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Heterogeneous Dose-Response Analyses of Alcohol Abuse and Dependence

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Abstract

Background: Survey-based estimates of the prevalence of alcohol abuse, dependence and disorders in the US rely upon self-reports of drinking patterns (e.g., binge drinking), social problems (e.g., trouble at work), physiological responses to use (e.g., tolerance) and desistance from use (e.g., withdrawal). Diagnostic criteria derived from these reports enable prevalence estimates of abuse and dependence, but moderating structural relationships among symptom groups may lead some light and moderate drinkers to appear to exhibit an alcohol use disorder.

Methods: A dynamic model of drinking and problems predicts that symptoms of dependence will moderate relationships between drinking measures and symptoms of abuse. Wave 1 NESARC data on DSM-IV diagnoses of abuse and dependence were used to test predictions from this model and assess whether moderating effects were observed among lighter and heavier drinkers (those who drink 1–3 vs. 4 or more drinks on average). A dose-response model that accounts for other known sources of risk heterogeneity related to drinking and problems enabled us to test these predictions.

Results: As expected from previous work, symptoms of abuse and dependence and dependence criteria were nonlinearly related to drinking patterns; more symptom reports appeared and criteria were met among less frequent drinkers who drank more on each occasion and this pattern of dose-response was substantially moderated among heavier drinkers. Controlling for these effects, relationships between drinking and symptoms of abuse were moderated among respondents who met more dependence criteria. These effects were observed among both lighter and heavier drinkers.

Conclusions: Moderating relationships observed between measures of drinking, abuse and dependence criteria among lighter and heavier drinkers suggest that the same etiologic forces are at play among all drinking groups. Greater symptoms of dependence among lighter drinkers may lead to greater reports of symptoms of abuse and an AUD diagnosis.

Keywords

Alcohol Use Disorder; Abuse; Dependence; DSM-IV; Drinking Problems

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Estimates of the population prevalence of alcohol abuse, dependence and alcohol use disorders (AUDs) in the U.S. have historically relied upon symptom reports obtained from self-report population surveys of adults. Over the past three decades great progress has been made toward developing reliable and valid survey instruments to assess DSM-IV diagnoses of abuse and dependence in the National Epidemiologic Survey of Alcohol use and Related Conditions (NESARC) and its successors (Grant & Dawson, 2006). And in recent years these have been extended to assessments of diagnoses of alcohol use disorders in DSM-5 (Grant, et al., 2015). Not surprisingly, statistical estimates of relationships between measures of drinking (e.g., average quantity of alcohol consumed) and survey-based diagnoses of abuse and dependence universally find greater prevalence among “heavier” drinkers; so much so that heavier drinking on its own has been used to index AUDs (Dawson, et al., 2005a). However, these survey instruments do not identify all “heavier” drinkers as having abuse or dependence and survey-based diagnoses of abuse and dependence can be found among persons typically classified as “light” or “moderate” drinkers.

Although there are no firm criteria that define “light”, “moderate” and “heavier” drinking (see Gruenewald, et al., 2016), some drinkers who consume relatively small quantities of alcohol appear to meet some AUD diagnostic criteria. As shown by a cross-tabulation of Wave 1 NESARC data presented in Figure 1, national estimates of the percent of drinkers consuming successively larger average quantities of alcohol decreases from 1 to 12 drinks while the prevalence of DSM-IV dependence diagnoses increases. Surprisingly, some diagnoses appear among those drinkers who consume on average just two drinks on each drinking occasion. This may be due to measurement error in assessments of diagnostic outcomes (Saha, et al., 2006; Caetano, 2015); misclassification rates among “lighter” drinkers may lead some to be classified as dependent due to measurement error alone. These cases may also arise from biased self-reports; if some dependent drinkers under-report drinking, dependence will appear at lower drinking levels (Devaux and Sassi, 2015).

The appearance of dependence diagnoses among “lighter” drinkers may also arise because these drinkers do, indeed, experience dependence symptoms, although at drinking levels considerably lower than those of “heavier” drinkers. Symptoms of dependence may appear at lower drinking levels due to predisposing genetic determinants or impacts related to the neurobiological life course of addiction that appear at early stages of abuse (Koob and Le Moel, 2006; Zucker, 2006). “Lighter” quantity dependent drinkers may report drinking more than they normally would, report that their usual drinking quantity had less of an effect than it once did, put aside other pleasurable activities to drink, and/or report having unsuccessfully tried to cut down drinking and continued to drink despite problems. If so, these “lighter” quantity dependent drinkers may have more problems than others drinking at the same level, may be drinking despite the problems they experience at these “lighter” drinking levels and appear, despite their lower drinking levels, to be dependent (West and Brown, 2013). Consequently, structural relationships between measures of drinking and symptoms of abuse and dependence may be qualitatively the same among “lighter” and “heavier” drinkers but with “lighter” drinkers drinking, of course, much less. Thus, we suggest that symptoms of dependence among “lighter” drinkers will moderate the relationships between drinking and self-report symptoms of abuse in the same way as

observed among “heavier” drinkers. Neither measurement errors nor self-report biases predict these relationships

A Model of Drinking, Problems and Dependence

In this article, we argue that symptoms of dependence moderate relationships between drinking and problems (including symptoms of abuse) regardless of quantities consumed. Based on our previous work, we assume that under most conditions drinking is a self-regulating behavior; greater drinking leads to more problems and, under most circumstances, those problems regulate further use (Gruenewald and Mair, 2015). This negative feedback control generally constrains heavier drinking, but can be mitigated by exogenous forces that encourage drinking (e.g., peer pressure) or endogenous forces that maintain drinking (e.g., tolerance). Quantities of alcohol consumed on any drinking event, Q_e , are contingent upon problems, P_{e-1} , and benefits, B_{e-1} , associated with drinking on previous occasions, Q_{e-1} (Figure 2). Problems, P_{e-1} , and benefits, B_{e-1} , are assumed to be directly proportional to drinking quantities, βQ_{e-1} and αQ_{e-1} , with problems constraining subsequent use, $-\delta P_{e-1}$, and benefits encouraging subsequent use, γB_{e-1} .

Formulated in discrete terms (de Vries, et al., 2006), quantity consumed, Q_e , is a function of that consumed on the prior event, $Q_e = KQ_{e-1}$, which is moderated by problems and benefits:

$$Q_e = (K - \beta\delta Q_{e-1} + \alpha\gamma Q_{e-1})Q_{e-1} \quad (1)$$

with equilibrium quantities representing a balance of problems and benefits:

$$Q^* = (K - 1) / (\beta\delta - \alpha\gamma) \quad (2)$$

Rearranging equation 2, dose-response, the function relating drinking problems to drinking quantities in equilibrium, $b^* \equiv P^*/Q^*$, will be inversely related to Q^* (heterogeneous dose-response, Gruenewald and Mair, 2015) and directly related to benefits, $\alpha\gamma$:

$$\beta^* = (K - 1) / \delta Q^* + \alpha\gamma / \delta \quad (3)$$

Since b^* is inversely related to Q^* “heavier” drinkers will exhibit fewer additional problems for each additional drink consumed while “lighter” drinkers will exhibit more problems for each additional drink consumed (Gruenewald and Mair, 2015). In addition, greater benefits related to drinking, larger values of $\alpha\gamma$, and reduced negative feedback control, smaller values of δ , will be related to more problems for each additional drink consumed. Considering the benefits related to heavier drinking, $\alpha\gamma$, heavier drinkers may need to drink more to achieve the same benefits (or same level of intoxication, tolerance) or to avoid negative consequences related to less use (withdrawal). Considering failures to incorporate problems into future drinking decisions, δ , compulsions to drink may overcome feedback control. Thus, symptoms of dependence are expected to have direct and, more critically, moderating effects on dose-response.

DSM Diagnostic Criteria and Dose-Response

We assess DSM-IV abuse and dependence symptom counts and criteria for AUD using AUDADIS-IV questionnaire items established in NESARC (American Psychiatric Association, 1994; Grant et al., 2004). These have been shown to be reliable and valid in previous work (Grant et al., 1995, 2003). In order for a drinker to be categorized as having AUD, one of four abuse criteria must be met and three of seven dependence criteria must cluster within a 12 month period. Representing problems related to drinking, symptoms of abuse include failures in role obligations, interpersonal problems, hazards related to drinking, and legal problems. Symptoms of dependence include compulsive drinking (e.g., drinking despite problems, unsuccessful efforts to cut down) and persistent heavy alcohol use (tolerance and withdrawal). Withdrawal is measured as a syndrome, requiring at least two positive symptoms of withdrawal or one positive symptom of withdrawal relief/avoidance. Thus, each dependence symptom represents a psychological or physiological inducement to drink that defeats negative feedback control.

The recent shift from DSM-IV diagnostics for alcohol abuse and dependence to DSM-5 diagnostics for AUDs would appear to limit the relevance of DSM-IV to the estimation of AUDs in the current US population. However, symptoms assessed in DSM-IV and DSM-5 instruments are essentially the same, with the DSM-5 eliminating one symptom of abuse (legal problems) and adding one related to dependence (craving). For this reason, other than differences that arise due to changing criteria for AUD, the results of epidemiological surveys using DSM-5 instrumentation do not substantively diverge from those for DSM-IV (Grant, et al., 2015) and the correlates of AUD remain similar (Dawson, et al, 2013). In addition, although clinical interpretation of symptom scores from DSM-5 is currently focused solely on diagnoses of AUD rather than abuse and dependence *per se*, the internal relationships between measures of abuse, as problems related to drinking, and dependence, as that collection of symptoms reflecting among other things indicators of tolerance and withdrawal, remain relevant. In particular, the expected role of reduced negative feedback control among respondents reporting greater symptoms of dependence will remain in DSM-5 symptom reports of symptoms related to abuse much as it is predicted to arise in DSM-IV.

With these thoughts in mind, we use equation 3 to guide an examination of dose-response relationships between drinking patterns and symptoms of abuse and dependence. We first assess whether DSM-IV abuse and dependence symptoms exhibit heterogeneous dose-response relationships like other problems related to drinking; symptom counts should increase over greater quantities consumed but in a decelerating manner reflecting the reciprocal relationship between problems and Q^* as demonstrated by Gruenewald and Mair (2015). We then examine whether dose-response relationships between drinking and symptoms of abuse are directly affected and moderated by greater symptoms of dependence for all drinkers and drinkers who consume relatively few (1–3 drinks) vs. more average drinks per occasion. If symptoms of dependence affect dose-response relationships in similar ways among light and heavier drinkers, it can be argued that dependence symptoms affect abuse reports in both groups.

Materials and Methods

We examine relationships between drinking, abuse and dependence among heavier vs. lighter drinkers using Wave 1 NESARC data, collected in 2001–2002. Although this source is almost two decades old, these data have been carefully studied, have been the source of many estimates of the etiologic supports and demographic distributions of AUD and AUD symptoms in the US, and include essentially the same symptom reports covered in DSM-5. Importantly, while there have been some changes in the composition and levels of drinking among some groups (e.g., especially among women, Dawson, et al., 2015), and these will likely be related to greater reports of AUD symptoms, patterns of drinking and problems in the US population as a whole have remained stable over time and there is no evidence that structural relationships between demographic characteristics of the drinking population and AUD symptom reports have changed.

Statistical analyses are informed by the model outlined in Figure 2 (equation 1) and its equilibrium conditions (equations 2 and 3). Noting that the dimension of b^* in equation 3 is number of problems (symptoms) associated with a one unit increase in average drinking quantity, estimates of this parameter can be obtained using an empirical dose-response measurement model developed for this purpose (Gruenewald and Mair, 2015).

NESARC

NESARC is a large, nationally representative sample of adults in the United States focused on the occurrence of psychological and substance use disorders (Grant and Dawson, 2006). Diagnostic classifications were assessed using a semi-structured diagnostic interview schedule (AUDADIS-IV) defined in accordance with DSM-IV criteria. The sample was designed to represent the adult population of the United States, using the sampling frame of the 2000 Census Supplementary Survey. African Americans, Hispanics, and young adults (ages 18–24) were oversampled to provide adequate sample sizes. 43,093 respondents were enrolled, with a response rate of 81% (Dawson, 2005b; Chen, 2004). Nearly two thirds (65.4%) of respondents reported past-year drinking. NESARC's complex sampling design requires the use of calculated weights to account for design effects. Once weighted, the data were adjusted to be representative of the US population based on the 2000 Census. These weights have made NESARC particularly important in describing nationally representative associations between alcohol use and dependence, drinking patterns, and psychiatric and other substance use disorders (e.g., Grant, 2004; Dawson, 2004).

Symptoms of abuse were measured as the sum of symptom reports related to (1) failure to fulfill major role obligations, (2) continuing to drink despite social or interpersonal problems, (3) recurrent drinking in hazardous situations, and (4) alcohol-related legal problems. Symptoms of dependence were measured as the sum of symptom reports related to persistent drinking despite problems, drinking larger amounts over time, activities given up or reduced due to drinking, unsuccessful efforts to cut down, time spent in activities to obtain drink or recover from drinking, and symptoms of tolerance and withdrawal. Since tolerance and withdrawal were measured as syndromes represented by responses to symptom groups, we summarized the number of symptom criteria met for each respondent

(zero through seven criteria). We then characterized each respondent as meeting no, one-or-two, or three-or-more dependence criteria.

NESARC measures of frequencies of drinking over the previous year, average quantities consumed across these occasions, and total volume were used in all analysis models. Frequency was assessed by asking how often respondents drank alcohol in the last 12 months (10 response categories, recoded to the lowest value in each category) (mean 76.4 (SD 105.1)). Average quantity was assessed as the number of drinks of any alcohol usually consumed on days when respondents drank alcohol in last 12 months (mean 2.5 (SD 2.3), range 1–48). Total volume was calculated as past-year frequency*average quantity. All models were also adjusted for a set of effect coded covariates. These included individuals' gender, age (18–29, 30–44), race/ethnicity (white, black), marital status (married, divorced/separated), education (high school graduate, college graduate), and family income (\$20,000–\$35,000, \$35,001–\$70,000, \$70,000+).

Measuring Dose-Response

Correlational assessments of relationships between drinking problems and self-reported drinking quantities or volumes do not adequately represent dose-response effects (see Gruenewald and Mair, 2015). Since the accumulation of drinking problems over any time frame is a strong function of drinking “exposures,” the frequencies which alcohol is used, the impacts of these exposures must be modeled in a specific way to obtain meaningful estimates of dose-response. Thus, if it is assumed that the rate at which drinking problems arise over F successive drinking occasions, R_f , is proportional to the number of days on which drinking takes place, bF , and that risks increasing linearly for each additional drink consumed beyond the first drink on each occasion, then it can be shown that problem rates are a function of drinking frequencies and additional volumes consumed over time, $c(V-F)$:

$$R_f = a + bF + c(V-F) \quad (4)$$

where parameter c in this equation reflects the dose-response effect, β^* , in equation 3, the additional rate of problems over F drinking occasions related to an additional drink consumed. If, as also indicated in equation 3, dose-response is an inverse function of average drinking quantities, $1/Q_m$, then parameter c can be represented by the function $c+d/Q_m$, relating β^* to equilibrium drinking quantities, Q^* . Intuitively, the function $c+d/Q_m$ reflects the decline in negative feedback control over drinking that we expect to observed among heavier drinkers who consume greater average drinking quantities, Q_m (Gruenewald and Mair, 2015) which, when introduced into equation (4) leads to this measurement model for dose-response:

$$R_f = a + bF + c(V-F) + d(V-F)Q_m^{-1} \quad (5)$$

In the current case, R_f will represent symptom counts of abuse or dependence over F drinking occasions in the previous year and the parameters of the model will reflect

unexplained sources of risk, a, risks related to each drinking event regardless of drinking quantity, b, increased risks related alcohol consumed beyond the first drink, c, and attenuation in growth of these risks typically seen among heavier drinkers, d.

Statistical Approach

Our statistical approach is dictated by theoretical argument and the equations presented above. As suggested by equation 3 and shown in Figure 2, symptoms of dependence are expected to affect both the intercepts and slopes of dose-response functions, represented by parameters c and d in equation 5. In order to test these hypotheses we used censored regression models to relate symptoms of abuse and dependence to measures of drinking patterns, F, V-F, and $(V-F)Q_m^{-1}$ and sociodemographic covariates, with controls for biases due to heteroscedasticity related to F and V identified by Gruenewald, et al. (2016). We then assessed the degree to which dose-response relationships between drinking and symptoms of abuse were moderated across three levels of dependence criteria (none, 1–2, 3+ symptoms). Stata Version 14 tobithtem procedures enabled corrections for multiplicative heteroscedasticity using survey data from complex multistage sampling designs and survey weights (Shehata, 2011). The dose-response model in equation 5 identifies linear relationships between cumulated problems (symptoms) per unit time, R_f , and patterns of alcohol use. Although Poisson and Negative Binomial models are preferred for what are, ostensibly, count data, the log-linear form of these models precludes application in quantitative contexts which dictate that predictors and outcomes be linearly related. In this case, Tobit models are a reasonable alternative approach (Hilbe, 2011).

Results

Table 1 provides descriptive statistics for measures used in the current study. Table 2 summarizes the results of dose-response analyses of symptoms of abuse and dependence and dependence criteria. A number of statistical controls for demographic variables and all controls for heteroscedasticity were significant in all models. Statistically controlling for these effects, significant dose-response effects were also observed for all three outcomes. Effects related to F were negative; spreading drinking volumes across greater numbers of drinking occasions was associated with fewer symptoms of abuse, dependence, and dependence criteria. Effects related to continued drinking volumes, V-F, and heterogeneous risks, $(V-F)(1/Q_m)$, were both positive and significant, demonstrating greater risks related to heavier use and decreasing dose-response among heavier drinkers. Thus, all three outcomes behave much as expected from previous dose-response analyses relating drinking and problems; although heavier drinking was associated with more abuse and dependence symptoms on average, lighter drinkers were more dose-responsive than heavier drinkers.

The derived dose-response functions from the parameter estimates presented in Table 2 are shown in Figure 3. Each plot represents the association of average drinking quantities with symptoms of abuse (top left), dependence (top right), and dependence criteria (bottom) reported over the past year. Scaled to an annual average drinking frequency of $F=76.45$ occasions, the ordinate of each figure provides an estimate of the average number of symptoms reported over a one year period. The black curve in each figure shows that overall

risks increased across drinking quantities but in a decelerating manner, increasing less at higher quantities. The gray lines show that dose-response decreased across drinking quantities (shown for even numbered values). Thus, heavier drinkers had less dose-response but greater problems at average levels of use.. Non-negligible symptoms of abuse and dependence and dependence criteria were observed among drinkers consuming an average of two and three drinks. These drinkers were also reported more symptoms of abuse and dependence for each additional drink consumed than heavier drinkers (heterogenous dose-response).

Table 3 presents an analysis of symptoms of abuse examining dose-response effects for persons meeting greater numbers of dependence criteria. The reference group for the analysis was those respondents who met no symptom criteria, with dummy variables indicating those who had met 1 or 2, or 3 or more criteria. Covariates related to demographic effects and controls for heteroscedasticity continued to be significant but, in addition, model parameters b, c and d from equation 5, estimated respectively in relation to measures F, V-F, and $(V-F)/(1/Q_m)$, significantly differed across dependence criteria groups [$F(6,60)=39.15$, $p<0.001$]. Looking at each parameter separately, coefficients b and d differed across groups [$F(2,64)=16.29$, $p<0.001$; $F(2,64)=6.02$, $p=0.004$] while c did not [$V-F$, $F(2,64)=0.94$, $p=0.3972$]. Average numbers of symptoms associated with each drinking occasion, coefficient b, increased with numbers of dependence criteria met. Average dose-response, coefficient c, did not differ between groups. And, finally, heterogeneous dose-response, coefficient d, differed between groups, decreasing in association with greater symptom criteria.

Noting that the reference group for coding of dependence criteria groups was that meeting no dependence criteria, the parameter estimates for dose-response to the left of the table were used to calculate the group-level dose-response effects appearing to the right. These can be directly interpreted and show that the parameter related to F was greater among those with more dependence criteria; greater numbers of dependence criteria were associated with more reported symptoms of abuse. The parameter related to $(V-F)/(1/Q)$ declined over greater dependence criteria; greater numbers of dependence criteria were related to decreased dose-response suggesting less negative feedback control over drinking at higher drinking quantities. The overall pattern of reduced negative feedback control over drinking among those drinkers meeting more symptom criteria is shown by the functions displayed for each group in Figure 4. Each line in the plot is limited to those drinking levels that constituted 95% of each group's drinking events. Thus, many of those who met no dependence criteria averaged a single drink per occasion while those who reported one or more typically averaged more than a single drink. While the measure of negative feedback control declined over drinks for all groups those respondents with no dependence criteria showed markedly greater negative feedback control over drinking than others. (An additional set of specification tests showed that the same effects were observed among men, women, and the different age groups in the study; confidence intervals for all dose-response parameters overlapped those displayed in Table 3.)

Finally, the analysis comparing dose-response effects among those drinkers who consumed average quantities of 1 through 3 drinks vs. those who consumed 4 or more demonstrated no

significant differences between groups in coefficient estimates with respect to parameters b [$F(3,63)=1.33$, $p=0.271$], c [$F(3,63)=0.50$, $p=0.683$], or d [$F(3,63)=0.60$, $p=0.620$]. Thus, while number of dependence criteria met was related to differences in model parameters (Table 3, Figure 4), these effects were the same among drinkers who consumed an average of 1 through 3 or 4 or more average drinks per occasion. Estimated impacts of dependence criteria on dose-response were the same for both groups.

Discussion

The results of the study clearly indicate that there are substantive nonlinear dose-response relationships between drinking patterns, symptoms of abuse and dependence, and dependence criteria (Figure 3). This observation affirms those made in our previous investigations relating drinking patterns to problems; heavier drinkers who consume greater average quantities of alcohol exhibit greater risks for self-reported problems, but these problems are less dose-responsive over each additional average drink consumed. By argument, drinking problems serve as less of a constraint over use among heavier than lighter drinkers. While this observation is not surprising in light of previous work and current modeling efforts (equation 3), it reflects an important observation regarding individual vs. population assessments of problem risks. Among individual drinkers, problem risks will increase monotonically across drinking quantities (Figure 3), but across populations of drinkers risks for problems will peak at relatively moderate drinking levels (2 through 4 drinks; Gruenewald and Mair, 2015). The much larger population of light and moderate drinkers in the US (Figure 1) will present substantially greater numbers of symptoms of abuse and dependence than that of heavier drinkers. Thus it should be no surprise that some light and moderate drinkers are found to exhibit clinically significant indicators of AUD. Among heavier drinkers, relatively small population sizes and increased heteroskedasticity related to symptom reports make identification of respondents with clinically significant indicators of AUD more difficult.

The results also provide evidence of reduced negative feedback control over drinking across groups of drinkers who meet more dependence criteria (Figure 4). Once again, problems related to drinking have less influence over drinking among heavier drinking groups. But, in addition, these effects are moderated by in the presence of symptoms of dependence; meeting any number of dependence symptom criteria was related to reduced negative feedback control over drinking. That this same effect appeared among drinkers who consumed average quantities of 1 through 3 vs. 4 or more drinks per occasion is important; expected moderating relationships between dependence symptoms, symptoms of abuse and drinking patterns appeared the same among these lighter and heavier drinkers suggesting that the same mechanisms of use and dependence are in effect in both drinking groups. While this argument is supported by a null hypothesis test, making it somewhat weak, there is little evidence at this stage of investigation that any substantive differences appear between these lighter and heavier drinkers. Thus, among lighter drinkers, symptoms of dependence are related to greater symptom reports of abuse and this effect will further increase the likelihood that clinically significant indicators of AUD will sometimes appear in the much larger population of lighter drinkers. We conclude from these observations that there are good reasons to believe that alcohol dependence affects relationships between

drinking and problems among low quantity drinkers and that the presence of AUD cases among low quantity drinkers may be a prodromal indication of continued AUD among at least some of these drinkers. The obvious challenge for researchers is to determine which of these users will progress to heavier use and dependence, which will remain lighter drinkers with some indications of dependence, and which will desist from exhibiting further symptoms of dependence.

A final important theoretical question is whether the behavioral model outlined by equations 1–3 can be used to generally characterize human drinking behavior. The model asserts that drinking quantities will be responsive to problems experienced on previous drinking occasions and that these quantities will be autocorrelated over time. In addition to our own efforts, there is accumulating time series data that suggests that risk response is conditional upon the average amount consumed (Scaglione, et al., 2014), that drinkers take previous problems into account when they drink (Nguyen, et al., 2013), and that the negative autoregressive effects implied by equation 1 are observed in drinking quantities over time (Labhart and Kuntsche, 2014; Gruenewald, et al., 2005). Particularly relevant to clinical symptoms of dependence, it has been shown that craving intensity predicts and is predicted by daily drinking quantities measured from-one-day-to-the-next (Fazzino, et al., 2013). A related and equally important empirical question is whether the parameters of the reduced form equilibrium equation 3 are well-represented by the measurement model in equation 5. While we think there are good reasons to believe this is true, there is a dearth of empirical research on dose-response models in the epidemiological literature. In the absence of formalized measurement models relating drinking patterns to drinking problems, correlational assessments of relationships between measures of drinking and problem outcomes will remain uninformed and uninformative to the field (Gruenewald, et al, 2016).

Relevance to DSM-5

With the advent of DSM-5, some concern may be expressed that the findings obtained here have limited relevance to DSM-5 diagnoses of AUD. This would be the case if symptom reports assessed using the different instruments differed in substance, but they do not. Since, as noted in the introduction, almost the same measures of abuse and dependence appear in both DSM-IV and DSM-5, and symptoms that fall under both constructs remain clinically relevant to diagnoses of AUD, we can say with some confidence that the class of symptoms of dependence measured using both instruments will moderate relationships between measures of drinking and the class of symptoms of abuse, again using both instruments (or, in fact, any instrument assessing the same classes of symptoms of AUD). Thus, our work suggests that the constructs of abuse and dependence exhibit the theoretical relationships posited here, with greater symptoms of dependence moderating relationships between drinking and symptoms of abuse. Our observation that problems related to drinking, at least as represented by symptoms of abuse, have less influence over drinking among heavier drinking groups, would then appear to also obtain for abuse symptoms measured in DSM-5.

In terms of clinical practice using new DSM-5 criteria the primary message of this work, noting that it still bears replication, is that heavy drinking *per se*, however measured, does not necessarily lead to AUD among heavier drinkers and that light drinking *per se* does not

necessarily protect against AUD symptoms, or preclude the occasional AUD diagnosis, among lighter drinkers. Rather, this work suggests that there is reason to be cautious about interpreting an AUD diagnosis as spurious if the patient presents as a lighter drinker; such a diagnosis may represent a lighter drinkers response to her drinking that is problematic and potentially predictive of future problems.

Limitations

As noted in the introduction, survey-based studies of drinking and problems suffer from many limitations that can bias parameter estimates from statistical models. Measurement errors in diagnostic outcomes, misclassification rates among “lighter” drinkers, and under-reporting of drinking levels may all lead to the appearance of greater numbers of AUDs among lighter drinkers. None of these limitations are addressed in the current work and all are generally neglected in assessments of drinking problems in the extent literature; indeed the statistical methodologies necessary to simultaneously address these concerns are just becoming available (see McElreath, 2016). Our goal in this study has been to present a more formal approach to the assessment of dose-response and outline some of its implications for measuring abuse and dependence. Given the nonlinear relationships to be expected between measures of drinking, problems, abuse and dependence, future research will require that both structural and measurement issues be addressed using more comprehensive statistical approaches.

Putting these basic measurement issues aside, the theoretical and empirical analyses presented here suggest that among the difficulties that currently confront research examining drinking, problems, and symptoms of AUD, the identification of those problems proximal to alcohol use that regulate drinking is most important. As problem outcomes related to drinking, symptoms of abuse reflect this larger class of day-to-day problems that drinkers experience when drinking and which may regulate day-to-day drinking behaviors. While this broader class of problems has long been considered as critical to assessments of college student drinking (e.g., Gruenewald and Mair, 2015), they have not been introduced into most studies of adult alcohol use, and they have not been introduced into any studies of AUD. Thus, while the current study bears replication using data from NESARC II and III, absent of better measures of drinking problems and their reciprocal regulatory impacts on use, progress on these issues will be stymied by this problem.

Many deep and difficult concerns remain about epidemiological assessments of population relationships between drinking and problems, in general, and drinking and symptoms of AUD, in particular. This contribution is intended to aide in elucidating some of the ways in which dose-response models of drinking and problems can help clarify these relationships. It does so by deploying a comprehensive model of drinking-problem relationships in the service of understanding how symptoms of dependence, themselves an outcome of use, may come to moderate the appearance of symptoms of abuse. Other concerns about the complex social and behavioral dynamics linking drinking and AUD outcomes remain in play; for example, it remains possible that the appearance of AUD diagnoses among those who drink relatively low quantities of alcohol may arise because lighter more moderate drinkers who meet AUD criteria are in recovery and may have reduced use. This observation, and others

like it, underline our current limited understandings of AUD symptomatology in the general population.

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DRINKER DISTRIBUTIONS BY DRINKING QUANTITIES IN THE US POPULATION

Figure 1:
Distributions of average drinking levels (left axis, bar graph) and dependence diagnoses (right axis, line graph).

Q_e : Quantities consumed at event e

P_e : Problems related to drinking at event e

B_e : Benefits from drinking at event e

Figure 2:

Linear discrete dynamic model incorporating moderating impacts of drinking “benefits.”

Figure 3:
Heterogeneous dose-response functions for symptoms of abuse and dependence.

CONTROL FUNCTIONS FOR DEPENDENCE SYMPTOM CRITERIA GROUPS

Figure 4:
Impacts of dependence criteria classifications on feedback control function.

Table 1.

Descriptive Characteristics (n=26,641)

Drinking Measures	n (%)	Mean (SD)
Mean quantity (Q)*		2.50 (2.31)
Frequency (F)*		76.44 (105.13)
Continued volumes (V-F)*		165.83 (473.17)
Problem Measures		
Alcohol abuse	2,734 (10.26%)	
Abuse symptom counts		0.18 (0.65)
Alcohol dependence	1,466 (5.50%)	
Dependence symptom counts		0.59 (1.68)
Number of dependence criteria met		0.42 (1.05)
Dependence: No criteria	21,157 (79.42%)	
Dependence: 1–2 criteria	4,018 (15.08%)	
Dependence: 3+ criteria	1,466 (5.50%)	
Other Covariates		n (%)
Age	18–29	6,079 (22.82%)
	30–44	9,363 (35.15%)
	45+	11,199 (42.04%)
Race/ethnicity	White non-Hispanic	16,562 (62.17%)
	Black Non-Hispanic	4,130 (15.50%)
	Other	5,949 (22.33%)
Marital Status	Married/Living as married	14,137 (53.06%)
	Separated/Divorced/Widowed	5,912 (22.19%)
	Never married	6,592 (24.74%)
Education	Less than high school	3,319 (12.46%)
	High school graduate	15,901 (59.69%)
	College graduate	7,421 (27.86%)
Median family income	< \$20,000	5,938 (22.29%)
	\$20,000–\$35,000	5,598 (21.01%)
	\$35,000–\$69,999	8,798 (33.02%)
	\$70,000 +	6,307 (23.67%)
Gender	Male	12,879 (48.34%)

Table 2:

Heterogeneous dose-response analyses of abuse and dependence symptom counts and number of dependence criteria.

Variables:	Abuse Symptom Counts:				Dependence Symptom Counts:				Dependence Criteria:			
	b:	se:	t:	p:	b:	se:	t:	p:	b:	se:	t:	p:
Dose-Response												
F	-0.0047	0.0017	-2.72	0.004	-0.0037	0.0014	-2.74	0.004	-0.0025	0.0009	-2.71	0.005
V-F	0.0004	0.0001	3.56	0.001	0.0020	0.0003	6.97	<0.001	0.0006	0.0001	4.77	<0.001
(V-F)/(1/Q)	0.0165	0.0023	7.04	<0.001	0.0202	0.0025	8.02	<0.001	0.0168	0.0016	10.65	<0.001
Demographics												
Age												
18–29	0.6421	0.0544	11.81	<0.001	1.2961	0.0623	20.79	<0.001	0.9425	0.0421	22.40	<0.001
30–44	0.1350	0.0456	2.96	0.002	0.1682	0.0537	3.13	0.001	0.1115	0.0366	3.05	0.001
Ethnicity												
White	0.1890	0.0486	3.89	<0.001	-0.0106	0.0616	-0.17	n.s.	0.0040	0.0433	0.09	n.s.
Black	-0.2782	0.0713	-3.90	<0.001	-0.2227	0.0829	-2.69	0.009	-0.1624	0.0576	-2.82	0.003
Male	0.3080	0.0350	8.80	<0.001	0.0995	0.0397	2.51	0.008	0.0941	0.0277	3.40	0.001
Marital Status												
Married	-0.4226	0.0467	-9.05	<0.001	-0.5813	0.0570	-10.20	<0.001	-0.4065	0.0396	-10.26	<0.001
Divorced / Separated	0.2731	0.0626	4.36	<0.001	0.1598	0.0757	2.11	0.019	0.1091	0.0527	2.07	0.021
Education												
High School Graduate	0.1734	0.0505	3.44	0.001	0.0318	0.0611	0.52	n.s.	0.0205	0.0430	0.48	n.s.
College Graduate	-0.2621	0.0684	-3.83	<0.001	-0.3863	0.0770	-5.02	<0.001	-0.2792	0.0536	-5.21	<0.001
Income												
\$20K - \$35K	0.0396	0.0651	0.61	n.s.	-0.1022	0.0755	-1.35	n.s.	-0.0617	0.0529	-1.16	n.s.
\$36K - \$70K	-0.0129	0.0495	-0.26	n.s.	-0.2116	0.0621	-3.41	0.001	-0.1475	0.0437	-3.37	0.001
More Than \$70K	0.650	0.0659	0.99	n.s.	0.0055	0.0734	0.08	n.s.	0.0014	0.0510	0.03	n.s.
Constant	-3.5216	0.1298	-27.13	<0.001	-3.3880	0.1061	-31.94	<0.001	-2.3718	0.0643	-36.90	<0.001
Heteroskedasticity*												
F	0.4926	0.0334	14.73	<0.001	0.4010	0.0379	10.59	<0.001	0.4077	0.0314	12.98	<0.001

Variables:	Abuse Symptom Counts:				Dependence Symptom Counts:				Dependence Criteria:			
	b:	se:	t:	p:	b:	se:	t:	p:	b:	se:	t:	p:
I ²	-0.0012	0.0001	-15.67	<0.001	-0.0009	0.0001	-8.65	<0.001	-0.0009	0.0001	-11.48	<0.001
V-F	0.0070	0.0025	2.76	0.004	0.0142	0.0026	5.53	<0.001	0.0038	0.0022	1.70	0.046
Σ	1.9069	0.0618	30.87	<0.001	2.8106	0.0789	35.60	<0.001	2.0313	0.0412	49.29	<0.001

* Coefficients and standard errors multiplied by 100 for clarity

Table 3:

Heterogeneous dose-response model of abuse symptom counts moderated by dependence criteria.

Variables:	Symptoms of Abuse:				D-R Effects:
	b:	se:	t:	p:	** b ² :
Dose-Response – No Dependence Criteria					
F	−0.0108	0.0025	−4.28	<0.001	−0.0108
V-F	−0.0001	0.0003	−0.26	n.s.	-----
(V-F)(1/Q)	0.0170	0.0035	4.92	<0.001	0.0170
Dose-Response – Meet 1 or 2 Criteria					
F	0.0117	0.0024	4.96	<0.001	0.0009
V-F	−0.0001	0.0003	−0.30	n.s.	-----
(V-F)(1/Q)	−0.0072	0.0041	−1.75	0.043	0.0098
Dose-Response – Meet 3 Criteria					
F	0.0202	0.0034	5.93	<0.001	0.0094
V-F	0.0002	0.0003	0.64	n.s.	-----
(V-F)(1/Q)	−0.0094	0.0052	−1.82	0.037	0.0076
Demographics					
Age					
18–29	0.4671	0.0496	9.42	<0.001	-----
30–44	0.1071	0.0409	2.62	0.006	-----
Ethnicity					
White	0.1925	0.0448	4.30	<0.001	-----
Black	−0.2842	0.0686	−4.14	<0.001	-----
Male	0.3164	0.0313	10.11	<0.001	-----
Marital Status					
Married	−0.3539	0.0430	−8.22	<0.001	-----
Divorced / Separated	0.2348	0.0577	4.07	<0.001	-----
Education					
High School Graduate	0.1790	0.0488	3.67	<0.001	-----
College Graduate	−0.2084	0.0615	−3.39	<0.001	-----
Income					
\$20K - \$35K	0.0524	0.0587	0.89	n.s.	-----
\$36K - \$70K	0.0109	0.0457	0.24	n.s.	-----
More Than \$70K	0.0488	0.0621	0.79	n.s.	-----
Constant	−3.1026	0.1194	−25.98	<0.001	-----
Heteroskedasticity[*]					
F	0.5369	0.0367	14.64	<0.001	-----
F ²	−0.0013	0.0001	−15.65	<0.001	-----

Variables:	Symptoms of Abuse:				D-R Effects:
	b:	se:	t:	p:	b ^{**} :
V-F	0.0031	0.0026	1.20	0.118	-----
Σ	1.7183	0.0579	29.70	<0.001	-----

* Coefficients and standard errors multiplied by 100 for clarity.

** Estimated effects for dependence criteria groups.