dynamics, it is important to identify and examine the aforementioned literature gap. While mechanistic immunology models exist for allergic and immunotherapy processes in a broad range, they are often too biologically specialized to apply the modeling of clinical desensitization trajectories (12, 13). On the other hand, a simple dynamic model may help demonstrate how the probability of achieving a clinically meaningful tolerance threshold changes over time, while providing an interpretable way to compare the treatment patterns, estimating rates of desensitization, and generating hypotheses for the future study.

Accordingly, this study develops a first-order mathematical model for the progression of peanut tolerance during oral immunotherapy by using published clinical trial benchmarks. Instead of modeling individual immune-cell behavior, the model proposed in this study focuses on desensitization dynamics in a population-level, reflecting challenge-defined tolerance outcomes over time. This approach aims to provide a tractable quantitative framework of treatment progression in a close connection with clinically relevant endpoints.

To achieve the goal of filling the aforementioned literature gap, this study seeks to answer the research question about whether the progression of peanut allergen tolerance can be quantitatively represented during oral immunotherapy by using a first-order dynamic model based on published clinical outcomes. This study hypothesized that the chance of achieving a clinically defined peanut tolerance threshold increases over time in a decelerating manner during oral immunotherapy and can be estimated by a first-order approach toward a plateau rather than by indefinite linear growth.

METHODS AND MATERIALS

In this study, a simulation-based mathematical modeling was used, describing the progression of peanut allergen tolerance during peanut oral immunotherapy (OIT). This study was based on aggregate clinical trial outcomes reported in the U.S. Food and Drug Administration statistical review of PALFORZIA (peanut allergen powder-dnfp) rather than analyzing patient-level raw data. Additional conceptual framing was drawn from the manuscript draft. The goal of the analysis was to generate a simple quantitative model to represent the population-level trajectory of desensitization during treatment.

Python was used to perform all model calculations, parameter estimation, and figure generation. The differential equation was analytically solved, and the fitted rate constants were calculated from the closed-form first-order model using the published 12-month response proportions. The simulated model outputs and FDA-reported aggregate response rates were used to generate figures. Since this study used only publicly available aggregate data from an FDA statistical review without involving direct interaction with human participants or access to identifiable private information, institutional review board approval was not required.

Data Source and Clinical Benchmark

The main reference source for model parameterization was the FDA statistical review of Phase 3 Study ARC005 (POSEIDON). This was a randomized, double-blind, placebo-controlled trial that evaluated AR101 in peanut-allergic children in the ages from 1 to 3 years. According to the review, a total of 146 subjects were randomized that 98 were assigned to AR101, and 48 were assigned to placebo. An initial dose-escalation phase was included in the treatment protocol, followed by an up-dosing period of approximately 24 to 40 weeks and a maintenance phase with daily 300mg dosing for an overall treatment period of around 12 months before exit double-blind, placebo-controlled food challenge (DBPCFC).

The proportion of subjects who tolerated a single dose of at least 600mg of peanut protein with no more than mild symptoms during the exit DBPCFC was the main efficacy endpoint in the FDA review. This 600mg of threshold was used in this study as it was the prespecified primary endpoint in the trial, representing a clinically meaningful and regulator-reviewed benchmark for desensitization. In the intent-to-treat population, 73.5% of AR101-treated subjects achieved this endpoint compared with 6.3% of placebo-treated subjects after the period of approximately 12 months of therapy.

Model Variables and Assumptions

Clinical peanut tolerance was modeled as a time-dependent population process. P(t) was used to denote the proportion of participants who were able to tolerate at least 600mg of peanut protein without the symptoms of limiting the dose at time t, where t was measured in months from the start of oral immunotherapy. Therefore, P(t) takes the values in the interval [0,1], representing a tolerance probability at the population level rather than the exact threshold dose of an individual patient. This definition was informed by the FDA primary endpoint to operationalize tolerance.

The model assumes that the P(t) increases at a rate proportional to the remaining proportion of participants who have not achieved the defined tolerance endpoint yet. In a biological perspective, this aligns with the idea that many participants remain below the target threshold early in the treatment. Therefore, improvement may occur relatively rapidly, while fewer participants remain to transition later in treatment, leading to slower growth and eventual saturation. This assumption was maintained throughout the analysis since it yields a simple first-order approach with a plateau that is consistent with the general clinical pattern of rapid early improvement followed by gradual slowdown during OIT.

A second assumption maintained in this study is that the population proportion tolerating 600mg is almost zero at baseline. Using the ARC005 eligibility criteria about how enrolled subjects needed to demonstrate dose-limiting allergic symptoms after consuming single doses greater than 3mg and up to 300mg during the screening DBPCFC, the aforementioned assumption is justified. Therefore, participants who were able to tolerate 600mg at baseline were excluded from the study population for the analysis.

Mathematical Model

Under these assumptions, the first-order differential equation for the temporal progression of tolerance was generated as follows:

$$\frac{dP}{dt} = k\,(1 - P)$$

Where $k > 0$ is the constant for the desensitization rate. Since k represents a first-order rate constant, its units are inverse time; in this study, k is reported in $month^{-1}$. The term 1-P is the proportion of participants who remain below the 600mg tolerance threshold at time t. This formulation demonstrates that few participants have reached the endpoint during the initial rapid increase in tolerance probability, followed by gradual deceleration as the population approaches plateau.

When solving this differential equation subject to the initial condition of P(0)=0, it yields the following analytical solution:

$$P(t) = 1 - e^{-kt}$$

This is a closed-form function used as the principal simulation model for the treatment group. For the comparison, the same functional form was descriptively

used to the placebo group even though the placebo curve is interpreted only as a benchmark of low-response trajectory instead of an active process in desensitization.

Parameter Estimation and Derived Quantities

Matching the model to the observed 12-month treatment outcome reported in the FDA review, the rate constant k was estimated. For the AR101 group, the model was generated using P(12)=0.735, yielding

$$0.735 = 1 - e^{-12k}$$

Solving for k yields

$$k = -\frac{1}{12}\ln(1 - 0.735)$$

This parameter shows how model-derived monthly desensitization rate constant is at the population level. A tolerance half-time was also calculated as

$$t_{\frac{1}{2}} = \frac{ln2}{k}$$

Where this value represents the time required for the modeled proportion to reach one-half of its eventual asymptotic level using the first-order framework. For the placebo group, the reported 12-month response proportion of 0.063 was used to perform the analogous descriptive calculation.

Uncertainty and Comparison

This study reported the FDA-provided confidence intervals for the treatment and placebo response rates to summarize uncertainty in the observed clinical proportions. The regulator-reviewed treatment difference and confidence interval reported in the statistical review were used to interpret the difference between groups at 12 months. No individual-level regression or subject-specific fitting was performed as only aggregate endpoint data were available. Therefore, the model should be interpreted as an explanatory simulation of desensitization dynamics performed in the population-level instead of a validated predictive model for individual patients.

RESULTS

Observed Clinical Outcomes at the Primary Endpoint

The simulation performed in this study was anchored to the aggregate efficacy result as reported in the FDA statistical review of Phase 3 Study ARC005. 73.5% of participants in the intent-to-treat population who were treated with AR101 tolerated a single dose of at least 600mg of peanut protein with no more than mild symptoms at the exit double-blind, placebo-controlled food challenge (DBPCFC). On the other hand, only 6.3% of participants in the placebo group tolerated it. The corresponding 95% confidence intervals were 63.6% to 81.9% for AR101 and 1.3% to 17.2% for placebo. The treatment difference was reported to be 67.2 percentage point, and a 95% confidence interval was 50.0 to 84.5 percentage points. This confirmed a large separation between the treatment and placebo groups at the study endpoint (Figure 1). With these values, the primary benchmark was provided for the tolerance probabilities at the population level in the dynamic model used in this analysis. These response percentages are observed aggregate clinical outcomes from the FDA-reviewed trial, whereas the desensitization rate constant, tolerance half-time, and continuous tolerance curves reported below are modeled-derived quantities calculated using the first-order framework.

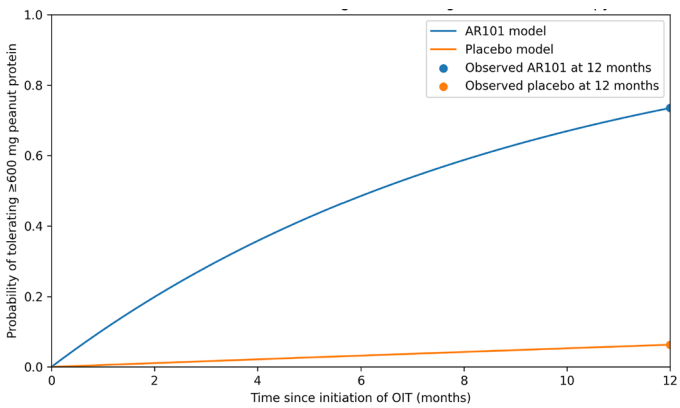

Figure 1. *Simulated peanut tolerance progression during oral immunotherapy. The x-axis shows time since initiation of oral immunotherapy in months, and the y-axis shows the modeled probability of tolerating at least 600 mg of peanut protein. The AR101 curve represents a first-order increase toward the FDA-reported 12-month endpoint of 73.5%, while the placebo curve is an illustrative assumption-driven curve calibrated only to the 6.3% placebo response at 12 months.*

The overall desensitization advantage of AR101 was supported by additional efficacy outcomes. At the 300mg threshold, 79.6% of subjects treated with AR101 achieved the tolerance endpoint compared with 22.9% in the placebo group. At the 1000mg threshold, 68.4%

of the group treated with AR101 achieved the tolerance endpoint compared with 4.2% of the placebo group. These results support that the treatment effect extended across multiple clinically relevant challenge doses without being limited to a single threshold (Figure 2).

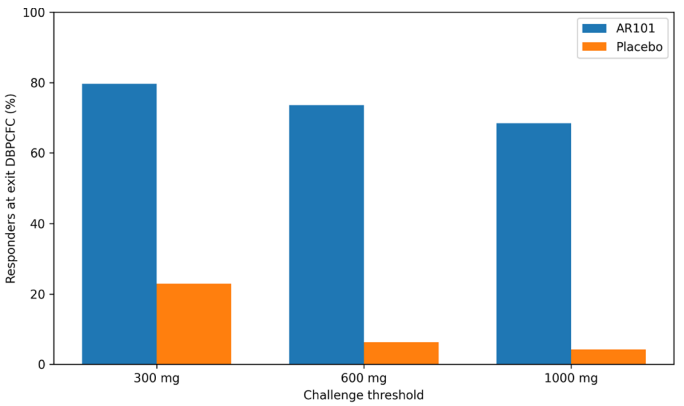

Figure 2. *Observed desensitization response rates at three peanut protein challenge thresholds. The x-axis indicates the peanut protein dose threshold tested at exit double-blind, placebo-controlled food challenge (DBPCFC), and the y-axis shows the percentage of participants who tolerated each dose. Data are from the FDA statistical review of Phase 3 Study ARC005 and show higher response rates for AR101 than placebo at 300 mg, 600 mg, and 1000 mg.*

Model-Based Characterization of Tolerance Progression

The probability of achieving the 600mg tolerance threshold was modeled by using the first-order dynamic framework as follows:

$$P(t) = 1 - e^{-kt}$$

Where P(t) represents the proportion of participants who tolerated at least 600mg of peanut protein without symptoms of limiting doses at time t in months, and k is the constant of desensitization rate. This function was calibrated to match the modeled treatment-group probability with the FDA-reported 12 months outcome for AR101.

Substituting P(12) = 0.735 for the AR101 group yields

$$0.735 = 1 - e^{-12k}$$

Therefore, the model-derived value of k was calculated to be $-\frac{1}{12}\ln(1 - 0.735)$ that was around 0.111 month^{-1}.

Based on this estimate, it was implied that the trajectory of the tolerance shown in the treated-group rose rapidly at the beginning of therapy, followed by gradual slowdown as the modeled population approached the plateau. The corresponding half-time for the tolerance was calculated as follows:

$$t_{\frac{1}{2}} = \frac{ln2}{k}$$

The model-derived tolerance half-time was approximately 6.26 months (Figure 3). Therefore, about half of the population-level approach toward the endpoint was eventually achieved under the fitted first-order model within the first half-year of treatment. This finding was consistent with the general clinical structure of the ARC005 trial where subjects experienced initial elevation and up-dosing during the early and middle phases of the intervention followed by the maintenance dosing.

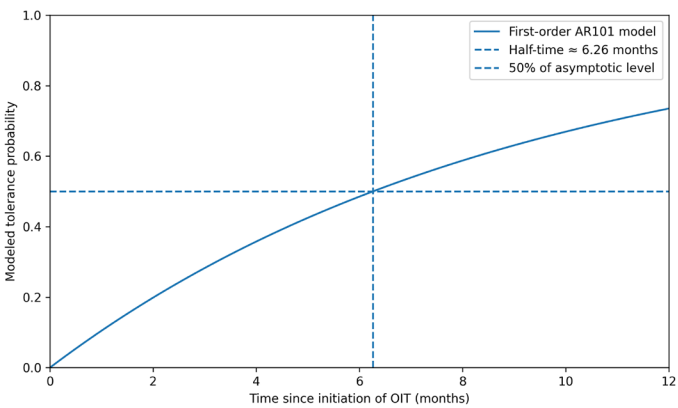

Figure 3. *First-order desensitization curve with estimated tolerance half-time. The x-axis represents time since initiation of oral immunotherapy in months, and the y-axis represents the modeled probability of reaching the 600 mg peanut protein tolerance endpoint. The plotted curve indicates the fitted AR101 first-order model, with the dashed lines marking the estimated half-time of around 6.26 months, when the model reaches 50% of its asymptotic progression.*

Placebo Comparison

The same functional form was applied to the placebo group for descriptive comparison. Using the observed 12-month tolerance probability of 0.063 and substituting P(12) = 0.063 into the same equation, the following was obtained:

$$0.063 = 1 - e^{-12k}$$

Which yields a model-derived placebo rate constant of approximately

$$k_{placebo} \approx 0.0054\ month$$

Compared to the corresponding AR101 estimate, this value is substantially smaller. This should not be interpreted as an observed month-by-month placebo trajectory. Since only the 12-month placebo endpoint was available, the placebo curve is an assumption-driven illustrative trajectory calibrated to the single endpoint of 6.3%. In practical terms, the assumed placebo curve remains close to zero under the same first-order model form, whereas the AR101 model curve reaches a much higher endpoint by month 12. This difference between these two fitted trajectories both visually and quantitatively reinforces how effective the treatment was as observed in the clinical trial.

Interpretation of the Dynamic Pattern

The fitted treatment-group model reported the expected decelerating pattern of desensitization. At the initiation of treatment, nearly all participants remained below the 600mg threshold. At this time, the model predicted a relatively fast increase in tolerance probability. As treatment continued with a larger proportion of the population reaching the endpoint, the remaining proportion below threshold decreased, along with slowed rate of improvement. This behavior follows directly from the model term 1-P that becomes smaller as P(t) increases. Therefore, the first-order formulation captures a clinically intuitive pattern to report substantial improvement during early treatment followed by gradual slowdown approaching a plateau than increasing indefinitely.

This dynamic interpretation also aligns with the observed structure of oral immunotherapy in ARC005. Subjects experienced a progress through escalation of doses in stages followed by up-dosing approximately every two weeks and finally a period of maintenance dosing at 300mg/day before the exit challenge. This result is reasonably expected to generate active gain in the early period followed by a slower maintenance phase to the decelerating trajectory produced in the model.

Supportive Analysis and Robustness

Sensitivity analyses were also reported by the FDA review to be consistent with the primary endpoint findings. In the population of subjects who completed tolerating the dose endpoint, the desensitization response rate at 600mg was calculated to be 86.7% in the AR101 group compared with 6.7% in the placebo group. In the per-protocol population, the corresponding rates were 87.8% and 7.1%, respectively. In addition, a large treatment effect was shown from missing data of a worst-case imputation analysis, with a treatment difference of 61.0 percentage points. These supportive analyses show that it took more than one analysis set to drive the favorable treatment outcome where they strengthened the rationale for using the 12-month AR101 response as a reasonable benchmark for simulation.

Overall, the results show that a plausible and interpretable quantitative representation of peanut tolerance progression during oral immunotherapy is provided by the first-order quantitative framework. More specifically, it reproduces the observed 12-month treatment response, distinguishing clearly between AR101 and placebo. Furthermore, it also yields clinically intuitive derived measures, including the constant of desensitization rate and tolerance half-time. Although the model is based not on individual-level data but aggregate population-level data, its behavior aligns well with the reported trial outcomes that the use of the first-order quantitative model is supported to describe population-level desensitization dynamics.

DISCUSSION

The quantitative model developed in this study provides a simplified but useful framework for describing the process of desensitization observed during peanut oral immunotherapy. The model provides an explanatory representation of a clinically intuitive pattern in which the chance of achieving a meaningful tolerance threshold rapidly increases in the early period of treatment followed by gradual slowdown as it approaches a limiting level by representing the increase in tolerance in the use of a first-order differential equation. This pattern aligns well with the ARC005 trial structure, including the staged elevation, prolonged up-dosing, and maintenance therapy over approximately 12 months. The observed difference between the AR101 and placebo trajectories supports the idea that observed improvement demonstrates not just background variation alone but also an active treatment effect.

One strength of this study is that regulator-reviewed clinical outcomes are translated into a quantitative framework for convenient interpretation. Rather than

trying to reproduce the full complexity of immune-cell signaling, cytokine interactions, or biomarker changes, the model proposed in this study focuses on a clinically intuitive and meaningful endpoint, namely: the proportion of participants tolerating at least 600mg of peanut protein. The model in this study becomes especially useful for conceptualizing the progression of treatment at the population level, while generating a hypothesis about how tolerance may evolve over time under oral immunotherapy.

This modeling approach also differs from prior mechanistic descriptions of allergy desensitization and immune tolerance. Biological pathways, such as allergen-specific IgE, IgG4, basophil activation, mast-cell responsiveness, and T-cell regulation during immunotherapy, have been emphasized by earlier immunology-focused models and reviews. With those frameworks, explaining the cellular and molecular mechanisms underlying desensitization was available. However, they often were too biologically detailed to directly describe the population-level progression of a clinical tolerance endpoint. In contrast, the first-order model proposed in this study intentionally simplifies the biological process into a single clinically interpretable outcome: the proportion of participants reaching the 600mg peanut protein threshold. This simplification is a meaningful trade-off. Although it cannot explain individual immune mechanisms, it offers a transparent way to estimate the pace of desensitization, compare treatment and placebo trajectories, and connect published clinical trial outcomes to a reproducible mathematical structure.

However, there are several limitations in this study. First, the model proposed in this study is based on aggregate benchmark data. Since it is not based on patient-level longitudinal observations, the model cannot capture individual-level variability in treatment response. Second, a single primary endpoint time anchor is used in the model. Since the model was calibrated using only the assumed baseline condition $P(0) = 0$, and the 12-month treatment endpoint $P(12) = 0.735$, the desensitization rate constant and tolerance half-time were mathematically determined by these two values rather than independently estimated from longitudinal observations. As a result, the model reproduces the 12-month endpoint by construction, and goodness-of-fit cannot be assessed from the available aggregate data. Intermediate clinical time points during up-dosing and maintenance would be needed to test whether the first-order functional form accurately describes the actual desensitization trajectory over time.

In spite of aforementioned limitations, the model proposed in this study provides a ground that a simple mathematical framework can offer meaningful insight into peanut OIT dynamics. It is recommended for future studies to improve this work by applying additional time points, patient-specific factors, or immunologic variables to generate more detailed and clinically informative models.

CONCLUSION

In this study, a simplified mathematical model was presented to describe the progression of peanut tolerance during oral immunotherapy. The model captured the general pattern for an increase of the proportion of participants achieving a clinically meaningful tolerance threshold over time, followed by a gradual approach to a plateau by using a first-order differential equation and FDA-reviewed clinical trial benchmarks. There was a clear advantage of the simulated trajectory for AR101 over placebo, reflecting the overall pattern of desensitization in the ARC005 trial.

Although the model does not apply detailed immunologic mechanisms or patient-level variability, it still demonstrates that a simple quantitative framework generated at the population level can provide useful insight into treatment dynamics. In this way, mathematical modeling may complement clinical evidence by providing an interpretable result about how tolerance progresses over time during therapy. It is recommended for future studies to focus on strengthening this framework by incorporating additional longitudinal endpoints, biological variables, and individualized response factors to improve the predictive value as well as realism.

CONFLICT OF INTEREST

The author declares no conflicts of interest related to this work.

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