A Multi-ethnic Mendelian Randomization Study of Moderate Alcohol Use and the Risk of Atherosclerotic Cardiovascular Disease in Women’s Health Initiative

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Presenter Disclosure Information

• FINANCIAL DISCLOSURE:
  No relevant financial relationship exists
Background

- Alcohol (EtOH) linked to risk of CVD
- High dose → harmful, moderate → protective
- Control for confounding?
- Protective effect never been demonstrated in Randomized Controlled Trials (RCT)
  - Feasible?

Source: BMJ 2011;342:d671
An alternative strategy to RCT: Mendelian Randomization (MR) study

- Leverage genetic variants with well-understood effects on exposure to estimate its causal effect on an outcome
- In MR, the genetic variant is the instrumental variable (IV). MR also called IV analysis.
  - Old concept (econometrics), new application (epidemiology)
- variants are randomly assigned at conception
  - Unlinked to confounders
IV assumptions and two-stage method of analysis

i. the IV is associated with the exposure

ii. the IV is not associated with any (measured and unmeasured) confounder of the exposure-outcome association

iii. the IV does not affect the outcome, except possibly via its association with the exposure.

1st stage: IV - E

2nd stage: \( \hat{E} \mid IV - O \)

Continuous: linear

Binary: logistic

The causal estimate is this 2nd-stage regression coefficient for the change in outcome caused by a unit change in the exposure.
Hypothesis & Study population

• **Hypothesis**

  • protective effect of moderate EtOH on risk of CVD is not causal in nature

• **Sample**

  • Subjects with history of CVD at baseline were excluded.
  
  • 154,643 European (EA), African (AA), and Hispanic American (HA) participants in the Women’s Health Initiative (WHI).
  
  • Subset with imputed genetic data for IV analysis
Exposure and Outcome

• Exposure
  • non drinker
  • Moderate (>0 drinks/week <15): divided into 4 equal sized groups
  • Heavy: ≥15 drinks/week

• Outcome
  • incident Atherosclerotic Cardiovascular Disease (ASCVD): adjudicated fatal and non-fatal myocardial infarction (MI), coronary revascularization, angina, ischemic stroke, carotid artery disease, peripheral artery disease
Observational analyses of EtOH and ASCVD

Multivariable logistic regression: N=154,643

**Minimally adjusted:** age, race  **Fully adjusted:** + BMI, hypertension status, systolic blood pressure, diabetes status, smoking status, physical activity, education, and income
Observational association between EtOH and ASCVD in each race

<table>
<thead>
<tr>
<th>N cases/controls</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA</td>
<td>-0.024</td>
<td>0.008</td>
<td>0.002</td>
<td>0.977 (0.962, 0.992)</td>
</tr>
<tr>
<td>HA</td>
<td>-0.025</td>
<td>0.055</td>
<td>0.647</td>
<td>0.975 (0.876, 1.086)</td>
</tr>
<tr>
<td>AA</td>
<td>0.020</td>
<td>0.032</td>
<td>0.547</td>
<td>1.019 (0.957, 1.087)</td>
</tr>
<tr>
<td>EA+HA+AA</td>
<td>-0.022</td>
<td>0.007</td>
<td>0.004</td>
<td>0.978 (0.964, 0.993)</td>
</tr>
</tbody>
</table>

EtOH: log-base-2 transformed # of drinks/week; fully adjusted logistic regression; N=72,497 moderate drinkers

2.2% reduction in the risk of ASCVD per doubling of the # drinks/week
Strength of Instrumental variable (IV) in the WHI (Stage 1: IV - EtOH)

• IV: rs1229984, a missense variant in ADH1B known to be strongly associated with the degree of lifetime alcohol consumption

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minor Allele Frequency</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA</td>
<td>11,590</td>
<td>0.07</td>
<td>0.38</td>
<td>0.05</td>
<td>5.49E-13</td>
<td>52.1</td>
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<tr>
<td>HA</td>
<td>1,562</td>
<td>0.10</td>
<td>0.38</td>
<td>0.11</td>
<td>6.89E-04</td>
<td>11.6</td>
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<tr>
<td>AA</td>
<td>2,912</td>
<td>0.02</td>
<td>0.03</td>
<td>0.18</td>
<td>0.86</td>
<td>0.03</td>
</tr>
<tr>
<td>EA+HA+AA</td>
<td>16,064</td>
<td>0.06</td>
<td>0.36</td>
<td>0.05</td>
<td>6.11E-15</td>
<td>61.0</td>
</tr>
</tbody>
</table>

Effect allele: allele associated with an increase of EtOH in moderate drinkers
Subset of the moderate drinkers with imputed genetic data for the IV
F >10 suggests the IV is strong enough to be used in Stage 2.
SNP r² = 0.74
MR analyses of causal association between EtOH and ASCVD (Stage 2: \( EtOH \) - ASCVD)

<table>
<thead>
<tr>
<th>N cases/controls</th>
<th>( \beta )</th>
<th>SE</th>
<th>( P )</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA</td>
<td>3,274/8,316</td>
<td>0.27</td>
<td>0.11</td>
<td>0.008</td>
</tr>
<tr>
<td>HA</td>
<td>146/1,416</td>
<td>0.72</td>
<td>0.40</td>
<td>0.077</td>
</tr>
<tr>
<td>AA</td>
<td>432/2,480</td>
<td>1.26</td>
<td>2.93</td>
<td>0.667</td>
</tr>
<tr>
<td>AA+HA+EA</td>
<td>3,852/1,2212</td>
<td>0.35</td>
<td>0.11</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Risk of ASCVD increased by 42% per doubling of # drinks/week

Subset of moderate drinkers with imputed genetic data for the IV
How can an IV analysis result in an estimate of the causal association that is in the opposite direction of the observation analysis?

Adapted from Burgess S, Thompson SG, Mendelian Randomization, methods for using genetic variants in causal estimation, 2015 by Taylor & Francis Group, LLC
Mediation vs. pleiotropy through risk factors for ASCVD?

In moderate drinkers

Continuous Trait
AGE
BMI
SBP
PA
EDUCATION
INCOME
HOMA-IR

In never drinkers

Continuous Trait
AGE
BMI
SBP
PA
EDUCATION
INCOME
HOMA-IR

Regression of trait on genetic IV SNP rs1229984, stratified by drinking status

Never drinkers are a subset of non drinkers (n =4079 out of 15788)
Limitations

• Small number of events in non-European populations.

• Small sample size for never drinkers, and the power for the test of mediation vs pleiotropy is limited.

• Only women were included, not generalization to men.
Conclusions

• IV analysis suggests association between alcohol use and improved cardiovascular health is confounded.

• Alcohol use even among moderate users substantially increases risk of ASCVD in a multi-ethnic population of post-menopausal women.

• The potential mechanism of adverse effects of moderate alcohol use on ASCVD include the direct promotion of a lower SES, lower amounts of physical activity, higher blood pressure and higher BMI, all of which in turn increase risk of ASCVD.
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