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Change in Non-Abstinent World Health Organization Risk Drinking Levels and Alcohol Dependence: A 3-Year Follow-Up Study in the United States General Population

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Authors' Contribution

DSH planned the study, selected the variables for analysis, provided input into the statistical analyses and results, and wrote the initial and final drafts of the manuscript. MW developed the statistical analysis plan, MW and JS conducted the statistical analyses, and MW provided input on the initial and final manuscripts. RLR contributed to early design concepts and preliminary statistics. HK, KW, DF, RL, KM, SOM and RA provided input into the study design, interpretation of results, and the final manuscript.

Declaration of interests

Dr. Hasin is Principal Investigator of a study funded by contract from InVentiv Health Consulting that combines support from Actavis, Inc.; Endo Pharmaceuticals; Janssen Pharmaceuticals, Inc.; Mallinckrodt, LLC; Pfizer, Inc.; Purdue Pharma, L.P.; Rhodes Pharmaceuticals, L.P.; Roxane Laboratories, Inc.; and Zogenix, Inc. Dr. Wall is Principal Investigator of a contract to conduct statistical planning, analysis and interpretation on the Inventive Health Consulting contract. Dr. Kranzler has been a consultant, advisory group member, or CME lecturer for Alkermes, Lundbeck, Otsuka, and Indivior. Dr. Witkiewitz has been a consultant for Alkermes. Dr. O'Malley has been an advisory group member or consultant for Alkermes, Cerecor, Hazelden Betty Ford Foundation and Amydala, has received donated study medications from Pfizer and Astra Zeneca, and a clinical trial contract from Lilly. Dr. Anton has been a past consultant or on advisory boards for Lilly, Lundbeck, and Novartis. He has received grant support from Lilly. He is currently a consultant for Indivior and Xenoport. Dr. Mann has consulted for Novartis and Abbvie. He is a member of the advisory boards for Pfizer and Lundbeck, and has received speaker fees from Lundbeck. Drs. Witkiewitz, Kranzler, Mann, Hasin, O'Malley, Robinson and Anton are/were members of the American Society of Clinical Psychopharmacology's sponsored Alcohol Clinical Trials Initiative (ACTIVE), which has recently been supported by Abbvie, Alkermes, Ethypharm, Lilly, Lundbeck, Otsuka, Pfizer, Indivior, and Xenoport. Drs. Litten and Falk have no conflict of interest to declare.

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Abstract

Background—Alcohol dependence often goes untreated. Although abstinence is often the aim of alcohol treatment, many drinkers prefer drinking-reduction goals. Therefore, if supported by evidence of benefit, drinking-reduction goals could broaden the appeal of treatment. Regulatory agencies are considering non-abstinent outcomes as clinical trial efficacy indicators, including reduction in the World Health Organization (WHO) drinking risk levels: very high, high, moderate and low, defined in terms of average grams of ethanol per day. Little is known about the relationship between reductions in WHO risk levels and subsequent reduction in the risk for alcohol dependence.

Methods—In a U.S. national sample, 22 005 drinkers participated in Wave 1 interviews in 2001–2002 and Wave 2 follow-ups 3 years later. Alcohol consumption and alcohol dependence were assessed at both waves. Logistic regression tested the relationship between change in WHO drinking risk levels between Waves 1 and 2, and Wave 2 alcohol dependence.

Findings—Reductions of 1, 2 or 3 WHO risk levels predicted significantly lower odds of alcohol dependence at Wave 2, particularly among very high and high risk drinkers at Wave 1, and among those with alcohol dependence at Wave 1.

Interpretation—Results support the use of reductions in WHO drinking risk levels as clinical trial efficacy indicators. Because the levels can readily be translated into average drinks per day using the standard drink equivalents of different countries, the WHO risk levels could also be used internationally to guide treatment goals and clinical recommendations on drinking reduction.

INTRODUCTION

Heavy drinking and alcohol dependence are associated with disability,[1] comorbidity,[2,3] mortality,[4] and global burden of disease.[5] Since 2000, the prevalence of binge drinking and alcohol disorders increased 28% and 49% in the U.S.,[3] but few with alcohol use disorders in

the U.S. or Europe receive treatment.[2,3,6,7] Treatments commonly aim for abstinence,[8] but many individuals with alcohol disorders do not accept abstinence goals,[9] at least initially, so drinking-reduction treatments or clinical recommendations may broaden appeal.[10] Further, in addition to psychosocial interventions, medications may broaden interest in treatment by expanding available options.[11] Naltrexone, disulfiram, and acamprosate are approved to treat alcohol disorders in the U.S.,[12] U.K.,[13] and Europe, plus nalmefene in Europe[14] and some Asian countries. However, these medications do not work for everyone, and progress on developing new medications has been slow.

Barriers to progress may lie in elements of clinical trial design[15,16] including outcome measures. Historically, the favored outcome for clinical trials has been abstinence. However, while few participants achieve complete abstinence, many reduce their drinking. If drinking reduction provides clinically meaningful improvement, then complete abstinence may not be necessary to achieve important benefits. Accordingly, the U.S. Food and Drug Administration now accepts either abstinence or no heavy drinking days as trial endpoints.[17] However, the latter may also be overly restrictive, e.g., participants with a one-day slip considered treatment failures. The European Medicines Agency (EMA) favors abstinence as the primary treatment goal, but also recognizes intermediate outcomes,[18] including reduction of two or more levels in the four World Health Organization (WHO) drinking risk categories:[19] very high, high, moderate and low, defined by mean grams of ethanol consumed per day (Table 1). An important advantage of the WHO risk drinking categories is that they can easily be “translated” into change in standard drinks per day using the standard drink equivalents of different countries (Table 1). The WHO risk drinking categories could therefore facilitate clearer clinical recommendations for drinking-reduction goals internationally.

Surprisingly little is known about the relationship between prospectively determined reductions in WHO risk drinking levels and clinically meaningful improvement. An important indicator of such improvement would be reduction in the likelihood of an alcohol dependence diagnosis. In contrast to the WHO risk drinking levels, alcohol dependence is not defined by drinking quantity or frequency, but rather, by drinking-related aspects of how individuals may feel or function, e.g., impaired control over drinking and drinking-related behaviors, important social, occupational or other activities given up/reduced due to drinking, and physiological dependence (Supplementary Table 1). Information is needed about whether the risk for alcohol dependence decreases after reduction in WHO drinking risk levels, and if this varies by initial WHO drinking level and the initial presence of alcohol dependence.[20]

With few exceptions,[21,22] clinical trial datasets are too limited to address these questions. Further, clinical trial participants may not represent the broader population of heavy drinkers,[23] some of whom may be seen in psychiatric or primary care settings. Thus, a larger, more representative source of data is needed. Accordingly, we investigated the relationship between reduction in WHO drinking risk levels and reduction in risk for alcohol dependence among participants in a US national survey who were re-interviewed three years later. We addressed two main questions: (1) Compared to no reduction, does reduction in WHO drinking risk level to a lower level predict reduced risk for alcohol dependence? (2)

Do results apply to participants with a diagnosis of alcohol dependence at their initial interview? Such information could not only inform the choice of clinical trial outcomes, but guide provider recommendations on drinking reduction for patients in psychiatric, primary care and addiction treatment settings who do not accept abstinence goals.

METHODS

Study design and participants

Data came from the U.S. National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Wave 1 (2001–2002),[24] and a Wave 2 re-interview three years later (2004–2005).[25] NESARC data were collected in face-to-face interviews conducted in participants' homes. The NESARC target population was non-institutionalized civilians ≥18 years in households and group quarters. Blacks, Hispanics, and those age 18–24 were oversampled; data were adjusted for oversampling, household- and person-level non-response, as has been described in detail elsewhere.[24–26] All procedures, including informed consent, were reviewed and approved by the U.S. Census Bureau and U.S. Office of Management and Budget. The Wave 1 overall response rate was 81.0%.[2] Excluding ineligible respondents (e.g., deceased), the overall Wave 2 response rate was 86.9%.[25] Combined with the Wave 1 response rate, the weighted cumulative Wave 2 response rate (i.e., Wave 1 × Wave 2 rates) was 70.2%[25] (see also Supplementary Table 2). Wave 2 weights adjusted for non-response and demographic factors to ensure that the Wave 2 sample approximated the target population.[25] This report includes Wave 1 drinkers (≥1 drink in the prior 12 months) who participated in Wave 2, with drinking data available (N=22 005). Wave 1 abstainers were excluded because they would not have been informative about drinking reduction between Waves 1 and 2.

Measure - The NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV)

AUDADIS-IV is a structured interview administered by lay interviewers.[27,28] It assesses the seven DSM-IV dependence criteria, with ≥3 required in the last 12 months for a diagnosis. AUDADIS-IV alcohol dependence measures have excellent reliability and validity in U.S. and international samples,[2,29] with mean reliability of AUDADIS-IV current alcohol dependence in six studies K=0.74. AUDADIS-IV also provides detailed drinking information. The four WHO drinking risk levels - very high risk, high risk, moderate risk and low risk (Table 1) - were defined using estimated average ethanol consumed per day in the prior 12 months. The WHO levels include values of zero for abstinent days, combining quantity and frequency. Some studies define consumption as ethanol per *drinking* day (quantity), so a sensitivity analysis examined ethanol per drinking day to determine whether results differed. (Full abstainers, i.e., those with no drinking for at least a year, are not considered WHO low risk drinkers). Reliability of AUDADIS alcohol consumption measures is generally very good to excellent, e.g., ICC=0.73–0.92 for average daily ethanol consumed. See Supplementary Text for detailed information about reliability and validity of AUDADIS alcohol consumption and dependence measures. AUDADIS-IV also covers depressive disorders (major depression, dysthymia) and anxiety disorders (panic, generalized anxiety, social, specific phobia) whose reliability and validity have been described

previously;[2] a variable was created indicating any vs. none of these at Wave 1, and used as a covariate in all models. The AUDADIS-IV also included a general functioning measure, the Mental Component Summary (MCS) of the Short-Form 12, Version 2 (SF-12v2; range=0–100; mean=50; standard deviation=10[2,30]).

Statistical Analysis

Weighted proportions of Wave 1 WHO drinking risk categories and proportions of individuals in the same or different WHO categories by Wave 2 were obtained. Logistic regression with Wave 2 alcohol dependence as the outcome was used to test associations with Wave 2 decreases in WHO drinking risk categories by each level of initial (Wave 1) WHO drinking risk, following work showing greater benefits of drinking reduction at initially high levels.[20] The number of possible levels that were decreased at Wave 2 depended on participants' Wave 1 level. Wave 1 very high risk drinkers could not change, or decrease one, two, or three WHO drinking risk categories. High risk drinkers could increase, not change, or decrease one or 2 categories. Moderate risk drinkers could increase, not change, or decrease one category. Low risk drinkers increase or not change. All Wave 1 drinkers could also become abstainers at Wave 2. A logistic regression model was fit among Wave 1 drinkers that included each of these combinations of WHO risk categories, controlling for gender, age, education, race/ethnicity, smoking, body mass index (BMI), health insurance, Wave 1 depressive/anxiety disorder, and Wave 1 alcohol dependence. A similar model was fit for the subset of drinkers with alcohol dependence at Wave 1. For Wave 1 very high risk, high risk, and moderate risk drinkers, adjusted odds ratios (aOR) and 95% confidence intervals (CI) of Wave 2 alcohol dependence are presented for each level of reduction in WHO drinking risk, compared to no change. Adjusted Wave 2 alcohol dependence prevalence or persistence was also obtained from the logistic regression for each combination of WHO risk change categories, using covariates fixed at their marginal distribution found in the sample.

We conducted two sensitivity analyses. First, we substituted mean ethanol *per drinking day* for ethanol *per day* in defining WHO categories. All analyses described above were redone using this definition of WHO risk levels. Second, we substituted impaired functioning (≥1 SD below the SF-12v2 MCS mean at Wave 2) for alcohol dependence as a possible indicator of clinically meaningful improvement. Logistic regressions parallel to those described for alcohol dependence were fit for the impairment outcome, with additional covariates likely to directly impact MCS: divorce/separation since Wave 1, bereavement, being unemployed, undergoing substantial financial crisis, and being below the federal poverty level. Proc Surveylogistic (SAS 9.4) was used to incorporate the NESARC complex clustered design and sampling weights.

Role of the funding source

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) funded the NESARC and a grant to Dr. Hasin that supported this secondary analysis of NESARC data (R01AA025309). New York State Psychiatric Institute and the Alcohol Clinical Trials Initiative (ACTIVE) group also contributed to support for the present study (Hasin, Wall). Study funders had no role in study design, data collection, data analysis, data interpretation,

or writing the first draft of this report. Program staff at NIAAA (Litten, Falk) provided input and co-authorship on the final draft, as did members of the ACTIVE group (Anton, Kranzler, Mann, O'Malley, Witkiewitz, Robinson). The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

WHO drinking risk levels at Wave 1, and change in level by Wave 2, three years later

At Wave 1, 2.5% of respondents were very high risk drinkers, 2.5% were high risk drinkers, 4.8% were moderate risk drinkers and the rest low risk drinkers. The proportion with diagnoses of current alcohol dependence increased as WHO drinking level increased, with ~30% alcohol dependent in the high risk group, and ~55% in the very high-risk group (Table 2). Table 3 shows the reductions in WHO risk levels by Wave 1 level among all drinkers and those who were alcohol dependent at Wave 1. For example, regardless of Wave 1 alcohol dependence, over two-thirds of very high risk drinkers decreased at least one WHO risk level by Wave 2.

Wave 2 alcohol dependence status, by change in WHO drinking risk level

Among those in the WHO very high risk group at Wave 1, each decrease in drinking level by Wave 2 was associated with significantly lower prevalence and adjusted odds of alcohol dependence at Wave 2 (Table 4). Specifically, among individuals whose drinking remained at the very high risk level, 36.6% were alcohol dependent at Wave 2, while among those who decreased their drinking by one, two or three WHO risk levels, 13.5%, 8.8%, and 3.8% were alcohol dependent (p-values <0.0001). (The risk of alcohol dependence among abstainers is zero). Similarly, among the subset of Wave 1 alcohol dependent very high risk drinkers (Table 4), each decrease in WHO risk level by Wave 2 was associated with significantly lower prevalence and adjusted odds of alcohol dependence at Wave 2 (p-values, 0.00030 to <0.0001). In this subset of alcohol dependent participants, among those whose drinking remained at the very high risk level, 77.4% were still alcohol dependent at Wave 2, while among those who reduced one, two or three levels, 49.6%, 18.1%, and 12.3% remained alcohol dependent.

Similarly, among those in the WHO high risk group at Wave 1, each decrease in drinking level by Wave 2 was associated with significantly lower prevalence and adjusted odds of Wave 2 alcohol dependence (p-values <0.0001; Table 4). Specifically, among individuals whose drinking remained at the high risk level, 27.2% were alcohol dependent at Wave 2, while 19.2%, and 4.1% were alcohol dependent if they decreased their drinking by one or two levels. Findings at Wave 2 were very similar for the subset of Wave 1 high risk drinkers who were alcohol dependent (p-values <0.0001; Table 4).

Among Wave 1 moderate risk drinkers, including those with alcohol dependence, decreasing drinking by one risk level at Wave 2 predicted lower prevalence and significantly lower odds of Wave 2 alcohol dependence compared to those remaining at the moderate risk level at Wave 2. Among individuals in the low risk group at Wave 1, the only decrease possible was to abstinence, with zero risk of alcohol dependence.

Among participants initially at the high risk level, an increase of one WHO risk level by Wave 2 did not significantly increase the risk of alcohol dependence (Table 4). Among individuals initially at moderate or low risk levels, an increased WHO risk level by Wave 2 significantly increased the risk of alcohol dependence.

Sensitivity analyses

Supplementary Tables 3, 4 and 5 show the findings defining WHO risk drinking levels as drinks *per drinking day*. This yielded more participants in the high and very high risk categories, with lower alcohol dependence prevalence in these groups compared to WHO risk groups defined by *drinks per day* (Supplementary Table 3). Results were largely similar to the main results (Supplementary Tables 4, 5), the only difference being that among Wave 1 alcohol dependent high risk drinkers, reduction in drinking level did not reduce the odds for Wave 2 alcohol dependence.

Initial exploration of bivariate associations of MCS with drinking found it unrelated to mean drinks per day at Waves 1 ($r_{spearman}$=−0.013, p=0.053) and 2 ($r_{spearman}$=−0.001, p=0.90). Among all Wave 1 very high risk drinkers, including those with Wave 1 alcohol dependence, reductions in WHO risk drinking levels predicted significantly lower risk of Wave 2 poor functioning (p-values, 0.005 to <0.001; Supplementary Table 6). Among the remaining participants initially at lower Wave 1 drinking levels, results varied. For example, among the Wave 1 high risk drinking group (all drinkers and the subset that was alcohol dependent at Wave 1), decreases in WHO risk drinking levels consisted of non-significant aORs, one aOR suggesting significantly reduced risk of SF-12 MCS impairment and one aOR suggesting significantly increased risk of SF-12 MCS impairment (Supplementary Table 6).

DISCUSSION

Non-abstinent drinking-reduction goals are increasingly of interest as a means of engaging problem drinkers and alcohol dependent individuals in treatment, and as outcome indicators for clinical trials of alcohol disorder treatments. In a large national survey with a three-year follow-up, we examined whether non-abstinent drinking reduction, defined by the World Health Organization drinking risk levels (very high risk, high risk, moderate risk and low risk), conferred clinically meaningful benefit by reducing the risk of alcohol dependence. Very high risk and high risk drinkers are those of greatest clinical concern. Results showed after three years, those who were initially very high and high risk drinkers who reduced their WHO risk category had substantial, significant reductions in risk for alcohol dependence, regardless of whether or not they initially met criteria for alcohol dependence. Even a reduction of one WHO risk drinking category significantly reduced the risk of alcohol dependence at follow-up. Greater reductions (two- or three-category shifts) led to even lower risk for alcohol dependence.

Sensitivity analyses using an alternative definition of the WHO drinking risk levels (ethanol consumed per *drinking* day, which ignores non-drinking days) produced results similar to the more standard definitions of WHO drinking risk levels, suggesting robustness of the findings. However, these two methods might be further compared in additional samples, if appropriate data sources could be found.

The findings show that reduction in WHO drinking risk levels offers meaningful and important clinical benefit, particularly among high risk drinkers initially diagnosed with alcohol dependence, who are most like participants in alcoholism clinical trials. While achieving abstinence brings the risk of alcohol dependence to zero, reduction in WHO levels to low-risk drinking greatly reduces the risk of alcohol dependence regardless of the initial drinking level, while even a one- or two-level reduction substantially and significantly reduces the risk for alcohol dependence.

These results have important implications for treatment goals and clinical recommendations, and for use of the WHO risk drinking levels as an efficacy outcome measure in clinical trials of alcohol treatment. Clinically, for individuals initially uninterested in abstinence, drinking-reduction goals can be offered in specific terms, including smaller or larger reductions in WHO risk drinking levels and their associated benefit. These WHO risk levels can readily be translated into approximate numbers of drinks per day, using the standard drink equivalents of the country in which the intervention occurs (Table 1). For clinical trials of alcohol treatment, the study findings support the WHO risk levels as efficacy outcome measures. For example, the two-level reduction used to evaluate the effects of nalmefene, which led to its approval in Europe, clearly offers considerable benefit, while one-level reductions offer benefit as well.

Our results are generally consistent with other studies. For example, an earlier NESARC study showed reduced risk for varied alcohol-related outcomes after drinking reduction,[31] although WHO risk drinking levels were not addressed specifically, or whether results varied depending on initial drinking level. Three studies of mortality risk also showed benefit from either reduced drinking or abstinence.[20,32,33] One of these suggested that the benefit of a given amount of reduction was greater among those initially at the highest drinking levels,[20] providing part of the rationale for our analysis by initial Wave 1 WHO risk drinking level. Another modeled reduction in mortality risk by WHO risk drinking levels using nalmefene clinical trial data.[32] Our results are also consistent with results from the multi-site COMBINE alcohol clinical trial[21] that also showed significant clinical improvements after reductions in WHO drinking risk levels.[22] The consistency of these earlier studies with our general population findings further supports their robustness, and therefore the value of the WHO risk drinking levels as a specific means of defining drinking reductions that can be used to guide clinical recommendations and evaluate efficacy in alcohol clinical trials.

This study capitalized on a large and rigorously-assessed epidemiologic sample. However, study limitations are noted. While alcohol dependence is an important indicator of how heavy drinkers feel and function, the relationship between reduction in WHO risk drinking levels to change in additional indicators should be examined, e.g., other substance disorders (to address substance substitution), other psychiatric disorders, other indicators of functioning, and mortality.[32,33] The indicator of functioning, the SF-12v2 MCS, was included because some consider it to indicate clinical improvement, despite its lack of correlation with the overall drinking level in the NESARC sample, and its lack of specificity to disease outcomes, as noted by the FDA.[34] The fact that results were obtained among very high risk drinkers attests to the value of the WHO risk drinking categories. Further, we note that among very heavy drinkers, the results were essentially unchanged when the SF-12v2

outcome was re-defined with a threshold indicating greater impairment (two SD below the mean, not shown), indicating the robustness of the overall finding. In contrast, the greater variability among participants initially at high, moderate or low risk drinking levels simply indicates that at these lower levels, other factors or issues become more salient to SF-12v2 scores than WHO risk drinking levels alone. Future studies should address the complex nexus of drinking-related and other factors that may impact SF-12v2 impairment scores. Further, our study addresses non-abstinent drinking reductions, but the ability to maintain non-abstinent reductions compared to maintaining abstinence is unknown and merits study. Finally, all data were based on self-report, leading to the possibility that set response bias contributed to the findings. However, the markedly different formats of items covering alcohol consumption and items covering alcohol dependence, and their location in different modules of the interview, suggests that set response bias is unlikely to explain the relationships we found between change in WHO risk drinking levels and change in alcohol dependence. Study limitations are offset by several strengths, including high response rates; detailed assessment of alcohol consumption and alcohol dependence at both waves; reliable, valid dependence diagnoses; a 3-year follow-up period, and a national sample with a high representation of participants by age, sex, race/ethnicity and socioeconomic status that was large enough to analyze WHO-defined risk groups, including those at very high and high risk levels. While a similar dataset with 3-year follow-ups collected more recently would enable us to determine whether details of our results changed, we can think of no reason that our main findings would be different now. However, the need to widen the options available for treating alcohol dependence (non-abstinence goals, additional medications) has grown more acute, given population increases in drinking and alcohol use disorders,[3] and the fact that so many with these disorders remain untreated.[3]

In summary, understanding non-abstinent drinking reductions among individuals at high or very high drinking levels in the general population is important to help inform the public, treatment providers, patients, investigators conducting clinical trials, and public health officials. Prior studies used NESARC data to address drinking and its relationship to alcohol diagnoses,[31,35] but none specifically examined change in the WHO risk levels, which offer a guide to specific non-abstinent goals that can be used by providers in a variety of settings and countries. Individuals whose very heavy drinking substantially reduces their functioning and survival would benefit most from becoming abstinent. However, not all such very heavy drinkers can do that, or are initially willing to try. Our results suggest that such drinkers benefit considerably from reducing WHO-defined risk drinking even by one level, with greater benefit from additional reductions. Thus, such reductions can be valid clinical trial outcome indicators, and have clinical utility as treatment goals discussed with patients, including those with alcohol dependence. The results also suggest that among heavy drinkers at a less extreme level, one or two decreases in WHO-defined drinking levels also confer meaningful benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

In 2000, based on existing knowledge about the relationship of drinking levels to harms in the general population, the World Health Organization (WHO) published a set of four drinking risk levels, based on average volume of ethanol intake: very high risk, high risk, moderate risk and low risk. In 2010, the European Medicines Agency accepted the WHO four-level drinking risk categories as an outcome to examine in clinical trials. However, for further use of the WHO risk drinking levels as a clinical trial outcome, information was needed on the correspondence between change in the four WHO risk drinking levels and clinical benefit, i.e., how individuals feel and function. An important indicator of how drinkers feel and function is whether they are diagnosed with alcohol dependence. Therefore, change in the risk for alcohol dependence can be used to indicate the value of using shifts in the WHO drinking risk levels as outcome indicators in clinical trials. Examining this risk prospectively in the general population would provide findings with the greatest representativeness and generalizability.

We therefore searched the literature for relevant articles. We searched for prospective studies of the relationship between change in the WHO risk drinking levels and change in the risk for alcohol dependence conducted in general population samples. We began with a search of the terms “alcohol dependence”, and “World Health Organization” between 2000 and January 24, 2017 in Pubmed and Scopus. These two searches yielded 48 and 77 articles, respectively, but none that met our criteria. Changing the spelling of “World Health Organization” to “World Health Organisation” and re-doing the searches failed to produce any relevant articles. We then searched “WHO” and “alcohol dependence” in Pubmed for articles from 2000 to January 24, 2017, which yielded 1 631 articles, none of which were relevant. We further searched Pubmed for the following terms paired with “alcohol dependence”: “OMS”, “organizacion mundial de la salud” and “organization mondiale de la sante”. None of these searches produced any relevant articles. We then searched for articles with “alcohol dependence” paired with the following: “prospective” and “volume”; and “prospective” and “ethanol”, none of which produced any articles.

Added value of this study

The present study accomplishes what no previous studies did, namely, used data from a large, general population sample with 3-year prospective follow-up to examine the relationship between change in WHO risk drinking level to the risk for follow-up alcohol dependence as a function of baseline WHO risk drinking level. This was done in the large sample of all drinkers (n=22 005), and among the subset of those with alcohol dependence at baseline (N=1 152). Further, the WHO categories are unclear about whether the risk drinking levels should be defined as average volume of ethanol consumed per day or per drinking day, and this study contributes information on these two different definitions as well. Our study showed that when defined in terms of average ethanol consumed per day, any decrease in WHO risk drinking level produced benefit by reducing the risk of alcohol dependence at the 3-year follow-up, in the full sample of drinkers and among those with alcohol dependence at baseline. Results defining the

WHO risk drinking levels as average ethanol per drinking day were less consistent, mainly diverging in the group initially classified as high risk drinkers, particularly among those with alcohol dependence.

Implications of all the available evidence

To previously existing evidence that among very heavy drinkers who do not become abstinent, reduction to lower drinking levels confers multiple benefits, the present study adds prospective evidence from the general population that one of these benefits is decreased risk for alcohol dependence. These findings are consistent with recent findings from the COMBINE clinical trial also showing that reduction in the WHO risk drinking levels decreases the risk of alcohol dependence. Thus, evidence supports use of the World Health Organization four-level drinking risk indicators (defined by average ethanol volume consumed per day) as an outcome measure in alcohol treatment clinical trials, since reduction to lower WHO drinking risk levels, even a single-level reduction, leads to significantly decreased risk of alcohol dependence.

Table 1

Mean Number of Standard Drinks Per Day For Each WHO Drinking Risk Level, Across Countries

			Mean number of drinks per day consumed at each WHO risk level, using standard drink equivalency (grams per standard drink) for each country[1]				
WHO Risk Drinking Level	**Sex**	**Mean grams of ETOH consumed per day**	**U.S. 14 grams**	**UK 8 grams**	**France 10 grams**	**Germany 12 grams**	**Netherlands 10 grams**
Very High	Men	**>100**	> 7.1	>12.5	> 10	> 8.3	> 10
	Women	**> 60**	> 4.3	>7.5	> 6	> 5	> 6
High	Men	**60–100**	4.3–7.1	7.5–12.5	6–10	5–8.3	6–10
	Women	**40–60**	2.9–4.3	5–7.5	4–6	3.3–5	4–6
Moderate	Men	**40–60**	2.9–4.3	5–7.5	4–6	3.3–5	4–6
	Women	**20–40**	1.4–2.9	2.5–5	2–4	1.7–3.3	2–4
Low	Men	**1–40**	< 2.9	< 5	< 4	< 3.3	< 4
	Women	**1–20**	< 1.4	< 2.5	< 2	< 1.7	< 2

[1]Columns show number of standard drinks at each WHO risk drinking level for each country. Number of drinks = mean grams of ETOH consumed per day divided by the number of grams in a standard alcoholic drink in each country shown

Table 2

Analytic sample: Wave 1 drinkers in NESARC by WHO Risk Drinking Levels, N = 22 005

WHO Risk Level	Definition: mean grams of alcohol (U.S. standard drinks) per day	Proportion at each WHO Risk Level	Prevalence of Wave 1 Alcohol Dependence[1], by Wave 1 WHO Risk level
Very High (n=512)	Men: 100+g (≥7.1 drinks) Women 60+g (≥4.3 drinks)	2.5%	55.2%
High (n=546)	Men: 60–100g (4.3–7.1 drinks) Women 40–60g (2.9–4.3 drinks)	2.5%	30.2%
Moderate (n=1 073)	Men: 40–60g (2.9–4.3 drinks) Women 20–40g (1.4–2.9 drinks)	4.8%	16.6%
Low (n=19 874)	Men: 1–40g (<2.9 drinks) Women 1–20g (<1.4 drinks)	90.2%	2.8%

[1] DSM-IV alcohol dependence, last 12 months

Table 3

Changes in WHO[1] drinking risk level at Wave 2 (3-year follow-up) by Wave 1 WHO drinking risk level: all drinkers, and alcohol dependent drinkers

Part A. All Wave 1 drinkers (n=22 005) Wave 1 WHO Risk Level	**Proportion of participants by change in WHO drinking risk level at Wave 2, by Wave 1 WHO risk level[2]**						
	Increased	**No change**	**Decreased 1 level**	**Decreased 2 levels**	**Decreased 3 levels**	**Total Decreased**	**Became Abstinent**
Very High (n=512)	–	0.26	0.14	0.11	0.41	0.66	0.07
High (n=545)	0.15	0.15	0.19	0.46	–	0.65	0.06
Moderate (n=1 073)	0.13	0.24	0.60	–	–	0.60	0.04
Low (n=19 874)	0.05	0.81	–	–	–	–	0.13
Part B. Wave 1 alcohol dependent drinkers (n=1 152) Wave 1 WHO Risk Level	**Proportion of alcohol dependent participants by change in WHO drinking risk level at wave 2, by wave 1 WHO risk level[2]**						
	Increased	**No change**	**Decreased 1 level**	**Decreased 2 levels**	**Decreased 3 levels**	**Total Decreased**	**Became Abstinent**
Very High (n=276)	–	0.27	0.14	0.10	0.43	0.67	0.06
High (n=153)	0.18	0.14	0.11	0.52	–	0.63	0.06
Moderate (n=175)	0.17	0.21	0.57	–	–	0.57	0.05
Low (n=548)	0.20	0.76	–	–	–	–	0.05

[1] WHO – World Health Organization

[2] The table shows the change in WHO risk drinking level of participants at Wave 2, by their risk level at Wave 1. For example, of all 512 Very High Risk drinkers at Wave 1 (Part A), 0.26 (26%) were still at the Very High Risk level (i.e. no change) at Wave 2, while 0.14 (14%) had decreased one level and 0.07 (7%) had become abstinent. Of the 276 alcohol dependent Very High Risk drinkers at Wave 1 (Part B), 0.27 (27%) were still at the Very High Risk level (i.e., no change) at Wave 2, while 0.14 (14%) had decreased one level and 0.06 (6%) had become abstinent. Being at the highest level at Wave 1, Very High Risk drinkers could not increase their WHO level by Wave 2, but High, Moderate and Low risk drinkers could increase their WHO risk level, as exemplified by the 0.15, 0.13 and 0.05 (15%, 13% and 5%) of the high, moderate and low risk drinkers who did increase their drinking risk level by Wave 2 (Part A).

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Table 4

Alcohol Dependence at Wave 2, by WHO[1] drinking risk level at Wave 1 and change in WHO level, Wave 1 to Wave 2

All Wave 1 Drinkers (n=22 005):					Wave 1 drinkers with Alcohol Dependence (n=1 152)				
Wave 1 WHO risk level	**Wave 2 change in WHO level**	**% with Wave 2 Alcohol Dependence[2]**	**aOR[3] (95% CI)**	**p-value 1**	**Wave 1 WHO risk level**	**Wave 2 change in WHO level**	**% with Wave 2 Alcohol Dependence[2]**	**aOR[3] (95% CI)**	**p-value**
Very High (n=512)					Very High (n=276)				
	no change	36.57	reference			no change	77.35	reference	
	decrease 1	13.54	0.27 (0.18–0.41)	<0.0001		decrease 1	49.59	0.29 (0.15–0.57)	0.00030
	decrease 2	08.83	0.17 (0.10–0.27)	<0.0001		decrease 2	18.11	0.06 (0.04–0.10)	< 0.0001
	decrease 3	03.78	0.07 (0.05–0.10)	<0.0001		decrease 3	12.30	0.04 (0.03–0.06)	< 0.0001
	abstainer	00.00				abstainer	00.00		
High (n=546)					High (n=153)				
	increase	21.99	0.76 (0.52–1.11)	0.15		increase	53.97	0.95 (0.48–1.87)	0.88
	no change	27.17	reference			no change	55.24	reference	
	decrease 1	19.21	0.64 (0.54–0.75)	<0.0001		decrease 1	24.94	0.27 (0.16–0.45)	< 0.0001
	decrease 2	04.12	0.12 (0.09–0.15)	<0.0001		decrease 2	11.21	0.10 (0.06–0.16)	< 0.0001
	abstainer	00.00				abstainer	00.00		
Moderate (n=1 073)					Moderate (n=175)				
	increase	20.56	1.44 (1.06–1.95)	0.019		increase	48.17	2.21(1.45–3.38)	0.00023
	no change	15.25	reference			no change	29.57	reference	
	decrease 1	04.98	0.29 (0.23–0.37)	<0.0001		decrease 1	12.64	0.34 (0.24–0.49)	< 0.0001
	abstainer	00.00				abstainer	00.00		
Low (n=19 874)					Low (n=548)				
	increase	19.02	8.23 (7.26–9.32)	<0.0001		increase	37.79	3.82 (2.98–4.88)	< 0.0001
	no change	02.78	reference			no change	13.73	reference	
	abstainer	00.00				abstainer	00.00		

[1]WHO World Health Organization

[2]The percentages in this column indicate the % of respondents in each row (representing a WHO risk drinking category at Wave 1) who had alcohol dependence at Wave 2 based on the logistic regression model that included adjustment for covariates fixed at their marginal distributions found in the sample. For example, among all participants who were very high risk drinkers at Wave 1, an estimated 36.57%

of those whose risk level did not change by Wave 2 had alcohol dependence at Wave 2; among participants who were very high risk drinkers and also alcohol dependent at Wave 1, an estimated 77.35% of those whose risk level did not change by Wave 2 had alcohol dependence at Wave 2.

[3] aOR = adjusted odds ratio. Odds ratios indicate the effect of the predictor variable (change in WHO risk drinking level) on the outcome (Wave 2 alcohol dependence), relative to a comparison group (in this case, participants whose WHO risk drinking level did not change between Waves 1 and 2). Odds ratios >1.00 indicate increased odds relative to the comparison group, Odds ratios=1.00 indicate no difference in risk, and odds ratios <1.00 indicate decreased risk relative to the comparison group. Statistical significance of an aOR is indicated by a 95% confidence interval that does not include 1.00 between its lower and upper limit.