Alcohol consumption and its association with long-term prognosis among cardiovascular disease patients

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Declaration

I, Chengyi Ding confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Moderate alcohol consumption has been reported to be cardio-protective among apparently healthy individuals, but it remains unclear if this association is also present in those with cardiovascular disease (CVD). Inconsistency exists across guidelines regarding the recommended drinking limits for CVD patients. This thesis consists of three studies aiming to better understand alcohol consumption in this patient population and its association with long-term prognosis.

By pooling the results from de novo analyses of three cohorts and 12 published studies identified through a systematic review, meta-analyses of 48423 CVD patients (Study 1) found lower risk of mortality and subsequent cardiovascular events for an alcohol consumption up to 105 grams per week compared to current non-drinking. These effects, however, were significantly attenuated or absent after distinguishing former drinkers from non-drinkers. Meanwhile, little is known about the longitudinal dynamics of alcohol consumption in CVD patients and the associated health risks.

With repeated-measures data from two cohorts (n=12502), Study 2 plotted CVD patients' mean trajectory of weekly alcohol consumption as a function of time, centred on the date of diagnosis and spanning up to 30 years before and after the diagnosis. For male patients, mean consumption increased over time, peaked at eight years before diagnosis at 95 grams per week, and declined afterwards. A flatter trajectory was seen in female patients, which remained stable at around 30 grams per week and started to decline after diagnosis.

In Study 3, alcohol consumption trajectory was further differentiated into six distinct groups in an inception cohort of 1306 patients with incident CVD and related to their subsequent mortality risk from all causes. Patients who consistently drank moderately (within 112 grams per week) had a similar risk of mortality as those who were continuous non-drinkers. While increases in risk were found among patients who stopped drinking compared to continuous moderate drinkers, former drinkers also had the worst self-rated health.

Temporal variability in alcohol consumption highlights the importance of taking a longitudinal approach to examine alcohol health relations. Findings indicating

protective effects of baseline moderate drinking in CVD patients may be largely explained by a referent group contaminated by less healthy former drinkers and are not seen when considering long-term drinking trajectories. This thesis provides novel knowledge about alcohol's relation to cardiovascular health, which could be used to inform CVD patient care and low-risk drinking guidelines.

Impact statement

While the notion of potential health benefits related to moderate alcohol consumption has been widely studied among general populations, very few reports have looked at patients who have already experienced a CVD event and the methodology used is flawed in several important respects. It therefore has remained unclear what drinking advice should be given to CVD patients regarding their subsequent health, with varying consumption limits recommended in different clinical guidelines. This thesis addresses this research gap through three separate studies. Taken independently and together, these studies showcase novel research contributions which both advance future research and have implications for guidelines and patient care.

In addition to consolidating 20 years of existing evidence on the topic of alcohol consumption and prognosis in CVD patients, the meta-analyses outlined in this thesis (Study 1) bring in new insights by adding additional data from cohort analyses and, for the first time, evaluate the role of alcohol in experiencing a subsequent cardiovascular event. Findings from this body of work highlight several critical issues that need to be accounted for when modelling alcohol-related health risks. This work serves as a definitive contemporary source of evidence for CVD patients and their physicians worldwide to consult when making clinical decisions about their drinking and provides preliminary support for downward revisions of low-risk drinking limits in existing guidelines.

With prospectively recorded alcohol consumption across multiple assessment times, this thesis also presents the first attempt to show amongst CVD patients specifically how weekly consumption changes over a prolonged period from pre- to post-diagnosis, first assessed by plotting mean trajectories (Study 2) and then by differentiating between trajectory groups (Study 3). These findings can inform future inquiry into how alcohol drinking in an at-risk population is related to initial and subsequent disease onset and mortality. Additionally, this thesis has furthered the understanding of how long-term drinking profiles are associated with CVD patients' mortality risk (Study 3). In particular, it shows the additional insights obtainable from longitudinal exposure assessment, clarifying how a life course approach would be a fruitful avenue for future alcohol research.

Findings from this thesis have been disseminated through publications, conference presentations, and the media. The results of meta-analyses have been published in *BMC Medicine* and press released through the communications team at Springer Nature. The resulting media attention was extensive, including coverage from The Times, CNN, Reuters and UCL News. The remaining two pieces of work have been presented and discussed at international conferences and have resulted in two peer-reviewed publications.

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List of abbreviations

ACCF	American College of Cardiology Foundation
ACE	Angiotensin-converting enzyme
ADH	Alcohol dehydrogenase
AHA	American Heart Association
AIC	Akaike information criterion
ALDH2	Aldehyde dehydrogenase 2
Apo	Apolipoprotein
AvePP	Average posterior probability
BIC	Bayesian information criterion
BMI	Body mass index
CABG	Coronary artery bypass grafting
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CSE	Certificate of Secondary Education
CVD	Cardiovascular disease
EPIC	European Prospective Investigation of Cancer Study
FP	Fractional polynomial
GBTM	Group-based trajectory modelling
GCSE	General Certificate of Secondary Education
GENIUS-CHD	Genetics of Subsequent Coronary Heart Disease
GGT	Gamma-glutamyl transferase
GWAS	Genome-wide association study
HDL	High-density lipoprotein
HES	Hospital Episode Statistics
HF	Heart failure
HNC	Higher National Certificate
HND	Higher National Diploma
HR	Hazard ratio
HSE	Health Survey for England
ICD	International Classification of Diseases
IL	Interleukin
IQR	Interquartile range
IV	Instrumental variable
LVEF	Left ventricular ejection fraction

MI	Myocardial infarction
MICE	Multiple imputation by chained equations
MR	Mendelian randomisation
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
NVQ	National Vocational Qualification
OPCS4	Office of Population Censuses and Surveys' Classification of Interventions and Procedures Version 4
PCI	Percutaneous coronary intervention
PVC	Premature ventricular contraction
RR	Relative risk
SE	Standard error
SD	Standard deviation
SHeSs	Scottish Health Survey
SNP	Single nucleotide polymorphism
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization

Introduction to the thesis

This thesis starts with an overview of the definition and epidemiology of cardiovascular disease (CVD) in **Chapter 1**, describing its profound negative impact on public health and economic costs around the globe. With UK cohorts being used in the thesis, UK-specific CVD statistics will be provided in addition to global data.

As a leading modifiable risk factor for the global disease burden, alcohol consumption will be singled out as the exposure of interest, summarising current research that indicates the possibility of a cardio-protective effect at moderate levels of drinking in the general population. Evidence that suggests the impact of drinking patterns and underlying mechanisms will also be presented.

The chapter will then highlight the importance of secondary prevention in the healthcare of CVD patients and a possible role that alcohol can play in it. By summarising current guidelines and research on alcohol's association with CVD patients' prognosis, this chapter will point out the evidence gap in this area.

Chapters 2 to 4 comprise three different studies. Each chapter has four sections relating to the introduction, methodology, findings, and discussion of the study.

A previous meta-analysis, from over a decade ago, on the association between alcohol and CVD patients' prognosis was limited to mortality. **Chapter 2 (Study 1)** reports the results of an updated and expanded meta-analysis study that has included recent published studies, de novo findings from three large-scale UK cohorts – the Health Survey for England (HSE), the Scottish Health Survey (SHeSs) and the UK Biobank study, as well as morbidity outcomes. In addition to identifying reductions in risk of both mortality and cardiovascular morbidity at moderate levels of drinking compared to non-drinking among CVD patients, the new meta-analysis study will also outline some potential shortcomings underlying current investigations, such as inappropriate reference group selections and the use of single time-point alcohol observations.

Addressing these shortcomings, **Chapter 3 (Study 2)** presents a longitudinal nested case-control study illustrating how weekly alcohol consumption changes

over a prolonged period of up to 30 years before and after the onset of CVD, with repeated measures of alcohol intake from two ongoing UK cohorts – the Whitehall II study and the European Prospective Investigation of Cancer (EPIC)-Norfolk study. The chapter draws attention to the possible bias from single time-point alcohol assessments and the heterogeneity in drinking profiles over time across CVD patients, concluding that additional insights may be gained by applying a longitudinal, trajectory-based approach when modelling health risk in relation to alcohol consumption.

Chapter 4 (Study 3) includes a prospective cohort study that addresses several limitations in existing methods and formally examines whether long-term drinking profiles influence CVD patients' prognosis. Using repeated-measures data spanning up to three decades from the Whitehall II study, different trajectory groups of alcohol consumption are determined in an inception cohort of patients with incident CVD and linked to their subsequent risk of death from all causes. The results will also be compared to those of analyses based on single alcohol intake assessment in the same cohort to explore the utility of taking a longitudinal approach in examining the association of alcohol with health outcomes.

Finally, in **Chapter 5**, the findings from Chapters 2 to 4 are brought together and summarised. The Chapter also discusses the strengths and limitations, implications for practice and further work.

Chapter 1 Background

1.1 Global burden of CVD

CVD refers to a group of diseases that involve the heart and/or blood vessels, mainly including coronary heart disease [CHD, angina and myocardial infarction (MI)], stroke, congenital heart disease and vascular dementia [1].

CVD is the leading cause of mortality and a major contributor to disability across the world [2], responsible for an estimated 18.6 million deaths or one-third of all global deaths in 2019 [3]. Over the past few decades, due to modifications in risk factors and advances in medical treatments, large declines in CVD mortality have been seen in most regions of the world [4, 5]. In the UK for example, in 1969 the age standardised mortality rate from total CVD was 1045 per 100000 and this had fallen to 255 per 100000 in 2019 [6]. According to the 'Heart and Circulatory Disease Statistics 2021' report published by the British Heart Foundation [6], the main types of CVD are CHD and stroke, with nearly half of CVD deaths throughout the UK caused by CHD and a quarter by stroke. CHD by itself is the greatest single cause of death in the UK. In 2019, around 64000 deaths were due to CHD, accounting for 13% of all male deaths and 8% of all female deaths.

The improvements in survival have led to a high prevalence of people living with CVD and consequently huge amounts of healthcare and economic costs. Data from the Global Burden of Disease Study show that the number of prevalent CVD cases worldwide has increased rapidly since 1990, reaching 523 million in 2019 [3]. The total cost attributed to CVD was estimated at US$863 billion in 2010, more than half (55%) of which came from direct healthcare costs and the remaining from indirect costs (productivity loss from disability or premature death and lost work time because of medical care). Overall, the global CVD cost is expected to rise and exceed US$1 trillion by 2030 [7]. In the UK, it is estimated that currently 2.3 million people are suffering from CHD and 1.3 million people have survived a stroke [8]. With such a large patient population, the UK spent £9 billion on treating CVD each year. Taking indirect costs into account, CVD results in an economic impact of £19 billion to the UK economy each year [8].

In summary, CVD imposes a tremendous public health and economic burden around the globe, including the UK. Despite the declining trend in mortality, the huge number of patients who survive with the condition and the related costs underscore the importance of improving healthcare for CVD patients.

1.2 Alcohol consumption and related harms

Alcohol is a widely used psychoactive substance, which has toxic and dependence-producing properties [9]. Population levels of alcohol consumption are typically presented as three indicators: prevalence of current drinkers, total alcohol per capita consumption in litres of pure alcohol per person per year, and consumption in grams of pure alcohol per person per day. According to the most recent data published by the World Health Organization (WHO) [10], almost half of the global adult population (43%), which is 2.348 billion people of the population aged 15 years and over, are current drinkers. Taking into account both recorded and unrecorded alcohol (alcohol that is not accounted for in official statistics owing to unregulated production or importation), per capita consumption in the adult population worldwide was 5.5 litres of pure alcohol in 2005 (which translated into 11.9 grams of pure alcohol per person per day) and this had increased to 6.4 litres (13.9 grams per day) in 2016. Among drinkers per capita consumption rose globally from 11.5 litres (25.0 grams per day) to 15.1 litres (32.8 grams per day) over the same period, with about one quarter of all alcohol estimated to be consumed in the form of unrecorded alcohol.

Alcohol consumption is deeply ingrained within Western society. In 2017, an estimated 29.2 million people in the UK population drank alcohol [11]. In England, latest data from the HSE 2019 show that 80% of people aged 16 years and over drank alcohol in the previous year, and 48% drank alcohol at least once per week; there was a higher proportion of men than women who drank alcohol in 2019 (83% and 78%, respectively), with 55% of men and 41% of women drinking alcohol at least once per week [12]. Over the past few decades, the UK has seen a marked increase in recorded per capita consumption, from 7.1 litres (15.4 grams per day) in 1961 to 9.8 litres (21.3 grams per day) in 2016 [13]. Together with consumption of unrecorded alcohol, the annual per capita consumption in the UK reaches 11.4 litres (24.8 grams

per day), which is higher than the European average of 9.8 litres (21.3 grams per day). The UK also has a higher prevalence of heavy episodic drinking (29.8%; defined as 60 grams or more of pure alcohol on at least one single occasion at least once per month) compared to European (26.4%) or global (18.2%) averages [10].

Alcohol is associated with a large range of health conditions and remains one of the leading modifiable risk factors for the global disease burden [14]. Using a comparative risk assessment approach, Shield et al. [15] estimated that worldwide in 2016, alcohol was responsible for 5.3% of all deaths (3.0 million deaths) and 5.0% of all disability-adjusted life years (that is 131.4 million years of healthy life lost through disability and premature mortality), with the main contributors being injuries (intentional and unintentional) and digestive diseases. In keeping with the trend in alcohol consumption (as described above), the UK recorded 8974 deaths from alcohol-specific causes in 2020, an increase of 18.6% compared with 2019. More than three-quarters of these deaths were caused by alcoholic liver disease [16]. Indeed, within the UK, liver disease is the only major cause of death that is still rising year on year, with numbers increased by 400% since 1970, and is the biggest cause of death in people aged between 35-49 years old [17]. Consequently, the annual financial burden of alcohol on the UK society, through the increased costs of healthcare, policing, absenteeism, and other social problems, has been estimated at around £21 billion [18].

The huge burden and predicted increase in use until at least 2030 [19] highlight the need to implement the best evidence-based alcohol policies. Reducing the use of alcohol may also have a beneficial impact on other behavioural health risk factors, with studies consistently suggesting that alcohol changes affect tobacco more than tobacco changes affect alcohol [20]. Existing interventions tend to focus solely on heavier drinkers, through healthcare and social services and awareness-raising activities. Although treating alcohol dependence is important, clinical addiction treatment has not been shown to reduce population-level consumption and related harms [21]. Information dissemination and education alone that seek to change individuals' drinking behaviour have been largely unsatisfactory [22]. Despite being recommended by the WHO as the most cost-effective alcohol policies, across-the-board measures addressing

the physical availability, marketing, and price and taxation of alcohol are being implemented at a very slow pace. Data from 173 countries, which responded to the 2016 Global Survey on Alcohol and Health [10], show increasing number of licences to distribute and sell alcohol, with about two in five countries reporting growth in the number of licences to produce alcohol. Almost half of the countries have no restrictions on advertising alcoholic beverages on the internet and social media, and fewer than half of them use price strategies such as adjusting taxes to keep up with inflation and income levels, imposing minimum unit pricing or banning below-cost selling or volume discounts. A common argument against more stringent regulations and advocated by the alcohol industry is that these control policies would penalise the majority of drinkers who consume alcohol moderately, and that, because of the perceived benefits of alcohol on health conditions like CVD, moderate drinkers should be free from most interventions.

1.3 Alcohol consumption and CVD

1.3.1 Cardio-protective effect of alcohol in general population

Unlike the well-established adverse effects of alcohol use on conditions such as liver cirrhosis, injuries and certain cancers [23], moderate drinking has been associated with a lower risk of CVD versus non-drinking or heavier consumption (termed the J-shaped curve) in an extensive body of research on general populations, though whether the association is causal in nature remains under debate [24-26]. A comprehensive study addressing the association of alcohol with CVD outcomes in general population was undertaken by Ronksley et al. in 2011 [27]. By pooling data from 84 longitudinal cohort studies, Ronksley et al. assessed a broad array of relevant cardiovascular outcomes which included mortality from total CVD, CHD or stroke, and incidence of CHD or stroke. In accordance with many meta-analyses on this topic [28-33], their results showed that, compared with non-drinking, 2.5-14.9 grams of alcohol per day was associated with a 14-25% reduction in the risk of all five outcomes, while larger amounts of alcohol increased risks for stroke incidence and mortality. When studies were pooled chronologically, they found that the overall relations between alcohol intake and CVD/CHD became apparent at least one decade ago, and subsequent studies have made little changes to the estimated

associations. Similar observations have also been reported in more recent large-scale studies [34-37]. For example, a population-based cohort study, which included over 1.9 million participants and removed former/occasional drinkers from the non-drinking group, found an elevated risk of CHD, CVD and all-cause mortality among non-drinkers compared with moderate drinkers (within contemporaneous UK guidelines of 21 units per week for men and 14 units per week for women), whereas drinking exceeding the guidelines increased the risk of experiencing all outcomes except CHD [37].

1.3.1.1 Roles of drinking patterns and beverage type

In addition to the amount of alcohol consumed, the effect of alcohol on cardiovascular health can also vary depending on the pattern of consumption. In particular, binge or episodic heavy drinking has been found to increase the risk of CVD, modifying the protective association seen for average moderate drinkers. In a meta-analysis of 14 studies involving 4718 coronary events, heavy irregular drinking occasions (>60 grams of pure alcohol per occasion) were significantly associated with a 45% increased risk of CHD morbidity and mortality after controlling for average total alcohol intake [38]. Similar results have been reported in another meta-analysis of seven studies comparing two distinct drinking groups with the same average alcohol intake [31]: moderate drinkers (average intake >0 and <30 grams per day) who engaged in heavy episodic drinking, as compared with lifetime abstainers, had a pooled relative risk (RR) for developing CHD of 1.12 [95% confidence interval (CI)=0.91-1.37], whereas drinkers with the same average amount but without heavy drinking occasions had a pooled RR of 0.64 (95%CI=0.53-0.71). Using two large datasets from a community and an outpatient population, respectively, a recent study from USA [39] examined drinking frequency of 434321 participants and found elevated risk of cardiovascular and total mortality in binge drinkers (consuming 5 or more drinks on an occasion) and very frequent drinkers (6-7 times weekly), compared to those who consumed alcohol in moderate amounts 3 times weekly. Previous studies have also linked binge drinking pattern with higher stroke risk [40-42]. Binge drinking can lead to excessive concentrations of alcohol at the tissue level, accelerates alcohol metabolism and generation of reactive oxygen species and alcohol metabolites, and disrupts the antioxidant mechanisms [43]. Consequently, the UK Chief Medical Officers have advised

people who regularly drink as much as 14 units a week to spread their drinking evenly over 3 or more days per week [44].

Furthermore, there has been much discussion about whether different types of alcoholic beverage have differential influences on health. Some postulate that drinking wine may confer a greater cardiovascular benefit than other forms of alcohol, because wine contains polyphenols (like resveratrol and flavonoids) which have antioxidant, anti-inflammatory, and cytoprotective properties [45]. Regular consumption of wine, especially red wine, has often contributed to explain the so-called French Paradox – the observation of a low incidence of and mortality rates from CHD in France despite the fact that saturated fat intakes, serum cholesterol, blood pressure and prevalence of smoking are no lower there than elsewhere [46]. However, most studies investigating the role of beverage type have found no major differences in CVD outcomes [33, 47, 48], indicating that the substantial portion of the apparent protection is from alcohol itself, rather than other, variable components [49]. Significant imbalances present between drinkers of different beverages with respect to various socio-demographic and lifestyle factors [50]. The differential cardio-protective effect of wine is accordingly most likely confounded by an overall more favourable cardiovascular risk profile among wine drinkers, as well as by the fact that wine is more often consumed in moderation in comparison to beer or spirit [51].

A recent published cohort study on 309123 UK participants suggested that consuming alcohol without food was associated with higher mortality (HR=1.10, 95%CI=1.02-1.17) relative to consumption with food when the same amount of alcohol was consumed overall; drinking with or without food however did not have an association with the risk of major cardiovascular events, liver cirrhosis, accidents/self-harm and cancer incidence [52]. In an Italian study, compared to drinkers of wine with meals, drinkers of wine outside meals were found to be at higher risk of all-cause, non-CVD and cancer mortality independent of the amount of alcohol consumed [53]. It is hypothesised that the presence of food causes prolonged gastric emptying, and that alcohol is absorbed more slowly in the intestine, resulting in lower and delayed peak blood alcohol levels [54, 55].

1.3.1.2 Putative biological mechanisms

Meanwhile, there is also some evidence that indicates the existence of

mechanisms by which alcohol might protect against CVD [56, 57]. Lipoproteins, namely high-density lipoprotein (HDL, commonly known as the 'good' cholesterol), have been considered as the primary biological pathway involved in the alcohol-CVD association [47]. In a meta-analysis of 63 feeding studies in this area, Brien et al. systematically reviewed the effects of alcohol intake on 21 candidate causal biomarkers and found that moderate alcohol consumption benefited a variety of the assessed biomarkers [58]. Specifically, for 30 grams alcohol (or about 3.5 UK units) consumed per day Brien et al. reported an increase in circulating HDL-cholesterol level of 3.66 mg/dL (95%CI=2.22-5.13) and an increase in apolipoprotein A-I (Apo A-I, the main structural and functional protein component of HDL) of 8.67 mg/dL (95%CI=6.81-10.32). Similar results have been found in a more recent randomised feeding trial conducted among men at high cardiovascular risk and without documented CVD, where serum HDL-cholesterol, Apo A-I and Apo A-II significantly increased by 5%, 6% and 7%, respectively, after four weeks of moderate alcohol use (30 grams per day) [59]. It is, however, noteworthy that the extent to which changes in HDL-cholesterol alter risk of cardiovascular adverse outcomes remains controversial. Pharmaceutical drugs that simply raise the amount of circulating HDL-cholesterol have not consistently resulted in decreased CVD and mortality risk [60, 61], bringing into doubts the potential cardiovascular benefits of alcohol-induced increase in HDL concentration.

Low-density lipoprotein (LDL, the 'bad' cholesterol) is a well-established risk factor for CVD. While the meta-analysis by Brien et al. [58] found no association between levels of alcohol consumption and LDL-cholesterol, others suggested that an association might exist and vary by population characteristics [62]. With increasing alcohol intake, circulating LDL-cholesterol has been reported to be decreased in Japanese [63] and Danish men and women [64] but increased in elderly Italian men [65] and Turks [66]. Discrepancies in analyses of different populations may partly result from allele-specific genetic effects [67]. For example, a previous study identified interactions between three ApoA5 genotypes and alcohol in determining serum LDL-cholesterol levels [68], and analysis of the Spanish EPIC cohort found that higher LDL-cholesterol with alcohol intake was primarily restricted to those carrying at least one copy of the Apo E4 allele [69].

Observational studies and meta-analyses have reported that moderate alcohol consumption was associated with lower risk of type 2 diabetes mellitus (T2DM) [70-72]. A comprehensive meta-analysis of 38 studies, representing 125926 incident T2DM cases in 1.9 million individuals, found a J-shaped relationship between alcohol intake and T2DM risk [70]. Compared with abstainers, reductions in risk were recorded at drinking levels of less than 63 grams of alcohol per day, with risk increasing above this threshold. Peak risk reduction was observed at 10-14 grams per day, with a decrease of 18% in hazards. Moderate drinking is demonstrated to increase insulin sensitivity and glucose metabolism by inhibiting fatty acid release from adipose tissue and elevating levels of adiponectin [73, 74]. Consumption of 30 grams of alcohol per day has been found to reduce insulin concentration during fasting by 19.2% and improve insulin sensitivity by 7.2% in nondiabetic postmenopausal women [75]. Also, similar alterations in glucose metabolism have been seen in patients with diabetes [76] and metabolic syndrome [77]. Increased insulin sensitivity, which is the converse of insulin resistance, is related to a decreased risk of developing T2DM and CVD.

Systemic inflammation is associated with cardiovascular risk [78, 79], and alcohol appears to have anti-inflammatory properties at low dose, most likely mediated through changes in cytokine profiles and cell signalling pathways [80-82]. It has been reported that, compared with non-drinkers and heavy drinkers, moderate drinkers tended to have lower levels of C-reactive protein (CRP), interleukin (IL)-6 and IL-1 receptor antagonist, an inflammatory marker profile which is consistent with conferring a reduced risk of developing CHD [83]. Although investigated to a lesser extent, alcohol in moderation may also have favourable effects on clotting-fibrinolysis system [84-86] and endothelial function [87, 88]. Given the crucial role of thrombosis/atherosclerotic arteries in major cardiovascular events, these effects may be important in mediating the posited benefits conferred by alcohol and require further evaluation.

1.3.1.3 Controversies over the cardio-protective effect

Nevertheless, many continue to question the cardio-protective effect of moderate drinking due to a number of methodological limitations in the current evidence base, which is comprised mainly of observational studies [25, 89].

Important among these are residual confounding and reverse causality, issues that plague epidemiological research more generally in efforts to establish causal inference [90]. Specifically, many cardiovascular risk factors have been found to be more prevalent among non-drinkers than moderate drinkers [91]; these factors, if not adequately accounted for, can lead to spurious conclusions. There are also concerns about misclassification and selection bias that are more pertinent to the investigation of alcohol-CVD association [92]. The best-known example of the former is 'sick quitter' bias, whereby individuals who may have quit drinking owing to illness are included in the non-drinking reference group, making moderate drinkers appear to be at lower risk of adverse outcomes by comparison [93]. Healthier or more resilient drinkers are more likely to be enrolled into studies later in life, resulting in selection bias that favours drinkers in relation to non-drinkers [94]. Furthermore, although moderate alcohol consumption has been reported to promote beneficial changes in several biomarkers of cardiovascular health in short-term interventional studies (as described above), such benefits may only be transitory [90]. Alcohol can have delayed and/or cumulative effects [95], which can only be clarified with a long duration of follow-up. As long-term clinical trials of moderate alcohol use seem impractical and unethical, observational studies with more sophisticated designs are warranted to confirm or refute the currently still probably beneficial effect of moderate drinking [24].

Mendelian randomisation (MR) is an approach that has become increasingly popular in recent years for investigating the causal effect of alcohol on health. As a type of instrumental variable (IV) analysis, MR utilise genetic variants as proxies for exposures [96]. Unlike the exposures of interest, genetic variants are randomly assorted at meiosis. As such, observational studies based on this approach mimic the features of a randomised trial and are therefore not generally susceptible to bias from unmeasured confounding and reverse causation (that are typical of conventional observational epidemiology as discussed above), provided that all assumptions underlying the MR design hold true [97]. Additionally, effects derived from MR research are thought to be equivalent to lifetime differences, thereby reducing issues pertinent to transient fluctuations in exposures [98].

MR studies examining the causal role of alcohol in moderation on

cardiovascular health have yielded mixed results and varied in their methodology. For example, using the single nucleotide polymorphism (SNP) rs1229984 in alcohol dehydrogenase 1B (ADH1B) as the genetic instrument, Silverwood et al. [99] performed a MR study among 80057 individuals of European ancestry (sourced from the Alcohol-ADH1B Consortium) and found evidence for a non-linear effect of alcohol consumption on several cardiovascular traits, such as CRP, body mass index (BMI) and waist circumference, suggesting that moderate drinkers had a more favourable cardiovascular risk profile compared to non-drinkers. Such causality, however, was not found in MR studies of Chinese populations, where aldehyde dehydrogenase 2 (ALDH2)-rs671 alone [100] or combined with ADH1B-rs1229984 [101] served as the instruments. Given that MR is relatively new and substantial methodological heterogeneity (and weakness) exists across current MR studies on alcohol's relation to CVD, it is not yet possible to draw definite conclusions about causality of the associations found. Particularly, MR should not yet be considered as a substitute for long-term randomised trials and has its own potential sources of bias, including weak instruments, collider bias and residual population stratification [102]. Nevertheless, being a rapidly evolving approach, MR provides new opportunities to test causality in alcohol research. With continuous progress in methodology, MR is expected to add significantly to the ongoing debate about the potential health benefits of moderate drinking; this is discussed further in Chapter 5 Section 5.3.2.

1.3.2 Impact of alcohol on CVD patients

As indicated in Section 1.1, despite the worldwide falling trend in CVD mortality rates, the number of CVD patients may actually be increasing because of the more advanced treatments of these patients and also the ageing of populations [103]. More importantly, this enlarging patient group carries a very high risk for subsequent events [104]. Therefore, CVD patients have been recognised as top priority for reducing CVD burden, while improving wellbeing and preventing cardiovascular events (secondary prevention) have been regarded as essential goals of their healthcare [105].

Lifestyle and dietary habits interventions are the cornerstone of CVD prevention efforts [106]. However, the impact of alcohol consumption on CVD patients'

long-term prognosis remains less well documented and recommendations for patients regarding upper limits of drinking vary substantially across different guidelines (with some examples listed in Box 1.1) [107-110]. Noteworthily, these recommendations are supported mainly by evidence from general population studies. While light to moderate drinking appears to be cardio-protective in general populations (see Section 1.3.1), it may be erroneous to extend the posited cardio-protective effects to CVD patients due to their more advanced age, higher rate of comorbidities, compromised blood vessels as well as the prescribed medications they take to prevent future events [111, 112]. Specifically, with the possibility of disease progression and recurrent events, patients with established CVD may derive considerable benefit from any protection conferred by moderate drinking. Alternatively, these patients may become more sensitive to alcohol's adverse effects on several cardiovascular functions such as raised heart rate and blood pressure levels [113, 114], shifting the overall association away from a clinical benefit. Though not fully understood, epidemiological evidence indicates that the biological mechanisms by which alcohol may influence CVD prognosis are different from those mediating the initial disease onset (detailed further in Chapter 2 Section 2.4) [115, 116]. Alcohol has been reported to have no direct protective effect on myocardium following ischaemia-reperfusion injury in some experimental studies [117, 118]. These findings further stress the need for clarifying the role of alcohol in the patient groups, despite a significant body of literature on alcohol consumption and primary events from the general population.

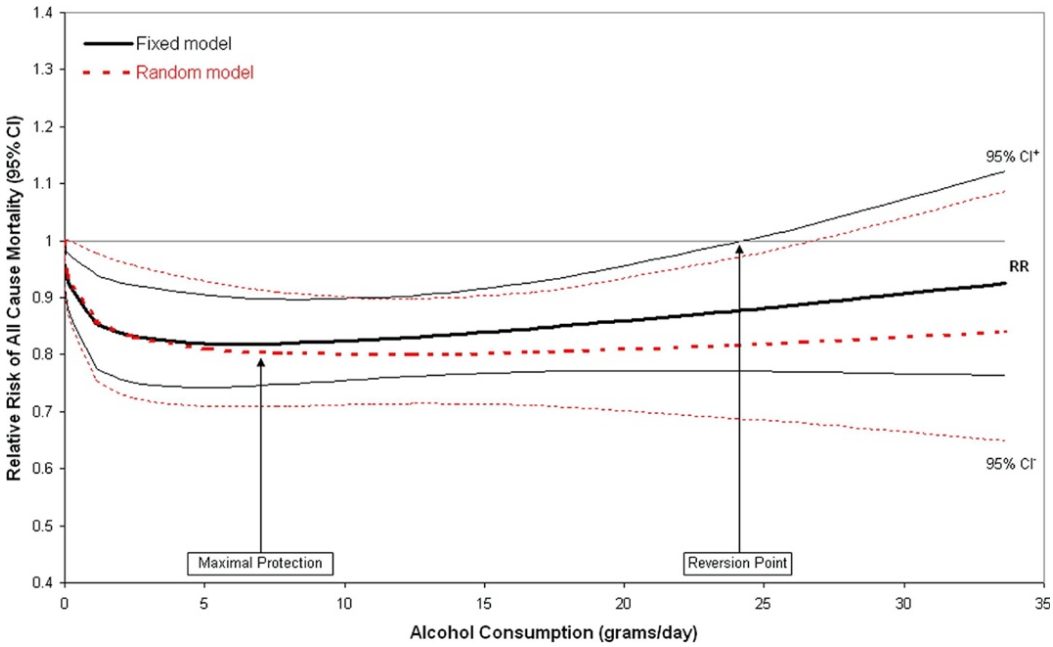
Box 1.1 Recommendations on alcohol consumption for CVD secondary prevention

- ***AHA/ACCF (American Heart Association/American College of Cardiology Foundation) Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update:*** "All patients should be counselled regarding the need for lifestyle modification: weight control; increased physical activity; alcohol moderation – up to 1 drink per day for women and up to 2 drinks per day for men according to the national dietary guidelines with 1 drink equal to 14 grams of ethanol [119]; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products [108]."
- ***Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the AHA/American Stroke Association (2014):*** "Patients with ischemic stroke, TIA, or haemorrhagic stroke who are heavy drinkers should eliminate or reduce their consumption of alcohol; light to moderate amounts of alcohol consumption (up to 2 drinks per day for men and up to 1 drink per day for nonpregnant women, with 1 drink equal to 14 grams of ethanol) may be reasonable, although non-drinkers should not be counselled to start drinking [109]."
- ***Acute coronary syndromes NICE (National Institute for Health and Care Excellence) guideline (2020), 1.9 Lifestyle changes after an MI:*** "For advice on alcohol consumption, see the UK government drinking guidelines [107] – men and women should not regularly drink more than 14 units (or equivalent to 112 grams) of alcohol per week [44]."
- ***Prevention of Cardiovascular Disease: Pocket Guidelines for Assessment and Management of Cardiovascular Risk (WHO, 2007), Part 2 Management of people with established CHD, CeVD or peripheral vascular disease (secondary prevention):*** "Individuals who take more than 3 units (or equivalent to 30ml≈23.7 grams) of alcohol per day should be advised to reduce alcohol consumption [110]."

Research on the relations between alcohol consumption and prognosis among CVD patients has been sparse and inconsistent. The most recent meta-analysis to have investigated this association was conducted by Costanzo et al. in 2010 (referred to as the 2010 meta-analysis below) [120]. By pooling data of 16351 patients with a history of MI, angina, or stroke from eight studies published between 1998 and 2008, they found a J-shaped dose-response relationship between alcohol and mortality, with the greatest reduction in risk evident at about 7 grams per day for all-cause mortality (RR=0.82, 95%CI=0.90-0.75) and 8 grams per day for cardiovascular mortality (RR=0.78, 95%CI=0.87-0.70) relative to non-drinkers (Figure 1.1).

Unfortunately, the 2010 meta-analysis was limited to studies on mortality and did not include any non-fatal outcomes. CVD patients are at high risk of recurring events and those non-fatal events can severely impair their quality of life [121, 122], it is therefore of great importance to examine the association of alcohol with cardiovascular morbidity, thereby providing a more complete picture of how alcohol consumption can be managed for optimal secondary CVD prevention. Furthermore, all the individual study estimates contributing to the 2010 meta-analysis were calculated according to a single baseline measure of alcohol intake, despite apparent changes in drinking behaviour across the life course [123] and findings that instability in drinking behaviour over time increases CHD/mortality risk among general populations (discussed further in Chapter 4 Section 4.1) [124-126]. While several new studies addressing alcohol and CVD patients' prognosis [127-129] have been published in the decade since the 2010 meta-analysis, no study to date has examined the impact of changing drinking levels in this patient population. Large knowledge gaps remain regarding alcohol consumption over time amongst CVD patients and the associated health consequences.

(a)



(b)

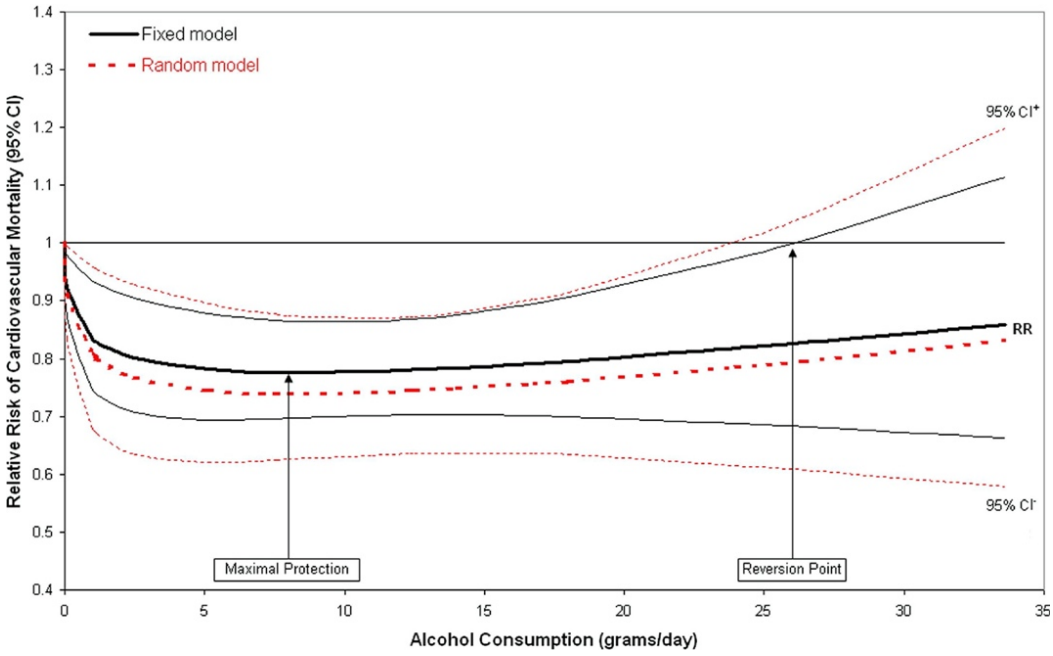


Figure 1.1 Association of alcohol consumption with the risk of (a) all-cause mortality and (b) cardiovascular mortality in CVD patients, a study by Costanzo et al. [120]

1.4 Aims and objectives

The overarching aim of this thesis is to investigate the association between alcohol consumption and long-term prognosis in patients with established CVD. This will include determining the upper thresholds of patients' alcohol intake

associated with lower risk for mortality as well as cardiovascular morbidity, to help in the formulation of evidence-based low-risk drinking guidelines. There will also be particular focus on a longitudinal, trajectory-based approach that illustrates and accounts for the dynamic diverse nature of alcohol use in CVD patients, thereby improving the validity of estimates of the association between alcohol and health risks.

The specific objectives of this thesis are as follows:

(1) To estimate the dose-response relationships between alcohol consumption and risk of mortality and subsequent cardiovascular events in CVD patients (Chapter 2),

(2) To describe patients' mean trajectories of alcohol consumption and possible changes in mean consumption in relation to their CVD onset (Chapter 3),

(3) To explore the heterogeneity in trajectories of alcohol consumption among CVD patients (Chapter 4),

(4) To investigate how different trajectories of alcohol consumption are associated with patients' mortality risk (Chapter 4), and

(5) To assess the utility of taking a longitudinal approach in developing a better understanding of the association between alcohol and health outcomes (Chapter 4).

Chapter 2 Association of alcohol consumption with morbidity and mortality in CVD patients: update and expanded meta-analysis (Study 1)[1]

2.1 Introduction to the study

As discussed in the previous chapter (see Section 1.3.2), the latest meta-analysis study (the 2010 meta-analysis [120]) to have explored the association between alcohol and CVD patients' long-term prognosis included only mortality outcomes and was published over one decade ago. This chapter therefore presents an updated and expanded meta-analysis study that has included de novo findings from three large-scale contemporary cohorts as well as those from 12 published studies identified through a systematic review. In addition to estimating risk of mortality among CVD patients, this meta-analysis also examined the dose-response association between alcohol intake and subsequent cardiovascular events. Quantitative syntheses were conducted on each outcome of interest and reported in this chapter following a two-step framework, first calculating estimates of the association separately in the contributing cohorts (see the sections below on 'De novo cohort analyses') and then meta-analysing the results together with those available in published literature (see the sections below on 'Systematic review and meta-analysis').

2.2 Methods

2.2.1 De novo cohort analyses

2.2.1.1 Study cohorts and participants

Data were derived from participants in HSE [130], SHeSs [131], and UK Biobank [132]. The datasets were chosen for their large sample size and coverage of pertinent variables (alcohol intake data, relevant covariates and verified outcome data). Complete cohort profiles are available via the above citations. Briefly, HSE/SHeSs is a series of surveys which use a multistage stratified design to draw a nationally representative sample of the general

[1] Some of the findings presented in this chapter have informed the journal article: Ding C, O'Neill D, Bell S, Stamatakis E, Britton A. Association of alcohol consumption with morbidity and mortality in patients with cardiovascular disease: original data and meta-analysis of 48423 men and women. BMC Med. 2021;19(1):167. Please see Appendix 2.1 for full paper.

population living in England/Scottish households. Each survey year consists of a new sample of private residential addresses and participants and entails a household interview followed by a nurse visit to collect baseline information on demographics, anthropometry, self-reported health, and health-related behaviours. Participants have been asked for consent to follow-up through data linkage, thus converting cross-sectional survey data into a longitudinal study with samples from different survey years assessed across a range of health outcomes. The present analyses combined data from the 1994-2008 HSE datasets and the 1995, 1998 and 2003 SHeSs datasets and were restricted to participants aged 16 years and over self-reporting diagnosis of MI/angina (not recorded separately) or stroke prior to baseline.

UK Biobank is a prospective study of more than 500000 participants, aged 40-69 years when recruited in 2006-2010. Participants were invited to attend one of 22 centres across England, Scotland, and Wales, where a touchscreen questionnaire was completed, a nurse-led interview was performed, and physical measurements were taken. Participants were included in the data analyses if they had MI, angina, or stroke before recruitment based on record linkage to the Hospital Episode Statistics (HES, 2 December 1980 onwards). Algorithmic definitions developed by the UK Biobank Outcome Adjudication Group were applied for identification of MI [133] and stroke [134]; overall accuracy of algorithmically defined events using hospital records in UK Biobank was high, with an estimated positive predictive value of 75-100% for MI and 68-90% for stroke [135]. Classification algorithms for angina were developed using the process and data fields (diagnoses in the primary or any secondary position) recommended by the Group [135] with relevant codes from the International Classification of Diseases (ICD) Edition 9 and Edition 10 listed in Appendix 2.2 [136].

2.2.1.2 Alcohol assessment

At baseline of each cohort, participants were asked about their drinking status (never, former, or current drinker) and were asked to report their average weekly or monthly consumption of different types of alcoholic beverages. These measures were then converted into standard UK units and summed to obtain an average alcohol consumption in units per week, where one unit contains 8

grams of ethanol [137] and is equivalent to half a pint of beer/cider, half a glass of wine, one measure of spirits, or one glass of fortified wine [138]. A large glass of alcopops and other forms of alcohol count as 1.5 units [139]. Former drinkers were categorised separately from never drinkers, and never drinkers were used as the reference group to provide additional data for meta-analyses on different non-drinking reference group. Current drinkers were categorized into three groups in line with the NICE definitions: low-level drinkers (≤14 units per week), medium-level drinkers (>14 to ≤50 units per week for men, >14 to ≤35 units per week for women), and high-level drinkers (>50 units per week for men, >35 units per week for women) [140]. Additional information on drinking patterns (the timing of consuming alcohol in relation to food and frequency of binge drinking) was obtained from UK Biobank, but not available from HSE/SHeSs.

2.2.1.3 Covariates

Covariates considered in analyses were assessed at baseline and included age, sex, smoking status (never, ex-smoker, or current smoker), self-reported history of diabetes and hypertension, socioeconomic position or education, BMI, and regular medications (cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin). In HSE/SHeSs, socioeconomic position was defined using the participant's occupational classification, categorised as low (semi-skilled or unskilled manual), intermediate (skilled non-manual or manual) or high (professional or managerial technical) [141]. For UK Biobank participants, highest educational qualification was used as a proxy for socioeconomic position and categorised into four levels: (1) none; (2) O levels, General Certificate of Secondary Education (GCSE), Certificate of Secondary Education (CSE) or equivalent; (3) A/AS levels, National Vocational Qualification (NVQ), Higher National Diploma (HND), Higher National Certificate (HNC) or other professional qualification; and (4) college, university degree or higher [142].

2.2.1.4 Outcome

Alcohol consumption was assessed in relation to three outcomes: all-cause mortality, cardiovascular mortality (ICD-10 codes I00-I99) [143] and major cardiovascular events (as defined below). Date and underlying cause of death (coded with ICD-10) were ascertained by national death registries and all

cohorts contributed to the mortality analyses. Participants were censored at their date of death (if not from cardiovascular causes), the date they left the UK or the end of follow-up (until 14 February 2011 in HSE, 31 December 2009 in SHeSs or 9 February 2018 in UK Biobank), whichever came first.

Cardiovascular events were defined as a composite of angina, fatal and non-fatal MI and stroke, revascularization procedures (angioplasty or coronary artery bypass graft), death from heart failure (HF), and sudden cardiac death, and only UK Biobank contributed data to the analysis on cardiovascular events. Non-fatal events were identified from linked HES records using primary diagnoses coded with ICD-10 and procedures coded with OPCS4 (the Office of Population Censuses and Surveys' Classification of Interventions and Procedures Version 4), as given in Appendix 2.2. Any hospital or death records that occurred within 28 days of the date for a detected event were considered to relate to the same event [144]. Participants were followed up until the date of their first detected event or were censored on the date they left the UK or the last date of data linkage (31 March 2017).

2.2.1.5 Statistical analysis

Due to differing study designs and unavailability of identical covariates (see sections 2.2.1.1 and 2.2.1.3 above), pooled analysis (individual participant data meta-analysis) of HSE/SHeSs and UK Biobank was not considered appropriate. Instead, statistical analyses were conducted for each dataset independently. Multivariable Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% CIs for the associations of different drinking categories with each outcome of interest versus never drinkers. Adjustments were made for age, sex, and smoking status in initial models and then for all covariates in maximally adjusted models. For HSE/SHeSs datasets, additional adjustment for survey wave was made using shared-frailty models to account for within-group correlations. Plots of Schoenfeld residuals against time were inspected to ensure the validity of the proportional hazards assumption (see Appendix 2.3). In stratified analyses by primary cardiovascular events, models were mutually adjusted for each other (MI, angina, and stroke) as well as all covariates. For example, models were adjusted for all covariates plus previous angina and stroke in the stratified analysis for patients with a history of MI, and for stroke

patients models were adjusted for all covariates, previous angina and MI. Interactions between drinking category and sex in relation to each outcome of interest were tested using the likelihood ratio method, comparing models with and without the interaction term. Because BMI could act as both a confounder and a mediator of the effects, a sensitivity analyses was carried out by not adjusting BMI in the maximally adjusted models. Sensitivity analysis restricted to never smokers was also performed, diminishing any residual confounding by smoking status.

2.2.2 Systematic review and meta-analysis

2.2.2.1 Search strategy and study selection

This chapter followed PRISMA and MOOSE reporting guidelines for meta-analyses of observational studies [145, 146]. Medline and Embase were searched using subject headings and free-text terms for relevant studies up to 30 July 2020. No restriction was made on language or date of publication, and the full search strategy is presented in Appendix 2.4. Also, bibliographies of eligible studies and a previous systematic review [111] on this topic were hand-searched for any studies missed by the initial database searches.

After removing duplicates and multiple reports from the same dataset (retaining the study with the longer follow-up), citations were screened by Chengyi Ding (CD) to exclude any that did not report a prospective relationship between alcohol consumption and outcomes of interest among patients with established CVD. Full text of the remaining citations was then independently assessed by two pairs of reviewers – CD plus Professor Annie Britton (AB) or Dr. Dara O'Neill (DON) – for eligibility.

Studies were selected if they met all of the following criteria:

(1) Longitudinal study design, including randomized control trials where alcohol consumption was not part of the interventions,

(2) Study population were patients with a history of MI, angina, or stroke,

(3) Exposure to alcohol was reported across at least three categories of volume, inclusive of a non-drinking group (to allow for testing curvilinear associations),

(4) Outcome was all-cause mortality, cardiovascular mortality, or subsequent cardiovascular events, and

(5) Risk estimates were adjusted at least for age, sex, and smoking status.

Studies were excluded if the reported alcohol consumption could not be converted into grams per day or if frequency counts, risk estimate, and its corresponding 95%CI were not available after contacting the authors. The inter-rater agreement for this review process was high with a Fleiss kappa of 0.85. Any disagreements were resolved by consensus. If necessary, study authors were contacted to obtain data suitable for inclusion in the meta-analyses.

2.2.2.2 Data extraction and quality assessment

Data extraction was undertaken by one reviewer (CD) and then independently checked by a second reviewer (AB/DON), using a standardized data extraction form. Extracted information included study design (setting, sample size, length of follow-up), patient demographics (primary events, baseline age, sex), assessment of alcohol use and outcomes, frequency counts and risk estimates by drinking category and confounder adjustments. Whenever available, the amount of alcohol consumed was collected, using grams of alcohol per day as the common unit of measure. To convert the number of drinks to grams in four included studies (one conducted in Italy [127] and three in USA [147-149]) which did not specify the quantity of ethanol contained in one drink, country-specific standard drinks (Italy=12 grams, USA=14 grams [150]) were applied. A factor of 0.79 was used for the conversion of millilitres to grams (where 1 millilitre of ethanol equals to 0.79 grams [151]) in one study [152]. In six studies [129, 147, 153-156], exposures to alcohol were categorised according to time periods longer than one day and were transferred into daily estimates by assuming an even distribution; for example, weekly alcohol intakes were divided by seven. Where averages were not reported for each drinking category, the midpoints of the range were chosen. For open-ended upper categories, mean values were defined as 1.2 times the lower boundary as proposed by Berlin et

al. [157]. Similar findings were observed when multiplying the lower boundary for the open-ended upper categories by 1.0, 1.4, or 1.6 rather than 1.2 (see Appendix 2.5).

Given that a non-drinking reference group was used in all included studies except one [155], risk estimates for different drinking categories compared to non-drinkers were preferred. For a single study where occasional drinkers served as the reference group [155], the risk estimates were recalculated to obtain alternative estimates each versus a non-drinker group. An Excel spreadsheet developed by Hamling et al. was applied during the recalculation to account for the non-independence between risk estimates that shared a common reference group [158]. When a study reported risk estimates with different degrees of statistical adjustment for confounding, the most adjusted one was used. Furthermore, to investigate the possible impact of over-adjustment for potential mediators on the results, a sensitivity analysis was performed by using risk estimates that were only controlled for age, sex and smoking status, the three most relevant confounding factors for the alcohol-CVD relationship [31]. RRs were used as the common measure of association across studies, and HRs were considered equivalent to RRs [70]. Study quality was assessed using the Newcastle-Ottawa Scale (see Appendix 2.6) [159]. The scale consists of eight items assessing studies in the following three dimensions: (1) selection of cohorts, (2) comparability of study design and analysis, and (3) outcome ascertainment and adequacy of follow-up. A study is awarded stars for items within each dimension for a maximum of nine stars.

2.2.2.3 Data synthesis

For each outcome of interest, a family of second-degree fractional polynomial models (FP2) was generated to perform a power transformation of the exposure variable [160]:

$$\log\mathrm{RR} = \begin{cases} \beta_1 x^{p_1} + \beta_2 x^{p_2} & \text{if } p_1 \neq p_2 \\ \beta_1 x^{p_1} + \beta_2 x^{p_2}\log(x) & \text{if } p_1 = p_2 \end{cases}$$

whereby convention x^0 (with power p=0) equals log(x) rather than 1. p_1 and p_2 were taken from a predefined set P = (-2, -1, -0.5, 0, 0.5, 1, 2, 3) which allows for a very large and varied set of functions, including U- and J-shaped curves, to

be generated. Figure 2.1 shows some examples of the FP2 curve shapes [161]. For x=0, the function would start from log RR=0 and therefore no constant term (that is the intercept) was considered in the models for the present study [162]. Best fit was defined as the model with the lowest deviance.

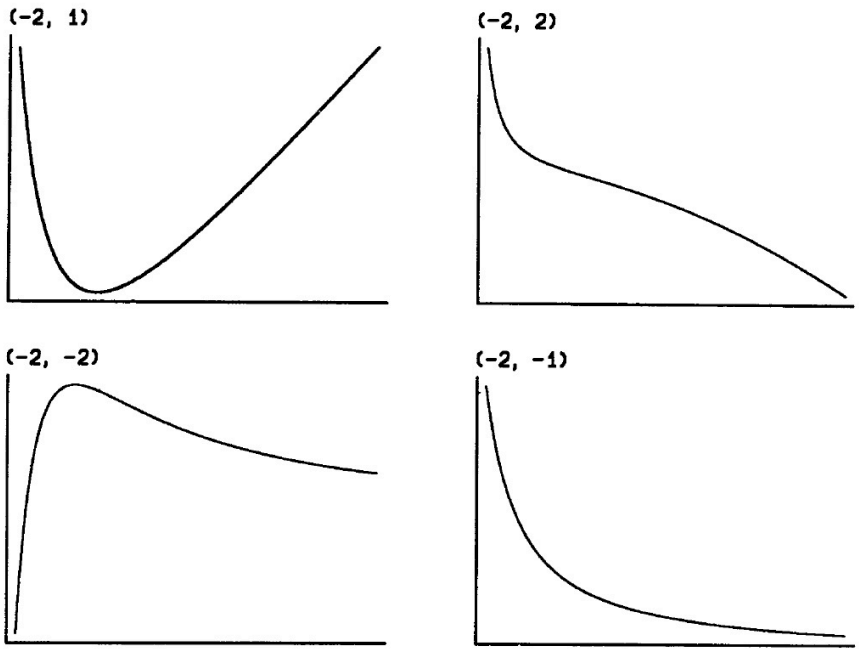


Figure 2.1 An illustration of examples of the FP2 curve shapes available with different power values of (p1, p2), a study by Royston et al. [161]

With the terms of exposure identified in the best-fitting FP2, a two-stage regression model was fitted to summarise the association between alcohol consumption and each outcome of interest. The first stage generated the dose-response model within each study and the second stage pooled study-specific trends using a random effect model to account for heterogeneity between studies [163, 164]. Heterogeneity between studies was quantified using the I^2 index [165], and a sensitivity analysis was performed using a fixed effect meta-analysis model when no heterogeneity existed. Additional sensitivity analysis was carried out by excluding studies of the lowest quality. Several pre-defined subgroup analyses were also performed according to sex, primary event, and type of non-drinking reference group and alcohol assessment for each outcome of interest.

Publication bias was assessed through visual inspection of funnel plots and Egger's regression test for asymmetry [166]. As asymmetry cannot be examined using continuous dose-response data, alcohol consumption in each study was reclassified into three groups (0-10, 10-20, and >20 grams per day) according to its averages of the reported categories. For each outcome, analysis of asymmetry was repeated for each of the three drinking groups. All statistical analyses were performed using Stata (version 15.1). A P-value (two-sided) <0.05 was considered statistically significant.

2.3 Results

2.3.1 Associations of alcohol with mortality and cardiovascular morbidity in study cohorts

As shown in Figure 2.2, complete data for the de novo cohort analyses were available for 2802 participants (MI/angina=2341, stroke=535) in HSE/SHeSs and 14386 participants (MI=5333, angina=9589, stroke=2064) in UK Biobank. Compared with participants who were included in analyses, those who were excluded due to missing data were more likely to be female, older, less educated; they also had higher BMI, a higher prevalence of diabetes, and reported less use of alcohol and cardiovascular drugs (Table 2.1).

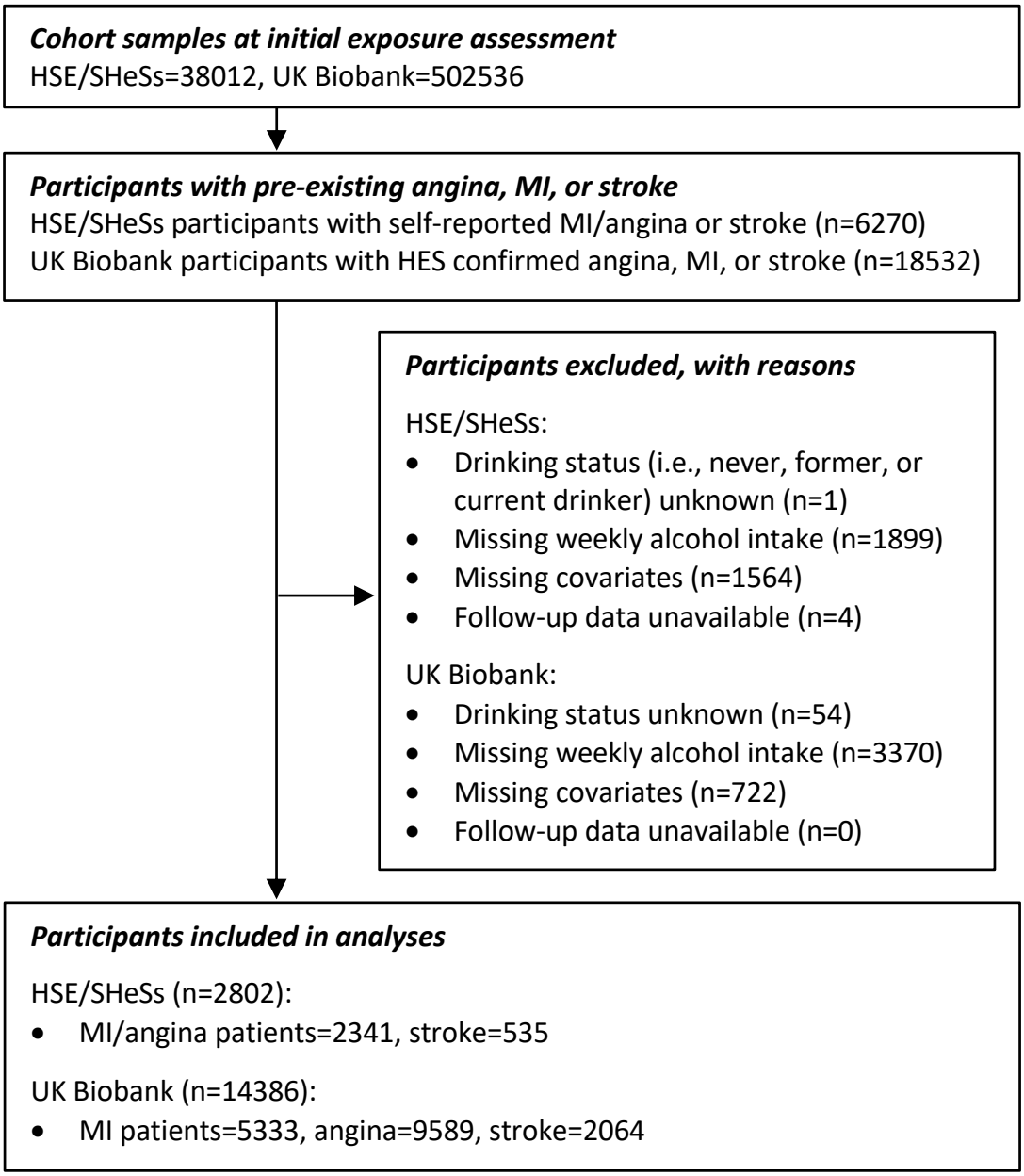


Figure 2.2 Flowchart of inclusion criteria for participants in HSE/SHeSs and UK Biobank

Table 2.1 Baseline characteristics of participants included versus excluded from analyses of HSE/SHeSs and UK Biobank

	Included	Excluded	P-value*
HSE/SHeSs			
Total N	2802	3468	
Age, mean (SD), years	67.3 (10.6)	69.1 (11.7)	<0.001
Missing	0 (0.0)	0 (0.0)	
Alcohol intake, mean (SD), g/day	9.0 (16.9)	6.3 (13.5)	<0.001
Missing	0 (0.0)	1899 (54.8)	
BMI, mean (SD), kg/m^2	28.1 (4.8)	28.7 (5.0)	<0.001
Missing	0 (0.0)	1244 (35.9)	
Sex			
Male	1598 (57.0)	1825 (52.6)	<0.001
Female	1204 (43.0)	1643 (47.4)	
Missing	0 (0.0)	0 (0.0)	
Smoking status			
Never	861 (30.7)	1197 (34.5)	0.005
Ex-smoker	1357 (48.4)	1566 (45.2)	
Current smoker	584 (20.8)	697 (20.1)	
Missing	0 (0.0)	8 (0.2)	
History of diabetes			
No	2474 (88.3)	2989 (86.2)	0.013
Yes	328 (11.7)	479 (13.8)	
Missing	0 (0.0)	0 (0.0)	
History of hypertension			
No	2408 (85.9)	2976 (85.8)	0.887
Yes	394 (14.1)	492 (14.2)	
Missing	0 (0.0)	0 (0.0)	
Socioeconomic position†			
Low	843 (30.1)	971 (28.0)	0.164
Intermediate	1312 (46.8)	1446 (41.7)	
High	647 (23.1)	807 (23.3)	
Missing	0 (0.0)	244 (7.0)	
Cholesterol-lowering medications			
No	2158 (77.0)	1244 (35.9)	<0.001
Yes	644 (23.0)	1037 (29.9)	
Missing	0 (0.0)	1187 (34.2)	
Antihypertensive medications			
No	1260 (45.0)	744 (21.5)	<0.001
Yes	1542 (55.0)	1537 (44.3)	
Missing	0 (0.0)	1187 (34.2)	
Antiplatelet agents			
No	1542 (55.0)	981 (28.3)	<0.001

Yes	1260 (45.0)	1300 (37.5)	
Missing	0 (0.0)	1187 (34.2)	
Digoxin			
No	2700 (96.4)	2167 (62.5)	0.017
Yes	102 (3.6)	114 (3.3)	
Missing	0 (0.0)	1187 (34.2)	
Warfarin			
No	2802 (100.0)	2281 (65.8)	NA
Yes	0 (0.0)	0 (0.0)	
Missing	0 (0.0)	1187 (34.2)	
UK Biobank			
Total	14386	4146	
Age, mean (SD), years	61.6 (6.2)	61.2 (6.5)	<0.001
Missing	0 (0.0)	0 (0.0)	
Alcohol intake, mean (SD), g/day	19.2 (21.4)	13.5 (17.1)	<0.001
Missing	0 (0.0)	3370 (81.3)	
BMI, mean (SD), kg/m^2	29.2 (4.9)	30.1 (5.4)	<0.001
Missing	0 (0.0)	250 (6.0)	
Sex			
Male	10161 (70.6)	2525 (60.9)	<0.001
Female	4225 (29.4)	1621 (39.1)	
Missing	0 (0.0)	0 (0.0)	
Smoking status			
Never	5360 (37.3)	1502 (36.2)	<0.001
Ex-smoker	7241 (50.3)	1768 (42.6)	
Current smoker	1785 (12.4)	675 (16.3)	
Missing	0 (0.0)	201 (4.8)	
History of diabetes			
No	11941 (83.0)	3259 (78.6)	<0.001
Yes	2445 (17.0)	887 (21.4)	
Missing	0 (0.0)	0 (0.0)	
History of hypertension			
No	6316 (43.9)	1829 (44.1)	0.809
Yes	8070 (56.1)	2317 (55.9)	
Missing	0 (0.0)	0 (0.0)	
Highest educational qualification‡			
None	4663 (32.4)	1581 (38.1)	<0.001
O levels or equivalent	2082 (14.5)	497 (12.0)	
A levels or equivalent	4623 (32.1)	1028 (24.8)	
Degree	3018 (21.0)	501 (12.1)	
Missing	0 (0.0)	539 (13.0)	
Cholesterol-lowering medications			
No	2459 (17.1)	727 (17.5)	0.001
Yes	11927 (82.9)	3032 (73.1)	

Missing	0 (0.0)	387 (9.3)	
Antihypertensive medications			
No	4313 (30.0)	1149 (27.7)	0.485
Yes	10073 (70.0)	2610 (63.0)	
Missing	0 (0.0)	387 (9.3)	
Antiplatelet agents			
No	2978 (20.7)	965 (23.3)	<0.001
Yes	11408 (79.3)	3181 (76.7)	
Missing	0 (0.0)	0 (0.0)	
Digoxin			
No	14177 (98.5)	4086 (98.6)	0.979
Yes	209 (1.5)	60 (1.4)	
Missing	0 (0.0)	0 (0.0)	
Warfarin			
No	13516 (94.0)	3914 (94.4)	0.278
Yes	870 (6.0)	232 (5.6)	
Missing	0 (0.0)	0 (0.0)	

Data are number (percentage) unless otherwise specified.
*One-way ANOVA was used on continuous data and the chi-squared test on categorical data; analyses were based on complete cases.
† Socioeconomic position was defined using the participant's occupational classification, categorised as low (semi-skilled or unskilled manual), intermediate (skilled non-manual or manual), or high (professional or managerial technical).
‡ Highest educational qualification was categorised into four levels: None; O levels/GCSE, CSE or equivalent; A/AS levels, NVQ, HND, HNC or other professional qualification; College or university degree or higher.
SD=standard deviation, NA=not applicable.

Characteristics of participants stratified by cohorts and drinking categories are presented in Table 2.2. On average, UK Biobank participants were younger and consumed more alcohol than HSE/SHeSs participants; they also had higher BMI and reported a higher prevalence of diabetes, hypertension, and taking cardiovascular drugs. Compared to never and low-level drinkers, high-level drinkers were more frequently male, current smokers and younger of age. Conversely, never drinkers had the highest proportions of female and never smokers.

It can also be seen in Table 2.2 that among 12103 current drinkers in the UK Biobank dataset, wine was the most commonly consumed beverage contributing a mean of 49.8% to total alcohol intake, followed by beer/cider (35.3%), spirits (12.9%) and fortified wine and other forms (1.9%). The same pattern was seen in all drinking categories, although high-level drinkers consumed relatively more wine than low- and medium-level drinkers; the mean percentage of alcohol derived from wine was 55.1% for high-level drinkers, 48.7% for medium-level drinkers and 50.1% for low-level drinkers. Drinkers in medium- and high-level categories more frequently reported consuming alcohol without meals than low-level drinkers.

Using online follow-up questionnaires, frequency of binge alcohol consumption (consuming six or more units of alcohol on one occasion) was measured in a very small subset of 2621 UK Biobank participants, of whom 834 (31.8%) reported binge drinking less than monthly to monthly and 489 (18.7%) weekly to daily (Table 2.2). Compared to other drinking categories, high-level drinkers had higher frequency of binge drinking, though caution is needed when interpreting the result due to large number of missing values.

Table 2.2 Characteristics of participants at baseline

	Never drinker	Former drinker	Low-level drinker	Medium-level drinker	High-level drinker	Overall
HSE/SHeSs*						
N	263 (9.4)	383 (13.7)	1630 (58.2)	458 (16.3)	68 (2.4)	2802 (100.0)
Age, mean (SD), years	69.0 (11.0)	67.1 (11.1)	68.2 (10.1)	64.2 (10.9)	60.4 (10.7)	67.3 (10.6)
Alcohol intake, mean (SD), g/day	0.0	0.0	4.0 (4.3)	28.0 (10.2)	85.1 (33.0)	9.0 (16.9)
BMI, mean (SD), kg/m^2	28.5 (5.5)	28.6 (5.7)	27.9 (4.6)	27.9 (4.1)	28.0 (4.2)	28.1 (4.8)
Female	187 (71.1)	189 (49.3)	758 (46.5)	65 (14.2)	5 (7.4)	1204 (43.0)
Smoking status						
Never	157 (59.7)	89 (23.2)	527 (32.3)	78 (17.0)	10 (14.7)	861 (30.7)
Ex-smoker	66 (25.1)	191 (49.9)	799 (49.0)	272 (59.4)	29 (42.6)	1357 (48.4)
Current smoker	40 (15.2)	103 (26.9)	304 (18.7)	108 (23.6)	29 (42.6)	584 (20.8)
History of diabetes	40 (15.2)	74 (19.3)	169 (10.4)	43 (9.4)	2 (2.9)	328 (11.7)
History of hypertension	50 (19.0)	60 (15.7)	224 (13.7)	54 (11.8)	6 (8.8)	394 (14.1)
Socioeconomic position†						
Low	104 (39.5)	138 (36.0)	494 (30.3)	83 (18.1)	24 (35.3)	843 (30.1)
Intermediate	106 (40.3)	186 (48.6)	764 (46.9)	230 (50.2)	26 (38.2)	1312 (46.8)
High	53 (20.2)	59 (15.4)	372 (22.8)	145 (31.7)	18 (26.5)	647 (23.1)
Cholesterol-lowering medications	70 (26.6)	128 (33.4)	328 (20.1)	107 (23.4)	11 (16.2)	644 (23.0)
Antihypertensive medications	168 (63.9)	247 (64.5)	883 (54.2)	217 (47.4)	27 (39.7)	1542 (55.0)
Antiplatelet agents	118 (44.9)	187 (48.8)	725 (44.5)	207 (45.2)	23 (33.8)	1260 (45.0)
Digoxin	9 (3.4)	19 (5.0)	62 (3.8)	10 (2.2)	2 (2.9)	102 (3.6)

UK Biobank						
N	1076 (7.5)	1207 (8.4)	5989 (41.6)	5222 (36.3)	892 (6.2)	14386 (100.0)
Age, mean (SD), years	61.6 (6.6)	61.1 (6.5)	61.9 (6.1)	61.6 (6.0)	60.5 (6.4)	61.6 (6.2)
Alcohol intake, mean (SD), g/day	0.0	0.0	7.9 (5.1)	30.6 (10.6)	76.7 (26.4)	19.2 (21.4)
Percentage contribution to total alcohol intake, mean (SD)						
Wine	NA	NA	50.1 (40.7)	48.7 (36.4)	55.1 (37.6)	49.8 (38.7) ‡
Beer/cider	NA	NA	32.3 (38.9)	38.9 (36.3)	32.9 (36.3)	35.3 (37.7) ‡
Spirits	NA	NA	14.7 (27.4)	11.4 (19.8)	11.1 (20.9)	12.9 (23.9) ‡
Fortified wine and others	NA	NA	2.9 (12.0)	1.0 (4.8)	0.9 (5.6)	1.9 (9.1) ‡
Alcohol usually taken with meals						
Yes	NA	NA	2685 (44.8)	1717 (32.9)	237 (26.6)	4639 (38.3) ‡
No	NA	NA	1691 (28.2)	1638 (31.4)	299 (33.5)	3628 (30.0) ‡
It varies	NA	NA	1588 (26.5)	1867 (35.8)	355 (39.8)	3810 (31.5) ‡
Missing	NA	NA	25 (0.4)	0 (0.0)	1 (0.1)	26 (2.1) ‡
Binge drinking §						
Never	NA	NA	884 (14.8)	392 (7.5)	22 (2.5)	1298 (10.7) ‡
Less than monthly	NA	NA	240 (4.0)	341 (6.5)	32 (3.6)	613 (5.1) ‡
Monthly	NA	NA	62 (1.0)	144 (2.8)	15 (1.7)	221 (1.8) ‡
Weekly	NA	NA	34 (0.6)	272 (5.2)	51 (5.7)	357 (3.0) ‡
Daily or almost daily	NA	NA	6 (0.1)	75 (1.4)	51 (5.7)	132 (1.1) ‡
Missing	NA	NA	4763(79.5)	3998 (76.6)	721 (80.8)	9480 (78.3) ‡
BMI, mean (SD), kg/m^2	30.0 (5.8)	30.2 (6.0)	29.1 (5.0)	28.8 (4.3)	29.0 (4.7)	29.2 (4.9)

Female	619 (57.5)	447 (37.0)	2242 (37.4)	743 (14.2)	174 (19.5)	4225 (29.4)
Smoking status						
Never	704 (65.4)	350 (29.0)	2616 (43.7)	1512 (29.0)	178 (20.0)	5360 (37.3)
Ex-smoker	252 (23.4)	638 (52.9)	2799 (46.7)	3045 (58.3)	507 (56.8)	7241 (50.3)
Current smoker	120 (11.2)	219 (18.1)	574 (9.6)	665 (12.7)	207 (23.2)	1785 (12.4)
History of diabetes	280 (26.0)	346 (28.7)	1026 (17.1)	676 (12.9)	117 (13.1)	2445 (17.0)
History of hypertension	637 (59.2)	764 (63.3)	3193 (53.3)	2940 (56.3)	536 (60.1)	8070 (56.1)
Highest educational qualification #						
None	432 (40.1)	564 (46.7)	1910 (31.9)	1510 (28.9)	247 (27.7)	4663 (32.4)
O levels or equivalent	141 (13.1)	150 (12.4)	900 (15.0)	742 (14.2)	149 (16.7)	2082 (14.5)
A levels or equivalent	315 (29.3)	295 (24.4)	1948 (32.5)	1760 (33.7)	305 (34.2)	4623 (32.1)
Degree	188 (17.5)	198 (16.4)	1231 (20.6)	1210 (23.2)	191 (21.4)	3018 (21.0)
Cholesterol-lowering medications	841 (78.2)	990 (82.0)	4876 (81.4)	4488 (85.9)	732 (82.1)	11927 (82.9)
Antihypertensive medications	746 (69.3)	855 (70.8)	4047 (67.6)	3774 (72.3)	651 (73.0)	10073 (70.0)
Antiplatelet agents	810 (75.3)	902 (74.7)	4655 (77.7)	4305 (82.4)	736 (82.5)	11408 (79.3)
Digoxin	16 (1.5)	29 (2.4)	86 (1.4)	66 (1.3)	12 (1.3)	209 (1.5)
Warfarin	59 (5.5)	106 (8.8)	358 (6.0)	313 (6.0)	34 (3.8)	870 (6.0)

Data are number (percentage) unless otherwise specified.
* None of the participants in HSE/SHeSs reported using warfarin on a regular basis. Data on drinking patterns were not available for HSE/SHeSs.
† Socioeconomic position was defined using the participant's occupational classification, categorised as low (semi-skilled or unskilled manual), intermediate (skilled non-manual or manual), or high (professional or managerial technical).
‡ Percentages were calculated among all current drinkers in the UK Biobank dataset (N=12103).
§ Binge drinking was defined as consuming six or more UK units of alcohol on one occasion.
# Highest educational qualification was categorised into four levels: None; O levels/GCSE, CSE or equivalent; A/AS levels, NVQ, HND, HNC or other professional qualification; College, university degree or higher.
SD=standard deviation. NA=not applicable.

During a median follow-up of 9.5 years (interquartile range [IQR]=5.7-13.0) in HSE/SHeSs and 8.7 years (IQR=8.0-9.5) in UK Biobank, there were 1257 deaths among HSE/SHeSs participants and 1640 deaths among UK Biobank participants, of which 492 (39.1%) and 631 (38.5%) deaths were from cardiovascular causes, respectively. Figure 2.3 illustrates the associations of different drinking categories with each outcome of interest, stratified by cohorts. Maximally adjusted analyses using the UK Biobank dataset found a J-shaped curve for both all-cause and cardiovascular mortality, with low- and medium-level drinkers showing a lower risk of death than never drinkers. However, no significant difference in risk was found for high-level or former drinkers compared to never drinkers. Similar J-shaped trends were observed for HSE/SHeSs, though none of the associations were statistically significant; this may be attributable to its relatively small sample size of each drinking subgroup.

As to cardiovascular events, a total of 2950 fatal and non-fatal subsequent events were recorded in the UK Biobank dataset, with a median follow-up of 7.5 years (IQR=6.8-8.5). A decreased risk was found in all categories of current drinkers compared to never drinkers (Figure 2.3).

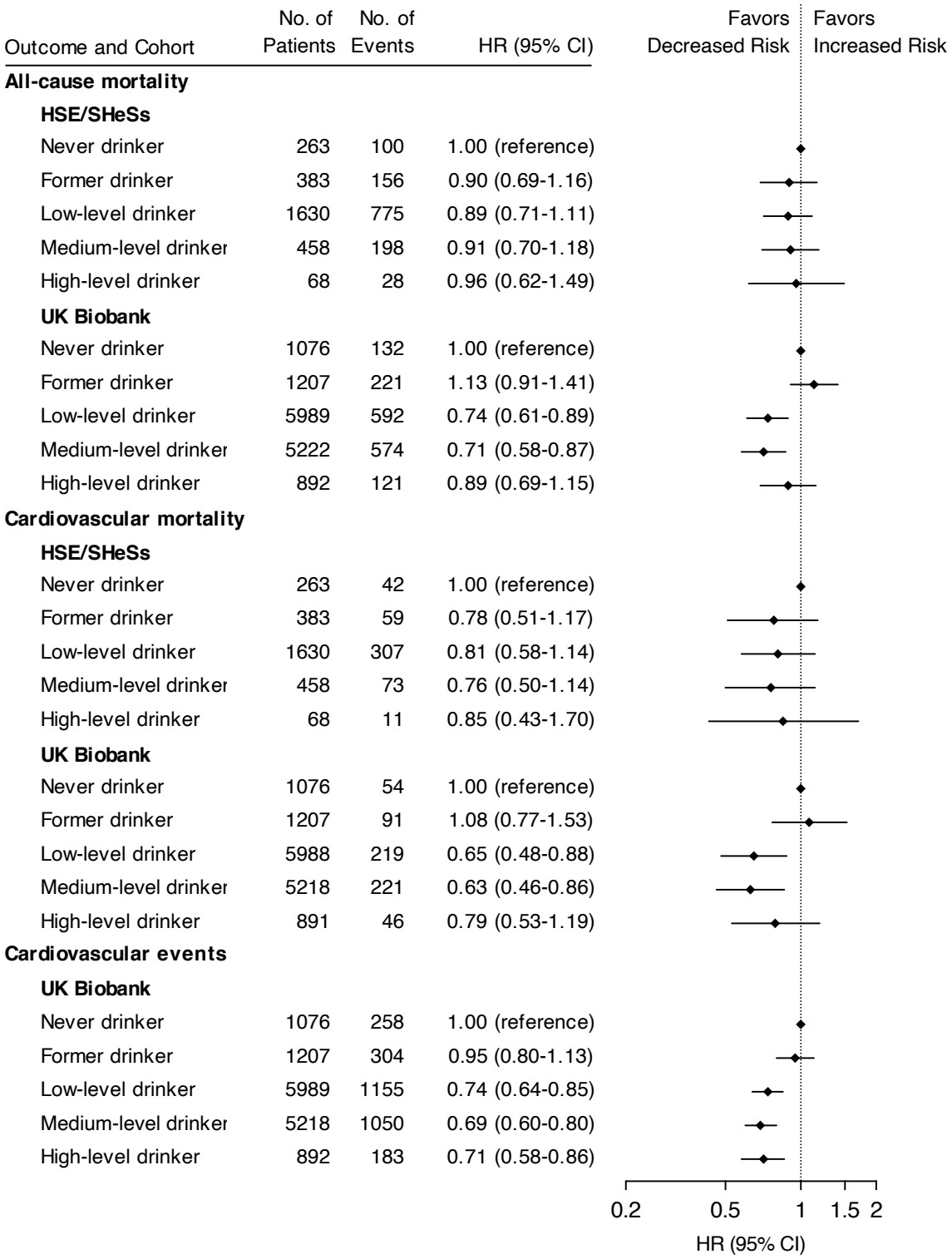
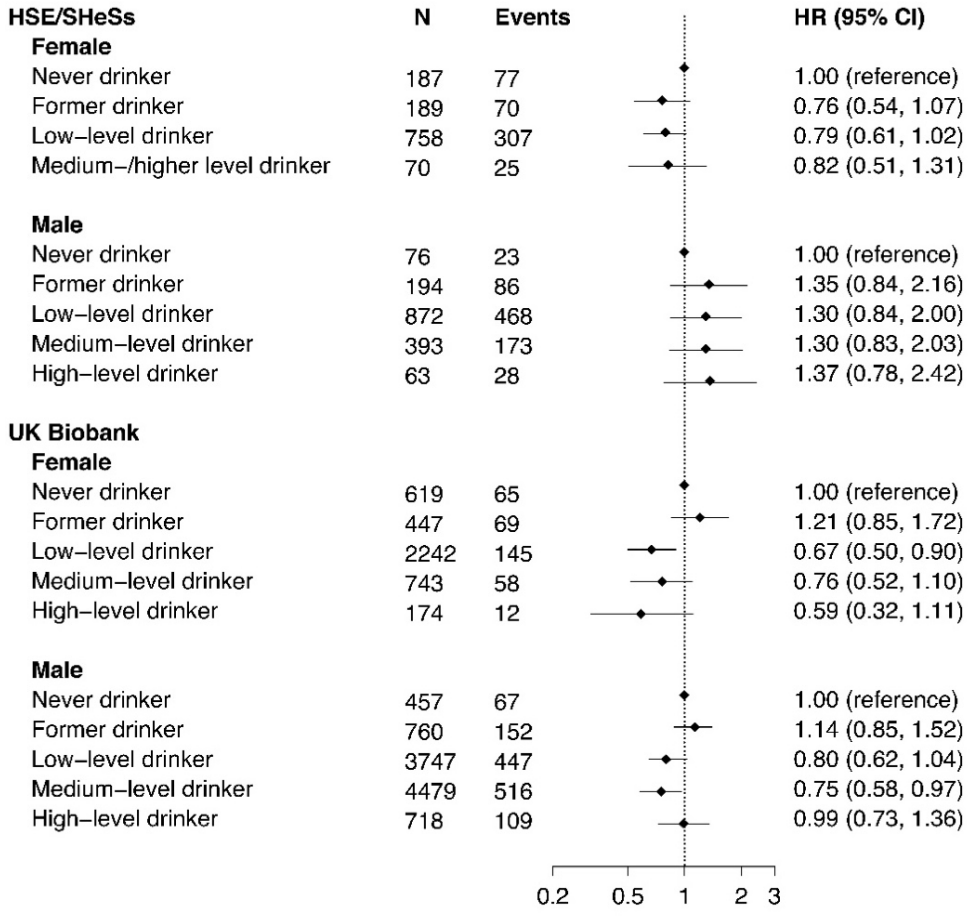


Figure 2.3 Association of drinking categories with mortality and cardiovascular events in CVD patients by study cohorts

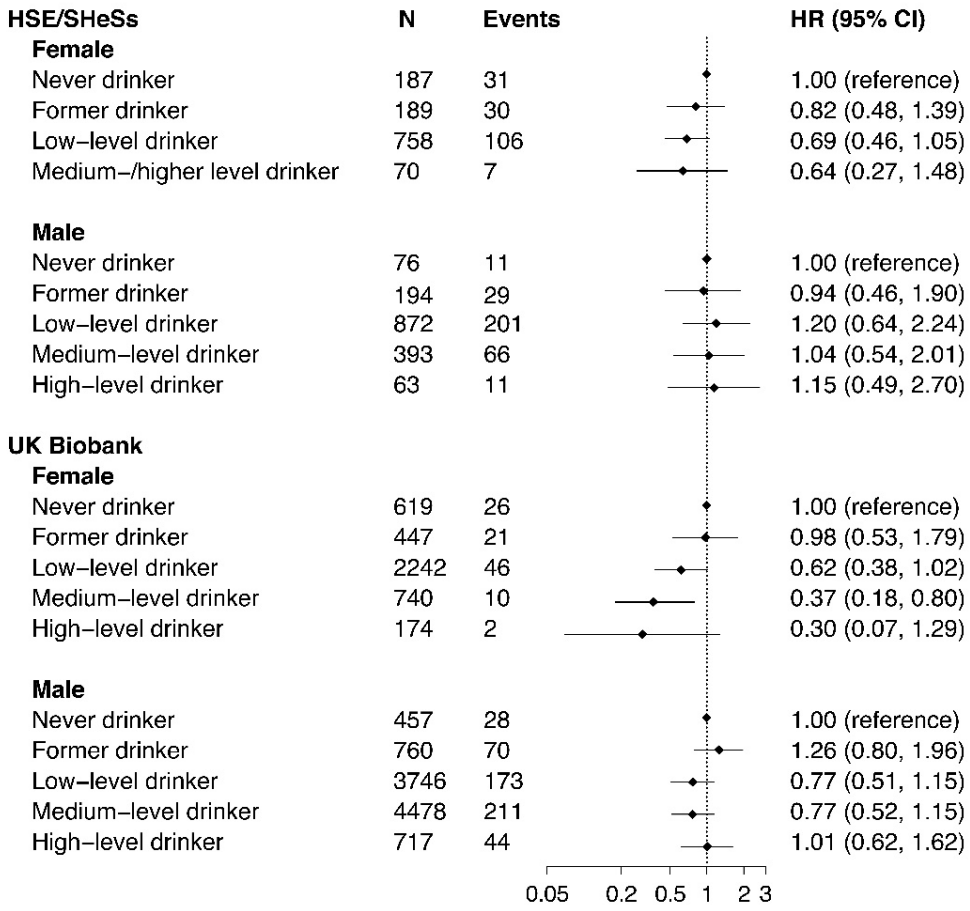
Notes: HRs are adjusted for age, sex, smoking status, prevalent diabetes and hypertension, socioeconomic position or education, BMI, and regular use of cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin.

In the stratified analyses, similar results were seen for both sexes (Figure 2.4) and participants having different primary events (Figure 2.5). There were no significant interactions of sex on the association of drinking categories with all-cause mortality (P-value=0.124 and 0.263 for HSE/SHeSs and UK Biobank, respectively), cardiovascular mortality (P-value=0.198 and 0.194 for HSE/SHeSs and UK Biobank, respectively), or cardiovascular events (P-value=0.189 for UK Biobank). Results were essentially unchanged in the sensitivity analysis which did not adjust for BMI (Table 2.3). Analysis restricted to never smoker showed comparable results, except that the CIs were much wider (due to reduced sample size) and for former and high-level drinking an association with increased risk of all-cause and cardiovascular mortality was suggested (Table 2.4).

(a) All-cause mortality



(b) Cardiovascular mortality



(c) Cardiovascular events

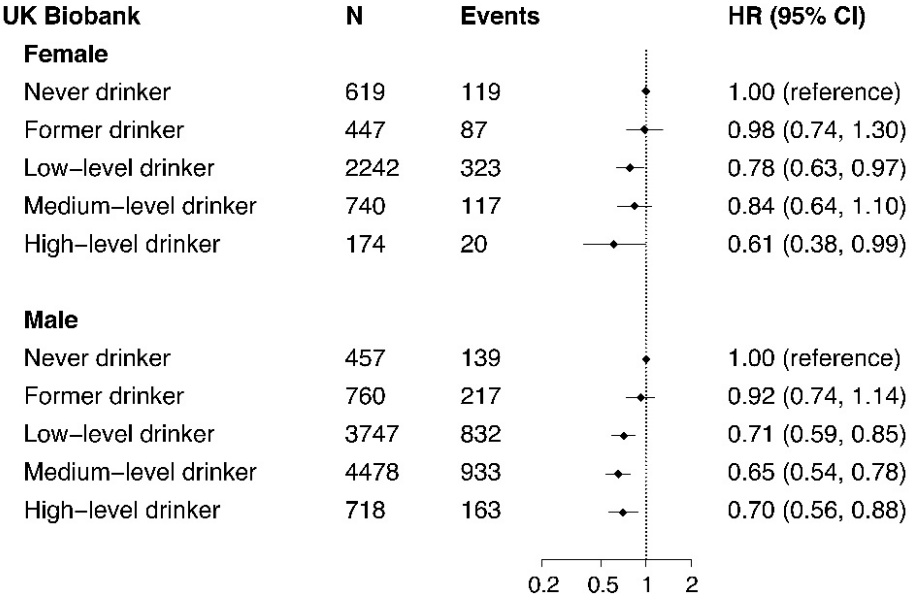
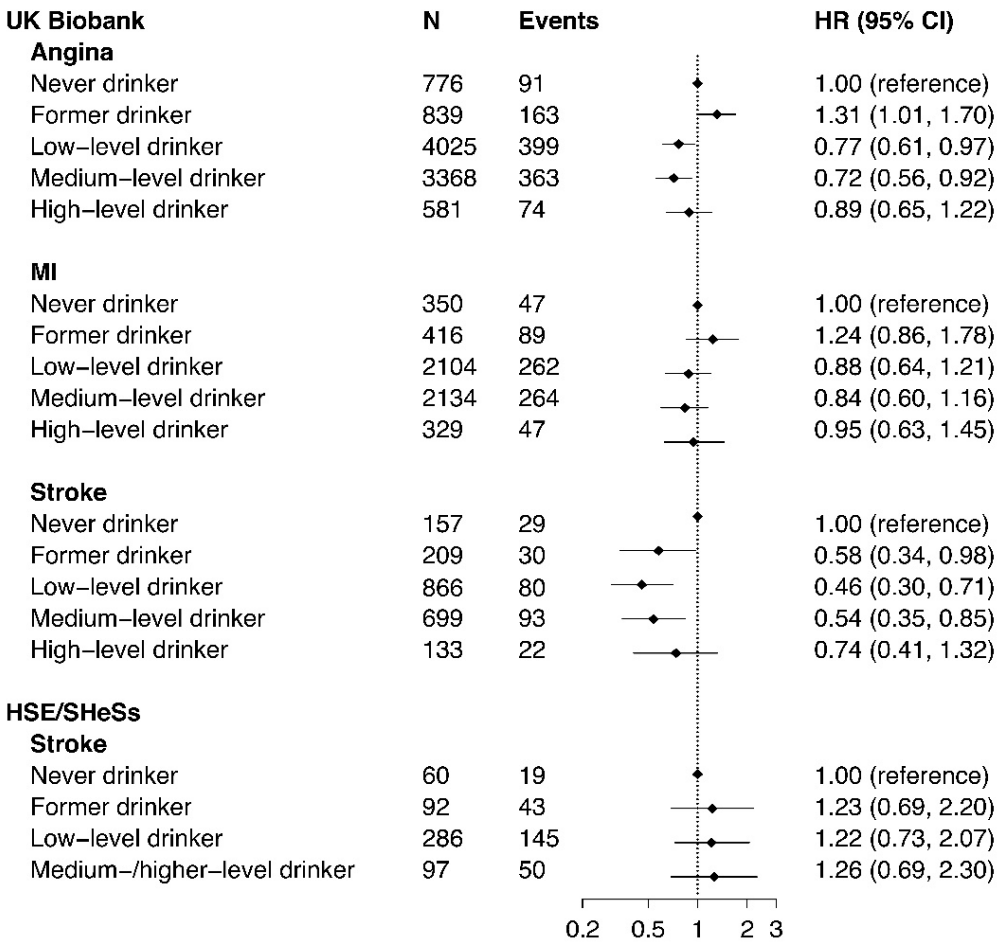


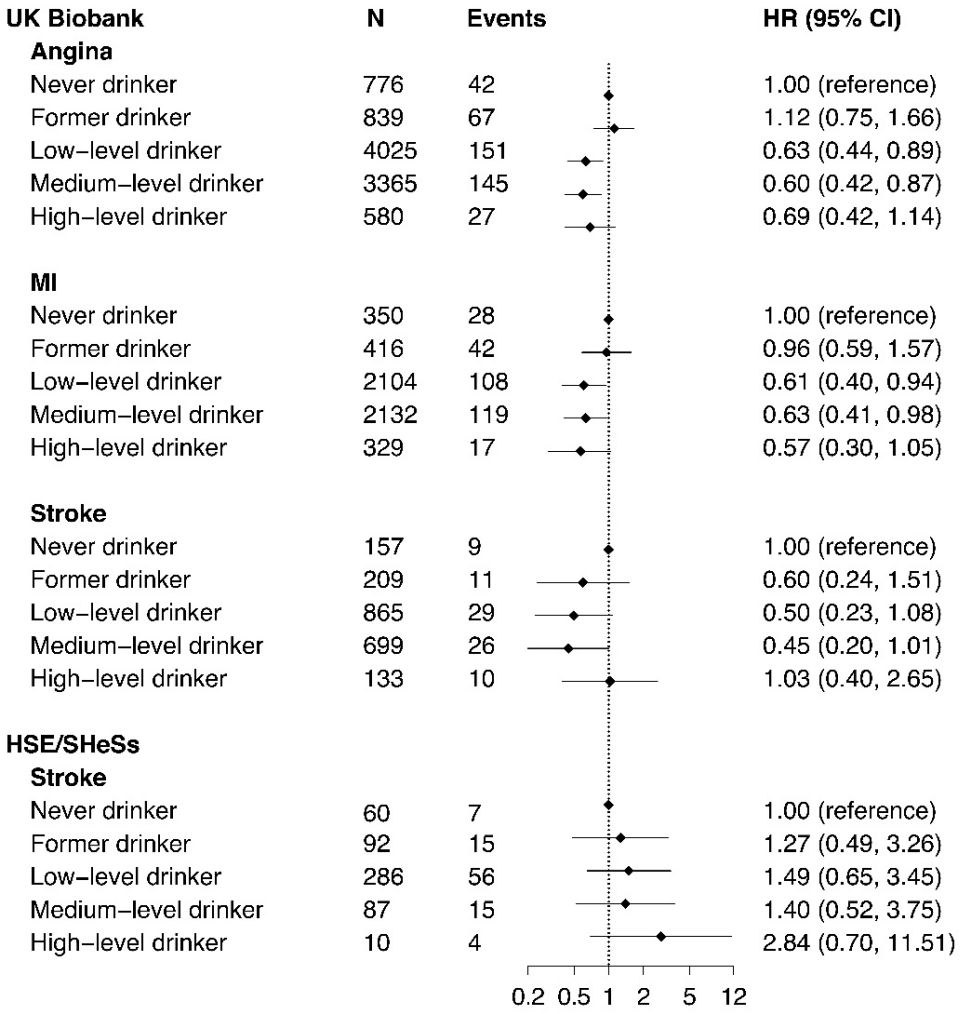
Figure 2.4 Association of drinking categories with (a) all-cause mortality, (b) cardiovascular mortality and (c) cardiovascular events in CVD patients, stratified by cohort and sex

Notes: All models were adjusted for the same covariates listed in Figure 2.3.

(a) All-cause mortality



(b) Cardiovascular mortality



(c) Cardiovascular events

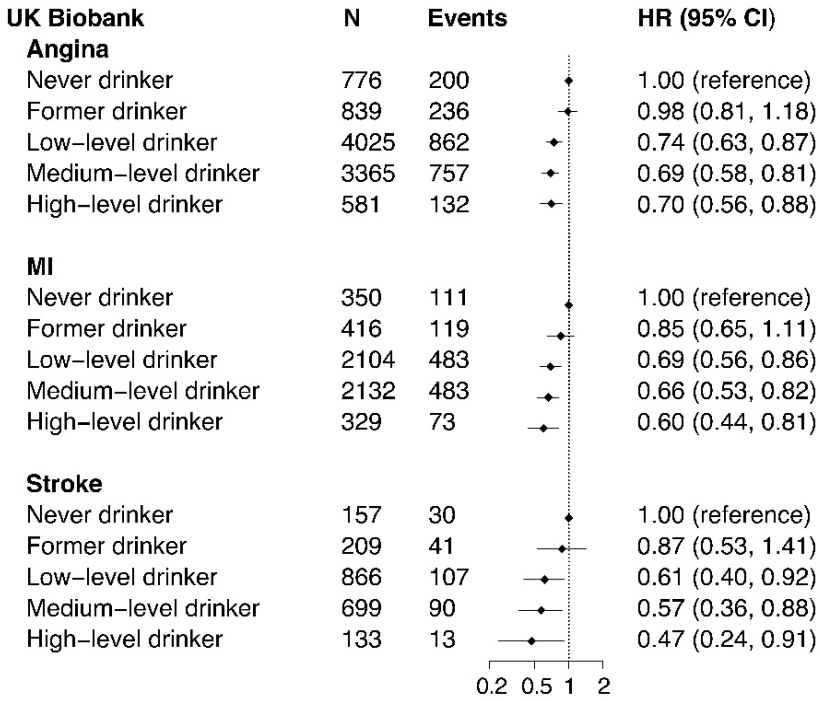


Figure 2.5 Association of drinking categories with (a) all-cause mortality, (b) cardiovascular mortality and (c) cardiovascular events in CVD patients, stratified by cohort and primary events

Notes: Models for MI, angina, and stroke as primary event were adjusted for each other as well as the same covariates listed in Figure 2.3.

Table 2.3 Sensitivity analyses for association of drinking categories with mortality and cardiovascular events in CVD patients, not adjusting for BMI

Outcome and cohort	No. of patients	No. of events	Hazard ratio (95% CI) *
All-cause mortality			
HSE/SHeSs			
Never drinker	263	100	1.00 (Reference)
Former drinker	383	156	0.90 (0.70-1.17)
Low-level drinker	1630	775	0.89 (0.72-1.11)
Medium-level drinker	458	198	0.92 (0.71-1.19)
High-level drinker	68	28	0.97 (0.63-1.50)
UK Biobank			
Never drinker	1076	132	1.00 (Reference)
Former drinker	1207	221	1.13 (0.91-1.41)
Low-level drinker	5989	592	0.74 (0.61-0.90)
Medium-level drinker	5222	574	0.72 (0.59-0.88)
High-level drinker	892	121	0.90 (0.70-1.16)
Cardiovascular mortality			
HSE/SHeSs			
Never drinker	263	42	1.00 (Reference)
Former drinker	383	59	0.78 (0.51-1.17)
Low-level drinker	1630	307	0.81 (0.58-1.14)
Medium-level drinker	458	73	0.76 (0.50-1.14)
High-level drinker	68	11	0.85 (0.43-1.70)
UK Biobank			
Never drinker	1076	54	1.00 (Reference)
Former drinker	1207	91	1.08 (0.76-1.52)
Low-level drinker	5988	219	0.65 (0.48-0.89)
Medium-level drinker	5218	221	0.63 (0.46-0.87)
High-level drinker	891	46	0.80 (0.53-1.20)
Cardiovascular events			
UK Biobank			
Never drinker	1076	258	1.00 (Reference)
Former drinker	1207	304	0.96 (0.81-1.13)
Low-level drinker	5989	1155	0.74 (0.64-0.85)
Medium-level drinker	5218	1050	0.69 (0.59-0.79)
High-level drinker	892	183	0.71 (0.58-0.86)

* Adjusted for the same covariates listed in Figure 2.3 **EXCLUDING** BMI.

Table 2.4 Sensitivity analyses for association of drinking categories with mortality and cardiovascular events in CVD patients, restricted to never smokers

Outcome and cohort	No. of patients	No. of events	Hazard ratio (95% CI)
All-cause mortality			
HSE/SHeSs			
Never drinker	196	81	1.00 (Reference)
Former drinker	120	45	1.10 (0.70-1.74)
Low-level drinker	619	253	0.83 (0.62-1.12)
Medium-level drinker	88	28	0.94 (0.58-1.52)
High-level drinker	11	5	2.33 (0.81-6.66)
UK Biobank			
Never drinker	712	67	1.00 (Reference)
Former drinker	353	42	1.31 (0.89-1.93)
Low-level drinker	2631	155	0.67 (0.50-0.90)
Medium-level drinker	1521	103	0.74 (0.54-1.03)
High-level drinker	178	18	1.21 (0.71-2.04)
Cardiovascular mortality			
HSE/SHeSs			
Never drinker	196	34	1.00 (Reference)
Former drinker	120	23	1.25 (0.63-2.51)
Low-level drinker	619	109	0.94 (0.59-1.50)
Medium-level drinker	88	10	0.97 (0.44-2.10)
High-level drinker	11	1	1.44 (0.19-11.12)
UK Biobank			
Never drinker	712	26	1.00 (Reference)
Former drinker	353	19	1.47 (0.81-2.67)
Low-level drinker	2631	60	0.66 (0.41-1.06)
Medium-level drinker	1521	40	0.72 (0.43-1.21)
High-level drinker	178	7	1.19 (0.51-2.78)
Cardiovascular events			
UK Biobank			
Never drinker	712	159	1.00 (Reference)
Former drinker	353	71	0.84 (0.63-1.11)
Low-level drinker	2631	440	0.68 (0.57-0.82)
Medium-level drinker	1521	294	0.72 (0.59-0.88)
High-level drinker	178	35	0.79 (0.55-1.15)

* Adjusted for the same covariates listed in Figure 2.3.

2.3.2 Characteristics of studies included in meta-analysis

As displayed in the flow diagram (Figure 2.6), 1722 unique citations were identified by the initial literature search, of which 12 fulfilled the selection criteria: six reported results separately for all-cause mortality and cardiovascular mortality, three for all-cause mortality only, one for cardiovascular mortality only and three for subsequent cardiovascular events. Data extracted from the 12 published studies represented 31235 CVD patients, among whom 5095 deaths and 1414 subsequent events were reported.

Table 2.5 outlines the characteristics of all studies selected for meta-analyses, inclusive of HSE/SHeSs and UK Biobank. Nine of the 14 studies had a cohort design and the remaining five [127, 147-149, 167] were randomized control trials for a certain drug or diet type with no specific inventions on alcohol consumption. Six studies strictly separated former drinkers from never drinkers within the non-drinking group. In terms of exposure assessment, only three studies utilised repeated measures of alcohol consumption – two reported risk estimates based on each patient's average intake during follow-up [128, 167] and the remaining one performed time-dependent analyses to allow changes in drinking levels [127]. The majority of included studies asked patients to report their average intake since the occurrence of their primary events (post-event alcohol assessment). Three studies used alcohol consumption in the year prior to primary events (pre-event), assuming drinking behaviours remained unchanged over time, even following events [129, 154, 168]. The quality of selected studies was moderate to high on average, with a median score of 8 stars on the Newcastle-Ottawa Scale. Additional details regarding categories of alcohol consumption, risk estimates, and confounder adjustment in each included study are provided in Tables 2.6-2.8.

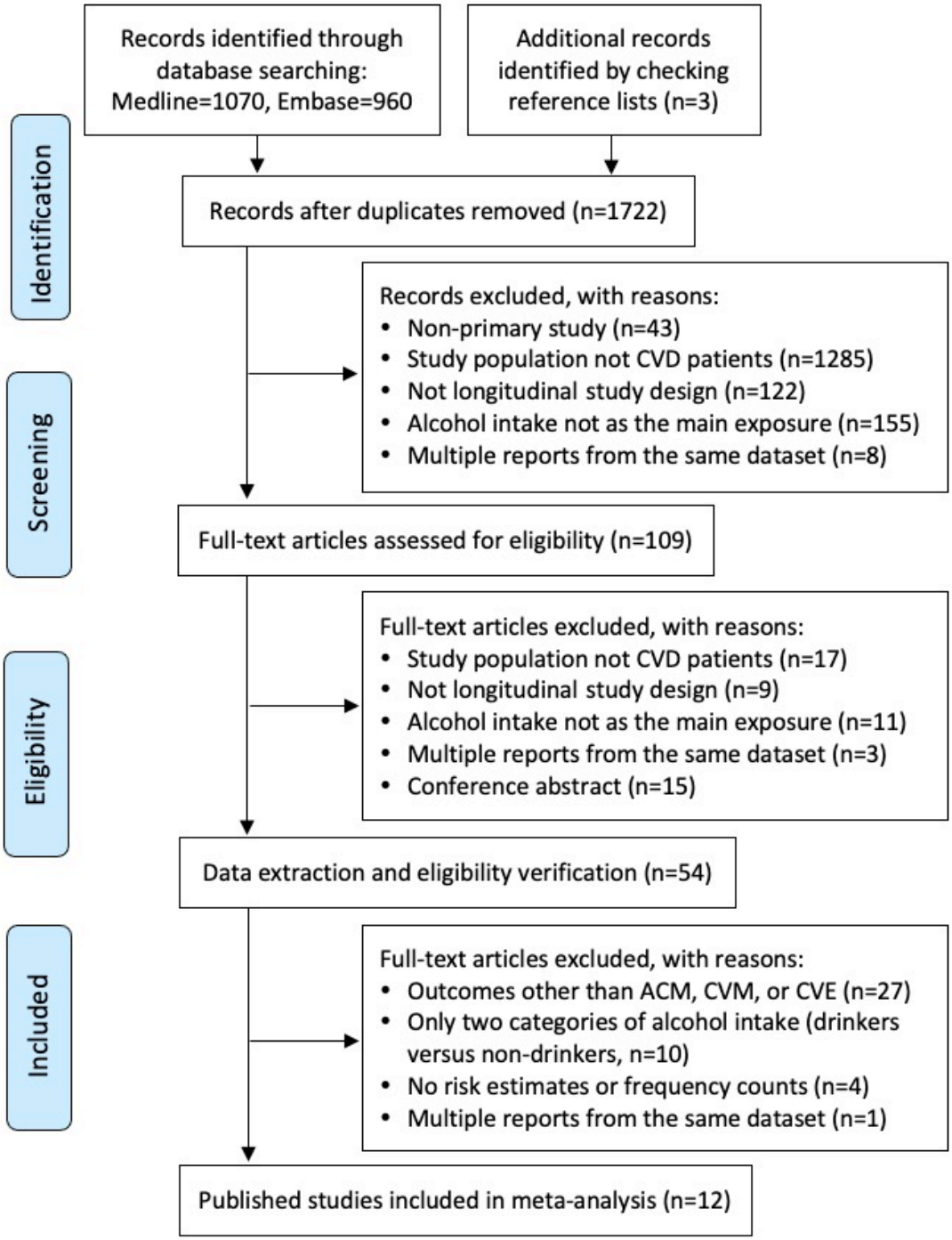


Figure 2.6 Study selection flowchart

Notes: ACM=all-cause mortality, CVE=cardiovascular events, CVD=cardiovascular disease, CVM=cardiovascular mortality.

Table 2.5 Characteristics of 14 studies included in meta-analyses

Source	Country	Dataset	Sex	Study size, No.	Meta-analyses Inclusion*			Follow up, y†	Baseline age, y‡	Reference group including former drinkers	Pre-/post-event alcohol assess-ment	Multiple alcohol measures	Quality assess-ment score	Primary event
					ACM case, No.	CVM case, No.	CVE case, No.							
HSE/SHeSs	UK	HSE (1994-2008)/SHeSs (1995, 1998, 2003)	M, F	2802	1257	492	NA	9.5	67.3	Both§	Post	No	9	MI/angina, stroke‖
UK Biobank	UK	Initial assessment visit (2006-2010)	M, F	14386	1640	631	2950	8.7	61.6	Both§	Post	No	9	MI, angina, stroke
Levantesi et al,[127] 2013	Italy	GISSI study	M, F	11248	1656	NA	1168	5.7	59.4	Yes	Post	Yes	7	MI
Pai et al,[128] 2012	USA	Health Professionals Follow-up Study	M	1818	468	243	NA	Up to 20	Range 40-75	Yes	Both	Yes	7	MI
Rosenbloom et al,[129]2012	USA	Onset study	F	1253	441	NA	NA	Up to 10	66.1	Yes	Pre	No	9	MI
Janszky et al,[168] 2008	Sweden	SHEEP study	M, F	1332	259	140	NA	8.6	59.4	No	Pre	No	9	MI
Masunaga et al,[152] 2006	Japan	Consecutive patients	M	3845	NA	NA	142	1.1	57.2	No	Post	No	8	MI
Aguilar et al,[147] 2004	USA, Canada	SAVE trial	M, F	2036	355	284	NA	3.5	59.2	Yes	Both	No	7	MI
Jackson et al,[148] 2003	USA	Physicians' Health Study	M	1320	369	267	NA	4.5	67.4	Yes	Post	No	6	Stroke
de Lorgeril et al,[167]2002	France	Lyon Diet Heart Study	M	353	NA	NA	104	4.0	54.0	Yes	Post	Yes	7	MI
Mukamal et al,[154]2001	USA	Onset study	M, F	1913	317	238	NA	3.8	61.8	Yes	Pre	No	8	MI

Shaper et al,[155]2000	UK	British Regional Heart Study	M	596	258	184	NA	12.8	Range 45-64	No	Post	No	9	MI, angina
Valmadrid et al,[169]1999	USA	WESDR	M, F	163	NA	52	NA	Up to 12.3	68.6	No	Post	No	9	MI/angina‖ #
Muntwyler et al,[149]1998	USA	Physicians' Health Study	M	5358	920	NA	NA	5.0	64.1	Yes	Post	No	6	MI

* Not applicable (NA) if the study was not included in meta-analysis on the outcome.
† Data are mean/median unless otherwise specified.
‡ Data are mean unless otherwise specified.
§ Former drinkers were included only in subgroup meta-analyses on different non-drinking reference group.
|| Results were not reported separately for angina and MI patients.
# Older-onset diabetic patients with a history of angina or MI.
ACM=all-cause mortality; CVE=cardiovascular events; CVM=cardiovascular mortality; F=female; M=male.

Table 2.6 Drinking categories, effect estimates, and confounder adjustment reported by studies on all-cause mortality

Source	Alcohol consumption		Risk of all-cause mortality				
	Reported exposure categories	Estimated g/day *†	Total (N)	Cases (n)	Measure of association	Effect estimates	Confounder adjustment
Levantesi et al, 2013	Never/almost never	0.0	3713	645	HR	1.00 (reference)	Age, gender, BMI, smoking, prior MI, history of hypertension, diabetes, peripheral vascular disease, electrical instability, exercise, LVEF, NYHA class, revascularization procedures, intakes of cooked vegetables, raw vegetables, fruit, fish, olive oil, other oil, butter, cheese, and coffee, use of n-3 PUFA, vitamin-E, antiplatelet agents, ACE inhibitor, lipid-lowering medication, beta-blockers
	≤0.5 L/day	20.4	5821	874		0.85 (0.76-0.95)	
	>0.5 L/day	49.0	985	137		0.80 (0.66-0.98)	
Pai et al, 2012	0 g/day	0.0	515	168	HR	1.00 (reference)	Age at diagnosis, questionnaire follow-up cycle, smoking, BMI, physical activity, diabetes, hypertension, lipid-lowering medication, aspirin use, heart failure at MI
	0.1-9.9 g/day	3.1	719	161		0.78 (0.62-0.97)	
	10.0-29.9 g/day	15.8	420	97		0.66 (0.51-0.86)	
	≥30.0 g/day	42.9	164	42		0.87 (0.61-1.25)	
Rosenbloom et al, 2012	None	0.0	761	331	HR	1.00 (reference)	Age, BMI, previous MI, congestive HF, angina, diabetes, hypertension, non-cardiac co-morbidity, previous medication use, smoking, physical activity, income, education, marital status, race, peak creatine kinase level, receipt of thrombolytic therapy, congestive HF, and ventricular tachycardia during hospitalization
	<1 serving/week	1.0	280	70		0.66 (0.50-0.86)	
	≥1 to <3 servings/week	3.8	75	15		0.65 (0.38-1.11)	
	≥3 servings/week	14.9	137	25		0.71 (0.46-1.09)	
Janszky et al, 2008	Longer-term abstainers	0.0	140	35	HR	1.00 (reference)	Age, sex, smoking, obesity, self-reported physical activity, history of diabetes, education
	>0 to <5 g/day	2.5	437	84		0.77 (0.51-1.15)	
	5-20 g/day	12.5	447	80		0.77 (0.50-1.18)	
	over 20 g/day	24.1	308	60		0.89 (0.56-1.40)	

Aguilar et al, 2004	0 drink/week	0.0	1437	274	HR	1.00 (reference)	Age, gender, LVEF, prior MI, history of hypertension, history of diabetes, BMI, tobacco use, NYHA classification, Killip class, beta-blocker use at the time of randomization, thrombolytic therapy with the qualifying MI, treatment (captopril) assignment
	1 to 10 drinks/week	11.0	532	74		0.91 (0.70-1.19)	
	>10 drinks/week	24.2	67	7		0.66 (0.31-1.41)	
Jackson et al, 2003	Rarely/never	0.0	361	128	RR	1.00 (reference)	Age, smoking, diabetes, BMI, exercise, angina, MI
	<1 drink/week	1.0	133	39		0.88 (0.60-1.28)	
	1-6 drinks/week	7.0	417	93		0.64 (0.48-0.85)	
	≥1 drink/day	16.8	409	109		0.71 (0.54-0.94)	
Mukamal et al, 2001	Abstainers	0.0	896	196	HR	1.00 (reference)	Age, sex, use of thrombolytic therapy, peak creatine kinase level, congestive HF during index hospitalization, ventricular tachycardia during index hospitalization, and propensity score
	<7 drinks/week	7.5	696	91		0.79 (0.60-1.03)	
	≥7 drinks/week	32.1	321	30		0.68 (0.45-1.05)	
Shaper et al, 2000	Teetotalers	0.0	43	18	RR ‡	0.96 (0.57-1.62)	Age, smoking, social class, BMI, pre-existing diabetes, stroke, and regular medication
	< 1 unit/week	0.6	199	85		1.00 (reference)	
	1-15 units/week	10.3	230	94		1.05 (0.78-1.42)	
	> 16 units/week	24.7	124	61		1.30 (0.93-1.83)	
Muntwyler et al, 1998	Rarely/never	0.0	1125	240	RR	1.00 (reference)	Age, smoking, diabetes, physical activity, BMI
	1-4 drinks/month	1.2	1227	211		0.85 (0.69-1.05)	
	2-6 drinks/week	8.0	1390	187		0.72 (0.58-0.89)	
	1 drinks/day	14.0	1424	249		0.79 (0.64-0.96)	
	≥2 drinks/day	33.6	192	33		0.84 (0.55-1.26)	
HSE/SHeSs §	Never drinker	0.0	263	100	HR	1.00 (reference)	Age, sex, smoking, socioeconomic position, history of diabetes, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin
	Low-level drinker	4.0	1630	775		0.89 (0.71-1.11)	
	Medium-level drinker	28.0	458	198		0.91 (0.70-1.18)	
	High-level drinker	85.1	68	28		0.96 (0.62-1.49)	

UK Biobank §	Never drinker	0.0	1076	132	HR	1.00 (reference)	Age, sex, smoking, education, history of diabetes, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, warfarin
	Low-level drinker	7.9	5989	592		0.74 (0.61-0.89)	
	Medium-level drinker	30.6	5222	574		0.71 (0.58-0.87)	
	High-level drinker	76.7	892	121		0.89 (0.69-1.15)	

* The upper limit of the highest exposure category defined as the lower bound multiplied by 1.2, unless explicitly defined within each publication.
† Average intake in each consumption category. Where unreported, the median of the upper and lower bounds was used.
‡ Effect estimates re-calculated according to a reference group other than that originally reported. This was undertaken using the method by Hamling et al, as described in text.
§ Measures of usual weekly consumption, categorized as never drinker, low-level drinker (≤14 units per week), medium-level drinker (>14 to ≤50 units per week for men, >14 to ≤35 units per week for women), or high-level drinker (>50 units per week for men, >35 units per week for women).
ACE=angiotensin-converting enzyme; BMI=body mass index; HF=heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NYHA=New York Heart Association; PUFA=polyunsaturated fatty acids.

Table 2.7 Drinking categories, effect estimates, and confounder adjustment reported by studies on cardiovascular mortality

Source	Alcohol consumption		Risk of cardiovascular mortality				
	Reported exposure categories	Estimated g/day *†	Total (N)	Cases (n)	Measure of association	Effect estimates	Confounder adjustment
Pai et al, 2012	0 g/day	0.0	515	92	HR	1.00 (reference)	Age at diagnosis, questionnaire follow-up cycle, smoking, BMI, physical activity, diabetes, hypertension, lipid-lowering medication, aspirin use, HF at MI
	0.1-9.9 g/day	3.1	719	81		0.74 (0.54-1.02)	
	10.0-29.9 g/day	15.8	420	47		0.58 (0.39-0.84)	
	≥30.0 g/day	42.9	164	23		0.98 (0.60-1.60)	
Janszky et al, 2008	Longer-term abstainers	0.0	140	23	HR	1.00 (reference)	Age, sex, smoking, obesity, self-reported physical activity, history of diabetes, education
	>0 to <5 g	2.5	437	44		0.61 (0.36-1.02)	
	5-20 g	12.5	447	42		0.62 (0.36-1.07)	
	over 20 g	24.1	308	31		0.69 (0.38-1.25)	
Aguilar et al, 2004	0 drink/week	0.0	1437	215	HR	1.00 (reference)	Age, gender, LVEF, prior MI, history of hypertension, history of diabetes, BMI, tobacco use, NYHA classification, Killip class, beta-blocker use at the time of randomization, thrombolytic therapy with the qualifying MI, treatment (captopril) assignment
	1 to 10 drinks/week	11.0	532	62		1.00 (0.75-1.34)	
	>10 drinks/week	24.2	67	7		0.87 (0.40-1.87)	
Jackson et al, 2003	Rarely/never	0.0	361	101	RR	1.00 (reference)	Age, smoking, diabetes, BMI, exercise, angina, MI
	<1 drink/week	1.0	133	29		0.89 (0.58-1.36)	
	1-6 drinks/week	7.0	417	62		0.56 (0.40-0.79)	
	≥1 drink/day	16.8	409	75		0.64 (0.46-0.88)	
Mukamal et al, 2001	Abstainers	0.0	896	153	HR	1.00 (reference)	Age, sex, use of thrombolytic therapy, peak creatine kinase level, congestive HF during index hospitalization, ventricular tachycardia during index hospitalization, and propensity score
	<7 drinks/week	7.5	696	64		0.75 (0.55-1.02)	
	≥7 drinks/week	32.1	321	21		0.67 (0.41-1.17)	

Shaper et al, 2000	Teetotallers	0.0	43	13	RR ‡	0.98 (0.53-1.82)	Age, smoking, social class, BMI, pre-existing diabetes, stroke, and regular medication
	< 1 unit/week	0.6	199	62		1.00 (reference)	
	1-15 units/week	10.3	230	62		0.94 (0.65-1.35)	
	> 16 units/week	24.7	124	47		1.34 (0.91-1.98)	
Valmadrid et al, 1999	Never drinkers	0.0	31	12	RR	1.00 (reference)	Age, sex, cigarette smoking, insulin use, glycosylated hemoglobin level, plasma C-peptide level, digoxin use, the presence and severity of diabetic retinopathy
	<2 g/day	1.0	87	27		0.51 (0.24-1.12)	
	2-13 g/day	7.5	20	8		0.43 (0.15-1.22)	
	≥14 g/day	16.8	25	5		0.26 (0.08-0.81)	
HSE/SHeSs §	Never drinker	0.0	263	42	HR	1.00 (reference)	Age, sex, smoking, socioeconomic position, history of diabetes, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin
	Low-level drinker	4.0	1630	307		0.81 (0.58-1.14)	
	Medium-level drinker	28.0	458	73		0.76 (0.50-1.14)	
	High-level drinker	85.1	68	11		0.85 (0.43-1.70)	
UK Biobank §	Never drinker	0.0	1076	54	HR	1.00 (reference)	Age, sex, smoking, education, history of diabetes, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, warfarin
	Low-level drinker	7.9	5988	219		0.65 (0.48-0.88)	
	Medium-level drinker	30.6	5218	221		0.63 (0.46-0.86)	
	High-level drinker	76.8	891	46		0.79 (0.53-1.19)	

* The upper limit of the highest exposure category defined as the lower bound multiplied by 1.2, unless explicitly defined within each publication.
† Average intake in each consumption category. Where unreported, the median of the upper and lower bounds was used.
‡ Effect estimates re-calculated according to a reference group other than that originally reported. This was undertaken using the method by Hamling et al, as described in text.
§ Measures of usual weekly consumption, categorized as never drinker, low-level drinker (≤14 units per week), medium-level drinker (>14 to ≤50 units per week for men, >14 to ≤35 units per week for women), or high-level drinker (>50 units per week for men, >35 units per week for women).
BMI=body mass index; HF=heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NYHA=New York Heart Association.

Table 2.8 Drinking categories, effect estimates, and confounder adjustment reported by studies on cardiovascular events

Source	Alcohol consumption		Risk of cardiovascular events				
	Reported exposure categories	Estimated g/day *†	Total (N)	Cases (n)	Measure of association	Effect estimates	Confounder adjustment
Levantesi et al, 2013	Never/almost never	0.0	4108	458	HR	1.00 (reference)	Age, gender, BMI, smoking, prior MI, history of hypertension, diabetes, peripheral vascular disease, electrical instability, exercise, LVEF, NYHA class, revascularization procedures, intakes of cooked vegetables, raw vegetables, fruit, fish, olive oil, other oil, butter, cheese, and coffee, use of n−3 PUFA, vitamin-E, antiplatelet agents, ACE inhibitor, lipid-lowering medication, beta-blockers
	≤0.5 L/day	20.4	5446	551		0.87 (0.76-0.99)	
	>0.5 L/day	49.0	1694	159		0.90 (0.74-1.09)	
Masunaga et al, 2006; age <65 years	Abstainers	0.0	1385	54	HR	1.00 (reference)	CABG, atrial fibrillation, PCI, cholesterol-lowering agents, obesity, antiplatelet agents, β-blockers, warfarin, Forrester class, nitrates, coronary thrombolysis, calcium antagonists, diabetes, smoking, PVC, Gout, Killip class, ACE inhibitors, vasospastic angina, hyperlipidemia, multi-vessel disease, hypertension, positive exercise ECG, antiarrhythmic agents, angina pectoris
	<30 ml/day	11.9	1053	20		0.56 (0.32-0.97)	
	≥30 ml/day	28.4	563	18		0.92 (0.51-1.66)	
Masunaga et al, 2006; age ≥65 years	Abstainers	0.0	533	24	HR	1.00 (reference)	Same as above
	<30 ml/day	11.9	250	14		1.02 (0.44-2.35)	
	≥30 ml/day	28.4	61	12		5.75 (2.21-14.90)	
de Lorgeril et al, 2002	Non-drinkers	0.0	96	36	RR	1.00 (reference)	Diet group, age, current smoking, serum total cholesterol, and systolic blood pressure
	<5.41% of total energy intake/day	8.9	83	34		0.74 (0.40-1.38)	
	>5.41 but <9.84%	24.1	89	18		0.41 (0.20-0.83)	
	>9.84%	51.8	85	16		0.48 (0.24-0.96)	

UK Biobank ‡	Never drinker	0.0	1076	258	HR	1.00 (reference)	Age, sex, smoking, education, history of diabetes, hypertension, BMI, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, warfarin
	Low-level drinker	7.9	5989	1155		0.74 (0.64-0.85)	
	Medium-level drinker	30.6	5218	1050		0.69 (0.60-0.80)	
	High-level drinker	76.7	892	183		0.71 (0.58-0.86)	

* The upper limit of the highest exposure category defined as the lower bound multiplied by 1.2, unless explicitly defined within each publication.
† Average intake in each consumption category. Where unreported, the median of the upper and lower bounds was used.
‡ Measures of usual weekly consumption, categorized as never drinker, low-level drinker (≤14 units per week), medium-level drinker (>14 to ≤50 units per week for men, >14 to ≤35 units per week for women), or high-level drinker (>50 units per week for men, >35 units per week for women).
ACE=angiotensin-converting enzyme; BMI=body mass index; CABG=coronary artery bypass grafting; HF=heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; PUFA=polyunsaturated fatty acids; PVC=premature ventricular contraction.

2.3.3 Alcohol and all-cause mortality among CVD patients

Eleven studies, comprising 41743 CVD patients, contributed to this analysis. As shown in Figure 2.7, an overall J-shaped association was observed between alcohol consumption and risk of death from all causes. The protective effect peaked at 7 grams per day, equating to a 21% decrease in risk compared to non-current drinkers (RR=0.79, 95%CI=0.73-0.85), and remained significant up to 62 grams per day (Table 2.9).

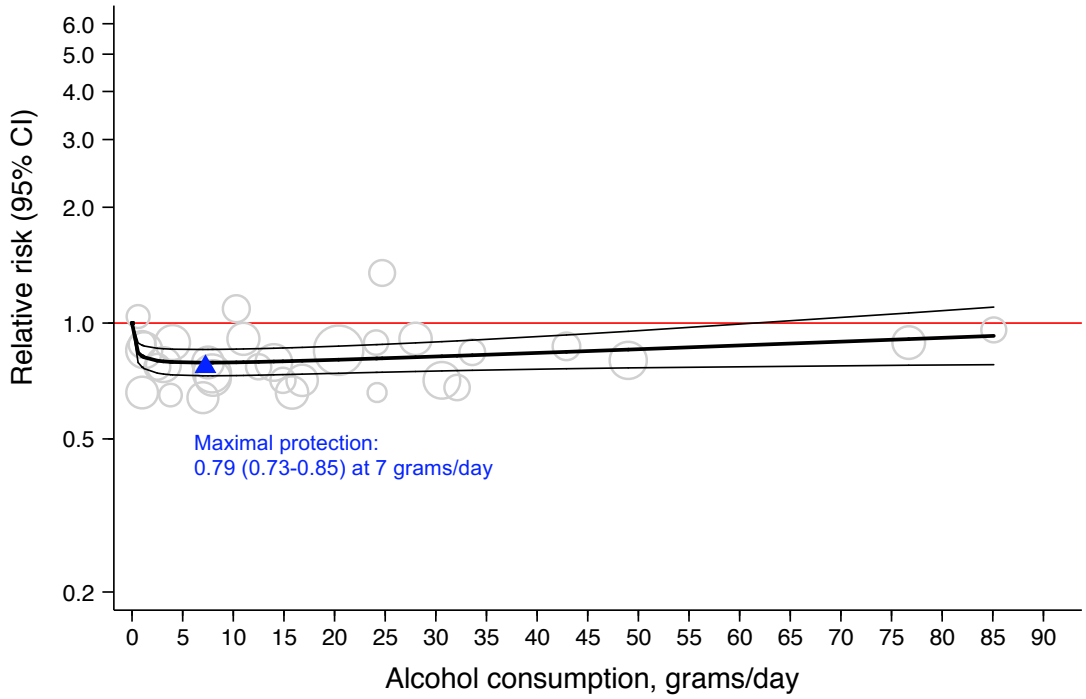


Figure 2.7 Overall dose-response association between alcohol consumption and risk of all-cause mortality in CVD patients, using maximally adjusted estimates
Notes: Best-fitting second-degree fractional polynomial models (with 95%CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk. The triangle represents the lowest point (maximal protection) of the dose-response curve within the range of dose reported by the data points.

Subgroup results are illustrated in Figures 2.8-2.11, with model details and risk estimates summarised in Table 2.9. Although the dose-response association was J-shaped in male patients, no increased risk was found among female patients who drank at higher levels. As to primary events, moderate alcohol consumption was associated with a lower risk for total mortality among patients

with a history of MI or angina, but not with stroke. Meta-analysis of estimates relative to non-current drinkers showed a reduction in risk of all-cause mortality for an alcohol intake up to 75 grams per day. This association, however, was remarkably attenuated when compared to a strictly defined reference group of never drinkers or when restricting to studies that utilised repeated measures of alcohol intake. Among those studies with post-event alcohol measures, the association did not change substantively.

Table 2.9 Best-fitting models and results of the meta-analysis on all-cause mortality in CVD patients

Outcome and subgroup	No. of studies (curves)	No. of patients	No. of deaths	Maximal effect size*		Reversion point, g/day†	Powers for the Best-Fitting FP2	
				RR (95% CI)	g/day		dose_1	dose_2
All-cause mortality								
Overall	11 (11)	41743	7563	0.79 (0.73-0.85)	7	62	-0.5	1
Male	6 (6)	19897	3846	0.82 (0.72-0.93)	9	39	0	0.5
Female	3 (3)	6046	1130	0.64 (0.36-1.14)	54	49	-2	3
MI as primary event	9 (9)	29554	5227	0.82 (0.68-0.99)	2	7	-1	0.5
Angina as primary event	2 (2)	8938	994	0.79 (0.64-0.98)	31	46	0.5	3
Stroke as primary event	3 (3)	3618	807	0.71 (0.42-1.20)	12	NA	0	0.5
Reference group including former drinkers	9 (9)	41405	7423	0.77 (0.69-0.85)	16	75	-0.5	2
Reference group excluding former drinkers	4 (4)	17526	3037	0.85 (0.71-1.00)	3	3	-0.5	-0.5
Post-event alcohol assessment	8 (8)	37245	6546	0.81 (0.74-0.88)	9	52	0	0.5
Multiple alcohol measures	2 (2)	12337	2124	0.78 (0.59-1.03)	16	NA	-0.5	-0.5

* Defined as the lowest point of the dose-response curve within the range of dose reported by the studies.
† Defined as the dose of alcohol at which protection against the outcome is no longer statistically significant at the 95% confidence level; not applicable (NA) if non-significant association was found at any level of consumption.

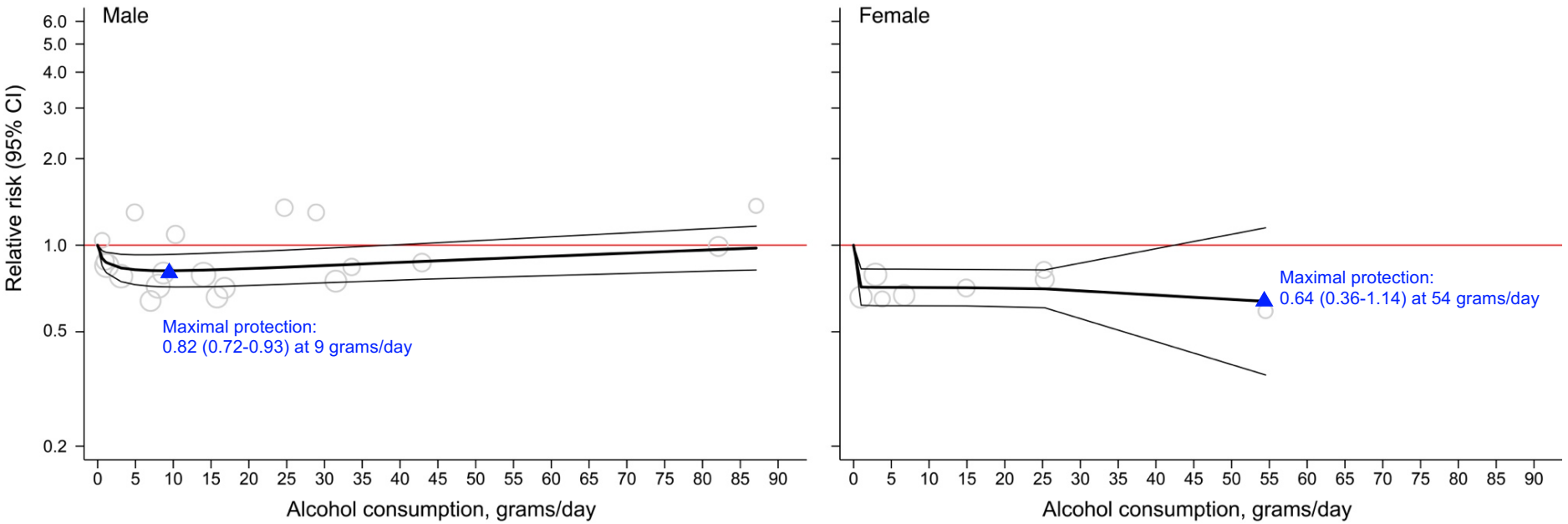


Figure 2.8 Association between alcohol and all-cause mortality in CVD patients, stratified by sex

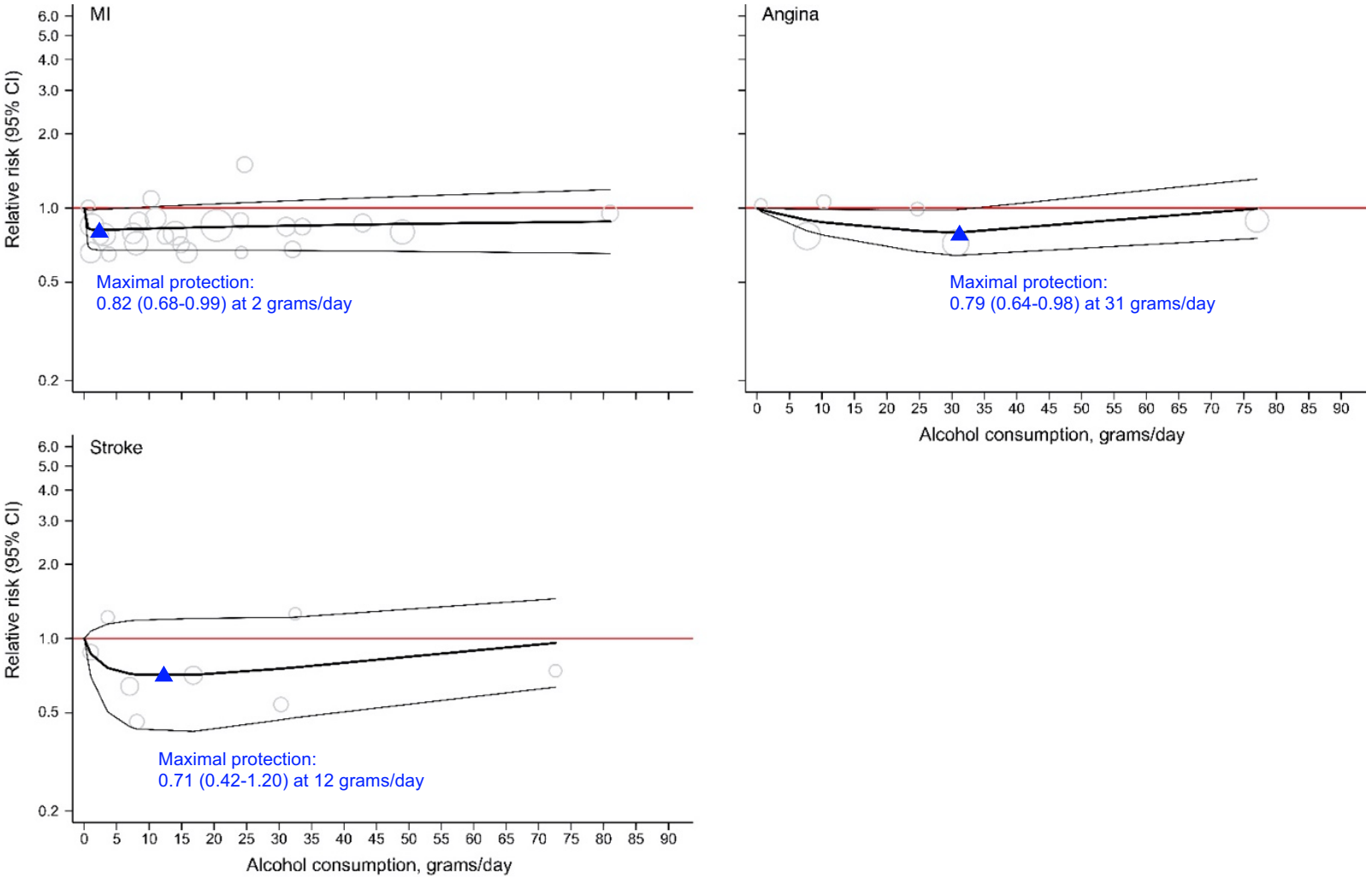


Figure 2.9 Association between alcohol and all-cause mortality in CVD patients, stratified by primary events

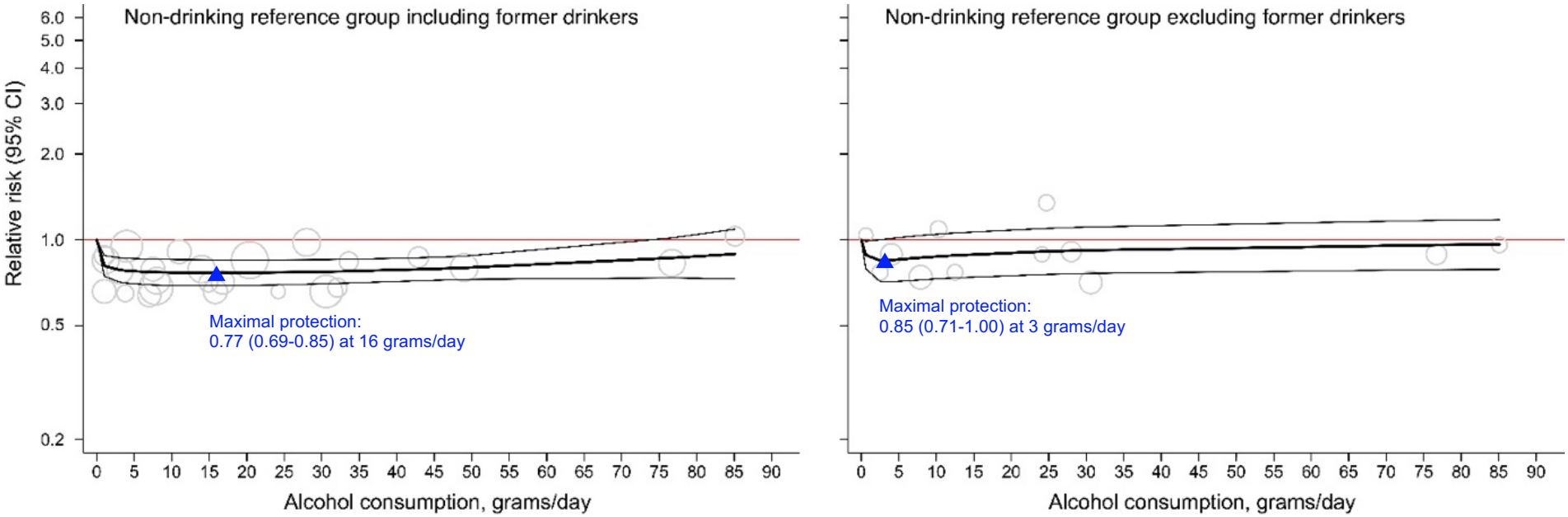


Figure 2.10 Association between alcohol and all-cause mortality in CVD patients, relative to different non-drinking groups

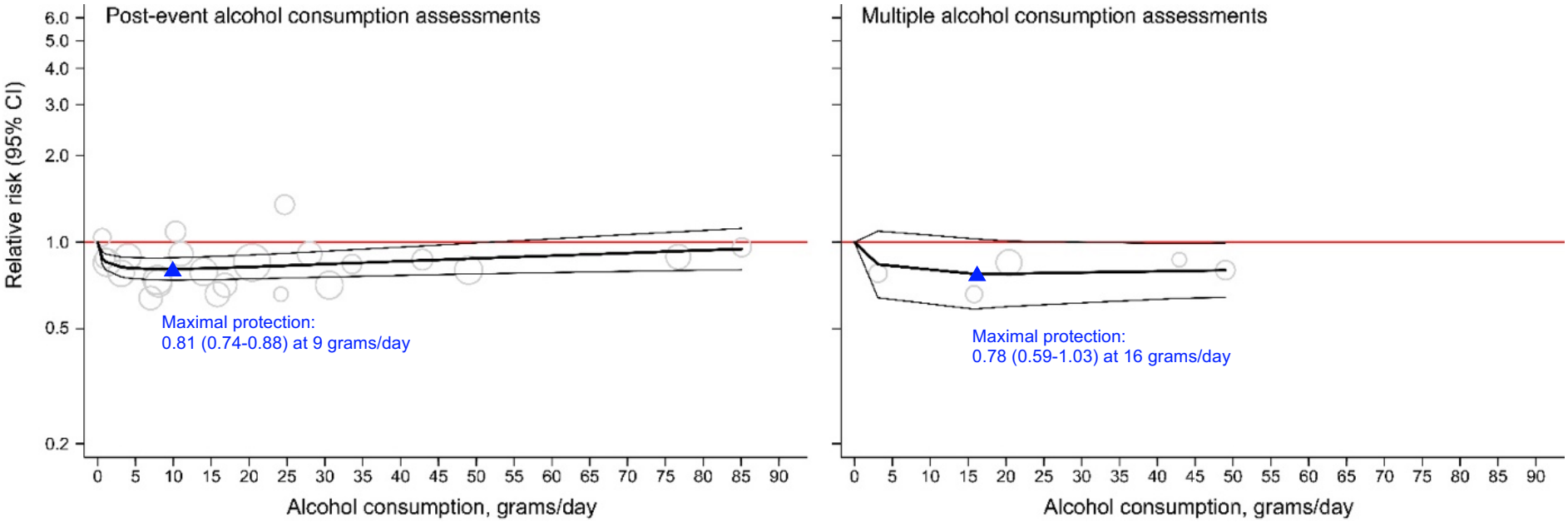


Figure 2.11 Association between alcohol and all-cause mortality in CVD patients, by different method of assessing alcohol consumption

2.3.4 Alcohol and cardiovascular mortality among CVD patients

A total of nine studies (24770 patients) were included in the meta-analysis on cardiovascular mortality, and the overall association with alcohol consumption was found to follow a J-shaped curve, as illustrated in Figure 2.12. The reduction in risk was greatest at 8 grams per day (RR=0.73, 95%CI=0.64-0.83) and evident up to 50 grams per day (Table 2.10).

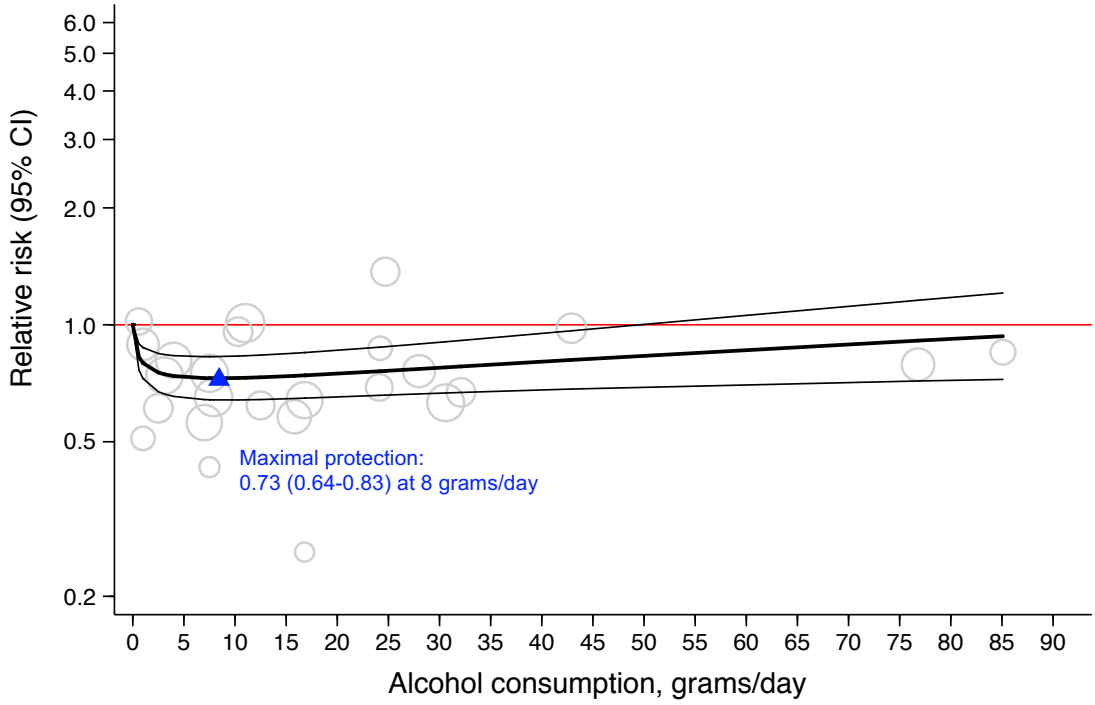


Figure 2.12 Overall dose-response association between alcohol consumption and risk of cardiovascular mortality in CVD patients, using maximally adjusted estimates
Notes: Best-fitting second-degree fractional polynomial models (with 95%CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk. The triangle represents the lowest point (maximal protection) of the dose-response curve within the range of dose reported by the data points.

As shown in Figures 2.13-2.16 and Table 2.10, the J-shaped association between alcohol consumption and cardiovascular mortality was little altered when restricting to male patients; however, again there was no increase in risk at higher levels of consumption among female patients. Similar results were obtained with different types of reference groups and alcohol assessments or

among patients with a previous MI. On the contrary, the overall association was close to null among those with angina or stroke.

Table 2.10 Best-fitting models and results of the meta-analysis on cardiovascular mortality in CVD patients

Outcome and subgroup	No. of studies (curves)	No. of patients	No. of deaths	Maximal effect size*		Reversion point, g/day†	Powers for the Best-Fitting FP2	
				RR (95% CI)	g/day		dose_1	dose_2
Cardiovascular mortality								
Overall	9 (9)	24770	2381	0.73 (0.64-0.83)	8	50	0	0.5
Male	5 (5)	14536	1439	0.72 (0.62-0.85)	9	32	0	0.5
Female	2 (2)	4790	228	0.29 (0.09-1.01)	54	54	0	2
MI as primary event	6 (6)	12422	1320	0.76 (0.64-0.91)	3	25	-2	3
Angina as primary event	2 (2)	8934	406	0.85 (0.66-1.10)	31	NA	3	3
Stroke as primary event	3 (3)	3617	423	0.63 (0.37-1.08)	26	NA	0	3
Reference group including former drinkers	6 (6)	24269	2155	0.73 (0.58-0.93)	13	27	0	0.5
Reference group excluding former drinkers	5 (5)	17683	1349	0.71 (0.55-0.90)	7	29	-0.5	0.5
Post-event alcohol assessment	7 (7)	21525	2003	0.73 (0.60-0.90)	8	43	0	0
Multiple alcohol measures	1 (1)	1818	243	0.58 (0.40-0.84)	17	33	-0.5	3

* Defined as the lowest point of the dose-response curve within the range of dose reported by the studies.
† Defined as the dose of alcohol at which protection against the outcome is no longer statistically significant at the 95% confidence level; not applicable (NA) if non-significant association was found at any level of consumption.

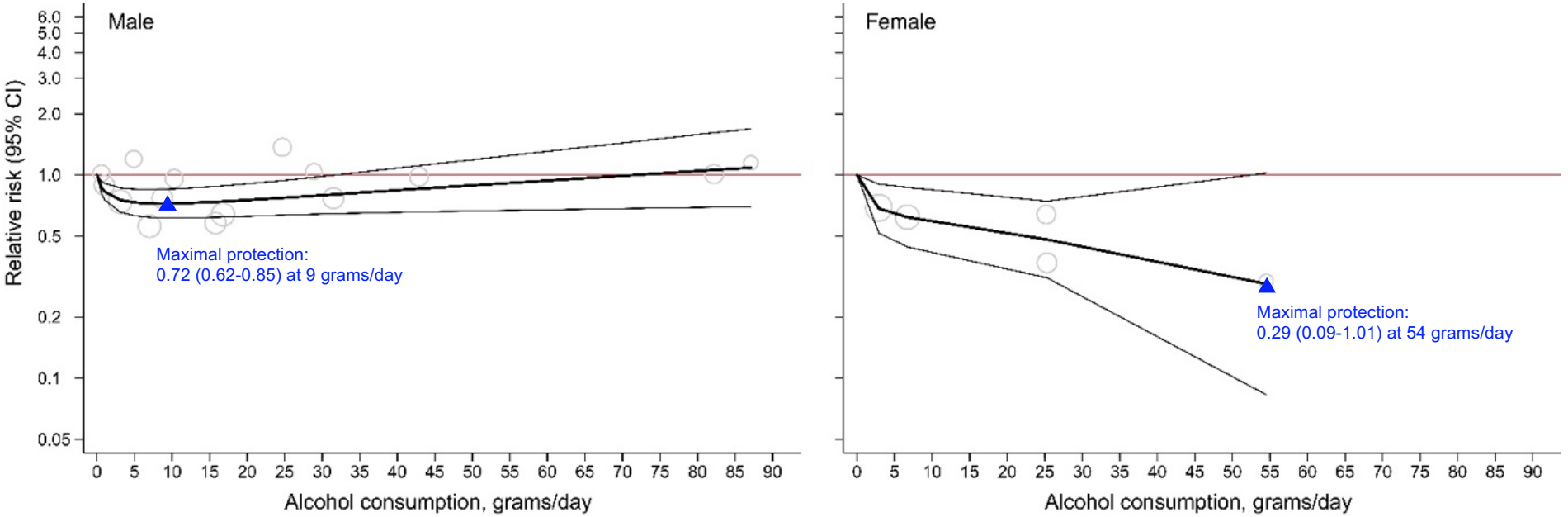


Figure 2.13 Association between alcohol and cardiovascular mortality in CVD patients, stratified by sex

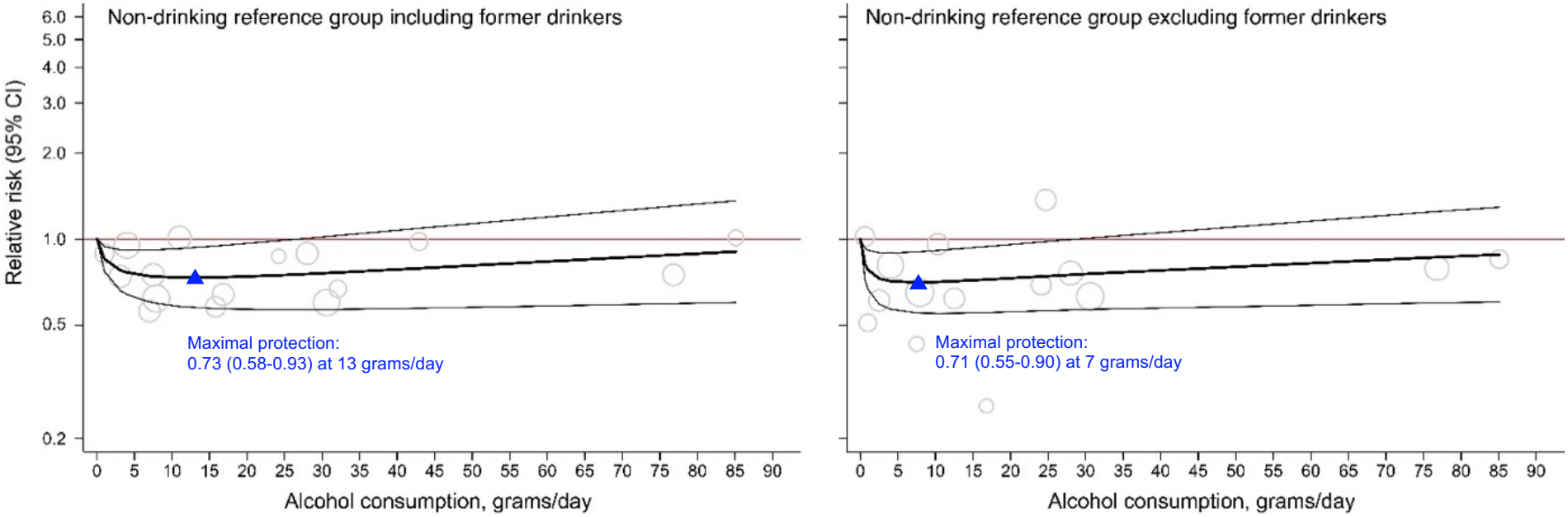


Figure 2.14 Association between alcohol and cardiovascular mortality in CVD patients, relative to different non-drinking group

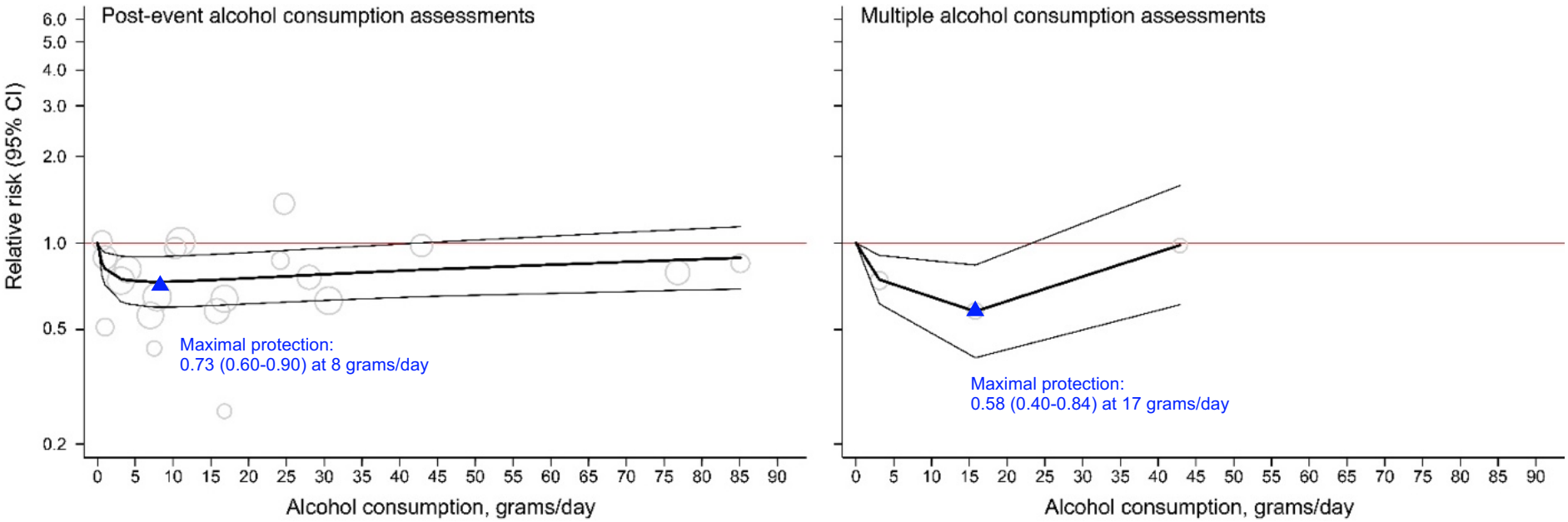


Figure 2.15 Association between alcohol and cardiovascular mortality in CVD patients, by different method of assessing alcohol consumption

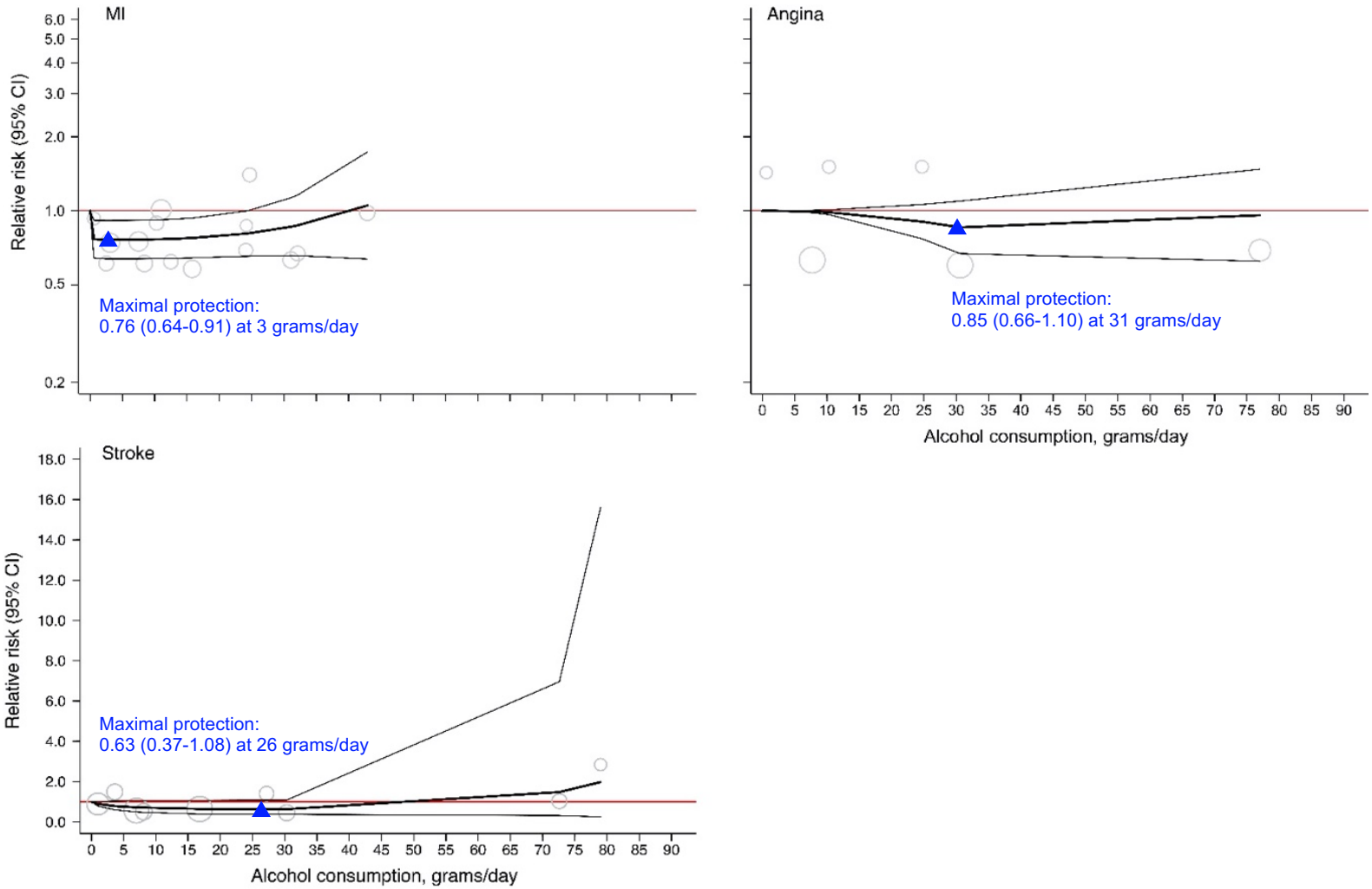


Figure 2.16 Association between alcohol and cardiovascular mortality in CVD patients, stratified by primary events

2.3.5 Alcohol and cardiovascular events among CVD patients

Four studies, comprising 28621 CVD patients, examined alcohol's relation to cardiovascular events and were included in this meta-analysis. One study reported dose-response relationship separately for two age groups and thus provided two curves. An alcohol intake up to 15 grams per day was associated with a significant decrease in the risk of subsequent events; the greatest risk reduction was seen at 6 grams per day (RR=0.56, 95%CI=0.34-0.93; Figure 2.17 and Table 2.11).

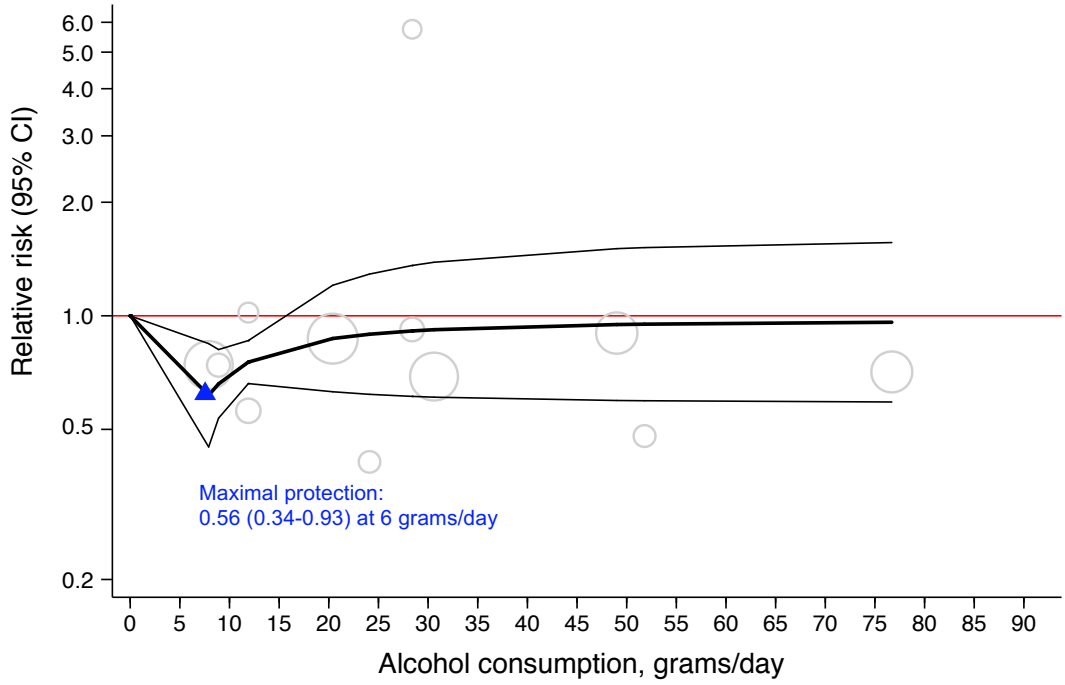


Figure 2.17 Overall dose-response association between alcohol consumption and risk of subsequent cardiovascular events in CVD patients, using maximally adjusted estimates

Notes: Best-fitting second-degree fractional polynomial models (with 95%CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk. The triangle represents the lowest point (maximal protection) of the dose-response curve within the range of dose reported by the data points.

Subgroup analysis stratified by sex showed wide CIs around the curves for both sexes and a decreased risk for an alcohol intake up to about 49 grams per day among female patients (Figure 2.18). Moderate drinking was found to confer a

protective effect among patients having different primary events or studies based on repeated alcohol measures (Figures 2.19 and 2.21). However, when studies including former drinkers in the reference group were excluded, the effect was weakened and became non-significant (Figure 2.20).

Table 2.11 Best-fitting models and results of the meta-analysis on subsequent cardiovascular events in CVD patients

Outcome and subgroup	No. of studies (curves)	No. of patients	No. of events	Maximal effect size*		Reversion point, g/day†	Powers for the Best-Fitting FP2	
				RR (95% CI)	g/day		dose_1	dose_2
Cardiovascular events								
Overall‡	4 (5)	28621	4060	0.56 (0.34-0.93)	6	15	-2	-2
Male	3 (4)	13598	2313	0.56 (0.23-1.34)	8	NA	-2	-2
Female	1 (1)	3775	579	0.67 (0.43-1.05)	54	49	-2	3
MI as primary event	4 (5)	20361	2564	0.79 (0.66-0.94)	11	35	-2	3
Angina as primary event	1 (1)	8747	1951	0.69 (0.59-0.81)	35	n.a.	-2	1
Stroke as primary event	1 (1)	1855	240	0.49 (0.26-0.92)	72	n.a.	-2	3
Reference group including former drinkers	3 (3)	25983	4222	0.72 (0.53-0.97)	40	45	1	1
Reference group excluding former drinkers	2 (3)	17020	2788	0.83 (0.58-1.17)	12	NA	3	3
Multiple alcohol measures	1 (1)	353	104	0.41 (0.20-0.83)	24	n.a.	2	3

* Defined as the lowest point of the dose-response curve within the range of dose reported by the studies.
† Defined as the dose of alcohol at which protection against the outcome is no longer statistically significant at the 95% confidence level; not applicable (NA) if non-significant association was found at any level of consumption; not available (n.a.) if the association remained significant within the range of dose reported by the studies.
‡ All of the four studies measured post-event alcohol consumption and had a quality score ≥7.

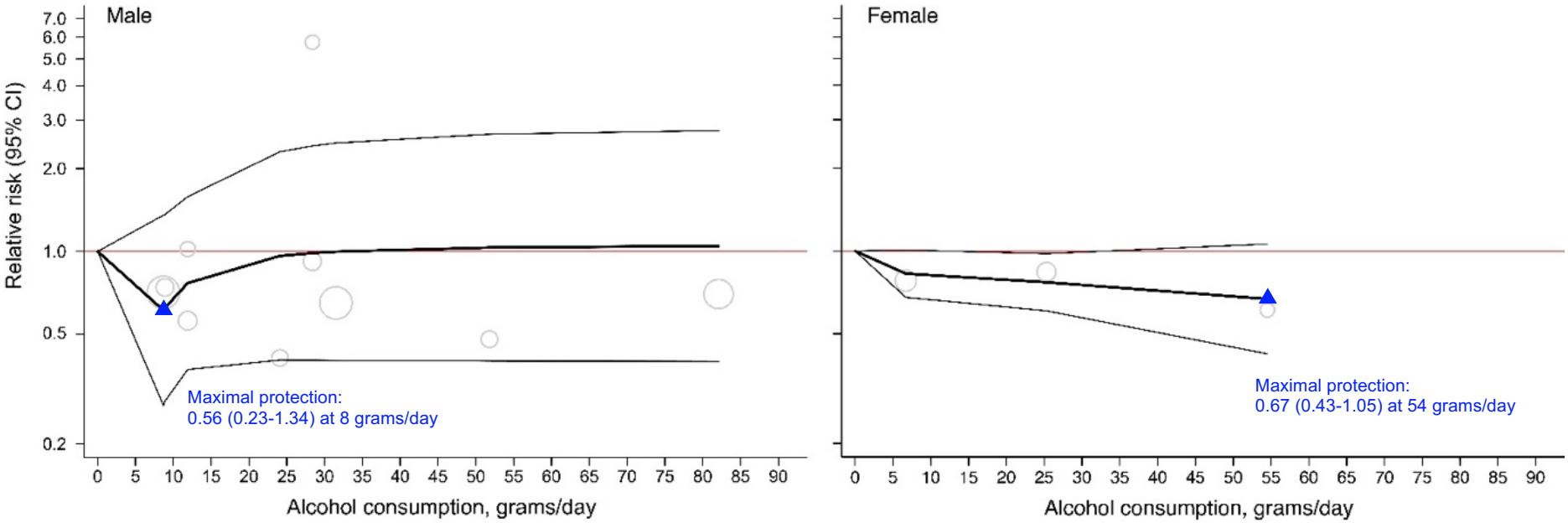


Figure 2.18 Association between alcohol and cardiovascular events in CVD patients, stratified by sex

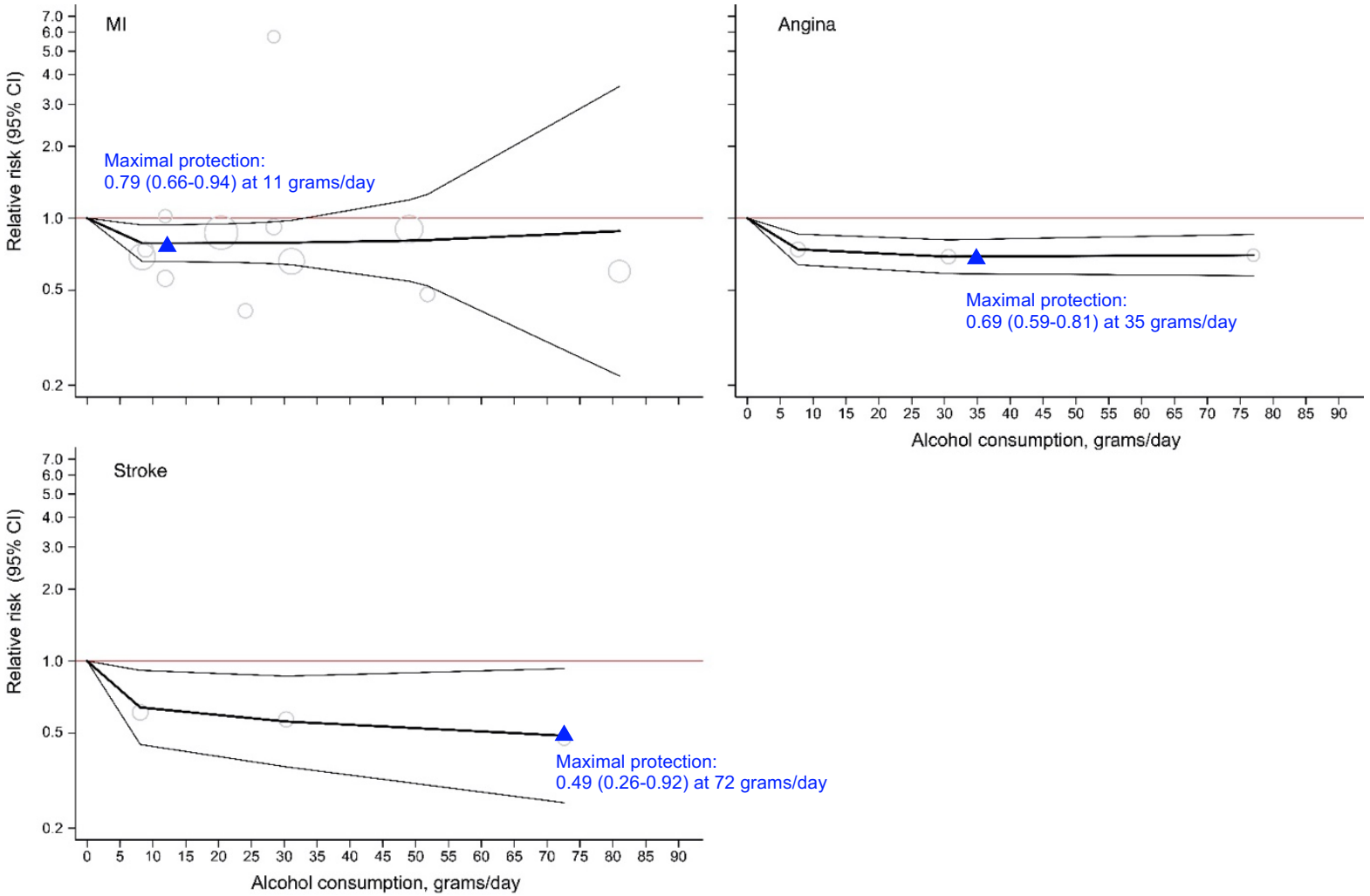


Figure 2.19 Association between alcohol and cardiovascular events in CVD patients, stratified by primary event

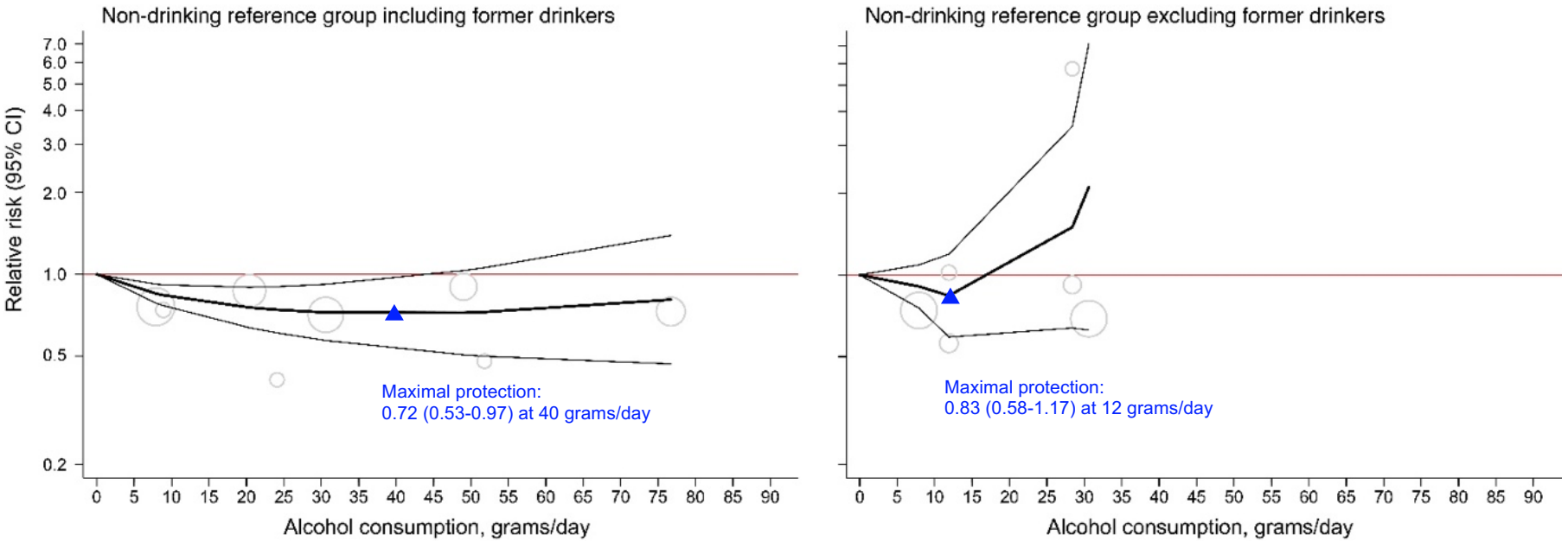


Figure 2.20 Association between alcohol and cardiovascular events in CVD patients, relative to different non-drinking group

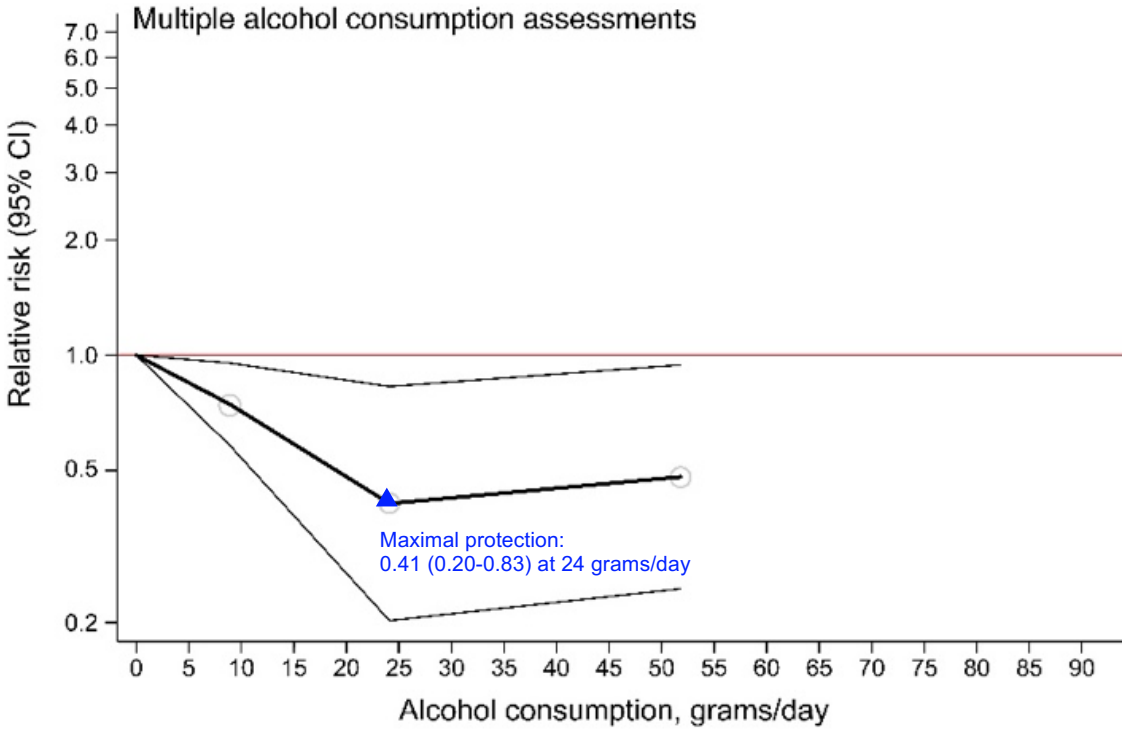


Figure 2.21 Association between alcohol and cardiovascular events in CVD patients, using multiple alcohol assessments

2.3.6 Sensitivity analyses

Sensitivity analyses showed that the overall dose-response associations remained robust after excluding studies of the lowest quality (score <7; Appendix 2.7) or restricting analysis to risk estimates that were only adjusted for age, sex, and smoking status (Appendix 2.8). For all-cause and cardiovascular mortality outcomes, there was no evidence of heterogeneity across the first- and second-order polynomial (both I^2=0%). Meta-analyses using a fixed effect model yielded similar pooled estimates with slightly narrower CIs (Table 2.12 and Appendix 2.9): the reduction in risk was greatest at 7 grams per day (RR=0.79, 95%CI=0.74-0.84) for all-cause mortality and 9 grams per day (RR=0.73, 95%CI=0.65-0.82) for cardiovascular mortality and remained significant up to 66 and 56 grams per day, respectively. Because of large heterogeneity between studies (I^2=75% for both first- and second-order polynomial), it was not considered appropriate to use a fixed effect meta-analysis model for the outcome of subsequent cardiovascular events [170].

Results of Egger's test and funnel plots, as presented in Appendix 2.10, found no evidence of publication bias for all outcomes assessed.

Table 2.12 Results of meta-analysis on mortality in CVD patients using fixed effect model

Outcome and subgroup	No. of studies (curves)	No. of patients	No. of deaths	Maximal effect size*		Reversion point, g/day†
				RR (95% CI)	g/day	
All-cause mortality						
Overall	11 (11)	41743	7563	0.79 (0.74-0.84)	7	66
Male	6 (6)	19897	3846	0.80 (0.73-0.88)	9	51
Female	3 (3)	6046	1130	0.64 (0.36-1.14)	54	49
MI as primary event	9 (9)	29554	5227	0.78 (0.72-0.85)	2	63
Angina as primary event	2 (2)	8938	994	0.79 (0.64-0.98)	31	46
Stroke as primary event	3 (3)	3618	807	0.66 (0.54-0.80)	12	41
Reference group including former drinkers	9 (9)	41405	7423	0.78 (0.73-0.82)	15	72
Reference group excluding former drinkers	4 (4)	17526	3037	0.83 (0.73-0.94)	3	22
Post-event alcohol assessment	8 (8)	37245	6546	0.80 (0.75-0.86)	9	64
Multiple alcohol measures	2 (2)	12337	2124	0.81 (0.72-0.91)	12	52
Cardiovascular mortality ‡						
Overall	9 (9)	24770	2381	0.73 (0.65-0.82)	9	56
Male	5 (5)	14536	1439	0.75 (0.64-0.87)	10	42
Female	2 (2)	4790	228	0.29 (0.09-1.01)	54	54
MI as primary event	6 (6)	12422	1320	0.78 (0.66-0.91)	43	43
Angina as primary event	2 (2)	8934	406	0.85 (0.66-1.10)	31	NA
Stroke as primary event	3 (3)	3617	423	0.59 (0.44-0.79)	28	52
Reference group including former drinkers	6 (6)	24269	2155	0.72 (0.64-0.80)	16	76
Reference group excluding former drinkers	5 (5)	17683	1349	0.72 (0.60-0.86)	7	49
Post-event alcohol assessment	7 (7)	21525	2003	0.74 (0.65-0.84)	7	53

* Defined as the lowest point of the dose-response curve within the range of dose reported by the studies.
† Defined as the dose of alcohol at which protection against the outcome is no longer statistically significant at the 95% confidence level; not applicable (NA) if non-significant association was found at any level of consumption.
‡ Only one study measured alcohol consumption at multiple time points.

2.4 Discussion

Meta-analysis of new findings from three major UK cohorts together with those from 12 published studies showed J-shaped associations between alcohol consumption and mortality in patients with established CVD. Compared to current non-drinkers, the reduction in risk was largest at 7 grams per day for all-cause mortality and 8 grams per day for cardiovascular mortality and held up to 62 and 50 grams per day, respectively. The associations were found in accordance with the 2010 meta-analysis [120] and have also been reported in other high-risk populations, such as patients with hypertension [171] and diabetes [172].

The work presented in this chapter is the first meta-analysis to examine the association between alcohol consumption and any subsequent cardiovascular events among CVD patients. Decreases in risk were evident for any alcohol intake up to about 15 grams per day, an upper limit much lower than those seen for the mortality outcomes. Taken together, findings of this chapter indicated that, among CVD patients, the upper drinking limit for lower risks of mortality and cardiovascular morbidity was approximately 105 grams per week, which was lower than those recommended in most current guidelines. For example, the UK NICE 2020 guidelines recommend MI survivors to drink within 112 grams per week [107]; the AHA/American Stroke Association 2014 guidelines [109] and the AHA/ACCF 2011 guidelines [108] recommend no more than 196 grams per week for male patients with stroke or atherosclerotic vascular disease and 98 grams per week for the female patients; and WHO 2007 recommendations for prevention of recurrent MI and stroke were up to about 166 grams per week [110]. For more details as regards the above guideline recommendations, please refer to Box 1.1 in Chapter 1 Section 1.3.2.

The biological mechanisms whereby alcohol may influence long-term prognosis in CVD patients are not fully understood. While epidemiological studies suggest that HDL-cholesterol mediates approximately half of alcohol's relation to CVD incidence [173], HDL-cholesterol does not appear to be the main pathway responsible for the protective effect of moderate drinking on CVD prognosis. Specifically, in the study by Janszky et al. [116] among survivors of a first MI, adjustment for lipids, including HDL-cholesterol, LDL-cholesterol, Apo A, and

total cholesterol, did not appreciably alter the strength of association between alcohol intake and total mortality. Another study found that moderate drinking was associated with reduced progression of coronary atherosclerosis (as measured by mean luminal diameter change) in women hospitalized with CHD; the effect, however, was only attenuated by 12-13% after further control for HDL-cholesterol [115]. Experimental animal models also showed that alcohol suppressed the progression of existing atherosclerotic lesions and reduced plasma HDL-cholesterol level, indicating that HDL-cholesterol plays little or no role in amelioration of atherogenesis [174]. On the other hand, in line with data from the general population, adjustment for circulating amounts of insulin, insulin-like growth factor binding protein-1, and fibrinogen significantly weakened the association of alcohol with mortality post-MI, as found by Janszky et al [116]. Hence, the prognostic effect of alcohol may be partly explained by its favourable impact on glucose metabolism and prothrombotic factors. Alcohol was also found to inhibit ischemic-induced arrhythmias and significantly reduce the percentage of the ischemic area that underwent necrosis in experimental MI (a rat model of ischemia and reperfusion) [175]. Other proposed mechanisms that remain to be further elucidated within the context of prevalent CVD include lower levels of inflammation [83], decreased platelet activity [84] and better endothelial function [87, 88]. For more detailed description on possible mechanisms that underlie the alcohol-CVD association, please refer to Chapter 1 Section 1.3.1.2.

With almost triple the sample size (48423 CVD patients in total), this chapter expands the findings of the 2010 meta-analysis [120]. In particular, both HSE/SHeSs and UK Biobank provide long-term follow-up of large contemporary samples from the UK general population. The inclusion of these new datasets enables assessments of the risk of drinking within various subgroups, some of which are not available or too small to reliably investigate in published studies on CVD patients. For example, the results from the current chapter suggest that the dose-response associations may be more pronounced among patients with a previous MI than angina or stroke, raising the question of whether differential drinking limits should be recommended in patient subgroups and require further examination.

Furthermore, there is evidence that reductions in risk of all-cause mortality and subsequent events might have been overestimated due to the inclusion of former drinkers in the non-drinking reference group. By comparison, in the 2010 meta-analysis [120], inclusion of former drinkers in the reference group did not seem to bias the association between alcohol consumption and mortality. One possible reason for the discrepancy is that the 2010 meta-analysis adopted a unified ($p_1 = p_2 = 0.5$) rather than a best-fitting transformation when modelling each dose-response curve and thus might have obscured the differences between curves. Former drinkers may include individuals who have stopped drinking because of worsening health (often referred to as 'sick quitters', as discussed in Chapter 1 Section 1.3.1.3), particularly past heavy drinkers [176], therefore making current drinkers appear healthy relative to less healthy non-current drinkers [177]. Indeed, in a previous meta-analysis of studies conducted in the general population, reductions in mortality risk among low-volume drinkers were attenuated and insignificant after adjustment for abstainer reference group bias, that is mixing former and occasional drinkers with lifetime abstainers [178]. These could lead to a low-risk drinking limit less than the estimated 105 grams per week. However, this chapter cannot definitely determine the extent of this overestimation with only two studies (one is UK Biobank) that explicitly excluded former drinkers in their analysis on subsequent cardiovascular events, resulting in wide CIs around the corresponding pooled curve.

In the present chapter, there was no increase in risk of mortality and subsequent events among patients with higher alcohol intake. This accords with the 2010 meta-analysis and another meta-analysis of hypertensive individuals [120, 179], but contradicts some research reports from general populations [27, 34]. The discordance between findings from the present chapter and those of general population studies may be partly explained by CVD patients' advancing age. The mean/median age at baseline was greater than 59 years in most datasets utilised in this work (see Table 2.5). Because alcohol-related harms are relatively higher in younger age groups than in the elderly [180], enrolling participants of older age in studies would downplay the risk association compared to an analysis based on drinkers of all ages. Particularly, the likelihood for drinkers to become former drinkers would rise in studies with older

participants, resulting in larger bias from sick quitters (that is when the non-drinking reference group also includes former drinkers who have quit drinking in response to ill health) as discussed above. Patients who drink heavily and remained/enrolled in studies at older ages are more likely to represent 'healthy survivors' or have safer drinking practices [92, 176]. Notably, heavy drinkers are known to be under-represented in some of the included datasets, such as HSE/SHeSs [181] and the Physicians' Health Study [182]. Therefore, potential selection bias may have occurred and led to an underestimation of associations between heavy intake and risks of mortality and subsequent events. Furthermore, most epidemiological studies did not capture the extremes of alcohol use and thus may not have sufficient power to look at the effects of very heavy drinking. As a result, the lack of effects at higher drinking levels seen in this work should be interpreted cautiously, especially in light of the known profound health and societal impact of such elevated intake levels [183], as well as the increasing concerns about alcohol misuse in older populations [184].

The work reported in this chapter has several additional limitations that should be noted. Firstly, as a composite of cardiac mortality and several non-fatal cardiovascular endpoints, the definition of cardiovascular events varied across the three published studies [127, 152, 167], and thus this chapter defined the outcome in UK Biobank based on the most frequently reported events in these studies. However, there was still a significant heterogeneity in the meta-analysis. Recent observational and genetic research has suggested that moderate alcohol consumption is associated with a decreased risk of some but not all types of CVD [37, 101, 185, 186]. Therefore, this heterogeneity might have reflected the complex and diverse impacts of alcohol consumption on different CVD phenotypes.

Secondly, episodic heavy drinking has been suggested to modify the relationship between average alcohol intake and CVD/mortality risk, as detailed in Chapter 1 Section 1.3.1.1. So, there might have been confounding by the drinking pattern, as the selected studies did not exclude 'binge' drinkers. Additionally, data on alcohol intake were self-reported and hence subject to bias. However, self-reported drinking data was validated against HDL-cholesterol and gamma-glutamyl transferase (GGT) in HSE/SHeSs and UK Biobank (see Appendix 2.11). Although this meta-analysis attempted to

minimise confounding by using the most adjusted estimates, residual confounding may still exist. Information on factors such as regular use of medications, dietary behaviour or physical activity was not available in all studies included in this meta-analysis and so there is a possibility of residual confounding by these factors. However, sensitivity analyses found consistent results when using risk estimates that were only adjusted for age, sex, and smoking status, indicating that additional adjustment for these factors is unlikely to substantively influence the associations.

Thirdly, the results of this chapter must be interpreted with caution when it comes to some subgroups that have been investigated in only a limited number of studies. Relatedly, further analyses for beverage type were not possible with sufficient beverage-specific data reported in very few studies. However, the proposed differences in the associations across different beverage types are believed to be more attributed to differences in lifestyle among drinkers rather than a direct effect of the beverage per se (see Chapter 1 Section 1.3.1.1). Similar beverage types were found among drinkers at different levels in UK Biobank. Although the included studies scored as moderate to high quality on the Newcastle-Ottawa Scale, this may not account for some pertinent design/reporting characteristics of many of the studies which had problems that were specific to alcohol exposure and not covered in the scale. In meta-analyses, a relatively strong effect was observed at very low levels of drinking, and this may reflect some under-estimation of alcohol intake expected from studies with self-reported measures. Particularly, despite evidence that drinking levels fluctuate over time [123] and that the experience of ill health could lead to subsequent reduction or cessation of alcohol use [187], the majority of included studies relied upon only single alcohol observations. Little is therefore known about the temporal changes within individuals' drinking behaviour both after primary event and during follow-up, and this will be explored in depth in the next chapter.

In summary, this chapter shows that, amongst CVD patients, an alcohol intake up to about 15 grams per day is associated with lower risks of both mortality and subsequent cardiovascular events relative to non-drinking. At the same time, there is also the possibility that reductions in risk may have been overestimated by studies using a referent group contaminated by less healthy

former drinkers. No evidence of elevated risk among heavy drinkers was found but this was potentially attributable to selection bias and under-representation of such drinkers in the datasets. The findings therefore indicate that, for secondary prevention of CVD, current drinkers may not need to stop drinking but should be informed that lower levels of intake – up to 105 grams (or equivalent to 13 UK units) per week – may be associated with reduced risks. However, non-drinking patients should not be encouraged to take up light drinking because of well-known adverse effects on other health outcomes, including certain cancers [188].

Chapter 3 Trajectories of alcohol consumption before and after CVD diagnosis: a longitudinal case-control study (Study 2)[2]

3.1 Introduction to the study

As outlined in Chapter 2 Table 2.5, much of the existing evidence linking alcohol to the long-term prognosis among CVD patients arises from observational studies that measured exposure to alcohol at a single point in time (typically at baseline, either before [129, 154, 168] or after being diagnosed with CVD [148, 152, 155, 169]), In doing so, these studies assume that levels of alcohol consumption remain stable over time, but there are reasons to doubt this. Drinking behaviour varies across the life course [123, 189]. There is also possibility that the onset of disease may lead individuals to re-evaluate their lifestyles and foster positive behaviour changes to enjoy better health outcomes. Analysis of drinking trajectories with repeat alcohol measures is therefore needed to examine longitudinal stability of consumption among CVD patients, particularly possible changes in consumption in relation to the diagnosis. Such information can be used to inform ongoing investigation into how drinking behaviour is associated with the onset and long-term prognosis of CVD.

Few studies have assessed drinking trajectories over time among CVD patients. Levantesi et al. found that most patients reduced their wine consumption during the first six months after the onset of MI [127]. With no drinking data prior to MI, the authors did not examine the impact of MI diagnosis itself on alcohol use. Pai et al. reported a high correlation between levels of consumption assessed immediately before and after MI [128]. However, their analysis included men only. Notably, change in consumption was based on only two time-point assessments of alcohol and, therefore, the authors were unable to estimate the shape of trajectories or distinguish true change from measurement error [190].

[2] Some of the findings presented in this chapter have informed the journal article: Ding C, O'Neill D, Britton A. Trajectories of alcohol consumption up to 30 years before and after the diagnosis of cardiovascular diseases: a longitudinal case-control study of 12502 participants. J Epidemiol Community Health. doi:10.1136/jech-2021-217237. Please see Appendix 3.1 for full paper.

Estimations of longitudinal drinking trajectories have also been drawn from studies linking alcohol to broader categories of life events which include newly occurring CVD [191-193]. However, these analyses were characterised by heterogeneous results as well as different methodological limitations such as (1) reliance on crudely categorised measures of alcohol intake, (2) short durations of observation and (3) utilisation of a small number of measurement occasions, which in combination limited insights into trajectories of alcohol consumption from pre- to post-CVD diagnosis over an extended time frame.

The work presented in this chapter aims to describe the mean trajectories of alcohol consumption among CVD patients, highlighting any possible changes in mean consumption after their CVD diagnosis. It examines the extent to which alcohol consumption changes over a prolonged period of up to 30 years before and after the onset of CVD with repeated alcohol measures from two large UK cohorts. By using a case-control study design, a group of controls were also sampled from the same source population that gave rise to the CVD cases but without the condition. Given that the present work aimed to offer perspectives on a changing behaviour (rather than defining its health risk), this control group served as a background reference, which helped to illustrate potential fluctuations in alcohol intake as individuals age over the life course rather than being a comparator about how drinking trajectories might be related to the occurrence of CVD.

3.2 Methods

3.2.1 Study design and population

A ‘nested’ case-control study was conducted within two ongoing UK cohorts: the Whitehall II study, comprising 10308 British civil servants aged 35-55 years at enrolment during 1985-88 [194], and the EPIC-Norfolk study, comprising 25639 residents in Norfolk aged 39-79 years at enrolment in 1993 [195]. The cohorts were chosen because they both measured alcohol intake (and covariates) repeatedly for the same individuals over a considerable time span and had reliable information on the date of CVD diagnosis through linkage to electronic health records. Participants with a previous diagnosis of CHD (angina or MI) or stroke prior to the enrolment date were excluded from the analysis. Cases were

defined as participants who developed incident CHD or stroke during follow-up (until 31 March 2019 in Whitehall II and 31 March 2016 in EPIC-Norfolk), as ascertained from linked data, and had at least one alcohol measure both before and after the date of diagnosis. Up to four controls were randomly selected for each case from those who were free of CHD and stroke during follow-up and provided at least one alcohol measure both before and after the time of diagnosis of the case. Cases and controls were individually matched by cohort, sex, and age at baseline (±1 year).

3.2.2 Alcohol consumption

Data on alcohol consumption were extracted from eight phases of the Whitehall II study and three phases of the EPIC-Norfolk study. At each phase, participants were asked to report the number of alcoholic drinks (measures of spirits, small glasses of wine, and pints of beer/cider) they had consumed in the week prior to interview. Drinks were converted into grams of ethanol in the same way as described in the preceding chapter (see Section 2.2.1.2), by assuming 8 grams per measure of spirits or small glass of wine and 16 grams per pint of beer/cider [150]. These converted measurements were then added up to define the total volume of weekly alcohol consumption in grams. The date of interview was compared with the date of diagnosis (for controls the date of diagnosis of their matched case) to determine whether an alcohol measure reflected the drinking level before or after the onset of disease.

3.2.3 Covariates

Covariates were drawn from each phase along with alcohol assessment and included age, sex, ethnicity (white or non-white) and marital status (married/cohabiting or other). Socioeconomic position was measured using occupational information and categorised as high, intermediate or low, representing income and status at work [83]. Additional data on health behaviours were obtained on smoking status (current, former, or never), physical activity (active or inactive) and dietary behaviour (frequency of fruit and vegetables consumed in a week). Information on BMI (kg/m^2), self-reported history of hypertension or use of anti-hypertensive drugs and self-rated health (excellent/good, fair, or poor) was also collected.

3.2.4 Statistical analysis

3.2.4.1 Trajectory modelling

Time (in years) was centred on the date of diagnosis for cases and for controls the date of diagnosis of their matched case, which were each coded as year zero. Volume of alcohol consumed as a function of time prior to or following diagnosis was estimated using multilevel growth curve models in which observations were nested within individuals within cohorts. The models were fit with a random intercept and random slope on time at the individual level, and a random intercept at the cohort level. This allowed each individual to have their own drinking trajectory and accounted for the clustered nature of the data. The fixed effects of the models thus described the population mean trajectories. Detailed model equations are given below [196]:

The Level-1 (observation level) model equation was

$$y_{tij} = \alpha_{0ij} + \alpha_{1ij} f(time_{tij}) + e_{tij}$$

where y_{tij} was the volume of alcohol consumed at time t for individual i nested within cohort j. α_{0ij} and α_{1ij} represented the intercept and slope for individual i in cohort j. $f(time_{tij})$ was the best fitting first- or second-degree fractional polynomial (FP) transformations of the 'time' variable at time t for individual i in cohort j (see Chapter 2 Section 2.2.2.3 and below for further information on FP modelling). e_{tij} was the time-, individual-, and cohort-specific residual.

The Level-2 (individual level) equations were

$$\alpha_{0ij} = \beta_{00j} + \nu_{0ij}$$
$$\alpha_{1ij} = \beta_{10j} + \nu_{1ij}$$

where β_{00j} and β_{10j} were the cohort-specific intercept and slope of the drinking trajectory, interpreted as the mean initial value and the mean rate of change for all of the individuals who were nested within cohort j. The residuals ν_{0ij} and ν_{1ij} were individual-specific random effects, capturing the variability of each individual's trajectory around their own cohort-specific mean trajectory.

Finally, given the possible cohort differences and clustering of data by cohort, a further random effect was included in the models to allow cohort-specific intercepts. The Level-3 (cohort level) equation was thus

$$\beta_{00j} = \gamma_{000} + u_{00j}$$

where γ_{000} was the overall mean intercept pooling over all individuals in both cohorts. The residual u_{00j} captured the variability of each cohort-specific intercept around the overall mean value.

Models were fit separately for cases and controls and for males and females. To examine how drinking may change following the onset of CVD, separate models were constructed according to whether alcohol measures were reported before or after the documented date of diagnosis. Models were then incrementally adjusted for sociodemographic factors, health behaviours and health status. All of the covariates were allowed to vary over time, except for sex and ethnicity.

FP has been applied in the multilevel framework to model the longitudinal trajectory of alcohol consumption according to T2DM status [197]. Using height growth in girls during infancy and early childhood as an illustrative example, Tilling et al. compared FP and linear spline (also called 'piecewise model', which assumes implausible linearity and models trajectory as a series of connected lines jointed at 'knots') in the multilevel setting and concluded that the two approaches performed similarly [198]. Considering that linear spline does not have the same smoothness as FP and that the optimal methods for selecting knots in spline fitting remains unsettled [199], this work used FP terms (power p = -2, -1, -0.5, 0, 0.5, 1, 2 and 3) to best describe the shape of alcohol trajectory in CVD patients and their matched controls [200]:

The first-degree FP equations were defined as

$$f_1(time_{tij}) = \begin{cases} \beta_0 + \beta_1 time_{tij}^{\,p_1} & \text{if } p_1 \neq 0 \\ \beta_0 + \beta_1 \log(time_{tij}) & \text{if } p_1 = 0 \end{cases}$$

And the second-degree FP equations were

$$f_2(time_{tij}) = \begin{cases} \beta_0 + \beta_1 time_{tij}^{\,p_1} + \beta_2 time_{tij}^{\,p_2} & \text{if } p_1 \neq p_2 \\ \beta_0 + \beta_1 time_{tij}^{\,p_1} + \beta_2 time_{tij}^{\,p_2} \log(time_{tij}) & \text{if } p_1 = p_2 \end{cases}$$

Model fit was assessed using the Bayesian information criterion (BIC), with fit statistics for each model reported in Appendix 3.2. An improvement in fit was defined as any reduction in the BIC ≥10 [201]. Robust standard errors were calculated for the best fitting model.

3.2.4.2 Multiple imputation

Missing covariate data were handled with multiple imputation by chained equations (MICE) [202, 203], using the *mi* commands in Stata. MICE treat repeated measurements in longitudinal studies as distinct variables (often referred to as 'Just Another Variable' [204]) and impute incomplete variables iteratively via a sequence of separate regression models that predicted missing values conditional on all other variables within the models. All covariates, having missing values or not, in the substantive analysis of interest (that is growth curve models in the trajectory analysis) were included in the imputation models. Variables on 'volume of alcohol consumption' and 'time to diagnosis' were also included in the imputation models but only observed values of these variables were used in the substantive analysis.

For different variable types, the most appropriate regression model was chosen. Specifically, logistic regressions were used for binary variables and ordinal logistic regressions for ordered categorical variables. In the case of alcohol consumption, truncated regression models were used, restricting the lower limit of predicted value to zero. Data were log transformed for skewed continuous variables. The 'augment' option was selected to avoid perfect prediction, by adding random observations with very small weights to the dataset during estimation. Imputations were done separately by cohort and 50 imputations were run within each cohort – a value equal to at least the total proportion of participants without complete case data [202]. Table 3.1 shows the proportions of missing values for each variable stratified by cohort and case/control status.

Sensitivity analysis was carried out by comparing imputed data (primary analysis) to complete case data. Results derived using complete case methods were broadly concordant with those obtained using multiple imputation (see

Appendices 3.3-3.4). Upon identifying age as the main influencing factor, in a series of post hoc analyses, drinking trajectories were examined either within subgroups defined by age at the time of diagnosis or using age (in years) as the time scale. All analyses were performed using Stata 15.1. All P-values were two-sided and a P-value <0.05 was considered statistically significant.

3.3 Results

3.3.1 Sample characteristics

As presented in Figure 3.1, of the 35947 participants enrolled at baseline, there were 9178 incident CVD cases during a median follow up of 21.2 (IQR=19.8-31.3) years. Among these, 2501 cases had at least one alcohol measure both before and after the time of diagnosis, providing 12285 observations. Eligible cases were predominantly male (71.6%) and had a mean age of 65.39 (SD=9.33) years at diagnosis.

Table 3.1 shows the characteristics of the cases and their matched controls (control: n=10001, observations=50357) at the most recent phase prior to the diagnosis. Median time from this phase to diagnosis was 2.6 (IQR=1.3-3.9) years among the Whitehall II participants and 4.0 (IQR=2.3-6.7) years among the EPIC-Norfolk participants.

On average, cases showed a worse cardiovascular risk profile than controls, with a greater proportion of the participants currently smoking, being physically inactive and having higher BMI. Cases were also more likely to have hypertension and rate their health as poor. In terms of alcohol consumption, cases in the EPIC-Norfolk study reported slightly lower levels of drinking than matched controls, whereas drinking levels were similar for the two groups in the Whitehall II study.

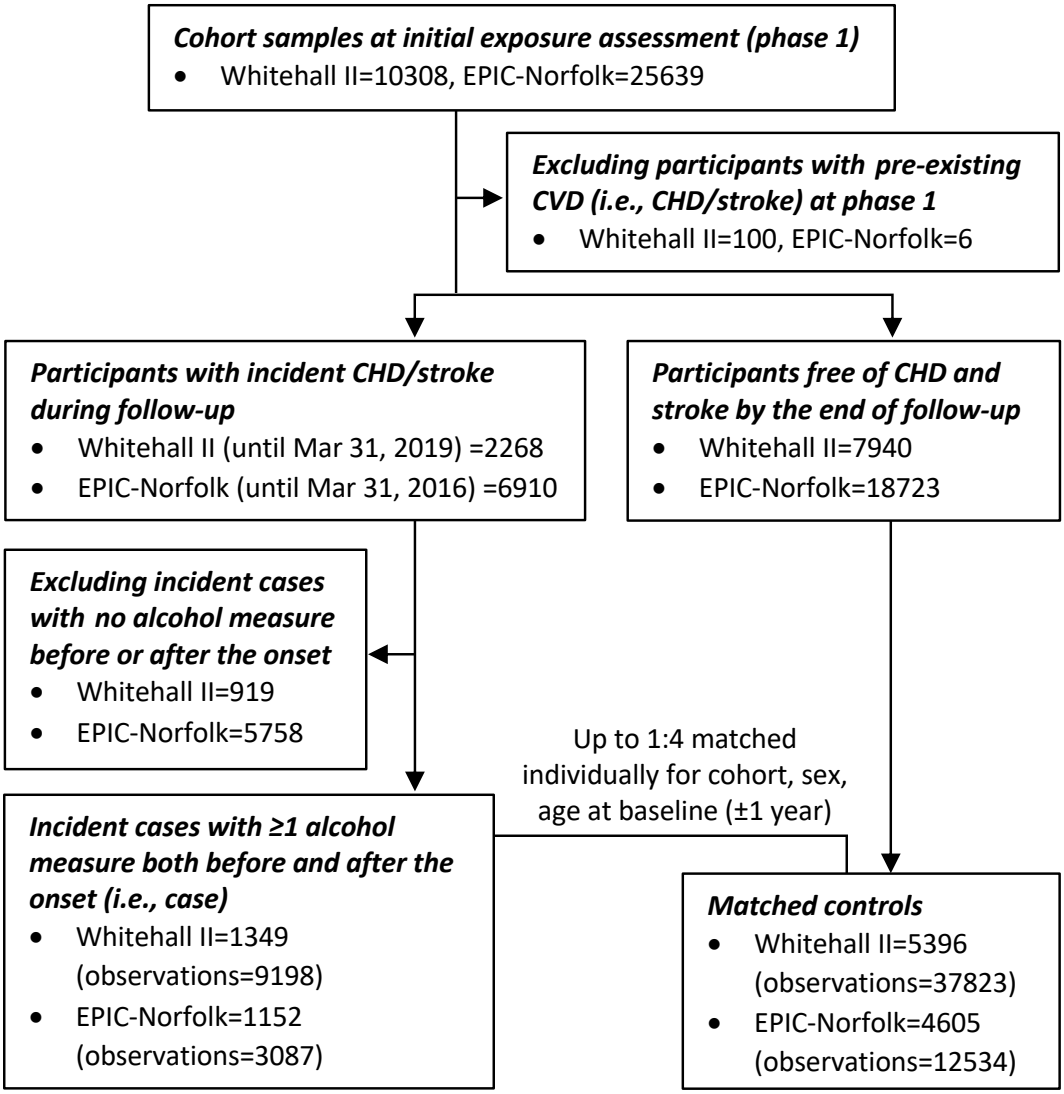


Figure 3.1 Flowchart of the case selection for each study

Table 3.1 Sample characteristics at the most recent phase before diagnosis

	The Whitehall II study					The EPIC-Norfolk study				
	Case (n=1349)		Control (n=5396)		P-value*	Case (n=1152)		Control (n=4605)		P-value*
Age (years) †	62.05	(9.04)	61.87	(8.98)	0.509	69.30	(8.07)	69.13	(8.06)	0.522
Male	1027	(76.13)	4108	(76.13)	1.000	764	(66.32)	3053	(66.30)	0.989
Alcohol intake in last week (grams) ‡	56	(8, 128)	56	(16, 128)	0.446	28	(10, 80)	36	(12, 92)	0.031
Ethnicity										
White	1161	(86.06)	5054	(93.66)	<0.001	1146	(99.48)	4582	(99.50)	0.169
Non-white	186	(13.79)	328	(6.08)		1	(0.09)	15	(0.33)	
Missing	2	(0.15)	14	(0.26)		5	(0.43)	8	(0.17)	
Marriage										
Married/cohabiting	1054	(78.13)	4191	(77.67)	0.748	943	(81.86)	3918	(85.08)	0.003
Other	295	(21.87)	1201	(22.26)		205	(17.80)	656	(14.25)	
Missing	0	(0.00)	4	(0.07)		4	(0.35)	31	(0.67)	
Socioeconomic position										
High	538	(39.88)	2546	(47.18)	<0.001	524	(45.49)	2254	(48.95)	0.128
Intermediate	604	(44.77)	2191	(40.60)		446	(38.72)	1659	(36.03)	
Low	207	(15.34)	659	(12.21)		161	(13.98)	636	(13.81)	
Missing	0	(0.00)	0	(0.00)		21	(1.82)	56	(1.22)	
Smoking										
Never smoker	574	(42.55)	2691	(49.87)	<0.001	413	(35.85)	2052	(44.56)	<0.001
Ex-smoker	578	(42.85)	2217	(41.09)		616	(53.47)	2198	(47.73)	
Current smoker	197	(14.60)	484	(8.97)		114	(9.90)	329	(7.14)	
Missing	0	(0.00)	4	(0.07)		9	(0.78)	26	(0.56)	

Physical activity										
Active	1222	(90.59)	4988	(92.44)	0.024	746	(64.76)	3393	(73.68)	<0.001
Inactive	124	(9.19)	397	(7.36)		406	(35.24)	1212	(26.32)	
Missing	3	(0.22)	11	(0.20)		0	(0.00)	0	(0.00)	
Fruit and vegetable consumption										
≥ Daily	915	(67.83)	3833	(71.03)	0.021	1122	(97.40)	4472	(97.11)	0.908
< Daily	434	(32.17)	1563	(28.97)		4	(0.35)	17	(0.37)	
Missing	0	(0.00)	0	(0.00)		26	(2.26)	116	(2.52)	
BMI (kg/m^2) †	26.83	(4.08)	25.88	(3.93)	<0.001	27.35	(3.74)	26.41	(3.51)	<0.001
Missing	0	(0.00)	1	(0.02)		1	(0.09)	6	(0.13)	
Hypertension										
No	931	(69.01)	4319	(80.04)	<0.001	582	(50.52)	3566	(77.44)	<0.001
Yes	415	(30.76)	1056	(19.57)		570	(49.48)	1039	(22.56)	
Missing	3	(0.22)	21	(0.39)		0	(0.00)	0	(0.00)	
Self-rated health										
Excellent/good	983	(72.87)	4611	(85.45)	<0.001	813	(70.57)	4072	(88.43)	<0.001
Fair	300	(22.24)	680	(12.60)		289	(25.09)	496	(10.77)	
Poor	66	(4.89)	102	(1.89)		36	(3.13)	21	(0.46)	
Missing	0	(0.00)	3	(0.06)		14	(1.22)	16	(0.35)	

Covariates were drawn from the phase just before the date of diagnosis for cases and for controls the date of diagnosis of their matched case.
Values are numbers (percentages) unless otherwise specified.
* To examine within-cohort differences between case and control groups, one-way ANOVA was used on continuous data and the chi-squared test on categorical data; analyses were based on complete cases.
† Mean (standard deviation).
‡ Median (interquartile range).

Table 3.2 presents the percentage contribution of different beverage types to total alcohol intake in a subset of Whitehall II participants who reported drinking in the past week at both phases immediately before and after diagnosis (noting that binge drinking and drinking with meals were not consistently examined in Whitehall II; no data on drinking patterns were available from EPIC-Norfolk). Overall, wine contributed most to total weekly alcohol intake in both cases and controls before and after CVD diagnosis, followed by beer/cider and spirits. While total consumption was similar between cases and controls, controls drank relatively more wine and less beer/cider. The mean percentage of alcohol derived from wine was slightly higher after diagnosis, as well as in controls than in cases.

Table 3.2 Contribution of different beverage types to total alcohol intake in the Whitehall II study

	Case (n=902)	Control (n=4061)
At the most recent phase before diagnosis*		
Total alcohol intake in grams/week †	88 (48-160)	80 (48-160)
Wine %	49.71 (35.24)	53.05 (35.28)
Beer/cider %	32.40 (33.58)	29.70 (32.66)
Spirits %	17.89 (25.14)	17.25 (25.27)
At the phase immediately after diagnosis ‡		
Total alcohol intake in grams/week †	80 (40-144)	80 (48-144)
Wine %	52.66 (35.98)	56.88 (35.39)
Beer/cider %	30.71 (33.69)	27.33 (32.00)
Spirits %	16.63 (25.79)	15.78 (24.61)

Values are means (standard deviations) unless otherwise specified.
* Median time from this phase to diagnosis was 2.5 (IQR=1.3-3.8) years among cases and 2.7 (IQR=1.4-4.0) years among controls.
† Median (interquartile range).
‡ Median time from this phase to diagnosis was 2.4 (IQR=1.3-3.6) years among cases and 2.2 (IQR=1.1-3.4) years among controls.

3.3.2 Trajectories of alcohol consumption prior to diagnosis

Drinking trajectories prior to diagnosis were estimated based on 5367 observations among 1791 male cases and 1868 observations among 710 female cases. For trajectories among matched controls, there were 7161 men and 2840 women, providing 37395 and 12962 observations, respectively.

Overall, among male cases, mean consumption increased over time, peaking at around eight years before diagnosis at 95 (95%CI=60-130) grams per week and declining afterwards. At 30 years prior to diagnosis, the mean weekly volume of alcohol consumed among male cases was higher than among controls; however, by the time of diagnosis, the consumption was estimated to be roughly equivalent between the two groups, at around 90 grams per week (Figure 3.2).

Mean consumption among female cases remained stable over time, at about 30 grams per week. There was little difference in the average volume of alcohol consumption between female cases and controls at 30 years prior to diagnosis, whereas controls had a weekly consumption about 10 grams higher than cases by the time of diagnosis (Figure 3.2).

The crude models were incrementally adjusted to assess the effect of a broad range of sociodemographic characteristics, lifestyle, and health-related factors on disparities in alcohol consumption between cases and controls. Results are reported in Table 3.3 and displayed in Figure 3.3. Up to the time of diagnosis, variation in alcohol volume grew substantially among female cases. Differences in consumption at the time of diagnosis were greater between male cases and controls following adjustments but attenuated between female cases and controls.

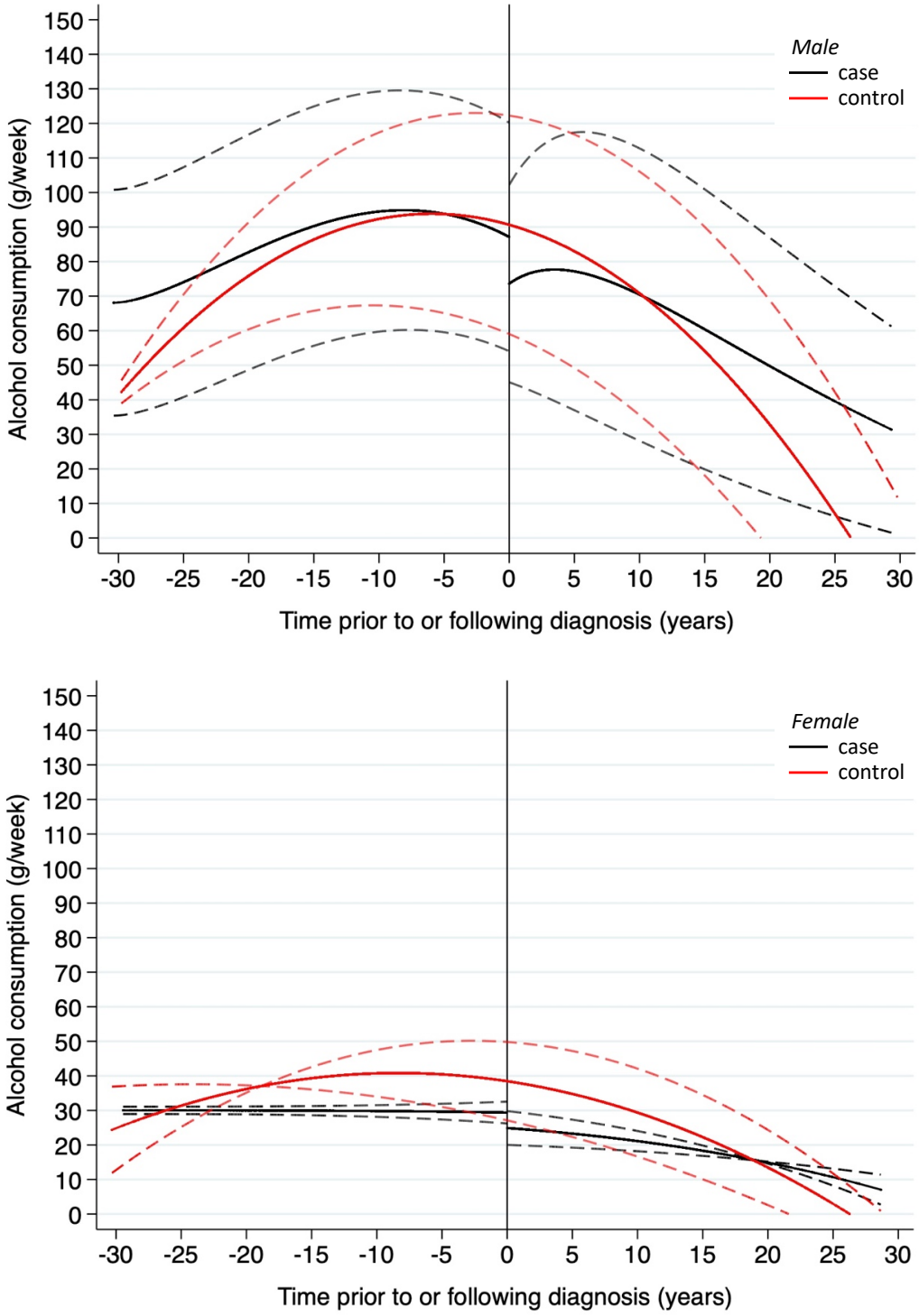


Figure 3.2 Trajectories of the mean volume of weekly alcohol consumption prior to and following the diagnosis of cardiovascular diseases, stratified by sex and case/control group (crude models using imputed data)

Notes: Dashed curves represent 95%CIs.

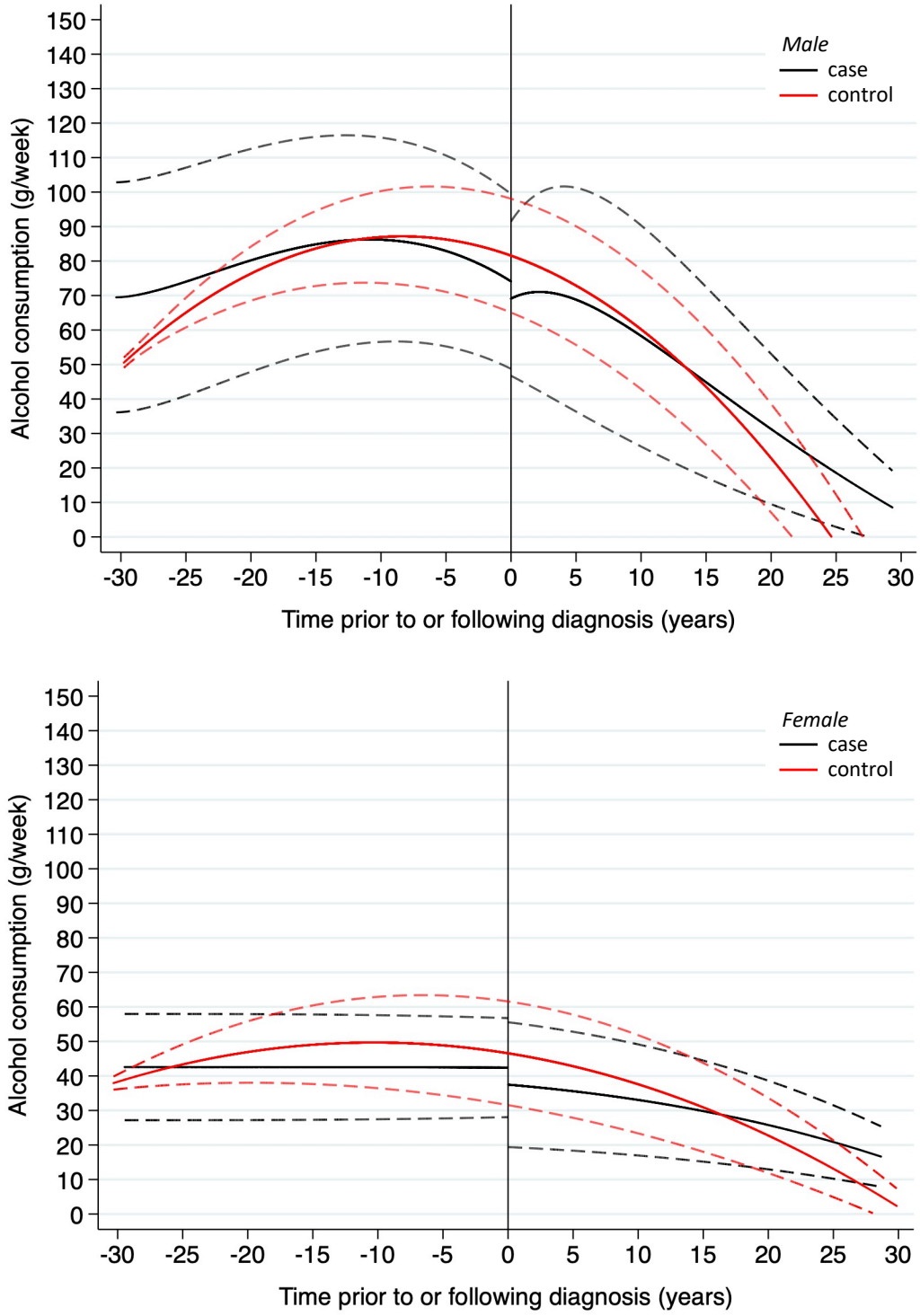


Figure 3.3 Trajectories of the mean volume of weekly alcohol consumption prior to and following the diagnosis of cardiovascular diseases, stratified by sex and case/control group (maximally adjusted models using imputed data)

Notes: Figures are reported according to mean and referent held values (that is 65 years old at diagnosis, white, married, high socioeconomic position, never-smoking, physically active, eating fruits/vegetable daily, self-rated health as excellent/good, reporting no history of hypertension and with a BMI value of 26 kg/m^2).

3.3.3 Trajectories of alcohol consumption following diagnosis

Drinking trajectories following diagnosis were estimated using the same set of cases as in the pre-diagnosis analysis above. A total of 3722 observations from male cases and 1328 observations from female cases contributed to the post-diagnosis estimation.

As shown in Figure 3.2, the mean volume of alcohol consumption among male cases dropped from 87 (95%CI=54-120) grams per week to 74 (95%CI=45-102) grams per week after the date of diagnosis, and then slightly rose to 78 (95%CI=40-116) grams per week at the subsequent three and a half years, before gradually declining to 31 (95%CI=2-61) grams per week at 30 years after diagnosis. By contrast, a continuous steeper decrease in consumption was found for their matched controls. These results, however, should be interpreted with caution as the CIs continued to be wide and greatly overlapped.

Among female cases, mean consumption fell marginally to 25 (95%CI=20-30) grams per week after the date of their diagnosis. Consumption kept decreasing in both female cases and controls during the 30 years following diagnosis, with a steeper rate of decrease in the latter.

Similar regression coefficients and drinking trajectories were obtained from adjusted models, except that a markedly attenuated drop in the average volume of alcohol consumption after the date of diagnosis was found among male cases and a greater variation in alcohol consumed was seen among female cases (Table 3.3 and Figure 3.3).

Table 3.3 Regression coefficients for the fixed effects of the best-fitting multilevel growth curve models using imputed data

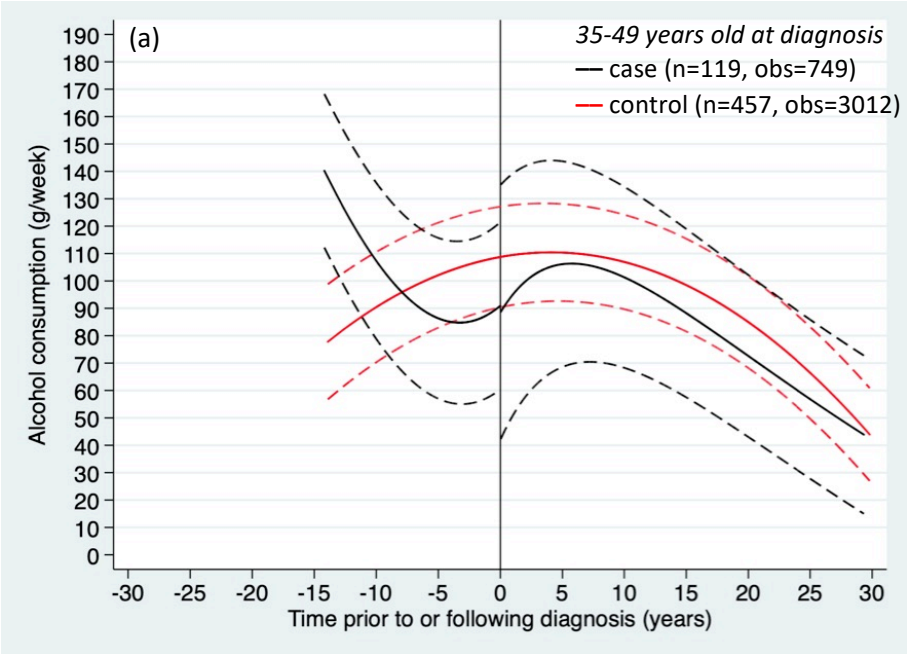
Best-fitting models *		Obs	n	Model 1			Model 2			Model 3			Model 4		
				Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value
Male															
Case,	Time ^{2}	5367	1791	14.02	0.68	<0.001	13.15	1.19	<0.001	13.68	1.14	<0.001	10.31	0.52	<0.001
pre-	Time ^{2}			-10.77	0.59	<0.001	-10.35	0.92	<0.001	-10.69	0.85	<0.001	-8.83	0.12	<0.001
onset	Intercept			68.09	16.68	<0.001	113.90	1.89	<0.001	88.99	5.01	<0.001	23.21	29.99	0.439
Case,	Time $^{-2}$	3722	1791	-2436.96	919.61	0.008	-2837.56	1164.62	0.015	-2808.99	1214.59	0.021	-2635.08	1092.75	0.016
post-	Time $^{-2}$			3386.79	1042.04	0.001	4088.46	1386.48	0.003	4030.64	1435.09	0.005	3873.59	1335.15	0.004
onset	Intercept			-70.03	11.21	<0.001	38.80	10.75	<0.001	20.13	8.55	0.019	-35.36	40.10	0.378
Control	Time ^{1}	37395	7161	44.32	7.17	<0.001	43.81	7.45	<0.001	44.08	7.40	<0.001	35.17	4.70	<0.001
	Time ^{2}			-9.07	0.75	<0.001	-9.16	0.85	<0.001	-9.17	0.83	<0.001	-8.00	0.61	<0.001
	Intercept			39.70	1.28	<0.001	141.43	0.91	<0.001	128.35	4.76	<0.001	60.39	15.74	<0.001
Female															
Case,	Time ^{3}	1868	710	-0.02	0.04	0.553	-0.06	0.02	0.021	-0.02	0.02	0.134	-0.01	0.02	0.785
pre-onset	Intercept			30.01	0.54	<0.001	52.13	4.65	<0.001	42.88	11.41	<0.001	54.15	7.84	<0.001
Case,	Time ^{3}	1328	710	-0.10	0.03	<0.001	-0.12	0.03	<0.001	-0.11	0.03	<0.001	-0.12	0.03	<0.001
post-onset	Intercept			27.72	3.24	<0.001	66.70	20.69	0.001	61.86	21.54	0.004	60.92	16.83	<0.001

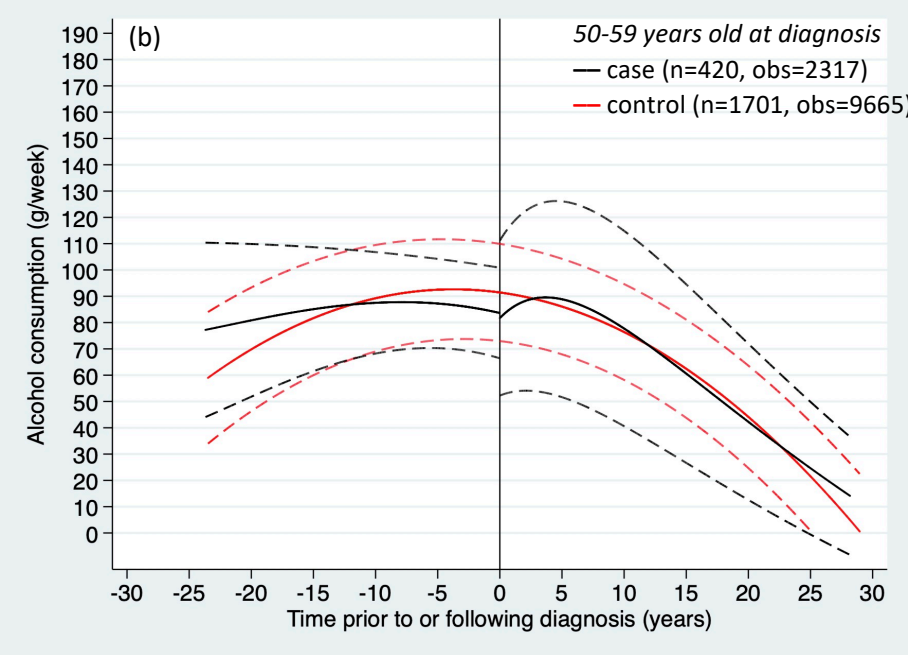
Control	Time [1]	12962	2840	15.00	6.51	0.021	13.72	5.84	0.019	13.27	5.82	0.023	11.77	4.24	0.005
	Time [2]			-3.41	0.82	<0.001	-3.29	0.79	<0.001	-3.18	0.80	<0.001	-2.93	0.66	<0.001
	Intercept			24.31	6.41	<0.001	71.88	12.75	<0.001	66.30	14.76	<0.001	62.58	10.93	<0.001

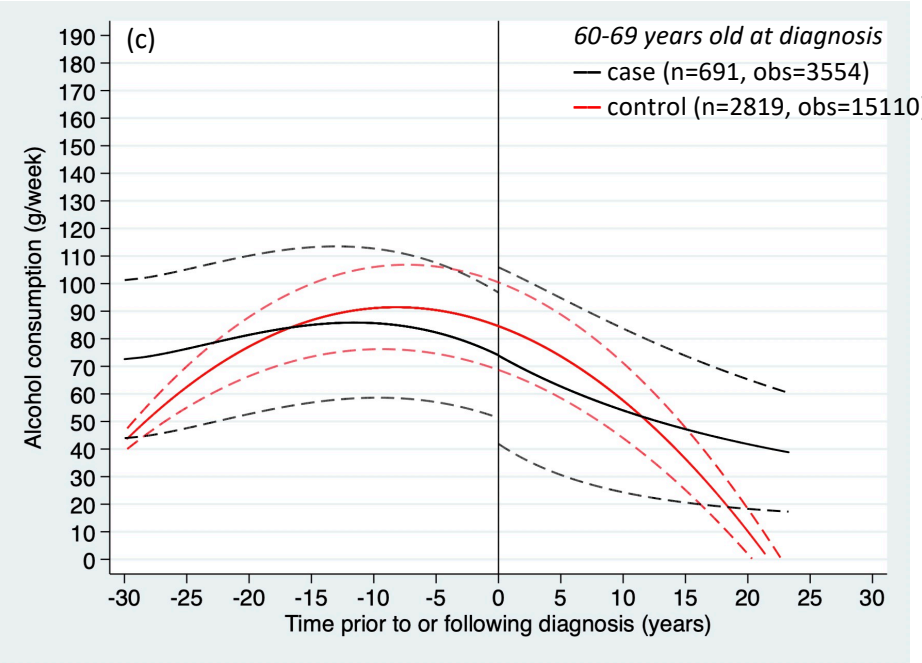
* To describe the shape of each trajectory, a group of first- and second-degree fractional polynomials with powers from a predefined set (-2, -1, -0.5, 0, 0.5, 1, 2, 3) was used to derive a power transformation of the 'Time' variable. The superscript numbers following 'Time' in the table above refer to power terms that provide the best fit.
Obs=observations, SE=standard error.
Model 1: unadjusted.
Model 2: as Model 1, plus adjustment for age at diagnosis, ethnicity, marital status, and socioeconomic position.
Model 3: as Model 2, plus adjustment for smoking, physical activity, frequency of fruit and vegetables consumed in a week.
Model 4: as Model 3, plus adjustment for prevalent hypertension (self-reported doctor diagnosed hypertension or use of antihypertensive drugs), BMI, self-rated health.

3.3.4 Post hoc analyses

Alcohol consumption trajectories prior to and following diagnosis within different age groups (35-49, 50-59, 60-69, ≥70 years at the time of diagnosis) are shown in Figures 3.4-3.5. Among females, age groups 35-49 and 50-59 years were combined due to the small number of cases in the former (n=31). For both sexes, trajectories from adjusted analyses (with adjustment for the same covariates listed in Table 3.3 Model 4) had highly overlapping CIs, indicating little difference in mean weekly consumption of alcohol between cases and controls in any specific age group. As presented in Figures 3.6-3.7, similar trajectories of mean consumption were also found between cases and controls when using age as the time scale.


(a)
35-49 years old at diagnosis
case (n=119, obs=749)
control (n=457, obs=3012)
Alcohol consumption (g/week)
Time prior to or following diagnosis (years)


(b)
50-59 years old at diagnosis
case (n=420, obs=2317)
control (n=1701, obs=9665)
Alcohol consumption (g/week)
Time prior to or following diagnosis (years)



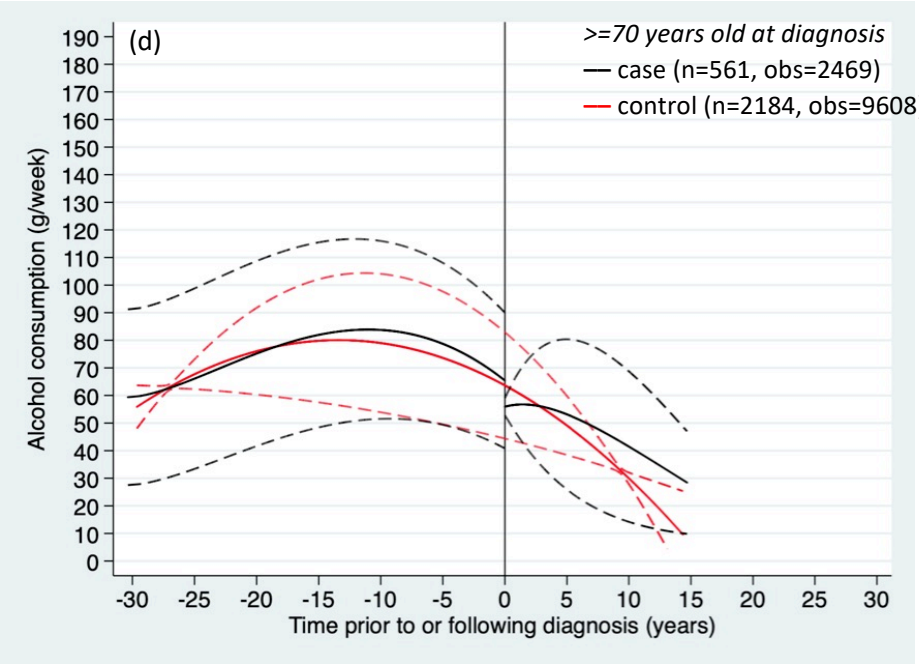
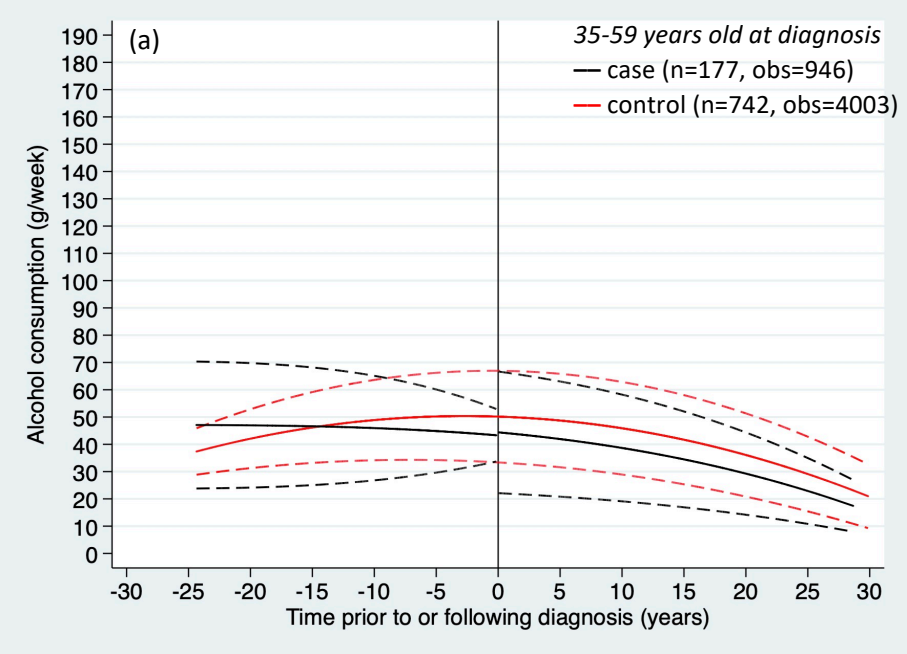
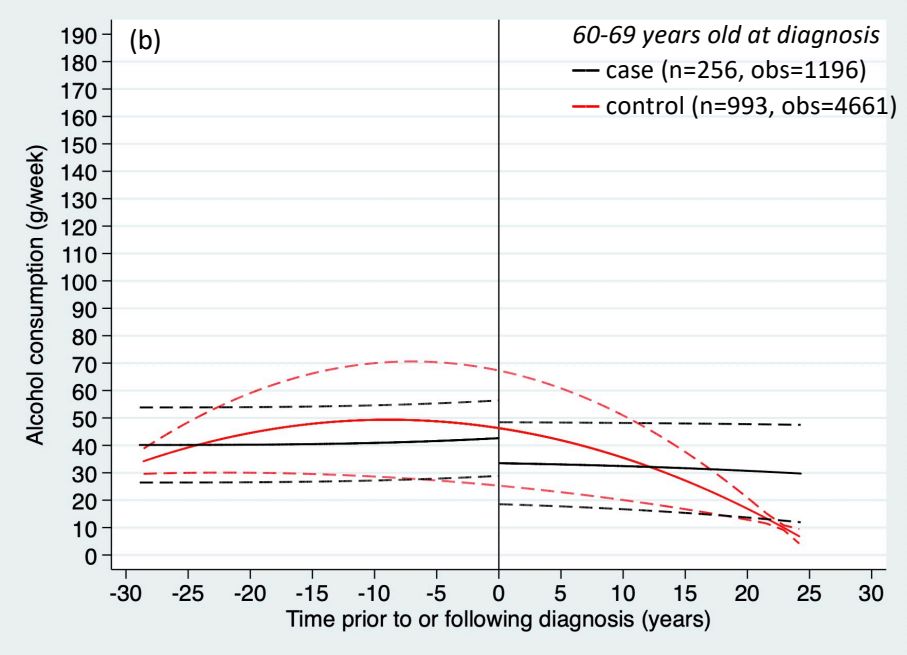


Figure 3.4 Trajectories of the mean weekly alcohol consumption among males, stratified by case/control and age group (maximally adjusted models using imputed data)

Notes: Figures are reported according to mean and referent held values, that is 46 years old at diagnosis for (a), 56 years old for (b), 65 years old for (c), or 75 years old for (d) PLUS other values as specified in the legend of Figure 3.3. obs=observations.


(a)
35-59 years old at diagnosis
case (n=177, obs=946)
control (n=742, obs=4003)
Alcohol consumption (g/week)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Time prior to or following diagnosis (years)


(b)
60-69 years old at diagnosis
case (n=256, obs=1196)
control (n=993, obs=4661)
Alcohol consumption (g/week)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Time prior to or following diagnosis (years)

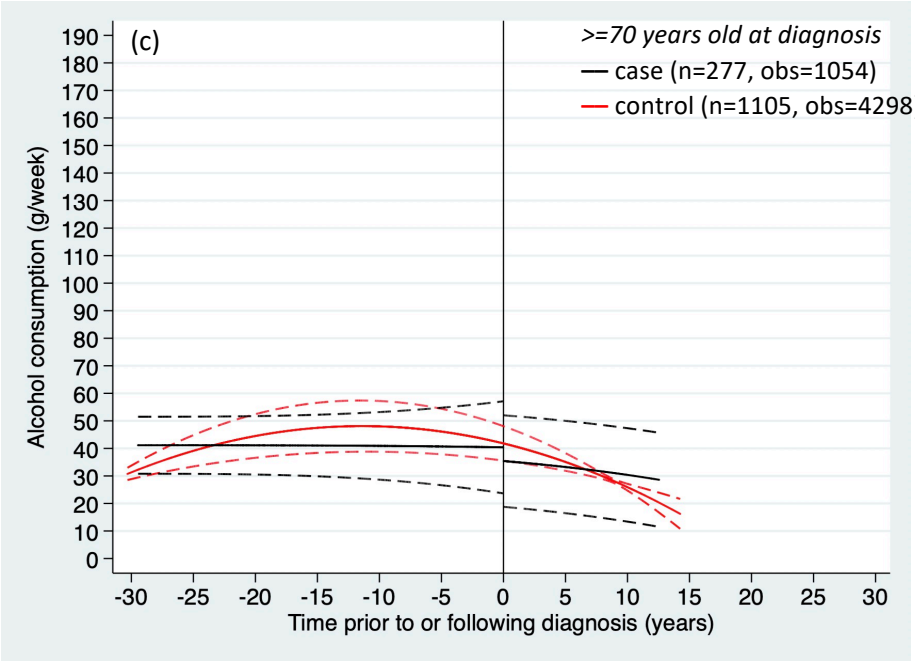
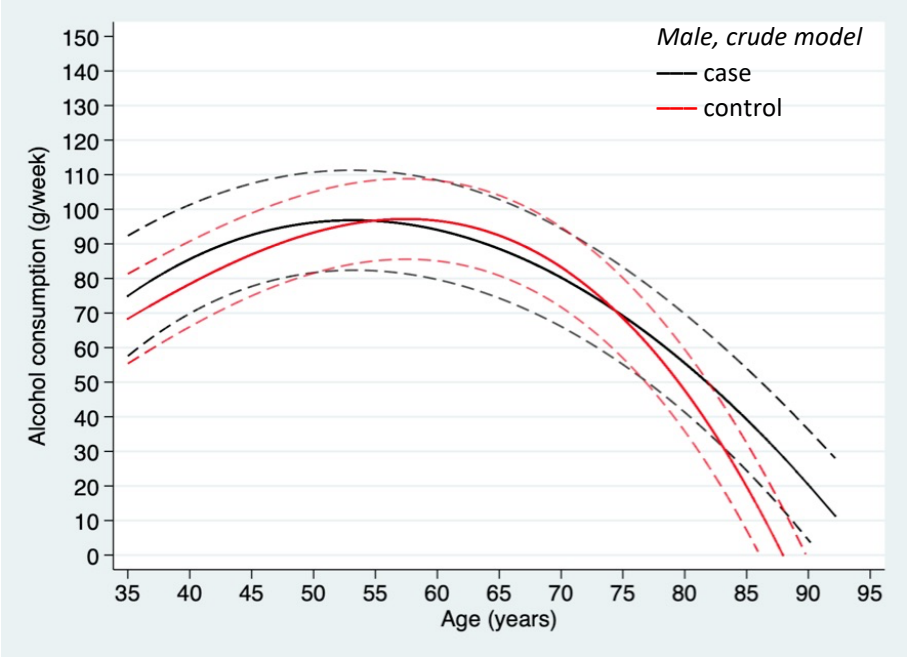


Figure 3.5 Trajectories of the mean weekly alcohol consumption among females, stratified by case/control and age group (maximally adjusted models using imputed data)

Notes: Figures are reported according to mean and referent held values, that is 54 years old at diagnosis for (a), 65 years old for (b), or 75 years old for (c) PLUS other values as specified in the legend of Figure 3.3. obs=observations.



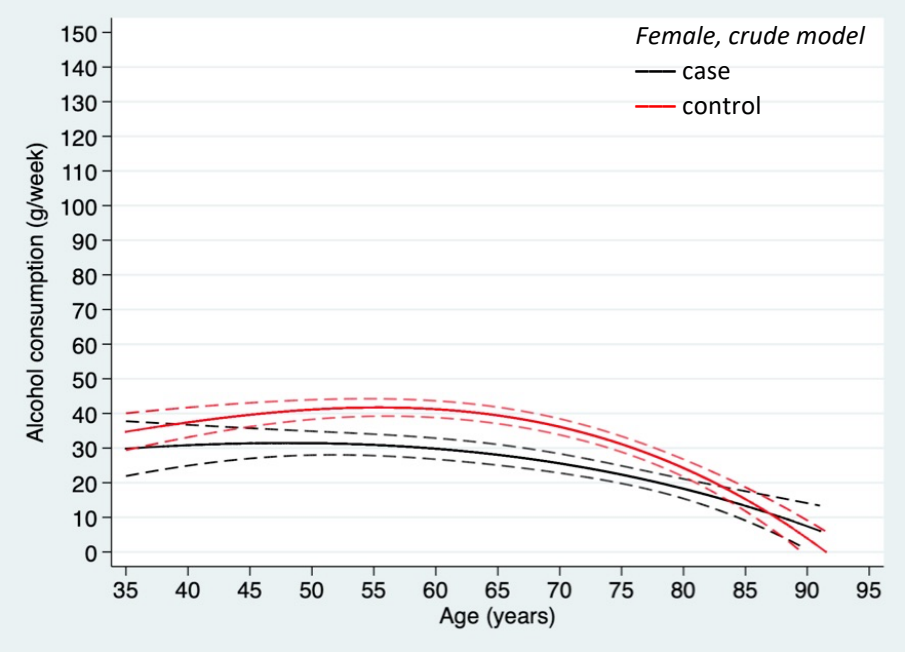
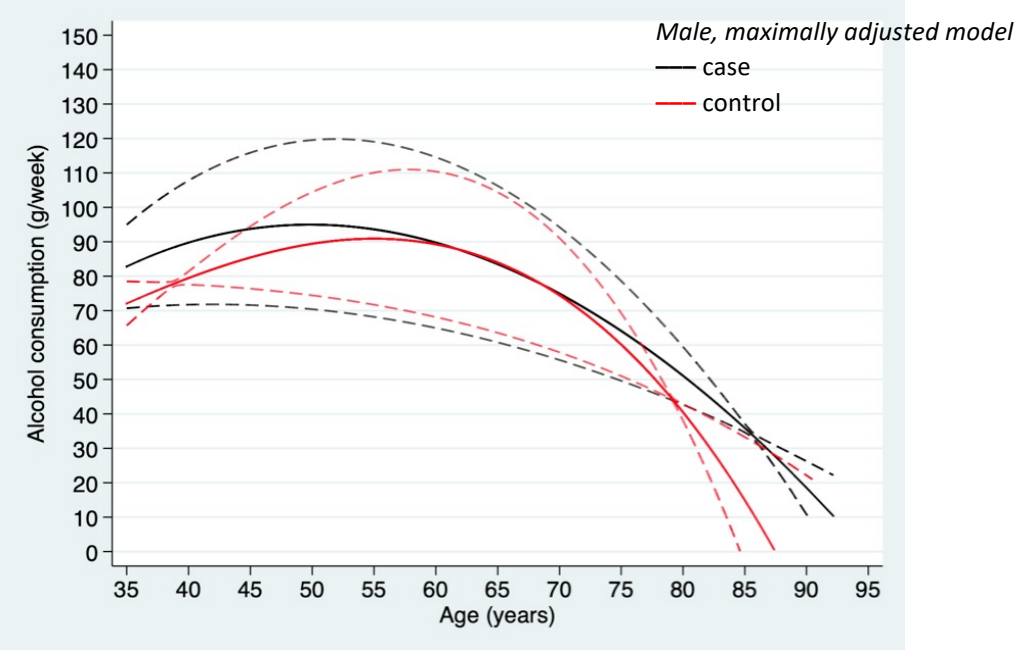


Figure 3.6 Trajectories of the mean weekly alcohol consumption across age, stratified by sex and case/control group (crude models using imputed data).

Notes: Dashed curves represent 95%CIs.



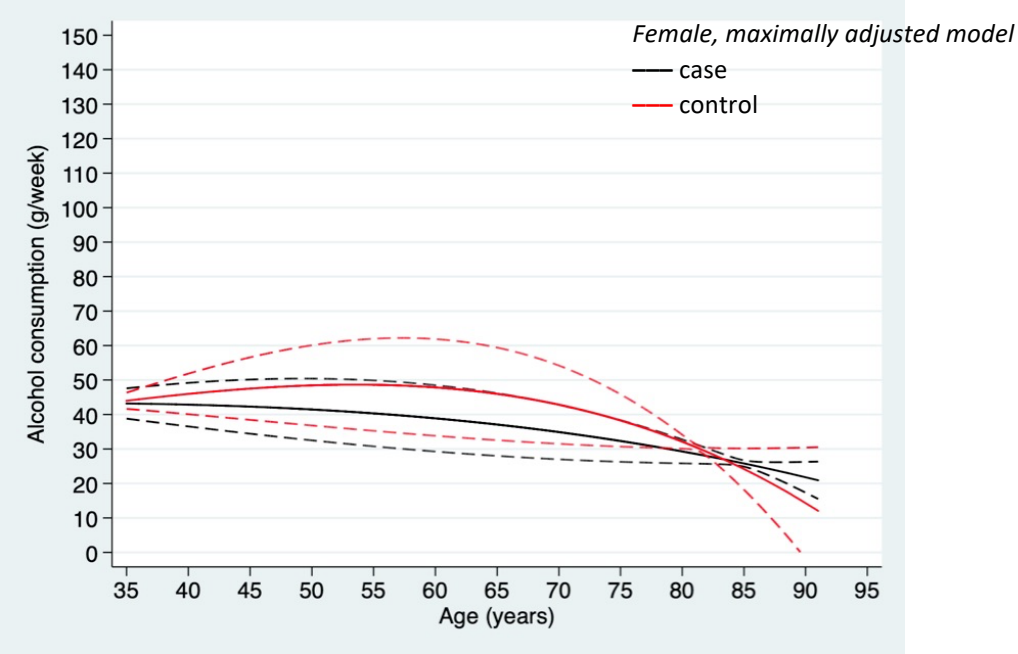


Figure 3.7 Trajectories of the mean weekly alcohol consumption across age, stratified by sex and case/control group (maximally adjusted models using imputed data).
Notes: Figures are reported according to mean and referent held values as specified in the legend of Figure 3.3.

3.4 Discussion

The work reported in this chapter is the first study to describe the mean trajectory of weekly alcohol consumption spanning up to 30 years before and

after CVD diagnosis. With repeated measures of alcohol from two large UK cohorts, this work benefited from its prospective case-control design, reliable ascertainment of CVD cases and wide coverage of the adult life span (with data collected from ages 35 to 92 years). By mapping and centring alcohol data on the date of diagnosis, drinking trajectories pre- or post-CVD were fitted with separate models, allowing curves to have different shapes. Overall, little difference was found in the mean volume of alcohol consumed among those diagnosed with CVD and those without the condition. For patients of both sexes, there was a small reduction in alcohol consumption in the years straddling the diagnosis. Altogether, the findings from this chapter provide novel insights into how engagement in a known determinant of health changes before and after the onset of disease. These insights can inform future inquiry into how drinking behaviour in an at-risk population is related to initial/subsequent disease onset as well as mortality.

The drinking trajectories observed among controls in this chapter are broadly in agreement with studies on lifetime drinking patterns among general population samples which report that alcohol consumption increases from adolescence to middle age and then decreases as people get older, with lower overall consumption in women than men [123]. The present work extended these findings by looking at CVD patients and found consumption trajectories that were roughly similar to the consumption patterns observed in their matched controls; similarities between cases and controls regarding drinking trajectories were seen within different age groups, suggesting that changes in consumption over time may be largely attributable to the effect of age. This is an important observation which has not typically been reflected in current evidence base for alcohol drinking among CVD patients. Studies linking alcohol to long-term prognosis of CVD have predominantly used just one measure of exposure, mostly at baseline (as shown in Chapter 2 Table 2.5), and thus overlook the changes in drinking during follow up (which may be several decades for some health outcomes) and are at risk of misclassification bias, with longer intervals increasing the likelihood of misclassification [205]. For the few studies with serial measures of alcohol, levels of consumption were commonly categorized according to each individual's average intake during follow up [128, 167]. Such

aggregation can still mask the pattern of changes in consumption within individuals over time and its possible impact on subsequent health risks.

In the present chapter, wide CIs were observed for estimates of population mean trajectories, which are likely to be attributable to a high variability in trajectories across individual CVD patients. Addressing heterogeneity in drinking pattern over time has been the research focus of alcohol epidemiology in recent years [92]. Many efforts have been made to differentiate between long-term trajectories of alcohol intake among the general population in terms of drinker typologies (for instance, persistent moderate drinker, mostly heavy drinker, increasing drinker, etc.) [206, 207] and link these typologies to health outcomes such as incidence of T2DM [208] and CHD [124]. However, such a trajectory approach has yet to be used to examine the health consequences of alcohol among CVD patients. Future research needs to investigate the benefits/harms of well-classified drinking patterns in secondary prevention of CVD to better inform lifestyle choices and health education in regard to these.

Over the years surrounding diagnosis, there was a drop in the mean volume of alcohol consumed among CVD patients, although the overlapping CIs limits interpretation of this finding. A similar pattern of results has been reported for a new diagnosis of T2DM [197] and other medical conditions including cancer [191, 193]. Mechanisms underlying the reductions in drinking following CVD onset could not be identified with information from the source cohorts. Likely reasons for the reductions include ill health (and related reduction in ability to socialise or enjoy alcohol consumption), health precaution, pharmacological contraindication, or adherence to medical advice. Patients included in the present study were diagnosed across a broad span of time (spanning the years 1986 to 2016) where different drinking advice and CVD management were applied. In the UK, low risk drinking guidelines were first released in 1987 with recommendations of no more than 21 units (1 unit equals 8 grams of pure ethanol) per week for men and 14 units per week for women [209]. The recommended limits were transited to daily (no more than 3-4 units per day for men and 2-3 units per day for women) in 1995 [210], before reverting to weekly (no more than 14 units per week for both men and women) in the latest drinking guidelines published in 2016 [44]. For secondary prevention of CVD, it has been recommended that advice on alcohol consumption should be given in line

with the above-mentioned national recommendations [211, 212]. Unfortunately, it was not possible to ascertain what advice the CVD participants in each cohort were told in real clinical practice where drinking decisions need to be made appropriate to the circumstances of each individual.

The work presented in this chapter has additional limitations that warrant consideration. First, as with other longitudinal cohort studies, the findings from this chapter were prone to selection attrition. Heavier drinkers might be more likely to drop out and be under-represented in the datasets, which could have biased downwards the mean estimates. Secondly, the measurement of alcohol was based on self-reports; although it is subject to estimation error and the strength of some alcohol beverages is likely to have increased over time [213], research has shown that drinking data collected through this method remains valid and reliable, especially when involving specified time-frames ('past week' instead of 'usual' reference frames) and beverage-specific questions [214, 215]. Thirdly, analyses of drinking trajectories in the present study were dependent on drinking volume only. Sufficient data on other characteristics of alcohol consumption, such as drinking frequency and context, may provide a more detailed illustration of how drinking behaviour changes over time. Furthermore, many major life events, such as retirement [216], could affect alcohol drinking and were not included in the present analyses; however, a comprehensive discussion of possible predictors of changes in alcohol consumption is beyond the scope of this chapter. Data presented here were collected from two UK cohorts: one being a 'white collar' occupational cohort (the Whitehall II study) and the other a population-based cohort. Clearly, there were some cohort differences, most likely due to demographic characteristics such as socioeconomic position. Apart from adjustments for these characteristics, the inclusion of cohort-level random effects in the modelling took into account data clustering and thereby improved the validity of the results obtained. Although the present analysis attempted to account for concurrent changes in many other lifestyle and health-related factors, residual confounding owing to unmeasured factors might still be possible.

In summary, this chapter is the first piece of research to show amongst CVD patients specifically how weekly alcohol intake changes across a wide span of the life course, covering a period of up to 30 years before and after the

diagnosis. The findings provide a basis of evidence that can inform future inquiry into how drinking behaviour in an at-risk population is related to initial/subsequent disease onset as well as mortality. Future research needs to examine the drinking behaviour in other ways, such as the frequency and context of consumption (for example, with meal or role in wider dietary guidance) as well as address the impact of changes in drinking behaviour on CVD patients to better inform lifestyle advice and healthcare policy. To shed light on the latter, the next chapter will present a further investigation into the heterogeneity in patients' alcohol consumption trajectories (as indicated by the wide CIs and discussed above); efforts will also be made to clarify the mortality risk associated with different drinking trajectories in CVD patients.

Chapter 4 Alcohol trajectories in relation to all-cause mortality in CVD patients: a prospective cohort study (Study 3)[3]

4.1 Introduction to the study

As summarised earlier in Chapter 1 Section 1.3, the association between moderate alcohol consumption and reduced risk of CVD is well documented and heatedly debated; however, relatively few studies have focused on patients who have already experienced a CVD event and the effects that alcohol drinking may have on their subsequent health. Findings from Chapter 2 suggest that drinking up to 105 grams of ethanol per week is associated with lower risks of mortality and subsequent cardiovascular events than non-drinking in those with established CVD; this threshold is lower than the upper limits of drinking recommended in most current guidelines (as listed in Box 1.1).

Similar to the critiques of studies on general populations [92, 217], the evidence among CVD patients is far from robust for several important reasons. Firstly, most studies (11 out of 14) included in the meta-analyses presented in Chapter 2 only looked at the association with single baseline measure of alcohol intake, despite evidence from Chapter 3 and the literature that drinking behaviours change over time and that misclassification of alcohol intake has the potential to bias the risk estimates [218, 219]. Longitudinal prospective assessment of intake is needed to accurately measure long-term exposure to alcohol, and this is particularly relevant when studying biological processes that cause chronic effects on health [220]. Secondly, in those few studies of CVD patients that did include longitudinal assessment of alcohol and subsequent health risks [127, 128, 167], the methodology used can be questioned. In most cases these studies categorised the patients into different drinking groups according to each patient's average intake during follow-up, with no accounting for intra-individual variation in drinking levels over time. Failure to capture such variation may result in over-simplistic interpretation of alcohol use and consequent outcomes, as there is evidence from general population samples that unstable drinking

[3] Some of the findings presented in this chapter have informed the journal article: Ding C, O'Neill D, Britton A. Trajectories of alcohol consumption in relation to all-cause mortality in patients with cardiovascular disease: a 35-year prospective cohort study. Addiction. doi:10.1111/add.15850. Please see Appendix 4.1 for full paper.

patterns confer increased risks for CHD and total mortality independent of average intake [124-126]. Thirdly, these studies were often limited by the inclusion of former drinkers in the non-drinking group. As discussed in Chapter 2, patients may quit drinking in response to ill health, and such sick quitters could potentially bias risk estimates if not analysed separately [70]. Fourth, most studies also had a heterogeneous group of patients with incident or recurrent CVD events and did not adequately account for concurrent changes in other lifestyle and health factors – such as smoking which is associated with both levels of drinking and with mortality [221], and thus might confound the results.

It therefore remains unclear what advice should be given to CVD patients in terms of their alcohol consumption and subsequent prognosis. The present chapter contributes to this deficit in evidence using data with repeated measures of alcohol intake spanning up to three decades, with aims to (1) describe the heterogeneity in longitudinal trajectories of alcohol consumption in patients with incident CVD events, (2) link different trajectories to risk of all-cause mortality, and (3) compare these associations with findings based on single time-point assessment of alcohol intake in the same cohort to assess the utility of taking a longitudinal approach in examining alcohol's relation to health.

4.2 Methods

4.2.1 Study design and population

The Whitehall II study (used previously in Chapter 3) was chosen for the present analyses as it was able to provide reliable information on CVD incidence and subsequent mortality (tracked through linkage with administrative databases) and collected alcohol intake data repeatedly from the same individuals across study phases. Phase 1 of the Whitehall II study (at enrolment) involved a clinical examination as well as a self-administered questionnaire to collect information including demographics, health status and lifestyle factors. Subsequent phases of data collection have alternated between questionnaire alone and questionnaire accompanied by a clinical examination. Data used in the chapter came from phase 1 (1985-88), 2 (1989-90), 3 (1991-93), 5 (1997-99), 7 (2002-04), 9 (2007-09), 11 (2012-13) and 12 (2015-16) of the study.

After excluding participants with previously diagnosed CHD, stroke or cancer at phase 1 (n=178), an inception cohort of 1705 was identified, who survived an incident CHD/stroke event from phase 1-12. All patients with repeated measures of alcohol (at least two measures, starting from the most recent phase pre-incident CVD; Figure 4.1) were included, resulting in an analytical sample of 1306.

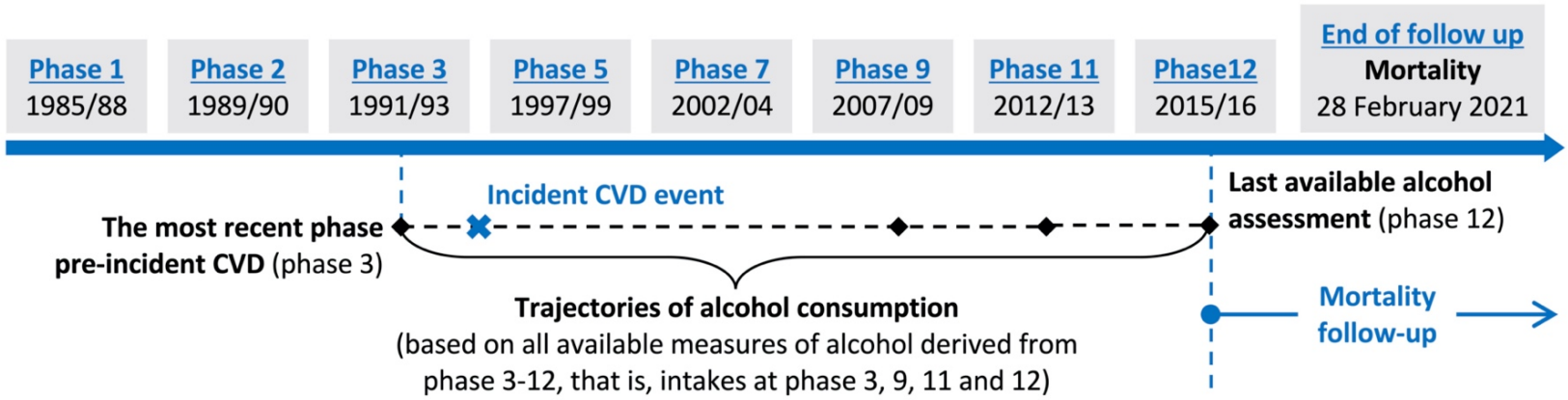


Figure 4.1 An illustration of study design

Notes: This is an illustrative example of how drinking trajectory was constructed for a participant who had an incident CVD event in the year 1995 and was alive at the end of follow-up.

4.2.2 Alcohol consumption

At each phase, participants were asked to report the number of alcoholic drinks (measures of spirits, glasses of wine, and pints of beer/cider) they had consumed in the previous week. Drinks were converted into UK units of alcohol using the same conversion protocol implemented in earlier chapters. For more information regarding the drinks-to-units conversion, please refer to Chapter 2 Section 2.2.1.2. These converted measurements were summed to define the total weekly alcohol intake in units. Intakes at each phase were then categorised into none, moderate (1-14 units per week) and heavy (>14 units per week) to reflect the current UK drinking guidelines [44].

The present analysis used all available alcohol category data (divided into 0, 1-14 and >14 units per week and coded as 0, 1 and 2, respectively) collected at the most recent phase pre-incident CVD (defined as assessment occasion 1) and from all subsequent phases post-incident CVD to better represent long-term drinking trajectories, with an illustrative example presented in Figure 4.1.

Group-based trajectory modelling (GBTM) was applied to identify groups of patients following different trajectories of alcohol consumption, using the *traj* command in Stata [222]. GBTM is an application of the finite mixture models for longitudinal data. Unlike growth mixture modelling (which is also based on finite mixture models), GBTM does not assume that the population is composed of discrete groups defined by different trajectories. Instead, GBTM uses groups as a statistical device for approximating the unknown distribution of trajectories in the population and thus is more appropriate for elucidating heterogeneity in alcohol use over time (as population differences in drinking trajectories are unlikely to be clear-cut) [223]. Trajectory models were estimated with 3-6 groups and for each group a polynomial function of assessment occasion (up to second order) was considered, as suggested by previous research [224, 225]. BIC and Akaike information criterion (AIC) values were used to select optimal number and shape of groups. Patients were assigned to the group for which their posterior membership probability was highest. Model adequacy was assessed using the recommended average posterior probability, with AvePP ≥0.7 in all groups demonstrating a high assignment accuracy [226].

Results of the best-fitting model in the GBTM analysis are reported in Figure 4.2 and Table 4.1. Model fit statistics are given in Appendix 4.2. A six-group model provided best fit to the data and showed adequate classification accuracy; AvePP for each trajectory group was between 0.75-0.93. The identified trajectory groups are labelled a posteriori as: (1) long-term abstainers, (2) stable moderate drinkers, (3) reducing moderate drinkers, (4) former drinkers, (5) occasional heavy drinkers, and (6) stable heavy drinkers.

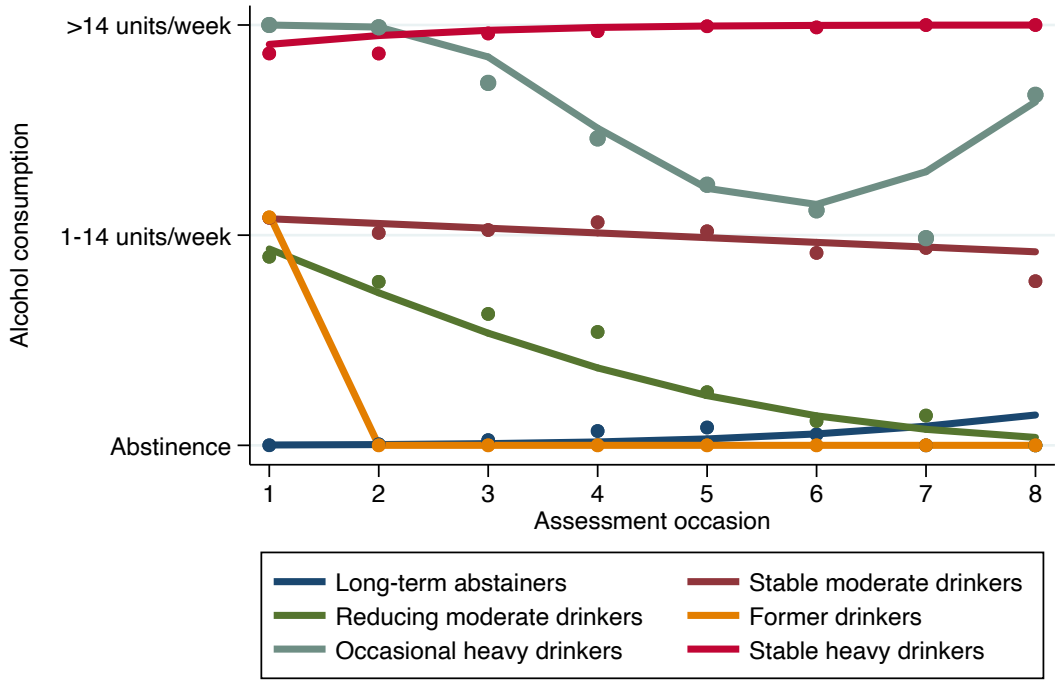


Figure 4.2 Alcohol consumption trajectories of the six groups identified using group-based trajectory modelling

Notes: Models were based on repeated measures of drinking category (0, 1-14 and >14 units per week and coded as 0, 1 and 2, respectively) derived from the most recent phase pre-incident CVD (assessment occasion 1) and all subsequent phases post-incident CVD (assessment occasions 2-8). Solid lines indicate estimated trajectories and dot symbols indicate observed group means at each assessment occasion.

Table 4.1 Regression coefficients for the best-fitting group-based trajectory model

Trajectory group	Allocated group membership	Average posterior probabilities *	Parameter	Estimate	SE	P-value
Long-term abstainers	15.5%	0.93	Intercept	-1.821	0.236	<0.001
			Linear	0.190	0.050	<0.001
Stable moderate drinkers	53.9%	0.86	Intercept	1.116	0.036	<0.001
			Linear	-0.026	0.010	0.010
Reducing moderate drinkers	6.0%	0.77	Intercept	1.171	0.121	<0.001
			Linear	-0.247	0.040	<0.001
Former drinkers	6.3%	0.75	Intercept	7.400	208.059	0.972
			Linear	-6.987	235.822	0.976
			Quadratic	0.700	29.544	0.981
Occasional heavy drinkers	8.5%	0.80	Intercept	5.873	0.553	<0.001
			Linear	-1.616	0.247	<0.001
			Quadratic	0.139	0.026	<0.001
Stable heavy drinkers	9.8%	0.81	Intercept	2.260	0.154	<0.001
			Linear	0.223	0.067	0.001

Trajectories were modelled with alcohol category data that were divided into 0, 1-14 and >14 units per week and coded as 0, 1 and 2, respectively.
* Posterior probabilities of group membership for individuals assigned to each group, an average of >0.7 demonstrates good classification accuracy.
SE=standard error.

4.2.3 Outcome

All-cause mortality was traced through the national mortality register until 28 February 2021. Patients contributed person time from the date of last available alcohol assessment (which was defined as the current work's baseline) until the occurrence of death or censoring.

4.2.4 Covariates

Sociodemographic variables included age, sex, and ethnicity (white or non-white). Socioeconomic position was defined using either current or last recorded employment grade as high, intermediate, or low. Health behaviours were assessed and comprised smoking (current, former, or never), physical activity (meeting or below WHO recommendations [227], that is ≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week) and dietary behaviour (frequency of fruit and vegetables consumed in a week). Further medical information was obtained on self-reported use of cardiovascular drugs, prevalent diabetes (defined as reported doctor-diagnosed diabetes or use of antidiabetic drugs, or clinically measured fasting blood glucose ≥7.0 mmol/L) and hypertension (defined as reported doctor-diagnosed hypertension or use of antihypertensive drugs, or clinically measured systolic/diastolic blood pressure ≥140/90 mmHg). Covariates were assessed at the most recent phase pre-incident CVD. To account for variability in the exposure assessment interval, the time difference between the date of first and last available alcohol assessment was calculated for each patient and included as a further covariate. Follow-up observations on health behaviours and medical status were also derived from the same phase when the last available alcohol assessment was recorded.

4.2.5 Statistical analysis

Prior to undertaking inferential analyses, MICE was completed to address missing covariate data [202]. Outcome (the Nelson-Aalen hazard and outcome indicator) and exposure (alcohol intakes at each phase) variables were also included in the imputation model but only observed values of these variables were used in the substantive analysis (that is survival analysis, please see below) [228, 229]. Repeated measurements were treated as distinct variables in

the imputation model [204]. Simulation studies show that this approach performs well in similar longitudinal settings [203, 230]. Altogether, 100 imputations were run. For more information regarding the construction of imputation models, please refer to Chapter 3 Section 3.2.4.2.

HRs for all-cause mortality in relation to drinking trajectories were estimated using Cox proportional hazards regression models. Models were first adjusted for age, sex, and intake assessment interval (Model 1), then additionally for ethnicity, socioeconomic position, health behaviours and medical status (Model 2). Covariates in Models 1 and 2 were from the most recent phase pre-incident CVD. To account for changes in health behaviours as well as updates to medical status, in Model 3 further adjustment was made for covariates (smoking, physical activity, dietary behaviour, use of cardiovascular drugs, prevalent diabetes and hypertension) assessed at the phase of last available alcohol assessment. The reference group for the present analysis was stable moderate drinkers [231]. Schoenfeld residuals were plotted to ascertain that the proportional hazards assumption had not been violated (see Appendix 4.3).

A further analysis was performed with drinking categories defined using *only* data from the last available alcohol assessment, so that findings from the main analyses (trajectory approach) can be compared to those that would have been obtained using the conventional approach in which exposure to alcohol was only assessed at one time-point. Sensitivity analyses were conducted on a number of patient characteristics (sex and primary events), allowing for a more homogenous sample. A stricter inclusion criterion of having at least three alcohol measures was applied to minimise the potential misclassification of exposure. Complete case analysis was performed to assess the influence of multiple imputation on the results.

As shown in Chapter 2 Figure 2.7, the intake threshold associated with significantly increased risk of mortality among CVD patients may be higher than 14 units per week, so in exploratory post hoc analyses, average weekly intake during the assessment interval was calculated for each patient in the group of stable heavy drinkers. The group was then divided into two subgroups based on the group mean value of average weekly intakes, and their associations with mortality were examined. Additional post hoc analysis was conducted with

further adjustment for concurrent changes in patients' self-rated health (excellent/good, fair, or poor). Self-rated health has been shown to be a valid measure of overall health status as well as a predictor of mortality among participants of the Whitehall II study [232, 233]. Such analyses help to reveal whether changes in alcohol consumption occur as a consequence of worsening health. All analyses were performed using Stata 15.1. A two-sided P-value <0.05 was considered statistically significant.

4.3 Results

4.3.1 Sample characteristics

Table 4.2 shows the characteristics of the study population stratified by alcohol trajectories, as well as the proportion of missingness. The most common derived trajectory groups were stable moderate drinker (53.9%), followed by long-term abstainers (15.5%) and stable heavy drinkers (9.8%). Overall, the resultant trajectories comprised a median assessment interval of 12.2 (IQR=7.0-18.0) years, with each patient contributing an average of 4 (IQR=3-5) measures of alcohol.

Mean age at the most recent phase pre-incident CVD ranged from 56.8 (SD=7.9) years for stable heavy drinkers to 64.1 (SD=9.1) years for former drinkers. Long-term abstainers were more likely to be female, non-white and of lower socioeconomic position. Heavy drinkers (occasional or stable) were more likely to be male, of white ethnicity and high socioeconomic position; they were also more frequently past or current smokers at the most recent phase pre-incident CVD.

Across all trajectory groups, the proportions of patients currently smoking or meeting physical activity recommendations decreased from the most recent phase pre-incident CVD to the phase of last available alcohol assessment. The prevalence of cardiovascular drug use, diabetes and hypertension increased over the same period.

Table 4.2 Patient characteristics by alcohol consumption trajectories

	Stable moderate drinkers	Long-term abstainers	Reducing moderate drinkers	Former drinkers	Occasional heavy drinkers	Stable heavy drinkers	Overall
No. of patients	704 (53.9)	203 (15.5)	78 (6.0)	82 (6.3)	111 (8.5)	128 (9.8)	1306 (100)
Intake assessment interval, median (IQR) years	12.2 (6.9-17.9)	10.8 (5.2-17.2)	17.8 (12.9-23.3)	7.2 (4.2-12.6)	12.4 (6.4-18.2)	14.2 (11.2-19.1)	12.2 (7.0-18.0)
No. of alcohol measures, median (IQR)	4 (3-5)	3 (2-4)	5 (4-5)	3 (2-4)	4 (2-5)	4 (3-5)	4 (3-5)
At the most recent phase pre-incident CVD							
Age, mean (SD) years	60.4 (8.9)	61.1 (9.2)	57.3 (8.1)	64.1 (9.1)	59.1 (9.1)	56.8 (7.9)	60.1 (9.0)
Male	574 (81.5)	97 (47.8)	44 (56.4)	53 (64.6)	107 (96.4)	123 (96.1)	998 (76.4)
Ethnicity							
White	635 (90.2)	131 (64.5)	65 (83.3)	69 (84.1)	109 (98.2)	123 (96.1)	1132 (86.7)
Non-white	68 (9.7)	71 (35.0)	13 (16.7)	13 (15.9)	2 (1.8)	5 (3.9)	172 (13.2)
Missing	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Socioeconomic position							
High	314 (44.6)	29 (14.3)	14 (17.9)	24 (29.3)	63 (56.8)	81 (63.3)	525 (40.2)
Intermediate	321 (45.6)	92 (45.3)	41 (52.6)	43 (52.4)	43 (38.7)	47 (36.7)	587 (44.9)
Low	69 (9.8)	82 (40.4)	23 (29.5)	15 (18.3)	5 (4.5)	0 (0.0)	194 (14.9)
Smoking status							
Never smoker	279 (39.6)	91 (44.8)	36 (46.2)	41 (50.0)	35 (31.5)	32 (25.0)	514 (39.4)
Ex-smoker	302 (42.9)	61 (30.0)	21 (26.9)	33 (40.2)	56 (50.5)	67 (52.3)	540 (41.3)
Current smoker	79 (11.2)	30 (14.8)	14 (17.9)	7 (8.5)	17 (15.3)	21 (16.4)	168 (12.9)
Missing	44 (6.3)	21 (10.3)	7 (9.0)	1 (1.2)	3 (2.7)	8 (6.3)	84 (6.4)
Physical activity *							

Met recommendations	242 (34.4)	42 (20.7)	13 (16.7)	27 (32.9)	42 (37.8)	34 (26.6)	400 (30.6)
Below recommendations	422 (59.9)	142 (70.0)	55 (70.5)	53 (64.6)	66 (59.5)	84 (65.6)	822 (62.9)
Missing	40 (5.7)	19 (9.4)	10 (12.8)	2 (2.4)	3 (2.7)	10 (7.8)	84 (6.4)
Fruit/vegetable consumption							
≥Daily	462 (65.6)	121 (59.6)	53 (67.9)	59 (72.0)	81 (73.0)	77 (60.2)	853 (65.3)
<Daily	204 (29.0)	65 (32.0)	18 (23.1)	23 (28.0)	25 (22.5)	42 (32.8)	377 (28.9)
Missing	38 (5.4)	17 (8.4)	7 (9.0)	0 (0.0)	5 (4.5)	9 (7.0)	76 (5.8)
Use of cardiovascular drugs							
Yes	248 (35.2)	84 (41.4)	23 (29.5)	30 (36.6)	40 (36.0)	39 (30.5)	464 (35.5)
No	437 (62.1)	110 (54.2)	54 (69.2)	52 (63.4)	69 (62.2)	85 (66.4)	807 (61.8)
Missing	19 (2.7)	9 (4.4)	1 (1.3)	0 (0.0)	2 (1.8)	4 (3.1)	35 (2.7)
Prevalent diabetes†							
Yes	73 (10.4)	50 (24.6)	10 (12.8)	13 (15.9)	16 (14.4)	17 (13.3)	179 (13.7)
No	612 (86.9)	145 (71.4)	67 (85.9)	69 (84.1)	93 (83.8)	107 (83.6)	1093 (83.7)
Missing	19 (2.7)	8 (3.9)	1 (1.3)	0 (0.0)	2 (1.8)	4 (3.1)	34 (2.6)
Prevalent hypertension ‡							
Yes	360 (51.1)	129 (63.5)	44 (56.4)	46 (56.1)	63 (56.8)	69 (53.9)	711 (54.4)
No	325 (46.2)	66 (32.5)	33 (42.3)	36 (43.9)	46 (41.4)	55 (43.0)	561 (43.0)
Missing	19 (2.7)	8 (3.9)	1 (1.3)	0 (0.0)	2 (1.8)	4 (3.1)	34 (2.6)
At the phase of last available alcohol assessment							
Smoking status							
Never smoker	259 (36.8)	83 (40.9)	29 (37.2)	31 (37.8)	31 (27.9)	27 (21.1)	460 (35.2)
Ex-smoker	376 (53.4)	81 (39.9)	26 (33.3)	34 (41.5)	65 (58.6)	91 (71.1)	673 (51.5)
Current smoker	27 (3.8)	13 (6.4)	7 (9.0)	1 (1.2)	8 (7.2)	4 (3.1)	60 (4.6)

Missing	42 (6.0)	26 (12.8)	16 (20.5)	16 (19.5)	7 (6.3)	6 (4.7)	113 (8.7)
Physical activity *							
Met recommendations	142 (20.2)	22 (10.8)	11 (14.1)	12 (14.6)	23 (20.7)	27 (21.1)	237 (18.2)
Below recommendations	510 (72.4)	163 (80.3)	57 (73.1)	56 (68.3)	79 (71.2)	93 (72.7)	958 (73.4)
Missing	52 (7.4)	18 (8.9)	10 (12.8)	14 (17.1)	9 (8.1)	8 (6.3)	111 (8.5)
Fruit/vegetable consumption							
≥Daily	500 (71.0)	125 (61.6)	43 (55.1)	57 (69.5)	78 (70.3)	87 (68.0)	890 (68.2)
<Daily	186 (26.4)	62 (30.5)	23 (29.5)	13 (15.9)	28 (25.2)	38 (29.7)	350 (26.8)
Missing	18 (2.6)	16 (7.9)	12 (15.4)	12 (14.6)	5 (4.5)	3 (2.3)	66 (5.1)
Use of cardiovascular drugs							
Yes	642 (91.2)	174 (85.7)	67 (85.9)	74 (90.2)	101 (91.0)	117 (91.4)	1175 (90.0)
No	60 (8.5)	28 (13.8)	11 (14.1)	8 (9.8)	10 (9.0)	11 (8.6)	128 (9.8)
Missing	2 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Prevalent diabetes†							
Yes	239 (33.9)	109 (53.7)	47 (60.3)	46 (56.1)	40 (36.0)	52 (40.6)	533 (40.8)
No	465 (66.1)	94 (46.3)	31 (39.7)	36 (43.9)	71 (64.0)	76 (59.4)	773 (59.2)
Prevalent hypertension ‡							
Yes	609 (86.5)	173 (85.2)	66 (84.6)	77 (93.9)	97 (87.4)	111 (86.7)	1133 (86.8)
No	93 (13.2)	29 (14.3)	12 (15.4)	5 (6.1)	14 (12.6)	17 (13.3)	170 (13.0)
Missing	2 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)

Values are numbers (percentages) unless stated otherwise.
* Physical activity meeting WHO recommendations defined as ≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week.
† Defined as reported doctor-diagnosed diabetes or use of antidiabetic drugs, or clinically measured fasting blood glucose ≥7.0 mmol/L.
‡ Defined as reported doctor-diagnosed hypertension or use of antihypertensive drugs, or clinically measured systolic/diastolic blood pressure ≥140/90 mmHg.

4.3.2 Alcohol consumption trajectories and all-cause mortality

During a median follow-up of 5.0 (IQR=4.4-5.7) years after the last alcohol assessment, there were 380 deaths. The associations between trajectories and all-cause mortality are presented in Table 4.3. Long-term abstainers, stable and occasional heavy drinkers all had a similar risk of mortality as stable moderate drinkers after adjustment for all included covariates (Model 3; HR=1.13, 95%CI=0.83-1.55; HR=1.10, 95%CI=0.76-1.60; and HR=1.25, 95%CI=0.86-1.81, respectively).

Compared to stable moderate drinkers, former drinkers had higher risk of mortality after adjustment for covariates from the most recent phase pre-incident CVD (Model 2; HR=1.84, 95%CI=1.26-2.68). The effect remained but was slightly attenuated in a maximally adjusted model with further adjustment for changes in other health behaviours and medical status (Model 3; HR=1.74, 95%CI=1.19-2.54).

4.3.3 Alcohol consumption categories based on single assessment

In analyses of drinking categories defined according to intakes from the last available alcohol assessment, former drinkers had a point estimate of mortality risk greater than one when compared with moderate drinkers and adjusted for covariates from the most recent phase pre-incident CVD (Model 2; HR=1.24, 95%CI=0.94-1.63); this effect, however, was not statistically significant and was further attenuated in a maximally adjusted model (Model 3; HR=1.16, 95%CI=0.87-1.53). There was little difference in mortality risk amongst abstainers and heavy drinkers compared to moderate drinkers (Table 4.3).

Table 4.3 Association between alcohol consumption and risk of all-cause mortality

Alcohol consumption	No. of death	No. of patients	Hazard ratio (95%CI)		
			Model 1*	Model 2†	Model 3‡
Trajectories					
Stable moderate drinkers	192	704	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Long-term abstainers	63	203	1.16 (0.86-1.56)	1.18 (0.87-1.62)	1.13 (0.83-1.55)
Reducing moderate drinkers	21	78	1.16 (0.73-1.84)	1.14 (0.72-1.83)	1.08 (0.67-1.73)
Former drinkers	35	82	1.77 (1.22-2.55)	1.84 (1.26-2.68)	1.74 (1.19-2.54)
Occasional heavy drinkers	34	111	1.28 (0.88-1.85)	1.24 (0.86-1.80)	1.25 (0.86-1.81)
Stable heavy drinkers	35	128	1.19 (0.83-1.72)	1.13 (0.78-1.64)	1.10 (0.76-1.60)
Categories based on single assessment only §					
Moderate drinkers	187	652	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Abstainers	59	187	1.08 (0.80-1.46)	1.11 (0.81-1.52)	1.04 (0.76-1.44)
Former drinkers	78	245	1.23 (0.94-1.61)	1.24 (0.94-1.63)	1.16 (0.87-1.53)
Heavy drinkers	56	222	0.91 (0.67-1.23)	0.86 (0.63-1.17)	0.85 (0.62-1.15)

* Adjusted for sex, age, and intake assessment interval.
†Additionally adjusted for ethnicity, socioeconomic position, smoking, physical activity, dietary behaviour, use of cardiovascular drugs, prevalent diabetes and hypertension, assessed at the most recent phase pre-incident CVD.
‡ Additionally adjusted for smoking, physical activity, dietary behaviour, use of cardiovascular drugs, prevalent diabetes and hypertension, assessed at the phase of last available alcohol assessment.
§ Drinking categories defined using intakes from the last available alcohol assessment.

4.3.4 Sensitivity analyses

Results of sensitivity analyses are in Table 4.4. The findings did not alter substantially when restricting analyses to either male patients, those with ≥3 measures of alcohol or having CHD as first event. Similar associations were observed when using complete case data only.

Table 4.4 Sensitivity analyses for association between alcohol trajectories and all-cause mortality

Alcohol consumption trajectories	No. of death	No. of patients	Hazard ratio (95%CI) *
Restricting to patients with ≥ 3 alcohol measures (n=990)			
Stable moderate drinkers	130	533	1.00 (Reference)
Long-term abstainers	31	136	1.02 (0.66-1.57)
Reducing moderate drinkers	20	77	1.10 (0.67-1.81)
Former drinkers	17	45	1.78 (1.04-3.05)
Occasional heavy drinkers	23	80	1.33 (0.84-2.09)
Stable heavy drinkers	33	119	1.23 (0.83-1.83)
Restricting to patients with CHD (n=1212)			
Stable moderate drinkers	175	645	1.00 (Reference)
Long-term abstainers	60	189	1.22 (0.88-1.68)
Reducing moderate drinkers	20	75	1.11 (0.68-1.81)
Former drinkers	28	73	1.53 (1.01-2.33)
Occasional heavy drinkers	34	106	1.35 (0.93-1.97)
Stable heavy drinkers	35	124	1.12 (0.77-1.63)
Restricting to male patients (n=998)			
Stable moderate drinkers	162	574	1.00 (Reference)
Long-term abstainers	29	97	0.97 (0.64-1.46)
Reducing moderate drinkers	11	44	0.90 (0.48-1.70)
Former drinkers	23	53	1.56 (0.98-2.48)
Occasional heavy drinkers	33	107	1.22 (0.83-1.78)
Stable heavy drinkers	34	123	1.06 (0.72-1.55)
Complete case data only (n=1061)			
Stable moderate drinkers	170	579	1.00 (Reference)
Long-term abstainers	48	161	0.97 (0.69-1.37)
Reducing moderate drinkers	14	49	1.10 (0.63-1.92)
Former drinkers	26	64	1.54 (1.00-2.37)
Occasional heavy drinkers	29	93	1.08 (0.72-1.61)
Stable heavy drinkers	29	104	0.99 (0.66-1.48)

*Adjusted for the same covariates listed in Table 4.3 Model 3.

4.3.5 Post hoc analyses

Among the 128 stable heavy drinkers, mean weekly intake over the assessment interval was 30 (SD=12) units. Patients who died during follow-up had higher weekly intakes than survivors (mean±SD: 34±14 units versus 28±11 units, respectively). Compared to stable moderate drinkers, hazard ratio for all-cause mortality was 1.53 (95%CI=0.93-2.51) in stable heavy drinkers with weekly intakes >30 units and 0.77 (95%CI=0.45-1.30) in those with weekly intakes ≤30 units in maximally adjusted analysis (with adjustment for the same covariates listed in Table 4.3 Model 3).

As shown in Table 4.5, at the most recent phase pre-incident CVD, long-term abstainers had the lowest proportion of patients rating their health as excellent or good (55.7%), while occasional heavy drinkers had the highest (76.6%). The proportion decreased over the interval from the most recent phase pre-incident CVD to last alcohol assessment in all trajectory groups, with the greatest decrease seen in former drinkers (-36.8%, from 69.5% to 43.9%), followed by occasional heavy drinkers (-23.5%, from 76.6% to 58.6%,) and reducing moderate drinkers (-17.6%, from 65.4% to 53.8%). Further adjustment for changes in self-rated health attenuated the associations between trajectories and all-cause mortality, with risk estimates reported in Table 4.6.

Table 4.5 Self-rated health over the assessment interval by alcohol consumption trajectories

	Stable moderate drinkers	Long-term abstainers	Reducing moderate drinkers	Former drinkers	Occasional heavy drinkers	Stable heavy drinkers
Self-rated health at the most recent phase pre-incident CVD, n (%)						
Excellent/good	516 (73.3)	113 (55.7)	51 (65.4)	57 (69.5)	85 (76.6)	92 (71.9)
Fair	128 (18.2)	61 (30.0)	16 (20.5)	18 (22.0)	21 (18.9)	24 (18.8)
Poor	23 (3.3)	12 (5.9)	5 (6.4)	7 (8.5)	2 (1.8)	2 (1.6)
Missing	37 (5.3)	17 (8.4)	6 (7.7)	0 (0.0)	3 (2.7)	10 (7.8)
Self-rated health at last available alcohol assessment, n (%)						
Excellent/good	481 (68.3)	96 (47.3)	42 (53.8)	36 (43.9)	65 (58.6)	90 (70.3)
Fair	167 (23.7)	60 (29.6)	19 (24.4)	28 (34.1)	33 (29.7)	29 (22.7)
Poor	38 (5.4)	28 (13.8)	9 (11.5)	8 (9.8)	9 (8.1)	8 (6.3)
Missing	18 (2.6)	19 (9.4)	8 (10.3)	10 (12.2)	4 (3.6)	1 (0.8)

Table 4.6 Association between alcohol trajectories and all-cause mortality with further adjustment for changes in self-rated health

Alcohol consumption trajectories	No. of death	No. of patients	Hazard ratio (95%CI) *
Stable moderate drinkers	192	704	1.00 (Reference)
Long-term abstainers	63	203	1.03 (0.75-1.41)
Reducing moderate drinkers	21	78	1.04 (0.64-1.67)
Former drinkers	35	82	1.53 (1.04-2.25)
Occasional heavy drinkers	34	111	1.13 (0.78-1.64)
Stable heavy drinkers	35	128	1.12 (0.78-1.63)

*Adjusted for the same covariates listed in Table 4.3 Model 3 **PLUS** self-rated health assessed at the most recent phase pre-incident CVD and at the phase of last available alcohol assessment.

4.4 Discussion

In this inception cohort of patients with incident CVD events, six different drinking trajectories were derived with repeated assessments spanning up to 30 years and linked to their subsequent risk of total mortality. Through iterative modelling that accounted for changing lifestyle and health status, this chapter found no evidence that patients who consistently consumed alcohol within the recommended limit of 14 units per week had a lower risk of mortality compared to long-term abstainers. Meanwhile, former drinkers had greater mortality risk than stable moderate drinkers.

The elevated risk of mortality among former drinkers was only appreciable when considering long-term drinking trajectories and was not significantly detected in the analyses using single intake assessment. Indeed, a large proportion of patients in this cohort did not have stable drinking trajectories following their incident CVD. Apart from those transiting from drinking to non-drinking, this chapter also observed an overall decrease in alcohol intake over time among some continuers (reducing moderate drinkers and occasional heavy drinkers), as has also been reported elsewhere [127, 234]. The tendency towards desistance/lower levels of drinking with increasing age suggests that categorization of alcohol intake based on single time-point measurements may be problematic, especially when applied to cohorts with long follow-up periods and older participants. These highlight the importance of longitudinal measures

and a life course approach in examining the effect of alcohol on health and the work presented in this chapter should be replicated with other outcomes.

The findings from this chapter echo other research which suggests that former drinkers have poorer self-perceived general health [235] and are at higher risk of experiencing adverse outcomes including CHD and overall mortality than moderate drinkers [124, 236]. As a reason for the higher risk seen in former drinkers, the sick-quitter hypothesis proposes that a substantial number of former drinkers have quit drinking for health reasons [93, 237]. In line with this hypothesis, former drinkers were found to have a higher prevalence of poor self-rated health than other groups at the most recent phase pre-incident CVD and showed the biggest decrease in the proportion of patients reporting good to excellent health during follow-up. The association for former drinkers was weakened following further adjustment for self-rated health, suggesting that poorer general health may partially explain former drinkers' increased likelihood of death and perhaps may have driven the decision to abstain itself.

In the present work, no statistically significant protective effect was found in relation to consistent moderate drinking compared to long-term abstinence. This concurs with general population studies measuring alcohol intake over time (collected either as repeated measures or as recall of past drinking levels) and the risk of death from all causes [91, 238, 239]. For example, in a cohort of 24029 individuals from a nationally representative sample of USA adults aged more than 50 years, Goulden et al. measured alcohol use at three time points and found no evidence of an association between any level of regular alcohol consumption and reduced all-cause mortality; the HR in fully adjusted analyses was 1.02 (95%CI=0.94-1.11) for <7 drinks per week, 1.14 (95%CI=1.02-1.28) for 7-14 drinks per week, 1.13 (95%CI=0.96-1.35) for 14-21 drinks per week, and 1.45 (95%CI=1.16-1.81) for ≥21 drinks per week [91]. Regarding CVD patients, longitudinal assessment of alcohol has been reported in two previous studies, where low levels of consumption were found to be associated with lower mortality [127, 128]. However, both studies have used a reference group composed of former drinkers and lifetime abstainers. The lower mortality risk for moderate drinking compared with non-drinking could potentially be caused by a less healthy comparison group contaminated by sick quitters (as discussed above). This speculation is further supported by findings from Chapter 2, where

the removal of former drinkers from the reference group eliminated the protective effect of moderate drinking on all-cause mortality among CVD patients [240].

Furthermore, the variety of reasons for which people abstain from drinking throughout life may introduce other biases. For instance, non-drinkers in later life may include those who adopt lifelong teetotalism due to continual poor health, the so-called ‘sick non-starters’ [241]. In this work, only a small minority of CVD patients were long-term abstainers. Notably, this group consisted mainly of women from lower socioeconomic position with higher prevalence of cardiometabolic risk factors and disease as well as poorer self-rated health, a pattern that has also been reported in other study populations where alcohol use is normative [242, 243]. It has been suggested that members of this minority differ from drinkers on a number of health determinants and that unmeasured confounders may have contributed to the excess risk seen in this group [244, 245]. These motivated the choice of considering moderate drinkers as the reference group throughout this chapter and might explain the slightly increased point estimate for long-term abstainers, despite the extensive level of adjustment in the present analyses.

Although excessive drinking has been found to raise the risk of total mortality in the general population [186, 246], the level from which this effect is evident is less clear. This chapter assessed the impact of heavy drinking on CVD patients using the 14 units per week threshold advocated by the current UK guidelines and observed no elevated risk for those who consistently drank above this limit. Previous dose-response analyses using data from 83 general population cohorts have reported an intake threshold for increased mortality risk at ≥200 grams per week (25 units per week) [186]. This agrees with the results of post hoc analyses, where an increased risk was seen in stable heavy drinkers with higher average intakes (>30 units per week). Clearly, the small number of patients within this group precludes any firm conclusion. Further data is therefore needed to explore alternative intake thresholds and validate the findings of the current work. In addition, heavy drinkers who remain in the cohort are likely to be ‘healthy survivors’ [92]. At the most recent phase pre-incident CVD, the proportion of patients drinking in excess of guidelines (36% male and 13% female) is lower than the recent estimates from HSE (39% male

and 20% female aged 55-64 years) [12], which means that heavy drinkers may be under-represented in the Whitehall II study. These potential selections could have reduced the estimate of association between heavy drinking and mortality risk, and thus caution is required when interpreting the absence of effect among heavy drinkers seen in this chapter.

Immortal time in epidemiology refers to a period of observation or follow-up during which death (or an outcome that determines end of follow-up) cannot occur [247]. Immortal time bias can arise when this period of 'immortality' is either misclassified with respect to exposure status or excluded from the analyses [248]. Because participants must survive to have their drinking trajectories measured, the period between first and last available alcohol assessment is considered immortal. To avoid immortal time bias, this work studied only 'survivors' of the immortal period [249], by following patients for the outcome of all-cause mortality from the date of last available alcohol assessment. Additional adjustment was made for the length of alcohol assessment interval, accounting for the imbalance in immortal time across different trajectory groups.

There are several limitations that should be acknowledged. First, alcohol measures in the Whitehall II study are self-reported and thus prone to estimation error. However, as discussed previously (see Chapter 3 Section 3.4), drinking data collected via this method remains valid and reliable. Comparison of alcohol consumption reported by the Whitehall II participants also suggests patterns similar to those in other UK cohorts [123]. Secondly, because of power limitations restricting further refinement, this chapter was unable to incorporate other drinking characteristics into the construction of trajectories. Additional data may provide insights into other drinking patterns, such as binge drinking, which could further clarify the observed mortality risk associated with unstable drinking trajectories. Relatedly, subgroup analyses (for example, in female or by age groups) were not possible due to the small number of patients in certain trajectory groups. In addition, participants in the Whitehall II study are not a representative sample of the general population; however, it has been shown that cardiometabolic-related etiological evidence from this occupational cohort are broadly in agreement with those obtained from nationally representative cohorts [250]. Although this work considered a wide range of covariates and

accounted for their changes in the analyses, the possibility of residual confounding or confounding by unmeasured factors cannot be ruled out.

In summary, the work reported in this chapter has illustrated the dynamic and diverse nature of alcohol use in CVD patients and how long-term drinking profiles are associated with their subsequent risk of death from all causes. By demonstrating the differing insights obtainable from single time-point and repeated exposure assessment, this chapter has also confirmed the utility of taking a longitudinal approach in examining the association of alcohol with health outcomes. CVD patients who consistently drank within the UK guidelines of 14 units per week had a similar risk of mortality as those who were continuous abstainers; therefore, this chapter does not support a protective effect of moderate drinking on total mortality. Patients who stopped drinking following incident CVD were at greater risk of mortality than continuous moderate drinkers; however, the former drinkers also had the highest proportion with poor self-rated health before CVD onset and experienced the greatest degree of health deterioration during follow-up. These findings contribute to the dearth of evidence on health effects of alcohol consumption among CVD patients.

Chapter 5 General discussion

5.1 Summary of findings

The concept of a potentially cardio-protective effect of moderate drinking has been largely studied and debated among general populations (see Chapter 1 Section 1.3.1). However, relatively few data are available in those who have already experienced a cardiovascular event; there is also inconsistency across guidelines regarding the recommended limits of alcohol intake for these patients (see Chapter 1 Section 1.3.2; Box 1.1). This thesis aimed to contribute to filling this gap by presenting a comprehensive meta-analysis and two longitudinal studies, evaluating alcohol consumption among CVD patients and its association with long-term prognosis.

Firstly, in Chapter 2, a series of meta-analyses were performed to consolidate all available evidence on the topic of alcohol consumption and CVD patients' prognosis and, for the first time, to evaluate the role of alcohol in experiencing a second cardiovascular event. The synthesis of data from three large-scale cohorts and 12 existing published studies corroborated previously reported J-shaped associations between alcohol intake and mortality relative to non-drinking, with a risk reduction that peaked at 7 grams per day for all-cause mortality and 8 grams per day for cardiovascular mortality and remained significant up to 62 and 50 grams per day, respectively (Figures 2.7 and 2.12). Reductions in risk of subsequent cardiovascular events were found among patients who consumed no more than 15 grams per day and were greatest at 6 grams per day (Figure 2.17). Taken collectively, the most up-to-date observational data suggested that, among CVD patients, the upper drinking limit for lower risks of both mortality and cardiovascular morbidity compared to non-drinkers was about 105 grams (or equivalent to 13 UK units) per week, which was lower than those recommended in most current guidelines (as listed in Box 1.1).

Meanwhile, several methodological issues were identified through the meta-analyses that may undermine the validity of inferences drawn from the results. Particularly, reductions in risk seen with moderate alcohol consumption were significantly attenuated or absent when restricted to the few studies that

excluded former drinkers from the non-drinking reference group (Figures 2.10 and 2.20). This concurs with the hypothesis that current non-drinkers include sick quitters, and this can erroneously lead to suggested protective effects of drinking compared to non-drinking. No evidence of elevated risk among heavy drinkers was found but this was potentially attributable to selection bias, where heavy drinkers most susceptible to alcohol may have died or stopped drinking at earlier ages and be under-represented in the datasets. With existing studies relying predominantly on single time-point alcohol observations (Table 2.5), there was also a lack of consideration given to changes in consumption levels over time and its possible impact upon the observed associations.

To provide in-depth evidence of the extent to which alcohol consumption changes in relation to the onset of CVD, Chapter 3 went on to plot patients' mean trajectory of weekly alcohol intake as a function of time, centred on the date of diagnosis and spanning up to 30 years before and after the diagnosis (Figure 3.2). Specifically, for trajectories prior to diagnosis, mean volume of alcohol consumed among male patients increased over time, peaking at around eight years before diagnosis at 95 grams per week. Trajectories following diagnosis showed mean consumption in male patients dropped from 87 to 74 grams per week after the date of diagnosis and then slightly rose to 78 grams per week at the subsequent 3.5 years, before gradually declining to 31 grams per week at 30 years after diagnosis. Flatter and lower trajectories were seen in female patients. Here, the mean consumption remained stable prior to diagnosis (at about 30 grams per week), fell marginally to 25 grams per week after the date of diagnosis, and kept decreasing afterwards. Moreover, for both sexes, there was a high variability in drinking trajectories across patients, as indicated by the wide CIs. These observations draw attention to the risk of misclassification bias inherent to conventional analyses that had only alcohol data at one time point. The evidence base may be further improved by accounting for the heterogeneity within long-term drinking profiles in the context of secondary CVD prevention.

Therefore, in Chapter 4, the longitudinal association between differential drinking profiles and subsequent risk of total mortality was examined in an inception cohort of 1306 patients with incident CVD events, using data with repeated measures of alcohol intake spanning up to three decades. A total of

six trajectory groups were identified (Figure 4.2). Besides those with stable drinking patterns (long-term abstainers, stable moderate or heavy drinkers), there were also groups of patients who stopped (former drinkers) or reduced drinking (reducing moderate drinkers or occasional heavy drinkers) following the onset of CVD. This finding remains in line with the declining trends in mean consumption post-CVD reported in Chapter 3 Figure 3.2 and highlights the dynamic and changeable character of alcohol use among CVD patients.

In multivariable models adjusted for changing lifestyle and health status (Model 3 in Table 4.3), patients who consistently drank within the UK guidelines of 14 units per week (stable moderate drinkers) had a similar risk of mortality from all causes as those who were continuous abstainers. This finding was robust to a range of sensitivity analyses (Table 4.4) and in accordance with findings from Chapter 2 Figure 2.10, which reported an attenuated and non-significant reduction in mortality risk among current drinkers when former drinkers were excluded from non-drinkers. Furthermore, patients who stopped drinking following the events were at greater risk of mortality than stable moderate drinkers; this finding was not seen when only using single time-point intake assessment (Table 4.3), thus confirming the utility of taking a longitudinal approach in examining the association of alcohol with health outcomes. In consistent with sick quitter hypothesis, former drinkers had the highest proportion with poor self-rated health before CVD onset and reported the greatest deterioration in their health during follow-up (Table 4.5). The association was significantly weakened following further adjustment for self-rated health (Table 4.6), suggesting that the increased risk of mortality in former drinkers was more likely attributable to their poorer general health rather than a lack of ‘protection’ from alcohol. Although the sample size was too small to draw firm conclusions, patients who consistently drank far above the guidelines (for example, with an average intake of more than 30 units per week) appeared to have an elevated risk of mortality compared to stable moderate drinkers.

5.2 Strengths and limitations

Major strengths of this thesis include a more recent and in-depth meta-analysis (Chapter 2) and the ability to use repeated measures of alcohol intake on the

same individuals across multiple time-points. To overcome limitations of studies utilising single time-point alcohol observations, a trajectory-based approach was applied in the longitudinal analyses presented in Chapters 3 and 4. In addition to minimising bias due to misclassification (for example, when alcohol intake assessed at the time of enrolment does not accurately represent intake during follow-up), such an approach also allows for differentiation between long-term profiles of alcohol consumption among CVD patients, taking into account both drinking volume and its stability within an individual over time. The derived trajectories reflect UK government's drinking guidelines [44], and thus facilitate the translation of evidence and have policy relevance (which will be discussed later in Section 5.3.1). Importantly, access to prospectively recorded alcohol intake data before the incidence of CVD enables distinguishing between recent and longer-term abstainers, each presumed and later confirmed to have disparate risks of mortality compared to continuous moderate drinkers. The longitudinal analyses also benefit from the long study period of over three decades, reliable ascertainment of CVD or mortality outcomes as well as repeated assessments on a broad range of sociodemographic, lifestyle and health-related factors.

Discussion of weakness specific to each study are provided in detail in the relevant chapters (see Sections 2.4, 3.4 and 4.4). However, there are some important limitations that may impact the overall interpretation of the findings presented in this thesis and hence need to be pointed out.

Firstly, as discussed earlier in each of the Chapters 2-4, alcohol consumption in this thesis was measured using self-reports. Most commonly, participants in the study cohorts were asked to report the number of alcoholic drinks that they had consumed during the last week, assuming that the snapshots of alcohol consumption in the week prior to the interview were reflective of the usual (habitual) weekly consumption over the period between assessments. Although this may introduce error into the results, the repetition of these snapshots helps to improve the accuracy in estimating long-term alcohol exposure, which is likely to be more aetiologically relevant than a single baseline measure [220].

Secondly, both categories of alcohol consumption in Chapter 2 and trajectories constructed in Chapters 3 and 4 were based on variables of drinking volume

only, and so this thesis was not equipped to assess the role of other characteristics pertaining to alcohol use such as frequency and context (for example, consume with or without food or water). In the general population, drinking more frequently is arguably a greater determinant of men's risk for incident MI than the actual volume consumed [251]. Similarly, binge drinking pattern or the timing of alcohol use in relation to meals may confound or modify the associations between average alcohol intake and CVD (see Chapter 1 Section 1.3.1.1); unfortunately, these data were not adequately captured in the datasets utilised. Relatedly, detailed information on drinking history prior to recruitment to the Whitehall II study was also not available. It is therefore possible that long-term abstainers identified in Chapter 4 might have included some individuals who ceased drinking in young adulthood due to awareness of familial health risk or impaired health, and the possibility of sick quitter bias cannot be definitively excluded.

Thirdly, data presented in this thesis came from individuals who took part in epidemiological studies (for example, the Physicians' Health Study contributed to meta-analyses in Chapter 2 and the Whitehall II study used in Chapters 3 and 4) and were available for follow-up lasting up to several decades. This may result in selection bias (healthy cohort effect) [252], especially for heavy drinkers. Indeed, a consistent under-representation of heavy drinkers was found across the present work, meaning that any effect reported for heavy intake is likely to be an underestimate of the 'true' association.

Another form of selection bias that may present in this thesis is index event bias. It arises when the occurrence of a particular event (index event) is required for inclusion in a study [253]. The requirement represents a source of selection, which can induce correlations between previously independent risk factors among those selected and hence can lead to biased conclusions [254]. Index event bias explains the antithetical observation that obesity increases the risk for CHD onset but protects against recurrent coronary events (the obesity paradox) [255]. Prior use of aspirin reduces the risk for primary MI but elevates the risk for MI recurrence (the aspirin paradox) [256]. As to alcohol consumption, moderate drinking has been reported to be associated with lower risk of developing CVD in general populations (as described in Chapter 1 Section 1.3.1). Therefore, it can be assumed that patients who developed CVD

despite being moderate drinkers had other risk factors contributing to the disease onset that surpassed any protection conferred by alcohol consumption. There remains a possibility that these other risk factors (both known and unknown) could have influenced the subsequent course of patients following the initial cardiovascular events, causing additional recurrence risk and mortality among moderate drinkers included in the analyses.

Finally, this thesis is underpowered to assess very heavy drinking, which may be associated with increased mortality risk amongst CVD patients (as indicated in Chapter 4 Section 4.3.4). As with much of the earlier work in this area [238, 257], this thesis is constrained by the relatively low number of female drinkers (female heavy drinkers in particular), which precludes further investigations into sex-specific effects. Likewise, the small sample size of patients included in Chapter 4 limits the statistical power and prevents additional subgroup/cause-specific analyses as well as a more sophisticated trajectory modelling. Also, findings of this thesis should be interpreted keeping in mind the observational nature of the datasets, which precludes firm conclusions about causal inferences.

5.3 Implication and future work

5.3.1 Implications for guidelines and patient care

For patients with established CVD, consistently moderate alcohol consumption does not associate with reduced mortality risk compared to long-term abstinence. In terms of subsequent cardiovascular events, available observational evidence suggestive of protective effects at moderate levels of drinking are methodologically weak, with underlying causal mechanisms yet to be clearly established. There are strong indications that the proposed cardio-benefit accruing to moderate drinkers has been overstated due to an already unhealthy comparison group of non-drinkers; and such cardio-benefit, if it exists, is most likely to occur and be greatest at lower intake levels (for example, 6 grams per day or equivalent to 5 UK units per week, as indicated by Figure 2.17) than those recommended in most current guidelines.

Although additional data are needed to make robust recommendations about the exact drinking limits in this patient population, the findings from this thesis may still have important implications for optimising guidelines in regard to these. Currently, guidelines for secondary prevention of CVD only warn specifically against heavier alcohol consumption [107-110], keeping the upper drinking limits in line with guidelines for the general population [44, 119]. Perhaps more stringent recommendations on alcohol use should be applied to CVD patients, for example advising all current drinking patients to further reduce their consumption even within the recommended limits. In addition to benefiting from any possible protection against a second event (which is likely to be present at intake levels much less than the recommended limits), the net burden of harms associated with alcohol would also be lowered through an overall reduction in patients' alcohol consumption, given that drinking even at the modest level increases risk of developing certain cancers [258-260] and liver disease [21]. Because unhealthy lifestyle behaviours (including smoking, poor nutrition, alcohol, and physical inactivity, collectively known as 'SNAP') usually cluster [261, 262] and that alcohol is commonly comorbid with other substance use such as illicit drugs, prescription painkillers and gabapentinoid drugs [263], a decrease in alcohol intake may also lead to improvements in these risk factors and thus has a wider range of positive impacts on health.

This is of particular concern when considering patients' generally older age and that the old are more physiologically sensitive to alcohol-related harms due to the effects of ageing, more co-morbidity and medication use [264-266]. Such a view is further supported by the latest report 'Our Invisible Addicts, 2nd edition' from the Royal College of Psychiatrists [263], arguing that UK's current low-risk drinking guidelines (no more than 14 units of alcohol per week) may still be too high for the older population, especially those with physical and mental disabilities and taking medications. As such, the report recommends that people aged 65 years and over should drink no more than 11 UK units per week, with no more than 3 units per day. Similar recommendations are made by the National Institute on Alcohol Abuse and Alcoholism, USA [267], that is no more than 7 USA-standard drinks (or equivalent to 12 UK units) per week and no more than 1-2 drinks on any single day for those older than 65 years.

Meanwhile, recommendations to initiate light to moderate drinking for perceived

cardio-benefits should not be made in the absence of evidence from randomized controlled trials, as well as the risk of non-vascular conditions and alcohol dependency [268]. Particularly, patients who fully abstain from alcohol may do so for reasons such as persistent poor health, low alcohol tolerance, a history of misuse, or pharmaceutical contraindication. Other lifestyle recommendations, including smoking cessation, increased physical activity, and combined dietary interventions with more convincing evidence of benefits in CVD patients (approximate 25% to 45% mortality risk reduction) [112], should therefore be given higher priority in the healthcare and management of patients at this time.

5.3.2 Future research directions

The work presented in Chapter 4 has illustrated the additional insights that can be obtained when capturing long-term drinking profiles in lieu of relying solely on baseline alcohol intake. An important next step would be replication studies with other outcomes, using different longitudinal datasets where repeated measures are available for a considerable period and of sufficient regularity. Based on lessons learned from this work and wider evidence including that from the general population, the following are suggestions for conducting such investigations in future research:

- Firstly, apart from aggregated cardiovascular mortality or events, future research may benefit from using more homogeneous phenotypes as outcomes of interest (for example, ischaemic/haemorrhagic stroke), as there is growing evidence from general population samples that diverse or even opposite dose-response associations may exist between alcohol and the risk of developing different CVD phenotypes [37, 186].

- Secondly, larger sample sizes are needed to facilitate analyses by patient subgroups as well as to enable testing of possible interactions for factors such as sex and age groups. Capacity for modelling non-linear associations would also be improved with an increasing number of heavier drinkers. Where sample size permitted, long-term occasional drinkers should be singled out and used as the reference group. This is because they are more comparable to moderate drinkers than long-term

abstainers in terms of potential confounders, and it seems implausible that alcohol would have any prolonged physiologic effect given their infrequent and very small consumption [92, 269].

- Thirdly, exposure to alcohol should be measured as accurately as possible, with adequate information about 'basic' drinking patterns which include frequency and amount of alcohol consumption and binge drinking [49]. Although self-reported alcohol data are generally considered valid and reliable, future studies may benefit from emerging technologies such as transdermal alcohol sensors which provide objective measures of alcohol use and thereby may serve as a means of validating/correcting estimates from self-reports [270].

- Lastly, research suggests that light to moderate alcohol consumption has no protective effect on MI survivors whose cardiac function has been severely impaired – for example, patients with a left ventricular ejection fraction less than 40% post MI [147], or having anterior wall infarcts [128] that generally cause greater infarct size and more extensive left ventricular remodelling and dysfunction than non-anterior infarcts [271]. Hence, studies examining patient cohorts with more detailed clinical data may be fruitful.

While the importance of longitudinal assessments has been widely recognised in alcohol epidemiology, there is no generally agreed way to analysing such datasets. In addition to trajectory-based approaches, whereby drinking patterns over time are first established (either pre-defined by the researchers or determined with statistical models) and then related to health outcomes, future studies may also consider the joint modelling framework, for example using shared random effects models [272] or latent class models [273]. Joint modelling allows simultaneous analyses for repeated measurement and time-to-event outcome data. It has been shown to reduce bias and improve efficiency compared to separate analyses and has been applied in several research areas such as CD4 counts and AIDS [274, 275], aortic valve function [276], renal disease [277-279] and cancer [280]. Furthermore, there is no consistent practice as to how to handle former drinkers in analyses of alcohol-related risks. The most common practice is to separate former drinkers from long-term

abstainers (to avoid sick-quitter bias) and treat them as a single exposure group. Some argue that doing so may result in selecting a healthier current drinker sample [281]. A possible solution to overcome this problem is to perform 'intention-to-treat' analysis, that is putting former drinkers back to one of the current drinking categories based on their past consumption levels [282]. However, this solution can only be applied in studies that assess the association with baseline drinking categories (not used in the de novo cohort analyses in Chapter 2 due to lack of data on former drinkers' earlier consumption in both HES/SHeSs and UK Biobank datasets). How to deal with issues of former drinkers in the context of longitudinal analysis represents a key area for future work.

MR is a promising approach to test causality in observational studies (as detailed in Chapter 1 Section 1.3.1.3) and should continuously be leveraged in alcohol epidemiology. Most MR studies to date examining alcohol's relation to cardiovascular health have focused on functional variants in alcohol metabolizing genes, mainly ALDH2-rs671. Less important variants include ADH1B-rs1229984 and ADH1C-rs698. In east Asians, these variants are common, jointly affect alcohol exposure to a great extent and thus can be suitable instruments for MR analyses [283]. Among populations of European ancestry, however, ALDH2-rs671 is monomorphic; the functional variants end up explaining only little variance in alcohol consumption, resulting in weak instrument bias and low power of analyses [284]. With the availability of large-scale genome-wide association studies (GWAS) [285], researchers wishing to conduct MR studies are now able to select a set of strong and robust genetic variants associated with alcohol consumption, without knowing the underlying biological mechanisms. The use of multiple variants increases the variance in alcohol consumption explained (especially for European-descent populations), enabling a broader assessment relating to the robustness of findings to pleiotropy and validity of the instruments chosen [286]. Indeed, data from GWAS have been used in a most recent MR study examining alcohol consumption instrumented by up to 94 SNPs in relation to several CVD phenotypes [287].

Furthermore, because observational literature suggests a non-linear (often J-shaped) association between alcohol consumption and CVD/mortality

outcomes, it is of particular relevance to explore the possible non-linearity in the context of MR. Common statistical methods for MR design (such as two-stage least squares regression) assume a linear exposure-outcome relationship. In recent years, several different strategies, for example modelling the localized average causal effects with fractional polynomials or a piecewise linear function, have been proposed to deal with non-linearity in MR [288, 289]. But so far only very few non-linear MR analyses have been performed about alcohol and cardiovascular health, with some finding evidence of non-linear trends [99, 290] and others not [100, 101]. Significant research gaps also exist in the field of MR between alcohol and CVD prognosis, most likely due to the barriers associated with poor data availability, collider bias and measurement of disease progression [291]. In the absence of single large-scale data source, the Genetics of Subsequent Coronary Heart Disease (GENIUS-CHD) Consortium has been established, to bring together over 50 cohorts of CHD patients with data on biomarkers, genes, and subsequent events [292]. Future MR studies with large samples and advanced methodology are warranted to yield a more complete picture of the role alcohol plays in both CVD aetiology and prognosis.

This thesis was written during the ongoing COVID-19 pandemic, which has already caused the loss of over 4.9 million lives and infected more than 243 million people worldwide by 26 October 2021 [293]. Patients with cardiovascular conditions are disproportionately affected by the pandemic, given their higher risk of complications and mortality from the infection [294]. In addition to deferring necessary care due to the fear of contracting the virus or restructuring of health services [295-297], CVD patients are also subject to sustained social distancing or even shielding (staying at home to reduce exposure risk), which can cause significant disruptions to daily routines and alter their lifestyles, including drinking habits [298]. Preliminary data suggest that drinking has become more polarised at early stages of the pandemic: in a survey of 1797 regular drinkers with cardiometabolic disease from 13 countries, 11.3% reported an increase in their alcohol consumption since the outbreak began, while 45.4% said they drank less [299]. As the relaxation of social distancing measures (for example, resurgence of physical social interactions and reopening of bars and restaurants) may offset or intensify any previous changes in patients' alcohol use [300, 301], an important question that needs to be addressed in future

research is the temporal evolution of these changes in drinking and the associated consequences. Such research would subsequently guide management of CVD patients in current and future pandemics, as well as adding to the knowledge regarding alcohol in relation to cardiovascular health.

5.4 Concluding remarks

The body of research presented in this thesis has advanced the understanding of alcohol use as a changing behaviour and its long-term implications on the wellbeing of CVD patients.

Among patients with established CVD, this thesis has shown no evidence of lower mortality risk for consistent moderate drinkers compared to continuous abstainers. Within the context of recurrent events, findings of protective effects associated with baseline moderate drinking may be largely attributable to an already unhealthy comparison group of non-drinkers; such cardio-protective effects, if real, are most likely to occur at lower consumption levels (up to 105 grams per week) than those recommended in most current guidelines. This thesis therefore encourages the downward revision of low-risk drinking limits in existing guidelines to both promote cardiovascular health in this patient population and reduce alcohol-related harm.

From a research standpoint, this thesis provides the first in-depth evidence on the dynamics and differentiation of alcohol consumption among CVD patients, highlighting the importance of taking a longitudinal approach. Future research should seek to replicate this work and expand on it to include more homogeneous outcomes, other populations and drinking characteristics. There is also a need for the development of methodologies aiming to better incorporate longitudinal and genetic data for the analyses of alcohol health relations.

Appendices

Appendices for Chapter 2

Appendix 2.1 Publication of results from meta-analyses

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Association of alcohol consumption with morbidity and mortality in patients with cardiovascular disease: original data and meta-analysis of 48,423 men and women

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Abstract

Background: Light-to-moderate alcohol consumption has been reported to be cardio-protective among apparently healthy individuals; however, it is unclear whether this association is also present in those with disease. To examine the association between alcohol consumption and prognosis in individuals with pre-existing cardiovascular disease (CVD), we conducted a series of meta-analyses of new findings from three large-scale cohorts and existing published studies.

Methods: We assessed alcohol consumption in relation to all-cause mortality, cardiovascular mortality, and subsequent cardiovascular events via de novo analyses of 14,386 patients with a previous myocardial infarction, angina, or stroke in the UK Biobank Study (median follow-up 8.7 years, interquartile range [IQR] 8.0–9.5), involving 1640 deaths and 2950 subsequent events, and 2802 patients and 1257 deaths in 15 waves of the Health Survey for England 1994–2008 and three waves of the Scottish Health Survey 1995, 1998, and 2003 (median follow-up 9.5 years, IQR 5.7–13.0). This was augmented with findings from 12 published studies identified through a systematic review, providing data on 31,235 patients, 5095 deaths, and 1414 subsequent events. To determine the best-fitting dose-response association between alcohol and each outcome in the combined sample of 48,423 patients, models were constructed using fractional polynomial regression, adjusting at least for age, sex, and smoking status.

Results: Alcohol consumption was associated with all assessed outcomes in a J-shaped manner relative to current non-drinkers, with a risk reduction that peaked at 7 g/day (relative risk 0.79, 95% confidence interval 0.73–0.85) for all-cause mortality, 8 g/day (0.73, 0.64–0.83) for cardiovascular mortality and 6 g/day (0.50, 0.26–0.96) for cardiovascular events, and remained significant up to 62, 50, and 15 g/day, respectively. No statistically significant elevated risks were found at higher levels of drinking. In the few studies that excluded former drinkers from the non-drinking reference group, reductions in risk among light-to-moderate drinkers were attenuated.

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Conclusions: For secondary prevention of CVD, current drinkers may not need to stop drinking. However, they should be informed that the lowest risk of mortality and having another cardiovascular event is likely to be associated with lower levels of drinking, that is up to approximately 105g (or equivalent to 13 UK units, with one unit equal to half a pint of beer/lager/cider, half a glass of wine, or one measure of spirits) a week.

Keywords: Alcohol, Cardiovascular disease, Mortality, Secondary prevention, Meta-analysis

Background

Lifestyle and dietary habits play an important role in the secondary prevention of cardiovascular disease (CVD) [1]. However, the impact of alcohol consumption on CVD patients' prognosis is unclear and recommendations for patients regarding upper limits of drinking vary substantially across different guidelines [2–5]. While light-to-moderate alcohol consumption is associated with a lower risk of developing multiple cardiovascular outcomes in general population cohorts [6, 7], it is difficult to extend the posited cardio-protective effects to CVD patients because of their typically older age and compromised vasculature as well as the medications they take to prevent secondary events [8]. In addition, for CVD patients, there are concerns about the potential detrimental effects of alcohol on the circulatory system, such as hypertension, arrhythmias, and haemorrhagic stroke, which may exacerbate their existing pathological conditions [9].

The most recent meta-analysis to have explored the association between alcohol consumption and prognosis among CVD patients was undertaken by Costanzo et al. in 2010 [10]. Pooling data from eight observational studies published between 1998 and 2008, they identified a maximal 22% relative risk (RR) reduction at approximately 8 g/day for cardiovascular mortality and 18% at 7 g/day for all-cause mortality among patients with myocardial infarction (MI), angina, or stroke, relative to non-drinkers, with risk increasing in a dose dependent manner above these levels. However, their analysis was limited to studies only on mortality and did not consider any non-fatal outcomes. Understanding how alcohol consumption is related to cardiovascular morbidity is of great importance to CVD patients because this population is at high risk of recurring cardiovascular events which can significantly compromise the patients' quality of life [11]. Including morbidity information will complement the existing evidence base to provide a more complete picture of how alcohol consumption can be managed for optimal secondary CVD prevention. Additionally, further studies [12–14] have been published in the decade since the last meta-analysis. Given the growing debate on this topic, a more detailed and comprehensive reassessment of the evidence is warranted in the absence of long-term clinical trials [9].

We thus analysed individual data from three large-scale cohorts. In addition to estimating risk of mortality among CVD patients, we also examined the association between alcohol intake and subsequent cardiovascular events. To consolidate all available evidence on this topic, we conducted meta-analyses of our results with those from published studies identified through a systematic review.

Methods

De novo cohort analyses

Study cohorts and participants

Data were obtained from participants in the Health Survey for England (HSE), the Scottish Health Survey (SHeSs), and UK Biobank. Descriptions of each cohort are provided in Additional file 1 (Appendix S1). The present analyses combined data from the 1994–2008 HSE datasets and the 1995, 1998, and 2003 SHeSs datasets and were restricted to participants aged ≥16 years reporting to have been diagnosed with MI/angina (not recorded separately) or stroke prior to baseline. For UK Biobank, we identified participants with MI, angina, or stroke before recruitment based on record linkage to the Hospital Episode Statistics (HES), using algorithms defined in Additional file 1 (Appendix S1 and Table S1 [15–29]).

To be eligible for the analysis, participants in HSE/SHeSs and UK Biobank had to have baseline information about their drinking status and average alcohol intakes, plus age, sex, smoking status, self-reported history of diabetes and hypertension, socioeconomic position/education, body mass index, and regular medications. We separated former drinkers from never drinkers and categorised current drinkers into three groups: low-level drinkers (≤ 14 units/week, one unit contains 8g of ethanol [30] and is equivalent to half a pint of beer/lager/cider, half a glass of wine, or one measure of spirits/fortified wine [31]), medium-level drinkers (>14 to ≤50 units/week for men, >14 to ≤35 units/week for women), and high-level drinkers (>50 units/week for men, >35 units/week for women) [32]. Further details of the alcohol assessment and covariates are described in Additional file 1 (Appendix S1).

We assessed alcohol consumption in relation to three outcomes (each ascertained by national death registries or HES records): all-cause mortality, cardiovascular mortality, and major cardiovascular events. We defined cardiovascular events as a composite of angina, fatal and

non-fatal MI and stroke, revascularisation procedures (angioplasty or coronary artery bypass graft), death from heart failure, and sudden cardiac death, and only UK Biobank contributed data to the analysis on cardiovascular events. Participants were followed up until the date of their death or first detected event, or were censored on the date they left the UK or the last date of data linkage (cohort specific). Additional details of outcome ascertainment and follow-up procedures are in Additional file 1 (Appendix S1).

Statistical analysis

We used multivariable Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of different drinking categories with each outcome of interest relative to never drinkers. Adjustments were made for age, sex, and smoking status in initial models and then for all covariates in maximally-adjusted models. For HSE/SHeSs datasets, we additionally adjusted for survey wave using shared-frailty models to account for within-group correlations. Schoenfeld residuals were plotted to ascertain that the proportional hazards assumption had not been violated (see Additional file 1: Figure S1). Models for MI, angina and stroke as primary event in further stratified analyses were adjusted for each other as well as all covariates.

Systematic review and meta-analysis

Search strategy and study selection

This study followed PRISMA and MOOSE guidelines [33, 34]. MEDLINE and Embase were searched for relevant studies up to 30 July 2020, using a combination of subject headings and free-text terms with no restrictions on language or publication date (see Additional file 1: Table S2). In addition, the reference lists of eligible studies and a previous systematic review [35] on this topic were manually checked to add any studies missed by the initial database searches.

After removing duplicates, citations were screened to exclude any that did not report a prospective relationship between alcohol consumption and outcomes of interest among patients with pre-existing CVD. Full text of the remaining citations were then independently assessed by two pairs of reviewers (CD and AB/DON) for eligibility. Studies were retained if they met the selection criteria for study design (longitudinal study including randomised control trials not involving alcohol), study population (MI, angina, or stroke patients), exposure (alcohol consumption reported across ≥3 categories, inclusive of a non-drinking group, to allow for testing a curvilinear relationship), outcomes (all-cause or cardiovascular mortality, cardiovascular events), and risk estimates (at least adjusted for age, sex, and smoking). We excluded studies if the reported alcohol consumption could not be converted into gram per day or if frequency counts, risk estimate, and its corresponding 95%CI were not available after contacting the authors. The inter-rater agreement for this review was high (Fleiss κ= 0.85).

Data extraction and quality assessment

Data extraction was conducted by one reviewer (CD) and then verified by a second reviewer (AB/DON). When available, we collected data on the amount of alcohol consumed. Given that most studies included in our analyses reported alcohol consumption on a daily basis, we used grams of alcohol per day as the common unit of measurement. To convert the number of drinks to grams in four included studies (one conducted in Italy [12] and three in USA [36–38]) which did not specify the quantity of alcohol in one drink, we assumed country-specific standard drinks (i.e. Italy 12g, USA 14g) [39]. A factor of 0.79 was used for the conversion of millilitres to grams (i.e. 1 ml alcohol = 0.79 g [40]) in one study [41]. Exposures categorised according to time periods longer than 1 day were transferred into daily estimates, assuming an even distribution of consumption over the reference period. Where averages were not reported for each drinking category, the midpoints of the range were chosen. For open-ended upper categories, mean values were defined as 1.2 times the lower boundary as suggested by Berlin et al. [42]. Similar results were obtained when multiplying the lower boundary for the open-ended upper categories by 1.0, 1.4, or 1.6 instead of 1.2 (see Additional file 1: Figure S2).

Multiple alcohol measures were used in three included studies, two of which reported risk estimates based on the average intakes during follow-up [13, 43] and the remaining one performed time-dependent analyses to allow changes on drinking habits [12]. In addition, most of the included studies asked patients to report their average consumption since the occurrence of their primary events (post-event alcohol assessment), whereas three studies used alcohol intake in the year prior to primary events (pre-event), assuming drinking habits remained stable over time, even following events [14, 44, 45].

Because all included studies except one [46] used a non-drinking reference group, we preferred risk estimates for different drinking categories versus non-drinkers. For a single study that used occasional drinkers as the reference group [46], the risk estimates were recalculated to derive alternative estimates each relative to a non-drinker group. A Microsoft Excel spreadsheet developed by Hamling et al. was used during the recalculation to account for the non-independence between estimates sharing a common reference group [47]. When a study reported risk estimates with different degrees of statistical adjustment for confounding, we used the

most-adjusted one. Furthermore, to investigate the possible impact of over-adjustment for potential mediators on our results, we performed a sensitivity analysis by using risk estimates that were only controlled for age, sex, and smoking, the three most important confounding factors for the alcohol-CVD relationship. With all estimates reported being RR or HR, RR served as the common measure of association across studies. HRs were treated as measures of RRs [48]. Study quality was assessed using the Newcastle-Ottawa Scale (see Additional file 1: Appendix S2) [49].

Data synthesis

For each analysis, a family of second-degree fractional polynomial models (FP2: log RR = $\beta_1 x^{p1} + \beta_2 x^{p2}$, x^0 equals log(x) rather than 1 and the model becomes log RR = $\beta_1 x^p + \beta_2 x^p \log(x)$ when $p_1 = p_2$) was generated to derive a power transformation of the exposure variable [50]. p_1 and p_2 were taken from a predefined set P= (−2, −1, −0.5, 0, 0.5, 1, 2, 3) which allows for a very large and varied set of functions, including U- and J-shaped curves, to be generated. For x = 0, the function would start from log RR = 0 and therefore no constant term (i.e. the intercept) was considered in our models [51]. The best fit among the family of models was defined as that with the lowest deviance.

With the terms of exposure identified in the best-fitting FP2, a two-stage regression model was fitted to summarise the relationship between alcohol consumption and each outcome of interest. The first stage generated the dose-response model within each study and the second stage pooled study-specific trends using a random effect model to accommodate the heterogeneity across studies [52, 53]. A sensitivity analysis was done by excluding studies of the lowest quality and pre-defined subgroup analyses according to sex, primary event, and type of non-drinking reference group and alcohol assessment for each outcome of interest.

The overall degree of heterogeneity was quantified using the I^2 index [54]. We assessed evidence of publication bias through visual inspection of funnel plots and Egger's regression test for asymmetry [55]. All statistical analyses were performed using Stata (version 15.1).

Results

Associations of alcohol consumption with mortality and cardiovascular morbidity in study cohorts

Complete data for the de novo cohort analyses were available for 2802 participants (MI/angina=2341, stroke=535) in HSE/SHeSs and 14,386 (MI=5333, angina=9589, stroke=2064) in UK Biobank (see Additional file 1: Figure S3). On average, UK Biobank participants were younger and reported higher consumption of alcohol than HSE/SHeSs participants (Table 1).

During a median follow-up of 9.5 years (interquartile range [IQR], 5.7–13.0) in HSE/SHeSs and 8.7 years (IQR, 8.0–9.5) in UK Biobank, we identified 1257 deaths among HSE/SHeSs participants and 1640 deaths among UK Biobank participants, of which 492 (39.1%) and 631 (38.5%) deaths were due to cardiovascular causes, respectively. Maximally adjusted models of UK Biobank dataset revealed a J-shaped association for both all-cause and cardiovascular mortality, with low- and medium-level drinkers having a decreased risk compared with never drinkers but no difference in risk for high-level or former drinkers (Fig. 1). Although similar J-shaped trends were observed for HSE/SHeSs, none of the associations were statistically significant, probably due to the relatively small sample size of each drinking subgroup (Fig. 1). We noted differential associations by sex and primary cardiovascular events in stratified analyses (see Additional file 1: Figures S4 and S5).

A total of 2950 fatal and non-fatal subsequent cardiovascular events were recorded in UK Biobank, with a median follow-up of 7.5 years (IQR, 6.8–8.5). A lower risk of cardiovascular events was observed across all categories of current drinkers (Fig. 1), within participants of both sexes and with different primary events (see Additional file 1: Figures S4 and S5).

Characteristics of studies included in meta-analysis

Of the initial 1722 unique citations, 12 published studies fulfilled the selection criteria (see Additional file 1: Figure S6). Table 2 outlines the characteristics of all studies selected for meta-analyses, inclusive of HSE/SHeSs and UK Biobank. Nine of the 14 studies had a cohort design and the remaining five [12, 36–38, 43] were randomised control trials for certain drug or diet type with no specific inventions on alcohol consumption. The quality of selected studies was moderate to high on average, with a median score of 8 on the Newcastle-Ottawa Scale. Additional details regarding alcohol consumption, effect estimates, and confounder adjustment are provided in Additional file 1 (Tables S3–S5).

Alcohol consumption and all-cause mortality among CVD patients

Eleven studies, comprising 41,743 CVD patients, contributed to this analysis. Overall, a J-shaped association was observed, with a protective effect that peaked at 7 g/day and remained significant up to 62 g/day (Fig. 2A, Table 3). Although the dose-response trend followed a J-curve in men, we found no increased risk among women at higher levels of drinking (see Additional file 1: Figure S7). Regarding primary events, moderate drinking was associated with a lower risk for total mortality among patients with a previous MI or angina, but not with stroke (see Additional file 1: Figure S8). Pooled analysis

Table 1 Characteristics of participants at baseline

	HSE/SHeSs						UK Biobank					
	Never drinker	Former drinker	Low-level drinker	Medium-level drinker	High-level drinker	Overall	Never drinker	Former drinker	Low-level drinker	Medium-level drinker	High-level drinker	Overall
N	263 (9.4)	383 (13.7)	1630 (58.2)	458 (16.3)	68 (2.4)	2802 (100.0)	1076 (7.5)	1207 (8.4)	5989 (41.6)	5222 (36.3)	892 (6.2)	14386 (100.0)
Age, mean (SD), y	69.0 (11.0)	67.1 (11.1)	68.2 (10.1)	64.2 (10.9)	60.4 (10.7)	67.3 (10.6)	61.6 (6.6)	61.1 (6.5)	61.9 (6.1)	61.6 (6.0)	60.5 (6.4)	61.6 (6.2)
Alcohol intake, mean (SD), g/day	0.0	0.0	4.0 (4.3)	28.0 (10.2)	85.1 (33.0)	9.0 (16.9)	0.0	0.0	7.9 (5.1)	30.6 (10.6)	76.7 (26.4)	19.2 (21.4)
BMI, mean (SD), kg/m^2	28.5 (5.5)	28.6 (5.7)	27.9 (4.6)	27.9 (4.1)	28.0 (4.2)	28.1 (4.8)	30.0 (5.8)	30.2 (6.0)	29.1 (5.0)	28.8 (4.3)	29.0 (4.7)	29.2 (4.9)
Female	187 (71.1)	189 (49.3)	758 (46.5)	65 (14.2)	5 (7.4)	1204 (43.0)	619 (57.5)	447 (37.0)	2242 (37.4)	743 (14.2)	174 (19.5)	4225 (29.4)
Smoking status												
Never	157 (59.7)	89 (23.2)	527 (32.3)	78 (17.0)	10 (14.7)	861 (30.7)	704 (65.4)	350 (29.0)	2616 (43.7)	1512 (29.0)	178 (20.0)	5360 (37.3)
Ex-smoker	66 (25.1)	191 (49.9)	799 (49.0)	272 (59.4)	29 (42.6)	1357 (48.4)	252 (23.4)	638 (52.9)	2799 (46.7)	3045 (58.3)	507 (56.8)	7241 (50.3)
Current smoker	40 (15.2)	103 (26.9)	304 (18.7)	108 (23.6)	29 (42.6)	584 (20.8)	120 (11.2)	219 (18.1)	574 (9.6)	665 (12.7)	207 (23.2)	1785 (12.4)
History of diabetes	40 (15.2)	74 (19.3)	169 (10.4)	43 (9.4)	2 (2.9)	328 (11.7)	280 (26.0)	346 (28.7)	1026 (17.1)	676 (12.9)	117 (13.1)	2445 (17.0)
History of hypertension	50 (19.0)	60 (15.7)	224 (13.7)	54 (11.8)	6 (8.8)	394 (14.1)	637 (59.2)	764 (63.3)	3193 (53.3)	2940 (56.3)	536 (60.1)	8070 (56.1)
Socioeconomic position[a]												
Low	106 (40.3)	186 (48.6)	764 (46.9)	230 (50.2)	26 (38.2)	1312 (46.8)	NA	NA	NA	NA	NA	NA
Intermediate	104 (39.5)	138 (36.0)	494 (30.3)	83 (18.1)	24 (35.3)	843 (30.1)	NA	NA	NA	NA	NA	NA
High	53 (20.2)	59 (15.4)	372 (22.8)	145 (31.7)	18 (26.5)	647 (23.1)	NA	NA	NA	NA	NA	NA
Highest educational qualification[b]												
None	NA	NA	NA	NA	NA	NA	432 (40.1)	564 (46.7)	1910 (31.9)	1510 (28.9)	247 (27.7)	4663 (32.4)
O levels or equivalent	NA	NA	NA	NA	NA	NA	141 (13.1)	150 (12.4)	900 (15.0)	742 (14.2)	149 (16.7)	2082 (14.5)
A levels or equivalent	NA	NA	NA	NA	NA	NA	315 (29.3)	295 (24.4)	1948 (32.5)	1760 (33.7)	305 (34.2)	4623 (32.1)
Degree	NA	NA	NA	NA	NA	NA	188 (17.5)	198 (16.4)	1231 (20.6)	1210 (23.2)	191 (21.4)	3018 (21.0)
Cholesterol-lowering medications	70 (26.6)	128 (33.4)	328 (20.1)	107 (23.4)	11 (16.2)	644 (23.0)	841 (78.2)	990 (82.0)	4876 (81.4)	4488 (85.9)	732 (82.1)	11927 (82.9)
Antihypertensive medications	168 (63.9)	247 (64.5)	883 (54.2)	217 (47.4)	27 (39.7)	1542 (55.0)	746 (69.3)	855 (70.8)	4047 (67.6)	3774 (72.3)	651 (73.0)	10073 (70.0)
Antiplatelet agents	118 (44.9)	187 (48.8)	725 (44.5)	207 (45.2)	23 (33.8)	1260 (45.0)	810 (75.3)	902 (74.7)	4655 (77.7)	4305 (82.4)	736 (82.5)	11408 (79.3)
Digoxin	9 (3.4)	19 (5.0)	62 (3.8)	10 (2.2)	2 (2.9)	102 (3.6)	16 (1.5)	29 (2.4)	86 (1.4)	66 (1.3)	12 (1.3)	209 (1.5)
Warfarin[c]	NA	NA	NA	NA	NA	NA	59 (5.5)	106 (8.8)	358 (6.0)	313 (6.0)	34 (3.8)	870 (6.0)

Data are number (percentage) unless otherwise specified
BMI, body mass index; *HSE*, the Health Survey for England; *NA*, not applicable; *SD*, standard deviation; *SHeSs*, the Scottish Health Survey
[a]Socioeconomic position was defined using the participant's occupational classification, categorised as low (semi-skilled or unskilled manual), intermediate (skilled non-manual or manual), or high (professional or managerial technical)
[b]Highest educational qualification was categorised into four levels: None, O levels/GCSEs, CSEs or equivalent; A/AS levels, NVQ or HND or HNC or equivalent, or other professional qualification; college or university degree
[c]None of the participants in HSE/SHeSs reported using warfarin on a regular basis

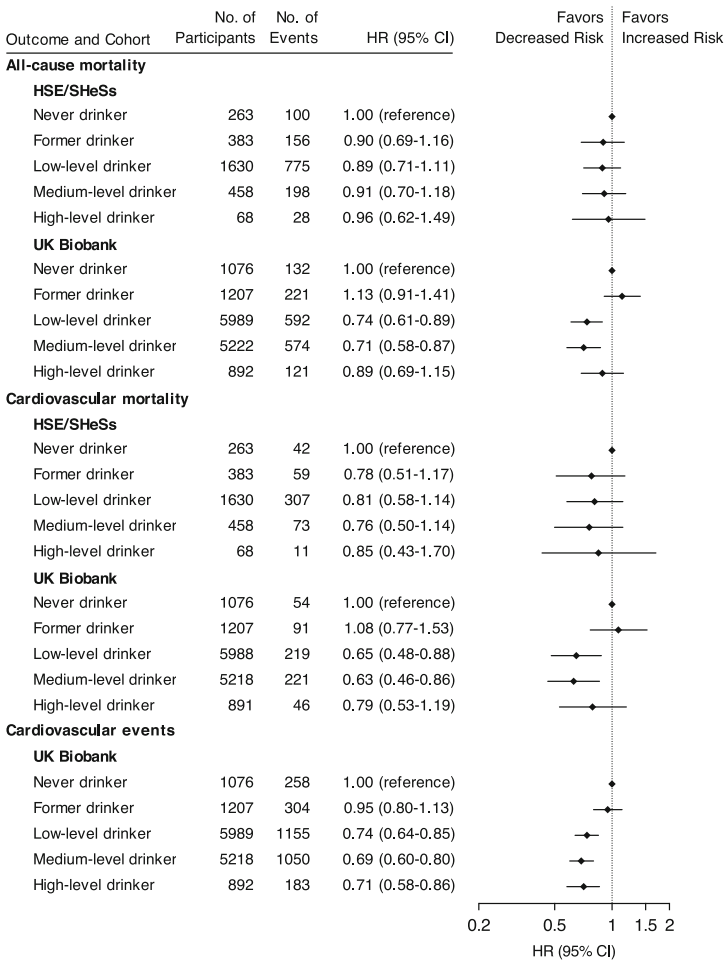

Fig. 1 Association of drinking categories with all-cause mortality, cardiovascular mortality, and cardiovascular events by study cohorts. Hazard ratios are adjusted for age, sex, smoking status, diabetes, hypertension, socioeconomic position or education, body mass index, and regular use of cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin. CI indicates confidence interval; HR, hazard ratio; HSE, the Health Survey for England; SHeSs, the Scottish Health Survey

of estimates relative to non-current drinkers showed a reduced mortality risk for an alcohol intake up to approximately 75 g/day. However, when studies with former drinkers in the reference group were excluded, the association was considerably weakened (see Additional file 1: Figure S9). In addition, among those studies using post-event alcohol measures, the result did not change substantively; a similar trend was seen in studies with multiple measures but failed to reach statistical significance, probably because of the low number of curves (n=2) in this subgroup (see Additional file 1: Figure S10).

Alcohol consumption and cardiovascular mortality among CVD patients

Nine studies, comprising 24,770 patients, were included in the meta-analysis on cardiovascular mortality, and the overall association with alcohol consumption was interpreted as a J-curve. The maximal reduction in mortality risk was found to be 27% at 8 g/day and the reversion

Table 2 Characteristics of 14 studies included in meta-analyses

Source	Country	Dataset	Sex	Study size, No.	Meta-analyses Inclusion[a]			Follow up, y[b]	Baseline age, y[c]	Reference group including former drinkers	Pre-/post-event alcohol assessment	Multiple alcohol measures	Quality assessment score	Primary event
					ACM case, No.	CVM case, No.	CVE case, No.							
HSE/SHeSs	UK	HSE (1994–2008) / SHeSs (1995, 1998, 2003)	M, F	2802	1257	492	NA	9.5	67.3	Both[d]	Post-	No	9	MI/angina, stroke[e]
UK Biobank	UK	Initial assessment visit (2006–2010)	M, F	14,386	1640	631	2950	8.7	61.6	Both[d]	Post-	No	9	MI, angina, stroke
Levantesi et al., 2013 [12]	Italy	GISSI study	M, F	11,248	1656	NA	1168	5.7	59.4	Yes	Post-	Yes	7	MI
Pai et al., 2012 [13]	USA	Health Professionals Follow-up Study	M	1818	468	243	NA	Up to 20	Range 40–75	Yes	Both	Yes	7	MI
Rosenbloom et al., 2012 [14]	USA	Onset study	F	1253	441	NA	NA	Up to 10	66.1	Yes	Pre-	No	9	MI
Janszky et al., 2008 [44]	Sweden	SHEEP study	M, F	1332	259	140	NA	8.6	59.4	No	Pre-	No	9	MI
Masunaga et al., 2006 [41]	Japan	Consecutive patients	M	3845	NA	NA	142	1.1	57.2	No	Post-	No	8	MI
Aguilar et al., 2004 [36]	USA, Canada	SAVE trial	M, F	2036	355	284	NA	3.5	59.2	Yes	Both	No	7	MI
Jackson et al., 2003 [37]	USA	Physicians' Health Study	M	1320	369	267	NA	4.5	67.4	Yes	Post-	No	6	Stroke
de Lorgeril et al., 2002 [43]	France	Lyon Diet Heart Study	M	353	NA	NA	104	4.0	54.0	Yes	Post-	Yes	7	MI
Mukamal et al., 2001 [45]	USA	Onset study	M, F	1913	317	238	NA	3.8	61.8	Yes	Pre-	No	8	MI
Shaper et al., 2000 [46]	UK	British Regional Heart Study	M	596	258	184	NA	12.8	Range 45–64	No	Post-	No	9	MI, angina
Valmadrid et al., 1999 [56]	USA	WESDR	M, F	163	NA	52	NA	Up to 12.3	68.6	No	Post-	No	9	MI/angina[e, f]
Muntwyler et al., 1998 [38]	USA	Physicians' Health Study	M	5358	920	NA	NA	5.0	64.1	Yes	Post-	No	6	MI

ACM all-cause mortality, *CVE* cardiovascular events, *CVM* cardiovascular mortality, *F* female, *HSE* the Health Survey for England, *M* male, *MI* myocardial infarction, *SHeSs* the Scottish Health Survey

[a]Not applicable (NA) if the study was not included in meta-analysis on the outcome

[b]Data are mean/median unless otherwise specified

[c]Data are mean unless otherwise specified

[d]Former drinkers were included only in subgroup meta-analyses on different non-drinking reference group

[e]Results were not reported separately for angina and MI patients

[f]Older-onset diabetic patients with a history of angina or MI

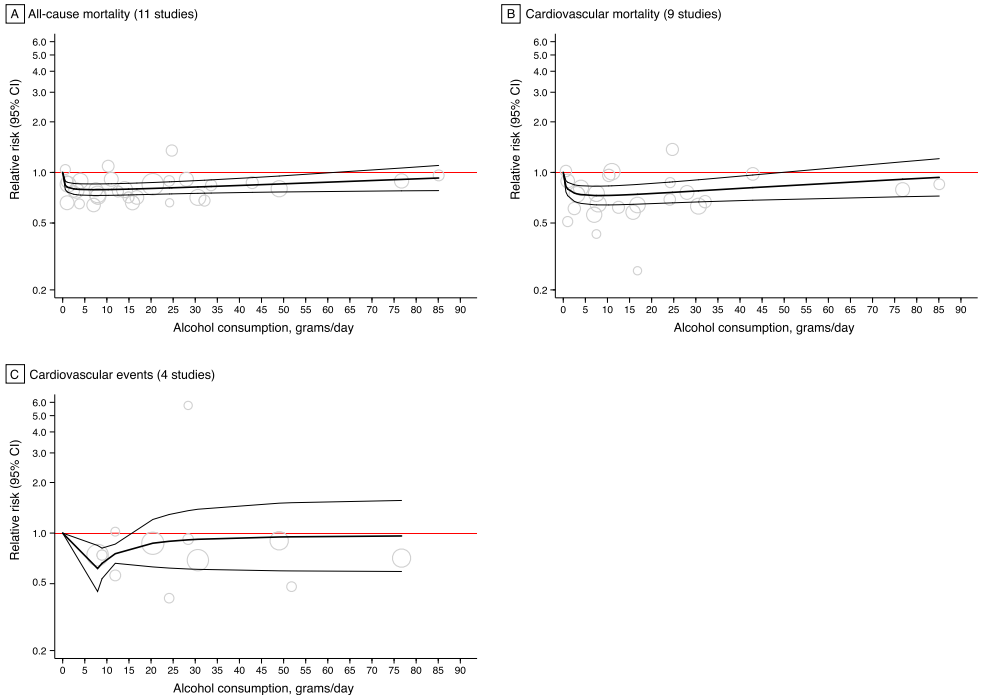

Fig. 2 Overall dose-response relationship between alcohol consumption and risk of mortality and subsequent cardiovascular events, using maximally-adjusted estimates. Best-fitting second-degree fractional polynomial models (with 95% CIs) are shown in solid curves with each data point overlaid as circles. Circle size indicates the weighting of each data point and is inversely proportional to the variance of the log-transformed relative risk

point was reached at 50 g/day (Fig. 2B, Table 3). Our results remained little altered when considering studies on men only, or using different types of reference groups or alcohol assessments (see Additional file 1: Figures S7, S9 and S10). Unlike the J-curve observed for men, there was no excess risk of mortality among women at higher levels of consumption (see Additional file 1: Figure S7). Stratified analyses by primary events showed that moderate drinking was associated with a lower risk of cardiovascular mortality among patients with a previous MI; however, among those with angina or stroke, the overall dose-response trend was close to null (see Additional file 1: Figure S8).

Alcohol consumption and cardiovascular events among CVD patients

Among the four studies (28,621 patients) addressing drinking and cardiovascular events, one reported dose-response trend separately for two age groups and thus provided two curves. Alcohol intake was associated with a significant reduction in the risk of cardiovascular events up to 15g/day (Fig. 2C, Table 3). Pooled analysis of studies on women showed a declined risk for an alcohol intake up to approximately 49 g/day, whereas no reduction in risk was seen in men at any level of consumption (see Additional file 1: Figure S7). Moderate drinking was found to be protective against cardiovascular events within patients of different primary events and studies with multiple alcohol measures (see Additional file 1: Figures S8 and S10). However, when studies including former drinkers in the reference group were excluded, the overall protective effect was attenuated and became non-significant (see Additional file 1: Figure S9).

Sensitivity analyses

Sensitivity analyses excluding studies of the lowest quality (score <7) revealed similar curves (see Additional file 1: Figure S11). Results were consistent when restricting analysis to estimates that were only adjusted for age, sex, and smoking status (see Additional file 1: Figure S12). For mortality outcomes, there was no evidence of heterogeneity across the first- and second-order polynomial (both I^2 = 0%); however, a high degree of heterogeneity (both I^2 = 75%) was noted in studies

Table 3 Best-fitting models and results of the meta-analysis on alcohol consumption and risk of mortality and subsequent cardiovascular events

Outcome and subgroup	No. of studies (curves)	No. of patients	Maximal effect size[a]		Reversion point, g/day[b]	Powers for the Best-Fitting FP2	
			RR (95% CI)	g/day		dose_1	dose_2
All-cause mortality							
Overall	11 (11)	41,743	0.79 (0.73–0.85)	7	62	−0.5	1
Male	6 (6)	19,897	0.82 (0.72–0.93)	9	39	0	0.5
Female	3 (3)	6046	0.64 (0.36–1.14)	54	49	−2	3
MI as primary event	9 (9)	29,554	0.82 (0.68–0.99)	2	7	−1	0.5
Angina as primary event	2 (2)	8938	0.79 (0.63–0.99)	39	46	0.5	3
Stroke as primary event	3 (3)	3618	0.71 (0.42–1.20)	12	NA	0	0.5
Reference group including former drinkers	9 (9)	41,405	0.77 (0.69–0.85)	16	75	−0.5	2
Reference group excluding former drinkers	4 (4)	17,526	0.85 (0.71–1.00)	3	3	−0.5	−0.5
Post-event alcohol assessment	8 (8)	37,245	0.81 (0.74–0.88)	9	52	0	0.5
Multiple alcohol measures	2 (2)	12,337	0.78 (0.59–1.03)	16	NA	−0.5	−0.5
Cardiovascular mortality							
Overall	9 (9)	24,770	0.73 (0.64–0.83)	8	50	0	0.5
Male	5 (5)	14,536	0.72 (0.62–0.85)	9	32	0	0.5
Female	2 (2)	4790	0.29 (0.09–1.01)	54	54	0	2
MI as primary event	6 (6)	12,422	0.76 (0.64–0.91)	3	25	−2	3
Angina as primary event	2 (2)	8934	0.72 (0.42–1.23)	56	NA	3	3
Stroke as primary event	3 (3)	3617	0.63 (0.37–1.08)	26	NA	0	3
Reference group including former drinkers	6 (6)	24,269	0.73 (0.58–0.93)	13	27	0	0.5
Reference group excluding former drinkers	5 (5)	17,683	0.71 (0.55–0.90)	7	29	−0.5	0.5
Post-event alcohol assessment	7 (7)	21,525	0.73 (0.60–0.90)	8	43	0	0
Multiple alcohol measures	1 (1)	1818	0.58 (0.40–0.84)	17	33	−0.5	3
Cardiovascular events							
Overall[c]	4 (5)	28,621	0.50 (0.26–0.96)	6	15	−2	−2
Male	3 (4)	13,598	0.56 (0.23–1.34)	8	NA	−2	−2
Female	1 (1)	3775	0.67 (0.43–1.05)	54	49	−2	3
MI as primary event	4 (5)	20,361	0.79 (0.66–0.94)	11	35	−2	3
Angina as primary event	1 (1)	8747	0.69 (0.59–0.81)	35	n.a.	−2	1
Stroke as primary event	1 (1)	1855	0.49 (0.26–0.92)	72	n.a.	−2	3
Reference group including former drinkers	3 (3)	25,983	0.72 (0.53–0.97)	40	45	1	1
Reference group excluding former drinkers	2 (3)	17,020	0.78 (0.46–1.31)	17	NA	3	3
Multiple alcohol measures	1 (1)	353	0.32 (0.14–0.71)	38	n.a.	2	3

FP2 second-degree fractional polynomial model, *MI* myocardial infarction

[a]Defined as the lowest point of the dose-response curve within the range of dose reported by the studies

[b]Defined as the dose of alcohol at which protection against the outcome is no longer statistically significant at the 95% confidence level; not applicable (NA) if non-significant association was found at any level of consumption; not available (n.a.) if the association remained significant within the range of dose reported by the studies

[c]All of the four studies measured post-event alcohol consumption and had a quality score ≥ 7

contributing results for cardiovascular events. For all outcomes assessed, we found no evidence of publication bias (see Additional file 1: Figure S13).

Discussion

Meta-analysis of the results from three major UK cohorts together with those from 12 published studies found J-curve relationships between alcohol consumption and mortality in those with cardiovascular disease, with the greatest risk reduction being observed at 7 g/day for all-cause mortality and 8 g/day for cardiovascular mortality relative to current non-drinkers. This dose-response trend remains consistent with the last published meta-analysis [10] and has also been reported in

other high-risk populations, such as hypertensive [57] and diabetic individuals [58].

To our knowledge, this is the first meta-analysis of alcohol consumption and any subsequent cardiovascular events in patients with previous CVD, in which UK Biobank contributed nearly half of the total sample size. We found a reduction in risk for an alcohol intake up to approximately 15 g/day, an upper limit much lower than those for the mortality outcomes. Taken together, our study suggested that, among CVD patients, the upper drinking limit for lower risks of mortality and cardiovascular morbidity was about 105 g/week, which was lower than those recommended in most current guidelines. For example, the American Heart Association (AHA) and American College of Cardiology Foundation 2011 guidelines on secondary prevention recommend "alcohol moderation"—up to 196 g/week (2 USA drinks/day) for male and 98 g/week (1 USA drink/day) for female according to the national dietary guidelines [59]—for patients with atherosclerotic vascular disease [2]; the same recommendations apply in the AHA/American Stroke Association 2014 guidelines for secondary stroke prevention [5]; the UK National Institute for Health and Care Excellence 2020 guidelines recommend to keep alcohol intake within 112 g/week (14 UK units/week) for both men and women after having an MI [4]; and WHO 2007 recommendations for prevention of recurrent MI and stroke were no more than about 166 g/week (3 units/day, 1 unit contains 10 ml of pure alcohol) [3].

Strengths and limitations of study

With almost triple the number of CVD patients, our study expands the findings of the last comprehensive review published a decade ago [10]. In particular, both HSE/SHeSs and UK Biobank provide long-term follow-up of large contemporary samples from the UK general population. The inclusion of these new datasets allows us to examine the risk of drinking within various subgroups, some of which are not available or too small to reliably investigate in published studies. For example, our data suggest that the dose-response associations of alcohol with mortality and morbidity differ by sex and are more pronounced among patients with MI than angina or stroke. These findings raise the question of whether differential drinking limits should be recommended in patient subgroups and warrant further investigation. Furthermore, there is evidence that reductions in risk of all-cause mortality and subsequent events might have been overestimated due to the inclusion of former drinkers in the non-drinking reference group. Former drinkers may include individuals who have quit drinking in response to ill health (i.e. "sick quitters"), particularly past heavy drinkers [60], therefore making current drinkers appear healthy relative to less healthy non-current drinkers. This could lead to a low-risk drinking limit less than the estimated 105g/week; however, we cannot definitely determine the extent of this overestimation with very few studies that explicitly excluded former drinkers.

Many medications commonly used by CVD patients can interact with alcohol by altering the metabolism or effects of the medication and/or alcohol [61]. The interactions may occur with lower amounts of alcohol or follow a dose-response relationship, with the risk and severity of interactions increasing with increasing levels of alcohol consumption [62]. For example, moderate drinking in combination with statins use may be synergistic to confer a lower risk of all-cause mortality [63]. Concurrent heavy drinking with warfarin enhance the anticoagulant effect and may lead to major bleeding [64]. In the present meta-analyses, most (9 out of 14) but not all included studies adjusted for medication use (including antihypertensives, cholesterol-lowering and oral antiplatelet agents) in their most-adjusted models and so there is a possibility of residual confounding by medications. However, sensitivity analyses showed consistent results when using risk estimates that were only adjusted for age, sex and smoking, suggesting that further adjustment for medication use is unlikely to materially impact on our findings.

In the present study, no elevated risk of mortality and cardiovascular events was found at higher levels of alcohol consumption, which is in line with other meta-analysis among CVD patients [10, 65] but contradicts evidence from some of the general population studies [66, 67]. The discrepancy between the present study and previous general population studies may be partly due to the generally older age of CVD patients. The mean/median age at baseline was greater than 59 years in most datasets used in our analyses. Because alcohol-related risk is relatively higher among younger people compared with the elderly [68], enrolling older participants in studies would minimise the risk relationship compared with an analysis that included drinkers of all ages. Notably, with older age of the study participants comes increased likelihood for drinkers to become former drinkers, which might exacerbate the "sick quitters" bias (i.e. when the non-drinking reference group also includes former drinkers who have stopped drinking due to poor health) as discussed above. Patients who drink heavily and enrolled in studies at older ages are more likely to represent "healthy survivors" or have safer drinking patterns [60, 69]. Particularly heavy drinkers are known to be under-represented in some datasets used in our analyses, such as the Physicians' Health Study [70] and HSE/SHeSs [71]. These potential selections may have biased downwards the estimated associations between heavy intake and risks of mortality and subsequent events.

Furthermore, most included studies did not capture the extremes of drinking and therefore may be underpowered to look at the effects of very heavy drinking. Consequently, the absence of effects at higher levels of consumption seen in our study should be interpreted cautiously, particularly in light of the increasing concerns about alcohol misuse among older people [72] as well as the known wider health and societal impacts in regard to these [73].

The present study has some further limitations. First, as a composite of cardiac mortality and several non-fatal cardiovascular endpoints, the definition of cardiovascular events varied across the three published studies [12, 41, 43], and thus, we defined the outcome in UK Biobank using the most frequently reported events in these studies. However, there was still a significant heterogeneity in the pooled analysis. Recent observational and genetic evidence has suggested that drinking at moderate levels is associated with a decreased risk of some but not all forms of CVD [6, 74–76]. Therefore, this heterogeneity might have reflected the complex and diverse impacts of alcohol consumption on different CVD outcomes.

Secondly, our results must be interpreted with caution when it comes to some subgroups that have been examined in only a limited number of studies. Although the included studies scored as moderate-to-high quality on the Newcastle-Ottawa Scale, this may not account for some pertinent design/reporting characteristics of many of the studies which had problems that were specific to alcohol exposure and not covered in the scale. For example, by relying upon only a single measurement of alcohol consumption, some studies did not consider the effect of temporal changes in drinking behaviour both after primary event and during follow-up; however, our results remained consistent in the analyses restricted to studies using post-event or multiple measures. Further analyses for beverage type were not possible with sufficient beverage-specific data reported in very few studies.

Thirdly, episodic heavy drinking has been suggested to modify the relationship between average alcohol consumption and CVD/mortality risk [77]. Our results might have been confounded by the drinking pattern, as the selected studies did not exclude "binge" drinkers. Additionally, as with all observational studies and self-reported alcohol intake, our findings are prone to bias; however, self-reported drinking data was validated against high-density lipoprotein cholesterol and gamma-glutamyl transferase in HSE/SHeSs and UK Biobank (see Additional file 1: Table S6). Although we attempted to minimise confounding by using the most adjusted estimates, information on dietary habits or physical activity was not available in all studies included in our meta-analysis and residual confounding may still persist.

Conclusions

In summary, our study shows that an alcohol intake up to about 105g (or equivalent to 13 UK units, with one unit equal to half a pint of beer/lager/cider, half a glass of wine, or one measure of spirits) a week is associated with lower risks of both mortality and subsequent cardiovascular events among CVD patients. While this threshold is somewhat lower than those recommended in most current guidelines, specific recommendations regarding the downward revision of such guidelines cannot be made. There is some indication that reductions in risk may have been overestimated by studies using a referent group contaminated by less healthy former drinkers. No evidence of elevated risk among heavy drinkers was found but this was potentially attributable to selections and under-representation of such drinkers in the datasets. Moreover, when developing drinking thresholds for use within guidelines, we must consider the totality of evidence and balance pragmatic concerns [78]. Our findings therefore indicate that, for secondary prevention of CVD, current drinkers may not need to stop drinking but should be informed that lower levels of intake (up to 105g/week) may be associated with reduced risks. However, non-drinking patients should not be encouraged to take up light drinking because of well-known adverse effects on other health outcomes, such as cancers [79].

Abbreviations

AHA: American Heart Association; BMI: Body mass index; CI: Confidence interval; CVD: Cardiovascular disease; FP2: Second-degree fractional polynomial model; HES: Hospital Episode Statistics; HR: Hazard ratio; HSE: Health Survey for England; IQR: Interquartile range; MI: Myocardial infarction; RR: Relative risk; SHeSs: Scottish Health Survey

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-021-02040-2.

Additional file 1: Supplementary Materials. Supplementary methods for de novo cohort analyses (**Appendix S1** and **Table S1**). Quality assessment checklist (**Appendix S2**). Literature search strategy (**Table S2**). Alcohol consumption, effect estimates, and confounder adjustment reported by studies selected for meta-analyses (**Table S3-S5**). Associations of alcohol intake with HDL-cholesterol and gamma-glutamyl transferase in UK Biobank and HSE/SHeSs (**Table S6**). Schoenfeld residuals (**Figure S1**). Results of subgroup and sensitivity analyses for dose-response relationship between alcohol consumption and risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (**Figure S2, S7-S12**). Patients inclusion flowchart for HSE/SHeSs and UK Biobank (**Figure S3**). Association of drinking categories with all-cause mortality, cardiovascular mortality, and cardiovascular events by cohort, sex, and primary events (**Figure S4-S5**). Study flow diagram (**Figure S6**). Funnel plots (**Figure S13**).

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Not applicable.

Authors' contributions

All authors contributed to study design. CD searched the literature. CD, DON, and AB selected the studies and extracted the data. CD analysed the data

and wrote the first draft of the manuscript. ES led the data acquisition and harmonisation of the HSE/SHeSs. DON, SB, and AB were involved in the interpretation of results and critically reviewed the manuscript. All authors approved the submission of the final manuscript.

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Availability of data and materials
Data from UK Biobank (http://www.ukbiobank.ac.uk/) and the Health Survey for England and the Scottish Health Survey (https://www.ukdataservice.ac.uk/) are available to researchers upon application.

Declarations

Ethics approval and consent to participate
This study is a secondary analysis of previously collected data and so additional ethical approval was not required. Ethics approvals for HSE 1994-97 were granted by Local Research Ethics Committees in England, HSE 1998-99 by London North Thames Multicentre Research Ethics Committee (MREC/97/2/9, MREC/98/2/89), HSE 2000-07 by London Multicentre Research Ethics Committee (MREC/99/2/91, MREC/00/2/81, MREC/01/2/82, MREC/02/2/72, MREC/03/2/97, 04/MRE02/50, 05/MRECO2/47, 06/MRE02/62), and HSE 2008 by Oxford A-Research Ethics Committee (07/H0604/102). SHeSs 1995 and 1998 were approved by all fifteen of the Research Ethics Committees for all Area Health Boards in Scotland, and SHeSs 2003 by Multicentre Research Ethics Committee for Scotland. All participants gave verbal consent to be interviewed for the survey. UK Biobank received approval from the North West Centre for Research Ethics Committee (11/NW/0382) and all participants gave written informed consent.

Consent for publication
Not applicable.

Competing interests
Dr Steven Bell is Editorial Board Member for BMC Medicine. The authors declare that they have no competing interests.

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Publisher's Note

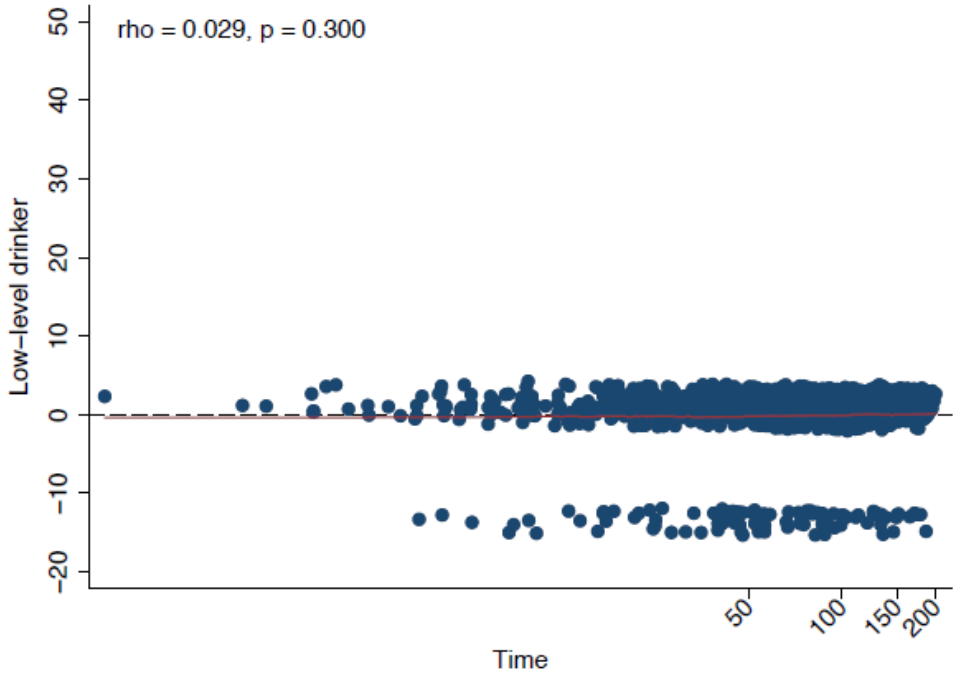
Appendix 2.2 ICD and OPCS codes used in analyses of UK Biobank and HSE/SHeSs

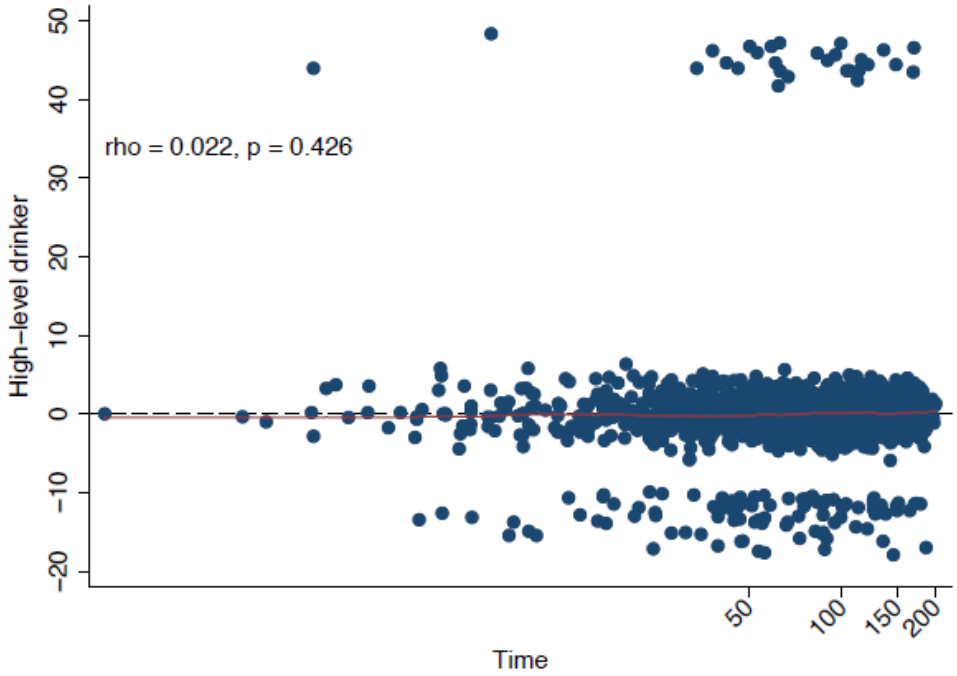
Angina [136]		
ICD-9	411, 4119, 413, 4139	
ICD-10	I20, I20.0, I20.1, I20.8, I20.9	
MI [133]		
ICD-10	MI, unclassified	I21, I22, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.1, I25.2
ICD-10	ST elevation MI	I21.0, I21.1, I21.2, I21.3, I22.0, I22.1, I22.8
ICD-10	Non-ST elevation MI	I21.4, I21.9, I22.9
Stroke [134]		
ICD-10	Ischaemic stroke	I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64.X
ICD-10	Intracerebral haemorrhage	I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9
ICD-10	Subarachnoid haemorrhage	I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9
Heart failure [302]		
ICD-10	I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.8, I42.9, I50.0, I50.1, I50.9	
Sudden death [303]		
ICD-10	I46.1, I49.9, R96, R96.0, R96.1	
Revascularization procedures [304]		
OPCS4	Coronary artery bypass graft	K40, K41, K42, K43, K44, K45, K46
OPCS4	Percutaneous transluminal coronary angioplasty	K49, K50, K75

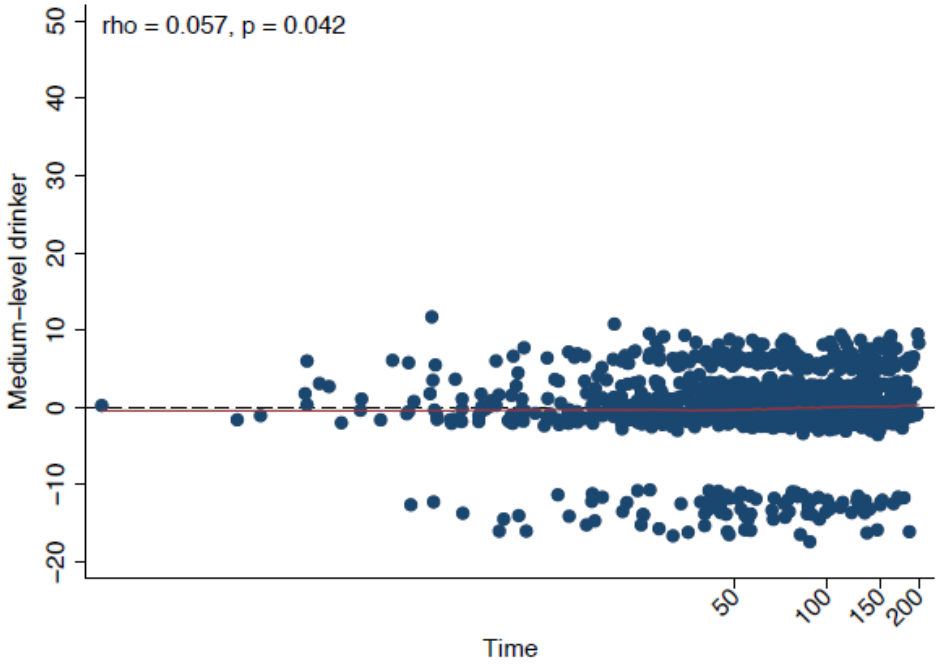
ICD=the International Classification of Diseases, MI=myocardial infarction, OPCS=OPCS Classification of Interventions and Procedures

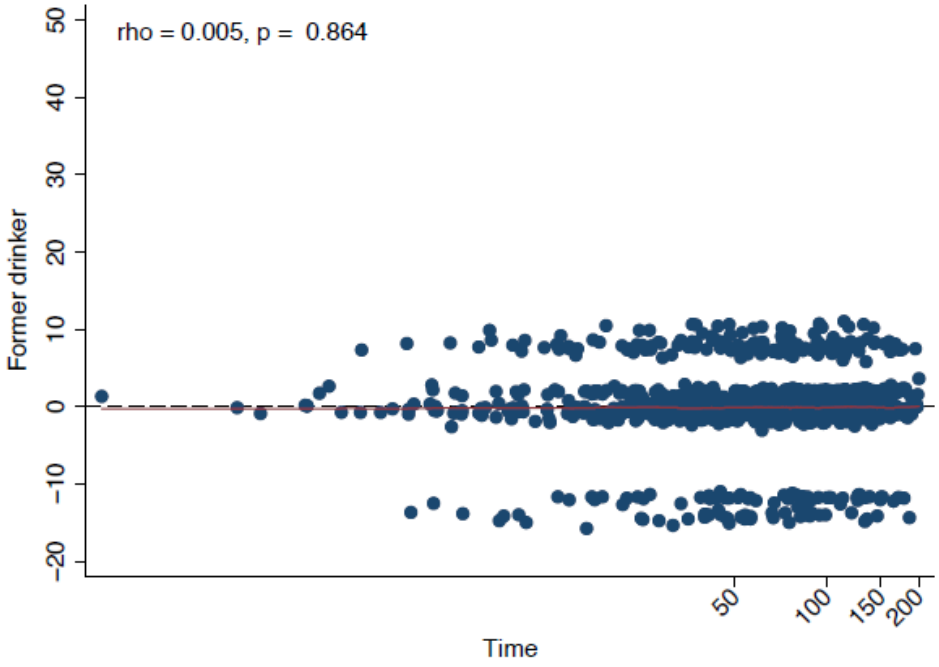
Appendix 2.3 Schoenfeld residuals for UK Biobank and HSE/SHeSs

(a) All-cause mortality for Health Survey for England/Scottish Health Survey models

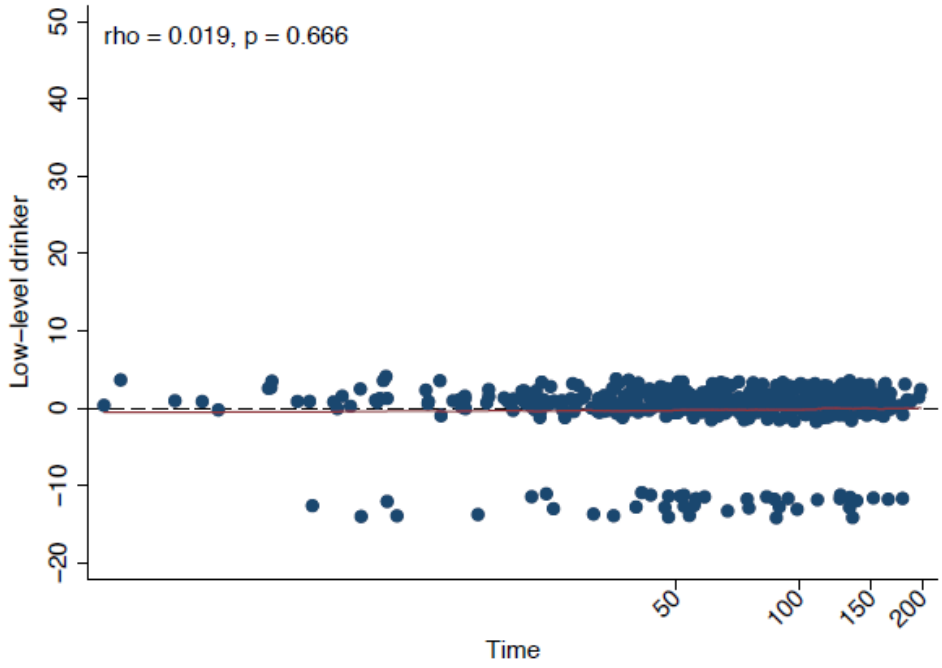


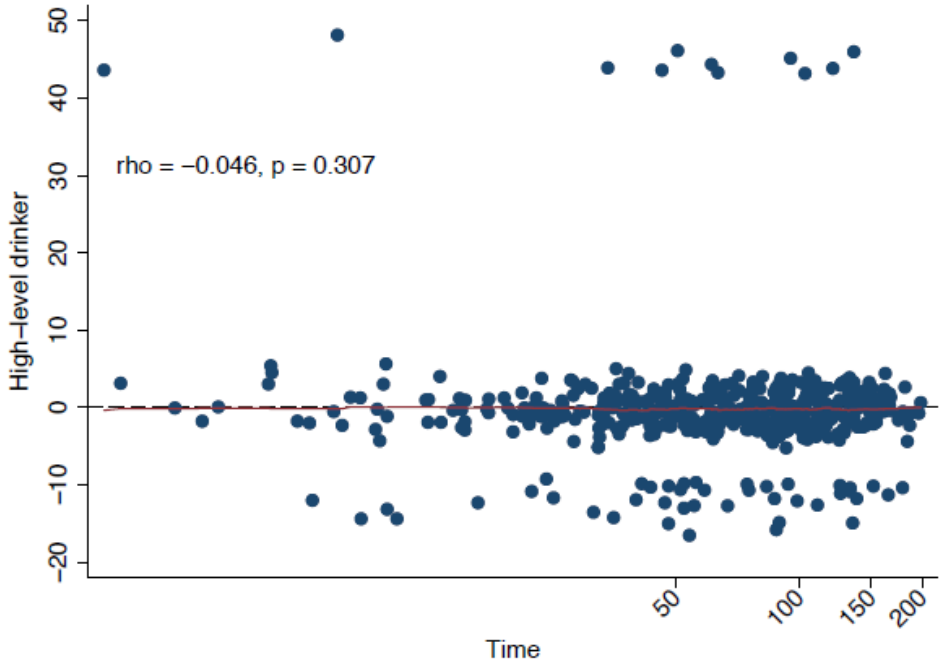


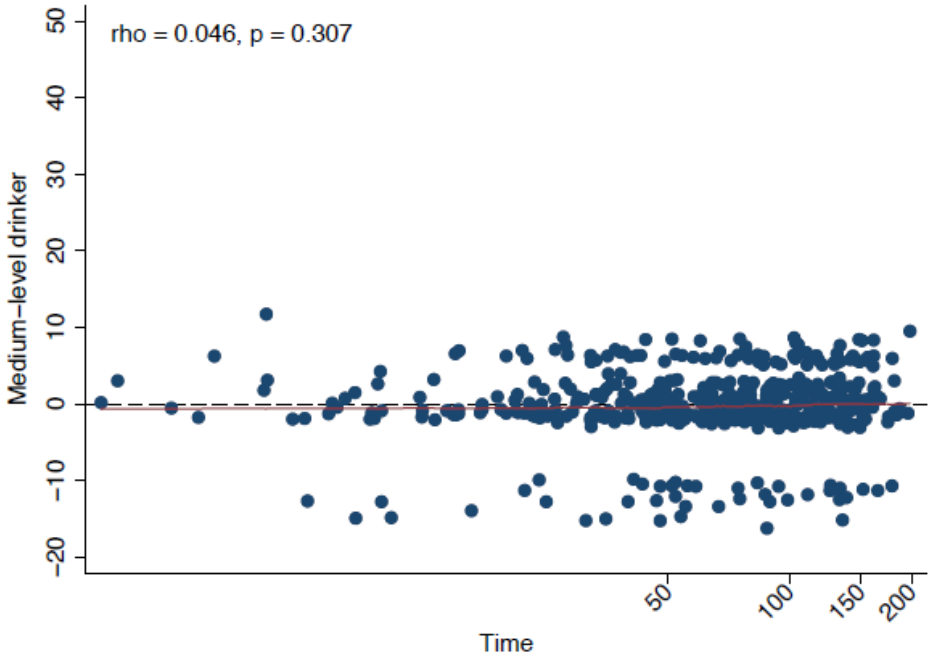

rho = 0.057, p = 0.042
Medium−level drinker
50
40
30
20
10
0
−10
−20
50
100
150
200
Time

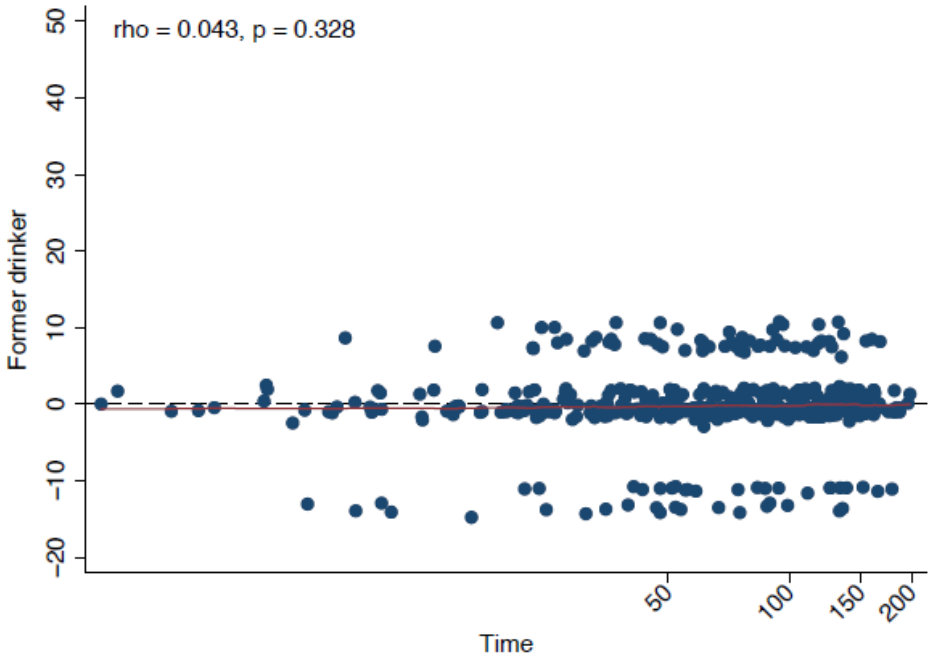

rho = 0.005, p = 0.864
Former drinker
50
40
30
20
10
0
−10
−20
50
100
150
200
Time

(b) Cardiovascular mortality for Health Survey for England/Scottish Health Survey models

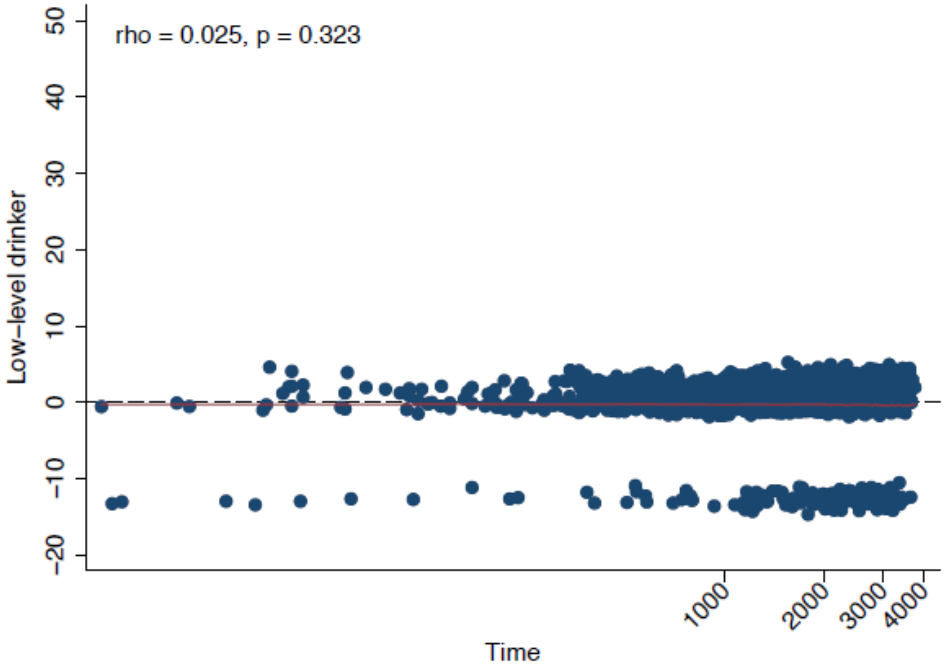


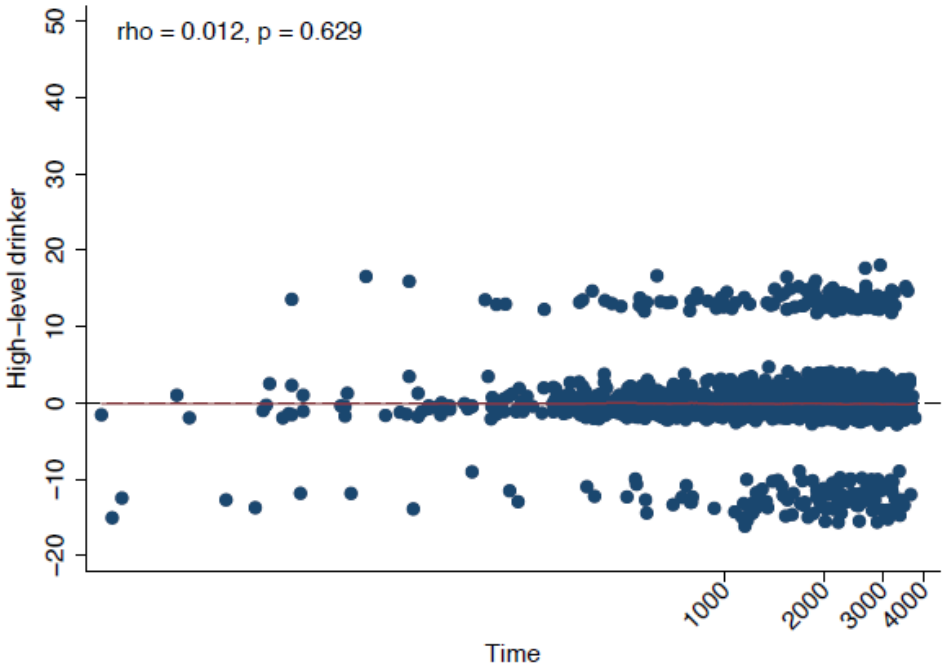


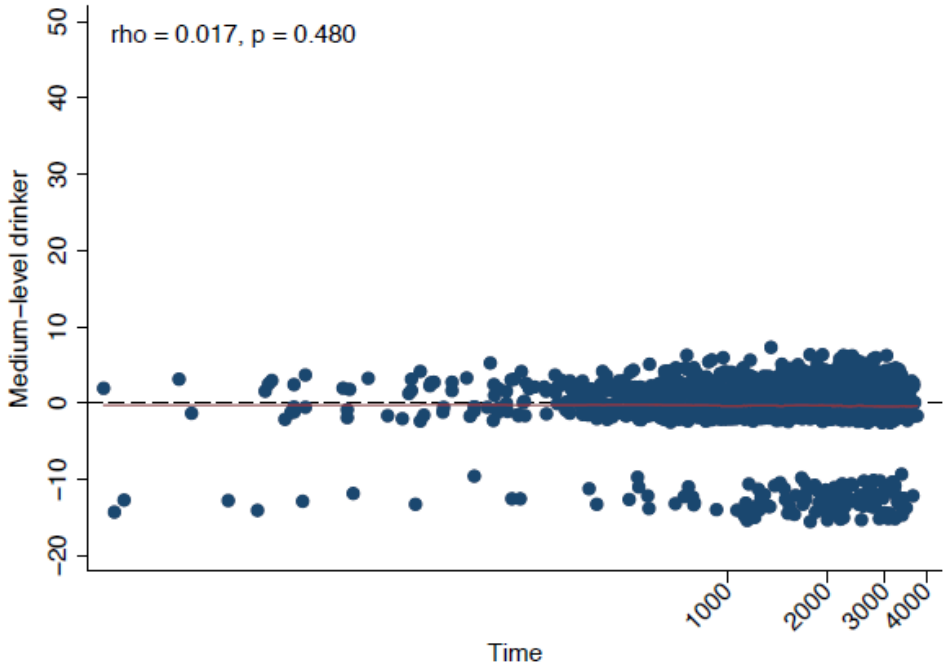

rho = 0.046, p = 0.307
Medium−level drinker
50
40
30
20
10
0
−10
−20
50
100
150
200
Time

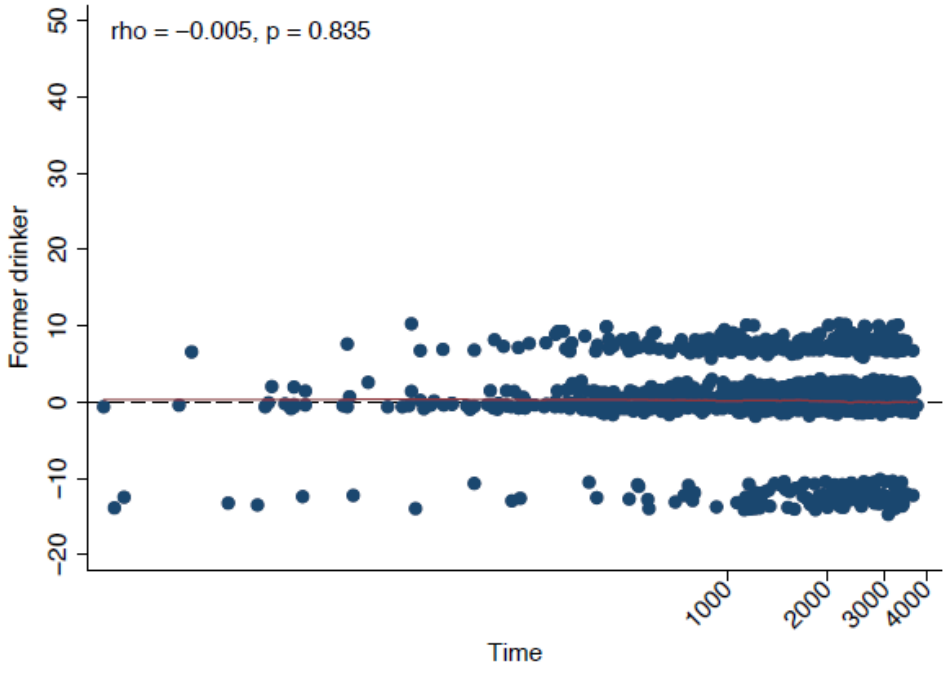

rho = 0.043, p = 0.328
Former drinker
50
40
30
20
10
0
−10
−20
50
100
150
200
Time

(c) All-cause mortality for UK Biobank models

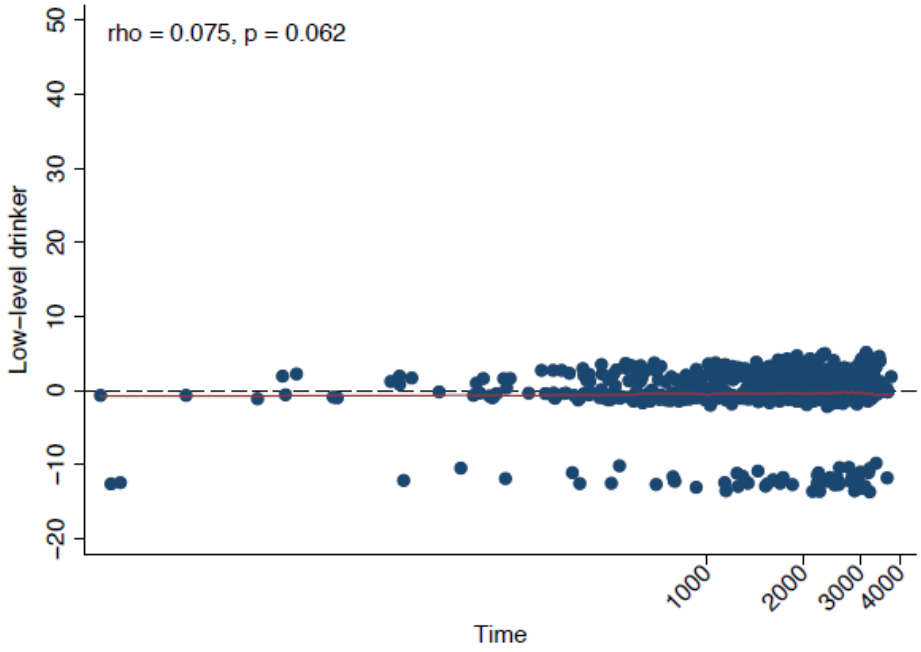


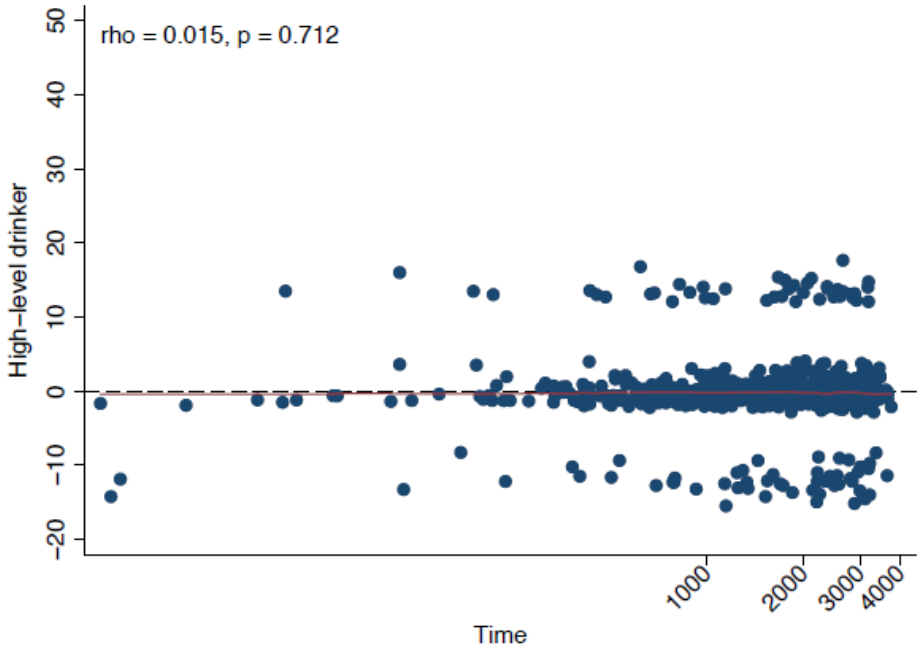


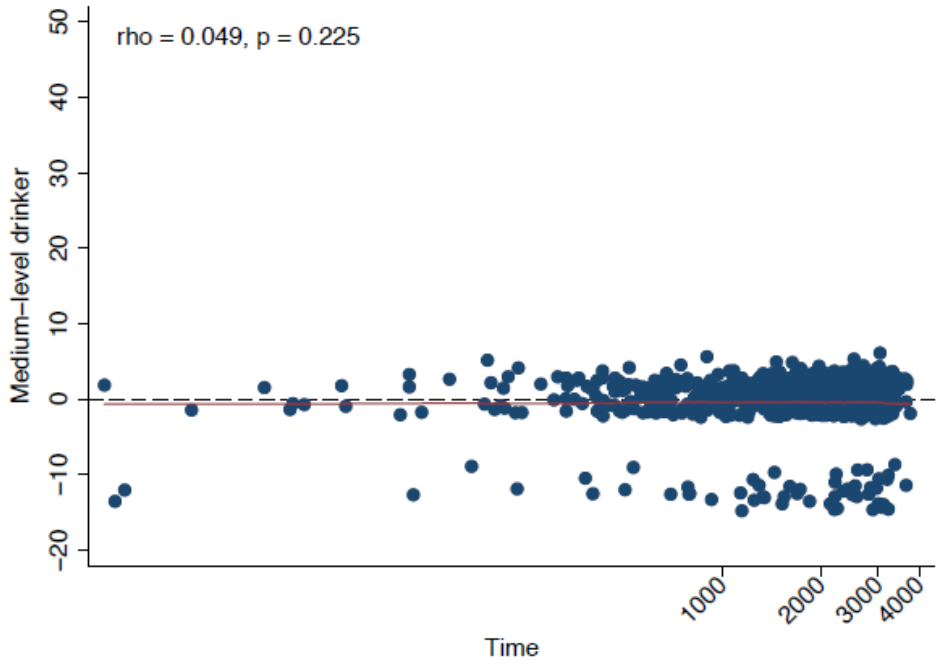

rho = 0.017, p = 0.480
Medium−level drinker
50
40
30
20
10
0
−10
−20
1000
2000
3000
4000
Time

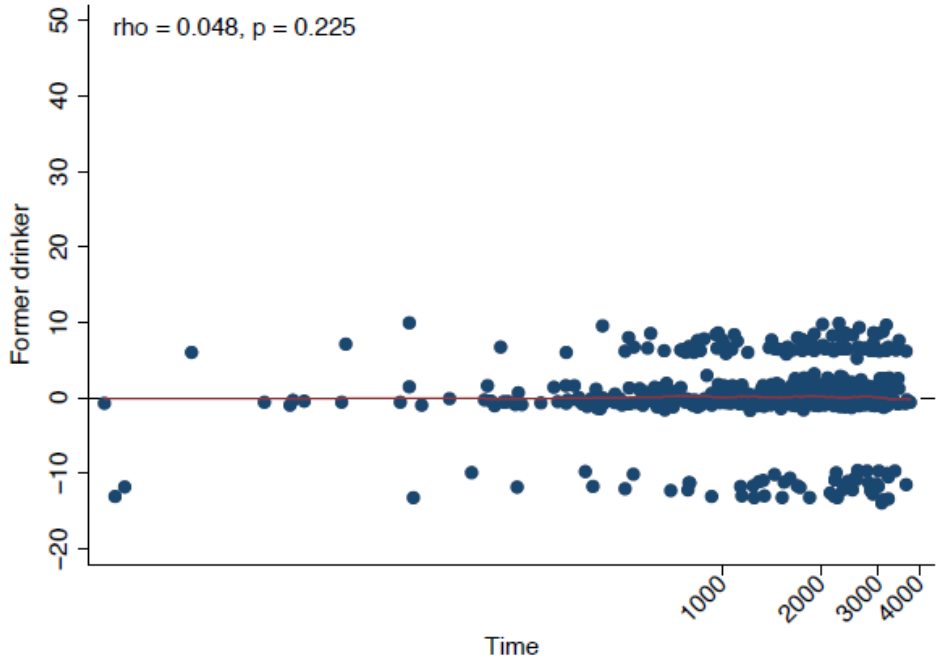

rho = −0.005, p = 0.835
Former drinker
50
40
30
20
10
0
−10
−20
1000
2000
3000
4000
Time

(d) Cardiovascular mortality for UK Biobank models

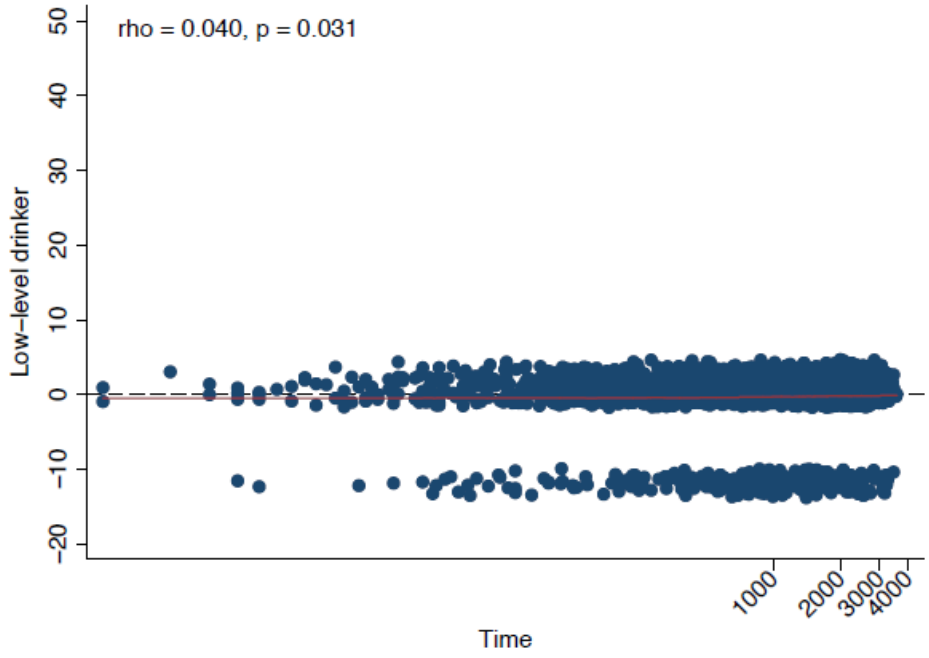


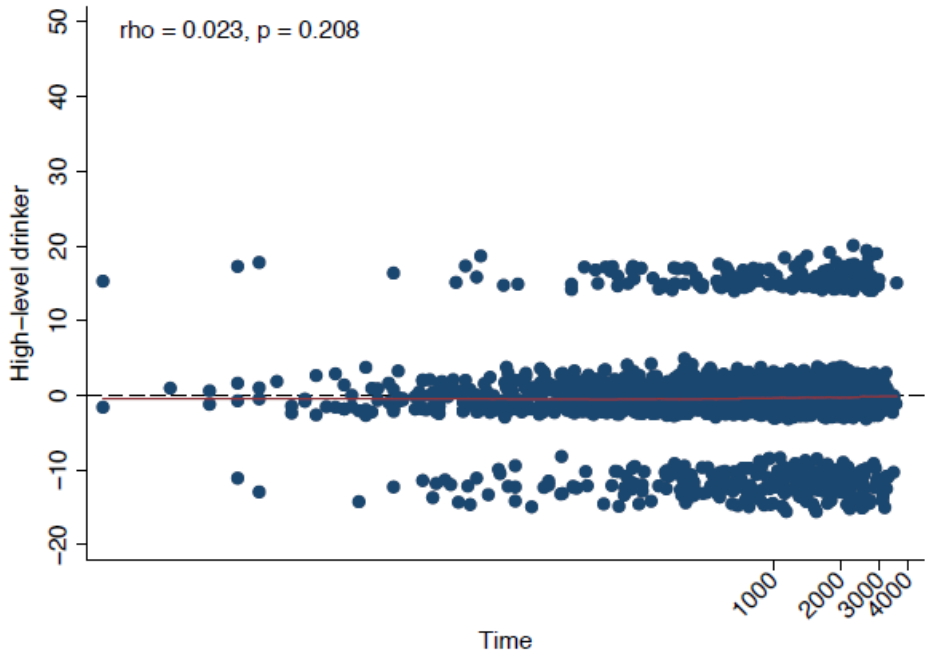


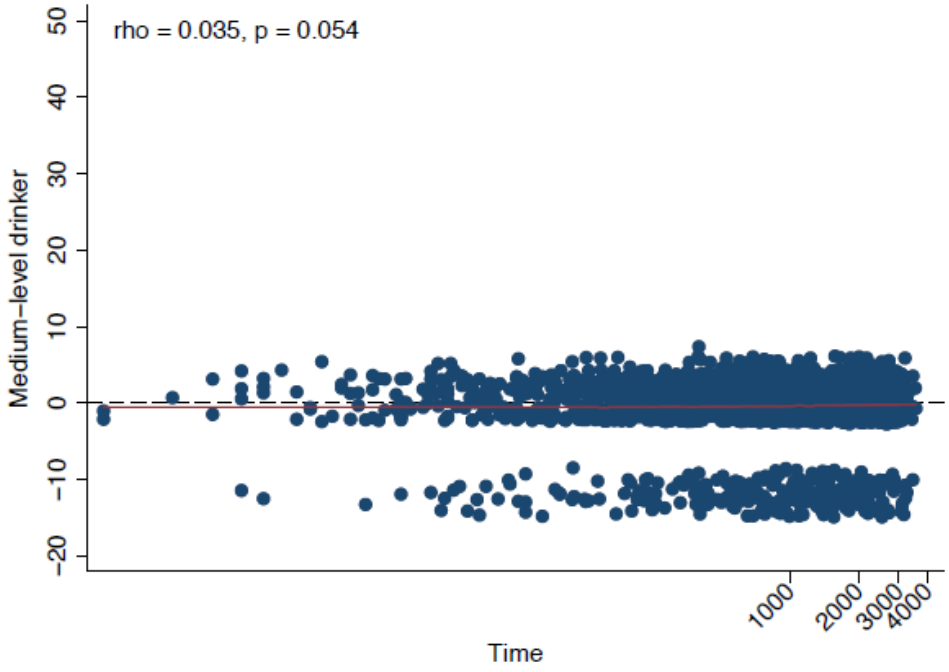

rho = 0.049, p = 0.225
Medium−level drinker
50
40
30
20
10
0
−10
−20
1000
2000
3000
4000
Time

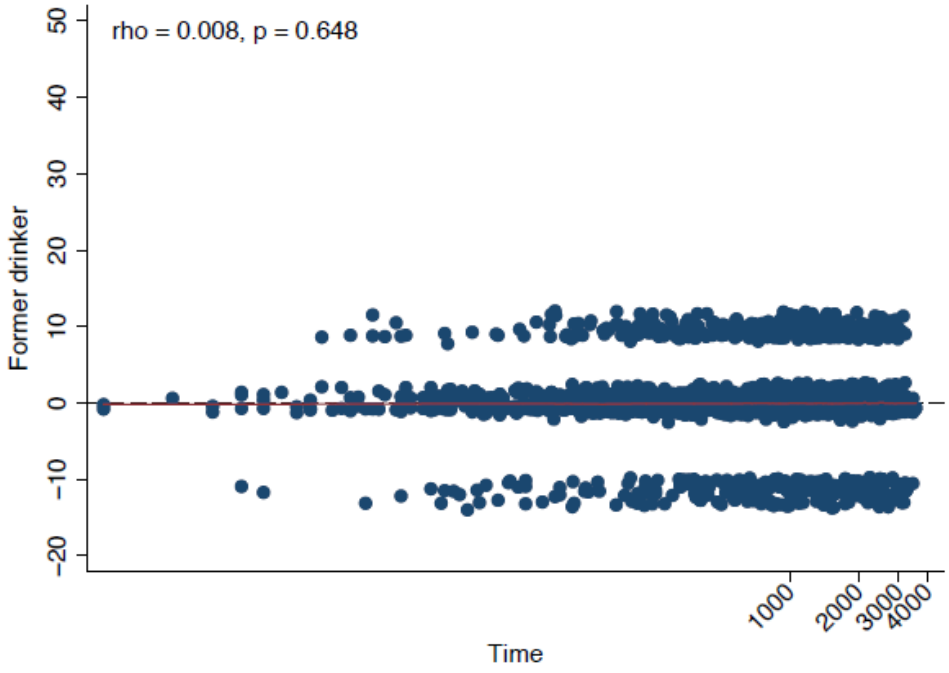

rho = 0.048, p = 0.225
Former drinker
50
40
30
20
10
0
−10
−20
1000
2000
3000
4000
Time

(e) Cardiovascular events for UK Biobank models






rho = 0.035, p = 0.054
Medium−level drinker
50
40
30
20
10
0
−10
−20
1000
2000
3000
4000
Time


rho = 0.008, p = 0.648
Former drinker
50
40
30
20
10
0
−10
−20
1000
2000
3000
4000
Time

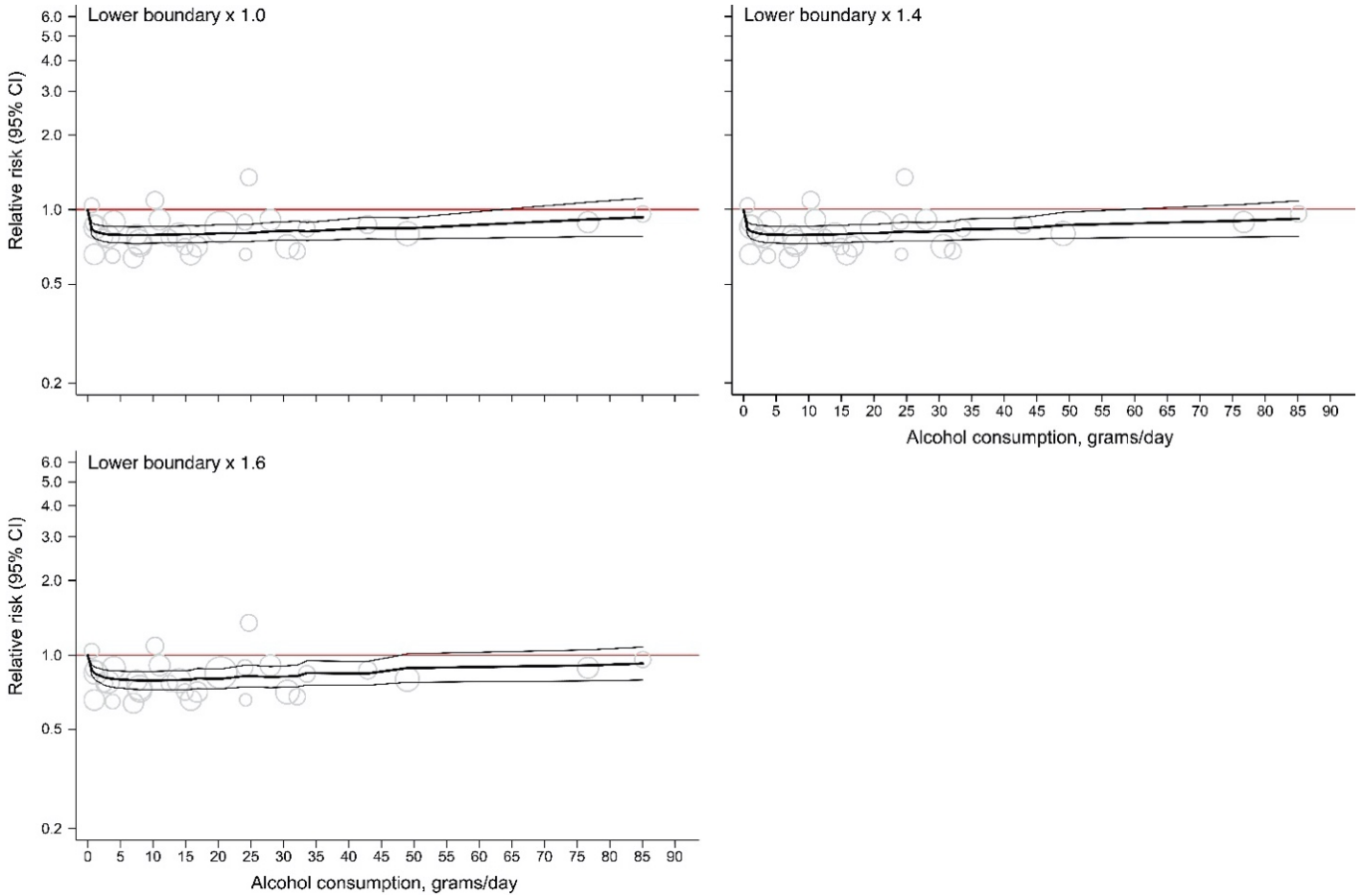
Appendix 2.4 Literature search strategy

#	Medline (Ovid)	Results
1	Alcohol Drinking/	66993
2	((alcohol or beer$1 or wine$1 or spirit or spirits or liquor$1 or liqueur$1) adj2 (intake$1 or consum$ or drink$)).ab,ti.	68862
3	exp myocardial infarction/ or exp coronary disease/	363351
4	((isch?emic heart disease$1 or IHD or myocardial isch?emia or myocardial infarct$ or MI or acute myocardial infarct$ or MI or coronary disease$1 or coronary artery disease$1 or CAD or coronary heart disease$1 or CHD or heart disease$1 or cardiovascular disease$1 or CVD or angina) adj2 (patients or people or women or men)).ab,ti.	78580
5	((myocardial infarct$ or MI or acute myocardial infarct$ or MI) adj2 (surviv$ or after or following)).ab,ti.	31387
6	exp STROKE/	134621
7	((stroke or strokes or acute cerebrovascular accident$1 or cerebrovascular accident$1 or CVA$1 or apoplexy or brain vascular accident$1) adj2 (patients or people or women or men or surviv$ or after or following)).ab,ti.	67330
8	exp cohort studies/ or exp follow-up studies/ or longitudinal studies/	2014690
9	(comment or editorial or letter or case reports or news or review or meta analysis).pt.	6532171
10	1 or 2	106345
11	3 or 4 or 5 or 6 or 7	551960
12	8 and 10 and 11	1128
13	limit 12 to humans	1128
14	13 not 9	1070
#	Embase (Ovid)	Results
1	exp drinking behavior/	47562
2	((alcohol or beer$1 or wine$1 or spirit or spirits or liquor$1 or liqueur$1) adj2 (intake$1 or consum$ or drink$)).ab,ti.	94229
3	exp heart infarction/ or exp coronary artery disease/	593221
4	((isch?emic heart disease$1 or IHD or myocardial isch?emia or myocardial infarct$ or MI or acute myocardial infarct$ or MI or coronary disease$1 or coronary artery disease$1 or CAD or coronary heart disease$1 or CHD or heart disease$1 or cardiovascular disease$1 or CVD or angina) adj2 (patients or people or women or men)).ab,ti.	115149
5	((myocardial infarct$ or MI or acute myocardial infarct$ or MI) adj2 (surviv$ or after or following)).ab,ti.	42351
6	exp cerebrovascular accident/	209214
7	((stroke or strokes or acute cerebrovascular accident$1 or cerebrovascular accident$1 or CVA$1 or apoplexy or brain vascular accident$1) adj2 (patients or people or women or men or surviv$ or after or following)).ab,ti.	111595

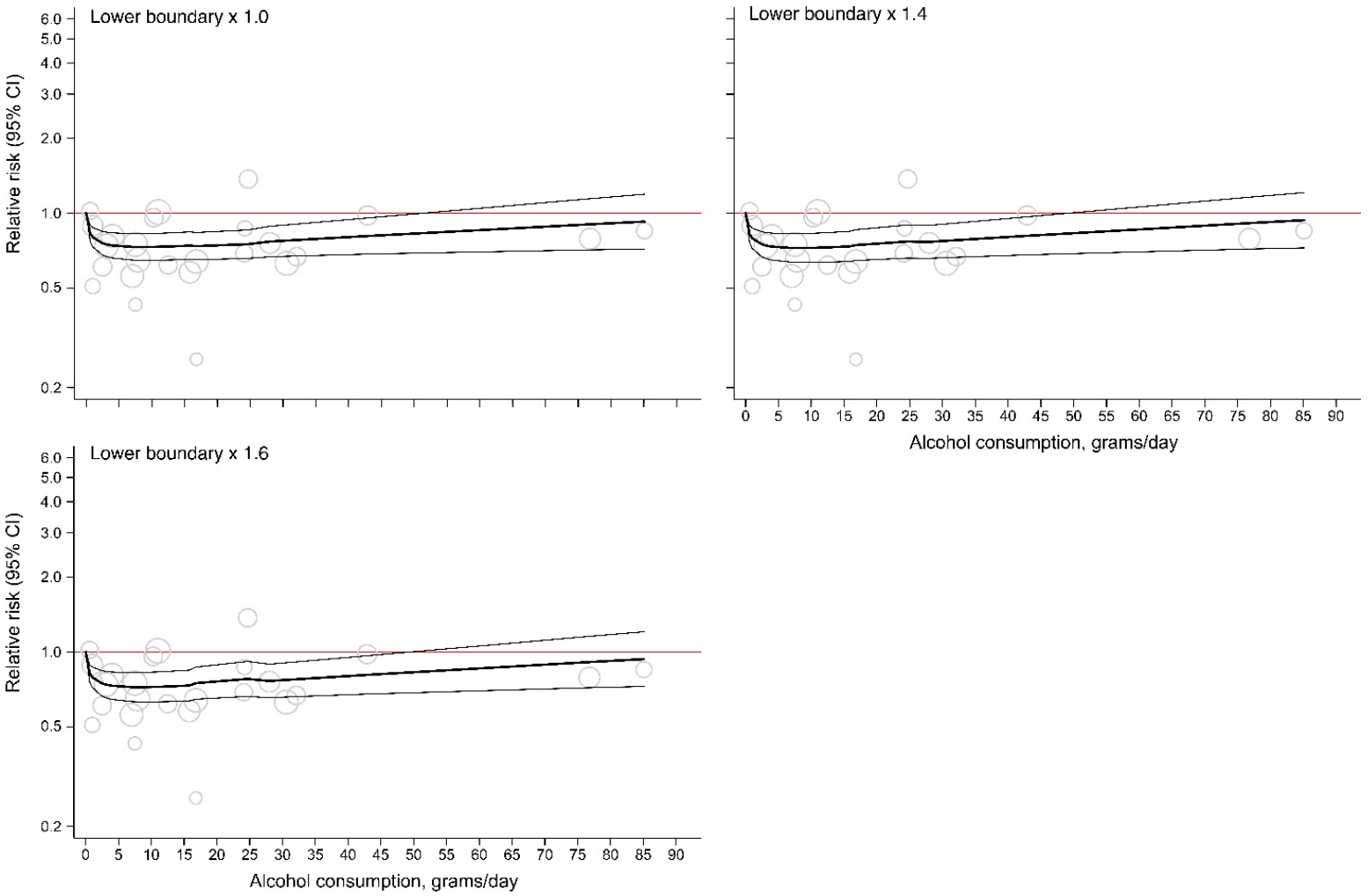
8	exp follow up/ or longitudinal study/	1663997
9	(Patent or Tombstone or Note or Editorial or Letter or Erratum or Books or Chapter or Review).pt.	5351012
10	1 or 2	122144
11	3 or 4 or 5 or 6 or 7	859770
12	8 and 10 and 11	1039
13	limit 12 to human	996
14	13 not 9	960

Appendix 2.5 Association of alcohol with mortality and cardiovascular events in CVD patients: For open-ended upper categories, mean values were defined as lower boundary×1, ×1.4, and ×1.6

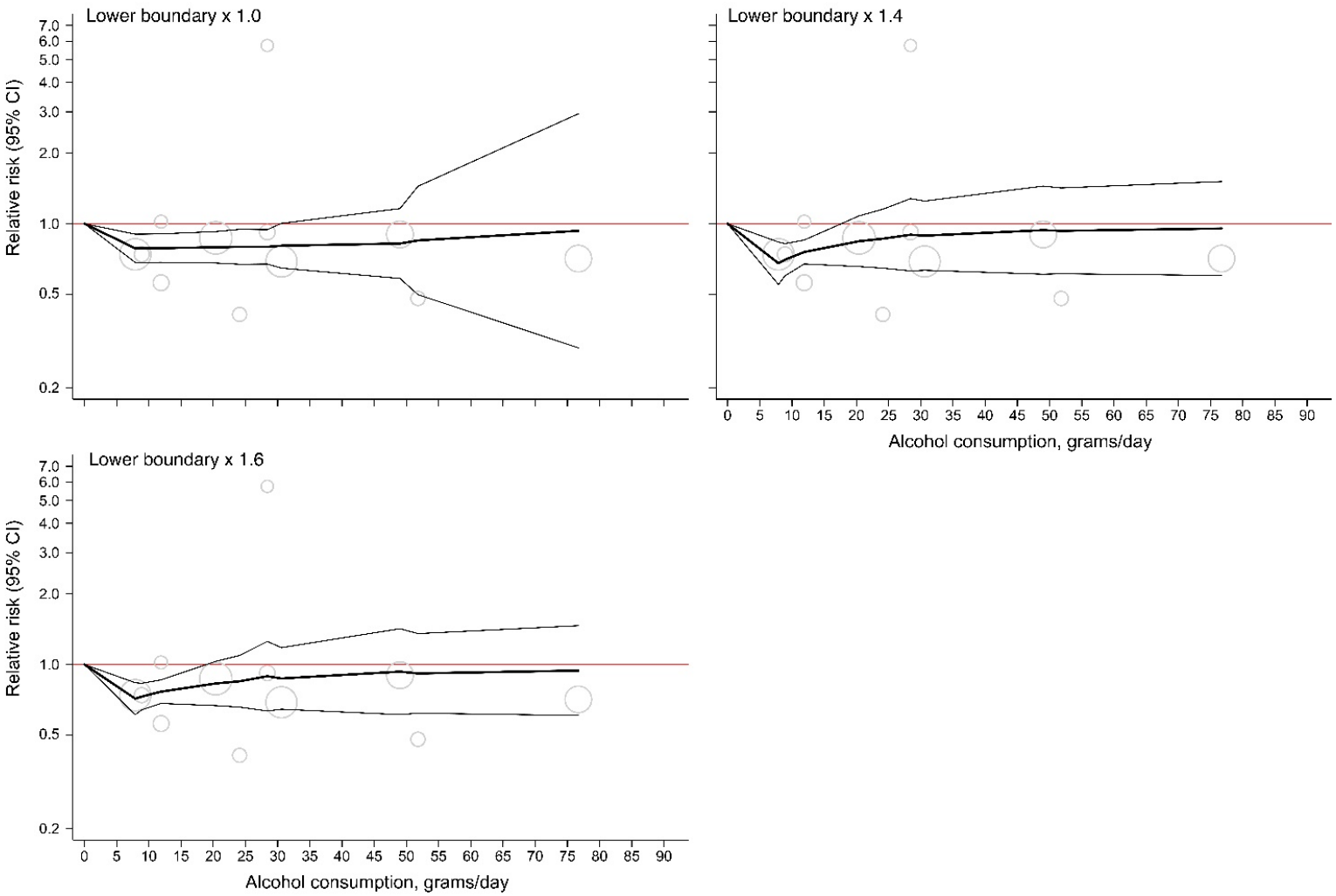
(a) All-cause mortality



(b) Cardiovascular mortality



(c) Cardiovascular events



Appendix 2.6 Quality assessment checklist

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Notes: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average current drinkers in the community *
   b) somewhat representative of the average current drinkers in the community *
   c) selected group of users (e.g., nurses, volunteers)
   d) no description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort *
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) secure record (e.g., surgical records) *
   b) structured interview *
   c) written self-report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes *
   b) no

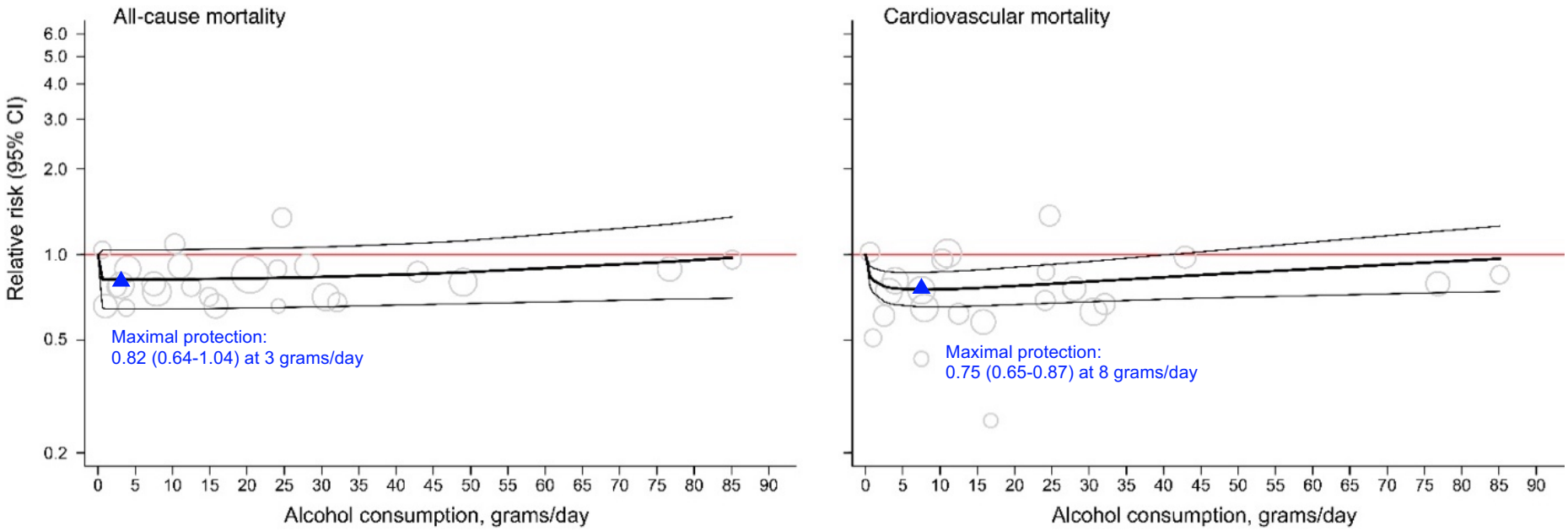
Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for smoking status *
   b) study controls for any additional factor *

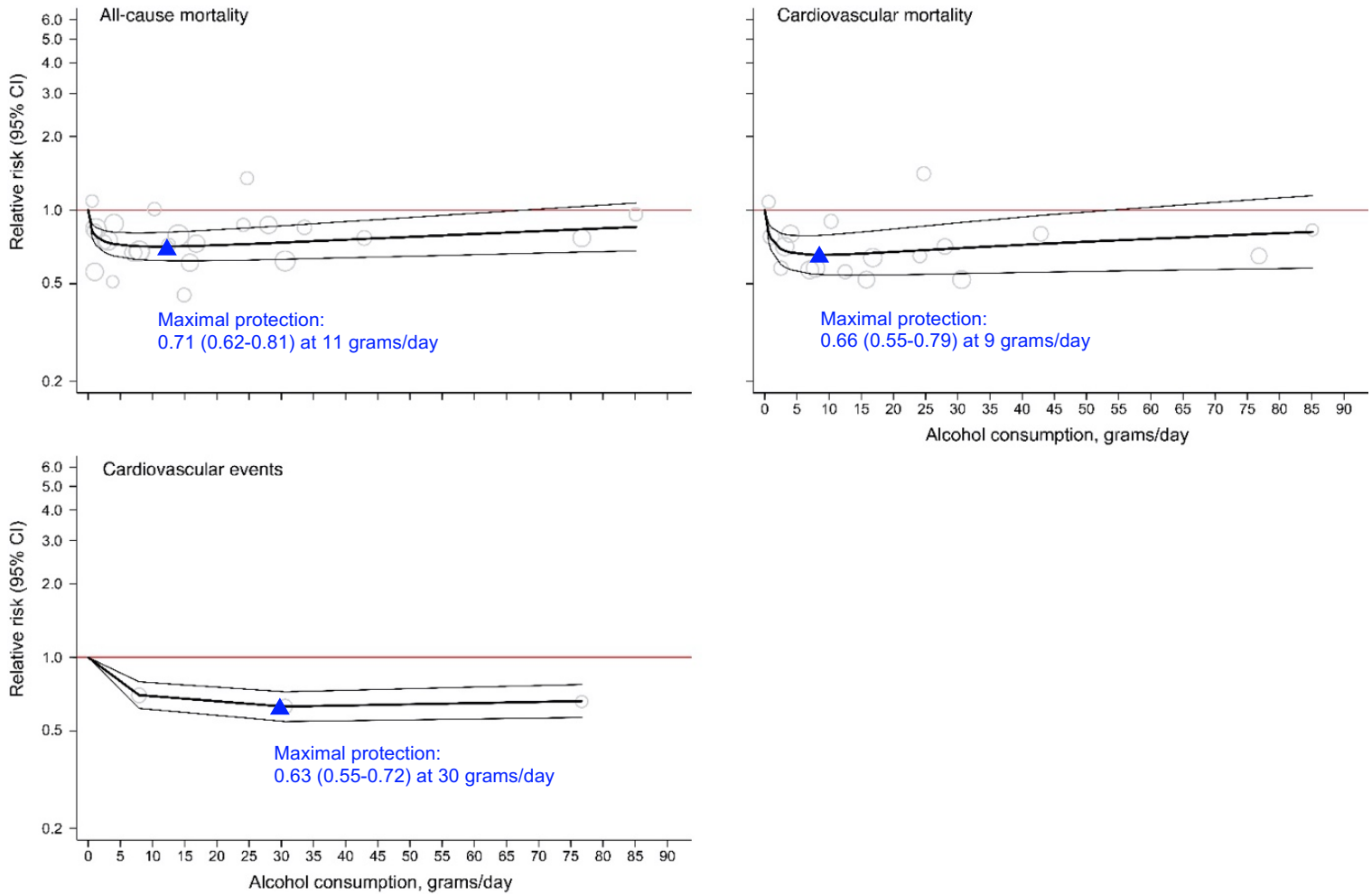
Outcome

1) Assessment of outcome
   a) independent blind assessment *
   b) record linkage *
   c) self-report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes, at least six years duration *
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up: all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias:
      small number lost (>95% follow up) or description provided of those lost *
   c) follow up rate <95% and no description of those lost
   d) no statement

Appendix 2.7 Association of alcohol with mortality and cardiovascular events in CVD patients excluding studies with a quality assessment score <7

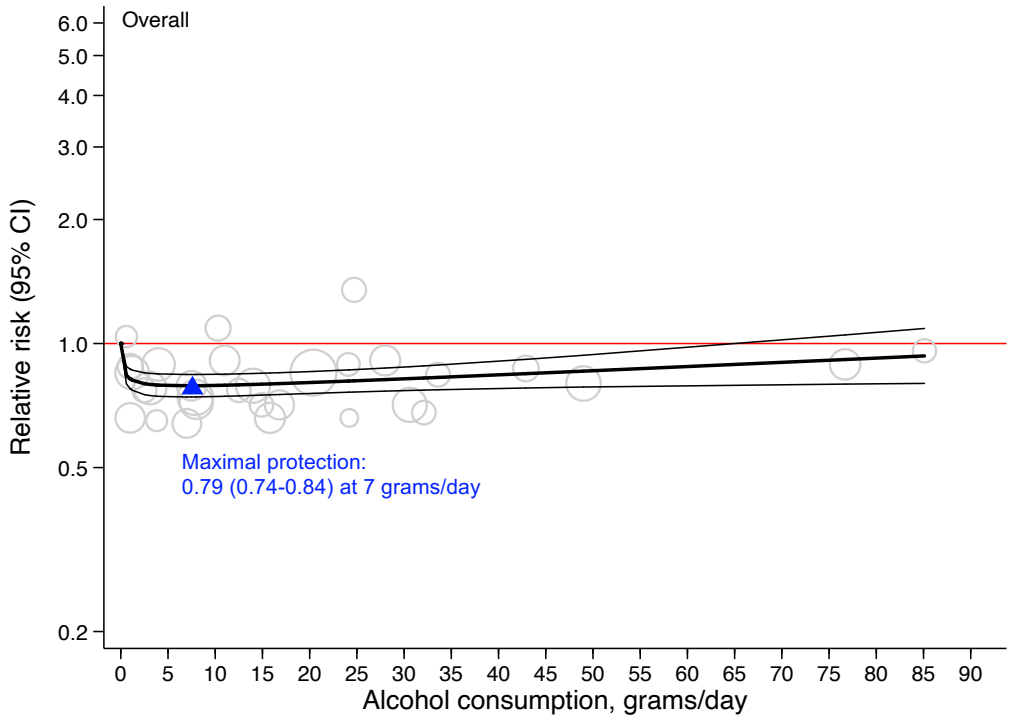


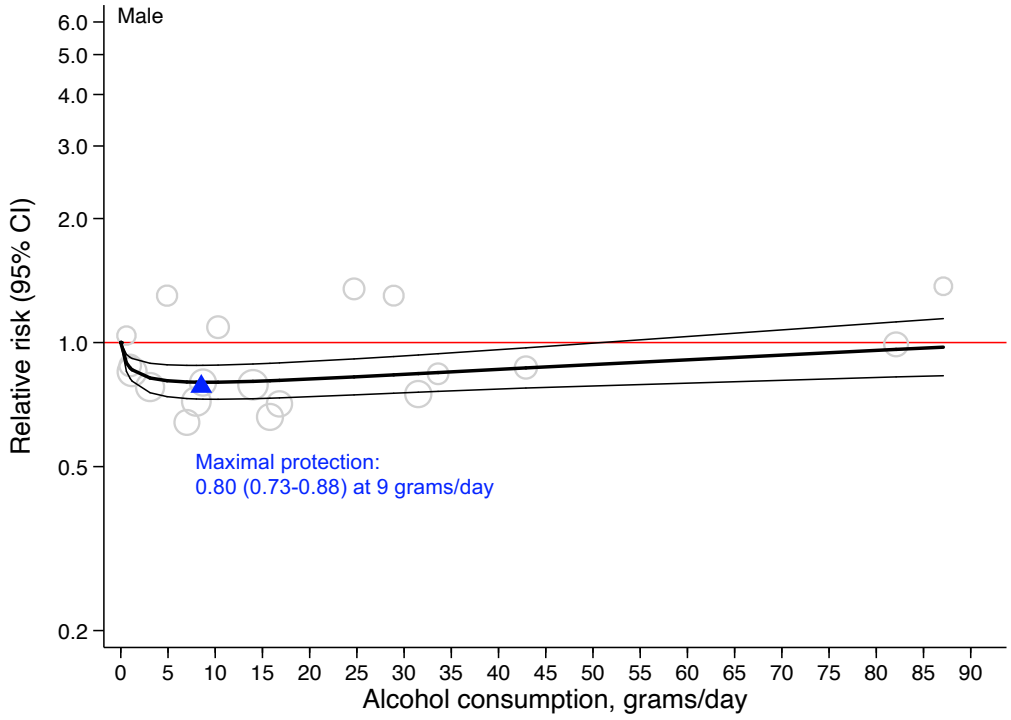
Appendix 2.8 Association of alcohol with mortality and cardiovascular events in CVD patients using least adjusted estimates (adjusted for age, sex, and smoking status only)

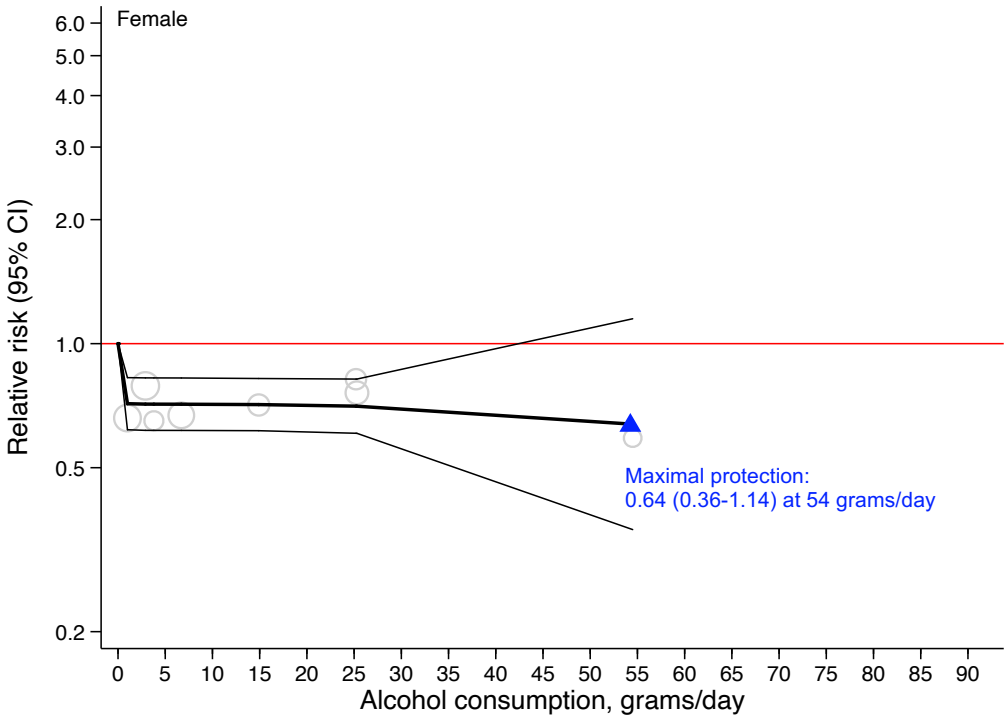


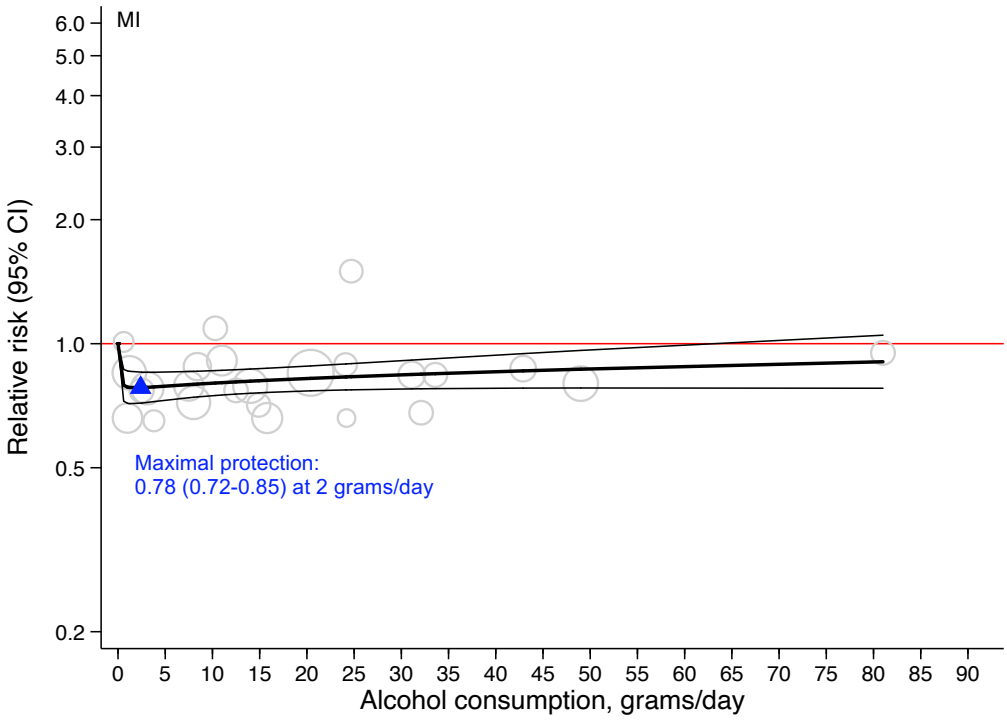
Appendix 2.9 Association of alcohol with mortality in CVD patients using a fixed effect meta-analysis model

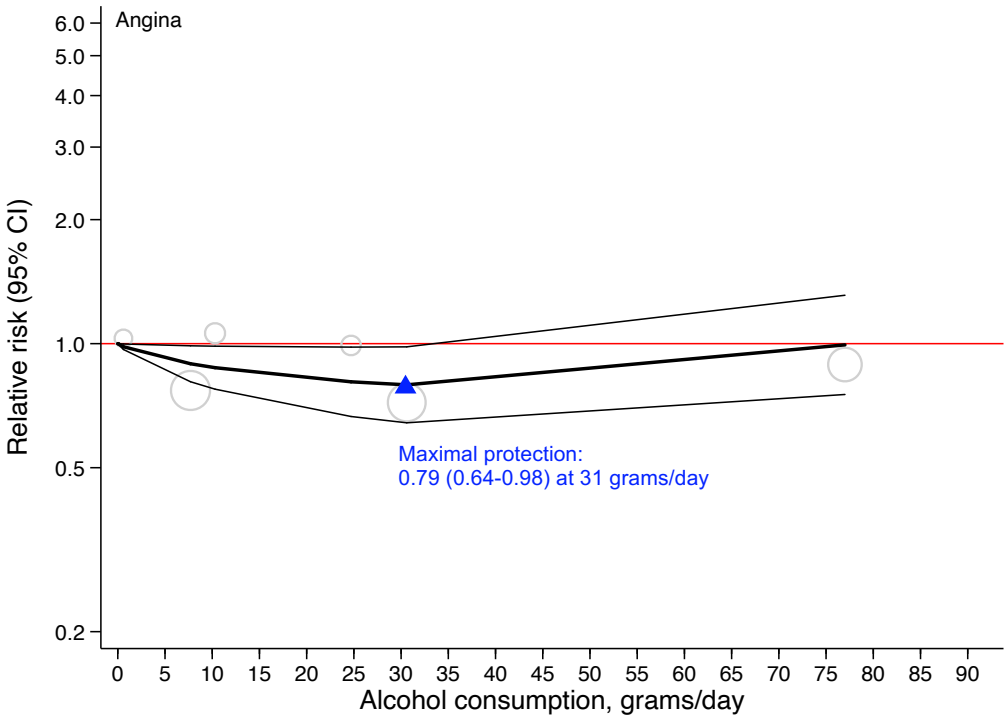
(a) All-cause mortality

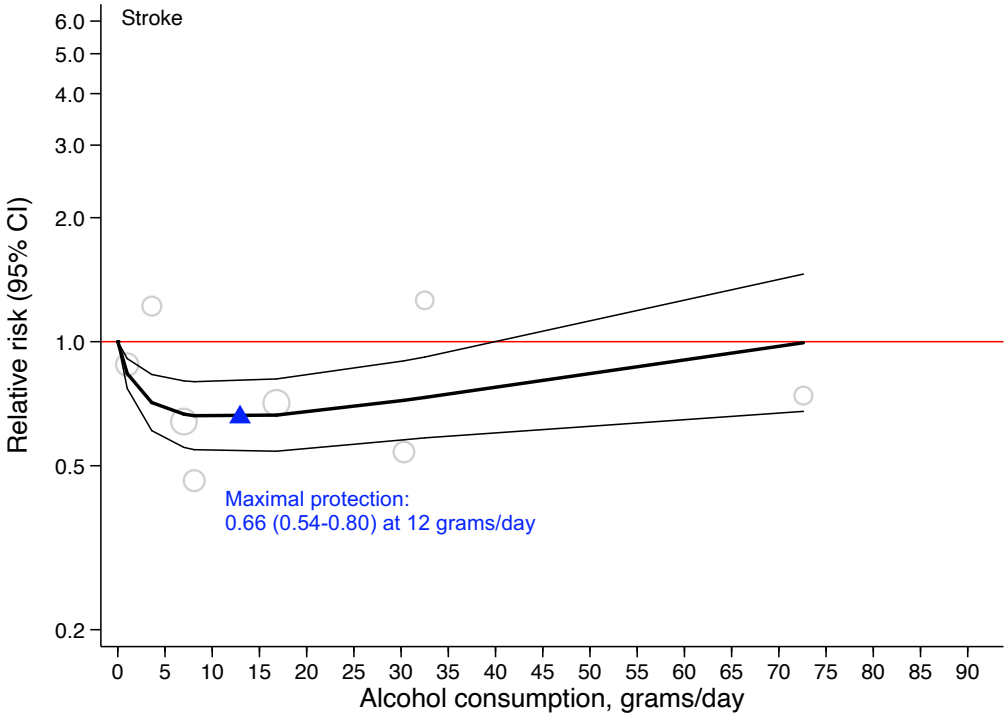


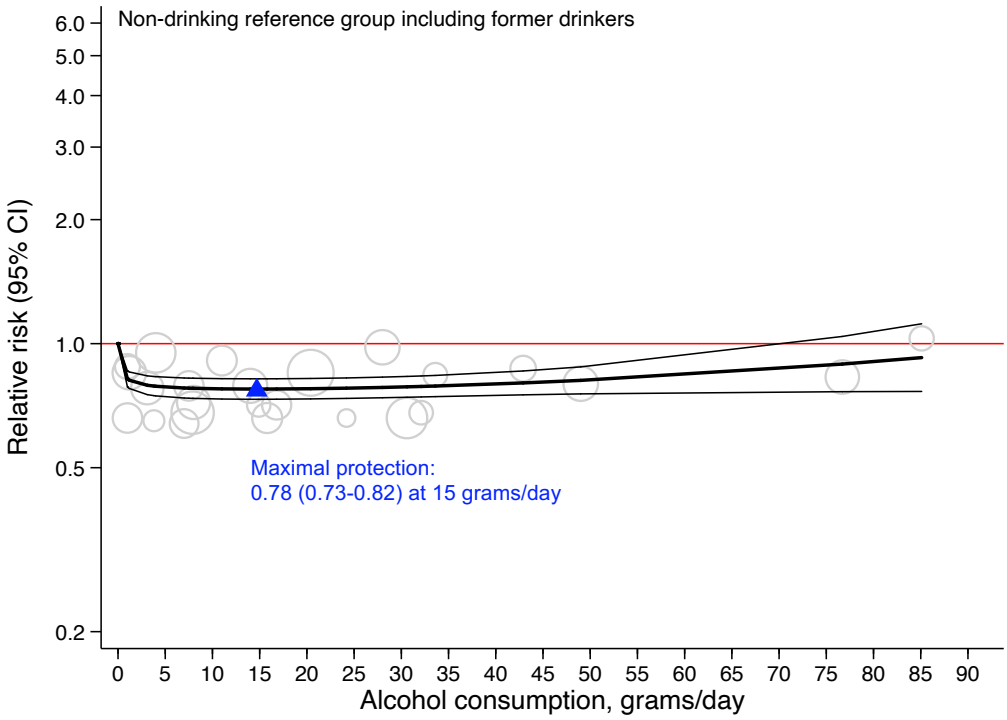


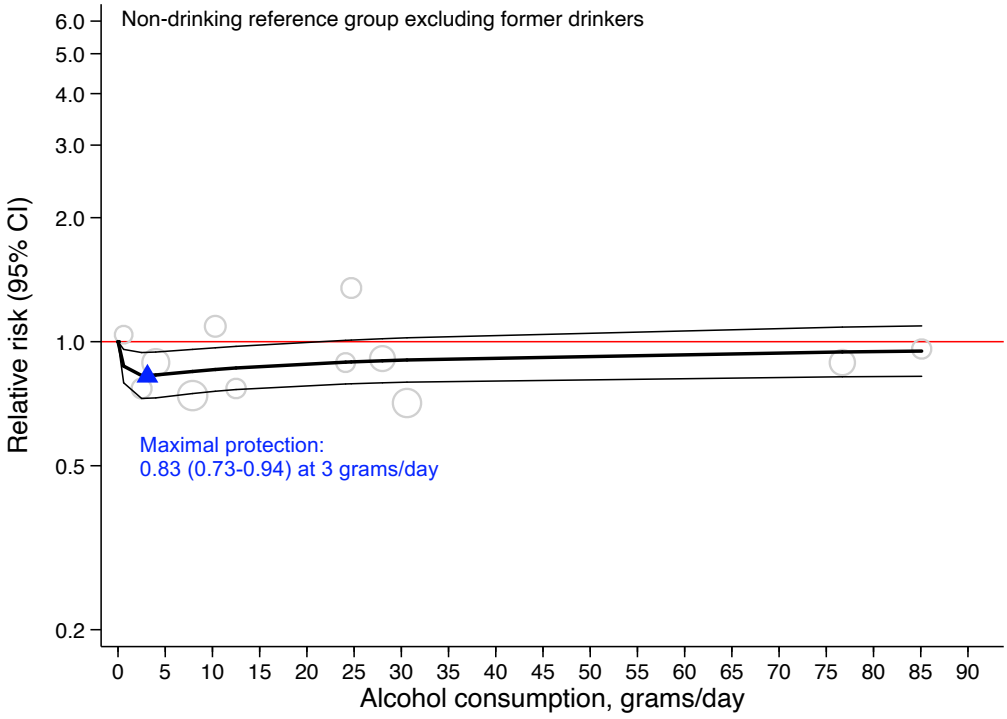

Female
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day
Maximal protection:
0.64 (0.36-1.14) at 54 grams/day

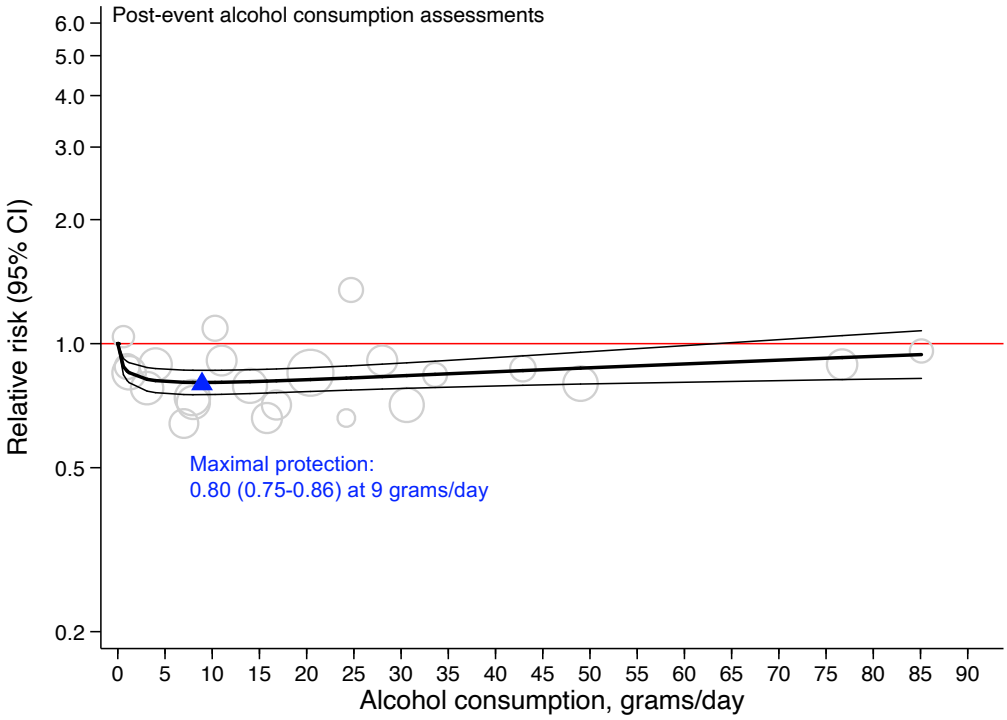

MI
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day
Maximal protection:
0.78 (0.72-0.85) at 2 grams/day

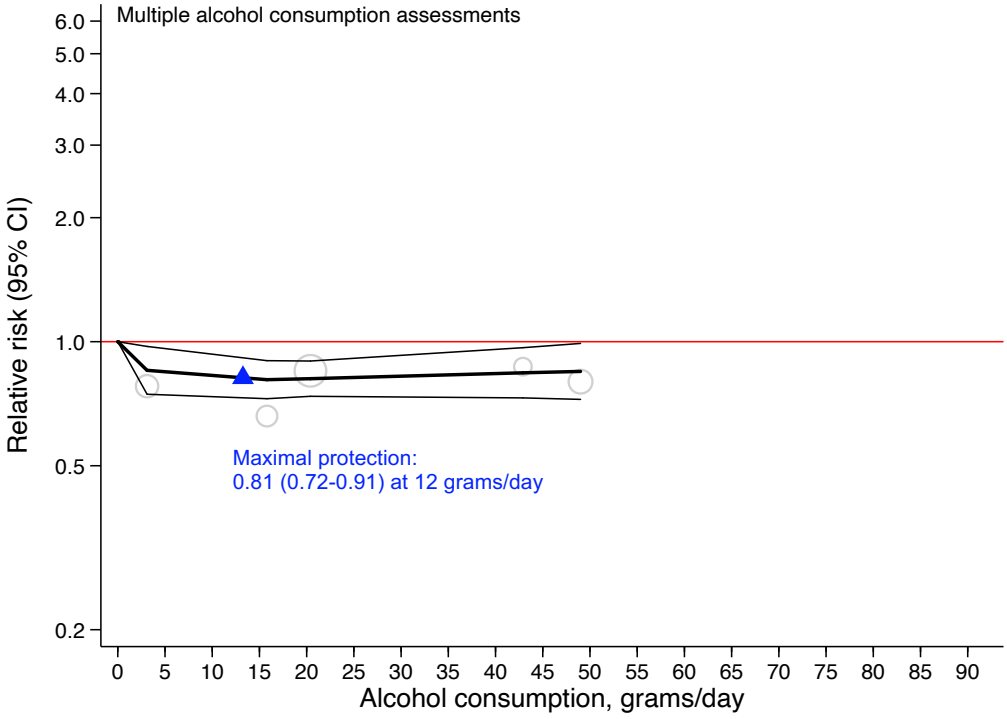

Angina
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.79 (0.64-0.98) at 31 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day


Stroke
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.66 (0.54-0.80) at 12 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

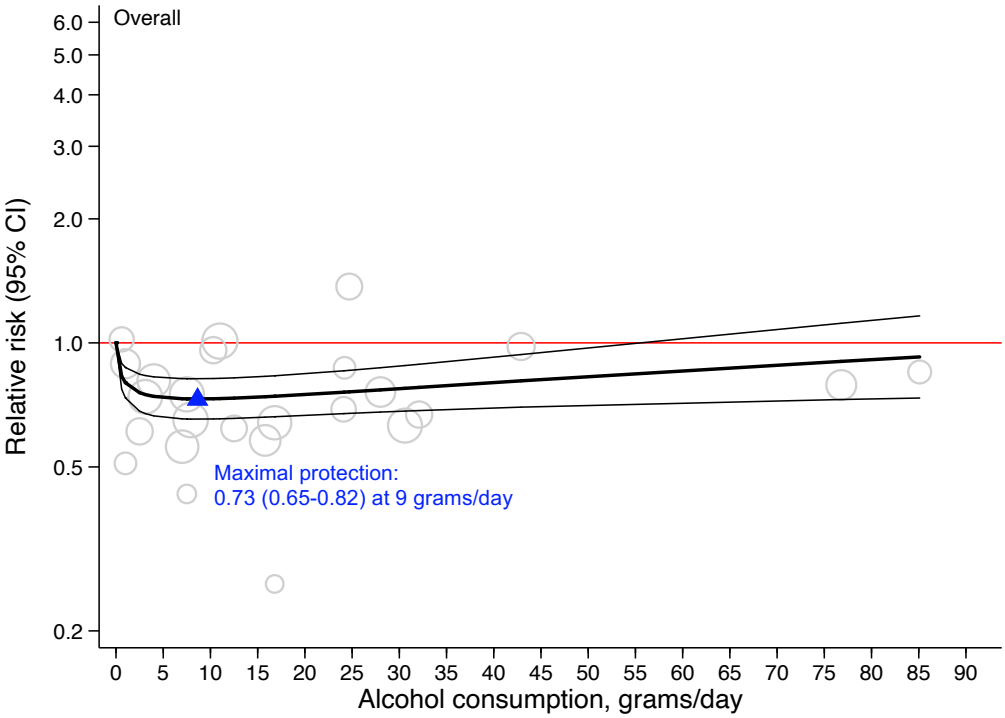

Non-drinking reference group including former drinkers
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.78 (0.73-0.82) at 15 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

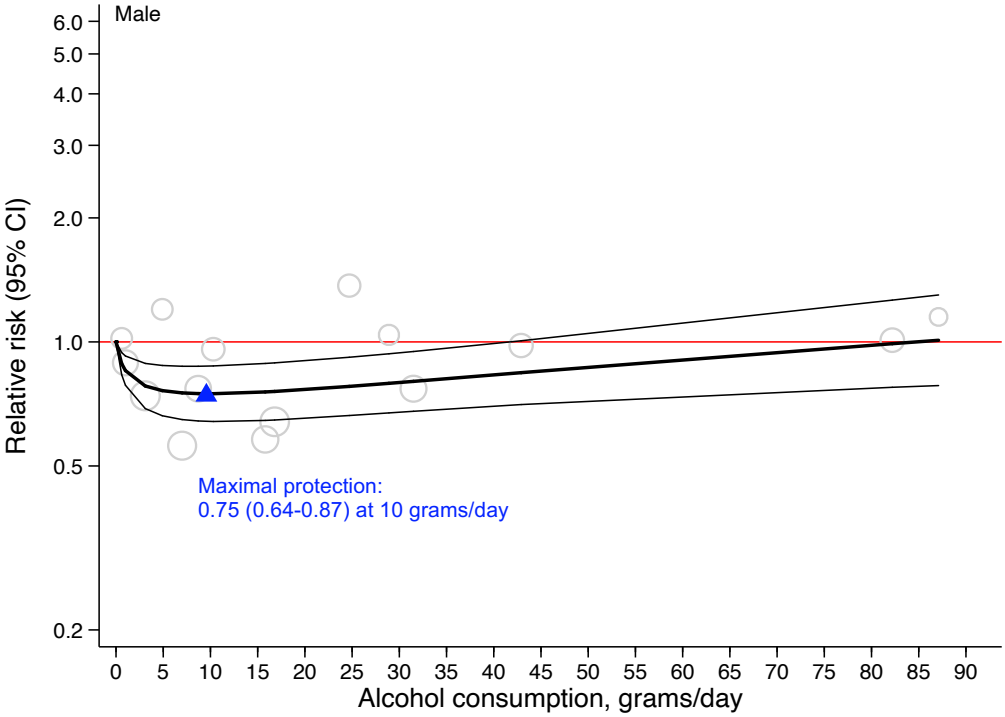

Non-drinking reference group excluding former drinkers
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.83 (0.73-0.94) at 3 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

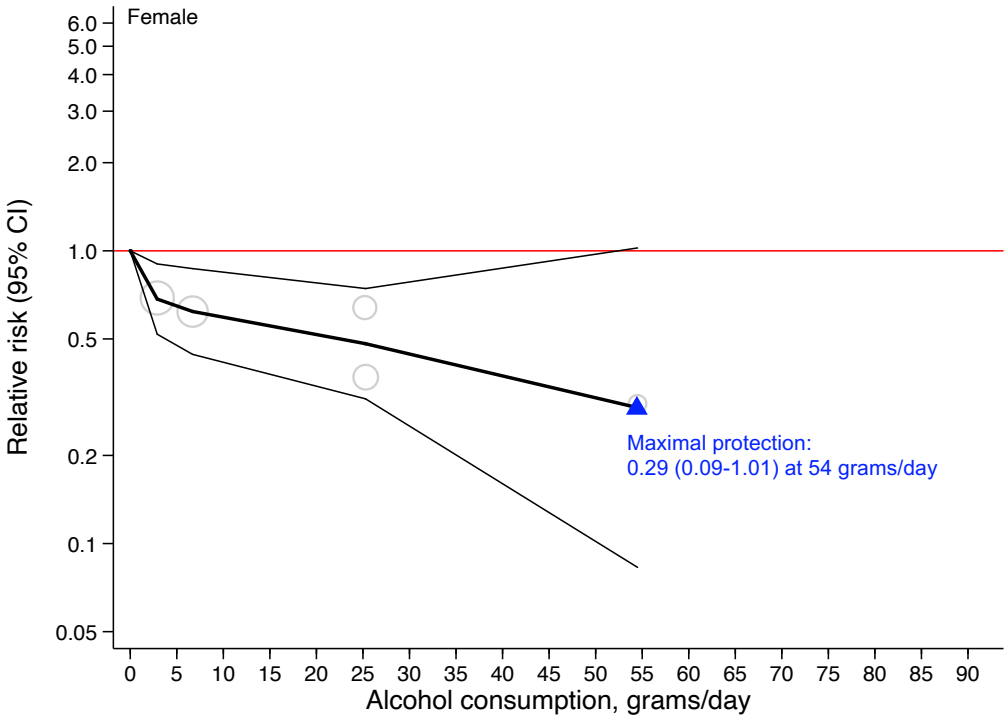

Post-event alcohol consumption assessments
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.80 (0.75-0.86) at 9 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

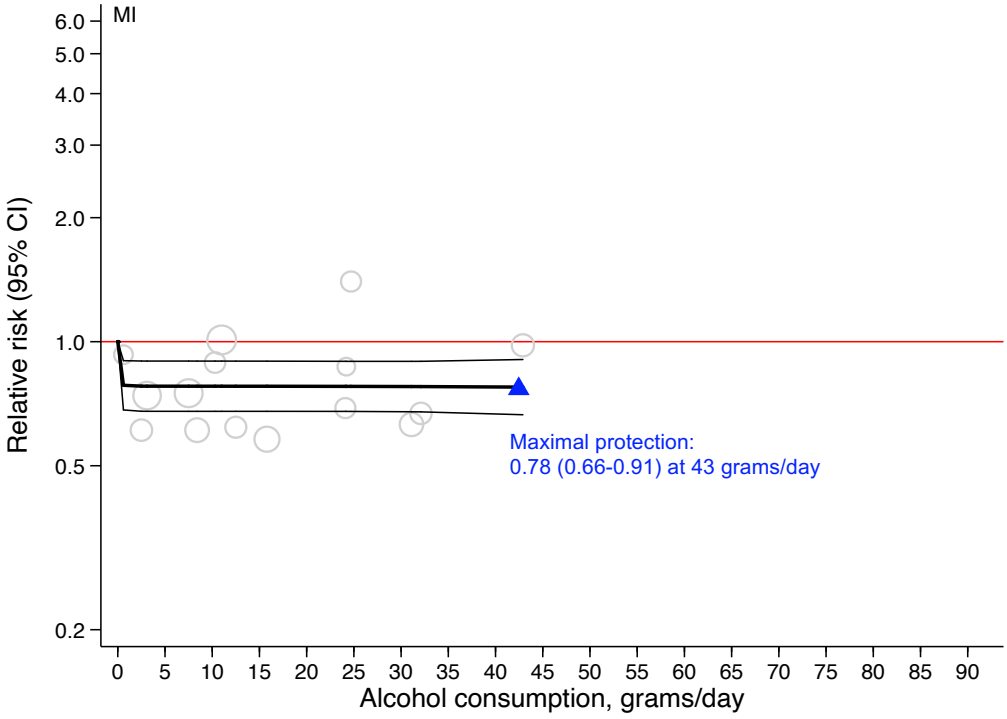

Multiple alcohol consumption assessments
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.81 (0.72-0.91) at 12 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

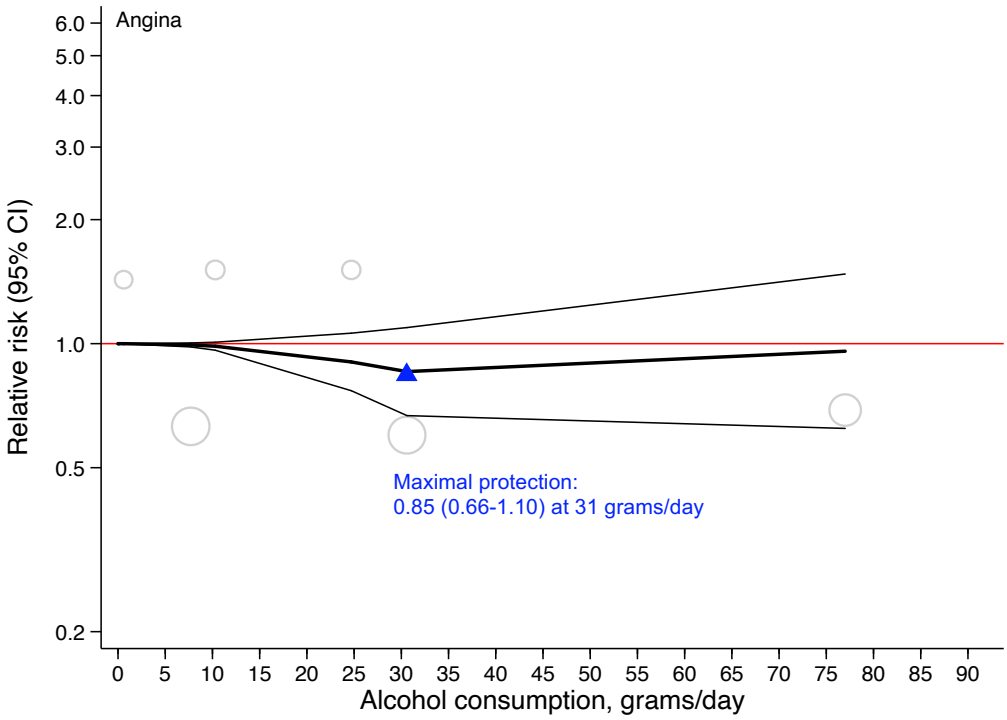
(b) Cardiovascular mortality

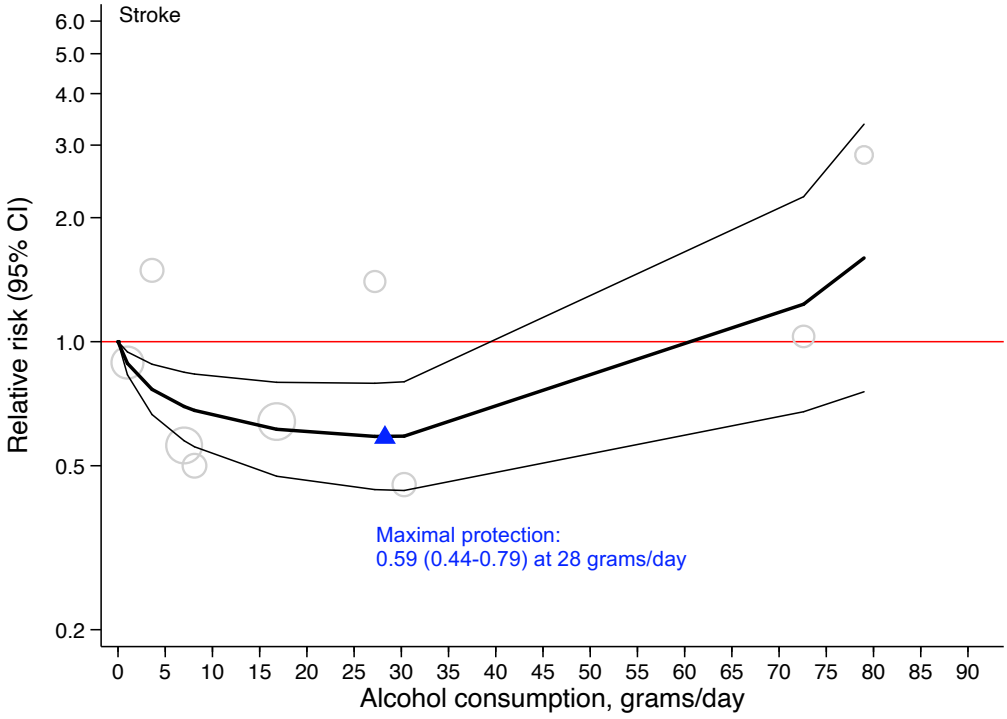


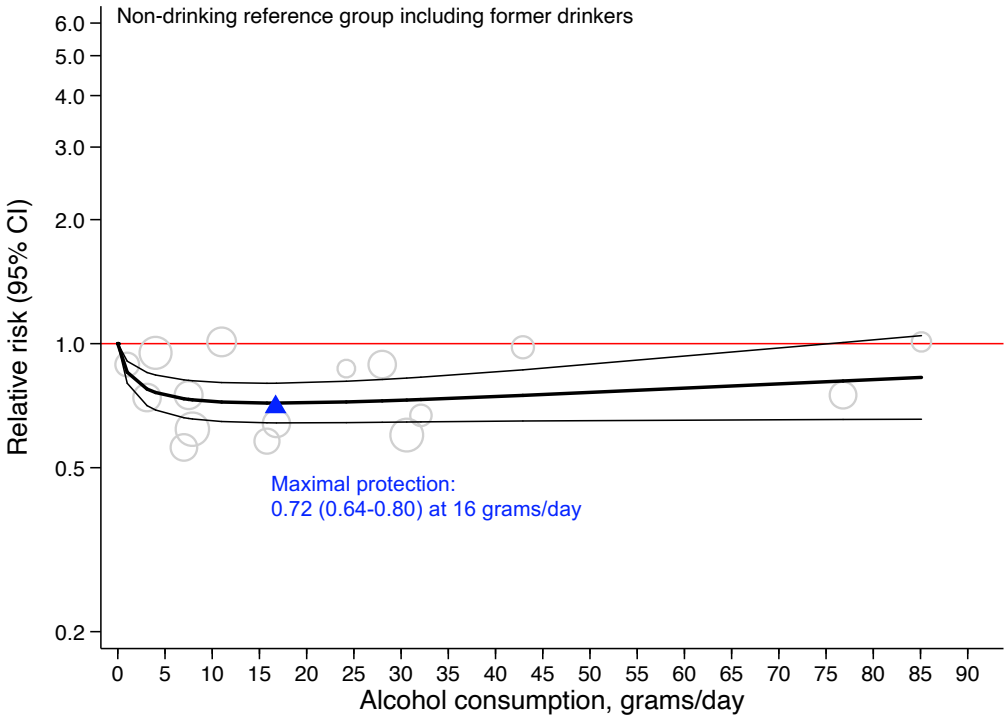


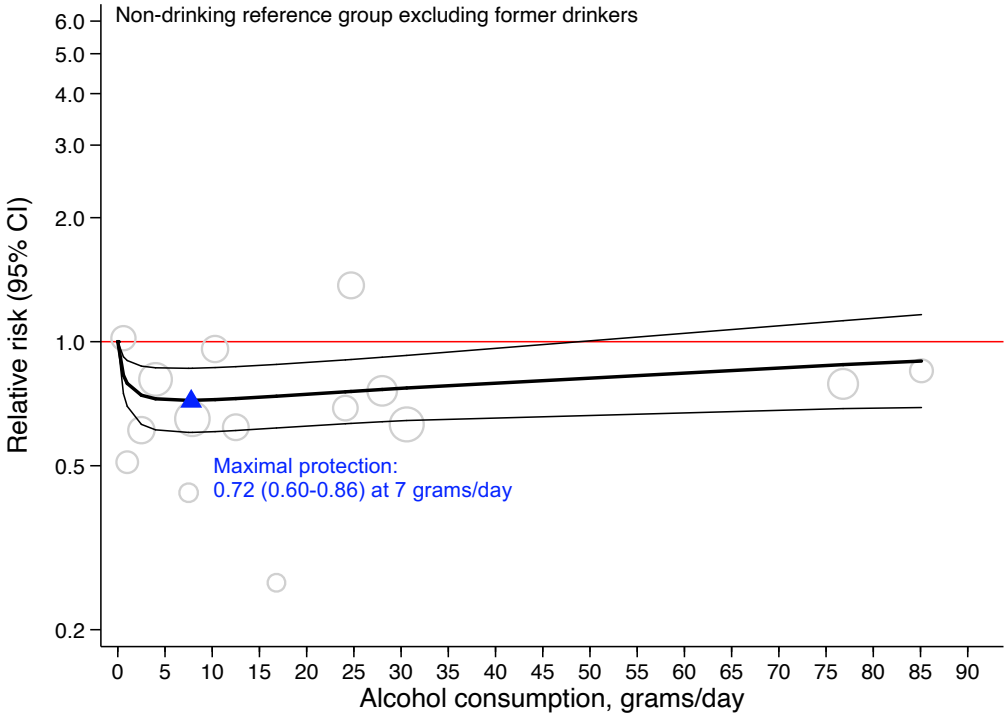

Female
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
0.1
0.05
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day
Maximal protection:
0.29 (0.09-1.01) at 54 grams/day

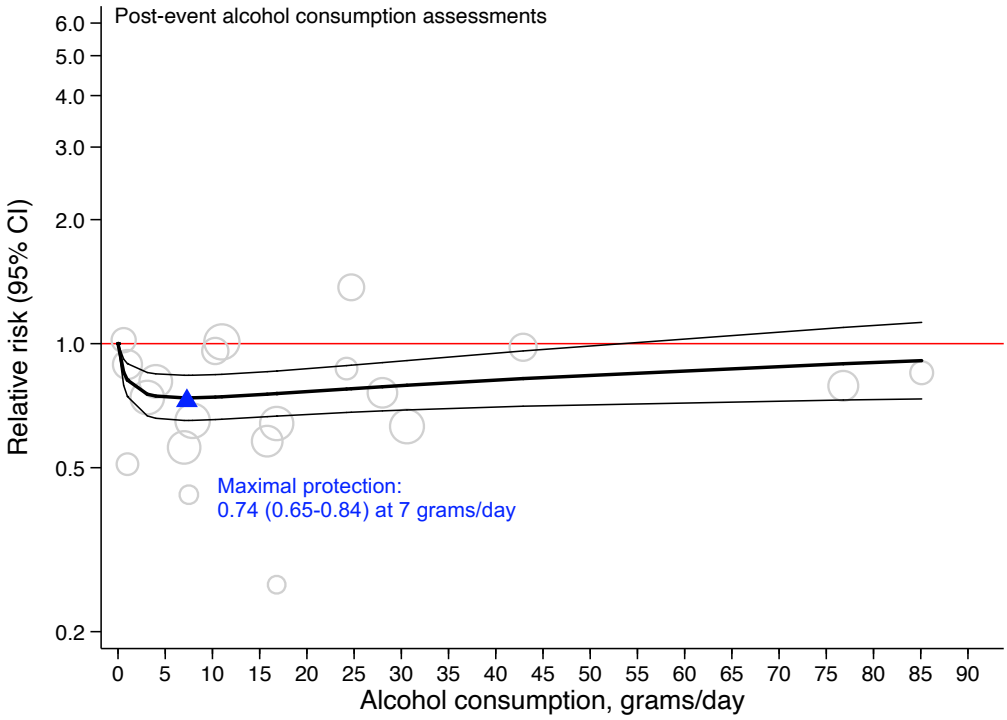

MI
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day
Maximal protection:
0.78 (0.66-0.91) at 43 grams/day


Angina
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.85 (0.66-1.10) at 31 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day


Stroke
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.59 (0.44-0.79) at 28 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

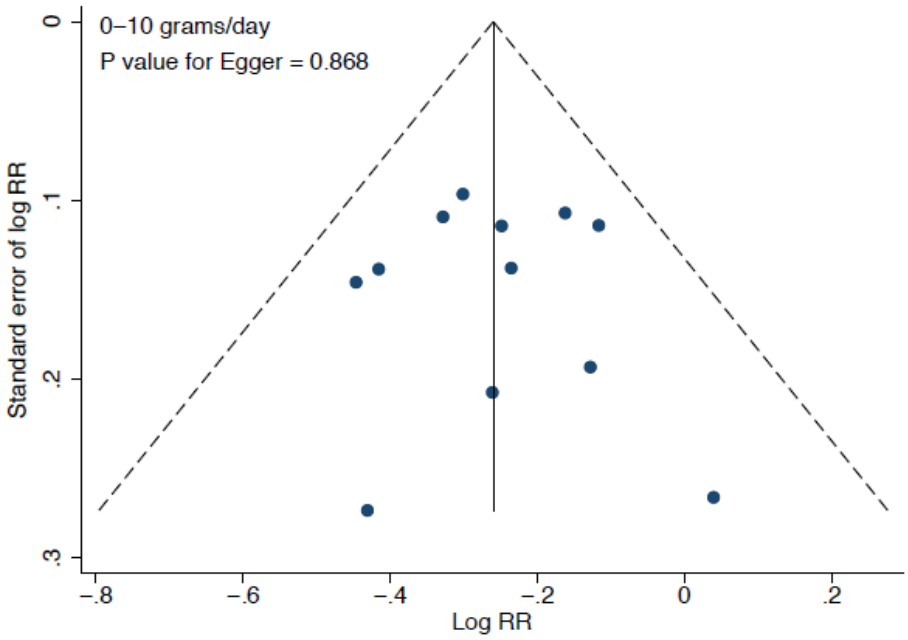

Non-drinking reference group including former drinkers
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.72 (0.64-0.80) at 16 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

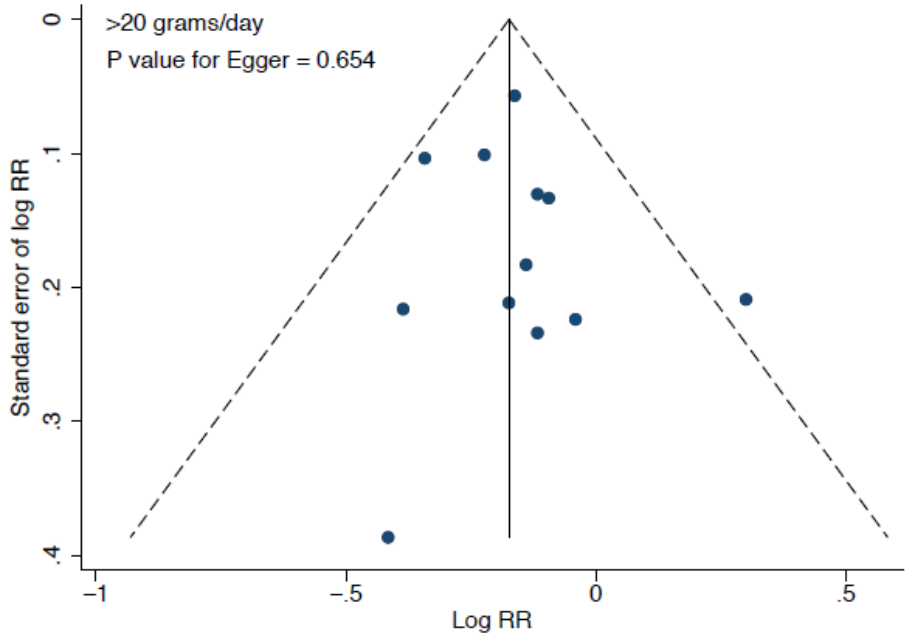

Non-drinking reference group excluding former drinkers
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.72 (0.60-0.86) at 7 grams/day
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Alcohol consumption, grams/day

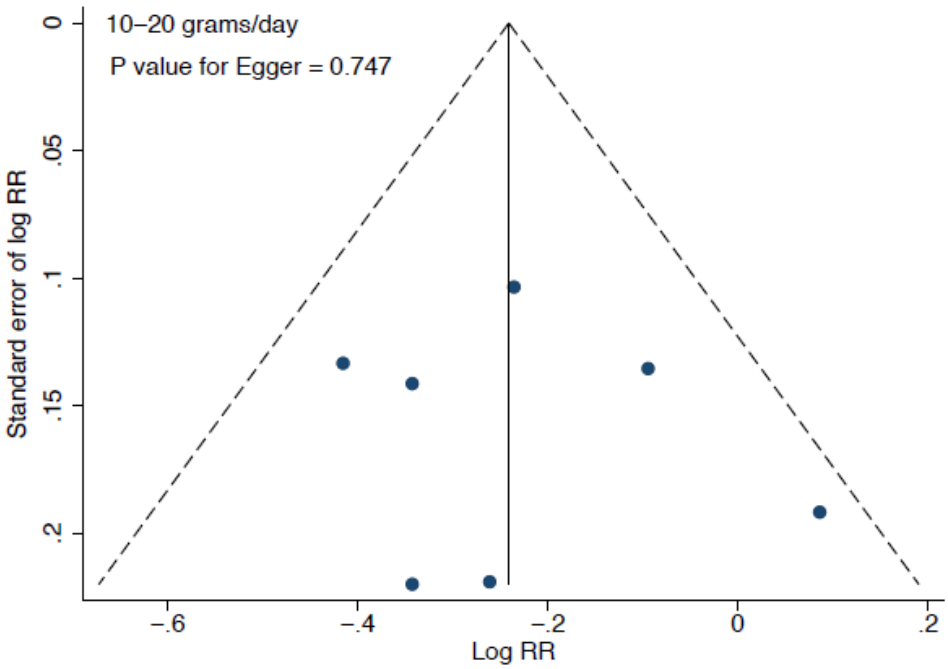

Post-event alcohol consumption assessments
Relative risk (95% CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.5
0.2
Maximal protection:
0.74 (0.65-0.84) at 7 grams/day
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
Alcohol consumption, grams/day

Appendix 2.10 Funnel plots

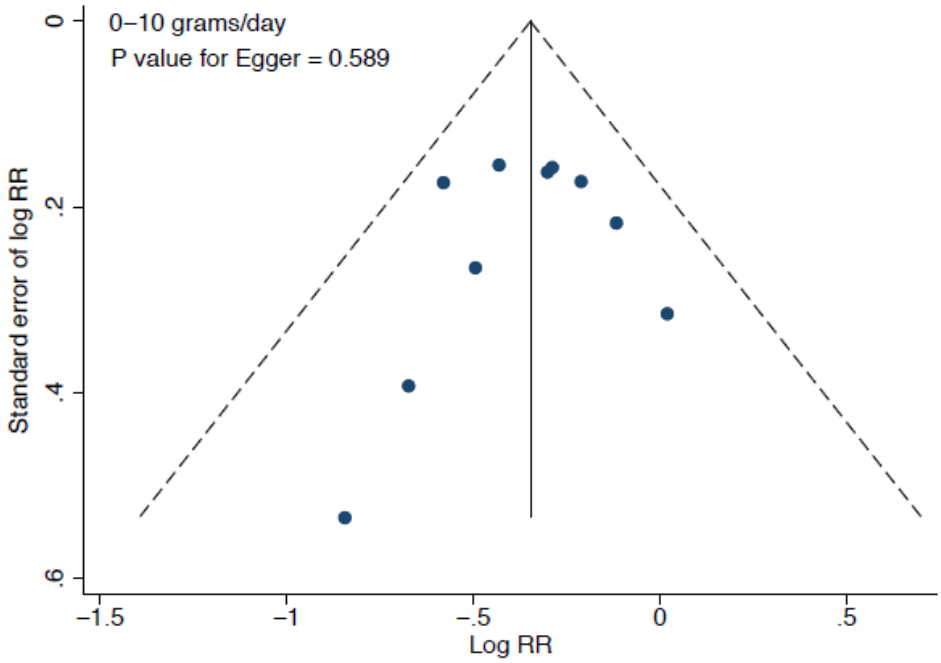
(a) All-cause mortality

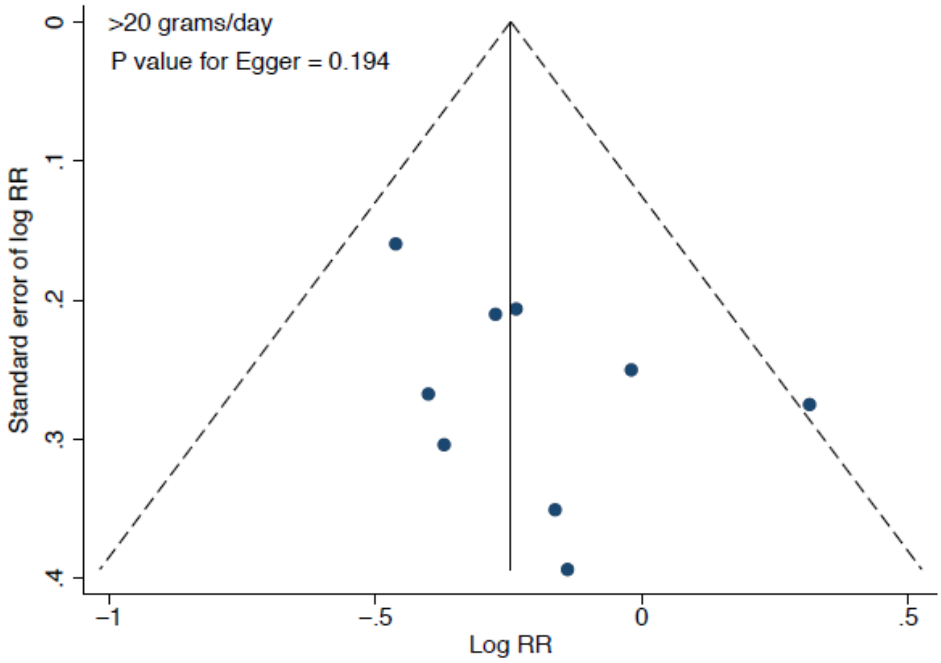


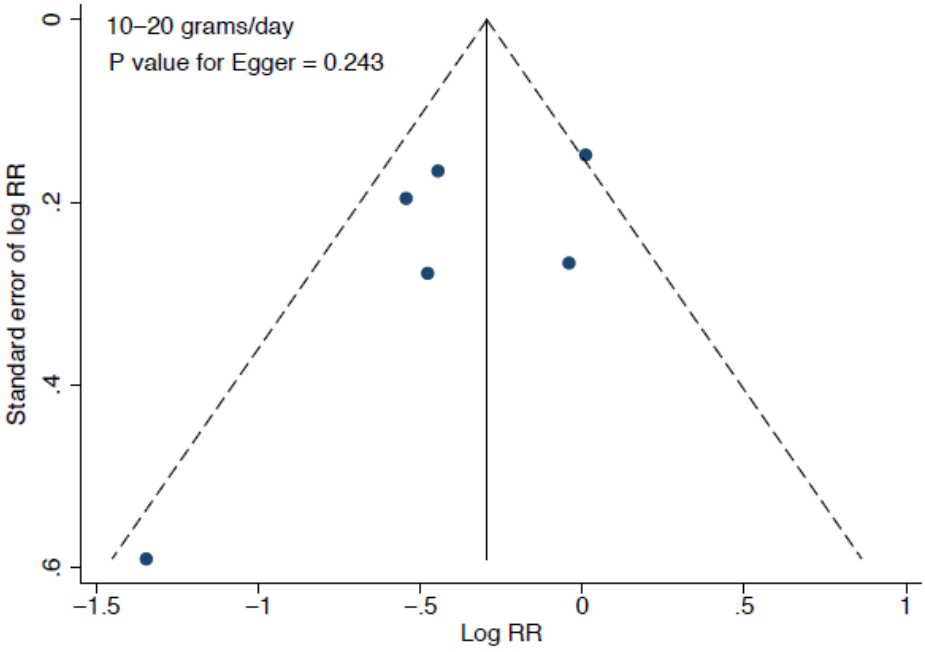



10–20 grams/day
P value for Egger = 0.747
Standard error of log RR
0
.05
.1
.15
.2
−.6
−.4
−.2
0
.2
Log RR

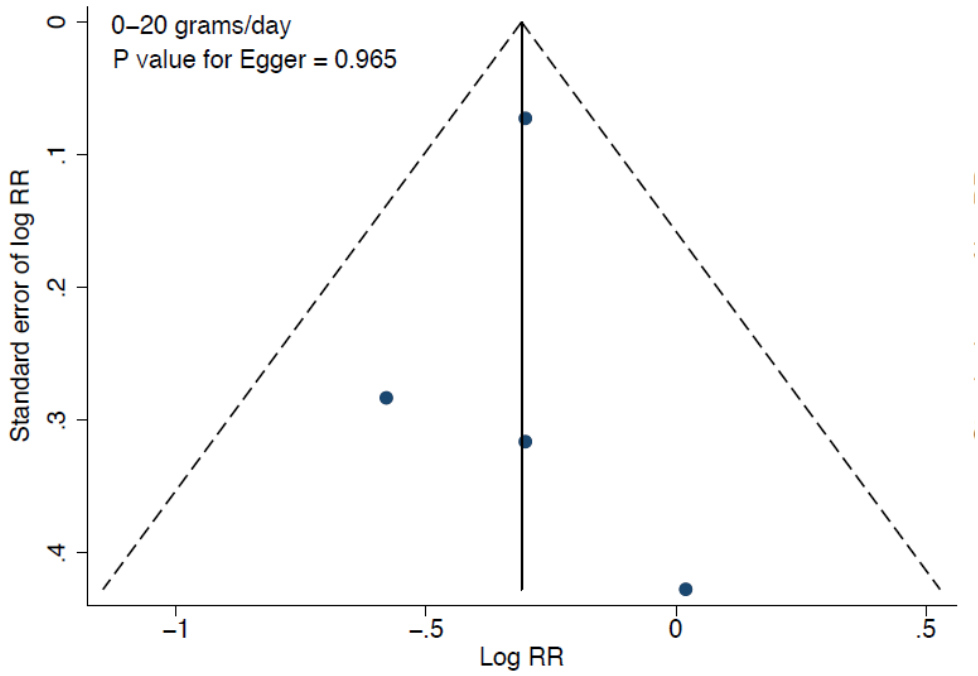
(b) Cardiovascular mortality

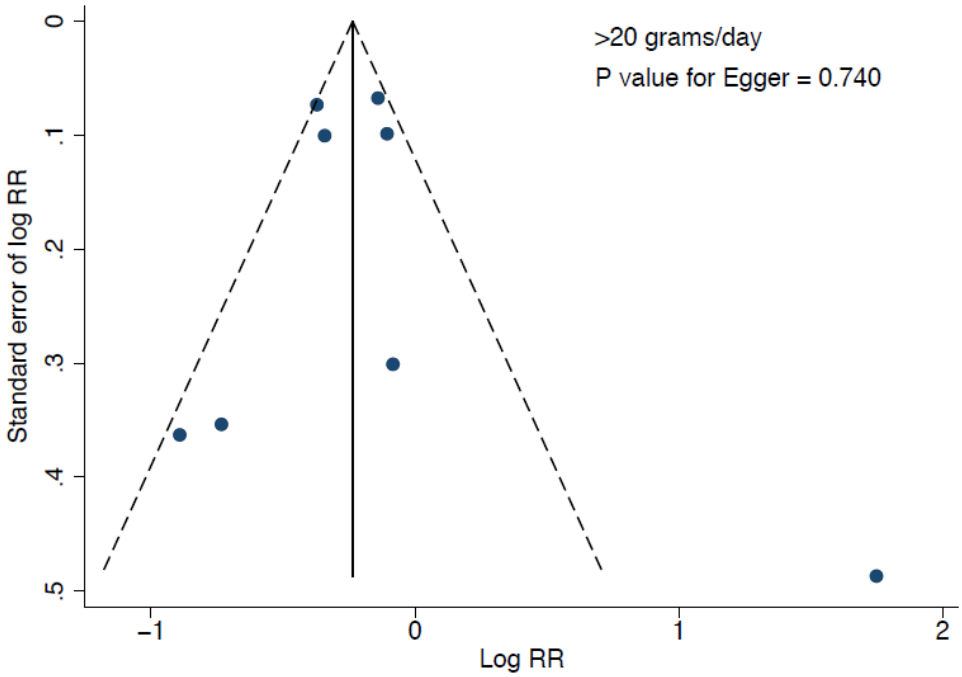





10–20 grams/day
P value for Egger = 0.243
Standard error of log RR
0
.2
.4
.6
−1.5
−1
−.5
0
.5
1
Log RR

(c) Cardiovascular events





Appendix 2.11 Associations of alcohol intake with HDL-cholesterol and gamma-glutamyl transferase in UK Biobank and HSE/SHeSs

Study cohort	Alcohol consumption category					Alcohol intake (per 100 grams per day) *	
	Never drinker	Low-level drinker	Medium-level drinker	High-level drinker	Former drinker	β (95% CI)	P-value
UK Biobank, Gamma-glutamyl transferase (U/L) (N=13477)							
n	1000	5611	4908	836	1122		
Mean	40.09	41.79	53.08	79.75	38.87	59.11	<0.001
(95% CI) †	(36.46-43.72)	(40.10-43.49)	(51.16-54.99)	(75.83-83.66)	(35.46-42.27)	(54.40-63.82)	
UK Biobank, HDL-cholesterol (mmol/L) (N=12334)							
n	917	5123	4481	766	1047		
Mean	1.19	1.26	1.35	1.49	1.20	0.39	<0.001
(95% CI) †	(1.17-1.21)	(1.25-1.27)	(1.34-1.36)	(1.47-1.51)	(1.18-1.22)	(0.36-0.41)	
HSE/SHeSs, HDL-cholesterol (mmol/L) (N=385)							
n	60	196	55	6	68		
Mean	1.24	1.31	1.43	1.54	1.26	0.40	0.003
(95% CI) †	(1.15-1.34)	(1.26-1.37)	(1.33-1.53)	(1.25-1.83)	(1.17-1.34)	(0.14-0.67)	

* β (95% CI) and P-values were derived from multivariable linear regression models by treating alcohol intake as a continuous variable
† Means (95% CI) were derived from multivariable linear regression models by treating alcohol consumption as a categorical variable
All models were adjusted for age, sex, smoking status, diabetes, hypertension, socioeconomic position or education, body mass index, cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, digoxin, and warfarin
HDL=high-density lipoprotein

Appendix 3.2 Goodness of fit statistics for linear and non-linear trajectories of mean weekly alcohol consumption

(a) Models for control group

Control group Fractional polynomial terms		Female		Male	
		Log-likelihood	BIC	Log-likelihood	BIC
time -2		-65015.16	130096.60	-212293.6	424660.9
time -1		-64800.01	129666.30	-211565.0	423203.7
time -0.5		-64701.16	129468.60	-211156.1	422385.9
time 0		-64635.56	129337.40	-212610.5	425263.1*
time 0.5		-64606.02	129278.30	-210773.7	421621.1
time 1		-64605.54	129277.40	-210797.6	421669.0
time 2		-64651.05	129368.40	-211007.7	422089.1
time 3		-64718.35	129503.00	-211245.8	422565.3
time -2 +	time -2	-64767.03	129638.20	-211278.1	422671.9
time -2 +	time -1	-64678.00	129460.20	-210832.9	421781.6
time -2 +	time -0.5	-64640.94	129386.00	-210651.6	421419.0
time -2 +	time 0	-64613.25	129330.70	-210532.9	421181.6
time -2 +	time 0.5	-64605.01	129238.40	-210485.4	421086.7
time -2 +	time 1	-64605.05	129238.50	-210496.8	421109.5
time -2 +	time 2	-64603.58	129311.30	-210617.8	421351.3
time -2 +	time 3	-64639.26	129382.70	-210801.7	421719.2
time -1 +	time -1	-64613.30	129330.80	-210496.5	421108.8
time -1 +	time -0.5	-64578.40	129261.00	-210357.4	420830.7
time -1 +	time 0	-64543.49	129191.10	-210260.8	420637.5
time -1 +	time 0.5	-64511.36	129126.90	-210208.0	420531.7
time -1 +	time 1	-64485.66	129075.50	-210191.5	420498.9
time -1 +	time 2	-64460.75	129025.70	-210236.8	420589.4
time -1 +	time 3	-64470.82	129045.80	-210365.8	420847.3
time -0.5 +	time -0.5	-64536.76	129177.70	-210220.2	420556.2
time -0.5 +	time 0	-64491.08	129086.30	-210111.8	420339.5
time -0.5 +	time 0.5	-64447.45	128999.10	-210034.7	420185.2
time -0.5 +	time 1	-64411.26	128926.70	-209986.8	420089.5
time -0.5 +	time 2	-64373.83	128851.80	-209975.5	420066.9
time -0.5 +	time 3	-64380.99	128866.10	-210075.7	420256.6

time 0 +	time 0	-64433.95	128972.10	-209977.4	420070.5
time 0 +	time 0.5	-64380.93	128866.00	-209864.5	419844.7
time 0 +	time 1	-64339.94	128784.00	-209779.7	419675.2
time 0 +	time 2	-64303.26	128710.70	-209721.2	419558.2
time 0 +	time 3	-64314.93	128734.00	-209817.5	419750.9
time 0.5 +	time 0.5	-64324.50	128753.20	-209713.2	419542.3
time 0.5 +	time 1	-64285.17	128674.50	-210484.4	421052.9
time 0.5 +	time 2	-64257.39	128619.00	-209530.4	419176.7
time 0.5 +	time 3	-64277.49	128659.10	-209659.8	419435.4
time 1 +	time 1	-64250.93	128606.00	-209475.0	419065.9
time 1 +	time 2	-64235.65	128575.50	-209436.3	418988.5
time 1 +	time 3	-64265.48	128635.10	-209623.1	419362.1
time 2 +	time 2	-64244.99	128594.10	-209521.1	419158.0
time 2 +	time 3	-64290.50	128685.20	-209823.7	419763.2
time 3 +	time 3	-64341.13	128786.40	-210140.8	420397.4

Numbers following ‘time’ refer to power terms. BIC=Bayesian information criterion.
* Fit statistics calculated on models with fixed slopes due to issues of convergence for some transformations when random slopes were expressed.

(b) Models for case group (pre-onset)

Case group, pre-onset Fractional polynomial terms		Female		Male	
		Log-likelihood	BIC	Log-likelihood	BIC
time -2		-9437.36	18919.91	-31418.84	62880.62*
time -1		-9435.98	18924.68	-31372.82	62805.76
time -0.5		-9433.76	18912.72	-31340.04	62740.19
time 0		-9430.70	18906.60	-31317.23	62694.58
time 0.5		-9425.98	18904.70	-31307.48	62675.07
time 1		-9419.71	18884.62	-31306.69	62673.50
time 2		-9409.58	18871.90	-31315.43	62690.98
time 3		-9404.40	18854.00	-31328.27	62716.65
time -2 +	time -2	-9437.30	18927.33	-31418.52	62888.57*
time -2 +	time -1	-9435.91	18924.55	-31372.74	62814.18
time -2 +	time -0.5	-9433.74	18920.21	-31339.98	62748.66
time -2 +	time 0	-9437.29	18897.17	-31317.22	62703.14
time -2 +	time 0.5	-9423.88	18870.35	-31307.46	62683.62
time -2 +	time 1	-9417.94	18858.47	-31306.62	62681.94
time -2 +	time 2	-9409.30	18871.34	-31315.31	62699.32
time -2 +	time 3	-9404.05	18860.84	-31328.13	62724.97
time -1 +	time -1	-9435.97	18932.21	-31328.37	62682.50
time -1 +	time -0.5	-9433.75	18920.23	-31339.85	62748.41
time -1 +	time 0	-9424.95	18872.49	-31315.63	62657.02
time -1 +	time 0.5	-9419.61	18861.81	-31307.02	62639.80
time -1 +	time 1	-9419.38	18891.50	-31306.40	62638.56
time -1 +	time 2	-9408.97	18870.67	-31306.74	62707.95
time -1 +	time 3	-9403.62	18867.50	-31301.20	62696.86
time -0.5 +	time -0.5	-9433.76	18920.25	-31316.72	62659.21
time -0.5 +	time 0	-9430.58	18913.88	-31317.18	62703.07
time -0.5 +	time 0.5	-9415.54	18906.41	-31306.44	62638.65
time -0.5 +	time 1	-9409.97	18895.26	-31300.64	62695.74
time -0.5 +	time 2	-9401.58	18886.03	-31283.18	62660.83
time -0.5 +	time 3	-9397.13	18869.58	-31274.12	62642.72
time 0 +	time 0	-9415.72	18906.76	-31308.00	62710.46
time 0 +	time 0.5	-9409.62	18894.56	-31303.47	62632.70
time 0 +	time 1	-9404.28	18883.88	-31281.09	62656.65
time 0 +	time 2	-9396.66	18868.64	-31261.38	62617.22

time 0 +	time 3	-9392.95	18861.22	-31252.19	62598.84
time 0.5 +	time 0.5	-9403.88	18883.09	-31305.29	62679.28
time 0.5 +	time 1	-9398.99	18873.30	-31303.23	62675.16
time 0.5 +	time 2	-9392.41	18860.15	-31245.35	62585.16
time 0.5 +	time 3	-9389.76	18854.84	-31238.88	62572.22
time 1 +	time 1	-9394.65	18864.62	-31250.23	62594.93
time 1 +	time 2	-9389.33	18853.99	-31236.11	62566.69
time 1 +	time 3	-9387.87	18851.07	-31233.93	62562.32
time 2 +	time 2	-9386.67	18856.20	-31232.32	62559.11
time 2 +	time 3	-9387.59	18850.51	-31237.85	62570.16
time 3 +	time 3	-9390.41	18856.15	-31247.81	62590.10

Numbers following 'time' refer to power terms. BIC=Bayesian information criterion.
* Fit statistics calculated on models with fixed slopes due to issues of convergence for some transformations when random slopes were expressed.

(c) Models for case group (post-onset)

Case group, post-onset Fractional polynomial terms		Female		Male	
		Log-likelihood	BIC	Log-likelihood	BIC
time -2		-6883.73	13817.80	-21912.83	43883.22
time -1		-6881.56	13813.46	-21910.24	43878.03
time -0.5		-6879.94	13803.02	-21909.25	43876.05
time 0		-6877.92	13798.99	-21908.52	43874.59
time 0.5		-6883.424	13802.81*	-21908.07	43873.70
time 1		-6883.172	13802.30*	-21907.94	43873.44
time 2		-6866.20	13782.73	-21908.71	43874.97
time 3		-6858.92	13761.00	-21910.83	43879.22
time -2 +	time -2	-6880.63	13811.61	-21863.43	43817.30
time -2 +	time -1	-6878.60	13807.54	-21864.13	43818.71
time -2 +	time -0.5	-6877.08	13804.49	-21864.65	43819.75
time -2 +	time 0	-6875.18	13807.88	-21899.12	43864.02
time -2 +	time 0.5	-6872.90	13796.13	-21866.02	43822.49
time -2 +	time 1	-6870.25	13790.84	-21866.87	43824.18
time -2 +	time 2	-6864.06	13785.66	-21868.83	43828.11
time -2 +	time 3	-6857.15	13771.83	-21871.10	43832.64
time -1 +	time -1	-6878.39	13807.13	-21865.32	43821.09
time -1 +	time -0.5	-6876.88	13804.10	-21899.87	43865.51
time -1 +	time 0	-6878.21	13806.75	-21899.75	43865.28
time -1 +	time 0.5	-6872.73	13795.79	-21899.66	43865.09
time -1 +	time 1	-6870.10	13790.53	-21868.90	43828.24
time -1 +	time 2	-6863.93	13785.39	-21871.18	43832.80
time -1 +	time 3	-6857.04	13771.61	-21873.67	43837.77
time -0.5 +	time -0.5	-6876.79	13803.92	-21866.93	43824.30
time -0.5 +	time 0	-6874.91	13800.16	-21900.32	43866.43
time -0.5 +	time 0.5	-6876.63	13810.79	-21900.25	43866.28
time -0.5 +	time 1	-6876.56	13803.47	-21870.04	43830.52
time -0.5 +	time 2	-6863.87	13785.27	-21872.46	43835.37
time -0.5 +	time 3	-6856.99	13764.32	-21875.04	43840.52
time 0 +	time 0	-6874.83	13800.01	-21868.93	43828.30
time 0 +	time 0.5	-6874.76	13799.87	-21870.06	43822.34
time 0 +	time 1	-6874.70	13799.75	-21871.26	43832.95
time 0 +	time 2	-6863.82	13785.16	-21873.81	43838.06

time 0 +	time 3	-6856.95	13771.42	-21876.46	43843.36
time 0.5 +	time 0.5	-6871.06	13792.45	-21902.00	43869.78
time 0.5 +	time 1	-6880.508	13804.16*	-21901.97	43869.72
time 0.5 +	time 2	-6863.77	13785.07	-21875.19	43840.83
time 0.5 +	time 3	-6856.91	13764.15	-21877.90	43846.24
time 1 +	time 1	-6867.48	13785.29	-21903.16	43872.09
time 1 +	time 2	-6863.73	13784.99	-21876.61	43843.66
time 1 +	time 3	-6869.74	13789.83	-21879.35	43849.15
time 2 +	time 2	-6860.17	13770.68	-21879.46	43849.36
time 2 +	time 3	-6856.83	13764.01	-21882.22	43854.87
time 3 +	time 3	-6852.85	13763.22	-21884.94	43860.31

Numbers following ‘time’ refer to power terms. BIC=Bayesian information criterion.
* Fit statistics calculated on models with fixed slopes due to issues of convergence for some transformations when random slopes were expressed.

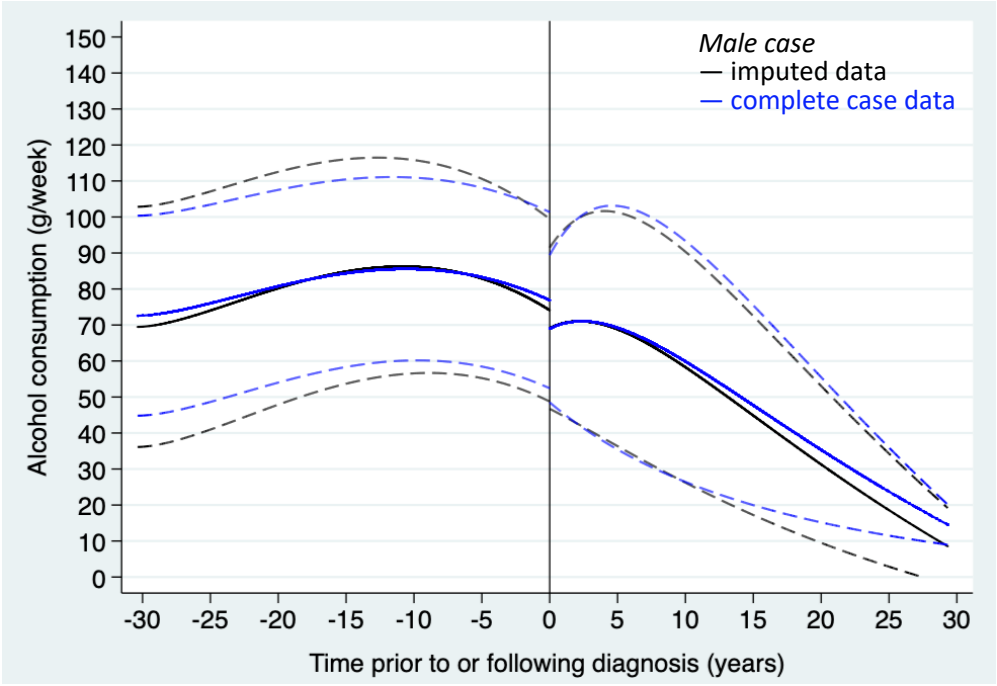
Appendix 3.3 Regression coefficients for the fixed effects of the best-fitting multilevel growth curve models using complete case data

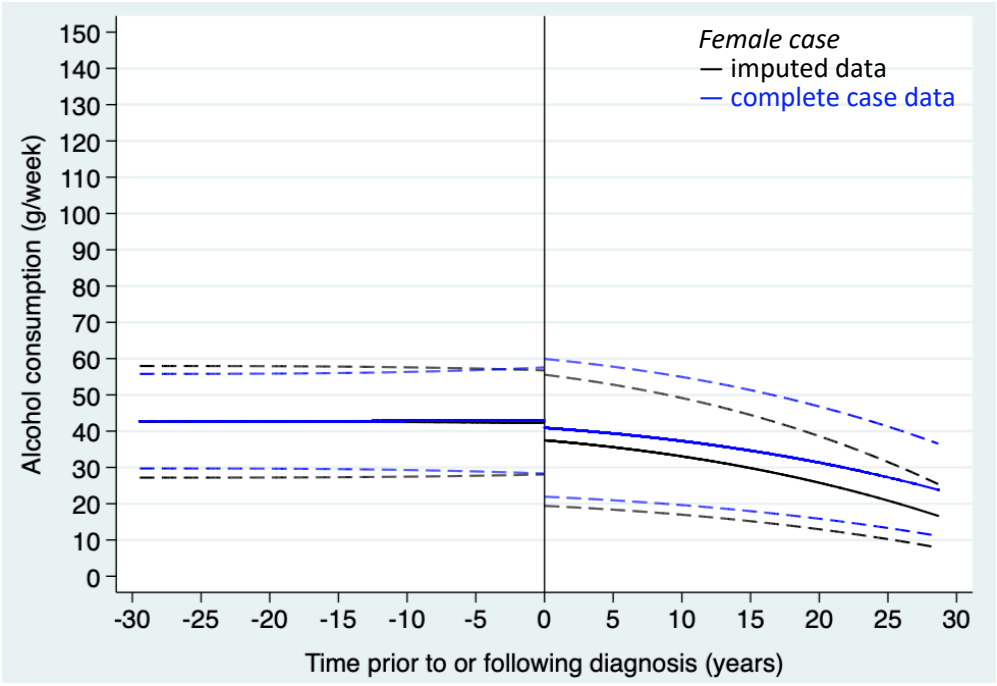
Best-fitting models*		Obs	n	Model 1			Model 2			Model 3			Model 4		
				Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value	Coefficient	Robust SE	P-value
Male															
Case,	Time ^{2}	4633	1734	10.99	0.20	<0.001	10.28	0.88	<0.001	11.02	0.86	<0.001	7.87	0.49	<0.001
pre-onset	Time ^{2}			-8.19	0.03	<0.001	-7.92	0.49	<0.001	-8.39	0.44	<0.001	-6.66	0.28	<0.001
	Intercept			71.98	16.31	<0.001	116.06	6.45	<0.001	89.89	10.34	<0.001	27.80	28.53	0.330
Case,	Time $^{-2}$	2835	1388	-2628.45	1209.39	0.030	-2633.68	1443.08	0.068	-2493.58	1506.76	0.098	-2456.12	1429.41	0.086
post-	Time $^{-2}$			3549.34	1384.11	0.010	3736.08	1704.33	0.028	3551.20	1788.95	0.047	3581.64	1742.05	0.040
onset	Intercept			-68.77	21.10	0.001	52.65	4.87	<0.001	39.46	1.19	<0.001	-27.39	48.87	0.575
Control	Time ^{1}	31137	6989	37.90	8.43	<0.001	36.40	8.72	<0.001	36.35	8.55	<0.001	28.19	6.01	<0.001
	Time ^{2}			-7.78	0.87	<0.001	-7.69	0.95	<0.001	-7.65	0.90	<0.001	-6.65	0.69	<0.001
	Intercept			47.84	1.06	<0.001	129.43	14.46	<0.001	116.51	19.36	<0.001	44.67	29.30	0.127
Female															
Case,	Time ^{3}	1587	671	0.01	0.10	0.934	-0.05	0.07	0.452	-0.01	0.03	0.799	0.01	0.03	0.822
pre-onset	Intercept			30.65	0.21	<0.001	55.41	3.27	<0.001	44.83	10.44	<0.001	57.55	11.40	<0.001
Case,	Time ^{3}	916	495	-0.08	0.03	0.011	-0.10	0.02	<0.001	-0.08	0.02	<0.001	-0.10	0.02	<0.001
post-onset	Intercept			30.19	3.96	<0.001	73.56	16.28	<0.001	68.27	18.49	<0.001	66.66	12.83	<0.001
Control	Time ^{1}	10250	2745	13.90	4.90	0.005	12.18	3.90	0.002	11.75	3.80	0.002	10.46	2.26	<0.001
	Time ^{2}			-2.98	0.43	<0.001	-2.83	0.36	<0.001	-2.73	0.35	<0.001	-2.54	0.22	<0.001
	Intercept			25.42	4.44	<0.001	67.51	10.16	<0.001	62.06	12.53	<0.001	56.13	8.78	<0.001

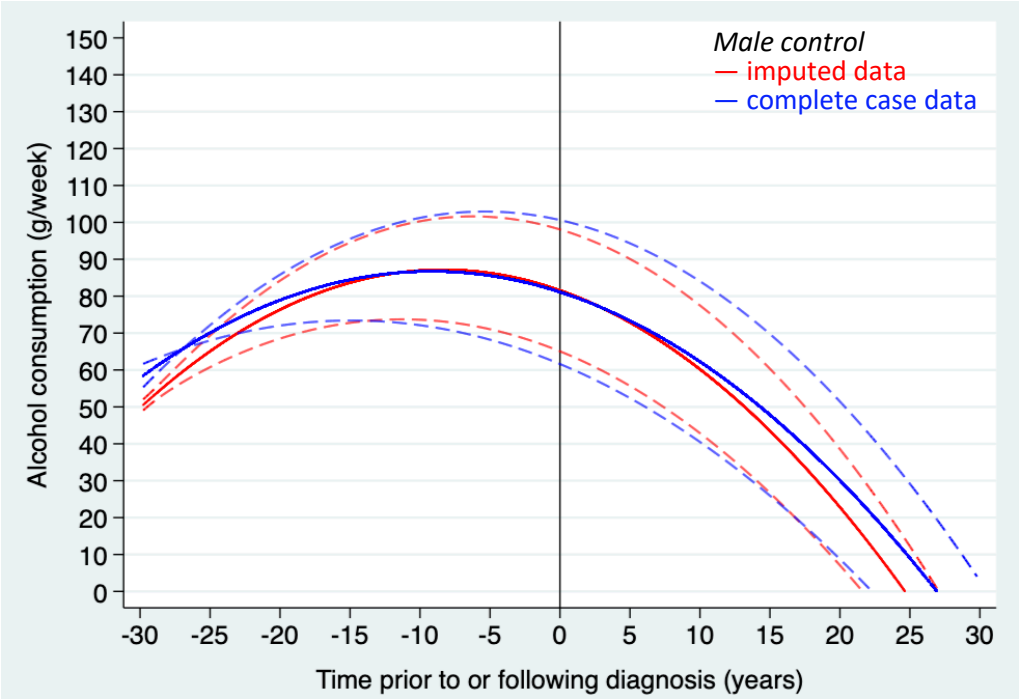
*To describe the shape of each trajectory, a group of first- and second-degree fractional polynomials with powers from a predefined set (-2, -1, -0.5, 0, 0.5, 1, 2, 3) was used to derive a power transformation of the 'Time' variable. The superscript numbers following 'Time' in the table above refer to power terms that provide the best fit.
Obs=observations, SE=standard error.
Model 1: unadjusted.
Model 2: as Model 1, plus adjustment for age at diagnosis, ethnicity, marital status and socioeconomic position.
Model 3: as Model 2, plus adjustment for smoking, physical activity, frequency of fruit and vegetables consumed in a week.
Model 4: as Model 3, plus adjustment for prevalent hypertension (self-reported doctor diagnosed hypertension or use of antihypertensive drugs), body mass index, self-rated health.

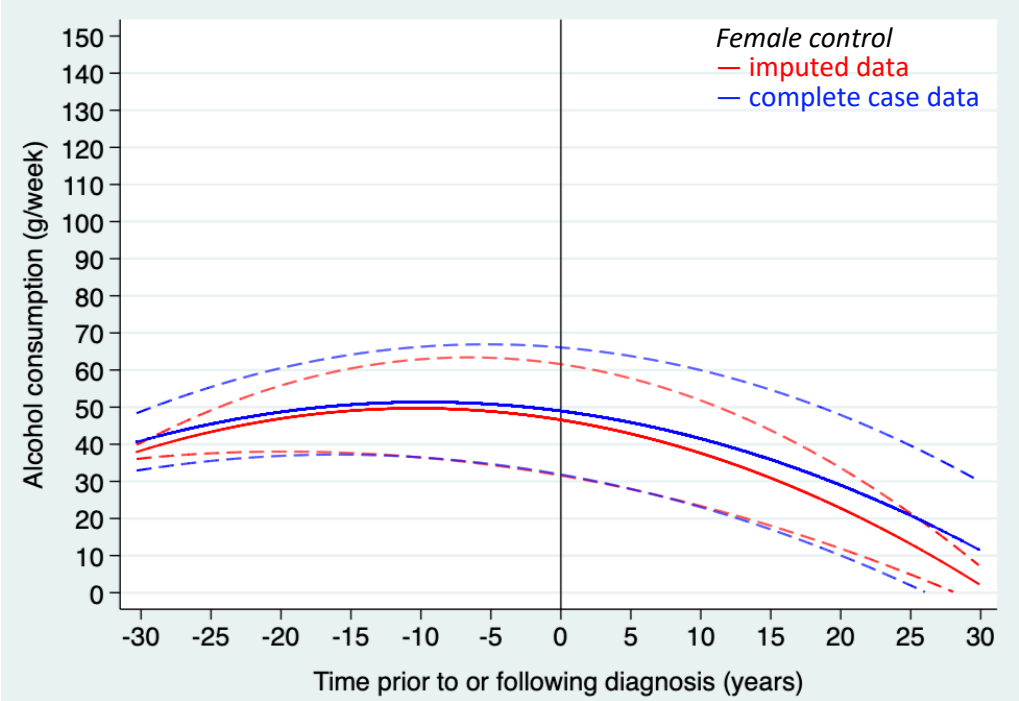
Appendix 3.4 Trajectories of the mean volume of weekly alcohol consumption prior to and following CVD diagnosis, stratified by sex and case/control group (maximally adjusted models using imputed data versus complete case data)

Notes: Figures are reported according to mean and referent held values (i.e., 65 years old at diagnosis, white, married, high socioeconomic position, never-smoking, physically active, eating fruits/vegetable daily, self-rated health as excellent, reporting no history of hypertension, with a BMI value of 26 kg/m^2). Dashed curves represent 95% CIs.






Male control
imputed data
complete case data
Alcohol consumption (g/week)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Time prior to or following diagnosis (years)


Female control
imputed data
complete case data
Alcohol consumption (g/week)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Time prior to or following diagnosis (years)

Appendices for Chapter 4

Appendix 4.1 Publication of results on alcohol trajectory and mortality risk

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RESEARCH REPORT

ADDICTION SSA

Trajectories of alcohol consumption in relation to all-cause mortality in patients with cardiovascular disease: a 35-year prospective cohort study

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Abstract

Background and Aims: Research into alcohol consumption and cardiovascular disease (CVD) patients' prognosis has largely ignored the longitudinal dynamics in drinking behaviour. This study measured the association between alcohol consumption trajectories and mortality risk in CVD patients.

Design: Prospective cohort study.

Setting: UK-based Whitehall II Study.

Participants: A total of 1306 participants with incident non-fatal CVD (coronary heart disease/stroke) events.

Measurements: Up to eight repeated measures of alcohol intake were available for each patient from the most recent assessment phase pre-incident CVD and all subsequent phases post-incident CVD, spanning up to three decades. Six trajectory groups of alcohol consumption were identified using group-based trajectory modelling and related to the risk of all-cause mortality, adjusting for demographics and changes in life-style and health status.

Findings: Three hundred and eighty deaths were recorded during a median follow-up of 5 years after patients' last alcohol assessment. Compared with patients who consistently drank moderately (≤ 14 units/week), former drinkers had a greater risk of mortality (hazard ratio = 1.74, 95% confidence interval = 1.19–2.54) after adjustment for covariates. There was no significantly increased risk of mortality in long-term abstainers, reduced moderate drinkers, stable or unstable heavy drinkers. Cross-sectional analyses based only on drinking information at patients' last assessment found no significant differences in mortality risk for abstainers, former or heavy drinkers versus moderate drinkers.

Conclusions: Cardiovascular disease patients who consistently drink ≤ 14 units/week appear to have a similar risk of mortality to those who are long-term abstainers, which does not support a protective effect of moderate drinking on total mortality. Cardiovascular disease patients who stop drinking appear to have increased mortality risk compared with continuous moderate drinkers, but this may be linked to poor self-rated health before cardiovascular disease onset.

KEYWORDS
Alcohol, cardiovascular disease, former drinker, longitudinal, mortality, trajectory

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of premature mortality and a major contributor to disability [1]. Globally, the number of prevalent CVD cases has increased rapidly since 1990, reaching 523 million in 2019 [2]. The association between moderate alcohol consumption and reduced risk of CVD is well-documented and heatedly debated [3–5]. However, relatively few studies have focused on patients who have already experienced a CVD event and the effects that alcohol drinking may have on their subsequent health. A recent meta-analysis suggests that drinking up to 105 g of ethanol per week is associated with lower risks of mortality and subsequent cardiovascular events than non-drinking in those with established CVD [6]. It is noteworthy that this threshold is lower than the upper limits of drinking recommended in most current guidelines [7–9].

Similar to the critiques of studies on general populations [10, 11], the evidence among CVD patients is far from robust for several important reasons. First, most studies (11 of 14) included in the meta-analysis only looked at the association cross-sectionally, despite evidence that drinking behaviours change over time and that misclassification of alcohol intake has the potential to bias the risk estimates [12, 13]. Longitudinal prospective assessment of intake is needed to accurately measure long-term exposure to alcohol, and this is particularly relevant when studying biological processes that cause chronic effects on health [14]. Secondly, in those few studies of CVD patients that did include longitudinal assessment of alcohol and subsequent health risks [15–17], the methodology used can be questioned. In most cases these studies categorized the patients into different drinking groups according to each patient's average intake during follow-up, with no accounting for intra-individual variation in drinking levels over time. Failure to capture such variation may result in over-simplistic interpretation of alcohol use and consequent outcomes, as there is evidence from general population samples that unstable drinking patterns confer increased risks for coronary heart disease (CHD) and total mortality independent of average intake [18–20]. Thirdly, these studies often included former drinkers (who might have quit in response to ill health) in the non-drinking group, which could erroneously lead to a suggested protective effect of drinking compared to non-drinking. Indeed, when former drinkers were excluded from the meta-analysis [6], the protective effect of moderate drinking on all-cause mortality among CVD patients was eliminated. Fourthly, most studies also had a heterogeneous group of patients with incident or recurrent CVD events and did not adequately account for concurrent changes in other life-style and health factors, such as smoking, which is associated both with levels of drinking and with mortality [21] and thus might confound the results.

It therefore remains unclear what advice should be given to CVD patients in terms of their alcohol consumption and subsequent prognosis. We contribute to this deficit in evidence using data with repeated measures of alcohol intake spanning up to three decades. We aimed to (1) describe the longitudinal trajectories of alcohol consumption in patients with incident CVD events, (2) link these trajectories to risk of all-cause mortality and (3) compare these associations with cross-sectional findings in the same cohort.

METHODS

Study design and population

The Whitehall II Study is an ongoing cohort study of 10 308 British civil servants aged 35–55 years at enrolment (phase 1), recruited from 20 London-based offices during 1985–88 [22]. Phase 1 involved a clinical examination and a self-administered questionnaire to collect information including demographics, health status and life-style factors. Subsequent phases of data collection have alternated between questionnaire alone and questionnaire accompanied by a clinical examination. A linkage was made to the National Health Service (NHS) Hospital Episode Statistics database, which has been found valid for CVD ascertainment in the Whitehall II study [23, 24]. Incident CVD event was defined as a primary or secondary CHD/stroke diagnosis in the linked data set (using the procedure and International Classification of Diseases codes listed in Supporting information, Table S1), with additional cases identified on the basis of 12-lead resting electrocardiogram recording (for CHD only) or self-reports that had been verified with information from general practitioners or manual retrieval of medical records.

Data used for the present analyses came from phases 1 (1985–88), 2 (1989–90), 3 (1991–93), 5 (1997–99), 7 (2002–04), 9 (2007–09), 11 (2012–13) and 12 (2015–16) of the Whitehall II study. We included participants who survived an incident CHD/stroke event during phases 1–12 and for whom repeated measures of alcohol were available (at least two measures, starting from the most recent phase pre-incident CVD; Figure 1). Participants with previously diagnosed CHD/stroke or cancer at phase 1 were excluded from analyses to reduce reverse causality. The analysis was not pre-registered and thus the results should be considered exploratory.

Alcohol consumption

At each phase, participants were asked if they had consumed alcohol in the previous year, and if not whether they have always been non-drinkers. Those who reported having consumed alcohol in the previous year were then asked about the number of alcoholic drinks they had consumed during the previous week. Drinks were converted into UK units of alcohol (1 unit equivalent to 8 g of ethanol) using a conservative estimate of 1 unit for each measure of spirits and small glass of wine, and 2 units for each pint of beer [25]. These converted measurements were summed to define the total weekly alcohol intake in units. We then categorized intakes at each phase into none, moderate (1–14 units/week) and heavy (> 14 units/week) to reflect the current UK drinking guidelines [26].

Outcomes

All-cause mortality was traced through the national mortality register. For each patient, follow-up time began on the date of the patient's

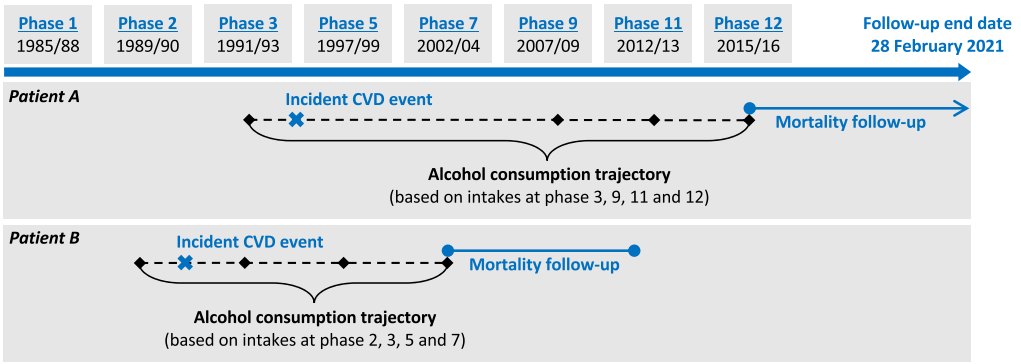

FIGURE 1 An illustration of study design. This figure provides two illustrative examples of how drinking trajectories were constructed for patient A, who had an incident cardiovascular disease (CVD) event in 1995 and was alive at the end of follow-up, and for patient B, who had an incident event in 1990 and later died in 2012, using all available measures of alcohol intake for each patient starting from the most recent phase pre-incident CVD. Duration of mortality follow-up was calculated from date of each patient's last available alcohol assessment to the earliest of date of death, emigration or last follow-up

last available alcohol assessment and ended on the date of death, emigration, or 28 February 2021, whichever occurred first.

Covariates

Socio-demographic variables included age, sex and ethnicity. Socioeconomic position was defined using either current or last recorded employment grade as high, intermediate or low [27]. Health behaviours were assessed and comprised smoking (current, former or never), physical activity [meeting or below World Health Organization (WHO) recommendations] [28] and dietary behaviour (frequency of fruit and vegetables consumed in a week). Further medical information was obtained on self-reported use of cardiovascular drugs, prevalent diabetes and hypertension. Covariates were assessed at the most recent phase pre-incident CVD. To account for variability in the exposure assessment interval, the time difference between the date of first and last available alcohol assessment was calculated for each patient and included as a further covariate. Follow-up observations on health behaviours and medical status were also derived from the same phase when the last available alcohol assessment was recorded.

Statistical analysis

Group-based trajectory modelling (GBTM), an extension of finite mixture modelling (FMM), was applied to identify groups of patients following different trajectories of alcohol consumption [29], with all available alcohol data (categorized into 0, 1–14 and > 14 units/week and coded as 0, 1 and 2, respectively) collected at the most recent phase pre-incident CVD and from all subsequent phases post-incident CVD (see Figure 1 for illustrative examples). Unlike growth mixture modelling (which is also FMM-based), GBTM does not assume that the population is composed of discrete groups defined by different trajectories. Instead, GBTM uses groups as a statistical device for approximating the unknown distribution of trajectories in the population and is thus more appropriate for elucidating heterogeneity in alcohol use over time (as population differences in drinking trajectories are unlikely to be clear-cut) [30]. We estimated trajectory models with three to six groups and for each group a polynomial function of time (up to second order) was considered, as suggested by previous research [31, 32]. The Bayesian information criterion was used to select optimal number and shape of groups. Patients were assigned to the group for which their posterior membership probability was highest (maximum-probability rule). Model adequacy was evaluated using the recommended average posterior probability (AvePP ≥ 0.7 is indicative of a high assignment accuracy) [33].

Prior to undertaking inferential analyses, multiple imputation by chained equations was completed to address missing covariate data [34]. Outcome (the Nelson–Aalen hazard and outcome indicator) and exposure (alcohol intakes at each phase) variables were also included in the imputation model, but only observed values of these variables were used in the substantive analysis [35, 36]. We treated repeated measurements as distinct variables in the imputation model [37]. Simulation studies show that this approach performs well in similar longitudinal settings [38, 39]. Altogether, 100 imputations were run.

Hazard ratios (HRs) for all-cause mortality in relation to drinking trajectories were estimated using Cox proportional hazards regression models. Models were first adjusted for age, sex and intake assessment interval (model 1), then additionally for ethnicity, socioeconomic position, health behaviours and medical status (model 2). Covariates in models 1 and 2 were from the most recent phase pre-incident CVD. To account for changes in health behaviours as well

as updates to medical status, further adjustment was made in model 3 for covariates (smoking, physical activity, dietary behaviour, use of cardiovascular drugs, prevalent diabetes and hypertension) assessed at the phase of last available alcohol assessment. Our reference group for analyses was stable moderate drinkers [40]. The proportional hazards assumption was tested using Schoenfeld residuals and found not to be violated (Supporting information, Figure S1).

We performed cross-sectional analyses with drinking categories defined using only data from the last available alcohol assessment, so that findings from the main analyses (trajectory approach) can be compared to those that would have been obtained using the conventional approach in which exposure to alcohol was only assessed at one time-point. Former drinkers were separated from abstainers in cross-sectional analyses based on whether they reported at that phase to be always non-drinkers.

Sensitivity analyses were conducted restricting analyses to either male patients, those with ≥ 3 alcohol measures, having CHD as first event or having complete-case data. Previous research has suggested that the intake threshold associated with increased risk of mortality among CVD patients may be higher than 14 units/week [6, 41], so in exploratory *post-hoc* analyses the average weekly intake during the assessment interval was calculated for each patient in the group of stable heavy drinkers. The group was then divided into two subgroups based on the group mean value of average weekly intakes, and their associations with mortality were examined. Additional *post-hoc* analysis was conducted with further adjustment for concurrent changes in patients' self-rated health (excellent/good, fair or poor). Self-rated health has been shown to be a valid measure of overall health status as well as a predictor of mortality among participants of the Whitehall II study [42, 43]. Such analyses help to reveal whether changes in alcohol consumption occur as a consequence of worsening health. All analyses were performed using Stata version 15.1.

RESULTS

GBTM and sample characteristics

Of 10 308 Whitehall II participants, 178 were excluded due to a diagnosis of CHD/stroke or cancer before phase 1. A total of 1705 survived an incident CHD/stroke event from phases 1–12, 1306 of whom had repeated measures of alcohol and were included in this study.

In GBTM analysis, a six-group model provided the best fit to the data (see Supporting information, Table S2 for model fit statistics) and showed adequate classification accuracy, with AvePP between 0.75–0.93. The identified trajectory groups are shown in Figure 2 (where occasion 1 corresponds to the most recent phase - pre-incident CVD), labelled *a posteriori* as: long-term abstainers (15.5%), stable moderate drinkers (53.9%), reduced moderate drinkers (6.0%), former drinkers (6.3%), unstable heavy drinkers (8.5%) and stable heavy drinkers (9.8%). Overall, the resultant trajectories comprised a median assessment interval of 12.2 [interquartile range (IQR) = 7.0–18.0] years, with each patient contributing an average of four (IQR = 3–5) measures of alcohol.

Table 1 shows the characteristics of the study sample, as well as the proportion of missingness. Heavy drinkers (unstable or stable) were more likely to be male, of white ethnicity and high socio-economic position; they were also more frequently past or current smokers at the most recent phase pre-incident CVD. Across all trajectory groups, the proportions of patients currently smoking or meeting physical activity recommendations decreased from the most recent phase pre-incident CVD to the phase of last available alcohol assessment. The prevalence of cardiovascular drug use, diabetes and hypertension increased during the same period.

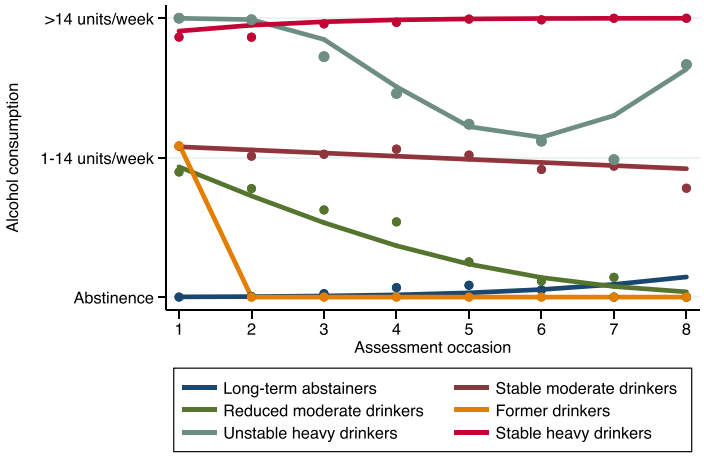

FIGURE 2 Alcohol consumption trajectories of the six groups identified using group-based trajectory modelling. Assessment occasion 1 corresponds to the most recent phase pre-incident CVD and assessment occasions 2–8 represent subsequent phases post-incident cardiovascular disease (CVD). Solid lines indicate estimated trajectories and dot symbols indicate observed group means at each assessment occasion

TABLE 1 Patient characteristics by alcohol consumption trajectories

	Stable moderate drinkers	Long-term abstainers	Reduced moderate drinkers	Former drinkers	Unstable heavy drinkers	Stable heavy drinkers	Overall
No. of patients	704 (53.9)	203 (15.5)	78 (6.0)	82 (6.3)	111 (8.5)	128 (9.8)	1306 (100)
Intake assessment interval, median (IQR) years	12.2 (6.9–17.9)	10.8 (5.2–17.2)	17.8 (12.9–23.3)	7.2 (4.2–12.6)	12.4 (6.4–18.2)	14.2 (11.2–19.1)	12.2 (7.0–18.0)
No. of alcohol measures, median (IQR)	4 (3–5)	3 (2–4)	5 (4–5)	3 (2–4)	4 (2–5)	4 (3–5)	4 (3–5)
At the most recent phase pre-incident CVD							
Age, mean (SD) years	60.4 (8.9)	61.1 (9.2)	57.3 (8.1)	64.1 (9.1)	59.1 (9.1)	56.8 (7.9)	60.1 (9.0)
Male	574 (81.5)	97 (47.8)	44 (56.4)	53 (64.6)	107 (96.4)	123 (96.1)	998 (76.4)
Ethnicity							
White	635 (90.2)	131 (64.5)	65 (83.3)	69 (84.1)	109 (98.2)	123 (96.1)	1132 (86.7)
Non-white	68 (9.7)	71 (35.0)	13 (16.7)	13 (15.9)	2 (1.8)	5 (3.9)	172 (13.2)
Missing	1 (0.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Socio-economic position							
High	314 (44.6)	29 (14.3)	14 (17.9)	24 (29.3)	63 (56.8)	81 (63.3)	525 (40.2)
Intermediate	321 (45.6)	92 (45.3)	41 (52.6)	43 (52.4)	43 (38.7)	47 (36.7)	587 (44.9)
Low	69 (9.8)	82 (40.4)	23 (29.5)	15 (18.3)	5 (4.5)	0 (0.0)	194 (14.9)
Smoking status							
Never smoker	279 (39.6)	91 (44.8)	36 (46.2)	41 (50.0)	35 (31.5)	32 (25.0)	514 (39.4)
Ex-smoker	302 (42.9)	61 (30.0)	21 (26.9)	33 (40.2)	56 (50.5)	67 (52.3)	540 (41.3)
Current smoker	79 (11.2)	30 (14.8)	14 (17.9)	7 (8.5)	17 (15.3)	21 (16.4)	168 (12.9)
Missing	44 (6.3)	21 (10.3)	7 (9.0)	1 (1.2)	3 (2.7)	8 (6.3)	84 (6.4)
Physical activity[a]							
Met recommendations	242 (34.4)	42 (20.7)	13 (16.7)	27 (32.9)	42 (37.8)	34 (26.6)	400 (30.6)
Below recommendations	422 (59.9)	142 (70.0)	55 (70.5)	53 (64.6)	66 (59.5)	84 (65.6)	822 (62.9)
Missing	40 (5.7)	19 (9.4)	10 (12.8)	2 (2.4)	3 (2.7)	10 (7.8)	84 (6.4)
Fruit/vegetable consumption							
≥ Daily	462 (65.6)	121 (59.6)	53 (67.9)	59 (72.0)	81 (73.0)	77 (60.2)	853 (65.3)
< Daily	204 (29.0)	65 (32.0)	18 (23.1)	23 (28.0)	25 (22.5)	42 (32.8)	377 (28.9)
Missing	38 (5.4)	17 (8.4)	7 (9.0)	0 (0.0)	5 (4.5)	9 (7.0)	76 (5.8)
Use of cardiovascular drugs							
Yes	248 (35.2)	84 (41.4)	23 (29.5)	30 (36.6)	40 (36.0)	39 (30.5)	464 (35.5)
No	437 (62.1)	110 (54.2)	54 (69.2)	52 (63.4)	69 (62.2)	85 (66.4)	807 (61.8)
Missing	19 (2.7)	9 (4.4)	1 (1.3)	0 (0.0)	2 (1.8)	4 (3.1)	35 (2.7)
Prevalent diabetes[b]							
Yes	73 (10.4)	50 (24.6)	10 (12.8)	13 (15.9)	16 (14.4)	17 (13.3)	179 (13.7)
No	612 (86.9)	145 (71.4)	67 (85.9)	69 (84.1)	93 (83.8)	107 (83.6)	1093 (83.7)

(Continues)

TABLE 1 (Continued)

	Stable moderate drinkers	Long-term abstainers	Reduced moderate drinkers	Former drinkers	Unstable heavy drinkers	Stable heavy drinkers	Overall
Missing	19 (2.7)	8 (3.9)	1 (1.3)	0 (0.0)	2 (1.8)	4 (3.1)	34 (2.6)
Prevalent hypertension[c]							
Yes	360 (51.1)	129 (63.5)	44 (56.4)	46 (56.1)	63 (56.8)	69 (53.9)	711 (54.4)
No	325 (46.2)	66 (32.5)	33 (42.3)	36 (43.9)	46 (41.4)	55 (43.0)	561 (43.0)
Missing	19 (2.7)	8 (3.9)	1 (1.3)	0 (0.0)	2 (1.8)	4 (3.1)	34 (2.6)
At the phase of last available alcohol assessment							
Smoking status							
Never smoker	259 (36.8)	83 (40.9)	29 (37.2)	31 (37.8)	31 (27.9)	27 (21.1)	460 (35.2)
Ex-smoker	376 (53.4)	81 (39.9)	26 (33.3)	34 (41.5)	65 (58.6)	91 (71.1)	673 (51.5)
Current smoker	27 (3.8)	13 (6.4)	7 (9.0)	1 (1.2)	8 (7.2)	4 (3.1)	60 (4.6)
Missing	42 (6.0)	26 (12.8)	16 (20.5)	16 (19.5)	7 (6.3)	6 (4.7)	113 (8.7)
Physical activity[a]							
Met recommendations	142 (20.2)	22 (10.8)	11 (14.1)	12 (14.6)	23 (20.7)	27 (21.1)	237 (18.2)
Below recommendations	510 (72.4)	163 (80.3)	57 (73.1)	56 (68.3)	79 (71.2)	93 (72.7)	958 (73.4)
Missing	52 (7.4)	18 (8.9)	10 (12.8)	14 (17.1)	9 (8.1)	8 (6.3)	111 (8.5)
Fruit/vegetable consumption							
≥ Daily	500 (71.0)	125 (61.6)	43 (55.1)	57 (69.5)	78 (70.3)	87 (68.0)	890 (68.2)
< Daily	186 (26.4)	62 (30.5)	23 (29.5)	13 (15.9)	28 (25.2)	38 (29.7)	350 (26.8)
Missing	18 (2.6)	16 (7.9)	12 (15.4)	12 (14.6)	5 (4.5)	3 (2.3)	66 (5.1)
Use of cardiovascular drugs							
Yes	642 (91.2)	174 (85.7)	67 (85.9)	74 (90.2)	101 (91.0)	117 (91.4)	1175 (90.0)
No	60 (8.5)	28 (13.8)	11 (14.1)	8 (9.8)	10 (9.0)	11 (8.6)	128 (9.8)
Missing	2 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Prevalent diabetes[b]							
Yes	239 (33.9)	109 (53.7)	47 (60.3)	46 (56.1)	40 (36.0)	52 (40.6)	533 (40.8)
No	465 (66.1)	94 (46.3)	31 (39.7)	36 (43.9)	71 (64.0)	76 (59.4)	773 (59.2)
Prevalent hypertension[c]							
Yes	609 (86.5)	173 (85.2)	66 (84.6)	77 (93.9)	97 (87.4)	111 (86.7)	1133 (86.8)
No	93 (13.2)	29 (14.3)	12 (15.4)	5 (6.1)	14 (12.6)	17 (13.3)	170 (13.0)
Missing	2 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)

Values are numbers (percentages) unless stated otherwise.

[a]Physical activity meeting WHO recommendations defined as ≥ 150 min of moderate-intensity or ≥ 75 min of vigorous-intensity activity per week.

[b]Prevalent diabetes defined as reported doctor-diagnosed diabetes, fasting blood glucose ≥ 7.0 mmol/l or use of antidiabetic drugs.

[c]Prevalent hypertension defined as reported doctor-diagnosed hypertension, systolic/diastolic blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs. CVD = cardiovascular disease; IQR = interquartile range; SD = standard deviation.

Alcohol consumption trajectories and all-cause mortality

There were 380 deaths, with the median time from the last alcohol assessment to death being 5.0 (IQR = 4.4–5.7) years. Long-term abstainers, stable and unstable heavy drinkers all had a similar risk of mortality as stable moderate drinkers after adjustment for all included covariates (Table 2). Compared to stable moderate drinkers, former drinkers had a higher risk of mortality after adjustment for covariates from the most recent phase pre-incident CVD (model 2; HR = 1.84, 95% confidence interval (CI) = 1.26–2.68). The effect remained but was slightly attenuated in a maximally adjusted model with further adjustment for changes in other health behaviours and medical status (model 3; HR = 1.74, 95% CI = 1.19–2.54).

Cross-sectional analyses

In cross-sectional analyses, former drinkers had a point estimate of mortality risk greater than 1 when compared with moderate drinkers and adjusted for covariates from the most recent phase pre-incident CVD (model 2; HR = 1.24, 95% CI = 0.94–1.63); this effect, however, was not statistically significant and was further attenuated in a maximally adjusted model (model 3; HR = 1.16, 95% CI = 0.87–1.53). There was little difference in mortality risk among abstainers and heavy drinkers compared to moderate drinkers (Table 2).

Sensitivity analyses

Results of sensitivity analyses are in Supporting information, Table S3. The findings did not alter substantially when we restricted analyses to either male patients, those with ≥ 3 measures of alcohol or having CHD as first event. Similar associations were observed when using complete case data only.

Post-hoc analyses

Among the 128 stable heavy drinkers, mean weekly intake over the assessment interval was 30 [standard deviation (SD) = 12] units. Patients who died during follow-up had higher weekly intakes than survivors (mean ± SD = 34 ± 14 units versus 28 ± 11 units, respectively). Compared to stable moderate drinkers, HR for all-cause mortality was 1.53 (95% CI = 0.93–2.51) in stable heavy drinkers with weekly intakes > 30 units and 0.77 (95% CI = 0.45–1.30) in those with weekly intakes ≤ 30 units in maximally adjusted analysis (with adjustment for the same covariates listed in Table 2, model 3).

At the most recent phase pre-incident CVD, long-term abstainers had the lowest proportion of patients rating their health as excellent or good (55.7%), while unstable heavy drinkers had the highest (76.6%). The proportion decreased over the interval from the most recent phase pre-incident CVD to last alcohol assessment in all trajectory groups (Supporting information, Table S4), with the greatest decrease seen in former drinkers (−36.8%, from 69.5 to 43.9%), followed by unstable heavy drinkers

TABLE 2 Association between alcohol consumption and risk of all-cause mortality

Alcohol consumption	No. of death	No. of patients	Hazard ratio (95% CI)		
			Model 1[a]	Model 2[b]	Model 3[c]
Trajectories					
Stable moderate drinkers	192	704	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Long-term abstainers	63	203	1.16 (0.86–1.56)	1.18 (0.87–1.62)	1.13 (0.83–1.55)
Reduced moderate drinkers	21	78	1.16 (0.73–1.84)	1.14 (0.72–1.83)	1.08 (0.67–1.73)
Former drinkers	35	82	1.77 (1.22–2.55)	1.84 (1.26–2.68)	1.74 (1.19–2.54)
Unstable heavy drinkers	34	111	1.28 (0.88–1.85)	1.24 (0.86–1.80)	1.25 (0.86–1.81)
Stable heavy drinkers	35	128	1.19 (0.83–1.72)	1.13 (0.78–1.64)	1.10 (0.76–1.60)
Categories based on single assessment only[d]					
Moderate drinkers	187	652	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Abstainers	59	187	1.08 (0.80–1.46)	1.11 (0.81–1.52)	1.04 (0.76–1.44)
Former drinkers	78	245	1.23 (0.94–1.61)	1.24 (0.94–1.63)	1.16 (0.87–1.53)
Heavy drinkers	56	222	0.91 (0.67–1.23)	0.86 (0.63–1.17)	0.85 (0.62–1.15)

CI = confidence interval, Ref = reference; CVD = cardiovascular disease.
[a]Adjusted for sex, age and intake assessment interval.
[b]Additionally adjusted for ethnicity, socio-economic position, smoking, physical activity, dietary behaviour, use of cardiovascular drugs, prevalent diabetes and hypertension, assessed at the most recent phase pre-incident CVD.
[c]Additionally adjusted for smoking, physical activity, dietary behaviour, use of cardiovascular drugs, prevalent diabetes and hypertension, assessed at the phase of last available alcohol assessment.
[d]Drinking categories defined using intakes from the last available alcohol assessment.

(−23.5%, from 76.6 to 58.6%,) and reduced moderate drinkers (−17.6%, from 65.4 to 53.8%). Further adjustment for changes in self-rated health attenuated the associations between trajectories and all-cause mortality (Supporting information, Table S5).

DISCUSSION

In this inception cohort of patients with incident CVD events, we derived drinking trajectories with repeated assessments spanning up to 30 years and examined their association with subsequent risk of total mortality. Through iterative modelling that accounted for changing life-style and health status, we found no evidence that patients who consistently consumed alcohol within the recommended limit of 14 units/week had a lower risk of mortality compared to long-term abstainers. We also found that former drinkers had a greater mortality risk than stable moderate drinkers.

The elevated risk of mortality among former drinkers was only appreciable when considering long-term drinking trajectories and was not significantly detected in our cross-sectional analyses. Indeed, a large proportion of patients in this cohort did not have stable drinking trajectories following their incident CVD. Apart from those transiting from drinking to non-drinking, this study also observed an overall decrease in alcohol intake over time among some continuers (reduced moderate drinkers and unstable heavy drinkers), as has also been reported elsewhere [16, 44]. The tendency towards desistance/lower levels of drinking with increasing age suggests that categorization of alcohol intake based on single time-point measurements may be problematic, especially when applied to cohorts with long follow-up periods and older participants. These highlight the importance of longitudinal measures and a life-course approach in examining the effect of alcohol on health and our study should be replicated with other outcomes.

Our findings echo other research which suggests that former drinkers have poorer self-perceived general health [45] and are at higher risk of experiencing adverse outcomes including CHD and overall mortality than moderate drinkers [18, 46]. As a reason for the higher risk seen in former drinkers, the sick-quitter hypothesis proposes that a substantial number of former drinkers have quit drinking for health reasons [47, 48]. In line with this hypothesis, we found that former drinkers had a higher prevalence of poor self-rated health than other groups at the most recent phase pre-incident CVD and showed the biggest decrease in the proportion of patients reporting good to excellent health during follow-up. The association for former drinkers was weakened following further adjustment for self-rated health, suggesting that poorer general health may partially explain former drinkers' increased likelihood of death and perhaps may have driven the decision to abstain itself.

In the present study, no statistically significant protective effect was found in relation to consistent moderate drinking compared to long-term abstinence. This concurs with general population studies measuring alcohol intake over time (collected either as repeated measures or as recall of past drinking levels) and mortality [49–51], as well as several Mendelian randomization studies where alcohol's cardioprotective effect has been tested and refuted [52–54]. Regarding CVD patients, longitudinal assessment of alcohol has been reported in two previous studies, where low levels of consumption were found to be associated with lower mortality [16, 17]. However, both studies have used a reference group composed of former drinkers and lifetime abstainers. The lower mortality risk for moderate drinking compared with non-drinking could potentially be caused by a less healthy comparison group contaminated by sick quitters (as discussed above). Furthermore, the variety of reasons for which people abstain from drinking throughout life may introduce other biases. For instance, non-drinkers in later life may include those who adopt life-long teetotalism due to continual poor health [55]. In this study, only a small minority of CVD patients were long-term abstainers. Notably, this group consisted mainly of women from a lower socio-economic position with a higher prevalence of cardiometabolic risk factors and disease as well as poorer self-rated health, a pattern that has also been reported in other study populations where alcohol use is normative [56, 57]. It has been suggested that members of this minority differ from drinkers on a number of health determinants and that unmeasured confounders may have contributed to the excess risk seen in this group [58, 59]. These motivated our choice of considering moderate drinkers as the reference group throughout this work and might explain the slightly increased point estimate for long-term abstainers, despite the extensive level of adjustment in our analyses.

Although excessive drinking raises the risk of total mortality, the level from which this effect is evident is less clear. We assessed the impact of heavy drinking on CVD patients using the 14 units/week threshold advocated by the current UK guidelines and observed no elevated risk for those who consistently drank above this limit. Previous dose–response analyses using data from 83 general population cohorts have reported an intake threshold for increased mortality risk at ≥ 200 g/week (25 units/week) [41]. This agrees with the results of our *post-hoc* analyses, where an increased risk was seen in stable heavy drinkers with higher average intakes (> 30 units/week). Clearly, the small number of patients within this group precludes any firm conclusion. Further data are therefore needed to explore alternative intake thresholds and validate the findings of the current study. In addition, heavy drinkers who remain in the cohort are likely to be 'healthy survivors' or have safer drinking patterns and practices [10, 60]. At the most recent phase pre-incident CVD, the proportion of patients drinking in excess of guidelines (36% male and 13% female) is lower than the recent estimates from Health Survey for England (39% male and 20% female aged 55–64 years) [61], which means that heavy drinkers may be under-represented in our data set. These potential selections could have biased downwards the estimate of association between heavy intake and mortality risk, and thus caution is required when interpreting the lack of effect among heavy drinkers seen in our study.

There are other limitations that should be noted. First, our alcohol measures are self-reported; however, self-reports of drinking have shown reasonable levels of validity and reliability, especially when

involving specified time-frames ('past week' instead of 'usual' reference frames) and beverage-specific questions [62, 63]. Comparison of alcohol consumption reported by the Whitehall II participants also suggests patterns similar to those in other UK cohorts [64]. Alcohol measures utilized in this study reflect intake only over the week immediately prior to each assessment, and may not be representative of participants' general consumption. Although this may introduce some exposure misclassification, the repeated assessment of alcohol over such a long period is unique. By integrating these repeated assessments, we were able to estimate trajectories, providing a more accurate account of longitudinal exposure than a cross-sectional approach. Secondly, on the basis of maximum-probability assignment rule, a level of uncertainty remains in individual-level trajectory group membership. However, such uncertainty is unlikely to materially alter the profiles (characteristics and outcomes) that emerge from well-fitting models such as the one in our GBTM analysis [33]. Because of power limitations restricting further refinement, we were unable to incorporate other drinking characteristics into the construction of trajectories. Additional data may provide insights into other drinking patterns, such as binge drinking, which could further clarify the observed mortality risk associated with unstable drinking trajectories. Relatedly, subgroup analyses (for example, in female or by age groups) were not possible due to the small number of patients in certain trajectory groups. In addition, participants in the Whitehall II study are not a representative sample of the general population; however, it has been shown that cardiometabolic-related etiological evidence from this occupational cohort are broadly in agreement with those obtained from nationally representative cohorts [65]. Although we considered a wide range of covariates and accounted for their changes in the analyses, the possibility of residual confounding or confounding by unmeasured factors cannot be ruled out.

CONCLUSION

In conclusion, this study has illustrated the dynamic and diverse nature of alcohol use in CVD patients and how long-term drinking profiles are associated with their subsequent risk of death from all causes. By demonstrating the differing insights obtainable from cross-sectional and repeated exposure assessment, this study has also confirmed the utility of taking a longitudinal approach in examining the association of alcohol with health outcomes. We found that CVD patients who consistently drank within the UK guidelines of 14 units/week had a similar risk of mortality as those who were continuous abstainers; therefore, this study does not support a protective effect of moderate drinking on total mortality. Patients who stopped drinking following incident CVD were at greater risk of mortality than continuous moderate drinkers; however, the former drinkers also had the highest proportion with poor self-rated health before CVD onset and experienced the greatest degree of health deterioration during follow-up. This study contributes to the dearth of evidence on health effects of alcohol consumption among CVD patients.

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DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Chengyi Ding: Conceptualization; formal analysis. **Dara O'Neill:** Conceptualization; formal analysis; supervision. **Annie Britton:** Conceptualization; formal analysis; supervision.

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SUPPORTING INFORMATION

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Appendix 4.2 Model fit statistics for estimation of alcohol consumption trajectories (group-based trajectory models)

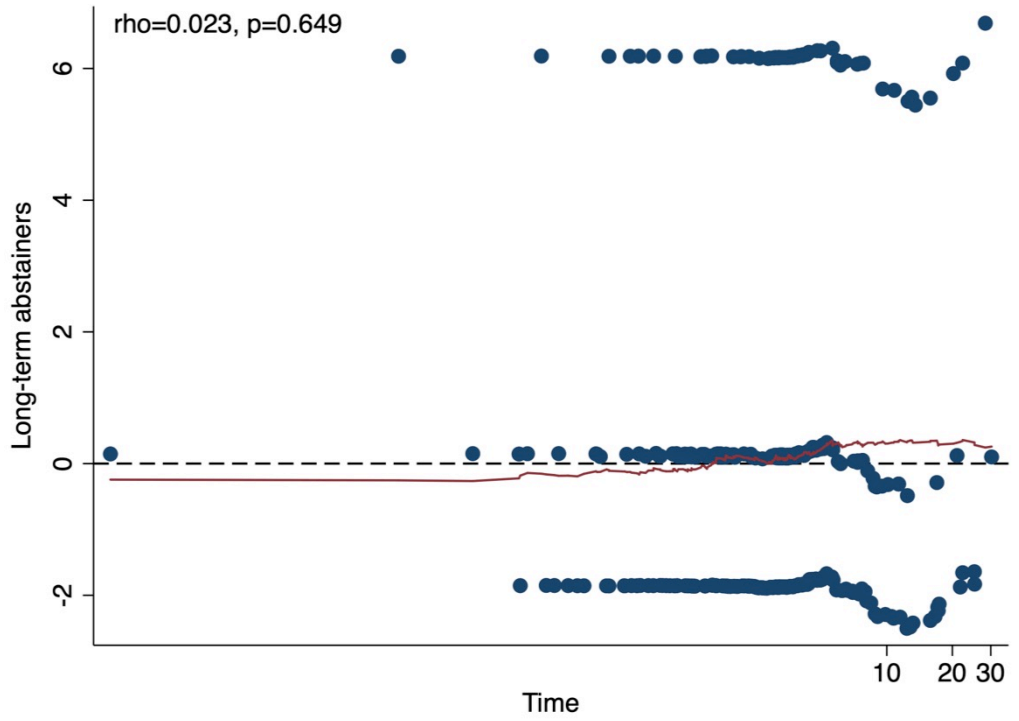
Number of groups	Trajectory shapes*	BIC †	BIC ‡	AIC
3	1 1 1	-5456.48	-5450.46	-5427.18
	2 2 2	-5476.88	-5468.86	-5437.81
4	1 1 1 1	-5416.72	-5408.69	-5377.65
	2 2 2 2	-5430.96	-5420.26	-5378.86
5	1 1 1 1 1	-5380.88	-5370.85	-5332.04
	2 2 2 2 2	-5402.02	-5388.65	-5336.90
6	1 1 1 1 1 1	-5371.05	-5359.02	-5312.45
6	2 1 1 1 1 1	-5357.42	-5344.71	-5295.55
	1 2 1 1 1 1	-5349.47	-5336.77	-5287.61
	1 1 2 1 1 1	-5369.88	-5357.17	-5308.01
	1 1 1 2 1 1	-5371.29	-5358.58	-5309.42
	1 1 1 1 2 1	-5371.29	-5358.58	-5309.42
	1 1 1 1 1 2	-5385.29	-5372.59	-5323.43
6	2 2 1 1 1 1	-5353.73	-5340.36	-5288.61
	2 1 2 1 1 1	-5353.73	-5340.36	-5288.61
	2 1 1 2 1 1	-5360.41	-5347.04	-5295.30
	2 1 1 1 2 1	-5375.54	-5362.17	-5310.42
	2 1 1 1 1 2	-5379.57	-5366.20	-5314.45
	1 2 2 1 1 1	-5374.35	-5360.98	-5309.24
	1 2 1 2 1 1	-5335.95	-5322.58	-5270.83
	1 2 1 1 2 1	-5375.54	-5362.17	-5310.42
	1 2 1 1 1 2	-5353.73	-5340.36	-5288.61
	1 1 2 2 1 1	-5348.46	-5335.09	-5283.35
	1 1 2 1 2 1	-5354.81	-5341.44	-5289.69
	1 1 2 1 1 2	-5379.23	-5365.86	-5314.11
	1 1 1 2 2 1	***-5332.79***	***-5319.42***	***-5267.67***
	1 1 1 2 1 2	-5345.52	-5332.15	-5280.40
	1 1 1 1 2 2	-5358.44	-5345.07	-5293.32
6	2 2 2 1 1 1	-5376.03	-5361.99	-5307.65
	2 2 1 2 1 1	-5352.69	-5338.65	-5284.32
	2 2 1 1 2 1	-5352.72	-5338.68	-5284.35
	2 2 1 1 1 2	-5357.98	-5343.94	-5289.61
	2 1 1 2 2 1	-5340.41	-5326.37	-5272.04
	2 1 1 2 1 2	-5357.98	-5343.94	-5289.61
	2 1 1 1 2 2	-5357.98	-5343.94	-5289.61
	2 1 2 2 1 1	-5359.73	-5345.69	-5291.35

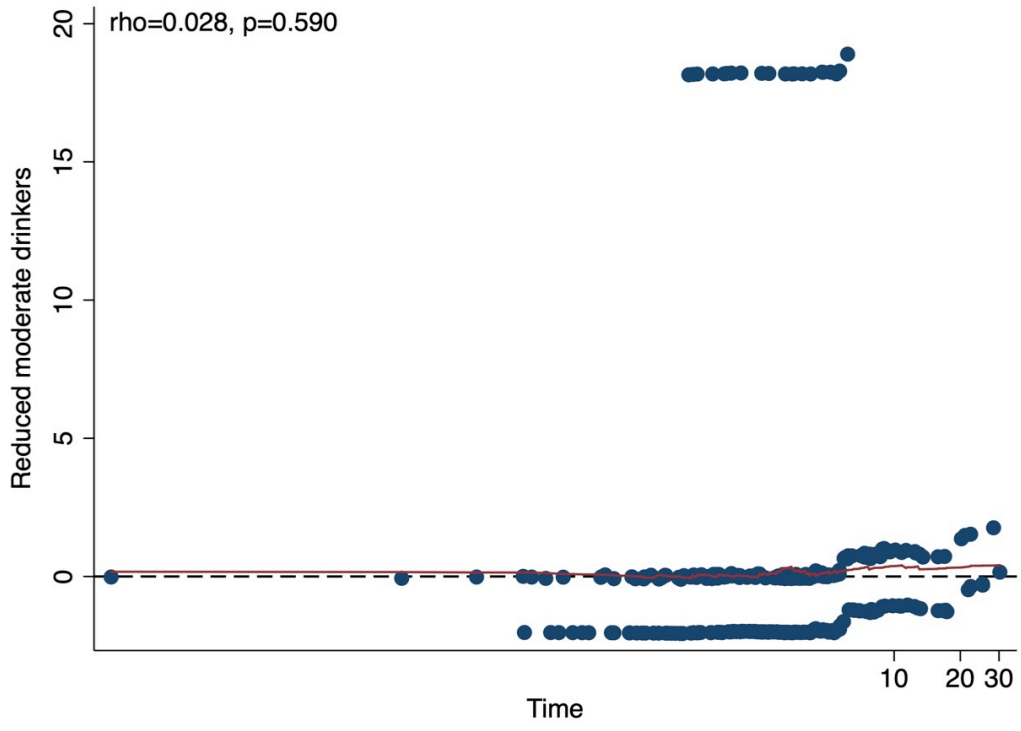
	2 1 2 1 2 1	-5352.69	-5338.65	-5284.32
	2 1 2 1 1 2	-5386.55	-5372.51	-5318.18
	1 2 2 2 1 1	-5379.47	-5365.44	-5311.10
	1 2 2 1 2 1	-5372.91	-5358.87	-5304.53
	1 2 2 1 1 2	-5340.51	-5326.47	-5272.13
	1 2 1 2 2 1	-5350.83	-5336.79	-5282.46
	1 2 1 2 1 2	-5340.51	-5326.47	-5272.13
	1 2 1 1 2 2	-5378.61	-5364.57	-5310.24
	1 1 2 2 2 1	-5329.48	-5315.44	-5261.11
	1 1 2 2 1 2	-5340.51	-5326.47	-5272.13
	1 1 2 1 2 2	-5357.90	-5343.86	-5289.53
	1 1 1 2 2 2	-5349.65	-5335.61	-5281.27
6	1 1 2 2 2 2	-5376.33	-5361.62	-5304.70
	1 2 1 2 2 2	-5363.11	-5348.40	-5291.48
	1 2 2 1 2 2	-5382.80	-5368.09	-5311.17
	1 2 2 2 1 2	-5361.84	-5347.13	-5290.21
	1 2 2 2 2 1	-5388.56	-5373.85	-5316.93
	2 1 1 2 2 2	-5385.52	-5370.81	-5313.89
	2 1 2 1 2 2	-5390.78	-5376.07	-5319.15
	2 1 2 2 1 2	-5356.95	-5342.24	-5285.32
	2 1 2 2 2 1	-5390.76	-5376.06	-5319.14
	2 2 1 1 2 2	-5413.91	-5399.20	-5342.28
	2 2 1 2 1 2	-5356.95	-5342.24	-5285.32
	2 2 1 2 2 1	-5358.14	-5343.43	-5286.51
	2 2 2 1 1 2	-5380.28	-5365.58	-5308.65
	2 2 2 1 2 1	-5363.90	-5349.19	-5292.27
	2 2 2 2 1 1	-5356.91	-5342.20	-5285.28
6	1 2 2 2 2 2	-5380.58	-5365.21	-5305.70
	2 1 2 2 2 2	-5367.36	-5351.98	-5292.48
	2 2 1 2 2 2	-5374.77	-5359.40	-5299.89
	2 2 2 1 2 2	-5373.73	-5358.35	-5298.84
	2 2 2 2 1 2	-5361.16	-5345.79	-5286.28
	2 2 2 2 2 1	-5362.34	-5346.97	-5287.46
6	2 2 2 2 2 2	-5377.97	-5361.93	-5299.83

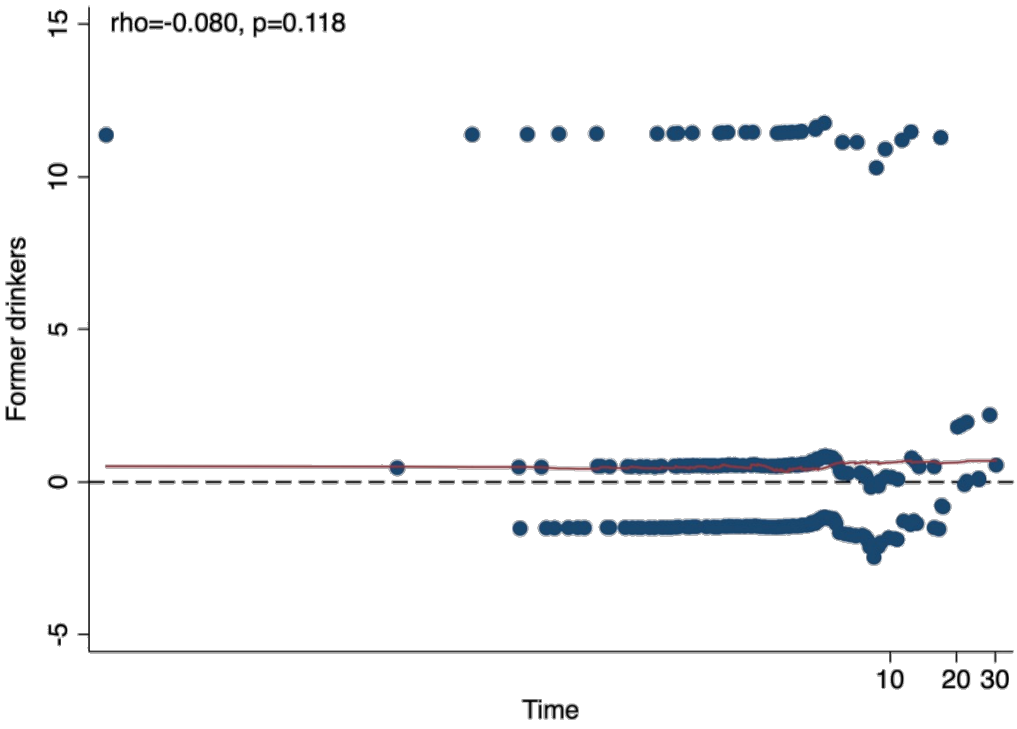
* Polynomial type for each group trajectory (0 intercept only, 1 linear, 2 quadratic).
† BIC for the total number of alcohol measurements (N=4973). A difference of 10 is strong evidence in favour of the model with a greater BIC; model with the highest (least negative) value of BIC has best fit.
‡ BIC for the total number of patients (N=1306).
BIC=Bayesian information criterion, AIC=Akaike information criterion

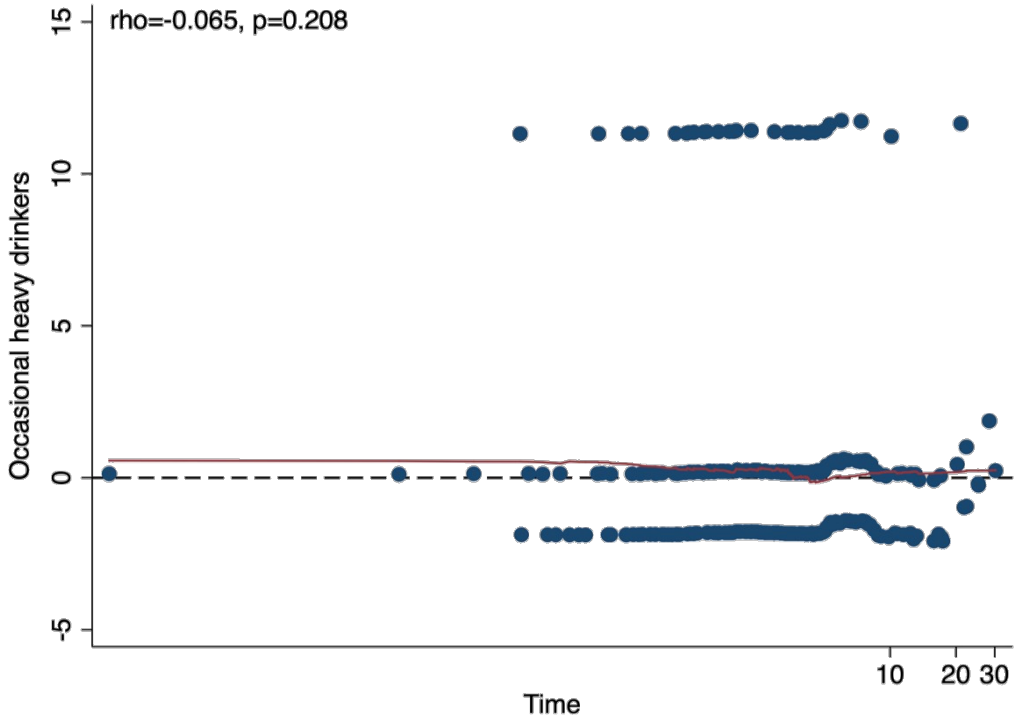
Appendix 4.3 Schoenfeld residuals for Whitehall II

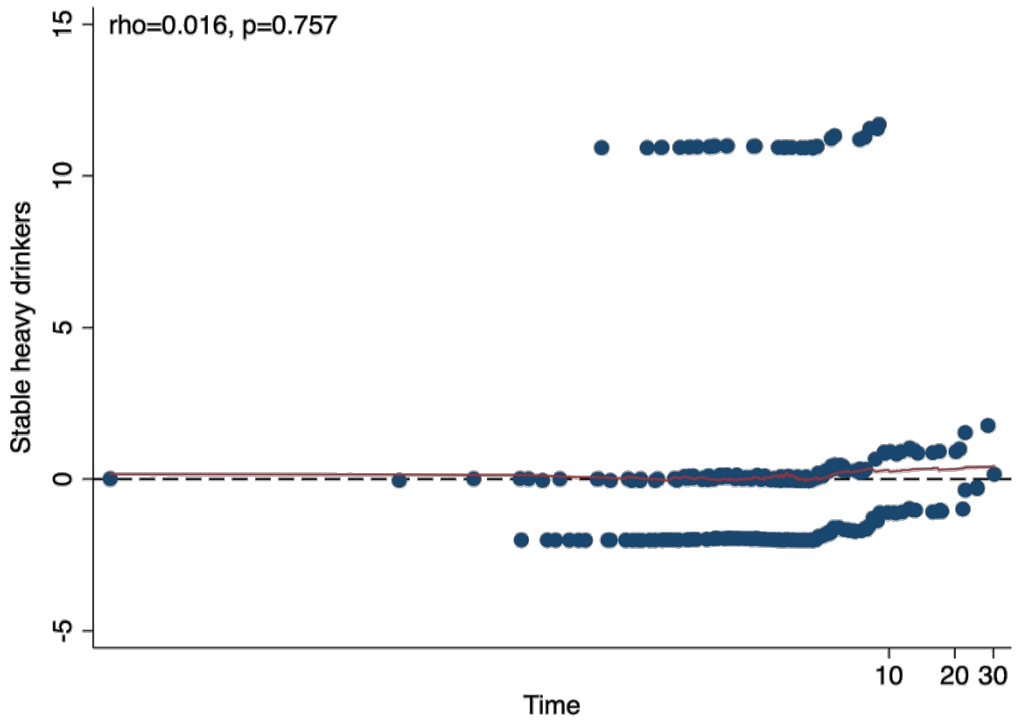
(a) All-cause mortality for models using alcohol consumption trajectories



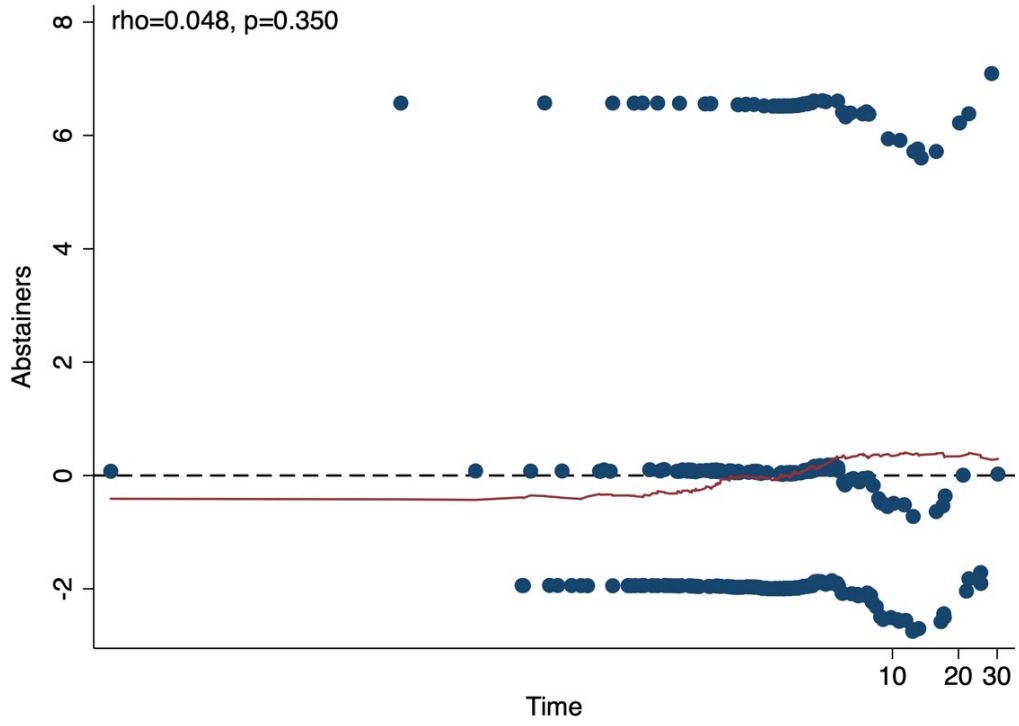


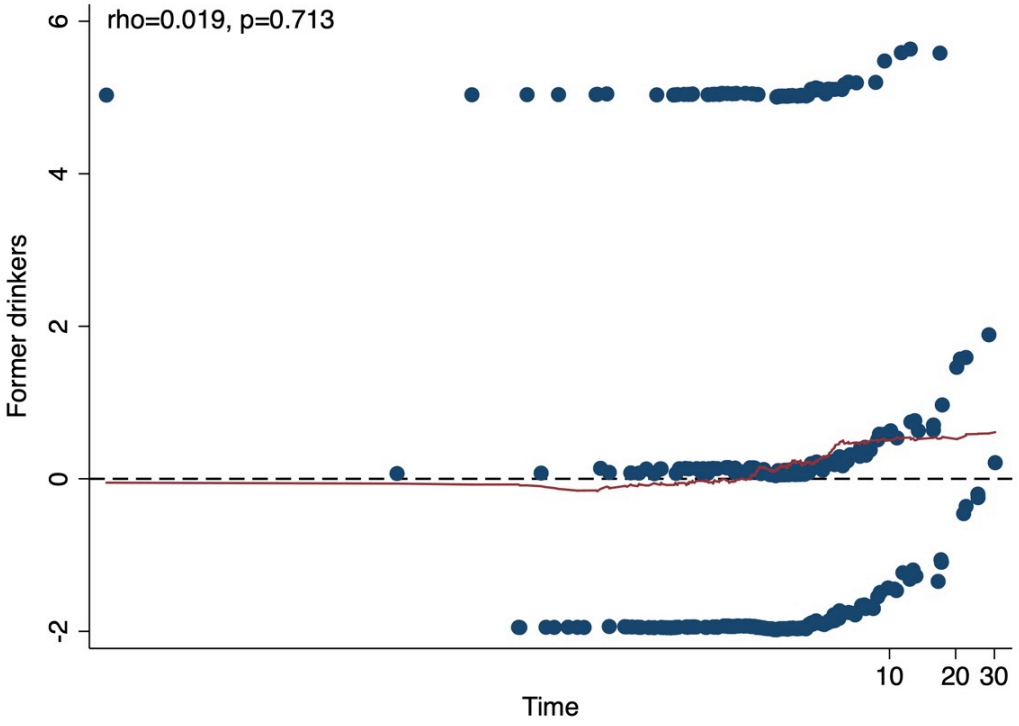

rho=-0.080, p=0.118
Former drinkers
15
10
5
0
-5
10
20
30
Time

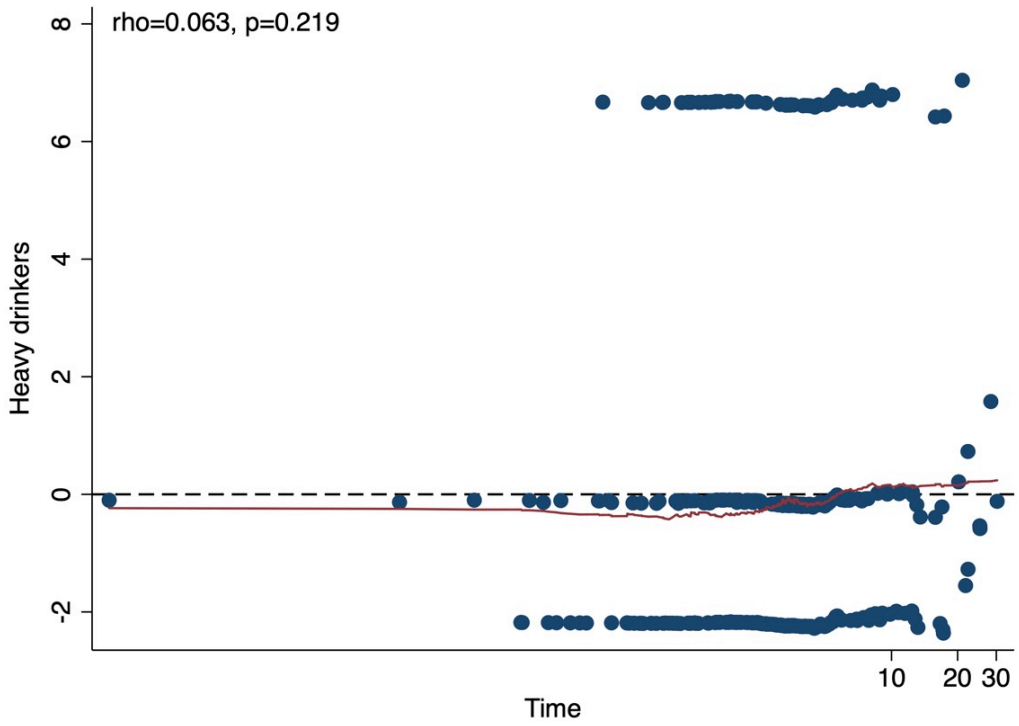

rho=-0.065, p=0.208
Occasional heavy drinkers
15
10
5
0
-5
10
20
30
Time


rho=0.016, p=0.757
Stable heavy drinkers
15
10
5
0
-5
10
20
30
Time

(b) All-cause mortality for models using alcohol consumption categories based on single assessment only






rho=0.063, p=0.219
Heavy drinkers
8
6
4
2
0
-2
10
20
30
Time

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