Why benefits of “moderate drinking” may be overestimated – and risks underestimated

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There has been a broad scientific consensus across multiple disciplines that alcohol use in moderation confers health benefits, in particular in relation to coronary heart disease and diabetes – and it is also evident in the J shape risk relationship between drinking and all-cause mortality.
This is important for:

- The framing of public policy on alcohol
- Estimating the Global Burden of Disease
- Establishing guidelines for low risk drinking
- Verification of health claims by commercial interest groups
The J-Shape Curve for Alcohol and All Cause Mortality

- Mortality nadir <1 drink/day
- Based on average daily consumption
- "Adjusting" changes results
- Size of "benefit", shape of curve vary by country

Di Castelnuovo et al. Arch Intern Med. 2006;166(22):2437-2445
Our Thesis

Systematic biases, mainly about how “abstainers” are defined, result in an exaggeration of alcohol’s benefits – and underestimation of it’s risks

We explore this with two new meta-analyses of alcohol’s associations with

  a) mortality from all causes
  b) mortality from prostate cancer
“Abstainer biases” in prospective studies of alcohol and health

1. Including former drinkers with lifetime abstainers in reference group
2. Including occasional drinkers with lifetime abstainers in reference group

Fillmore et al (2006), Addiction Research and Theory
Dr Kaye Middleton Fillmore (1941-2013)
Medical Sociologist, University of San Francisco
The authors of two meta-analyses published in the *British Medical Journal* in 2011 (Ronksley et al; Brien et al) suggested that all of the Bradford Hill criteria for a causal association in epidemiological research are met and it is time to consider how best to communicate this fact to the general public.
Results of Fillmore et al (2006) meta-analysis

Only 7/54 studies of all cause mortality corrected for both errors (Fillmore et al, 2006) – they found no protection.

Apparent protection created by artificially introducing the errors.

Criticised for including two studies with subjects too young to benefit from protection against heart disease.

[NB reference group = ‘long term’ abstainers]
Of their 84 studies, how many included some form of misclassification error?

How many also failed to meet 5 other basic quality criteria?

Summary of analysis of 84 Ronksley et al, 2011 studies

84 articles met criteria

67 unique studies

63 studies retained

4 had no control for smoking or health

4 assessed drinking for less than 30 days

59 studies retained

10 did not assess quantity and frequency of use

49 studies retained

32 had former drinker bias

17 studies retained

7 had occasional drinker bias

17 duplicates excluded

49 studies retained

8 had occasional drinkers mixed with moderate drinkers

2 studies retained
New meta-analysis of all-cause mortality published online March 22\textsuperscript{nd} 2016

Funded by a US NIH R01 grant on which Kaye Fillmore was the original PI, Tanya Chikritzhs was CI, Jinhui Zhao was employed on the project, Timothy Naimi was a consultant.

**Aim** was to update the Fillmore et al (2006) with stricter definition of “abstainer”, adjust for other measurement problems, include new studies and correct previous errors.

Other analyses also completed on breast cancer, **prostate cancer**, stroke and CHD.
Inclusion criteria

- Prospective studies (cohort, longitudinal) of average daily alcohol consumption and all cause mortality
- Published up to and including 2014
- Identified by systematic searches of PubMed, Web of Science and reference list checking of previous meta analyses
- Original studies not reviews or other meta analyses
- Where multiple studies published from same cohort the latest results are used unless earlier are more complete
Study selection process

2,662 articles from databases and meta-analyses

240 articles retained

2,422 excluded on review of abstracts for relevant disease outcome and alcohol measure

153 excluded after article review, not original study, sample with pre-existing disease, no drinking categories, cross-sectional study

87 studies retained
Study characteristics

- **RR estimates**: 523 of drinkers v “abstainers”
- **Countries**: USA (44%), Asia (14%)
- **Age**: <50 (37%), 50-59 (33%), 60+ (30%)
- **Length of follow-up**: <10 years (43%) years
- **Former drinker bias**: 75%
- **Occasional drinker bias**: 57%
- **Neither bias**: 15%
- Quantity and Frequency of alcohol use for at least 7 days: 74%
Definitions of drinkers

- **Life-term abstainers**: (< 2 drinks in life)
- **Former drinkers**: a current abstainer who drank previously
- **Occasional**: < 1 drink per week
- **Low**: up to 24g or 2 drinks per day
- **Medium**: 25-44g or 2-4 drinks per day
- **High**: 44-64g or 4-6 drinks per day
- **Higher**: 65+g or 6+ drinks per day
1. Meta Analyses of all 87 Studies

<table>
<thead>
<tr>
<th>Model:</th>
<th>Former</th>
<th>Occ’l</th>
<th>Low</th>
<th>Med</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.22***</td>
<td>0.84**</td>
<td>0.86***</td>
<td>0.95*</td>
<td>1.29***</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.38***</td>
<td>0.95</td>
<td>0.97</td>
<td>1.07</td>
<td>1.44***</td>
</tr>
</tbody>
</table>

* p<0.05; *** p<0.0001

Multi-level regression models controlling for between study variation and precision of estimates. Adjusted models also controlled for gender, age, ethnicity, drinking measure, abstainer biases and whether controls used for health, smoking and diet.
DO “MODERATE” DRINKERS LIVE LONGER?

On the surface, they show that moderate alcohol consumption reduces your risk of dying earlier.
When we adjusted the studies for these factors, we found the protective effect of light drinking disappeared.

- **Increased Risk**
  - Former Drinkers
  - Medium Volume Drinkers (3-4 drinks per day)
  - High Volume Drinkers (5-6 drinks per day)

- **No Risk**
  - Abstainers
  - Occasional Drinkers (<1 drink per week)
  - Low Volume Drinkers (1-2 drinks per day)

Only 13 of the 87 studies avoided “abstainer bias”.

**WE ALSO FOUND...**

Only 6 of the 87 studies were considered high quality.
Figure 2. All-cause mortality relative risk estimates for low volume alcohol consumers versus 'lifetime abstainers' with and without influential covariates (N=81 studies, 229 risk estimates)

Adjustment level

- Fully-adjusted
- Outliers removed
- Abstainer biases removed
- Caucasian or not removed
- Smoking status removed
- All covariates removed

Relative risk (95% CI)

- 0.97 (0.88 - 1.07)
- 0.97 (0.89 - 1.05)
- 0.96 (0.87 - 1.06)
- 0.95 (0.88 - 1.03)
- 0.91 (0.84 - 0.97)
- 0.86 (0.83 - 0.90)
2. Higher Quality Studies

a) No abstainer biases  
b) adequate drinking measures  
c) smoking status controlled  
d) <60 years at intake  
e) 55+ at follow up

Multi-level regression models with adjustment only for sampling variability and between study variation.

<table>
<thead>
<tr>
<th>Model: +/- 1 influential study</th>
<th>RRs for different categories of drinker</th>
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<tbody>
<tr>
<td></td>
<td>Former</td>
</tr>
<tr>
<td>N=7</td>
<td>1.14</td>
</tr>
<tr>
<td>N=6</td>
<td>1.31**</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01; *** p<0.0001
1. With adjustment for abstainer biases and other study characteristics in studies of all cause mortality, evidence for health protection seems to vanish

2. This only suggests there may be no net health benefits of low volume consumption

3. Similar meta analyses have been conducted for CHD and diabetes outcomes – some limited protective effects
New meta-analysis of alcohol use and prostate cancer

**Meta Analyses of all 27 Studies**

<table>
<thead>
<tr>
<th></th>
<th>Former</th>
<th>Occasional</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RRs</strong></td>
<td>1.10</td>
<td>0.95</td>
<td>1.08***</td>
<td>1.07*</td>
<td>1.14***</td>
<td>1.18***</td>
</tr>
</tbody>
</table>

* * p<0.01; *** p<0.0001

Multi-level regression models controlling for between study variation, precision of estimates, age, ethnicity, abstainer biases and whether controls used for smoking.

**Significant dose-response relationship**
Meta Analyses of studies by type of abstainer bias

<table>
<thead>
<tr>
<th>RRs for Low Volume drinkers by extent of bias</th>
</tr>
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<tbody>
<tr>
<td>No bias</td>
</tr>
<tr>
<td>N=6</td>
</tr>
<tr>
<td>1.23*</td>
</tr>
</tbody>
</table>

* p<0.05

Multi-level regression models controlling for between study variation, precision of estimates, country and whether controls used for smoking.
1. First meta analysis to confirm a significant dose response relationship for alcohol and prostate

2. Evidence for abstainer bias in this literature – only 6 studies used lifetime abstainers as reference

3. When abstainer biases minimised, increased risk from low volume intake (up to 2 drinks/day) increased from 8% to 22%

Interpretation
But note....

1. Not enough to separate former drinkers from abstainers – they should be re-allocated to drinking groups to avoid bias

2. Not enough to separate occasional drinkers from abstainers – they need to be reported separately from low volume drinkers as well to avoid bias

3. No Study of all-cause mortality or prostate cancer or CHD has met all these conditions
Conclusions

1. Abstainer biases contribute to over-estimating benefits and under-estimating risks of moderate drinking

2. We need a new generation of unbiased prospective studies to get more accurate risk estimates

3. Corrected studies will likely find higher mortality risks for all categories of drinker – and few if any benefits