CLINICAL VALIDATION OF WORLD HEALTH ORGANIZATION (WHO) DRINKING RISK LEVELS IN A LARGE ALCOHOL CLINICAL TRIAL (COMBINE)

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Disclosures & Acknowledgements

- No personal disclosures

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- Members of the Alcohol Clinical Trials Initiative (ACTIVE) Workgroup provided intellectual input in this work during attendance at Workgroup meetings:

  - Bernard Silverman, Henri Jean Aubin, Roger Meyer, Charles O'Brien, Anne Andorn, Jay Graham, Didier Meulien, Francoise Trinquet, Benjamin Zakine, Joanne Fertig, Megan Ryan, David McCann

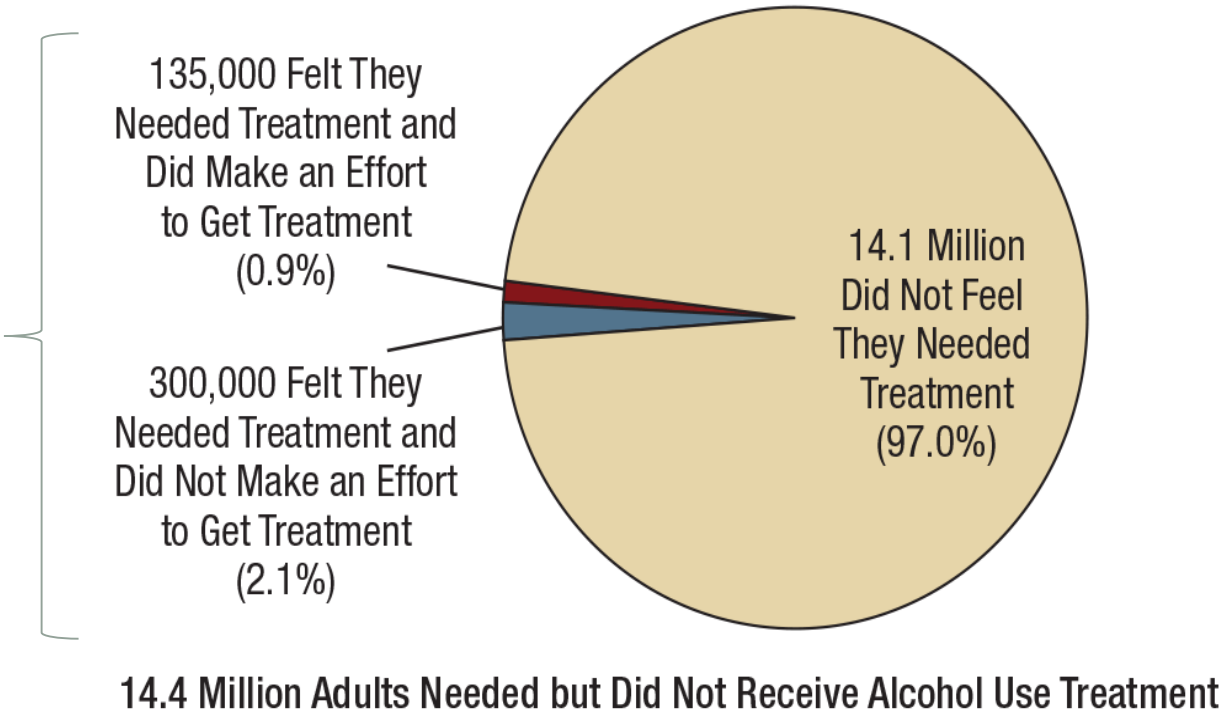
Objectives

- To explore whether reductions in World Health Organization (WHO) Drinking Risk Levels are associated with improvements in “feeling and functioning” in a large **clinical trial** for alcohol use disorder
  - Drinking Consequences
  - Mental health
  - Quality of Life
  - Physiological measurements (blood pressure & liver function)
- How many WHO levels of reduction are needed to see improvements in “feeling and functioning”?
- How do improvements associated with reductions in WHO levels compare to current FDA-endorsed endpoints?

BACKGROUND

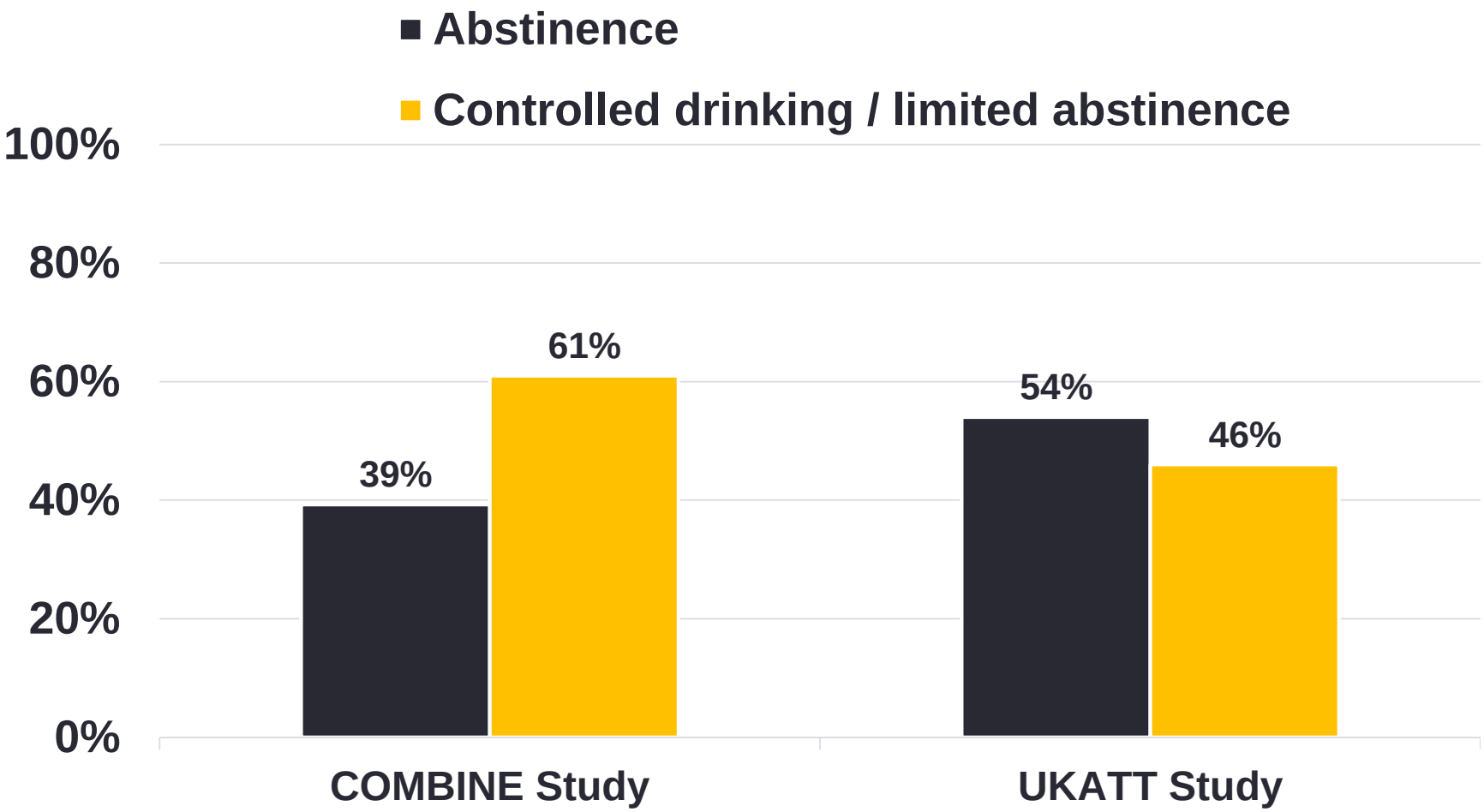
Abstinence is a Barrier to Receiving Specialty Treatment

Of those who felt they needed treatment but did not receive specialty treatment, **51.9%** report not receiving treatment because they **did not want to abstain**



Park-Lee, E., Lipari, R. N., Hedden, S. L., Copello, E. A. P., & Kroutil, L. A. (2016, September). *Receipt of services for substance use and mental health issues among adults: Results from the 2015 National Survey on Drug Use and Health*. NSDUH Data Review. Retrieved from http://www.samhsa.gov/data/

Abstinence is the most desirable outcome, but many patients entering treatment prefer non-abstinence goals



Growing support for non-abstinent treatment goals among treatment providers

Alcohol and Alcoholism Vol. 49, No. 4, pp. 447–452, 2014
Advance Access Publication 12 June 2014
doi: 10.1093/alcalc/agu036

Acceptance of Controlled Drinking Among Treatment Specialists of Alcohol Dependence in Japan

Susumu Higuchi*, Hitoshi Maesato, Atsushi Yoshimura and Sachio Matsushita

Alcohol and Alcoholism Vol. 46, No. 5, pp. 586–591, 2011
Advance Access Publication 18 July 2011
doi: 10.1093/alcalc/agr08

TREATMENT

Is Controlled Drinking an Acceptable Goal in the Treatment of Alcohol Dependence? A Survey of French Alcohol Specialists

A. Luquiens[1], M. Reynaud[1,2,3] and H.J. Aubin[1,2,3,4,*]

Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment



Journal of Substance Abuse Treatment 46 (2014) 214–218

Differences in the acceptability of non-abstinence goals by type of drug among American substance abuse clinicians

Harold Rosenberg, Ph.D.*, Alan K. Davis, M.A.

Department of Psychology, Bowling Green State University, Bowling Green, OH 43403, USA

44%-66%of addiction treatment providers support initial goal of non-abstinence

Growing body of evidence that non-abstinent reductions in drinking are feasible & have benefit

- Reducing drinking to moderate, lower-harm levels is feasible among individuals who have previously been diagnosed with AUD (Dawson et al., 2005; Hasin et al., 2013).

- Long-term (7-year) psychosocial functioning and healthcare costs are similar for patients who achieve low-risk drinking* vs abstinence following AUD treatment

*<4 / 5 drinks on a day for women/men (Kline-Simon et al., 2013, 2014)

European Medicines Agency (EMA) Guidance (2010)

1.3 Risk levels of drinking

There is a strong correlation between extent of alcohol consumption and the risk of development of dependence and physical harm.

According to the WHO "International guide for monitoring alcohol consumption and related harm" (WHO 2000), alcohol consumption in general is categorised in different health risk levels.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

WHO-Criteria for risk of consumption on a single drinking day in relation to acute problems

	Males	Females
Low Risk	1 to 40g,	1 to 20g
Medium Risk	41 to 60g,	21 to 40g
High Risk	61 to 100g	41 to 60g
Very High Risk	101+g	61+g

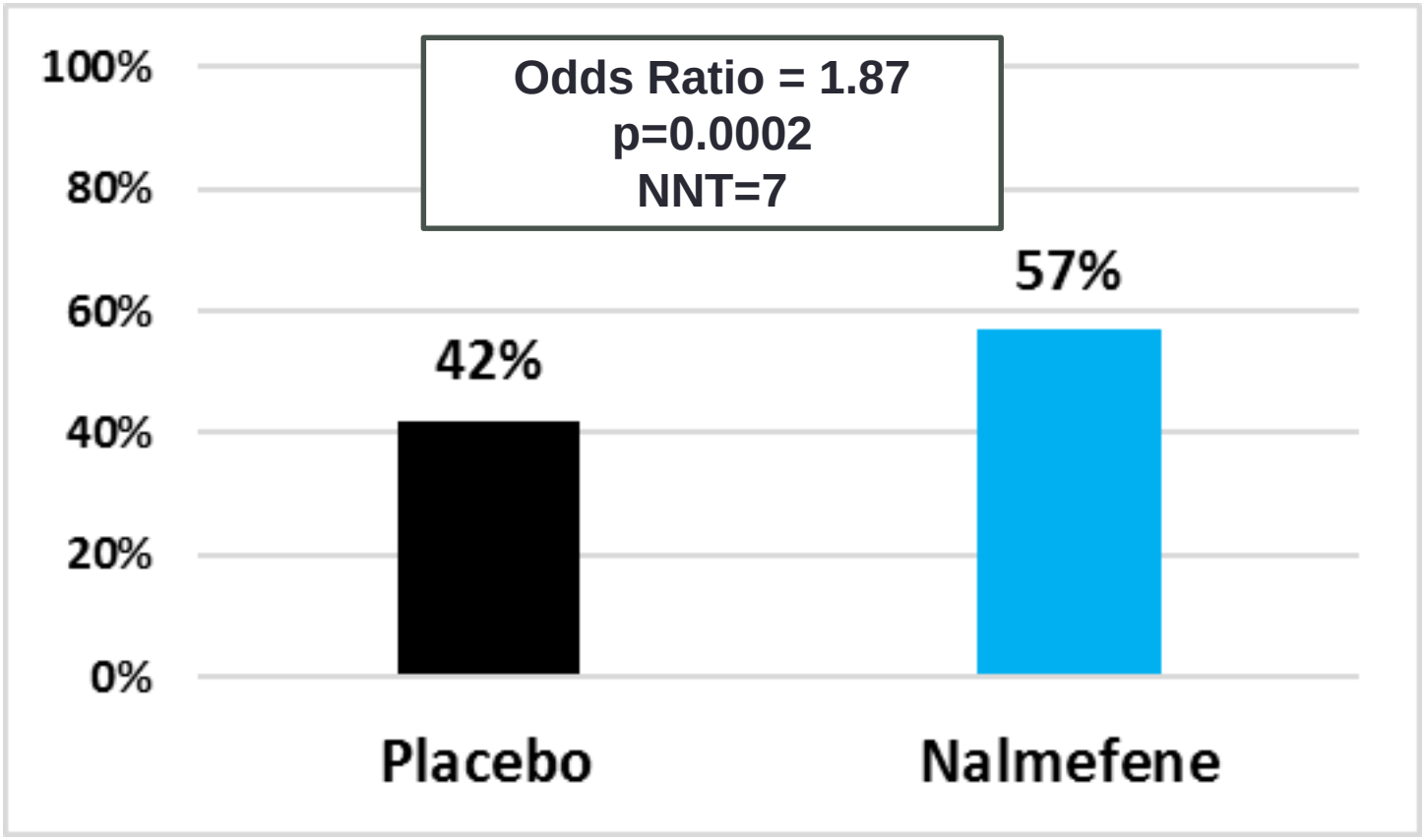
WHO-Criteria for risk of chronic harm

	Males	Females
Low Risk	1 to 40g,	1 to 20g
Medium Risk	41 to 60g,	21 to 40g
High Risk	61+ g	41+ g

EMA suggests an intermediate harm-reduction endpoint as a key secondary endpoint in clinical trials :

"the proportion of subjects with a significant categorical shift in WHO risk levels of drinking"
(i.e., at least a 2-level reduction)

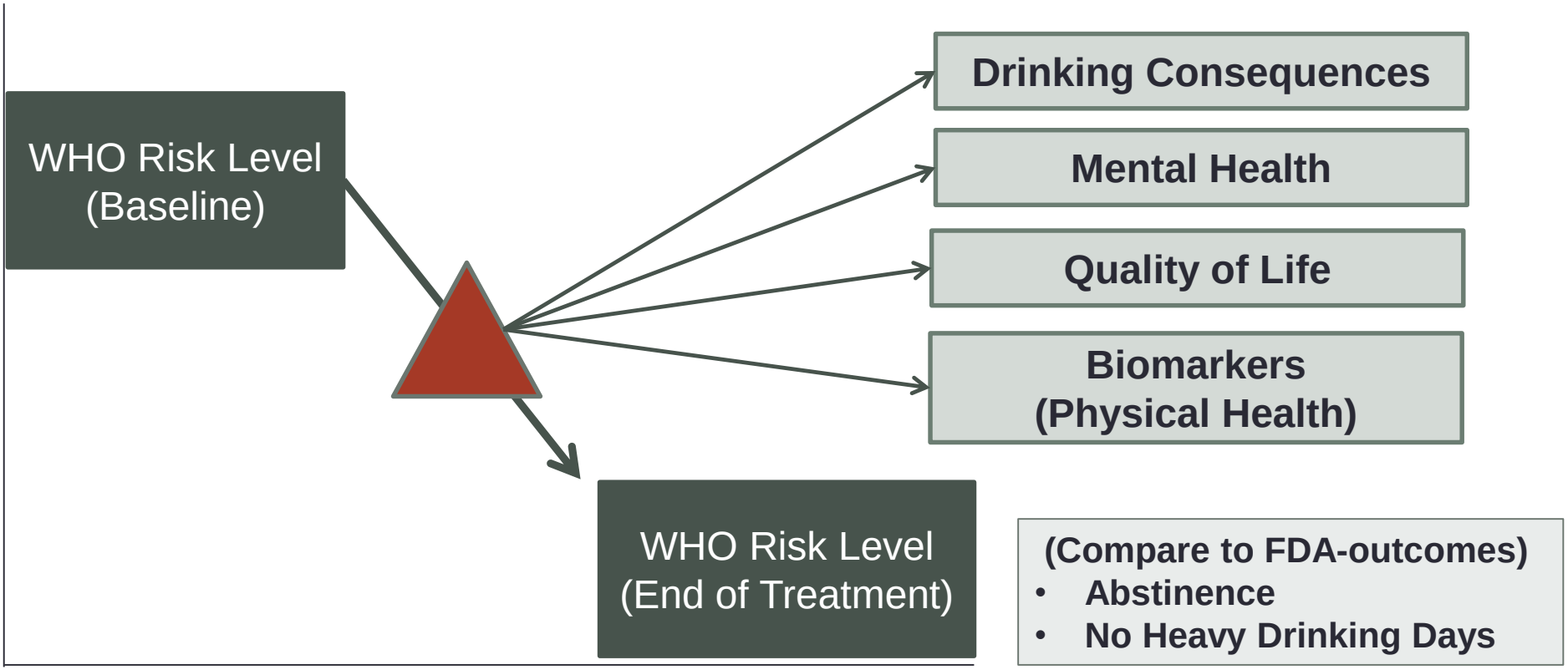
WHO 2-Level Reduction as Endpoint in Nalmefene Trial



Aubin et al. (2015)

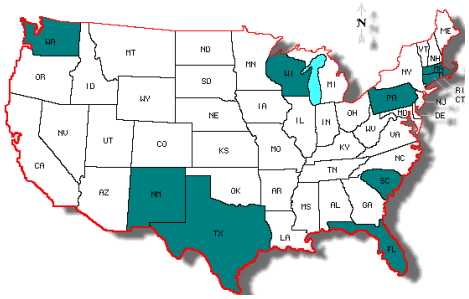
Design of Current Study

Examine association between reductions in WHO Risk Drinking Levels of alcohol consumption and clinically meaningful outcomes among individuals receiving treatment for alcohol dependence



METHODS

Validation of the WHO Drinking Risk Levels in an Alcohol Clinical Trial



- **COMBINE study** (Anton et al., 2005)
  - 16-week randomized, double-blind, placebo-controlled clinical trial
  - Individuals with DSM-IV alcohol dependence
  - 11 clinical sites (recruitment: Jan 2001 – Jan 2004)
  - Acamprosate x naltrexone x psychosocial intervention (n=1226)

Measure	Assessment Method
WHO Drinking Risk Levels	Timeline followback = Drinks/Day
Drinking-Related Consequences	Drinker Inventory of Consequences (DrInC)
Mental Health	Short Form Health Survey (SF-12)
Systolic Blood Pressure, Liver Enzymes	Clinic visits
Quality of Life	WHO Quality of Life – Brief version

WHO Drinking Risk Levels

Original WHO Levels (grams)

WHO Category	Males	Females
Low Risk	1 to 40g	1 to 20g
Medium Risk	41 to 60g	21 to 40g
High Risk	61 to 100g	41 to 60g
Very High Risk	101+g	61+g

Converted to Drinks (14g = .6 oz = 1 drink) & added Abst.

WHO Category	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

WHO 2+ Level Reduction Endpoint

% of subjects who shift downwards by at least 2 levels

- **Very High** to Medium/Low/Abst

WHO Category	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

- **High** to Low/Abst

WHO Category	Males	Females
Abstinent	0	0
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Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

- **Medium** to Abst

WHO Category	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

WHO 1+ Level Reduction Endpoint

% of subjects who shift downwards by at least 1 level

- **Very High** to High/Medium/Low/Abst

WHO Category	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

- **High** to Medium/Low/Abst

WHO Category	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

- **Medium** to Low/Abst

WHO Category	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+

- **Low** to Abst

WHO Category	Males	Females
Abstinent	0	0
Low Risk	>0 to 2.86	>0 to 1.43
Medium Risk	2.87 to 4.29	1.44 to 2.86
High Risk	4.30 to 7.14	2.87 to 4.29
Very High Risk	7.15+	4.30+



Drinker Inventory of Consequences (DrInC)

- **Alcohol-related consequences (past 2 months)**
- **45-items capturing of 5 categories of consequences**
  - **Physical** (e.g., “I have been sick and vomited after drinking”)
  - **Intrapersonal** (e.g., “I have been unhappy because of my drinking”)
  - **Social responsibility** (e.g., “I have gotten in trouble because of drinking”)
  - **Interpersonal** (e.g., “I have lost a friend because of my drinking”)
  - **Impulse control** (e.g., “I have had an accident while drinking or intoxicated”)
- **Higher total score = more drinking consequences**

Miller, Tonigan, & Longabaugh, 1995

Short Form Health Survey (SF-12)

- Derived from the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)
- **6-item Mental Health subscale (past 4 weeks)**
  - Accomplished less than you would like?
  - Did work or other activities less carefully than usual?
  - Have you felt calm and peaceful?
  - Did you have a lot of energy?
  - Have you felt downhearted or blue?
  - How much of the time has your physical health or emotional problems interfered with your social activities?
- **Mental Health Component Score** (T-score: Mean = 50, SD = 10)
  - Higher scores = greater mental health

(World Health Organization (1998)

WHO Quality of Life Brief version

25-items capturing 4 quality of life (QoL) domains:

- **Physical health** (max=35)
  - e.g.,“How satisfied are you with your sleep?
- **Psychological health** (max=30)
  - e.g., “How much do you enjoy life?”
- **Social relationships** (max=15)
  - e.g., “How satisfied are you with your personal relationships?”
- **Environmental** (max=40)
  - e.g., “How satisfied are you with the conditions of your living place?”

- **Higher scores on each domain = better quality of life**

(Ware, Kosinski, & Keller, 1996)

Biomarkers of Physical Health

Systolic Blood Pressure (SBP)

Liver Enzymes

- **CDT**: carbohydrate-deficient transferrin (%) } Alcohol-specific biomarker
- **AST**: aspartate aminotransferase
- **ALT**: alanine aminotransferase } Reflects liver cell damage
- **GGT**: c-glutamyltransferase

- **All biomarkers are associated with heavy drinking and AUD**
  (Baros et al., 2008; LoCastro et al., 2009; Stewart et al., 2008).

- **Lower levels = more positive health outcomes**
  (Kwo et al., 2017; Strandberg and Pitkala, 2003)

Analyses

- **Multiple regression analyses**
- **Outcomes**: DrInC, SF-12, WHO QoL, Biomarkers at end of treatment
- **Predictors**:
  - Reduction in WHO risk level from baseline - end of treatment
  - Covariates
    - Baseline WHO risk level
    - Baseline equivalent of the outcome
    - Gender
    - Age
    - Body mass index
    - Smoking status
    - Race (white vs. not white) – for DrinC & SF-12 analyses
    - Years of education – for DrinC & SF-12 analyses
- **Statistics:**
  - Unadjusted means (95% confidence Intervals)
  - Cohen's d (small=.2, medium=.5, large=.8)
  - Unstandardized regression coefficients (Beta) (95% confidence intervals)
  - P-value (adjusted for covariates)

RESULTS

Participant Characteristics in COMBINE Trial

Demographics

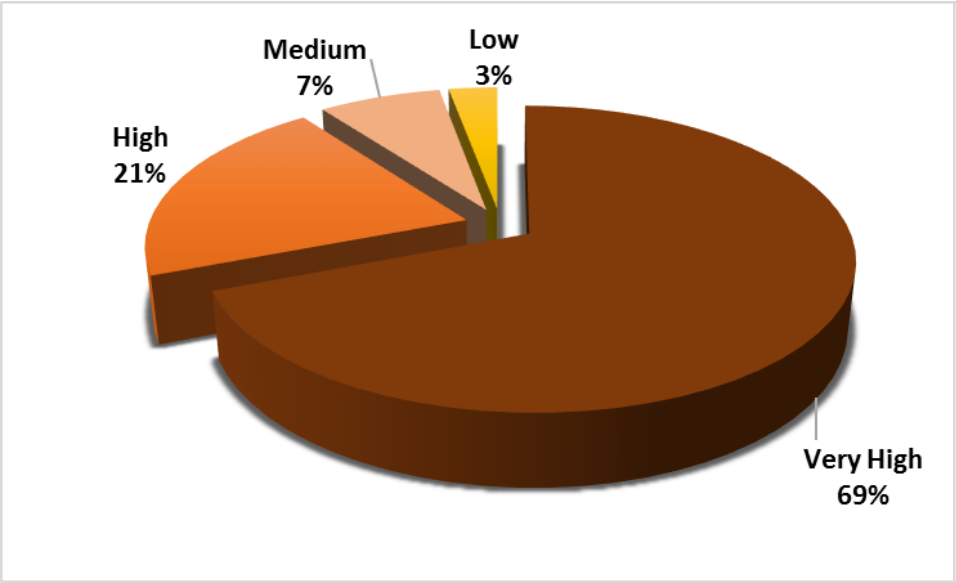
- Age = 44
- 70% male
- 78% White, 8% Black, 12% Hispanic, 3% Other
- 28% < High School education

Drinking:

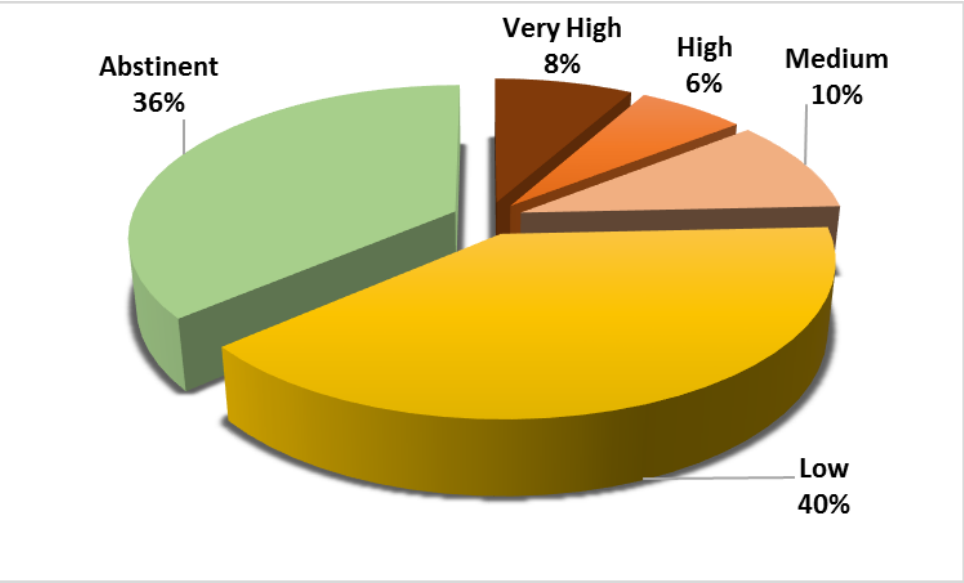
- 25% days abstinent
- 71% heavy drinking days
- 9 drinks/day

WHO Drinking Risk Levels

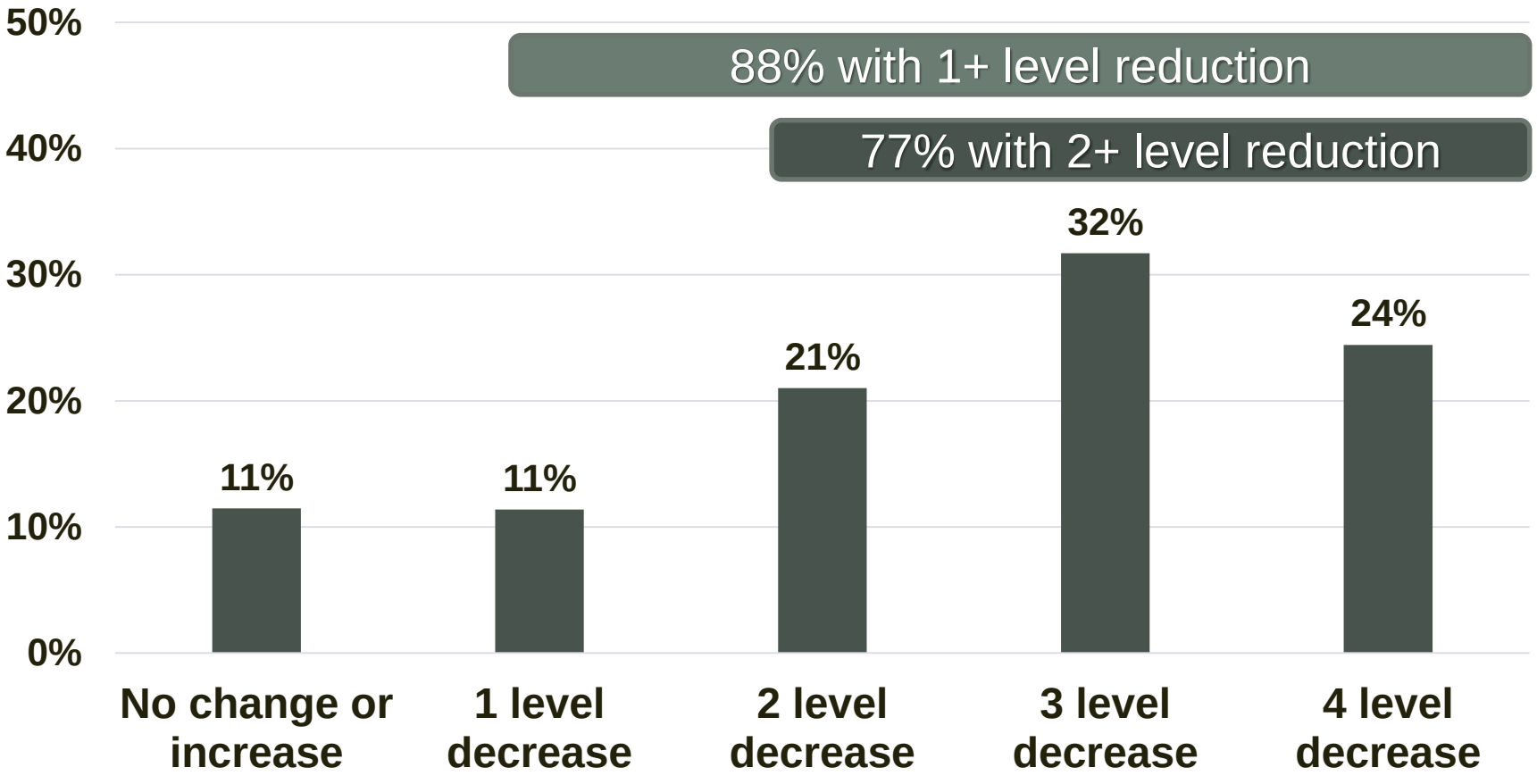
Baseline



Last Month of Treatment (4)



Change in WHO Risk Level: Baseline - Last Month of Treatment (Month 4)



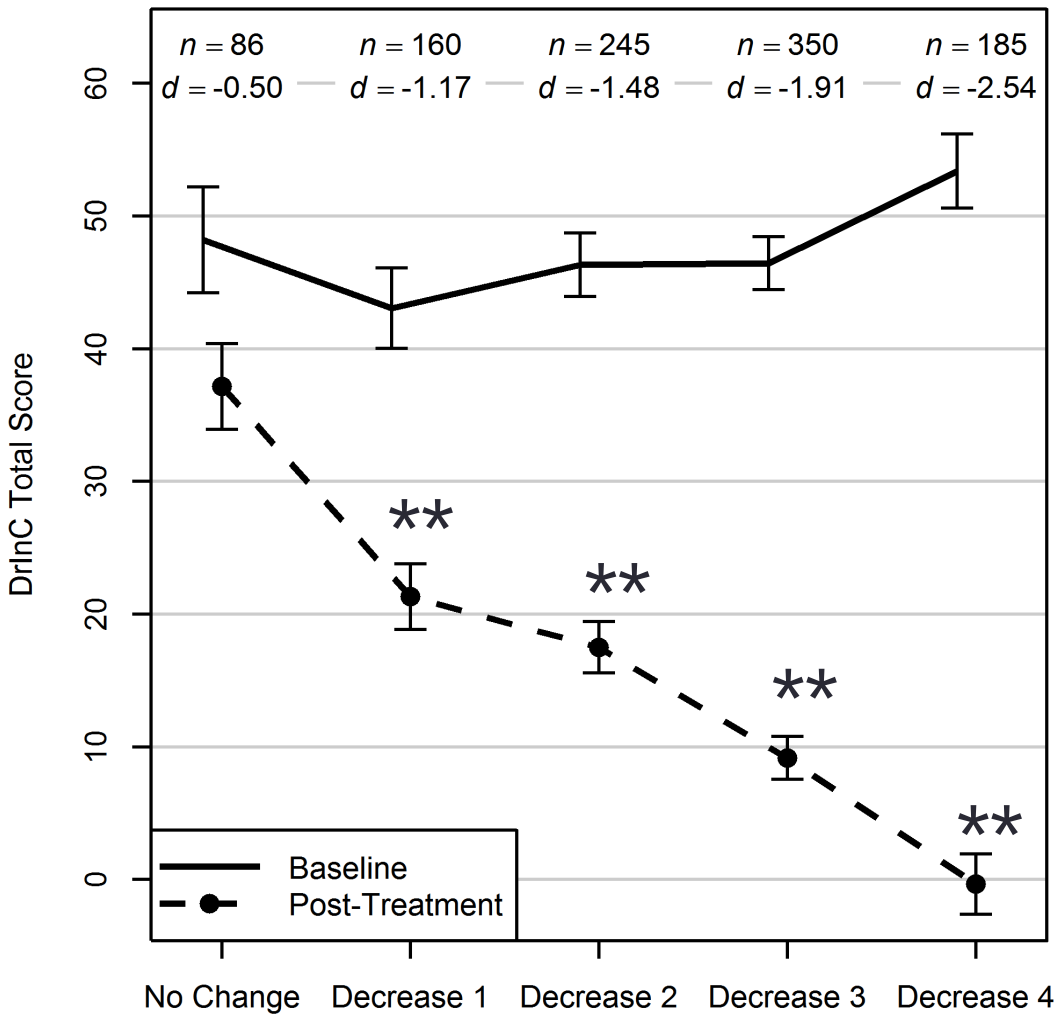
SELF-REPORT FUNCTIONING

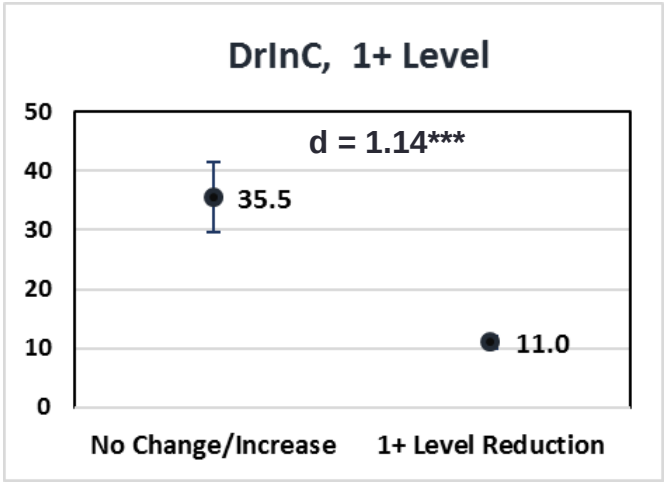
Drinker Inventory of Consequences

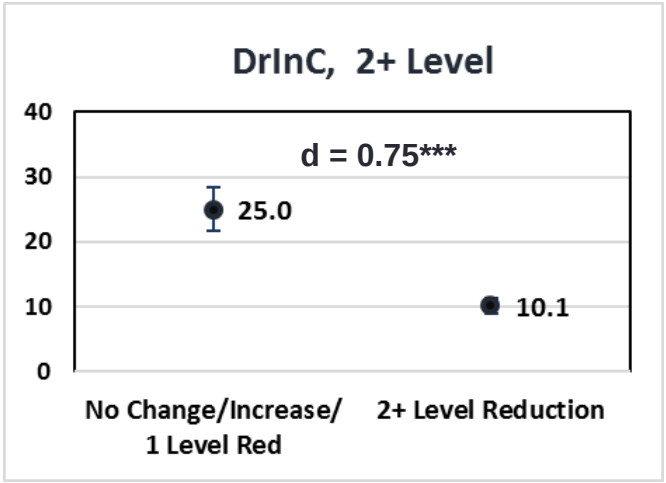
Short Form Health Survey Mental Health

World Health Organization Quality of Life Measure

Drinking Consequences (DrInC)



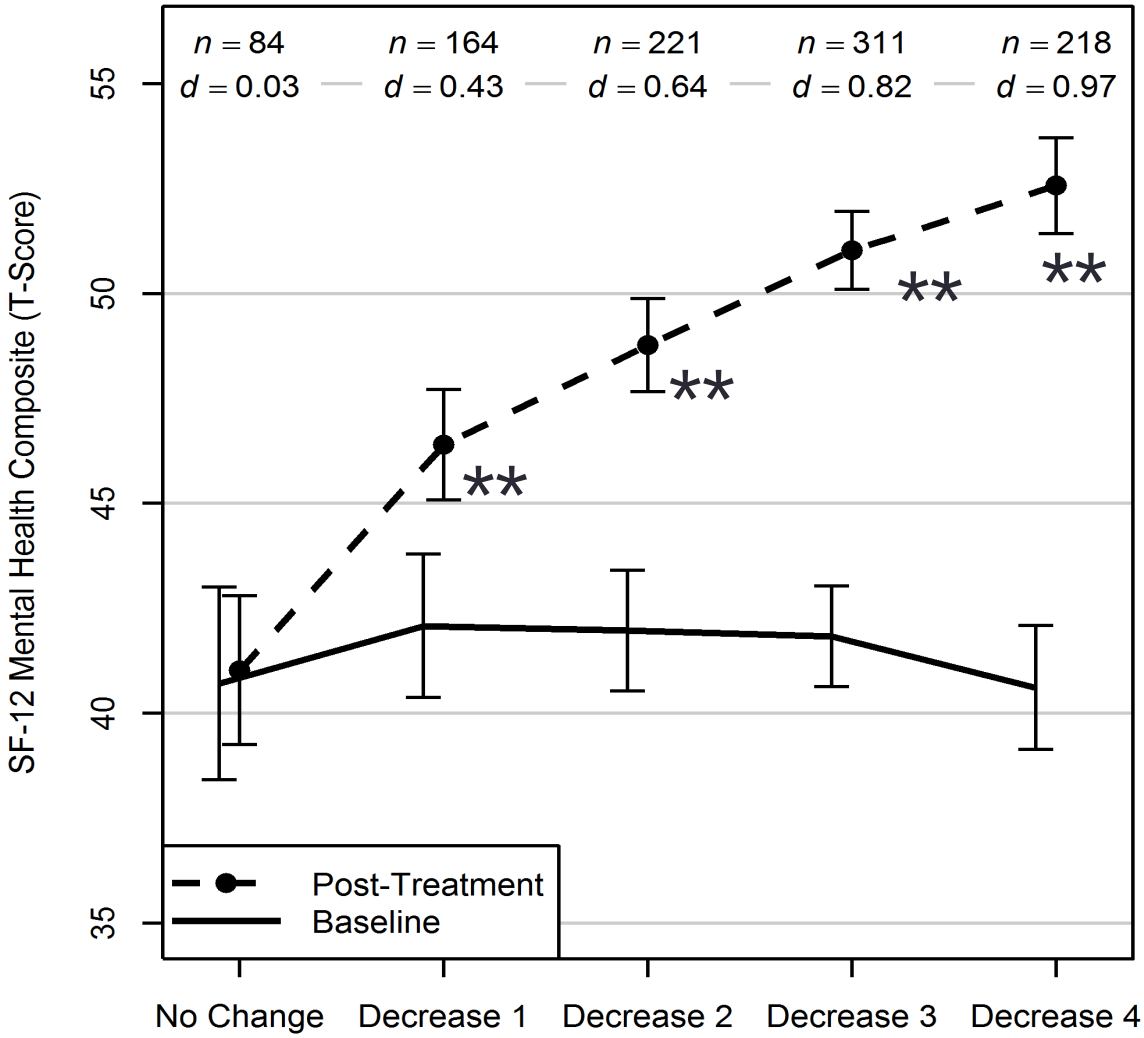


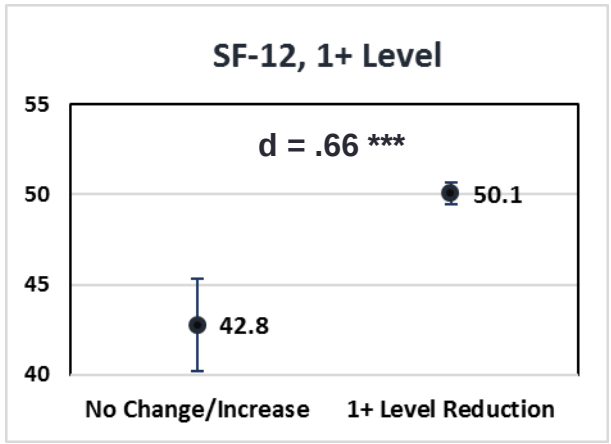


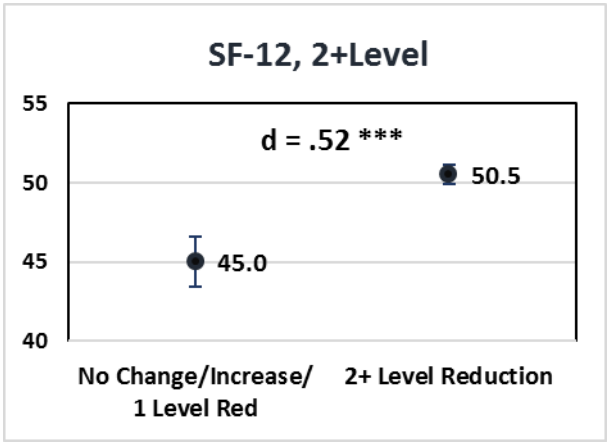
** $p < 0.001$ in adjusted regression models versus no change (reference group)

Witkiewitz et al (2017). *ACER*

SF-12 Mental Health



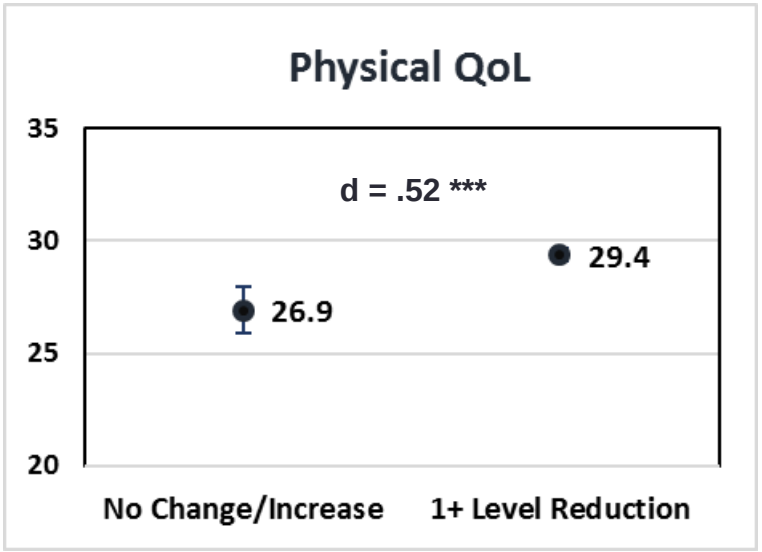


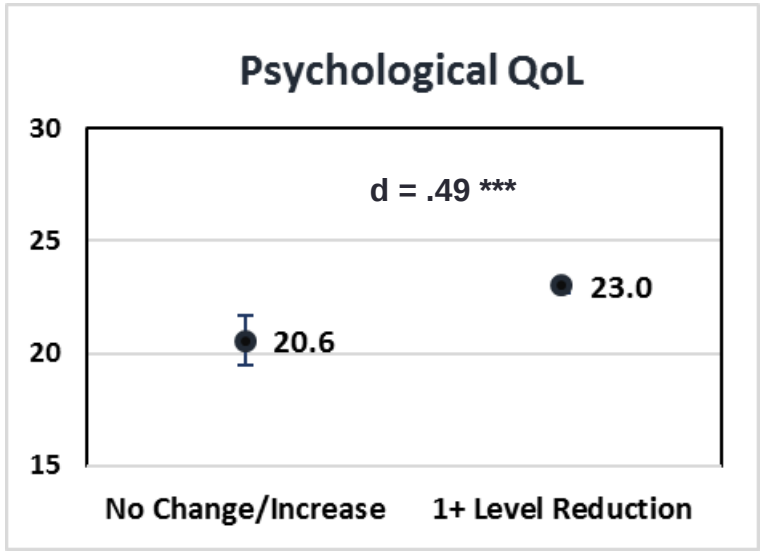


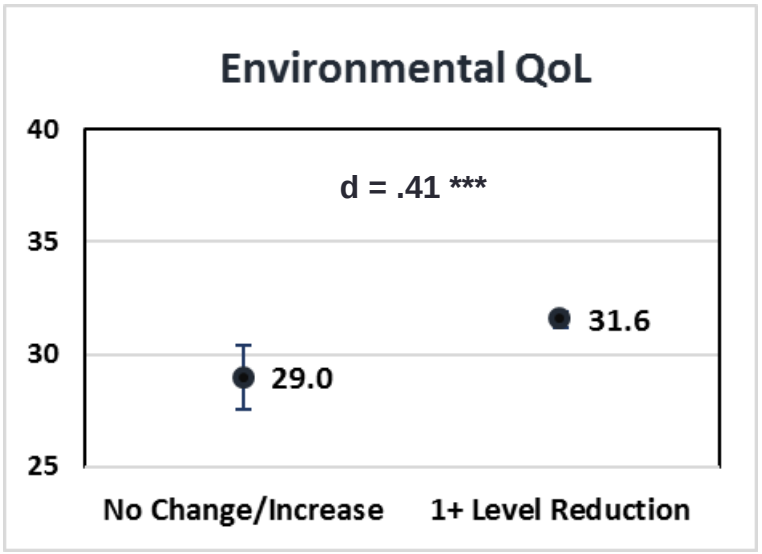
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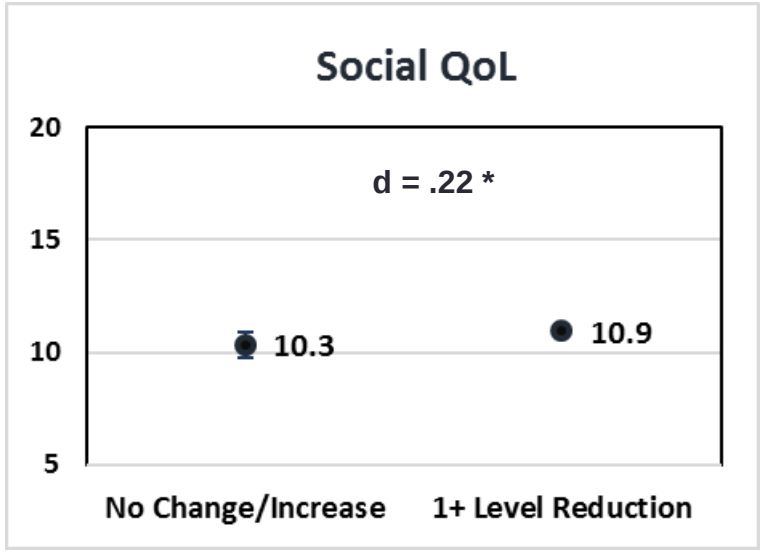
Witkiewitz et al (2017). *ACER*

Quality of Life: 1+ WHO Drinking Level Reduction



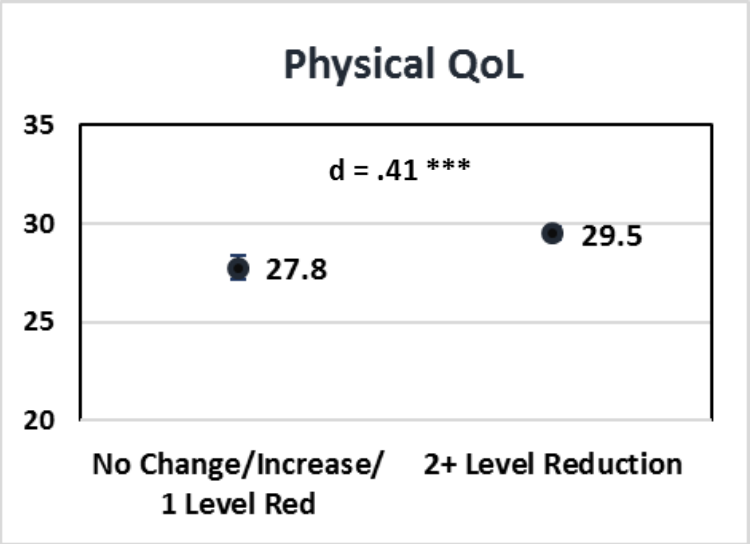


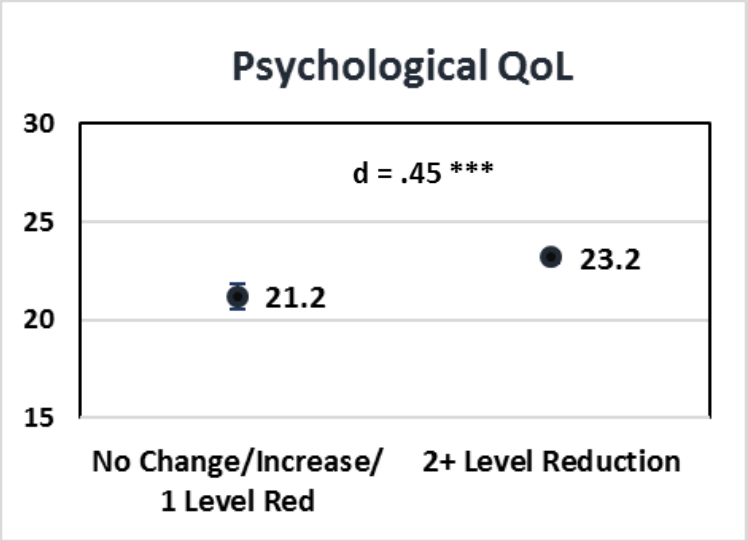


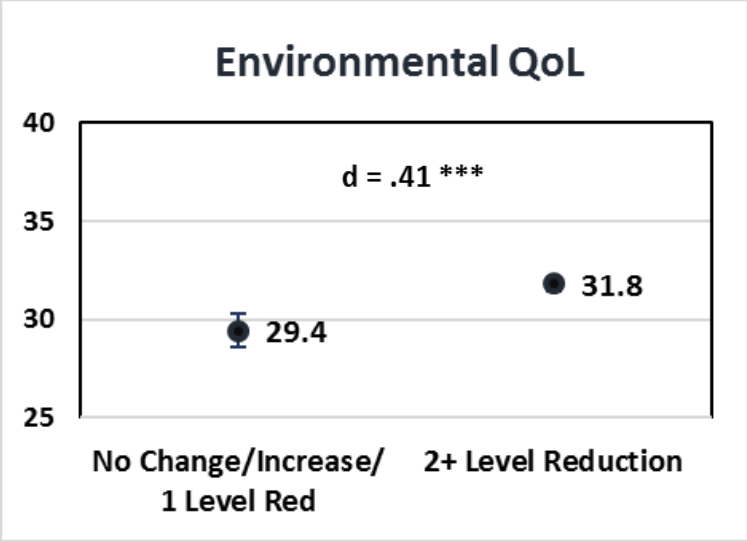


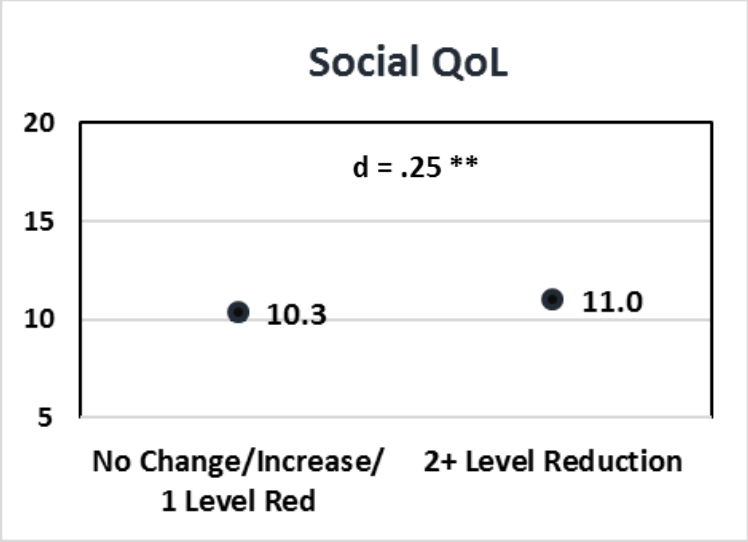
Witkiewitz et al (2018). *ACER*

Quality of Life: 2+ WHO Drinking Level Reduction



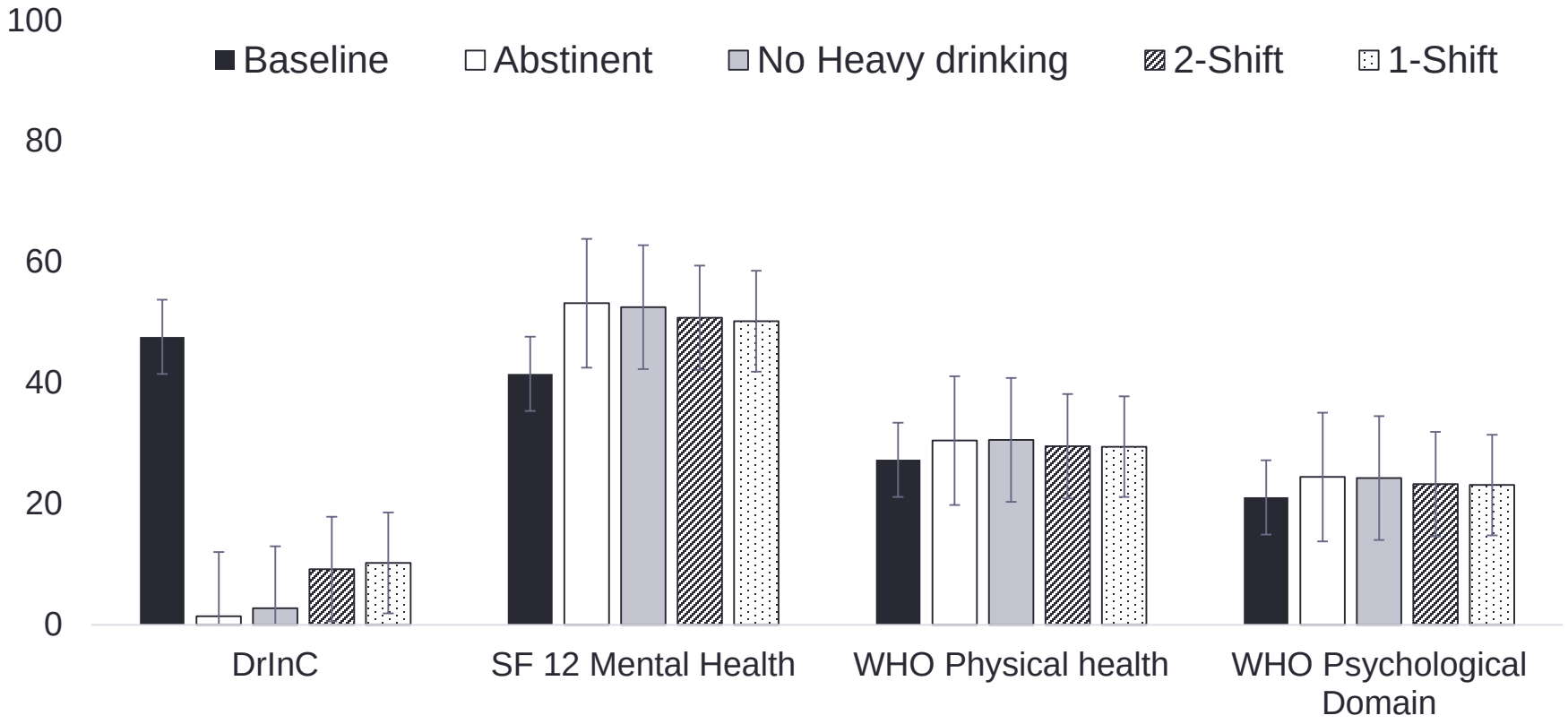






Witkiewitz et al (2018). *ACER*

How do WHO level reduction outcomes compare to FDA-approved outcomes?



BIOMARKERS OF PHYSICAL HEALTH

Systolic Blood Pressure

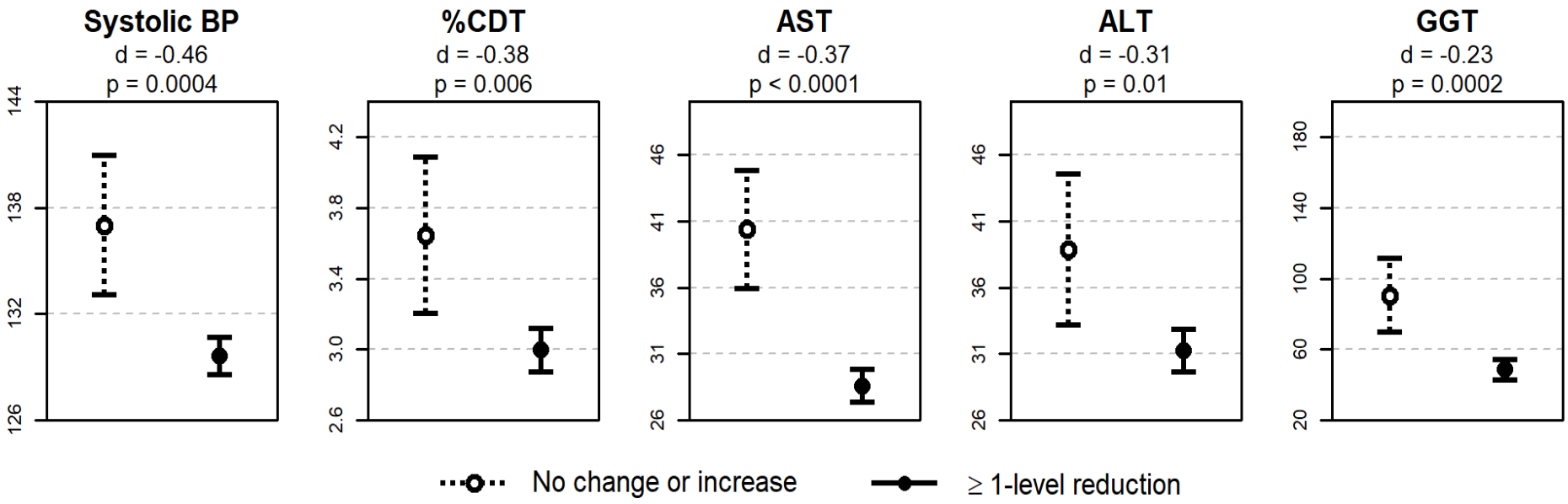
%CDT

ALT

AST

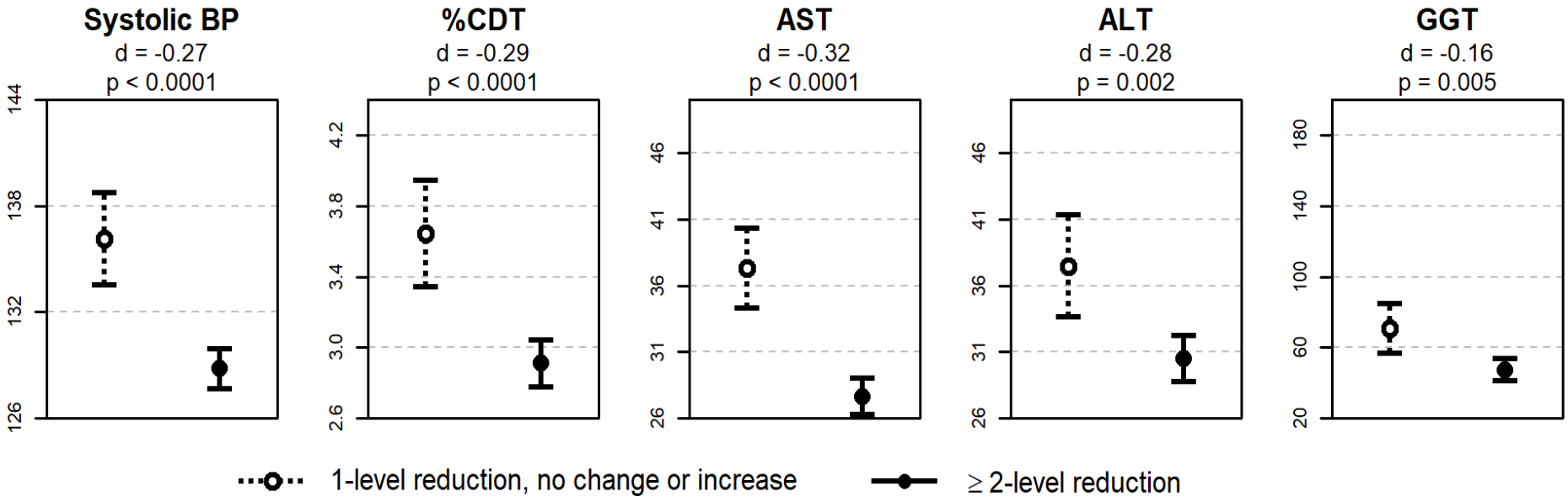
GGT

1+ level reduction: improved (lower) markers of physical health



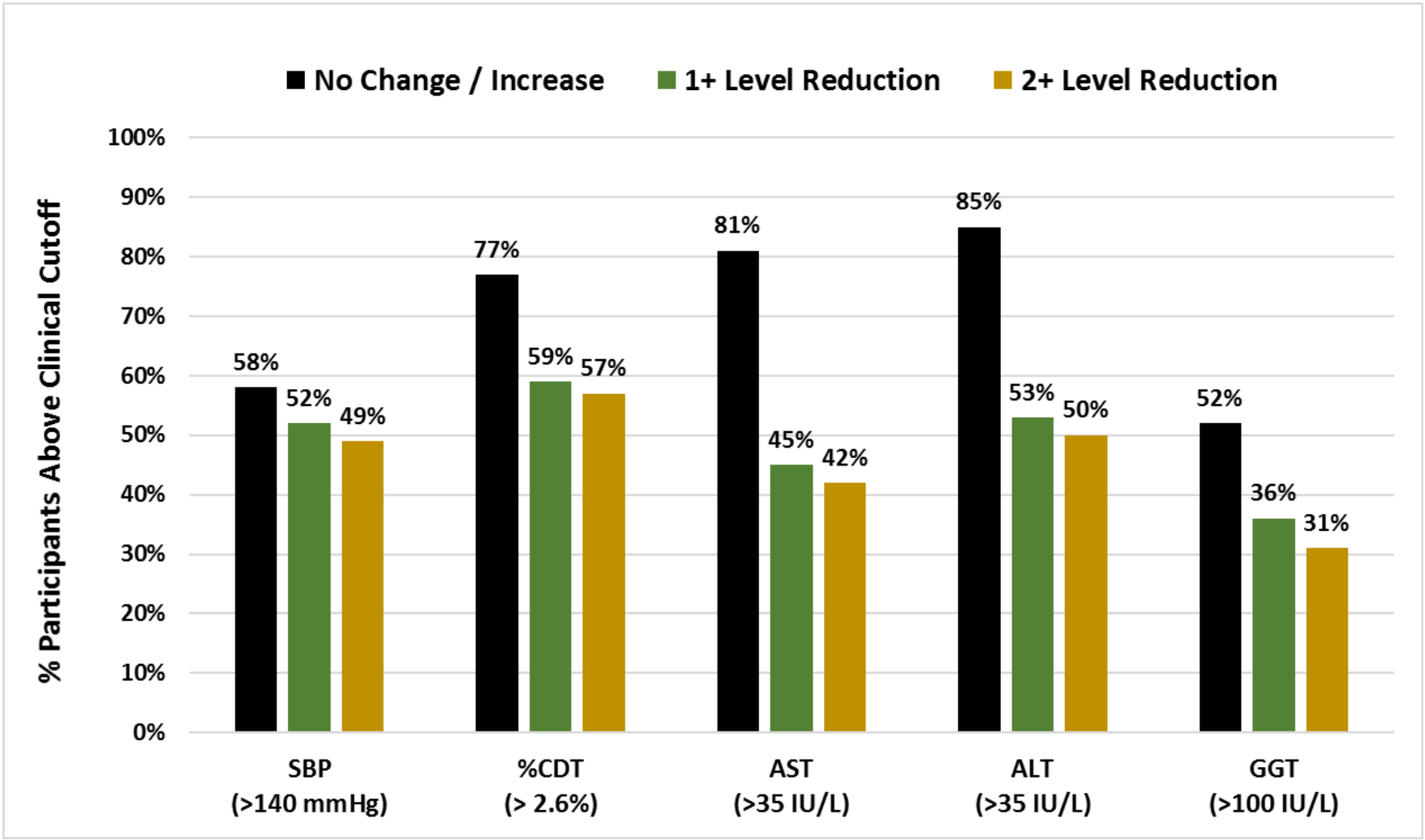
Witkiewitz et al (2018). *ACER*

2+ level reduction: improved (lower) markers of physical health



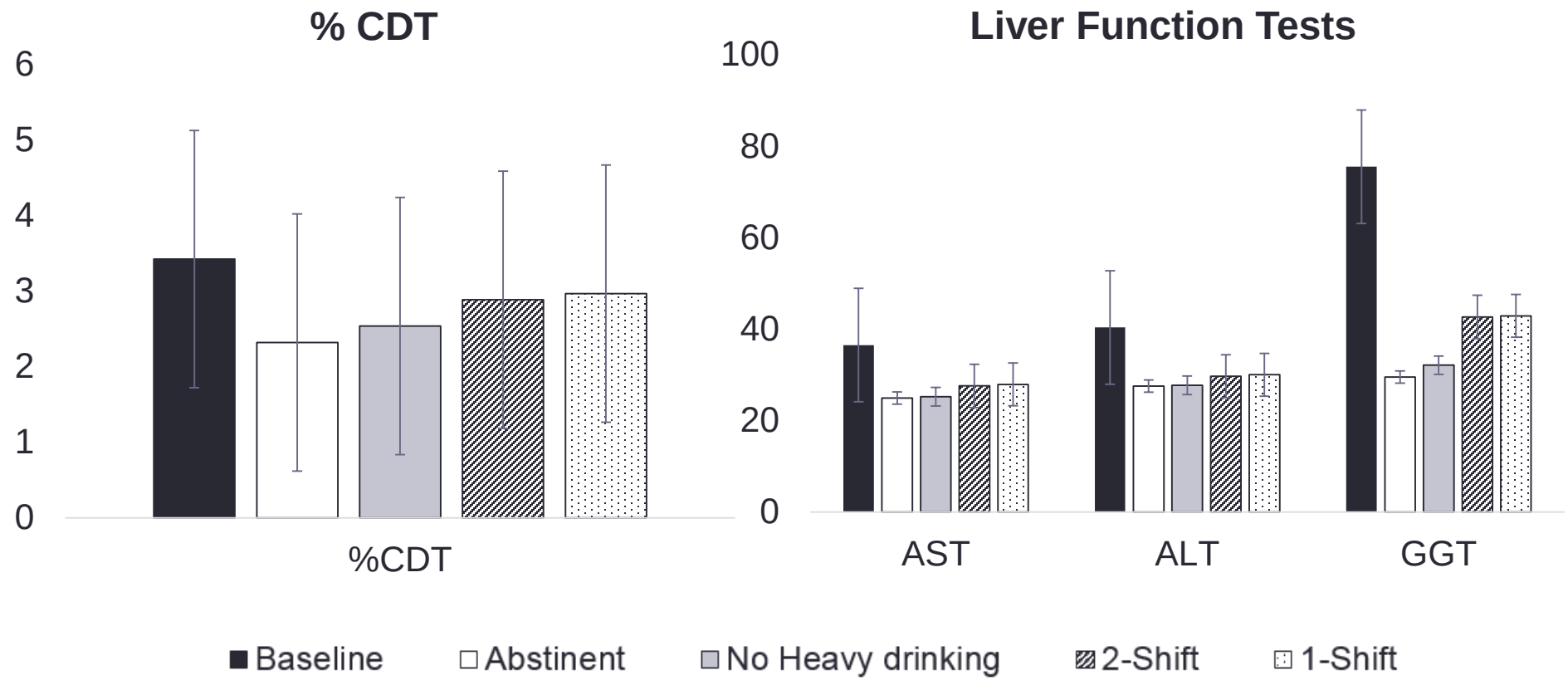
Witkiewitz et al (2018). *ACER*

% Patients above clinical cutoffs - markers of physical health



Witkiewitz et al (2018). *ACER*

How do WHO level reduction outcomes compare to FDA-approved outcomes?



Summary of Results

Unstandardized Regression Results (B (95% CI))		
	WHO Risk Level Reduction	
Outcomes	1+ level reduction vs. no change / increase	2+ level reduction vs. 1-level red, no change, increase
Drinking Consequences	-26.3 (-31.7, -20.9)	-20.8 (-23.0, -18.5)
SF-12 Mental Health	7.8 (5.3, 9.8)	6.9 (5.5, 8.2)
Physical QoL	2.2 (1.9, 2.5)	2.2 (1.7, 2.7)
Psychological QoL	2.2 (1.7, 2.8)	2.2 (1.8, 2.7)
Social QoL	0.8 (0.4, 1.2)	0.83 (0.5, 1.2)
Environmental QoL	2.1 (1.1, 3.2)	2.3 (1.5, 3.2)
Systolic Blood Pressure	-7.9 (-11.8, -4.0)	-7.3 (-11.0, -3.6)
%CDT	-0.7 (-1.0, -0.3)	-0.7 (-1.1, -0.4)
AST	-11.6 (-21.0, -2.2)	-9.9 (-14.2, -5.6)
ALT	-8.1 (-15.2, -1.0)	-7.7 (-11.3, -4.2)
GGT	-41.1 (-72.2, -10.0)	-23.7 (-38.3, -9.0)

Sensitivity Analyses: Additional models

- Results are similar using different methods to handle missing data
    - Missing = “no change or increase”
    - Multiple imputation

- Results are similar when stratified by baseline WHO level (e.g., among individuals with baseline “Very High” WHO level vs. those with “High” or “Moderate” levels)

SUMMARY & CONCLUSION

Summary of Findings: Current Study & ACTIVE group

1+ and 2+ level reductions in WHO risk levels are associated with clinically meaningful improvements in…

- Alcohol-related consequences (Witkiewitz et al. 2017, ACER)
- Mental health (Witkiewitz et al. 2017, ACER)
- Quality of Life (Witkiewitz et al. 2018, ACER)
- Systolic blood pressure and liver function (Witkiewitz et al., 2018)

Consistent with improvements found in…

- Risk of alcohol dependence (Hasin et al. 2017, Lancet Psychiatry)
- Risk of alcohol problems and liver disease (Knox et al., 2018 ACER)
- Health care costs (Aldridge, Zarkin et al., in preparation)
- Treatment effects (Falk et al., in press)

Summary (cont…)

- WHO 1+ and 2+ level reductions are comparable with those obtained using the current FDA endpoints -- abstinence and no heavy drinking -- when examining a range of functioning and physical health outcomes

- **Reductions in WHO drinking risk levels are predictive of clinical benefit (i.e., how a patient "feels and functions")**

Thank you!

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