Moderate alcohol and cardiovascular health trial
MACH15

A trial to determine if telling people to not drink 15g of alcohol a day vs telling them to do so along with substantial efforts at adherence lowers CVD risk (with unknown effects on mortality or cancer) among older adults at low cancer risk, high CVD risk, without depressive symptoms liver or kidney disease, and who have been drinking without drinking too much and without any consequences

Richard Saitz MD, MPH, FACP, DFASAM
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Professor of Community Health Sciences & Medicine

CHS Mission:
To apply the social and behavioral sciences to enhance the health and well-being of communities and promote health equity

Clinical Addiction Research and Education Unit
Section of General Internal Medicine
Boston Medical Center
Boston University School of Medicine
As required by the Alcohol Policy 18 Conference, I/we have signed a disclosure statement and note the following conflict(s) of interest:

Systembolaget, the Swedish government alcohol monopoly, supported meeting travel in 2016 through a grant to Karolinska Institutet.

Alkermes is providing injectable naltrexone to Boston University for a study medication for alcohol use disorder supported by NIAAA for which I am principal investigator.
MACH15 considerations

- Study design
- Scientific justification
- Significance
- Funding context
- Conclusions and discussion
Design overview

- Seven (up to 16) site randomized trial in 7800 adults with stable CVD or 15% 10-year risk of a CVD event, of ~15g of alcohol daily versus abstinence, for 4.5 to 7.5 years
- 80% power to detect a 18% difference in a composite CVD outcome (anticipated 2.6%)
  - non-fatal myocardial infarction
  - non-fatal ischemic stroke
  - hospitalization for angina
  - coronary/carotid revascularization
  - all-cause mortality
- Secondary: 1) diabetes, 2) above limited to CVD death

https://clinicaltrials.gov/ProvidedDocs/30/NCT03169530/Prot_000.pdf
Outcome determination

- 3-monthly interviews, annual visit, medical record review, determination by unblinded* investigator, standard definitions (blood testing for fasting glucose or HBA$_1$C)

*according to protocol. Clinical trials.gov says “masked”
Main inclusion criteria

- 50+, postmenopausal
- Clinical or subclinical CVD or 15% risk (AHA/ACC Risk Score) or age 75+
- 1+ drink in past 5 years

~16.5% prevalence
Goff DC et al. Circ 2014;129:S49-S73
Exclusions (speak to generalizability)

1. High alcohol consumption, defined by any one of the following:
   a) Alcohol Use Disorders Identification Test (AUDIT) score >5 at screening
   b) Drinking, on average, >7 alcoholic beverages/week during the past 6 months
   c) Drinking 6 or more alcoholic beverages on one occasion during the past 6 months.
2. Yale-Brown Obsessive Compulsive Scale-heavy drinking (Y-BOCS-hd) total score of ≥6 on questions 7, 8, and 10
3. Within the 6 months prior to randomization, cardiovascular disease event (MI, revascularization procedure, or stroke)
4. AHA Class III-IV heart failure
5. History of alcohol or substance abuse (medical record confirmed or self-reported history)
6. Other intolerance or allergy to alcohol
7. Dual antiplatelet therapy
8. History of gastric bypass surgery
9. Any serious chronic liver disease (e.g., active hepatitis B and C infections) or liver tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and gamma-glutamyl transpeptidase [GGT]) >2 times the upper limit of the normal range using local standards
10. Personal history of any colon or liver cancer
11. Any other cancer with a life expectancy of less than 3 years
12. Diagnosed with breast cancer that required either surgery or removal of breast tissue or chemotherapy
13. Mother or sister ever diagnosed with breast cancer that required either surgery or removal of breast tissue or chemotherapy
14. Estimated glomerular filtration rate (eGFR) <30 ml/min /1.73m² or end-stage renal disease (ESRD)
15. Ongoing use of any medication for which alcohol consumption is contraindicated
16. A Patient Health Questionnaire (PHQ-9) ≥15 at screening or a positive response on question 9 dealing with suicide ideation
17. History of any organ transplant
18. Unintentional weight loss >10% in last 6 months
19. Currently participating in another clinical trial (intervention trial) with CVD outcomes. Note: Participant must wait until the completion of his/her activities or the completion of the other trial before being screened for MACH15. Local restrictions for entry by participants can be more conservative if mandated.
20. Not willing or able to provide a name and contact information for at least one additional contact person other than self
21. Diagnosis of dementia
22. Investigator discretion regarding appropriateness of participation or concern about intervention adherence, examples include: moderate – severe psychiatric illness, behavioral concerns regarding likelihood of low adherence to trial protocol, a medical condition likely to limit survival to less than 3 years, or an advanced chronic disease, such as cognitive impairment without a dementia diagnosis or any condition that requires 24-hour care.
23. Not willing or able to provide a signed and dated informed consent form
24. Unable to successfully complete the washout period
25. Not willing or able to comply with all trial procedures
Exclusions

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Exclusions (continued…)

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Intervention

▪ Assignment to abstain vs. to consume ~15 g (a standard U.S. serving) of alcohol (in any form)
  ▪ “only after activities that require dexterity and alertness are completed for the day (i.e., at night) and will be advised to consume alcohol as part of a healthy diet.”
  ▪ Abstinent group: exceptions for “special occasions” (up to 8)

▪ Reimbursement for or distribution of beverage*; may reimburse nonalcoholic beverage as well

▪ Adherence assessed by self report (interviews and electronic) and HDL-C
  ▪ Optional subset urine or hair testing
  ▪ Monitoring (7d TLFB, blood pressure, liver enzymes, triglycerides)
  ▪ “Alcohol, the product of interest in this trial, does not concern a medicinal product but a food substance.”

▪ If not adherent, counseling for adherence or excessive use

▪ Optional run-in period of drinking or not drinking

*75% cost of beer
Validity

- Dose and adherence
  - It is possible the dose taken will be
    - higher (and riskier for outcomes that are not the primary outcome—e.g. cancer, injuries, falls, death) (may still see effect on primary outcome, or bias to $H^0$)
    - lower (selected by participants with lower risk of heart disease) (bias to $H'$)
- Outcome: assessment (adequacy of/any blinding), composite
Generalizability

- Many exclusions
  - but not reflux, insomnia, falls, pain…common symptoms, often not attributed to ETOH
- People who never drink who would start?
- People who are 50+ who drink low amounts no longer include those who might have had harms
- To whom will the results apply?
  - People like those in the trial (exclusions, adherence)
  - 2/3 of elderly do not drink; 1/3 of those who do, exceed limits

MACH15 considerations

- Study design
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Scientific justification

- Short-term and experimental trials suggest
  - Some adherence (one 24-month study with unclear results [Gepner et al. 2015])
  - Some effects on CHD biomarkers (4 of 11 studies in one review, Brien et al 2011)
- Observational studies suggest possible benefits
- But…
Do “Moderate” Drinkers Have Reduced Mortality Risk? A Systematic Review and Meta-Analysis of Alcohol Consumption and All-Cause Mortality

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ABSTRACT. Objective: Previous meta-analyses of cohort studies indicate a J-shaped relationship between alcohol consumption and all-cause mortality, with reduced risk for low-volume drinkers. However, low-volume drinkers may appear healthy only because the “abstainers” with whom they are compared are biased toward ill health. The purpose of this study was to determine whether misclassifying former and occasional drinkers as abstainers and other potentially confounding study characteristics underlie observed positive health outcomes for low-volume drinkers in prospective studies of all-cause mortality. Method: A systematic review and meta-regression analysis of studies investigating alcohol use and mortality risk after controlling for quality-related study characteristics was conducted in a population of 3,998,626 individuals, among whom 367,103 deaths were recorded. Results: Without adjustment, meta-analysis of all 87 included studies replicated the classic J-shaped curve, with low-volume drinkers (1.3–24.9 g ethanol per day) having reduced mortality risk (RR = 0.86, 95% CI [0.83, 0.90]). Occasional drinkers (<1.3 g per day) had similar mortality risk (RR = 0.84, 95% CI [0.79, 0.89]), and former drinkers had elevated risk (RR = 1.22, 95% CI [1.14, 1.31]). After adjustment for abstainer biases and quality-related study characteristics, no significant reduction in mortality risk was observed for low-volume drinkers (RR = 0.97, 95% CI [0.88, 1.07]). Analyses of higher-quality bias-free studies also failed to find reduced mortality risk for low-volume alcohol drinkers. Risk estimates for occasional drinkers were similar to those for low- and medium-volume drinkers. Conclusions: Estimates of mortality risk from alcohol are significantly altered by study design and characteristics. Meta-analyses adjusting for these factors find that low-volume alcohol consumption has no net mortality benefit compared with lifetime abstention or occasional drinking. These findings have implications for public policy, the formulation of low-risk drinking guidelines, and future research on alcohol and health. (J. Stud. Alcohol Drugs, 77, 185–198, 2016)
ABSTRACT. Objective: Previous meta-analyses estimate that low-volume alcohol consumption protects against coronary heart disease (CHD). Potential errors in studies include systematic misclassification of drinkers as abstainers, inadequate measurement, and selection bias across the life course. Method: Prospective studies of alcohol consumption and CHD mortality were identified in scholarly databases and reference lists. Studies were coded for potential abstainer biases and other study characteristics. The alcohol-CHD risk relationship was estimated in mixed models with controls for potential biases. Stratified analyses were performed based on variables identified as potential effect modifiers. Results: Fully adjusted meta-analysis of all 45 studies found significantly reduced CHD mortality for current low-volume drinkers (relative risk [RR] = 0.80, 95% CI [0.69, 0.93]) and all current drinkers (RR = 0.88, 95% CI [0.78, 0.99]). There was evidence of effect modification by cohort age, gender, ethnicity, and heart health at baseline. In stratified analyses, low-volume consumption was not significantly protective for cohorts ages 55 years or younger at baseline (RR = 0.95, 95% CI [0.75, 1.21]), for studies controlling for heart health (RR = 0.87, 95% CI [0.71, 1.06]), or for higher quality studies (RR = 0.86, 95% CI [0.68, 1.09]). In studies in which the mean age was 55 years or younger at baseline, there were significantly increased RRs for both former (RR = 1.45, 95% CI [1.08, 1.95]) and occasional drinkers (RR = 1.44, 95% CI [1.09, 1.89]) compared with abstainers. Conclusions: Pooled analysis of all identified studies suggested an association between alcohol use and reduced CHD risk. However, this association was not observed in studies of those age 55 years or younger at baseline, in higher quality studies, or in studies that controlled for heart health. The appearance of cardio-protection among older people may reflect systematic selection biases that accumulate over the life course. (J. Stud. Alcohol Drugs, 78, 375–386, 2017)
MACH15 considerations

- Study design
- Scientific justification
- **Significance**
- Funding context
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**NIH definition:** “…how will scientific knowledge and/or clinical practice be improved? How will [the study] change treatments or preventative interventions…”
Significance

- Calls for randomized trials as the only way to settle the question
- Not powered to determine mortality or cancer risk, thus even positive findings will be difficult to know how to apply
- Not generalizable

- What is the question?
  - Does recommending low dose alcohol prevent CVD in…?
  - Is alcohol beneficial for health in the way it is used by the public?

- Will the trial settle the question?
  - An addictive substance that is a carcinogen (including at low doses) that risks numerous consequences when used by a substantial proportion of the population for prevention
Significance

▪ Is it to inform those already drinking low amounts? Shouldn’t inform non-drinkers starting. How many people will results apply to?

▪ NIAAA senior advisor reports study would not have been done without industry funds given to NIH Foundation to give to NIAAA ($67 million)(at a time when NIAAA budget was ~$440 million)
  ▪ Anheuser-Busch InBev
  ▪ Diageo
  ▪ Pernod Ricard
  ▪ Heineken
  ▪ Carlsberg

▪ Are firewalls enough when scientists know what industry wants?

“…to spend that kind of money…would never fly…”

NYT Mar 17, 2018
Wired Oct 26 2017
FY18 NIAAA budget $509,573
FY17 NIAAA budget $483,363
MACH15 considerations

- Study design
- Scientific justification
- Significance
- **Funding context**
- Conclusions and discussion

*For a cardiovascular disease prevention trial (NHLBI would be expected funder)*
PAR-13-363

Applicants for the U10 Clinical Trial Implementation Cooperative Agreement must be able to begin the trial without further planning activities when the U10 is awarded.

Therefore, investigators who have already completed planning activities through an NIAAA-funded U34 clinical trial planning grant are expected to apply.

Department of Health and Human Services
Part 1. Overview Information
Participating Organization(s)
National Institutes of Health (NIH)

Components of Participating Organizations
National Institute on Alcohol Abuse and Alcoholism (NIAAA)
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute on Aging (NIA)

Funding Opportunity Title
Multi-Site Randomized Controlled Clinical Trial Research Center on Alcohol's Health Effects (U10)
NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM SPECIAL EMPHASIS PANEL

ZAA1 - (05)
NIHAA1: AA1 & AA3 MEMBER CONFLICT REVIEWS
07/14/17 - 07/14/17
Meeting Roster

Notice of NIH Policy to All Applicants: Meeting rosters are provided for informational purposes only and do not reflect a commitment to any particular individual. Failure to observe this policy will create a serious breach of integrity in the peer review process.

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### Project Information

- **Project Title:** Symposium on the Health Effects of Moderate Alcohol
- **Contact PI / Project Leader:** Mukamel, Kenneth J.
- **Program Official Information:** Available
- **Other PI Information:** Not Applicable

### Details

- **Organization:** Beth Israel Deaconess Medical Center
- **City:** Boston
- **Country:** United States (US)
- **State Code:** MA
- **Congressional District:** 07
- **FOA:** PA-16-293

### Funding Details

- **DUNS Number:** 071723021
- **CFDA Code:** 275
- **Project Start Date:** 11-May-2017
- **Budget Start Date:** 1-Jan-2018
- **Project End Date:** 31-Dec-2018
- **Budget End Date:** 31-Dec-2018

### Industry Funding

- **5 of 10 with known/reported current or past industry funding**

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**New NIAAA conference grant:**

**MACH15**

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Presentation to DISCUS: opportunity “to show that moderate alcohol consumption is safe and lowers risk of common diseases”

NIH will examine ethics of its study on the health effects of a daily glass of wine

NIH rejected a study of alcohol advertising while pursuing industry funding for other research

By Sharon Begley

The New York Times

Is Alcohol Good for You? An Industry-Backed Study Seeks Answers

By KELLI CARTER RAEHAN / JUNE 22, 2017

2014 meeting to make a business case to industry

EXCLUSIVE

Anheuser-Busch InBev launches Global Smart Drinking Goals: consumers are encouraged to make smart drinking choices at all times

NIH rejected a study of alcohol advertising while pursuing industry funding for other research
CONFLICT OF INTEREST POLICY

The MACH15 investigators have established a policy regarding Conflict of Interest, which is presented in the Manual of Procedures (MOP).

The independence of this trial from any **actual or perceived** influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The trial leadership in conjunction with the NIAAA has established policies and procedures for all members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

https://www.mach15trial.org/
MACH15 considerations

- Study design
- Scientific justification
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Conclusions and discussion

- Design
  - Not consistent with equipoise (…to prove safe, healthy…)
  - Will not determine risk/benefit balance (cancer/mortality)
  - Limited generalizability. NB: it is really a trial of *not* drinking (all eligible drink already)

- Scientific justification (merit)
  - Questionable

- Significance
  - Questionable given insufficient merit to be funded w/o industry funds according to NIAAA

- Funding context
  - At a minimum, perception of industry influence

- Conclusions
  - At best, will answer narrow question that would beg other trials (the norm in CVD prevention) that will not be done; will not be definitive (and null study will be ignored)
    - Q: ‘should someone who drinks low amounts stop or continue for CVD health only?’
  - Results will likely be applied too broadly, with harmful public health effects