

# Selection bias in estimates of alcohol's contribution to cancer, heart disease and all-cause mortality – and how to fix it

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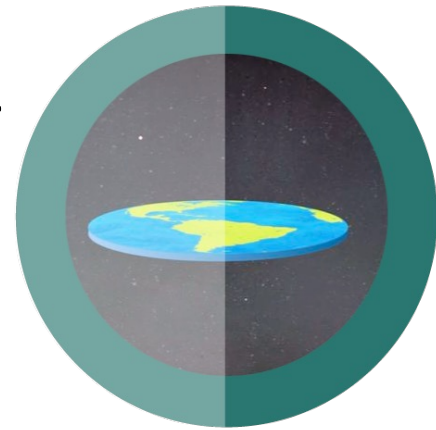
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# There used to be a consensus that health benefits from alcohol were real

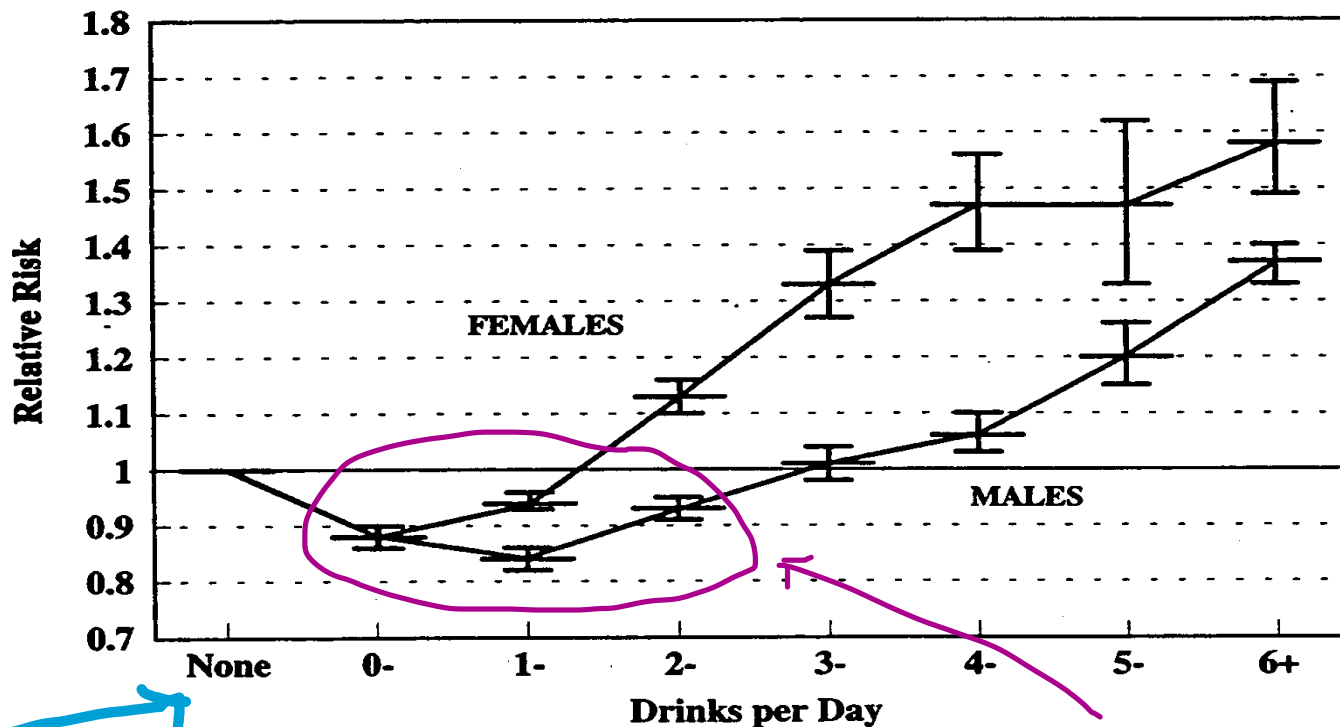
“The evidence amassed . . . (is) . . . sufficient to bracket sceptics of alcohol’s protective effects with doubters of manned lunar landings and members of the Flat Earth Society”



- Editorial, *Medical Journal of Australia*, p.116, vol 117, 2000

# The J-shape curve

**Figure 3-1: Relationship of All-cause mortality to Alcohol Intake Based on Pooled Results of 16 Cohort Studies**



**“Abstainers”**

Source: English et al (1995)

**“Lower volume drinkers”**

# Estimates of IHD protection matter

- GBD Collaborators (2022) estimated reduced risk of ischaemic heart disease (IHD) up to **9 drinks per day** and global deaths from alcohol at **1.8 million** in 2020
- Griswold et al (2020) estimated reduced IHD risk at **~5 drinks per day** and **2.8 million** global deaths in 2016
- Zhao et al (2017) estimated non-significantly reduced IHD death risk at up to **one drink per day** – this might equate to **~4 million** deaths per year??



# Our Systematic Reviews and Meta Analyses

Fillmore, Stockwell et al (2006) *AddResTh* – IHD+All-cause

Zeisser, Stockwell et al (2014) *ACER*, Breast cancer

Stockwell, Zhao et al (2016) *JSAD*, All-cause mortality\*\*

Zhao, Stockwell et al (2016) *BMC Cancer*, Prostate cancer

Zhao, Stockwell et al (2017) *JSAD*, IHD

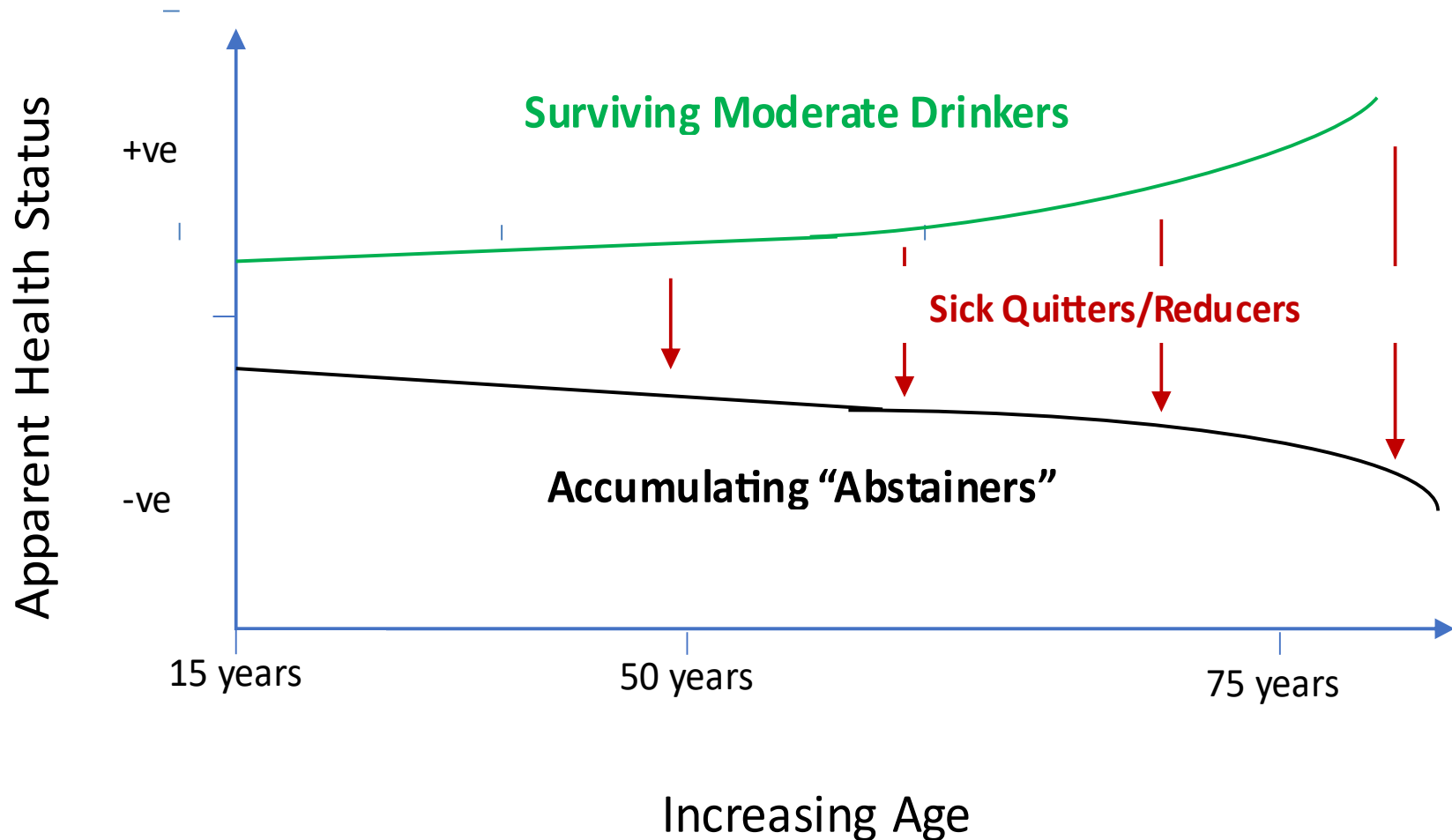
Zhao, Stockwell et al (2023) *JAMA*, All-cause mortality

Stockwell, Zhao et al (2024) *JSAD*, All-cause mortality

All applied quality criteria to reduce **lifetime selection biases** (Naimi et al, 2017) e.g. “sick quitter” effects

# Non-drinkers are biased towards ill health

**Lifetime Selection Bias:** As people become frail/unwell with advancing age they tend to stop drinking alcohol – or to cut down (Naimi et al, 2017)



# Selection Bias: More than “Sick Quitters”

1. **Occasional drinkers** bias reference groups: people cut down as well as stop drinking when unwell
2. **Light/moderate former drinkers** also quit or cut down drinking with ill-health
3. **Lifetime abstainers start out less healthy** than drinking peers as young adults
4. **Biases accumulate with age** – abstainers in older cohorts are increasingly biased towards ill-health
5. **Healthy survivor biases** – removing former drinkers does not deal with this, need to reassign as drinkers

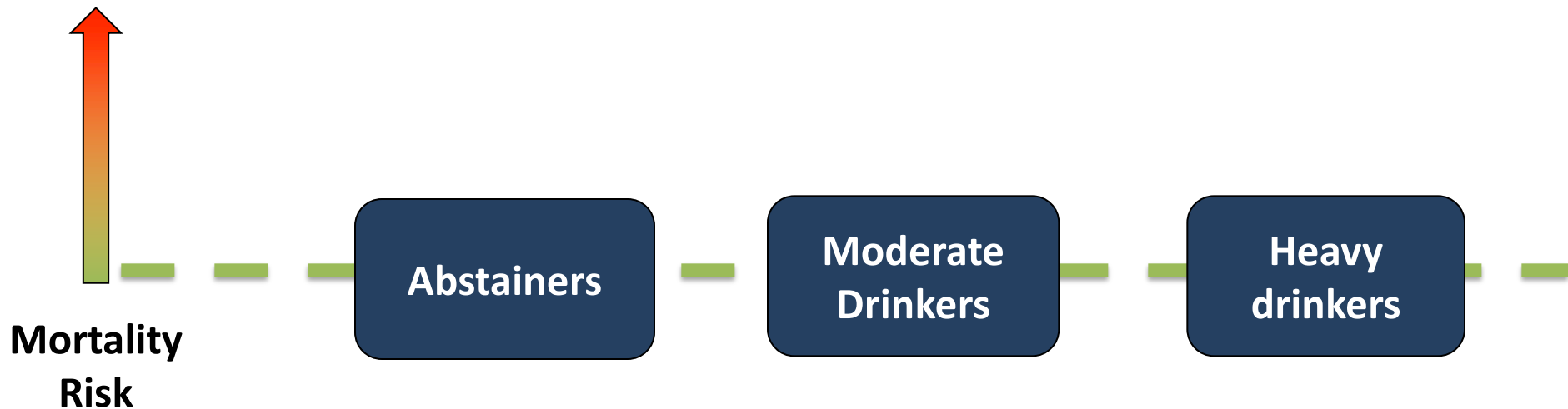
# Former light drinkers also less healthy

**Table 3** Hazard rate ratios of cause specific deaths across categories of lifetime pattern of alcohol use among **men** participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study Bergmann et al, 2013, Int J Epi

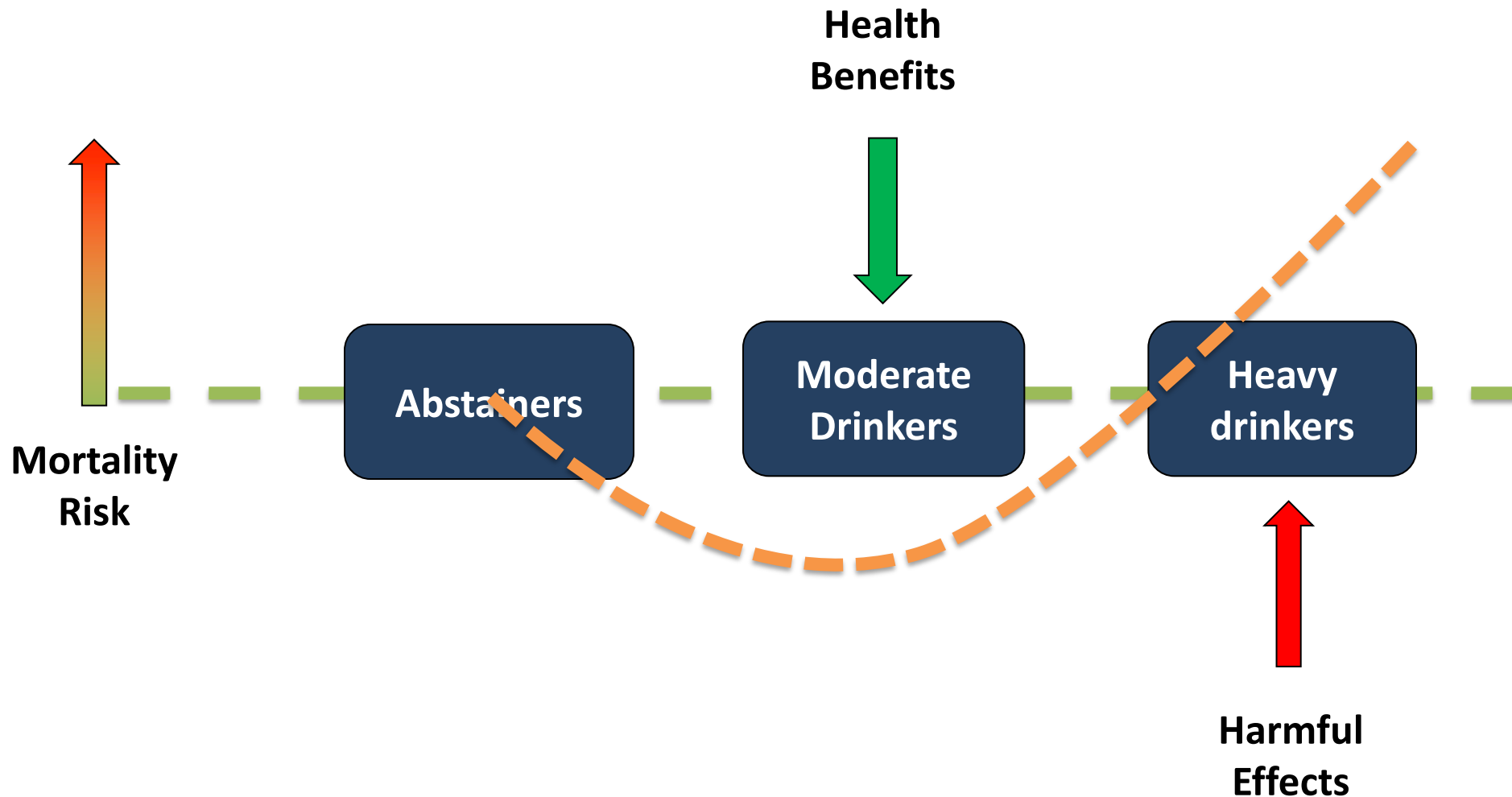
| Exclusive categories of pattern of alcohol use |                    | Former <sup>b</sup>                   |                           | Lifetime <sup>c</sup> |                                |                                |                                 |                    |                          |  |
|------------------------------------------------|--------------------|---------------------------------------|---------------------------|-----------------------|--------------------------------|--------------------------------|---------------------------------|--------------------|--------------------------|--|
| Cause of death                                 | Never <sup>a</sup> | Former light to moderate <sup>d</sup> | Former heavy <sup>e</sup> | Light <sup>f</sup>    | Below rec. limits <sup>g</sup> | Light to moderate <sup>d</sup> | Occasionally heavy <sup>e</sup> | Heavy <sup>e</sup> | P for trend <sup>h</sup> |  |
| Person-years                                   | 21 087             | 41 918                                | 16 108                    | 39 168                | 490 252                        | 477 358                        | 212 821                         | 24 645             |                          |  |
| CHD <sup>k</sup>                               |                    |                                       |                           |                       |                                |                                |                                 |                    |                          |  |
| Deaths N = 1755                                | 43                 | 103                                   | 48                        | 92                    | 665                            | 502                            | 278                             | 24                 |                          |  |
| HR <sup>i</sup>                                | 1.39               | 1.45                                  | 2.49                      | REF                   | 1.01                           | 1.05                           | 1.34                            | 1.26               | 0.001                    |  |
| (95% CI)                                       | (0.95; 2.02)       | (1.06; 1.98)                          | (1.71; 3.62)              |                       | (0.79; 1.28)                   | (0.82; 1.35)                   | (1.03; 1.75)                    | (0.78; 2.04)       |                          |  |



# Core Assumption: Drinkers and Abstainers start out with same premature mortality risks

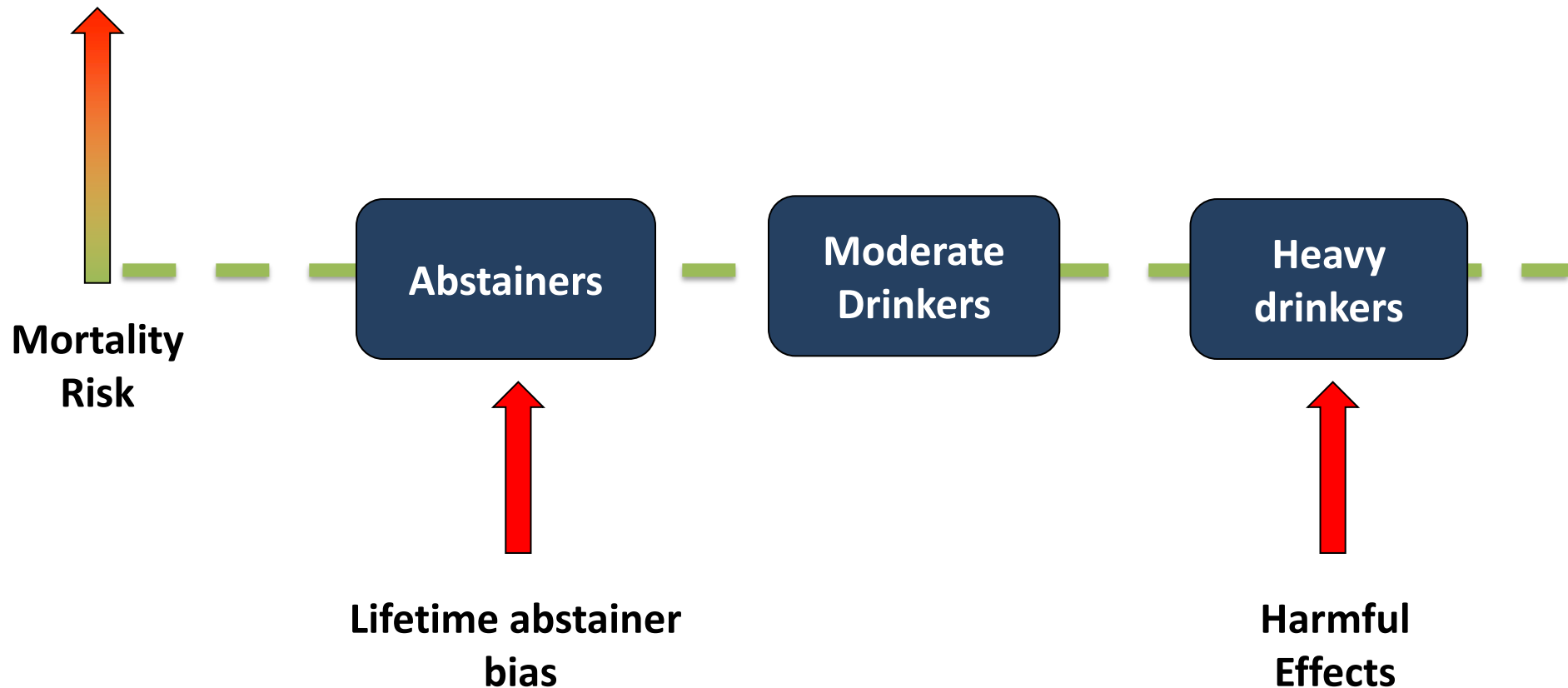


# Assumed Physiological Effects Behind J-Shape Curve

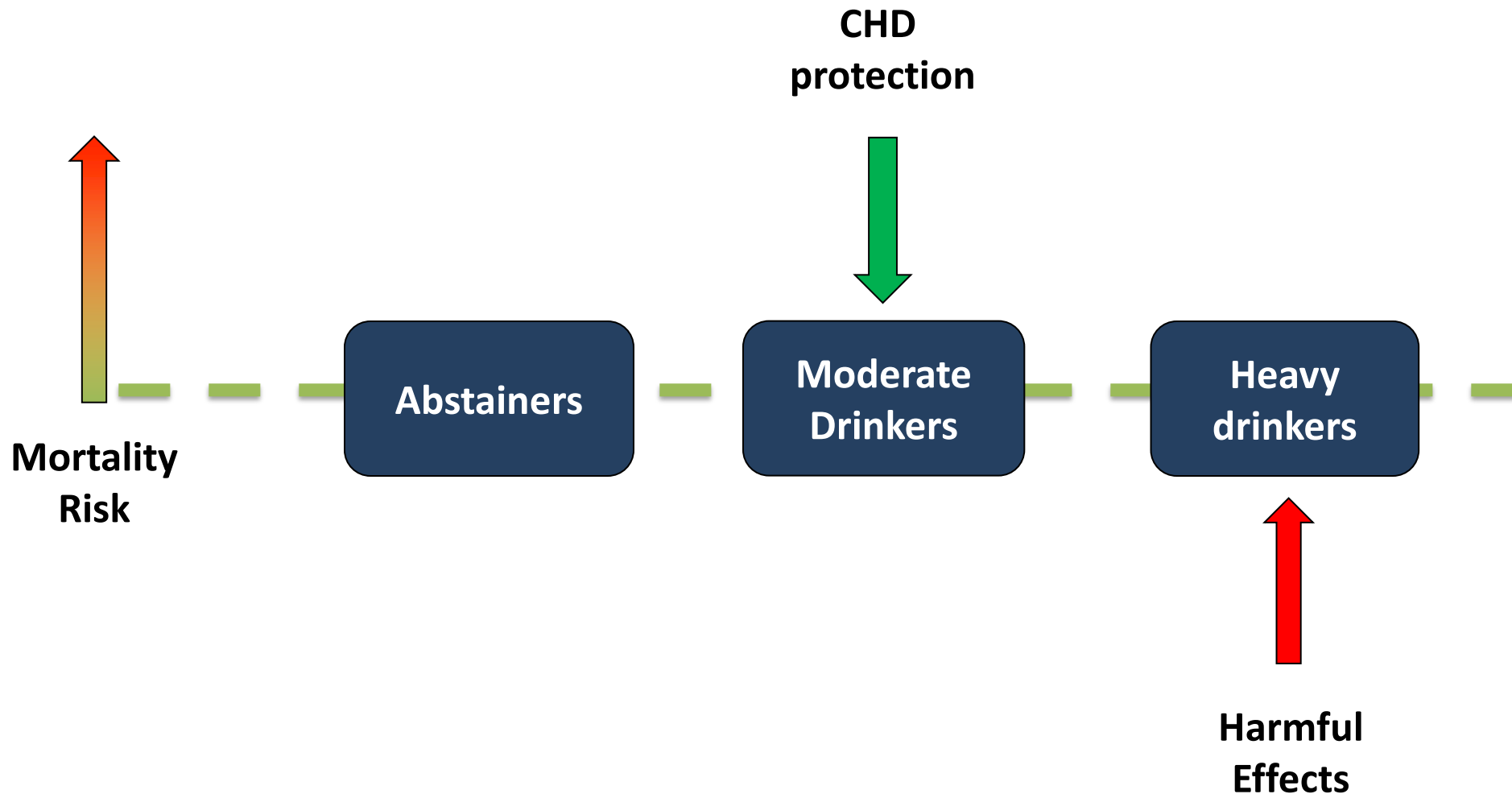


Ng Fat et al (2015):

Young adult abstainers have lower incomes and more disabilities than drinking peers



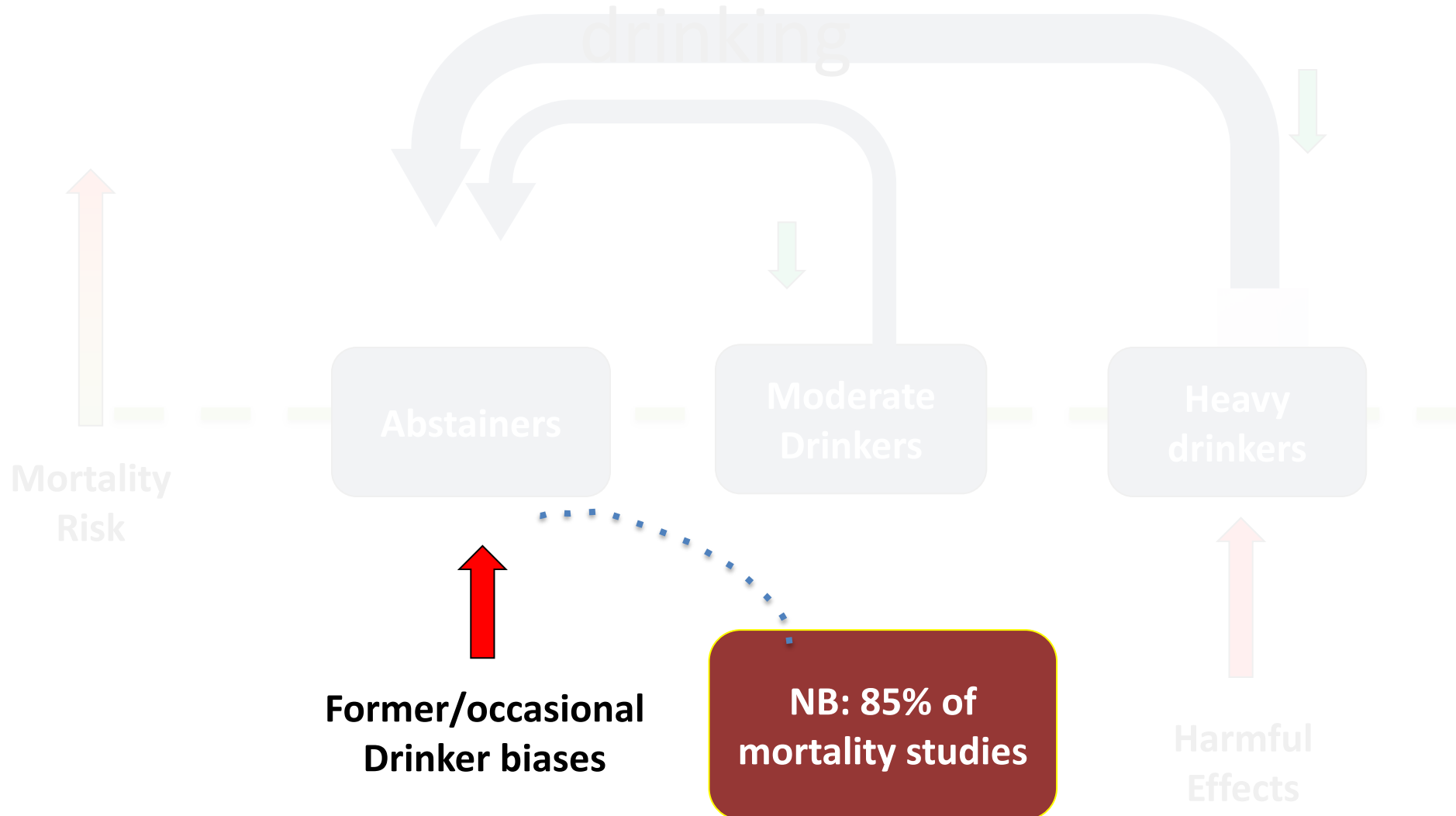
Moderate drinkers have less CHD risk than abstainers on multiple risk measures unrelated to alcohol (e.g. Naimi et al, 2007)



Fillmore et al (2006):

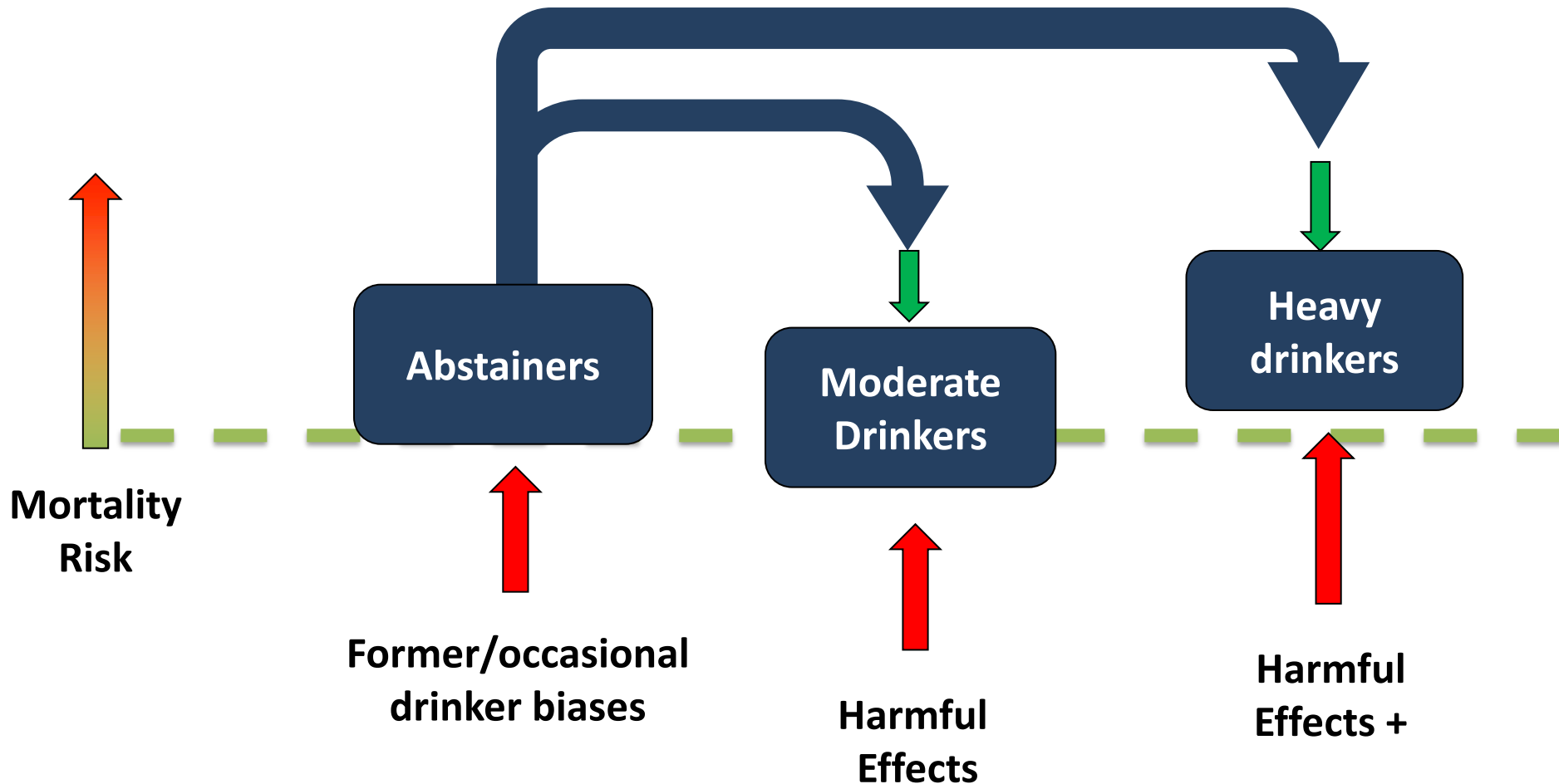
As people become unwell they are more likely stop or cut down on their

drinking



Laing & Chikritzhs (2013):

To reduce bias need to place less healthy former drinkers back in with the drinkers





## OR Use Mean Lifetime Drinking Measures

Using multiple measures of drinking over time and/or using retrospective measures of lifetime drinking can also reduce lifetime selection biases

Ortola CHD cohort study (2018):  
Results from Spanish cohort aged  $\geq 60$  years  
comparing baseline and lifetime alcohol measures

|                 | RRs for different categories of drinker |       |      |      |       |
|-----------------|-----------------------------------------|-------|------|------|-------|
| Alcohol Measure | Former                                  | Occ'l | Low  | Med  | High  |
| Baseline        | 1.68*                                   | 0.80  | 0.90 | 1.06 | 1.54  |
| Lifetime        | n/a                                     | 1.23  | 1.20 | 1.55 | 2.15* |

\* $p < 0.05$ ;

Both models adjusted for sex, age, socioeconomic & smoking status ,  
other CHD risk factors,

Source: Ortola et al (2018) *Addiction*

## Other Findings Supporting Scepticism

- **Fekjaer** (*Add.*, 2013) Identified multiple studies finding implausible health benefits of moderate drinking e.g. deafness, hip fractures, common cold, liver cirrhosis, infant health
- **Stamatakis et al** (*Epid.*, 2021) Health benefits vanish when a sample representative of general population used
- **Biddinger et al** (*JAMA*, 2022): Mendelian Randomisation (close to an RCT) studies find less drinking means lower not higher CHD risk

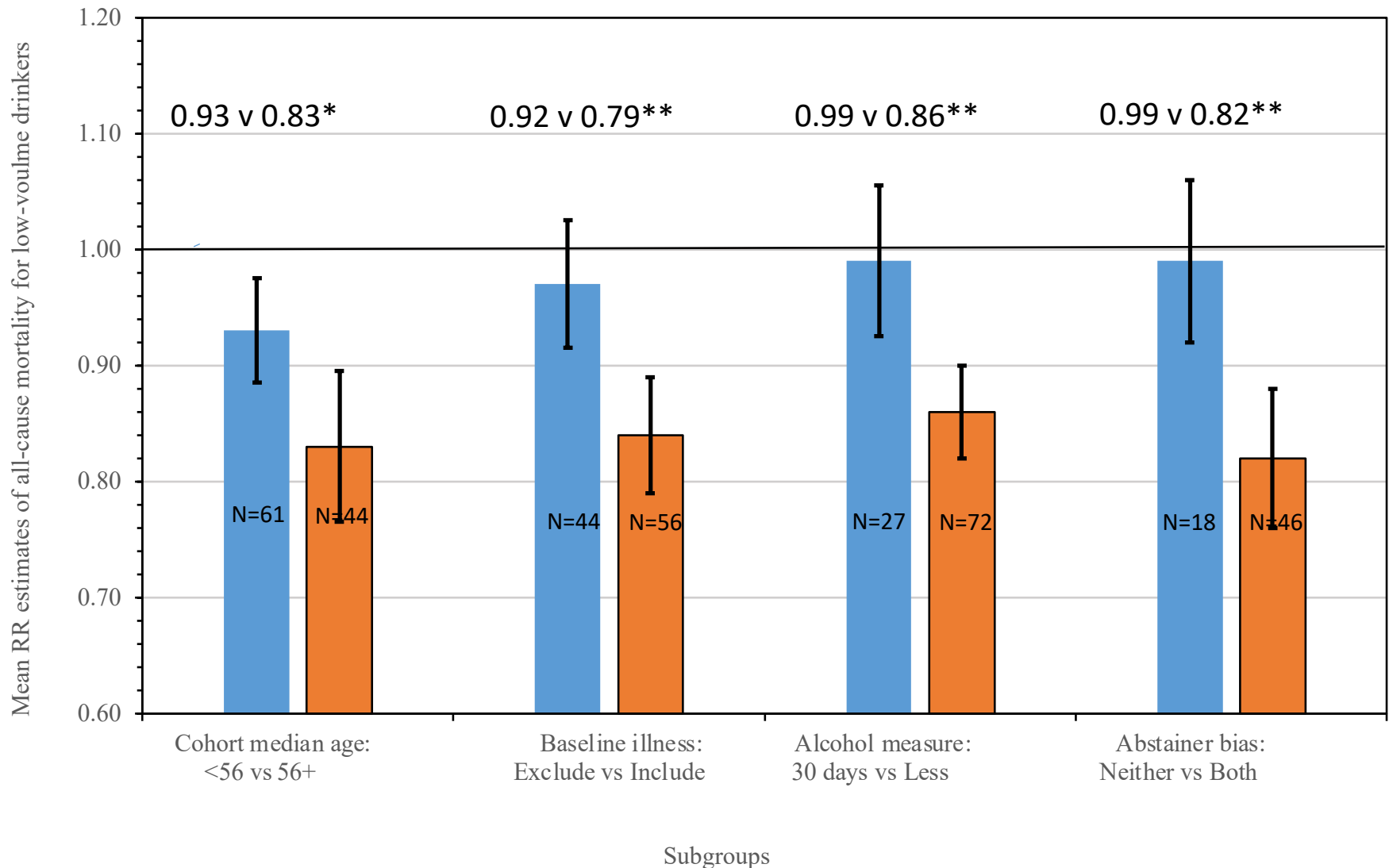
# Our most recent all-cause mortality study

1. Exploratory and pre-registered analyses of 107 cohort studies with RR estimates for **“lower volume” drinkers versus abstainers**
2. *Exploratory:* Compare mean RR values in sub-groups of studies contrasted on a range of potentially relevant quality criteria
3. *Pre-registered:* Conduct meta-analyses to compare higher versus lower quality study sub-groups in relation to likely degree of lifetime selection bias

Stockwell, Zhao et al (2024) *Journal of Studies on Alcohol and Drugs*

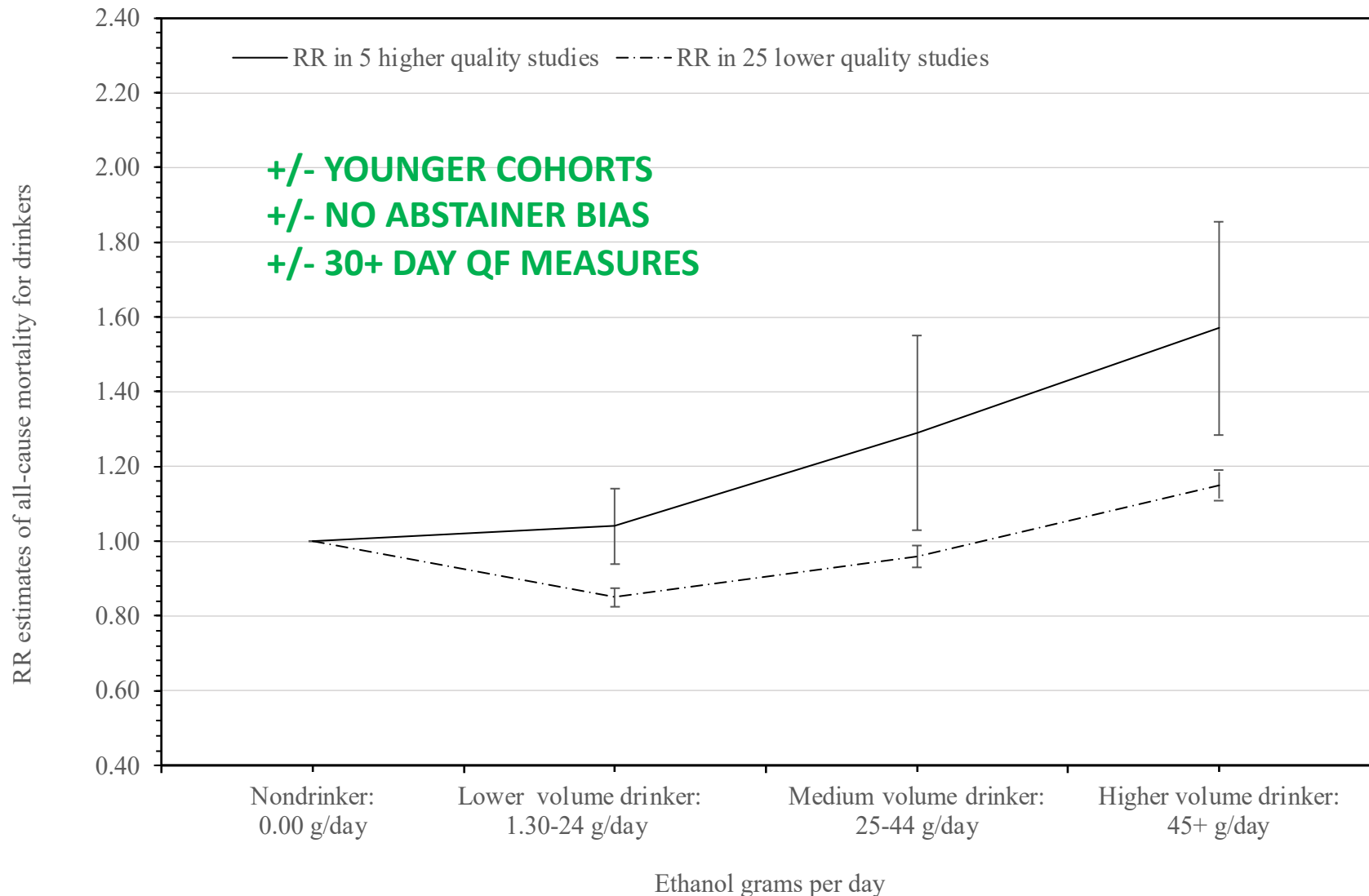
# Bivariate analyses of mean RRs: as predicted

**Figure 1.** Mean RR estimates of all-cause mortality for low-volme drinkers versus abstainers between different study subgroups, 1980-2022



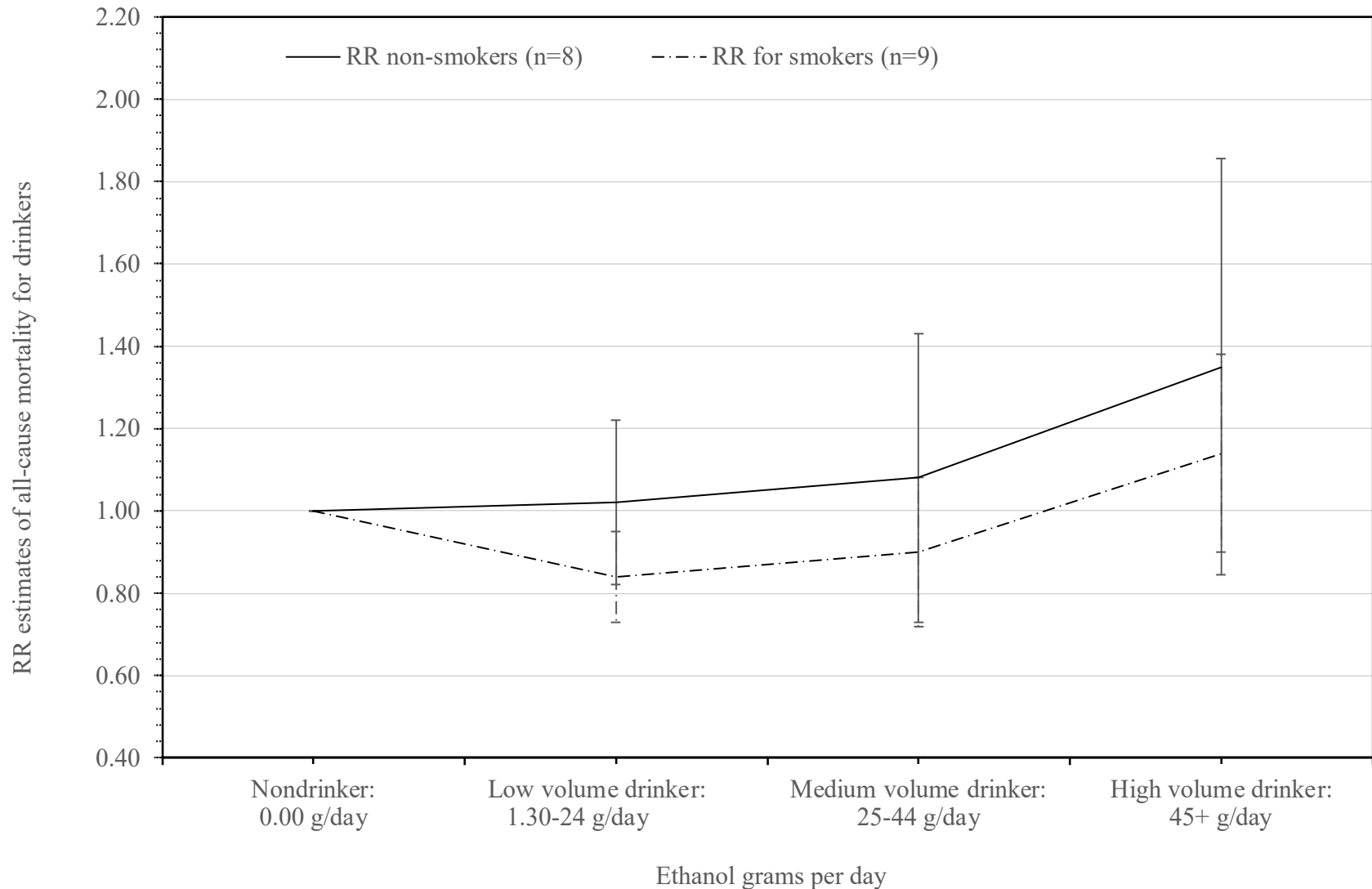
# Mortality risk for high v low quality studies

**Figure 1.** Weighted RR adjusted for between-study variation of all-cause mortality for drinkers versus abstainers in higher and lower quality studies



# Stratified analyses: Non-smokers v Smokers

**Figure 2.** Unadjusted RR of all-cause mortality for drinkers (versus nondrinker) by smoking status (non-smokers and smokers), 1980-2022



# Conclusions

- Results support the Lifetime Selection Bias hypothesis re health benefits of lower volume alcohol use: J-shape curve vanishes in higher quality studies with less bias
- Conversely, lower quality studies find markedly reduced mortality risk for lower volume drinkers
- These issues affect estimates of alcohol's contribution to other diseases e.g. cancers
- Need more higher quality studies to confirm this pattern of results



# Recommendations

Ensure main estimates of alcohol's contribution to mortality *minimise lifetime selection bias*, specifically:

1. Use study estimates with *strictly defined* lifetime abstainers (or lifetime occasional drinkers)
2. Use cohorts with younger ages at baseline (e.g. <50) with follow up to ages when IHD possible (e.g. >60)
3. Use lifetime drinking measures OR assess over at least 30 days AND/OR reassign former drinkers to current drinkers