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ORIGINAL ARTICLE

Crowdsourced Asparagus Urinary Odor Population Kinetics

Anuradha Ramamoorthy[1°], Brian M. Sadler[2°], J.G. Coen van Hasselt[3°], Jeroen Elassaiss-Schaap[3,4], Sreeneeranj Kasichayanula[5], Alena Y. Edwards[6], Piet H. van der Graaf[3,7], Lei Zhang[1] and John A. Wagner[8*]

The consumption of asparagus is associated with the production of malodorous urine with considerable interindividual variability (IIV). To characterize the urinary odor kinetics after consumption of asparagus spears, we conducted a study with consenting attendees from two American Society for Clinical Pharmacology and Therapeutics (ASCPT) meetings. Subjects were randomized to eat a specific number of asparagus spears, and then asked to report their urinary odor perception. Eighty-seven subjects were included in the final analysis. A mixed effect proportional odds model was developed that adequately characterized the dose-response relationship. We estimated the half-life of the asparagus effect on malodorous urine to be 4.7 hours (relative standard error (RSE) = 13.2%), and identified a dose-response slope term with good precision (24.3%). Age was found as the predictor of IIV in slope estimates. This study design and tools can be used as a demonstration "crowdsourcing" project for studying population kinetics in organizational and educational settings.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The consumption of asparagus is associated with the production and perception of malodorous urine with considerable variability. Perceived urinary odor kinetics after consumption of asparagus spears has not previously been characterized. In addition, there is a need to educate more broadly on clinical pharmacology, pharmacokinetics, and clinical trials.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This crowdsourced clinical study aimed to characterize asparagus urinary odor perception kinetics and associated variability in healthy subjects.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ A mixed effect proportional odds model was developed that adequately characterized the dose-response relationship. The half-life of the effect of the number of spears of asparagus consumed on the urinary odor scores was approximately 4.7 hours. Age was a predictor of variability in slope estimates.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

☑ Asparagus consumption and quantitative measurement of malodorous urine perception provides a unique opportunity to study and educate on important topics related to pharmacokinetics and clinical trials. This study design and tools can be used as a demonstration "crowdsourcing" project for studying population kinetics in organizational and educational settings.

Asparagus is a vegetable that has been eaten by humans for thousands of years. The production of odorous urine after consumption of asparagus is well-known, and is associated with significant interindividual variability (IIV) in the ability to produce and/or detect the odor.[1–3] The reported odor, described as the smell of rotten cabbage, is attributed to the production of volatile sulfurous metabolites.[2] A number of sulfated asparagus metabolites, including methanethiol, dimethyl disulfide, dimethyl sulfide, dimethyl sulfone, and dimethyl trisulfide, have been found in the urine of individuals who consumed asparagus. However, there is no consensus on which compounds contribute to the distinct smell.[4,5] Additionally, not all individuals produce these sulfurous metabolites (i.e., they are "nonexcretors") and not all individuals who produce malodorous urine may be able to perceive it (i.e., they are "nonperceivers").[1,5–7]

The cause(s) for variability in the production and perception of malodorous urine after consuming asparagus has not been

[1]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA; [2]Pharmacokinetics, Pharmacodynamics, Modeling & Simulation, ICON Plc, Cary, North Carolina, USA; [3]Cluster Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands; [4]PD-Value BV, Houten, The Netherlands; [5]Clinical Pharmacology, Modeling and Simulation, Amgen Inc, Thousand Oaks, California, USA; [6]Pharmacokinetics, Pharmacodynamics, Modeling & Simulation, ICON Plc, Marlow, UK; [7]Certara QSP, Canterbury, UK; [8]Takeda Pharmaceuticals International Co, Cambridge, Massachusetts, USA. *Correspondence: J A Wagner (john.wagner.md.phd@gmail.com)
°Anuradha Ramamoorthy, Brian M. Sadler, and J.G. Coen van Hasselt contributed equally to this work.
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clearly elucidated. Genetic variability is likely to contribute to the heterogeneity observed in the population. First, genetic variability in drug or xenobiotic metabolizing enzymes can be involved; however, no specific genes or enzymes involved in the production of these metabolites have been identified so far. Second, genetic variability in olfactory genes can be associated with the inability to detect certain urinary asparagus metabolites, also known as asparagus anosmia.[5,8] In fact, a recent genomewide association study involving 6,909 individuals identified 871 single nucleotide polymorphisms associated with asparagus anosmia.[9]

At present, there is a need to educate more broadly on the subjects of clinical pharmacology, pharmacokinetics, and clinical trials. On the one hand, clinical pharmacology training programs have declined and the public understanding of clinical trial conduct is poor, while on the other hand, quantitative approaches are increasingly being used in drug discovery and development.[10–13] Asparagus consumption and quantitative assessment of malodorous urine, as measured by perceived odor, provides a unique opportunity to study and educate on important topics related to pharmacokinetics and conduct of clinical trials.

Here, we conducted, what we believe to be, the first ever crowdsourced clinical study aimed to characterize asparagus urinary odor kinetics and associated IIV in healthy subjects. The novel aspects of the current study include crowdsourcing of a population kinetic study, a semiquantitative asparagus urine odor perception assessment, resulting model-based analysis, and the educational aspects. The study was conducted by involving attendees from two American Society for Clinical Pharmacology and Therapeutics (ASCPT) meetings in 2014–2015. The consenting study participants were randomized to eat prepared asparagus spears and report their perception of the odor in their urine over a period of time. Odor production as measured by the intensity of perceived odor was the pharmacodynamic end point. The intensity of perceived odor was measured using an analog scale that subjectively measured the magnitude of asparagus odor in urine. Data on demography, dose, olfactory function, time of urine void, and odor perceived were collected to understand the asparagus urinary odor kinetics. The specific aims of this study were to characterize the time course, dose-response dynamics, and half-life ($t_{1/2}$) of urinary asparagus odor perception after receiving a single, specified dose of asparagus in a group of subjects. This study design and the associated data analysis can be used as a demonstration project for clinical trials and population kinetics in many settings, including schools, universities, and scientifically oriented organizations. In addition, there is a potential to link results through crowdsourcing by allowing other researchers to add their data to our dataset and build on the current analysis.

METHODS

Clinical studies

Two clinical studies were conducted: (1) a pilot study conducted at an ASCPT subcommittee meeting (2014); and (2) a main study at the ASCPT 2015 Annual Meeting. An overview of these studies is provided in **Supplementary Table S1**. As both the pilot and the main studies involved participation of human subjects, the protocols, informed consent forms, and instruction documents for the participants were reviewed and approved by the Integ Review Institutional Review Board (IRB). The IRB approval was sponsored by ICON.

The pilot study was conducted in October 2014 during an ASCPT subcommittee meeting. In this open-label study, consenting participants were randomized into one of the four study groups to eat 0, 5, 10, or 15 spears of asparagus. In order to evaluate general olfactory function, participants were also required to smell the contents of bottles containing water (blank) and 2-mercaptoethanol (diluted to 0.5, 0.25, and 0.125 ppm with water), and to report on their ability to smell the contents. The distinct odor of 2-mercaptoethanol was detectable by most people at all three nonhazardous concentrations of 2-mercaptoethanol.[14] The goal of the pilot study was to aid in the development of the parameters and other logistics for the main study, including qualifying the questionnaire scale used for reporting the intensity of asparagus odor in urine. The differences between the pilot study and the main study are outlined in **Supplementary Table S1**. The supporting documents for the pilot study (informed consent, CRFs, etc.) are not included.

The main study was conducted at the March 2015 ASCPT Annual Meeting. In this open-label study, consenting participants were randomized into one of the four study groups to eat 0, 3, 6, or 9 spears of asparagus. The participants were asked to eat fewer asparagus spears based on the participant reports from the pilot study. The participants were instructed to eat the specified number of asparagus spears within ~15 minutes, and to document the actual number of asparagus spears consumed in the demography case report form (CRF; see **Supplementary Materials S2 and S3**). In order to evaluate general olfactory function, participants were also required to smell the contents of two bottles containing water and a commercially available perfume, and to report on their ability to smell the contents. This switch was done in order to simplify the logistics for the main study. Of note, the original intent of the olfactory "challenge" was to distinguish perceivers from nonperceivers using a compound (mercaptoethanol) with a similar odor to the substance(s) responsible for malodorous urine after asparagus consumption. When perfume replaced mercaptoethanol in the main study, the olfactory "challenge" became a test for nasal congestion. In the analysis, the covariate for perfume/mercaptoethanol perception was uniformly positive in all study participants and the distinction between perceivers and nonperceivers was assessed using mixture modeling methods.

The demography CRF was required to be submitted at the end of the opening reception after the participants were randomized and ate the asparagus spears. The sample CRFs were required to be completed after every micturition to subjectively describe the intensity of the asparagus odor on a scale of 0–6 (0 being no odor or not offensive and 6 being very intense or offensive odor). The participants had the option of turning in the CRFs either in the digital or paper format (**Supplementary Material S3**). To facilitate

data handling and analyses, the study participants were encouraged to use digital CRFs. Digital submission required downloading the ASCPT Annual Meeting app on a smart device and registering it for use. A free t-shirt was offered to the first 100 asparagus study participants.

For data analysis, subjects were excluded from the analysis if they did not report the time for asparagus consumption or the number of spears consumed. Observation records were excluded when the time of urination or the odor perception score was missing.

The final, approved protocol is included as **Supplementary Material S4**.

Model development

Model development was conducted using NONMEM version 7.3.[15] The first order conditional estimation method was used for parameter estimation. A mixed effect proportional odds kinetic-pharmacodynamic model was used to associate dose with odor scores.[16,17] The relationship between the number of asparagus spears consumed ($Dose_{Asparagus,i}$) for individual *i* and the associated effect half-life ($t_{1/2}$) was described as follows:

$$A_i(t,i) = Dose_{Asparagus,i} \cdot \exp\left(-\frac{\ln 2}{t_{1/2,i}} \cdot t\right)$$

If $y_{i,n}$ represents the observed score for individual *i* and observation *n*, then the probability to observe a score $\geq j$ was defined as follows:

$$P(y_{i,n} \geq j) = \frac{e^{f_{i,n}}}{1+e^{f_{i,n}}}$$

$f_{i,j}$ is defined as the sum of baseline coefficient β_1 and additional coefficients β_n for the remaining *m* score levels, as follows:

$$f_{i,j} = \sum_{n=1}^{m} \beta_n + S_{Asp} \cdot A_i(t)$$

Here, S_{Asp} is a dose-response slope parameter relating the asparagus effect time course to the observed scores.

To estimate the probability of being a urinary odor perceiver or nonperceiver, a mixture model was considered. Nonperceivers were defined as individuals who consumed asparagus but did not report a change in their urinary odor (i.e., with a flat response curve). Estimation of IIV was considered for the parameters $t_{1/2}$, baseline β_1, and S_{Asp} according to log-normal distributions, except for β_1, which was modeled according to an additive relationship. Available participant demographics (age, sex, prior asparagus consumption, and reported history of odor after eating asparagus) were evaluated as predictors for IIV in parameter estimates. Model selection was based on the decrease in the objective function value (OFV), adequate parameter estimation precision, and adequate description of the data using visual predictive checks.[18] The NONMEM model code and final dataset are included as **Supplementary Materials S5 and S6**, respectively.

Table 1 Characteristics of participants included for the data analysis

No. of participants with evaluable data	**87**
No. of men/women	51/34[a]
Age, years (median, range)	41 (24–64)[b]
Known ability to smell odor after eating asparagus (no.)	No (30), yes (57)
Consumed asparagus prior to study	No (83), yes (4)

[a]Sex was missing for 2 participants.
[b]Age was missing for 6 participants.

RESULTS

Study participation and compliance

A total of 158 subjects signed the informed consent; however, only a total of 120 participants participated (14 and 106 in the pilot and main studies, respectively). After excluding participants who did not report sufficient data, a total of 87 participants had odor scores available, 79 of whom received a nonzero dose of asparagus. A total of 412 odor scores were available for the data analysis.

With respect to compliance in data entry, 31% of the subjects (43/137; note: 137 demography forms were submitted) reported neither the nominally randomized nor the actual number of spears consumed. With respect to compliance in following the dose per protocol (i.e., eating the number of spears a subject was randomized to), 12% of the subjects (11/94) reporting their randomized number of spears did not consume the assigned number of asparagus spears. Digital CRFs were available only for the main study, and about 99% of the data submission was done via this mechanism. The demographics of participants included in the analysis are provided in **Table 1**; about 57% of the subjects were women, and the age range was wide with a mean of 43 years (range, 24–64 years). The frequency of distribution of the reported odor scores after the time of asparagus administration are provided in **Figure 1a**. The IIV for the duration and magnitude of reported odor scores was clearly present, as shown for representative individuals (**Figure 1b**). Individual curves are included as **Supplementary Material S7**.

Asparagus odor population kinetics

A six-score odor scale was used in this study. However, for scores of four and five, we ultimately could only reliably estimate a single coefficient due to insufficient data. The parameter estimates of the final model are shown in **Table 2**. Because the majority of participants reported a change in odor perception, perceivers could not be reliably separated from nonperceivers. The half-life of the asparagus effect was estimated at 4.7 hours, with good precision (relative standard error (RSE) = 13%). A dose-response term (S_{Asp}) could be identified with good precision (24.3%), and found to be equal for different score levels.

The IIV could be estimated for S_{Asp} and for the baseline variability of the score for responders (**Table 2**). The IIV estimates for S_{Asp} and baseline parameters were large: 56.1 of coefficient of variation percentage (CV%) and 63.1 CV%, respectively. The IIV could not be estimated simultaneously for both $t_{1/2}$ and S_{Asp}; a large correlation between these parameters was present during estimation, as could

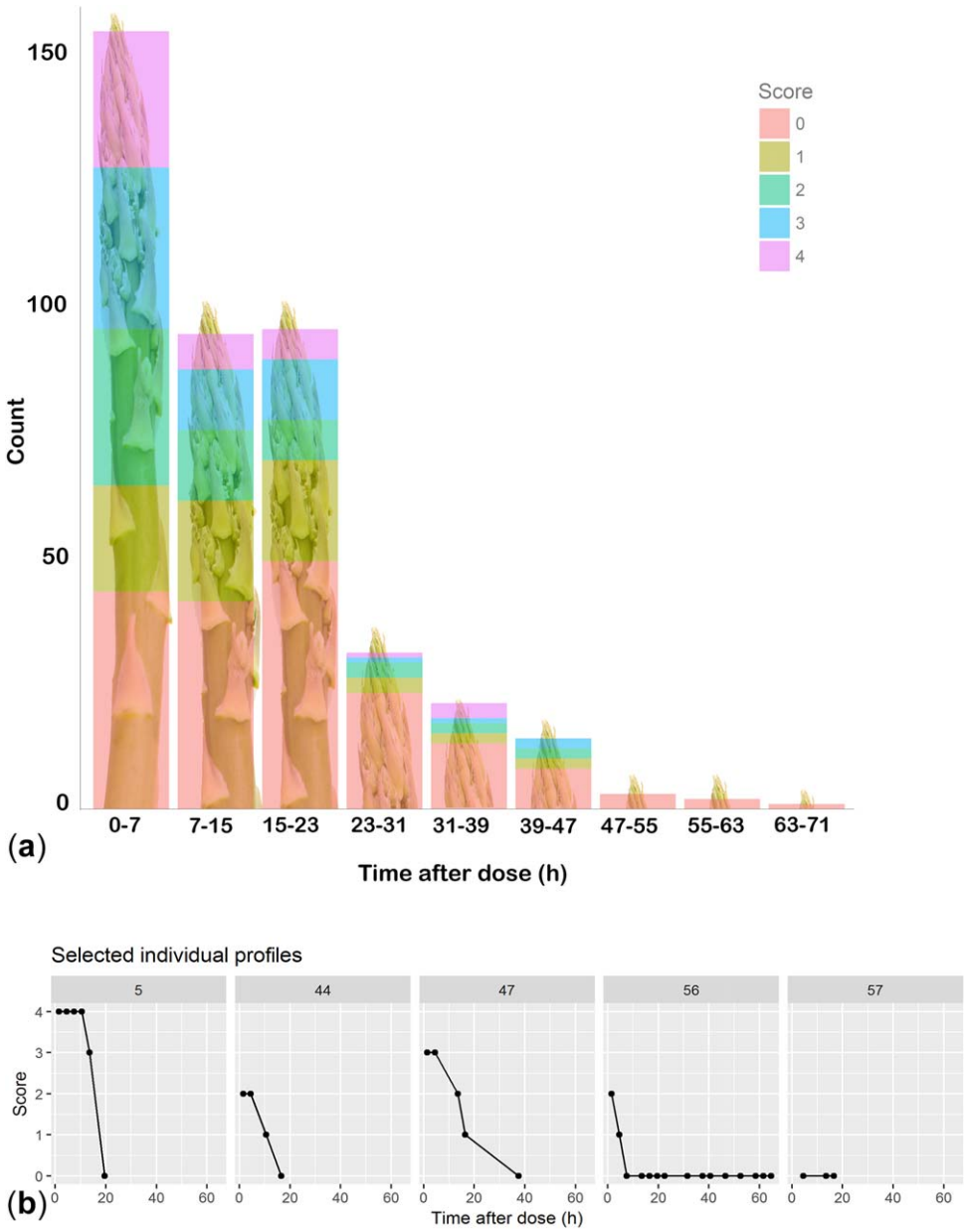

Figure 1 (**a**) Frequency counts of reported odor scores versus time after dose. (**b**) Representative selection of individual reported odor scores vs. time.

be expected. Although estimation of IIV for $t_{1/2}$ resulted in a 1 point drop in OFV, estimation of IIV for S_{Asp} resulted in a 10 point drop in OFV, and IIV for S_{Asp} was, therefore, retained.

We evaluated collected demographics as predictors for IIV in these parameters. Interestingly, a correlation between age and S_{Asp} was identified, and retained as covariate in the model (**Figure 2**). The typical dose-response relationship, as predicted by the model for different age groups, is illustrated in **Figure 3**. The visual predictive check ($n = 2{,}000$) indicated the model provided an adequate description of the data (**Figure 4**).

DISCUSSION

We successfully conducted, what we believe to be, the first ever crowdsourced population study to characterize the kinetics in perception of urinary odor, dose response, and IIV after asparagus consumption. The numbers of participants who were ultimately available for analysis were sufficient to develop a population kinetic model, which characterized a half-life, dose-response relationship, and associated IIV for asparagus odor scores. For 5.7% of the participants (5/87), a flat odor perception curve was observed, and these individuals could potentially be

Table 2 Parameter estimates of the final kinetic-pharmacodynamic mixed effect proportional odds model

Description	Parameter	Estimate	RSE (%)	IIV (CV%)[a]
Structural model				
Log, half-life of asparagus effect (h)	$t_{1/2}$	1.55 (ns 4.7 h)	13.2	–
Level ≥1, baseline	β_1	−0.505	46.1	69.9[b]
Level ≥2	β_2	−0.861	13.8	–
Level ≥3	β_3	−0.889	13.3	–
Level ≥4	β_4	−1.41	15.5	–
Log, slope of asparagus effect[b]	S_{Asp}	−0.879 (ns 0.42)	24.3	60.8[c]
Effect of age on slope[c]	$AGE\text{-}S_{Asp}$	−1.5	45	–

CV, coefficient of variation; IIV, interindividual variability; ns, normal (non-log) scale; RSE, relative standard error; $t_{1/2}$, half-life.
[a]Calculated as sqrt(exp(OMEGA)-1).
[b]β_1 *for individual i given by* $\beta_{1,i} = \beta_1 + \eta_{\beta 1}$.
[c]Slope for individual i given by $SLOPE_i = \exp(S_{Asp}*(AGE_i/41)^{AGE\text{-}SASP} + \eta_{SASP})$.

considered as nonperceivers. However, for several of these individuals, only two observations were available, and, therefore, we did not separately distinguish between these populations in the analysis. The percentage of subjects who both produce and perceive odorous urine after consuming asparagus was within the range of previous observations.[1,3,7]

In addition to the main model-based analysis described, we conducted an initial preliminary analysis using a simple one-compartment model and treating the odor-rating scale as a continuous variable. The $t_{1/2}$ estimated in the preliminary and final analyses had different meanings. In the preliminary analysis, the $t_{1/2}$ directly represented the rate of decline in urine odor. In the present analysis, the $t_{1/2}$ represented the decline in the effect of the amount of asparagus eaten on the logit of the probability of successive decreases in the odor score. The preliminary model also required the estimation of a "volume" term that served as a scalar between the number of spears of asparagus eaten and the reported odor score. The present model did not require a scalar term as the effect of the amount of asparagus eaten (declining over time with the reported $t_{1/2}$) was incorporated as an element in the logit transduction function and used to compute the likelihoods of the odor scores in their (more appropriate) ordered categorical domain.

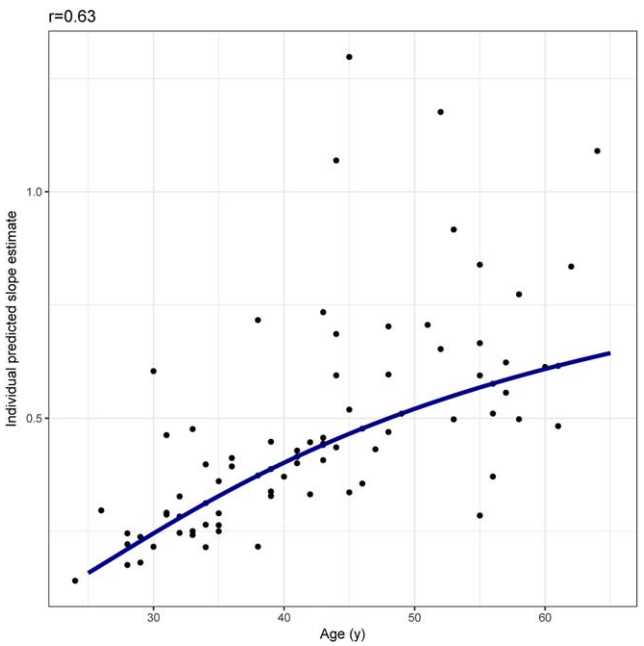

Figure 2 Relationship between individual predicted estimate for slope and associated age of participant. The blue solid line indicates the prediction for the effect of age on slope included in the final model.

This study was the first to quantify the $t_{1/2}$ and the "dose"-response for the effect of the number of consumed spears on the intensity of asparagus-associated malodorous urine. The $t_{1/2}$ of the asparagus effect on malodorous urine was 4.7 hours. Moreover, we identified age to be correlated with the individual estimate for the dose-response slope term. It should be noted that IIV for $t_{1/2}$ and the dose-response slope were highly correlated. This age effect may be attributable to the decrease of renal function with age,[19] resulting in odor time courses with increased intensity and duration of perceived odors, as was illustrated in **Figure 3**.

Some of the parameter estimates were still associated with significant uncertainty (e.g., baseline β_1 and age effect); more data could result in more precise estimates of these parameters. Moreover, increasing the number of participants could also provide additional insights in patient-associated characteristics predictive of the kinetics of urinary odor profiles, and better separation of perceiver and nonperceiver subgroups. Finally, collection of additional data may ultimately allow explaining the IIV associated with the ability to perceive odorous urine.

A pilot study with a small number of subjects helped with ironing out the logistics of the study details. For example, in the pilot study, the participants were randomized into one of the four study groups selected to eat 0, 5, 10, or 15 spears of asparagus. As the participants reported that eating 15 spears was a challenge, for the subsequent main study, the dose was modified to 0, 3, 6, or 9 spears of asparagus. The participants were asked to eat fewer asparagus spears based on the participant reports from the pilot study. Also in this study, to evaluate the olfactory function, participants were asked to take a whiff (exposure duration of about 5–10 seconds) from the control bottles and 2-mercaptoethanol dilutions (pilot study) or commercially available perfume (main study). Ideally, the test of olfactory function should have used sulfurous odor similar to the expected odor in urine after consuming asparagus.

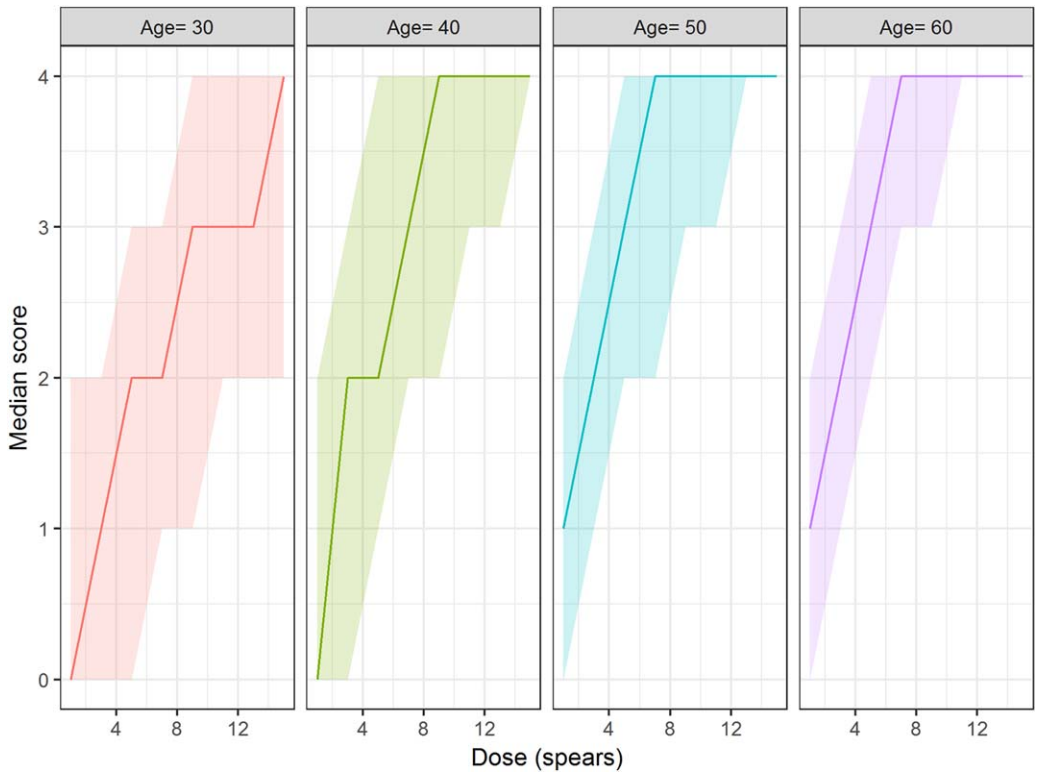

Figure 3 Simulated median and interquartile range of dose-response relationship between the number of consumed asparagus spears and the peak score ($n = 2{,}000$ individuals), for different age groups.

One surprising observation from this study was that clinical pharmacologists were not particularly compliant study subjects. Usable data for this analysis was available from 72.5% of the subjects ($n = 87/120$) who participated in the study, and this represented 55% of the subjects ($n = 87/158$) who signed the informed consent to participate in the study. In many instances, subjects did not report the time of asparagus consumption, number of spears consumed, time of urination, or odor perception score. In defense of the subjects, free-format text fields were used in the case report forms with no edit checks in place to prevent data entry errors. The study team was unable to resolve the resulting data queries as subjects departed for home after the meeting and were lost to follow-up.

There were a number of lessons learned from the practical execution of this study. First, as with many volunteer collaborations,[20] focus, organization, and pace of the project was a challenge. Although ultimately successful, the overall project duration was lengthy from design to completion. Mitigations include robust project management with accountability, a clear and concise project plan with precise objectives is mandatory, and so are setting and adhering to deadlines. Second, despite advertising before and at the annual meeting as well as an incentive t-shirt, the rate of participation was relatively low (about 10% of the annual meeting attendees) and noncompliance was relatively high, especially given that meeting participants were mostly scientists with keen interest in clinical pharmacology and clinical trials. Mitigations might also include increasing advertising, better explaining goals, and offering additional incentives, such as a lottery. Finally, the study itself was complicated and it may be possible to simplify different elements in the future studies. For example: (1) both digital and paper CRFs were offered, but the vast majority of subjects used the digital option. In the future, only the digital option would need to be offered; (2) the design of the CRF could be improved by text controlling most field entries to ensure uniformity of the entry data in order to expedite data assembly; and (3) simplifying the odor scale. In our analysis, we collapsed the upper two odor scores into a single score because model parameters could not be reliably estimated for these score levels separately. Therefore, for subsequent studies, a five-point scale to quantify asparagus odor perception may be sufficient.

This study and the associated data analysis could be considered as a demonstration project for population kinetics studies in many settings, including schools and a wide variety of organizations. We have provided supplementary materials as supportive documentation. Moreover, we also provide the raw data and the code of the final model developed (**Supplementary Material S5**). Unlike blood concentrations of a drug, the questions about consumption of asparagus and its associated malodorous urine are straightforward and the endpoint—perception of malodorous urine—is clear. Thus, the asparagus study can be utilized to teach principles of pharmacokinetics and population kinetics.

A recent trend in clinical trials is the “crowdsourcing” different aspects of clinical studies, such as mining and

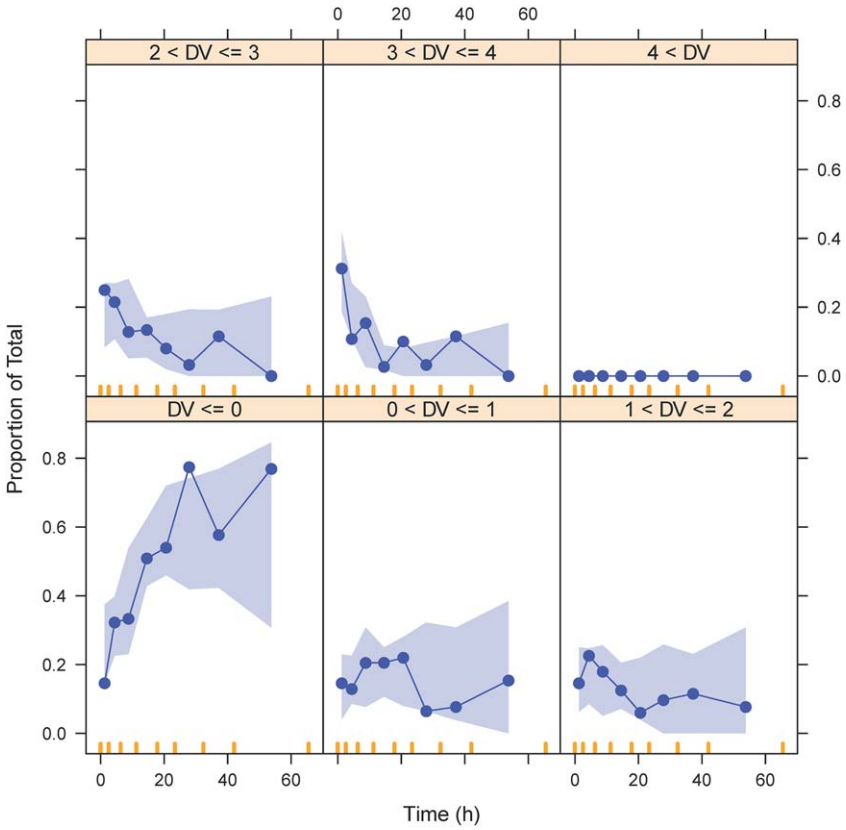

Figure 4 Visual predictive check showing the observed (solid circles) and 95% prediction intervals for each score (DV) interval.

analyzing clinical trial data and informing the design of a clinical trial.[21–23] The hope is that crowdsourcing, by harnessing the wisdom of the researcher, clinician, patient, and advocate community, will lead to accelerated research and development. In our study, we used crowdsourcing to help with the logistics of the study, including running the study, ensuring that informed consent was executed, providing instructions to the participants, aiding in randomization, entering data from the paper CRFs, etc. Additionally, we also hope to use crowdsourcing to build on the current study. Our study design can be used as a demonstration project for clinical trials and population kinetics in many settings, including schools, universities, and scientifically oriented organizations. Consequently, there is a potential to link results through crowdsourcing by allowing other researchers to add their data and build on the current database.

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