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A regression-based model to predict chemical migration from packaging to food

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Abstract

Packaging materials can be a source of chemical contaminants in food. Process-based migration models (PMM) predict the chemical fraction transferred from packaging materials to food (F_C) for application in prioritisation tools for human exposure. These models, however, have a relatively limited applicability domain and their predictive performance is typically low. To overcome these limitations, we developed a linear mixed-effects model (LMM) to statistically relate measured F_C to properties of chemicals, food, packaging, and experimental conditions. We found a negative relationship between the molecular weight (MW) and F_C , and a positive relationship with the fat content of the food depending on the octanol-water partitioning coefficient of the migrant. We also showed that large chemicals (MW > 400 g/mol) have a higher migration potential in packaging with low crystallinity compared with high crystallinity. The predictive performance of the LMM for chemicals not included in the database in contact with untested food items but known packaging material was higher (Coefficient of Efficiency (CoE) = 0.21) compared with a recently developed PMM (CoE = −5.24). We conclude that our empirical model is useful to predict chemical migration from packaging to food and prioritise chemicals in the absence of measurements.

Keywords Mixed-effects model · Deterministic model · Chemical risk assessment · Life cycle assessment · Food contact material

Introduction

Plastics are widely used as a food contact material (FCM) to ensure the safety and protection of foodstuffs [1]. However,

chemical migrants in plastic FCMs can transfer into the food and therefore the use of FCMs is regulated to ensure consumer safety [2, 3]. Regulations on chemicals in FCM change as new evidence becomes available [4, 5]. For instance, in Europe, bisphenol A has been banned in baby bottles in 2011 [6] and the European Food Safety Authority is currently looking into revising the tolerable intake rates of perfluoroalkylated substances found, amongst other, in food packaging applications [7]. Safety regulations tend to focus on limiting exposure to single chemicals. However, given the increased number of chemicals in use, risk-based chemical priority setting is of increasingly relevance for example using aggregate human exposure predictions to different chemicals found across different products [8].

One way to predict human exposure to chemical migrants is by quantifying the amount of chemical migration. Migration experiments, which measure the amount of migrant transferred from the FCM into food, are accurate but costly, time consuming, and difficult to conduct on food products. As a result, regulatory bodies accept the use of recognised process-based migration models (PMM) as alternatives to testing. Such chemical migration models are

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not only used in a regulatory context, but also in high-throughput aggregate exposure predictions developed to prioritise human exposure to chemicals [9–11]. Pocas et al. [12], and more recently Gavriil, Kanavouras [13], reviewing migration models, concluded that PMMs are computationally complex, require measured chemical diffusion coefficients, and are applicable to a limited set of FCMs only.

Here, we developed a linear mixed-effects model (LMM) of chemical migration from packaging into food as a function of the properties of the food, chemical migrant, and FCM. LMMs can link measured chemical transfer to a number of relevant predictor variables, including chemical, food and packaging properties. LMMs are particularly useful to control for potential bias and correlation in the data available, e.g., from overrepresented packaging or food material [14]. This is a major advantage in the case of repeated measurements or hierarchical data, as it allows for accurate predictions despite the presence of correlated errors [15]. In various scientific domains, including ecology and atmospheric pollution research, LMM have shown high predictive performance and large applicability domains [16–18]. To our knowledge, LMMs have never been applied to predict the transfer of chemicals from food packaging materials into food. We compare our results with a recently developed PMM [19].

Methods

Chemical transfer fraction data

The specific fraction of chemical, also called migrant, transferred from the FCM, hereafter packaging, into food (F_C) was defined as shown in Eq. (1) [19].

$$F_C = \frac{m_{C, \text{food}}}{m_{C, \text{packaging}}} \quad (1)$$

Where $m_{C, \text{food}}$ represents the mass of the chemical in the food at the end of the migration experiment and $m_{C, \text{packaging}}$ the mass of the chemical present in the packaging at the beginning of the migration experiment. More information about how this measure of migration was derived is provided in the Supporting Information (SI, S1). The data used to derive F_C was accessed by Ernststoff et al. [19] and consisted of experimental outcomes reported to the US Environmental Protection Agency (US EPA). The database can be accessed upon request to Ernststoff et al. [19]; and more information on the database can be found at [20]. Overall, the database summarised 12,773 experimental results stemming from 127 different literature sources. We focused our analysis on food and food simulants, so that 572 data points representing non-food experiments or unclear food simulants were discarded. We also removed migration values reported for wax-coated paper and

PVC-PA-PVC-PU since it was not clear what type of material they described (51 data points). Further, 369 data points did not report the polymer's surface area or the polymer's thickness so that the F_C could not be calculated. We also discarded data that were considered to be clear outliers in the database. For example, experimental results with exposure times equal to 0 (19 data points), initial or final chemical masses equal to 0 (120 data points), and final masses higher than initial ones (79 data points). Our final database included 11,563 migration experiment results for 23 different food simulants and 94 different foods. All the experimental results included were from time-dependent migration experiments conducted on mono-layer polymeric packaging. Further details about the data cleaning procedure are provided in SI, S2, Tables S1, S2.

Predictor variables

We selected a number of predictor variables influencing migration and classified them in the following groups: (a) migrant properties, (b) food properties, (c) packaging material properties, and (d) differences in experimental design. When the study did not provide values for the properties of interest, we used literature values and assumptions to fill the data gap ($N = 3,277$). For example, we used food proxies or the indications of the EU Annex III [21] to assign specific fat contents to some of the data (e.g. heptane, a food simulant, was assigned the same value as olive oil) (SI, S3).

A final set of predictor variables was then selected based on their explanatory power, their correlation to the other variables, and the number of missing data (see S1, S4, Tables S3–S5, Figs. S1, S2 and Table 1). A total of 10,235 migration experiment results had information for all of the predictor variables chosen (see SI, S4 Tables S3–S5, Figs. S1, S2 for more details). In the final predictor set, the migrant's ability to transfer from packaging material into food is described by the molecular weight and the octanol-water partitioning coefficient as these are recurring drivers of migration in literature [22–28]. According to the European legislation, the food is best described by its pH and fat content so both were kept as predictor variables [29]. The crystallinity of the packaging as well as the ability of the migrant to dissolve in the packaging, the latter summarised as the total Hansen solubility, also influence migration (Table 1) [23, 24, 30, 31]. Finally, the experimental conditions, described by the temperature and contact duration time, can influence the migration modelling results: higher temperature and contact duration times are known to increase the fraction migrated [22, 23, 31–34]. Given the data availability and the current mechanistic knowledge on migration modelling, the predictor variables chosen are expected to describe most of the variability found in the database.

Table 1 Predictor variables considered for the modelling of the fraction of chemical transferred from packaging into food

Predictor variables	Importance in migration modelling
M Molecular weight	The lower the molecular weight, the smaller the molecule, the larger its diffusion into the food [1–4].
Octanol-Water partitioning coefficient (K_{OW})	Represents the lipophilicity of the migrant: the higher, the more lipophilic and therefore the more migration can be expected, given that the food has a high fat content [3, 5–7].
F Ethanol (EtOH) equivalency	The ethanol equivalency is a measure of the food's fat content [8]. Many migrants are lipophilic, thus the higher the fat content of the food, the higher the migration into the food [2, 5, 6, 9–11].
pH	Fang, Wang [12] found higher migration rates in acidic food.
P Crystallinity	The higher the degree of crystallinity, the lower the migration [2, 3, 9, 13].
Total Hansen solubility	The migration is likely to be lower when the solubility of the chemical in the polymer is high which can be quantified with the Hansen solubility [2, 3].
E Temperature	An increase in temperature increases the mobility of the migrant. Further it can lead to a swelling of the polymer and a decrease of its crystallinity thus creating more free space for the migrant [1, 2, 10, 13–15].
Duration of contact	The migration increases with prolonged contact between the packaging and the food [9, 10, 15, 16].

M stands for the migrant properties, F for food properties, P for packaging properties, and E for experimental design properties

Model fitting

We used LMMs to relate the log-transformed fraction of chemical transferred from the packaging into food with the predictor variables, also referred to as fixed effects. Chemical migration might be increasingly influenced under certain combinations of predictor variables, so we also included interactions in the model namely between: the experimental temperature and the duration [33], the migrant's molecular weight and the polymer's crystallinity, and the migrant's K_{OW} and the EtOH-equivalency of food. Further, we included a quadratic term for the experiment's duration to account for potential non-linear responses [34, 35]. The fraction of chemical transferred from the packaging was log-transformed (base 10 logarithm) to ensure normality in the model residuals, as were the migrant's K_{OW} , molecular weight, and the experiment's duration. In addition, the continuous variables were scaled for the model selection procedure.

LMMs allow to control for dependencies between experimental data or replicated experimental results using the so-called random effects [14]. The first step in the model selection procedure consisted of choosing the optimal random effects structure by comparing fitted models with the same full fixed effects structure and different random effects. The models were fitted with the restricted maximum likelihood method (REML). The random effect structure of the LMM with the smallest Bayesian Information criteria (BIC) value was kept [14]. It included the citation ID, analytical method, migrant, packaging, and food name nested in the EU food simulant categories [29, 36]. The second step was to fit all possible fixed effects structures with the maximum likelihood method, using the optimal random effects structure [14], and to choose the best fixed effects structure based on the lowest BIC value. Finally, the best LMM, with optimal random and fixed effects structure and used for inferences and predictions, was fitted using REML. The validity of the assumptions of normality, homogeneity, and independence was tested.

We assessed the best LMM's fit based on the marginal and the conditional R^2 (R^2_M and R^2_C), where R^2_M describes how much of the variability can be explained by the fixed effects of the best model, and the R^2_C by both the fixed and random effects [37]. The relative importance of the random effects was then quantified following Assink and Wibbelink [38], and for the fixed effects by comparing the changes in explained variance after randomising the values of each variable [39].

Predictive performance

The predictive performance of the best LMM was quantified using a fivefold block cross-validation (CV), with folds based on the random effect with the largest variation (migrant name) [40]. We used the coefficient of efficiency (CoE Eq. (2)) and the root mean squared error (RMSE, Eq. (3)) as predictive performance metrics.

$$\text{CoE} = 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i (y_i - \bar{y})^2} \quad (2)$$

$$\text{RMSE} = \sqrt{\frac{\sum_i (y_i - \hat{y}_i)^2}{N}} \quad (3)$$

With y_i being the measured migrated fraction, $\hat{y}_i$ the predicted migrated fraction, $\bar{y}$ the average of the measured migrated fractions, and N the number of observations. A CoE of 1 represents a perfect fit, while negative values indicate that the observed mean is a better predictor than the model. For the RMSE, the higher the value, the larger the difference between predicted and observed values, thus the poorer the fit.

The predictive performance of regression models can drop when predicting for random effect levels that were not included during model fitting. Given that we wanted to expand the applicability domain of our model to untested migrants, food types, and packaging materials, we assessed

the variation in the model's predictive performance for several scenarios:

- (1) an untested migrant,
- (2) an untested migrant in an unknown laboratory using another analytical method,
- (3) an untested migrant transferring to an untested food type in an unknown laboratory using another analytical method, and
- (4) an untested migrant present in an untested packaging transferring to an untested food type in an unknown laboratory using another analytical method.

Comparison with process-based model

The performance of the LMM was further assessed by comparing its predictive power to the PMM, recently developed by Ernstoff, Fantke [19]. This PMM incorporates mechanistic descriptions of the Fick's law of diffusion and chemical partitioning into a single equation describing the migrated fraction of chemicals. We used the PMM as published by Ernstoff et al. [19], including the implemented equations for the diffusion and packaging-food partitioning coefficients. The comparison of the LMM and PMM was based on two subsets of the US EPA database. Subset 1 consisted of 4,949 data points where measured diffusion coefficients were available, excluding the data points of the study named "Models for the Migration of Low Molecular Weight Additives in Polyolefins. National Bureau of Standards. Report NBSIR 81 e 2264, April 1981." because the reported diffusion coefficients represented clear outliers compared with the other reported values (SI, S5 Figs. S3, S4). Subset 2 included all data points for which the diffusion coefficients could be estimated ($N = 10,235$). The performance of the PMM was compared with the predictive performance of the LMM for an untested migrant in an unknown laboratory using another analytical method by comparing the coefficient of efficiencies and root mean squared errors of both models. Higher CoE and smaller RMSE mean a better predictive performance of the model considered. Further, we chose to consider all data points for which both models could be applied, disregarding the applicability domain of the PMM (meaning the requirement for K_{OW} and EtOH-equivalency values to be inside the range of empirical data used to derive the partitioning coefficient).

Results

Mixed-effects model

The final LMM included, as fixed effects, the experiment's duration (both linear and quadratic terms) and the

temperature, the crystallinity of the polymer, the ethanol equivalency of the food, and the migrant's molecular weight and K_{OW} . In addition, the interactions between the migrant's molecular weight and polymer's crystallinity, the migrant's K_{OW} and the food's EtOH equivalency, and the experiment's duration and temperature were also included. The formula describing the model is shown in Eq. (4). The ten models with lowest BIC are shown in the SI, Table S6.

$$\begin{aligned} \log(F_C) = & \log(MW_{\text{Migrant}}) + \log(KOW_{\text{Migrant}}) + \text{EtOH} - \text{eq}_{\text{Food}} \\ & + \text{Crystallinity}_{\text{Polymer}} + \text{Temperature} + \log(\text{Time}) \\ & + (\log(\text{Time}))^2 + \log(MW_{\text{Migrant}}) \text{Crystallinity}_{\text{Polymer}} \\ & + \log(KOW_{\text{migrant}}) \text{EtOH} - \text{eq}_{\text{Food}} + \text{Temperature} \\ & + \log(\text{Time}) + (1|\text{Name}_{\text{Migrant}}) + (1|\text{Name}_{\text{Polymer}}) \\ & + (1|\text{Food Simulant}/\text{Name}_{\text{Food}}) + (1|\text{Reference}) \\ & + (1|\text{Analytical Method}), \end{aligned} \quad (4)$$

where the superscript "2" stands for quadratic term, "1" denote the random effects, and "/" shows the nested structure of the random effects.

For the final model fitted to the entire dataset, the fixed effects accounted for 10.4% of the observed variability (R^2_m) while both random and fixed effects explained 93.5% (R^2_C). The model met the homogeneity and independence assumptions, with a slight deviation from normality for the extreme residuals, which had a small influence on the overall model fit (SI, S7, Tables S7, S8 Figs. S5–S11).

Amongst the random effects, the migrant's name contributed the most to the total variance (31.1%), followed by the citation ID (23.0%), the polymer name (22.7%), the food name and simulant category (11.8%), and the analytical method (4.1%).

Predictive power

The CV shows that the median CoE is 0.30 (standard deviation $SD = 0.18$) for the model predictions for chemicals not included in the database. Further excluding the citation ID and analytical method as prior information reduced the median CoE to 0.22 ($SD = 0.12$). Excluding also the food name in the prediction of the transfer fractions resulted in a median CoE of 0.09 ($SD = 0.30$). Finally excluding all random effects results led to a CoE of -0.11 ($SD = 0.51$). In other words, for predictions of unknown chemicals in known food products and/or packaging materials, the LMM has added value. However, model predictions for combinations of a new chemical, food item, and packaging material are likely to be worse than the average measured transfer fraction from the full dataset. Comparing the root mean squared error leads to the same conclusions (SI, S7, Fig. S11).

Transfer fraction relationships

From all fixed effects included in the model, the migrant's molecular weight and the experiment duration influenced the fraction migrated the most followed by the temperature and the EtOH equivalency of the food (SI, S7, Table S8). Overall, the fraction of chemical migrated increases with increasing experimental time and temperature (Fig. 1). For higher temperatures (above 75 °C), however, this relationship seems to plateau after experiment durations of 4 days. Figure 1 also shows that the fraction of chemical migrating from packaging into food increases with increasing EtOH-equivalency value, representing the fat content, of the food. The overall influence of the migrant's K_{OW} is rather small. Still, it can be seen that for food with higher EtOH equivalencies, a higher K_{OW} of the migrant implies an increase in migrated values (Fig. 1). On the contrary, food with EtOH equivalencies around 25% show a decrease in migration with increasing K_{OW} . A similar but less strong relationship applies for food with EtOH equivalencies around 50%. Finally, Fig. 1 illustrates that larger chemicals (molecular weight above approximately 400 g/mol) migrate more from packaging materials with low crystallinity values (45%) than packaging with high crystallinity values (65%). The opposite is true for chemicals with molecular weights below 400 g/mol. Overall, larger chemicals migrated less than smaller ones.

Comparison to process-based model

The coefficient of efficiency of the LMM derived here is always larger than the one for the PMM developed by Ernstoff et al. [19] (Fig. 2). The negative CoE of the PMM shows that its performance is worse than using the measured average of the data selected. This, therefore, shows that the LMM has a larger predictive power than the PMM. In addition, the applicability domain of the LMM is larger than that of the PMM. In fact, Fig. 2 highlights in blue the points outside the applicability domain of the PMM but within the one of the LMM.

The 90% confidence interval (CI) of the ten logarithm of the predicted migrated fraction from the deterministic model is ± 4.6 for measured diffusion coefficients, and ± 4.8 for modelled diffusion coefficients. For the LMM the 90% CI of the prediction is ± 1.4 and ± 1.5 for measured and modelled diffusion coefficients respectively.

Discussion

We showed that it is possible to predict the transfer of chemicals using a limited set of properties for the chemical migrant, food, and packaging material, combined with

Fig. 1 Relationship between the common logarithm of the chemical fraction migrated and the common logarithm of the experiment's time for three different temperatures (a), the common logarithm of the K_{OW} value for three different food ethanol equivalency values (b), and the common logarithm of the chemical's molecular weight for three different packaging crystallinities (c)

descriptors of experimental design by using a data-driven LMM approach. The LMM clearly has a better predictive performance compared with the PMM given the higher CoE and lower RMSE. Below, we compare our results with other findings in the literature.

Parameters influencing migration

From all the parameters kept in the LMM, the migrant's molecular weight influenced the migrated fraction the most. The K_{OW} , another predictor variable of the migrant's properties, was the least influential parameter. While the

Fig. 2 Scatterplots displaying the fraction migrated estimated with the deterministic model of Ernstoff et al. [19] compared with the linear mixed effects model without citation ID, analytical method and migrant name in the random effects for data points with measured

diffusion coefficients (**a**, **b**) and data points with estimated diffusion coefficients (**c**, **d**). The points shown in blue display the data points that are outside the applicability domain of the deterministic model of Ernstoff et al. [19]

importance of the molecular weight is supported by previous findings (e.g. Fang and Vitrac [22]), the small influence of the K_{OW} is more surprising given research stressing its importance in migration modelling [8, 49]. The primary explanation probably lies in the fact that the database includes results of migration in early stages, thus likely not capturing partitioning effects. It is, therefore, not possible to clearly state that migration is less influenced by the hydrophilic character of the migrant than the fat content of the food material it is in contact with. This is supported by the importance of the EtOH-equivalency of the food in the LMM. Another explanation could relate to the difference in partitioning behaviour between food and food simulants:

the K_{OW} might influence partitioning differently when food simulants are considered instead of food [23]. Further, the importance of the EtOH equivalency of the food also indicates that diffusion as well as partitioning influence the migration of chemicals from the FCM into the food. In fact, the food's fat content was shown to be one of the main drivers of the partitioning behaviour of migrants [23, 50].

Some of the relationships found with the LMM have also been described in previous studies. For example, in accordance with previous findings [22, 23, 28], the LMM shows an overall increase in the migrated fraction of molecules with lower molecular weights. Smaller molecules tend to have a larger ability to migrate than larger

ones [22–25]. While this relationship might not apply to all molecules, the LMM identified this general tendency across the 10,235 migration experiment results. The model also demonstrated that crystalline packaging materials were associated with lower migration values, which is in line with observations by, amongst others, Canellas, Aznar [24]. This is explained by the fact that crystalline materials have more ordered polymer structures, which will typically allow less movement of the migrants [51]. More interestingly, the LMM showed an interaction between the crystallinity of the packaging and the migrant's molecular weight. The higher the crystallinity, the larger the difference in migrated fraction between low and high molecular weight migrants. A potential explanation might be related to the swelling of the packaging which occurs when rather hydrophilic FCM is put into contact with food with a high water content [34]. One might argue that the swelling of FCM with higher crystallinity will impact on the migration of small migrants more than for an FCM with lower crystallinity, where parameters other than the available space are likely to influence migration more. So, while the swelling of the packaging was not directly represented by the predictors included in the LMM, the identified interaction between the crystallinity of the packaging and the migrant's molecular weight likely accounts for this behaviour. The LMM also showed that for fatty food (high EtOH equivalency), increased K_{OW} of the migrant, thus increased lipophilicity, meant increased migrated fractions. The positive relationship between K_{OW} and migrated fraction was also reported by Sanches-Silva et al. [28], Cai et al. [52]. Less attention is given in literature to the possible dependency of this relationship on the EtOH equivalency of the food. In fact, models considering both partitioning and diffusion processes usually include a directly positive relationship between migrated fraction and the food's fat content. The LMM accounts for this relationship, as well as taking into account that lipophilic migrants (higher K_{OW} values) will remain in the packaging (known to be rather lipophilic) rather than migrate when in contact with food with lower EtOH equivalencies (e.g. Kawamura et al. [53]). Finally, similarly to the PMM of migration, the LMM predicts an increase in the migrated fraction for higher temperatures and longer contact times. Higher temperatures imply higher diffusion rates for the migrant from the packaging into the food [22, 54], while longer contact times give chemicals a longer time-window to migrate [35, 55].

Explained variance

Most of the explained variance was captured by the random effects. Differences in how the studies were conducted, represented by the citation ID, explained an important share

of the total variance of the reported results (23.0%) as did the name of the migrant (31.1%) and packaging type (22.7%). These results indicate that even though great care was given to choose all of the potentially relevant parameters explaining migration, additional variables related to packaging, migrant characteristics, and experimental conditions might be necessary to model the migration from plastics into food more accurately. While the importance of citation ID probably simply reflects expected variabilities between different laboratories, or research groups, the importance of the migrant and packaging name will require more investigation. As a preliminary test, we assessed the performance of a model including additional molecular variables from chemo-informatics [56], which have been related to physico-chemical properties [57, 58], metabolic characteristics [59–61], and ecotoxicity values [62]. Including these predictor variables in the model selection procedure, only slightly improved the performance of our model (SI, S8, Tables S9, S10, Fig. S12). Considering the increased level of complexity implied when these predictors are added, we did not present this model in this work. We only considered 2D predictor variables while 3D variables, such as the Van der Waal's volume, can also be relevant (Fang and Vitrac [22], Vitrac et al. [63]).

The small share of variance explained by the food and food simulant category (11.8%) indicates that the identified relationships most likely apply invariably for both.

Unlike citation ID and migrant and packaging name, the analytical method explained a relatively low fraction of the total explained variance. (4.1%), suggesting that migration experiments conducted with any of the recognised analytical methods will lead to comparable results.

The model developed here is, to our knowledge, the first mixed-effects migration model estimating the fraction of migrants transferred from packaging into food. Our model outperforms the predictive accuracy of previous PMMs [19] independently of whether estimated or experimental diffusion coefficients are used. We also showed, that our LMM could be applied to a larger set of chemicals than the PMM developed by Ernststoff et al. [19], thus showing its larger applicability domain. Despite the careful choice of the predictor variables, the LMM is still a simplification of reality and might not capture all complex interactions. In addition, the performance of this LMM is also highly dependent on the a priori knowledge of the food and/or packaging tested. In fact, the model performed best when predicting the migrated fraction for packaging and food combinations for which experimental results were available in the database used for model fitting. As a result, the predictions of migrated fractions for new migrants of our LMM are most accurate whenever the packaging and food materials are known. While the prediction accuracy of the LMM is not high enough for application in packaging compliance or consumer protection purposes, this

model can be very useful when combined with prioritisation techniques for human exposure to chemicals. In fact, while for packaging compliance it is important to quantify in absolute terms whether a migration level is too high or not, such prioritisation relies on a comparative assessment of the migration in different packaging-food applications. In risk assessment, such a model is useful when screening packaging materials for potential health impacts as it can be applied quickly to a large set of packaging, migrants, and food types and could help refine dietary exposure models [64].

Code availability

All the analyses were carried out in R version 3.5.1 [41] using the following packages: *dplyr* and *reshape2* to rearrange the data [42, 43], *ggplot2* and *ggeffects* to generate the figures presented [44, 45], *lme4* to fit the models [46], *MuMIn* and *hydroGOF* to compute the goodness of fit measures [47, 48]. The code necessary to generate the models can be accessed upon request to the corresponding author.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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