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Reduction in non-abstinent WHO drinking risk levels and change in risk for liver disease and positive AUDIT-C scores: Prospective 3-year follow-up results in the US general population

Justin Knox, PhD[1,2], **Melanie Wall, PhD**[1,2], **Katie Witkiewitz, PhD**[3], **Henry R. Kranzler, MD**[4,5], **Daniel Falk, PhD**[6], **Raye Litten, PhD**[6], **Karl Mann, MD**[7], **Stephanie S. O'Malley, PhD**[8], **Jennifer Scodes, MS**[2], **Raymond Anton, MD**[9], **Deborah S. Hasin, PhD**[1,2], and **Alcohol Clinical Trials (ACTIVE) Workgroup**

[1]Columbia University, New York, NY, USA

[2]New York State Psychiatric Institute, New York, NY, USA

[3]Department of Psychology, University of New Mexico, Albuquerque, NM, USA

[4]Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

[5]Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA

[6]National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, USA

[7]Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[8]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA

[9]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Abstract

Background—Abstinence is often the treatment aim for AUD, but this may deter individuals who prefer drinking-reduction goals from entering treatment, and be an overly restrictive endpoint in alcohol clinical trials. Non-abstinent drinking reductions that predict improvement in how

Correspondence to: Deborah Hasin, Department of Psychiatry, Columbia University Medical Center, New York, NY 10032, USA, Phone: 646-774-7909; Fax: 646-774-7920; deborah.hasin@gmail.com.

Conflict of Interest

The following authors have disclosed potential sources of conflict of interest. Drs. Witkiewitz, Kranzler, Mann, Hasin, Falk, Litten, O'Malley, and Anton are members of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative (ACTIVE Workgroup), which during the time in which this paper was developed, was supported by Abbvie, Alkermes, Arbor, Amygdala, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, and Pfizer. Dr. Mann has received speaker's fees from Lundbeck and the advisory board of Pfizer, Germany. Dr. Kranzler has served as a consultant, advisory board member, and CME lecturer for Alkermes, Lundbeck, and Indivior. Dr. Anton previously was a consultant for Lilly, Lundbeck, Novartis, Indivior, Laboratorio Farmaceutico CT, and Alkermes; served on advisory boards for Alkermes, Indivior, and Lundbeck; and received grant funds from Lilly and Laboratorio Farmaceutico CT. Dr. Hasin is Principal Investigator of a study funded by a contract from InVentiv Health Consulting that combines support from Actavis, Endo Pharmaceuticals, Janssen Pharmaceuticals, Mallinckrodt, Pfizer, Purdue Pharma, Rhodes Pharmaceuticals, Roxane Laboratories, and Zogenix. All other authors (Knox, Wall, Scodes) have no conflicts of interest to declare.

individuals feel or function may be useful clinical trial outcomes, e.g., reductions in the 4-category World Health Organization (WHO) drinking risk levels. To investigate the clinical relevance of these reductions, we examined their relationship to two outcomes of interest to medical providers: liver disease, and positive scores on an alcohol screening measure.

Methods—Current drinkers in a U.S. national survey (n=21,925) interviewed in 2001–02 (Wave 1) and re-interviewed 3 years later (Wave 2). WHO drinking risk levels, liver disease and the Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) were assessed at both waves. Adjusted odds ratios (aOR) were used to indicate the association of change in WHO drinking risk levels with Wave 2 liver disease and AUDIT-C scores.

Results—Wave 1 very-high-risk drinkers who reduced one, two, or three WHO drinking risk levels had significantly lower odds of Wave 2 liver disease (aOR=0.34, 0.23, 0.17) and positive AUDIT-C scores (aOR=0.27, 0.09, 0.03). Wave 1 high-risk drinkers who reduced one or two WHO risk levels had significantly lower odds of positive AUDIT-C scores (aOR=0.61, 0.25). Adjusting for alcohol dependence or AUDIT-C scoring variations did not affect results.

Conclusions—In the highest-risk drinkers, reductions in WHO drinking risk levels predicted lower likelihood of liver disease and positive AUDIT-C scores. Results add to findings that reductions in the 4-category WHO drinking risk levels are a meaningful indicator of how individuals feel and function, and could serve as non-abstinent endpoints in clinical trials. Results also connect the WHO risk drinking levels to commonly-used alcohol screening questions, which may be more familiar to health care providers.

Keywords

alcohol use disorder; WHO risk drinking categories; liver disease; drinking reduction; AUDIT-C

Introduction

Heavy drinking and alcohol use disorders (AUD) have many adverse consequences (Centers for Disease Control and Prevention, 2018, Grant et al., 2015, Grant et al., 2017, Greenfield et al., 2015, Hasin et al., 2017, Lewis-Laietmark et al., 2017), contributing to morbidity and mortality worldwide (Rehm et al., 2003, Rehm et al., 2017, Room et al., 2005). In U.S. adults over the past 10 years, the prevalence of heavy drinking and AUD has increased (Grant et al., 2015, Grant et al., 2017). Nevertheless, many with AUD who could benefit from some form of treatment, including those with severe disorders, do not receive it (Cohen et al., 2007, Grant et al., 2015, Grant et al., 2017, Hasin et al., 2007, Mann et al., 2017a, Mann et al., 2017b, Shield et al., 2014). To reduce the personal and societal burden of AUD, engaging those who could benefit from treatment is an increasingly important public health priority.

In treatment of AUD or alcohol dependence, goals most commonly involve complete abstinence (DeMartini et al., 2014). However, many individuals with AUD do not want to stop drinking entirely (Mann et al., 2017a, Mann et al., 2017b, Probst et al., 2015), deterring them from seeking treatment. Offering drinking *reduction* goals could broaden interest in treatment among individuals who could benefit from it (Mann et al., 2017a), but evidence is needed that non-abstinent reductions also provide clinical benefit. Offering a greater number

of effective medication options could also broaden interest in treatment. The Food and Drug Administration (FDA) has approved only three medications as effective for alcohol dependence (National Institute on Alcohol Abuse and Alcoholism, 2017). Aspects of clinical trial design may have posed barriers to identifying additional medications (Anton et al., 2012, Witkiewitz et al., 2015), including overly restrictive, insensitive outcome measures that are often not acceptable to patients and that cannot differentiate between active and placebo conditions. While the favored outcome for clinical trials of alcohol dependence has historically been abstinence, many patients improve substantially without attaining complete abstinence (Maisto et al., 2018, Wilson et al., 2016, Witkiewitz et al., 2017c). Therefore, abstinence may be an overly narrow, insensitive outcome. Recognizing this, the FDA now accepts an additional outcome, i.e., no heavy drinking days (HDD; >3 drinks for females, >4 for males) (US Food and Drug Administration, 2015), with % of participants having no HDD compared between treatment arms. However, the no-HDD outcome may also be overly narrow and insensitive, since it classifies patients as treatment failures after any HDD, although some of these patients substantially reduce their drinking and improve in how they feel and function (Maisto et al., 2018, Wilson et al., 2016, Witkiewitz et al., 2017c).

As an alternative, the European Medicines Agency (EMA) accepts as an outcome a 2-level reduction in the World Health Organization (WHO) 4-level classification of risk drinking levels (very-high-risk, high-risk, moderate-risk and low-risk; (World Health Organization, 2000) (European Medicines Agency, 2010) The validity of this 4-level outcome has been under investigation since 2012 by the Alcohol Clinical Trials Initiative (ACTIVE) Group (Anton et al., 2012) (Litten et al., 2017), with greatest interest in the two highest levels, i.e., very-high-risk and high-risk drinkers, the WHO levels most relevant to clinical trials for alcohol dependence (Witkiewitz et al., 2017a). For the FDA to accept reductions in the WHO drinking risk levels as a clinical trials outcome, information is needed about the clinical benefit provided by reductions in the WHO risk drinking levels, i.e., whether such reductions predict improvements in how individuals feel and function.

Two studies have shown clinical benefit from reductions in the four-level WHO drinking risk levels. In the COMBINE Study (Anton et al., 2006), a multisite treatment trial for alcohol dependence (n=1,383), reduced alcohol consequences on the DrinC (Miller et al., 1995) and improved mental health functioning on the SF-12 scale (Ware et al., 1996) were predicted by reductions in WHO risk drinking levels (Witkiewitz et al., 2017a). In US drinkers (n=22,005) followed prospectively for 3 years, (Hasin et al., 2017), reductions from the very high- and high-risk levels of the 4-level WHO drinking risk category predicted decreased rates of alcohol dependence and improved SF-12 mental health functioning (Hasin et al., 2017). These studies support reductions in the 4-level WHO risk drinking categories as a valid clinical trial outcome, but information is needed on additional outcomes. Below, we report on reductions in the 4-level WHO risk drinking categories and outcomes likely to be of interest to general medical practitioners.

One of these outcomes is liver disease (Kozarevic et al., 1983, Maddrey, 2000, Verschuren, 1993). Liver disease, when severe, can necessitate liver transplantation (Reuben, 2008, Sheron, 2016, Yoon and Yi, 2010) and is the 12th leading cause of death in the US. Alcohol contributes to 50%−80% of liver disease mortality (Rehm, 1996, Rehm et al., 2003, Rehm et

al., 2010, Rehm and Roerecke, 2013). The prevalence of US alcoholic liver disease and liver cirrhosis is increasing (Doycheva et al., 2017, Yoon and Chen, 2016). Liver disease is therefore highly relevant to medical practitioners.

The other outcome is the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) (Bradley et al., 2004, Bush et al., 1998), used in slightly varied versions as a screen for excessive drinking or "alcohol problems" (Dawson et al., 2005) in medical settings. For example, the AUDIT-C is used annually to screen all patients in the US Veterans Affairs (VA) healthcare system (Bradley et al., 2016, Hawkins et al., 2007), which serves over 9 million patients a year (US Department of Veterans Affairs, 2018). The AUDIT-C consists of three items on drinking quantity and frequency, including binge drinking (Bradley et al., 2003, Bush et al., 1998, Dawson et al., 2005, Dawson et al., 2012). Since 2002, most U.S. adults (78.2%−79.6%) have recognized binge drinking as incurring great or moderate risk (Shmulewitz and Hasin, In preparation), and medical providers are also generally familiar with binge drinking definitions (Chander et al., 2016). Therefore, while the AUDIT-C is not a direct measure of how patients feel or function, providing information on the correspondence of positive AUDIT-C scores (sometimes the only specific alcohol measure available) to the WHO risk drinking levels should help clarify the meaning and importance of the WHO risk levels to medical practitioners, helping them to gauge findings from clinical trials of medications for alcohol dependence or AUD that use the WHO risk drinking levels as outcome indicators.

Therefore, to provide more information about whether reductions in the WHO 4-level risk drinking categories are clinically meaningful, we investigated the relationship between a reduction in WHO risk drinking levels and two variables that are relevant to medical practitioners: 1) liver disease, including cirrhosis, which has obvious health implications; and 2) positive AUDIT-C scores, which are a well-recognized indicator of unhealthy alcohol use. Using baseline and 3-year follow-up data from a nationally representative sample of US adult drinkers, we examined whether a reduction in WHO risk drinking levels was associated with reduced risk for liver disease or a positive AUDIT-C score.

Materials and Methods

Study design and participants

Data were derived from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Grant et al., 2004). Data were collected in two waves of face-to-face interviews in participants' homes: Wave 1 (2001–2002) and Wave 2 (2004–2005) (Grant et al., 2009). The NESARC target population was non-institutionalized civilians aged at least 18 years in households and group quarters (e.g., group homes, worker dormitories). Black individuals, Hispanic individuals, and those aged 18–24 years were oversampled; data were adjusted for oversampling, household- and person-level nonresponse (Compton et al., 2007, Grant et al., 2004, Grant et al., 2009). All procedures, including written informed consent, were reviewed and approved by the US Census Bureau and US Office of Management and Budget. The overall response rate in Wave 1 was 81.0%. Excluding ineligible respondents (e.g., those who died before the follow-up), the overall response rate in Wave 2 was 86.9% (Grant et al., 2009). Combined with the Wave 1 response rate, the weighted cumulative

Wave 2 response rate (i.e., Wave 1 × Wave 2 rates) was 70.2% (Grant et al., 2009). Wave 2 data were weight-adjusted for non-response and demographic factors to ensure that the Wave 2 sample approximated the target population (Grant et al., 2009). The present analytic sample consisted of Wave 1 drinkers (participants who had at least one drink in the prior 12 months) who participated in Wave 2 and had drinking data available (N=21,925). Wave 1 abstainers were excluded because they were not informative about drinking *reduction* by Wave 2.

Measures

The Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV) is a modularized structured interview administered by lay interviewers (Grant et al., 2003, Ruan et al., 2008) covering numerous topics related to health. The AUDADIS-IV alcohol consumption module includes many questions on drinking, including those used to derive AUDIT-C scores for the present report. reliability of AUDADIS-IV alcohol consumption measures is very good to excellent (e.g., intraclass correlation coefficient=0.73–0.92 for mean daily ethanol consumption).

The four WHO drinking risk levels are defined for men and women using estimated mean ethanol consumption (grams) in the prior 12 months (Table 1). The estimated annual ethanol consumption was divided by the number of drinking days over the past year to calculate the mean number of drinks per drinking day, incorporating information on drinking quantity only on days participants drank, ignoring non-drinking days. Risk levels are expressed in terms of US standard drinks (14 grams of pure alcohol). The four levels include very-high-risk (>100 gm/day for men and >60 gm/day for women, or >7.1 or >4.3 standard drinks for men and women), high-risk (60–100 gm/day for men and 40–60 gm/day for women, or 4.3–7.1 standard drinks for men and 2.9–4.3 for women), moderate-risk (40–60 gm/day for men and 20–40 gm/day for women, or 2.9–4.3 standard drinks for men and 1.4–2.9 for women), and low-risk (1–40 gm/day for men and 1–20 gm/day for women, or <2.9 standard drinks for men and <1.4 for women). Full abstainers, i.e., non-drinkers for at least a year, are not considered WHO low-risk drinkers.

The original WHO document defining the risk drinking levels (World Health Organization, 2000) and earlier reports (English et al., 1995) offered an additional definition of WHO drinking risk levels: mean drinks *per day*. Mean drinks per day includes both drinking and non-drinking days, leading to somewhat different distributions, especially for infrequent heavy drinkers. Previous studies examined WHO drinking risk level reductions in terms of drinks per day (Hasin et al., 2017, Witkiewitz et al., 2017b), so we also conducted sensitivity analyses defining the WHO drinking risk levels this way, since both mean drinks *per day* and drinks *per drinking day* are potentially useful measures. Eighty participants did not report on the frequency of drinking days and thus we could not calculate drinks per drinking day for these participants, who were excluded from the analyses in the main paper, but were included in the supplementary results, which present results for drinks per day.

Liver disease, including cirrhosis, was coded from two questions: “Now I’d like to ask some questions about your health. In the past 12 months, have you had… cirrhosis of the liver? or any other form of liver disease?” For liver disease to be considered positive, a positive

response to an additional question was also required: “Did a doctor or other health professional tell you that you had cirrhosis of the liver? or any other form of liver disease?”.

The AUDIT-C score was derived from points assigned to responses on three questions about drinking in the 12 months (Dawson et al., 2005). Two of these covered frequency: “How often did you drink ANY alcoholic beverage?” and “How often did you drink FIVE OR MORE drinks in a single day?”. Eleven response categories were offered to participants, grouped in analysis for scoring purposes as follows: never (0 points); 1 or 2 times, 3–6 times, 7–11 times (all scored as 1 point); once a month, 2–3 times a month, once a week (scored as 2 points); 2 times a week, 3–4 times a week (scored as 3 points) and nearly every day and every day (scored as 4 points). An additional question covered usual number of drinks: “Counting all types of alcohol combined, how many drinks did you USUALLY have on days when you drank?” with response options: ≥10 drinks (scored as 4 points); 7–9 drinks (3 points); 5 or 6 drinks (2 points) 3 or 4 drinks (1 point) and 1 or 2 drinks (0 points). AUDIT-C scores of ≥4 points for men or ≥3 points for women were considered positive (Bradley et al., 2007, Dawson et al., 2005). Questions with missing values (unknown, refused) were scored 0 points; participants with such values (0.3%) were retained in the analysis because they represent part of the population to be screened and their removal could bias results, although in a sensitivity analysis, their removal had little effect on results.

AUDADIS-IV modules also included the covariates used in the statistical analyses: sex, age, education, race and ethnicity, smoking, body-mass index, and health insurance. Measures of Wave 1 psychiatric disorders included DSM-IV depressive disorders (major depression, dysthymia) and anxiety disorders (panic, generalized anxiety, social or specific phobia). Reliability and validity of these were described previously (Hasin et al., 2007). A variable indicating any of these psychiatric disorders at Wave 1 was also used as a covariate in all models.

Statistical analysis

We obtained weighted proportions of individuals in the four WHO drinking risk categories at Wave 1 and proportions of individuals in the same or different WHO categories by Wave 2. Wave 2 liver disease and positive AUDIT-C scores were the two outcomes. We used logistic regression to test associations of the outcomes with decreases between Wave 1 and Wave 2 WHO drinking risk levels by each level of initial (Wave 1) risk level, following work showing greater benefit of drinking reduction among those at high levels (Rehm and Roerecke, 2013). The number of possible Wave 2 non-abstinent reduction levels depended on participants’ Wave 1 level. Very-high-risk drinkers in Wave 1 could have no change in WHO drinking risk level, or decrease by one, two, or three levels. High-risk drinkers could increase (by one level, to very high risk), have no change, or decrease by one or two levels. Moderate-risk drinkers could increase, have no change, or decrease by one level. Low-risk drinkers could increase or have no change. All Wave 1 drinkers could also become abstainers at Wave 2. We fit logistic regression models among Wave 1 drinkers that included each of these combinations of WHO risk categories, controlling for sex, age, education, race and ethnicity, smoking, body-mass index, health insurance, any depressive or anxiety disorder at Wave 1, and the respective outcome (liver disease or AUDIT-C score) at Wave 1.

For very-high-risk, high-risk, and moderate-risk drinkers at Wave 1, we calculated adjusted odds ratios (aORs) and 95% CIs of Wave 2 liver disease and positive AUDIT-C score for each level of reduction in WHO drinking risk, compared with no change in risk. Similarly, we calculated aORs and 95% CIs of positive AUDIT-C score persistence using logistic regression for each combination of WHO risk level change. (We did not analyze persistence of liver disease due to the low frequency of this outcome in the sample). The adjusted prevalence or persistence of each outcome at Wave 2 was calculated using covariates fixed at their marginal distribution found in the sample.

We conducted three main sensitivity analyses. In one, we also controlled for alcohol dependence at Wave 1. In the second, we re-scored as negative participants originally scored as positive only because of their score on the AUDIT-C question on frequency (daily or near-daily drinking, scored as 4) while their responses to the other two questions were zero (never drank more than one or two drinks on drinking days). In the third, we defined the WHO risk drinking levels in terms of drinks *per day*. In all analyses, Proc Surveylogistic (SAS version 9.4) was used to incorporate the NESARC complex clustered design and sampling weights.

Results

At Wave 1, 12.7% of the respondents were very-high-risk drinkers, 13.2% were high-risk drinkers, 23.2% were moderate-risk drinkers, and most (50.9%) were low-risk drinkers (Table 1). The prevalence of liver disease at Wave 1 was greater at higher levels of the WHO risk drinking levels: 0.4% among low- and moderate-risk drinkers, 0.7% among high-risk drinkers, and 1.0% among very-high-risk drinkers. The proportion of individuals screening positive on the AUDIT-C was also higher at higher levels of WHO drinking risk, ranging from 21.8% among low-risk drinkers to 88.3% among very-high-risk drinkers.

Change in WHO risk levels between Waves 1 and 2 by Wave 1 WHO risk level is shown in Table 2 for all drinkers, and for the subset of individuals with a positive AUDIT-C score at Wave 1. Regardless of Wave 1 AUDIT-C score, 56% of very-high-risk drinkers decreased their drinking by at least one WHO risk level by Wave 2.

Liver disease results are shown in Table 3. Among Wave 1 very-high-risk drinkers whose drinking remained unchanged, 1.6% had liver disease at Wave 2. In those who decreased one, two, or three WHO drinking risk levels, 0.5%, 0.4%, and 0.3% had liver disease at Wave 2. Compared to those with no change, each decrease in WHO risk level predicted significantly lower prevalence and adjusted odds of Wave 2 liver disease (all $p<.0001$). The prevalence of liver disease among abstainers, 3.1%, likely indicates “sick quitters”, i.e., those who stop drinking due to illness. Among Wave 1 high-risk drinkers, reductions in risk for liver disease by reduction in WHO drinking risk levels were not significant, although significantly lower prevalence and adjusted odds of liver disease were found among those who became abstainers. Compared to Wave 1 moderate-risk drinkers with no change in WHO risk level, reduction of one WHO risk level predicted lower prevalence and adjusted odds of Wave 2 liver disease (p=.001).

AUDIT-C results are shown in Table 4. Among Wave 1 very-high-risk drinkers whose drinking remained unchanged, 93.0% had a Wave 2 positive AUDIT-C. In those who decreased one, two, or three WHO risk levels, 78.0%, 55.0%, and 27.0% had a Wave 2 positive AUDIT-C score ($p<0.0001$). Compared to those with no change, each decrease in WHO risk level predicted significantly lower prevalence and adjusted odds of a Wave 2 positive AUDIT-C (all $p<.0001$). Table 4 also shows Wave 2 *persistence* of positive AUDIT-C scores among respondents with positive Wave 1 AUDIT-C scores. Of very-high-risk drinkers at Wave 1 whose drinking level remained unchanged, 98.1% had persistent Wave 2 positive AUDIT-C scores. Among respondents whose drinking decreased one, two, or three levels, persistent positive AUDIT-C scores were found in 91.9%, 76.0%, and 52.2%. Compared to respondents with no change in WHO risk level, each decrease predicted significantly lower persistence and adjusted odds of a persistent Wave 2 positive AUDIT-C score (all $p<.0001$).

Results for high-risk drinkers were similar (Table 4). Among Wave 1 high-risk drinkers whose drinking increased to the very-high-risk level, 89.5% had a positive Wave 2 AUDIT-C score, in those whose Wave 2 level remained unchanged, 67.8% had a positive Wave 2 AUDIT-C score, and among those whose drinking decreased 1 or 2 WHO risk levels, 56.1% and 34.9% had a positive Wave 2 AUDIT-C score. All changes in WHO risk levels were associated with significant changes in the same direction as the prevalence and adjusted odds of a positive Wave 2 AUDIT-C score ($p<0.0001$). Wave 2 *persistence* of positive AUDIT-C score among high-risk drinkers reflected similar, significant changes (increase or decrease) in persistence and adjusted odds of a Wave 2 positive AUDIT-C score in the same direction as the changes in WHO risk level. Among Wave 1 moderate-risk drinkers, a decrease in WHO drinking risk level was associated with a significantly lower prevalence, persistence and corresponding adjusted odds of Wave 2 positive AUDIT-C scores (Table 4).

Results of sensitivity analyses that additionally controlled for Wave 1 alcohol dependence were very similar to the main results, as were sensitivity analyses re-coding as negative on the AUDIT-C participants who had a positive screening result only because of their score on the first AUDIT-C question (daily/near-daily drinking); no result was changed in either in its direction or whether it was statistically significant (Supplementary Table 1).

Results of sensitivity analyses that used WHO risk levels based on drinks per day were largely similar to the main results. Supplementary Table 2 shows the distribution of participants by Wave 1 WHO risk drinking levels *per day*, and the prevalence of positive AUDIT-C scores and liver disease. Compared to the prevalences in Table 1 (WHO risk levels defined as drinks per drinking day), Supplementary Table 2 shows lower prevalences of participants at very-high-risk, high-risk and moderate-risk levels; higher prevalence of positive AUDIT-C scores (virtually all participants at very-high-risk, high-risk and moderate-risk levels were positive) and higher prevalence of liver disease in the very–high-, high- and moderate-risk levels. The prevalence of respondents that changed WHO risk levels between Waves 1 and 2 by Wave 1 WHO risk level is shown in Supplementary Table 3 for all drinkers and for those with a Wave 1 positive AUDIT-C score. Results for liver disease are shown in Supplementary Table 4. Among the Wave 1 very-high-risk drinkers, results were very similar to those shown in Table 3, i.e., significantly decreased odds of Wave 2

liver disease by reductions in WHO risk levels (all $p<.0001$). Among Wave 1 high-risk drinkers, only a decrease to abstinence predicted significantly decreased risk of liver disease, while decreases to abstinence in moderate- and low-risk drinkers predicted significantly *increased* risk of liver disease, again suggesting the "sick quitter" phenomenon.

The Wave 2 prevalence of positive AUDIT-C scores by change in WHO risk drinking level is shown in Supplementary Table 5. Because of the very high proportions of participants at the WHO very-high-risk and high-risk drinking levels with Wave 1 positive AUDIT-C scores, adjusted odds of positive Wave 2 AUDIT-C scores by change in WHO risk drinking level could not be produced because the models did not converge.

Discussion

Using data from a large national survey with a 3-year follow-up, we examined whether non-abstinent drinking reduction, defined by reductions in the 4-category WHO drinking risk levels, conferred clinically meaningful benefit for an outcome likely to be of interest to medical providers, i.e., liver disease. We also examined whether reduction in the WHO risk levels predicted change in risk for a positive AUDIT-C score, an indicator of excess drinking and/or alcohol problems likely to be known to medical providers. Of particular interest in this study were very-high-risk and high-risk drinkers, i.e., those of greatest clinical concern.

Among the heaviest Wave 1 drinkers, the WHO very-high-risk drinkers, drinking reduction of one, two or three levels was associated with a sizeable, significant reduction in the risk of liver disease, regardless of whether WHO risk levels were defined by drinks per drinking day or drinks per day. This finding provides information about the clinically meaningful benefit of reducing the risk level of drinking among those whose drinking is of highest concern. The effects of reduction in WHO risk drinking level on risk of liver disease were less consistent among high-, moderate- and low-risk drinkers, perhaps because the prevalence of liver disease was lower among these groups, providing less power to detect significant relationships or because of the sick quitter phenomenon. We also found that very-high-risk and high-risk drinkers who reduced their WHO risk category had significant reductions in the risk of having positive AUDIT-C scores, regardless of whether they were initially positive on the AUDIT-C or not.

Results of this study have important implications. Clinically, for individuals uninterested in abstinence, initial drinking reduction goals can be offered in specific terms, including reductions in WHO drinking risk levels and their associated benefit. Indeed, offering drinking reduction goals may not just be useful and appropriate for patients who do not want abstinence; it may be the best approach for less severe AUD patients whose drinking pattern and consequences do not require abstinence. The WHO risk levels can be readily translated into goals involving approximate numbers of drinks per drinking day or drinks per day using the standard drink equivalents of the country in which the intervention occurs (Hasin et al., 2017). For clinical trials, our findings, particularly those regarding reduced risk of liver disease, support the use of WHO drinking risk levels as an efficacy outcome measure.

We conducted sensitivity analyses to determine if results differed when the WHO risk drinking levels were defined by mean drinks per day rather than mean drinks per drinking day. Drinks per day is a higher-threshold measure because (unlike mean drinks per drinking day), days with zero drinks are included in the mean. To illustrate with an extreme hypothetical example, a male drinking one day, 8 drinks in the prior year would be classified as very high risk (mean=8) using drinks per drinking day but low risk (mean=0.022) using mean drinks per day (8/365). At the other extreme, a male drinking 8 drinks every day in the prior year would be very high risk whether defined by drinks per drinking day or drinks per day. Defining WHO risk levels in terms of drinks per day, fewer participants are classified at very-high- and high-risk level, but at these levels, prevalences of positive AUDIT-C scores and liver disease are higher. Models did not converge for AUDIT-C scores when WHO risk levels were defined as drinks per day because virtually all participants other than low-risk drinkers had positive Wave 1 AUDIT-C scores, offering little variance to analyze. However, the models for liver disease produced similar results for very-high-risk drinkers regardless of how the WHO risk levels were defined, underscoring the robustness of these results for this serious drinking outcome when very-high-risk drinkers were considered.

The most important difference between the AUDIT-C version used in this study and other versions is that the AUDADIS-IV alcohol consumption questions assessed the frequency of consuming ≥5 drinks, while other versions of the AUDIT-C assess the frequency of consuming ≥6 drinks. The AUDIT-C questions, designed by an international team, assume that a standard drink has 10 g of ethanol, so the question on ≥6 drinks referred to an intake of 60 g of ethanol or more (the threshold between moderate and high levels of risk). In the US, where the standard drink size has 12–14 g, this is more accurately captured by asking the frequency of consuming ≥5 drinks. We also note slight differences between the AUDIT-C used in this study and other versions, as described by (Dawson et al., 2005). First, respondents who never drank in the preceding 12 months were determined from a separate question rather than as a response option to the drinking frequency question. Second, a broader range of response options to the frequency questions was offered, with higher frequencies placed at the top of the list rather than at the bottom as in other AUDIT-C versions. Finally, a frequency category of “3 to 4 times a week” meant that respondents drinking four times a week were combined with those drinking two to three times a week rather than with those drinking more than four times a week, as in other versions of the AUDIT-C. Whether these differences affected the present results cannot be determined. However, we suggest that their effect appears likely to be slight. Further, few busy clinicians follow the exact wording of any screening measure, including the AUDIT-C (Chander et al., 2016). Given the tendency of clinicians not to use screening questionnaire wording exactly (Chander et al., 2016), the differences in wording of this version of the AUDIT-C relative to other versions should not have a large impact on the utility for medical providers of our overall findings on the relationship of a reduction in WHO risk drinking levels to positive AUDIT-C scores. However, future work might utilize other AUDIT-C versions to replicate the results presented here.

Our results are consistent with other studies (Anton et al., 2006, Dawson et al., 2008, Rehm and Roerecke, 2013, Roerecke et al., 2013, Roerecke et al., 2015, Witkiewitz et al., 2017a) that non-abstinent drinking reduction confers clinically meaningful benefit. Furthermore,

sensitivity analyses controlling for alcohol dependence gave similar results, indicating robustness of the findings. The consistency of previous studies with our new findings in the general population additionally supports their robustness, and therefore the value of the WHO drinking risk levels as a means of defining drinking reductions that can be used to guide clinical recommendations and assess efficacy in clinical trials.

Ideally, drinking risk guidelines for the public and for medical providers would be presented in terms of whole standard drinks. The WHO risk drinking levels, based on the metric system, translate into whole standard drinks for some but not all countries because standard drink sizes vary across countries (e.g., 14 g of ethanol for the US; 8 g for the UK; 10 g for France, the Netherlands, Australia; 12 g for Germany) (Hasin et al., 2017). Working out an accurate system to communicate risk levels in terms of whole standard drinks for each country would serve an important public health purpose. However, for the purpose of the present paper, i.e., determining benefit of a reduction in the WHO 4-level risk drinking categories to allow use of the risk levels as outcomes in clinical trials, the fact that the levels do not exactly translate into standard drinks (US or other) does not appear to pose a problem. On the contrary, regulatory agencies would benefit from and find useful a standardization of clinical trial results across countries, leaving each country to translate the grams per day into a metric that best fits local standards.

The AUDIT-C is an important and widely used screening tool for alcohol use. The AUDIT-C and WHO risk drinking levels share a feature, i.e., they are both scored based on drinking measures, albeit different ones. The AUDIT-C results provide information that can help medical professionals link a measure with which they are more familiar, the AUDIT-C, to the WHO risk drinking levels, which have not seen widespread dissemination efforts. This information can help clinicians interpret clinical trials results presented in terms of reduction in WHO risk drinking levels.

Study limitations are noted. Because all data were based on self-report, set response bias could have contributed to the findings. While our measure of liver disease required medical confirmation to be scored as positive, it is still based on participant self-report. Future studies should incorporate direct examinations or medical record variables. Further, while the relatively low prevalence of liver disease in the sample was sufficient to show significant correspondence to reductions in WHO risk drinking levels, replication of the findings in other samples would be useful. In addition, the increased risk of liver disease shown among Wave 1 moderate or low-risk drinkers who became abstainers at Wave 2 could be attributed to the “sick quitters” phenomenon (i.e., individuals who reduced or quit drinking based on the presence of liver disease). However, future surveys that include motives for continuing to drink despite health problems such as liver disease (Elliott et al., 2017, Elliott et al., 2018), and reasons for reducing drinking (Elliott et al., 2014) would provide valuable information on this question, especially among individuals with medical problems related to drinking. Also, the relationship between a reduction in WHO drinking risk levels and a change in additional indicators should be examined (in this or other datasets), including other more acute conditions, e.g., hypertension, and other substance use disorders, psychiatric disorders, and indicators of functioning. Lastly, the AUDIT-C, like any screening instrument, has the potential to generate false positives (i.e. healthful drinkers with a positive AUDIT-C score).

Sensitivity analysis were run to explore the impact of re-scoring as negative participants originally scored as positive only because of their score on the AUDIT-C question on frequency (daily or near-daily drinking, scored as 4) while their responses to the other two questions were zero (never drank more than one or two drinks on drinking days). However, traditional cut-off scores (≥4 points for men or ≥3 points for women) were still used for these analyses, which may result in individuals at the lower end of the drinking spectrum being misclassified with a positive AUDIT-C score. Fortunately, this is not likely to impact the findings regarding our primary interest for this study, i.e., drinkers at the high ends of the spectrum.

Study limitations are offset by several strengths, including a large and rigorously assessed epidemiological sample; high response rates; detailed assessment of alcohol consumption and misuse at both waves; a 3-year follow-up period; and the use of a national sample with a high representation of participants by age, sex, race and ethnicity, and socioeconomic status that was large enough to analyze WHO defined risk groups, including those at very-high- and high-risk levels. The need to widen the options available for treating AUD (e.g., non-abstinence goals and additional medications) has grown increasingly acute, given population increases in drinking and AUD prevalence in the US (Grant et al., 2017) and the fact that so many individuals with these disorders remain untreated (Cohen et al., 2007, Grant et al., 2015, Grant et al., 2017, Hasin et al., 2007, Shield et al., 2014).

Untreated problem drinkers and individuals with an alcohol use disorder (AUD) who do not want to stop drinking are unlikely to enter treatment requiring an abstinence goal. Non-abstinent goals could therefore help engage those who need alcohol treatment and are warranted if such goals are accompanied by improvements in how patients feel and function. Further, non-abstinent drinking reductions defined by the 4-category WHO risk drinking levels could also serve as valuable outcome indicators in clinical trials of AUD treatment, as already accepted by the European Medicines Agency (European Medicines Agency, 2010). Previously, drinking reductions defined with the 4-category WHO risk drinking levels were shown to predict lower risk of alcohol dependence, mental health functioning, and drinking consequences (Witkiewitz et al., 2017a) (Hasin et al., 2017). This study offers additional information that non-abstinent reductions in the 4-category WHO risk drinking levels may be a useful clinical trials outcome measure. Our results suggest that such reductions offer considerable benefit to very heavy drinkers, even those that reduce their WHO-defined drinking risk by only one level. Thus, such reductions can be valid clinical trial outcome indicators, and also serve a valuable clinical use as treatment goals to be discussed with patients. Therefore, the information provided in this study is important to inform the public, public health officials, clinicians (including physicians and other health care providers in primary care settings), patients, and investigators conducting clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Wave 1 current drinkers in the NESARC sample, by the four WHO drinking risk levels (n = 21,925)

Wave 1 WHO risk drinking level	Definition of each level, in grams (US standard drinks)	n	Prevalence of participants at each WHO risk level	Prevalence of liver disease, Wave 1	Prevalence of positive AUDIT-C scores at Wave 1*
	>100 g (>7.1 drinks) for men;				
Very high	>60 g (>4.3 drinks) for women	2,729	12.7%	1.0%	88.3%
	60–100 g (4.3–7.1 drinks) for men;				
High	40–60 g (2.9–4.3 drinks) for women	2,961	13.2%	0.7%	68.6%
	40–60 g (2.9–4.3 drinks) for men;				
Moderate	20–40 g (1.4–2.9 drinks) for women	5,269	23.2%	0.4%	43.9%
	1–40 g (<2.9 drinks) for men;				
Low	1–20 g (<1.4 drinks) for women	10,966	50.9%	0.4%	21.8%

*Positive AUDIT-C score: ≥4 points for men; ≥3 points for women

Table 2:

Changes in WHO risk drinking level at Wave 2 by Wave 1 WHO drinking risk level (drinks per drinking day) for all drinkers and Wave 1 positive AUDIT-C score drinkers

All Wave 1 drinkers (n=21925)								
	n	**Increased**	**No change**	**Decreased by one level**	**Decreased by two levels**	**Decreased by three levels**	**Total decreased**	**Became abstinent**
Very high	2729	NA	35%	21%	20%	16%	57%	8%
High	2961	16%	22%	27%	27%	NA	54%	8%
Moderate	5269	21%	30%	40%	NA	NA	40%	10%
Low	10966	26%	56%	NA	NA	NA	NA	18%
Wave 1 positive AUDIT-C score drinkers (n=9145)								
	n	**Increased**	**No change**	**Decreased by one level**	**Decreased by two levels**	**Decreased by three levels**	**Total decreased**	**Became abstinent**
Very high	2410	NA	38%	21%	19%	15%	55%	7%
High	2031	20%	25%	26%	23%	NA	49%	6%
Moderate	2313	28%	32%	33%	NA	NA	33%	6%
Low	2391	38%	55%	NA	NA	NA	NA	7%

Table 3:

Liver disease prevalence at Wave 2, by WHO drinking risk level (drinks per drinking day) at Wave 1 and change in WHO risk level between Waves 1 and 2

	All Wave 1 drinkers (n=21925)		
	Prevalence of liver disease at Wave 2	**Adjusted OR (95% CI)**	**p value**
Very high risk			
No change	1.6%	Reference	--
Decreased by one level	0.5%	0.34 (0.21–0.54)	<.0001
Decreased by two levels	0.4%	0.23 (0.15–0.36)	<.0001
Decreased by three levels	0.3%	0.17 (0.10–0.29)	<.0001
Became abstainer	3.1%	2.03 (1.18–3.51)	0.011
High risk			
Increased	0.3%	0.43 (0.09–2.11)	0.30
No change	0.8%	Reference	--
Decreased by one level	0.6%	0.71 (0.36–1.41)	0.33
Decreased by two levels	0.5%	0.63 (0.34–1.14)	0.13
Became abstainer	0.1%	0.16 (0.05–0.54)	0.003
Moderate risk			
Increased	0.3%	0.54 (0.39–0.75)	0.0003
No change	0.6%	Reference	--
Decreased by one level	0.4%	0.65 (0.51–0.85)	0.001
Became abstainer	0.6%	0.99 (0.71–1.37)	0.95
Low risk			
Increased	0.5%	1.37 (1.07–1.76)	0.012
No change	0.4%	Reference	--
Became abstainer	0.8%	1.98 (1.45–2.70)	<.0001

Table 4:

Positive AUDIT-C score prevalence at Wave 2, by WHO drinking risk level (drinks per drinking day) at Wave 1 and change in WHO risk level between Waves 1 and 2

	All Wave 1 drinkers (n=21925)			Wave 1 positive AUDIT-C score drinkers (n=8924)		
	Prevalence of positive AUDIT-C scores at Wave 2	Adjusted OR (95% CI)	p value	Prevalence of positive AUDIT-C scores at Wave 2	Adjusted OR (95% CI)	p value
Very high risk						
No change	93.0%	Reference	--	98.1%	Reference	--
Decreased by one level	78.0%	0.27 (0.20–0.36)	<.0001	91.9%	0.22 (0.15–0.32)	<.0001
Decreased by two levels	55.0%	0.09 (0.07–0.12)	<.0001	76.0%	0.06 (0.05–0.08)	<.0001
Decreased by three levels	27.0%	0.03 (0.02–0.04)	<.0001	52.2%	0.02 (0.02–0.03)	<.0001
Became abstainer	0.0%	--	--	0.0%	--	--
High risk						
Increased	89.5%	4.03 (3.36–4.84)	<.0001	98.8%	10.86 (9.46–12.47)	<.0001
No change	67.8%	Reference	--	88.5%	Reference	--
Decreased by one level	56.1%	0.61 (0.54–0.69)	<.0001	76.1%	0.41 (0.36–0.47)	<.0001
Decreased by two levels	34.9%	0.25 (0.23–0.29)	<.0001	59.1%	0.19 (0.17–0.21)	<.0001
Became abstainer	0.0%	--	--	0.0%	--	--
Moderate risk						
Increased	73.5%	2.33 (2.05–2.64)	<.0001	87.6%	1.69 (1.39–2.05)	<.0001
No change	54.3%	Reference	--	80.7%	Reference	--
Decreased by one level	35.4%	0.46 (0.43–0.50)	<.0001	63.3%	0.41 (0.35–0.48)	<.0001
Became abstainer	0.0%	--	--	0.0%	--	--
Low risk						
Increased	59.5%	3.80 (3.57–4.06)	<.0001	78.8%	2.44 (2.18–2.73)	<.0001
No change	27.9%	Reference	--	60.4%	Reference	--
Became abstainer	0.0%	--	--	0.0%	--	--