Alcohol as a trigger of migraine attacks in people with migraine. Results from a large prospective cohort study in English-speaking countries

Marina Vives-Mestres PhD[1,2], Amparo Casanova MD PhD[1], Xavier Puig PhD[3], Josep Ginebra PhD[3], Noah Rosen MD[4]

[1] Curelator Inc., Cambridge, United States of America

[2] Departament d'Informàtica i Matemàtica Aplicada, Universitat de Girona, Girona, Spain

[3] Department of Statistics and Operations Research, Universitat Politècnica de Catalunya, Barcelona, Spain

[4] Northwell Health, New York, United States of America

Conflict of interest:

Marina Vives-Mestres and Amparo Casanova have received consulting fees from Curelator Inc. and hold stock options in Curelator Inc. Xavier Puig and Josep Ginebra have no conflict. Noah Rosen has served as an advisor and/or participated in speakers panel in Allergan, Biohaven, Eli Lilly and Lundbeck. He is section editor for Current Pain and Headache Reports and speaker for the American Headache Society.

Key Words: alcohol; headache; individual differences; migraine; mixed models; migraine trigger

Funding information:

This study was partially funded by Curelator, Inc. Curelator Inc. provided the data for this study.

Abbreviations:

EM: Episodic Migraine

ICHD-3: International Classification of Headache Disorders International (3rd Edition)

CI: Credibility Interval

Acknowledgements:

We would like to acknowledge Curelator Inc. for providing pseudonymized data.

Abstract

***Objective**:* To assess whether alcohol intake is associated with the onset of migraine attacks up to two days after consumption in individuals with episodic migraine.

***Background**:* Although alcohol has long been suspected to be a common migraine trigger, studies have been inconclusive in proving this association.

***Methods**:* This was an observational prospective cohort study among individuals with migraine who registered to use a digital health platform for headache. Eligible individuals were aged ≥18 years with episodic migraine who consumed alcohol and had tracked their headache symptoms and alcohol intake for ≥90 days. People who did not drink any alcohol were excluded. The association of alcohol intake (Yes/No) and of the number of alcoholic beverages in the two preceding days with migraine attack was assessed accounting for the presence of migraine on day-2 and its interaction with alcohol intake on day-2, and further adjusted for sex, age and average weekly alcohol intake.

***Results**:* Data on 487 individuals contributing 5,913 migraine attacks and a total of 40,165 diary days were included in the analysis. Presence of migraine on day-2 and its interaction with alcohol intake on day-2 were not significant and removed from the model. At the population level, alcohol intake on day-2 was associated with a lower the probability of migraine attack (OR[95% CI]=0.75 [0.68, 0.82]; event rate 1,006/4,679 (21.5%)), while the effect of alcohol intake on day-1 was not significant (OR[95% CI]=1.01 [0.91, 1.11]; event rate 1,163/4,679 (24.9%)), after adjusting for sex, age and average weekly alcohol intake. Similar results were obtained with the number of beverages as exposure.

***Conclusions**:* In this English-speaking cohort of individuals with episodic migraine that identified themselves as alcohol consumers, mostly low alcohol-dose consumers, there was no significant effect

on the probability of a migraine attack in the 24 hours following consumption, and a slightly lower likelihood of a migraine attack from 24 to 48 hours following use.

Introduction

Alcohol has been with human ancestors likely over a million years since primates began to eat fermenting fruit. Early Egyptian and Sumerian writings extoll the medicinal and dietary use of alcohol and evidence has been found of use dating back to 7000-6600 BCE.[1] The relationship between alcohol and headache was also described throughout history, however, the direct association with migraine took much longer to develop.[2] The concept of migraine being separate or different from other headaches took centuries to be established, with the scientific definition still being modified today.[3]

The International Headache Society currently classifies alcohol-induced headache as a secondary headache, and distinguishes immediate and delayed (or hangover) headache.[4] Some individuals see an immediate reaction to alcohol (within three hours from ingestion) with regards to stimulating a headache. More often, however, individuals experience a delayed effect of alcohol (5 hours or more after ingestion). In both cases, the headache resolves spontaneously within 72 hours.[45] People with migraine might find it difficult to distinguish between a migraine attack triggered by alcohol and a delayed alcohol-induced headache, as symptoms may overlap.[5] Moreover, no specific biomarkers have been found helpful in differentiating these conditions. Immediate alcohol-induced headache usually appears in people without migraine after consuming large amounts of alcohol, while smaller amounts may induce a migraine headache in persons with migraine.[4]

In this study we focused on alcohol as a potential trigger of migraine attacks within 24-48 hours after consumption. This delayed effect of alcohol on migraine attack onset may be much more difficult to ascertain by an individual. Consumption varies greatly between cultures, regions and between individuals, which may explain why different studies have found opposing results. An extensive review including twenty-two studies in migraine populations, in thirteen different countries, found that - overall- close to one-third of participants self-reported retrospectively alcohol (any type) as an occasional trigger and about 10% as a consistent trigger.[6] The prevalence of alcohol as a trigger of

migraine attacks estimated in prospective studies is lower.[7–9] One possible explanation is alcohol avoidance and/or low alcohol consumption in migraine populations.

The study of migraine triggers is complex. About 70% of people can identify a factor that is likely to predispose them to a migraine attack (triggers).[10] Among self-reported triggers there are endogenous events, like menses,[11] and exogenous events, like dietary factors[12] (including alcohol[6,13], chocolate[14,15], aspartame[16,17]), weather conditions[18,19] or air pollution[20,21]. Interventional studies to test whether a potential trigger is indeed a trigger are rare. Oftentimes individuals with migraine give up trying to figure out which of the multiple potential triggers reported in population-level analyses may apply to them and may decide to avoid some if they cannot confirm whether the event is a trigger for them, or cannot develop some coping strategy.

Given that alcohol is a part of the social lives of many people, it would be most helpful that study designs and analytical techniques that are specifically capable of identifying individuals for whom alcohol is indeed a trigger, and individuals for whom it is not, be implemented.

Individual-level analysis plays a very important role in the study of migraine-associated exposures.[22] Mixed effects models may be the method of choice to study the association between potential triggers/protectors and migraine attacks. They provide specific estimates of the exposure effect for each individual while making optimal use of population-level data.[23] This balance between expected norms for the population and the individuals' experience may provide a more tailored approach to the issue, and guidance for good self-care. In a recent individual-level analysis of the association between triggers and migraine attack onset among people with episodic migraine (EM), our group found that same-day alcohol consumption was associated with increased risk of an attack in less than 0.5% of drinkers.[9]

The objective of the present study is to explore the relationship between alcohol intake and risk of migraine attack onset at the individual level among people with EM who consume alcohol. We hypothesized that any alcohol intake, as well as number of alcoholic drinks, on a given day may be associated with the onset of migraine attacks during the day after consumption or up to two days after consumption, and the effect of the association may vary among individuals.

Methods

This is an observational prospective cohort study of individuals with migraine, who used a digital health platform (N1-Headache™) to prospectively track headache symptoms and risk factors daily.[24–26] After downloading the app and registering, participants answered baseline questionnaires which were used to customize the daily diary. Subsequently, they used the app to track daily headache symptoms and exposure to potential migraine risk factors. Participants could set a daily alert (by default set at 9PM). Daily self-monitoring entry took approximately 2-3 minutes.

Participants Selection and Characteristics

Participants registered to use the platform through physician referral, via the website or the App Store between October 2014 and March 2018 were eligible. At the time of the study, the app was only available to users of iOS.

Inclusion criteria were: 1) aged ≥18 years 2) who tracked their symptoms and factors daily for 90 days within 120 calendar-days, 3) with migraine who did not meet the International Classification of Headache Disorders (3rd Edition, ICHD-3) diagnostic criteria for chronic migraine during the study period,[4] and 4) stated at registration that they consumed alcohol. Eligible participants were excluded if they stated that they drank alcohol but never tracked its consumption. Note that individuals who

did not meet ICHD-3 criteria for chronic migraine during the study period might have met it outside the studied period or have it successfully in remission or under control with treatment.

At that time the App was only available in English.

IRB Approval and Subject Consent

Individuals gave consent to their anonymized data being collected and analyzed for research purposes, by agreeing to the Curelator Inc. Terms and Conditions and Privacy Policy.[27] The Biomedical Research Alliance of New York (BRANY) IRB granted full waiver from informed consent on 10 October 2019.

Data collection and measures

At registration, participants recorded sex and date of birth. Females and other genders were asked about their menstrual cycles: regular, menopausal, post-menopausal or amenorrheic. Age was calculated from date of birth, and categorized into [18, 30], (30, 50] and >50 years old.

This study's two main exposures were daily alcohol consumption ("Yes/No") and total daily number of alcoholic beverages. Participants' alcohol consumption and regular frequency was determined at registration with the question "How often do you drink alcoholic beverages?", with possible answers "never/ sometimes/ often". If they answered "never" then no further alcohol-related questions were included in the daily questionnaire. Otherwise, the following "Yes/No" question was asked daily: "Did you drink alcohol?". If they answered Yes then they were asked about types and number of alcoholic drinks intaken: glasses of red wine, white wine, sparkling wine and spirits, and number of beers. Total

number of daily alcoholic beverages (all types) was computed and categorized into 0, 1, 2, 3, 4, 5 or more.

The primary outcome in this study was the first day of each migraine attack. A migraine attack was defined as a series of consecutive migraine days. A new attack could only start if there was a non-migraine day between two migraine days. In the baseline questionnaire, participants indicated the type(s) of headache(s) they believe they experienced. Those indicating migraine were asked whether a physician had diagnosed it. Each recorded headache was classified as migraine or "other headache" based on daily recorded symptoms using an algorithm following the ICHD-3 criteria.[4] A migraine day with aura was defined as a day during which the participant reported experiencing an aura, regardless of whether or not it was followed by a headache. A definite migraine day was defined as a headache day fulfilling ICHD-3 criteria B (headache duration), C (headache characteristics) and D (associated symptoms of migraine without aura). The definition of a day with "probable migraine" was similar except that either criterion C or D could be lacking, or the episode could have lasted 2-4 hours and been treated with acute medication for headache. Both probable and definite migraine days with and without aura were labeled as migraine days in this analysis.

Statistical methods

Descriptive statistics were used to summarize baseline participant characteristics and alcohol consumption. For alcohol intake behavior, weekly statistics were calculated using natural weeks composed of five or more tracked days. In those weeks, weekly alcohol consumption (number of days with any consumption and number of alcoholic beverages) was calculated assuming zero consumption during missing days (≤2 days per week). Means (standard deviations, SD) were used to describe normally distributed data, medians [25th, 75th] for ordinal or skewed data, and proportions

(percentages) for categorical or ordinal data. Percentiles and standard deviation of the number of daily alcoholic drinks (all types and by type of alcoholic drink) were calculated over all person-days, within-person means, and within-person standard deviations. Mean differences between two groups were assessed using independent samples t-tests with Welch correction, and differences in percentages were analyzed using Chi-square tests. Spearman correlation was used to describe the relationship between numerical variables. Where appropriate, all hypotheses are two-tailed with $p<0.05$ interpreted for statistical significance.

Migraine attack onset was modeled as a binary outcome; migraine days after the first day of attack were removed from the analysis. Logistic (logit-normal) models were used to estimate an individual's probability of having a migraine attack on a given day and its association with alcohol intake up to two previous days (day-1 and day-2). Random intercepts by subject and random slopes in day-1 and day-2 alcohol-intake covariates were included. Random effects allow for individual differences in daily migraine attack risk and in the effect of alcohol consumption on the risk of migraine attack onset. The initial model also included the presence of migraine on day-2 and its interaction with alcohol intake on day-2 to account for the possible effect of a migraine headache on how alcohol intake may affect migraine onset in the following days.[28] Sex, age (categorical) and average weekly alcohol intake (categorized into 0, [1,7) and $\geq$7 units) were used as adjustment covariates.[29] Non-significant terms would be removed from the initial model (called Model 1) leading to the simplest, final model (Model 2). See Appendix 1 for model specifications. The same modeling strategy was applied to build another model with total daily number of alcoholic beverages (for both day-1 and day-2) as the main exposure, leading to a final model (Model 3).

Bayesian statistics were used for model parameters estimation using Markov Chain Monte Carlo (MCMC) simulation with non-informative prior distributions (fixed effects were assumed to follow a Normal distribution with mean 0 and variance 1000, and the variances of the random effects were

assumed to follow an inverse Gamma distribution with mean 1 and variance 100). Chain convergence was assessed through visual inspection of the sample traces and by monitoring diagnostic measures, like their sample autocorrelations and the R-hat.[30] Two chains were run until convergence, discarding the first 50,000 iterations of each chain and keeping one out of ten iterations afterwards. The final analysis was therefore based on 20,000 realizations, 10,000 from each chain. Plots of iterations vs. sampled values for each variable were inspected to check model convergence. Instead of confidence intervals, Bayesian statistics calculates Credibility Intervals (CI) on the basis of the posterior probability distribution, and they are defined as the range of values within which an unobserved parameter value falls with a particular probability, e.g. 95%. Hereafter CI refers to Credibility Interval. A parameter is considered statistically significant when zero does not belong to the 95% credibility interval. Observations with missing information in any of the independent variables were handled with listwise deletion, that is, only complete cases were used for parameter estimation.

Given the observational, post-hoc nature of this study there was no a priori statistical power calculation used to guide sample size, all eligible available data were analyzed (90 days per individual in 487 individuals). Houle et al. (2021) showed that forecasting models using Bayesian methods in N=95 individuals yield reliable estimates after 45 daily measurements, even when using very weak informative priors, the way we did, and suggested that models may further improve with longer observation periods.[31]

All analyses were performed using R version 3.4.3 (2017-11- 30).[32] Bayesian estimation was performed with JAGS (Just Another Gibbs Sampler)[33] through the R package R2jags.[34]

Data Availability Policy

Anonymized data will be made available to qualified researchers on written request to the investigators.

Results

A total of 7,877 people with migraine registered to use the headache app from October 2014 to March 2018. Among these, 787 were ≥18 years old who had tracked ≥90 days with ≥75% adherence. Of these, 651 met criteria for EM retrospectively, and 493 reported drinking alcohol. Further 6 individuals were excluded because they never tracked alcohol consumption. The final sample size was 487 individuals. who contributed data on 43,830 diary days, from which 9,578 were migraine days and 5,913 were the first days of a migraine attack.

Subject sociodemographics

Table 1 summarizes participants' demographics. The majority were female (419/487, 86.0%), actively working (293/378, 77.5%). The mean age (SD) was 42.4 (12.2) years. Most of the females had regular menstrual cycles (247/419, 58.9%). Individuals contributed a mean (SD) of 6.1 (3.3) migraine days per month and 3.7 (1.7) migraine attacks per month.

Table 1: Demographic data for the sample (n = 487).

Variable alcohol intake had 10.6% missing values on day-1 and 11.6% on day-2; migraine on day-2 was missing in 7.4%. Same-day alcohol intake (Yes/No), and quantity of each type of alcoholic drink had 4.7% missing values.

Alcohol intake behavior

Out of 487 individuals who reported alcohol consumption at registration, 59 (59/487, 12.1%) indicated that they consumed “a lot”, and the remainder consumed “some”. During 90 days, the average number of drinks per week was <1 in 132 (132/487, 27.1%) individuals, between [1, 7) in 289 (289/487, 59.3%) and ≥7 in 66 individuals (66/487, 13.6%).

Table 2 shows alcohol consumption overall and by sex. Consumption differed by sex in both frequency and quantity: the median daily and weekly number of alcoholic beverages drunk were higher in men compared to women; there were more men having ≥7 drinks per week; similarly, men consumed alcohol on significantly more days per week (all p-values <0.001).

Table 2: Alcohol consumption overall and by sex

People with lower migraine frequency consumed more alcohol: the correlation between the average monthly migraine (headache) frequency and the average weekly drinks was -0.28 (-0.22).

Individuals mostly drank alcohol on non-migraine days (85.4%, 9,332/10,928) while they drank alcohol on 17.4% of migraine days (17.4%, 1,596/9,163). Fifty percent of individuals consumed ≤3 different types of alcoholic drinks (out of the 5 asked types) during the 90 days (interquartile range=2-4). Beer was intaken at least once by 311 individuals (311/487, 63.9%), red wine by 265 (256/487, 52.6%), white wine by 358 (358/487, 73.5%), sparkling wine by 255 (255/487, 52.4%) and spirits by 370 (370/487, 76.0%).

Table 3: Distribution of daily alcoholic beverages consumption (total daily quantity and by type of alcoholic drink) for: all person-days, within-person means, and within-person standard deviations.

Table 3 shows the distribution of daily alcoholic beverages consumption. Overall, consumption was very low.

Association between alcohol intake and migraine attack

The total number of follow-up days was 46,820. There were a total of 2,990 embedded missing days (6.4%, 2,990/46,820) resulting in 43,830 days (90 for each individual) eligible for analysis. Migraine days after the first day of attack (3,665 migraine days) were removed from the models leading to a dataset with 40,165 diary entries. The embedded missing days, as well as incomplete entries during tracked days, resulted in 7,254 day-cases with missing values (7,254 /40,165, 18.1%) in one or more of the independent variables, which were further removed from the analysis. Missing days were observed more often during weekends (15.9% and 16.2% of the 7,254 missing days occurred on Saturday and Sunday, respectively, compared to 14.3% missing on Mondays, 13.1% on Tuesdays, 13.7% on Wednesdays, 13.4% on Thursdays and 13.4% on Fridays). A total of 32,911 complete cases including 4,679 migraine attacks were analyzed.

Model 1 was estimated (Table 4) with no convergence issues. Neither the interaction term nor the presence of migraine on day-2 were significant and they were removed (one at a time) from the final model (Model 2). No convergence issues were identified in Model 3 (neither in the full nor in the simplified, final model).

Table 4: Results of the logistic regression models of the log odds of migraine attack in relation to alcohol consumption.

Table 4 shows that, at a population level, the probability of a migraine attack two days after alcohol intake was 25% lower compared to the probability of an attack two days after no alcohol consumption (OR = 0.75, 95% CI = 0.68-0.82, event rate 21.5% (1,006/4,679)) while the effect of alcohol intake on day-1 was not significant (OR = 1.01, 95% CI = 0.91-1.11, event rate 24.9% (1,163/4,679)), after adjusting for sex, age and average number of alcoholic beverages per week. In the adjusted model,

the higher the average number of alcoholic beverages the individual consumed per week during the study period, the lower the probability of having a migraine attack (17% lower for those drinking [1,7) vs [0,1) and 27% lower for those drinking ≥7 vs [0,1)). This was consistent with the descriptive statistics on the migraine frequency by average weekly alcoholic beverages intake. Sex and age had no significant effect. In the model with the total daily number of alcoholic beverages as covariates (Model 3), the number of beverages on day-1 also had no significant effect, while the probability of a migraine attack was 12% lower for each unit-increase in the number of beverages on day-2 (OR = 0.88, 95% CI = 0.84-0.92). These results were consistent with the binary alcohol intake model.

Mixed models obtain the differences between each individual effect and the population estimates, thus estimates from Table 4 can be adjusted to provide an individualized model for each user. Figure 1 shows the results of the predicted probabilities (median and 95% CI) of migraine attack for each of the 487 individuals.

Figure 1: Individual probability of migraine attack (median and 95% CI) under four scenarios: A) No alcohol consumption on either the day before (day-1) or two days before (day-2), "No/No", B) Alcohol consumption on day-1 but not on day-2, "Yes/No", C) Alcohol consumption on day-2 but not on day-1, "No/Yes" and D) Alcohol consumption on both days, "Yes/Yes". Individual probabilities are estimated from a Bayesian model with the following covariates: fixed and random intercept, fixed and random day-1 alcohol intake and day-2 alcohol intake, and adjusted for sex, age, and average weekly alcohol consumption.

Figure 1A shows the individual probabilities of migraine attack, when no alcohol was consumed on neither day-1 nor day-2. Red dots represent median individual probability, and vertical lines represent the individual 95%CI. These probabilities (red dots) serve as reference in the other three figures. Figure 1C shows the median (blue dots) and 95%CI of the individual probability of migraine attack onset when

individuals consumed alcohol on day-2 but no alcohol on day-1; blue dots lay below red dots, which indicate a lower probability of migraine attack two days after alcohol consumption (with respect to no consumption). When there was alcohol intake on day-2 (regardless of intake on day-1, Figures 1C and 1D) the probability of migraine attack was lower compared to when there was no alcohol intake in both day-1 and day-2 (red dots). On the other hand, the probability of migraine attack when there was no intake on day-2 was similar regardless of whether there was alcohol intake on day-1 (Figures 1A and 1B).

Figure 2 shows data on two individuals selected at random among those who tracked more than 600 days. In each case, individual predicted probabilities are compared to the population predictions (in purple) after updating Model 2 to account for all available tracked data for each individual (not only the first 90 tracked days).

Figure 2: Individual probability of migraine attack (median and 95% CI) corresponding to two individuals selected at random among participants who tracked ≥600 days. Individual probabilities are estimated using a Bayesian model and all available tracked days, with the following covariates: fixed and random intercept, fixed and random day-1 (day before) alcohol intake and day-2 (two days before) alcohol intake, and adjusted for sex, age, and average weekly alcohol consumption. Scenarios are defined according to alcohol consumption on day-1 and on day-2.

Discussion

The relationship between alcohol use and migraine is complicated. Its use differs tremendously cross-culturally and has meaningful social, religious and economic associations. In this prospective observational study of 487 mostly English-speaking females with EM who consumed low doses of alcohol, and used a digital health platform to track their headache symptoms and factors, we found that alcohol intake appears to have no effect on the probability of an attack on the next day, after

adjusting for sex, age and average number of alcoholic beverages consumed per week. There was a statistically significant decrease in the probability of an attack two days after consumption on average. A model including number of alcoholic beverages instead of simply alcohol consumption (Yes/No) led to the same conclusions. Even though the statistical model did not include medication use, since the participants reported taking relief medication only in 8.5% (501/5,913) of the 5,913 migraine attacks considered in this analysis (data not shown) we may conclude that this finding was also independent of any attempt to prevent or treat the headaches more acutely.

Most individuals self-reported moderate use of alcohol at registration (428/487, 87.9%) and a low number of a range of different beverages were consumed during the study (as previously reported).[6,35,36] Alcohol was consumed more among people with lower migraine frequency, and consumption occurred more often during non-migraine days. This inverse relationship has been consistently shown in previous population-based studies.[37,38] One may argue that patients with migraine might be avoiding alcohol if they believe it triggers their attacks. In a recent study of the mechanisms of alcohol-induced headache, however, Panconesi presents counter-arguments in favor of lower consumption being a personal choice.[37,39] One of the arguments is that, in a large study of patients with migraine, only 3% of those who did not drink alcohol reported that the reason was that alcohol triggered their attacks.[40] An additional argument was that the percentage of individuals who never or seldom consumed alcohol was higher among people with both migraine and non-migraine headache types when compared to patients without migraine.[38,41] In this study we combined definite and probable migraine as the primary outcome: there were 4.6% (215/4,679) of migraine attacks that had been classified as probable migraine and were preceded by alcohol intake within 12 hours from onset. In the present cohort, a separate study on self-reported triggers showed that no individuals identified alcohol as the only trigger of their headaches suggesting none of these events represented hangover headache alone. Despite not being able to capture data on the immediate response to alcohol consumption due to the daily resolution of the questionnaire, we were able to look at various

time points following the initial use of alcohol. Alcohol appears to be related to different risks of migraine depending on how distant temporally the use occurred.

This study has several strengths. First, to our knowledge, this is the largest study to examine self-reported alcohol consumption in relation with migraine attack onset in this population (>30,000 diary entries analyzed). This included a cross-cultural population, although all spoke English, representing social differences in alcohol use. Second, we applied the gold-standard criteria to define the primary outcome, using a validated algorithm reflecting the ICHD-3 definition of migraine. Third, we employed robust statistical modeling techniques to estimate the effect of alcohol consumption on migraine attack onset. We used Bayesian statistics for parameter estimation and included random effects to allow for individual differences in their daily migraine attack risk and for individual differences in the effect of alcohol consumption. In addition to population-level estimates, we were able to compute individual probabilities of migraine attack onset based on alcohol consumption on day-1 and/or day-2, with very high accuracy in many cases (the higher the number of days tracked, the higher the accuracy). The models were assessed for potential confounding: migraine presence on day-2, weekly average alcohol consumption, age and sex.

This analysis also has several limitations which suggest areas that require further research and delineation. Units of alcohol consumption were not collected in a standardized manner and may differ in cross-cultural use, therefore we were not able to standardize the number of alcoholic drinks according to type of alcohol or accurately estimate the actual dose of ethanol. Other observational studies in people with migraine have taken a similar approach, which seems appropriate given the low alcohol consumption in this population.[28,35] The measure of alcohol consumption used in this study has not been formally validated or psychometrically tested for reliability. However, self-reports of drinking show adequate reliability and validity when the assessment situations are structured to minimize bias, which is the case of the N1-Headache™ app by 1) ensuring anonymity and confidentiality, 2) minimizing recall bias through prospective daily data collection and 3) giving clear

and simple instructions regarding data to be reported.[42] Although similar measures have been used in prior published work[35] results may have differed if a validated measure was used in its place. Furthermore, alcohol consumption on the same day (of the outcome analysis) was not included, since the exact time of intake was not collected, and it was not possible to determine whether migraine onset was before or after alcohol intake on the same day. However, by assessing the effect of day-1 consumption we expect to have captured the potential effect of alcohol within 12 hours of intake in many instances (if it occurred in the evening of day-1). This may not capture individuals who experienced a rapid onset of headache following alcohol use, particularly if it had occurred in the morning. Third, we excluded people who do not consume alcohol, and we were not able to assess whether the reason for abstaining from alcohol is related to their belief that alcohol may trigger their migraine attacks and accounts for a separate phenotype from the rest of the analyzed sample. However, based on previous reports we expect the number of people for whom this belief was the reason for not drinking to be very small.[40] We assessed the differences between the (excluded) nondrinkers and the analysis sample to explore possible bias (data not shown). We found a higher frequency of migraine and headache attacks among those who do not drink ($p<0.001$, $p=0.004$, respectively), which is consistent with other similar studies. Furthermore, excluded individuals had greater disability ($p=0.024$) and were more likely to come from the US ($p=0.015$). Another limitation is that there were a total of 18.1% missing entries. Participants skipped data entry more often during weekends (approximately 16% of missing entries occurred during Saturdays and also Sundays, compared to approximately 14% each of the weekdays). This may have caused under-reporting of both alcohol consumption and headache. Finally, included individuals were only iOS users with frequent phone use who have a more severe disability than would be expected at least in the US;[43] this study sample has more than 80% of users who self-report having a doctor diagnosis, which may impact the generalizability of our findings. Moreover, prior research has shown that people with migraine who are adherent with completing daily data entry in the N1-Headache™ application are not representative of the general population of people with migraine.[24]

In conclusion, the results of this large multicultural, English-speaking cohort of people with migraine and that consumes low doses of alcohol suggest that the role of alcohol as a migraine trigger might have been overestimated. Our findings do not support recommending alcohol avoidance to all people with migraine. Finally, looking as to whether any other associated behaviors may increase or decrease the risk of migraine in association with alcohol may also give us further insight into the complexities of this condition and better ways to help direct care.

References

1. McGovern PE, Zhang J, Tang J, Zhang Z, Hall GR, Moreau RA, et al. Fermented beverages of pre- and proto-historic China. *Proc Natl Acad Sci U S A*. 2004;101(51):17593–17598.
2. Susruta, Translated by Prof.Murthy Srikantha K.R. Illustrated Susruta samhita. Varanasi. Vol. 3. India: CHAUKHAMBHA ORIENTALIA; 2007.
3. Goadsby PJ, Evers S. International Classification of Headache Disorders - ICHD-4 alpha. *Cephalalgia*. 2020;40(9):887–888.
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1–211.
5. García-Azorín D, Aparicio-Cordero L, Talavera B, Johnson A, Schytz HW, Guerrero-Peral ÁL. Clinical characterization of delayed alcohol-induced headache: A study of 1,108 participants. *Neurology*. 2020;95(15):e2161–e2169.
6. Panconesi A. Alcohol and migraine: Trigger factor, consumption, mechanisms. A review. *Journal of Headache and Pain*. 2008;9(1):19–27.
7. Wöber-Bingöl C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P. Prospective analysis of factors related to migraine attacks: The PAMINA study. *Cephalalgia*. 2007;27(4):304–314.
8. Leone M, Vila C, McGown C. Influence of trigger factors on the efficacy of almotriptan as early intervention for the treatment of acute migraine in a primary care setting: The START study. *Expert Rev Neurother*. 2010;10(9):1399–1408.
9. Casanova A, Vives-Mestres M, Donoghue S, Mian A, Martin PR. An observational study of self-reported migraine triggers and prospective evaluation of the relationships with occurrence of attacks enabled by a smartphone application (App). *Headache: The Journal of Head and Face Pain*. 2022;00:1–10.
10. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia*. 2007;27(5):394–402.
11. Goldberg J, Wolf A, Silberstein S, Gebeline-Myers C, Hopkins M, Einhorn K, et al. Evaluation of an electronic diary as a diagnostic tool to study headache and premenstrual symptoms in migraineurs. *Headache: The Journal of Head and Face Pain*. 2007;47(3):384–396.
12. Finocchi C, Sivori G. Food as trigger and aggravating factor of migraine. *Neurological Sciences*. 2012;33:77–80.
13. Nicolodi N, Sicuteri F. Wine and migraine: compatibility or incompatibility? *Drugs Exp Clin Res*. 1999;25(2–3):147–153.
14. Lippi G, Mattiuzzi C, Cervellin G. Chocolate and migraine: The history of an ambiguous association. *Acta Biomed*. 2014;85(3):216–221.
15. Marcus DA, Scharff L, Turk D, Gourley LM. A double-blind provocative study of chocolate as a trigger of headache. *Cephalalgia*. 1997;17(8):855–862.
16. Schiffman SS, Buckley CE, Sampson HA, Massey EW, Baraniuk JN, Follett JV, et al. Aspartame and Susceptibility to Headache. *New England Journal of Medicine*. 1987;317(19):1181–1185.
17. Lipton RB, Newman LC, Cohen JS, Solomon S. Aspartame as a Dietary Trigger of Headache. *Headache: The Journal of Head and Face Pain*. 1989;29(2):90–92.
18. Piorecky J, Becker WJ, Rose MS. Effect of chinook winds on the probability of migraine headache occurrence. *Headache*. 1997;37(3):153–158.

19. Lipton RB. Fair winds and foul headaches. *Neurology*. 2000;54(2):280–280.
20. Szyszkowicz M, Stieb DM, Rowe BH. Air pollution and daily ED visits for migraine and headache in Edmonton, Canada. *American Journal of Emergency Medicine*. 2009;27(4):391–396.
21. Li W, Bertisch SM, Mostofsky E, Buettner C, Mittleman MA. Weather, ambient air pollution, and risk of migraine headache onset among patients with migraine. *Environ Int*. 2019;132.
22. Peris F, Donoghue S, Torres F, Mian A, Wöber C. Towards improved migraine management: Determining potential trigger factors in individual patients. *Cephalalgia*. 2017;37(5):452–463.
23. Lipton RB, Pavlovic JM, Haut SR, Grosberg BM, Buse DC. Methodological issues in studying trigger factors and premonitory features of migraine. *Headache*. 2014;54(10):1661–1669.
24. Seng EK, Prieto P, Boucher G, Vives-Mestres M. Anxiety, Incentives, and Adherence to Self-Monitoring on a Mobile Health Platform: A Naturalistic Longitudinal Cohort Study in People With Headache. *Headache*. 2018;58(10):1541–1555.
25. Vives-Mestres M, Casanova A, Buse DC, Donoghue S, Houle TT, Lipton RB, et al. Patterns of Perceived Stress Throughout the Migraine Cycle: A Longitudinal Cohort Study Using Daily Prospective Diary Data. *Headache*. 2021;61(1):90–102.
26. Vives-Mestres M, Casanova A, Hershey AD, Orr SL. Perceived stress and pain severity in individuals with chronic migraine: A longitudinal cohort study using daily prospective diary data. *Headache*. 2021;61(8):1245–1254.
27. N1-Headache. Privacy Policy [Internet]. [cited 2022 Mar 4]. Available from: https://n1-headache.com/privacy-policy/
28. Turner DP, Lebowitz AD, Chtay I, Houle TT. Headache Triggers as Surprise. *Headache*. 2019;59(4):495–508.
29. Smyth A, Teo KK, Rangarajan S, O'Donnell M, Zhang X, Rana P, et al. Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: A prospective cohort study. *The Lancet*. 2015;386(10007):1945–1954.
30. Gelman A, Rubin DB. Inference from Iterative Simulation Using Multiple Sequences. *https://doi.org/101214/ss/1177011136*. 1992;7(4):457–472.
31. Houle TT, Deng H, Tegeler CH, Turner DP. Continuous updating of individual headache forecasting models using Bayesian methods. *Headache*. 2021;61(8):1264–1273.
32. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2021.
33. Plummer M. JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling. *Proceedings of the 3rd international workshop on distributed statistical computing*. 2003;124(125.10):1–10.
34. Su Y-S, Yajima M. R2jags: Using R to run "JAGS". R package version 0.7-1. 2021.
35. Holsteen KK, Hittle M, Barad M, Nelson LM. Development and Internal Validation of a Multivariable Prediction Model for Individual Episodic Migraine Attacks Based on Daily Trigger Exposures. *Headache*. 2020;60(10):2364–2379.
36. MJ M. Triggers, Protectors, and Predictors in Episodic Migraine. *Curr Pain Headache Rep*. 2018;22(12).
37. Panconesi A, Bartolozzi ML, Guidi L. Alcohol and migraine: What should we tell patients? *Curr Pain Headache Rep*. 2011;15(3):177–184.

38. Le H, Tfelt-Hansen P, Skytthe A, Kyvik KO, Olesen J. Association between migraine, lifestyle and socioeconomic factors: A population-based cross-sectional study. *Journal of Headache and Pain*. 2011;12(2):157–172.
39. Panconesi A. Alcohol-induced headaches: Evidence for a central mechanism? *J Neurosci Rural Pract*. 2016;7(2):269–275.
40. Panconesi A, Franchini M, Bartolozzi ML, Mugnai S, Guidi L. Alcoholic drinks as triggers in primary headaches. *Pain medicine*. 2013;14(8):1254–1259.
41. Kurth T, Schürks M, Logroscino G, Buring JE. Migraine frequency and risk of cardiovascular disease in women. *Neurology*. 2009;73(8):581–588.
42. Del Boca FK, Darkes J. The validity of self-reports of alcohol consumption: state of the science and challenges for research. *Addiction (Abingdon, England)*. 2003;98 Suppl 2(SUPPL. 2):1–12.
43. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343–349.

Table 1: Demographic data for the sample (n = 487).

	Mean (SD) or n (%)
Age (years)	42.5 (12.2)
Sex – female	419 (86.0)
Employment status¶	
Employed	261 (69.0)
Self-employed	32 (8.5)
Homemaker	28 (7.4)
Student	23 (6.1)
Retired	16 (4.2)
Other	18 (4.8)
Country	
United States	192 (39.4)
Great Britain	172 (35.3)
Other	123 (25.3)
Migraine diagnosed by doctor§	431 (88.7)
Migraine years¶¶§	20.6 (13.0)
Average pain level (rated on a 0-10 scale)§	6.0 (1.8)

Headache days/month	9.3 (4.2)
Migraine days/month	6.1 (3.3)
Migraine attacks/month	3.7 (1.7)
Disability $\oint$	
MIDAS Grade I	42 (8.6)
MIDAS Grade II	39 (8.0)
MIDAS Grade III	91 (18.7)
MIDAS Grade IV	314 (64.6)

¶ Available in n=378

¶¶ Available in n=251

$\oint$ self reported at registration

Table 2: Alcohol consumption overall and by sex.

	Overall (n=487)	Female (n=419)	Male (n=68)
Daily drinks (median, Q1-Q3)	0.3 (0.1-0.7)	0.3 (0.3-0.7)	0.6 (0.2-1.2)
Weekly drinks (median, Q1-Q3)	2.1 (0.8-4.8)	1.9 (0.8-4.3)	3.4 (1.2-7.7)
Average drinks intaken per week (n, %)			
[0, 1)	132 (27.1)	118 (28.2)	14 (20.6)
[1,2)	101 (20.7)	93 (22.2)	8 (11.8)
[2,3)	66 (13.6)	56 (13.4)	10 (14.7)
[3,4)	42 (8.6)	39 (9.3)	3 (4.4)
[4,5)	31 (6.4)	26 (6.2)	5 (7.4)
[5,6)	30 (6.2)	27 (6.4)	3 (4.4)
[6,7)	19 (3.9)	15 (3.5)	4 (5.9)
$\geq$7	66 (13.6)	45 (10.7)	21 (30.9)
Days per week with intake (median, Q1, Q3)	1.3 (0.6-2.4)	1.2 (0.5-2.2)	2.2 (0.9-4.0)
Alcohol intake in $\geq$50% of days (n, %)	60 (12.3)	39 (9.3)	21 (30.9)

Note: all comparison tests p-value<0.001

Table 3: Distribution of daily alcoholic beverages consumption (total daily quantity and by type of alcoholic drink) for: all person-days, within-person means, and within-person standard deviations.

All person-days									
Variable	Units	5th	10th	25th	50th	75th	90th	95th	SD
Alcoholic beverages	drinks	0	0	0	0	1	2	3	1.2
Beer	beers	0	0	0	0	0	0	1	0.7
Red wine	glasses	0	0	0	0	0	0	1	0.4
White wine	glasses	0	0	0	0	0	0	1	0.6
Sparkling wine	glasses	0	0	0	0	0	0	0	0.4
Spirits	glasses	0	0	0	0	0	0	1	0.6
Within-person means									
Alcoholic beverages	drinks	0	0	0.1	0.3	0.8	1.3	1.8	0.6
Beer	beers	0	0	0	0	0.1	0.4	0.6	0.3
Red wine	glasses	0	0	0	0	0.1	0.2	0.5	0.2
White wine	glasses	0	0	0	0	0.2	0.4	0.6	0.3
Sparkling wine	glasses	0	0	0	0	0	0.1	0.2	0.1
Spirits	glasses	0	0	0	0	0.2	0.3	0.4	0.2
Within-person standard deviations									
Alcoholic beverages	drinks	0.1	0.2	0.4	0.7	1.2	1.7	2.0	0.6
Beer	beers	0	0	0	0.2	0.5	0.8	1.1	0.5
Red wine	glasses	0	0	0	0.1	0.4	0.6	0.8	0.3
White wine	glasses	0	0	0	0.2	0.5	0.8	1.1	0.4
Sparkling wine	glasses	0	0	0	0.1	0.3	0.6	0.8	0.3
Spirits	glasses	0	0	0	0.2	0.6	0.9	1.2	0.4

*SD: standard deviation

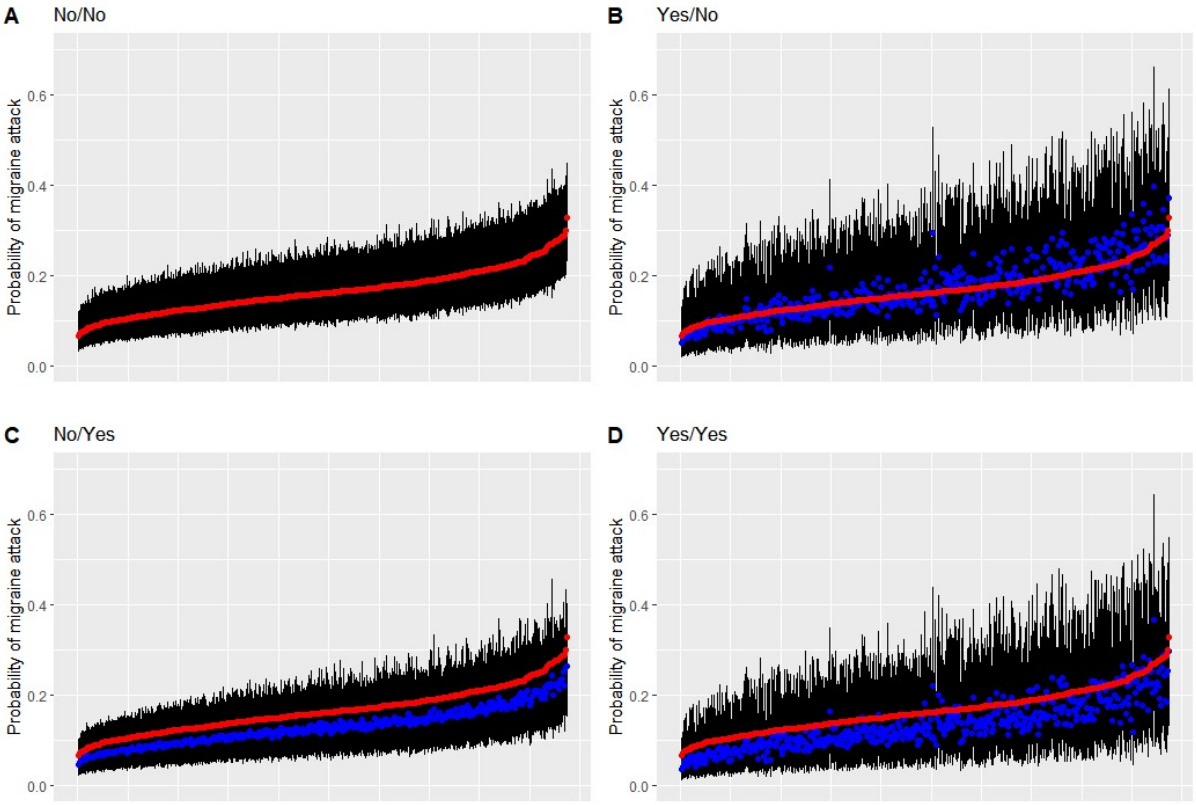
Table 4: Results of the logistic regression models of the log odds of migraine attack in relation to alcohol consumption.

	Model 1	Model 2	Model 3
	OR (95% CI)[†]	OR (95% CI) [†]	OR (95% CI) †
Intercept	0.198 (0.169, 0.232)	0.197 (0.169, 0.229)	0.196 (0.169, 0.229)
day-1 alcohol intake	1.01 (0.91, 1.11)	1.01 (0.91, 1.11)	Not applicable
day-2 alcohol intake	0.75 (0.68, 0.83)	0.75 (0.68, 0.82)	Not applicable
day-1 number of alcoholic beverages	Not applicable	Not applicable	1.03 (0.98, 1.08)
day-2 number of alcoholic beverages	Not applicable	Not applicable	0.88 (0.84, 0.92)
day-2 migraine	0.96 (0.88, 1.05)	--	–
day-2 alcohol * day-2 migraine	0.98 (0.79, 1.20)	--	–
Sex - male	0.89 (0.75, 1.05)	0.89 (0.75, 1.05)	0.88 (0.75, 1.04)
Age (30,50] vs $\leq$30	0.95 (0.82, 1.09)	0.95 (0.82, 1.09)	0.95 (0.82, 1.09)
Age >50 vs $\leq$30	1.00 (0.85, 1.18)	1.00 (0.85, 1.17)	1.00 (0.85, 1.09)
Alcohol doses per week [1,7) vs [0,1)	0.85 (0.75, 0.96)	0.85 (0.75, 0.96)	0.83 (0.75, 0.94)
Alcohol doses per week $\geq$7 vs [0,1)	0.76 (0.62, 0.93)	0.76 (0.62, 0.93)	0.73 (0.60, 0.90)

[†] Odds ratios and their 95% credibility intervals (95% CI) have been calculated from the log odds estimates for ease of interpretation

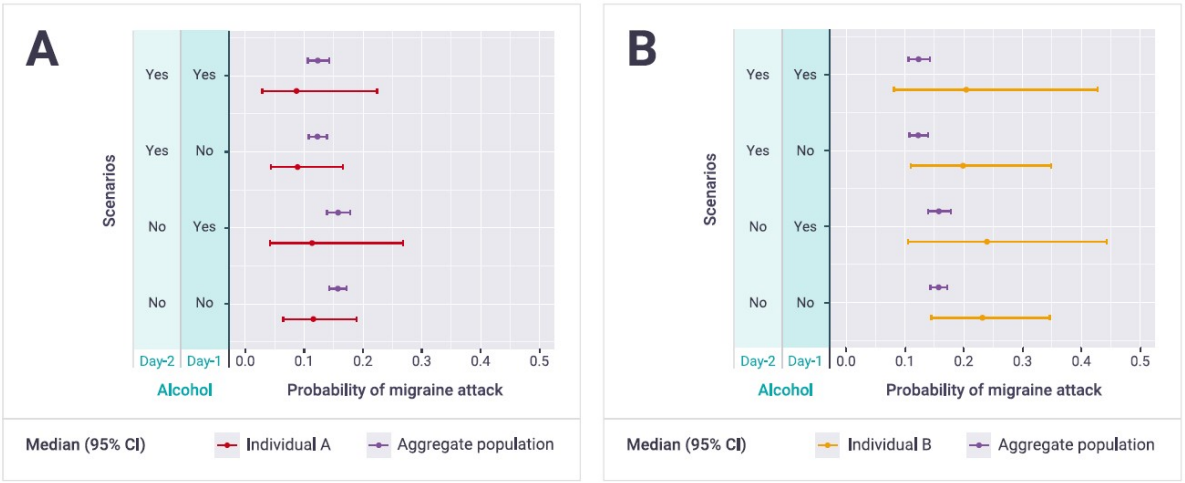
Figure 1: Individual probability of migraine attack (median and 95% CI) under four scenarios: A) No alcohol consumption on either the day before (day-1) or two days before (day-2), "No/No", B) Alcohol consumption on day-1 but not on day-2, "Yes/No", C) Alcohol consumption on day-2 but not on day-1, "No/Yes" and D) Alcohol consumption on both days, "Yes/Yes". Individual probabilities are estimated from a Bayesian model with the following covariates: fixed and random intercept, fixed and random day-1 alcohol intake and day-2 alcohol intake, and adjusted for sex, age, and average weekly alcohol consumption.

.



Note: Individuals are ordered by probability of migraine attack under the assumption of no alcohol intake on day-1 and no intake on day-2 (red dots). For reference this baseline probability (red dots line) is reproduced in all graphs.

Figure 2: Individual probability of migraine attack (median and 95% CI) corresponding to two individuals selected at random among participants who tracked ≥600 days. Individual probabilities are estimated using a Bayesian model and all available tracked days, with the following covariates: fixed and random intercept, fixed and random day-1 (day before) alcohol intake and day-2 (two days before) alcohol intake, and adjusted for sex, age, and average weekly alcohol consumption. Scenarios are defined according to alcohol consumption on day-1 and on day-2.



Note: Individual A is a 50-year old female, consumer of 1.1 alcoholic drinks per week (on average, first 90 days), 858 days tracked; Individual B is a 46 year-old female, consumer of 0.1 alcoholic drinks per week (on average, first 90 days), 1052 days tracked.

Appendix 1

The statistical model is specified as follows: let n be the number of individuals and n_i the number of tracked days of individual i (that is, n_i is the number of repeated measurements of individual i); let $r = 1,\ldots,n_i$be the index of the repeated measurement (tracked day). Let $y_{ir}|p_{ir}$ be the presence (or absence) of migraine for individual i on the r-th tracked day, which is assumed to follow a Bernoulli probability distribution with parameter p_{ir} , that is,

$$y_{ir}|p_{ir} \sim Bern\ (p_{ir}),$$

for $i = 1,\ldots,n$, and $r = 1,\ldots,n_i$. Then, for each individual i , Model 1 can be specified as

$$logit(p_{ir}) = (b_0 + a_{0i}) + (b_1 + a_{1i}) \cdot alcohol_{ir-1} + (b_2 + a_{2i}) \cdot alcohol_{ir-2} + b_3 \cdot migraine_{ir-2} + b_{23} \cdot alcohol_{ir-2} \cdot migraine_{ir-2} + b_4 \cdot male + b_5 \cdot age_{(30,50]} + b_6 \cdot age_{>50} + b_7 \cdot alcoholD_{[1,7)} + b_8 \cdot alcoholD_{>7}\ ,$$

where $b_0$is the fixed intercept and $b_1, b_2, b_3, b_{23}, b_4, b_5, b_6, b_7, b_8$ are the fixed slopes, $a_{ji}$is the random intercept when $j = 0$ and the random slopes for the covariates when $j > 0$: alcohol on day-1 ($j = 1$), alcohol on day-2 ($j = 2$). The a_{ji} are assumed to follow a normal distribution with mean 0 and unknown variance σ_j^2 for $j = 0,\ldots,3$. The adjusting covariate alcoholD is the average weekly alcohol intake in doses. As a prior distribution of every fixed effect, an independent normal distribution with prior mean 0 and prior variance 1000 is chosen, which corresponds to a non-informative prior distribution. As a prior distribution of the variance of each random effect, an inverse Gamma distribution with prior mean 1 and prior variance 100 is chosen, which is the standard noninformative choice for the dispersion parameter.