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Drinking Risk Level Reductions Associated with Improvements in Physical Health and Quality of Life among Individuals with Alcohol Use Disorder

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Abstract

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Disclosures.

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Background.—Abstinence and no heavy drinking days are currently the only Food and Drug Administration (FDA) approved endpoints in clinical trials for alcohol use disorder (AUD). Many individuals who fail to meet these criteria may substantially reduce their drinking during treatment and most individuals with AUD prefer drinking reduction goals. One- and two-level reductions in World Health Organization (WHO) drinking risk levels have been proposed as alternative endpoints that reflect reduced drinking and are associated with reductions in drinking consequences, improvements in mental health, and reduced risk of developing alcohol dependence. The current study examined the association between WHO drinking risk level reductions and improvements in physical health and quality of life in a sample of individuals with alcohol dependence.

Methods.—Secondary data analysis of individuals with alcohol dependence (n=1142) enrolled in the longitudinal, prospective COMBINE study (Anton et al. 2006), a multi-site randomized placebo-controlled clinical trial, examining the association between reductions in WHO drinking risk levels and change in blood pressure, liver enzyme levels, and self-reported quality of life following treatment for alcohol dependence.

Results.—One- and two-level reductions in WHO drinking risk level during treatment were associated with significant reductions in systolic blood pressure ($p<0.001$), improvements in liver enzyme levels (all $p<0.01$), and significantly better quality of life ($p<0.001$).

Discussion.—One- and two-level reductions in WHO drinking risk levels predicted significant improvements in markers of physical health and quality of life, suggesting that the WHO drinking risk level reduction could be a meaningful surrogate marker of improvements in how a person "feels and functions" (FDA, 2015) following treatment for alcohol dependence. The WHO drinking risk levels could be useful in medical practice for identifying drinking reduction targets that correspond with clinically significant improvements in health and quality of life.

Keywords

World Health Organization Drinking risk levels; Alcohol Use Disorder; Reduced Alcohol Consumption; Alcohol Treatment Outcomes; Liver Enzymes; Quality of Life; Blood Pressure

Introduction

Excessive alcohol consumption is associated with significant morbidity and all-cause mortality (GBD 2016 Alcohol Collaborators, 2018; Rehm et al., 2014, 2003; Shield et al., 2013) and is one of the leading causes of preventable death worldwide (Whiteford et al., 2013; World Health Organization, 2011). Evidence of a curvilinear relationship exists between increased alcohol consumption and risk of cardiovascular disease (Wood et al., 2018), with 50% of heavy drinkers estimated to have elevated blood pressure (Estruch et al. 2005). Most of the studies examining the association between alcohol use and morbidity and mortality have focused on population-based samples, which tend to have lower average alcohol intake than clinical samples of individuals with alcohol use disorder (AUD). Importantly, those with AUD who continue to drink heavily have the greatest mortality risk, whereas those who reduce their alcohol consumption have significantly lower mortality risk (Laramée et al., 2015) and estimated disease burden (Francois et al., 2014), even among those who do not achieve abstinence.

Abstinence has long been considered the goal of AUD treatment (Betty Ford Institute Consensus Panel, 2007; Mann et al., 2017). However, multiple studies have shown that reductions in alcohol consumption during treatment are associated with significant improvements in physical health, as reflected by reductions in blood pressure (Baros et al., 2008; Stewart et al., 2008) and improvements in liver tests and quality of life (LoCastro et al., 2009). Further, individuals with AUD who achieve low-risk drinking (typically defined as not exceeding 3 drinks for women and 4 drinks for men on a drinking day) have been shown to be similar to abstainers on a variety of physical and mental health outcomes (Kline-Simon et al., 2017; Maisto et al., 2010; Witkiewitz, 2013; Witkiewitz et al., 2017b), as well as on healthcare costs (Aldridge et al., 2016; Kline-Simon et al., 2014). Some individuals in AUD treatment who exceed the low-risk drinking cutoffs have improved post-treatment social functioning and quality of life, and reduced mental health symptoms and alcohol-related problems, similar to those of abstainers and low-risk drinkers (Wilson et al., 2016; Witkiewitz et al., 2018). These findings are particularly important in light of the fact that most individuals who seek treatment (especially those in clinical trials and those presenting to other medical settings, such as primary care) are interested primarily in nonabstinent drinking reduction goals (DeMartini et al., 2014). Moreover, many individuals with AUD report not seeking treatment because they do not want to abstain from alcohol (Center for Behavioral Health Statistics and Quality, 2017). Extending treatment options to target reductions in drinking, rather than complete abstinence, could expand the reach of alcohol treatment and have an important impact on public health (Mann et al., 2017; Maremmani et al., 2015; van Amsterdam and van den Brink, 2013).

Endpoint Definitions in Alcohol Clinical Trials

Abstinence is one of the primary endpoints (i.e., treatment outcomes) that is currently accepted by the Food and Drug Administration (FDA) for Phase III clinical trials (Food and Drug Administration, 2015). The FDA also accepts no heavy drinking days (defined as more than 3 drinks for women and more than 4 drinks for men in a day) as a primary endpoint. Both abstinence and no heavy drinking days are considered surrogate endpoints that are "reasonably predictive of clinical benefit (e.g., improvement in the way the patient feels or functions)" (p. 2, FDA, 2015). Meanwhile, the European Medicines Agency (EMA; European Medicines Agency, 2010) not only accepts abstinence as a primary endpoint for Phase III alcohol clinical trials, but also accepts intermediate harm reduction endpoints, including reductions in total alcohol consumption, heavy drinking days, or in the World Health Organization (WHO) drinking risk levels (WHO, 2000), which are defined by sex-specific limits for grams of alcohol consumed per day (Figure 1). Similar to the FDA guidance, the EMA guidance notes that intermediate harm reduction endpoints should be evaluated in terms of significantly "improved health outcome on an individual patient level" (p. 10, EMA, 2010).

World Health Organization Drinking Risk Levels as a Drinking Reduction Endpoint

The EMA-approved intermediate endpoints of reductions in total alcohol consumption and heavy drinking days are continuous measures and provide more statistical power to detect treatment effects than binary outcomes such as abstinence or no heavy drinking days (MacCallum et al., 2002; Yoo, 2010). However, continuous measures may also be more

difficult to translate into real-world clinical practice. In clinical practice, it is often useful to create a binary threshold to differentiate a successful outcome (i.e., normal range) from an unsuccessful outcome (i.e., abnormal range) (Perlis, 2011). The EMA-approved binary endpoint of reduction in WHO drinking risk levels defines a categorical reduction in WHO drinking risk level to capture a decrease in average alcohol consumption from pre-treatment to an *a priori* defined treatment endpoint (e.g., the last month of treatment).

Patients who initiate treatment at the very high risk WHO level can reduce 1, 2, or 3 levels to high risk, medium risk, or low risk, or they can become abstinent. Patients who initiate treatment at the high risk level can reduce 1 or 2 levels to medium risk or low risk, or become abstinent. The EMA defines at least a two-category reduction (from very high risk to medium or low risk, or from high risk to low risk) as a binary endpoint for alcohol clinical trials that may be useful for capturing clinically meaningful changes in consumption (Aubin et al., 2015).

Recent work has shown that reductions in WHO drinking risk levels correspond to significant improvements in mental health and drinking consequences in a clinical sample (Witkiewitz et al., 2017a). Similarly, in a nationally representative, population-based sample in the United States, reductions in the WHO drinking risk level were associated with significantly lower risk of developing alcohol dependence (Hasin et al., 2017) and lower risk of liver disease (Knox et al., in press).

Current Study

Despite recent studies, gaps remain in evaluating the utility of the WHO drinking risk level reductions. First, although population-based data show that WHO drinking risk level reductions may be associated with reduced risk of liver disease (Knox et. al. in press), it is unclear whether WHO drinking risk level reductions are associated with improvements in more proximal measures of physical health, particularly liver enzyme levels and blood pressure, among individuals in treatment for AUD. Second, to our knowledge, no studies have examined the association between WHO drinking risk level reductions and patient-reported quality of life.

The current study examined reductions in WHO drinking risk level as a predictor of proximal indicators of physical health (blood pressure and liver enzyme levels) and self-reported quality of life. We conducted a secondary data analysis among patients who participated in a large multi-site clinical trial for alcohol dependence to examine whether at least 1- and 2-level reductions in WHO drinking risk levels from pre-study (i.e., baseline) to the last month of treatment were associated with improvements in systolic blood pressure and liver enzyme levels at the end of treatment and self-reported quality of life assessed at 10 weeks following treatment. We hypothesized that at least 1- and 2-level reductions would be associated with significant improvements in physical health and self-reported quality of life.

Materials and Methods

Participants and procedures

Data were derived from the COMBINE study (Anton et al., 2006), a multi-site, randomized, double-blind placebo-controlled clinical trial conducted in the United States examining combinations of medications and behavioral interventions in the treatment of alcohol dependence. To be included in COMBINE, all participants met the criteria for alcohol dependence based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994) and reported at least 2 heavy drinking days in a consecutive 30-day period within the 90 days prior to the baseline assessment. Exclusion criteria included the presence of another substance use disorder (other than nicotine or cannabis), a psychiatric disorder requiring medication, or unstable medical conditions, including serum liver enzyme levels that were more than three times the upper limit of normal.

Participants for the current analyses (n=1226) were randomized using a 2 × 2 × 2 design in which they received: 1) active naltrexone (100 mg/day) or placebo naltrexone, 2) active acamprosate (3000 mg/day) or placebo acamprosate, and 3) medication management with a combined behavioral intervention (CBI) or medication management (MM) alone. An additional group received the CBI intervention without MM or pills (n=157) and this subset was excluded from the current analyses because we were most interested in examining the WHO risk reduction endpoints among those who received medications as part of an alcohol clinical trial.

Participants completed follow-up assessments at the end of treatment (week 16) and at three post-treatment follow-ups: 10 weeks (week 26 after baseline), 36 weeks (week 52 after baseline), and one year following treatment (week 68 after baseline).

Measures

Demographics.—Demographics, including age, sex, and race/ethnicity, were assessed at baseline using a self-report demographic questionnaire.

Alcohol consumption.—Daily alcohol consumption was measured using the Form-90 (Miller, 1996) and Timeline Follow-Back interview (Sobell and Sobell, 1992). We calculated WHO drinking risk levels (see Figure 1) based on participants' reports of the number of standard drinks (defined as 0.6 ounces of absolute alcohol) consumed, which were converted to grams of pure alcohol (0.6 ounces=14 grams). WHO drinking risk levels were then calculated based on the average grams of alcohol consumed per day (i.e., drinks per day). Importantly, the WHO drinking risk level is based on average grams per day, thus both drinking days and abstinent days are included to define average alcohol consumption across days over a specific time period (in the current study we averaged over one month time periods). For the baseline period, we calculated the WHO drinking risk level using data from the month prior to the screening. The final endpoint WHO drinking risk level during treatment was defined using the average grams of alcohol consumed per day during the last month of treatment, assessed at week 16.

For all analyses, we computed two binary variables that reflected at least 1- or 2-level reductions in the WHO drinking risk levels based on the reduction (i.e., "shift") from baseline to the last month of treatment. The reference group for the 1-level reduction was no change or an increase in the WHO drinking risk level from baseline to the last month of treatment and the reference group for the 2-level reduction was the 1-level reduction, no change, or increase in the WHO risk level from baseline to the last month of treatment. This reference group was chosen to be consistent with the EMA guidelines which define a responder as achieving at least a 2-level reduction (and thus a non-responder would be not achieving those reductions). Only 14 individuals had an increase in WHO risk level from baseline to the last month of treatment. As supplementary analyses we examined at least a 2-level reduction in WHO drinking risk level with no change or an increase in WHO drinking risk level as the reference group (excluding individuals with a 1-level reduction from the reference group).

Biological Markers.—Systolic blood pressure (SBP) was assessed at each clinic visit by clinical staff. Blood samples for liver enzyme levels and liver cell pathology, including percent carbohydrate-deficient transferrin (%CDT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT), were collected at specified clinic visits and sent to a central laboratory (Quintiles Laboratories, Marietta, GA) which performed the GGT, AST and ALT clinical assays utilizing automatic analyzer procedures. The Clinical Neurobiology Laboratory at the Medical University of South Carolina performed the %CDT analysis (Anton et. al. 2006). All samples were analyzed with the same assay techniques over the course of the entire study. AST, ALT, and GGT are liver enzyme markers which typically reflect liver cell damage while %CDT is a sensitive and alcohol specific biochemical marker of alcohol's effects on the protein transferrin. SBP and liver enzyme/pathology levels were included as biological markers of physical health that have been shown to be associated with heavy drinking and AUD (Baros et al., 2008; LoCastro et al., 2009; Stewart et al., 2008). SBP was examined rather than diastolic blood pressure (DBP), because prior research has shown SBP is more impacted by reductions in alcohol use than DBP (Stewart et al., 2008) and SBP is also a better predictor of cardiovascular risk (Strandberg & Pitkala, 2003). Lower SBP and liver enzyme/pathology levels are associated with more positive health outcomes (Kwo, Cohen, & Lim, 2017; Strandberg & Pitkala, 2003).

Quality of life.—Quality of life was assessed with the World Health Organization Quality of Life Brief version (WHOQOL-BREF; World Health Organization, 1998), the use of which was validated in the COMBINE study (Kirouac et al., 2017; LoCastro et al., 2009). This 25-item measure had response options ranging from 1 ("not at all") to 5 ("an extreme amount") and measured quality of life in four domains: physical health (e.g., "How satisfied are you with your sleep?"), psychological health ("How much do you enjoy life?"), social relationships (e.g., "How satisfied are you with your personal relationships?"), and environmental quality of life (e.g., "How satisfied are you with the conditions of your living place?"). Higher scores on each domain indicate better quality of life with maximum possible domain scores of 35 (physical health), 30 (psychological health), 15 (social health) and 40 (environmental domain). Scores in the COMBINE sample represented the full range

of possible scores on each domain. The WHOQOL-BREF was administered at baseline, 10 weeks following treatment (week 26) and 36 weeks following treatment (week 52). Internal consistency reliabilities for each domain exceeded Cronbach's α=.70 at all time points.

Statistical analysis

Using multiple regression analyses, we examined biomarkers assessed at the end of treatment and quality of life assessed at 10 weeks following treatment by regressing them on the WHO 1- and 2-level reduction endpoints. For all regression models, we controlled for the following covariates: baseline measures of the corresponding biomarkers or WHOQOL domains, age, sex, body mass index, and smoking status, and WHO drinking risk level at baseline. All covariates were mean centered prior to analysis. Results are reported as unstandardized regression coefficients (with standard errors), which can be interpreted as the decrease in outcomes based on achieving at least the 1- and 2-level reductions, holding all other covariates constant. The Cohen's *d* effect sizes, which represent the standardized mean differences between groups (e.g., no change or increases versus at least a 1-level reduction), at the end of treatment are also reported, where d=.2 is a small effect, d=.5 is a medium effect, and d= 0.8 is a large effect (Cohen, 1992). Potential effects of clinical research site were included as a clustering variable with standard errors adjusted using a sandwich estimator. All models were estimated in Mplus version 8 (Muthén and Muthén, 2017) with maximum likelihood estimation to accommodate missing outcome data (Witkiewitz et al., 2014).

Drinking data required to calculate the WHO level reduction were missing for 84 participants (6.9% of the total sample). Attrition analyses indicated that only participant age (with younger participants having more missing data) was associated with missing data on the WHO drinking risk level variables ($t(1218)=3.27$, $p<0.001$). None of the outcome measures at baseline or follow-up were associated with missing data on the WHO drinking risk level, thus the data were assumed to be missing at random with age included in the regression models. A set of sensitivity analyses that imputed "no change" in WHO drinking risk level when WHO level reduction data were missing (i.e., worst case scenario imputation) did not substantively change the results (available from first author).

Sensitivity analyses were conducted to examine the effect of excluding abstainers in the WHO drinking risk level reduction analysis by examining a subgroup of participants (n=806) that started treatment at the high- or very-high-risk levels of drinking and did not achieve total abstinence during treatment. These regression analyses provided a more sensitive test of whether reductions in high- and very-high-risk drinking at treatment intake to low-, medium-, or high-risk drinking (short of abstinence) at the end of treatment were associated with significant improvements in physical health and quality of life.

Similarly, we examined the effect of at least a 2-level reduction versus no change or increase in WHO risk level. These regression analyses excluded the 1-level reduction group from the comparison (i.e., reference) group, thus the focus is on those who achieved at least a 2-level reduction versus those who did not change or increased WHO levels. We also conducted regression analyses that included individuals who exceeded cutoffs for high levels of systolic blood pressure (SBP of 140 or above), %CDT (2.6% or above; Anton and Youngblood,

2006), AST and ALT (35 or above; Gueorguieva et al., 2015), and GGT (30 or above; Gueorguieva et al., 2015) at baseline.

Finally, reductions in WHO risk levels were further examined by estimating their associations with the percent of subjects who moved from above pre-determined cutoffs at baseline (elevated SBP, %CDT, AST, ALT, and GGT) to below pre-determined cutoffs at the end of treatment (below cutoffs on SBP, %CDT, AST, ALT, and GGT) using Pearson chi-square tests and Mantel-Haenszel odds ratios (with 95% confidence intervals).

Results

Participants in this secondary analysis were mostly male (68.8%) and non-Hispanic white (76.7%) [Black/African American (7.9%), Asian (0.3%), Hispanic (11.2%), American-Indian/Alaskan Native (1.3%), multi-racial (1.3%), and other race (1.2%)], with an average age of 44.4 years (*SD*=10.2).

The number of participants categorized at each WHO drinking risk level based on drinking during the 28 days prior to screening and the last month of treatment were examined using frequency statistics. At baseline, the majority of individuals (69.1%) were in the "very high risk" category (drinking over 101/61 [males/females] grams of pure alcohol per day on average) and there were no abstainers. During the last month of treatment (month 4), 36.3% of the sample was abstinent, 39.4% categorized as "low risk" drinkers, 9.9% categorized as "medium risk" drinkers, 6.3% categorized as "high risk drinkers", and 8.1% categorized as "very high risk" drinkers. As shown in Table 1, abstinence and low risk drinking were the most common WHO drinking risk levels in each month of treatment.

The binary WHO drinking risk level reduction variables were then created by calculating the reduction in drinking risk level from baseline to the last month of treatment. The majority of the sample reduced at least 1 (n=1011, 88.5%) or at least 2 levels (n=881, 77.1%) from baseline to the last month of treatment. Descriptive statistics for all outcomes by risk reduction levels are provided in Table 2.

Regression models

Regression analyses examined the binary 1- and 2-level WHO drinking risk reductions as predictors of biomarkers at the end of treatment and quality of life at 10 weeks following treatment. As shown in Figure 2 and Table 3, both the 1- and 2-level reduction measures were associated with significantly lower systolic blood pressure, %CDT, AST, ALT, and GGT, which indicates better functioning. The Cohen's *d* effect sizes can be interpreted as the standardized mean differences in outcomes based on achieving the 1- and 2-level reductions. For example, at least a 1-level reduction was associated with a 0.46 standard deviation lower SBP (p=0.0004) and a 0.38 standard deviation lower %CDT (p=0.006), as compared to those with no change or an increase in the WHO drinking risk level. At least a 2-level reduction was associated with a 0.27 standard deviation lower SBP (p<0.0001) and a 0.29 standard deviation lower %CDT (p<0.0001), as compared to those with 1-level reduction, no change, or an increase in the WHO drinking risk level. Effect size differences in AST, ALT,

and GGT were in the small to medium range for both 1- and 2-level reductions and statistically significant (all $p<0.01$).

Unstandardized regression coefficients, which can be interpreted as the decrease in outcomes based on achieving at least a 1- and 2-level reduction, are provided in Table 3. For example, at least a 1-level reduction was associated with 7.99 mm Hg lower SBP ($p<0.001$) and 0.70 lower %CDT ($p<0.001$), indicating better functioning, as compared to those with no change or an increase in the WHO drinking risk level. At least a 2-level reduction was associated with 7.38 mm Hg lower SBP ($p<0.001$) and 0.76 lower %CDT ($p<0.001$), as compared to those with 1-level reduction, no change, or an increase in the WHO drinking risk level.

Results from the regression analyses of quality of life outcomes are shown in Table 3 and Figure 3. The 1- and 2-level reduction measures were associated with significantly greater quality of life in all domains (all $p<0.001$). For example, at least a 1-level reduction was associated with a 2.36 higher physical domain score, a 2.26 higher psychological domain score, and a 2.11 higher environment domain score, as compared to those with no change or an increase in the WHO drinking risk level (all $p<0.001$ and Cohen's d>.40).

Sensitivity analyses

Sensitivity analyses were conducted with only the subgroup of participants ($n=806$) that started treatment at the high risk or very high risk levels and who did not achieve abstinence during treatment. In this subgroup, at least a 2-level reduction (n=631) was associated with a statistically significant decrease in SBP, %CDT, AST, and ALT; and at least a 1-level reduction ($n=702$) was associated with a statistically significant decrease in SBP (see Supplementary Table 1). At least 1- and 2-level reductions were also associated with significantly higher quality of life across all domains (all $p<0.001$).

Additionally, sensitivity analyses were conducted with only the subgroup of participants ($n=1012$) who achieved at least the 2-level reduction with no change or increase as the reference group (excluding the 1-level reduction from the reference group). As shown in Figure 4, the 2-level reduction was associated with significantly lower SBP ($p<0.0001$), %CDT ($p=0.003$), AST ($p<0.0001$), ALT ($p=0.01$), and GGT ($p=0.0007$). The 2-level reduction was also associated with significantly higher quality of life across all domains (all $p<0.01$). Importantly, at least a 1-level reduction (Figure 2) versus no change or increase, and at least a 2-level reduction (Figure 4) versus no change or increase produced similar effect sizes (Cohen's d) for each outcome (SBP: 1-level d=−.46, 2-level d=−.47; %CDT: 1-level d=−.38, 2-level d=−.40, AST: 1 level d=−.37, 2-level d=−.39; ALT: 1-level d=−.31. 2-level d=−.33; GGT: 1-level d=−.23, 2-level d=−.23).

Sensitivity analyses were also conducted for the subgroup of participants whose SBP (≥140 mm Hg; $n = 394$), %CDT (≥2.6%; $n = 552$), AST (≥35 IU/L; $n=385$), ALT (≥35 IU/L; $n=467$), and GGT (≥30 IU/L; $n=720$) were elevated at baseline. Among those with elevated SBP at baseline, at least a 2-level reduction was associated with significantly lower SBP at the end of treatment ($p=.001$; see Supplementary Table 2). The subgroup with at least a 1-level reduction did not show a significant reduction in SBP at end of treatment ($p=.09$),

despite a reduction in the magnitude of SBP that was similar to that of the 2-level reduction. Among participants with elevated %CDT, AST, ALT, and GGT at baseline, the 1- and 2-level reductions were associated with significantly lower concentrations of these liver enzymes at the end of treatment (see Supplementary Table 2, all $p<0.05$).

As shown in Figure 5, among participants with elevated %CDT, AST, ALT, and GGT at baseline, both the 1- and 2-level reductions in WHO risk were associated with significantly lower odds (all $p<0.05$) of being above the cutoffs for all of these measures at the end of treatment. For %CDT, achieving at least a 1- or 2-level reduction reduced the participants' odds of remaining above the 2.6 %CDT cutoff by 58% and 61%, respectively (see Supplementary Table 3). Odds of remaining elevated on AST, ALT, and GGT were significantly decreased by more than 72% with at least a 1- or 2-level reduction. (Supplementary Table 3). For participants whose SBP was above 140 mm Hg at baseline, achieving at least a 2-level reduction significantly reduced the participants' odds of remaining above the 140 mm Hg cutoff by 54%. Sex specific cutoffs for ALT and GGT (ALT ≥50 IU/L for males and ALT ≥35 IU/L for females; GGT ≥60 IU/L for males and GGT ≥40 IU/L for females), as well as a higher cutoff for GGT (GGT ≥100 IU/L) yielded substantively identical results (shown in Figure 5).

Discussion

Many people do not endorse abstinence as a goal of treatment (DeMartini et al., 2004) and an intermediate goal of harm reduction has been proposed as a reasonable and acceptable goal in both clinical trials and treatment settings (EMA, 2010; Witkiewitz, 2013). The current study examined whether drinking reductions, defined by achieving at least 1- or 2-level categorical reductions in the World Health Organization (WHO) drinking risk levels (WHO, 2000), were associated with significant improvements in physical health and quality of life measures in a large, well-conducted clinical trial. Results indicated that at least 1- and 2-level reductions in the WHO drinking risk levels from baseline to the last month of treatment were associated with significantly lower systolic blood pressure (SBP) and lower liver enzyme levels and liver cell pathology indicating better functioning, and improved self-reported quality of life at the end of treatment. Sensitivity analyses that excluded abstainers showed that at least a 2-level reduction remained a significant predictor of lower SBP, lower %CDT, and lower AST and ALT levels, and at least 1- or 2-level reductions remained significant predictors of improvements in quality of life. Likewise, using a less conservative reference group for the 2-level reduction endpoint (i.e., no change or increase in WHO risk levels) resulted in even greater improvements in physical health and quality of life. In addition, those individuals with elevated SBP (≥140 mm Hg) or liver enzymes (%CDT ≥2.6%, AST ≥35, ALT ≥35, GGT ≥30, sex specific cutoffs for ALT and GGT, and GGT ≥100) at baseline also significantly benefited from reductions in drinking. Achieving at least a 2-level reduction was associated with significantly lower SBP at the end of treatment among those with elevated blood pressure at baseline and achieving at least 1- or 2-level reductions were each associated with significantly lower %CDT, AST, ALT, and GGT at the end of treatment among those with elevated liver enzymes and liver cell pathology at baseline. Additional analyses, not reported here, found the effects of at least 1- and 2-level reductions on physical health and quality of life outcomes were not impacted by medication

condition or adherence to medications. Likewise, medication condition and adherence did not change the association between WHO risk level reduction and health or quality of life outcomes.

Intermediate harm reduction targets are currently accepted by the European Medicines Agency (EMA) as positive endpoints for alcohol clinical trials. Both the Food and Drug Administration (FDA) and EMA require that endpoints for alcohol clinical trials reflect meaningful clinical improvement in how patients feel or function (EMA, 2010; FDA, 2015). The results from the current study show that 1- and 2-level WHO drinking risk reductions are associated with statistically significant and clinically meaningful improvement in measures of health and quality of life among patients with alcohol dependence enrolled in a large alcohol clinical trial. The current findings are consistent with prior work showing that reductions in drinking are associated with meaningful improvement in health and quality of life among individuals with AUD (Kline-Simon et al., 2017; Laramée et al., 2015; LoCastro et al., 2009; Witkiewitz et al., 2017b, Stewart et. al. 2008) and extend this work by indicating that 1- and 2-level WHO drinking risk reductions predict improvements. Results are also consistent with a population-based study that showed reductions in the WHO drinking risk levels to be associated with reduced risk of liver disease (Knox et al., in press).

The identification of valid endpoints that can be used to identify clinically meaningful drinking reduction in AUD treatment is important for treatment development, translation to clinical practice, and public health. Reductions in WHO drinking risk levels provide a clear threshold for clinicians to use in recommending reduced drinking goals and evaluating the effectiveness of treatment for a given patient. When compared to abstinence, reductions in drinking risk levels are also more likely to be achieved by patients. In the current analyses, the majority achieved a 1-level reduction (88.5%) or a 2-level reduction (77.1%) from baseline to the last month of treatment, whereas only a minority of patients with AUD were abstinent in the last month of treatment (36.3% in the current study). Developing treatments that specifically target drinking reduction may also be more attractive to the millions of individuals with AUD who do not seek treatment because they do not want to stop drinking (Center for Behavioral Health Statistics and Quality, 2017).

Recent studies have shown that reductions in alcohol consumption on a broader scale could substantially reduce morbidity and mortality at the population level, positively affecting public health (François et al., 2014; GBD 2016 Alcohol Collaborators, 2018; Laramée et al., 2016; Rahhali et al., 2015). It is well known that heavy alcohol consumption leads to sustained high blood pressure, which in turn predisposes to arterial disease that can lead to stroke and myocardial infarction. Liver disease is also a well-known consequence of sustained heavy alcohol use (Rehm, 2010), with more than 20% of costly liver transplants being performed in individuals with alcoholic cirrhosis (Lucey, 2014). Therefore, reductions in blood pressure and liver enzyme levels could lead to important public health benefits through reduced medical costs and improved quality of life.

The current study is not without limitations. Most importantly, we were limited to the available data in the COMBINE study, which was designed as a clinical trial that evaluated medication response, rather than physical/psychological health per se. Thus, some of the

procedures, such as blood pressure measurement, were not standardized. The %CDT assay used in this study was a second-generation assay and there are newer, more sensitive and specific assays currently available (Schellenberg et. al. 2017). However, both threats to the precision of measurement would be expected to bias the results against finding significant relationships by reducing effect sizes, due to greater error variance. The fact that significant relationships were observed despite measurement imprecision suggests that even greater effects may exist than were detected here. The COMBINE study also did not include assessments of quality of life during treatment and did not extend the measurement of biological markers of physical health into the months following treatment. The difference in sample sizes between groups (i.e., fewer individuals in the no change or increase reference group) is also a limitation, particularly with respect to potential violations of the assumptions of regression. Importantly, non-parametric tests of differences in outcomes by the WHO level reductions resulted in the same substantive conclusions. Also, although minimal compared to many clinical trials, some data were missing, which we accommodated using maximum likelihood estimation. While we also conducted sensitivity analyses with alternative imputation strategies, these are, at best, estimations of how individuals with missing data were functioning at the end of treatment and/or 10 weeks following treatment. Future studies should expand the range of physical and psychological variables that might be associated with WHO drinking risk level changes and extend the analyses over longer periods of time.

The current findings add to the growing body of literature in support of the WHO drinking risk levels as an alternative to abstinence or no heavy drinking as targeted endpoints/outcomes in clinical trials (Falk et al. in press; Hasin et. al. 2017; Knox et al. in press; Witkiewitz et. al. 2017). The 1- and 2-level WHO drinking risk level reductions corresponded to significant and meaningful improvements in blood pressure and liver enzyme levels and liver cell pathology. It also appears that a change in WHO drinking-risk level is sensitive to medication effects in clinical trials (Aubin et al., 2015; Falk et. al. in press). Taken together, the reduction in WHO drinking-risk level is a clinically meaningful outcome that reflects meaningful reductions in alcohol consumption that could be used in clinical practice. This approach to measuring change in drinking could be more attractive to clinicians and patients than the measures currently available and could encourage greater interest in developing effective treatments for AUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Aldridge A, Zarkin GA, Dowd W, Bray JW, 2016 The relationship between end of treatment alcohol use and subsequent health care costs: Do heavy drinking days predict higher health care costs? Alcohol Clin Exp Res 40, 1122–1128. [PubMed: 27110675]

American Psychiatric Association, 1994 Diagnostic and statistical manual of mental disorders (4th ed.; DSM-IV), 4th ed. ed. Author, Washington, DC.

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A, 2006 Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 295, 2003–17. [PubMed: 16670409]

Anton RF, Youngblood M, 2006 Factors affecting %CDT status at entry into a multisite clinical treatment trial: experience from the COMBINE Study. Alcohol Clin Exp Res 30, 1878–83. [PubMed: 17067352]

Aubin H-J, Reimer J, Nutt DJ, Bladström A, Torup L, François C, Chick J, 2015 Clinical relevance of as-needed treatment with nalmefene in alcohol-dependent patients. Eur Addict Res 21, 160–8. [PubMed: 25832297]

Baros AM, Wright TM, Latham PK, Miller PM, Anton RF, 2008 Alcohol consumption, %CDT, GGT and blood pressure change during alcohol treatment. Alcohol Alcohol 43, 192–197. [PubMed: 18039674]

Betty Ford Institute Consensus Panel, 2007 What is recovery? A working definition from the Betty Ford Institute. J Subst Abuse Treat 33, 221–228. [PubMed: 17889294]

Center for Behavioral Health Statistics and Quality, 2017 2016 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD.

Cohen J (1992). A power primer. Psychol Bull 112, 155–159. [PubMed: 19565683]

DeMartini KS, Devine EG, DiClemente CC, Martin DJ, Ray LA, O'Malley SS, 2014 Predictors of pretreatment commitment to abstinence: results from the COMBINE study. J Stud Alcohol Drugs 75, 438–46. [PubMed: 24766756]

Dunn KE, Harrison JA, Leoutsakos J-M, Han D, Strain EC, 2017 Continuous Abstinence During Early Alcohol Treatment is Significantly Associated with Positive Treatment Outcomes, Independent of Duration of Abstinence. Alcohol Alcohol 52, 72–79. [PubMed: 27567268]

European Medicines Agency, 2010 Guideline on the development of medicinal products for the treatment of alcohol dependence. European Medicines Agency, United Kingdom.

Falk DE, O'Malley SS, Witkiewitz K, Anton RF, Litten RZ, Slater M, Mann K, Hasin DS, Johnson B, Meulien D, Ryan M, Fertig J (in press). Reductions in drinking risk level as outcomes in alcohol pharmacotherapy trials. JAMA Psychiatry.

Food and Drug Administration, 2015 Alcoholism: Developing drugs for treatment (No. FDA D-0152–001). Silver Spring, MD.

François C, Laramée P, Rahhali N, Chalem Y, Aballéa S, Millier A, Bineau S, Toumi M, Rehm J, 2014 A Predictive Microsimulation Model to Estimate the Clinical Relevance of Reducing Alcohol Consumption in Alcohol Dependence. Eur Addict Res 20, 269–284. [PubMed: 25228120]

GBD 2016 Alcohol Collaborators 2018 Alcohol use and burden for 195 coutnries and territories, 1990–2016: A systematic analysis for the global burden of disease study 2016. Lancet. online first https://doi.org/10.1016/S0140-6736(18)31310-2.

Gueorguieva R, Wu R, Tsai W-M, O'Connor PG, Fucito L, Zhang H, O'Malley SS, 2015 An analysis of moderators in the COMBINE study: Identifying subgroups of patients who benefit from acamprosate. Eur Neuropsychopharmacol 25, 1586–99. [PubMed: 26141511]

Hasin DS, Wall M, Witkiewitz K, Kranzler HR, Falk D, Litten R, Mann K, O'Malley SS, Scodes J, Robinson RL, Anton R, Fertig J, Isenberg K, McCann D, Meulien D, Meyer R, O'Brien C, Ryan M, Silverman B, Trinquet F, Wong C, Zakine B, 2017 Change in non-abstinent WHO drinking risk levels and alcohol dependence: a 3 year follow-up study in the US general population. The Lancet Psychiatry 4, 469–476. [PubMed: 28456501]

Kirouac M, Stein ER, Pearson MR, Witkiewitz K, 2017 Viability of the World Health Organization quality of life measure to assess changes in quality of life following treatment for alcohol use disorder. Qual Life Res 26, 2987–2997. [PubMed: 28647889]

Kline-Simon AH, Litten RZ, Weisner CM, Falk DE, 2017 Posttreatment Low-Risk Drinking as a Predictor of Future Drinking and Problem Outcomes Among Individuals with Alcohol Use Disorders: A 9-Year Follow-Up. Alcohol Clin Exp Res 41, 653–658. [PubMed: 28072453]

Kline-Simon AH, Weisner CM, Parthasarathy S, Falk DE, Litten RZ, Mertens JR, 2014 Five-year healthcare utilization and costs among lower-risk drinkers following alcohol treatment. Alcohol Clin Exp Res 38, 579–86. [PubMed: 24117604]

Knox J, Wall M, Witkiewitz K, Kranzler H, Falk DE, Litten R, Mann K, O'Malley SS, Scodes J, Anton R, Hasin D (in press). Reductions in non-abstinent WHO drinking risk levels are associated with reductions in rates of positive AUDIT-C score and liver disease: A 3-year follow-up study in the US general population. Alcohol Clin Exp Res.

Kwo PY, Cohen SM, Lim JK 2017 ACG Clinical Guideline: Evaluation of abnormal liver chemistries. Am J Gastroenterol, 112, 18–35. [PubMed: 27995906]

Laramée P, Leonard S, Buchanan-Hughes A, Warnakula S, Daeppen J-B, Rehm J, 2015 Risk of All-Cause Mortality in Alcohol-Dependent Individuals: A Systematic Literature Review and Meta-Analysis. EBioMedicine 2, 1394–404. [PubMed: 26629534]

Laramée P, Millier A, Rahhali N, Cristeau O, Aballéa S, François C, Chalem Y, Toumi M, Rehm J, 2016 A Trial-Based Predictive Microsimulation Assessing the Public Health Benefits of Nalmefene and Psychosocial Support for the Reduction of Alcohol Consumption in Alcohol Dependence. Appl Health Econ Health Policy 14, 493–505. [PubMed: 27283839]

LoCastro JS, Youngblood M, Cisler RA, Mattson ME, Zweben A, Anton RF, Donovan DM, 2009 Alcohol treatment effects on secondary nondrinking outcomes and quality of life: the COMBINE study. J Stud Alcohol Drugs 70, 186–96. [PubMed: 19261230]

Lucey MR 2014 Liver transplantation for alcoholic liver disease. Nat Rev Gastroenterol Hepatol 11, 300–307. [PubMed: 24393837]

MacCallum RC, Zhang S, Preacher KJ, Rucker DD, 2002 On the practice of dichotomization of quantitative variables. Psychol Methods 7, 19–40. [PubMed: 11928888]

Maisto SA, Clifford PR, Witkiewitz K, 2010 Alcohol use in the first year post-treatment initiation and its relationship to longer term functioning in individuals presenting for AUD treatment. Alcohol Clin Exp Res 34, 289A.

Mann K, Aubin H-J, Witkiewitz K, 2017 Reduced Drinking in Alcohol Dependence Treatment, What Is the Evidence? Eur Addict Res 23, 219–230. [PubMed: 28934736]

Maremmani I, Cibin M, Pani PP, Rossi A, Turchetti G, 2015 Harm Reduction as "Continuum Care" in Alcohol Abuse Disorder. Int J Environ Res Public Health 12, 14828–41. [PubMed: 26610535]

Miller WR, 1996 Form 90: A structured assessment interview for drinking and related behaviors, Project MA. ed. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Muthén LK, Muthén BO, 2017 Mplus users guide (Version 8).

Perlis RH, 2011 Translating biomarkers to clinical practice. Mol Psychiatry 16, 1076–87. [PubMed: 21709685]

Rahhali N, Millier A, Briquet B, Laramée P, Aballéa S, Toumi M, François C, Rehm J, Daeppen J-B, 2015 Modelling the consequences of a reduction in alcohol consumption among patients with alcohol dependence based on real-life observational data. BMC Public Health 15, 1271. [PubMed: 26690081]

Rehm J, Dawson D, Frick U, Gmel G, Roerecke M, Shield KD, Grant B, 2014 Burden of disease associated with alcohol use disorders in the United States. Alcohol Clin Exp Res 38, 1068–77. [PubMed: 24428196]

Rehm J, Gmel G, Sempos CT, Trevisan M, 2003 Alcohol·related morbidity and mortality. Alcohol Res Heal 27, 39–51.

Shield KD, Gmel G, Kehoe-Chan T, Dawson DA, Grant BF, Rehm J, 2013 Mortality and Potential Years of Life Lost Attributable to Alcohol Consumption by Race and Sex in the United States in 2005. PLoS One 8, e51923. [PubMed: 23300957]

Sobell LC, Sobell MB, 1992 Timeline Follow-Back In: Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Humana Press, pp. 41–72.

Strandberg TE & Pitkala K. 2003 What is the most important component of blood pressure: systolic, diastolic, or pulse pressure? Curr Opin Nephrol Hypertens, 12(3), 293–7. [PubMed: 12698068]

Stewart SH, Latham PK, Miller PM, Randall P, Anton RF, 2008 Blood pressure reduction during treatment for alcohol dependence: results from the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) study. Addiction 103, 1622–1628. [PubMed: 18821872]

van Amsterdam J, van den Brink W, 2013 Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. J Psychopharmacol 27, 987–997. [PubMed: 23824247]

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJL, Vos T, 2013 Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575–86. [PubMed: 23993280]

Wilson AD, Bravo AJ, Pearson MR, Witkiewitz K, 2016 Finding success in failure: using latent profile analysis to examine heterogeneity in psychosocial functioning among heavy drinkers following treatment. Addiction 111, 2145–2154. [PubMed: 27367263]

Witkiewitz K, 2013 "Success" following alcohol treatment: moving beyond abstinence. Alcohol Clin Exp Res 37 Suppl 1, E9–13. [PubMed: 23075307]

Witkiewitz K, Falk DE, Kranzler HR, Litten RZ, Hallgren KA, O'Malley SS, Anton RF, 2014 Methods to analyze treatment effects in the presence of missing data for a continuous heavy drinking outcome measure when participants drop out from treatment in alcohol clinical trials. Alcohol Clin Exp Res 38, 2826–34. [PubMed: 25421518]

Witkiewitz K, Hallgren KA, Kranzler HR, Mann KF, Hasin DS, Falk DE, Litten RZ, O'Malley SS, Anton RF, 2017a Clinical Validation of Reduced Alcohol Consumption After Treatment for Alcohol Dependence Using the World Health Organization Risk Drinking Levels. Alcohol Clin Exp Res 41, 179–186. [PubMed: 28019652]

Witkiewitz K, Masyn KE, 2008 Drinking trajectories following an initial lapse. Psychol Addict Behav 22, 157–67. [PubMed: 18540713]

Witkiewitz K, Roos CR, Pearson MR, Hallgren KA, Maisto SA, Kirouac M, Forcehimes AA, WIlson AD, Robinson CS, McCallion EA, Tonigan JS, Heather N, 2017b How much is too much? Patterns of drinking during alcohol treatment and associations with post-treatment outcomes across three alcohol clinical trials. J Stud Acohol Drugs 78, 59–69.

Witkiewitz K, Wilson AD, Pearson MR, Montes KS, Kirouac M, Roos CR, Hallgren KA, Maiso SA 2018 Profiles of recovery from alcohol use disorder at three years following treatment: can the definition of recovery be extended to include high functioning heavy drinkers? Addiction. doi: 10.1111/add.14403

Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, Bell S, Astle W, Stevens D, Koulman A, Selmer RM, Verschuren WMM, Sato S, Njølstad I, Woodward M, Salomaa V, Nordestgaard BG, Yeap BB, Fletcher A, Melander O, Kuller LH, Balkau B, Marmot M, Koenig W, Casiglia E, Cooper C, Arndt V, Franco OH, Wennberg P, Gallacher J, de la Cámara AG, Völzke H, Dahm CC, Dale CE, Bergmann MM, Crespo CJ, van der Schouw YT, Kaaks R, Simons LA, Lagiou P, Schoufour JD, Boer JMA, Key TJ, Rodriguez B, Moreno-Iribas C, Davidson KW, Taylor JO, Sacerdote C, Wallace RB, Quiros JR, Tumino R, Blazer DG, Linneberg A, Daimon M, Panico S, Howard B, Skeie G, Strandberg T, Weiderpass E, Nietert PJ, Psaty BM, Kromhout D, Salamanca-Fernandez E, Kiechl S, Krumholz HM, Grioni S, Palli D, Huerta JM, Price J, Sundström J, Arriola L, Arima H, Travis RC, Panagiotakos DB, Karakatsani A, Trichopoulou A, Kühn T, Grobbee DE, Barrett-Connor E, van Schoor N, Boeing H, Overvad K, Kauhanen J, Wareham N, Langenberg C, Forouhi N, Wennberg M, Després J-P, Cushman M, Cooper JA, Rodriguez CJ, Sakurai M, Shaw JE, Knuiman M, Voortman T, Meisinger C, Tjønneland A, Brenner H, Palmieri L, Dallongeville J, Brunner EJ, Assmann G, Trevisan M, Gillum RF, Ford I, Sattar N, Lazo M, Thompson SG, Ferrari P, Leon DA, Smith GD, Peto R, Jackson R, Banks E, Di Angelantonio E, Danesh J, Wood AM, Kaptoge S, Butterworth A, Willeit P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, Bell S, Astle W, Stevens D,

Koulman A, Selmer RM, Verschuren M, Sato S, Njølstad I, Woodward M, Veikko S, Nordestgaard BG, Yeap BB, Flecther A, Melander O, Kuller LH, Balkau B, Marmot M, Koenig W, Casiglia E, Cooper C, Arndt V, Franco OH, Wennberg P, Gallacher J, Gómez de la Cámara A, Völzke H, Dahm CC, Dale CE, Bergmann M, Crespo C, van der Schouw YT, Kaaks R, Simons LA, Lagiou P, Schoufour JD, Boer JM, Key TJ, Rodriguez B, Moreno-Iribas C, Davidson KW, Taylor JO, Sacerdote C, Wallace RB, Quiros JR, Rimm EB, Tumino R, Blazer III DG, Linneberg A, Daimon M, Panico S, Howard B, Skeie G, Salomaa V, Strandberg T, Weiderpass E, Nietert PJ, Psaty BM, Kromhout D, Salamanca-Fernandez E, Kiechl S, Krumholz HM, Grioni S, Palli D, Huerta JM, Price J, Sundström J, Arriola L, Arima H, Travis RC, Panagiotakos DB, Karakatsani A, Trichopoulou A, Kühn T, Grobbee DE, Barrett-Connor E, van Schoor N, Boeing H, Overvad K, Kauhanen J, Wareham N, Langenberg C, Forouhi N, Wennberg M, Després J-P, Cushman M, Cooper JA, Rodriguez CJ, Sakurai M, Shaw JE, Knuiman M, Voortman T, Meisinger C, Tjønneland A, Brenner H, Palmieri L, Dallongeville J-P, Brunner EJ, Assmann G, Trevisan M, Gillumn RF, Ford IF, Sattar N, Lazo M, Thompson S, Ferrari P, Leon DA, Davey Smith G, Peto R, Jackson R, Banks E, Di Angelantonio E, Danesh J, 2018 Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 391, 1513–1523. [PubMed: 29676281]

World Health Organization, 1998 World Health Organization Quality of Life. World Health Organization, Geneva, Switzerland.

World Health Organization, 2011 Global Status Report on Alcohol and Health. Geneva.

World Health Organization (WHO), 2000 International guide for monitoring alcohol consumption and related harm. World Health Organization, Geneva, Switzerland.

Yoo B, 2010 The impact of dichotomization in longitudinal data analysis: a simulation study. Pharm Stat 9, 298–312. [PubMed: 19904810]

	World Health Organization Alcohol Risk Levels (for males)			
	Low Risk	Medium Risk	High Risk	Very High Risk
Drinks per day (in grams)	1 to 40 g	41 to 60 g	61 to 100 g	101+ g
Drinks per day (in standard drinks)	0 to 2.9 drinks	3.0 to 4.3 drinks	4.4 to 7.1 drinks	7.2+ drinks

	World Health Organization Alcohol Risk Levels (for females)			
	Low Risk	Medium Risk	High Risk	Very High Risk
Drinks per day (in grams)	1 to 20 g	21 to 40 g	41 to 60 g	61+ g
Drinks per day (in standard drinks)	0 to 1.4 drinks	1.5 to 2.8 drinks	2.9 to 4.3 drinks	4.4+ drinks

Figure 1.
WHO Drinking Risk Levels and Approximate United States Standard Drinks

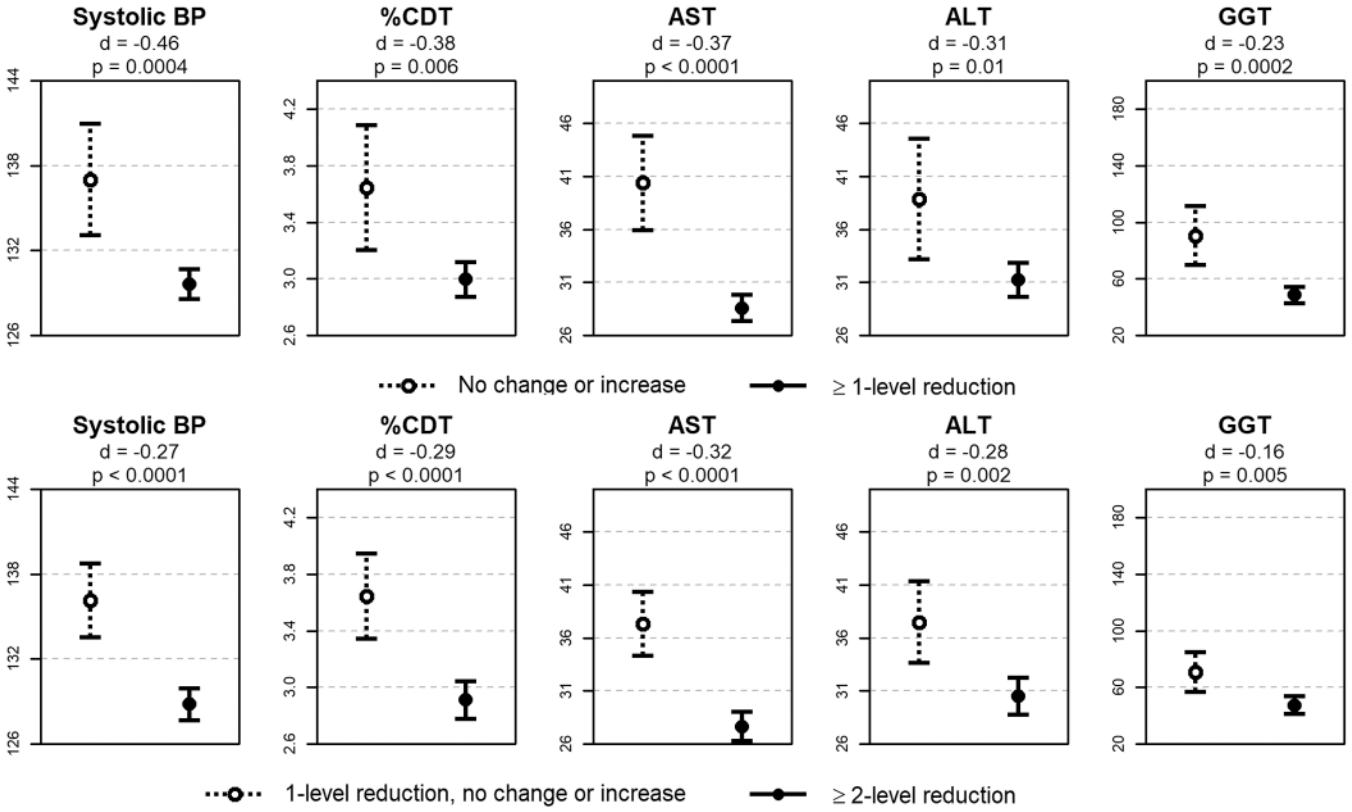

Figure 2. Risk Level Reductions from Baseline to End of Treatment Predicting End of Treatment Biomarkers (N=1142) for 1- and 2-Level Reduction with 95% Confidence Intervals

Figure Note. Systolic BP=Systolic Blood Pressure; CDT=% carbohydrate-deficient transferrin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=γ-glutamyltransferase. d =Cohen's d, which is the standardized mean effect size difference between groups (e.g., >1 level reduction versus no change or increase) at end of treatment. p = p-value for group difference in regression models including the following covariates: baseline levels of outcome (BP or biomarker), sex, age, body mass index, smoking status, and WHO drinking risk level at baseline.

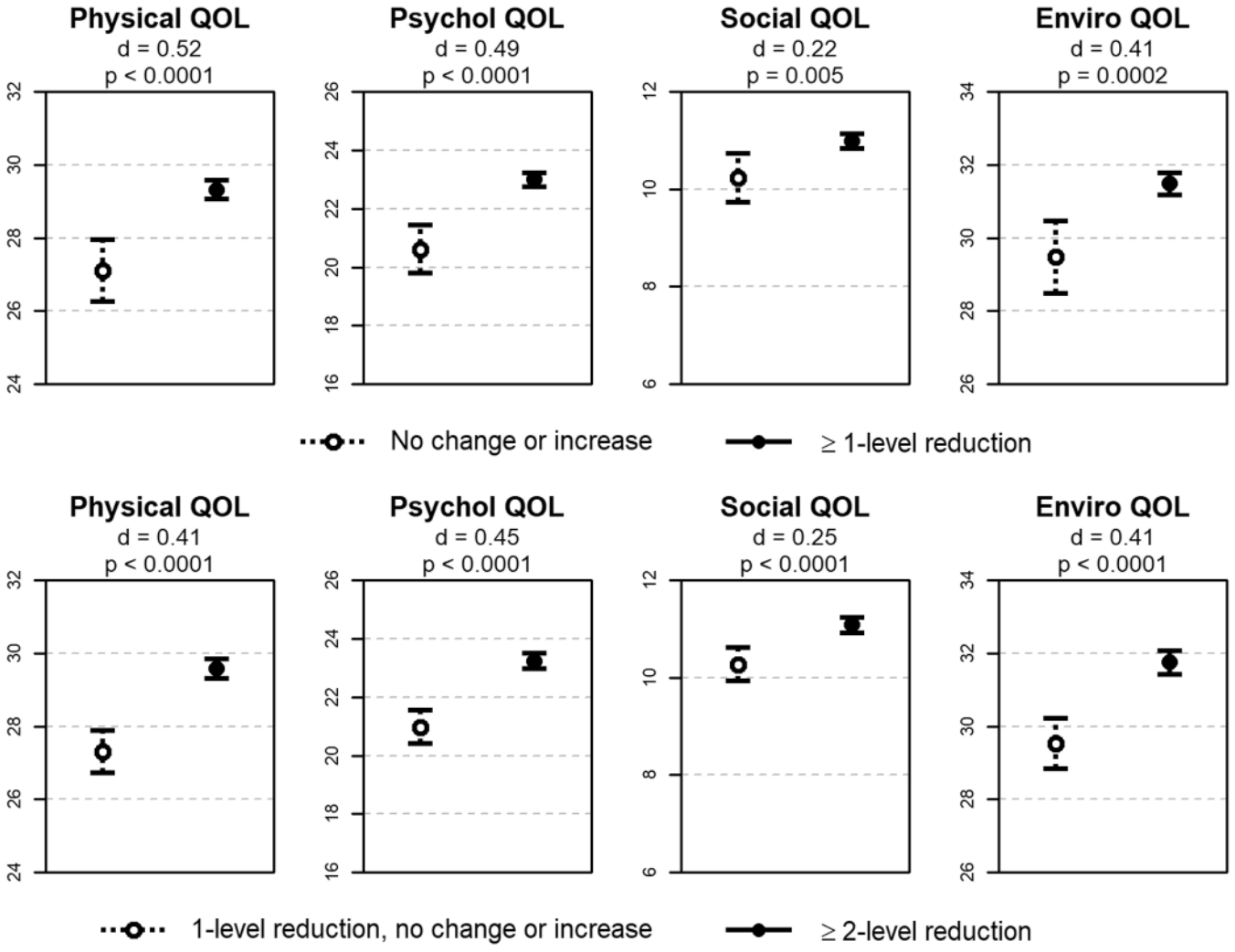

Figure 3. Risk Level Reductions from Baseline to End of Treatment Predicting End of Treatment Quality of Life (QoL) (N=1142) for 1- and 2-Level Reduction with 95% Confidence Intervals

Figure Note. QOL = Quality of Life. d =Cohen's d, which is the standardized mean effect size difference b. p = p-value for group difference in regression models including the following covariates: baseline levels of quality of life, sex, age, body mass index, smoking status, and WHO drinking risk level at baseline. Error bars are 95% confidence intervals.

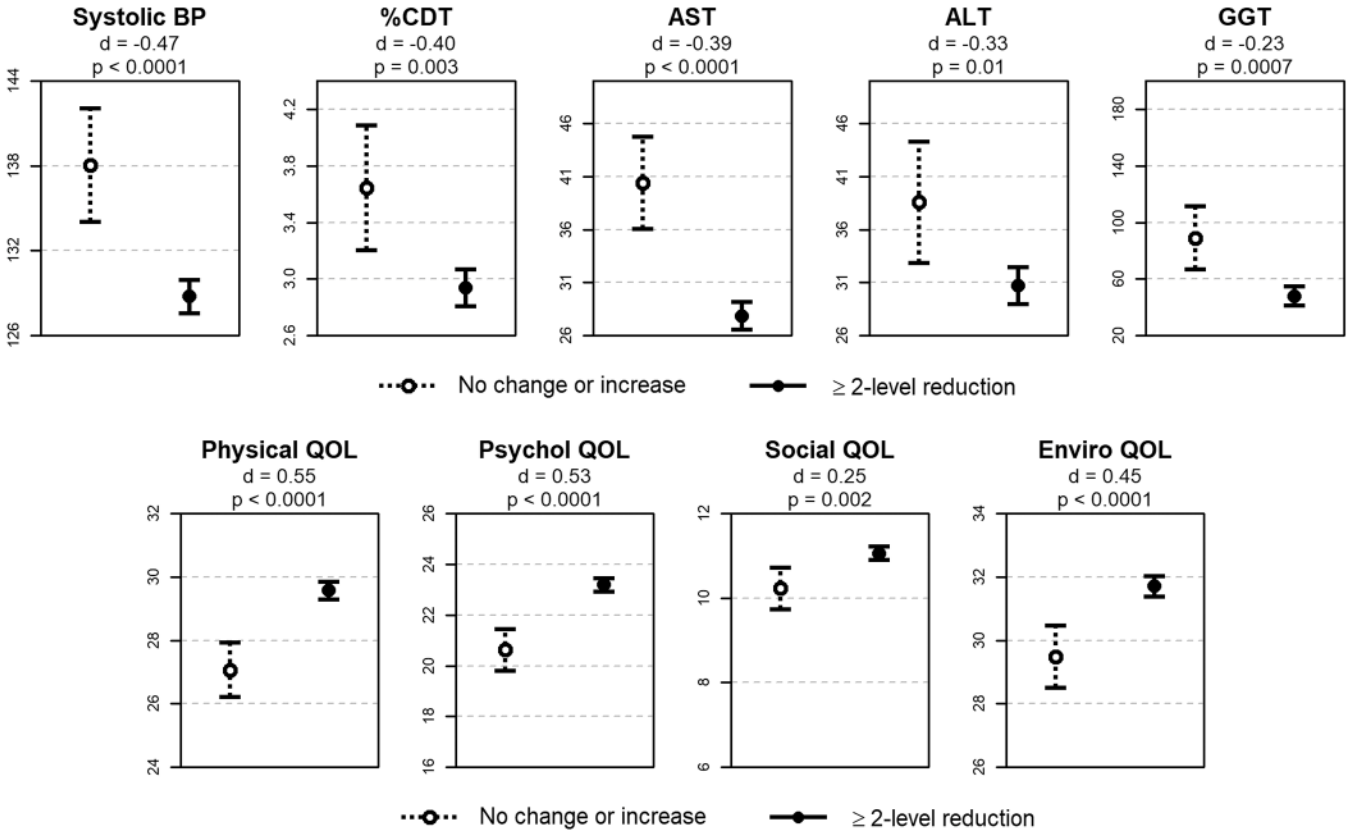

Figure 4. Risk Level Reductions from Baseline to End of Treatment Predicting End of Treatment Biomarkers and Quality of Life (N=1142) for 2-Level Reduction with 95% Confidence Intervals

Figure Note. Systolic BP=Systolic Blood Pressure; CDT=% carbohydrate-deficient transferrin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=γ-glutamyltransferase. QOL = Quality of Life. d =Cohen's d, which is the standardized mean effect size difference between groups (e.g., >2 level reduction versus no change or increase) at end of treatment. p = p-value for group difference in regression models including the following covariates: baseline levels of outcome (BP or biomarker or QOL), sex, age, body mass index, smoking status, and WHO drinking risk level at baseline.

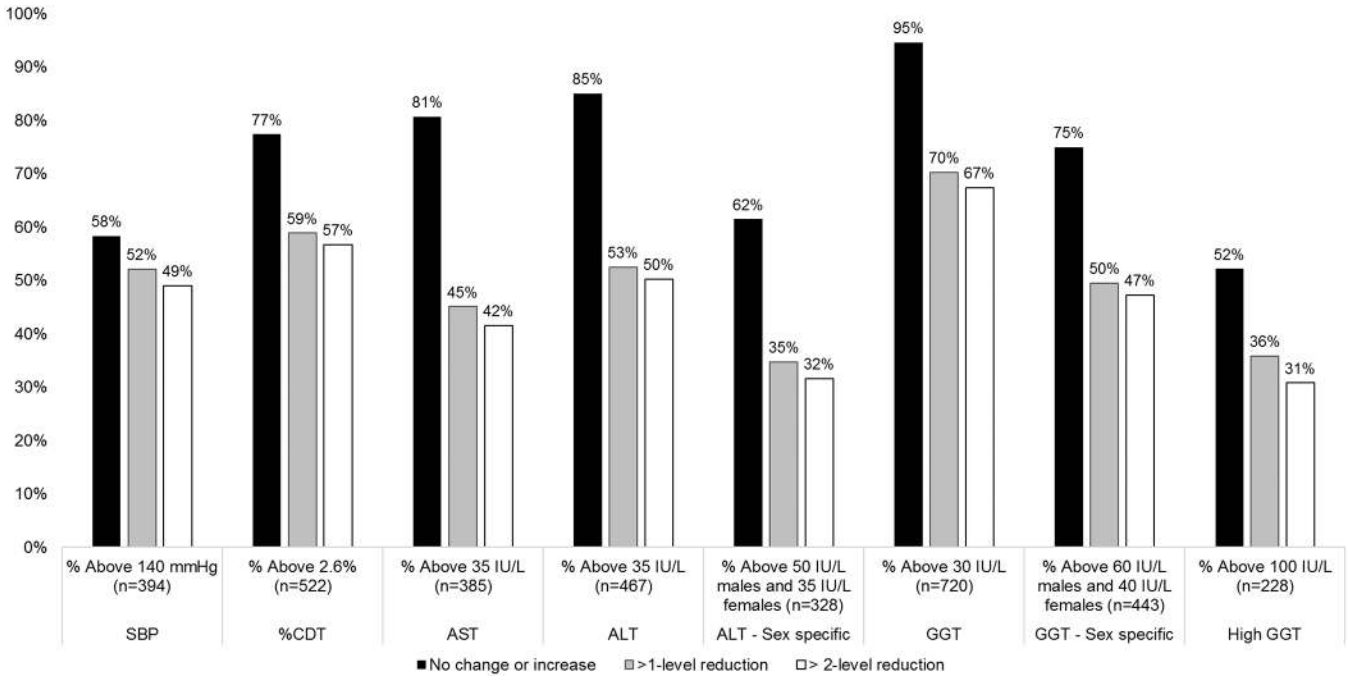

Figure 5.

Percent of Individuals with Elevations at the End of Treatment, among those with Elevations on Biomarkers at Baseline Figure Note. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; SBP=Systolic Blood Pressure; CDT=% carbohydrate-deficient transferrin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=γ-glutamyltransferase. IU/L=International Units per Liter. 1-level reduction = > 1-level reduction; 2-level reduction = > 2-level reduction.

Table 1.

WHO Drinking Risk Levels and Frequencies (N (%)) at each Risk Level

WHO drinking risk level (grams (g) of pure alcohol per day for males / females)	Baseline	Month 1	Month 2	Month 3	Month 4
Abstinence (0 g)	0 (0.0%)	443 (36.3%)	399 (33.8%)	426 (36.9%)	415 (36.3%)
Low risk (1 to 40 g / 1 to 20 g)	36 (2.9%)	560 (45.9%)	515 (43.6%)	484 (41.9%)	450 (39.4%)
Medium risk (41 to 60 g / 21 to 40 g)	89 (7.3%)	101 (8.3%)	110 (9.3%)	91 (7.9%)	113 (9.9%)
High risk (61 to 100 g / 41 to 60 g)	254 (20.7%)	69 (5.7%)	71 (6.0%)	67 (5.8%)	72 (6.3%)
Very high risk (101+ g / 61+ g)	846 (69.1%)	46 (3.8%)	86 (7.3%)	87 (7.5%)	92 (8.1%)

Note. WHO drinking risk levels were derived from patient reports of the number of standard drinks (defined as 0.6 ounces of absolute alcohol) consumed, which were converted to grams of pure alcohol (0.6 ounces=14 grams).

Table 2.

Baseline and End of Treatment Mean (Standard Deviation) Blood Pressure, Liver Enzymes, and Quality of Life (QOL) by WHO Drinking Risk Level Reduction

	No change or increase (n=131)	WHO 1-level reduction (n=1011)	1 level reduction, no change or increase (n=261)	WHO 2-level reduction (n=881)
SBP (mm/Hg) Baseline	135.8 (17.6)	133.5 (18.2)	133.7 (19.3)	133.7 (17.8)
SBP (mm/Hg) End of treatment	137.9 (17.6)	129.8 (16.6)	134.2 (17.1)	129.5 (16.6)
%CDT (%) Baseline	4.3 (3.3)	3.3 (1.9)	3.8 (2.8)	3.3 (1.9)
%CDT (%) End of treatment	3.8 (1.1)	2.9 (1.8)	3.5 (2.3)	2.9 (1.7)
AST (IU/L) Baseline	44.6 (34.8)	35.5 (34.2)	38.4 (28.4)	35.9 (35.9)
AST (IU/L) End of treatment	41.0 (35.7)	28.2 (16.0)	36.2 (29.1)	27.7 (14.7)
ALT (IU/L) Baseline	46.9 (35.7)	39.6 (38.3)	41.8 (29.7)	40.0 (40.2)
ALT (IU/L) End of treatment	40.8 (32.6)	30.8 (23.5)	38.0 (28.9)	30.1 (23.1)
GGT (IU/L) Baseline	120.2 (270.4)	69.6 (96.9)	91.3 (201.3)	70.7 (99.0)
GGT (IU/L) End of treatment	145.1 (467.1)	43.5 (61.9)	87.3 (303.6)	42.9 (63.3)
QOL Physical Baseline	26.9 (4.3)	27.3 (4.2)	27.5 (4.1)	27.2 (4.3)
QOL Physical End of treatment	26.9 (4.8)	29.4 (4.2)	27.8 (4.3)	29.5 (4.2)
QOL Psychological Baseline	20.8 (4.0)	21.1 (3.9)	21.3 (3.8)	21.0 (4.0)
QOL Psychological End of treatment	20.6 (4.9)	23.0 (4.1)	21.2 (4.4)	23.2 (4.1)
QOL Social Baseline	9.8 (2.7)	9.8 (2.6)	9.8 (2.5)	9.8 (2.6)
QOL Social End of treatment	10.3 (2.6)	10.9 (2.6)	10.3 (2.6)	11.0 (2.6)
QOL Environment Baseline	29.1 (5.5)	29.9 (5.4)	29.5 (5.3)	29.8 (5.4)
QOL Environment End of treatment	28.9 (6.4)	31.6 (5.4)	29.4 (6.0)	31.8 (5.3)

Note. SBP=Systolic Blood Pressure; CDT=% carbohydrate-deficient transferrin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=γ-glutamyltransferase. IU/L=International Units per Liter. QOL=Quality of Life.

Table 3.

WHO Risk Level Reductions from Baseline to End of Treatment in Predicting End of Treatment Biomarkers and Quality of Life (N=1142)

Predictor	SBP (mm/Hg) B (SE)	%CDT (%) B (SE)	AST (IU/L) B (SE)	ALT (IU/L) B (SE)	GGT (IU/L) B (SE)
Model R^2	0.29	0.29	0.11	0.15	0.66
1-level reduction (n=1011)	−7.99 (1.96)***	−0.70 (0.17)***	−11.65 (4.91)*	−8.01 (3.67)*	−43.05 (16.36)**
Baseline WHO level	2.29 (0.57)***	0.10 (0.07)	0.48 (0.68)	−1.09 (1.02)	−3.53 (2.28)
Baseline outcome	0.42 (0.04)***	0.44 (0.05)***	0.11 (0.06)	0.17 (0.07)*	0.87 (0.22)***
Sex	4.77 (1.42)**	0.11 (0.09)	5.28 (1.30)***	6.83 (2.26)**	−2.95 (9.30)
Age	0.10 (0.04)*	−0.003 (0.004)	−0.04 (0.05)	−0.14 (0.07)	−0.67 (0.35)
Body mass index	0.08 (0.12)	−0.03 (0.01)*	−0.08 (0.14)	0.55 (0.20)**	−0.77 (0.40)
Smoking status	1.15 (0.96)	0.22 (0.11)*	0.45 (1.01)	−1.40 (1.87)	0.33 (2.85)
Model R^2	0.32	0.31	0.10	0.15	0.66
2-level reduction (n=881)	−7.38 (1.89)***	−0.76 (.19)***	−9.82 (2.17)***	−7.61 (1.73)**	−24.32 (7.58)**
Baseline WHO level	3.47 (0.78)***	0.23 (0.10)*	1.96 (1.06)	0.11 (1.21)	−0.79 (2.79)
Baseline outcome	0.42 (0.04)***	0.43 (0.05)***	0.12 (0.06)	0.17 (0.07)*	0.88 (0.22)***
Sex	4.98 (1.38)***	0.13 (0.08)	5.47 (1.32)***	7.01 (2.25)**	−2.81 (9.48)
Age	0.10 (0.04)*	−0.003 (0.004)	−0.04 (0.05)	−0.15 (0.08)	−0.66 (0.35)
Body mass index	0.10 (0.12)	−0.03 (0.01)*	−0.08 (0.13)	0.55 (0.19)**	−0.73 (0.40)
Smoking status	1.07 (0.87)	0.19 (0.10)	0.30 (1.07)	−1.55 (1.92)	0.30 (2.89)

Predictor	QoL Physical B (SE)	QoL Psychological B (SE)	QoL Social B (SE)	QoL Environment B (SE)
Model R^2	0.32	0.34	0.34	0.43
1-level reduction (n=1011)	2.36 (0.15)***	2.26 (0.24)***	0.76 (0.22)***	2.11 (0.52)***
Baseline WHO level	0.02 (0.13)	0.09 (0.17)	0.004 (0.07)	0.13 (0.22)
Baseline outcome	0.54 (0.04)***	0.60 (0.05)***	0.56 (0.04)***	0.61 (0.05)***
Sex	−0.23 (0.27)	−0.27 (0.28)	0.01 (0.13)	−0.30 (0.30)
Age	0.02 (0.01)	0.01 (0.01)	0.01 (0.01)	0.05 (0.01)***
Body mass index	0.02 (0.01)	0.05 (0.01)***	0.02 (0.02)	0.07 (0.02)**
Smoking status	−0.14 (0.23)	−0.06 (0.38)	−0.26 (0.13)	−0.14 (0.33)
Model R^2	0.34	0.36	0.34	0.44
2-level reduction (n=881)	2.27 (0.24)***	2.25 (0.21)***	0.83 (0.17)***	2.32 (0.44)***
Baseline WHO level	−0.34 (0.16)*	−0.27 (0.20)	−0.13 (0.09)	−0.26 (0.24)
Baseline outcome	0.55 (0.04)***	0.60 (0.06)***	0.56 (0.04)***	0.61 (0.05)***
Sex	−0.30 (0.28)	−0.35 (0.28)	−0.02 (0.13)	−0.38 (0.29)
Age	0.02 (0.01)	0.01 (0.01)	0.005 (0.01)	0.05 (0.01)***

Predictor	QoL Physical B (SE)	QoL Psychological B (SE)	QoL Social B (SE)	QoL Environment B (SE)
Body mass index	0.02 (0.01)	0.05 (0.01) **	0.02 (0.01)	0.07 (0.02) **
Smoking status	−0.10 (0.24)	−0.02 (0.36)	−0.24 (0.12)	−0.09 (0.32)

Note.

* $p < 0.05$;

** $p < 0.01$;

*** $p < 0.001$;

SBP=Systolic Blood Pressure; CDT=% carbohydrate-deficient transferrin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=γ-glutamyltransferase. IU/L=International Units per Liter; QoL = Quality of Life Domains. B (SE)=unstandardized regression coefficient (standard error). Models include the following covariates: baseline levels of outcome (BP or biomarker), sex (male=1), age, body mass index, smoking status (smoker=1), and WHO drinking risk level at baseline; and adjusted for treatment site. The reference group (1-level reduction=0) for the 1-level reduction (1-level reduction=1) is no change or increase in WHO drinking risk level and the reference group (2-level reduction=0) for the 2-level reduction (2-level reduction=1) is 1-level reduction, no change, or increase in WHO drinking risk level during any month of treatment.