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# Maintenance of World Health Organization Risk Drinking Level Reductions and Post-Treatment Functioning Following a Large Alcohol Use Disorder Clinical Trial

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## Abstract

**Background.—**Reductions in the World Health Organization (WHO) risk drinking levels have been proposed as an alternative primary outcome for alcohol clinical trials. Yet, little is known about whether reductions in WHO risk drinking levels can be maintained over time. The current study examined whether reductions in WHO risk drinking levels were maintained for up to one year following treatment, and whether reductions over time were associated with improvements in functioning.

**Methods.—**Secondary data analysis of individuals with alcohol dependence (n=1226) enrolled in the COMBINE study (Anton et al. 2006), a multi-site randomized placebo-controlled clinical trial. Logistic regression was used to examine the maintenance of end-of-treatment WHO risk level reductions and WHO risk level reductions at the one-year follow-up. Repeated measures mixed

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models were used to examine the association between WHO risk level reductions and functional outcomes over time.

**Results.—**Achieving at least a one- or two-level reduction in risk by the end of treatment was significantly associated with WHO risk level reductions at the one-year follow-up assessment ($p$<0.001). Among individuals who achieved at least a one-level reduction by the end of treatment, 85.5% reported at least a one-level reduction at the one-year follow-up. Among individuals who achieved at least a two-level reduction by the end of treatment, 77.8% reported at least a two-level reduction at the one-year follow-up. WHO risk level reductions were associated with significantly lower alcohol consumption, better physical health ($p$<0.01), and fewer alcohol-related consequences ($p$<0.001) up to one year following treatment.

**Conclusion.—**One- and two-level reductions in WHO risk levels during alcohol treatment were maintained after treatment and associated with better functioning over time. These findings support the use of the WHO risk level reductions as an outcome measure that reflects clinically significant improvement in how individuals seeking treatment for AUD feel and function.

### Keywords

World Health Organization Risk Drinking Levels; Alcohol Use Disorder; Reduced Alcohol Consumption; Alcohol Treatment Outcomes; Low Risk Drinking; Alcohol Dependence

## Introduction

For individuals treated for alcohol use disorder (AUD), engaging in some level of drinking following treatment is common (Hunt et al., 1971; Maisto et al., 2018; Witkiewitz and Masyn, 2008). Sustained abstinence has long been considered the optimal outcome of AUD treatment (Betty Ford Institute Consensus Panel, 2007; Mann et al., 2017) and most research historically focused on abstinence as a primary measure of treatment outcomes (e.g., percent days abstinent from alcohol; Anton et al., 2006; Maisto et al., 2016). Yet, individuals seeking treatment for AUD are increasingly interested in drinking reduction goals (DeMartini et al., 2014; Haug et al., 2018; Ryan et al., 2017) and AUD treatment professionals have become more accepting of patients' drinking reduction goals (Davis and Rosenberg, 2013; Rosenberg and Davis, 1994). Given a growing interest in drinking reduction as a goal of AUD treatment (Mann et al., 2017; van Amsterdam and van den Brink, 2013), examining whether drinking reductions are maintained over time and associated with improvements in patients' functioning is an important question for AUD treatment outcomes research.

### Primary Measures of AUD Treatment Outcomes

The Food and Drug Administration's (FDA's) draft guidance on the development of alcohol treatment medications (Food and Drug Administration, 2015) recommended two potential AUD treatment outcomes (i.e., endpoints) for medications development: 1) sustained abstinence or 2) no heavy drinking days, with heavy drinking days defined as more than 3 drinks in a day for women and 4 drinks in a day for men (National Institute on Alcohol Abuse and Alcoholism, 2005). The European Medicines Agency (EMA; European Medicines Agency, 2010) recommends abstinence as a primary endpoint, but acknowledges

the utility of drinking reduction endpoints for alcohol clinical trials, including reductions in total alcohol consumption, heavy drinking days, or in the World Health Organization (WHO) risk drinking levels (WHO, 2000), which are defined by sex-specific limits on the number of grams (g) of alcohol consumed per day. Specifically, as shown in Figure 1, individuals can be abstinent (0 g males/females), low risk (1 to 40 g males / 1 to 20 g females), medium risk (41 to 60 g males / 21 to 40 g females), high risk (61 to 100 g males / 41 to 60 g females), or very high risk (101+ g males / 61+ g females). Importantly, guidance from both the FDA and the EMA highlights that endpoints for alcohol clinical trials should be associated with improvements in patient functioning.

Reduction in the WHO risk levels as a potential outcome measure has recently been studied in both populations of individuals receiving treatment for AUD (Aubin et al., 2015; O'Malley et al., 2018; Witkiewitz et al., 2017a, 2018) and a general population sample of alcohol drinkers (Hasin et al., 2017; Knox et al., 2018). Findings across studies show that reductions in WHO drinking-risk levels are associated with significant differences between active medication treatments and placebo (Aubin et al., 2015; Falk et al., in press; O'Malley et al., 2018), improvements in physical health and the quality of life (Knox et al., in press; Knox et al., 2018; Witkiewitz et al., 2018), reduced risk of alcohol dependence (Hasin et al., 2017), and reductions in drinking-related consequences and improvements in mental health (Witkiewitz et al., 2017a).

## Current Study: Examining the Maintenance of Drinking Reduction Outcomes

A major concern with non-abstinent drinking reduction outcomes is that they may not be maintained over time (Anton et al., 2012). For example, the FDA recommends that clinical trials be 6 months in duration based on the notion that "drinking patterns over shorter durations of time, such as 12 weeks, may not be stable or representative of future experience" (p. 5; FDA, 2015). Recent work in the field has supported the maintenance of low-risk drinking outcomes, defined as not exceeding heavy drinking limits, over one year (Witkiewitz et al., 2017b), three years (Maisto et al., 2007), and up to nine years following treatment (Kline-Simon et al., 2017). However, the maintenance of the WHO risk drinking level reductions has not been studied extensively. Aubin and colleagues (2015) examined whether individuals who received nalmefene, compared to placebo, had a higher likelihood of achieving a two-level reduction in WHO risk drinking level over a 6-month clinical trial, but did not examine the maintenance of the two-level reduction outcome beyond 6 months. Witkiewitz and colleagues (2017a, 2018) examined whether reductions in WHO risk levels during a 4-month clinical trial, the COMBINE Study, predicted functioning for up to one year following treatment, but did not examine whether reductions in WHO risk drinking levels themselves were maintained beyond the 4-month trial period. To address this gap in the literature, the current study examined the maintenance of the WHO risk level reductions for up to one year following treatment. In line with FDA and EMA guidance, we also tested whether WHO risk level reductions were associated with functional improvement. We hypothesized that one- and two-level reductions in WHO risk levels would be maintained over time and that reductions in WHO risk levels would be associated with better functional outcomes over time.

## Materials and Methods

### Participants and procedures

The data for the current study were from the COMBINE Study (Anton et al., 2006), a U.S. multi-site, randomized, double-blind, placebo-controlled, clinical trial that examined combinations of medications and behavioral interventions for treating alcohol dependence. 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 had at least 2 heavy drinking days (defined as more than 3 drinks for women and more than 4 drinks for men) in a consecutive 30-day period within the 90 days prior to the baseline assessment. Exclusion criteria were a current substance use disorder (other than nicotine or cannabis), a psychiatric disorder requiring medication, or unstable medical conditions. Participants in the current analyses (n=1226) were randomized to receive: 1) active naltrexone (100 mg/day) or placebo naltrexone, 2) active acamprosate (3000 mg/day) or placebo acamprosate, and 3) medication management (MM) or combined behavioral intervention (CBI) with MM.

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

### Measures

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

**Alcohol consumption.—**Daily standard drinks were measured using the Form-90 (Miller, 1996) and Timeline Follow-Back interview (Sobell and Sobell, 1992). We calculated WHO drinking-risk levels based on the number of standard drinks (defined as 0.6 ounces of absolute alcohol =14 grams of pure alcohol). WHO risk levels were calculated based on the average number of grams of alcohol consumed per day (i.e., drinks per day) over a specific time period (in the current study we averaged over one-month time periods). For the baseline period, we calculated the WHO risk drinking level using data from the month prior to the screening.

For all analyses, binary variables were included that reflected at least one- or two-level reductions in the WHO risk drinking levels from baseline to each month of treatment (post-baseline months 1 through 4) and from baseline to each follow-up month (post-baseline months 5 through 16). The reference group for the one-level reduction was no change or an increase in the WHO risk drinking level from baseline to the treatment/follow-up months, and the reference group for the two-level reduction was the one-level reduction, no change, or increase in the WHO risk level from baseline to the treatment/follow-up months.

Data from the Form-90 (Miller, 1996) and Timeline Follow-Back interview (Sobell and Sobell, 1992) were also used to calculate the alcohol consumption outcomes–percent heavy drinking days, percent drinking days, and drinks per drinking day–at the end of treatment

(post-baseline week 16), 10 weeks post-treatment (post-baseline week 26), 36 weeks post-treatment (post-baseline week 52), and one year post-treatment (post-baseline week 68).

**Functioning outcomes.—**Biological functioning was assessed at end of treatment (post-baseline week 16), 10 weeks post-treatment (post-baseline week 26), and 36 weeks post-treatment (post-baseline week 52), and included systolic blood pressure (SBP), and levels of the liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT). SBP was assessed at each clinic visit by clinical staff, and blood samples were sent to a central laboratory (Quintiles Laboratories, Marietta, GA) which performed the AST, ALT, and GGT clinical assays utilizing automatic analyzer procedures. Lower levels of SBP, AST, ALT, and GGT are associated with better health outcomes (Kwo et al., 2017; Strandberg and Pitkala, 2003).

Alcohol-related consequences were assessed with the Drinker Inventory of Consequences (DrInC; Miller et al. 1995), a 50-item measure that uses a four-level response scale (0=never, 3=daily or almost daily). The DrInC total score (based on 45 drinking consequences, excluding the five control items) was used to assess alcohol-related consequences at the one-year follow-up (Cronbach's $\alpha$=0.97).

## Statistical analysis

Descriptive and inferential analyses were used to examine the maintenance of risk level reductions over time. Descriptive frequencies were used to determine the observed monthly prevalence of risk drinking level reductions. For inferential analyses, we used logistic regression and repeated measures mixed models to examine associations between WHO risk level reductions and functioning outcomes up to one-year post-treatment. First, we examined the association between risk level reductions achieved in the last month of treatment and at one-year post-treatment using logistic regression. Specifically, these analyses examined the odds of maintaining one- and two-level reductions at the one-year follow-up assessment as a function of achieving one- and two-level reductions at the end of treatment, respectively. Second, to examine associations across all follow-up months, general linear repeated measure mixed models with an identity link function were used to assess the association between WHO risk level reductions in each month over time and functional outcomes at each assessment over time. All mixed models were estimated using M*plus* version 8.2 (Muthén and Muthén, 2017) using maximum likelihood estimation with robust estimation of standard errors to account for clustering within treatment sites (Yuan and Bentler, 2010). Missing data were accommodated via maximum likelihood estimation procedures, which provide an estimate of the variance-covariance matrix given all available data and allow for some missing data across months (Hallgren and Witkiewitz, 2013; Witkiewitz et al., 2014). Consistent with prior analyses examining the WHO risk level reductions in the COMBINE study data (Witkiewitz et al., 2017a, 2018), we controlled for the following covariates in all analyses: age, sex, body mass index, smoking status, and baseline WHO risk level. All covariates were grand-mean centered.

**Sensitivity analyses.—**For all analyses, we performed two sets of sensitivity analyses. First, we re-estimated all models with no change/increase imputed for individuals with

missing drinking data, which was a small percent of the sample in each month (range of 1% in month 1 to 20% in month 16) given excellent retention in the COMBINE Study (Anton et al., 2006). This method of imputing "failure" for missing outcomes has been shown to produce biased estimates (Hallgren et al., 2016), however it is commonly recommended as a sensitivity analysis by regulatory agencies, including the FDA. Second, we examined the effect of excluding abstainers by conducting analyses among individuals who achieved one- and two-level reductions and were not abstinent. These analyses provided a test of whether reductions in drinking, short of abstinence, were associated with maintenance of risk level reductions (short of abstinence) and improvements in functioning over time.

## Results

### Descriptive Analyses

Participants 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). 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. As shown in Figure 1, more than half of the sample was categorized as abstinent or low risk in every month following baseline (note that one person was missing drinking data at baseline for a baseline sample size of n=1225).

The binary WHO risk level reduction variables were then created by calculating the reduction in drinking-risk level from baseline to each month of treatment (month 1–4) and up to 12 months post-treatment (months 5–16). The majority of the sample reduced their drinking from baseline to the last month of treatment (month 4) by at least one level (n=1011, 88.5%) or at least two levels (n=881, 77.1%). The percentage of individuals who achieved at least one- and at least two-level reductions ranged from 79.0–84.2% and 63.8–70.4%, respectively, across the follow-up months (see Figure 2).

### Logistic Regression

Results from the logistic regression models indicated that reduction in WHO risk levels in the last month of treatment was significantly associated with at least one- and two-level reductions in WHO risk levels at one year following treatment. Achieving at least a one- or two-level reduction during the last month of treatment was associated with nine to 10 times the odds of reporting at least a one- or two-level reduction, respectively, at one year following treatment (one-level reduction: Nagelkerke $R^2$=0.20; B(SE)=2.33 (0.24), $p$<0.001; OR (95% CI)=10.25 (6.44, 16.29); two-level reduction: Nagelkerke $R^2$=0.27; B(SE)=2.24 (0.20), $p$<0.001; OR (95% CI)=9.40 (6.42, 13.78)). Among individuals who achieved at least a one-level reduction by the end of treatment, 85.5% reported at least a one-level reduction at the one-year follow-up. Similarly, among individuals who achieved a least a two-level reduction by the end of treatment, 77.8% reported at least a two-level reduction at the one-year follow-up.

## Linear Mixed Models

Next, we examined whether one- and two-level reductions in WHO risk levels over time were associated with physical health, drinking consequences, and other measures of alcohol consumption over time. Descriptive statistics for functional outcomes by one- and two-level-reduction groups are provided in Table 1 (physical health outcomes) and Table 2 (drinking outcomes). Results from the linear mixed models are provided in Table 3. The reference group for the one-level reduction showed no change or an increase in the WHO risk drinking level, and the reference group for the two-level reduction showed a one-level reduction, no change, or an increase in the WHO risk level from baseline to the treatment/follow-up months. Unstandardized coefficients, which can be interpreted as the decrease in outcomes over time based on achieving at least a 1- and 2-level reduction over time, at the average level of covariates (covariate effects shown in Supplementary Table 1). For example, at least a 1-level reduction over time was associated with a 6.42 mm Hg reduction in SBP ($p<0.001$), a 7.87 IU/L reduction in AST ($p<0.001$), a 6.33 IU/L reduction in ALT ($p<0.001$), a 26.92 IU/L reduction in GGT ($p=0.01$), a reduction of 19.24 in DrInC total score ($p<0.001$), and lower drinking intensity and drinking frequency over time (all $p<0.001$). These findings reflect better functioning, on average over time, than in individuals with no change or an increase in the WHO drinking-risk level over time. At least a 2-level reduction was associated with a 6.00 mm Hg reduction in SBP ($p<0.001$), a 7.19 IU/L reduction in AST ($p<0.001$), a 6.00 IU/L reduction in ALT ($p<0.001$), a 21.84 IU/L reduction in GGT ($p=0.005$), a reduction of 17.40 in DrInC total score ($p<0.001$), and lower drinking intensity and frequency (all $p<0.001$) than in individuals with a 1-level reduction, no change, or an increase in the WHO drinking-risk level over time.

## Sensitivity Analyses

**Imputing failure for missing data.—**All models were re-estimated with failure imputed for missing data. For the one-level reduction outcome, failure was defined as no change or an increase in WHO risk level. For the two-level reduction outcome, failure was defined as a one-level reduction, no change, or an increase in WHO risk level. The logistic regression models were nearly identical. Achieving at least a one- or two-level reduction during the last month of treatment was associated with nine to 10 times the odds of reporting at least a one- or two-level reduction, respectively, at one year post-treatment (one-level reduction: B(SE)=2.33 (0.19), $p<0.001$; OR (95% CI)=10.31 (7.01, 15.16); two-level reduction: B(SE)=2.26 (0.18), $p<0.001$; OR (95% CI)=9.55 (6.77, 13.47)). The results from the linear mixed models were substantively unchanged (see Table 3).

**Excluding abstainers.—**Sensitivity analyses included only individuals who did not achieve abstinence (n=1052). In this subgroup, the results of the logistic regression models with abstainers excluded were nearly identical to the prior models in which they were included. Achieving at least a one- or two-level reduction during the last month of treatment (short of abstinence) was associated with greater than eight times the odds of reporting at least a one- or two-level reduction (short of abstinence), respectively, at one year post-treatment (one-level reduction: B(SE)=2.39 (0.29), $p<0.001$; OR (95% CI)=10.90 (6.14, 19.36); two-level reduction: B(SE)=2.16 (0.26) , $p<0.001$; OR (95% CI)=8.69 (5.25, 14.39)). Of those who achieved at least a one-level reduction by the end of treatment and were not

abstinent, 80.4% reported at least a one-level reduction by the one-year follow-up. Similarly, of those who achieved a least a two-level reduction by the end of treatment and were not abstinent, 69.5% reported at least a two-level reduction at the one-year follow-up. The results from the linear mixed models were similar (see Table 3), although effects on functional outcomes were smaller with abstainers excluded. In particular, the effects of one- and two-level reductions on GGT were not significant with abstainers excluded.

## Discussion

The current study examined whether one- and two-level reductions in World Health Organization (WHO) risk levels were maintained over time in a large sample of individuals with alcohol dependence who received four months of treatment and were followed for 12 months after treatment. Consistent with study hypotheses, the one- and two-level reductions were maintained over time and associated with significant improvements in functioning over time up to one-year post-treatment. Results were robust to sensitivity analyses that imputed failure (e.g., no change or increase in WHO risk level) for missing data. The findings were also consistent when abstainers were excluded from the model, with one notable difference: at least one- and two-level reductions were not significantly associated with lower GGT.

The results from the current study are consistent with prior work demonstrating that low-risk-drinking outcomes are maintained up to and beyond one year post-treatment (Kline-Simon et al., 2017; Maisto et al., 2007; Witkiewitz et al., 2017b). The current study makes an important new contribution by specifically focusing on WHO risk level reductions, showing that they are maintained across time and associated with improvements in functional outcomes over time.

The current study was limited by the data available in the COMBINE Study, a clinical trial that did not include measures of all outcomes over time. For example, biomarkers were measured through nine months following treatment and were thus unavailable at the one-year follow-up. More sensitive biomarkers, such as phosphatidylethanol (PEth) and ethyl glucuronide (EtG), were not available in the COMBINE Study data. Percent carbohydrate-deficient transferrin (%CDT), a biochemical marker that has previously been associated with the WHO risk-level reductions (Witkiewitz et al., 2018), was not measured at follow-up months in the COMBINE Study. Also, all drinking data was obtained by verbal report. These results were also limited to a one-year follow-up and there is the possibility that reductions would not be maintained for longer follow-ups, although there is evidence that reductions in drinking can be sustained over three-year and up to nine-year follow-ups (Kline-Simon et al., 2017; Maisto et al., 2007). Future studies should extend the current analyses by examining the maintenance of WHO risk level reductions over longer periods of time and with other life functional assessments, such as medical outcomes and costs.

The current findings build on other recent studies that have provided support for the reduction in WHO drinking-risk levels as primary outcomes in clinical trials (Falk et al., in press; Hasin et al., 2017; Knox et al., in press; Knox et al., 2018; Witkiewitz et al., 2018b, 2017a). We found that one- and two-level WHO risk drinking level reductions were maintained across a one-year follow-up for most participants and reductions in WHO risk

drinking levels over time corresponded to statistically significant and clinically meaningful differences in blood pressure, liver enzyme levels, alcohol consumption, and drinking-related consequences, as compared to those among individuals who did not achieve reductions.

Sensitivity analyses provided further support for the maintenance of drinking reductions, even when abstainers were excluded from the analysis. These findings are particularly important because the majority of individuals with AUD who are seeking treatment prefer non-abstinence goals (DeMartini et al., 2014; Haug et al., 2018; Ryan et al., 2017). Moreover, many people with AUD do not seek treatment because they do not want to completely abstain from alcohol (Park-Lee et al., 2017). More individuals with AUD may be interested in seeking treatment if they are aware of the possibility that drinking reduction goals are achievable, sustainable, and associated with improvements in functioning (Mann et al., 2017; van Amsterdam and van den Brink, 2013). The expansion of treatment options to be more inclusive of drinking reduction goals is critically important. The current findings show a high probability that such drinking reductions are maintained over time.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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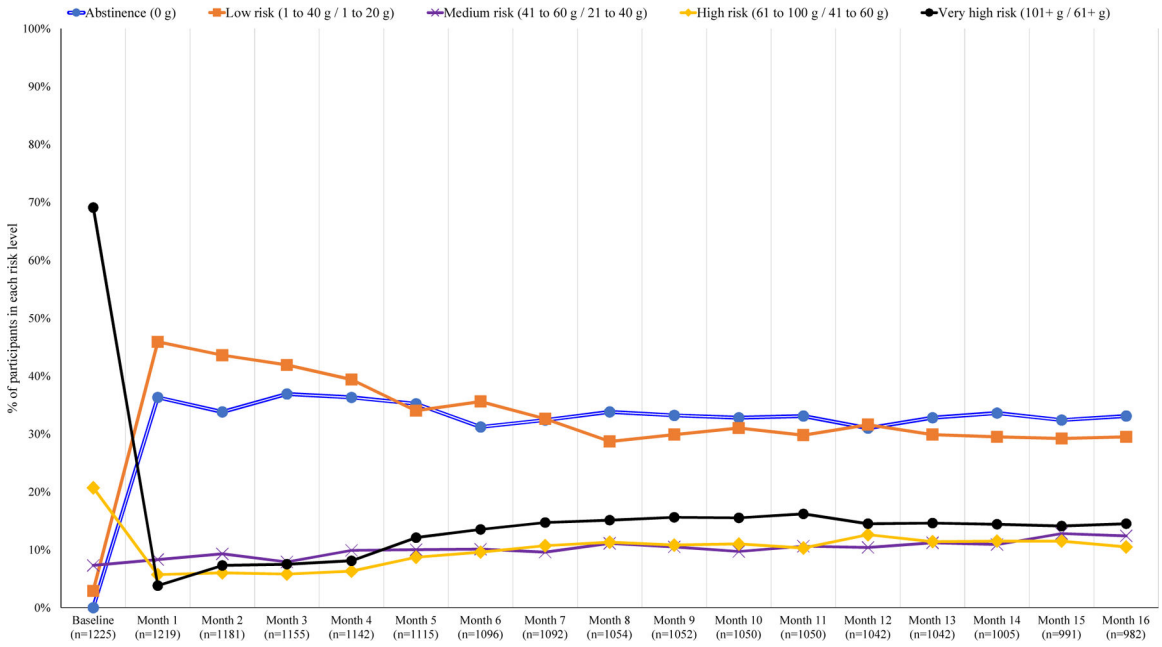


**Figure 1.**

WHO Risk Drinking Level (grams (g) of pure alcohol per day for males / females) by Months from Baseline, During Treatment (Months 1 – 4), and at Each Follow-up Month (Months 5 – 16).

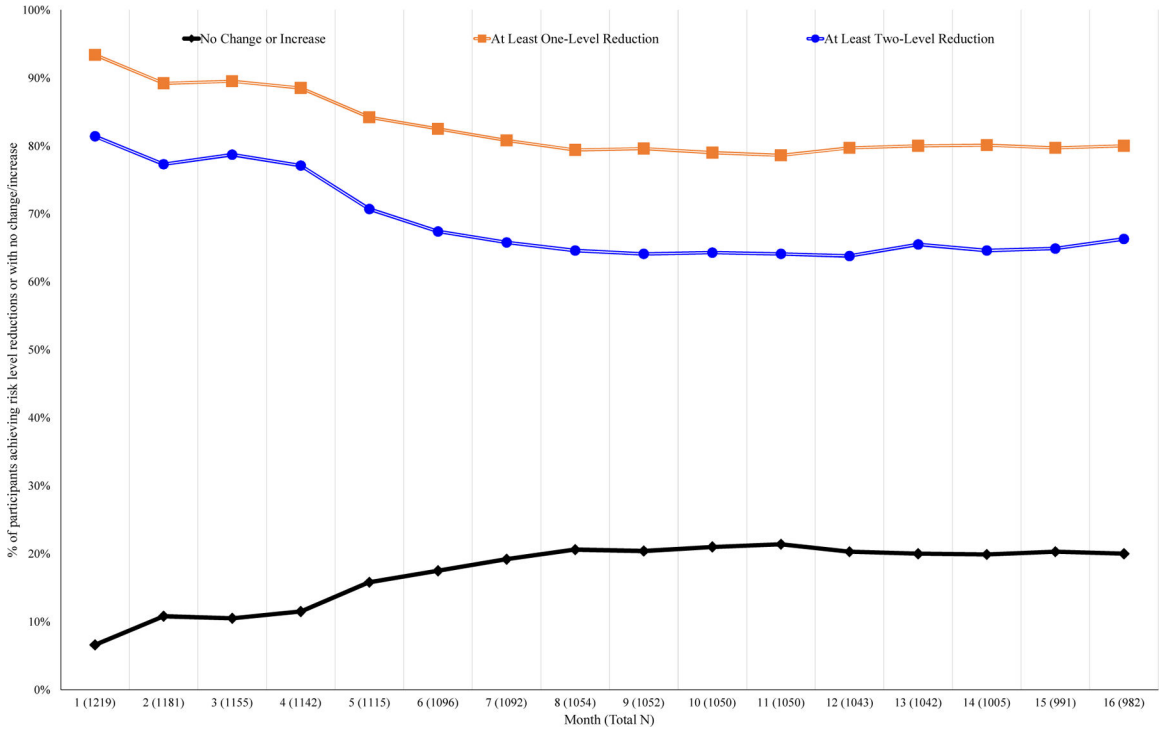


**Figure 2.**

Percentage of Participants Achieving WHO Risk Level Reductions from Baseline to each Month of Treatment (Months 1 – 4) and Post-Treatment (Months 5 – 16).

**Table 1.**

Means (Standard Deviations) for Each Physical Health Outcome by At Least One- and Two-Level Reductions at Each Assessment Timepoint

| Outcome | No change or increase Mean (SD) | At least 1-level reduction Mean (SD) | 1-level reduction, no change, or increase Mean (SD) | At least 2-level reduction Mean (SD) |
|---|---|---|---|---|
| | | | | |
| SBP (mm/Hg) | | | | |
| Week 16 | 137.9 (17.6) | 129.8 (16.6) | 134.2 (17.1) | 129.5 (16.6) |
| Week 26 | 138.6 (17.5) | 130.3 (17.9) | 135.5 (19.2) | 129.9 (17.3) |
| Week 52 | 136.7 (16.9) | 130.6 (17.2) | 134.4 (17.7) | 130.3 (16.9) |
| | | | | |
| AST (IU/L) | | | | |
| Week 16 | 41.0 (35.7) | 28.2 (16.0) | 36.2 (29.1) | 27.7 (14.7) |
| Week 26 | 38.5 (34.9) | 29.6 (26.8) | 35.4 (29.8) | 29.2 (27.7) |
| Week 52 | 40.3 (37.5) | 31.2 (29.9) | 37.7 (33.8) | 30.5 (30.3) |
| | | | | |
| ALT (IU/L) | | | | |
| Week 16 | 40.8 (32.6) | 30.8 (23.5) | 38.0 (28.9) | 30.1 (23.1) |
| Week 26 | 40.8 (38.9) | 30.9 (22.2) | 36.7 (31.5) | 30.8 (22.9) |
| Week 52 | 41.3 (29.7) | 33.9 (33.9) | 40.4 (30.8) | 32.8 (34.3) |
| | | | | |
| GGT (IU/L) | | | | |
| Week 16 | 145.1 (467.1) | 43.5 (61.9) | 87.3 (303.6) | 42.9 (63.3) |
| Week 26 | 86.6 (223.3) | 47.2 (73.2) | 73.8 (172.6) | 44.9 (72.8) |
| Week 52 | 108.6 (245.4) | 53.4 (79.4) | 29.5 (197.3) | 51.2 (75.1) |
| | | | | |
| | | | | |

*Note.* All numbers are observed (percentages are based on valid number of cases) with no imputation for missing data. Biomarker assessments were conducted at the end of treatment (week 16 after baseline) and at two assessments after treatment: 10 weeks post-treatment (post-baseline week 26), and 36 weeks post-treatment (post-baseline week 52). SBP=Systolic blood pressure; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=γ-glutamyltransferase; IU/L=International Units per Liter.

**Table 2.**

Means (Standard Deviations) for Each Drinking Outcome by At Least One- and Two-Level Reductions at Each Assessment Timepoint

| Outcome | No change or increaseMean (SD) | At least 1-level reductionMean (SD) | 1-level reduction, no change, or increaseMean (SD) | At least 2-level reductionMean (SD) |
|---|---|---|---|---|
| | | | | |
| DrInC | | | | |
| Week 16 | 35.3 (14.3) | 11.0 (16.5) | 24.8 (22.9) | 10.1 (16.1) |
| Week 26 | 37.7 (25.2) | 13.6 (18.1) | 31.6 (24.2) | 11.3 (16.5) |
| Week 52 | 39.9 (23.2) | 16.8 (19.5) | 33.5 (22.8) | 14.8 (18.9) |
| Week 68 | 38.6 (22.9) | 15.7 (20.1) | 33.7 (22.0) | 13.2 (18.3) |
| | | | | |
| PHDD | | | | |
| Week 16 | 71.3% (32.9%) | 9.1% (17.5%) | 50.7% (38.2%) | 5.9% (11.3%) |
| Week 26 | 62.2% (35.4%) | 12.8% (21.9%) | 49.6% (36.6%) | 8.9% (15.6%) |
| Week 52 | 67.1% (33.1%) | 15.9% (24.5%) | 55.6% (35.8%) | 10.6% (18.3%) |
| Week 68 | 71.4% (32.4%) | 14.9% (23.6%) | 58.9% (35.7%) | 9.5% (16.8%) |
| | | | | |
| PDD | | | | |
| Week 16 | 77.6% (28.8%) | 18.9% (26.7%) | 59.9% (36.6%) | 15.4% (23.4%) |
| Week 26 | 70.5% (32.4%) | 23.9% (29.6%) | 61.2% (34.7%) | 18.2% (25.3%) |
| Week 52 | 73.7% (29.8%) | 27.7% (31.9%) | 65.8% (33.4%) | 21.6% (27.8%) |
| Week 68 | 78.4% (27.2%) | 27.1% (31.8%) | 69.9% (31.7%) | 20.7% (27.4%) |
| | | | | |
| DPDD | | | | |
| Week 16 | 12.2 (7.5) | 5.9 (4.1) | 9.9 (6.7) | 5.6 (4.0) |
| Week 26 | 11.8 (7.2) | 4.6 (5.4) | 9.6 (6.6) | 4.1 (5.6) |
| Week 52 | 11.7 (7.1) | 5.7 (6.2) | 9.7 (6.8) | 5.4 (6.4) |
| Week 68 | 11.6 (6.5) | 7.1 (5.7) | 10.1 (6.1) | 6.8 (5.9) |
| | | | | |

*Note.* All numbers are observed (percentages are based on valid number of cases) with no imputation for missing data. Alcohol consumption and consequences were measured at weeks 16, 26, 52, and 68. DrInC = Drinker Inventory of Consequences Total Score; PHDD = Percent heavy drinking days; PDD = Percent drinking days; DPDD = Drinks per drinking day.

**Table 3.**

Linear Mixed Models Results for Functioning Outcomes Over Time following Treatment as Predicted from One- and Two-Level Reductions Over Time (n=1226) and Sensitivity Analyses with Missing=Failure Imputation (n=1226) and Excluding Abstainers (n=1052)

| | SBP (mm/Hg) | AST (IU/L) | ALT (IU/L) | GGT (IU/L) | DrInC | PHDD | PDD | DPDD |
|---|---|---|---|---|---|---|---|---|
| | B (SE) | B (SE) | B (SE) | B (SE) | B (SE) | B (SE) | B (SE) | B (SE) |
| Linear Mixed Models (n=1226) | | | | | | | | |
| 1-level reduction | –6.42 (1.11)*** | –7.87 (2.18)*** | –6.33 (2.09)*** | –26.92 (10.47)* | –19.24 (1.32)*** | –39.89 (1.76)*** | –32.69 (1.62)*** | –4.86 (.36)*** |
| 2-level reduction | –6.00 (.84)*** | –7.19 (1.55)*** | –6.00 (1.53)*** | –21.84 (7.97)** | –17.40 (1.08)*** | –38.55 (1.45)*** | –33.65 (1.39)*** | –4.16 (.28)*** |
| Missing = Failure Models (n=1226) | | | | | | | | |
| 1-level reduction | –5.69 (1.09)*** | –7.62 (2.09)*** | –6.12 (2.01)** | –25.60 (10.07)* | –18.21 (1.27)*** | –29.71 (1.62)*** | –24.53 (1.49)*** | –3.23 (.31)*** |
| 2-level reduction | –5.56 (.84)*** | –7.13 (1.53)*** | –5.86 (1.50)*** | –21.37 (7.67)** | –16.84 (1.06)*** | –32.07 (1.41)*** | –28.37 (1.33)*** | –3.25 (.26)*** |
| Excluding Abstainers (n=1052) | | | | | | | | |
| 1-level reduction | –5.14 (1.13)*** | –6.36 (2.15)** | –4.17 (1.99)* | –12.64 (6.82) | –14.39 (1.22)*** | –38.27 (1.77)*** | –28.10 (1.63)*** | –3.54 (.41)*** |
| 2-level reduction | –4.26 (.89)*** | –5.49 (1.60)** | –3.87 (1.56)* | –8.24 (5.21) | –13.14 (1.02)*** | –38.19 (1.54)*** | –29.34 (1.45)*** | –2.96 (.33)*** |

Note.

*$p<0.05$

**$p<0.01$

***$p<0.001$, B (SE) = Unstandardized regression coefficients (standard error), which can be interpreted as the decrease in outcomes based on achieving at least a 1- and 2-level reduction, at the average of all covariates (covariate effects reported in Supplementary Table 1); SBP=Systolic blood pressure; AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT=γ-glutamyltransferase; IU/L=International Units per Liter; DrInC = Drinker Inventory of Consequences Total Score; PHDD = Percent heavy drinking days; PDD = Percent drinking days; DPDD = Drinks per drinking day. The

reference group for the one-level reduction was no change or an increase in the WHO risk drinking level from baseline to the treatment/follow-up months, and the reference group for the two-level reduction was the one-level reduction, no change, or increase in the WHO risk level from baseline to the treatment/follow-up months.