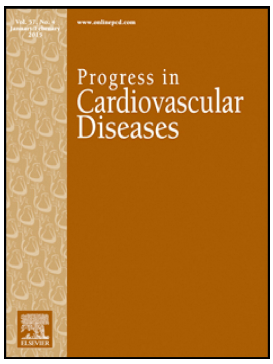

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Evan L. O'Keefe, James J. Di Nicolantonio, James H. O'Keefe, Carl J. Lavie

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Alcohol and CV Health: Jekyll and Hyde J-Curves

Short Title:

Alcohol's Jekyll & Hyde Nature

Evan L O'Keefe, MD[1], James J DiNicolantonio, PharmD[2],

James H O'Keefe, MD[2], Carl J Lavie, MD[1]

Affiliations:

[1] Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA

[2] Saint Luke's Mid America Heart Institute, Kansas City, MO

Corresponding Author:

James H O'Keefe, MD

4321 Washington Street, Suite 2400

Kansas City, MO 64111

jokeefe@saint-lukes.org

816-751-8480 - phone / 816-751-8665 – fax

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Abbreviations

ADA – American Diabetes Association

AF – Atrial Fibrillation

ARIC – Atherosclerosis Risk in Communities

BP – Blood Pressure

CAC – Coronary Artery Calcium

CHD – Coronary Heart Disease

CI – Confidence Interval

CV – Cardiovascular

HDL – High-Density Lipoprotein

HR – Hazard Ratio

HTN – Hypertension

LDL – Low-Density Lipoprotein

MI – Myocardial Infarction

NHIS – National Health Interview Surveys

T2D – Type 2 Diabetes

US – United States

Abstract

A routine of light or moderate alcohol consumption (≤1 drink/day for women and 1 to 2 drinks/day for men) were associated with a lower risk for all-cause mortality, coronary artery disease (CAD), type 2 diabetes mellitus (T2D), heart failure (HF), and stroke. Conversely, heavy drinking, (>4 drinks/day) is associated with an increased risk for death and cardiovascular (CV) disease (CVD). Excessive alcohol intake trails behind only smoking and obesity among the 3 leading causes of premature deaths in the United States (US). Heavy alcohol use is a common cause of reversible hypertension (HTN), nonischemic dilated cardiomyopathy, atrial fibrillation (AF), and stroke (both ischemic and hemorrhagic). Among males aged 15 to 59 years, alcohol abuse is perhaps the leading cause of premature death. As such, the risk-to-benefit ratio of drinking is less favorable in younger individuals. A daily habit of light to moderate drinking is ideal for those who choose to consume alcohol regularly. Red wine in particular before or during the evening meal is linked with the best long-term CV outcomes. Most of the studies on alcohol and health are observational, and correlation does not prove causation. Health care professionals should not advise nondrinkers to begin drinking because of the paucity of randomized outcome data coupled with the potential for alcohol abuse even among seemingly low risk individuals.

Introduction

In Robert Louis Stevenson's 1886 novel Dr. Henry Jekyll—a mild-mannered physician/healer drinks a potion that temporarily transforms him into an alter ego named Mr. Hyde—a homicidal sociopath.[1] Alcohol's association on health are analogous to the apocryphal *Strange Case of Dr. Jekyll and Mr. Hyde*. Prudent consumption of this dimorphic potion appears to improve cardiovascular (CV) health, but when consumed in excess, benefit transforms into detriment as alcohol unveils a deadly nature. In common parlance ethanol is referred to as "alcohol", and consumption of alcoholic beverages is known as "drinking", which has been a custom in many cultures throughout recorded human history.[2]

When alcohol assumes the malevolent Mr. Hyde identity, it is recognized as 1 of the 4 most common preventable and modifiable causes of major non-communicable diseases.[3] Excessive alcohol intake is responsible for 4% of all deaths, and it plays a causal role in 60 different diseases including atrial fibrillation (AF), stroke, hypertension (HTN), heart failure (HF), seizures, cirrhosis, poisonings, accidents, violence, and many malignancies including cancers of the larynx, colon, rectum, breast, and liver.[4] Alcohol abuse also tends to harm the health and well-being of people around the drinker. The annual health care and economic costs related to alcohol are over $224 billion in the United States (US) alone.[4,5]

In stark contrast, when alcohol is consumed responsibly in light to moderate amounts it largely retains its benign Dr. Jekyll demeanor, and were associated with a lower risk for CV disease (CVD)—the leading cause of death in the US.[6] Prudent habitual alcohol use also appears to be linked to lower risks for type 2 diabetes mellitus (T2D), stroke, HF, and all-cause mortality.[4,7]

This review article will present the risks and benefits associated with alcohol consumption, outline the potential mechanisms of action whereby alcohol bestows benefits or induces harm, and suggest safe drinking practices, types and quantities of alcohol that optimize CV outcomes and minimize risk and detriment for those choosing to consume. The findings in this review were based on a literature search of PubMed for the 20-year period 1997 through 2017 using the search terms *alcohol*, *ethanol*, *cardiovascular disease*, *coronary artery disease*, *heart failure*, *hypertension*, *stroke*, and *mortality*. Studies were included in this review if they were judged to be methodologically sound, high quality, objective, and reproducible.

US Adult Drinking Habits

Among all US adults, about two-thirds report that they at least occasionally have a drink, and 44% drink regularly—defined as consuming at least 1 drink/week.[8] These regular drinkers imbibe a mean of 4.2 alcoholic drinks per week. While a similar proportion of men and women drink alcohol, men drinkers on average

ingest 6.2 alcoholic beverages/week, whereas women drinkers have a mean of 2.2 drinks/week. Whites are more likely to drink alcohol than nonwhites, and on average, whites also tend to consume more drinks—4.5/week compared to 3.3/week among nonwhites.[8] Beer and wine are the favored drinks for men and women, respectively. Twenty percent of drinkers admit to occasional over-consumption of alcohol, and this is a more common problem among males and younger individuals.[8]

A standard drink, regardless of the variety, contains 13 to 14 grams of ethanol (0.6 fl oz of pure alcohol),[9,10] which translates to 12 oz of beer (~5% ethanol), 5.5 oz of table wine (~12% ethanol), or 1.5 oz of distilled spirits or hard liquor (~40% ethanol).[9,10] Alcohol intake can also be quantitated in units, whereby 1 unit equals 10 mL or 8 grams of ethanol, which corresponds to the amount of alcohol an average adult can metabolize in 1 hour. Thus, for example, 25 mL of whiskey, or 6 oz of beer, or 3 oz of wine would each contain about 1 unit of alcohol.[9,10]

Epidemiological Studies

The quantity and pattern of ethanol consumption largely determine the health effects of drinking.[7] Epidemiological studies consistently find that light and moderate drinkers are observed to be at lower risk for CVD than nondrinkers, whereas heavy drinkers are at the highest risk. A meta-analysis comprising 1

million individuals found that light or moderate alcohol consumption was associated with highly significant reductions in mortality during follow up; maximum potential benefit noted at one-half to 1 drink daily for females (18% reduction in all-cause mortality; 99% CI, 13%-22%).[11] Among males, maximal potential benefit was seen at 1 to 2 drinks/day, with an associated reduction of 17% (95% CI, 15%-19%) in all-cause mortality. However, consumption in excess of 2.5 drinks/day in women and [>4 drinks/day in men was associated with proportionately higher death rates in a dose-dependent fashion (Fig 1). Another study evaluated one-quarter million US adults, finding that alcohol intakes of both light (≤3 drinks/week) and moderate (4-7 drinks/week for women, 4-14 drinks/week for men) levels were associated with lower CVD mortality compared with either heavy users (>7 drinks/week in females or >14 drinks/week in males) or lifetime nondrinkers (Fig 2).[12]

National Health Interview Surveys Study

A scientifically impressive, statistically rigorous study from the National Health Interview Surveys (NHIS) examined the association between alcohol consumption and risk of mortality from all causes, and deaths specifically from cancer, and CVD.[13] This study included 333,247 adults from the US and collected 2.7 million person-years of follow up data. Compared to lifetime abstainers, light drinkers (3 or less drinks/week) or moderate drinkers (>3-7 drinks/week for women, and >3-14 drinks/week for men) were observed to have a lower risk of all-cause mortality (light—hazard ratio [HR]: 0.79; 95% confidence

interval [CI]: 0.76 to 0.82; moderate—HR: 0.78; 95% CI: 0.74 to 0.82). Lower risks for CVD were also observed for both light drinkers (HR: 0.74; 95% CI: 0.69 to 0.80), and moderate drinkers (HR: 0.71; 95% CI: 0.64 to 0.78). However, heavy drinking (>14 drinks/week) was associated with elevated risks for all-cause mortality (HR: 1.11; 95% CI: 1.04 to 1.19) and cancer mortality (HR: 1.27; 95% CI: 1.13 to 1.42). Binge drinking (consuming ≥5 drinks during 1 day) at least 1 day per week was also associated with significantly increased risks for both all-cause mortality (HR: 1.13; 95% CI: 1.04 to 1.23) and cancer mortality (HR: 1.22; 95% CI: 1.05 to 1.41). The maximal observed protection against both all-cause mortality (Fig 3) and CVD (Fig 4) was noted at approximately 7 to 9 drinks/week for both men and women. Furthermore, compared to never-drinkers, those who consumed up to 10 drinks/week were not observed to have an increased risk of cancer mortality (Fig 5).[13]

The associated risk reductions of consuming light or moderate amounts of alcohol were most significant for older (≥60 years of age or older), and middle-aged adults (40 to 59 years of age), but were less significant in younger adults (18 to 39 years of age), likely in part due to this younger cohort's lower baseline risk of adverse health events such as coronary disease.[13] Other large observational studies have also shown that the more favorable risk-benefit ratio of drinking is noted among the middle-aged and older cohorts as compared to younger individuals.[14]

For younger individuals, baseline risks for CVD are very low and this

younger cohort is also more likely to engage in excessive and/or binge drinking and accordingly suffers a higher risk of alcohol-related accidents, violence, and poisoning.[3-5] Thus, from a health and wellness perspective, the risks of drinking outweigh the benefits for many younger men and women.[13] In contrast, middle-aged and older individuals generally show more significant CVD risk reductions associated with light to moderate drinking.[15]

Secondary Prevention

Light and moderate drinking has also been shown to be associated with improved outcomes in individuals with established CVD. A meta-analysis of 8 prospective studies comprising 16,351 patients with a previous diagnosis of CVD, the well-known J-shaped curve was again noted, with maximal observed risk reduction seen at ethanol intakes of about 26 grams/day (or about 2 drinks daily).[16] Observational studies of patients with a myocardial infarction (MI) also have noted the familiar J-shaped relationship between alcohol intake and CVD events or mortality.[17,18] A large prospective study of 45 US hospitals with a median follow-up of 4 years observed a lowered risk-adjusted post-MI, all-cause mortality rate among drinkers when compared with nondrinkers.[19] Light to moderate habitual alcohol intake has also been associated with significantly less atherosclerotic progression in the grafts following coronary artery bypass surgery,[20] and a lower prevalence of peripheral arterial disease and its complications.[21-23]

Arrhythmias

Previous generations of physicians used the term “holiday heart” for the patients who presented with cardiac rhythm disturbances after excessive drinking.[4] Indeed binge drinking markedly increases risk of acute cardiac arrhythmias, most commonly AF.[24,25] In the Copenhagen City Heart Study, alcohol intakes > 35 drinks/week correlated with higher risk of AF in men.[26] Above a benign threshold of approximately 1 drink/day, the relative risk of AF rises about 10% for each daily drink (Fig 6).[27,28]

Excessive alcohol consumption, whether acutely in the form of binge drinking or due to heavy long-term drinking, can also trigger ventricular arrhythmias and rarely even sudden cardiac arrest.[11,29] The proarrhythmic association of heavy alcohol consumption are likely due in part to its proclivity for QT interval prolongation and shortening of the atrial effective refractory period.[30] Acute alcohol intoxication and withdrawal both commonly are linked with hypomagnesemia and hypokalemia.[31] Alcohol withdrawal also augments cardiac sympathetic activity and blunts both heart rate variability and baroreflex sensitivity— all of which are autonomic disturbances that predispose to cardiac arrhythmias.[32]

Heart Failure

In a large recent meta-analysis, light alcohol drinking (1 to 7 drinks/week) was inversely associated with risk of HF (RR, 0.86; 95% confidence interval, 0.81-0.90). In this study, no statistically significant association was noted between moderate (7 to 14 drinks/week), high (14 to 28 drinks/week), or heavy (>28 drinks/week) alcohol consumption and HF risk.[33] Other studies also show that light to moderate alcohol consumption is associated with significantly reduced risk of HF,[34] witnessed even among older individuals and HTN patients, albeit not due to a reduction in coronary heart disease (CHD).[35-37]

Nevertheless, ethanol at higher doses is a well-documented cardiotoxin. Chronic heavy alcohol consumption can cause a specific cardiac condition known as alcoholic cardiomyopathy, which causes about one-third of all cases of nonischemic dilated cardiomyopathy in the US.[38] Individuals who imbibe more than 90 grams/day of alcohol (>7 drinks/day) for at least 5 years, are at increased risk for developing alcoholic cardiomyopathy and HF. If a patient with alcoholic cardiomyopathy continues to drink, the 4-year mortality rate may be as high as 50%; and this is a common cause of death among individuals who are chronic alcohol abusers.[39] Crucially, abstinence from alcohol and treatment of HF dramatically improve both cardiac function and prognosis.[38]

Alcohol and Blood Pressure (BP)

Regular alcohol consumption elevates BP in a dose-dependent fashion. Consumption in excess of 14 drinks/week independently increases risk of HTN, an association that has been noted in blacks, whites, Asians, and Hispanics.[40,41] Chronic heavy drinking is among the most common reversible causes of HTN, and heavy drinking causes about 16% of HTN cases worldwide.[42] The American Society of Hypertension guidelines warn that intake of more than 2 alcoholic drinks/day increase BP.[43] Above 2 drinks per day, each additional alcoholic drink will raise BP by about 1.5 mm Hg. Upon complete cessation of drinking, or with a substantial reduction of intake, the alcohol-induced HTN usually resolves within 2 to 4 weeks. A multi-national meta-analysis showed a linear dose-response relationship between alcohol and BP whereby the relative risk for HTN was 1.7 for 50 grams of ethanol/day (about 4 drinks/day) and 2.5 at 100 grams/day (8 drinks/day).[41] Importantly, 1 or 2 drinks consumed once daily in conjunction with a meal has a neutral effect on long term BP.[44]

Alcohol and Stroke

Chronic heavy alcohol intake and chronic alcoholism are potent independent risk factors for stroke.[45-47] Yet even for this outcome, most studies report a J-shaped curve for the relationship between alcohol and ischemic stroke. As noted in other realms, a modest observed risk reduction was seen among light to moderate drinking, on the other hand heavy drinking was significantly associated with an

increased risk of stroke (Fig 7).[48-50] A study of approximately 50,000 Japanese women followed for a mean of 17 years found that drinking more 300 grams/week of ethanol (over 21 drinks/week) doubled the risk of stroke (a composite of both ischemic and hemorrhagic stroke).[51] A recent meta-analysis of 27 prospective studies reported that light and moderate alcohol intakes were associated with lower risk of ischemic stroke, whereas heavy drinking was associated with an increased risk of both ischemic and hemorrhagic strokes (Fig 7).[52] The American Stroke Association guidelines advise that heavy drinkers who have suffered an ischemic stroke or transient ischemic attack should eliminate or reduce their alcohol consumption. These guidelines also defined “reasonable” alcohol intake as not more than 2 drinks/day for males and 1 drink/day for females.[53]

Alcohol and Diabetes

Light or moderate alcohol intake is associated with a lower risk of developing CHD and its complications in the setting of T2D.[54] Furthermore, a large body of evidence indicates that for non-T2D individuals, light or moderate drinking is associated with a significant decrease in risk of developing new T2D.[55-57] With a mean of 12 years of follow-up, the Physicians’ Health Study found that light or moderate alcohol consumption was associated with a lowered risk of T2D.[58] However, heavy drinking (≥4 drinks/day) was not associated with reduced risk of new-onset T2D.[59] A recent comprehensive meta-analysis on this topic found that various alcohol-containing beverages had differing effects on risk reduction of

T2D.[60] Whereas wine was associated with a highly significant protection against new T2D, beer or spirits were associated with only slight reductions in T2D (Fig 8). The J-shaped alcohol relationship is also present for metabolic syndrome,[61] wherein a lower prevalence of metabolic syndrome is noted among individuals who are light or moderate drinkers.[62] These results were reproduced in a cohort of older Italians[63] and were also corroborated by a meta-analysis showing beneficial metabolic changes for ethanol intakes of <20 grams/day in women and <40 grams/day for men.[64] The American Diabetes Association recommends limiting alcohol intake to not more than 2 drinks/day for diabetic males and not more than 1 drink/day for diabetic women.[65]

How Moderate Drinking Might Reduce CV Risk

It is the ethanol, not any other compound present in alcoholic beverages, that is the main driver of the potential health benefits at low and moderate doses of alcohol and the toxic effects at high doses.[66,67] As mentioned above, light to moderate alcohol intake may augment insulin sensitivity, raise high-density lipoprotein (HDL) cholesterol, dampen inflammation, raise adiponectin, and improve endothelial function.[66,68,69] Ethanol in a dose-dependent fashion raises HDL (particularly the cardioprotective HDL2 subfraction) and apolipoprotein A-I.[70] A linear correlation exists for alcohol consumption in relation to lipoprotein particle size (higher alcohol intake is associated with larger low-density lipoprotein [LDL] and HDL particles). Yet, a U-shaped association is noted for

LDL particle number, whereby those who imbibed 7 to 13 drinks/week had lower numbers of LDL particles than nondrinkers or heavy drinkers.[71]

Light to moderate alcohol consumption has been reported to not protect against coronary artery calcium (CAC) accumulation, and although wine consumption was neutral for CAC, heavy drinking of distilled spirits or beer was associated with higher CAC scores.[72] In the Cardiovascular Risk Survey comprising 14,618 people, intakes of <4.5 drinks/day were associated with less peripheral atherosclerosis, whereas consumption of ≥4.5 drinks/day was associated with increased peripheral atherosclerosis.[73]

In the Pravastatin Inflammation/CRP Evaluation Study, moderate drinkers had lower C-reactive protein levels compared to nondrinkers, suggesting that light to moderate alcohol intake may be anti-inflammatory.[74] Notably, moderate alcohol consumption (1 to 2 drinks) improves insulin sensitivity and glucose metabolism for the ensuing 12 to 24 hours.[75] The biological mechanism whereby alcohol improves insulin sensitivity appears to involve suppression of fatty acid release from adipose tissue and elevation of adiponectin levels.[76,77] Consuming 1 to 2 drinks/day will lower triglycerides modestly (7%-10%) and decrease abdominal obesity.[4,78,79] Above 2 drinks/day, abdominal obesity and triglycerides increase proportionately with the amount of alcohol consumed.[79,80]

Red wine is generally high in polyphenols, which have antioxidant, anti-

inflammatory, and antiplatelet properties.[81-83] In fact, small, randomized controlled trials have reported red wine improves insulin resistance, lipid profiles, and endothelial function compared with other alcoholic beverages.[81-83]

Potential Cardioprotection Varies Among Different Ethnicities

The health-enhancing association of light or moderate drinking are noted to be highly variable among the different races, ethnicities, and cultures.[84-86] In the landmark NHIS study discussed above, light or moderate drinking was associated with lower risk of all-cause mortality in whites but not in blacks;[87] Hispanics appeared to have risk reductions for all-cause and CVD mortality of similar magnitude to the benefits noted among whites, though the results were less statistically significant due to smaller numbers of study subjects in the Hispanic cohort.[13] The INTERHEART study,[88] a 27,000-patient multi-national epidemiological study, reported that regular alcohol consumption was associated with risk reduction of MI by 14% with this potential cardioprotection being noted in both genders. Subjects from 50 different countries were included in the INTERHEART study; of note, the alcohol-related cardioprotection was not significant among the cohort from India.[88] A study conducted in India comprising 4,465 participants replicated these findings, whereby those who consumed alcohol on a regular basis were observed to have a higher risk of CHD compared to nondrinkers.[84] Similarly, light and moderate alcohol consumption has not been consistently associated with improved health outcomes in Chinese

populations.[89,90]

Healthy vs Dangerous Drinking Patterns

The health benefits linked to drinking, similar to those conferred by exercise,[91] are most likely to be manifest when done daily and in moderation.[7,91] This is probably because a significant proportion of the benefits seen with light to moderate drinking are temporary—typically disappearing within 24 hours.[7]

The consensus scientific definition of light to moderate alcohol consumption is not more than 1 drink/day for women and not more than 2 drinks/day for men. Among the various alcoholic beverages, red wine, likely due to it being intrinsically rich in antioxidant compounds and generally low in sugar, may be the optimal choice from a health perspective.[18,81,82,92-94] However, the data is probably not strong enough to suggest red wine to people who prefer other alcoholic beverages. Binge drinking, typically defined as ≥5 drinks within a few hours, often with intoxication as an intended consequence, is linked to adverse health outcomes including a doubling of risk of mortality.[95,96] Even occasional binges diminish the protection associated with an otherwise light to moderate drinking pattern.[3] Moreover, heavy drinking often triggers disruptive and destructive social forces, such as depression, isolation, abuse and violence.[4,97]

Light to moderate alcohol consumption was identified as the single strongest correlate for predicting improved life expectancy noted among followers of the traditional Mediterranean diet.[97] In this study moderate alcohol consumption accounted for 25% of the longevity boost associated with lifelong adherence to the Mediterranean cuisine; other longevity-boosting factors were vegetable, fruit and nut consumption, olive oil use, and fish intake, but none appeared to be as strongly correlated as alcohol.

Cultures with exceptional longevity, such as societies adhering to the traditional Mediterranean diet, often incorporate light or moderate alcohol consumption before or during the largest meal of the day.[97,98] The potential advantages of drinking at dinnertime could be due to effectiveness of low to moderate doses of ethanol for blunting postprandial glucose spikes and associated inflammation,[99] and/or the potential pro-social association of light to moderate drinking, which could enhance emotional bonding and foster interpersonal connection. Notably, smoking tobacco appears to completely neutralize the potential cardioprotection otherwise afforded by light or moderate drinking.[13]

Caveats

For women, even light to moderate alcohol intake is associated with increased risk for breast cancer.[100,101] Recent studies show that chronic heavy alcohol use

adversely affects brain structure and function, with problem drinking causing atrophy of the hippocampus and cerebellum.[102] Even moderate alcohol intake (>2 drinks/day) is associated with increased risk of adverse brain changes (particularly in the hippocampal memory regions) and steeper age-related cognitive decline in verbal fluency.[103] In this recent study, no protective effect on brain structure or cognition was noted for light drinking compared to abstinence.[103]

The Atherosclerosis Risk in Communities (ARIC) study reported that among nondrinkers who are deemed by their physician to be at low risk for addiction, initiation of light or moderate alcohol intake was reasonably safe.[104] Yet, other studies report that it is very difficult to consistently predict individuals who might be at increased risk for problem drinking once they begin to consume alcohol on a regular basis.[4,5,7] In fact, habitual alcohol consumption seems to be a “slippery slope” that cannot be safely navigated by a substantial portion of the population. For this reason the American Heart Association recommends that nondrinkers should not be advised to start drinking.[105] Moreover, an estimated 5% of US adults meet diagnostic criteria for alcohol abuse; only 1 in 10 of these problem drinkers will seek and receive formal treatment, usually with dishearteningly low rates of chronic ethanol abstinence.[90] As of January 2018, a new clinical trial was initiated by Mukamal, “Moderate Alcohol and Cardiovascular Health (MACH15)”. This long term randomized trial will compare the effects of 1 standard serving (approximately 15 grams) of alcohol daily versus abstention for individuals aged 50 years and older with advanced CVD.[106]

Conclusion:

Alcohol consumption is a double-edged sword that can cut deeply in either direction—potentially beneficial to health and wellbeing in small doses, but toxic and potentially lethal in larger doses. Individuals who customarily consume alcohol should typically limit their daily intake to not more than 1 drink/day for women and not more than 2 drinks/day for men. Health care providers should not advise nondrinkers to begin drinking. Problem drinkers should be advised to abstain permanently and seek professional help to attain this.

Figure Legend

Fig 1 - Alcohol intake and total mortality. Data from *Arch Intern Med*.[11]

Fig 2 - Adjusted risks for cardiovascular (CV) disease as a function of alcohol intake. CHD = coronary heart disease; HR = hazard ratio. Error bars indicate 95% CIs. Data from *Journal of the American College of Cardiology*.[12]

Fig 3 – With median follow-up was 8.2 years, compared with lifetime abstainers, individuals who were light or moderate drinkers were at a lowered risk of all-cause mortality, but that risk increased significantly with heavy alcohol consumption, as seen in this J-shaped curve. HR = hazard ratio. Blue lines = 95% confidence interval.[13]

Fig 4 - Alcohol consumption and risk of CV disease (CVD) mortality.[13]

Fig 5 - Alcohol consumption and risk of cancer mortality.[13]

Fig 6 - Dose-response relationship between alcohol consumption and risk of atrial fibrillation (AF). At 10 drinks/day, the risk of AF is doubled. Confidence interval (CI) is marked by dashes.[28] Adapted from *European Journal of Cardiovascular Prevention and Rehabilitation* used with permission.

Fig 7 - The American Stroke Association guidelines advise that heavy drinkers who have suffered an ischemic stroke or transient ischemic attack should eliminate or reduce their alcohol consumption. These guidelines also defined “reasonable” alcohol intake as not more than 2 drinks/day for males and 1 drink/day for females.[53]

Fig 8 - Associations between alcoholic beverage consumption and development of new T2D for: (a) wine, (b) beer, and (c) distilled spirits.[60]

Fig 1

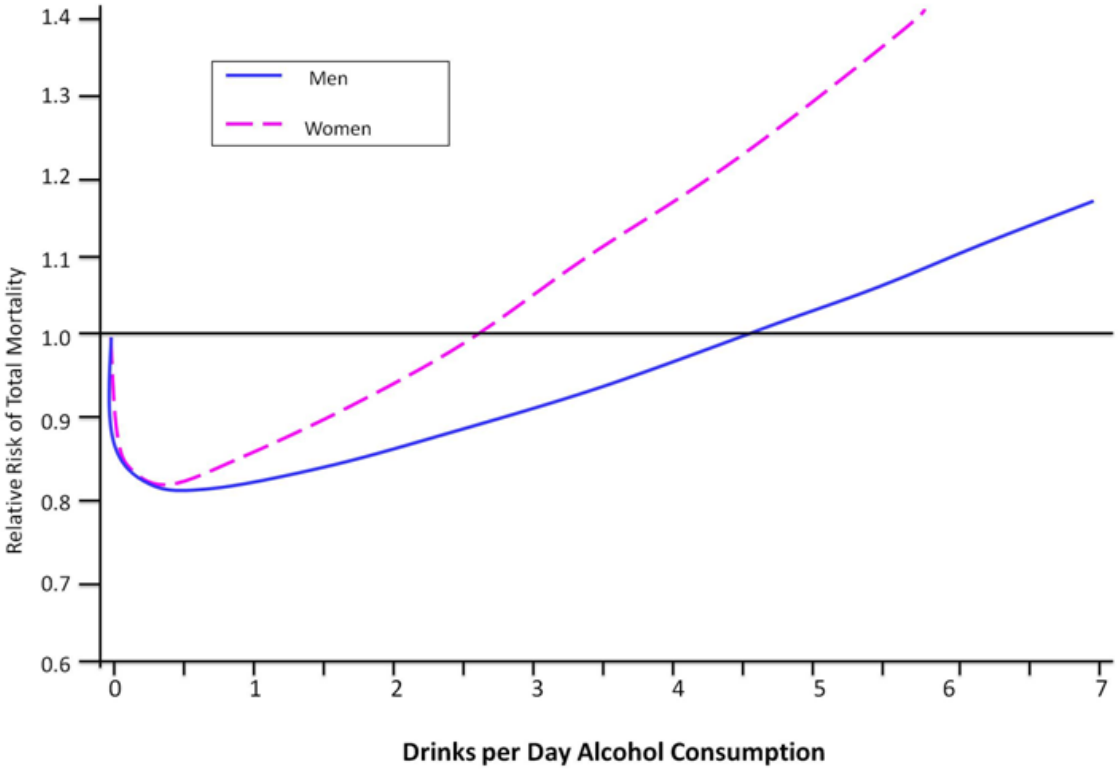


Fig 2

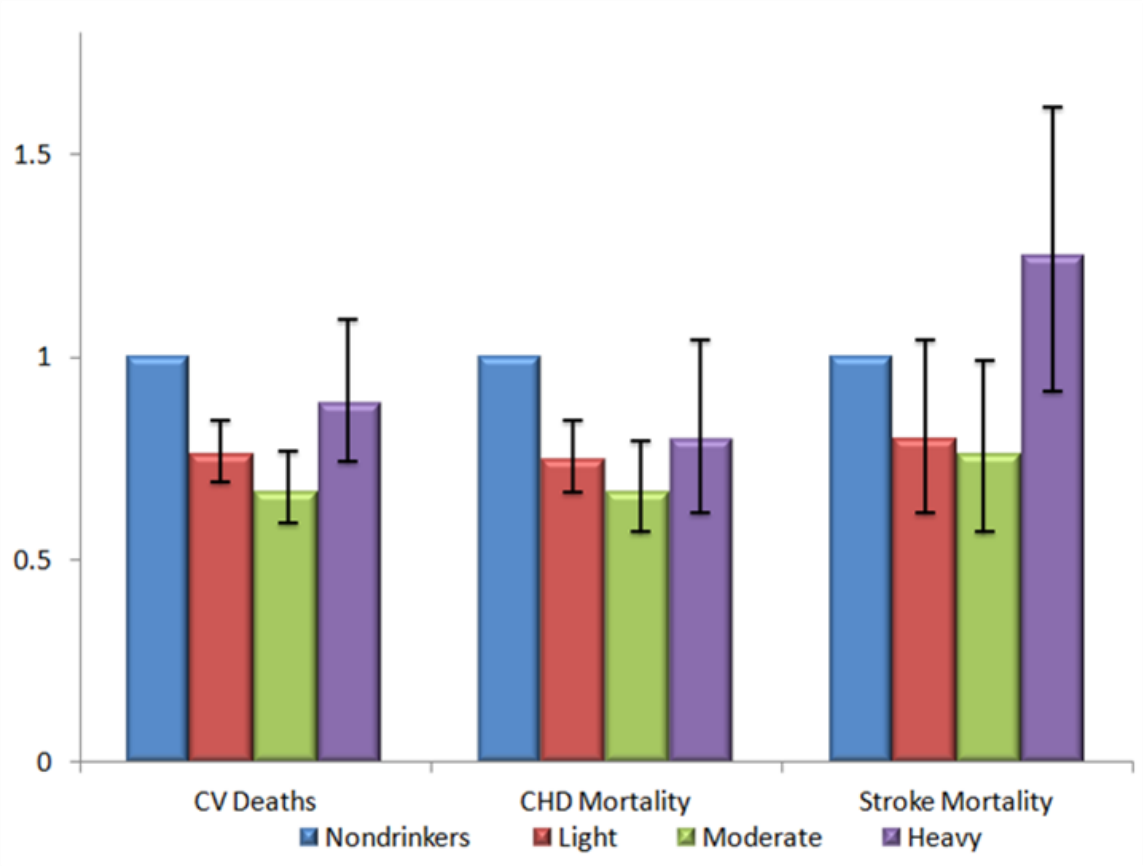


Fig 3

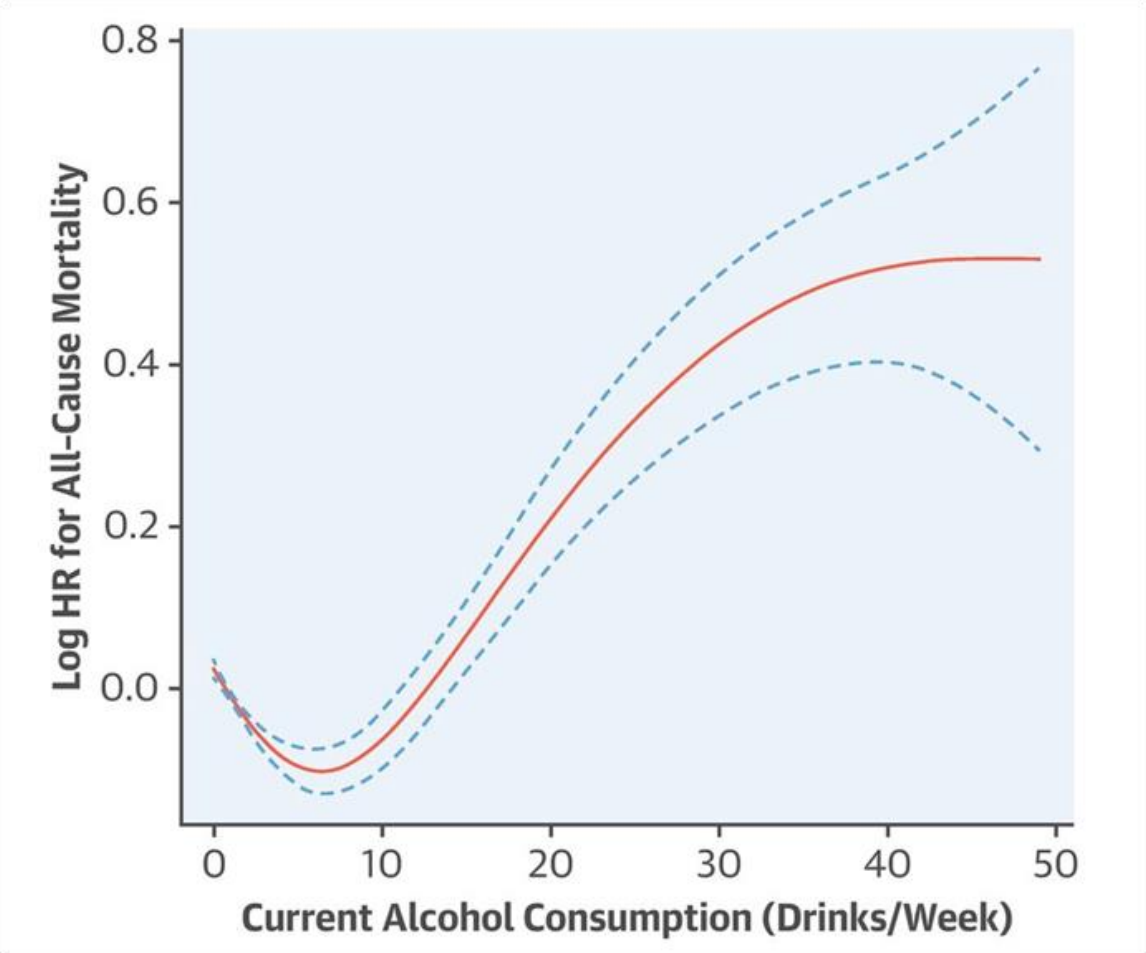


Fig 4

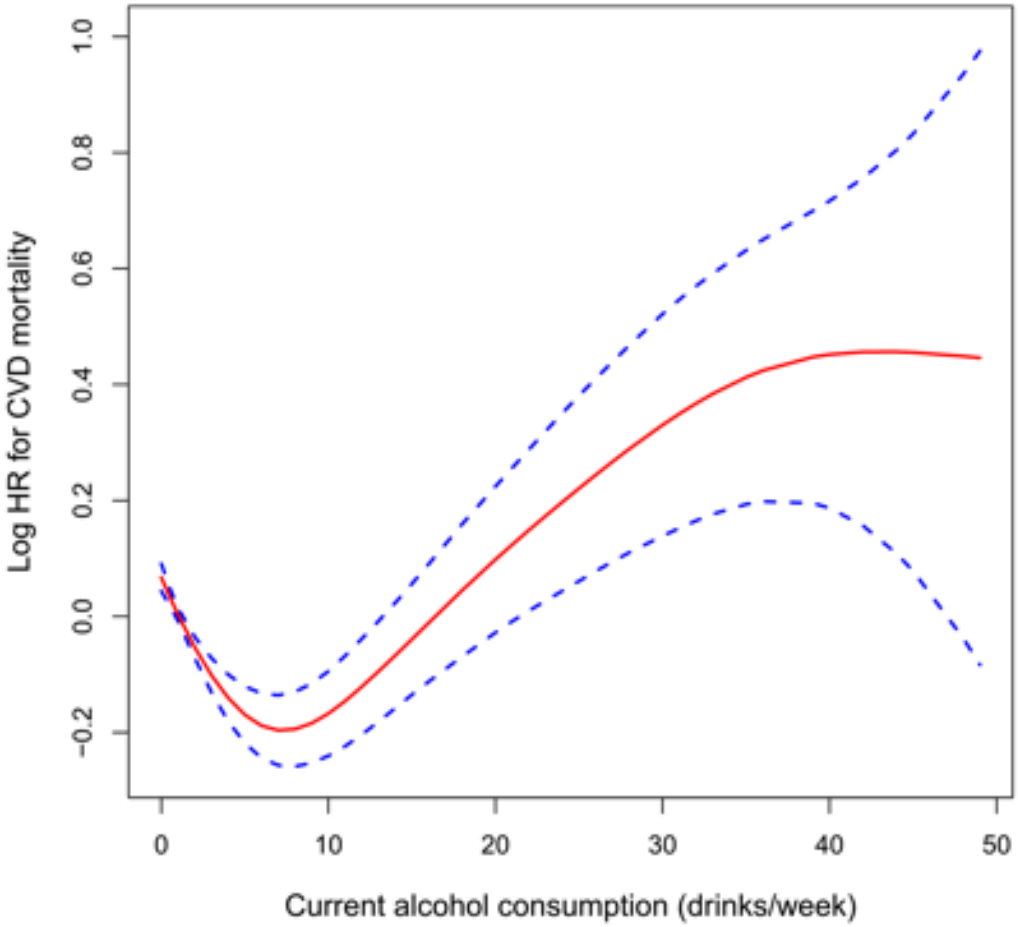


Fig 5

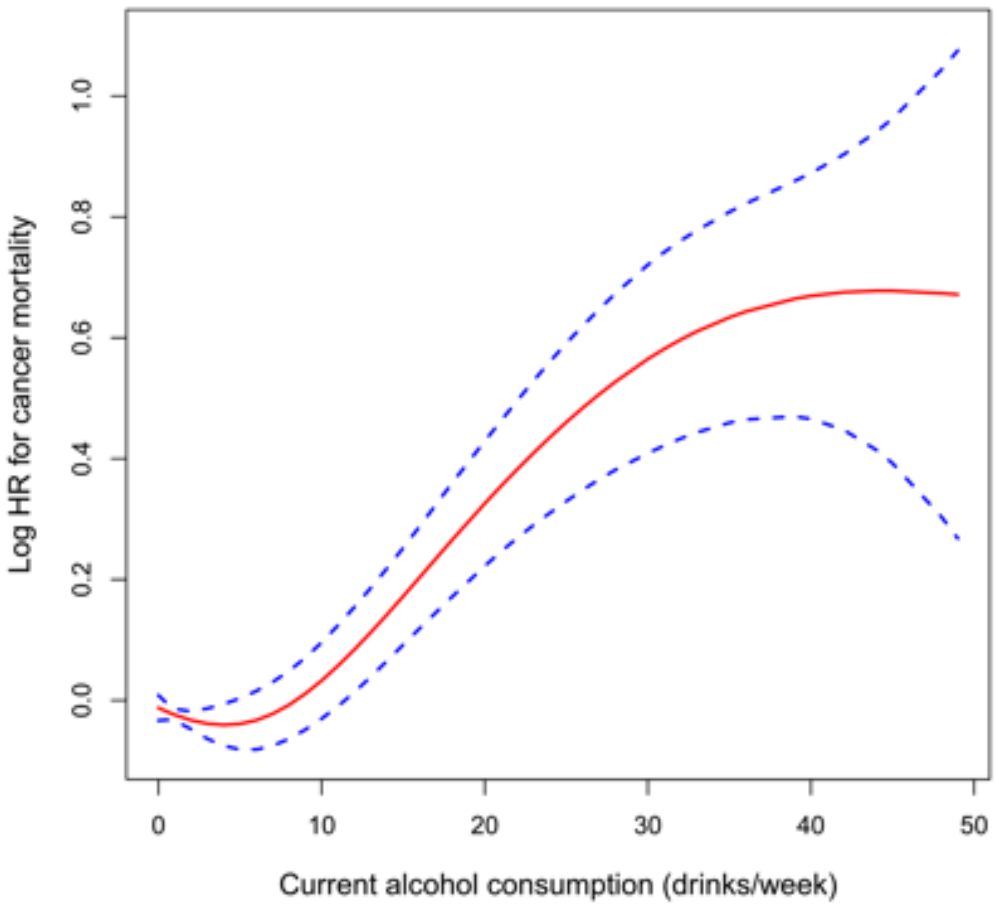


Fig 6

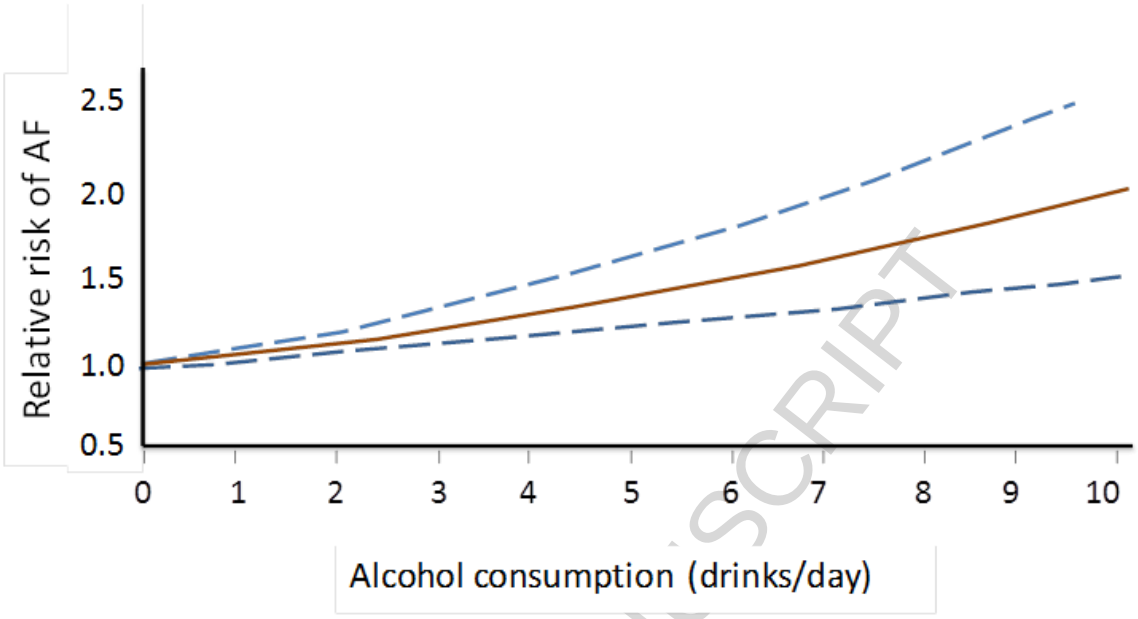


Fig 7

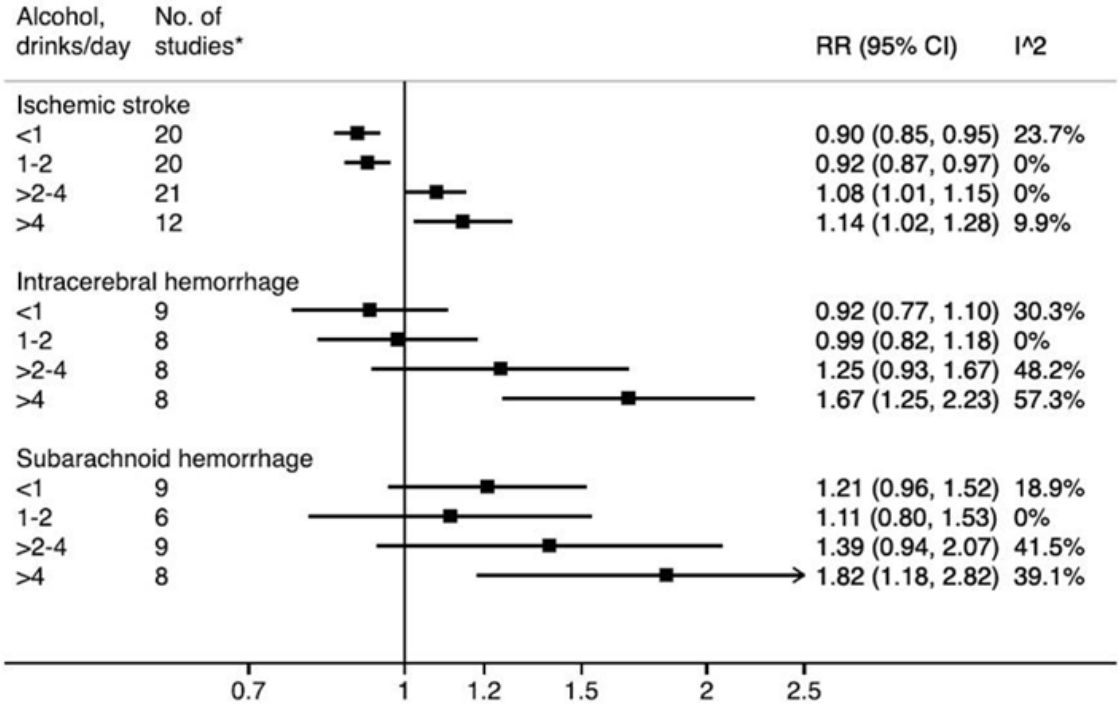
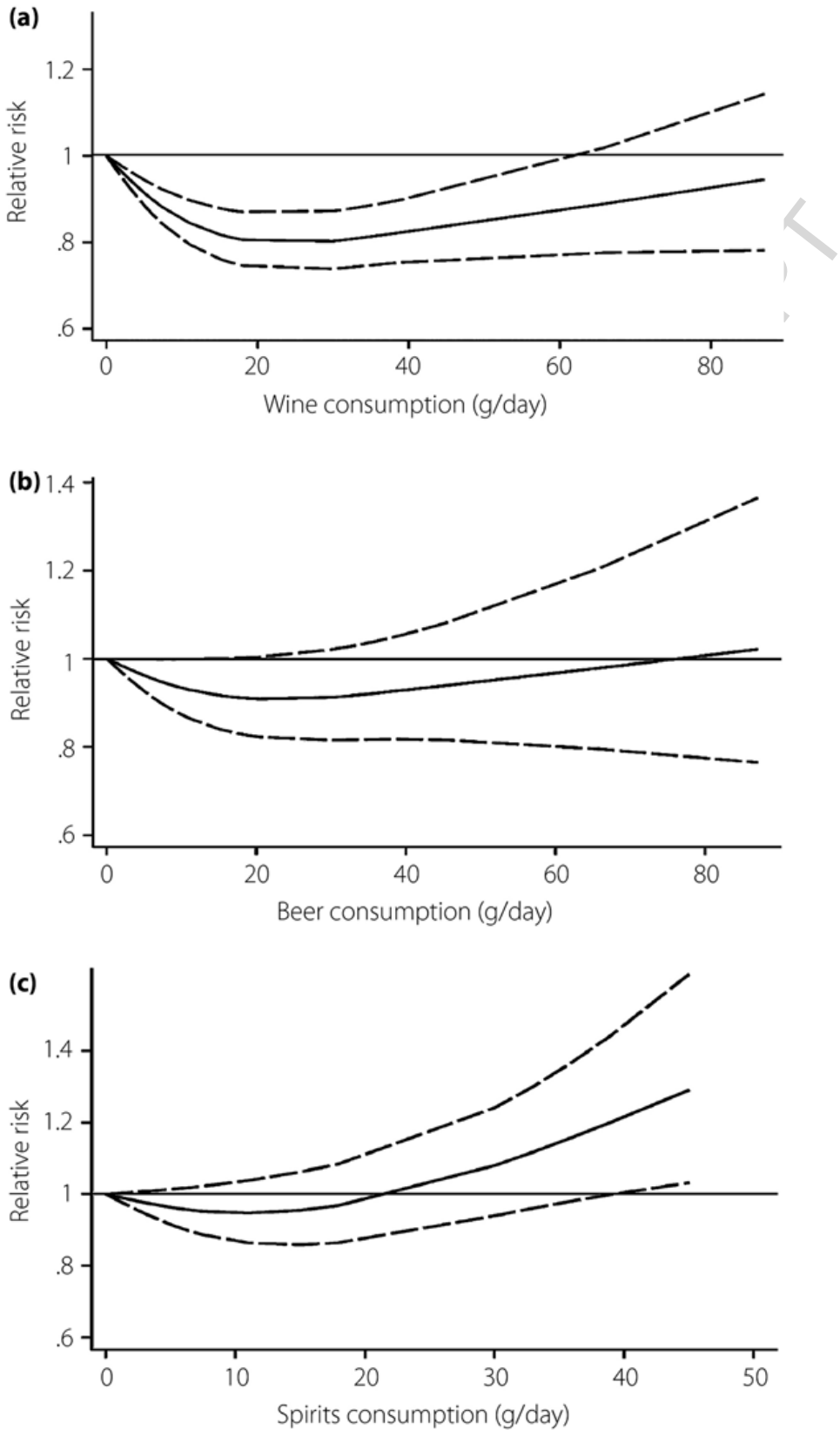


Fig 8



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