Received: 24 February 2022 | Revised: 6 June 2022 | Accepted: 14 August 2022

DOI: 10.1111/adb.13228

ORIGINAL ARTICLE

Addiction Biology SSA WILEY

Binge and high-intensity drinking—Associations with intravenous alcohol self-administration and underlying risk factors

Martin H. Plawecki[1] | Julian Boes[2] | Leah Wetherill[2] | Ann E. K. Kosobud[3] | Bethany L. Stangl[4] | Vijay A. Ramchandani[4] | Ulrich S. Zimmermann[5,6] | John I. Nurnberger Jr[1] | Marc Schuckit[7] | Howard J. Edenberg[2,8] | Gayathri Pandey[9] | Chella Kamarajan[9] | Bernice Porjesz[9] | Tatiana Foroud[2] | Sean O'Connor[1]

[1]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana, USA

[2]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA

[3]Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[4]Human Psychopharmacology Laboratory, Division of Intramural Clinical and Biological Research, NIAAA, Bethesda, Maryland, USA

[5]Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus of the Technische Universität Dresden, Dresden, Germany

[6]Department of Addiction Medicine and Psychotherapy, kbo Isar-Amper-Klinikum Haar/Munich, Munich, Germany

[7]Department of Psychiatry, University of California San Diego, San Diego, California, USA

[8]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana, USA

[9]Henri Begleiter Neurodynamics Laboratory, State University of New York Downstate Health Sciences University, Brooklyn, New York, USA

Correspondence
Martin Henry Plawecki, Indiana University School of Medicine, Neural Systems Laboratory, UH 5510 – General Clinical Research Center, 500 University Boulevard, Indianapolis, IN 46202, USA.
Email: mplaweck@iupui.edu

Funding information
The research was performed through the Alcohol Beverage Manufacturer's Research Foundation (MHP), NIAAA funding of the Indiana Alcohol Research Center (P60 AA07611; MHP, SOC, AK), and R01 AA027236 (MP), the IU Department of Psychiatry, and with Indiana Clinical and Translational Institute Clinical Research Center (prior M01 RR 750, now UL1TR001108 [National Center for Advancing Translational Sciences]) support. VAR and BLS supported by NIAAA Division of Intramural Clinical and Biological Research (Z1A AA000466). The Collaborative Study on the Genetics of Alcoholism (COGA), a national collaborative

Abstract

Some styles of alcohol consumption are riskier than others. How the level and rate of alcohol exposure contribute to the increased risk of alcohol use disorder is unclear, but likely depends on the alcohol concentration time course. We hypothesized that the brain is sensitive to the alcohol concentration rate of change and that people at greater risk would self-administer faster. We developed a novel intravenous alcohol self-administration paradigm to allow participants direct and reproducible control over how quickly their breath alcohol concentration changes. We used drinking intensity and the density of biological family history of alcohol dependence as proxies for risk. Thirty-five alcohol drinking participants aged 21–28 years provided analytical data from a single, intravenous alcohol self-administration session using our computer-assisted alcohol infusion system rate control paradigm. A shorter time to reach 80 mg/dl was associated with increasing multiples of the binge drinking definition ($p = 0.004$), which was in turn related to higher density of family history of alcoholism (FHD, $p = 0.04$). Rate-dependent changes in subjective response (intoxication and stimulation) were also associated with FHD (each $p = 0.001$). Subsequently,

study, is supported by NIH Grant U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA).

given the limited sample size and FHD range, associations between multiples of the binge drinking definition and FHD were replicated and extended in analyses of the Collaborative Study on the Genetics of Alcoholism database. The rate control paradigm models binge and high-intensity drinking in the laboratory and provides a novel way to examine the relationship between the pharmacokinetics and pharmacodynamics of alcohol and potentially the risk for the development of alcohol use disorders.

KEYWORDS
alcohol self-administration, ascending limb, binge drinking, high-intensity drinking, subjective response

1 | INTRODUCTION

Binge drinking is common[1] and associated with significant health risks (e.g., previous studies[2–5]). The impact on risk of how one consumes alcohol (how quickly and how high an alcohol concentration is achieved) is inherent in the definition of binge and high-intensity drinking. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) explicitly recognizes binging ("… a pattern of drinking that brings blood alcohol concentration (BAC) levels to [80 mg/dL]") as one pattern of risky drinking, typically occurring after four or five drinks for women and men—in about 2 h.[6] Breath alcohol concentration (BrAC) indexes the arterial concentration (as in Lindberg et al.[7]), to which the brain is exposed.[8] Unfortunately, many individuals consume more than four or five alcohol drinks on an occasion. This pattern, termed high-intensity drinking,[9] is associated with an elevated risk of developing an alcohol use disorder (AUD).[10–13] Binging and high-intensity drinking are also clearly influenced by genetic risk; existing and novel risk loci were associated with typical maximum alcohol consumption in the Million Veteran project,[14] with ~50% of the sample consuming *at least* four or five drinks on an occasion.

Several AUD risk models have been proposed based on the subjective response to alcohol, each derived using oral alcohol challenges and suggesting a relationship between alcohol pharmacokinetics and pharmacodynamics. The two models with the most support are the low level of response model and the differentiator model. The low level of response model is based on the finding that males with a positive family history of AUD (FHP) reported lesser subjective responses to an alcohol challenge than those without family history (family history negative, FHN).[15] The differentiator model posits that FHP individuals are more sensitive to the rewarding effects on the ascending limb (period of increasing BrAC), and more tolerant to the sedating effects on the descending limb (when BrAC is decreasing), compared with FHN controls.[16] Ingestion of alcohol, however, results in substantial variation in peak BrAC and latency to peak BrAC, limiting experimental control over how quickly alcohol exposures change (e.g., Norberg et al.[17] and Ramchandani et al.[18]). Consequently, most research has focused on the response to alcohol on the ascending versus descending limbs. Nonetheless, interest in the effects of rate of change of BrAC, per se, has existed for some time.[19–21]

Intravenous (IV) alcohol administration techniques document a relationship between the alcohol concentration time course and its effects, including the role of rate of change of brain exposure. The alcohol clamp comprises a linear rise to a target BrAC, which is then maintained for hours, thus eliminating rate of change as a contributing factor to measurements obtained during the clamp. Outcomes include subjective and physiological responses to both the investigator-defined initial positive rate of change of BrAC (initial response to alcohol) and changes in the response during maintenance of a steady BrAC (acute tolerance). The clamp paradigm has successfully examined family history of AUD,[22–24] genetic association of acute tolerance,[25] recent drinking history,[24] and other indicators of risk.[26] Conversely, using a paradigm where specific rates of BrAC ascent and descent were prescribed, we reported increased perceptions of "high" and "intoxicated" measured at the same BrAC and elapsed time on the ascending versus descending limb in moderate drinkers, and the reverse of that pattern in light drinkers.[27] Thus, the precise exposure control provided by IV alcohol administration techniques supports a relationship between positive and negative rates of change of BrAC and response to alcohol, drinking history, and other AUD risk factors. Taken together, the observations across the oral and IV alcohol challenge literature invited a study of how the steepness of self-controlled positive rates of change in BrAC relate to the subjective response to alcohol, family history, recent drinking history and risk for AUD.

Alcohol self-administration paradigms are increasingly common in human studies and suggest the importance of examining how quickly people consume alcohol, the relationship between how quickly BrAC changes and subjective response or other risk factors. Using oral alcohol self-administration techniques, investigators have primarily investigated the temporal dynamics of a drinking episode. Outcomes of interest have largely been limited to total volume of alcohol consumed, frequency or speed of consumption, and latency to start or finish a drink.[28–33] These studies provided minimal examination of alcohol concentration temporal dynamics beyond peak, ascending versus descending limb, or overall differences (for example, previous studies[30,34]), likely secondary to the aforementioned variability in alcohol exposure even after a standard "drink" and challenges collecting frequent alcohol concentration measures after oral consumption. Using an IV alcohol paradigm, Stangl et al. reported that those who self-infused more rewards in the first 30 min of the lab study reported

drinking more heavily in the past month and reported a greater rewarding subjective response compared with participants who infused less during the same interval.[35] Recently, the time to achieve a binge level exposure of 80 mg/dl was associated with AUD risk,[36] genetic risk,[37] and high-risk drinking.[38] In these studies, each IV alcohol reward is identical. Thus, participants only achieved *indirect* control of the overall rate of BrAC change through selection of *when* alcohol was delivered. Further, the rate of change associated with each reward was identical and thus may have been too rapid or too slow for an individual participant for whom the rate of change influences, if not determines, reward. Recently, investigators employed ecological momentary assessment and estimated blood alcohol concentrations to examine alcohol consumption in the community. Noting the limitations of the methodology, they reported that, within drinking episodes, "faster consumption" (determined as greater rates of change in *estimated* blood alcohol concentration) was associated with decreased negative affect and increased positive affect.[39] Consequently, while the alcohol self-administration literature consistently identifies a role for drinking rate and the resultant alcohol pharmacokinetics in multiple outcome measures, no study has yet to provide participants direct and reproducible control over their alcohol exposure time course.

We developed a novel IV alcohol self-administration paradigm to assess preference for high *rates of change of* BrAC as a potential underlying risk factor for AUD. By allowing participants to directly control how quickly their BrAC changed for each reward interval, we tested the primary hypothesis that their self-administered alcohol exposure profile is associated with recent binge and high-intensity drinking. In addition, we explored the underlying reasons including the role of subjective sensitivity to rate of change of alcohol exposure and family history density of AUD amongst other AUD-related risk. Then, based our results implicating family history density of AUD and recent binge and high-intensity drinking, we tested whether the interview-based associations found in our laboratory study replicated in a much larger sample population from the Collaborative Study on the Genetics of Alcoholism (COGA) (Appendix A).

2 | METHODS

See Supporting Information for expanded details.

2.1 | Laboratory participants

A total of 37 participants, 18 men and 19 women aged 21–27, completed the study. All were healthy, non-treatment seeking, and at-risk alcohol-consuming participants comprising 29 and 4 European and African ancestry respectively, with the remainder being of mixed, other, or unknown ancestry (Laboratory Session; Table 1A). All participants were heavy drinkers (≥7/14 drinks per week or ≥3/4 drinks on one occasion for women and men, respectively[6]). The study was

TABLE 1 Demographic analysis by drinking intensity group

	Low	Moderate	High	Extreme	*p* value
A: Laboratory sample: Drinking intensity group					
Number	2	11	14	8	
Age	–	22.9 (0.53)	23.4 (0.57)	23.0 (0.63)	0.83
Gender (%F)	–	73%	43%	50%	0.32
FHD	–	0.06 (0.03)	0.09 (0.03)	0.18 (0.04)	*0.04*
Craving (PACS)	–	6.1 (1.0)	8.7 (1.0)	7.1 (1.6)	0.39
SRE-total	–	5.92 (0.58)	6.81 (0.92)	7.46 (0.62)	0.28
AUDIT	–	8.0 (0.66)	11.1 (0.8)	8.8 (1.49)	0.39
Maxdrinks	–	6.2 (0.42)	10.7 (0.44)	15.9 (0.72)	*0.004*
DD/W	–	2.6 (0.2)	2.8 (0.27)	3.2 (0.55)	0.50
D/DD	–	3.5 (0.26)	5.5 (0.62)	5.5 (0.83)	*0.03*
B: COGA sample: Drinking intensity group					
Number	45	74	119	406	
Age	24.4 (0.36)	24.4 (0.27)	22.3 (0.21)	24.8 (0.11)	*0.033*
Gender (%F)	62.2%	70.3%	61.5%	38.9%	*<0.0001*
FHD	0.23 (0.03)	0.27 (0.03)	0.30 (0.02)	0.35 (0.01)	*<0.0001*
Maxdrinks	3.1 (0.18)	6.4 (0.12)	10.3 (0.15)	24.1 (0.56)	*<0.0001*

Note: Due to small number ($n = 2$), participants with membership the low drinking intensity group of the laboratory sample were excluded from all group-based analyses. Data show mean (standard error) or percent. Maxdrinks, DD/W, and D/DD: maximum number of drinks in a 24-h period, drinking days per week, and drinks per drinking day, respectively, over timeline followback interval. The italics were to emphasize statistically significant results.
Abbreviations: AUDIT: Alcohol Use Disorders Identification Test; FHD, family history density of biological relatives with an AUD; PACS, Penn Alcohol Craving Scale.

approved by the Indiana University School of Medicine Institutional Review Board. NIAAA guidelines for administering alcohol in human studies were followed. Participants were interviewed, providing demographic and medical information, a recent 35-day drinking (timeline follow-back[40,41]), an evaluation of antecubital vein access and vital signs, a blood sample for liver function testing, and a urine sample for drug use and pregnancy-testing. As tobacco use is also highly prevalent in heavier drinkers, $N = 8$ recent smokers were included.

2.2 | Alcohol self-administration sessions

Each participant undertook one IV alcohol self-administration session. Participants were instructed to avoid consuming alcohol after 4 PM on the previous day and to not eat anything after midnight. Each was admitted to the outpatient section of the Indiana Clinical Research Center at Indiana University Hospital at approximately 8 AM; all participants had a zero BrAC and females had a negative urine pregnancy test. Smokers were offered nicotine replacement during the session (none accepted). A standardized breakfast was provided, followed by antecubital IV catheter placement in the non-dominant arm. In response to the participant's experimental choices, the required infusion rate profile was calculated in real time, utilizing an individualized physiologically based pharmacokinetic model[42] and the computer-assisted alcohol infusion system (CAIS[43–45]). BrAC was measured frequently throughout the experiment. The safety limit, above which alcohol self-administration was suspended, was 150 mg/dl. Participants were not informed of their BrAC at any time.

Rate selection and subjective response assessments were repeated in 3 min epochs (Figure 1). Three min was determined to be the minimum interval over which the participant could experience the effects of the selected rate of BrAC based upon pharmacokinetic modelling of brain alcohol concentration and consistent with work by Gomez et al.[8] A visual display allowed the participant to choose the next rate of BrAC change by turning a dial. Participants were instructed that the experimental objective was to determine how much they enjoyed various alcohol exposure rates and that they would be able to increase, decrease, or keep their BrAC the same as they desired. They were encouraged to make decisions with minimal delay, during which their BrAC was held constant. The maximum ascending rate in each epoch was 5 mg/dl per min or whatever lesser rate would achieve a BrAC within 5 mg/dl of the safety limit. The maximum available descent rate was initially −5 mg/dl per min, reducing with equilibration of alcohol in the total body water,[46–49] and subsequently limited by the participant's alcohol elimination rate. The display was dynamically updated to present the current range of available choices.

Participants documented their current subjective perceptions over approximately 20 s at the end of each epoch, using a visual comparison to their preceding selection (Figure 1), consistent with our prior work.[25,50,51] The following subjective response questions were used, adapted from the Subjective High Assessment Scale[52] as implemented by Schuckit et al.,[15,53–55] the Brief Biphasic Alcohol Effects Scale,[56] and the Subjective Effects of Alcohol Scale.[57]

- How much am I feeling the effects of the drug right now? (INTOXICATED).
- How STIMULATED (energized, excited, up) do I feel right now?
- How ANXIOUS (tense, jittery, nervous) do I feel right now?
- How RELAXED (carefree, mellow, loose) do I feel right now?
- How SEDATED (slow thoughts, sluggish, difficulty concentrating) do I feel right now?

After the session, participants were transferred to a private room until the later of 5 PM or their BrAC fell below 20 mg/dl. We compensated participants $25 in cash at the time of the interview and $125 at release.

2.2.1 | Laboratory measures

Time to reach BrAC of 80 mg/dl

The elapsed time (minutes) at which the participant reached a BrAC of 80 mg/dl was employed as the primary outcome, as in our prior

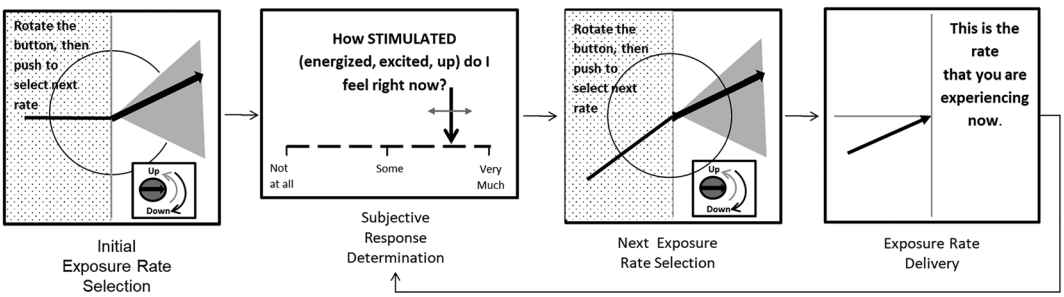

FIGURE 1 Exposure rate selection and subjective response determination sequence. The task began with an initial exposure rate selection, with the display indicating no past rate of change (baseline). During each 3 min epoch, beginning at 2.5 min, a set of subjective responses were collected over approximately 20 s after which time the next exposure rate selection prompt was displayed, indicating the prior selection in the left hand (shaded) portion of the display. The choice and subjective response sequence was repeated throughout the experiment. The next exposure rate was then selected by rotation of the response button (Griffin Technologies Powermate®, depiction inset) to a position within the available range depicted in grey. The arrow position followed the button rotation in real time, and the rate chosen is confirmed by a single button press.

work.[36–38] Two participants did not self-administer alcohol and post-session debriefing identified intentional manipulation to achieve an earlier discharge time in one case and, in the other, a significant recent stressor which would have precluded their involvement had it been reported at the screening interview. These individuals were excluded from all analyses.

Subjective response to alcohol

Operationalizing our prior work for repeated assessment,[58] subjective response to alcohol as a function of time was modelled as a linear combination of the current alcohol concentration, the preceding rate of change in alcohol concentration, and the cumulative exposure to alcohol at that time across all measured time points, using Matlab (Mathworks, Natick MA). The coefficient relating the rate of change in alcohol concentration to subjective response served as the analytical variable.

2.2.2 | Interview-based measures

Family history of AUD module of the SSAGA,[59] the Alcohol Use Disorders Identification Test (AUDIT[60]), Penn Alcohol Craving Scale (PACS[61]), and the retrospective Self-Reported Effects of Alcohol (SRE[62]) were collected. For safety and procedure-related purposes, the Clinical Institute Withdrawal Assessment for Alcohol[63] and the Center for Epidemiologic Studies Depression Scale[64] were completed.

Drinking intensity

Laboratory sample drinking intensity (DI) was characterized by the self-reported maximum number of drinks in a 24 h period (Maxdrinks) during the 35 day timeline follow-back interval, divided by four or five drinks for women and men respectively, a strategy comparable to that adopted in the epidemiological literature[9,12,13] and labelled as low-risk if DI < 1 ($N = 2$), moderate-risk if 1 ≤ DI < 2 ($N = 11$), high-risk if 2 ≤ DI < 3 ($N = 14$), and extreme-risk if DI ≥ 3 ($N = 8$). Given sample size concerns, the low-risk group was excluded from all group-based analyses, leaving a final analytical sample of 33 subjects. In the subsequent study, DI groups were created in COGA using the lifetime Maxdrinks variable. DI group demographic characteristics by sample are in Table 1A,B, with additional COGA sample data presented in Table S1B.

Family history density

A family history density (FHD) score[65] was calculated for each participant in both samples. FHD scores were based on degree of biological relatedness, in which parents and full-siblings with a lifetime history of DSM-IV alcohol dependence contributed 0.5 for each person, each dependent grandparent or sibling of parents contributed 0.25, and non-affected biological relatives contributed zero. We calculated FHD as the sum of weights divided by the number of counted relatives. A detailed description of Materials and Methods is provided in Supporting Information.

2.2.3 | Statistical analyses

Time to reach 80 mg/dl

Survival analyses used a Cox proportional hazards model to test if the time at which drinkers reached 80 mg/dl differed as a function of DI. The Akaike information criteria (AIC) was utilized to evaluate fit. Nicotine and gender were tested and included if significant ($p < 0.05$). FHD was tested in a separate model to avoid any confounds between FHD and DI group. To verify that our primary result was not a function of the DI group definition process, subsequent analyses examined the relationship between Maxdrinks and time to reach 80 mg/dl.

Subjective response

The individual contribution of FHD and DI group to the subjective response was evaluated using separate analyses of variance (ANOVA) model for FHD and for DI group. We included FHD, AUDIT, and the FHD*AUDIT interaction in each ANOVA model to account for the potential effect of high AUDIT scores in those with higher FHD.

Drinking intensity groups

An ANOVA model was used to examine the characteristics of the three DI groups for age, FHD, craving (PACS), and AUDIT (Table 1A) by using DI group as a predictor variable. Tukey-corrected pairwise comparisons were used to identify how the groups differed. A chi-square test was used to test whether gender and nicotine use was associated with the DI groups.

Family history density

To utilize risk information inherent in the DI group variable, an ordinal logistic regression model was employed to examine the hypothesis that FHD predicts DI group. The Score Test was employed to test the equal proportional odds assumption. ANOVA models were subsequently used to assess if FHD predicted the alcohol-related interview variables PACS/DAQ, SRE-total, and AUDIT/SC scores. Age and gender were excluded from the models because they were not significant.

Pearson correlation coefficients were estimated to aid in interpretation of associations between quantitative variables, when applicable. Odds ratios (OR) and 95% confidence intervals (CI) are reported when appropriate. An adjusted $\alpha = 0.01$ was used to correct for the five subjective responses analysed in the same model. An $\alpha = 0.05$ was employed for all other analyses. All analyses were completed using SAS v9.4.

3 | RESULTS

3.1 | Demographics

The (mean; standard deviation) age of participants in the laboratory sample was (23.1; 1.9) years and (24.8; 2.3) in the COGA sample. The laboratory sample reported (12.7; 6.0) drinks per week. There were slightly more women than men in both samples (laboratory sample = 55%, COGA sample = 51%).

3.2 | Alcohol self-administration

Many laboratory participants reached the safety limit of 150 mg/dl. DI group significantly predicted the time until a participant reached binge drinking BrAC threshold (80 mg/dl; overall $p = 0.004$, AIC = 153.7) with five participants not reaching 80 mg/dl (Figures 2 and 3). The extreme-risk DI group reached a BrAC of 80 mg/faster (mean 33.3 min) than the high-risk DI group (mean 57.2 min); hazard ratio = 3.33, 95% CI = [1.22, 9.09], $p = 0.02$, and faster than the moderate-risk DI group (mean 85.4 min); hazard ratio = 7.14, 95% CI = [2.22, 21.74], $p = 0.01$; There was an emerging trend in the difference in time between the high- and moderate-risk DI groups; hazard ratio = 2.13, 95% CI = [0.85, 5.26], $p = 0.10$. FHD, nicotine, and gender were not associated with time until binge level exposure occurred for the DI groups (all *p*s > 0.10).

Individuals with higher Maxdrinks also reached 80 mg/dl levels more quickly ($p = 0.004$, hazard ratio = 2.21, AIC = 162.4).

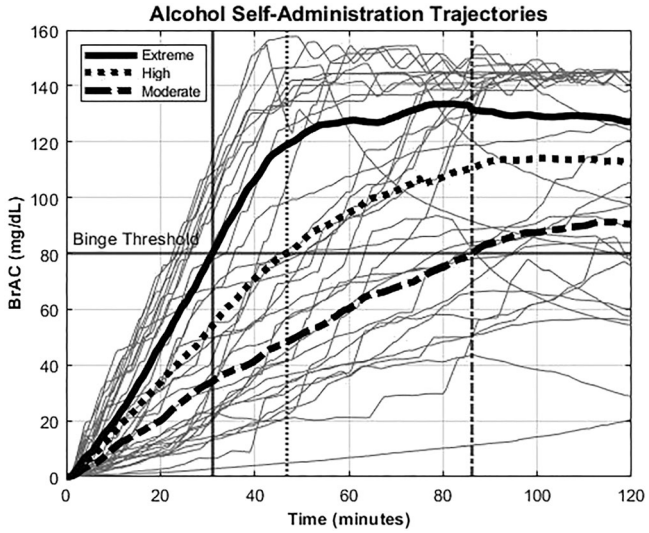

FIGURE 2 Alcohol self-administration trajectories. Individual BrAC time courses and average time course for the DI groups are displayed. Mean times to reach 80 mg/dl are noted by vertical lines.

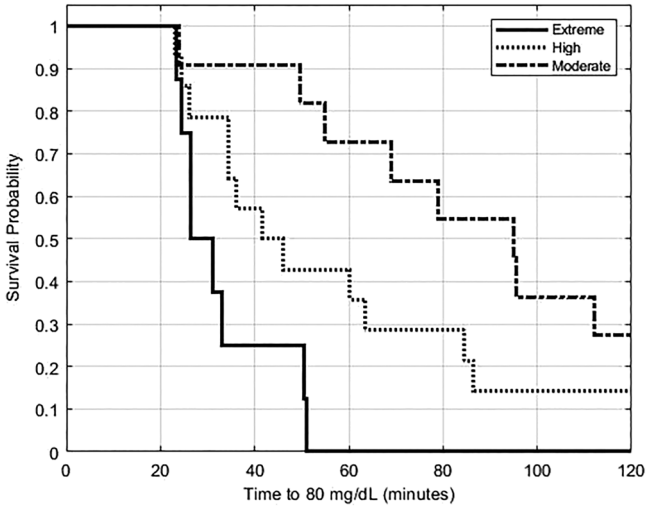

FIGURE 3 Survival analysis of time to a binge alcohol exposure of 80 mg/dl. Kaplan–Meier curves show that drinking intensity group significantly predicted the time until a subject reached binge drinking BrAC threshold ($p = 0.004$). Five total participants did not reach 80 mg/dl, demarcated by the high and moderate group's survival probability remaining non-zero at 120 min.

3.3 | Rate-dependent subjective response

DI group did not predict any rate-dependence of subjective responses (all *p*s ≥ 0.38). FHD by itself predicted rate sensitivity (at $p \leq 0.01$) for two of the five subjective responses to alcohol (Table 2).

3.3.1 | Intoxication

Higher FHD was associated with lower rate-dependent intoxication effects ($p = 0.001$). AUDIT score was not associated with intoxication, per se, ($p = 0.09$), but individuals with both a high FHD and high AUDIT scores reported feeling significantly more intoxication as a function of rate of alcohol exposure (FHD*AUDIT $p = 0.003$).

3.3.2 | Stimulation

Higher FHD was associated with lower rate-dependent stimulation ($p = 0.01$). As with intoxication, AUDIT score was not associated with rate sensitivity of stimulation ($p = 0.10$), although individuals with higher FHD and AUDIT scores reported moderately more stimulation (FHD*AUDIT $p = 0.05$).

3.3.3 | Anxious

There was an association between both higher FHD and higher AUDIT scores and a greater alcohol rate-dependent anxiety ($p = 0.04$ and $p = 0.03$, respectively); however, the significance did not survive correction. There was no significant interaction between AUDIT and FHD and anxiety ($p = 0.09$).

3.3.4 | Sedation and relaxation

No association between alcohol exposure rate and FHD, AUDIT, or their interaction was identified in the measure of Sedation or Relaxation (all *p*s > 0.2).

3.4 | Drinking intensity group

Individuals in the high-risk DI group had higher AUDIT scores than those in the moderate-risk DI group ($p = 0.04$, Table 1A). Those in the

TABLE 2 Beta and standard error of the general linear model rate of change of BrAC coefficients to each subjective response for the full analysis of variance model employing FHD, AUDIT, and FHD*AUDIT

Subjective response	FHD	AUDIT	FHD*AUDIT
Intoxication	−57.2 (15.87)	−0.49 (0.28)	5.66 (1.70)
	***p* = 0.001**	p = 0.088	***p* = 0.003**
Stimulation	−42.58 (15.30)	−0.45 (0.27)	3.40 (1.63)
	***p* = 0.001**	*p* = 0.103	*p* = *0.047*
Anxious	30.96 (14.18)	0.55 (0.25)	−2.68 (1.51)
	p = *0.038*	*p* = *0.034*	*p* = 0.088
Sedation	14.55 (22.22)	0.18 (0.38)	−0.44 (2.36)
	p = 0.516	*p* = 0.645	*p* = 0.855
Relaxation	18.69 (16.62)	0.35 (0.29)	−2.17 (1.78)
	p = 0.271	*p* = 0.240	*p* = 0.232

Note: The computation is shown for assessing FHD, AUDIT score, and the combination. Increasing biological family history of alcohol density was associated with less alcohol exposure rate-dependent sensitivity on the measures of intoxication, representing general drug effects, and on stimulation. Significant effects, based on an adjusted $\alpha \leq 0.01$, shown in bold; marginal effects italicized.
Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; FHD, family history density of biological relatives with an alcohol use disorder.

extreme-risk DI group had higher FHD compared to those in the moderate-risk DI group ($p = 0.036$). There were no pairwise differences between the groups for any other alcohol-related screening variable (all *p*s > 0.2).

3.5 | Family history density

FHD predicted DI group ($p = 0.02$; Score Test $p = 0.40$), a finding that prompted subsequent testing for replication in the COGA sample, given the small laboratory sample size and limited FHD range.

3.5.1 | COGA participants

The COGA sites began with recruitment of AUD probands from inpatient and outpatient treatment facilities and administered a polydiagnostic interview, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA),[66,67] and targeted families with a high density of first-degree relatives with alcohol dependence. Comparison families were recruited within the same communities.[68] To approximate the laboratory sample, COGA were included in analyses only if they were of European ancestry, between the ages of 21 and 28 at their most recent interview, and ever drank at least one full alcohol beverage. One person per extended family corresponding to the participant with the lowest identification number in the age range was retained. The final COGA sample contained $N = 644$ individuals, with 65% having a parent with AUD. FHD was computed in the COGA sample[58] in the same way as the laboratory sample. See Supporting Information for more discussion of the COGA sample.

Higher FHD was associated with greater drinking intensity in the COGA sample ($p = 0.0002$; Score Test $p = 0.54$, Figure S1). Individuals with a higher FHD were 7.75 times more likely to be in the extreme-risk DI group compared with the other DI groups (based on unit of 0.25 in FHD calculation; 95% confidence interval (CI) = [1.45, 40.76]). FHD was not associated with any of the alcohol-related screening measures (all *p*s > 0.30) in the laboratory sample.

4 | DISCUSSION

Rate control is the first human laboratory paradigm where participants had explicit, reproducible control over their *rate* of change of alcohol exposure. The results support our primary hypothesis—that people who report risky drinking self-administered alcohol to a binge level faster. This behaviour suggests that they may consume alcohol to raise their BrAC quickly versus simply achieving a higher level, potentially a pharmacodynamic mechanism underlying risky drinking. Clinically, this observation provides evidence of the importance of counselling people on not only how much and how often but also *how quickly* they drink, urging extra precaution for those with greater FHD. The results support FHD as a risk factor for elevated drinking intensity; it is also associated with subjective response, although in an indirect and complex manner. The findings also build upon previous studies that used retrospective evaluation of a free-access IV alcohol-self-administration paradigm to demonstrate that time to achieve binge levels during a drinking episode reflected risk factors for AUD such as gender, family history of AUD, impulsivity, and level of response.[35,36,38]

As a risk factor, FHD captures a combination of biological (genetic) and psychosocial/environmental factors. The genetics of alcohol consumption has garnered interest (e.g., previous studies[69,70]), yet binge and high-intensity phenotypes are relatively unexplored. Use of the AUDIT consumption subscale[71] has been

productive,[72–74] but this measure does not specifically capture the high-intensity drinking phenotype and may reflect non-problematic alcohol usage.[74] Further, some work suggests the prediction of clinical phenotypes based on AUDIT consumption-based polygenic risk scores may be sample-dependent.[75] Maxdrinks, which, at higher ranges, is more specific to Binge and High-Intensity Drinking, has proven a valuable phenotype in genetic studies.[14,76,77] Consequently, our laboratory finding of an association between FHD and drinking intensity group is congruent with the literature and significantly strengthened by replication in the much larger COGA sample. In fact, supplementary COGA analyses showed that drinking intensity accounted for more variability in the alcohol screening measures than FHD (See Supporting Information), highlighting the importance of collecting information on drinking patterns within and across events.

Our results suggesting that psychodynamic effects of alcohol may be exposure-rate dependent is not new, but remains relatively unexplored.[19–21] Studies using oral challenge techniques have been limited by the lack of control of the alcohol concentration trajectory. Under conditions in which participants could select their exposure rate, FHD, but not drinking intensity group, was associated with rate-dependent subjective response. Specifically, this negative relationship between FHD and the alcohol exposure-rate dependent term for both intoxication and stimulation, suggests that those with higher FHD perceive less of these effects for a given positive exposure rate. Such a person may have to drink faster if intoxication or stimulation is a goal, suggesting support for the low level of response model. Another possibility is that higher FHD is associated with greater, more rapid acute tolerance to intoxicating and stimulating effects.

Exposure-rate sensitivity should be applicable to the descending limb, but few participants in our study chose to reduce their alcohol exposures. Thus, extension of our results to the descending limb and directly comparing to the pre-existing subjective response models of risk is not advised.

Study limitations are primarily related to the small laboratory sample size, resulting in a limited range of FHD and diversity, and limited power to detect smaller effect sizes. Further, Maxdrinks was determined over the 35 day timeline follow-back interval in the laboratory sample compared with the lifetime assessment in the COGA dataset. However, variability in timeframe and drinking pattern assessment is also present in the larger literature,[9,11–14] and the optimal timeframe and metrics for assessing drinking intensity likely varies with the question of interest; potentially serving as either a state or trait risk factor. In the laboratory sample, however, the groups each consumed alcohol over a similar timescale—approximately 3 days per week, and across the entire sample, this was typically the weekend (Figure S2). Thus, the primary difference was the intensity of each event. In that context, our survival analysis results appear to be reflective of recent drinking intensity. Consequently, further study will be required to assess the potential impact of acute and/or chronic tolerance on our alcohol self-administration and subjective response measures, since each theoretically contributes to ongoing rapid alcohol self-administration in the laboratory and the community. Alcohol is not administered intravenously in the community, and our protocol did not include the sensory and environmental cues participants routinely experience when ingesting alcohol. The absence of such cues may have contributed to lack of association between drinking intensity and the subjective responses. The difference in route of administration and environment may limit generalizability, but we chose a controlled lab environment to assess alcohol's pharmacological effect and to allow exquisite control of exposure rates (in contrast to consumption rates) which is not possible with ingestion. Our sessions also began in the morning to allow for monitoring after alcohol-self-administration, and while not a common time-of-day for alcohol consumption for many, the time course of exposures suggests this was not a significant impediment (Figure 2). Finally, we asked subjects how much they enjoyed controlling their rates of exposure. While this positive valence focus is appropriate for those in an early stage of their drinking career (or within the binge-intoxication stage of AUD development, summarized in Koob and Volkow[78]), the instructions may need to be tailored to future populations under study. Despite these limitations, the strengths of this study include obtaining multiple assessments per subject to estimate the pharmacokinetic-pharmacodynamic relationship, constraining the age ranges in the COGA sample to reduce differences between the samples, and replicating Laboratory interview-based results in the much larger COGA sample.

There are several potential uses of the rate control paradigm. Most importantly, these results support the need for studies aiming to change how quickly people drink, the desire for rapidly increasing alcohol exposures, and their underlying neurobiology. Rate control could serve as an endpoint in studies aimed to screen interventions for efficacy prior to larger clinical trials. For example, a reduction (if not elimination) in the time to achieve 80 mg/dl could be considered a successful outcome of intervention, whether it is counselling about the dangers of binge drinking, a repurposed compound, or neuromodulation of reward circuitry. Further, pairing targeted analyses with objectively determined degrees of intense drinking may be a way to identify specific genes (or combinations) underlying subjective response, although obtaining a sufficient sample size may be challenging. Exploration of other contributors to drinking intensity, such as impulsivity[79] and sex as well as sexual identity differences,[80] are also warranted. Further, we envision rate control as an objective tool to examine the role of acute and chronic tolerance on the Binge and High-Intensity Drinking phenotype.

ACKNOWLEDGEMENTS

The cooperation and support of the IU research pharmacy in the preparation of 6% alcohol v/v infusate and of the Indiana Clinical and Translational Sciences Institute Clinical Research Center personnel in the preparation of participants for testing were essential for this research project. The diligent and expert performance of testing procedures by Jim Hays, James Millward, and David Haines are sincerely

appreciated. The programming expertise of Victor Vitvitskiy was vital to this project and most sincerely appreciated.

The Collaborative Study on the Genetics of Alcoholism (COGA), Principal Investigators B. Porjesz, V. Hesselbrock, T. Foroud; Scientific Director, A. Agrawal; Translational Director, D. Dick, includes eleven different centres: University of Connecticut (V. Hesselbrock); Indiana University (H.J. Edenberg, T. Foroud, Y. Liu, M. Plawecki); University of Iowa Carver College of Medicine (S. Kuperman, J. Kramer); SUNY Downstate Health Sciences University (B. Porjesz, J. Meyers, C. Kamarajan, A. Pandey); Washington University in St. Louis (L. Bierut, J. Rice, K. Bucholz, A. Agrawal); University of California at San Diego (M. Schuckit); Rutgers University (J. Tischfield, R. Hart, J. Salvatore); The Children's Hospital of Philadelphia, University of Pennsylvania (L. Almasy); Virginia Commonwealth University (D. Dick); Icahn School of Medicine at Mount Sinai (A. Goate, P. Slesinger); and Howard University (D. Scott). Other COGA collaborators include: L. Bauer (University of Connecticut); J. Nurnberger Jr., L. Wetherill, X., Xuei, D. Lai, S. O'Connor, (Indiana University); G. Chan (University of Iowa; University of Connecticut); D.B. Chorlian, J. Zhang, P. Barr, S. Kinreich, G. Pandey (SUNY Downstate); N. Mullins (Icahn School of Medicine at Mount Sinai); A. Anokhin, S. Hartz, E. Johnson, V. McCutcheon, S. Saccone (Washington University); J. Moore, Z. Pang, S. Kuo (Rutgers University); A. Merikangas (The Children's Hospital of Philadelphia and University of Pennsylvania); F. Aliev (Virginia Commonwealth University); H. Chin and A. Parsian are the NIAAA Staff Collaborators. We continue to be inspired by our memories of Henri Begleiter and Theodore Reich, founding PI and Co-PI of COGA, and also owe a debt of gratitude to other past organizers of COGA, including Ting-Kai Li, P. Michael Conneally, Raymond Crowe, and Wendy Reich, for their critical contributions. This national collaborative study is supported by NIH Grant U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA).

CONFLICT OF INTEREST

None of the authors has any financial or intellectual conflict of interest in this research.

AUTHOR CONTRIBUTIONS

MHP and SOC were responsible for study concept, design, and execution. MHP, JB, and LW performed statistical analyses. MHP, LW, JB, and SOC drafted the manuscript. AK oversaw day-to-day lab operations and provided review of the manuscript for important intellectual content. BS and VR provided insight into analytical strategy. UZ contributed to theoretical design and reviewed the manuscript. MS contributed to the subjective response interpretation. HJE, TF, and JN contributed to the genetic analysis and reviewed the manuscript for important intellectual content. GP, CK, and BP determined FHD in the COGA dataset. All authors critically reviewed content and approved the final version for publication.

INVITATIONS

Investigator interest in adapting the capabilities of the Computer-assisted Alcohol Infusion System to their own research is welcome and those interested should send an email to mplaweck@iupui.edu.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Martin H. Plawecki https://orcid.org/0000-0003-0708-9514
Leah Wetherill https://orcid.org/0000-0003-2888-9051
Vijay A. Ramchandani https://orcid.org/0000-0003-2474-2183

REFERENCES

1. World Health Organization. *Management of Substance Abuse Team*. Geneva, Switzerland: World Health Organization.
2. Naimi TS, Lipscomb LE, Brewer RD, Gilbert BC. Binge drinking in the preconception period and the risk of unintended pregnancy: implications for women and their children. *Pediatrics*. 2003;111(5 Pt 2):1136-1141. doi:10.1542/peds.111.S1.1136
3. Jarvenpaa T, Rinne JO, Koskenvuo M, Raiha I, Kaprio J. Binge drinking in midlife and dementia risk. *Epidemiology*. 2005;16(6):766-771. doi:10.1097/01.ede.0000181307.30826.6c
4. Miller JW, Naimi TS, Brewer RD, Jones SE. Binge drinking and associated health risk behaviors among high school students. *Pediatrics*. 2007;119(1):76-85. doi:10.1542/peds.2006-1517
5. Sundell L, Salomaa V, Vartiainen E, Poikolainen K, Laatikainen T. Increased stroke risk is related to a binge-drinking habit. *Stroke*. 2008;39(12):3179-3184. doi:10.1161/STROKEAHA.108.520817
6. Alcoholism NIoAAa. Drinking levels defined. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking. Accessed 6/22/21 2021.
7. Lindberg L, Brauer S, Wollmer P, Goldberg L, Jones AW, Olsson SG. Breath alcohol concentration determined with a new analyzer using free exhalation predicts almost precisely the arterial blood alcohol concentration. *Forensic Sci Int*. 2007;168(2-3):200-207. doi:10.1016/j.forsciint.2006.07.018
8. Gomez R, Behar KL, Watzl J, et al. Intravenous ethanol infusion decreases human cortical gamma-aminobutyric acid and N-acetylaspartate as measured with proton magnetic resonance spectroscopy at 4 tesla. *Biol Psychiatry*. 2012;71(3):239-246. doi:10.1016/j.biopsych.2011.06.026
9. Hingson RW, Zha W, White AM. Drinking beyond the binge threshold: predictors, consequences, and changes in the U.S. *Am J Prev Med*. 2017;52(6):717-727. doi:10.1016/j.amepre.2017.02.014
10. Linden-Carmichael AN, Vasilenko SA, Lanza ST, Maggs JL. High-intensity drinking versus heavy episodic drinking: prevalence rates and relative odds of alcohol use disorder across adulthood. *Alcohol Clin Exp Res*. 2017;41(10):1754-1759. doi:10.1111/acer.13475
11. Hingson RW, Zha W. Binge drinking above and below twice the adolescent thresholds and health-risk behaviors. *Alcohol Clin Exp Res*. 2018;42(5):904-913. doi:10.1111/acer.13627
12. Creswell KG, Chung T, Skrzynski CJ, et al. Drinking beyond the binge threshold in a clinical sample of adolescents. *Addiction*. 2020;115(8):1472-1481. doi:10.1111/add.14979
13. Patrick ME, Evans-Polce RJ, Parks MJ, Terry-McElrath YM. Drinking intensity at age 29/30 as a predictor of alcohol use disorder

symptoms at age 35 in a national sample. *J Stud Alcohol Drugs*. 2021; 82(3):362-367. doi:10.15288/jsad.2021.82.362
14. Gelernter J, Sun N, Polimanti R, et al. Genome-wide association study of maximum habitual alcohol intake in >140,000 U.S. European and African American veterans yields novel risk loci. *Biol Psychiatry*. 2019; 86(5):365-376. doi:10.1016/j.biopsych.2019.03.984
15. Schuckit MA. Self-rating of alcohol intoxication by young men with and without family histories of alcoholism. *J Stud Alcohol*. 1980;41(3): 242-249. doi:10.15288/jsa.1980.41.242
16. Newlin DB, Thomson JB. Alcohol challenge with sons of alcoholics: a critical review and analysis. *Psychol Bull*. 1990;108(3):383-402. doi: 10.1037/0033-2909.108.3.383
17. Norberg A, Jones AW, Hahn RG, Gabrielsson JL. Role of variability in explaining ethanol pharmacokinetics: research and forensic applications. *Clin Pharmacokinet*. 2003;42(1):1-31. doi:10.2165/00003088-200342010-00001
18. Ramchandani VA, Plawecki M, Li TK, O'Connor S. Intravenous ethanol infusions can mimic the time course of breath alcohol concentrations following oral alcohol administration in healthy volunteers. *Alcohol Clin Exp Res*. 2009;33(5):938-944. doi:10.1111/j.1530-0277.2009.00906.x
19. Martin CS, Earleywine M. Ascending and descending rates of change in blood alcohol concentrations and subjective intoxication ratings. *J Subst Abuse*. 1990;2(3):345-352. doi:10.1016/S0899-3289(10)80006-9
20. Fillmore MT, Vogel-Sprott M. Behavioral impairment under alcohol: cognitive and pharmacokinetic factors. *Alcohol Clin Exp Res*. 1998; 22(7):1476-1482. doi:10.1097/00000374-199810000-00016
21. Morris DH, Amlung MT, Tsai CL, McCarthy DM. Association between overall rate of change in rising breath alcohol concentration and the magnitude of acute tolerance of subjective intoxication via the Mellanby method. *Hum Psychopharmacol*. 2017;32(1):e2565. doi:10.1002/hup.2565
22. Ramchandani VA, O'Connor S, Blekher T, et al. A preliminary study of acute responses to clamped alcohol concentration and family history of alcoholism. *Alcohol Clin Exp Res*. 1999;23(8):1320-1330. doi:10.1111/j.1530-0277.1999.tb04353.x
23. Morzorati SL, Ramchandani VA, Flury L, Li TK, O'Connor S. Self-reported subjective perception of intoxication reflects family history of alcoholism when breath alcohol levels are constant. *Alcohol Clin Exp Res*. 2002;26(8):1299-1306. doi:10.1111/j.1530-0277.2002.tb02670.x
24. Ramchandani VA, Flury L, Morzorati SL, et al. Recent drinking history: association with family history of alcoholism and the acute response to alcohol during a 60 mg% clamp. *J Stud Alcohol*. 2002;63(6):734-744. doi:10.15288/jsa.2002.63.734
25. Kosobud AE, Wetherill L, Plawecki MH, et al. Adaptation of subjective responses to alcohol is affected by an interaction of GABRA2 genotype and recent drinking. *Alcohol Clin Exp Res*. 2015;39(7):1148-1157. doi:10.1111/acer.12749
26. Plawecki MH, Windisch KA, Wetherill L, et al. Alcohol affects the P3 component of an adaptive stop signal task ERP. *Alcohol*. 2018;70:1-10. doi:10.1016/j.alcohol.2017.08.012
27. Wetherill L, Morzorati SL, Foroud T, et al. Subjective perceptions associated with the ascending and descending slopes of breath alcohol exposure vary with recent drinking history. *Alcohol Clin Exp Res*. 2012;36(6):1050-1057. doi:10.1111/j.1530-0277.2011.01642.x
28. Caudill BD, Marlatt GA. Modeling influences in social drinking: an experimental analogue. *J Consult Clin Psychol*. 1975;43(3):405-415. doi:10.1037/h0076689
29. Collins RL, Parks GA, Marlatt GA. Social determinants of alcohol consumption: the effects of social interaction and model status on the self-administration of alcohol. *J Consult Clin Psychol*. 1985;53(2):189-200. doi:10.1037/0022-006X.53.2.189
30. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ. Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. *Psychopharmacology (Berl)*. 2002;160(1):19-29. doi:10.1007/s002130100919
31. Anton RF, Drobes DJ, Voronin K, Durazo-Avizu R, Moak D. Naltrexone effects on alcohol consumption in a clinical laboratory paradigm: temporal effects of drinking. *Psychopharmacology (Berl)*. 2004; 173(1–2):32-40. doi:10.1007/s00213-003-1720-7
32. Davidson D, Palfai T, Bird C, Swift R. Effects of naltrexone on alcohol self-administration in heavy drinkers. *Alcohol Clin Exp Res*. 1999;23(2): 195-203. doi:10.1111/j.1530-0277.1999.tb04099.x
33. Schneider VJ 2nd, Bush N, Vitus D, Carpenter RW, Robinson M, Boissoneault J. A virtual reality platform for the measurement of drinking topography. *Drug Alcohol Depend*. 2022;231:109246. doi:10.1016/j.drugalcdep.2021.109246
34. Corbin WR, Gearhardt A, Fromme K. Stimulant alcohol effects prime within session drinking behavior. *Psychopharmacology (Berl)*. 2008; 197(2):327-337. doi:10.1007/s00213-007-1039-x
35. Stangl BL, Vatsalya V, Zametkin MR, et al. Exposure-response relationships during free-access intravenous alcohol self-administration in nondependent drinkers: influence of alcohol expectancies and impulsivity. *Int J Neuropsychopharmacol*. 2017;20(1):31-39. doi:10.1093/ijnp/pyw090
36. Gowin JL, Sloan ME, Stangl BL, Vatsalya V, Ramchandani VA. Vulnerability for alcohol use disorder and rate of alcohol consumption. *Am J Psychiatry*. 2017;174(11):1094-1101. doi:10.1176/appi.ajp.2017.16101180
37. Hendershot CS, Claus ED, Ramchandani VA. Associations of OPRM1 A118G and alcohol sensitivity with intravenous alcohol self-administration in young adults. *Addict Biol*. 2016;21(1):125-135. doi:10.1111/adb.12165
38. Sloan ME, Gowin JL, Janakiraman R, et al. High-risk social drinkers and heavy drinkers display similar rates of alcohol consumption. *Addict Biol*. 2020;25(2):e12734. doi:10.1111/adb.12734
39. Carpenter RW, Merrill JE. How much and how fast: alcohol consumption patterns, drinking-episode affect, and next-day consequences in the daily life of underage heavy drinkers. *Drug Alcohol Depend*. 2021;218:108407. doi:10.1016/j.drugalcdep.2020.108407
40. Sobell LC, Sobell MB. *Timeline Follow-Back: A Technique for Assessing Self-Reported Alcohol Consumption*. Totowa, NJ: Humana Press; 1992; doi:10.1007/978-1-4612-0357-5_3
41. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the alcohol timeline followback when administered by telephone and by computer. *Drug Alcohol Depend*. 1996;42(1):49-54. doi:10.1016/0376-8716(96)01263-X
42. Plawecki MH, Decarlo R, Ramchandani VA, O'Connor S. Improved transformation of morphometric measurements for a priori parameter estimation in a physiologically-based pharmacokinetic model of ethanol. *Biomed Signal Process Control*. 2007;2(2):97-110. doi:10.1016/j.bspc.2007.04.001
43. Zimmermann US, Mick I, Laucht M, et al. Offspring of parents with an alcohol use disorder prefer higher levels of brain alcohol exposure in experiments involving computer-assisted self-infusion of ethanol (CASE). *Psychopharmacology (Berl)*. 2009;202(4):689-697. doi:10.1007/s00213-008-1349-7
44. Zimmermann US, Mick I, Vitvitskyi V, Plawecki MH, Mann KF, O'Connor S. Development and pilot validation of computer-assisted self-infusion of ethanol (CASE): a new method to study alcohol self-administration in humans. *Alcohol Clin Exp Res*. 2008;32(7):1321-1328. doi:10.1111/j.1530-0277.2008.00700.x
45. Plawecki MH, Wetherill L, Vitvitskiy V, et al. Voluntary intravenous self-administration of alcohol detects an interaction between GABAergic manipulation and GABRG1 polymorphism genotype: a

pilot study. *Alcohol Clin Exp Res*. 2013;37(Suppl 1):E152-E160. doi:10.1111/j.1530-0277.2012.01885.x
46. Loeppky JA, Myhre LG, Venters MD, Luft UC. Total body water and lean body mass estimated by ethanol dilution. *J Appl Physiol Respir Environ Exerc Physiol*. 1977;42(6):803-808. doi:10.1152/jappl.1977.42.6.803
47. Watson PE. *Total Body Water and Blood Alcohol Levels: Updating the Fundamentals*. Boca Raton, Fla.: CRC Press; 1989.
48. Endres HG, Gruner O. Comparison of D2O and ethanol dilutions in total body water measurements in humans. *Clin Investig*. 1994;72(11):830-837.
49. Norberg A, Sandhagen B, Bratteby LE, et al. Do ethanol and deuterium oxide distribute into the same water space in healthy volunteers? *Alcohol Clin Exp Res*. 2001;25(10):1423-1430. doi:10.1111/j.1530-0277.2001.tb02143.x
50. Plawecki MH, White K, Kosobud AEK, et al. Sex differences in motivation to self-administer alcohol after 2 weeks of abstinence in young-adult heavy drinkers. *Alcohol Clin Exp Res*. 2018;42(10):1897-1908. doi:10.1111/acer.13860
51. Plawecki MH, Durrani AM, Boes J, et al. Comparison of subjective responses to oral and intravenous alcohol administration under similar systemic exposures. *Alcohol Clin Exp Res*. 2019;43(4):597-606. doi:10.1111/acer.13970
52. Judd LL, Hubbard RB, Huey LY, Attewell PA, Janowsky DS, Takahashi KI. Lithium carbonate and ethanol induced "highs" in normal subjects. *Arch Gen Psychiatry*. 1977;34(4):463-467. doi:10.1001/archpsyc.1977.01770160097008
53. Schuckit MA. Subjective responses to alcohol in sons of alcoholics and control subjects. *Arch Gen Psychiatry*. 1984;41(9):879-884. doi:10.1001/archpsyc.1984.01790200061008
54. Schuckit MA, Gold EO. A simultaneous evaluation of multiple markers of ethanol/placebo challenges in sons of alcoholics and controls. *Arch Gen Psychiatry*. 1988;45(3):211-216. doi:10.1001/archpsyc.1988.01800270019002
55. Schuckit MA, Smith TL, Kalmijn J, Tsuang J, Hesselbrock V, Bucholz K. Response to alcohol in daughters of alcoholics: a pilot study and a comparison with sons of alcoholics. *Alcohol Alcohol*. 2000;35(3):242-248. doi:10.1093/alcalc/35.3.242
56. Rueger SY, King AC. Validation of the brief Biphasic Alcohol Effects Scale (B-BAES). *Alcohol Clin Exp Res*. 2013;37(3):470-476. doi:10.1111/j.1530-0277.2012.01941.x
57. Morean ME, Corbin WR, Treat TA. The Subjective Effects of Alcohol Scale: development and psychometric evaluation of a novel assessment tool for measuring subjective response to alcohol. *Psychol Assess*. 2013;25(3):780-795. doi:10.1037/a0032542
58. Plawecki MH, Zimmermann US, Vitvitskiy V, Doerschuk PC, Crabb D, O'Connor S. Alcohol exposure rate control through physiologically based pharmacokinetic modeling. *Alcohol Clin Exp Res*. 2012;36(6):1042-1049. doi:10.1111/j.1530-0277.2011.01706.x
59. Rice JP, Reich T, Bucholz KK, et al. Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcohol Clin Exp Res*. 1995;19(4):1018-1023. doi:10.1111/j.1530-0277.1995.tb00983.x
60. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption—II. *Addiction*. 1993;88(6):791-804. doi:10.1111/j.1360-0443.1993.tb02093.x
61. Flannery BA, Volpicelli JR, Pettinati HM. Psychometric properties of the Penn Alcohol Craving Scale. *Alcohol Clin Exp Res*. 1999;23(8):1289-1295. doi:10.1111/j.1530-0277.1999.tb04349.x
62. Schuckit MA, Smith TL. Changes over time in the self-reported level of response to alcohol. *Alcohol Alcohol*. 2004;39(5):433-438. doi:10.1093/alcalc/agh081
63. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict*. 1989;84(11):1353-1357. doi:10.1111/j.1360-0443.1989.tb00737.x
64. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*. 1997;12(2):277-287. doi:10.1037/0882-7974.12.2.277
65. Stoltenberg SF, Mudd SA, Blow FC, Hill EM. Evaluating measures of family history of alcoholism: density versus dichotomy. *Addiction*. 1998;93(10):1511-1520. doi:10.1046/j.1360-0443.1998.931015117.x
66. Bucholz KK, Cadoret R, Cloninger CR, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *JStudAlcohol*. 1994;55(2):149-158. doi:10.15288/jsa.1994.55.149
67. Hesselbrock M, Easton C, Bucholz KK, Schuckit M, Hesselbrock V. A validity study of the SSAGA-a comparison with the SCAN. *Addiction*. 1999;94(9):1361-1370. doi:10.1046/j.1360-0443.1999.94913618.x
68. Edenberg HJ, Bierut LJ, Boyce P, et al. Description of the data from the Collaborative Study on the Genetics of Alcoholism (COGA) and single-nucleotide polymorphism genotyping for Genetic Analysis Workshop 14. *BMC Genet*. 2005;6(Suppl 1):S2. doi:10.1186/1471-2156-6-S1-S2
69. Schumann G, Coin LJ, Lourdusamy A, et al. Genome-wide association and genetic functional studies identify autism susceptibility candidate 2 gene (AUTS2) in the regulation of alcohol consumption. *Proc Natl Acad Sci U S a*. 2011;108(17):7119-7124. doi:10.1073/pnas.1017288108
70. Clarke TK, Adams MJ, Davies G, et al. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). *Mol Psychiatry*. 2017;22(10):1376-1384. doi:10.1038/mp.2017.153
71. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Arch Intern Med*. 1998;158(16):1789-1795. doi:10.1001/archinte.158.16.1789
72. Kranzler HR, Zhou H, Kember RL, et al. Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nat Commun*. 2019;10(1):1499. doi:10.1038/s41467-019-09480-8
73. Sanchez-Roige S, Palmer AA, Fontanillas P, et al. Genome-wide association study meta-analysis of the Alcohol Use Disorders Identification Test (AUDIT) in two population-based cohorts. *Am J Psychiatry*. 2019;176(2):107-118. doi:10.1176/appi.ajp.2018.18040369
74. Mallard TT, Savage JE, Johnson EC, et al. Item-level genome-wide association study of the alcohol use disorders identification test in three population-based cohorts. *Am J Psychiatry*. 2021; PMID: appiajp202020091390.
75. Johnson EC, Sanchez-Roige S, Acion L, et al. Polygenic contributions to alcohol use and alcohol use disorders across population-based and clinically ascertained samples. *Psychol Med*. 2020;1-10.
76. Kapoor M, Wang JC, Wetherill L, et al. A meta-analysis of two genome-wide association studies to identify novel loci for maximum number of alcoholic drinks. *Hum Genet*. 2013;132(10):1141-1151. doi:10.1007/s00439-013-1318-z
77. Xu K, Kranzler HR, Sherva R, et al. Genomewide association study for maximum number of alcoholic drinks in European Americans and

African Americans. *Alcohol Clin Exp Res*. 2015;39(7):1137-1147. doi:10.1111/acer.12751
78. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760-773. doi:10.1016/S2215-0366(16)00104-8
79. Adan A, Forero DA, Navarro JF. Personality traits related to binge drinking: a systematic review. *Front Psych*. 2017;8:134. doi:10.3389/fpsyt.2017.00134
80. Fish JN, Hughes TL, Russell ST. Sexual identity differences in high-intensity binge drinking: findings from a US national sample. *Addiction*. 2018;113(4):749-758. doi:10.1111/add.14041

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Plawecki MH, Boes J, Wetherill L, et al. Binge and high-intensity drinking—Associations with intravenous alcohol self-administration and underlying risk factors. *Addiction Biology*. 2022;27(6):e13228. doi:10.1111/adb.13228