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

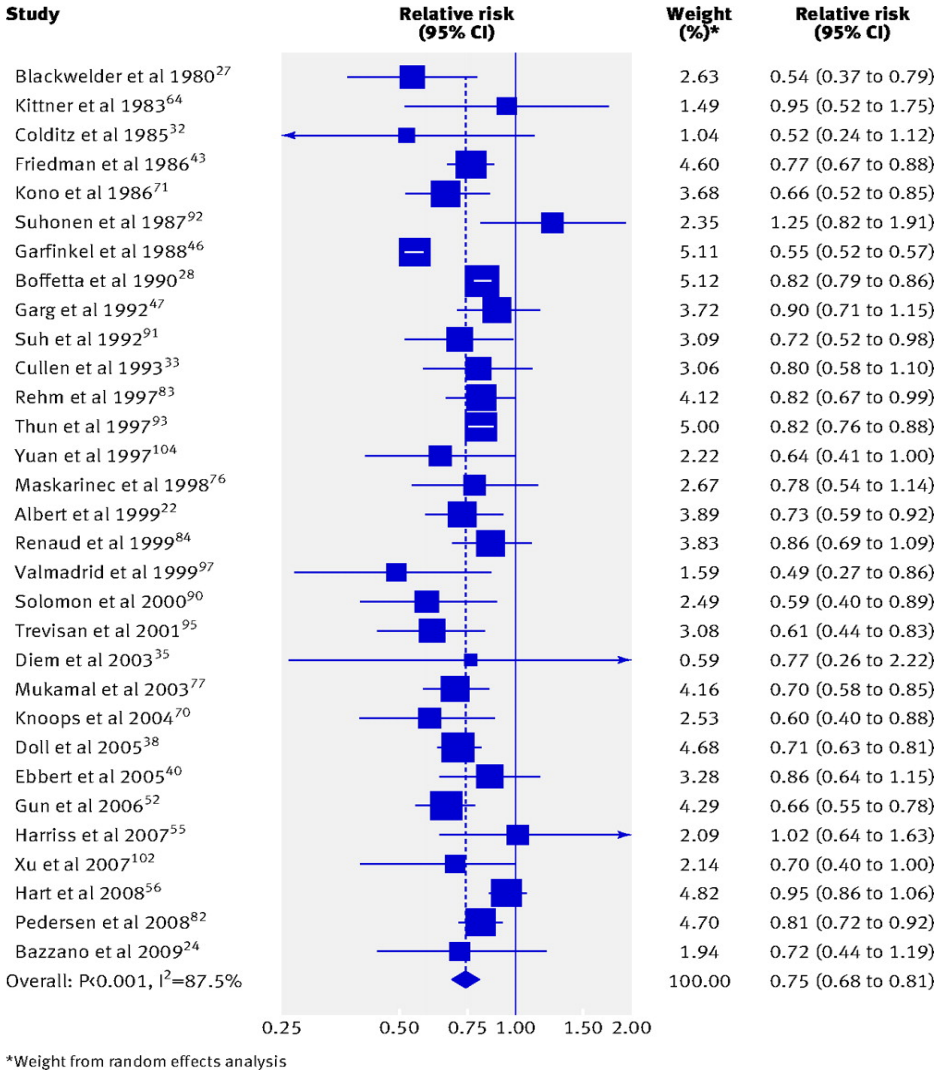
C. Mendelian Randomization to ↓Bias

D. Caveats of Mendelian Randomization

E. Concluding Remarks

A. Current Hypothesis from Observational Studies

Alcohol Intake & CHD Mortality

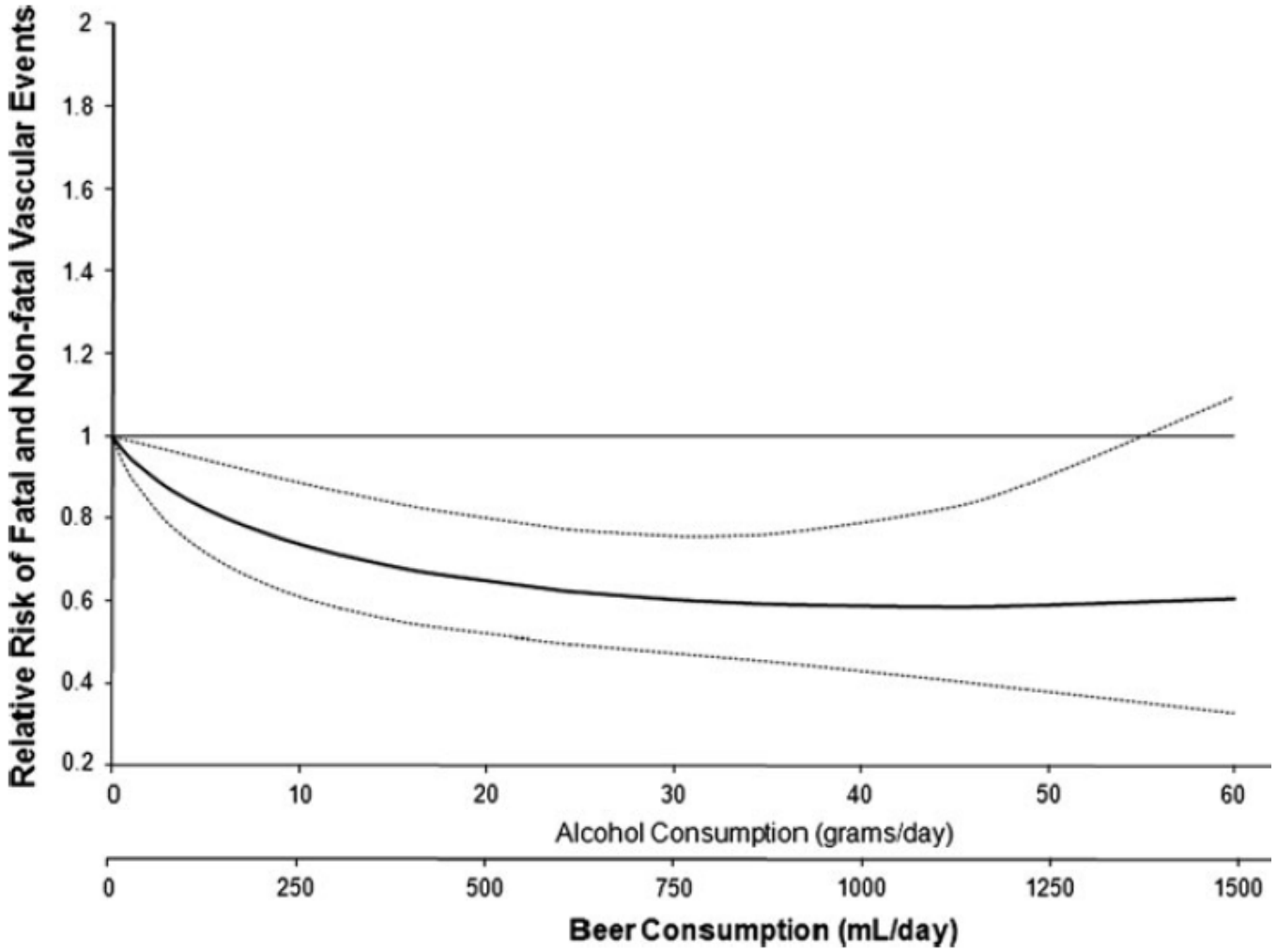


0.75 (0.68-0.81)

Beer and Health

Ronksley P E et al. BMJ 2011;342:bmj.d67

Beer and Fatal/Non-Fatal CVD



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Costanzo Eur J Epidemiol 2011;26:833-50

Alcohol and PAD

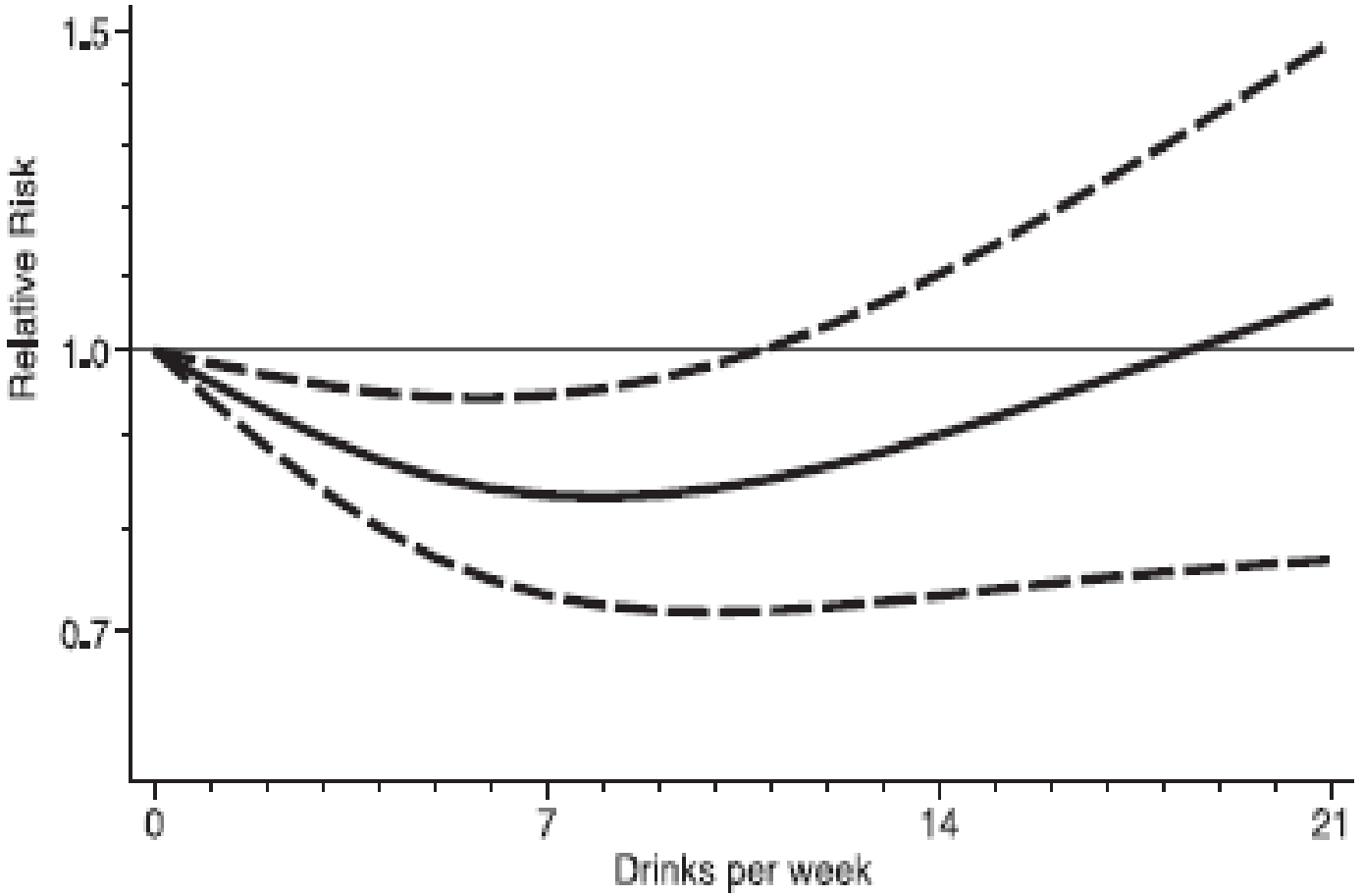
	Wine	Beer	Spirits
Drinks/wk			
0	1.0 (ref)	1.0 (ref)	1.0 (ref)
1-7	0.81 (0.64-1.03)	0.69 (0.52-0.91)	0.88 (0.69-1.10)
≥8	0.64 (0.38-1.07)	0.60 (0.43-0.83)	0.89 (0.68-1.18)
P for trend	0.013	0.0005	0.30

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

Djousse et al. Circulation 2000;102:3092-97

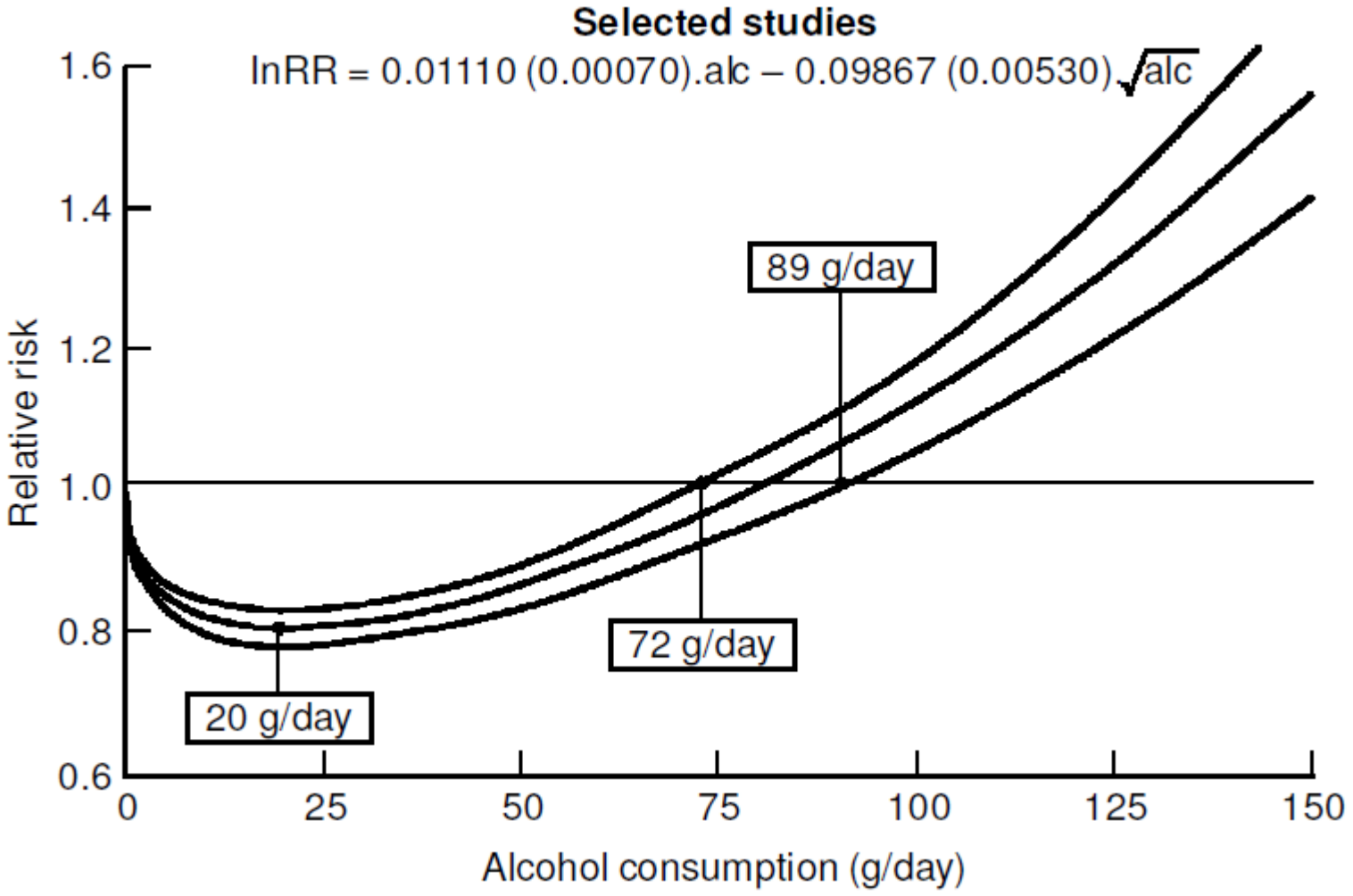
Alcohol Intake & Heart Failure

Meta-Analysis



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

Alcohol and Mortality



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Corrao et al. Addiction 2000;95:1505-23

Not All Findings Showed Benefits

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[a] with and without one influential study (Friesema et al., 2007)

	Model 1: Including Friesema et al.				Model 2: Excluding Friesema et al.			
Drinking categories[b]	n^b	RR[c]	[95% CI]	p	n^b	RR[c]	[95% CI]	p
Former drinker	19	1.14	[0.77, 1.69]	.4950	17	**1.31**	[1.11, 1.55]	.0022
Low volume (1.30–<25 g /day)	39	0.89	[0.62, 1.29]	.5279	35	1.04	[0.95, 1.15]	.3557
Medium volume (25–<45 g/day)	11	1.08	[0.72, 1.62]	.7123	9	**1.29**	[1.06, 1.56]	.0106
High volume (45–<65 g/day)	7	0.95	[0.62, 1.46]	.8113	5	1.07	[0.83, 1.36]	.6100
Higher volume (≥65 g/day)	11	**1.58**	[1.05, 2.38]	.0295	11	**1.85**	[1.51, 2.27]	.0001
All drinkers combined	87	1.10	[0.86, 1.41]	.3557	77	1.19	[0.94, 1.49]	.1065

Notes: **Bold** indicates statistical significance. CI = confidence interval. [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; [b]number of risk estimates; [c]estimates adjusted for sampling variability and between-study variation.

Stockwell et al. J Stud Alcohol Drugs 2016;77:185

Alcohol and All-Cause Mortality

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

	Alcohol Consumption Level over 4 y						
				Regular Alcohol Consumption (Drinks/Wk)			
Covariates Adjusted for	Lifetime Nondrinker	Former Drinker Now Abstinent	Occasional Drinker*	<7	7-<14	14-<21	≥21
Age and sex	1.12 (0.92-1.36)	1.53 (1.27-1.84)	1.00	0.80 (0.66-0.97)	1.03 (0.81-1.32)	1.22 (0.87-1.70)	1.76 (1.27-2.43)
Fully adjusted†	1.16 (0.95-1.43)	1.26 (1.05-1.53)	1.00	0.99 (0.82-1.21)	1.21 (0.91-1.61)	1.30 (0.88-1.91)	1.49 (0.97-2.29)

*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.

Goulden R. Am J Med 2016;129:180-6

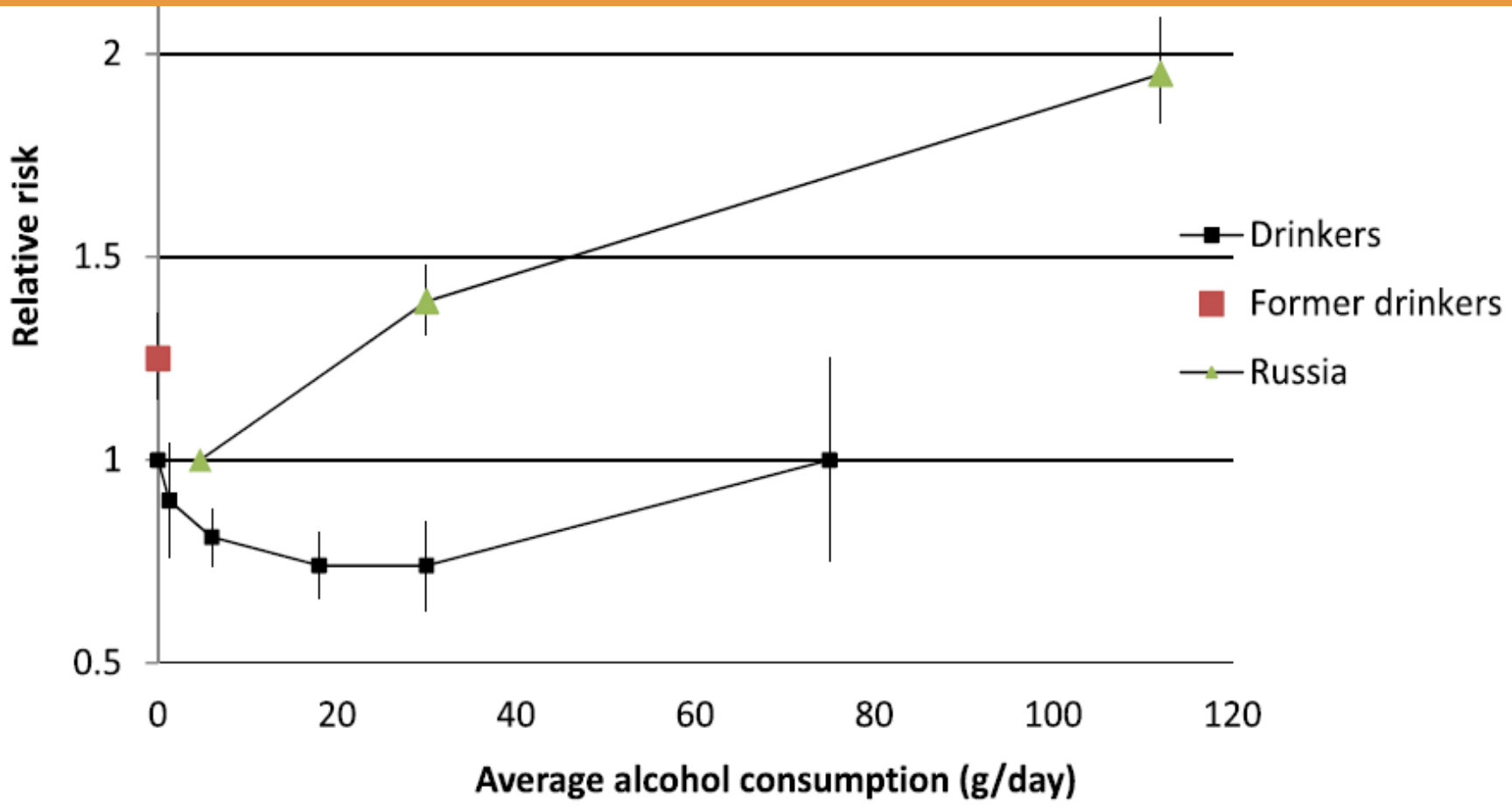
Is the Choice of Outcome Relevant?

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

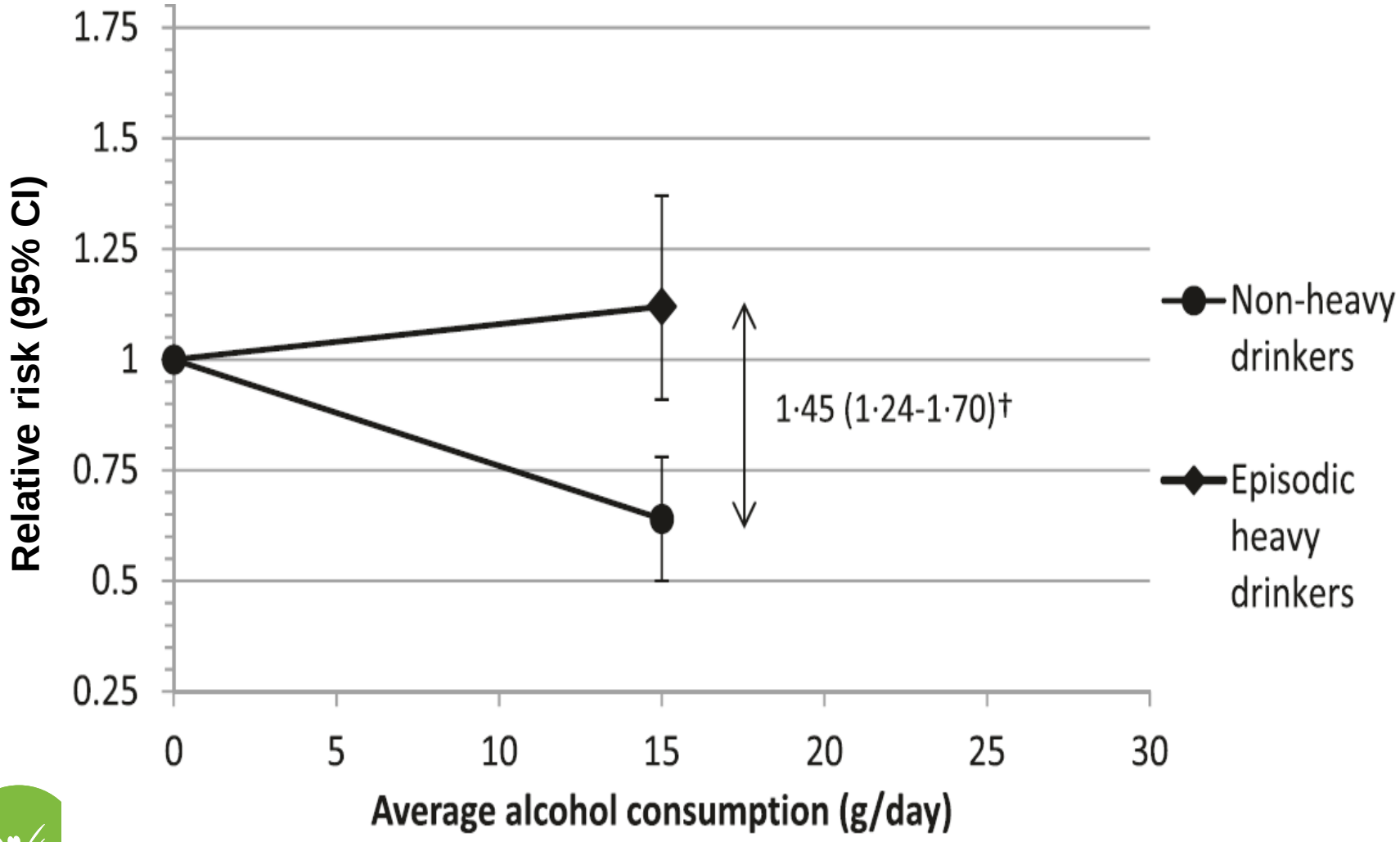
Alcohol & CHD Death with Lifetime Abstainers as Reference



Roerecke and Rehm BMC Medicine 2014;12:182

Drinking Patterns and CHD

Drinkers of <30 g/d vs. Lifetime Abstainers



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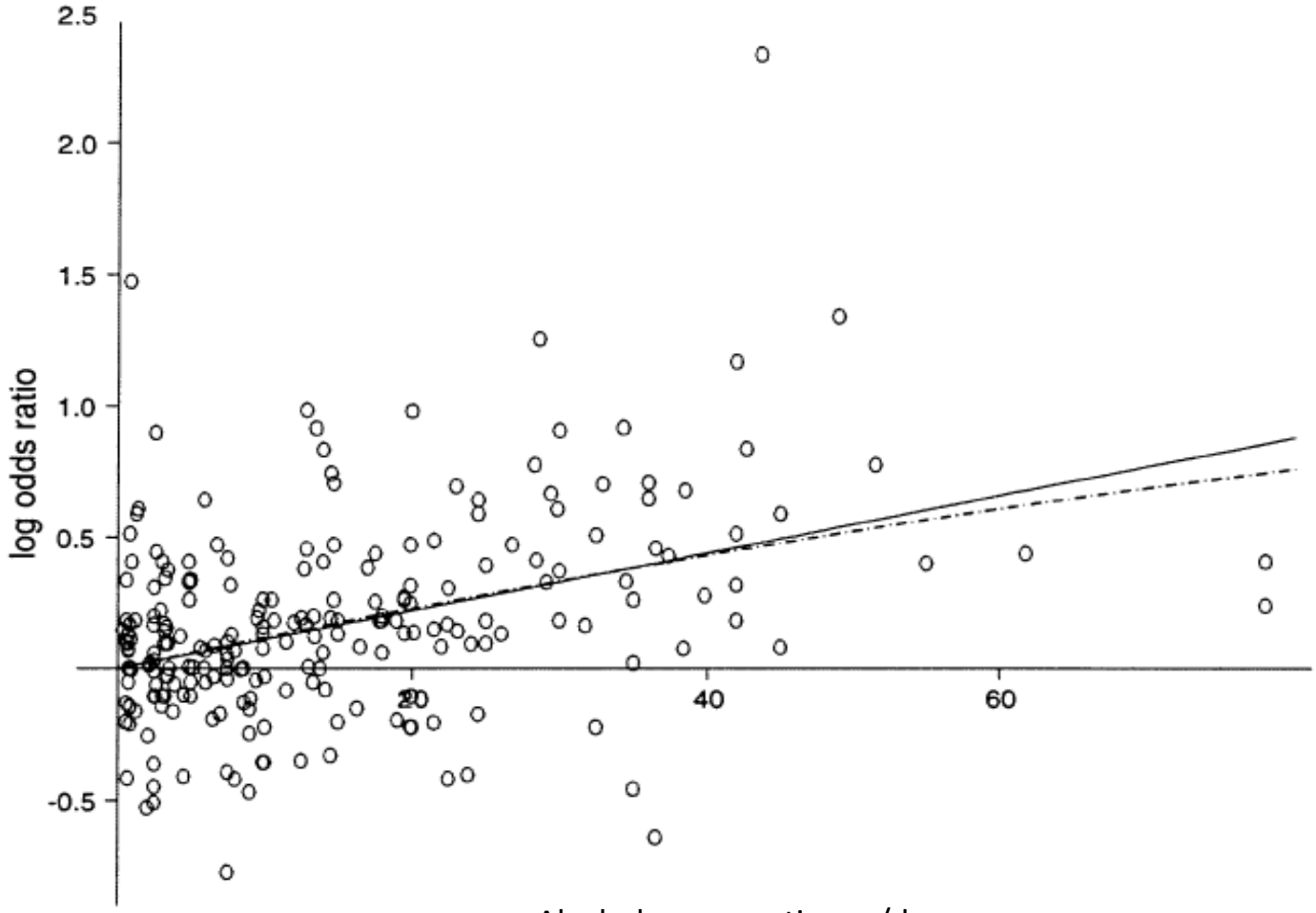
Roerecke and Rehm BMC Medicine 2014;12:182

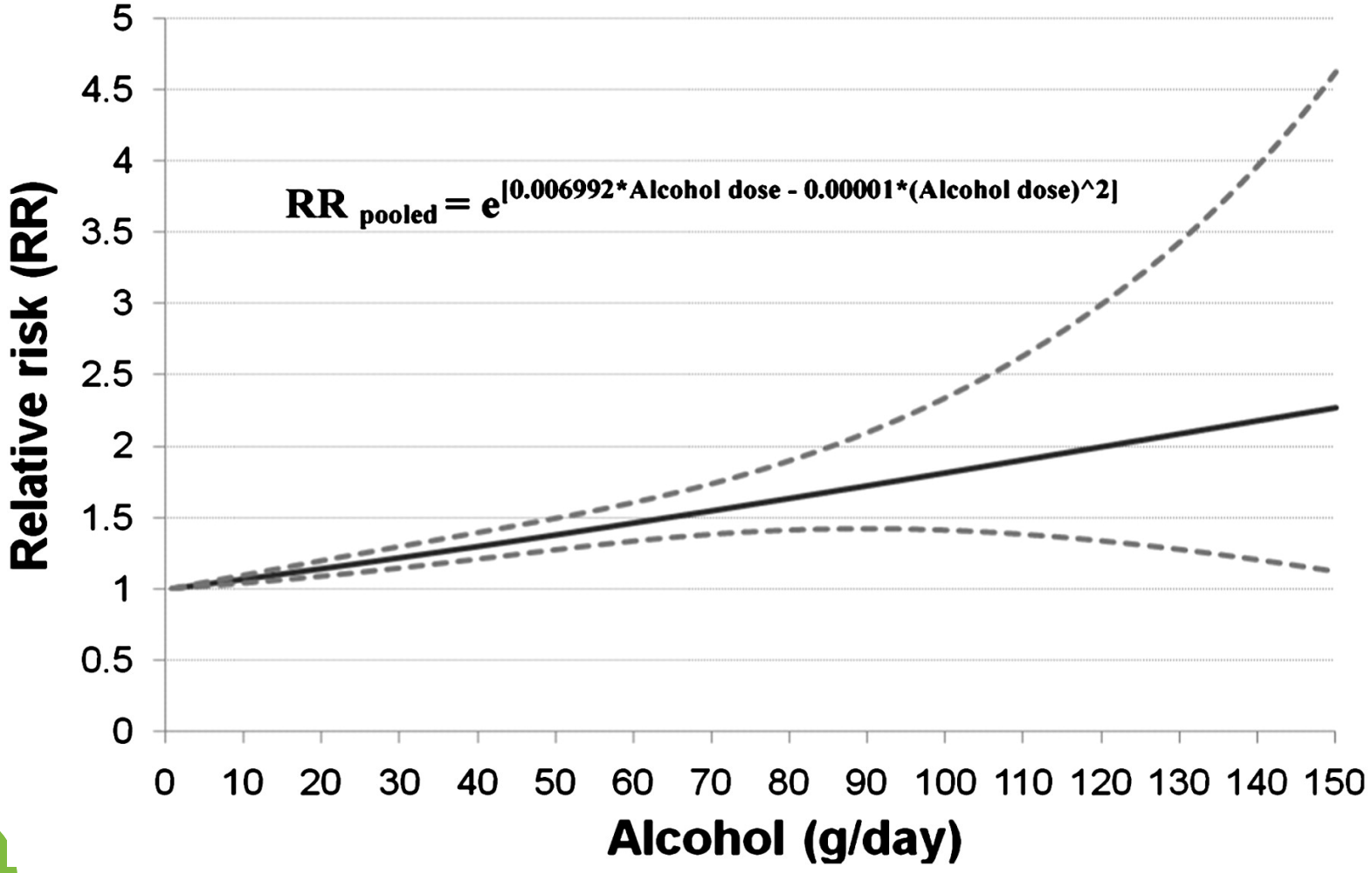
Alcohol & Breast Cancer Risk



Beer and Health

Key J et al. Cancer Causes Control 2006;17:759-70

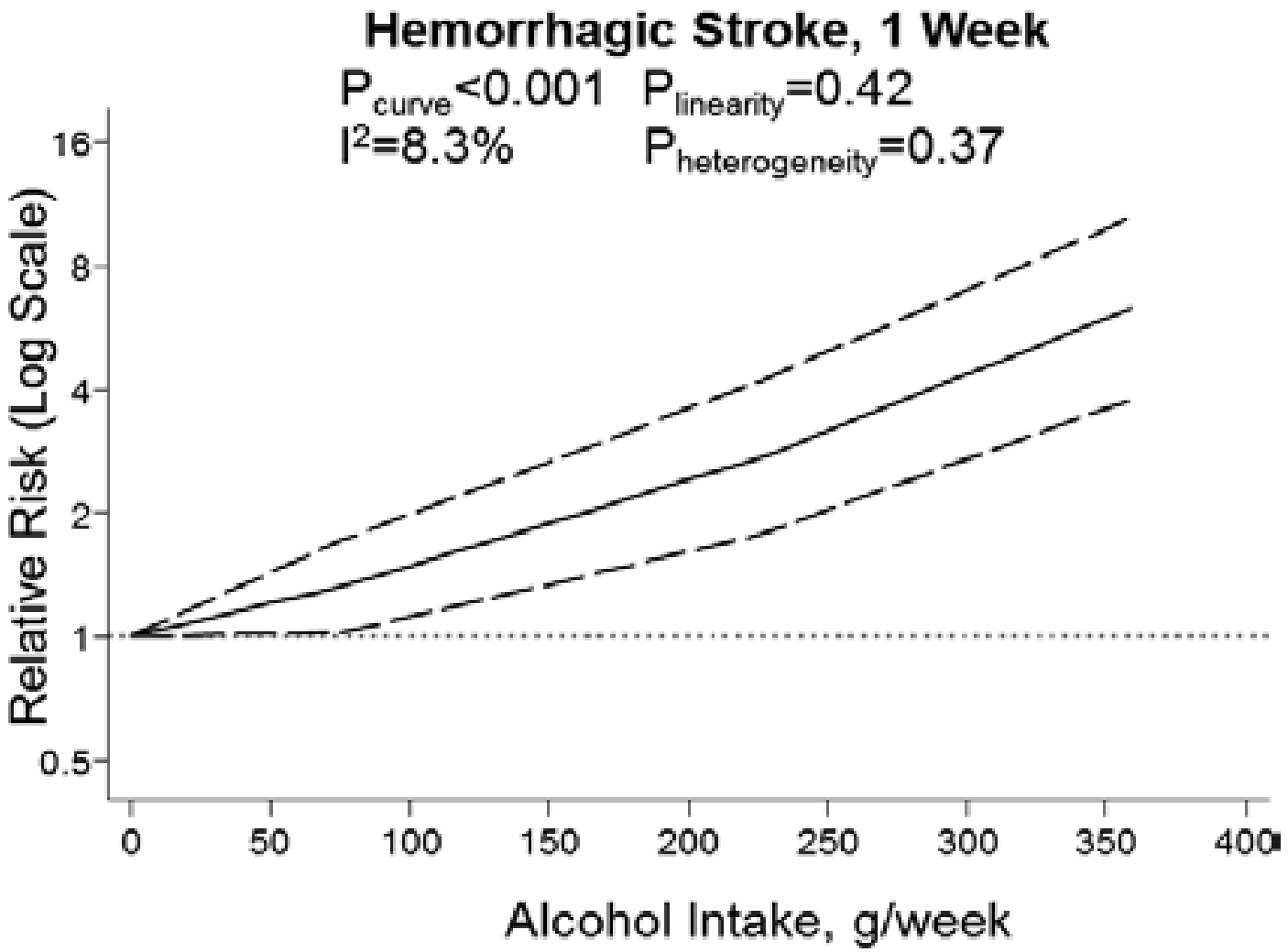
Alcohol and Colorectal Cancer



Beer and Health

Fedirko V et al. Ann Oncol 2011;22:1958-1972

Alcohol and Hemorrhagic Stroke



Beer and Health

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)

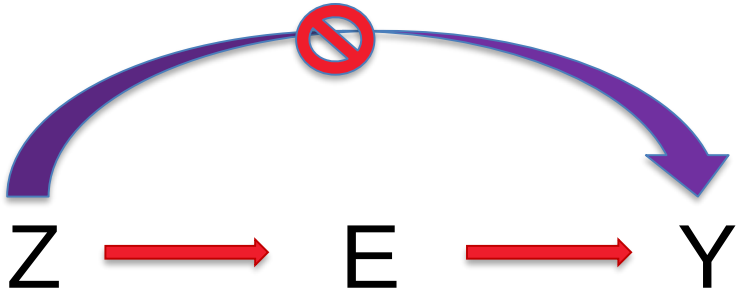
MR and Causal Inference

- 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

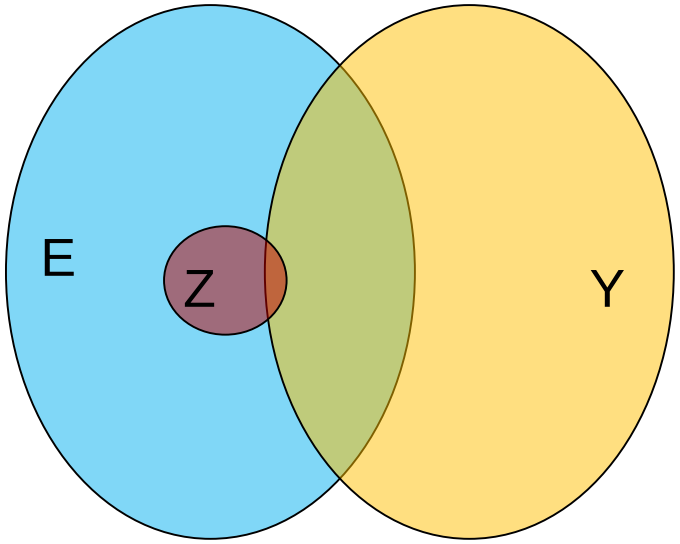
- Failure of exogeneity: IV influences outcome through variables that are different from the exposure
  - ➡ ⬆biases that are hard to quantify as they are unobserved

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

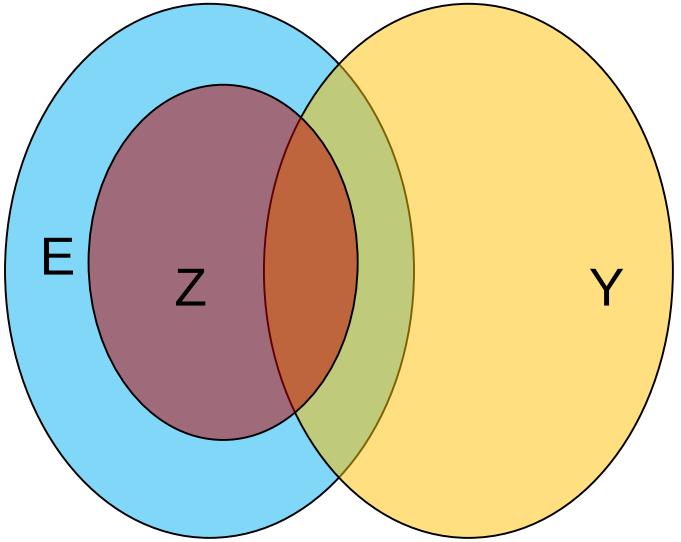
- IV is a large sample procedure (even when assumptions are met, no guarantee to obtain unbiased results in a small sample study)

% of Exposure Variance Explained by IV

Panel A: R^2 <10%



Panel B: R^2 >40%



E= exposure

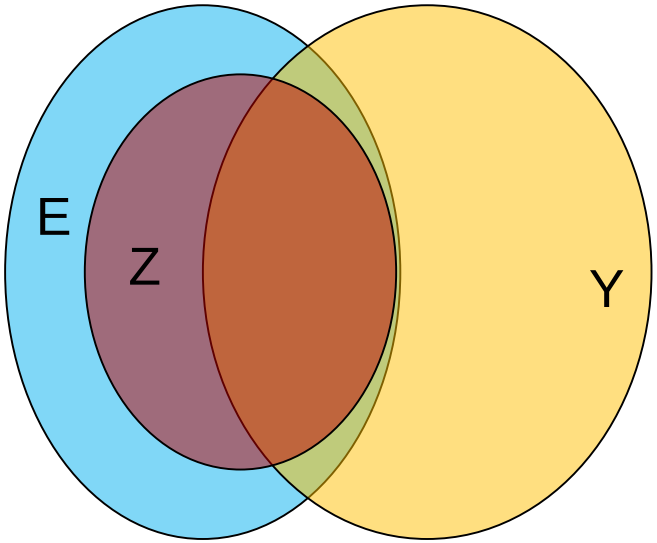
Y=outcome

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

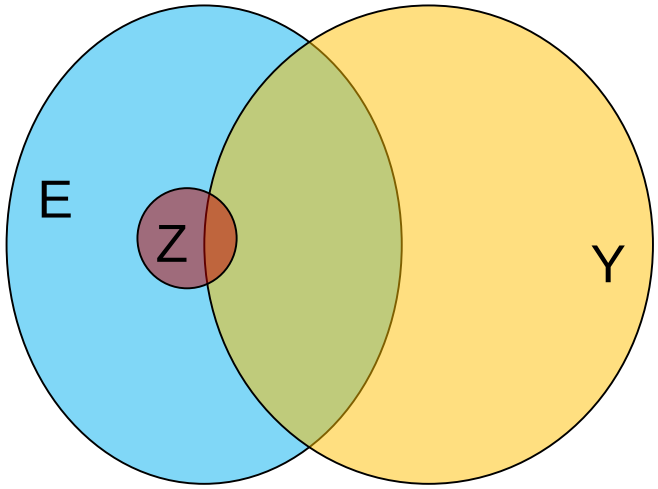
Y=outcome

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

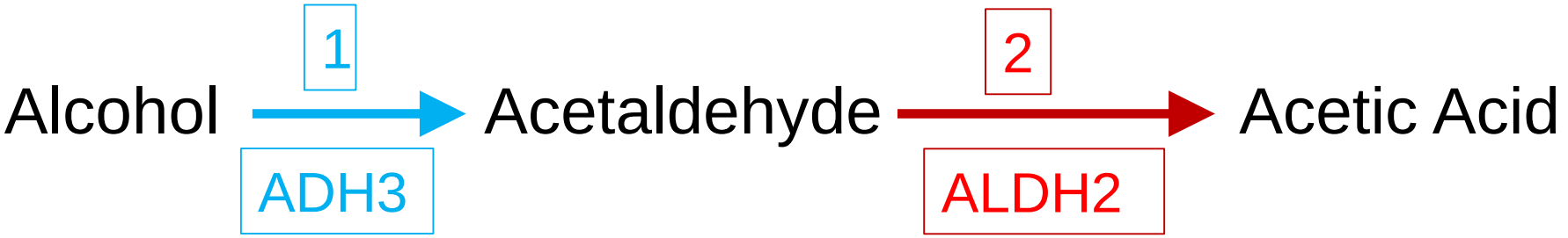


E= exposure

Y=outcome

Z=Instrumental variable

Beer and CHD Example



1 Alcohol dehydrogenase 3: γ_1 fast metabolizer and γ_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 (γ_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

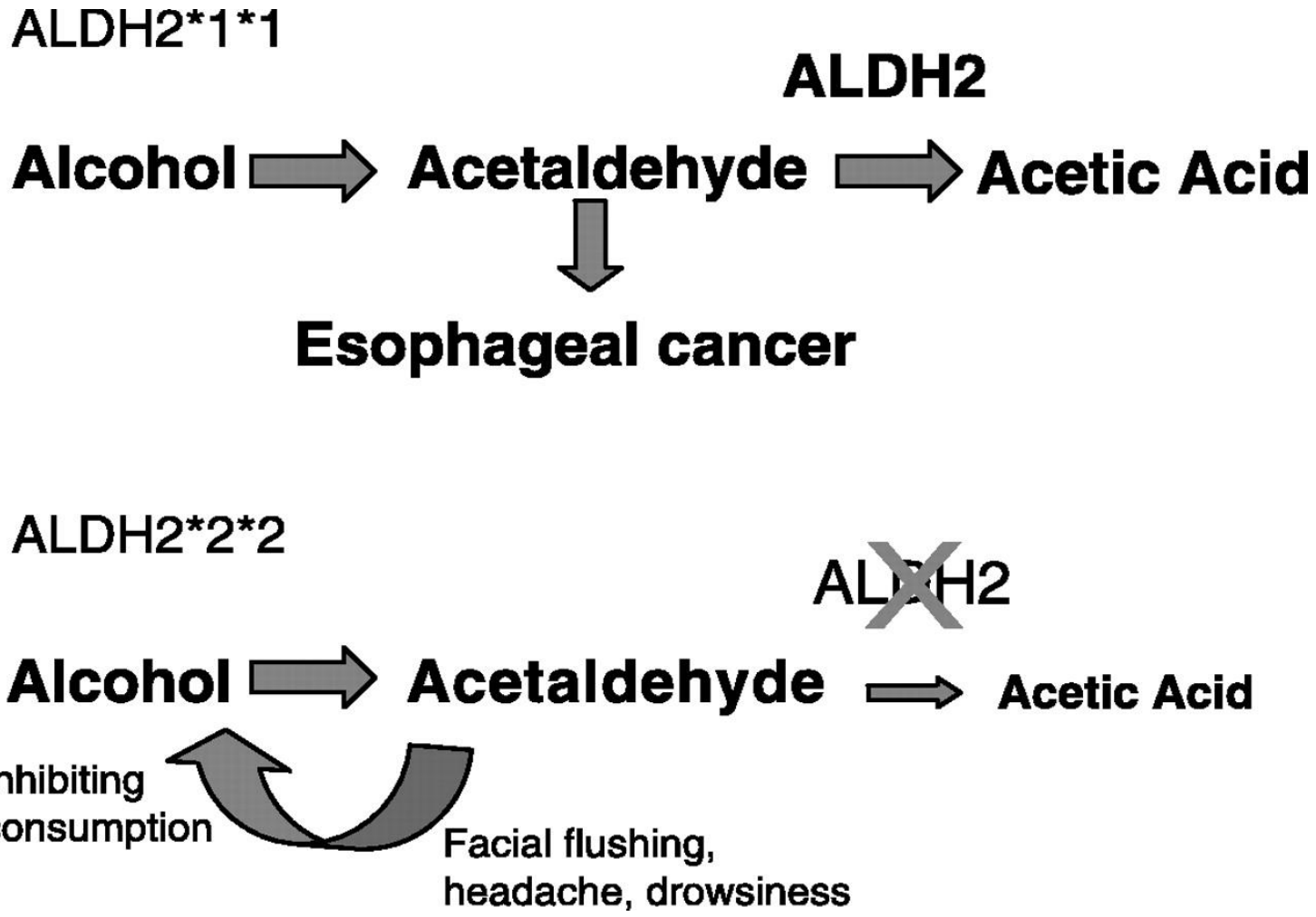
VARIABLE	*ADH3* GENOTYPE			P VALUE*
	$\gamma_1\gamma_1$	$\gamma_1\gamma_2$	$\gamma_2\gamma_2$	
No. of subjects (%)				
Patients	161 (41)	184 (46)	51 (13)	
Controls	279 (36)	361 (47)	130 (17)	
Relative risk (95% CI)†				
Matched	1.0‡	0.90 (0.69–1.17)	0.72 (0.50–1.05)	0.09
Multivariate	1.0‡	0.81 (0.61–1.09)	0.64 (0.43–0.98)	0.03
Multivariate, with adjustment for alcohol consumption§	1.0‡	0.83 (0.62–1.11)	0.65 (0.43–0.99)	0.04

*The P value is for the test for trend.

Hines LM et al. N Engl J Med 2001;344:549-555

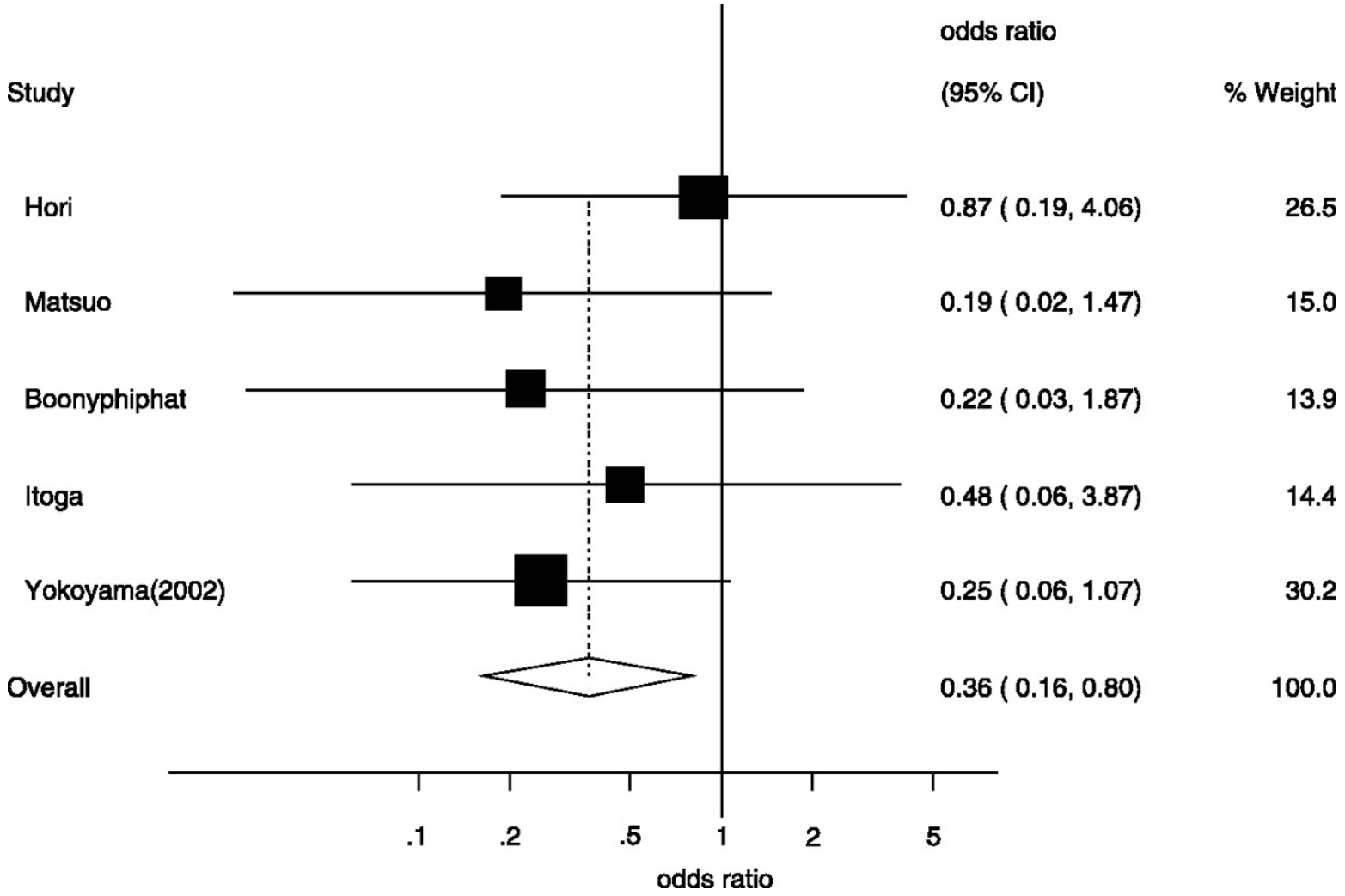
ALDH2 and Cancer Risk

ALDH2, Alcohol, Acetaldehyde, & Esophageal Ca



Slewis SJ Cancer Epidemiol Biomarkers Prev 2005;14:1967-1971

RR of Esophageal Cancer
ALDH2_22 vs. ALDH_11 Genotype



Beer and Health

Lewis SJ Cancer Epidemiol Biomarkers Prev 2005;14:1967-1971

D. Caveats of MR

Population Stratification

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

Adjust for population admixture

Linkage Disequilibrium (LD)

- 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

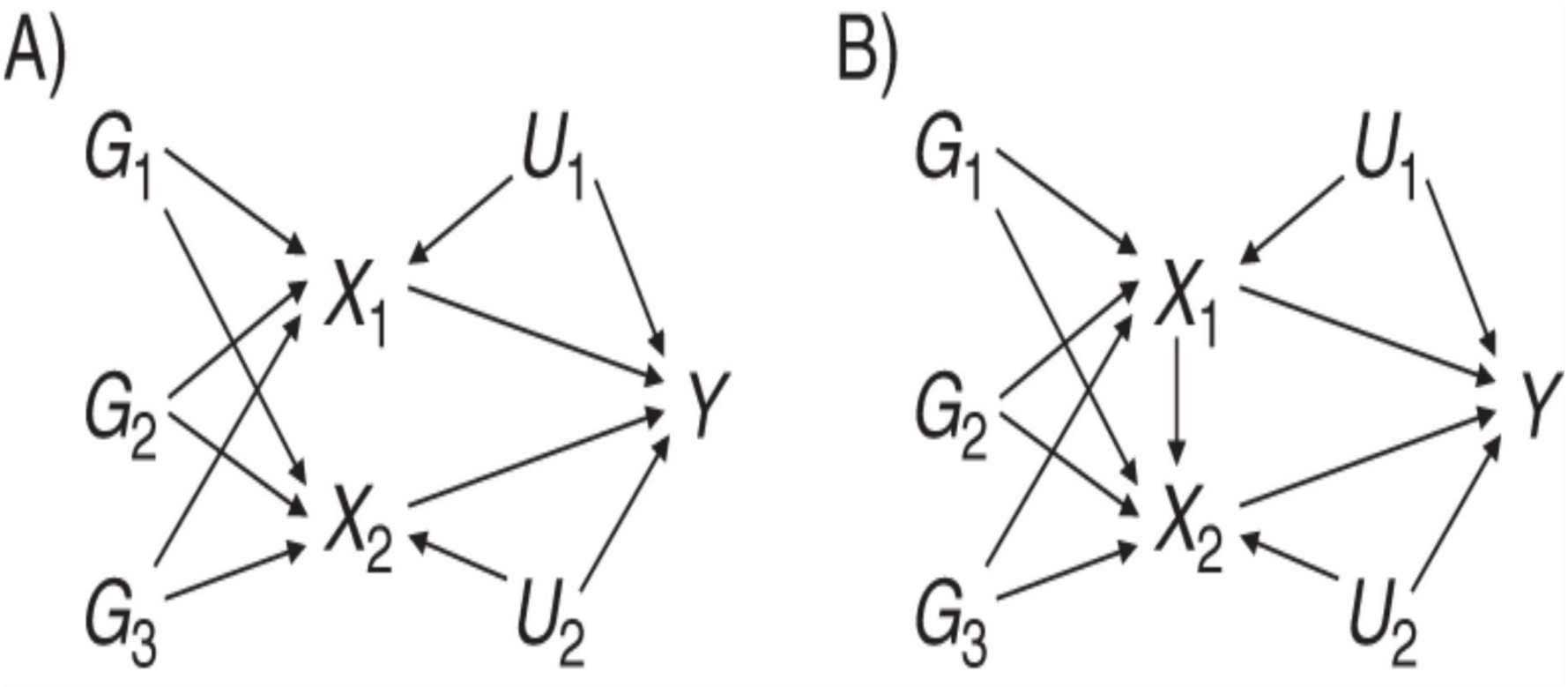
- A good IV requires well-defined and strong genetic risk factors with high penetrance

(e.g., Low penetrance: ALDH2 *2*2 subjects that tolerate alcohol intake)

Future Directions

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)

Burgess S & Thompson. Am J Epidemiol. 2015;181:251-260

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 !