Different Concepts in Alcohol Research: Are the Observed Protective Health Effects of Moderate Beer Consumption Still Valid?

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Beer and Health
THE 8TH EUROPEAN
BEER AND HEALTH SYMPOSIUM
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Outline

A. Hypothesis from Observational Studies

B. Limitations of Observational Studies

C. Mendelian Randomization to \(\downarrow\)Bias

D. Caveats of Mendelian Randomization

E. Concluding Remarks
A. Current Hypothesis from Observational Studies
# Alcohol Intake & CHD Mortality

Ronksley P E et al. BMJ 2011;342:bmj.d671

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
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<td>Blackwelder et al 1980</td>
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<td>Kittner et al 1983</td>
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<td>Colditz et al 1985</td>
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<td>Cullen et al 1993</td>
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<td>Diem et al 2003</td>
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<td>Bazzano et al 2009</td>
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<tr>
<td>Overall: P&lt;0.001, I²=87.5%</td>
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*Weight from random effects analysis

0.75 (0.68-0.81)
Beer and Fatal/Non-Fatal CVD

![Graph showing the relative risk of fatal and non-fatal vascular events against alcohol consumption and beer consumption.](Costanzo Eur J Epidemiol 2011;26:833-50)
## Alcohol and PAD

<table>
<thead>
<tr>
<th>Drinks/wk</th>
<th>Wine</th>
<th>Beer</th>
<th>Spirits</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>1-7</td>
<td>0.81 (0.64-1.03)</td>
<td>0.69 (0.52-0.91)</td>
<td>0.88 (0.69-1.10)</td>
</tr>
<tr>
<td>≥8</td>
<td>0.64 (0.38-1.07)</td>
<td>0.60 (0.43-0.83)</td>
<td>0.89 (0.68-1.18)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.013</td>
<td>0.0005</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Adjusted for age, diabetes, CHD, BP, smoking status, pack-years, and other types of beverage

Alcohol Intake & Heart Failure
Meta-Analysis

Larsson et al. Eur J Heart Fail 2015;17:367-73
Alcohol and Mortality

Selected studies

\[ \ln RR = 0.01110 (0.00070) \cdot \text{alc} - 0.09867 (0.00530) \sqrt{\text{alc}} \]

Relative risk vs Alcohol consumption (g/day)

- 20 g/day
- 72 g/day
- 89 g/day
Table 5. Adjusted relative risks (RRs) of all-cause mortality for different levels of alcohol consumption compared with lifetime abstainers estimated from higher quality studies\textsuperscript{a} with and without one influential study (Friesema et al., 2007)

<table>
<thead>
<tr>
<th>Drinking categories\textsuperscript{b}</th>
<th>Model 1: Including Friesema et al.</th>
<th></th>
<th>Model 2: Excluding Friesema et al.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n^b )</td>
<td>RR\textsuperscript{c}</td>
<td>[95% CI]</td>
<td>( p )</td>
</tr>
<tr>
<td>Former drinker</td>
<td>19</td>
<td>1.14</td>
<td>[0.77, 1.69]</td>
<td>.4950</td>
</tr>
<tr>
<td>Low volume (1.30–&lt;25 g/day)</td>
<td>39</td>
<td>0.89</td>
<td>[0.62, 1.29]</td>
<td>.5279</td>
</tr>
<tr>
<td>Medium volume (25–&lt;45 g/day)</td>
<td>11</td>
<td>1.08</td>
<td>[0.72, 1.62]</td>
<td>.7123</td>
</tr>
<tr>
<td>High volume (45–&lt;65 g/day)</td>
<td>7</td>
<td>0.95</td>
<td>[0.62, 1.46]</td>
<td>.8113</td>
</tr>
<tr>
<td>Higher volume (≥65 g/day)</td>
<td>11</td>
<td>1.58</td>
<td>[1.05, 2.38]</td>
<td>.0295</td>
</tr>
<tr>
<td>All drinkers combined</td>
<td>87</td>
<td>1.10</td>
<td>[0.86, 1.41]</td>
<td>.3557</td>
</tr>
</tbody>
</table>

Notes: Bold indicates statistical significance. CI = confidence interval. \textsuperscript{a}Studies in which only lifetime abstainers included in the reference group, adequate alcohol measure, median age <60 years at intake and ≥55 years at follow-up; \textsuperscript{b}number of risk estimates; \textsuperscript{c}estimates adjusted for sampling variability and between-study variation.
# Alcohol and All-Cause Mortality

N=24,029 from Health & Retirement Study, US

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Lifetime (95% CI)</th>
<th>Former Drinker (95% CI)</th>
<th>Occasional Drinker* (95% CI)</th>
<th>Regular Alcohol Consumption (Drinks/Wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for</td>
<td></td>
<td></td>
<td>&lt;7</td>
</tr>
<tr>
<td>Age and sex</td>
<td>Nondrinker (1.12 (0.92-1.36))</td>
<td>Former Abstinent (1.53 (1.27-1.84))</td>
<td>Occasional Drinker* (1.00)</td>
<td>0.80 (0.66-0.97)</td>
</tr>
<tr>
<td>Fully adjusted†</td>
<td>1.16 (0.95-1.43)</td>
<td>1.26 (1.05-1.53)</td>
<td>1.00</td>
<td>0.99 (0.82-1.21)</td>
</tr>
</tbody>
</table>

*Those who reported drinking on at least 1 occasion, but never more than less than once per week.

†Adjusted for age, sex, income quintile, wealth quintile, whether born in the United States, race, religiosity, smoking, BMI, exercise, binge drinking, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), diagnoses (cancer, lung disease, psychiatric disease, stroke, hypertension, diabetes, heart disease, and other diseases), mobility, activities of daily living, instrumental activities of daily living, and cognitive level.

Is the Choice of Outcome Relevant?

Inclusion criteria

Included studies were original English-language research articles published in the peer-reviewed literature that quantified the relationship between all-cause mortality and alcohol consumption among human populations in cohort studies.

Stockwell et al. J Stud Alcohol Drugs 2016;77:185
Alcohol & CHD Death with Lifetime Abstainers as Reference

The graph shows the relative risk of CHD death associated with different levels of alcohol consumption. The x-axis represents the average alcohol consumption (g/day), while the y-axis represents the relative risk.

- **Drinkers** show an increasing relative risk as alcohol consumption increases.
- **Former drinkers** show a different trend, with a peak at moderate consumption levels.
- **Russia** indicates a lower relative risk at higher consumption levels compared to drinkers.

Roerecke and Rehm BMC Medicine 2014;12:182
Drinking Patterns and CHD

Drinkers of <30 g/d vs. Lifetime Abstainers

Relative risk (95% CI)

1.45 (1.24-1.70)†

Average alcohol consumption (g/day)

Non-heavy drinkers

Episodic heavy drinkers

Roerecke and Rehm BMC Medicine 2014;12:182
Alcohol & Breast Cancer Risk

The graph shows the relationship between alcohol consumption (g/d) and the log odds ratio. There is a positive correlation, indicating that higher alcohol consumption is associated with a higher risk of breast cancer. The data points are spread across the graph, with a trend line indicating the increasing risk with alcohol consumption.
Alcohol and Colorectal Cancer

\[ \text{RR}_{\text{pooled}} = e^{0.006992 \times \text{Alcohol dose} - 0.00001 \times (\text{Alcohol dose})^2} \]

Beer and Health
Alcohol and Hemorrhagic Stroke

Hemorrhagic Stroke, 1 Week

$P_{\text{curve}} < 0.001$  $P_{\text{linearity}} = 0.42$

$I^2 = 8.3\%$  $P_{\text{heterogeneity}} = 0.37$

Relative Risk (Log Scale)

Alcohol Intake, g/week

Mostofsky et al. Circulation 2016;133:979-987
B. Limitations of Observational Studies
Potential Issues

1. Unmeasured & Residual Confounding

2. Reverse Causation

3. Information Bias

4. Misclassification
C. Mendelian Randomization (MR)
MR and Causal Inference

• Goal of MR is to minimize confounding and enhance study validity in observational studies where randomization may not be possible or may be unethical

• MR takes advantage of random assortment of chromosome during meiosis, and uses genetic loci that relate to the exposure (i.e., alcohol intake) as instrumental variables
What is an Instrumental Variable (IV)?

- Suppose we want to examine the relation between beer drinking (E) and risk of heart attack (Y).

- Variable Z (ADH3) is an instrumental variable only if Z affects heart attack ONLY through beer drinking.

- Z predicts beer drinking (E).
Two Assumptions for IV

1. IV must be a predictor of the exposure variable (i.e., beer consumption)

2. IV must be exogenous, that is, IV must be related to the outcome (heart attack) only through the exposure (beer intake)

Are these assumptions always satisfied in MR studies?
Challenges in IV Analysis

- Failure of exogeneity: IV influences outcome through variables that are different from the exposure
  - ↑biases that are hard to quantify as they are unobserved

- IV is only a weak predictor of the exposure (beer) – weak instrument (F-statistic < 20)

- IV is a large sample procedure (even when assumptions are met, no guarantee to obtain unbiased results in a small sample study)
% of Exposure Variance Explained by IV

Panel A: $R^2 < 10\%$

Panel B: $R^2 > 40\%$

$E$ = exposure
$Y$ = outcome
$Z$ = Instrumental variable
Best Scenario

- $R^2 > 60\%$ (IV explains most of variance of $E$)
- $>80\%$ of overlap between exposure and outcome explained

E= exposure
Y= outcome
Z= Instrumental variable
More Realistic Scenario

- $R^2 < 10\%$ (IV explains very little of the exposure variance)

- Very little of the explained exposure variance overlaps with outcome

$E=$ exposure  
$Y=$ outcome  
$Z=$ Instrumental variable
Beer and CHD Example

Alcohol $\rightarrow$ Acetaldehyde $\rightarrow$ Acetic Acid

1. Alcohol dehydrogenase 3: $\gamma_1$ fast metabolizer and $\gamma_2$ slow metabolizer
2. Aldehyde dehydrogenase 2: allele 2 for slow & 1 for fast metabolizer

SNPs associated with genes encoding ADH3 and ALDH2 can be used as IVs to assess causal effects of beer on CHD

*Slow means ↑substrate levels
ADH3 and CHD

• If Beer protects against CHD, slow metabolizers for ADH3 ($\gamma_2$) should have lower risk of CHD, given the same amount of beer

• Is there evidence that slow metabolizers ($\gamma_2\gamma_2$ or $\gamma_1\gamma_2$ genotypes) have a lower risk of CHD than wild type ($\gamma_1\gamma_1$)?
## RR of MI by ADH3 Genotype

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>ADH3 GENOTYPE</th>
<th>P VALUE*</th>
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<tbody>
<tr>
<td></td>
<td>$\gamma_1\gamma_1$</td>
<td>$\gamma_1\gamma_2$</td>
</tr>
<tr>
<td>No. of subjects (%)</td>
<td></td>
<td></td>
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<tr>
<td>Patients</td>
<td>161 (41)</td>
<td>184 (46)</td>
</tr>
<tr>
<td>Controls</td>
<td>279 (36)</td>
<td>361 (47)</td>
</tr>
<tr>
<td>Relative risk (95% CI)†</td>
<td></td>
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<tr>
<td>Matched</td>
<td>1.0 †</td>
<td>0.90 (0.69–1.17)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.0 †</td>
<td>0.81 (0.61–1.09)</td>
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<tr>
<td>Multivariate, with adjustment for alcohol consumption§</td>
<td>1.0 †</td>
<td>0.83 (0.62–1.11)</td>
</tr>
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</table>

*The P value is for the test for trend.

ALDH2 and Cancer Risk
ALDH2, Alcohol, Acetaldehyde, & Esophageal Ca

ALDH2*1*1

ALDH2

Alcohol ➔ Acetaldehyde ➔ Acetic Acid

Esophageal cancer

ALDH2*2*2

ALDH2

Alcohol ➔ Acetaldehyde ➔ Acetic Acid

Facial flushing, headache, drowsiness

Inhibiting consumption

D. Caveats of MR
Population Stratification

Different ethnic groups may have different genotype frequencies and different disease risks

Adjust for population admixture
There is an association between genetic variants due to small physical distance on the same chromosome

Variants in LD are inherited together
Genetic Canalization

• Extent to which a phenotype allows conclusions about its genotype

• With ↑canalization, the genotype cannot be reliably predicted from the phenotype (phenotype is expressed regardless of genetic variation)
Genetic Penetrance

• A good IV requires well-defined and strong genetic risk factors with high penetrance

(e.g., *Low penetrance*: ALDH2 *2*2 subjects that tolerate alcohol intake)
Multivariable MR
Use of Pleiotropic Genetic Variants to Estimate Causal Effects

Causal directed acyclic graph illustrating multivariable MR in associations between variants $G_1$, $G_2$, and $G_3$, risk factors $X_1$ and $X_2$, and outcome $Y$. Confounders $U_1$ and $U_2$ are assumed to be unknown.

A) Risk factors are causally independent (no causal effects between $X_1$ and $X_2$)
B) Risk factors are causally dependent ($X_1$ has a causal effect on $X_2$)

RCT of Moderate Alcohol Intake

The Moderate Alcohol and Cardiovascular Health Trial
2016 to 2021

- NIAAA (U10AA025286-01: PI- Mukamal KJ)
- N= 7800 adults 50+y, 10-y CVD risk of 15+%
- 16 Centers planned worldwide
- Planned 6-y of follow up
- Randomized to 14 g/d of alcohol or abstention
- Outcomes: CVD, mortality, and type 2 diabetes
E. Concluding Remarks
• With a suitable IV & sample size, MR can help establish causal relation of alcohol intake with disease in observational studies, but MR is no panacea

• Violation of IV assumptions can lead to wrong inference & contribute to heterogeneity across study results of alcohol and health

• Many observational studies support beneficial health effects of beer and other alcoholic beverages when consumed in moderation
Thank You!