Investigating the relationship between alcohol consumption and type 2 diabetes

A longitudinal analysis of the Whitehall II cohort, 1985-2013

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Declaration

I, Craig Knott, 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.

Abstract

Background: Although previous studies have reported a J-shaped association between the volume of alcohol consumption and incidence of type 2 diabetes (T2DM), a number of limitations weaken the validity of such findings. This thesis aims to systematically explore the effect of key methodological shortcomings.

Methods: Analyses were undertaken using Whitehall II data from 1985-2013. To examine the degree to which conventional survival analyses might be subject to misclassification error due to the use of a single baseline measure of drinking status, mixed effects models were used to plot the trajectory of alcohol intake according to baseline categories of consumption. Mixed effects models were also stratified by diagnosis status to shed light upon whether increases or decreases in risk are likely to accrue gradually over the life course or occur as a consequence of differences in intake specific to periods of heightened biological sensitivity. Finally, given changes in alcohol consumption across the life course, increasingly complex survival models were used to explore the relationship between different dimensions of the longitudinal trajectory and T2DM risk.

Results: Alcohol consumption within categories of baseline drinking converged over the adult life course toward moderate volumes, with moderate drinkers increasingly contaminated by participants defined at baseline as heavy or infrequent drinkers. Men who developed T2DM were found to increase their consumption up to their date of diagnosis, while drinking among women remained relatively stable up to diagnosis. Marked decreases in consumption were evident among both sexes following diagnosis. Reductions in the risk of T2DM were specific to or most pronounced among female current drinkers in middle age, with drinking in later life associated with an increased risk regardless of sex, after adjustment for prior consumption.

Conclusions: Variations in alcohol consumption across the adult life course highlight the importance of considering drinking histories when defining alcohol consumption categories, with the risk of misclassification error appearing to increase with age. Although reductions in the risk of T2DM were most pronounced among middle-aged women, evidence concerning the determinants of such a sex-specific disparity is lacking. That risks are heightened in older age suggest that any benefits from drinking earlier in the life course may be countered by age-related deteriorations to the alcohol metabolism.

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Glossary of units and abbreviations

ABV	Alcohol by volume
BIC	Bayesian information criterion
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DM	Diabetes mellitus
FFQ	Food frequency questionnaire
FP	Fractional polynomial
FPG	Fasting plasma glucose
g	Grams
GL	Glycaemic load
GWAS	Genome-wide association study
HbA1c	Glycated haemoglobin A1c
HDL	High density lipoprotein
HOMA	Homeostasis model assessment
HR	Hazard ratio
MAR	Missing at random
MCAR	Missing completely at random
MICE	Multiple imputation chained equations
MID	Multiple imputation, then deletion
ml	Millilitre
mmol/L	Millimoles per litre
NHS	National Health Service
nmol/L	Nanomoles per litre
OGTT	Oral glucose tolerance test
OR	Odds ratio
RR	Relative risk
SHBG	Sex hormone-binding globulin
SNP	Single nucleotide polymorphism
SMD	Standardised mean difference
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
THIN	The Health Improvement Network
TNF-α	Tumour necrosis factor alpha
UK	United Kingdom
US	United States
WHO	World Health Organisation
WW2	World War Two

Chapter 1
Introduction

1 Introduction

Diabetes mellitus (DM) is a condition implicated in the development of vascular dysfunction and thereby a heightened risk of numerous vascular conditions, including coronary heart disease (CHD) and ischaemic stoke,[1,2] as well as blindness, kidney failure and limb loss.[3] Beyond its human costs, the financial burden of the condition is sizeable, at up to £13.8bn of National Health Service (NHS) expenditure in 2010/11 and an estimated annual loss to the United Kingdom (UK) economy of £15.4bn through absenteeism and early mortality.[4]

Such factors are made all the more alarming by trend data indicating a rise in the prevalence of DM over recent decades, particularly within older age groups.[5] By 2014, DM was estimated to affect 6.4% of adults living in the United Kingdom, or around 2,913,538 people – an increase of 67% relative to 1994.[6] Thus, although the rate of newly diagnosed cases appears to have plateaued in recent years,[7] DM continues to pose considerable human and economic costs that represent a substantial public health challenge.

Fortunately, around 85% of known cases are of a type caused largely by exposure to deleterious yet modifiable lifestyle factors,[8] indicating that many future cases may be preventable. With this in mind, Public Health England published in 2015 a systematic review into the effectiveness of preventative lifestyle intervention programmes, of which the majority appeared to target improvements to physical activity and diet, including the regulation of fat and fibre consumption.[9]

In contrast to these programmes, a growing body of evidence has suggested that alcohol consumption may play a role in reducing the risk of type 2 diabetes mellitus (T2DM), with one meta-analysis from 2009 reporting that men and women who consumed ~22-24 g/day (154-168 g/week) of ethanol may be subject to a one-third reduction in the risk of T2DM, relative to never drinkers,[10] or a volume of intake equivalent to around 1.2 pints of 4% alcohol by volume (ABV) lager per day.[11]

With alcohol consumption appearing to represent a modifiable risk factor to which the majority of UK adults are exposed, Chapter 2 provides a more detailed overview of the evidence concerning alcohol consumption and T2DM, as well as a number of biological mechanisms by which alcohol consumption has been hypothesised to modify a person's risk of T2DM. The chapter also includes a summary of recent trends in alcohol consumption behaviour, and outlines a number of methodological limitations that may have led to an overestimation of reductions in T2DM risk at moderate volumes of alcohol intake. Acknowledging these

shortcomings, Chapter 3 reports results from an updated and revised meta-analysis that set out to explore the effect of such factors upon the observed dose-response relationship, with Chapter 4 providing a summary of the current literature, including gaps in the evidence base, such as a failure within conventional literature to consider the effect of longitudinal changes to drinking behaviour. Chapter 5 sets out a number of aims by which the longitudinal relationship between alcohol consumption and T2DM risk can be better understood, with Chapter 6 describing the selection and structure of a dataset for such an exploration and Chapter 7 establishing the suitability of the chosen cohort for quantifying the association between alcohol consumption and T2DM. Chapter 8 reports changes in alcohol consumption over the adult life course and investigates whether these trajectories differ according to T2DM diagnosis, while Chapter 9 utilises increasingly complex survival analyses to formally explore the relationship between different dimensions of the longitudinal trajectory and T2DM risk. Chapter 10 summarises findings from the analyses undertaken and documents a series of policy implications and areas for future research.

Chapter 2
Background

2 Background

2.1 Diabetes mellitus

DM is a chronic metabolic disorder characterised by the body's inability to effectively regulate the metabolism of carbohydrates and fats, leading to chronically elevated levels in the bloodstream. Such a homeostatic impairment is currently understood to take two primary forms:

- Type I diabetes (T1DM): an auto-immune disease in which an abnormal immune response leads to the destruction of insulin-producing pancreatic β-cells. Given the joint role of insulin in promoting the absorption of glucose from the blood into muscle and fat tissues, and the inhibition of glucose release from the liver, absolute insulin deficiency as associated with T1DM results in a build-up of carbohydrates and fats in the bloodstream.[12] T1DM has been identified as most common among younger individuals and estimated to represent around 5-10% of known cases worldwide, or around 15% of known cases in England.[8]

- Type 2 diabetes (T2DM): T2DM is characterised by relative insulin deficiency (reduced production) and/or the presence of insulin resistance (impaired response), which develop progressively over time and commonly following prolonged exposure to detrimental lifestyle factors, such as obesity.[8] Accounting for around 85-90% of known cases, T2DM represents both the most common and preventable component of DM.

Regardless of type, these metabolic abnormalities have been linked to an increased risk of numerous vascular complications and corollary costs to health services and the economy.

2.1.1 Costs

2.1.1.1 Morbidity and mortality

Although the precise nature of the relationship between DM and vascular pathogenesis appears complex and multifactorial, with biological mechanisms currently posited rather than conclusively established,[13,14,15] DM has been associated with the onset of numerous deleterious vascular conditions.[3]

Chief among these, macrovascular conditions appear to represent the leading cause of morbidity and mortality among diabetic patients worldwide, with cardiovascular disease (CVD) accounting for around half of all documented deaths.[16] This elevated cardiovascular risk profile

among people with DM was first identified in 1979, when data from the Framingham study indicated that participants with the condition were twice as likely to develop CVD as those without, even after adjustment for age, sex and common cardiovascular risk factors such as smoking.[17] Subsequent studies have consistently identified an elevated risk of macrovascular health complications among people with DM.[1] The latest macrovascular risk estimates are provided by an analysis of data obtained via the CALIBER programme, which links data from four English electronic health databases.[2] Based on a cohort of over 1.9 million participants, T2DM was positively associated with more than a 50% increase in the risk of heart failure (HR 1.56, 95% CI 1.45-1.69) and myocardial infarction (HR 1.54, 95% CI 1.42-1.67), as well as a 72% increase in the risk of ischaemic stroke (HR 1.72, 95% CI 1.52-1.95). Elsewhere, studies indicate that recovery from such conditions may also be impaired among persons with T2DM, with such individuals having exhibiting a heightened risk of stroke recurrence and post-stroke mortality,[18,19,20,21] physical disability[22] and dementia.[23,24]

Aside from macrovascular conditions and their negative consequences for health, diabetes-induced damage to the microvasculature represents a further serious concern, increasing the risk of conditions ranging from kidney failure and incontinence to limb loss and blindness.[3]

2.1.1.2 Primary care expenditure

Through its direct impact upon population health, DM necessitates investment in a wide range of health services. Applying estimates of disease prevalence and population size to inpatient and outpatient data available from Hospital Episode Statistics and other sources, two recent studies have attempted to calculate expenditures for healthcare resources including diagnostic tests, primary care consultations, prescription drugs and treatment for diabetes-attributable vascular conditions. Depending on the methods and data utilised, these direct costs have been estimated at between £9.8bn[25] and £13.8bn[4] in 2010/11, or around one-tenth of total NHS expenditure over the period.[26] These figures represent the latest published estimates of DM-related primary care expenditure.

2.1.1.3 Indirect costs

Costs associated with DM are not limited to health services. As a chronic and sometimes debilitating condition, DM can also introduce indirect costs to the economy through premature mortality, early retirement, absenteeism and an increased dependence on social welfare and care services.

Few sources of UK-specific data are available for determining indirect costs attributable to diabetes.[4,25] One approximation was undertaken by The Economist Intelligence Unit in 2007 using data from the United States (US),[27] which estimated foregone earnings attributable to absenteeism and mortality at £1.7bn/annum in the UK. Elsewhere, attempting to include indirect costs due to presenteeism, informal care and welfare, estimates of between £13.9bn[25] and £15.4bn[4] were estimated for 2010/11.

Whatever the precise figures, direct and indirect costs look to be sizeable – an observation notable given stagnated or reduced NHS, public health and social care budgets,[28,29,30] plus ongoing increases in the number of cases requiring treatment.

2.1.2 Prevalence and incidence

According to data published at the end of 2015,[5] the prevalence of self-reported DM cases among non-institutionalised adults in the England rose from 2.4% to 6.2% between 1994 and 2014 (Figures 2.1 and 2.2), reaching 2,707,850 cases by the end of the period.[31] Taking a more inclusive measurement, capturing both institutionalised and non-institutionalised residents from across the UK as a whole, objective data collected as part of the Quality and Outcomes Framework (QOF) indicated a prevalence of 6.4%, or 2,913,538 cases in 2014/15.[6] Temporal increases in the prevalence of T2DM appear most pronounced among older age groups, with prevalence consistently greatest among men.

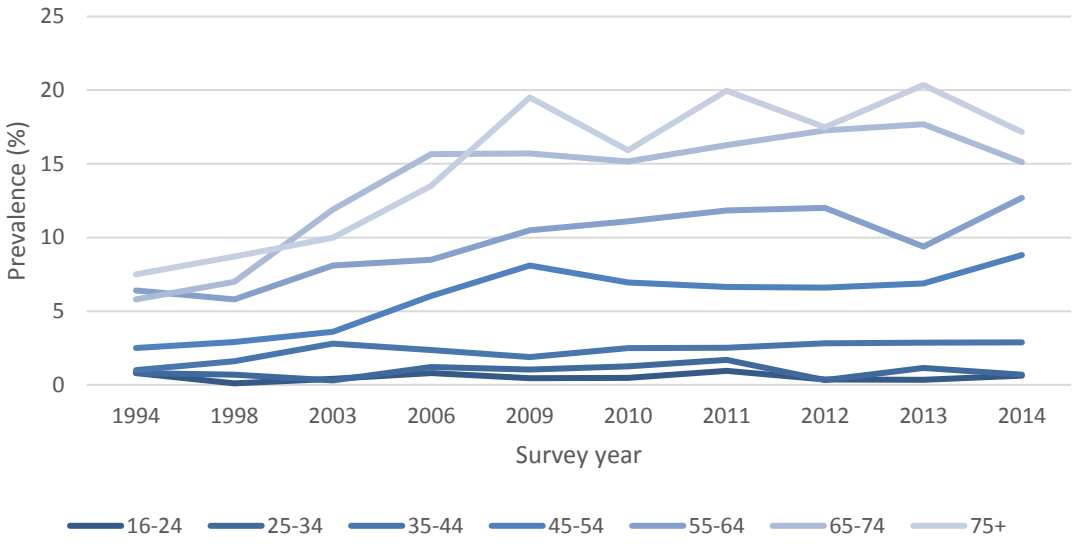


Figure 2.1 Age-specific prevalence of male self-reported doctor-diagnosed DM. Health Survey for England 1994-2014.

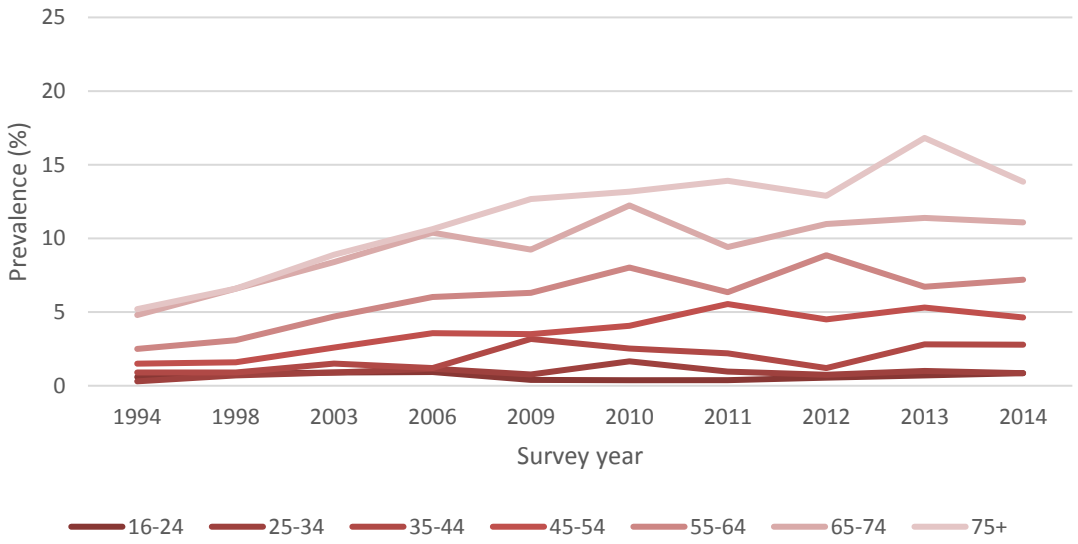


Figure 2.2 Age-specific prevalence of female self-reported doctor-diagnosed DM. Health Survey for England 1994-2014.

However, a marked rise in the prevalence of T2DM does not necessarily translate to a DM epidemic; an increase in prevalence may occur instead as a result of successful public health initiatives, such as improved disease management and consequent decreases in premature mortality.[32] Looking instead to the number of *new* cases diagnosed each year, trend data from The Health Improvement Network (THIN)[33,34] indicate that, while the incidence of T1DM has been low and constant over time, the age and sex standardised rate of T2DM rose by 63% between 1996 and 2005, to 4.31 cases per 1,000 person-years at risk.[35] Although alarming, more recent figures indicate that these earlier increases may now have stabilised, falling to 3.99 and 3.73 cases per 1,000 person-years at risk among men and women in 2013 (Figure 2.3).[7]

These figures indicate that increases in the prevalence of DM are most likely a consequence of improvements to the treatment and management of the condition, and resultant reductions in premature mortality. However, although an average 15,665 new T2DM cases were diagnosed annually between 2000 and 2013,[7] the human and economic costs of DM are not inexorable.

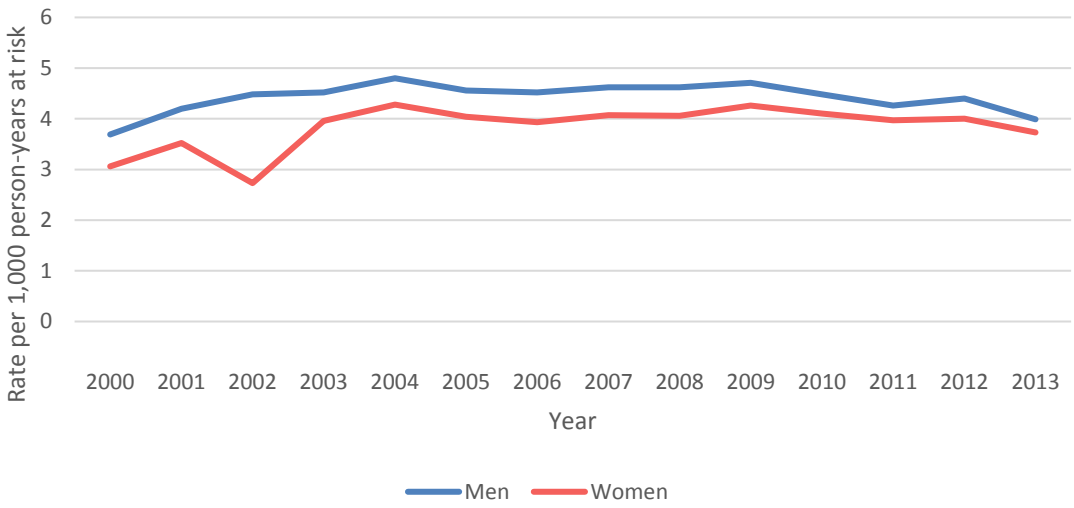


Figure 2.3 Crude annual incidence of T2DM per 1,000 person-years at risk. THIN 2000-2013.

2.1.3 Risk factors

A number of risk factors have been identified for the development of T2DM, ranging from adiposity and smoking, to alcohol consumption and physical activity.[36,37] While not all factors are modifiable, current epidemiologic evidence indicates that the risk of T2DM may be attenuated in large part through simple lifestyle changes. Several risk factors are discussed below, beginning with adiposity and ending with alcohol consumption.

2.1.3.1 Adiposity

Some of the rise in the incidence of T2DM observed between 1996 and 2005 was posited by researchers as attributable to rising obesity over the period, with the proportion of newly diagnosed patients presenting as obese having risen by 22% over the period, reaching 56% by 2005.[35] This was better substantiated by results from the British Regional Heart Study, which indicated that 25.9% (95% CI 16.5-38.3%) of the rise in T2DM incidence among men between 1984-1992 and 1999-2007 was attributable to an age-adjusted increase in average body mass index (BMI) of 1.42kg/m^2 (95% CI 1.10-1.74kg/m^2).[38]

An aetiological association between obesity and T2DM has been supported by multiple longitudinal studies, including a meta-analysis of 15 cohorts, which identified a standard deviation increase in BMI raised the relative risk (RR) of T2DM of by 55% (RR 1.55, 95% CI 1.43-1.69), with similar increases identified across alternative measures of adiposity, including waist circumference (RR 1.63, 95% CI 1.49-1.79) and waist-hip ratio (RR 1.52, 95% CI 1.40-1.66).[39] Although waist circumference was found to be a stronger predictor of T2DM risk than BMI and waist-hip ratio in primarily white study populations, this relationship differed according to a

diverse range of participant characteristics. Regardless of the measure adopted, the importance of adiposity as a predictor of T2DM risk is supported by studies that indicate decreased insulin-mediated glucose transport and metabolism within adipose tissues relative to skeletal muscle, contributing to the development of insulin resistance and hyperinsulinaemia.[40]

2.1.3.2 Diet

Given links between adiposity and T2DM risk, a number of dietary exposures are likely to be important modifiable risk factors for T2DM risk, including fat, carbohydrate and fibre consumption.

Fibre has been hypothesised to reduce T2DM risk by hastening intestinal transit, decreasing the amount of carbohydrates and fats digested and dispersed into the bloodstream.[41,42] Data pooled from 17 studies indicated a 9% reduction in risk per 10 g/day increase in total fibre consumption (RR 0.91, 95% CI 0.87-0.96).

Through their effect on blood sugar and obesity, carbohydrate-rich foods have been found to be linearly associated with the risk of T2DM. With foods ranked according to their glycaemic load (GL), with one unit equal to the effect on blood sugar of consuming 1 g of glucose, figures collated from 18 cohort studies indicated a 3% increase in T2DM risk for every 20 unit increase in GL per day (RR 1.03, 95% CI 1.00-1.05).[43]

By contrast, results reported by a recent meta-analysis of eight longitudinal studies indicated no dose-response association between saturated fat consumption and the risk of T2DM, with elevated risks observed only among crudely adjusted models.[44] Similarly, despite polyunsaturated fats commonly found in fish having properties thought advantageous toward a lowering of T2DM risk, including reductions in serum lipids, platelet aggregation and blood pressure,[45] data pooled from 18 cohorts identified no association between T2DM and fish consumption (RR per 100 g/day 1.12, 95% CI 0.94-1.34) or polyunsaturated fatty acids (RR per 250 mg/day 1.04, 95% CI 0.97-1.10).[46]

Reporting an array of positive, inverse and null associations, studies sampled as part of the saturated and polyunsaturated fat meta-analyses were notable in their considerable degree of heterogeneity, drawing into question the validity of reporting single summary measures. It was possible that real dose-response effects were lost due to noise resulting from marked differences in methods, populations and quality. While the proportion of variation in risk explained by between-study variance was low to moderate among fibre (I^2=29%) and GL studies (I^2=54%),[43] heterogeneity was considerable among those that investigated saturated fats

(I^2=91%)[44] and polyunsaturated fats (fish consumption, I^2=81%; polyunsaturated fat consumption, I^2=78%).[45] Additionally, the majority of sampled studies had adjusted for some measure of adiposity. With obesity likely positioned on the causal pathway between fat consumption and T2DM risk, it was possible that risks associated with dietary exposures had been biased toward the null by having controlled for an important intermediate factor.[47,48]

Taken collectively, fibre and carbohydrate appear to have an important influence upon T2DM risk beyond any effects they might have upon adiposity, while the effects of saturated and polyunsaturated fats remain inconclusive owing to substantial heterogeneity between studies.

2.1.3.3 Heritability

Although not modifiable, a predisposition to T2DM appears to be transferred vertically between generations via genetic inheritance. Compared with age-specific rates of T2DM as found in the US general population, individuals with a parental history of T2DM were found to have 2.3 times the risk of T2DM, while those with both a parent and a grandparent exhibited 3.5 times the risk of having developed the condition.[49]

Looking to the incidence of T2DM as documented by the largest twin study to have explored the heritability of T2DM, the degree of concordance was reported to be 34% (95% CI 27-41%) among monozygotic and 16% (95% CI 12-20%) among dizygotic twin pairs, with levels of concordance higher among female twins pairs[50] Indeed, the proportion of total variance calculated as attributable to genetic factors was highest among women, at 69% of male and 79% of female variance, suggesting that women may be more likely to inherit a genetic predisposition to the disease.[50] Other studies have reported higher levels of concordance, though sample sizes were substantially smaller and therefore subject to greater variance.[51,52]

Beyond twin studies, new data are becoming available from genome-wide association studies (GWASs), which sequence or impute the entire human genome and quantify the degree of association between SNPs and disease. To date, the number of SNPs associated with T2DM risk has risen in just a few years from 38[53] and 39[54] to more than 70,[55,56] with almost two dozen variants implicated in dysfunctional metabolic processes, including abnormalities in insulin secretion and insulin response.[53]

Despite such findings, SNPs that reach genome-wide statistical significance currently account for only around 6%[57] to 10%[53] of total variance in T2DM risk attributed to heritability, suggesting that more genes have yet to be discovered, have too small an effect on their own to be selected at the GWAS significance threshold,[58] or that heritability estimates derived from twin studies

may have been overestimated or unreliable, such as through their small sample sizes.[59] Until these issues are overcome, adjustment for family history of T2DM may present a pragmatic approach by which heritability may be accounted for in observational studies.

2.1.3.4 Physical activity

Physical activity is also a significant risk factor for T2DM, with longitudinal studies from a range of populations indicating an inverse relationship.[60,61] Specifically, results from the latest available meta-analysis indicates a 35% reduction in T2DM risk among study participants in the highest exposure category relative to those in the lowest category (RR 0.65, 0.59-0.71), with heterogeneity low across the 14 applicable studies (I^2=18%).[61] Reductions in risk were also evident among individuals who switched from low to moderate or higher categories (RR 0.64, 95% CI 0.50-0.70, n=7, I^2=0%), suggesting that any negative effects conferred by low physical activity may be reversible.

Although reductions in T2DM risk associated with physical activity may be mediated via an effect upon adiposity,[62] both factors has been identified as independent. This is supported by the results from physical activity meta-analyses, which identified large measures of effect despite adjustment for BMI across the majority of constituent studies. However, obesity appears to be the stronger determinant of risk.[63]

Accordingly, various additional mechanisms have been proposed beyond the direct effect of physical activity upon adiposity. These include exercise-induced increases to (a) the capillarisation of muscle tissue,[64,65] (b) the production of glucose transporter proteins,[66,67,68,69] and (c) muscle glycogen synthase activity, an enzyme involved in the conversion of glucose into glycogen for energy storage.[70,71] Together, these three processes have been posited to increase the rate at which glucose can be metabolised and transferred out of the bloodstream and into skeletal muscle tissue, resulting in improved insulin sensitivity as evident in the form of lower post-load blood glucose measurements among individuals who exercise for longer durations and with greater intensity.[72]

2.1.3.5 Smoking

The latest available meta-analysis of 84 longitudinal cohort studies and indicated that current smokers exhibit a 37% greater risk of T2DM relative to non-smokers (RR 1.37, 95% CI 1.33-1.42).[73] This relationship was also found to be dose-dependent, with risks largest among those classified as heavy smokers (RR 1.57, 95% CI 1.47-1.66). A stratification of non-smokers revealed an elevated risk among former smokers relative to those that reported never smoking (RR 1.14,

95% CI 1.10-1.18), suggesting that complete life-ling abstention may be optimal for reducing T2DM risk, but that elevated risks conferred by current smoking may still be attenuated by cessation. This latter inference is supported by the inverse relationship between the duration of cessation and T2DM risk.[74] Were a causal relationship present between smoking and the development of T2DM, the authors estimated that around 12% of male and 24% of female T2DM cases worldwide were attributable to active smoking.

Paradoxically, however, smoking has repeatedly been associated with advantageous changes in adiposity,[75] with BMI lowest among current smokers and smoking cessation linked to increases in BMI even after adjustment for baseline adiposity.[76] Putative mechanisms for such an inverse relationship range from smoking being a behavioural alternative to eating[75] to a direct genetic link between the two factors.[77] Whatever the underlying process, smoking appears associated with marked reductions in one of the leading risk factors for T2DM. Additionally, although smokers tend to exhibit a clustering of obesogenic health behaviours,[78] the dose-response nature of the association between smoking and T2DM risk and the magnitude of observed effect sizes were such that the relationship appeared unlikely to be attributable to residual confounding alone.

Any causal mechanism between smoke exposure and T2DM remains unclear, though there is some suggestion from experimental studies that smoking may increase insulin resistance,[79,80,81] with improvements to insulin sensitivity observed following cessation.[82] Such a relationship may be mediated by nicotine through its apparent effect upon insulin signalling proteins.[83]

2.1.3.6 Alcohol consumption

2.1.3.6.1 Average volume of alcohol consumed

An increasing body of evidence has highlighted the role that the average volume of alcohol consumed may play in modifying the risk of T2DM. According to a recent meta-analysis, which comprised 20 longitudinal studies, a J-shaped dose-response relationship exists between the volume of alcohol consumption and T2DM risk.[10] Relative to never drinkers, reductions in risk were reported to be greatest at 22 g/day (RR 0.87, 0.76-1.00) among men and 24 g/day (RR 0.60, 0.52-0.69) among women, with risks rising incrementally thereafter. A newer meta-analysis published after the analyses undertaken in Chapter 3 also reported a non-linear dose-response relationship, with risks lowest among adults that consumed 91-168 g/week (men: RR 0.80, 95% CI 0.72-0.89; women: RR 0.57, 95% CI 0.48-0.67), relative to the lowest consumption category

reported among constituent studies. Peak reductions in risk were evident at around 22 g/day (RR 0.57, 95% CI 0.51-0.62) among men and 30 g/day (RR 0.70, 0.64-0.76) among women.[84]

These findings have been countered by a Mendelian randomisation meta-analysis of 48 international cohorts.[85] Rather using a self-reported measure of alcohol intake, adults were instead categorised according to a genetic proxy for alcohol consumption. Because genotypes tend to be assigned at random during meiosis (assuming that the choice of partner was not associated with the genotype (panmixia)), groups of drinkers defined according to a genetic variant should benefit from a more even distribution of confounding factors akin to a randomised controlled trial, strengthening any inferences drawn.[86] However, despite being less prone to reverse causality and confounding, it should be noted that results derived using genetic data are subject to a unique set of assumptions. Aside from the requirement that a genetic polymorphism be associated with the exposure of interest, explaining a substantial proportion of variance in the volume of alcohol consumption consumed, it is assumed that a selected marker be associated with the outcome of interest solely through its effect on alcohol consumption, e.g. is unrelated to other genetic traits that may influence the outcome differentially (antagonistic pleiotropy).[86]

In this particular analysis, rs1229984 was selected as a single-nucleotide polymorphism (SNP) in the alcohol dehydrogenase 1B gene (*ADH1B*), responsible for encoding an enzyme implicated in the metabolism of alcohol.[87] Compared to the more common G-allele variant of the SNP (rs1229984(G)), carriers of an A-allele (rs1229984(A)) exhibit an impaired clearance rate of alcohol metabolites, leading to increased flushing, palpitations and drowsiness through a resultant accumulation of acetaldehyde, a metabolic by-product of alcohol.[88] Due to the adverse biological response it elicits following alcohol consumption, rs1229984(A) has been associated with lower volumes of daily alcohol consumption and a higher prevalence of non-drinking,[88] as well as a lower odds of alcohol dependence.[89]

Results from this Mendelian randomisation meta-analysis were in concordance with these negative effects. Although mean intake was not reported, carriers of the rs1229984(A) polymorphism had a 17% (95% CI 15.6-18.9%, I^2=64%) lower weekly volume of alcohol consumption and a 27% higher odds of being a non-drinker (OR 1.27, 95% 1.21-1.34, I^2=73%), relative to non-carriers (rs1229984(G)).[85] Notably, an analysis of all available individual participant data showed no difference in the odds of T2DM by genetic variant (p=0.627, n=145,063). Similarly, when data were restricted solely to those who defined themselves as current drinkers, no decrease in odds was detected among rs1229984(A) carriers (OR 0.97, 95%

CI 0.86-1.09, n=111,140) despite a lower volume of alcohol consumption. Such findings suggest that poor adjustment for confounding factors may have explained at least some of the apparent reduction in risk observed at moderate volumes of alcohol consumption present in observational studies, with around one-third of such studies having provided crude or age-adjusted estimates only.[10] Weak confounder adjustment among current observations studies is an issue discussed in more detail in Section 2.3.

A number of alternative explanations for a null result were possible. With consideration to the biological effect of the A-allele polymorphism, the absence of any reduction in risk among lighter drinkers with a genetically impaired alcohol metabolism might be attributable to higher concentrations of inflammatory alcohol metabolites, which may have offset any reduction in risk otherwise conferred by a more moderate volume of alcohol consumption. This was argued by authors of a paper which analysed participants from the Nurses' Health Study and Health Professionals Follow-Up Study.[90] While reductions in risk were observed among self-reported moderate drinkers in accordance with the 2009 meta-analysis, the presence of an alcohol dehydrogenase polymorphism was found to significantly attenuate the reductions in risk reported among moderate drinkers (p=0.02). Such a finding led the authors to conclude that, were there a causal relationship between the volume of alcohol intake and T2DM, the risk of T2DM may be mediated by an impaired clearance of inflammatory metabolites such as acetaldehyde[91,92,93] (see also Section 2.2.2.3).

Aside from this, a null result may also be a consequence of numerous statistical limitations.[94] Firstly, the Mendelian randomisation meta-analysis does not rule out a relationship between some other dimension of alcohol consumption and the risk of T2DM, such as the effect of drinking pattern. As highlighted in the following section, there are indications from some observational studies that the frequency of drinking or propensity for binge drinking may represent important determinants of T2DM risk beyond a simple measure of average volume consumed. Secondly, only a relatively small proportion of the variation in alcohol consumption was explained by the *ADH1B* genotypes. Were the mean volume of alcohol intake equal to a value of 50 g/week, for example, then the average difference in consumption between carriers and non-carriers would equate to just 8.5 g/week, or barely one unit. In this sense it was possible that the disparity in consumption between the two groups was too small to detect any effect. Thirdly, the prevalence of rs1229984(A) carriers within the pooled dataset was low, at just 7% of the sample, meaning that statistical power may have been insufficient to detect any effect, if present. Accordingly, though Mendelian randomisation studies can offer advantages over

observational studies, evidence from cohort and case-control studies still have an important role to play in developing a better understanding of the relationship between alcohol consumption and T2DM risk.

2.1.3.6.2 Drinking pattern

Beyond the volume of alcohol consumed on an average day or week, there is some suggestion that the pattern of alcohol consumption may represent a second and important component of T2DM risk. Of the 20 studies selected as part of the 2009 meta-analysis, just three were documented as having investigated some measure of consumption patterning.[10] The first, which utilised data from a US occupational cohort, found that the frequency of consumption over an average week was significantly associated with T2DM risk, even after adjustment for the average volume of alcohol consumption (p=<0.001).[95] Specifically, each additional drinking day per week was associated with an independent and multivariable adjusted reduction in risk of 7% (RR 0.93, 95% CI 0.90-0.97).

The second publication, a prospective cohort of monozygotic twins, looked instead at episodic heavy drinking. Although they provided no detailed dose-response analysis of the interaction between volume and pattern, they did document that female participants who reported consuming >179 g on any one occasion at least one a month during the preceding year had double the risk of T2DM relative to those that did not report binge drinking (RR 2.1, 95% CI 1.0-4.4).[96] No such association was observed among men, though the average volume of alcohol consumption among binge drinkers was not reported.

Finally, the third publication, based on a male multi-ethnic prospective cohort study, stratified volumes of weekly alcohol intake by the number of drinking days during the week.[97] Although sub-group sample sizes were small and confidence intervals consequently wide, point estimates revealed a notable interaction between weekly volume and frequency. At the lowest volume of alcohol consumption (<70 g/week), little difference in risk was evident when stratified by frequency of drinking over the week, suggesting that such a volume of intake may have been too low to detect an interaction effect in such a small sample. However, at higher volumes of consumption, risks were lower among those who distributed their consumption over a greater number of days. For instance, relative to non-drinkers, those who consumed >210 g/day over 1-3 days/week were five times more likely to have developed T2DM (RR 5.21, 95% CI 1.79-15.2), while those that distributed the same volume over a full seven days exhibited the lowest risk of T2DM (RR 0.68, 95% CI 0.39-1.20). Consumption within this group was equivalent to around 30

g/day, or a level almost equal to that associated with the peak reduction in risk reported by the 2009 meta-analysis.[10]

Although studies that investigated joint associations between the two dimensions of drinking and T2DM risk were few in number and explored the relationship in different ways, both the volume and frequency of consumption appeared to represent important risk factors, with T2DM risk appearing lowest among regular moderate drinkers, and any benefits potentially offset by concentrated periods of episodic heavy consumption.

2.2 Alcohol consumption

Representing a potentially modifiable risk factor for T2DM and appearing from observational studies to reduce risks at regular moderate volumes of alcohol consumption, trends in the volume and pattern of UK alcohol consumption are described below. With a peak reduction in risk appearing to be conferred at an volume of around 22-24 g/day, according to estimates from longitudinal observational studies,[10] trend data gave an indication as to the likely risk profile of the UK general population and thereby the degree to which the burden of T2DM could potentially be attenuated through population-level changes in alcohol consumption behaviour.

2.2.1 Trends

2.2.1.1 Volume of alcohol consumption

Current national alcohol guidelines advise that the total volume of consumption exceed no more than 21 units/week among men and 14 units/week among women.[98] A recent review of the available evidence recommended that these thresholds be revised to 14 units/week for both sexes.[99] This newly proposed threshold equates to 16 g/day, or a volume close to the 24 g/day nadir in T2DM risk reported by observational studies.[10]

In aggregate, data from the Health Survey for England 2014[5] and the Scottish Health Survey 2014[100] both indicate that consumption among men and women is close to or within current national guidelines, measuring an average 19.0 g/day among English men and 9.9 g/day among English women,[5] with values slightly lower in Scotland. Even within age groups where consumption is highest, volumes are not of a level associated with an increased risk of T2DM. For instance, among English men aged 65-74 years, consumption measured 23.0 g/day on average (Figure 2.4), with 11.9 g/day consumed by English women aged 16-24 years (Figure 2.5). However, it was unlikely that the volume of drinking is distributed uniformly across all seven days. As discussed in the next section, alcohol intake is marked by instances of episodic heavy consumption potentially associated with an increased risk of T2DM.[96,97]

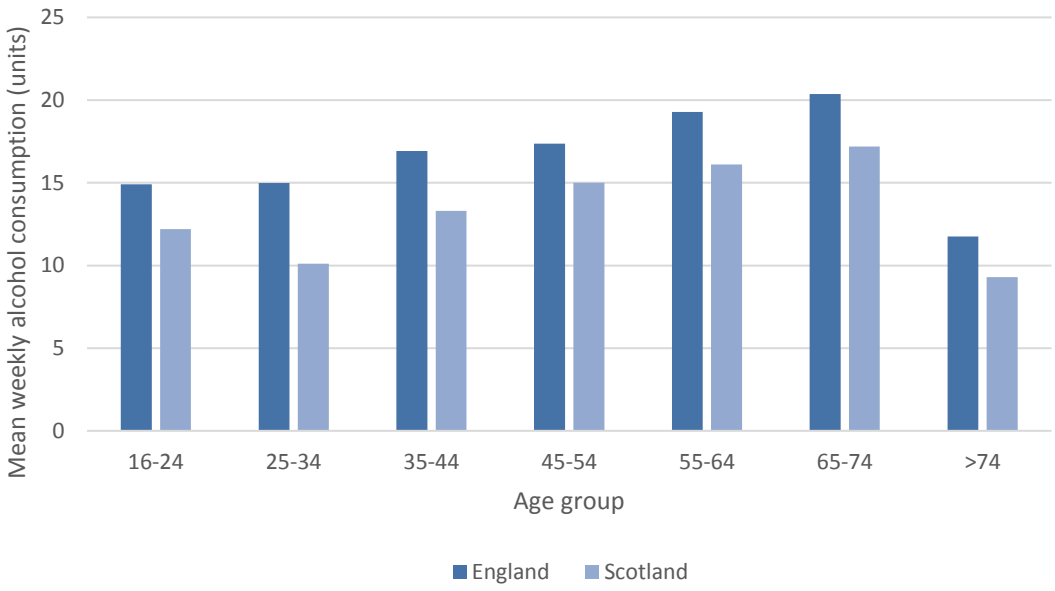


Figure 2.4 Mean volume of alcohol consumption among male current drinkers, stratified by age group and country. Health Survey for England and Scottish Health Survey, 2014.

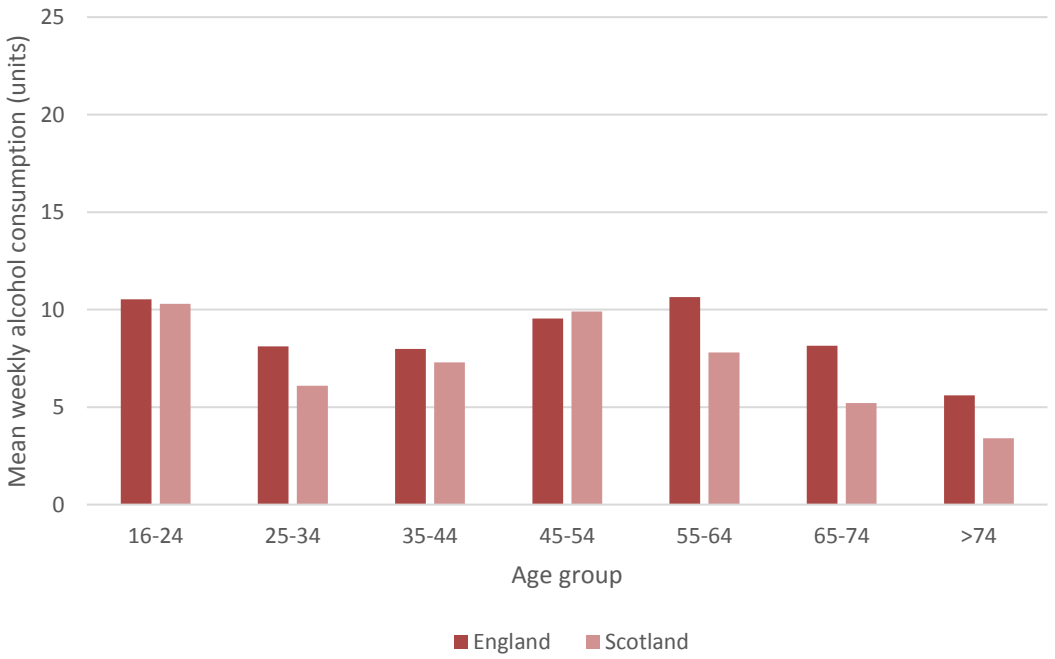


Figure 2.5 Mean volume of alcohol consumption among female current drinkers, stratified by age group and country. Health Survey for England and Scottish Health Survey, 2014.

2.2.1.2 Pattern of alcohol consumption

To get some idea as to the prevalence of episodic heavy consumption in the general population, data were obtained from the annual Opinions and Lifestyle Survey, which reported alcohol consumption from a random probability sample of UK residents.[101] Based on the data available, episodic heavy consumption was defined as any current drinker who reported consuming more than twice the recommended daily limit on their heaviest drinking day in the week prior to

interview, equating to >63 g among men and >47 g among women. The degree of episodic heavy consumption was lowest among women in all age groups (Figures 2.6 and 2.7). Although gradually declining over time, episodic heavy consumption is most common within younger age groups regardless of sex. By 2013, 20.9% of male and 15.8% of female current drinkers aged 16-24 years reported consuming more than twice the recommended limit on at least one day in the week.

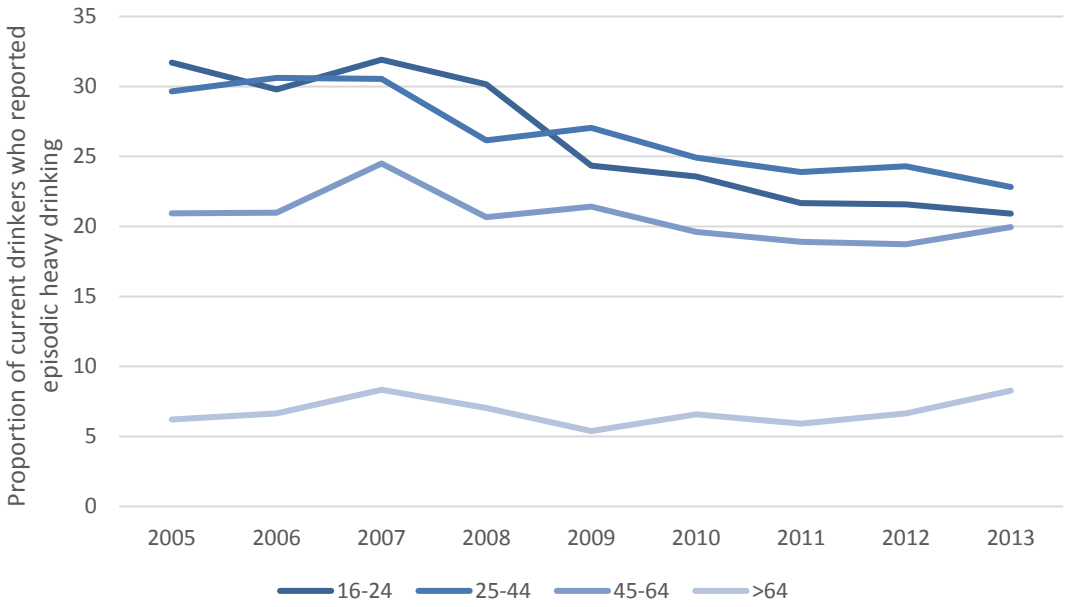


Figure 2.6 Proportion of male current drinkers who reported episodic heavy consumption. Opinions and Lifestyle Survey, 2005-2013.

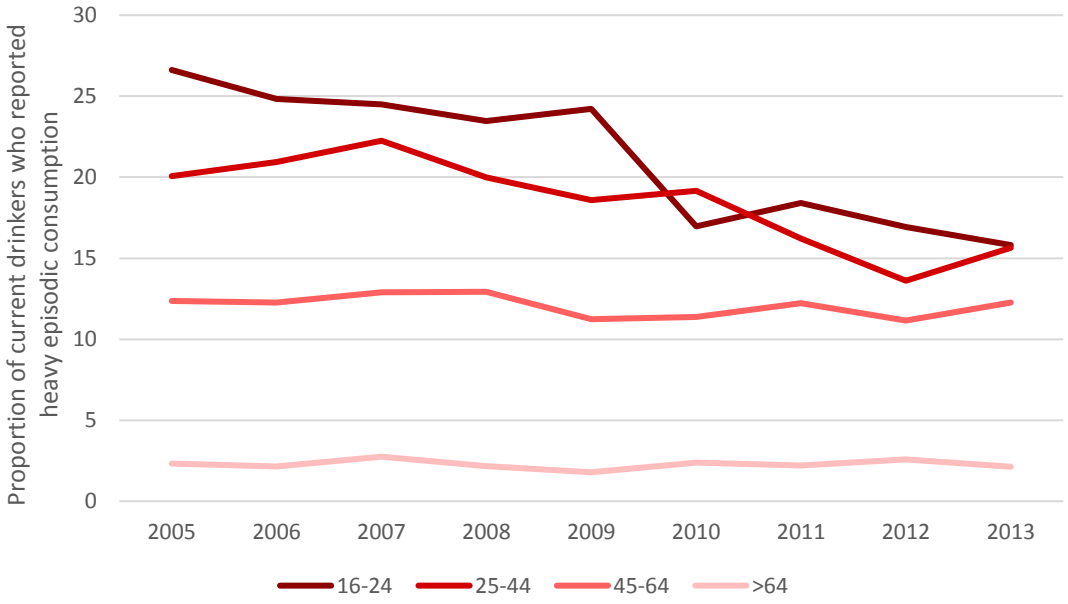


Figure 2.7 Proportion of female current drinkers who reported episodic heavy consumption. Opinions and Lifestyle Survey, 2005-2013.

If regular moderate alcohol consumption is causally associated with marked reductions in T2DM risk, relative to never drinkers, then the presence of episodic heavy drinking among around one-fifth of younger drinkers suggests that UK drinking behaviours may not be optimal for the attenuation of T2DM risk. Such trend data also suggest that an increase in the burden of T2DM may become apparent over coming decades as younger episodic heavy drinkers grow older.

2.2.2 Putative biological mechanisms

There are multiple proposed mechanisms by which alcohol consumption might influence the risk of T2DM. Three of the most commonly discussed hypothesised pathways are discussed below.

2.2.2.1 Insulin sensitivity

One pathway concerns the effect of alcohol upon insulin sensitivity, which refers to the rate of metabolic response following insulin exposure, including the metabolism, transport and storage of carbohydrates and fats.[102,103] High insulin sensitivity is marked by the prompt metabolism of carbohydrates and fats in the presence of nominal insulin concentrations. Here, elevations in blood sugar, such as those following meals, are acute and easily regulated without the need for dietary or medicinal control. Conversely, low insulin sensitivity is indicated by an impaired insulin response, resulting in chronically elevated levels of blood glucose. Often referred to as insulin resistance, these chronic elevations in blood glucose trigger a compensatory feedback loop that can result in a state of hyperinsulinaemia.

To date, analyses exploring the relationship between alcohol and insulin sensitivity have been predominantly cross-sectional,[104] with just three out of 16 non-interventional studies identified as part of a recent review having been longitudinal in design. Of all the observational data identified, both U-shaped and inverse linear associations with insulin sensitivity were found, as measured variously via fasting insulin, fasting glucose or homeostasis model assessment (HOMA).

Among studies that identified a U-shaped relationship, insulin sensitivity was greatest at volumes of alcohol consumption at which reductions in risk were reported by Baliunas *et al*,[10] ranging from 9 g/day[105] and 20 g/day[106] to anything below 40 g/day.[107] By contrast, upper limits in studies that identified a linear relationship ranged from >23 g/day[108] to >100 g/day.[109] Interestingly, although a cross-sectional analysis of data obtained from the French DESIR cohort identified a strong and sizeable linear relationship with average volume of alcohol consumption

among both sexes (p=<0.001),[110] no such association was identified in a three-year longitudinal analysis later undertaken on the same cohort bar a linear increase in glucose among men.[111]

A separate review and meta-analysis looked specifically at results from interventional studies that spanned at least a two-week period.[112] A total 14 studies were selected, with participant samples ranging in size from 17 to 51. Although no difference in fasting glucose concentration was identified among either male (p=0.48, study n=5) or female (p=0.94, n=6) drinkers, relative to controls, a significant sex interaction was reported between alcohol consumption and insulin sensitivity (p=0.018), which tended to be higher among female (SMD 0.16, 95% CI ⁻0.04-0.37, p=0.12, study n=5) but not male drinkers (SMD −0.30, 95% CI ⁻1.23-0.64, p=0.54, study n=5). However, heterogeneity among the studies was particularly high (I^2=95%). When a study largely responsible for such heterogeneity was removed, no significant difference in insulin sensitivity between men and women remained (p=0.180). With regard to the effect of alcohol upon fasting insulin, significant reductions in concentration were observed among women (p=0.02, study n=6). While no such effect was reported among men, analyses were based on estimates extracted from just two small interventional studies of low precision (men: p=0.59, study n=2). Data from the two studies indicated a similarly advantageous direction of effect.

Although a meta-analysis of alcohol consumption and T2DM risk found greater reductions in risk among moderate female drinkers than their male equivalents,[10] observational and interventional research were insufficient to conclude that this difference in dose-response may have occurred due to a sex-specific disparity in alcohol-induced insulin response. In addition to the majority of observational research thus far being cross-sectional, negating any conclusions concerning the direction of effect, results from interventional studies should also be viewed with caution. Such studies were small in size, few in number and reported heterogeneous levels of alcohol intake. Collectively, such limitations constrain any attempt to generalise interventional results to the general population.

2.2.2.2 High-density lipoprotein

Besides its putative effect upon markers of insulin sensitivity, alcohol may confer some reduction in the risk of T2DM through a causal relationship with the production of high-density lipoprotein (HDL). HDL has been linked to a number of positive metabolic processes, including the reverse cholesterol transport process, which transports lipids out of the bloodstream for storage in the liver.[113,114] Elsewhere, HDL has appeared to play a role in the transfer of glucose away from the bloodstream and into adipose tissue for storage, as well as the promotion of

glucose metabolism by skeletal muscle tissue.[115,116] Finally, there has been some suggestion that HDL may help promote insulin secretion by β-cells and protect them against apoptosis.[116]

Investigating alcohol-related changes to HDL concentration, data were abstracted from 25 interventional studies.[117] The researchers identified a linear dose-response relationship, whereby HDL concentrations increased by 0.133mg/dl per gram of daily alcohol consumption, relative to controls. At the average volume of alcohol consumption (30 g/day), which was close to the nadir in risk reported by the 2009 T2DM meta-analysis,[10] HDL concentration increased by 8.3% over a period of four weeks compared with controls (3.99 mg/dl, 95% CI 3.25-4.73).[117] This linear relationship was supported by a more recent meta-analysis of 33 studies (p=0.013),[118] with similarly positive findings reported by a recent trial of 224 participants followed over two years (2.0 mg/dL, 95% CI 1.6-2.2 mg/dL).[119] The earlier of the two meta-analyses reported the dose-response relationship by sex, and found a stronger association among men than women (men: β=0.134 mg/dl per 1 g/day alcohol; women β=0.095 mg/dl per 1 g/day alcohol), though differences between sexes were not significant (p=0.930).[117] However, the absence of a statistically significant interaction may have been due to low statistical power as opposed to the absence of a sex-specific dose-response, with only three small studies reporting female data.

Taking a different approach, a recent Mendelian randomisation meta-analysis found no overall difference in the concentration HDL (p=0.259) when data from 46 studies were stratified according to a genetic polymorphism predictive of variance in alcohol consumption,[85] though this null finding may have been a result of limitations outlined elsewhere (see Section 2.1.3.6.1).

That observed relationships in prospective cohort studies were linear as opposed to J-shaped suggested that any beneficial increase in HDL concentration following increased alcohol consumption may be offset by metabolic harms at higher intakes, such as a triggering of pancreatic β-cell apoptosis and signalling dysfunction.[120] Moreover, even if alcohol consumption is causally associated with increases in HDL concentration, there is an indication that HDL may not itself be associated with the onset of T2DM despite its apparent role in effective glucose transport and storage. For instance, in a recent Mendelian randomisation study based on 47,627 participants sampled by the Copenhagen City Heart Study and the Copenhagen General Population Study, no association was found between SNPs linked to HDL concentration and T2DM risk (p=0.550); significant dose-response relationships were specific to models that utilised observational data as opposed to a genetic indicator of HDL variance.[121]

2.2.2.3 Inflammation

A further hypothesis concerns the effect that alcohol may have upon inflammatory response,[122,123] a mechanism triggered following damage to human tissue or cellular function. Specifically, inflammation and a consequent production of pro-inflammatory proteins has been associated with the disruption of endothelial and pancreatic β-cell functioning, impairing the breakdown and transport of glucose, increasing blood glucose concentrations and thereby implicated in the pathogenesis of T2DM.[93,124,125]

As with studies investigating alcohol-related changes in HDL concentration, observational data concerning inflammatory markers is scarce and almost exclusively cross-sectional.[122,126] Focussing on results from interventional studies, a recent meta-analysis identified publications that reported dose-response relationships between alcohol consumption and a range of inflammatory biomarkers.[118] These included C-reactive protein (CRP), understood to increase in concentration during periods of inflammatory response but with an unknown function beyond its prognostic value,[127] and tumour necrosis factor alpha (TNF-α), a pro-inflammatory protein hypothesised to play a role in the development of insulin resistance through its suppression of insulin signalling.[128,129,130] The concentrations of such markers were not found to be influenced by the volume of alcohol consumption, though the number of constituent studies was small (e.g. CRP, n=5; TNF-α, n=3).[118] By contrast, a Mendelian randomisation meta-analysis of 42 longitudinal studies found CRP concentrations to be 3.4% (95% CI 1.1-5.7%) lower among A-allele carriers whose average volume of alcohol consumption was 17% lower than among non-carriers (p=<0.001).[85] Moreover, when a non-linear dose-response relationship was estimated based on data reported by 22 Mendelian randomisation studies, CRP concentrations were predicted to be elevated only at volumes of alcohol intake greater than around 166 g/week, relative to zero alcohol consumption.[131]

Data from these Mendelian randomisation studies therefore indicate an advantageous reduction in the concentration of CRP at relatively moderate volumes of weekly consumption, consistent with the J-shaped association observed between alcohol intake and T2DM risk.[10] However, in the absence of supporting evidence from interventional or longitudinal studies, the plausibility of such a pathway remains in question. This was especially so given a lack of robust evidence linking inflammatory intermediates to T2DM. For instance, while a study of the Whitehall II and Northwick Park Heart Study II datasets reported significant associations between baseline concentrations of CRP and the risk of insulin resistance (HOMA), hyperglycaemia and T2DM, null associations were present when data were stratified according

to SNPs significantly associated with variance in CRP concentration but independent of confounding factors such as obesity, blood pressure and socioeconomic position.[132] Elsewhere, consideration alternative inflammatory markers, a recent Mendelian randomisation meta-analysis reported null associations between genetic variants linked to concentrations of interleukin 1 receptor antagonist, a regulator of inflammatory response mechanisms, and T2DM risk (OR 0.99, 95% CI 0.97-1.01).[133] Although meta-analyses of Mendelian randomisation studies have linked SNPs associated with variance in the concentration of interleukin 6 (a cell signalling molecule implicated in the suppression of inflammatory response) to a slightly lower but statistically significant risk of CHD of between three[134] and five per cent,[135] no studies appear to have thus far explored associations between SNPs of interleukin 6 and T2DM risk.

2.2.2.4 Summary

Longitudinal observational studies that investigated putative mechanisms by which alcohol consumption might attenuate the risk of T2DM have tended to be lacking, with the majority of studies being cross-sectional in design and thus inappropriate for developing an understanding of cause and effect. Interventional studies have provided a better source of data, but their generalisability has been limited by heterogeneous designs, short durations and singular volumes of consumption, obfuscating any understanding of dose-response effects following chronic alcohol intake at the population level. Finally, with large-scale Mendelian randomisation studies having identified no association between either HDL or inflammatory markers and T2DM, the likelihood of such pathways being the route by which alcohol may confer differences in T2DM risk is low.

2.3 Reference groups and confounding

Although observational and experimental data have hinted at potential biological mechanisms by which alcohol may induce a reduction in T2DM risk, the validity of such studies was questionable. As an alternative to a direct biological effect, it is possible that observed reductions in T2DM risk among moderate drinkers may instead have been a statistical artefact attributable factors such as the selection of a reference group potentially predisposed to the condition under study, and a failure to account for any such predisposition.

For instance, of the 20 studies selected as part of the 2009 alcohol-diabetes meta-analysis, 18 calculated risks associated with current drinking relative to pooled non-drinkers.[10] Criticism has been levelled at this choice of abstention group on the grounds that is may capture former drinkers whose lifestyle behaviours and health status may place them at increased risk of negative health events, including T2DM.[136,137,138] Such criticism is supported by studies that

report a higher prevalence of T2DM risk factors among non-drinkers than moderate consumers of alcohol following adjustment for differences in age and sex,[139,140] including being of Asian ethnicity, having a high BMI and low physical activity. Elsewhere, studies also report a higher prevalence of poor self-reported health and limiting longstanding illness among non-drinkers than any other drinking category,[141,142,143] with the onset of ill-health associated with a subsequent cessation of alcohol consumption.[144,145,146] In at least one instance, the prevalence of limiting longstanding illness has been found to exhibit a J-shaped relationship, with the proportion of illness highest among non-drinkers and lowest among moderate consumers of alcohol.[141] Such data suggest that pooled non-drinking categories may indeed comprise a group of former drinking 'sick quitters' who cease alcohol consumption due to ill-health. Such individuals were likely to have health profiles that placed them at greater risk of T2DM than moderate drinkers, potentially confounding the dose-response relationship between drinking and T2DM risk in poorly adjusted studies.

Of the studies selected as part of the 2009 meta-analysis, risk estimates abstracted from 13 of the 20 selected studies had been adjusted for just three or fewer confounding factors, with one-third of studies providing only crude or age-adjusted estimates. There was therefore a possibility that estimated reductions in the risk of T2DM among healthier moderate drinkers may be overestimated. Unfortunately, the meta-analysis provides no sensitivity analysis examining the effect of confounder adjustment or abstention reference category upon the shape and magnitude of the dose-response relationship. Similarly, a new meta-analysis published after the analyses undertaken for Chapter 3 provided no adjustment or stratification according to the choice of reference category by consistent studies, opting only to use the lowest category of consumption in each case, however so defined.[84] As such, the impact of former drinkers and poor confounder adjustment upon reported dose-response relationships is currently unknown.

In the absence of such an analysis, the possibility that reductions in T2DM risk may have been overestimated is instead supported by a recent analysis of studies that explored the relationship between average volume of alcohol consumption and all-cause mortality.[136] Of the 21 all-cause mortality studies to have included former drinkers within a pooled non-drinking reference group, all reported a J-shaped association consistent with the 2009 T2DM meta-analysis. However, of a further seven studies that had explicitly excluded former drinkers, no difference in risk was reported between non-drinkers and moderate drinkers. Similarly, in a meta-analysis of 34 longitudinal studies,[147] reductions in the risk of all-cause mortality were lower and present across a narrower range of alcohol intake among studies that utilised a robust never drinking

reference category (n=27) rather than a group of pooled non-drinkers (n=21). These analyses and others[148] all support the assertion that former drinkers represent a less healthy drinking category predisposed to or already suffering from chronic health conditions.

Although these findings suggest that former drinkers should be excluded from among pooled non-drinkers so as to leave a category of never drinkers, it should be noted that even the use of a never drinking reference category has drawn criticism. This has included the impact of such a reference group upon statistical power given their relatively small sample size in populations where alcohol consumption is otherwise normative,[149,150] and evidence suggesting that morbidities in early adulthood may predict never drinking, potentially subjecting never drinkers to the same limitations as former drinkers.[151] These limitations have led some to recommend the use of an occasional drinking category as a reference group.[138,152] However, without knowing their average volume of consumption at each drinking occasion, such a category could capture either episodic heavy drinkers who appear to be at the greatest risk of T2DM, or episodic moderate drinkers that may drink infrequently due to the same morbidities as former drinkers. It is unclear why such a heterogeneous group would prove a better choice of reference category than robustly defined never drinkers, especially in a well-adjusted study of sufficient size.

Looking back to the 2009 meta-analysis, the authors attempted to work around the bias that may have arisen from selected studies having utilised a pooled non-drinking reference category confounded by less healthy former drinkers. Specifically, Baliunas *et al*[10] weighted risk estimates reported by such studies according to the sex-specific proportion of former drinkers documented by studies where non-drinkers had been explicitly bifurcated into groups of never and former drinkers.

The validity of such an approach is questionable. In addition to having calculated weights from just five studies, closer inspection revealed that two of the five studies had not utilised a robust never drinking category. One defined never drinkers as those that had never consumed more than 11 alcoholic drinks in any year,[97] while the second defined never drinkers as those that reported no alcohol consumption during the five years preceding baseline and consumption no greater than four drinks per day prior to those five years.[153] In the latter instance, never drinkers may actually have been former drinkers who had once routinely consumed 72.7 g/day, assuming that each drink was equal to one average (1750 ml) glass of 13% ABV wine.[11]

As well as estimating sex-specific proportions of former drinkers based on studies that had not defined abstention categories in a robust manner, it was unclear how reliably the baseline

prevalence of former drinkers averaged from five studies could be applied to 15 studies of disparate populations and demographics, with alcohol consumption differing according to factors beyond sex alone, including age, economic wealth, smoking and education,[154,155] plus both per capita consumption and the prevalence of non-drinking differing markedly between countries.[154]

In summary, an updated and revised meta-analysis was required to explore the impact of confounder adjustment and reference category selection upon the dose-response relationship between the volume of alcohol consumption and T2DM risk. Such analyses would help highlight the degree to which previous research may have overestimated any reductions in risk through a failure to properly account for a potential predisposition of former drinkers toward the development of T2DM.

Chapter 3

An updated and revised meta-analysis of the dose-response relationship between alcohol consumption and T2DM

3 An updated and revised meta-analysis

3.1 Introduction

Observational studies that utilised a self-reported measure of alcohol consumption appear to indicate a peak reduction in the risk of T2DM at levels of consumption below the equivalent of 8.5 pints of 4% ABV lager per week (22 g/day).[10] However, such studies predominantly calculated risks relative to pooled non-drinkers, a group likely to comprise former drinkers whose poor health and clustered negative lifestyle behaviours potentially predispose them to the development of T2DM.[136] In addition, two-thirds of selected studies adjusted for three or fewer confounding factors, with one-third providing only crude or age-adjusted estimates. As a consequence, an unequal distribution of risk factors for T2DM may have been largely unaccounted for, leaving observed reductions in risk less a consequence of a direct biological effect and more a statistical artefact. This possibility is hinted at by studies of all-cause mortality, which report an attenuation or nullification of reductions in risk following the removal of less healthy former drinkers from the abstention reference category,[136,147] as well as a Mendelian randomisation meta-analysis which found no relationship between drinking intensity and T2DM.[85]

To gauge the degree to which observed reductions in risk may have been overestimated, this chapter details an updated and revised meta-analysis of longitudinal observational studies, including sensitivity analyses chosen explicitly to explore the effect of confounder adjustment and choice of abstention reference category upon the dose-response relationship. The revised analyses also discuss new studies that report joint associations between the volume of alcohol consumption and drinking pattern. It was hypothesised that any reductions in risk would be shallower among studies that used a more robust abstention category or adjusted for a broader range of confounding factors. Results from the meta-analysis were later published.[156] A copy of the publication is included in Appendix 3.1.

3.2 Methods

3.2.1 Selection criteria

3.2.1.1 Types of study

Studies were limited to those of cohort and case-control design, and both community and occupational datasets were considered. Although occupational datasets may have captured a narrower spectrum of drinking and lifestyle behaviours,[157,158] data would still have captured

moderate levels of consumption – a range of particular interest given apparent reductions in T2DM risk at lower levels of intake.[10]

3.2.1.2 Types of participant

All adults aged ≥16 years were considered eligible regardless of sex, ethnicity or setting.

3.2.1.3 Types of exposure

Given apparent differences in dose-response between men and women,[10] sex-specific self-reported alcohol consumption was selected as the exposure of interest. With a non-linear dose-response relationship having previously been identified between alcohol consumption and T2DM risk,[10] studies were only considered if risks were reported across ≥3 categories denoting the average volume of alcohol consumption, inclusive of reference category. Studies were also excluded if the volume of alcohol consumption could not be converted into g/day, and if any abstention category was contaminated with participants other than non-drinkers (i.e. included light or occasional drinkers of some definition).

3.2.1.4 Types of outcome

T2DM was selected as the outcome of interest. Diagnostic tests and their respective thresholds have varied over time, with initial World Health Organisation (WHO) recommendations from 1965[159] having been revised in 1980,[160] 1985[161] and 1998,[162] with glycated haemoglobin A1C (HbA1c) added as a new diagnostic indicator in 2011.[163]

Restricting selection to publications that defined T2DM according to current recommendations would have unnecessarily excluded publications prior to 2011, which were likely to have adopted the gold standard diagnostic criteria at the time they were published. Such an approach would also have excluded publications that utilised self-reported measures of T2DM. An inclusive range of diagnostic measures were thus considered in order to maximise the number of studies selected, including: all objective diagnoses, all self- or physician-reported diagnoses, any reported hypoglycaemic drug treatment, or linkage to clinical registry data. Where not explicitly defined, cases of DM among adults were assumed to be T2DM given the tendency for T1DM to occur early in life.[8]

3.2.2 Search methods

PubMed (MEDLINE), Embase, The Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Alcohol and Alcohol Problems Science (ETOH) databases were each searched for relevant studies.

Where possible, searches of each database identified publications with titles or abstracts containing the terms 'alcohol', 'ethanol' or 'drink*', plus 'diabet*', 'NIDDM' or 'T2D*', plus 'cohort', 'inciden*', 'prospective', 'longitudinal', 'case' or 'retrospective'. During each electronic search, no limits were placed upon the language or date of publication. Searches were undertaken on 18/02/2014.

Of publications selected for inclusion in the final meta-analysis, referenced and referencing publications were searched for additional literature not captured by initial electronic searches. Grey literature was excluded owing to its lack of peer review. Although technical reports and conference papers may reflect the latest research in a given field, results can be preliminary and not subject to peer review.[164]

3.2.3 Data extraction and analysis

3.2.3.1 Study selection

3.2.3.1.1 Screening

Duplicate publications were omitted by Craig Knott (CK), who then screened the titles, abstracts and full texts of remaining publications to exclude any that failed to report a longitudinal association between volume of alcohol consumption and T2DM among persons aged ≥16 years.

3.2.3.1.2 Shortlisting

Screened publications were then shortlisted by CK, Annie Britton (AB) and Steven Bell (SB) according to *a priori* selection criteria. These criteria were as follows:

- The full text was available, allowing the identification of population characteristics and methods used;
- Data were reported separately for men and women, enabling the analysis of differences in dose-response according to sex;
- The volume of alcohol consumption was defined across ≥3 categories so as to permit a dose-response analysis;
- The abstention category free of contamination by current drinkers, i.e. the inclusion of light current drinkers;
- Reported data were sufficient for determining both the average volume of alcohol intake and the degree of T2DM risk for each consumption category.

During shortlisting, CK reviewed all screened entries while AB and SB each acted as second reviewer for two-thirds of the screened entries. This ensured all studies were reviewed

independently by at least two individuals, with one-third reviewed by all three reviewers. In the presence of any differences of opinion, a publication was reviewed by all three reviewers and the majority decision upheld.

Agreement between pairs of reviewers was quantified via Cohen's kappa statistic (κ), while agreement between all three reviewers was determined via the calculation of a Fleiss' kappa coefficient. The Fleiss kappa coefficient served as an extension of κ and permitted the calculation of agreement across more than two reviewers.[165] Inter-rater agreement could take any value from −1 to +1, standardised such that a value of +1 was indicative of perfect agreement between reviewers and -1 a complete absence of agreement across all shortlisted publications.[166]

3.2.3.2 Data requests

If a publication was agreed not to meet shortlisting criteria, contact was made with authors in an effort to obtain revised data, such as risks calculated relative to an uncontaminated reference category. Similarly, authors of publications that met shortlisting criteria were contacted if published data were found to be insufficient for the extraction or calculation of risk estimates, or sex-specific data were not reported.

In each instance, authors were given one month in which to respond. If no additional data were received, the publication was excluded (Figure 3.1). Where revised data were provided, this was noted in tables describing the characteristics of selected studies (Tables 3.1 and 3.2).

3.2.3.3 Duplicate studies

Publications that analysed the same dataset were identified and duplicates omitted with consideration to their respective degree of confounder adjustment, sample size and length of follow-up. Decisions were reached qualitatively by consensus, as detailed in Section 3.3.1.

3.2.3.4 Exposure data

A variety of methods were used for deriving volumes of alcohol consumption from categories of intake. Where the central tendency of each category was explicitly reported, the median or mean value was used, with preference given to the former measure owing to the skewness of continuous alcohol consumption.

If studies reported no central tendency for a category of alcohol consumption, intake was estimated according to the median of the lower and upper limit. However, in some circumstances the upper limit of the heaviest drinking category was not reported. Looking to meta-analyses undertaken elsewhere, methods applied for estimating an unknown upper limit were found to be arbitrary and inconsistent. While some authors operated on the assumption

that the range of a category with an undefined upper limit was equal to that which preceded it,[167,168] or three-quarters the width of the preceding category,[10] others multiplied the category's lower limit by a value of 1.2.[169] With no reason to conclude that any method was better than the other, unspecified upper limits were defined as 1.2 times the value of the lower limit. Where no lower bound was defined for the bottom category of volume of alcohol consumption, a value of 0.1 g was assumed.

In circumstances where alcohol consumption was reported only as the total number of drinks consumed over a given period of time, intake in g/day was estimated assuming country-specific standard drinks[170] unless otherwise defined by the study authors.

Finally, the volume of alcohol consumption as categorised according to periods longer than a day were converted into daily estimates assuming an even distribution of consumption over the period. For instance, a weekly volume of alcohol consumption was divided by seven.

3.2.3.5 Risk estimates

Extracted risk estimates took a number of forms. The pooling of ORs alongside other effect estimates risked being inappropriate given indications from simulated cohorts that ORs tend to overestimate equivalent RRs the greater the incidence of an event.[171] In an effort to bring ORs and RRs into greater concordance, ORs and their respective CIs were adjusted according to the Zhang and Yu method shown in Formula 3.1.

$$RR=OR/(1-p)+(p*OR)$$

Formula 3.1 Approximation of relative risks according to reported odds ratios

Here, p is a value equal to the proportion of T2DM among unexposed participants. Although not perfect, such an approach improves the suitability of pooling extracted ORs alongside other risk estimates for a high-incidence event such as T2DM.

Of shortlisted studies, some reported risk estimates according to a reference category other than abstention. These risk estimates were recalculated such that all risk estimates were relative to an equivalent category of non-drinking. This was undertaken iteratively using the Hamling method.[172] In short, the method uses the total number of exposed and unexposed participants in conjunction with the original risk estimates reported for each consumption category (k) to derive an approximated kx2 table of either cases and controls (for case-control studies) or cases and at-risk participants (for cohort studies) at each level of alcohol consumption. This table can then be used to calculate adjusted risk estimates for any consumption category relative to a reference category of choice. The calculation of corresponding CIs incorporated the covariance

between the original risk estimates from which the kx2 table was constructed, ensuring that the degree of variance for each new estimate was not underestimated.[172]

In all cases, estimates were extracted from models that incorporated the maximum number of confounding variables without adjustment for putative mediators – i.e. markers of insulin sensitivity, HDL concentration or inflammation. Such models would likely have been subject to an overadjustment bias, effectively controlling for the very mechanisms under investigation and thereby biasing risk estimates toward the null to a degree proportionate to the magnitude of dose-response effect explained by the mediating factor.[47]

3.2.4 Data synthesis

3.2.4.1 Model selection

Although meta-analyses have explored dose-response relationships according to a series of pre-defined alcohol consumption categories,[173] step functions provide a crude operationalisation of the relationship under study. Although easily interpretable by lay audiences, categories simplify the dose-response association, modelling risk as constant across a category's entire range and changing only at the exact threshold of each category.[174] In so doing, dose-response relationships become conditional upon both the number and width of exposure categories chosen, with the potential to inadvertently conceal nuanced changes in risk when categories are broad and few in number.

Fractional polynomial (FP) regression models provided a more flexible means of analysing non-linear dose-response relationships, utilising alcohol consumption data in its continuous form.[175] An extension of standard linear regression, FP regression models use transformations of alcohol consumption according to a restricted range of fractional powers (x^{-2}, x^{-1}, $x^{-0.5}$, $\ln(x)$, $x^{0.5}$, x^{1}, x^{2} and x^{3}).[176] Added as a single term, these transformations are capable of modelling monotonic dose-response relationships, while as a pair can also form non-monotonic functions with a single turning point, such as the J-shaped dose-response association previously observed between volume of alcohol consumption and T2DM risk. For example, a FP regression that comprises two polynomial terms is expressed as per Formula 3.2, with x^{p1} and x^{p2} equal to any pre-defined transformation of alcohol consumption from the restricted range of fractional powers, $\beta_{1,\ldots,n}$ equal to the change in risk for every unit change in $x^{p1,\ldots,n}$, and β_0 equal to the constant.

$$RR=\beta_0+\beta_1 x^{p1}+\beta_2 x^{p2}+\varepsilon$$

Formula 3.2 Derivation of regression coefficients according to a polynomial exposure

To identify the best-fitting transformation, all possible FP combinations were compared against a null model containing only a constant parameter. Fit was determined according to the deviance statistic (D), equivalent to the sum of squared residuals under OLS regression, or the degree to which observed data differed from the fitted function. Accordingly, the best-fitting model was that which reported a D value closest to zero.

FP regression models were constructed using the -fp- command in Stata 13.[177] As the -fp- command calculates dose-response relationships using weighted least squares regression, any resulting coefficients are under the assumption that data are independent. Such an assumption is invalid in this instance given that groups of risk estimates are nested within selected studies and calculated relative to a common reference category. When applied to non-independent data, least squares regression produces estimates with too great a degree of precision.[178] Accordingly, using an approach similar to the Hamling method,[172] covariance present between groups of extracted risk estimates was used to inflate standard errors reported by the best-fitting FP regression models. This was undertaken using the -glst- command.[179]

3.2.4.2 Heterogeneity

An assumption commonly underlying the pooling of data for meta-analysis is that, for a given level of volume alcohol consumption, corresponding effect estimates extracted from each study (y_i) were approximations of the same underlying effect (θ), with the extracted estimates each distributed around θ according to random sampling error.[180] Under this assumption, an inverse variance weight is typically applied (Formula 3.3), providing less prominence to smaller studies on the grounds that more precise information about the same underlying effect would be provided by larger selected studies.

$$w=1/SE_i^2$$

Formula 3.3 Inverse variance weight

However, given that no two selected studies were likely to have been methodologically identical, some degree of between-study heterogeneity was expected beyond simple random error,[181] with each y_i thereby estimating an underlying effect specific to the characteristics of its design and population (θ_i). In such a circumstance, the use of an inverse variance weight would be inappropriate, giving prominence to a sub-sample of selected studies that may have estimated an underlying effect different to those given lower prominence. Accordingly, random effects models were used throughout. These assumed that each effect estimate (y_i) for a given level of

exposure approximated its own specific underlying effect (θ_i), and that each underlying effect (θ_i) was itself distributed around a 'grand' value for all possible effects (μ) at the given level of exposure. The introduction of random effects thereby added an additional variance component (τ) equal to the estimated deviation between each θ_i and μ, thereby attenuating the inverse variance weight proportionate to the estimated deviation of each effect estimate's underlying effect from the grand effect of interest (Formula 3.4). Results from the random effects models were more conservative, with wider confidence intervals in the presence of between-study heterogeneity. Where no between-study heterogeneity was present ($\tau=0$), however, and the random effects models would naturally report figures analogous to a fixed effect model.[180]

$$w=1/SE_i^2+\tau$$

Formula 3.4 Inverse variance weight plus a random effects variance component

The degree of between-study heterogeneity was quantified using the I^2 index.[181] This estimated the proportion of total variance in risk as attributable to factors other than random error, and was calculated for each fitted polynomial term according to Formula 3.1:

$$I^2=((Q-df)/Q)*100\%$$

Formula 3.5 Calculation of the I^2 statistic

Here, df was equal to the number of constituent studies minus one, and the Cochran Q statistic equal to the sum of squared differences between each abstracted data point and the fitted polynomial function, with the contribution of each data point equal to its weight in the dose-response meta-analysis. An I^2 of 0% would thus indicate complete homogeneity between studies, with no variability between risk estimates other than that which would be expected through random error. Beyond this, the following guidelines were used for interpreting the I^2 index: 0-40%, low heterogeneity; 30-60%, moderate heterogeneity; 50-90%, substantial heterogeneity; 75% to 100%: considerable heterogeneity.[182]

3.2.4.3 Publication bias

There was a possibility that studies that investigated the relationship between volume of alcohol consumption and T2DM risk were more likely to have been published if they reported a significant and beneficial dose-response association. For instance, in an analysis of publication rates among 29,729 biomedical abstracts presented at scientific conferences, half were eventually published in full and the probability of publication associated with positive directions of effect (RR 1.30, 95% CI 1.14-1.47) and statistically significant results (RR 1.17, 95% CI 1.02-1.35).[183] Similar findings have been identified elsewhere.[184] If such publication bias were present

in the field of alcohol research, published studies selected for meta-analysis would have underrepresented smaller studies or those that reported contrary results and thereby overestimated the apparently advantageous relationship between moderate alcohol consumption and T2DM risk.

Funnel plots have commonly been used as a means of visualising the degree of publication bias present across sampled studies, plotting effect estimates along the x-axis and an indicator of their precision rising along the y-axis. In the absence of bias, less precise studies would be distributed evenly around the base of the plot with more precise studies clustered near the top, collectively resembling an inverted and symmetrical funnel. Accordingly, an asymmetrical distribution of risk estimates would indicate that studies of a particular statistical significance or direction of effect may have been less likely to reach publication.

Funnel plots are conventionally constructed by including a single risk estimate from each selected study, with all risk estimates relating to a consistently defined binary exposure (i.e. the risk of exposure versus non-exposure) such that they are assumed to be distributed around the same overall effect in a manner akin to a fixed effect meta-analysis.[185,186] Given that dose-response meta-analyses required the abstraction of multiple risk estimates from each selected study, with estimates pertaining to differing volumes of alcohol intake, such an assumption would have been invalidated were all extracted data included in a single plot.

Accordingly, new risk estimates were recalculated using the Hamling method so as to represent the risk of current drinking relative to non-drinking in each study.[172] These new estimates were then plotted against their respective standard errors. The contribution of each risk estimate to the calculation of an overall risk of current drinking was then estimated according to an inverse variance weighted linear regression equivalent to a fixed effects meta-analysis.[188] Random effects were not used when calculating the summary estimate and doing so risked shifting the summary estimate such that the small study effects being investigated may become masked.[188] Risk estimates were plot on a logarithmic scale to ensure that effects in opposite directions but of the same magnitude were all equidistant from a risk of 1.0.[182] A formal test of funnel plot asymmetry was also undertaken using the Egger's test, which tested the null hypothesis of no difference in effect according to sample size by way of an inverse variance weighted linear regression of standardised risk estimates against their SEs.[187]

Although a customary to view funnel plots as indicators of publication bias, such an interpretation should be made with consideration to factors other than publication bias that

may have produced an asymmetrical distribution. Alternative explanations include selection bias (selection criteria may have inadvertently excluded studies distributed around specific areas of the funnel plot, such as if negative associations between an exposure and event were most common among occupational cohorts but such populations had been excluded) and heterogeneity among selected studies (that, free of selection bias, selected studies still differed by characteristics associated with the relationship of interest, such as primarily representing a population sub-group in whom a particular direction of effect was more common). Accordingly, any funnel plots should only be used as a rough guide and best interpreted as a graphical representation of small-study effects – i.e. the tendency for studies of lower power to show lower levels of precision.[188]

3.2.4.4 Quality assessment

The quality of selected studies was assessed using the Newcastle-Ottawa quality assessment scale (Appendix 3.2).[189] It comprised eight questions ranging from the representativeness of the sample, the method of case ascertainment and the length of follow-up. A single point could be awarded for each question apart from one concerning confounder adjustment for which up to two points could be awarded. One point was awarded for adjustment for any confounding factors, with an additional point awarded if a study adjusted for 'the most important factor'. This was defined as adiposity, based on a study by Hu *et al*, which identified excess body fat as the strongest predictor of T2DM in a cohort of female nurses.[190] Study quality was thus ranked on a scale from 0-9 points, with larger scores indicative of higher quality.

Besides confounder adjustment, a number of other questions had to be subjectively defined. For instance, an 'adequate' period of aggregate follow-up was defined as at least six years in total. This threshold was decided upon with consideration to research by Tabak *et al*,[191] which examined 13-year trajectories of fasting and post-load glucose prior to the development of T2DM. They identified a gradual increase in glucose concentration over time, followed by a rapid elevation in concentration around three (fasting glucose) and six (post-load glucose) years prior to T2DM diagnosis. Assuming that study participants were free of T2DM at baseline with normative blood glucose readings, it was thus expected that a period of at least six years would have been required for blood glucose levels to reach a concentration sufficient for the formal diagnosis of T2DM.

3.2.4.5 Sub-group analyses

In addition to a summary dose-response analysis of all extracted data combined, a series of secondary analyses were undertaken to explore whether the relationship differed according to pre-specified factors.

3.2.4.5.1 Sex interaction

Given a higher incidence of T2DM[35] and a slower metabolism of alcohol among men,[192,193,194] it was possible that the relationship between the volume of alcohol consumption and T2DM risk may have differed according to sex. Such a hypothesis was supported by data from the last available meta-analysis,[10] which indicated that female drinkers experienced greater reductions in T2DM risk across a wider range of alcohol consumption than men, relative to quasi-never drinkers. Accordingly, in addition to the primary analysis of all data combined, consideration was given to a possible sex interaction. In addition to formally testing a sex interaction, the dose-response relationship was reported separately for men and women.

3.2.4.5.2 Reference group

To explore the effect of reference group selection upon the dose-response relationship, abstracted data were adjusted for any differences in dose-response according to sex and then an interaction term tested according to whether risk estimates had been calculated relative to never or pooled non-drinkers. Data were then stratified and dose-response relationships reported separately according to reference category. It was hypothesised that the magnitude of any reductions in T2DM risk at moderate volumes of alcohol consumption would be smaller among studies that excluded former drinkers from their reference category.

3.2.4.5.3 Confounder adjustment

As noted previously, it was hypothesised that confounder adjustment was likely to have a marked impact upon whether reductions in T2DM risk were observed at moderate levels of alcohol intake, with the magnitude of any reduction posited to be smaller among studies with more comprehensive adjustment for confounding factors.

To test this, dose-response data were adjusted for sex and reference group, with an interaction term then tested according to each study's degree of confounder adjustment. Confounder adjustment was defined according to a binary variable denoting whether extracted risk estimates were either crude or age-adjusted only, or multivariable-adjusted. In addition to formally testing whether the dose-response relationship differed according to the degree of

confounder adjustment, results were reported separately for each category of the binary variable.

3.2.4.5.4 Other sub-group analyses

Aside from sex, reference category and confounder adjustment, a number of other factors were posited to be likely modifiers of the observed dose-response relationship and thereby sources of heterogeneity between studies. These included the baseline age of participants, method of case ascertainment, population type, population region[195] and overall study quality assessment score. The reasoning behind the selection of such factors was as follows:

- **Baseline age**: It was hypothesised that any reduction in risk would be lower among older participants owing to age-related decreases in liver function and body water, increasing and prolonging the concentration of blood alcohol and alcohol metabolite beyond those seen in younger individuals at equivalent volumes of alcohol consumption.[196,197,198,199] Accordingly, any reductions in risk at moderate intakes might therefore be smaller within older populations as a consequence of prolonged accumulations of alcohol metabolites and their impact upon oxidative stress and a triggering of inflammatory response.[200,201]
- **Case ascertainment**: Subjective diagnoses of T2DM may have been subject to recall or self-reporting biases, leading to cases of T2DM being underreported. Depending on how any underreporting was distributed according to the volume of alcohol consumption, studies that utilised a subjective measure of T2DM diagnosis may have either overestimated or underestimated the magnitude of any dose-response relationship. Although an analysis investigating the validity of self-reported T2DM in epidemiologic studies found subjective measures to be reliable.[202]
- **Follow-up duration**: It was possible that studies with shorter periods of follow-up may have captured few new cases of T2DM and thereby have both insufficient power for the detection of dose-response effects.
- **Population region**: Given a genetic susceptibility among Asian populations to impaired alcohol metabolism[203] and increased T2DM risk,[204] it was hypothesised that any reductions in risk among moderate drinkers would be less pronounced among Asian studies in much the same way as older drinkers.
- **Population type**: Termed the 'healthy worker effect', studies have found participants in occupational cohorts to be healthier than those sampled in general population studies.[205] Accordingly, were a reduction in risk observed among moderate drinkers, any

such reduction in risk may have been shallower in studies of general populations whose participants were less healthy and potentially at greater risk of T2DM beyond any adjusted confounding factors.

- **Quality assessment**: With studies scoring low on the Newcastle-Ottawa assessment scale[189] potentially being less well adjusted for confounding factors, utilising self-reported outcome data, short follow-up periods and unrepresentative samples, it was posited that dose-response relationships reported by publications of lower quality would differ markedly in some fashion from those of higher quality.

Unfortunately, in the absence of individual participant data, the effect of differences in baseline age and follow-up duration were not explored due to the risk of aggregation bias, which would have inappropriately treated all study participants as having shared the same average age or length of observation.[206] For all remaining factors, interaction terms were formally tested in a mutually exclusive manner following adjustment for sex, reference category and confounder adjustment, if found to be significant modifiers of the dose-response relationship. Data were then stratified according to the value of each factor.

To explore the role of case ascertainment as a modifier of the dose-response relationship, a categorical variable was created denoting whether case ascertainment was subjective, objective or some combination of the two. A binary variable was created to investigate population type, indicating whether studies sampled occupational groups or the general population. Asian and non-Asian studies were identified and coded into a binary variable, studies also coded according to whether they fell below the median quality assessment score.

3.2.4.6 Sensitivity analyses

Having identified a study that contributed a substantial proportion of sampled data, an *a posteriori* sensitivity analysis was undertaken to explore the effect of including such a study upon the pooled analyses. An additional sensitivity analysis was also carried out to compare the dose-response relationship according to whether selected studies had been sampled by the preceding meta-analysis. Such an analysis would highlight whether the results of any newly analysed studies differed markedly to those previously examined.

3.3 Results

3.3.1 Excluded studies

As shown in the study flow diagram (Figure 3.1), 2,357 unique publications were identified by the initial search procedure, with preliminary screening by CK leading to the exclusion of 2,255

publications that reported no temporal association between volume of alcohol consumption and T2DM risk. The remaining 102 publications were then shortlisted by three reviewers against *a priori* selection criteria.

CK assessed all 102 publications, while AB shortlisted the first two-thirds (n=68) and SB shortlisted the last two-thirds (n=72), providing an overlap of one-third (n=38) for which shortlisting was undertaken by all three reviewers. Agreement between reviewers was high, with a κ of 0.86 between CK and SB, 0.91 between CK and AB, and 0.82 between all three reviewers.

Of the 102 publications that reported a temporal association between volume of alcohol consumption and T2DM risk, reviewers agreed that the full text of one was unobtainable, 45 reported <3 levels of alcohol intake, and seven provided data insufficient for estimating drinking in g/day. A further seven publications provided no sex-specific risk estimates, one reported information insufficient for calculating risk estimates for each consumption category (i.e. a figure without numbered axes or estimates), and one reported an abstention category contaminated by current drinkers.

With 40 shortlisted publications agreed to have m*et* all selection criteria, a further six suitable publications were identified following an examination of their referenced and referencing material. The resulting 46 publications were then checked to ensure that cohorts were each sampled only once. Where the same dataset was analysed by multiple publications, risk estimates were included from only the most robust analysis. Agreed upon by all three reviewers, the qualitative rationale in each instance was as follows:

- Four of the 46 shortlisted publications analysed the US Nurses' Health Study. Two of these were excluded for providing substantially shorter periods of follow-up and smaller sample sizes than the chosen publication.[207,208] Although the third publication provided almost twice the follow-up duration of any other paper, it was excluded due to its much smaller sample size and stratification of risk estimates for each consumption category according to a genetic polymorphism as opposed to the volume of alcohol consumption.[90]

- Three studies analysed the US Health Professionals' Follow-up Study. The first was excluded for providing data on 46,000 fewer participants than the chosen publication.[90] Although the second paper included adjustment for two additional confounding factors

than the chosen publication,[209] it sampled over 5,000 fewer participants and utilised half the period of follow-up than the third publication.

- Three studies also analysed the multi-centre European Prospective Investigation into Cancer and Nutrition (EPIC) study, each with roughly equivalent levels of confounder adjustment. The first sampled over 10,000 fewer participants than the chosen publication and was thus excluded.[210] While the second publication sampled 8,800 more participants than the chosen study,[211] it was excluded in preference of a paper that sampled a much wider range of European countries (Netherlands versus Denmark, France, Germany, Italy, Netherlands, Spain, Sweden and the United Kingdom).

- Two papers were published in 2010 by the same primary author, each sampling the same Japanese Gifu Prefectural Center for Health Check and Health Promotion cohort. Reporting similar levels of confounder adjustment and follow-up duration, the publication with the smaller sample size was excluded.[212]

- Two other shortlisted publications were also published by an identical primary author, with each sampling employees from the same Japanese gas company with equivalent levels of confounder adjustment and follow-up. Here, the study with the smaller sample size was excluded.[213]

The removal of these eight duplicate studies left a final sample of 38 unique studies.

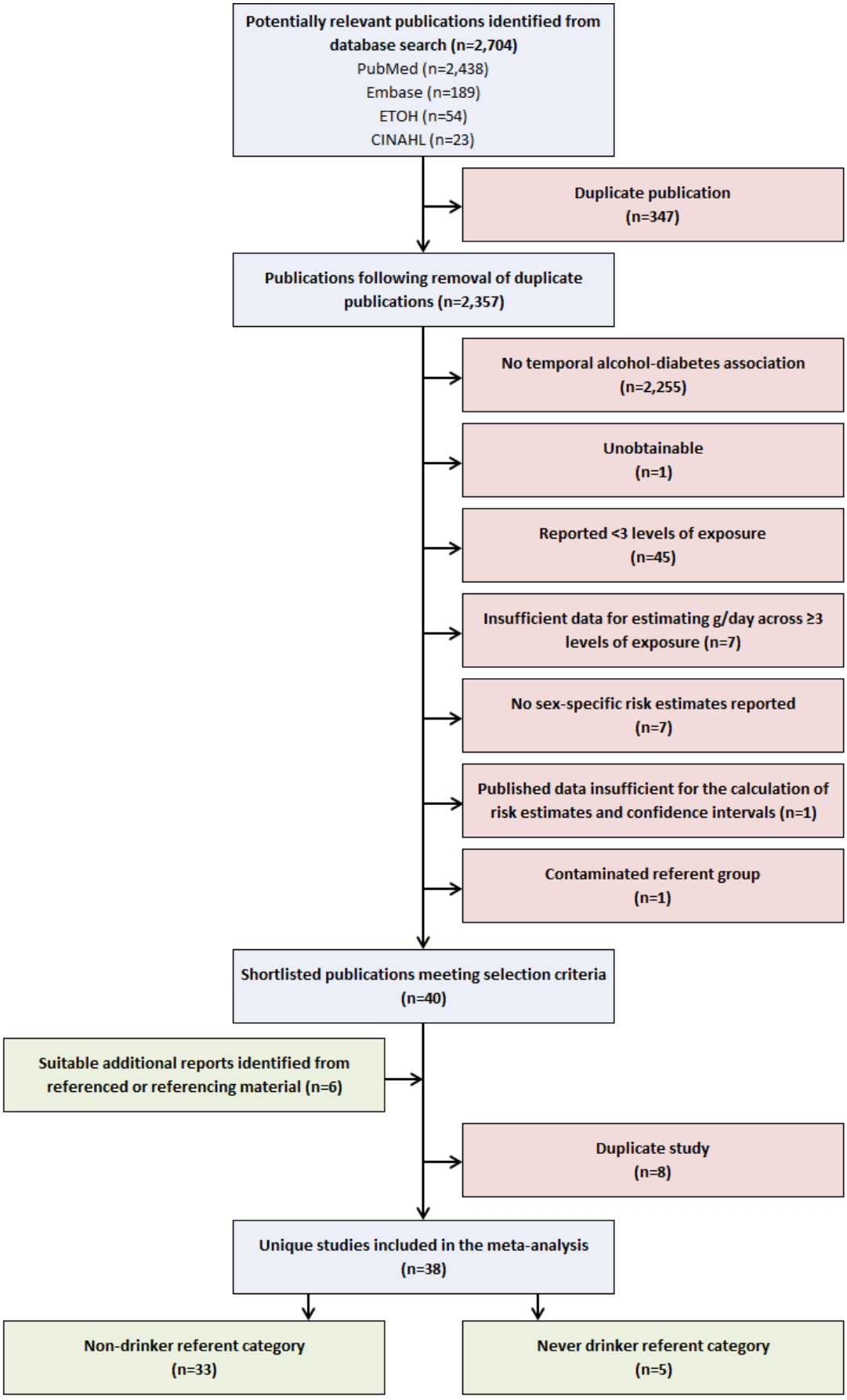


Figure 3.1 Study flow diagram

3.3.2 Included studies

As per the study flow diagram in Figure 3.1, 38 unique studies met *a priori* selection criteria out of an initial 2,704 search results. Of these, nine had provided additional, updated or recalculated risk estimates via personal correspondence.

Data extracted from the 38 studies represented 1,082,639 male and 819,966 female participants, among whom 79,633 and 46,293 cases of T2DM were reported. Crude or age-adjusted estimates were provided by 15 (39.5%) studies. Of the 23 remaining studies, measures of adiposity were universally accounted for, with smoking controlled by 16 (69.6%) studies, physical activity by 15 studies (65.2%), and familial heritability by 10 studies (43.4%). Other confounding factors included education (n=9, 39.1%), dietary variables (n=6, 26.1%), blood pressure (n=5, 21.7%), ethnicity (n=3, 13.0%) and some marker of social status such as occupational grade (n=3, 13.0%). More detailed information concerning the characteristics of the selected studies are reported in Table 3.1, while Table 3.2 lists the risk estimates for each level of alcohol consumption.

Despite capturing an additional 18 studies relative to the preceding alcohol-T2DM meta-analysis, only five studies were identified as having used a never drinking category strictly defined as complete abstention across the life course.[96,219,225,230,244] These included Kao *et al*,[219] who defined never drinkers as those who answered in the negative to the two following questions: “Do you presently drink alcoholic beverages?” and “Have you ever consumed alcoholic beverages?” Similarly, Carlsson *et al*,[96] defined never drinkers as baseline non-drinkers who also reported no change in alcohol consumption at any time prior, while Wannamethee *et al*[225] defined never drinkers as those who reported no consumption at all periods of follow-up (ages 15-17, 18-22, 23-30, and 31-40 years of age). Where a study’s definition of never drinking was deemed inadequate, such as through an inclusion of infrequent[97] or former drinkers,[153,234] such studies were classified as having use a pooled non-drinking reference category.

Table 3.1 Characteristics of selected studies

First author	Year	Country	Dataset	Design	Population	Age (years)	Duration (years)	Exposure ascertainment	Case ascertainment
Holbrook[214]	1990	US	Rancho Bernardo	Cohort	Community	40-79	14	Self-reported average weekly consumption of any alcoholic drinks.	A positive FPG or OGTT result, or a self-reported doctor-diagnosed diabetes.
Kawakami[215]	1997	Japan	Large electrical company	Cohort	Occupational	18-53	7.9	Self-reported mean consumption of alcoholic drinks usually consumed per week during the past year.	A positive FPG result among participants identified following a urine sample as having glycosuria.
Tsumura[216]	1999	Japan	Osaka Health Survey	Cohort	Occupational	35-61	9.7	Self-reported usual daily volume consumption.	A positive FPG or OGTT result.
Ajani[217]	2000	US	Physicians' Health Study	Cohort	Occupational	40-85	12.1	Self-reported frequency of consumption. Responses interpreted as number of standard drinks consumed.	Self-reported doctor diagnosis.
Wei[218]	2000	US	Cooper Clinic Study	Cohort	Community	30-79	6.1	Self-reported average weekly volume consumption of beer, wine or hard liquor. Alcohol content estimated as 1.1 g/1 oz beer, 2.7 g/1 oz wine, and 15.1 g /1 oz liquor.	A positive FPG result. Of those without a positive result, a self-reported history of diabetes or use of hypoglycaemic medication.
Conigrave[95]	2001	US	Health Professionals' Follow-up Study	Cohort	Occupational	40-75	10.9	Self-reported average frequency of consumption, with average daily volume estimated assuming 12.8g/beer, 11.0g/glass of wine, 14.0g/glass of liquor.	A positive FPG, non-FPG or OGTT result, or an elevated plasma glucose reading on two different occasions, or self-reported hypoglycaemic treatment.

Hu[190]	2001	US	Nurses' Health Study	Cohort	Occupational	30-55	15.3	Self-reported average frequency of beer, wine and liquor consumption. Daily volume estimated according to assumed nutrient content by drink type.	Self-reported cases confirmed following a positive FPG result, or an elevated randomly measured plasma glucose concentration.
Kao[219]	2001	US	ARIC	Cohort	Community	45-64	Men: 5.3 Women: 5.4	Self-reported average number of drinks consumed per week. Assumed 12.0 g/drink.	A positive FPG, or the self-reported use of hypoglycaemic medication, or a self-report of doctor diagnosis.
Meisinger[220]	2002	Germany	MONICA	Cohort	Community	35-74	Men: 7.5 Women: 7.6	Self-reported volume of beer, wine and spirit consumption on the previous workday and the previous weekend.	Self-reported doctor diagnosis or self-reported use of hypoglycaemic medication.
Wannamethee[221]	2002	UK	British Regional Heart Study	Cohort	Community	40-59	16.8	Self-reported frequency, quantity, and type of alcohol consumption.	Self-reported T2DM, confirmed via primary care records.
Carlsson[96]	2003	Finland	Finnish Twin Cohort	Cohort	Community	≥18	28	Self-reported volume of alcohol consumed during an average week (beer, wine) or month (spirits).	Death certificates, the National Hospital Discharge Register and the Medication Register of the Social Insurance Institution.
Lee[222]	2003	Korea	Steel company	Cohort	Occupational	25-55	4	Self-reported data. No further detail published.	A positive FPG result.

Nakanishi[223]	2003	Japan	Building contractor	Cohort	Occupational	35-59	6.1	Self-reported frequency of alcohol consumption per week, and usual amount consumed per day in units of “go” (23 g ethanol).	A positive FPG result, or self-reported use of hypoglycaemic medication.
Sawada[224]	2003	Japan	Gas company	Cohort	Occupational	20-40	13.6	Self-administered questionnaire. No further detail published.	A positive FPG or OGTT result, or the self-reported prescription of hypoglycaemic medication.
Wannamethee[225]	2003	US	Nurses' Health Study II	Cohort	Occupational	25-42	8.1	Self-reported beverage-specific frequency of consumption during the past year. Volume consumption estimated according to assumed drink-specific ABVs.	A positive FPG or OGTT result, or elevated plasma glucose levels on two different occasions, or self-reported hypoglycaemic treatment.
Lee[226]	2004	US	Iowa Women’s Health Study	Cohort	Community	55-69	9.3	Self-administered questionnaire. No further detail published.	Self-reported doctor diagnosis.
Waki[227]	2005	Japan	JPHC Study	Cohort	Community	40-59	10	Self-reported type and frequency of alcohol consumption per week, and the usual amount of alcohol consumed per day.	Self-reported doctor diagnosis.
Hodge[97]	2006	Australia	Melbourne Collaborative Cohort Study	Cohort	Community	40-69	4	Self-reported beverage-specific average frequency and quantity of consumption, plus volume via a seven-day diary.	Self-reported doctor diagnosis.

Hu[228]	2006	Finland	FINMONICA	Cohort	Community	35-74	Men: 13.0 Women: 13.8	Self-administered questionnaire. No further detail published.	National Hospital Discharge Register or National Social Insurance Drug Register, confirmed via a positive FPG or OGTT result, or self-reported hypoglycaemic drug treatment.
Strodl[229]	2006	Australia	Australian Women's Health Survey	Cohort	Community	70-74	3	Self-administered questionnaire. No further detail published.	Self-reported doctor-diagnosis.
Burke[230]	2007	Australia	Kimberley Aborigines	Cohort	Community	15-88	12.9	A contextualised diary of the last two 48-hour drinking periods.	Linkage to hospital admission and mortality records.
Djoussé[153]	2007	US	Cardiovascular Health Study	Cohort	Community	≥65	6.3	Self-reported usual frequency of beer, wine and liquor consumption, and quantity consumed on an average occasion.	A positive FPG result or self-reported hypoglycaemic drug treatment.
Maty[231]	2008	US	Alameda County Study	Cohort	Community	17-94	34	Self-reported frequency of consumption, and quantity consumed on an average occasion.	Self-reported doctor-diagnosed diabetes.
Onat[232]	2009	Turkey	Turkish Adult Risk Factor Study	Cohort	Community	≥18	7.4	Self-administered questionnaire. No further detail published.	A positive FPG result or self-reported hypoglycaemic drug treatment.
Roh[233]	2009	Korea	Annual health evaluation	Cohort	Community	Not reported	4	Self-reported frequency of consumption, and quantity consumed on an average occasion.	A positive FPG result.

Boggs[234]	2010	US	Black Women's Health Study	Cohort	Community	21-69	9.4	Self-reported average frequency of beer, wine, and liquor consumption during the previous year. Volume consumption estimated assuming 12.0 g/drink.	Self-reported doctor diagnosis, excluding cases among participants aged <30 years.
Jee[235]	2010	Korea	Korean Cancer Prevention Study	Cohort	Community	30-95	14	Self-administered questionnaire. No further detail published.	Outpatient treatment for diabetes (at least three visits for diabetes care per 365 days).
Nagaya[236]	2010	Japan	Gifu Center for Health Promotion	Cohort	Community	30-59	Men:8.2 Women: 7.7	Self-administered questionnaire reconfirmed by a personal interview with a public health nurse. No further detail published.	A positive FPG result or self-reported hypoglycaemic drug treatment.
Balkau[237]	2011	France	DESIR	Cohort	Community	30-65	9	Self-reported usual daily consumption of wine, beer, cider and spirits. The following volumes were assumed: 10.0 g/125 ml wine or 250 ml of beer/cider, and 7.0 g/20 ml of spirits.	A positive FPG or HbA1c result, or self-reported treatment for diabetes.
Beulens[238]	2012	Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, UK	EPIC–InterAct	Nested case–cohort	Community	35-70	9.9	Self-reported number and frequency of glasses of beer, cider, wine, sweet liquor, distilled spirits or fortified wines consumed during the previous 12 months. Volume estimated according to assumed glass volume and ethanol content for each drink type.	Self-reported doctor-diagnosed diabetes or self-reported treatment for diabetes, or linkage to primary or secondary care registers or diabetes and pharmaceutical registers.

Cullmann[239]	2012	Sweden	Stockholm Diabetes Prevention Program	Cohort	Community	35-56	8-10	Self-reported frequency and quantity of medium and strong beer, wine, dessert wine and spirits.	A positive FPG or OGTT reading.
Sato[240]	2012	Japan	Kansai Healthcare Study	Cohort	Occupational	40-55	3.5	Self-reported weekly frequency of alcohol consumption and quantity consumed per average drinking day. Volume estimated according to a Japanese standard drink equivalent to 23.0 g/180 ml sake.	A positive FPG result or self-reported hypoglycaemic drug treatment.
Stringhini[241]	2012	UK	Whitehall II	Cohort	Occupational	35-55	14.2	Self-reported quantity of drinks consumed in the previous week, converted to UK units. No further detail published.	A positive FPG or OGTT result, or self-reported doctor-diagnosed diabetes, or self-reported hypoglycaemic drug treatment.
Teratani[242]	2012	Japan	Steel company	Cohort	Occupational	Not reported	4.4	Self-reported quantity of daily alcohol consumption. Volume estimated assuming 22.0 g/180 ml sake, 500 ml beer, 60 ml whiskey, 180 ml wine, or 110 ml shochu.	Self-reported doctor diagnosis, or a positive HbAlc result, or ≥6.1% or self-reported hypoglycaemic drug treatment.
Abbasi[243]	2013	Netherlands	PREVEND	Cohort	Community	28-75	8	Self-administered questionnaire. No further detail published.	A positive FPG or random plasma glucose result, or a self-reported doctor diagnosis, or objective hypoglycaemic drug treatment.

Heianza[244]	2013	Japan	TOPICS 11	Cohort	Community	26-80	10.2	Self-reported frequency of consumption and average quantity of alcohol consumed per occasion.	Positive FPG or HbA1c result, or self-reported doctor-diagnosed diabetes.
Rasouli[245]	2013	Norway	Nord-Trøndelag Health Survey	Cohort	Community	≥20	11	Self-reported, beverage-specific average quantity of beer, wine or spirits consumed over a two-week period. Assumed 16g/beer, 12g/glass of wine or spirits.	Of those with self-reported diabetes, T1DM was tested using a marker of pancreatic autoimmune damage. Those with a negative result were classified as having T2DM.
Shi[246]	2013	China	Shanghai Men's Health Study	Cohort	Community	40-74	5.4	Self-reported type, frequency, and usual quantity of alcohol consumed (wine, beer, and liquor).	Self-reported cases confirmed via a positive FPG or OGTT result or use of hypoglycaemic medication.

FPG: Fasting plasma glucose test; OGTT: oral glucose tolerance test; UK: United Kingdom; US: United States.

Table 3.2 Measures of alcohol consumption, confounder adjustment and effect estimates reported by selected studies

		Alcohol consumption		Risk of T2DM					
First author	**Sex**	**Exposure categories[a]**	**Estimated g/day[b]**	**Cases (n)**	**Non-cases (n)**	**Measure**	**Effect estimates**	**Confounder adjustment**	**Quality**
Holbrook[214]	Men	Non-drinkers	Non-drinkers	6	31	Relative risk	1.00 (reference)	Age	7
		0.1-84.3 g/week	6.0	7	53		0.72 (95% CI 0.26-1.98)		
		84.4-176.0 g/week	18.6	6	55		0.61 (95% CI 0.21-1.74)		
		176.1-750 g/week	66.2	16	47		1.57 (95% CI 0.67-3.65)		
	Women	Non-drinkers	Non-drinkers	16	68		1.00 (reference)		
		0.1-41.3 g/week	6.0	7	67		0.50 (95% CI 0.22-1.14)		
		41.4-117.4 g/week	18.6	12	60		0.88 (95% CI 0.44-1.73)		
		117.5-750 g/week	66.2	12	61		0.86 (95% CI 0.44-1.70)		
Kawakami[215]	Men	0 ml/week	0.0	11[c]	590[c]	Hazard ratio	1.00 (reference)	Age; BMI; education; family history of T2DM; occupation; physical activity; smoking; shift pattern	7
		<300 ml/week	16.9	23[c]	1,595[c]		1.04 (95% CI 0.47-2.32)		
		≥300 ml/week	40.6	12[c]	533[c]		1.09 (95% CI 0.44-2.67)		
Tsumura[216]	Men	Non-drinkers	Non-drinkers	76	1,058	Relative risk	1.00 (reference)	Age	6
		0.1-19.0 ml/day	7.5	95	1,226		0.98 (95% CI 0.73-1.33)		
		19.1-29.0 ml/day	19.0	120	1,386		1.08 (95% CI 0.81-1.44)		
		29.1-50.0 ml/day	31.2	60	1,057		0.80 (95% CI 0.57-1.12)		
		≥50.1 ml/day	47.4	105	1,179		1.40 (95% CI 1.04-1.88)		
Ajani[217]	Men	Rarely/Never drinkers	Rarely/Never drinkers	145	2,900	Relative risk	1.00 (reference)	Age; BMI; physical activity; smoking; treatment group	6
		1-3 drinks/month	0.9	111	2,189		1.03 (95% CI 0.80-1.33)		
		1 drinks/week	2.0	122	2,806		0.89 (95% CI 0.70-1.14)		
		2-4 drinks/week	6.0	157	4,614		0.74 (95% CI 0.59-0.93)		
		5-6 drinks/week	11.0	80	2,613		0.67 (95% CI 0.51-0.88)		
		≥1 drink/day	16.8	151	5,063		0.57 (95% CI 0.45-0.73)		

Wei[218]	Men	Non-drinkers	Non-drinkers	36	1,811	Relative risk[d,e]	1.00 (reference)	Age; family history of T2DM; years of follow-up	6
		1-61.8 g/week	4.8	21	1,675		0.78 (95% CI 0.44-1.37)		
		61.9-122.7 g/week	13.1	16	1,682		0.56 (95% CI 0.31-1.00)		
		122.8-276.6 g/week	26.6	35	1,655		1.22 (95% CI 0.75-1.98)		
		≥276.6 g/week	83.5	41	1,661		1.32 (95% CI 0.83-2.11)		
Conigrave[95]	Men	0 g/day	0.0	416	10,656	Relative risk	1.00 (reference)	Age; BMI	5
		0.1-4.9 g/day	2.3	450	11,356		1.09 (95% CI 0.95–1.24)		
		5.0-9.9 g/day	7.3	214	6,941		0.88 (95% CI 0.74–1.04)		
		10.0-14.9 g/day	12.3	163	6,050		0.77 (95% CI 0.64–0.92)		
		15.0-29.9 g/day	19.7	174	6,321		0.80 (95% CI 0.67–0.96)		
		30.0-49.9 g/day	38.1	116	4,419		0.72 (95% CI 0.58–0.88)		
		≥50.0 g/day	70.1	38	1,419		0.64 (95% CI 0.46–0.89)		
Hu[190]	Women	0 g/day	0.0	1,715	27,165	Relative risk	1.00 (reference)	Age; family history of T2DM; menopausal status; time; use of postmenopausal hormone therapy	6
		0.1-5 g/day	2.6	1,034	26,997		0.78 (95% CI 0.72–0.84)		
		5.1-10.0 g/day	7.6	189	9,155		0.56 (95% CI 0.48–0.65)		
		>10 g/day	12.0	358	17,480		0.59 (95% CI 0.52–0.66)		
Kao[219]	Men	Lifetime abstainers	Lifetime abstainers	69	600	Relative risk[d,e]	1.00 (reference)	Age; BMI; education; ethnicity; family history of T2DM; history of hypertension; physical activity; smoking; total energy intake; waist-hip ratio	7
		Former drinkers	Former drinkers	118	978		0.93 (95% CI 0.70-1.24)		
		≤1 drink/week	0.1	74	741		0.88 (95% CI 0.64-1.23)		
		1.1-7 drinks/week	6.1	139	1,227		0.98 (95% CI 0.74-1.30)		
		7.1-14 drinks/week	17.7	55	670		0.72 (95% CI 0.50-1.02)		
		14.1-21 drinks/week	29.3	32	281		0.94 (95% CI 0.62-1.41)		
		>21 drinks/week	57.4	60	379		1.75 (95% CI 1.26-2.44)		
	Women	Lifetime abstainers	Lifetime abstainers	236	1,987		1.00 (reference)		
		Former drinkers	Former drinkers	108	872		1.00 (95% CI 0.75-1.34)		
		≤1 drink/week	0.1	110	1,626		0.92 (95% CI 0.72-1.17)		
		1.1-7 drinks/week	5.7	90	1,226		0.99 (95% CI 0.74-1.33)		
		7.1-14 drinks/week	16.7	18	378		0.75 (95% CI 0.45-1.25)		
		14.1-21 drinks/week	28.9	5	125		0.60 (95% CI 0.24-1.47)		
		>21 drinks/week	49.6	2	56		0.39 (95% CI 0.10-1.55)		

		0 g/day	0.0	23	439	1.00 (reference)		
	Men	0.1-39.9 g/day	20.0	46	1,518	0.59 (95% CI 0.36-0.96)		
		≥40 g/day	48.0	58	968	1.14 (95% CI 0.71-1.82)		
Meisinger[220]						Relative risk	None	6
		0 g/day	0.0	48	1,212	1.00 (reference)		
	Women	0.1-19.9 g/day	10.0	26	1,199	0.56 (95% CI 0.35-0.89)		
		≥20 g/day	24.0	12	618	0.50 (95% CI 0.27-0.93)		
		Non-drinkers	Non-drinkers	4	285	1.00 (reference)		
		<1 unit/week	0.6	62	1,150	0.91 (95% CI 0.50-1.65)	Age; BMI; history of CHD; physical activity; smoking; social class	9
Wannamethee[221]	Men	1-15 units/week	7.9	99	1,612	Relative risk[e] 0.74 (95% CI 0.45-1.20)		
		15-42 units/week	32.7	64	1,361	0.60 (95% CI 0.36-0.99)		
		>42 units/week	63.2	18	566	0.87 (95% CI 0.50-1.51)		
		Lifetime abstainers	Lifetime abstainers	64	1,045	1.00 (reference)		
		Former drinkers	Former drinkers	11	151	0.91 (95% CI 0.46-1.80)		
	Men	<5 g/day	3.1	181	2,525	1.06 (95% CI 0.78-1.42)		
		5–30 g/day	10.7	261	4,480	0.86 (95% CI 0.63-1.16)		
		>30 g/day	42.8	75	1,023	0.90 (95% CI 0.61-1.32)		
Carlsson[f,96]						Hazard ratio	Age; BMI; smoking	8
		Lifetime abstainers	Lifetime abstainers	280	2,977	1.00 (reference)		
		Former drinkers	Former drinkers	2	75	0.93 (95% CI 0.23-3.73)		
	Women	<5 g/day	2.3	273	5,655	0.79 (95% CI 0.66-0.95)		
		5–20 g/day	6.9	55	2,173	0.66 (95% CI 0.47-0.91)		
		>20 g/day	25.9	10	303	0.79 (95% CI 0.40-1.55)		
		Non-drinkers	Non-drinkers	23	816	1.00 (reference)		
		≤90 g/week	6.5	33	1,793	0.66 (95% CI 0.39-1.12)		
Lee[222]	Men	91-180 g/week	19.4	11	733	Relative risk 0.54 (95% CI 0.26-1.10)	None	3
		181-360 g/week	38.6	11	497	0.79 (95% CI 0.39-1.61)		
		>360 g/week	61.7	5	133	1.32 (95% CI 0.51-3.42)		
		0 g/day	0.0	63	358	1.00 (reference)		
		0.1-22.9 g/day	11.5	67	467	0.87 (95% CI 0.60-1.26)	Age; BMI; family history of T2DM; physical activity; smoking	7
Nakanishi[223]	Men	23.0-45.9 g/day	34.5	66	632	Relative risk[e] 0.66 (95% CI 0.47-0.93)		
		46.0-68.9 g/day	57.5	107	774	0.78 (95% CI 0.56-1.10)		
		≥69 g/day	82.8	67	352	0.95 (95% CI 0.65-1.38)		

Sawada[224]	Men	Non-drinkers	Non-drinkers	50	1,412	Relative risk	1.00 (reference)	Age; BMI; family history of T2DM; fitness; high blood pressure; smoking	7
		1-45 g/day	23.5	206	2,814		1.59 (95% CI 1.16-2.17)		
		≥46 g/day	55.2	24	239		1.68 (95% CI 1.03-2.76)		
Wannamethee[225]	Women	Lifelong abstainers	Lifelong abstainers	181	14,736	Relative risk	1.00 (reference)	Age	4
		Former drinkers	Former drinkers	334	23,791		1.18 (95% CI 0.98-1.41)		
		0.1-4.9 g/day	2.5	336	44,048		0.67 (95% CI 0.56-0.80)		
		5.0-14.9 g/day	10.0	70	18,309		0.34 (95% CI 0.25-0.44)		
		15.0-29.9 g/day	22.5	8	2,308		0.29 (95% CI 0.15-0.60)		
		≥30 g/day	36.0	6	758		0.63 (95% CI 0.28-1.42)		
Lee[226]	Women	Non-drinkers	Non-drinkers	1,168	15,829	Rate ratio	1.00 (reference)	None	4
		1-14 g/day	8.0	675	15,592		0.60 (95% CI 0.55-0.66)		
		≥15 g/day	18.0	78	2,356		0.47 (95% CI 0.37-0.59)		
Waki[227]	Men	Non/infrequent drinkers	Non/infrequent drinkers	196	3,834	Relative risk[d]	1.00 (reference)	Age; BMI; family history of T2DM; hypertension; physical activity; smoking	6
		≤23.0 g/day	11.55	169	3,162		1.08 (95% CI 0.88-1.32)		
		23.1-46.0 g/day	34.55	174	2,735		1.24 (95% CI 1.02-1.52)		
		>46.0 g/day	55.32	164	2,479		1.23 (95% CI 1.00-1.52)		
	Women	Non/infrequent drinkers	Non/infrequent drinkers	436	13,919		1.00 (reference)		
		≤4.9 g/day	2.5	15	465		1.14 (95% CI 0.69-1.90)		
		5.0-11.5 g/day	8.25	16	636		0.81 (95% CI 0.49-1.34)		
		>11.5 g/day	13.92	13	481		0.79 (95% CI 0.45-1.38)		

Hodge[97]	Men	Lifetime abstainer	Lifetime abstainer	25	1,795	Relative risk[d]	1.00 (reference)	Age; BMI; country of birth; dietary glycaemic index; dietary energy intake; waist-hip ratio	8
		Former drinkers	Former drinkers	17	500		2.44 (95% CI 1.29-4.52)		
		<10 g/day	4.3	56	3,031		1.55 (95% CI 0.95-2.50)		
		10-19.9 g/day	15.0	30	2,247		1.21 (95% CI 0.69-2.07)		
		20-29.9 g/day	24.2	13	1,333		0.80 (95% CI 0.40-1.59)		
		≥30 g/day	45.0	38	3,129		0.86 (95% CI 0.50-1.57)		
	Women	Lifetime abstainers	Lifetime abstainers	114	7,729		1.00 (reference)		
		Ex-drinkers	Ex-drinkers	9	589		1.12 (95% CI 0.55-2.24)		
		<10 g/day	3.5	32	5,659		0.66 (95% CI 0.44-1.00)		
		10-19.9 g/day	15.0	18	2,838		0.82 (95% CI 0.49-1.37)		
		≥20 g/day	30.2	10	2,210		0.60 (95% CI 0.30-1.17)		
Hu[228]	Men	Non-drinkers	Non-drinkers	223	3,608	Hazard ratio	1.00 (reference)	Age; BMI; food consumption (bread; coffee, fruit, tea, sausage, vegetable); education; physical activity; smoking; study year; systolic blood pressure	8
		1-100 g/week	7.2	190	3,661		0.91 (95% CI 0.75-1.11)		
		>100 g/week	17.1	104	2,402		0.74 (95% CI 0.58-0.95)		
	Women	Non-drinkers	Non-drinkers	357	6,350		1.00 (reference)		
		1-100 g/week	7.2	87	3,877		0.74 (95% CI 0.57-0.94)		
		>100 g/week	17.1	3	523		0.23 (95% CI 0.07-0.73)		
Strodl[229]	Women	Non-drinkers	Non-drinkers	87	2,698	Relative risk[d]	1.00 (reference)	None	3
		Rarely drinkers	Rarely drinkers				1.00 (95% CI 0.74-1.35)		
		1-2 drinks/day	15.0	54	2,922		0.58 (95% CI 0.42-0.82)		
		≥3 drinks/day	36.0	12	306		1.21 (95% CI 0.67-2.17)		
Burke[230]	Men	Life-long abstainers	Life-long abstainers	7	14	Relative risk	1.00 (reference)	None	6
		Ex-drinkers	Ex-drinkers	14	40		0.78 (95% CI 0.37-1.65)		
		<150 g/day	88.0	12	86		0.37 (95% CI 0.16-0.82)		
		≥150 g/day	209.0	8	48		0.43 (95% CI 0.18-1.04)		
	Women	Life-long abstainers	Life-long abstainers	25	66		1.00 (reference)		
		Ex-drinkers	Ex-drinkers	11	38		0.82 (95% CI 0.44-1.52)		
		<100 g/day	57.0	10	48		0.63 (95% CI 0.33-1.21)		
		≥100 g/day	136.0	9	18		1.21 (95% CI 0.65-2.28)		

Djoussé[153]	Men	Never drinkers	Never drinkers	37	476	Relative risk	1.00 (reference)	Age; BMI; education; smoking	8
		Former drinkers	Former drinkers	10	183		0.7 (95% CI 0.3-1.4)		
		<1 drink/week	0.4	13	326		0.5 (95% CI 0.3-0.9)		
		1-6 drinks/week	4.0	24	421		0.6 (95% CI 0.4-1.1)		
		≥7drinks/week	30.0	25	384		0.8 (95% CI 0.4-1.3)		
	Women	Never drinkers	Never drinkers	74	1,221		1.00 (reference)		
		Former drinkers	Former drinkers	10	143		1.2 (95% CI 0.6-2.3)		
		<1 drink/week	0.4	23	582		0.7 (95% CI 0.4-1.1)		
		1-6 drinks/week	4.0	13	400		0.6 (95% CI 0.3- 1.1)		
		≥7 drinks/week	30.0	5	285		0.4 (95% CI 0.2-1.0)		
Maty[231]	Men	0 drinks/month	0.0	21	373	Relative risk	1.00 (reference)	None	4
		1-45 drinks/month	10.6	85	1,652		0.92 (95% CI 0.58-1.46)		
		≥46 drinks/month	25.4	34	591		1.02 (95% CI 0.60-1.73)		
	Women	0 drinks/month	0.0	42	771		1.00 (reference)		
		1-45 drinks/month	10.6	116	1,969		1.08 (95% CI 0.76-1.52)		
		≥46 drinks/month	25.4	9	250		0.67 (95% CI 0.33-1.36)		
Onat[f,232]	Men	Non-drinkers	Non-drinkers	102	936	Relative risk	1.00 (reference)	Age; physical activity; smoking	6
		<3 drinks/day	16.0	46	434		1.23 (95% CI 0.88-1.73)		
		>3 drinks/day	38.4	14	71		1.91 (95% CI 1.06-3.45)		
	Women	Non-drinkers	Non-drinkers	157	1,384		1.00 (reference)		
		<3 drinks/day	16.0	2	63		0.38 (95% CI 0.11-1.23)		
		>3 drinks/day	38.4	0	4		Too few data		
Roh[233]	Men	Non-drinkers	Non-drinkers	150	276	Relative risk	1.00 (reference)	None	5
		1-14 g/day	8.0	251	412		1.08 (95% CI 0.91-1.26)		
		15-29 g/day	22.5	166	200		1.29 (95% CI 1.09-1.53)		
		≥30 g/day	36.0	123	139		1.33 (95% CI 1.11-1.60)		

Boggs[234]	Women	Never drinkers	Never drinkers	1,669	20,457	Relative risk	1.00 (reference)	Age; questionnaire cycle; energy intake	5
		Former drinkers	Former drinkers	1,159	9,966		1.22 (95% CI 1.13-1.31)		
		1-3 drinks/week	4.0	552	7,658		0.84 (95% CI 0.76-0.93)		
		4-6 drinks/week	10.0	132	2,530		0.60 (95% CI 0.51-0.72)		
		7-13 drinks/week	20.0	97	1,484		0.70 (95% CI 0.57-0.86)		
		≥14 drinks/week	33.6	43	654		0.71 (95% CI 0.52-0.96)		
Jee[f,235]	Men	0 g/day	0.0	14,407	172,786	Hazard ratio	1.00 (reference)	Age; age^2; BMI; physical activity	8
		1-24 g/day	13.0	33,332	418,536		0.95 (95% CI 0.93–0.97)		
		25-4 g/day	37.5	7,588	80,680		0.99 (95% CI 0.96–1.02)		
		50-99 g/day	75.0	4,188	41,104		1.05 (95% CI 1.01–1.08)		
		≥100 g/day	120.0	1,440	13,703		1.04 (95% CI 0.99–1.10)		
	Women	0 g/day	0.0	24,860	359,916		1.00 (reference)		
		1-24 g/day	13.0	3,596	60,024		0.90 (95% CI 0.87–0.93)		
		25-49 g/day	37.5	6	210		1.85 (95% CI 0.77–4.43)		
		≥50 g/day	60.0	2	46		1.03 (95% CI 1.00–1.06)		
Nagaya[236]	Men	0 g/day	0.0	212	3,940	Relative risk	1.00 (reference)	None	6
		<25 g/day	12.5	198	4,035		0.92 (95% CI 0.76-1.11)		
		25-40 g/day	32.5	223	4,071		1.02 (95% CI 0.85-1.22)		
		≥40 g/day	48.0	236	3,913		1.11 (95% CI 0.93-1.33)		
	Women	0 g/day	0.0	188	6,434		1.00 (reference)		
		<25 g/day	12.5	30	1,413		0.73 (95% CI 0.50-1.07)		
		≥25 g/day	30.0	6	297		0.70 (95% CI 0.31-1.56)		
Balkau[f,237]	Men	0 g/day	0.0	18	206	Relative risk[d]	1.00 (reference)	Education; physical activity; smoking	5
		<20 g/day	2.0	27	411		0.77 (95% CI 0.42-1.40)		
		20-39 g/day	23.0	79	844		0.84 (95% CI 0.49-1.40)		
		≥40 g/day	67.0	47	244		1.27 (95% CI 0.73-2.16)		
	Women	0 g/day	0.0	35	206		1.00 (reference)		
		<20 g/day	1.0	35	411		0.95 (95% CI 0.59-1.48)		
		≥20 g/day	21.0	22	1088		0.87 (95% CI 0.51-1.43)		

Beulens[238]	Men	0 g/day	0.0	485	452	Hazard ratio[e]	1.00 (reference)	Age; BMI; education; food consumption (coffee, fruit, meat, total energy, vegetable); physical activity; smoking;	8
		0.1-6.0 g/day	3.1	1,303	1,262		1.03 (95% CI 0.86-1.24)		
		6.1-12.0 g/day	9.1	890	891		0.93 (95% CI 0.79-1.09)		
		12.1-24.0 g/day	18.1	1,116	1,166		0.97 (95% CI 0.83-1.13)		
		24.1-60.0 g/day	42.1	1,448	1,555		0.89 (95% CI 0.77-1.02)		
		60.1-96.0 g/day	78.1	393	363		0.80 (95% CI 0.65-0.99)		
		>96.0 g/day	115.2	126	85		1.10 (95% CI 0.79-1.54)		
	Women	0 g/day	0.0	1,601	2,013		1.00 (reference)		
		0.1-6.0 g/day	3.1	2,429	3,828		0.91 (95% CI 0.86-0.96)		
		6.1-12.0 g/day	9.1	743	1,483		0.75 (95% CI 0.66-0.84)		
		12.1-24.0 g/day	18.1	623	1,322		0.79 (95% CI 0.70-0.90)		
		>24 g/day	28.8	402	838		0.81 (95% CI 0.69-0.95)		
Cullmann[239]	Men	Non-drinkers	Non-drinkers	10	62	Relative risk[d,e]	1.00 (reference)	Age; BMI; education; family history of T2DM; physical activity; smoking	8
		0.01-6.79 g/day	3.4	46	501		0.62 (95% CI 0.32-1.19)		
		6.80-13.01 g/day	9.9	28	488		0.41 (95% CI 0.23-0.73)		
		13.02-22.13 g/day	17.6	41	505		0.56 (95% CI 0.33-0.96)		
		≥22.14 g/day	26.6	50	486		0.56 (95% CI 0.33-0.96)		
	Women	Non-drinkers	Non-drinkers	6	94		1.00 (reference)		
		0.01-1.49 g/day	0.8	34	724		0.92 (95% CI 0.37-2.26)		
		1.50-4.71 g/day	3.1	14	766		0.39 (95% CI 0.18-0.83)		
		4.72-8.75 g/day	6.7	20	739		0.69 (95% CI 0.34-1.41)		
		≥8.76 g/day	10.5	24	755		0.87 (95% CI 0.43-1.75)		
Sato[240]	Men	Non-drinkers	Non-drinkers	142	1,479	Hazard ratio	1.00 (reference)	Age	5
		0.1-2.0 drinks/day	14.7	350	4,055		0.94 (95% CI 0.78-1.15)		
		2.1-4.0 drinks/day	42.7	268	3,093		0.94 (95% CI 0.77-1.15)		
		≥4.1 drinks/day	68.9	118	1,126		1.16 (95% CI 0.91-1.48)		
Teratani[f,242]	Men	Non-drinkers	Non-drinkers	131	2,287	Hazard ratio	1.00 (reference)	None	5
		1-76 g/week	6.3	71	1,677		0.81 (95% CI 0.61, 1.08)		
		77-153 g/week	15.7	73	1,243		0.94 (95% CI 0.70, 1.26)		
		154-307 g/week	22.0	85	1,469		0.95 (95% CI 0.72, 1.25)		
		≥308 g/week	44.0	104	1,283		1.14 (95% CI 0.88, 1.49)		

Stringhini[f,241]	Men	0 units/week	0.0	85	623	Hazard ratio	1.00 (reference)	Age; ethnicity	4
		1-21 units/week	12.4	369	3,037		0.96 (95% CI 0.75-1.22)		
		≥21 units/week	25.2	102	825		1.04 (95% CI 0.77-1.39)		
	Women	0 units/week	0.0	111	540		1.00 (reference)		
		1-14 units/week	8.5	139	1,198		0.73 (95% CI 0.56-0.94)		
		≥14 units/week	16.8	13	195		0.51 (95% CI 0.28-0.92)		
Abbasi[f,243]	Men	No/Almost never	No/Almost never	47	496	Relative risk	1.00 (reference)	None	6
		1-4 drinks/month	0.8	32	379		0.90 (95% CI 0.58-1.38)		
		2-7 drinks/week	6.3	76	1,121		0.73 (95% CI 0.52-1.04)		
		1-3 drinks/day	19.8	53	768		0.75 (95% CI 0.51-1.09)		
		≥4 drinks/day	47.5	18	257		0.76 (95% CI 0.45-1.28)		
	Women	No/Almost never	No/Almost never	70	1,106		1.00 (reference)		
		1-4 drinks/month	0.8	39	655		0.94 (95% CI 0.65-1.38)		
		2-7 drinks/week	6.3	34	1,084		0.51 (95% CI 0.34-0.76)		
		1-3 drinks/day	19.8	22	491		0.72 (95% CI 0.45-1.15)		
		≥4 drinks/day	47.5	3	69		0.70 (95% CI 0.23-2.17)		
Heianza[f,244]	Men	Lifetime abstainers	Lifetime abstainers	15	138	Relative risk	1.00 (reference)	Age	7
		Former drinkers	Former drinkers	10	30		2.83 (95% CI 1.27-6.31)		
		8-54 g/week	2.9	35	199		1.74 (95% CI 0.95-3.19)		
		55-98 g/week	10.9	31	214		1.54 (95% CI 0.83-2.86)		
		99-160 g/week	17.6	23	221		0.94 (95% CI 0.49-1.80)		
		161-229 g/week	24.7	30	230		1.43 (95% CI 0.76-2.66)		
		230-287 g/week	32.9	37	236		1.61 (95% CI 0.88-2.93)		
		288-748 g/week	66.3	35	166		2.38 (95% CI 1.29-4.38)		

Rasouli[f,244]	Men	Abstainers	0.0	44	1,513	Hazard ratio	1.00 (reference)	Age; BMI; education; family history of T2DM; physical activity; smoking	7
		0.01-4.9 g/day	1.7	324	11,343		0.94 (95% CI 0.66-1.35)		
		5.0-9.9 g/day	6.9	96	3,855		0.81 (95% CI 0.54-1.22)		
		10.0-14.9 g/day	11.7	18	1,387		0.46 (95% CI 0.25-0.85)		
		≥15 g/day	19.7	16	807		0.79 (95% CI 0.42-1.46)		
	Women	Abstainers	0.0	74	3,342		1.00 (reference)		
		0.01-4.9 g/day	1.1	330	15,774		1.34 (95% CI 0.99-1.83)		
		5.0-9.9 g/day	6.6	33	2,220		1.37 (95% CI 0.86-2.20)		
		≥10 g/day	12.0	5	504		1.12 (95% CI 0.44-2.85)		
Shi[f,246]	Men	Non-drinker	Non drinker	894	33,415	Hazard ratio	1.00 (reference)	Age; BMI; education; energy intake; family history of T2DM; hypertension; income; occupation; physical activity; smoking; wait-hip ratio	6
		<1 drink/day	9.6	74	3,115		0.88 (95% CI 0.70-1.12)		
		1-2.9 drinks/day	26.0	169	8,349		0.80 (95% CI 0.67-0.94)		
		≥3 drinks/day	53.6	101	3,973		0.91 (95% CI 0.74-1.13)		

[a] The upper limit of the highest exposure category was conservatively defined as 1.2 times the value of the lower bound, unless explicitly defined within each publication.

[b] Conversions into g/day were undertaken according to the median volume of alcohol consumption in each category. Means were used if medians were unreported. If neither indicator of central tendency were reported for each category, the median of the upper and lower bounds was used.

[c] Figures were obtained via personal correspondence and reflected the crude number of cases and non-cases in each exposure category. These figures therefore differed slightly from those contained within the analytical sample of the original study. Figures reported via personal correspondence were used only for the estimation of covariance between reported coefficients. Total of cases and non-cases in the analytical sample were 41 and 2,271 respectively.

[d] RRs were estimated based on reported ORs using the Zhang and Yu formula.[171]

[e] The Hamling method was used to recalculate risk estimates according to a reference category other than that originally reported.[172]

[f] Additional, updated or recalculated risk estimates were provided via personal correspondence and may thus have differed from those reported by the original publication.

3.3.3 All data

Data pooled from all 38 selected studies are presented in Figure 3.2. Constituent studies each contributed ≥3 point estimates, inclusive of reference group. In the figure, each risk estimate is plotted as a bubble of size proportionate to the inverse of its standard error such that larger bubbles represent more precise estimates.

Visual inspection of plotted risk estimates suggested sizable heterogeneity between data points at equivalent volumes of alcohol consumption. This was corroborated by the calculation of an I^2 index for each fitted polynomial, which revealed an I^2 of 75% (95% CI 67-80%) along the first polynomial, and 50% (95% CI 31-63%) along the second.

The greatest reduction in risk is evident at an alcohol intake of 12 g/day, equating to an 18% decrease in risk relative to pooled non-drinkers (RR 0.82, 95% 0.79-0.85). Risks increased incrementally above this volume, with significant reductions in risk evident up to 64 g/day. The best-fitting FP model provided a substantially better parameterisation of the dose-response relationship than a standard linear regression (p=<0.001).

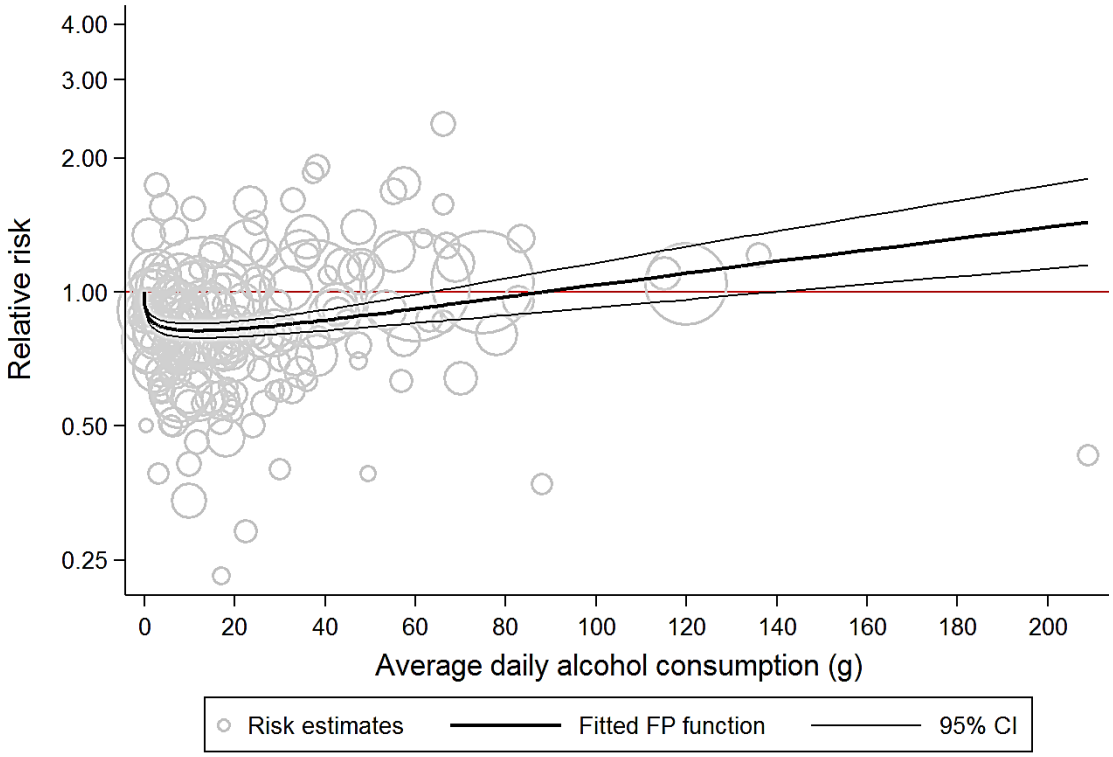


Figure 3.2 Dose-response relationship between the average volume of alcohol consumption and T2DM risk, utilising all data combined

3.3.4 Sex

A scatter diagram of risk estimates stratified by men and women revealed that the dose-response association differed by sex, with a reduction in risk at moderate volumes of alcohol consumption appearing most pronounced among women (Figure 3.3).

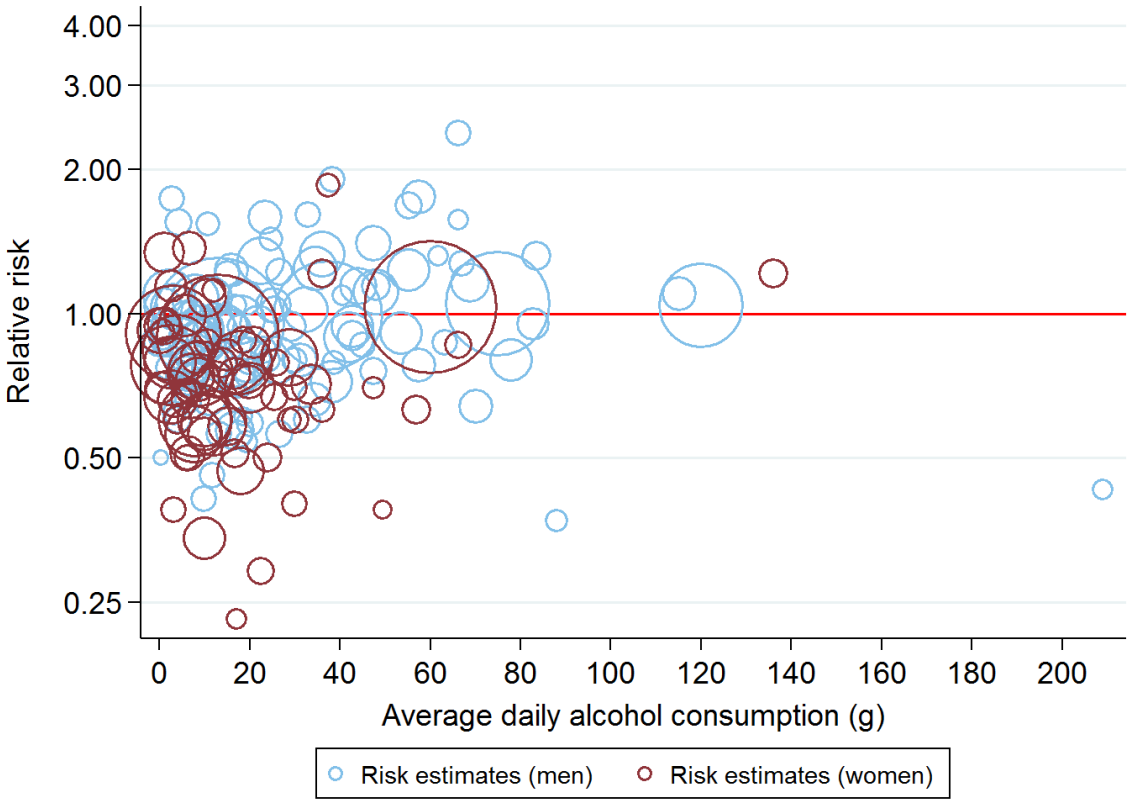


Figure 3.3 Scatter diagram of extracted risk estimates, stratified by sex

A sex-interaction was thus introduced against each polynomial term and a likelihood ratio test run to compare the basic FP model to one inclusive of a sex interaction. The interaction was significant overall (Wald test, p=<0.001) and improved the fit of the basic model (p=<0.001).

Sex-stratified results are reported in Figure 3.4. The dose-response relationships shown in Figure 3.4 were restricted to levels <140 g/day due to a dearth of risk estimates concerning higher volumes of alcohol intake. The results shown in Figure 3.4 appear to indicate that any reduction in risk relative to pooled non-drinkers may have been specific to women. While men show no reduction in risk at any volume, statistically significant reductions in the risk of T2DM are observed among women who reported average volume of alcohol consumption of <71 g/day. Reductions in risk were greatest at 35 g/day (RR 0.66, 95% CI 0.55-0.78), or close to two pints of 4% ABV lager.[11]

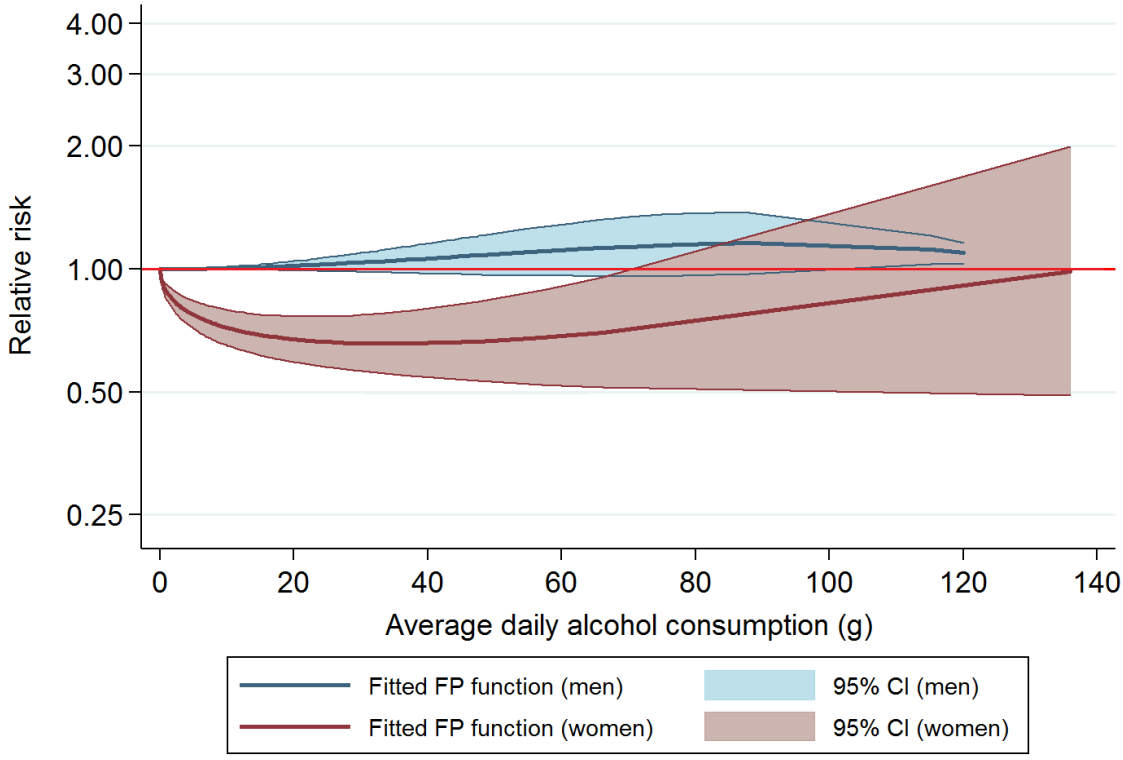


Figure 3.4 Dose-response relationship between average volume of alcohol consumption and T2DM risk, stratified by sex

3.3.5 Reference group

Only five studies were deemed to have utilised a strictly-defined never-drinking category, with four studies having reported risk estimates for men, and four for women. Having identified a significant interaction by sex, an additional interaction was included according to whether constituent studies had calculated risks relative to never or pooled non-drinkers. The dose-response relationship differed significantly by both sex (p=<0.001) and reference group (p=<0.001), with the addition of a reference group interaction improving the fit of the dose-response relative to one containing an interaction only for sex (p=0.009).

To visualise differences in dose-response according to abstention category, risk estimates were stratified by reference group and adjusted for sex through an inclusion in each model of a sex interaction term. Sex-adjusted differences in dose-response are reported in Figure 3.5, with the level of consumption restricted to <100 g/day due to the small number of risk estimates available above that level of consumption among studies that utilised a never drinking reference category. Reductions in risk appear most pronounced among studies that calculated risks relative to pooled non-drinkers, evident up to 82 g/day and largest at 12 g/day (RR 0.80, 95% 0.83-0.86). Although a U-shaped dose-response relationship is also evident among studies that

used a strictly-defined never drinking reference category, decreases in risk are smaller in magnitude and not statistically significant, peaking at 41 g/day (RR 0.94, 95% CI 0.72-1.20).

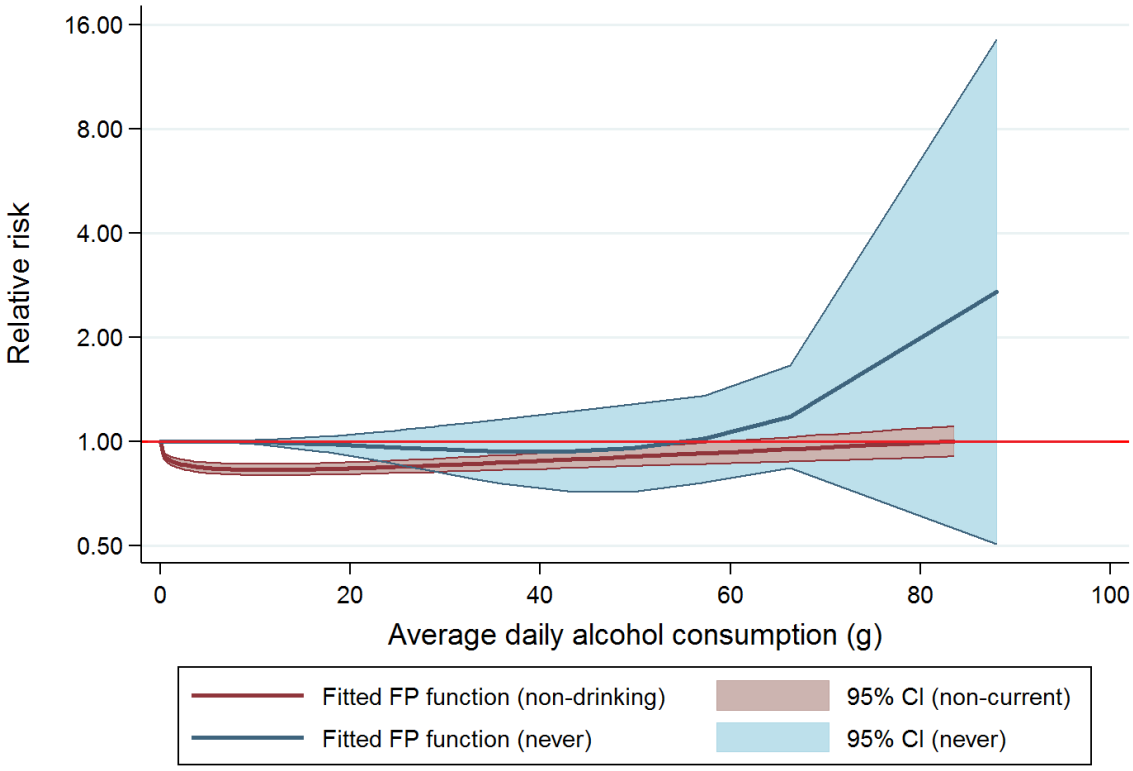


Figure 3.5 Sex-adjusted dose-response relationship between average volume of alcohol consumption and T2DM risk, stratified by reference group

The dose-response relationship was then calculated based solely on studies that reported a never-drinking abstention category. As shown in Figure 3.6, risk estimates were sparse particularly at higher volumes of alcohol consumption. As such, the plotted results shown in Figure 3.7 are restricted to values of alcohol consumption <140 g/day due to the wide confidence intervals reported by the model. Given the small number of constituent studies, Figure 3.7 should be interpreted with caution. Nevertheless, the results indicated that potential reductions in risk at moderate volumes of alcohol consumption remained specific to women when studies excluded former drinkers from the reference category.

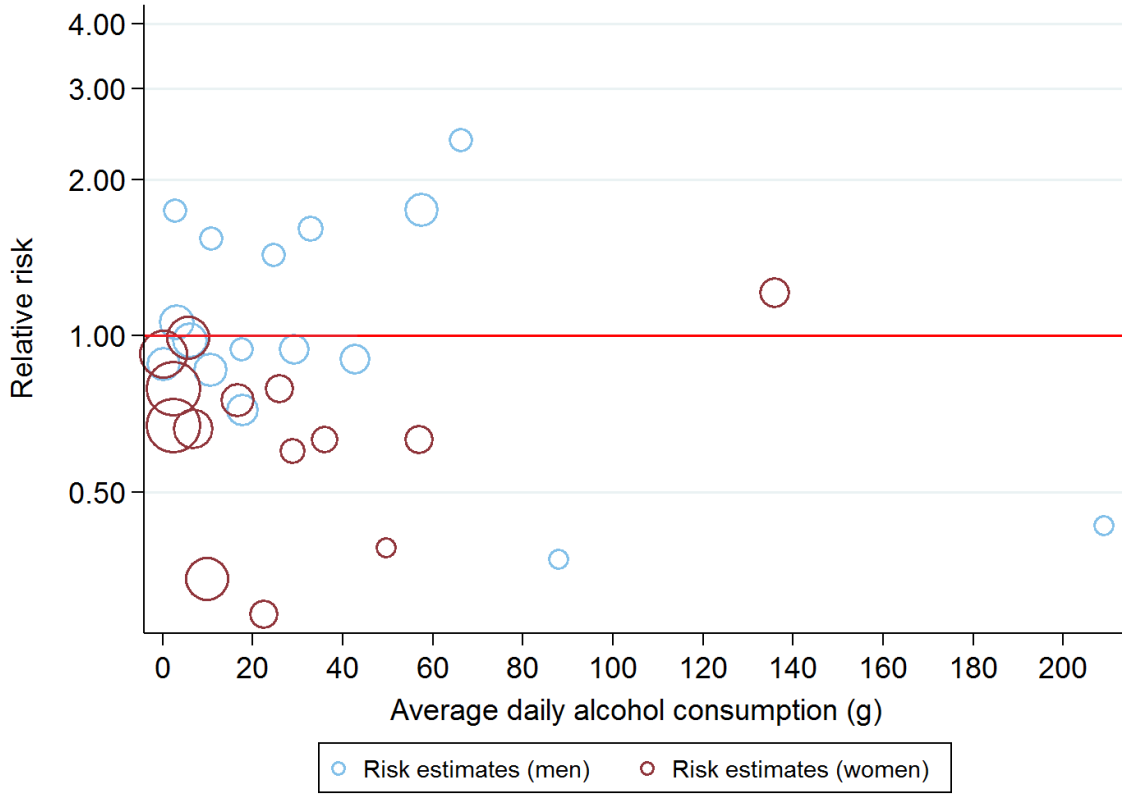


Figure 3.6 Scatter diagram of extracted risk estimates calculated relative to never drinkers, stratified by sex and inverse weighted by SE

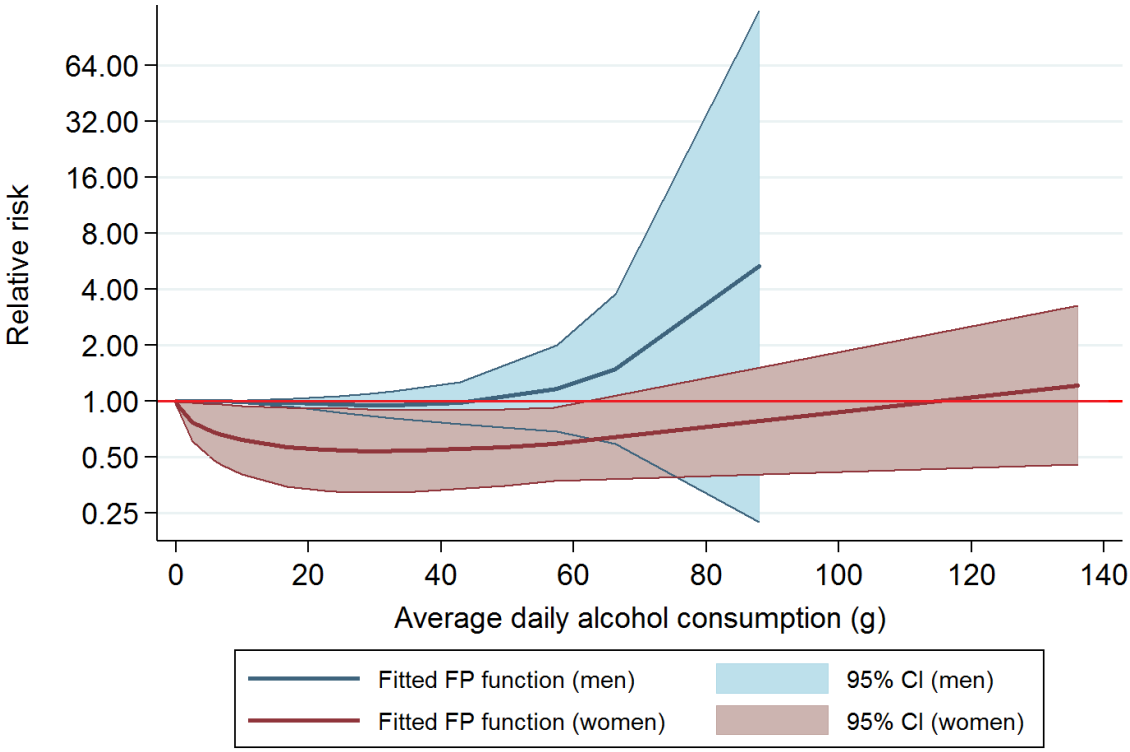


Figure 3.7 Dose-response relationship between average volume of alcohol consumption and T2DM risk, relative to never drinkers, stratified by sex

3.3.6 Confounder adjustment

A total 15 studies reported crude or age-adjusted estimates (n=15), with the rest providing more comprehensively adjusted data (n=23). Although sex (p=<0.001) and reference category (p=<0.001) remained statistically significant modifiers of the dose-response relationship, little statistical difference was evident according to whether or not risk estimates had been extracted from crude or age adjusted studies or those with more comprehensive confounder adjustment (p=0.165). The addition of a confounder adjustment interaction provided no marked improvement in model specification of a sex-adjusted model (p=0.168).

When data were stratified by confounder adjustment and adjusted for differences in dose-response attributable to sex and reference group, multivariable-adjusted estimates appear to show shallower reductions in risk at moderate levels of alcohol consumption (Figure 3.8). This relationship was little changed when using an alternative confounding variable that defined studies according to whether their degree of adjustment was above or below the mean of four confounding factors.

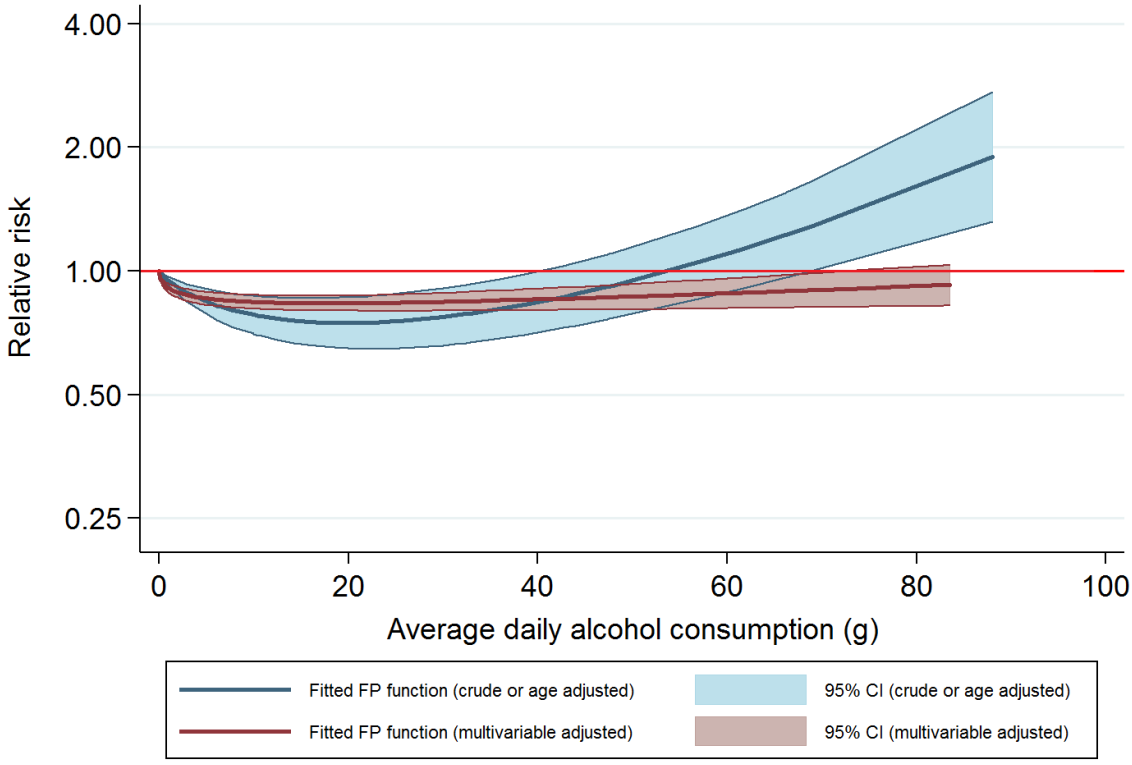


Figure 3.8 Dose-response relationship between average volume of alcohol consumption and T2DM risk, adjusted for sex and reference group, stratified by confounder adjustment

3.3.7 Sub-group analyses

Beyond analyses stratified according to factors of primary interest, a number of further sub-group analyses were undertaken, investigating the effect of putative modifiers of the dose-response relationship.

3.3.7.1 Case ascertainment

Cases of T2DM were defined according to a variety of methods, summarised as participant self-reports (n=11), objective ascertainment (n=21), or a combination thereof (n=6). Given the small number of studies to have employed mixed methods of case ascertainment, attention was focussed upon the subset of studies that used either a subjective or objective methods. Accordingly, data were restricted to the 32 applicable studies. The addition of an interaction according to method of case ascertainment provided little improvement over a dose-response model adjusted for differences by sex and reference category. While sex (p=<0.001) and reference category (p=<0.001) remained statistically significant modifiers, this was not the case for method of case ascertainment overall (p=0.166).

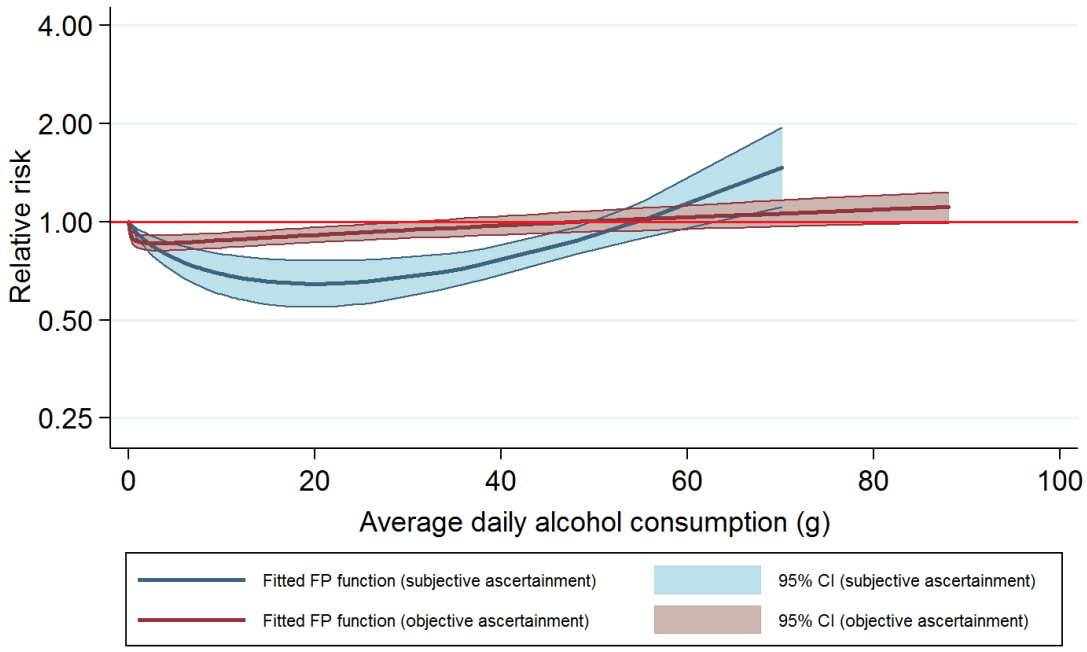


Figure 3.9 Dose-response relationship between average volume of alcohol consumption and T2DM risk, adjusted for sex and reference group, stratified by method of case ascertainment

Looking to the stratified dose-response relationship reported in Figure 3.9, studies that utilised an objective measure of case ascertainment reported reductions in risk of smaller magnitude and across a narrower range of consumption than studies with cases defined according to subjective self-reports. Among the latter, a peak 35% reduction in T2DM risk was observed at

20 g/day (RR 0.65, 95% CI 0.55-0.76) versus a 14% reduction in risk at 4 g/day (RR 0.86, 95% CI 0.82-0.91) among studies that defined cases using an objective measure, relative to pooled non-drinkers after adjustment for sex and reference group.

3.3.7.2 Population region

A total 13 studies sampled participants from Asian regions, with the remaining 25 studies having sampled participants from non-Asian countries. Population region represented a statistically significant modifier of the dose-response relationship (p=<0.001), even after accounting for the effect of sex (p=<0.001) and reference category (p=0.029). Inclusion of an interaction according to population region improved specification over a model that comprised interactions only for sex and reference category (p=<0.001).

Looking to the stratified dose-response relationship shown in Figure 3.10, risk estimates extracted from Asian studies reported no reduction in T2DM risk at any level of average volume of alcohol consumption. By comparison, estimates from non-Asian countries exhibited a J-shaped association even after adjustment for sex and reference category, with an intake of an average 26.5 g/day associated with a 27% reduction in risk relative to adjusted non-drinkers (RR 0.73, 95% CI 0.67-0.78).

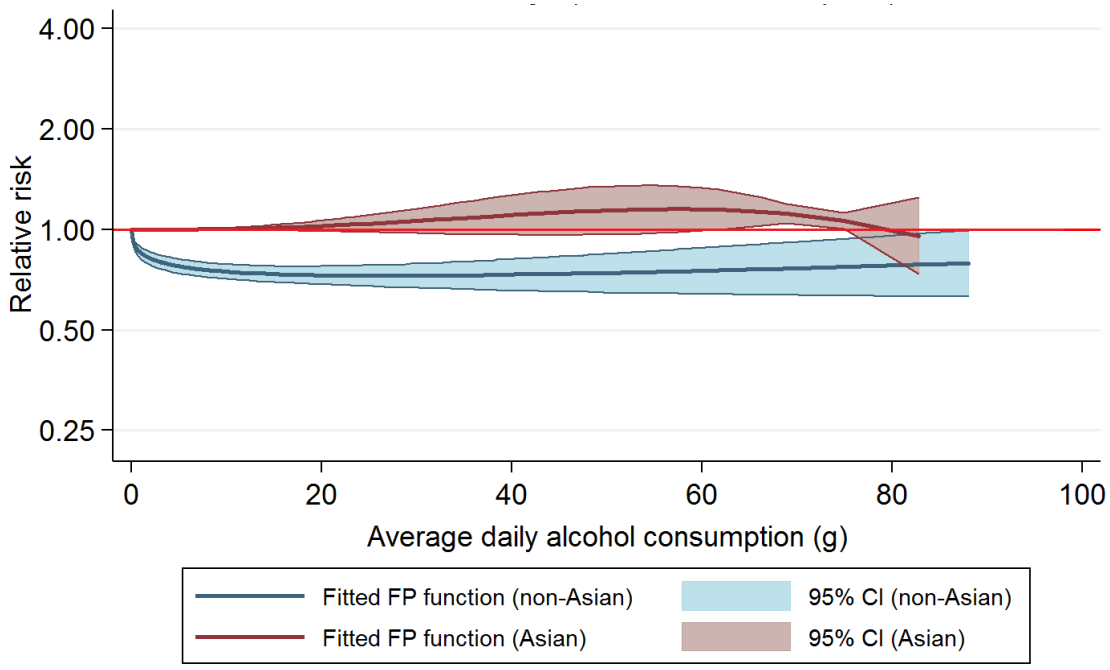


Figure 3.10 Dose-response relationship between average volume of alcohol consumption and T2DM risk, adjusted for sex and reference group, stratified by population region

3.3.7.3 Population type

Another factor posited as a modifier of the relationship between volume of alcohol consumption and T2DM was population type. Of selected studies, 12 sampled occupational cohorts and 26 analysed participants from the general population. Alongside the addition of sex (p=<0.001) and reference group (p=0.008) interaction terms, the dose-response relationship did not differ significantly according to population type (p=0.407). The inclusion of an interaction by population type did not improve a model already adjusted for differences according to sex and reference category (p=0.410).

Little difference in dose-response was observed when data were stratified according to population type, though reductions in risk among general population studies may have been less pronounced than those reported by occupational samples (Figure 3.11).

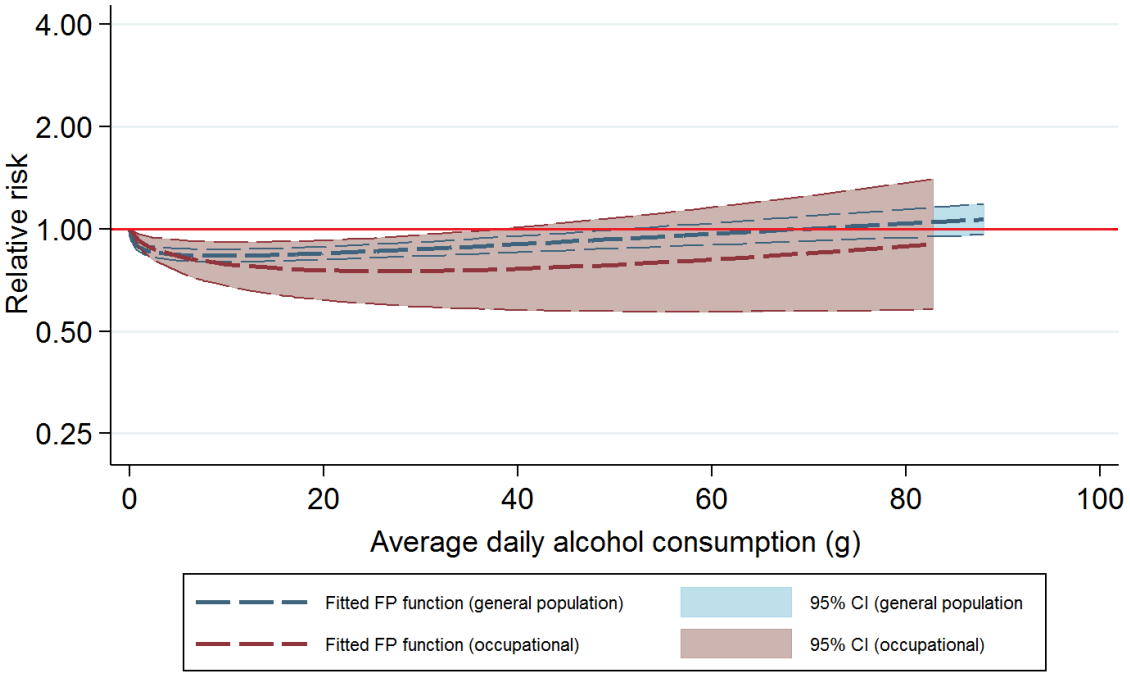


Figure 3.11 Dose-response relationship between average volume of alcohol consumption and T2DM risk, adjusted for sex and reference group, stratified by population type

3.3.7.4 Quality assessment

The quality of selected studies ranged from three to nine points out of nine. One study received the maximum score of nin e,[225] while two studies received a score of just three[222,229] for limitations including the use of a self-reported measure of T2DM, no information concerning the derivation of alcohol consumption volume, short periods of follow-up and no adjustment for confounding factors. The median score was six, indicating a moderate level of quality on average.

There was no significant difference in overall dose-response according to whether studies fell below a median quality assessment score of six points (p=0.837) after adjustment for differences according to sex (p=<0.001) and reference category (p=0.01). Although reductions in risk appeared greater among studies of below median quality, the difference was small and not significant (Figure 3.12).

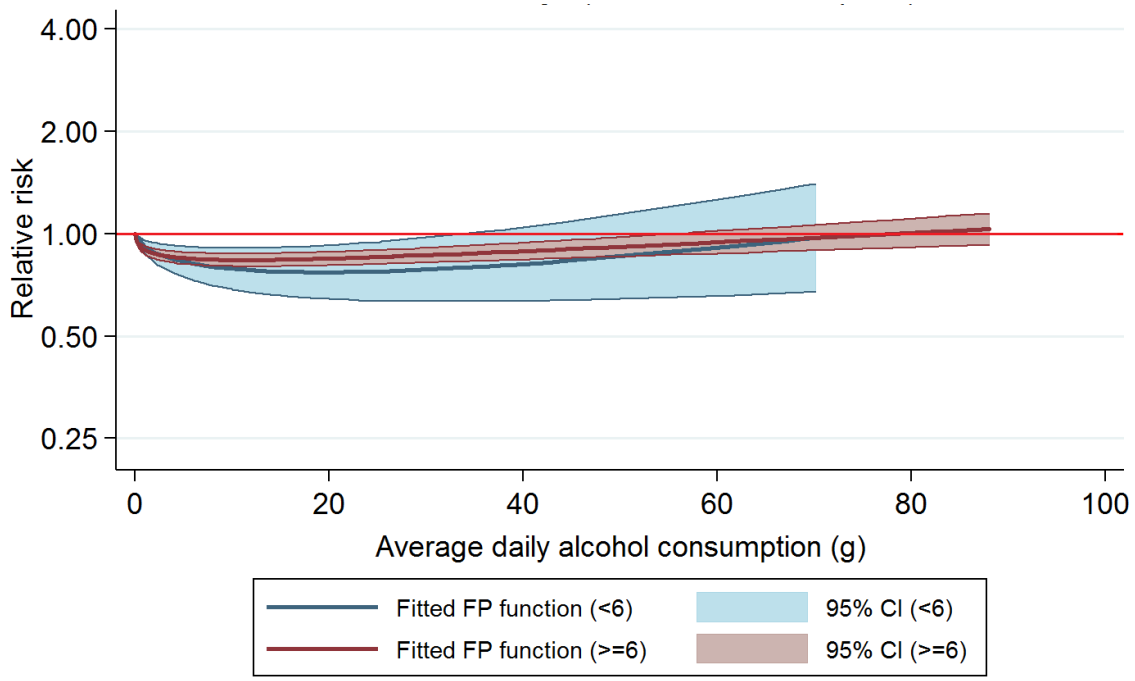


Figure 3.12 Dose-response relationship between average volume of alcohol consumption and T2DM risk, adjusted for sex and reference group, stratified by quality assessment score

3.3.8 Sensitivity analyses

3.3.8.1 Newly analysed studies

Of the 20 publications analysed by the preceding meta-analysis of volume of alcohol consumption and T2DM, 17 had been selected for analysis as part of the revised meta-analysis. Of those not selected, two were superseded by newer analyses of the same studies that also benefitted from larger samples and periods of follow-up,[207,210] whilst the remaining study did not report sex-specific estimates.[247] This left 21 publications with analyses that were either updated since the last meta-analysis, or else missed by the previous authors.

A statistically significant difference in dose-response was identified according to whether studies had been previously sampled by Baliunas *et al*[10] (p=<0.001) after accounting for any differences attributable to sex (p=<0.001) or choice of reference category (p=0.357). Stratifying the data revealed that newly analysed studies appeared to report a shallower reduction in risk at

moderate volumes of alcohol intake after adjustment for sex and reference category (Figure 3.13). Of studies sampled in the previous meta-analysis, a peak 29% reduction in risk was observed at 20.5 g/day (RR 0.71, 95% CI 0.61-0.82) versus a 13% reduction at 14 g/day (RR 0.87, 95% CI 0.83-0.91) among newly analysed studies, relative to adjusted non-drinkers.

Potentially explaining at least some of this discrepancy, sex-specific logistic regression analyses comprising putative sources of heterogeneity reported that previously analysed studies of men were more likely to have used subjective case ascertainment (p=<0.001) and sampled non-Asian populations (p=<0.001), while studies reporting female data adjusted for a greater number of confounders (p=0.029), less likely to have analysed occupational samples (p=0.028) and were more likely to have utilised subjective measures of case ascertainment (p=0.020) and a strictly-defined never drinking category (p=0.003).

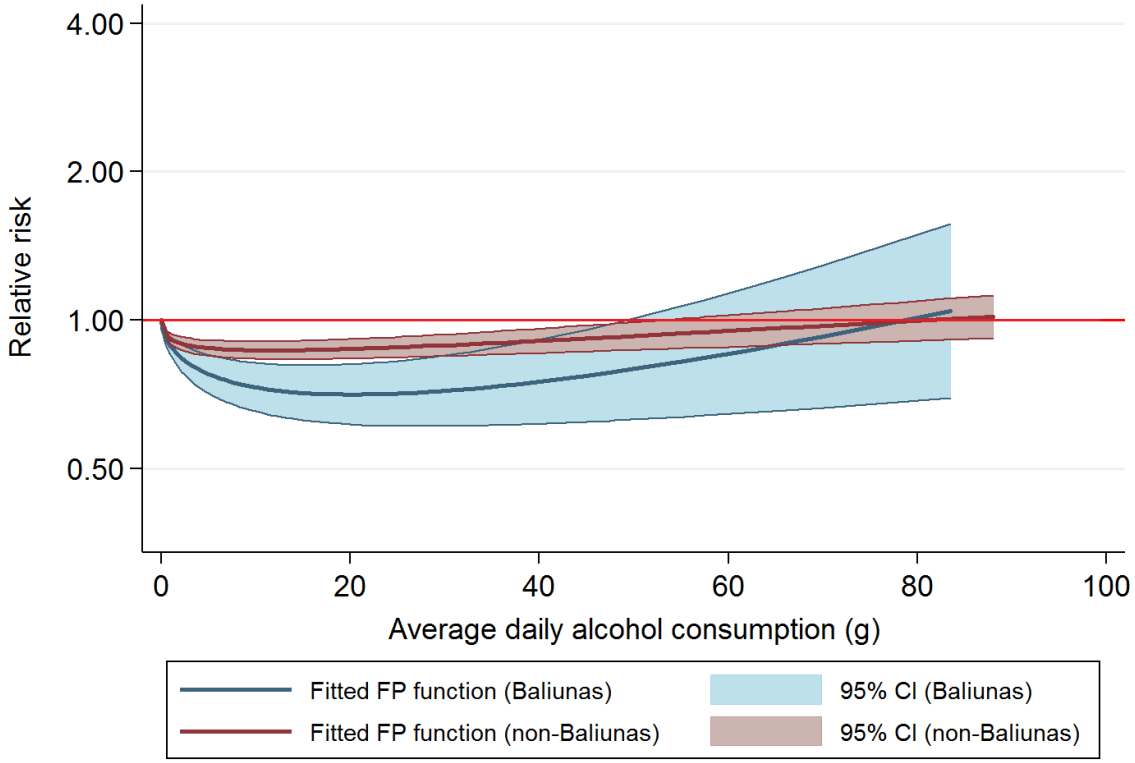


Figure 3.13 Dose-response relationship between average volume of alcohol consumption and T2DM risk, adjusted for sex and reference group, stratified according to selection in the preceding meta-analysis

3.3.8.2 Sensitivity of dose-response to a high precision study

Having extracted data from all selected studies, 63% of constituent participants were found to have been sampled by a single, high quality study.[235] Questioning the generalisability of any results where more than half of participants had been drawn from a single publication, a sensitivity analysis was undertaken to compare the impact of the study upon the observed dose-

response relationship. As shown in Figure 3.14, the inclusion of the large study had little overall effect upon the dose-response relationship beyond contributing to a reduction in variance. This was posited to be attributable to the calculation of dose-response relationships using random effects, which applies a lower weight to larger studies. On this basis, as well as its high quality assessment score, the study was considered appropriate for inclusion in all reported analyses. As per the sex-specific analyses reported in Figure 3.4, plots were restricted to volumes of consumption below 140 g/day due to a dearth of risk estimates at higher levels.

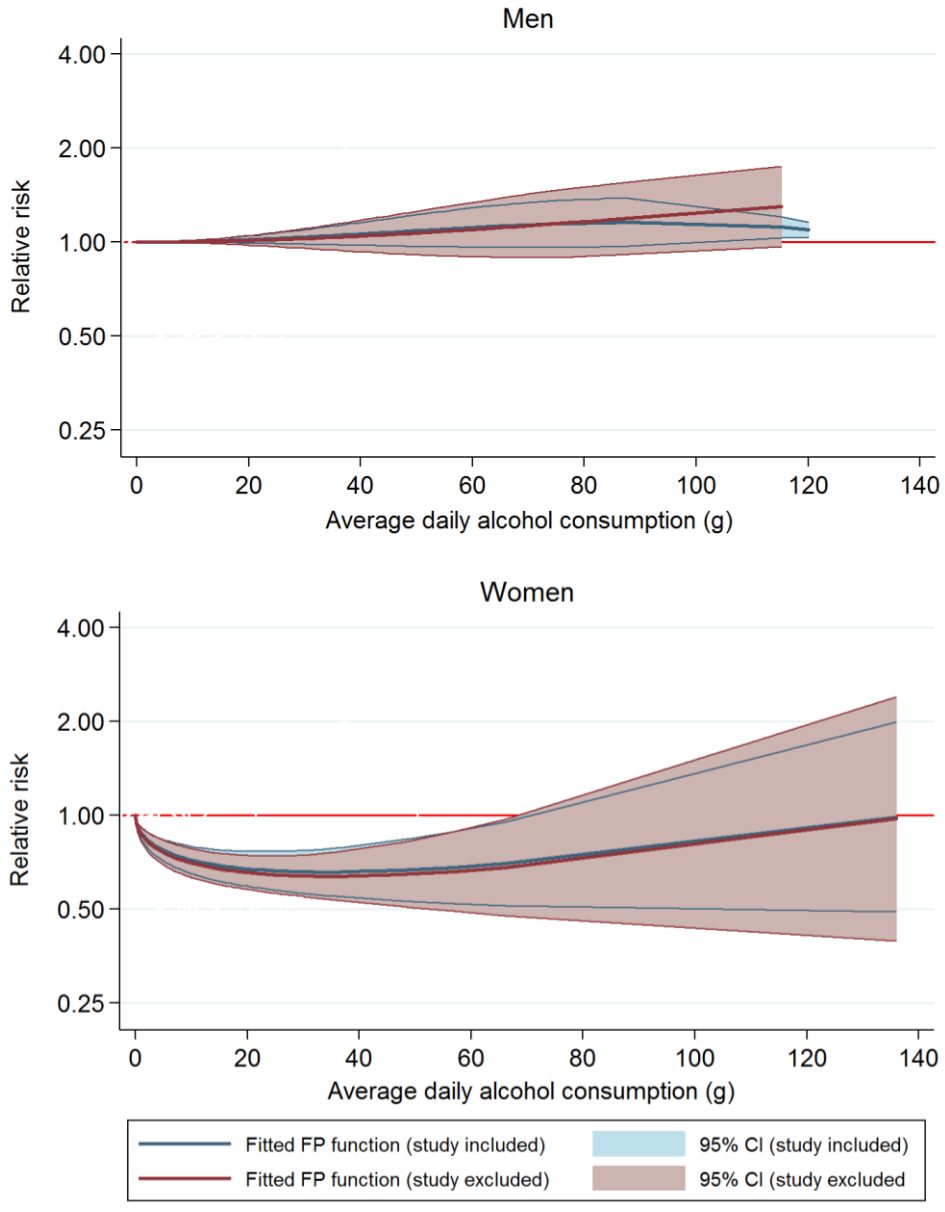


Figure 3.14 Dose-response relationship between average daily alcohol consumption and T2DM risk: sex-specific data, stratified by Jee *et al*[235]

3.3.9 Small-study effects

Recalculated estimates denoting the risk of current drinking versus non-drinking were plotted against the standard error of their log (Figure 3.15). The resulting funnel plots indicated that, while male risk estimates appeared largely symmetrically dispersed around a summary estimate denoting the overall level of risk reported for current drinkers (p=0.181), female estimates may have been asymmetrical (p=0.063), with selected risk estimates appearing more likely to report a reduction in T2DM than might have been expected in the absence of small-study effects.

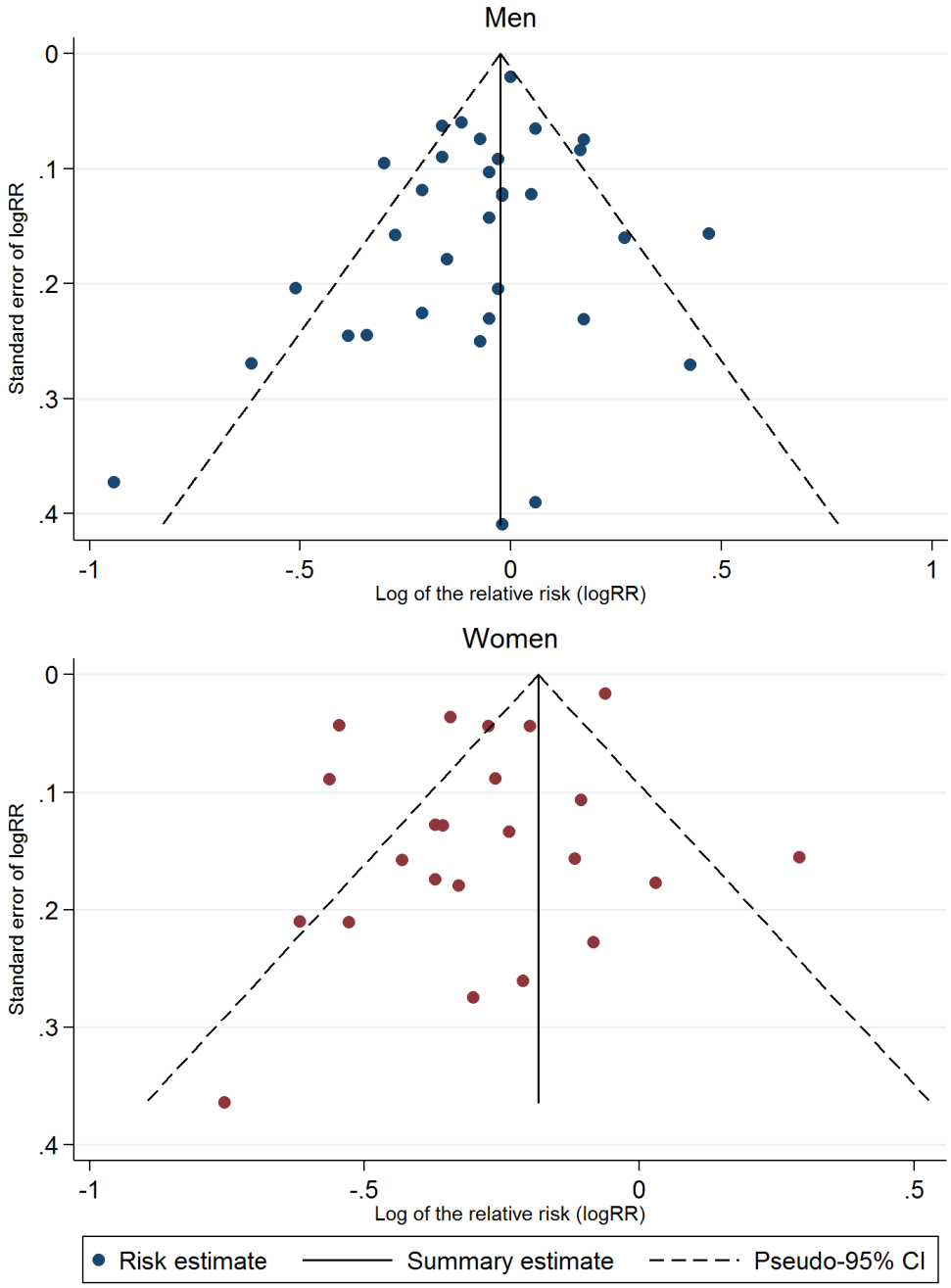


Figure 3.15 Funnel plot of current drinking versus non-drinking, stratified by sex

Given the summary estimates were calculated using a simple inverse variance weight,[188] asymmetry was hypothesised to be a consequence of a high precision study that reported results contrary to the majority of other studies. A prime suspect for such an effect was a large, high quality Korean study, which represented 65% of sampled participants and reported a smaller reduction in risk than many other selected studies.[235] The impact of the Korean study upon estimated small study effects is reported in Figure 3.16. After its exclusion, observed asymmetry among female risk estimates was indeed attenuated, with no significant different in risk estimates according to the degree of study precision among either men (p=0.610) or women (p=0.508). Small study effects and the risk of any potential publication bias was low.

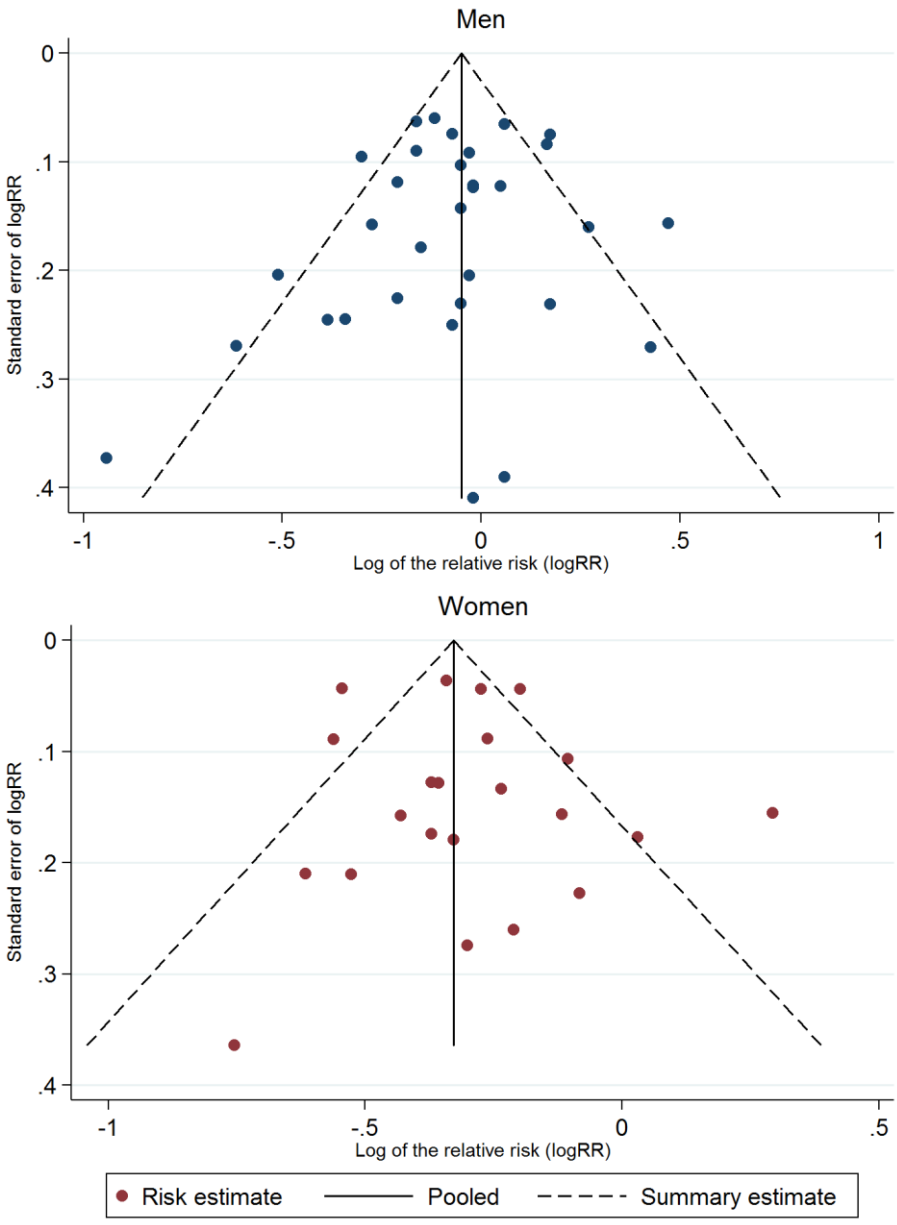


Figure 3.16 Funnel plot of current drinking versus non-drinking, stratified by sex and excluding Jee *et al*.[235]

3.3.10 Pattern of consumption

Of the 21 newly analysed studies, only three of their associated publications included a joint analysis of both the volume of alcohol consumption and drinking pattern. The first publication reported that middle-aged male binge drinkers (>1 bottle of wine on any one occasion ≥1/month, or around 95.6 g assuming a 750 ml bottle of 13% ABV wine[11]) had a 67% (OR 1.67, 95% CI 1.11-1.20) greater odds of T2DM relative to light drinkers (0.01-6.79 g/day).[239] This finding was in keeping with a previously discussed study, which reported double the risk of T2DM among women that consumed >179 g on any one occasion at least once a month during the preceding year (RR 2.1, 95% CI 1.0-4.4).[96] In both cases, however, reporting of the joint association between volume and pattern was limited, providing no indication as to the average volume of alcohol consumption among binge drinkers. It was possible their elevated risk of T2DM may have been attributable to a high average intake as opposed to infrequent periods of episodic heavy consumption.

A more comprehensive analysis was reported by Sato *et al*,[240] which explicitly set out to explore the joint association between the frequency and volume of alcohol consumption in a cohort of Japanese men. While no difference in the risk of T2DM was observed among men who consumed low volumes of alcohol (≤28 g/day) infrequently throughout the week (1-3 days), relative to pooled non-drinkers (RR 0.93, 95% CI 0.72-1.20), reductions in risk were apparent when the same low volume was consumed on at least four days in an average week (RR 0.74, 95% CI 0.58-0.95). Such a result indicated that moderate volumes of alcohol consumption may only confer a reduction in risk when drinking is regular.

The third and final study to have investigated the two dimensions of alcohol consumption was authored by Heianza *et al*.[244] Sampling 1,605 Japanese men, risks associated with the average volume of alcohol consumption per drinking occasion were stratified according to four weekly frequencies. Consistent with the preceding analysis, risks were lowest among participants who frequently (≥6 days/week) consumed moderate volumes of alcohol (23 g/day). Relative to this group, those who consumed the same moderate volume of alcohol across just 2-3 days/week reported a 48% greater risk of T2DM (RR 1.48, 0.65-3.37). Notably, risks were consistently greatest at all frequencies within a light drinking category that also included pooled non-drinkers, providing further indications as to the unsuitability of pooled non-drinkers as a reference category.

3.4 Strengths

In revising the 2009 meta-analysis, these most recent results benefitted from the addition of new studies published after the last search in 2008, plus the inclusion of two historic papers missed or discounted during previous meta-analyses. Thus, while Baliunas *et al*[10] sampled 20 studies, 477,200 participants and 12,556 cases, revised analyses were based on data obtained from 38 studies, 1,902,605 participants and 125,926 cases. Although the majority of these additional observations were extracted from a single Korean study,[235] a sensitivity analysis that compared results calculated with and without the large study showed negligible difference in the dose-response relationship beyond an expected change in precision (Figure 3.14).

Some alcohol researchers have argued that never drinkers may present a more suitable abstention category than pooled non-drinkers.[136] Although the preceding meta-analysis reportedly adopted a never drinking reference category when calculating the risk of T2DM among current drinkers, the never drinking category was only approximated. Specifically, effect estimates reported by 15 studies that used a non-drinking reference category were weighted according to the average sex-specific proportion of former drinkers reported by five studies that included a never drinking abstention category. This approach assumed that the average prevalence of former drinkers reported by the five studies was equal to that unreported by the remaining 15 studies and their varying population characteristics. In addition to the possibility that the study-specific proportion of former drinkers was determined by factors other than sex alone, two of the five studies from which an average proportion of former drinkers had been estimated did not define never and former drinking in a robust manner. For instance, one study defined never drinkers as participants who described themselves as non-drinkers at baseline and who also reported (a) not having changed consumption during the five years prior to baseline, and (b) never having regularly consumed ≥5 drinks/day.[153] Here, never drinkers were likely to comprise a number of former or infrequent moderate drinkers. Accordingly, it was possible that the previous meta-analysis may not have reliably estimated the proportion of never drinkers contained among pooled non-drinking categories. Contrary to their method, the updated meta-analysis opted instead to test for an interaction in dose-response according to type of reference category defined by selected studies. Such an approach avoided the potential for having weighted data under inappropriate assumptions. Beyond this, the revised meta-analysis also tested the effect of hypothesised modifiers of the dose-response relationship, providing insight into their effect upon summary dose-response estimates.

3.5 Limitations

3.5.1 Heterogeneity

Heterogeneity between sampled studies was high, with the breadth of effect estimates at equivalent volumes of consumption complicating interpretation of the overall dose-response relationship. In order to better understand the effect of such heterogeneity upon the observed dose-response relationship, potential explanatory factors were posited *a priori* and, where appropriate, explored individually through the inclusion of a corresponding interaction term along each fitted polynomial, with results then reported separately at each level of the a priori factor. The use of meta-regression to jointly test differences in dose-response according to all putative sources of heterogeneity was avoided owing to the potential for low statistical power, even when effect sizes and the number of studies are large.[248,249,250] Though suggested that statistical power may have been sufficient in instances where the number of factors did not exceed a ratio of one to every 10 studies,[251] simulations have suggested that power may remain low in circumstances where heterogeneity is high.[252]

3.5.2 Quality assessment

Although the quality of selected studies was assessed using the Newcastle-Ottawa assessment scale,[189] with studies found to be of moderate quality on average (a score of 6/9), quality assessment tools are subject to notable limitations. Although a wide range of instruments have thus far been devised for the assessment of quality among non-randomised studies, each comprised assessment criteria that were disparate in both number and nature.[253] In addition to the use of different rating scales or summary scores that risked weighing the importance of component items in ways disproportionate to their impact upon the validity of a given study, their differing designs were such that the choice of tool was likely to have had a sizeable bearing upon the assessment of study quality.[254,255] Alongside such general limitations, the Newcastle-Ottawa tool used to assess the quality of studies selected as part of the revised meta-analysis had criticisms ranging from the tool's focus upon the generalisability of results as opposed to a study's internal validity,[256] to weak inter-rater reliability on some questions.[257,258] With these limitations in mind, results from the Newcastle-Ottawa quality assessment tool should be considered only as a rough guide as opposed to a definitive measure of study quality.

3.5.3 Stability of consumption

In defining alcohol consumption using only one baseline measure, almost all studies sampled as part of the meta-analysis had modelled risk under an assumption that alcohol consumption was stable over the course of the study. However, having investigated datasets for which repeated

measures of alcohol consumption were available, researchers identified numerous disparate trajectories of alcohol consumption behaviour as a function of time.[259] As such, the cross-sectional categorisation of alcohol consumption may have been an inappropriate approach for defining drinking, with baseline categories potentially subject to misclassification error.[150]

Defined as latent classes, numerous discrete trajectories have been identified across the adult life course.[260,261,262,263] For example, looking to analyses that captured alcohol consumption data between the ages of 16 and 42 years, five distinct classes were observed in a Finnish cohort.[264] Here, in addition to stable categories of light (22%), moderate (35%) and heavy consumption (23%), 9% of participants decreased and 11% increased their consumption between the ages of 16 and 42.[264] Elsewhere, in a study of Canadians aged ≥50 years, nine different classes were identified over an average six years.[265] As well as stable light (7%), moderate (11%), heavy (2%) never (6%) and former drinkers (8%), plus those who increased (16%) or decreased (31%) their consumption, this older cohort also captured U-shaped (10%) and inverted U-shaped (9%) trajectories.[265]

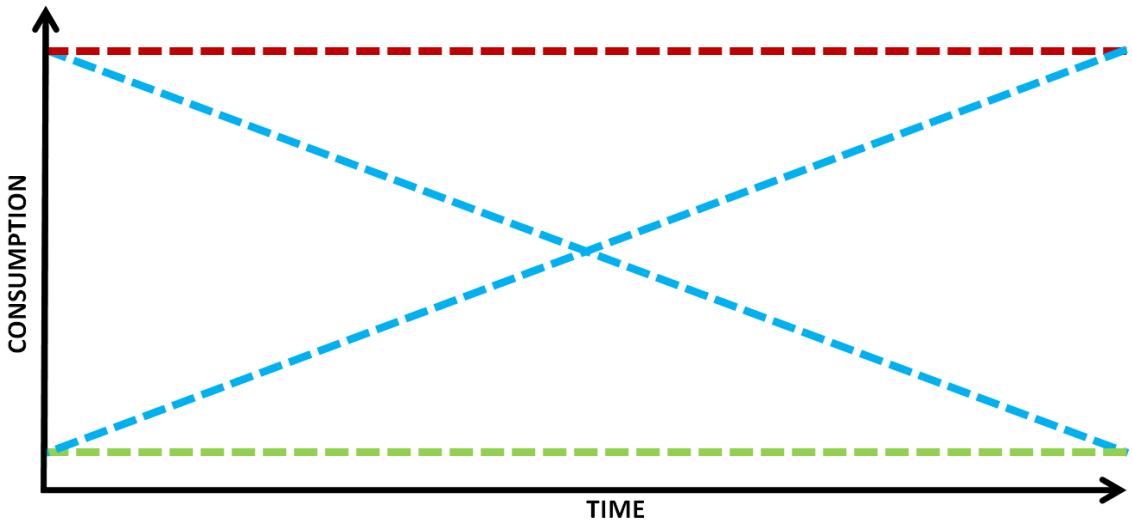


Figure 3.17 Common latent trajectories of volume of alcohol consumption: the 'cat's cradle'

As evident from just two examples, exact trajectories identified within cohorts will differ according to their baseline age, duration of observation and frequency of repeated measures. Despite this, four trajectories appear robust to such factors, having been consistently observed across cohorts: stable non-drinking and current drinking, increasing consumption and decreasing consumption – a so-called 'cat's cradle' of latent classes (Figure 3.9).[259] Of these four classes, increasing consumption may be most common during early adulthood, with younger participants typified by never drinking and therefore exhibiting little opportunity for alternative trajectories of consumption. Conversely, in later life, decreased consumption may become the

dominant trajectory following factors including age-related deteriorations to health status. This disparity was hinted at by the examples above,[264,265] and supported by findings from an analysis of mean volume consumption calculated from nine UK-based cohort studies (Figure 3.10).[266]

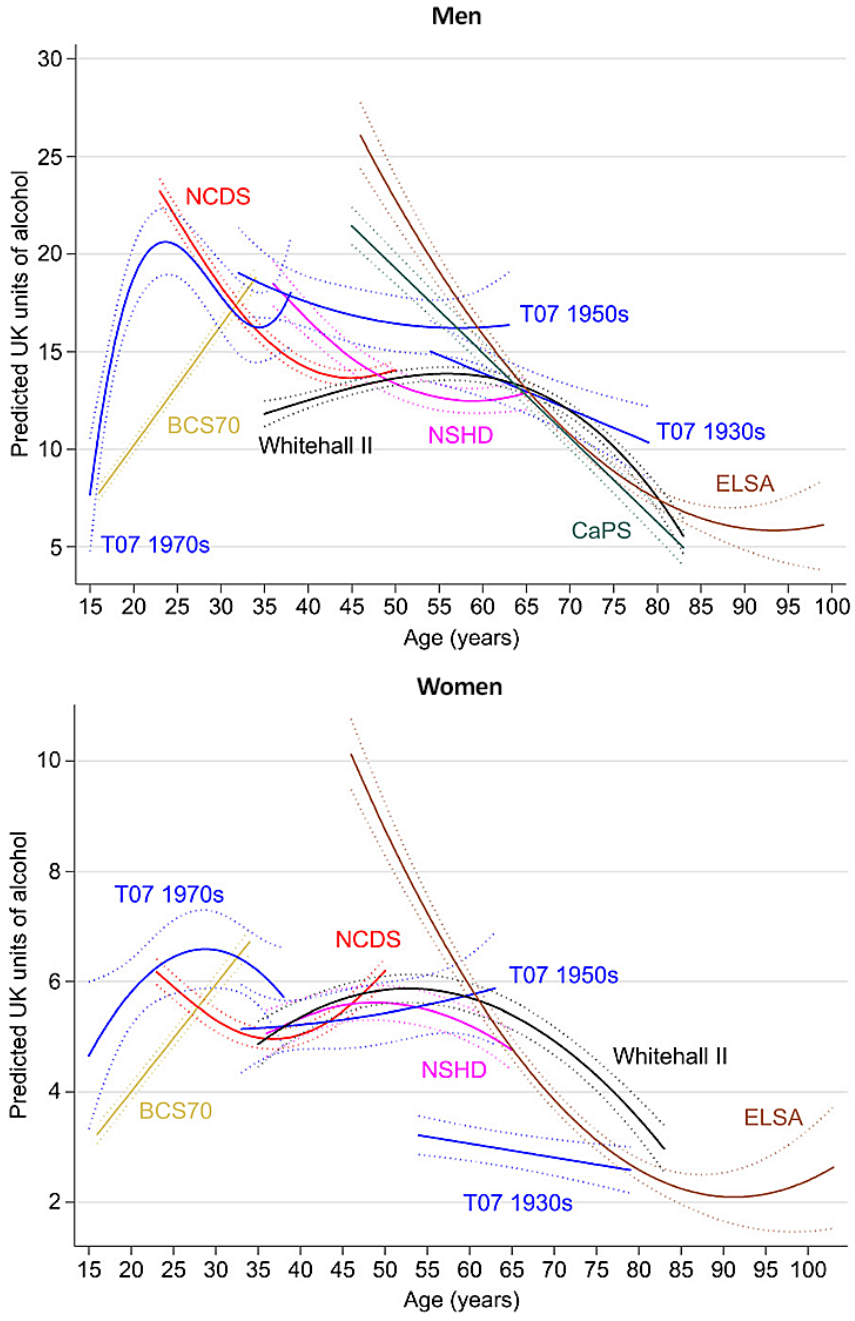


Figure 3.18 Predicted mean alcohol consumption trajectories (in units/week) across the life course in UK cohort studies. Reproduced from Britton *et al*[266] in BMC Medicine under a Creative Commons Attribution License (4.0).

Despite such evidence highlighting the variability in the volume of alcohol consumption as a function of time, the vast majority of alcohol-T2DM studies modelled the dose-response relationship according to a single baseline measurement, with just one out of the 38 selected publications having utilised repeated measures of alcohol consumption. The authors of the

paper modelled the dose-response relationship using an unconditional logistic regression model equivalent to an extended Cox survival model with time-varying covariates updated at six-month intervals over a period of 10 years.[153] Relative to never drinkers, results showed attenuated and non-significant reductions in risk across all levels of current drinking after accounting for changes to alcohol consumption over time.[153]

A second publication, which was excluded from the meta-analysis, reported analyses of male participants in the Health Professionals Follow-Up Study.[267] Compared with stable none or light drinkers (0-4.9 g/day), those who increased their consumption to moderate levels (5.0-29.9 g/day) in any four-year period exhibited a statistically significant 25% reduction in hazard (HR 0.75, 95% CI 0.62-0.90), while those who became heavy drinkers (≥30.0 g/day) showed a sizeable but not significant 65% reduction in hazard (HR 0.35 95% CI 0.11–1.10). Of moderate drinkers that reduced their consumption to none or light drinking, a 9% increase in hazards was observed (HR 1.09, 95% CI 0.92-1.30). Such participants may have reduced their intake due to poor health, though no such increase in risk was evident among heavy drinkers who switched to none or light consumption (HR 0.78, 95% CI 0.44-1.38). Such inconsistent results may have been a consequence of particularly small sample size in a number of sub-groups, with estimates subject to sampling error.

The variability of alcohol consumption across the life course suggests that the dose-response relationship may be more complex than modelled by conventional analytical methods. With the validity of existing research potentially limited by a failure to account for the effect of such variability upon T2DM risk, epidemiological research needs to explicitly adopt analytical approaches capable of giving consideration to changes in drinking over time.

3.6 Discussion

Although few additional studies were found to have reported a strictly-defined never drinking abstention category, sex-adjusted analyses confirmed that the choice of reference category had a marked and statistically significant impact upon the observed dose-response relationship, with reductions in risk at moderate volumes of alcohol intake appearing specific to studies that excluded less healthy former drinkers from their abstention category (Figure 3.5). Results from Figure 3.5 thus mirror findings from meta-analyses of other health conditions, which reported attenuations in risk reduction when former drinkers were explicitly excluded from an abstention reference category.[136,147] Such a difference in dose-response provides support to arguments made by some academics against the use of a pooled non-drinking category,[136,137] and suggested

that reductions in risk at moderate volumes of alcohol consumption may thus have been overestimated by close to 95% of observational studies.

Beyond the impact of reference category, little independent difference in the overall dose-response relationship was observed according to whether or not risk estimates were multivariable-adjusted. Such a finding suggests either that confounder adjustment had little additional impact after the exclusion of former drinkers, or that the type as opposed to number of confounding factors may have been a more important determinant of heterogeneity in observed dose-response.

Reductions in risk were previously identified as smallest among men.[10] These were rendered completely absent in revised analyses following the addition of new data (Figures 3.4 and 3.6). These new data were more likely to have been obtained from Asian countries (53% versus 21%) and have utilised an objective measure of ascertainment (89% versus 71%) – two factors associated with less pronounced reductions in risk even after accounting for differences attributable to sex and reference category (Figures 3.10 and 3.9 respectively). Among women, peak reductions in risk were broadly comparable between the two meta-analyses: a 40% peak reduction was reported at 24 g/day among women (RR 0.60, 95% CI 0.52-0.69) sampled in the earlier meta-analysis,[10] and a 34% peak reduction at 35 g/day (RR 0.66, 95% CI 0.55-0.78) in the revised meta-analysis.

It was unclear why the dose-response relationship between the volume of alcohol consumption and T2DM risk operated differently according to sex, though five conceivable hypotheses were proposed: systematic differences in study characteristics; sex-specific differences in drinking pattern; sex-specific differences in the effect of alcohol upon putative biological pathways; sex hormones; and drink type. These were explored separately and in detail below:

1. It was possible that sex-specific disparities in dose response may have been in some part a consequence of systematic differences in study characteristics. Following a stratification of study characteristics by sex, female data was found more likely to have been extracted from studies of non-Asian regions (61% versus 87%) or that utilised a subjective measure of case ascertainment (35% versus 18%). Both factors were associated with more pronounced reductions in risk than in studies of Asian regions (Figure 3.10) and that used an objective measure of defining T2DM (Figure 3.9). Although studies of women were also more likely to have sampled the general

population (87% versus 70%), population type was observed to have very little independent effect upon dose-response (Figure 3.11).

An *a posteriori* analysis was thus undertaken to explore the significance of case ascertainment and population region interactions solely among female data. Both case ascertainment (p=0.002) and population region (p=0.010) were found to be statistically significant modifiers of the female dose-response relationship, with plotted results similar to those reported in Figures 3.9 and 3.10 when both sexes were combined.

Although no sizeable difference was found in the proportion of studies that reported multivariable-adjusted risk estimates (men: 64%; women: 61%), it was possible that the degree of confounder adjustment was less important than the type of confounders for which dose-response relationships were adjusted. For instance, male studies were more often adjusted for a number of key risk factors for T2DM, including adiposity (45% versus 39%), family history of T2DM (24% versus 17%) and smoking (39% versus 30%).

Given the association between these risk factors and the risk of T2DM, as well as the possibility that they appear most prevalent among non-drinkers than moderate drinkers,[136,139] it is plausible that discrepancies in the type of confounder adjustment alongside other differences in study characteristics may have explained at least some of the difference in dose-response between men and women. Such a conclusion is supported in part by the absence of any alcohol-T2DM relationship in a recent Mendelian randomisation meta-analysis, in which confounding factors should have been more randomly distributed between drinking groups.[85]

2. With the risk of T2DM modelled exclusively according to the volume of alcohol consumption, no account was given to drinking pattern upon T2DM. The importance of such a consideration is illustrated by a recent meta-analysis of seven observational studies that reported data on both dimensions of alcohol consumption investigating the risk of ischaemic heart disease (IHD).[268] Here, relative to never drinkers, a 36% (RR 0.64, 95% CI 0.53, 0.71) reduction in risk was documented among those that reported a moderate level of average volume of alcohol consumption (<30 g/day) and no episodic heavy drinking. By contrast, no reduction in risk was evident among those who reported the same moderate level of average volume consumption but additionally indicated episodic heavy drinking (RR 1.12, 95% CI 0.91, 1.37). Of studies selected as part of the revised meta-analysis, few had considered the effect of consumption pattern, but

largely mirrored findings reported by Roerecke *et al* when researching IHD:[268] that regular moderate alcohol consumption was associated with the lowest incidence of T2DM,[95,97,240,244] with risks most pronounced among infrequent heavy drinkers.[96,239,244]

Such results indicate a possibility that any putative health benefit conferred by regular exposure to moderate volumes of alcohol may be countered by infrequent episodes of heavy consumption. Unfortunately, data for IHD were not stratified by sex, with the majority of T2DM studies having only analysed men or women separately. Accordingly, it was unclear whether a volume-pattern interaction operated similarly among both men and women. Nevertheless, assuming a comparable effect in both sexes, sex-specific differences in the relationship between the volume of alcohol consumption and T2DM risk may have been attributable to sex-specific disparities in the prevalence of episodic heavy drinking.

The possibility of a difference in consumption pattern between men and women is supported by data collated from 7,193 attendees at European 172 general practices.[269] Among participants, the odds of episodic heavy drinking (≥6 drinks on any one occasion at least once every month) among non-hazardous male drinkers (an AUDIT score of <8) was four times that of women following adjustment for country, age, employment status, mental and physical health (OR 4.38, 95% CI 3.27, 5.85). Similarly, of data reported by the Opinions and Lifestyle Survey, episodic heavy drinking was found to be greatest among men.[101]

Although more data are required, current evidence indicates that both the volume and pattern of alcohol consumption are likely to be important modifiers of T2DM risk. Differences in dose-response between men and women may therefore have been a consequence of differences in consumption pattern. Specifically, a greater prevalence of episodic heavy drinking among men.

3. Observed differences in dose-response between men and women may have been attributable to sex-specific disparities in the effect of alcohol upon putative biological pathways. Evidence in support of such a hypothesis was limited, however.

Looking to research concerning a possible effect of alcohol upon insulin sensitivity, a meta-analysis of 10 interventional studies identified a significant sex interaction between average volume of alcohol consumption and insulin sensitivity (p=0.018).[112] Specifically, insulin sensitivity was found to be higher among female but not male

drinkers, relative to controls. However, heterogeneity among the studies was high, and when a study largely responsible for such heterogeneity was removed, no significant difference in insulin sensitivity between men and women remained (p=0.180). Although women were also found to exhibit significant reductions in fasting insulin concentration, the absence of any detectable effect among men was due to a dearth of data; men were represented by just two small interventional studies that, despite low precision, each reported similar reductions in fasting insulin following alcohol consumption.

A second potential pathway concerned alcohol-mediated increases in HDL concentration. Although a linear dose-response relationship was identified across 33 interventional studies,[118] a sex interaction was not statistically significant. Such a result was mirrored by analyses reported in a Mendelian randomisation meta-analysis, which found no alcohol-mediated change to HDL concentration and no significant difference in mediation between men and women.[85]

Finally, regarding the effect of alcohol consumption upon inflammatory response, a meta-analysis of interventional studies to have researched various inflammatory biomarkers found no difference in concentration by alcohol consumption,[118] and while a Mendelian randomisation meta-analysis of 42 longitudinal studies found concentrations of CRP to be lower among A-allele carriers whose average volume of alcohol consumption was 17% lower than non-carriers, the magnitude of the difference was small and not stratified by sex.[85]

Aside from the methodological weaknesses that underpinned such studies, evidence indicating a difference in alcohol-mediated biological response between men and women was lacking.

4. A fourth possibility was that sex hormones may have played a role in altering the effect of alcohol upon T2DM risk. Associated with levels of insulin resistance and glucose concentrations independent of adiposity,[270,271,272] at least two hormonal biomarkers have been implicated as modifiers of T2DM risk, including estradiol, a female sex hormone, and sex hormone-binding globulin (SHBG), a protein responsible for the transport of sex hormones. Of nine case-control studies to have reported concentrations of estradiol according to T2DM status, levels were significantly higher among those who developed T2DM (SMD 12.8 nmol/L, 95% CI 3.44, 22.2 nmol/L), though with no apparent interaction by sex (p=0.870).[273] Of 20 case-control studies to

have reported on SHBG, concentrations were significantly lower among female cases than controls (SMD -16.23 nmol/L, 95% CI -20.24, -12.22 nmol/L), with little difference observed among men (SMD -5.07, 95% CI -11.92, 1.77).[273] Effect modification of SHBG concentrations by sex were statistically significant (p=<0.001). Lower levels of circulating SHBG were also identified in cohort studies, where the risk of T2DM was substantially lower in participants with higher concentrations of SHBG, particularly among women.[273]

In addition a lack of understanding concerning the precise biological mechanism by which factors such as SHBG may modify T2DM risk,[273] research investigating the effect of alcohol upon circulating concentrations of sex hormones is scarce, particularly how moderate volumes of alcohol consumption might specifically elicit advantageous changes in female sex hormone concentration. One cross-sectional analysis data from Women's Health Study stratified alcohol consumption according to whether or not participants consumed in excess of 25 g/day. Estradiol concentrations were elevated only within the higher consumption category, relative to pooled infrequent and non-drinkers (β=0.17, 95% CI 0.05, 0.29).[274] While concentrations of SHBG also appeared to be higher among regular current drinkers, differences in SHBG were not statistically significant (β=0.02, 95% CI -0.11, 0.15). Elsewhere, a cross-sectional study of 202 pre-menopausal women reported that those who consumed ≥10 g/day had an 18% higher mean salivary estradiol concentrations than those who consumed <10 g/day (p=0.034).[275] Similar findings have been reported by cross-sectional studies elsewhere,[276] as well as linear increases in estradiol concentrations across categories of weekly alcohol consumption,[277] and acute elevations in small placebo-controlled studies of female participants following dosages of 0.5 g/kg (or around 27.5 g in a 55 kg woman)[278] and 0.7 g/kg (or around 38.5 g in a 55 kg woman).[279]

Such studies were limited by only having sampled a single sex, meaning that side-by-side comparisons of alcohol-related changes to estradiol concentration were not possible. Similarly, with most studies having reported concentrations according to only a one or two volumes of alcohol consumption, a more complete understanding of the dose-response relationship was unclear. However, based on the few small studies available, there was an indication that the association between alcohol consumption and estradiol concentration may sit contrary to what is expected, with concentrations appearing elevated at volumes of alcohol consumption otherwise associated with a peak reduction in T2DM risk among women.[10] The validity of beneficial alcohol-induced

changes to endogenous sex hormone concentrations having served as a pathway by which women might experience the greatest reductions in T2DM risk therefore seemed weak.

5. Finally, there was a possibility that sex-specific differences in dose-response may have been a consequence of men and women having consumed different types of alcoholic drink; that reductions in risk were less to do with the total volume of ethanol so much as some other drink-specific component. Such a possibility was plausible given a purported role of flavonoids and stilbenes commonly found in fruit-based drinks as anti-oxidants capable of impairing inflammatory response, and promoting both good blood flow and endothelial function for the effective transport of blood glucose.[280,281]

   Of the studies selected as part of the revised meta-analysis, seven reported multivariable-adjusted risk estimates according to drink type. However, in many cases, the stratification of risk estimates by drink type and categories of volume consumption led to small sub-group samples and high imprecision, weakening inferences drawn concerning any effect modification by drink type.

   In one study, risks stratified by drink type were only reported for men owing to the low volume of consumption among women. Among the 5,423 male US participants, multivariable-adjusted odds of T2DM showed no independent association for any drink type.[219] Although point estimates indicate greater reductions in risk among men who drank wine at higher frequencies (e.g. OR 0.63 at >25 g/day, 95% CI 0.08-4.95), relative to non-drinkers, the estimates were subject to substantial imprecision given the small number of male wine drinkers. In a male cohort that benefitted from a much larger sample size, reductions in risk were statistically significant among moderate wine drinkers (HR 0.80 at 25 g/day, 95% CI 0.65-0.97), relative to pooled non-drinkers, with no reduction evident among beer or spirit drinkers.[246] By contrast, a final male cohort reported independent linear reductions in risk per 15 g/day increase in consumption for beer (RR 0.80, 95% 0.70-0.91), white wine (RR 0.77, 95% CI 0.65-0.90), and spirits (RR 0.85, 95% CI 0.76-0.94), plus some indication of a reduction in risk among red wine drinkers (RR 0.91, 95% CI 0.78-1.08).[95] However, in this instance confounder adjustment was much lower, accounting only for age and BMI. Nevertheless, in another model with greater covariate adjustment, but with additional adjustment for potential mediators of the alcohol-T2DM relationship, significant associations were unchanged.

In a US cohort study, participants were categorised according to their preferred drink type.[245] Unfortunately, to boost sample size, data were adjusted for sex as opposed to stratified. All current drinkers showed reductions in risk relative to non-drinkers, but with no difference in risk according to whether participants consumed beer (RR 0.7, 95% CI 0.4-1.1), wine (RR 0.6, 95% CI 0.4-0.9) or spirits (RR 0.6, 95% CI 0.4-0.9). Conversely, in another cohort where sex-specific data were combined, reductions in risk were evident among wine drinkers only (HR 0.93 per g/day wine, 95% CI 0.87-0.99), with point estimates no different from the null for all other drink types.[153]

Relative to never drinkers, reductions in risk among Australian female drinkers were specific to those who reported wine consumption.[97] However, none of the relationships were statistically significant due to high imprecision owing to a small number of cases within sub-groups. Imprecision was also high among men, though with reductions in risk indicated across all drink types. In particular, a statistically significant linear association trend was observed between increased wine consumption and decreased T2DM risk (p=0.037). Benefiting from a much larger number of cases per sub-group, a European multicentre prospective case–cohort study also reported significant effect modification among male wine drinkers (p=0.003), with hazards lowest at 24.1-60.0 g/day (HR 0.82, 95% CI 0.71-0.95) relative to very light drinkers (0.1-6.0 g/day).[238] Little variation from the null was evident across categories of beer (p=0.660) or spirit (p=0.440) consumption in men. Among women, significant effect modification was documented for wine (p=0.048) and fortified wine (p=0.023) drinkers, with hazards lowest in each case among those who reported consuming 24.1-60.0 g/day (wine: HR 0.89, 95% CI 0.72-1.11; fortified wine: HR 0.64, 95% CI 0.24-1.70).

On balance, reductions in risk appeared most consistently reported among male and female participants who reported consuming wine, particularly in studies of greater precision.[238,246] Although in keeping with research indicating that chemical compounds in fruit-based drinks such as red wine may have anti-inflammatory effects,[280,281] with sex-specific reductions in T2DM thereby a result of compounds other than ethanol, a recent probabilistic study casts doubt on such a conclusion. Using dose-response data from animal models, researchers estimated the comparative risks and benefits of alcohol consumption according to the putative carcinogenicity of ethanol and the anti-carcinogenicity of the stilbene resveratrol.[282] Based on abstracted data, the authors estimated that a person would have to consume at least 111 glasses of wine before

reaching a therapeutic dose of resveratrol at which the risk of cancer would begin to decrease. Having an effect over 100,000 times more potent than resveratrol, the increased risk of cancer from ethanol consumption would far outweigh any anti-carcinogenicity from resveratrol.

Although equivalent analyses have yet to be published for T2DM risk, such a finding suggests that reductions in risk among wine drinkers may instead be confounded by differences in health and lifestyle according to drink preference. Although the few papers that did stratify T2DM risk by drink type were generally included a number of primary T2DM risk factors such as age, adiposity, physical activity and smoking, residual confounding was a possibility, with marked differences in the characteristics wine, beer and spirit drinkers according a wide range of socio-economic variables.[283,284] In the absence of high precision studies able to isolate the independent effect of drink-specific compounds, a clear conclusion concerning the clinical effect of different drinks at moderate levels of alcohol consumption remains in question.

Although sex-specific differences were observed in the dose-response relationship between volume of alcohol consumption and T2DM risk, it was not possible to say with certainty which factor or combination of factors contributed to reductions in risk at moderate levels of consumption being specific to women. Based upon the available literature, the most credible determinants included a statistical artefact arising from differences in study characteristics, or else the result of biological mechanisms modified by sex-specific variations in drinking behaviour, such as consumption frequency or drink preference.

Chapter 4

A summary of current evidence

4 A summary of current evidence

DM has been linked to the development of multiple vascular morbidities,[1,3] the management and treatment of which was estimated to have accounted for around one-tenth of the NHS budget in 2010/11, or £13.8bn.[4] The effects of DM are not restricted to health and healthcare systems, however, with deteriorations in health having sizeable impacts on patients' ability to maintain jobs and care for themselves independently.[4] Fortunately, of all known cases, T2DM represents by far the largest proportion, at around 85-90% of UK diagnoses.[8] As such, the burden of DM may be largely attributable to modifiable environmental exposures, such as obesity and smoking, with the potential to attenuate disease risk in the general population through modest lifestyle changes.

A growing literature has indicated that alcohol consumption may represent one such change. Results from an updated and revised meta-analysis indicated a J-shaped dose-response relationship relative to pooled non-drinkers (Figure 3.2), with reductions in risk most pronounced among women (Figure 3.4). Although few in number, studies have also indicated that the frequency of consumption may represent an important modifier of T2DM risk, with T2DM lowest among regular moderate drinkers, and any reductions in risk potentially offset by concentrated periods of episodic heavy consumption.

To date, a number of biological mechanisms have been proposed to explain apparent reductions in T2DM risk at moderate levels of alcohol consumption, including alcohol-related improvements to insulin sensitivity, increases in the concentration of the lipid transport protein HDL, and a reduction in the expression of inflammatory factors implicated in the disruption of endothelial and pancreatic β-cell functioning. Research investigating such pathways has tended to be limited, with most existing observational studies having been cross-sectional in nature, preventing causal inference. Where studies were interventional, these were commonly constrained by small sample sizes, acute durations and single levels of exposure, undermining a determination of dose-response within each sample.

Where results from interventional studies have been reported, acute improvements in insulin sensitivity and fasting insulin have been observed,[112] as well as linear increases in HDL cholesterol concentrations.[117,119] However, a beneficial relationship between alcohol consumption and HDL concentration has not been supported by Mendelian randomisation studies,[85] with such studies also reporting a null relationship between SNPs of HDL variance and T2DM risk.[121] In a reversal of this apparent disparity in the findings of interventional and

Mendelian randomisation research, acute interventional trials currently report no association between alcohol consumption and inflammatory markers (though the number of such studies is small),[118] while results from Mendelian randomisation studies indicate a J-shaped association between alcohol and CRP consistent with the dose-response between alcohol consumption and T2DM risk.[131] And although a longitudinal cohort study has found associations between the concentration of CRP and T2DK risk, such an association was not identified when T2DM risk was stratified according to SNPs of variance in CRP concentration.[132] Elsewhere, Mendelian randomisation studies have reported conflicting evidence concerning the relationship between inflammatory markers and vascular conditions.[133,134,135] Thus, although conceivable that alcohol may indeed act upon T2DM risk through such pathways, results from existing studies are inconsistent and limited by small sample sizes.

Studies included within the updated and revised meta-analyses were subject to their own shortcomings, undermining the inference that moderate volumes of alcohol consumption may confer a reduction in T2DM risk. In all but two of the cohorts analysed by Baliunas *et al*, risk estimates among drinkers had been calculated relative to a group of pooled non-drinkers.[10] Although conventional in epidemiological studies to measure the effect of an exposure relative to those who were not exposed, the use of a pooled non-drinking category has drawn criticism through the manner in which it captures a number of former drinkers whose health and lifestyle may predispose them to the development of T2DM.[136,137] As such, apparent reductions in T2DM risk at moderate levels of consumption may have been overestimated, particularly among studies with poor adjustment for determinants of T2DM risk, such as physical activity and diet.

To explore this further, the updated and revised meta-analysis included sensitivity analyses that explicitly documented the effect of reference group and confounder adjustment upon reductions in risk observed in aggregate data. These analyses supported a significant, sex-adjusted interaction according to the choice of reference group, with reductions in risk particular to studies that calculated risks relative to pooled non-drinkers (Figure 3.5). Furthermore, after accounting for the effect of sex and reference category upon the dose-response relationship, a weak interaction was observed according to the degree of confounder adjustment, with multivariable-adjusted reductions in risk at moderate volumes of alcohol consumption appearing less pronounced than those derived from crude or age-adjusted estimates, though present across a broader range of consumption (Figure 3.8). Alongside these two factors, population region also appeared to have a sizeable effect upon dose-response, with smaller reductions in risk reported by studies that sampled participants from Asian regions (Figure 3.10).

Aside from the issue of reference group selection and confounder adjustment, a further limitation of the current literature concerned the tendency of longitudinal studies to define alcohol consumption according to a single baseline measure. Despite growing evidence that drinking may vary markedly across the life course,[259] only one selected study was found to have explored the effect of changes in alcohol consumption upon the risk of T2DM.[153] Of studies not captured by the revised and updated meta-analysis, only one additional publication was found to give any consideration to the variability of alcohol intake over time.[267]

Results from the two available studies hint at a dose-response relationship more complex than captured by conventional analytical approaches. The first reported attenuated and non-significant reductions in T2DM risk after accounting for longitudinal changes to the volume of alcohol consumption among sampled participanst,[153] while the second reported significant differences in T2DM according to the longitudinal trajectory of alcohol consumption.[267] For instance, of moderate drinkers (5.0-29.9 g/day) that reduced their consumption to none or light drinking (0-4.9 g/day), a 9% increase in hazards was observed (HR 1.09, 95% CI 0.92-1.30) on average over each four-year period of follow-up, indicating a possible sick quitter effect. Although limited, such analyses suggest that the categorisation of participants according to their consumption at baseline risked introducing some degree of misclassification error.[150] Accordingly, future research should apply analytical approaches capable of describing and modelling longitudinal changes to alcohol consumption and their association with T2DM risk.

Chapter 5

Research aims

5 Research aims

Although results from the updated and revised meta-analysis suggest the presence of reductions in T2DM risk among women at moderate volumes of alcohol intake, with T2DM risk elevated even at low volumes among men, effect estimates abstracted from constituent studies were calculated according to a single baseline measure. Despite apparent changes in alcohol consumption behaviour across the adult life course,[259] very few studies appear to have investigated the impact of such variation upon a person's risk of T2DM. In the few instances where T2DM risk has been modelled as a function of longitudinal changes to alcohol consumption, results indicate a relationship more complex than captured by conventional analytical approaches,[153,267] supporting recent calls for alcohol studies to give a better account of variations in alcohol consumption across the life course.[266,285,286,287] With this in mind, a series of analyses will be undertaken to help better understand the longitudinal dynamics of the dose-response relationship, beginning with a preliminary survival analysis designed to confirm the suitability of the chosen dataset for the analysis of dose-response relationships between alcohol consumption and T2DM.

Aim 1: Establish whether baseline alcohol consumption is associated with T2DM risk (Chapter 7)

- Undertake a conventional multivariable-adjusted survival analysis, reporting the dose-response relationship between baseline categories of average weekly volume of alcohol consumption and T2DM risk.
- Investigate whether the volume of alcohol consumption alone was sufficient for modelling T2DM risk by testing an interaction between the volume and frequency of alcohol consumption.
- Compare results from the conventional survival analyses against those summarised as part of the revised meta-analysis in Chapter 3.

Aim 2: Determine the degree to which baseline categories of alcohol consumption risked being subject to misclassification error as a result of longitudinal changes in alcohol consumption (Chapter 8)

- Establish whether sex-specific trajectories of the mean weekly volume of alcohol consumption were constant over the captured life course.

- Establish the longitudinal stability of alcohol intake within categories defined by baseline consumption.

Aim 3: Describe differences in the mean volume of alcohol consumption over the life course according to T2DM diagnosis (Chapter 8)

- Determine whether trajectories of alcohol consumption differed according to whether or not participants developed T2DM.
- Describe the nature of any differences in the mean weekly volume of alcohol consumption over the period leading up to the time of censoring or T2DM diagnosis.

Aim 4: Formally explore the utility of more advanced survival models in developing a better understanding of the relationship between alcohol consumption and T2DM (Chapter 9)

- Conduct a series of increasingly advanced survival models to estimate the sex-specific risk of T2DM as a function of age-varying alcohol consumption.
- Compare dose-response relationships reported according to different parameterisations of the longitudinal trajectory.
- Investigate the effect of adjustment for heterogeneous non-drinking groups upon the sex-specific dose-response relationship.
- Establish whether declining trajectories represent a group of drinkers at elevated risk of T2DM.

With these aims established, Chapter 6 details the selection and structure of a dataset considered suitable for exploring longitudinal trajectories of alcohol consumption and their relationship with T2DM.

Chapter 6
Data selection and structure

6 Data selection and structure

6.1 Introduction

To investigate the sensitivity of conventional survival analyses to longitudinal changes in average volume of alcohol consumption and drinking patterns, it was necessary to identify a dataset with a number of fundamental characteristics.

Given that alcohol consumption behaviours appeared to change across all periods of adulthood,[264,265] it was important first of all to analyse a dataset that spanned as broad a period of the adult life course as possible, with repeated measures of alcohol consumption that were both comparable between waves and of sufficient frequency as to capture acute fluctuations in drinking over time. However, while many longitudinal datasets were found to include repeated measures of alcohol consumption, none detailed the full adult life course, each having documented a restricted life period, such as early adulthood[288] or older age.[289]

Of the numerous longitudinal cohorts available, Whitehall II provided the best compromise between the period of adulthood captured, frequency of repeated alcohol measures, sample size and availability of variables, including objectively defined measures of T2DM. For instance, while the English Longitudinal Study of Ageing benefits from regular repeated measures and a sample of similar size to Whitehall II, its coverage of the adult lifecourse is skewed toward later life and comprises just 14 years of follow-up relative to the three decades of data afforded by Whitehall II.[290] Elsewhere, in terms of coverage, the MRC National Survey of Health and Development 1946 is perhaps one of the closest to Whitehall II, with measures of alcohol consumption available between the ages of 36 and 64 years. However, it is limited by self-reported T2DM data, fewer repeated measures and a sample one third the size of that available in Whitehall II.[291] Other cohorts, such as the Twenty-07 Study[292] and the Caerphilly Prospective Study,[293] benefit from a similar number of repeated measures to Whitehall II but with very small sample sizes.

6.2 Whitehall II cohort profile

The Whitehall II cohort was established in 1985 as a longitudinal occupational study and comprised 10,308 (6,895 male and 3,413 female) civil servants aged 35-55 years who worked in the offices of 20 Whitehall departments.[294] All eligible employees were invited to participate via letter, of whom 73% consented.[295] Baseline measurements were obtained between 1985 and 1988 by way of a self-administered questionnaire and a clinical examination. Participants were

followed up at regular intervals of between a median 1.6 and 5.5 years, with self-administered questionnaires completed at each wave and a clinical examination undertaken once every two waves (Table 6.1).

Although Whitehall II represents a geographically-concentrated and occupationally-narrow cohort, a recent paper confirmed that aetiological associations identified within the cohort are consistent with those reported from studies of general population samples, implying that aetiological analyses based on Whitehall II data are likely to offer sound external validity.[296]

Table 6.1 Variable availability in Whitehall II by study wave

Age range	34-56	37-60	40-64	42-66	45-69	48-71	50-74	54-77	55-80	60-84
Wave number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**11**
Alcohol consumption										
Frequency										
Volume										
'Always non-drinker?'										
T2DM										
FPG[a]										
HbA1c[b]										
OGTT[c]										
Self-reported										
Covariates										
Age										
BMI[d]										
Diet[e]										
Education										
Ethnicity										
Employment status										
Family history of T2DM										
Government office region										
Household income										
Index of Multiple Deprivation										
Occupational grade										
Physical activity										
Sex										
Smoking status										

[a]Fasting plasma glucose; [b]Glycated hemoglobin A1c; [c]Oral glucose tolerance test; [d]Body mass index; [e]Dietary variables, including fibre and saturated fat.

The main aim of wave 10 was to validate self-completed measures of psychiatric morbidity in older people. As only 337 participants were sampled for the validation exercise, data for wave 10 are not listed.

6.3 Defining alcohol consumption

As shown in Table 6.1, estimates of average weekly alcohol consumption were available in waves one, two, three, five, seven, nine and 11. Participants were asked to report the number of alcoholic drinks they had consumed in the preceding week according to "measures" of spirits, "glasses" of wine, or "pints" of beer or cider. A standard measure of spirits and a glass of wine were each assumed to contain one unit of alcohol, and a pint of beer or cider two units of alcohol. Based on data provided by Drinkaware,[11] these volumes were roughly equivalent to a small (125 ml) glass of 10% ABV white wine (1.2 units) and a 4% ABV pint of lager (2.3 units).

Given recent increases to both the size of wine glasses (175 ml and 250 ml) and the average strength of wines (11.5-13.5% ABV),[297] it was likely that alcohol consumption from wine is conservatively estimated in Whitehall II.[298] This was supported by a number of small convenience studies that asked drinkers to pour self-defined usual glasses of various drink types. Among these, volumes of alcohol contained within a usual glass of wine were consistently greater than those assumed by Whitehall II, with mean alcohol content measuring 15 g of alcohol among 283 drinkers from six locations across South-East England,[299] or around double the volume assumed in Whitehall II. Elsewhere, almost half of participants from a Scottish convenience study poured in excess of 16 g alcohol.[300]

While wine consumption data could have been inflated retrospectively, any such alteration risked being arbitrary and simplistic given variations in underestimation between convenience studies according to factors such as age, sex and setting.[299] In a recent study that investigated the impact of increasing the assumed alcohol content of wine from 8 g/glass to 16 g/glass, doubling the value of wine consumption had the effect of reducing the risk of all-cause, CVD and cancer mortality among very heavy drinkers (men: ≥408 g/week, women: ≥288 g/week), relative to moderate drinkers (men: 1-168 g/week; women: 1-112 g/week).[300] Risks among former and pooled non-drinkers were attenuated, though not to a degree as to be statistically significant. Accordingly, any underestimation of wine consumption would not have influenced the direction of the dose-response association under study, but may lead to an overestimation of risk at higher volumes. With this in mind, the volume of alcohol consumption was left unchanged with the caveat that risks among very heavy, former and non-drinkers were likely to have been biased upward among participants who predominantly consumed wine.

The total volume of alcohol consumption was reported within the Whitehall II dataset as average units/week. These data were transformed into grams/week assuming a UK unit equal to 7.9 g ethanol, consistent with conversions undertaken as part of the revised meta-analysis. At wave

one, median reported alcohol consumption was 63.2 g/week (IQR 23.7-134.3 g/week, n=6,840) and 23.7 g/week (IQR 0.0-55.3 g/week, n=3,374) among men and women respectively (Table 6.2). Median weekly alcohol consumption varied over the course of the study, peaking among men and women at wave five (ages 45-69).

Whitehall II also included data concerning the pattern of alcohol consumption, operationalised as the frequency of alcohol consumption over the last 12 months. In wave 11, frequencies were defined as: 'never', '≤1 occasion/month', '2-4 occasions/month', '2-3 occasions/week' and '>3 occasions/week'. In all other waves, frequencies were recorded as: 'none', 'special occasions', '>1/month', '>1/week', 'daily' and 'almost daily'. To maintain consistency across waves in the classification of consumption frequency, new variables were derived for each wave of data and categories defined as: 'none', '<1 occasion/week', '1-3 occasions/week', 'daily or almost daily'. These derivations were in keeping with a prior publication that used alcohol consumption frequency data from Whitehall II.[266]

6.4 Defining T2DM

Self-reported T2DM was documented at all waves, defined as any self-reported doctor-diagnosis or self-reported prescription of anti-diabetic medication (Table 6.1). Given that close to one-third of T2DM cases may be missed by subjective measures of T2DM,[301] self-reports were supplemented by objective data. These were obtained using measures of blood glucose drawn during clinical examinations at waves three (1991-93, ages 39-64), five (1997-99, ages 45-69), seven (2003-04, ages 50-74), nine (2008-09, ages 55-79) and 11 (2012-2013, ages 61-85) following a minimum five-hour fast. At each clinical examination, cases of T2DM were defined according to the 1998 WHO criteria: a fasting plasma glucose (FPG) reading ≥7.0mmol/L.[302] Data following an oral glucose tolerance test (OGTT) were also available, for which participants consumed 389 ml of Lucozade (75 g anhydrous glucose) over a five-minute period, with a blood sample taken two hours later. However, as shown in Table 6.1, this measure was unavailable in wave 11. Similarly, while HbA1c concentrations were also documented as an alternative objective diagnostic indicator, such data were only available from wave seven onwards. To maintain a consistent definition of T2DM over time, FPG was thus selected as the objective measure of choice alongside self-reported data.

To ensure a baseline free of T2DM, known cases between waves one through three were excluded from any analyses involving T2DM. After wave three, a total 916 new cases were observed (men: 620; women: 296), with a median follow-up 20.1 years (IQR 14.8-20.6 years) among men and 19.8 years (IQR 12.8-20.4 years) among women (Table 6.2).

6.5 Confounding factors

All confounding factors identified during the literature review were available in Whitehall II, including adiposity, dietary variables (fats, carbohydrates and fibre), ethnicity, physical activity, smoking status and family history of T2DM (Table 6.1).

6.5.1 Adiposity

Despite its strong association with T2DM risk,[39] there was a possibility that adiposity may have operated as a mediator of the relationship between volume of alcohol consumption and T2DM risk, with evidence indicating that calories consumed via alcoholic drinks tended to be additional to those derived from other dietary sources such as evening meals, leading to an acute over-consumption of calories relative to non-drinkers.[303] However, research linking average volume of alcohol consumption to increases in adiposity itself is conflicting, with longitudinal studies having reported a variety of null, inverse and positive associations.[303,304] Notably, where positive associations have been identified, absolute differences in adiposity across alcohol consumption categories were modest. For example, over a period of three-years, each 14 g increase in alcohol consumption per drinking occasion was associated with an increase in BMI of 0.03 kg/m^2 (0.02, 0.04 kg/m^2) among men, or a rise of 0.03 kg/m^2 (95% CI -0.01, 0.07 kg/m^2) for each additional day of weekly consumption.[305] Coefficients among women were even smaller and non-significant. Elsewhere, in an analysis of three large occupational cohorts, each 14 g increase in the volume of consumption per drinking occasion was associated with an increase in weight of 0.19 kg (95% CI 0.10, 0.27 kg) over a period of four years, or just 0.05 kg/annum.[306] Similarly small increases in weight have been identified elsewhere.[307]

On balance, given the body of available evidence, it was decided that while calories derived from alcoholic drinks may have some direct effect upon adiposity, the magnitude of such an association appears diminutive relative to other risk factors for adiposity, such as physical inactivity and poor diet. Accordingly, adiposity was included as a confounding factor in all multivariable-adjusted models, with negligible risk of overadjustment.

Multiple measures of adiposity are available in Whitehall II, including BMI and waist circumference. Each has been strongly associated with an increased risk of T2DM, with risk estimates of comparable magnitudes and the predictive utility of each measure differing according to a range of participant characteristics.[39] BMI was selected as a well-known indicator of adiposity. Data on participants' height and weight were captured at each clinical examination. Mean BMI measured 24.6 kg/m^2 (95% CI 23.3, 25.8 kg/m^2, n=6,883) among men and 24.8 kg/m^2

(95% CI 23.1, 26.5 kg/m^2, n=3,441) among women at wave one, with mean BMI appearing to increase gradually at each successive wave (Table 6.2).

6.5.2 Diet

A number of dietary factors were considered in accordance with the literature review, including carbohydrates, fibre and dietary fats (e.g. polyunsaturated and trans fats). The consumption of such factors was estimated based on responses to an anglicised food frequency questionnaire (FFQ) based on that used in the US Nurses' Health study.[308] Foods commonly eaten in the UK were added to the FFQ as per the UK arm of the EPIC cohort study.[309] A common portion size was assigned to each food, and participants then asked how often, on average, they consumed such a portion during the previous year. Frequencies ranged from 'never or less than once per month' to 'six or more times per day'. The reported frequency for each food item was then converted to an estimated daily intake, with the consumption of constituent nutrients computed by multiplying the daily frequency of consumption by the estimated nutrient content of each portion.[310]

Unfortunately, dietary variables were only available in waves three, five and seven of the Whitehall II cohort. In order to explore the merit of truncating the number of repeated measures of alcohol consumption in favour of greater covariate adjustment, the contribution of dietary factors upon the alcohol-T2DM relationship was explored alongside other covariates of interest by way of multiple sex-stratified Cox survival models. The method adopted was consistent with studies selected as part of the revised meta-analysis, with all covariates modelled only according to their values at baseline. The sample was restricted to T2DM-free participants at wave three, with T2DM defined according to a positive FPG, self-reported doctor diagnosis or use of hypoglycaemic medication. Dietary variables were treated as continuous variables that denoted their proportion of total energy intake (g/100g). With the exception of fibre, all dietary variables were subjected to a logarithmic transformation owing to skewness. In keeping with conventional survival models, categorical average weekly volume of alcohol consumption was selected as the exposure of interest.

The reference model was adjusted for all *a priori* covariates (age, BMI, ethnicity, family history of T2DM, physical activity, sex, smoking and socio-economic status), excluding any dietary variables. Dietary variables were then added in a mutually exclusive manner, with a final model adjusted for all covariates and dietary variables. Results from these analyses identified a statistically significant inverse association between fibre consumption and T2DM risk among men, independent of adiposity (p=0.018), while all other dietary variables were far from

significant in both sexes (Appendix 6.1). In all models, dietary variables appeared to have little impact upon the relationship between alcohol consumption and T2DM risk. The relationship was similarly unchanged when alcohol consumption was modelled as a continuous variable, or when dietary variables were coded as tertiles.

Such a series of results indicated that other covariates, particularly BMI, may have captured much of the effect of diet upon T2DM risk. Dietary factors were thus omitted as covariates from any subsequent multivariable-adjusted model.

6.5.3 Ethnicity

The ethnic group of participants was self-reported during screening at waves one and five. The ethnicity of participants was coded as 'white', 'South Asian' or 'other', which isolated into a separate category any Asian participants who were likely to have a heightened genetic sensitivity to alcohol[203] and susceptibility to the development of T2DM.[204] At baseline, 92.0% (95% CI 91.3-92.6) of participants were of a white ethnic background (Table 6.2).

6.5.4 Family history of T2DM

Family history of diabetes was self-reported by participants in waves one and two. Data were coded as a dichotomous variable according to whether a participant reported a parent or sibling as having developed T2DM. The variable was thus limited by failing to capture familial cases that developed after the first two waves of study. Among those who participated at baseline, 10.4% (95% CI 9.7-11.2%, n=709) of men and 14.1% (95% CI 12.9-15.3%, n=470) of women reported a family history of T2DM (Table 6.2).

6.5.5 Physical activity

Information regarding physical activity was ascertained via a 20-item questionnaire that included questions on the frequency and duration of participation in activities including walking, cycling, housework, gardening and sports in the preceding four weeks. These responses were used to derive the average number of hours spent doing each activity per week. Activities were classified as either mildly (e.g. gardening and housework), moderately (e.g. walking), or vigorously (e.g. running and swimming) energetic, relative to laying at rest.[311] Time spent in mildly energetic physical activity was discounted as it predominantly captured women, potentially leading to a small sub-group in any adjusted analyses stratified by sex. This was consistent with a previous analysis using Whitehall II physical activity data.[312]

A categorical physical activity variable was created, with participants classified according to WHO physical activity recommendations:[313] meeting guidelines (≥150 minutes of moderate-

intensity exercise per week, or ≥75 minutes of vigorous-intensity activity); inactive (<60 minutes of moderate physical activity and <60 minutes of vigorous physical activity; below guidelines (anyone not inactive or meeting the WHO guidelines).

The proportion of participants who reported meeting WHO physical activity guidelines was greatest among men and women at wave five (ages 45-69), at 91.0% (95% CI 90.1-91.8%, n=4,234) and 79.6% (95% CI 77.8-81.4%, n=1,576) respectively (Table 6.2). This proportion then fell with increasing age up to the final wave of data, at 54.3% (95% CI 52.8-55.8%, n=2,389) among men and 36.6% (95% CI 34.4-38.8%, n=661) among women by wave 11.

6.5.6 Smoking status

Smoking data were collected at each wave and participants categorised according to whether they reported being a current, former or never smoker. The proportion of current smokers was greatest at wave one, at 15.9% (95% CI 15.1-16.8%, n=1,091) of men and 23.4% (95% CI 22.0-24.9%, n=795) of women (Table 6.2). The proportion of current smokers declined as the cohort grew older, falling to 3.4% (95% CI 2.9-3.9%, n=141) of men and 4.8% (95% CI 3.8-5.9%, n=80) of women by wave 11.

6.5.7 Socio-economic status

Given the long history of research highlighting a social gradient in health inequalities, socio-economic variables were considered as a means of capturing some degree of confounding not captured by other *a priori* selected variables. Such a decision was supported by research that indicated a social gradient in abstention and heavy drinking,[314,315] which were disproportionally concentrated among those of low education or in unskilled occupations. Elsewhere, heavy drinking has also been associated with being unemployed or materially deprived,[316,317] or living in deprived neighbourhoods.[318] Similarly, the risk of T2DM also appears greatest among study participants of low income,[319,320] education,[320] socio-economic status,[321] or area deprivation.[322]

Although income, education, government office region (GOR) and Index of Multiple Deprivation (IMD) score were all available as potential socio-economic variables, data were present on each for only a sub-set of the baseline sample: GOR and IMD data were only available for 33.0% (n=3,398) of participants at wave one, income for 69.5% (n=7,161), and education for 74.5% (n=7,681). In complete-case analyses, such a high proportion of missing data would have led to a substantial reduction in sample size.

Two alternative surrogate indicators of socio-economic status were thus selected: last known hierarchical occupational grade, based on salary and work role (administrative,

professional/executive, clerical/support), and employment status (employed, retired, redundant/sacked/sick/other). Where individuals lacked an occupational grade in waves after baseline measurement, such as due to having left the civil service through retirement, redundancy or long-term sickness, the last known occupational grade was used. Over 90.7% of male participants at wave one were among the top two tertiles of occupational grade, compared with 50.3% of female participants. The proportion of retired individuals rose at each successive wave to 77.7% (95% CI 76.5-78%, n=5,018) of men and 84.2% (95% CI 82.4-85.8%, n=1,554) of women by wave 11 (Table 6.2). To assess whether the inclusion of education, income, GOR and IMD would have helped capture additional confounding by socio-economic status, correlations were calculated between these factors and both employment status and occupational grade at wave three. The correlation between occupational grade and employment status was low (r=-0.02), indicating that each was likely to describe different dimensions of socio-economic status. Weak to moderate correlations were found between occupational grade and income, IMD and education, with Pearson's *r* ranging from 0.29-0.53, suggesting that such factors may have had some moderate additional predictive value in adjusted analyses. The weakest correlation was present between occupational grade and GOR (r=-0.08), indicating that area of residence may be an important socio-economic covariate despite the geographically concentrated nature of the cohort. Some degree of residual confounding within adjusted analyses was thus plausible.

6.5.8 Variables not included

6.5.8.1 Direct mediators

Some selected studies reported models that also adjusted for factors such as serum insulin, glucose or triglyceride concentration. However, these factors were likely to exist on the causal pathway (see Section 2.2.2). By adjusting for a factor on the causal pathway between alcohol consumption and T2DM risk, the primary dose-response relationship under investigation will be biased toward the null.[47] This is illustrated in Figure 6.1, where E indicates the exposure of interest (weekly volume of alcohol consumed), M the mediating mechanisms (insulin sensitivity, cholesterol, inflammation), and D the dependent event of interest (T2DM).

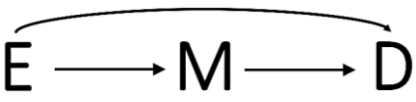


Figure 6.1 Directed acyclic graph illustrating direct overadjustment bias

6.5.8.2 Indirect mediators

Although self-rated general health was considered as a variable that may have helped adjust for confounding through an uneven distribution of poor health across alcohol consumption categories, and thereby potential differences in susceptibility to the development of T2DM, its inclusion was ruled out due to the possibility that it may also have served as a surrogate for mediating factors through which alcohol was hypothesised to modify T2DM risk. For instance, were moderate drinkers more likely to report good self-rated general health relative to non-drinkers, this may have been attributable in part to (a) advantageous differences in alcohol-induced insulin sensitivity, HDL cholesterol concentration and inflammation, and (b) a correspondingly lower burden of negative health conditions as a consequence of such a favourable metabolic profile, such as lower rates of stroke[323,324,325] and CHD.[326,327,328] The hypothesised role of self-rated general health as a surrogate mediator is illustrated in Figure 6.2, where U represents omitted mediators (inflammation, cholesterol and insulin sensitivity) and M the observed surrogate mediator (self-rated general health).

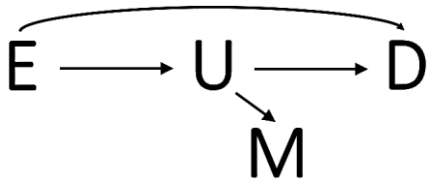


Figure 6.2 Directed acyclic graph illustrating indirect overadjustment bias

The exclusion of self-reported health as a covariate was supported by its absence as a confounding variable in models reported by selected studies, with preference given to lifestyle and demographic variables. Unfortunately, the degree to which a general health variable would have served as either a confounder or mediator could not be investigated statistically, each distinguishable only on a conceptual basis.[329]

Table 6.2 Descriptive summary of Whitehall II data, stratified by wave and sex

	Wave of study					
	1	3	5	7	9	11
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Variable	n	n	n	n	n	n
Men						
Participation (%)						
Participated	100.0	87.8	79.3	71.0	69.0	64.7
	6,895	6,057	5,473	4,893	4,759	4,459
Non-response	-	11.0	17.7	23.4	22.0	22.0
		757	1,218	1,613	1,515	1,521
Died	-	1.2	3.0	5.6	9.0	13.3
		81	204	389	621	915
Age						
Mean years	44.5 (44.4-44.7)[a]	49.9 (49.8-50.1)[a]	55.7 (55.5-55.9)[a]	61.1 (60.9-61.2)[a]	65.8 (65.7-66.0)[a]	69.7 (69.5-69.9)[a]
	6,895	6,057	5,473	4,893	4,759	4,459
Alcohol consumption frequency (%)						
None in past year	3.2 (2.8-3.6)	3.6 (3.2-4.2)	3.4 (2.9-3.9)	3.6 (3.1-4.1)	4.6 (4.0-5.2)	2.0 (1.6-2.5)
	220	209	168	171	213	83
<1/week	20.5 (19.5-21.4)	17.0 (16.1-18.0)	13.7 (12.8-14.7)	13.5 (12.6-14.5)	13.9 (12.9-14.9)	25.9 (24.6-27.3)
	1,407	977	682	645	644	1,083
1-3 times/week	42.5 (41.4-43.7)	39.4 (38.1-40.6)	33.0 (31.7-34.3)	30.5 (29.2-31.8)	30.1 (28.8-31.5)	26.7 (25.4-28.1)
	2,923	2,259	1,640	1,458	1,396	1,117
Daily or almost daily	33.8 (32.7-34.9)	40.0 (38.7-41.3)	49.9 (48.6-51.3)	52.4 (51.0-53.8)	51.4 (49.9-52.8)	45.4 (43.9-46.9)
	2,325	2,295	2,485	2,506	2,379	1,898
Alcohol consumption volume						
Median g/week	63.2 (23.7-134.3)[b]	63.2 (23.7-142.2)[b]	94.8 (31.6-181.7)[b]	79.0 (31.6-158.0)[b]	71.1 (23.7-142.2)[b]	63.2 (23.7-126.4)[b]
	6,840	5,734	4,984	4,765	4,619	4,400
BMI						
Mean kg/m^2	24.6 (24.5-24.6)[a]	25.1 (25.1-25.2)[a]	26.0 (25.9-26.1)[a]	26.6 (26.5-26.7)[a]	26.6 (26.5-26.7)[a]	26.6 (26.4-26.7)[a]
	6,883	5,591	3,996	4,569	4,424	4,039

Employment status (%)						
Employed	100.0	90.7 (90.0-91.4)	67.3 (66.0-68.5)	52.9 (51.5-54.3)	33.1 (31.8-34.5)	19.4 (18.2-20.6)
	6,895	7,981	5,001	3,413	2,039	1,101
Retired	-	7.4 (6.7-8.0)	26.4 (25.3-27.6)	42.1 (40.8-43.5)	63.0 (61.7-64.4)	77.7 (76.5-78.9)
		598	2,214	3,123	4,416	5,018
Other[c]	-	1.9 (1.6-2.3)	6.3 (5.7-7.0)	5.0 (4.4-5.6)	3.8 (3.3-4.4)	2.9 (2.5-3.5)
		236	606	403	295	185
Ethnicty (%)						
White	92.0 (91.3-92.6)	92.8 (92.1-93.4)	93.5 (92.8-94.1)	94.0 (93.3-94.6)	94.2 (93.5-94.8)	94.6 (93.9-95.2)
	6,306	5,602	5,116	4,592	4,472	4,211
South Asian	5.3 (4.8-5.9)	4.9 (4.4-5.5)	4.4 (3.9-5.0)	4.2 (3.7-4.8)	4.0 (3.5-4.6)	3.7 (3.2-4.3)
	366	297	243	207	191	166
Other[d]	2.7 (2.3-3.1)	2.3 (2.0-2.7)	2.0 (1.7-2.5)	1.8 (1.4-2.2)	1.8 (1.5-2.2)	1.7 (1.4-2.1)
	183	140	112	87	86	76
Family history of T2DM (%)						
Yes	10.4 (9.7-11.2)	10.5 (9.8-11.4)	10.3 (9.5-11.2)	10.1 (9.3-11.0)	9.9 (9.1-10.8)	9.8 (9.0-10.7)
	709	630	557	486	464	432
No	89.6 (88.8-90.3)	89.5 (88.6-90.2)	89.7 (88.8-90.5)	89.9 (89.0-90.7)	90.1 (89.2-90.9)	90.2 (89.2-91.0)
	6,078	5,342	4,836	4,336	4,232	3,972
Incident diabetes[c] (%)						
Yes	0.9 (0.7-1.2)	1.8 (1.4-2.1)	2.5 (2.1-3.0)	3.8 (3.3-4.4)	6.1 (5.4-6.9)	0.9 (0.7-1.2)
	63	108	129	177	276	38
No	99.1 (98.8-99.3)	98.2 (97.9-98.6)	97.5 (97.1-97.9)	96.2 (95.6-96.7)	93.9 (93.2-94.6)	99.1 (98.8-99.3)
	6,401	5,894	5,081	4,499	4,246	4,205
Occupational grade (%)						
Administrative (top)	38.4 (37.2-39.5)	48.0 (46.8-49.3)	50.9 (49.6-52.2)	53.5 (52.1-54.9)	54.4 (53.0-55.9)	13.9 (12.9-14.9)
	2,647	2,909	2,785	2,617	2,591	619
Professional (middle)	52.3 (51.1-53.5)	45.1 (43.9-46.4)	43.0 (41.7-44.3)	41.7 (40.3-43.0)	40.7 (39.4-42.1)	48.4 (47.0-49.9)
	3,607	2,733	2,352	2,038	1,939	2,160
Clerical (bottom)	9.3 (8.6-10.0)	6.9 (6.2-7.5)	6.1 (5.5-6.8)	4.9 (4.3-5.5)	4.8 (4.2-5.5)	37.7 (36.3-39.1)
	641	415	336	238	229	1,680

Physical activity[e] (%)						
Inactive	9.5 (8.8-10.2)	14.4 (13.5-15.3)	3.8 (3.3-4.4)	5.6 (5.0-6.3)	23.7 (22.5-25.0)	28.7 (27.4-30.1)
	645	826	177	267	1,110	1,264
Below guidelines	37.3 (36.1-38.4)	36.4 (35.1-27.6)	5.2 (4.6-5.9)	7.5 (6.8-8.3)	18.3 (17.2-19.4)	17.0 (15.9-18.1)
	2,544	2,087	243	357	854	746
Met guidelines	53.3 (52.1-54.5)	49.2 (47.9-50.5)	91.0 (90.1-91.8)	86.9 (85.9-87.8)	58.0 (56.6-59.4)	54.3 (52.8-55.8)
	3,636	2,826	4,234	4,138	2,715	2,389
Smoking (%)						
Never	47.7 (46.5-48.9)	44.7 (43.3-46.0)	46.8 (45.5-48.2)	45.3 (43.9-46.7)	44.0 (42.6-45.5)	42.5 (41.0-44.0)
	3,264	2,418	2,369	2,192	1,972	1,783
Former	36.3 (35.2-37.5)	42.1 (40.8-43.5)	43.6 (42.2-45.0)	47.1 (45.7-48.5)	49.9 (48.4-51.4)	54.2 (52.7-55.7)
	2,486	2,282	2,204	2,278	2,235	2,274
Current	15.9 (15.1-16.8)	13.2 (12.3-14.1)	9.6 (8.8-10.4)	7.6 (6.9-8.4)	6.1 (5.4-6.8)	3.4 (2.9-3.9)
	1,091	715	484	370	273	141
<u>Women</u>						
Participation (%)						
Participated	100.0	80.8	70.2	60.8	58.7	54.2
	3,413	2,758	2,397	2,074	2,002	1,849
Non-response	-	17.9	26.8	33.5	31.6	31.2
		611	914	1,144	1,078	1,065
Died	-	1.3	3.0	5.7	9.8	14.6
		44	102	195	333	499
Age						
Mean years	45.8 (45.6-46.0)[a]	51.1 (50.8-51.3)[a]	56.6 (56.3-56.8)[a]	61.7 (61.4-61.9)[a]	66.4 (66.2-66.7)[a]	70.1 (69.9-70.4)[a]
	3,413	2,758	2,397	2,074	2,002	1,849
Alcohol consumption frequency (%)						
None in past year	6.4 (5.6-7.2)	7.3 (6.4-8.4)	6.8 (5.8-7.9)	9.2 (8.0-10.5)	11.8 (10.4-13.3)	7.6 (6.4-9.0)
	217	189	141	183	224	124
<1/week	39.5 (37.9-41.2)	35.9 (34.0-37.7)	31.0 (29.0-33.0)	32.4 (30.4-34.5)	31.4 (29.3-33.5)	43.4 (41.0-45.8)
	1,345	925	644	648	598	708
1-3 times/week	34.3 (32.7-35.9)	34.8 (33.0-36.6)	30.6 (28.7-32.6)	27.9 (26.0-29.9)	27.0 (25.1-29.1)	21.7 (19.8-23.8)
	1,167	897	637	557	515	354
Daily or almost daily	19.8 (18.5-21.2)	22.0 (20.5-23.7)	31.6 (29.7-33.7)	30.5 (28.5-32.6)	29.9 (27.8-31.9)	27.3 (25.2-29.5)
	674	568	658	609	569	446

Alcohol consumption volume						
Median g/week	23.7 (0.0-55.3)[b]	23.7 (0.0-55.3)[b]	31.6 (0.0-79.0)[b]	25.7 (0.0-79.0)[b]	23.7 (0.0-63.2)[b]	15.8 (0.0-55.3)[b]
	3,374	2,578	2,098	1,986	1,902	1,827
BMI						
Mean kg/m^2	24.8 (24.6-24.9)[a]	25.7 (25.5-25.9)[a]	26.4 (26.2-26.7)[a]	27.2 (27.0-27.5)[a]	27.3 (27.1-27.6)[a]	27.2 (26.9-27.5)[a]
	3,411	2,483	1,685	1,881	1,769	1,576
Employment status (%)						
Employed	100.0	90.1 (88.9-91.2)	56.3 (54.3-58.3)	40.5 (38.4-42.6)	23.3 (21.5-25.2)	12.8 (11.4-14.4)
	6,895	2,485	1,342	836	465	237
Retired	-	5.5 (4.7-6.4)	32.6 (30.8-34.6)	51.8 (49.6-53.9)	71.1 (69.0-73.0)	84.2 (82.4-85.8)
		152	778	1,069	1,420	1,554
Other[c]	-	4.4 (3.7-5.2)	11.0 (9.8-12.4)	7.7 (6.7-9.0)	5.7 (4.7-6.8)	3.0 (2.3-3.9)
		121	263	160	113	55
Ethnicty (%)						
White	85.5 (84.3-86.7)	86.0 (84.6-87.3)	86.6 (85.2-87.9)	87.1 (85.6-88.5)	87.5 (85.9-88.9)	87.9 (86.3-89.3)
	2,875	2,353	2,070	1,801	1,746	1,622
South Asian	6.6 (5.8-7.5)	6.1 (5.2-7.0)	6.2 (5.3-7.2)	6.1 (5.2-7.3)	6.0 (5.0-7.1)	5.7 (4.8-6.9)
	222	166	147	127	120	106
Other[d]	7.9 (7.0-8.8)	7.9 (7.0-9.0)	7.2 (6.3-8.3)	6.8 (5.8-7.9)	6.5 (5.5-7.7)	6.3 (5.3-7.5)
	264	217	173	140	130	117
Family history of T2DM (%)						
Yes	14.1 (12.9-15.3)	13.9 (12.6-15.2)	13.7 (12.3-15.1)	13.8 (12.3-15.3)	13.6 (12.2-15.2)	13.3 (11.8-14.9)
	470	375	322	1,756	1,697	241
No	85.9 (84.7-87.1)	86.1 (84.8-87.4)	86.3 (84.9-87.7)	86.2 (84.7-87.7)	86.4 (84.8-87.8)	86.7 (85.1-88.2)
	2,874	2,329	2,032	280	268	1,573
Incident diabetes[c] (%)						
Yes	1.1 (0.8-1.5)	1.5 (1.1-2.0)	3.0 (2.4-3.8)	4.2 (3.4-5.2)	7.1 (6.0-8.3)	0.6 (0.3-1.1)
	37	42	68	84	134	10
No	98.9 (98.5-99.2)	98.5 (98.0-98.9)	97.0 (96.2-97.6)	95.8 (94.8-96.6)	92.9 (91.7-94.0)	99.4 (99.0-99.7)
	3,033	2,689	2,203	1,896	1,758	1,739

Occupational grade (%)						
Administrative (top)	11.2 (10.1-12.3)	15.4 (14.1-16.8)	18.6 (17.1-20.2)	21.2 (19.5-23.0)	22.1 (20.3-23.9)	6.5 (5.5-7.7)
	381	425	466	439	442	120
Professional (middle)	39.1 (37.5-40.8)	44.1 (42.2-46.0)	44.8 (42.8-46.8)	47.5 (45.3-49.6)	46.8 (44.6-48.9)	24.0 (22.1-26.0)
	1,336	1,216	1,074	985	936	443
Clerical (bottom)	49.7 (48.0-51.4)	40.5 (38.7-42.3)	36.6 (34.7-38.5)	31.3 (29.4-33.4)	31.2 (29.2-33.2)	69.6 (67.4-71.6)
	1,696	1,117	877	650	624	1,286
Physical activity[e] (%)						
Inactive	25.7 (24.3-27.3)	35.6 (33.8-37.5)	11.2 (9.9-12.7)	12.4 (11.0-13.9)	31.7 (29.7-33.8)	43.5 (41.3-45.8)
	856	919	222	245	613	787
Below guidelines	38.8 (37.1-40.4)	32.7 (30.9-34.5)	9.1 (8.0-10.5)	9.6 (8.4-11.0)	23.1 (21.3-25.1)	19.9 (18.1-21.8)
	1,289	844	181	190	447	360
Met guidelines	35.5 (33.9-37.1)	31.7 (29.9-33.5)	79.6 (77.8-81.4)	78.1 (76.2-79.8)	45.1 (42.9-47.4)	36.6 (34.4-38.8)
	1,180	817	1,576	1,548	872	661
Smoking (%)						
Never	53.2 (51.5-54.8)	51.2 (49.2-53.2)	54.1 (52.0-56.2)	53.8 (51.7-56.0)	53.6 (51.3-55.8)	52.3 (49.9-54.6)
	1,805	1,229	1,158	1,098	996	879
Former	23.4 (22.0-24.9)	30.9 (29.1-32.8)	32.7 (30.7-34.7)	36.1 (34.1-38.3)	40.3 (38.1-42.6)	43.0 (40.6-45.4)
	795	742	700	737	750	723
Current	23.4 (22.0-24.9)	17.9 (16.5-19.5)	13.2 (11.8-14.7)	10.0 (8.8-11.4)	6.1 (5.1-7.3)	4.8 (3.8-5.9)
	795	431	283	204	113	80

[a]Mean and 95% confidence interval; [b]Median and inter-quartile range; [c]Redundant, student, long-term sick, long-term carer; [d]e.g. black Caribbean, African and Arabic; [e]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (anyone not inactive or meeting guidelines)

6.6 Missing data

Evident in Table 6.2 were three sources of missing data: unit non-response, representing attrition by individuals who opted not to participate at all in a given wave; item non-response, characterised as individuals who participated but opted not to answer one or more questions in a given wave; and mortality.

Were data missing completely at random (MCAR), no systematic differences would exist between participants with and without missing values.[330] Under such a circumstance, missing data would be ignorable, with the only resultant limitation being a reduction in statistical power. In practice, however, data are rarely MCAR.[331]

The following sections explored whether individuals with missing data differed markedly from those that provided valid responses. If differences were present on characteristics associated with T2DM, missing data would be considered informative and non-ignorable due to its potential to introduce attrition or survivorship biases to any complete-case analyses of the alcohol-T2DM relationship.[332,333] For example, were individuals who opted not to answer certain questions found to have exhibited characteristics that placed them at greater risk of T2DM than those with complete covariate data, such as current smoking and physical inactivity, then complete-case analyses would have risked selecting a disproportionately healthy sub-sample and T2DM risk potentially underestimated as a consequence.

6.6.1 Mortality

Information concerning the mortality of study participants is available via linkage to the NHS Central Registry.[294] By wave 11, a total 13.3% (n=915) of men and 14.6% (n=499) of women were documented as having died (Table 6.2).

As with any other form of attrition, the death of participants risked producing results that were more optimistic than would otherwise be the case, with many of the risk factors for T2DM also being risk factors for mortality. If participants at high risk of T2DM had died prior to the development of the condition, the resulting dataset would have been biased, with the remaining cohort representing disproportionately healthy, low-risk participants relative to the original sample. To investigate the degree to participant characteristics differed according to mortality status, Table 6.3 summarises participant characteristics at wave one, stratified according to whether or not participants died during the course of the study.

Men and women who died were found to exhibit a higher proportion of negative risk factors for T2DM than those that survived, including older age and higher BMI, as well as lower levels of

physical activity and a higher prevalence of current smoking. Men who died were also more likely to be lighter, occasional drinkers than those that survived, though lower volumes of alcohol consumption and less frequent drinking may have been attributable to their poor health status at baseline. That participants lost to mortality appeared of poorer health and at greater risk of T2DM at baseline, it was possible that mortality produced a healthier analytical sub-sample in which T2DM risk was underestimated. In such an instance, mortality would be informative and represent a competing risk event, with death altering a participant's probability of experiencing T2DM.[334]

Unfortunately, no agreement was found concerning how best to deal with the informative effect of a competing risk such as mortality.[332] Approaches have included deriving an outcome measure that included both mortality and the primary outcome of interest,[335] or assigning those who died with the worst outcome value (e.g. coding all deceased individuals as having developed T2DM).[336] In each case, the modification of an outcome variable in such a manner rendered difficult the interpretation of results within the context of the primary relationship of interest.[337] With a lack of agreement over the most appropriate method, and existing methods potentially complicating any inferences concerning the alcohol-T2DM relationship, no attempt was made to account for the effect of mortality except to note that analyses potentially underestimated the risk of event.

Table 6.3 Descriptive summary of Whitehall II data at baseline, stratified by sex and survival

	Men			Women		
	Survived	Died	Difference[a]	Survived	Died	Difference[a]
Variables (wave 1)	% (95% CI) n	% (95% CI) n		% (95% CI) n	% (95% CI) n	
Age						
Mean years	44.0 (42.3-45.7)[b] 5,980	48.2 (46.5-49.8)[b] 915	<0.001	45.3 (43.5-47.0)[b] 2,914	48.8 (47.2-50.4)[b] 499	<0.001
Alcohol consumption frequency						
None in past year	2.9 (2.5-3.4) 173	5.2 (3.9-6.8) 47	<0.001	6.3 (5.4-7.2) 182	7.1 (5.1-9.7) 35	0.227
<1/week	19.8 (18.8-20.8) 1,181	24.9 (22.2-27.8) 226		38.9 (37.1-40.7) 1,131	43.1 (38.8-47.6) 214	
1-3 times/week	43.5 (42.3-44.8) 2,596	36.0 (32.9-39.2) 327		34.7 (33.0-36.5) 1,010	31.7 (27.7-35.9) 157	
Daily or almost daily	33.8 (32.6-35.0) 2,016	34.0 (31.0-37.1) 309		20.1 (18.7-21.6) 584	18.1 (15.0-21.8) 90	
Alcohol consumption volume						
Median g/week	63.2 (23.7-134.3)[c] 5,931	55.3 (15.8-150.1)[c] 909	0.040	23.7 (0.0-55.3)[c] 2,882	23.7 (0.0-55.3)[c] 492	0.167
BMI						
Mean kg/m^2	24.4 (23.3-25.6)[b] 5,971	25.4 (24.0-26.9)[b] 912	<0.001	24.6 (22.9-26.3)[b] 2,914	25.8 (23.9-27.7)[b] 497	<0.001
Ethnicity						
White	92.3 (91.6-92.9) 5,493	90.2 (88.1-92.0) 813	0.093	85.3 (84.0-86.6) 2,455	87.0 (83.6-89.7) 420	0.206
South Asian	5.1 (4.6-5.7) 305	6.8 (5.3-8.6) 61		6.9 (6.0-7.9) 199	4.8 (3.2-7.1) 23	
Other[d]	2.6 (2.2-3.1) 156	3.0 (2.1-4.3) 27		7.8 (6.9-8.8) 224	8.3 (6.1-11.1) 40	

Family history of T2DM						
No	89.9 (89.1-90.6)	87.3 (85.0-89.4)	0.021	86.3 (85.0-87.5)	83.8 (80.3-86.8)	
	5,298	780		2,465	409	0.142
Yes	10.1 (9.4-10.9)	12.7 (10.6-15.0)		13.7 (12.5-15.0)	16.2 (13.2-19.7)	
	596	113		391	79	
Incident diabetes from wave 3						
No	89.4 (88.5-90.2)	87.5 (84.6-90.0)	0.178	88.5 (87.1-89.7)	88.7 (84.4-91.8)	
	4,583	520		2,016	258	0.920
Yes	10.6 (9.8-11.5)	12.5 (10.0-15.4)		11.5 (10.3-12.9)	11.3 (8.2-15.6)	
	657	74		263	33	
Occupational grade						
Administrative (top)	12.7 (11.9-13.6)	12.3 (10.4-14.6)	0.016	5.0 (4.3-5.9)	3.6 (2.3-5.7)	<0.001
	760	113		146	18	
Professional (middle)	46.6 (45.4-47.9)	42.1 (38.9-45.3)		19.4 (18.0-20.8)	11.4 (8.9-14.5)	
	2,788	385		564	57	
Clerical (bottom)	40.7 (39.4-41.9)	45.6 (42.4-48.8)		75.6 (74.0-77.2)	85.0 (81.5-87.9)	
	2,432	417		2,204	424	
Physical activity[e]						
Inactive	9.0 (8.3-9.8)	12.1 (10.1-14.4)	0.001	24.4 (22.8-26.0)	33.6 (29.5-37.9)	<0.001
	536	109		692	164	
Below guidelines	36.9 (35.7-38.1)	39.7 (36.5-42.9)		39.5 (37.8-41.4)	34.2 (30.1-38.6)	
	2,186	358		1,122	167	
Met guidelines	54.0 (52.8-55.3)	48.2 (45.0-51.5)		36.1 (34.3-37.8)	32.2 (28.2-36.5)	
	3,201	435		1,023	157	
Smoking						
Never	49.3 (48.0-50.6)	37.4 (34.3-40.6)	<0.001	55.9 (54.1-57.7)	37.1 (33.0-41.5)	<0.001
	2,924	340		1,620	185	
Former	36.6 (35.4-37.8)	34.8 (31.7-37.9)		24.0 (22.4-25.5)	20.3 (17.0-24.1)	
	2,170	316		694	101	
Current	14.1 (13.3-15.0)	27.8 (25.0-30.8)		20.1 (18.7-21.6)	42.6 (38.3-47.0)	
	838	253		583	212	

The number of participants listed for each variable differed according to item non-response on each given variable at baseline.

[a]To explore differences between non-response groups, one-way ANOVA was used on continuous data, and the chi^2 test on categorical data (where continuous data exhibited a non-normal distribution, data were log-transformed prior to testing; [b]Mean and 95% confidence interval; [c]Median and inter-quartile range; [d]e.g. black Caribbean, African and Arabic; [e]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (not inactive or meeting guidelines).

6.6.2 Unit non-response

Some participant data were also missing due to unit non-response. Of participants who survived the course of the study, only 65.5% of male and 53.4% female baseline participants were found to have taken part at all waves (Table 6.4). Such a loss of data was likely to have a substantial impact upon statistical power and thereby inflate the risk of type 2 error in any complete-case analyses. To elucidate whether unit non-response may have introduced some degree of attrition bias, baseline characteristics of surviving participants were stratified according to the number of waves for which unit non-response was observed (Table 6.5).

Table 6.4 Proportion of surviving baseline participants with unit non-response

Number of waves with unit non-response	Men % n	Women % n
0	65.5 3,919	53.4 1,555
1	9.0 537	10.4 303
2	5.4 331	6.1 178
3	6.4 383	7.9 229
4	6.4 381	8.9 258
5	7.2 429	13.4 391

Figures excluded participants who died over the course of the study.

Differences in baseline characteristics are evident according to participants' degree of unit non-response. As shown in Table 6.5, those with greater levels of unit non-response were more likely to be from minority ethnic backgrounds, lower occupational grades, less physically active and have the greatest proportion of current smokers. Those with unit non-response across ≥4 waves were also found to have a lower volume and frequency of alcohol consumption, potentially due to poor health. In addition to a worse metabolic risk profile, participants with unit non-response had a lower incidence of T2DM, suggesting T2DM may have been underreported due to non-participation at clinical examinations. In summary, complete-case analyses may be subject to some degree of attrition bias, with any analytical sample skewed toward those with a more favourable risk profile.[338]

Table 6.5 Descriptive summary of Whitehall II data at baseline, stratified by sex and degree of unit non-response

	Unit non-response			
	0 waves	1-3 waves	≥4 waves	Difference[a]
Variables (wave 1)	% (95% CI) n	% (95% CI) n	% (95% CI) n	
Men				
Age				
Mean years	44.2 (44.0, 44.4)[b] 3,919	43.5 (43.2, 43.8)[b] 1,251	43.5 (43.1, 43.9)[b] 810	<0.001
Alcohol consumption frequency				
None in past year	2.2 (1.8, 2.7) 87	4.1 (3.1, 5.3) 51	4.3 (3.1, 6.0) 35	<0.001
<1/week	18.8 (17.6, 20.1) 736	19.1 (17.0, 21.4) 239	25.6 (22.7, 28.7) 206	
1-3 times/week	44.7 (43.1, 46.2) 1,747	42.5 (39.8, 45.3) 531	39.5 (36.1, 42.9) 318	
Daily or almost daily	34.3 (32.8, 35.8) 1,341	34.3 (31.7, 36.9) 428	30.6 (27.6, 33.9) 247	
Alcohol consumption volume				
Median g/week	63.2 (31.6, 134.3)[c] 3,891	71.1 (31.6, 150.1)[c] 1,239	47.4 (15.8, 126.4)[c] 801	<0.001
BMI				
Mean kg/m^2	24.3 (24.2, 24.4)[b] 3,912	24.8 (24.6, 24.9)[b] 1,250	24.6 (24.4, 24.8)[b] 809	<0.001
Ethnicity				
White	94.9 (94.1, 95.5) 3,716	89.1 (87.3, 90.8) 1,108	84.3 (81.5, 86.6) 669	<0.001
South Asian	3.7 (3.1, 4.3) 143	6.8 (5.6, 8.4) 85	9.7 (7.8, 12.0) 77	
Other[d]	1.5 (1.1, 1.9) 58	4.0 (3.1, 5.3) 50	6.0 (4.6, 7.9) 48	
Family history of T2DM				
No	9.9 (9.0, 10.9) 384	10.0 (8.4, 11.8) 123	11.2 (9.2, 13.6) 89	0.536
Yes	90.1 (89.1, 91.0) 3,485	90.0 (88.2, 91.6) 1,109	88.8 (86.4, 90.8) 704	
Occupational grade				
Administrative (top)	43.1 (41.6, 44.7) 1,689	31.7 (29.1, 34.3) 396	28.3 (25.3, 31.5) 229	<0.001
Professional (middle)	52.4 (50.8, 53.9) 2,052	55.3 (52.5, 58.1) 692	52.8 (49.4, 56.3) 428	
Clerical (bottom)	4.5 (3.9, 5.2) 178	13.0 (11.3, 15.0) 163	18.9 (16.3, 21.7) 153	
Physical activity[e]				
Inactive	7.6 (6.8, 8.5) 297	10.3 (8.7, 12.1) 126	14.1 (11.8, 16.7) 113	<0.001
Below guidelines	37.9 (36.4, 39.5) 1,476	33.9 (31.3, 36.6) 417	36.5 (33.3, 39.9) 293	
Met guidelines	54.4 (52.9, 56.0) 2,119	55.8 (53.0, 58.6) 686	49.4 (45.9, 52.8) 396	

Smoking				
Never	51.0 (49.4, 52.5) 1,983	45.9 (43.2, 48.7) 570	46.3 (42.9, 49.8) 371	<0.001
Former	37.0 (35.5, 38.5) 1,440	37.0 (34.3, 39.7) 459	33.8 (30.6, 37.2) 271	
Current	12.0 (11.0, 13.1) 467	17.1 (15.1, 19.3) 212	19.9 (17.2, 22.8) 159	
<u>Women</u>				
Age				
Mean years	44.6 (44.3, 44.9)[b] 1,555	45.9 (45.4, 46.3)[b] 710	46.2 (45.7, 46.6)[b] 649	<0.001
Alcohol consumption frequency				
None in past year	5.2 (4.2, 6.4) 80	7.6 (5.9, 9.8) 54	7.4 (5.6, 9.7) 48	<0.001
<1/week	35.2 (32.9, 37.7) 547	41.0 (37.4, 44.7) 290	45.4 (41.6, 49.2) 294	
1-3 times/week	36.9 (34.6, 39.4) 573	33.8 (30.4, 37.4) 239	30.6 (27.1, 34.2) 198	
Daily or almost daily	22.7 (20.7, 24.8) 352	17.5 (14.9, 20.5) 124	16.7 (14.0, 19.7) 108	
Alcohol consumption volume				
Median g/week	31.6 (7.9, 63.2)[c] 1,534	23.7 (0.0, 55.3)[c] 707	15.8 (0.0, 47.4)[c] 641	<0.001
BMI				
Mean kg/m^2	24.3 (24.1, 24.5)[b] 1,555	24.9 (24.6, 25.3)[b] 710	24.9 (24.6, 25.2)[b] 649	<0.001
Ethnicity				
White	88.8 (87.1, 90.3) 1,379	81.6 (78.6, 84.3) 573	80.7 (77.4, 83.7) 503	<0.001
South Asian	5.4 (4.4, 6.7) 84	8.3 (6.4, 10.5) 58	9.1 (7.1, 11.7) 57	
Other[d]	5.8 (4.7, 7.1) 90	10.1 (8.1, 12.6) 71	10.1 (8.0, 12.7) 63	
Family history of T2DM				
No	13.3 (11.7, 15.1) 203	13.3 (11.0, 16.0) 93	15.0 (12.4, 18.0) 95	0.539
Yes	86.7 (84.9, 88.3) 1,322	86.7 (84.0, 89.0) 606	85.0 (82.0, 87.6) 537	
Occupational grade				
Administrative (top)	16.7 (14.9, 18.6) 259	7.3 (5.6, 9.5) 52	5.4 (3.9, 7.4) 35	<0.001
Professional (middle)	46.9 (44.5, 49.4) 730	32.3 (28.9, 35.8) 229	31.7 (28.3, 35.4) 206	
Clerical (bottom)	36.4 (34.0, 38.8) 566	60.4 (56.8, 64.0) 429	62.9 (59.1, 66.5) 408	
Physical activity[e]				
Inactive	20.3 (18.3, 22.4) 310	28.5 (25.2, 32.0) 194	29.9 (26.5, 33.6) 188	<0.001
Below guidelines	42.5 (40.1, 45.0) 650	36.1 (32.6, 39.8) 246	36.0 (32.3, 39.8) 226	
Met guidelines	37.2 (34.8, 39.6) 568	35.4 (31.9, 39.1) 241	34.1 (30.5, 37.9) 214	

Smoking				
Never	59.4 (57.0, 61.9)	50.8 (47.1, 54.5)	53.1 (49.2, 56.9)	<0.001
	919	358	343	
Former	25.4 (23.2, 27.6)	24.5 (21.5, 27.9)	20.0 (17.1, 23.2)	
	392	173	129	
Current	15.2 (13.5, 17.1)	24.7 (21.6, 28.0)	26.9 (23.6, 30.5)	
	235	174	174	

Figures excluded participants who died over the course of the study. Figures included participants who had T2DM at waves 1-3. Number of participants listed under each variable differed according to the level of item non-response at baseline (wave one).

[a]To explore differences between non-response groups, one-way ANOVA was used on continuous data, and the chi^2 test on categorical data (where continuous data exhibited a non-normal distribution, data were log-transformed prior to testing; [b]Mean and 95% confidence interval; [c]Median and 25th and 75th percentiles; [d]e.g. black Caribbean, African and Arabic; [e]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (not inactive or meeting guidelines).

6.6.3 Item non-response

The third source of missing data within the Whitehall II cohort was among individuals who participated in a given wave but provided no answer to a specific question or provided no anthropometric measure or blood draw at clinical examination. Most *a priori* selected covariates were subject to some degree of item non-response, as summarised below in Table 6.6. Item non-response was greatest for the BMI variable at wave five, with measurements absent among 27.0% of male and 29.7% of female participants. This was understood to have been due to administrative problems at centres where clinical examinations were held. As a consequence, excess item non-response on BMI at this wave could be treated as MCAR.

In addition to a cumulative loss of 34.5% of male and 46.5% of female baseline participants through unit non-response in complete-case analyses (Table 6.4), analytic samples risked being attenuated even further by item non-response. To isolate differences in baseline characteristics according to item non-response, the dataset was restricted to the 5,474 individuals who participated at all waves, with descriptive statistics then reported for each variable as stratified according to whether complete-case data were provided at all waves (Table 6.7). Close to half of participants free of unit non-response provided complete-case data (n=2,673). Among both sexes, those with item non-response had a higher BMI and proportion of minority ethnic participants at baseline (wave one), as well as lower occupational grade, physical activity and average volume and frequency of alcohol consumption. As with unit non-response, the loss of data through item non-response appeared to represent a further source of attrition bias, with complete-case analyses inevitably sampling a subset of participants with a more favourable T2DM risk profile.

In order to reduce the impact of attrition bias upon any analyses, values missing due to unit or item non-response were estimated using multiple imputation. This process and its underlying assumptions are outlined in the following section.

Table 6.6 Degree of item non-response by wave, stratified by sex

	Wave 1	Wave 3	Wave 5	Wave 7	Wave 9	Wave 11
	%	%	%	%	%	%
Variables with item non-response	n	n	n	n	n	n
Men						
Alcohol consumption frequency	0.3	5.2	9.1	2.3	2.7	6.2
	20	317	498	113	127	278
Alcohol consumption volume	0.8	5.3	8.9	2.6	2.9	1.3
	55	323	489	123	135	58
BMI	0.2	7.7	27.0	6.6	7.0	9.4
	12	466	1,477	324	335	420
Employment status	-	0.0	0.6	0.4	0.2	0.0
		0	34	19	7	1
Ethnicity	0.6	0.3	0.0	0.1	0.2	0.1
	40	18	2	7	10	6
Family history of T2DM	1.6	1.4	1.5	1.5	1.3	1.2
	108	85	80	71	63	55
Incident diabetes from wave 3[a]	-	-	2.5	2.4	3.2	3.1
			134	115	148	135
Physical activity	1.0	5.2	15.0	2.7	1.7	1.4
	70	318	819	131	80	60
Smoking status	0.8	10.6	7.6	1.1	5.9	5.9
	54	642	416	53	279	261
Women						
Alcohol consumption frequency	0.3	6.5	13.2	3.7	4.8	11.7
	10	179	317	77	96	217
Alcohol consumption volume	1.1	6.2	12.3	4.1	4.8	1.2
	39	168	288	83	94	21
BMI	0.1	10.0	29.7	9.3	11.6	14.8
	2	275	712	1.3	233	273
Employment status	-	0.0	0.6	0.4	0.2	0.2
		0	14	9	4	3
Ethnicity	1.5	0.8	0.3	0.3	0.3	0.2
	52	22	7	6	6	4
Family history of T2DM	2.0	2.0	1.8	1.8	1.9	1.9
	69	54	43	38	37	35
Incident diabetes from wave 3[a]	-	-	3.1	2.8	3.9	3.8
			73	56	77	69
Physical activity	2.6	6.5	17.4	4.4	3.5	2.2
	88	178	418	91	70	41
Smoking status	0.5	12.9	10.7	1.7	7.1	9.0
	18	356	256	35	143	167

[a]Restricted to diabetes-free participants at wave 3

Table 6.7 Descriptive summary of Whitehall II data at baseline (wave one), stratified by sex and item non-response

	Item response		
	Complete	Incomplete	Difference[a]
Variables (wave 1)	**% (95% CI)** **n**	**% (95% CI)** **n**	
Men			
Age			
Mean years	44.1 (43.8, 44.3)[b] 1,976	44.3 (44.1, 44.6)[b] 1,943	0.163
Alcohol consumption frequency			
None in past year	0.8 (0.5, 1.3) 15	3.7 (3.0, 4.7) 72	<0.001
<1/week	19.0 (17.4, 20.8) 376	18.6 (16.9, 20.4) 360	
1-3 times/week	45.7 (43.6, 48.0) 904	43.6 (41.4, 45.8) 843	
Daily or almost daily	34.5 (32.4, 36.6) 681	34.1 (32.0, 36.3) 660	
Alcohol consumption			
Median g/week	71.1 (31.6, 142.2)[c] 1.976	63.2 (23.7, 126.4)[c] 1.915	<0.001
BMI			
Mean kg/m^2	24.2 (24.1,24.3)[b] 1.976	24.4 (24.2, 24.5)[b] 1.936	0.051
Ethnicity			
White	96.5 (95.6, 97.2) 1,907	93.2 (92.0, 94.2) 1,809	<0.001
South Asian	2.3 (1.7, 3.1) 46	5.0 (4.1, 6.1) 97	
Other[e]	1.2 (0.8, 1.7) 23	1.8 (1.3, 2.5) 35	
Family history of T2DM[d]			
No	91.1 (89.8, 92.3) 1,801	89.0 (87.5, 90.3) 1,684	0.023
Yes	8.9 (7.7, 10.2) 175	11.0 (9.7, 12.5) 209	
Incident diabetes from wave 3			
No	89.4 (87.9, 90.7) 1,766	88.2 (86.7, 89.6) 1,649	0.261
Yes	10.6 (9.3, 12.1) 210	11.8 (10.4, 13.3) 220	
Occupational grade			
Administrative (top)	43.3 (41.1, 45.5) 856	42.9 (40.7, 45.1) 833	0.006
Professional (middle)	53.2 (51.0, 55.4) 1,051	51.5 (49.3, 53.7) 1,001	
Clerical (bottom)	3.5 (2.8, 4.4) 69	5.6 (4.7, 6.7) 109	

Physical activity[e]			
Inactive	5.9 (4.9, 7.0)	9.4 (8.2, 10.8)	<0.001
	116	181	
Below guidelines	40.5 (38.4, 42.7)	35.2 (33.1, 37.4)	
	801	675	
Met guidelines	53.6 (51.4, 55.8)	55.3 (53.1, 57.5)	
	1,059	1,060	
Smoking			
Never	50.1 (47.8, 52.3)	51.9 (49.7, 54.2)	0.085
	989	994	
Former	38.6 (36.5, 40.8)	35.4 (33.3, 37.5)	
	763	677	
Current	11.3 (10.0, 12.8)	12.7 (11.3, 14.3)	
	224	243	
<u>Women</u>			
Age			
Mean years	43.7 (43.3, 44.1)[b]	45.3 (44.9, 45.7)[b]	<0.001
	697	858	
Alcohol consumption frequency			
None in past year	2.6 (1.6, 4.1)	7.3 (5.7, 9.2)	<0.001
	18	62	
<1/week	32.1 (28.8, 35.7)	37.8 (34.6, 41.1)	
	224	323	
1-3 times/week	38.5 (34.9, 42.1)	35.7 (32.5, 39.0)	
	305	305	
Daily or almost daily	26.8 (23.7, 30.3)	19.3 (16.8, 22.1)	
	165	165	
Alcohol consumption			
Median g/week	31.6 (7.9, 71.1)[c]	23.7 (0.0, 55.3)[c]	<0.001
	697	837	
BMI			
Mean kg/m^2	23.9 (23.6, 24.2)[b]	24.7 (24.4, 25.0)[b]	<0.001
	697	858	
Ethnicity			
White	92.8 (90.7, 94.5)	85.5 (83.0, 87.7)	<0.001
	647	732	
South Asian	2.4 (1.5, 3.9)	7.8 (6.2, 9.8)	
	17	67	
Other[e]	4.7 (3.4, 6.6)	6.7 (5.2, 8.5)	
	33	57	
Family history of T2DM[d]			
No	87.9 (85.3, 90.2)	85.6 (83.1, 87.9)	0.184
	613	709	
Yes	12.1 (9.8, 14.7)	14.4 (12.1, 16.9)	
	84	119	
Incident diabetes from wave 3			
No	90.4 (88.0, 92.4)	85.3 (82.8, 87.6)	0.003
	630	710	
Yes	9.6 (7.6, 12.0)	14.7 (12.4, 17.2)	
	67	122	

Occupational grade			
Administrative (top)	20.5 (17.7, 23.7)	13.5 (11.4, 16.0)	<0.001
	143	116	
Professional (middle)	51.4 (47.6, 55.1)	43.4 (40.1, 46.7)	
	358	372	
Clerical (bottom)	28.1 (24.9, 31.6)	43.1 (39.8, 46.5)	
	196	370	
Physical activity[e]			
Inactive	17.8 (15.1, 20.8)	22.4 (19.7, 25.3)	0.007
	124	186	
Below guidelines	46.6 (42.9, 50.4)	39.1 (35.8, 42.5)	
	325	325	
Met guidelines	35.6 (32.1, 39.2)	38.5 (35.3, 41.9)	
	248	320	
Smoking			
Never	58.2 (54.5, 61.9)	60.4 (57.1, 63.7)	0.222
	406	513	
Former	27.4 (24.2, 30.8)	23.7 (20.9, 26.7)	
	191	201	
Current	14.3 (11.9, 17.2)	15.9 (13.6, 18.5)	
	100	135	

Data were restricted to individuals who participated at all waves. Sample sizes differed according to item non-response at baseline (wave one).

[a]To explore differences between non-response groups, one-way ANOVA was used on continuous data, and the chi ^{2} test on categorical data (where continuous data exhibited a non-normal distribution, data were log-transformed prior to testing; [b]Mean and 95% confidence interval; [c]Median and 25th and 75th percentiles; [d]e.g. black Caribbean, African and Arabic; [e]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (not inactive or meeting guidelines).

6.6.4 Multiple imputation

Given the concomitant issues of reduced sample size and a potential introduction of attrition bias through unit and item non-response, the decision was made to try and populate any values deemed missing due to non-response.

A number of different imputation methods were available for handling missing data. One of the most basic was mean substitution, which would have replaced missing values with the observed variable mean. However, such an approach would have assumed that missing data were MCAR, such that the mean of the observed data provided a sound approximation of the missing values of a given variable, as in the case of excess item non-response on the BMI at wave five due to an administrative error, or a blood sample having been dropped at random in a laboratory. This assumption was not supported by the analyses undertaken in preceding sections. Additionally,

adding no new information to the dataset beyond what was already observed, mean substitution would have resulted in an underestimation of variance.[339] Alternative simple imputation methods, such as hot deck imputation and its replacement of missing data with an observed value selected at random from participants with similar characteristics, were each subject to the same two limitations.[339]

Among more complex methods, multiple imputation represented a popular and methodologically superior approach to those described above.[340] Unlike simple imputation methods, the most likely value of each missing data point was predicted multiple times via a series of iterative regression models, with each series of predictions forming its own datas*et al*ongside the observed data.[341] Values from each prediction were then averaged, and associated variances calculated according to two components: the standard variance present within each dataset, and the variance present between datasets. As a consequence, as well as adding new data as opposed to merely duplicating what has already been observed, variances following multiple imputation are larger and better reflect the uncertainty surrounding true values of the missing data. Given these benefits, multiple imputation was selected as the imputation method of choice.

6.6.4.1 Statistical analysis

Given the non-monotone nature of item non-response across waves (Table 6.2), as well as the presence of multiple variable types (e.g. categorical and continuous data), multiple imputation was undertaken using chained equations (MICE), which represented a method suited to handling such data characteristics.[342,343]

MICE offered a sequential approach to multiple imputation, whereby variables with missing data were imputed iteratively via a sequence of regression models that predicted missing data as conditional on all other observed variables.[342] For each variable missing data, the most appropriate regression model was utilised, including logistic regression models for binary data and multinomial logistic regression for non-ordered categorical variables. Given the difficulty with which linear regression models predict missing data on skewed continuous variables,[343] skewed data were log transformed prior to imputation, then converted back to their original scale post-imputation.

The imputation procedure began by populating all missing data with random values so as to permit the inclusion of missing data points within regression models. Then, starting with the variable for which the proportion of missing data was lowest (x_1), observed data on that variable

were regressed against all other covariates in the model (x_2,...,x_p). Missing values on x_1 were then replaced by data drawn from the predicted distribution of values missing on x_1, given x_2,...,x_p.[344] Once complete, the imputation procedure moved to the variable with the next lowest proportion of missing data (x_2). Observed values of x_2 were then regressed on all other covariates (x_1,x_3,…,x_p), with x_1 including all data predicted at the preceding stage.[344] This process continued iteratively until missing values had been imputed for all variables with missing data, representing one complete iteration of the imputation procedure.

At the start of a second iteration, missing data were populated with predictions from the previous iteration as opposed to random noise. The calculation of new iterations continued until the predicted values were consistent between iterations. In such a circumstance, any variation in predicted values between iterations appeared random and the data were said to have converged. At the point of convergence, predicted data were stored in a dataset as one complete imputation.[344]

In order to reliably capture the degree of uncertainty surrounding the predicted values, 50 imputations were run. This was in keeping with guidance which advises that the total number of imputed datasets should be equal to at least the total proportion of participants without complete-case data (see Tables 6.4 and 6.6).[344]

The imputation procedure was undertaken while data were stored in their wide format. This modelled each wave of a given variable as a separate covariate in each regression model, allowing for the modelling of missing data as a function of observations at all times that preceded and followed the wave of unit or item non-response. Data were imputed using Stata 13 and the -mi- package. The *augment* option was also applied to overcome any circumstances in which perfect prediction between variables may have occurred, adding random observations with very low weights to the included variables.

6.6.4.2 Diagnostics

Imputed estimates was examined to identify any incongruous values, such as negative alcohol consumption. Where any invalid values were identified, the imputation model was modified accordingly and re-run. In the case of average weekly volume of alcohol consumption, for example, this involved the use of a truncated regression model, which restricted the lower limit of predicted alcohol consumption to a value of zero.

Trace plots were then undertaken to check that predicted values of missing data had converged.[345] These plotted the mean predicted value of a variable at each iteration, indicating

visually whether any variation in values between iterations had become random such that additional iterations provided no further improvement to the predictions made. The optimal number of iterations recommended to reach convergence ranged from 10[344] to 20[346] depending upon the degree of correlation between variables. A total 20 iterations were initially run for each imputation, though convergence was not achieved on a minority of variables. The number of iterations was thus doubled to 40, which was found to be a sufficient number of iterations to reach convergence across all covariates. Examples of the resulting trace plots are reported in Appendix 6.2.

Once predictions had successfully converged and were deemed congruous, descriptive statistics were reported according to whether data were observed or imputed. Due to marked differences in participant characteristics according to the presence of missing data (Tables 6.5 and 6.7), the missingness process was considered informative and results thus documented according to both the imputed and observed datasets where possible within the limitations of Stata.

6.6.4.3 Variable selection

All variables identified *a priori* for use in any subsequent statistical analysis were included in the imputation model. These substantive variables thus comprised the frequency and total weekly volume of alcohol consumption plus an interaction term between these two dimensions, all confounding factors, and T2DM. Specifically, T2DM was represented by three variables: binary variable that denoted the number of new cases of T2DM captured at each wave of measurement, a continuous variable that represented the time to event, and the cumulative baseline hazard function. The inclusion of these outcome variables in the imputation model ensured that missing values on any independent variables each reflected the covariance that existed between observed covariate data and the risk of T2DM. Failure to include such variables risked biasing toward the null any associations subsequently calculated between covariates and T2DM risk when using imputed data.[347,348]

With missing values predicted conditional upon observed data, the multiple imputation model operated under the assumption that data were missing at random (MAR), i.e. that any systematic differences between participants with and without missing data could be entirely according to observed data included in the imputation model.[349] Accordingly, the plausibility of the MAR assumption and the performance of any imputation model was strengthened by an inclusive covariate selection strategy, including a broad range of auxiliary variables likely to covary with the variables upon which missing data were to be predicted.[342,350] A number of suitable auxiliary variables were theorised and are described in the section below.

Unfortunately, despite the inclusion of numerous auxiliary variables, it was possible that the MAR assumption may have been invalid; that some proportion of the systematic difference in participant characteristics evident between those with and without missing data (Tables 6.5 and 6.7) may have been a consequence of unobserved factors not included in the imputation model.[340,341] Nevertheless, in the case of both unit and item non-response, the MAR assumption was considered reasonable given the range of auxiliary variables considered.

6.6.4.3.1 Predictors of unit non-response

Although the reason for unit non-response was unknown, potential explanations were hypothesised to include instances were individuals were not solicited at all (e.g. due to inaccurate contact records) or participants who were solicited but unable to participate (e.g. due to physical or mental incapacity, or scheduling problems).

The first group was believed to represent a very small proportion of total unit non-response, given efforts by cohort administrators to maintain accurate contact information and actively trace those lost to postal contact.[294] Such individuals were assumed to be MCAR. Of those with unit non-response across just a couple of waves, attrition was most logically explained by scheduling problems such as work commitments or holidays, or the development of acute physical or mental incapacity sufficient to preclude participations. By contrast, of those with unit non-response across the majority of waves, attrition was most likely attributable to the development of chronic physical or mental incapacity that prevented participation over the long term.

In either case, it was thought possible to capture information concerning the probability of unit non-response through the inclusion of variables concerning mental and physical health prior to unit non-response, as well as factors likely to influence time available to participate. In the first instance, mental incapacity was included as an auxiliary variable via two variables. The first was the General Health Questionnaire (GHQ), a 30-item screening instrument administered at all waves and designed to capture self-reported symptoms of anxiety, depression and associated psychosocial dysfunction, with scores that ranged from 0 to 30.[351] Defined as any score greater than four,[352] the tool has been validated on Whitehall II data for the detection of mild psychiatric disorder.[352] Mild psychiatric disorder was thus included as a predictor of unit non-response by way of a binary GHQ variable. In addition to psychiatric morbidity, any unit non-response due to impaired mental cognition was captured via results from the Mini Mental State Examination (MMSE), a 30-point screening instrument for the quantitative assessment of global cognitive function.[353] The MMSE comprised a series of 11 questions concerning seven distinct cognitive

domains, including orientation to time, attention and recall, and has been validated as sensitive to the detection of moderate-to-severe cognitive impairment.[354] The MMSE was first introduced in wave 5 and applied only to persons aged ≥60 years. MMSE data were then available at all subsequent waves and delivered to all participants. In an effort to capture participants' physical health, participants' self-rated general health was also included, available at all waves and coded according to three categories: 'very good or excellent', 'good' and 'fair or poor'.

With regard to any unit non-response attributable to scheduling problems, the imputation model included data concerning the average number of hours worked in a week, as captured at wave three, as well as the amount of time participants reported being 'worn out' in the four weeks prior to each wave, defined as 'all of the time', 'most of the time', 'a good bit of the time', 'some of the time', 'a little of the time' or 'none of the time'. Regression models also included a variable that denoted whether family obligations reduced a participant's time available for relaxation. These data were documented at waves three, five and seven, with categories defined as 'not at all', 'to some extent', ' a great deal', or 'not applicable', e.g. no family obligations.

6.6.4.3.2 Predictors of item non-response

Alcohol consumption

Although alcohol consumption appeared lower at baseline (wave one) among those with item non-response at later waves (Table 6.7), it was possible that participants who opted not to disclose their consumption at later waves had experienced an alcohol use disorder.[355] Such individuals may not have disclosed their consumption behaviour out of shame or an inability to reliably recall volumes accurately due to inebriation. In case missing alcohol consumption data were associated with problematic levels of drinking, data from the CAGE questionnaire were included as a screening instrument for the detection of problem drinking,[356] which was found to correlate well with clinical diagnoses of alcoholism.[357] The CAGE questionnaire was first introduced in the Whitehall II study at wave 3 and comprises four questions concerning alcohol consumption behaviour and participants' perceptions thereof, such as whether they ever felt guilty about their drinking behaviour. Alcohol dependence was defined according to a score ≥2.[356]

With studies also having identified lower levels of alcohol intake among those in poor health,[144,145,146,141,358] self-rated general health was posited to provide a useful correlate of alcohol consumption. Alongside this, substantive ethnicity and socio-economic variables were thought to help explain any religious or genetic factors that might have influenced alcohol

consumption or the willingness of participants to report it,[359] as well as differences in alcohol consumption by socio-economic strata.[360]

BMI

Beyond substantive variables such as physical activity,[361] socio-economic factors,[362,363] and smoking,[361] potential correlates of BMI were thought to include: mild psychiatric disorder, as captured via the GHQ;[364] blood pressure;[365] plasma triglycerides and HDL;[366,367] and dietary factors identified during the literature review, including carbohydrate, polyunsaturated fat, trans fat and fibre.

Blood pressure readings were obtained at each clinical examination, averaged across two readings with continuous systolic and diastolic blood pressure variables documented in millimetres of mercury (mmHg).[368] Blood samples were also taken at each clinical examination, with triglyceride and HDL concentrations recorded in mmol/L.[369] Data concerning dietary factors were obtained via the FFQ, available at waves three, five and seven only.

It was possible that information on BMI was absent for some individuals due to hairstyles or clothing that would have rendered invalid any attempt to measure height or weight. Missing data in such cases were assumed to be MCAR, or else partially correlated with ethnicity, such as being unable to accurately measure height owing to religious headdresses.

Employment status

It was hypothesised that the probability of retirement would have been correlated with age, while the probability of exiting the labour market for reasons other than retirement was posited to be associated with indicators of mental health and self-reported general health.[370]

Ethnicity

Item non-response on the ethnicity variable was low (Table 6.6). However, given notable ethnic inequalities in labour participation in the UK,[371,372] it was hypothesised that any missing ethnicity data could be predicted through a partial correlation with variables that denoted employment status and occupational grade.

Family history of T2DM

Item non-response on this variable was also low, absent for just 1.6% of male and 2.0% of female baseline participants (Table 6.6). It was hypothesised that these data may have been missing because participants simply did not know whether there was a history of T2DM in the family. Such data were thus assumed to be MCAR.

Incidence of T2DM

Possible randomly distributed reasons for not having an objective indicator of T2DM diagnosis were posited to include refusal to have bloods taken, inability by the clinic nurse to obtain a suitable blood sample or poor adherence to the necessary protocol (e.g. had not fasted). Conversely, the lack of a subjective self-reported measure might have been attributable to the inability of a participant to recall whether or not T2DM had been reported by a doctor, or a lack of time with which to attend the clinic or complete all necessary measurements upon attendance. Missing values of T2DM were thus predicted according to indicators of availability and cognition, as described previously, as well as key risk factors for the disease, including age, BMI, ethnicity and both serum triglyceride and HDL concentration.

Physical activity

BMI was considered a key correlate of physical activity level, along with other clinical markers such as serum HDL and triglycerides.[373] Aside from such factors, studies indicate that, among employed individuals, time spent in leisure-time physical activity may be determined by factors that influence the amount of free time available to undertake such activity.[374] These factors were included as auxiliary predictors of physical activity, as described for unit non-response. Further correlates were thought to include socio-economic factors and self-rated general health, with different types and amounts of leisure-time physical activity undertaken across social strata.[375,376,377]

Smoking

As was likely with both BMI and physical activity, it was posited that item non-response may been greater among those participants who perceived their smoking behaviour to be less socially desirable. Given the clustering of negative health behaviours,[78,378] it was postulated that alcohol consumption, physical activity and BMI would all correlate with smoking, as well as clinical measures such as blood pressure[379] and serum HDL concentration.[380]

6.6.4.4 Results

6.6.4.4.1 Convergence

Trace plots indicated good convergence across all variables of interest, with between-iteration variation in predicted values appearing stable at the point of draw following 40 iterations. These data are reported in Appendix 6.2 and indicated that further iterations would have provided no improvement to the predicted values, with any variation between imputations having been a consequence of random error.

6.6.4.4.2 Summary of imputed data

Wave-specific characteristics of participants within the imputed dataset are reported below in Table 6.8, with observed cohort data reported in Table 6.2. After accounting for unit and item non-response, participants within the imputed dataset reported higher levels of average weekly volume consumption, particularly among women, suggesting that many may not have reported their consumption due to perceived social undesirability. The imputed data also predicted higher levels of BMI among women, relative to the observed dataset, suggesting that women may have systematically declined such a measurement for similar reasons. A higher proportion of imputed individuals were employed, relative to those that were observed, suggesting that many who did not participate may have done so due to scheduling problems and time constraints. Both sexes with missing data were also more likely to have been of minority ethnic origin, lower occupational grade and current smokers. Additionally, while not shown in Tables 6.2 and 6.8, the proportion of participants who reported being of very good or good general health was highest among those who were observed, with any discrepancies between the two datasets largest in later waves. For instance, of those who participated in wave 11, 48.0% of men and 44.2% of women reported being in good or very good general health. By contrast, within the imputed dataset, equivalent figures were just 40.4% and 34.8% respectively. Systematic differences between the observed (Table 6.2) and imputed data (Table 6.8) confirm that missing data were unlikely to have been MCAR, with complete-case analyses subject to attrition bias and the selection of a healthier sub-sample of participants.

6.7 Statistical power

Of the 3,413 women who participated at baseline, just 2,094 (61.4%) were free of prevalent T2DM at wave three and provided complete-case data concerning alcohol consumption, the confounding factors outlined in Section 6.5, and incident T2DM. Among these, only 247 incident cases were documented. There is therefore a possibility that statistical power may be insufficient to detect relatively small dose-response or interaction effects among women.[381]

To establish the power of any subsequent survival model to detect a difference in survivor functions for a one-unit change in consumption among women, the -stpower- package was used.[381] This assumed a conventional alpha level of 0.05, a sample of 2,094 participants, and survival in the reference group equal to the average observed among all female participants (88.2%). The power to detect a 20% reduction in hazards per unit increase in consumption was estimated at just 0.39, indicating a 61% probability of type II error. Based upon the graph in Figure 6.3, a sample of ~5,900 women would be required to reach a conventional power

threshold of 0.80. These calculations thus indicate that low statistical power may present a particular limitation for dose-response analyses of female Whitehall II participants.

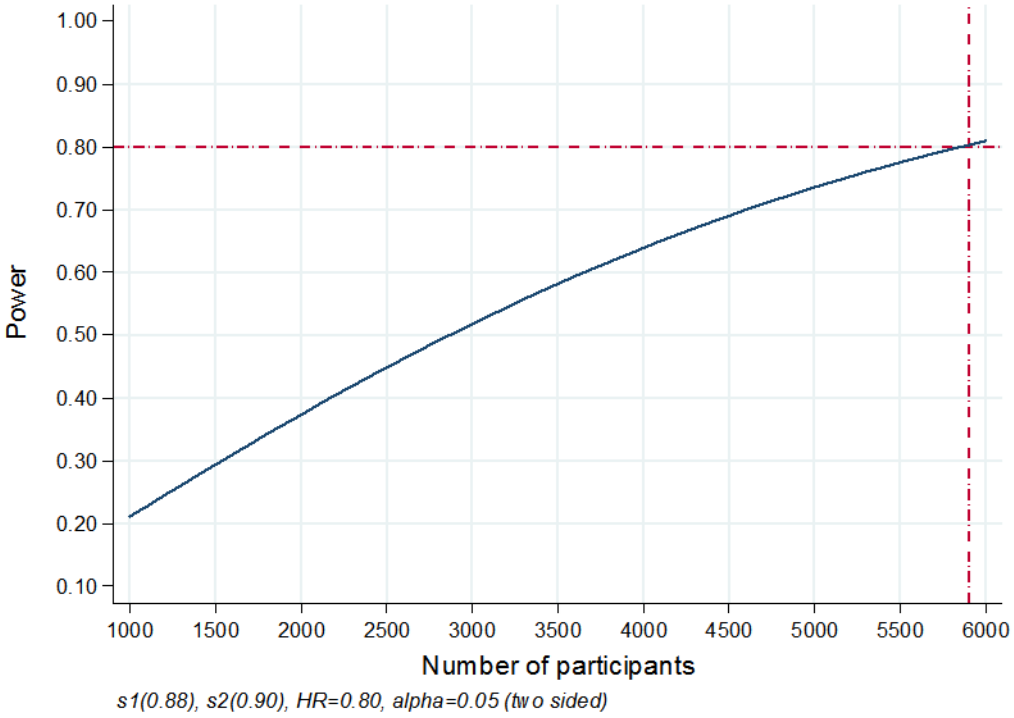


Figure 6.3 Power versus sample size for a log-rank test of differences in survivor functions

6.8 Summary of the dataset

Although numerous longitudinal cohorts are available, Whitehall II offers a number of benefits relevant to the study of longitudinal consumption trajectories and associations with T2DM. Perhaps of foremost importance, the cohort includes multiple waves of follow-up data for alcohol consumption and a wide range of potential confounders. The regular frequency of these follow-up data is such that acute fluctuations in health behaviours are more likely to be captured, increasing the accuracy of plotted trajectories and attempts to model risk with consideration to changes in participant characteristics across 50 years of the adult life course. Finally, the availability of an objective measure of T2DM reduces the potential for under-estimating the incidence of T2DM relative to the use of self-reported data.

However, with a predominantly male sample, statistical power is likely to be low for analyses of women. Additionally, as with any cohort, a number of participants were lost to follow-up or failed to answer all questions included in self-completion questionnaires, with complete-case data available for just 65.5% of men and 53.4% of women (Table 6.4). Systematic differences in baseline characteristics are apparent according to the presence of unit or item non-response, with observed participants having reported a lower metabolic risk profile at the beginning of the

study than those with missing data. Complete-case analyses thus risked being subject to selection bias, sampling a healthier sub-set of the source population in a manner that may impact the validity of any dose-response relationship estimated. Although missing data have been imputed using chained equations and a broad range of ancillary variables, the use of imputed data within analytical models is currently limited. As noted in forthcoming chapters, these limitations included variability in the predicted values of stratification variables between imputations and an inability to use imputed event data within survival models. These restrictions were such that little difference is reported between results based on the observed and imputed datasets. In addition to restrictions concerning the range of statistical tests that can be applied to imputation models, including goodness-of-fit statistics, it was decided to report results based upon the observed data as the primary analyses, with results obtained from the imputed dataset reported in the appendices.

Table 6.8 Descriptive summary of imputed Whitehall II data, stratified by wave and sex

	Wave of study					
Imputed variables	**1**	**3**	**5**	**7**	**9**	**11**
	% (95% CI)	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**
Men	**n=6,895**	**n=6,814**	**n=6,691**	**n=6,506**	**n=6,274**	**n=5,980**
Age						
Years	44.5 (44.4-44.7)[a]	49.8 (49.7-50.0)[a]	55.5 (55.4-55.6)[a]	60.9 (60.8-61.1)[a]	65.8 (65.6-65.9)[a]	69.6 (69.5-69.8)[a]
Alcohol cons. frequency						
None in past year	3.2 (2.8-3.6)	3.3 (2.9-3.8)	3.1 (2.7-3.6)	3.3 (2.8-3.8)	4.1 (3.6-4.7)	2.7 (2.2-3.1)
<1/week	20.4 (19.5-21.4)	15.9 (14.9-16.8)	12.3 (11.4-13.1)	12.4 (11.5-13.3)	12.6 (11.7-13.6)	27.1 (25.6-28.5)
1-3 times/week	42.5 (41.3-43.6)	37.2 (36.0-38.5)	31.7 (30.4-33.0)	28.6 (27.3-29.9)	28.7 (27.4-30.0)	26.6 (25.1-28.0)
Daily or almost daily	33.9 (32.8-35.0)	43.6 (42.3-44.8)	52.9 (51.4-54.4)	55.8 (54.4-57.2)	54.6 (53.0-56.1)	43.7 (41.9-45.5)
Alcohol cons. volume						
g/week	63.2 (23.7-135.2)[b]	63.2 (23.7-138.7)[b]	94.8 (39.5-181.4)[b]	82.8 (37.5-158.0)[b]	71.1 (31.6-134.1)[b]	65.9 (27.0-126.8)[b]
BMI						
kg/m^2	24.6 (24.5-24.6)[a]	25.2 (25.1-25.3)[a]	26.1 (26.0-26.2)[a]	26.6 (26.5-26.7)[a]	26.6 (26.5-26.8)[a]	26.6 (26.4-26.7)[a]
Employment status						
Employed	100.0	90.1 (89.4-90.9)	67.1 (65.9-68.4)	53.0 (51.6-54.4)	32.8 (31.3-34.2)	19.3 (18.0-20.5)
Retired	-	7.5 (6.8-8.2)	25.9 (24.8-27.1)	41.2 (39.8-42.5)	62.8 (61.4-64.3)	77.6 (76.2-79.0)
Other[c]	-	2.4 (1.9-2.8)	6.9 (6.2-7.7)	5.8 (5.1-6.6)	4.4 (3.6-5.2)	3.1 (2.5-3.7)
Ethnicity						
White	92.0 (91.4-92.6)	92.0 (91.4-92.7)	92.1 (91.4-92.7)	92.2 (91.5-92.8)	92.1 (91.5-92.8)	92.3 (91.6-92.9)
South Asian	5.3 (4.8-5.9)	5.3 (4.8-5.8)	5.2 (4.7-5.7)	5.1 (4.6-5.6)	5.2 (4.6-5.7)	5.1 (4.6-5.7)
Other[d]	2.7 (2.3-3.1)	2.7 (2.3-3.1)	2.7 (2.3-3.1)	2.7 (2.3-3.1)	2.7 (2.3-3.1)	2.6 (2.2-3.0)

Family history of T2DM						
Yes	10.5 (9.7-11.2)	10.5 (9.8-11.2)	10.4 (9.6-11.1)	10.3 (9.6-11.1)	10.2 (9.5-11.0)	10.1 (9.4-10.9)
No	89.5 (88.8-90.3)	89.5 (88.8-90.2)	89.6 (88.9-90.4)	89.7 (88.9-90.4)	89.8 (89.0-90.5)	89.9 (89.1-90.6)
Occupational grade						
Administrative (top)	38.4 (37.2-39.5)	46.0 (44.9-47.2)	48.0 (46.8-49.2)	49.3 (48.1-50.5)	49.8 (48.5-51.0)	12.7 (11.9-13.6)
Professional (middle)	52.3 (51.1-53.5)	45.7 (44.5-46.9)	43.9 (42.7-45.1)	43.0 (41.8-44.2)	42.4 (41.2-43.6)	46.6 (45.4-47.9)
Clerical (bottom)	9.3 (8.6-10.0)	8.2 (7.6-8.9)	8.1 (7.4-8.8)	7.7 (7.0-8.3)	7.8 (7.2-8.5)	40.7 (39.4-41.9)
Physical activity[c]						
Inactive	9.7 (9.0-10.4)	15.1 (14.1-16.0)	4.8 (4.1-5.4)	7.5 (6.4-8.5)	26.0 (24.5-27.5)	18.9 (17.9-19.9)
Below guidelines	37.2 (36.1-38.3)	36.1 (34.8-37.3)	5.8 (5.1-6.5)	8.5 (7.6-9.3)	18.9 (17.8-20.1)	14.7 (13.8-15.6)
Met guidelines	53.1 (51.9-54.3)	48.9 (47.6-50.2)	89.5 (88.5-90.4)	84.0 (82.6-85.4)	55.1 (53.3-56.8)	66.4 (65.2-67.6)
Smoking						
Never	47.8 (46.6-49.0)	46.3 (45.1-47.6)	45.4 (44.1-46.6)	44.1 (42.8-45.4)	44.2 (42.6-45.9)	44.3 (42.7-45.9)
Former	36.3 (35.1-37.4)	39.7 (38.5-41.0)	43.6 (42.2-44.9)	46.4 (45.0-47.8)	48.3 (46.7-49.8)	51.0 (49.4-52.6)
Current	15.9 (15.1-16.8)	13.9 (13.0-14.8)	11.0 (10.1-11.9)	9.5 (8.6-10.4)	7.5 (6.6-8.4)	4.7 (3.8-5.7)
	% (95% CI)	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**
Women	**n=3,413**	**n=3,369**	**n=3,311**	**n=3,218**	**n=3,080**	**n=2,914**
Age						
Years	45.7 (45.5-45.9)[a]	51.1 (50.9-51.3)[a]	56.8 (56.5-57.0)[a]	62.1 (61.9-62.3)[a]	67.0 (66.8-67.3)[a]	70.9 (70.6-71.1)[a]
Alcohol cons. frequency						
None in past year	6.4 (5.6-7.2)	6.6 (5.7-7.5)	6.6 (5.5-7.6)	7.5 (6.5-8.6)	9.6 (8.4-10.8)	7.2 (6.1-8.3)
<1/week	39.5 (37.9-41.1)	32.2 (30.5-33.9)	25.4 (23.6-27.1)	27.5 (25.6-29.4)	26.6 (24.6-28.6)	44.8 (42.2-47.4)
1-3 times/week	34.3 (32.7-35.9)	35.5 (33.7-37.2)	32.5 (30.5-34.4)	30.0 (27.8-32.2)	30.4 (28.4-32.3)	23.4 (21.6-25.2)
Daily or almost daily	19.9 (18.5-21.2)	25.7 (24.1-27.3)	35.6 (33.5-37.7)	35.0 (32.7-37.2)	33.4 (31.3-35.5)	24.6 (22.4-26.8)
Alcohol cons. volume						
g/week	23.7 (0.0-55.3)[b]	23.7 (6.3-61.5)[b]	39.4 (13.3-83.8)[b]	34.4 (11.2-78.8)[b]	28.5 (7.9-63.0)[b]	26.6 (5.5-61.5)[b]

BMI						
kg/m^2	24.8 (24.6-24.9)[a]	25.9 (25.7-26.0)[a]	26.8 (26.6-27.0)[a]	27.4 (27.2-27.6)[a]	27.5 (27.2-27.7)[a]	27.3 (27.0-27.5)[a]
Employment status						
Employed	100.0	89.5 (88.3-90.6)	54.3 (52.2-56.3)	38.3 (36.2-40.4)	21.0 (19.1-22.8)	11.4 (9.9-12.9)
Retired	-	5.5 (4.7-6.4)	33.5 (31.6-35.4)	52.7 (50.6-54.9)	72.8 (70.8-74.8)	85.5 (83.7-87.2)
Other[c]	-	5.0 (4.1-5.9)	12.2 (10.9-13.6)	8.9 (7.5-10.4)	6.2 (4.9-7.6)	3.1 (2.1-4.1)
Ethnicity						
White	85.5 (84.3-86.7)	85.4 (84.2-86.6)	85.3 (84.1-86.5)	85.2 (84.0-86.5)	85.2 (83.9-86.5)	85.3 (84.0-86.6)
South Asian	6.6 (5.7-7.4)	6.6 (5.8-7.5)	6.7 (5.9-7.6)	6.8 (5.9-7.7)	6.8 (5.9-7.7)	6.9 (6.0-7.8)
Other[d]	7.9 (7.0-8.8)	7.9 (7.0-8.9)	8.0 (7.1-8.9)	7.9 (7.0-8.9)	8.0 (7.1-9.0)	7.8 (6.8-8.8)
Family history of T2DM						
Yes	14.1 (12.9-15.2)	14.1 (12.9-15.3)	14.2 (13.0-15.4)	14.2 (13.0-15.4)	14.0 (12.7-15.2)	13.7 (12.4-15.0)
No	85.9 (84.8-87.1)	85.9 (84.7-87.1)	85.8 (84.6-87.0)	85.8 (84.6-87.0)	86.0 (84.8-87.3)	86.3 (85.0-87.6)
Occupational grade						
Administrative (top)	11.2 (10.1-12.3)	13.8 (12.6-14.9)	15.3 (14.1-16.6)	16.5 (15.2-17.8)	17.1 (15.8-18.4)	5.0 (4.2-5.8)
Professional (middle)	39.1 (37.5-40.8)	42.1 (40.4-43.8)	42.0 (40.3-43.6)	42.5 (40.8-44.2)	42.3 (40.5-44.0)	19.4 (17.9-20.8)
Clerical (bottom)	49.7 (48.0-51.4)	44.1 (42.5-45.8)	42.7 (41.0-44.4)	41.0 (39.3-42.7)	40.6 (38.9-42.4)	75.6 (74.1-77.2)
Physical activity[e]						
Inactive	26.3 (24.8-27.8)	36.4 (34.5-38.2)	13.3 (11.6-14.9)	16.2 (13.8-18.6)	35.0 (32.7-37.3)	35.3 (33.5-37.0)
Below guidelines	38.2 (36.6-39.9)	33.5 (31.7-35.4)	10.2 (8.7-11.6)	11.4 (10.0-12.8)	22.5 (20.7-24.2)	19.3 (17.9-20.8)
Met guidelines	35.5 (33.9-37.1)	30.1 (28.4-31.9)	76.6 (74.5-78.7)	72.4 (69.8-75.1)	42.5 (40.0-45.0)	45.4 (43.6-47.2)
Smoking						
Never	53.2 (51.5-54.9)	51.6 (49.9-53.3)	51.2 (49.4-53.0)	50.7 (48.8-52.6)	52.9 (50.7-55.2)	53.4 (51.1-55.6)
Former	23.4 (22.0-24.8)	28.7 (27.0-30.3)	33.1 (31.2-34.9)	36.3 (34.4-38.2)	39.2 (37.0-41.5)	40.4 (38.1-42.6)
Current	23.4 (22.0-24.8)	19.8 (18.3-21.2)	15.8 (14.2-17.3)	13.0 (11.5-14.5)	7.9 (6.4-9.3)	6.2 (4.8-7.7)

Wave-specific figures excluded participants who died.
No event data were reported as imputed dependent variables could not be used in any statistical model.
[a]Mean and 95% confidence interval; [b]Median and inter-quartile range; [c]Redundant, student, long-term sick, long-term carer; [d]e.g. black Caribbean, African and Arabic; [e]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (anyone not inactive or meeting guidelines).

Chapter 7

A preliminary conventional survival analysis

7 A preliminary conventional survival analysis

7.1 Introduction

Given changes to drinking behaviour across the life course as evidenced by multiple cohort studies,[266] it is possible that conventional survival models that define intake according to a single baseline measure may have been simplistic in their approach and subject to misclassification error through a failure to consider the effect of variations in alcohol consumption over time.

Prior to exploring such shortcomings in more detail, this chapter reports preliminary analyses undertaken to confirm the suitability of the Whitehall II dataset for such an analysis. Specifically, results are reported from a series of conventional survival models in order to establish whether observed dose-response relationships within the Whitehall II cohort were consistent with those identified in the revised meta-analysis. Although a conventional survival analysis of T2DM risk has previously been published using Whitehall II data, pooled heterogeneous non-drinking categories were used with adjustment only for age and ethnicity.[241]

Unlike the majority of existing studies, the conventional survival model reported in this chapter will also jointly examine two dimensions of alcohol consumption to ascertain whether drinking frequency represent an additional independent determinant of T2DM risk alongside the volume of consumption. The chapter will also explore the dose-response relationship between different drink types, given evidence discussed in Chapter 3 indicating the possibility of effect modification.

7.2 Objective

The objectives of the chapter were thus to:

- Undertake a conventional survival analysis, reporting the dose-response relationship between baseline categories of average weekly volume of alcohol consumption and T2DM risk.
- Investigate whether any interaction existed between the average volume of alcohol intake and the frequency of consumption.
- Establish whether independent dose-response relationships exist between drink type and T2DM risk.
- Compare results against those summarised as part of the revised meta-analysis in Chapter 3.

7.3 Hypotheses

Given that aetiological associations identified within Whitehall II are accordant with those found in general population cohorts,[296] it was hypothesised that results from conventional survival analyses applied to Whitehall II data would be broadly similar to those reported in Chapter 3. Specifically, that:

- Reductions in T2DM risk will be greatest among women who consumed alcohol at moderate volumes;
- Any elevated risks will be most pronounced among former drinkers and those that reported a low frequency of alcohol intake.
- After accounting for consumption of other drink types, reductions in risk will be most pronounced among wine drinkers.

7.4 Methods

7.4.1 Sample

The sample was restricted to T2DM-free individuals who participated at baseline plus at least one other wave from which longitudinal time-to-event data could be determined. The baseline was defined as wave three, the first wave at which cases of T2DM were identified via both subjective and objective measures.

7.4.2 Variables

7.4.2.1 Alcohol consumption

With wave three representing the first period at which data were sufficient for the demarcation of never and former drinkers, participants were defined according to categories of alcohol consumption reported at wave three.

Using the volume and frequency variables described in Section 6.3, abstainers were categorised as either never drinkers or non-current drinkers. Never drinkers were defined as those who reported never having consumed alcohol over the year preceding participation at wave three and as being 'always a non-drinker'. To provide a stricter definition of never drinkers, this category excluded any participant who reported 'always being a non-drinker' at wave three y*et al*so reported non-zero consumption at wave one (n=47), leaving a total 106 men and 111 women categorised as never drinkers. Non-current drinkers were thus defined as those who reported no alcohol consumption in the year preceding participation at wave three, and who reported not having always been a non-drinker. This category also included the 47 participants

who described themselves as never drinkers at wave three but reported non-zero consumption at wave one. The non-current drinkers were considered roughly analogous to a former drinking category and totalled 103 men and 78 women.

Current drinkers were defined according to their reported total volume of alcohol intake in the week preceding baseline. Male current drinkers were categorised as having consumed 0.1-50.0 g/week (n=1,692), 50.1-100.0 g/week (n=1,163), 100.0-150.0 g/week (n=725) or >150.0 g/week (n=1,316). For women, among whom the volume of alcohol consumption was lower, current drinkers were defined as having drunk 0.1-50.0 g/week (n=1,081), 50.1-100.0 g/week (n=387) or >100.0 g/week (n=323). Intervals of 50 g/week were chosen to strike a balance between being narrow enough to detect differences in T2DM risk across relatively small changes in the volume of alcohol consumption, and being broad enough to each capture an ample number of cases. Additionally, the use of regular intervals permitted a direct comparison of dose-response between men and women.

Alongside current drinkers, a separate group of 'infrequent drinkers' was defined, which represented participants who reported having consumed alcohol in the year preceding interview, but that did not drink alcohol in the week prior to measurement. The category of infrequent drinkers thus excluded participants who reported consuming alcohol at some point in the year prior to interview, but did not provide an answer to the questions concerning consumption in the last week; such individuals may have consumed alcohol in the last week, but missing data were such that this could not be determined. In total, 628 men and 597 women were classified as infrequent drinkers, among whom close to 85% reported drinking alcohol less than once a week, monthly or only on special occasions.

To test for an interaction between average weekly volume and the frequency with which alcohol was consumed over the week, a consumption pattern variable was defined according to whether or not participants reported 'daily or almost daily' alcohol consumption at wave three. This binary variable was chosen for consistency with previous studies that reported reductions in risk as greatest among participants that regularly consumed moderate volumes of alcohol throughout the week.[95,97,240,244]

Finally, continuous variables denoting the weekly volume of consumption of different drink types were derived based on responses to questions concerning the number of "measures" of spirits, "glasses" of wine, or "pints" of beer or cider consumed. A glass of wine and a measure of

spirits were each assumed to contain one unit of alcohol (7.9 g), with two units of alcohol (15.8 g) in and a pint of beer or cider.

7.4.2.2 T2DM

As documented in Section 6.4, cases of T2DM were defined according to any self-reported doctor diagnosis or use of hypoglycaemic medication, or a positive FPG result following clinical examination. Analyses focussed upon incident cases of T2DM and so therefore excluded any cases prevalent at baseline.

As the number of participants predicted to have developed T2DM over the course of the study varied between imputations, analyses applied to the imputed dataset were restricted to participants with observed T2DM diagnosis data such that the number of participants remained static between imputations.[342]

7.4.2.3 Covariates

All covariates selected *a priori* were included in multivariable-adjusted models, operationalised as described in Section 6.5. Included covariates were age, BMI, ethnicity, employment status, family history of T2DM, occupational grade, physical activity, and smoking status. As with alcohol consumption, all covariates were defined at baseline, with the exception of ethnicity for which data were obtained from waves one and five.

7.4.3 Statistical analyses

7.4.3.1 Data synthesis

7.4.3.1.1 Cumulative hazard functions

Where cumulative hazard functions were reported, these were calculated using the Nelson-Aalen estimator, which plotted the cumulative hazard as a function of the number of participants at risk and the number of events observed at each point in time. Differences in cumulative hazard functions were tested using the log-rank test of equality.

7.4.3.1.2 Categorical dose-response

In keeping with methods applied by conventional analyses, Cox proportional hazards models were used to investigate the relationship between categories of alcohol consumption and T2DM risk. At its most simple, the Cox survival model is expressed according to Formula 7.1.[382]

$$h_i(t)=h_0(t)\exp\{\beta x_i\}$$

Formula 7.1 Calculation of a Cox proportional hazard model

Here, the hazard of T2DM was calculated as a function of the baseline hazard of the sample at a given point in time ($h_0(t)$), which represented the hazard for a participant when all covariates were equal to zero, plus the effect of substantive covariate values (x_i) and their corresponding coefficients (β).

Results were reported separately for men and women based on apparent sex-specific differences in dose-response reported by the revised meta-analysis (Chapter 3). For each sex, age-adjusted and multivariable-adjusted dose-response relationships were described. Although few in number, never drinkers were selected as the reference group of choice for consistency with analyses undertaken as part of the revised and updated meta-analysis reported in Chapter 3, permitting a direct comparison of dose-response.

7.4.3.1.3 Frequency interaction

To investigate whether the effect of weekly volume of alcohol consumption differed according to the frequency of intake, a multiplicative interaction between the weekly volume of alcohol consumption and drinking frequency was included in the model. A categorical drinking variable denoting graduated volumes of intake was not used as part of the interaction analyses due to the small number of participants and cases when categories were divided according to values of the frequency variable. Instead, the weekly volume of alcohol consumption was modelled as a continuous variable, with a binary frequency variable denoting whether or not participants consumed alcohol on a daily or almost daily basis.

Non-current and infrequent drinkers were excluded from the interaction analysis so that relationships were calculated relative to never drinkers, consistent with preceding models. However, a sensitivity analysis was also run to examine the effect of their inclusion in a multivariable-adjusted interaction model.

Hazards were reported per 10 g/week increase in consumption and robust Huber-White standard errors were utilised for the calculation of confidence intervals due to the positive skewness of the continuous alcohol consumption variable.[383,384,385] These standard errors are robust to the heteroscedasticity of residuals when modelling skewed variables, and thereby account for the underestimation of variance that can occur in its presence.

Models that incorporated a continuous measure of alcohol intake assumed a linear dose-response relationship with T2DM incidence in conflict with the J-shaped associations previously observed. Accordingly, the possibility of a non-linear relationship was explored by raising the continuous measure of average volume of alcohol consumption according to a range of

fractional powers, as per the method described in Section 3.2.4.1. The fit of the non-linear dose-response models was then compared against the original linear model.

7.4.3.1.4 Drink type

To establish the association between different drink types and the risk of T2DM, the weekly volume of alcohol consumption from wine, spirits and beer or cider were each included concurrently within a multivariable-adjusted model as separate continuous variables. Consumption of each drink type was not categorised in an effort to avoid small sub-group sample size and low precision – a limitation inherent to a number of existing studies to have explored the effect of drink type upon T2DM risk.[97,219,245] No adjustment was made for total consumption to avoid overadjustment in instances where participants only consumed a single type of drink at baseline.

As described above, these models assumed a linear relationship between drink type and T2DM risk. Accordingly, the volume of each drink type was raised to a series of fractional powers as described in Section 3.2.4.1. Results from the best-fitting models were reported.

7.4.3.2 Goodness of fit

To determine which models best fit the underlying data, the Bayesian information criterion (BIC) was calculated in each instance. Developed as a tool to aid model selection, the BIC was calculated as follows:[386]

$$BIC=(-2*\ln(\ell))+(\ln(n_T))(n_p)$$

Formula 7.2 Calculation of the Bayesian information criterion

Here, ℓ refers to the likelihood function, or the probability of having reached the calculated effect estimates given the included parameters. As per the deviance statistic described in Section 3.2.4.1, a perfectly specified model would report a value of zero. The log of the total number of observations (or in the case of nested data, the effective sample size) was expressed as n_T, while n_p denoted the total number of included parameters. Unlike the likelihood function, which always improves when new parameters are introduced, the BIC includes a penalty to models of greater complexity due to their reduced parsimony and increased risk of overfitting, risking coefficients having modelled random error specific to the Whitehall II dataset and thereby reducing the generalisability of findings to other samples.

Likelihood and thereby BIC statistics could not be reported for analyses of imputed data, as the final estimates were not drawn from a single model but from identical models applied to

multiple different datasets.[342] At the time of writing, there was no clear solution to the derivation of summary fit statistics for analyses of imputed data.[387] Though one group of researchers proposed a method by which likelihood statistics could be averaged across imputations,[388] the package was not compatible with the latest -mi- commands and applicable only to a restricted range of regression models (i.e. linear, logistic and ordered logistic).[389] Simpler alternative recommendations included documenting the individual fit statistics for one, a sub-sample or all constituent imputation models.[387] Due to the time costs involved in calculating and storing 50 fit statistics for each statistical model, the mean and range of log-likelihood and BIC statistics are reported in each case according to just the first three imputations.

7.4.3.3 Proportionality assumption

Standard survival models operate under an assumption of proportional hazards: that relative differences in hazards between categories of volume of alcohol consumption are proportionate over time compared to the hazard of the reference group, such that the relative hazard of T2DM for a given category is approximately equal at all time points and thus suitable for reporting according to a single hazard ratio. This assumption was tested in each sex-specific multivariable-adjusted model through the inclusion of an interaction between categories of weekly alcohol consumption and a linear expression of time. Any violations of proportionality are reported.

7.4.3.4 Statistical package

Analyses of observed data were undertaken using the -st- package of commands available in Stata 13,[390] while results from analyses of imputed data were reported using the -mi- suite.[342] As Stata 13 did not permit the use of imputed diagnosis data due to differences in the predicted number of cases and duration of follow-up between imputations, analyses of both observed and imputed datasets were both restricted to participants with observed T2DM diagnosis data only. Similarly, due to the small number of never and non-current drinkers, it was not possible to derive imputed alcohol consumption categories at wave three; no imputation model would converge even when the number covariates against which never drinking was predicted were drastically reduced. Accordingly, imputed analyses reported in this chapter accounted only for attrition due to missing covariate data.

7.5 Results

7.5.1 Descriptive statistics

A total 5,456 men and 2,434 women provided valid alcohol consumption and T2DM data, with a median 20.2 and 20.0 years of follow-up respectively. Of those with valid alcohol consumption and T2DM diagnosis data, a total 589 incident cases of T2DM were documented among men and 279 cases among women, or 10.8% and 11.5% of the sample. In multivariable-adjusted analyses, complete-case data were available for 4,869 men and 2,094 women, among whom 527 and 247 cases of T2DM were documented. Women appeared to develop T2DM at a slightly faster rate over time (p=0.078, Appendix 7.1).

Notable differences in metabolic risk profile were evident at baseline between those that did and did not develop T2DM (Table 7.1). Consistent with findings from the literature review reported in Section 2.1.3, those who developed T2DM over the course of the study tended to be older, had higher values of BMI, were more likely to have been of Asian ethnicity, have a family history of T2DM, poorer self-reported general health, lower physical activity or be of lower occupational grade. The same differences were evident within the imputed dataset (Appendix 7.2).

Differences in crude cumulative hazards were present across categories of weekly volume of alcohol consumption, particularly among women (men: p=0.090; women: p=<0.001). Male non-current and never drinkers exhibited the greatest incidence of T2DM over the course of the study, with cumulative hazards roughly equivalent among current and infrequent drinkers (Appendix 7.3). By contrast, while female current drinkers also had a lower overall incidence of T2DM than non-current and never drinkers, cumulative hazards were greatest among those defined as infrequent drinkers (Appendix 7.3). For both men and women, the cumulative hazards were greatest among those who reported no consumption or a frequency of less than one occasion a week over the year preceding baseline interview (Appendix 7.4).

As might be expected given their higher incidence of T2DM, non-current and never drinkers exhibited a worse metabolic risk profile at baseline than current drinkers, with male and female abstainers having poorer self-reported general health, lower physical activity, a lower occupational grade, a greater proportion of South Asian participants and a higher prevalence of family history of T2DM than current drinking categories (Table 7.2). Similarly, differences in the baseline characteristics of current drinkers and infrequent drinkers were most pronounced among women. Specifically, female infrequent drinkers tended to be older, have a higher BMI,

lower occupational grade, lower physical activity, poorer self-reported general health, and a greater proportion of South Asian participants and individuals who were out of work for reasons such as long-term illness. In all cases, imputed descriptive data were comparable (Appendix 7.5).

Table 7.1 Baseline characteristics of participants free of T2DM at wave three and with valid follow-up data, stratified by sex. Observed data.

	Men			Women		
	T2DM	Censored	Difference[a]	T2DM	Censored	Difference[a]
Variables (wave 3)	**% (95% CI)**	**% (95% CI)**		**% (95% CI)**	**% (95% CI)**	
	n	**n**		**n**	**n**	
Age						
Mean years	50.4 (49.9-50.9)[b]	49.8 (49.6-49.9)[b]	0.017	52.1 (51.3-52.8)[b]	50.7 (50.5-51.0)[b]	<0.001
	620	5.103		296	2.274	
Alcohol consumption frequency						
None in past year	5.1 (3.6-7.2)	3.2 (2.7-3.7)	0.005	10.0 (7.0-14.1)	6.6 (5.6-7.7)	<0.001
	30	155		28	142	
<1/week	19.8 (16.8-23.3)	16.7 (15.6-17.7)		51.8 (45.9-57.6)	33.1 (31.1-35.1)	
	117	812		145	713	
1-3 times/week	34.7 (31.0-38.7)	40.2 (38.8-41.6)		25.7 (20.9-31.2)	36.4 (34.4-38.5)	
	205	1,959		72	785	
Daily or almost daily	40.3 (36.4-44.4)	40.0 (38.6-41.3)		12.5 (9.1-16.9)	23.9 (22.2-25.8)	
	238	1,947		35	516	
Alcohol consumption volume						
Never drinkers[c]	2.9 (1.8-4.6)	1.5 (1.2-1.9)	0.183	5.4 (3.2-8.7)	4.0 (3.2-4.9)	<0.001
	17	75		15	86	
Non-current drinkers[d]	2.2 (1.3-3.8)	1.6 (1.3-2.0)		4.6 (2.7-7.9)	2.6 (2.0-3.4)	
	13	80		13	56	
Infrequent drinkers[e]	10.3 (8.1-13.1)	11.1 (10.2-12.0)		37.1 (31.6-43.0)	20.9 (19.2-22.6)	
	61	540		104	450	
0.1-50.0g/week	27.6 (24.2-31.4)	29.6 (28.4-30.9)		38.9 (33.4-44.8)	42.7 (40.6-44.8)	
	163	1,445		109	920	
50.1-100.0g/week	19.5 (16.5-22.9)	20.5 (19.4-21.7)		8.6 (5.8-12.5)	16.0 (14.6-17.7)	
	115	1,000		24	346	
100.1-150.0g/week	12.7 (10.3-15.7)	12.9 (12.0-13.8)		5.4 (3.2-8.7)	13.9 (12.5-15.4)	
	75	627		15	299	
>150.0g/week[f]	24.7 (21.4-28.4)	22.7 (21.6-23.9)		-	-	
	146	1,107				

BMI						
Mean kg/m^2	26.9 (26.6-27.2)[b]	24.9 (24.8-25.0)[b]	<0.001	29.5 (28.8-30.2)[b]	25.1 (24.9-25.3)[b]	<0.001
	620	4,729		280	2,053	
Employment status						
Employed	90.8 (88.3-92.8)	90.9 (90.1-91.7)	0.033	88.5 (84.3-91.7)	90.7 (89.4-91.8)	0.213
	563	4,641		262	2,062	
Retired	6.3 (4.6-8.5)	7.5 (6.8-8.2)		5.4 (3.3-8.7)	5.4 (4.6-6.4)	
	39	382		16	123	
Other[g]	2.9 (1.8-4.6)	1.6 (1.3-1.9)		6.1 (3.9-9.5)	3.9 (3.2-4.8)	
	18	80		18	89	
Ethnicity						
White	84.8 (81.8-87.5)	94.6 (93.9-95.2)	<0.001	71.2 (65.7-76.1)	89.1 (87.7-90.3)	<0.001
	526	4,815		210	2,012	
South Asian	11.8 (9.5-14.6)	3.4 (3.0-4.0)		14.6 (11.0-19.1)	4.6 (3.8-5.5)	
	73	175		43	103	
Other	3.4 (2.2-5.1)	2.0 (1.6-2.4)		14.2 (10.7-18.7)	6.4 (5.4-7.5)	
	21	101		42	144	
Family history of T2DM						
No	81.1 (77.8-84.1)	91.2 (90.4-91.9)	<0.001	68.8 (63.1-73.9)	89.2 (87.8-90.4)	<0.001
	495	4,589		198	1,989	
Yes	18.9 (15.9-22.2)	8.8 (8.1-9.6)		31.3 (26.1-36.9)	10.8 (9.6-12.2)	
	115	444		90	242	
Occupational class						
Administrative (top)	42.4 (38.6-46.4)	49.9 (48.5-51.3)	<0.001	5.4 (3.3-8.7)	17.5 (16.0-19.1)	<0.001
	263	2,546		16	398	
Professional (middle)	48.5 (44.6-52.5)	44.3 (43.0-45.7)		42.2 (36.7-48.0)	45.9 (43.8-47.9)	
	301	2,263		125	1,043	
Clerical (bottom)	9.0 (7.0-11.6)	5.8 (5.2-6.4)		52.4 (46.6-58.0)	36.6 (34.7-38.6)	
	56	294		155	833	

Physical activity[h]						
Inactive	17.1 (14.3-20.4) 101	13.4 (12.5-14.4) 655	0.050	41.8 (36.1-47.7) 117	33.9 (32.0-36.0) 732	0.006
Below guidelines	35.6 (31.8-39.6) 210	36.8 (35.4-38.1) 1,791		33.9 (28.6-39.7) 95	33.2 (31.2-35.2) 716	
Met guidelines	47.3 (43.3-51.3) 279	49.8 (48.4-51.2) 2,426		24.3 (19.6-29.7) 68	32.9 (30.9-34.9) 709	
Self-reported general health						
Very good/Excellent	40.5 (36.6-44.5) 239	53.7 (52.3-55.1) 2,616	<0.001	31.1 (25.9-36.8) 87	43.5 (41.4-45.6) 937	<0.001
Good	45.1 (41.1-49.1) 266	37.9 (36.6-39.3) 1,848		44.6 (38.9-50.5) 125	42.8 (40.7-44.9) 922	
Fair/Poor	14.4 (11.8-17.5) 85	8.3 (7.6-9.1) 406		24.3 (19.6-29.7) 68	13.7 (12.3-15.3) 296	
Smoking						
Never	38.5 (34.5-42.6) 215	46.1 (44.6-47.5) 2,123	<0.001	54.0 (47.9-60.0) 141	51.1 (48.9-53.3) 1,029	0.645
Former	42.2 (38.2-46.4) 236	41.9 (40.5-43.3) 1,929		28.7 (23.5-34.6) 75	31.2 (29.2-33.3) 629	
Current	19.3 (16.2-22.8) 108	12.0 (11.1-13.0) 555		17.2 (13.1-22.4) 45	17.7 (16.1-19.4) 356	

[a]To explore differences between groups, one-way ANOVA was used on continuous data, and the chi [2] test on categorical data (where continuous data exhibited a non-normal distribution, data were log-transformed prior to testing; [b]Mean and 95% confidence interval; [c]Those who reported no consumption in the past week in waves 1 and 3, no consumption in the past year in waves 1 and 3, and stated they had 'always been a non-drinker'; [d]No consumption in the last week or in the last year; [e]Consumed alcohol in the past year but not in the past week; [f]Among women, this category was merged with those who reported consuming 100.0-150.0g/week; [g]Redundant, student, long-term sick, long-term carer; [h]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (anyone not inactive or meeting guidelines).

Table 7.2 Baseline characteristics of participants free of T2DM at wave three and with valid follow-up data, stratified by sex and categories of average weekly volume of alcohol consumption. Observed data.

	Alcohol consumption category				
	Current	Infrequent	Non-current	Never	Difference[a]
Variables (wave 3)	**% (95% CI)** **n**	**% (95% CI)** **n**	**% (95% CI)** **n**	**% (95% CI)** **n**	
Men					
Age					
Mean years	49.7 (49.5-49.9)[b] 4,678	50.2 (49.7-50.7)[b] 601	50.6 (49.4-51.9)[b] 92	50.1 (48.8-51.4)[b] 93	0.096
BMI					
Mean kg/m^2	25.1 (25.1-25.2)[b] 4,480	24.7 (24.4-24.9)[b] 568	25.0 (24.3-25.7)[b] 88	24.2 (23.5-24.9)[b] 88	<0.001
Employment status					
Employed	90.8 (89.9-91.6) 4,248	87.9 (85.0-90.2) 528	91.3 (83.4-95.6) 84	91.4 (83.5-95.7) 85	0.020
Retired	7.5 (6.8-8.3) 353	9.8 (7.7-12.5) 59	6.5 (2.9-14.0) 6	3.2 (1.0-9.7) 3	
Other[c]	1.6 (1.3-2.1) 77	2.3 (1.4-3.9) 14	2.2 (0.5-8.5) 2	5.4 (2.2-12.5) 5	
Ethnicity					
White	95.0 (94.3-95.6) 4,436	90.3 (87.7-92.4) 541	53.3 (42.9-63.4) 49	84.9 (76.0-91.0) 79	<0.001
South Asian	3.3 (2.8-3.8) 152	5.3 (3.8-7.5) 32	38.0 (28.6-48.5) 35	15.1 (9.0-24.0) 14	
Other	1.8 (1.4-2.2) 82	4.3 (3.0-6.3) 26	8.7 (4.4-16.6) 8	-	

Family history of T2DM					
No	90.5 (89.6-91.3)	88.9 (86.0-91.2)	80.0 (70.3-87.1)	89.2 (81.0-94.2)	0.006
	4,175	526	72	83	
Yes	9.5 (8.7-10.4)	11.1 (8.8-14.0)	20.0 (12.9-29.7)	10.8 (5.8-19.0)	
	438	61	18	10	
Incident T2DM					
No	89.3 (88.4-90.2)	89.9 (87.2-92.0)	81.5 (72.1-88.3)	86.0 (77.2-91.8)	<0.001
	4,179	540	75	80	
Yes	10.7 (9.8-11.6)	10.1 (8.0-12.8)	18.5 (11.7-27.9)	14.0 (8.2-22.8)	
	499	61	17	13	
Occupational class					
Administrative (top)	52.2 (50.8-53.7)	31.3 (27.7-35.1)	27.2 (18.9-37.3)	35.5 (26.3-45.9)	<0.001
	2,444	188	25	33	
Professional (middle)	43.0 (41.6-44.4)	56.9 (52.9-60.8)	52.2 (41.8-62.3)	49.5 (39.3-59.7)	
	2,012	342	48	46	
Clerical (bottom)	4.7 (4.2-5.4)	11.8 (9.5-14.7)	20.7 (13.5-30.3)	15.1 (9.0-24.0)	
	222	71	19	14	
Physical activity[d]					
Inactive	12.5 (11.6-13.5)	22.2 (19.0-25.7)	18.5 (11.7-27.9)	22.8 (15.3-32.7)	<0.001
	585	133	17	21	
Below guidelines	36.6 (35.2-38.0)	36.2 (32.4-40.1)	42.4 (32.6-52.9)	35.9 (26.6-46.3)	
	1,712	217	39	33	
Met guidelines	50.9 (49.5-52.3)	41.7 (37.8-45.7)	39.1 (29.6-49.6)	41.3 (31.6-51.8)	
	2,381	250	36	38	
Self-reported general health					
Very good/Excellent	53.1 (51.7-54.5)	46.7 (42.8-50.8)	56.5 (46.1-66.4)	43.5 (33.6-53.9)	<0.001
	2,483	280	52	40	
Good	38.9 (37.5-40.3)	38.4 (34.6-42.4)	31.5 (22.7-41.9)	37.0 (27.6-47.4)	
	1,821	230	29	34	
Fair/Poor	8.0 (7.2-8.8)	14.9 (12.2-17.9)	12.0 (6.7-20.5)	19.6 (12.6-29.1)	
	373	89	11	18	

Smoking					
Never	44.1 (42.6-45.5) 1,952	49.6 (45.5-53.8) 280	77.1 (66.6-85.0) 64	46.7 (36.5-57.2) 42	<0.001
Former	43.4 (41.9-44.8) 1,920	35.3 (31.4-39.3) 199	13.3 (7.4-22.6) 11	38.9 (29.2-49.5) 35	
Current	12.6 (11.6-13.6) 557	15.1 (12.3-18.3) 85	9.6 (4.8-18.3) 8	14.4 (8.5-23.5) 13	
Women					
Age					
Mean years	50.3 (50.0-50.6)[b] 1,713	52.0 (51.5-52.5)[b] 554	50.8 (49.5-52.0)[b] 101	50.7 (49.2-52.1)[b] 69	<0.001
BMI					
Mean kg/m^2	25.2 (25.0-25.4)[b] 1,613	26.7 (26.2-27.1)[b] 523	26.2 (25.1-27.3)[b] 95	27.5 (25.9-28.8)[b] 63	<0.001
Employment status					
Employed	91.2 (89.8-92.5) 1,563	86.3 (83.1-88.9) 478	91.1 (83.6-95.4) 92	84.1 (73.1-91.1) 58	0.021
Retired	5.7 (4.7-6.9) 98	6.0 (4.3-8.3) 33	4.0 (1.5-10.2) 4	5.8 (2.1-14.8) 4	
Other[c]	3.0 (2.3-4.0) 52	7.8 (5.8-10.3) 43	5.0 (2.0-11.5) 5	10.1 (4.8-20.1) 7	
Ethnicity					
White	92.3 (90.9-93.4) 1,573	82.2 (78.7-85.2) 452	42.0 (32.6-52.0) 42	59.4 (47.2-70.6) 41	<0.001
South Asian	2.3 (1.7-3.1) 39	7.8 (5.8-10.4) 43	41.0 (31.7-51.0) 41	20.3 (12.2-31.7) 14	
Other	5.5 (4.5-6.6) 93	10.0 (7.8-12.8) 55	17.0 (10.8-25.8) 17	20.3 (12.2-31.7) 14	

Family history of T2DM					
No	87.5 (85.8-89.0)	85.9 (82.7-88.6)	83.2 (74.4-89.4)	83.8 (72.8-90.9)	0.425
	1,468	468	84	57	
Yes	12.5 (11.0-14.2)	14.1 (11.4-17.3)	16.8 (10.6-25.6)	16.2 (9.1-27.2)	
	210	77	17	11	
Incident T2DM					
No	91.4 (89.9-92.6)	81.2 (77.7-84.3)	85.1 (76.6-90.9)	81.2 (69.9-88.9)	
	1,565	450	86	56	<0.001
Yes	8.6 (7.4-10.1)	18.8 (15.7-22.3)	14.9 (9.1-23.4)	18.8 (11.1-30.1)	
	148	104	15	13	
Occupational class					
Administrative (top)	21.0 (19.1-23.0)	5.2 (3.7-7.4)	5.0 (2.0-11.5)	5.8 (2.1-14.8)	<0.001
	359	29	5	4	
Professional (middle)	49.2 (46.8-51.6)	42.1 (38.0-46.2)	24.8 (17.2-34.3)	31.9 (21.8-44.0)	
	843	233	25	22	
Clerical (bottom)	29.8 (27.7-32.0)	52.7 (48.5-56.8)	70.3 (60.5-78.5)	62.3 (50.1-73.2)	
	511	292	71	43	
Physical activity[d]					
Inactive	29.9 (27.8-32.2)	45.5 (41.4-49.7)	51.5 (41.6-61.2)	46.4 (34.7-58.4)	<0.001
	513	252	52	32	
Below guidelines	35.9 (33.7-38.2)	26.7 (23.2-30.6)	25.7 (18.0-35.3)	31.9 (21.8-44.0)	
	615	148	26	22	
Met guidelines	34.2 (31.9-36.4)	27.8 (24.2-31.7)	22.8 (15.5-32.1)	21.7 (13.4-33.3)	
	585	154	23	15	
Self-reported general health					
Very good/Excellent	46.1 (43.8-48.5)	35.8 (31.9-39.9)	21.8 (14.7-31.1)	20.3 (12.2-31.7)	
	790	198	22	14	<0.001
Good	42.1 (39.7-44.4)	44.5 (40.4-48.7)	54.5 (44.5-64.0)	37.7 (26.8-49.9)	
	720	246	55	26	
Fair/Poor	11.8 (10.4-13.4)	19.7 (16.6-23.2)	23.8 (16.4-33.2)	42.0 (30.8-54.2)	
	202	109	24	29	

Smoking					
Never	48.2 (45.7-50.6) 776	53.2 (48.9-57.5) 272	87.9 (79.3-93.3) 80	67.7 (54.8-78.4) 42	<0.001
Former	34.1 (31.9-36.5) 550	26.8 (23.1-30.8) 137	4.4 (1.6-11.3) 4	21.0 (12.4-33.2) 13	
Current	17.7 (15.9-19.6) 285	20.0 (16.7-23.7) 102	7.7 (3.7-15.5) 7	11.3 (5.4-22.2) 7	

Table excluded consumption frequency owing to colinearity with consumption volume.

[a]To explore differences between groups, one-way ANOVA was used on continuous data, and the chi ^{2} test on categorical data (where continuous data exhibited a non-normal distribution, data were log-transformed prior to testing; [b]Mean and 95% confidence interval; [c]Redundant, student, long-term sick, long-term carer; [d]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (anyone not inactive or meeting guidelines).

7.5.2 Age-adjusted models

Although sex-specific differences in dose-response were evident from the meta-analysis reported in Chapter 3, the presence of such a disparity within Whitehall II was formally tested via an interaction was between sex and categories of baseline alcohol consumption. Following a likelihood ratio test of age-adjusted models with and without a sex interaction, the interaction term was found to provide a statistically significant improvement in fit (p=<0.001). This was consistent with results from the earlier meta-analysis and supported the case for the stratification of results by sex.

In age-adjusted analyses, male and female current drinkers showed significantly reduced risks of T2DM, relative to never drinkers (Table 7.3). Among men, risks were of a generally consistent magnitude across categories of current drinkers, at around a 41-50% reduction. Conversely, among women, an inverse dose-response relationship was apparent. Here, risks appeared to decline with each categorical increase in consumption, with a hazard ratio lowest among women who consumed >150.0 g/week (HR 0.28, 95% CI 0.14-0.58).

7.5.3 Multivariable-adjusted models

Adjustment for confounders improved the fit of both models and resulted in substantial attenuations to reductions in risk among current drinkers, with all estimates rendered statistically non-significant (Table 7.3). Among men, the largest reductions in risk were visible among those who reported consuming 0.1-50.0 g/week (HR 0.92, 95% CI 0.53-1.61). Above these volumes, risks were higher than the null except for among the heaviest drinkers (>150.0 g/week), for whom an insubstantial and likely artefactual 1% reduction in risk was observed (HR 0.99, 95% CI 0.56-1.79). For women, the risk of T2DM remained lowest in the highest drinking category, though attenuated from a 73% to a 45% reduction in risk relative to never drinkers (HR 0.55, 95% CI 0.24-1.24).

While not statistically significant, non-current drinkers showed a greater risk than never drinkers among both sexes (men: HR 1.38, 95% CI 0.65-2.94; women: HR 1.07, 95% CI 0.48-2.40). Further, while the risk of T2DM was marginally lower among male infrequent drinkers (HR 0.95, 95% CI 0.52-1.73), female infrequent drinkers showed an elevated risk (HR 1.44, 95% CI 0.79-2.62). Results from analyses that utilised imputed covariate data showed similar findings, though smaller reductions in risk were evident among female current drinkers (Appendix 7.6).

A sizeable change in dose-response was evident according to whether risks were adjusted only for age or all *a priori* risk factors concurrently. To identify the covariates most responsible for

the changes observed, a post-hoc analysis was undertaken for which groups of covariates were added in a mutually exclusive fashion: age only; age plus ethnic and genetic factors (ethnicity and family history of T2DM); age plus adiposity (BMI); age plus other lifestyle factors (physical activity and smoking status); and age plus socio-economic factors (employment status and occupational grade). For consistency between models, the post-hoc analysis was restricted to the multivariable-adjusted sample in Table 7.3. Among both sexes, the greatest improvement in fit is evident following adjustment for BMI and age, relative to age only, while coefficients vary markedly between models (Table 7.4).

Table 7.3 Age and multivariable-adjusted dose-response relationship between categories of average weekly volume of alcohol consumption and T2DM, stratified by sex. Observed data.

	Age adjusted			Multivariable adjusted		
Alcohol consumption (wave 3)	**Cases/non-cases**	**HR (95% CI)**	**p-value**	**Cases/non-cases**	**HR (95% CI)**	**p-value**
Men						
Never drinkers[a]	17/75	(reference)		15/64	(reference)	
Non-current drinkers[b]	13/80	0.77 (0.38-1.55)	0.486	13/72	1.37 (0.64-2.93)	0.412
Infrequent drinkers[c]	60/533	0.53 (0.31-0.95)	0.022	51/467	0.95 (0.52-1.73)	0.870
0.1-50.0g/week	163/1,445	0.50 (0.30-0.85)	0.006	143/1,296	0.92 (0.53-1.61)	0.769
50.1-100.0g/week	115/1,000	0.50 (0.30-0.85)	0.008	105/880	1.02 (0.58-1.81)	0.944
100.1-150.0g/week	75/627	0.52 (0.31-0.85)	0.015	69/566	1.04 (0.57-1.88)	0.907
>150.0g/week[d]	146/1,107	0.59 (0.36-0.95)	0.038	131/997	0.98 (0.56-1.75)	0.958
Log likelihood			*-4918*			*-4166*
BIC[d]			*9896*			*8494*
Women						
Never drinkers[a]	15/86	(reference)		14/71	(reference)	
Non-current drinkers[b]	13/56	1.13 (0.54-2.38)	0.740	11/45	1.07 (0.48-2.40)	0.869
Infrequent drinkers[c]	103/448	1.16 (0.67-2.00)	0.591	86/386	1.44 (0.79-2.62)	0.240
0.1-50.0g/week	109/920	0.62 (0.36-1.06)	0.082	100/781	1.06 (0.57-1.97)	0.845
50.1-100.0g/week	24/346	0.37 (0.19-0.70)	0.003	22/297	0.81 (0.39-1.70)	0.584
>100.0g/week	15/299	0.28 (0.14-0.58)	0.001	14/267	0.55 (0.24-1.24)	0.151
Log likelihood			*-2071*			*-1700*
BIC[d]			*4190*			*3538*

Age-adjusted models controlled for baseline age only. Multivariable-adjusted models controlled for baseline age plus baseline BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five. [a]Participants who reported no consumption in the past week in waves 1 and 3, no consumption in the past year in waves 1 and 3, and stated they had 'always been a non-drinker' at wave 3; [b]Participants who reported no consumption in the last year but had not 'always been a non-drinker'; [c]Consumed alcohol in the past year but not in the past week; [d]Bayesian information criterion.

Table 7.4 Iteratively-adjusted dose-response relationship between categories of average weekly volume of alcohol consumption and T2DM, stratified by sex. Observed data.

	Model 1		Model 2		Model 3		Model 4		Model 5	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Men (n=4,869)										
Never drinkers[a]	(reference)		(reference)		(reference)		(reference)		(reference)	
Non-current drinkers[b]	0.86 (0.41, 1.80)	0.684	1.25 (0.59-2.64)	0.554	0.95 (0.45-2.01)	0.902	0.77 (0.36-1.61)	0.483	0.88 (0.42-1.85)	0.731
Infrequent drinkers[c]	0.51 (0.29, 0.91)	0.022	0.90 (0.50-1.62)	0.729	0.50 (0.28-0.90)	0.020	0.46 (0.26-0.81)	0.008	0.53 (0.30-0.95)	0.031
0.1-50.0g/week	0.48 (0.28, 0.82)	0.007	0.88 (0.51-1.52)	0.642	0.48 (0.28-0.81)	0.007	0.46 (0.27-0.78)	0.004	0.54 (0.32-0.93)	0.025
50.1-100.0g/week	0.51 (0.30, 0.88)	0.016	0.97 (0.55-1.70)	0.914	0.49 (0.29-0.85)	0.011	0.48 (0.28-0.83)	0.008	0.60 (0.35-1.03)	0.062
100.1-150.0g/week	0.53 (0.30, 0.92)	0.024	1.04 (0.58-1.86)	0.897	0.50 (0.29-0.87)	0.015	0.48 (0.27-0.85)	0.011	0.63 (0.36-1.11)	0.110
>150.0g/week[d]	0.58 (0.34, 0.99)	0.047	1.13 (0.65-1.97)	0.663	0.50 (0.29-0.86)	0.012	0.49 (0.29-0.85)	0.011	0.68 (0.39-1.16)	0.155
Log likelihood		*-4344*		*-4289*		*-4242*		*-4322*		*-4327*
BIC[d]		*8747*		*8663*		***8552***		*8738*		*8747*
Women (n=2,094)										
Never drinkers[a]	(reference)		(reference)		(reference)		(reference)		(reference)	
Non-current drinkers[b]	1.14 (0.52-2.51)	0.749	1.40 (0.63-3.11)	0.408	0.94 (0.43-2.08)	0.886	1.11 (0.50-2.46)	0.791	1.24 (0.56-2.75)	0.587
Infrequent drinkers[c]	1.05 (0.60-1.85)	0.870	1.59 (0.87-2.88)	0.130	0.98 (0.56-1.73)	0.955	1.04 (0.59-1.84)	0.895	1.16 (0.66-2.05)	0.611
0.1-50.0g/week	0.62 (0.36-1.09)	0.099	1.02 (0.56-1.87)	0.949	0.69 (0.39-1.20)	0.188	0.63 (0.36-1.12)	0.118	0.75 (0.42-1.32)	0.314
50.1-100.0g/week	0.37 (0.19-0.71)	0.003	0.67 (0.33-1.37)	0.274	0.45 (0.23-0.88)	0.019	0.36 (0.18-0.72)	0.004	0.51 (0.26-1.01)	0.052
>100.0g/week	0.27 (0.13-0.57)	0.001	0.52 (0.24-1.15)	0.105	0.29 (0.14-0.60)	0.001	0.27 (0.13-0.58)	0.001	0.43 (0.20-0.93)	0.032
Log likelihood		*-1803*		*-1770*		*-1738*		*-1800*		*-1791*
BIC[d]		*3651*		*3608*		***3529***		*3677*		*3658*

Model 1 adjusted for age; Model 2 adjusted for age plus for ethnic and genetic factors (ethnicity and family history of T2DM). Model 3 adjusted for age plus adiposity (BMI); Model 4 adjusted for age plus other lifestyle factors (physical activity and smoking status); and Model 5 adjusted for age plus socio-economic factors (employment status and occupational grade). All variables were defined according to information available at baseline, apart from ethnicity which was derived from responses at waves one and five. [a]Participants who reported no consumption in the past week in waves 1 and 3, no consumption in the past year in waves 1 and 3, and stated they had 'always been a non-drinker' at wave 3; [b]Participants who reported no consumption in the last year but had not 'always been a non-drinker'; [c]Consumed alcohol in the past year but not in the past week; [d]Bayesian information criterion.

7.5.4 Frequency interaction

When multivariable-adjusted survival models included an interaction between the frequency and volume of consumption (Table 7.5), no relationship was observed among men for every 10 g/week increase in the weekly volume of alcohol intake (HR 1.00, 95% CI 0.99-1.01), while women showed a statistically significant 5% reduction in risk for each increment (HR 0.95, 95% CI 0.92-0.99). Among both sexes, the dose-response relationship between the volume of consumption and T2DM risk did not differ according to drinking frequency (men: p=0.361; women: p=0.450), with an interaction term having provided no improvement to the fit of any model. Results from analyses of imputed data are reported in Appendix 7.7, and also show no significant interaction among men (p=0.653) or women (p=0.324).

When non-current and infrequent drinkers were included (Appendix 6.8), the dose-response relationship was unchanged and interaction terms remained statistically insignificant (men: p=0.621; women: p=0.536). Results from analyses that utilised imputed data are reported in Appendix 7.9 and were comparable to those obtained from models applied to the observed data.

Given that models of continuous data assumed a linear dose-response relationship between the volume of alcohol consumption and T2DM, a range of non-linear transformations were tested to explore whether a non-linear association provided a better fit of the underlying data. The dose-response relationship was best described by a linear association.

Table 7.5 Multivariable-adjusted interaction between a continuous measure of average weekly volume of alcohol consumption and drinking frequency, stratified by sex and excluding non-current and infrequent drinkers. Observed data.

	Model 1		Model 2	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Men (n=4,266)				
Dose-response by volume				
Per 10 g/week increase	1.00 (0.99-1.01)	0.522	0.99 (0.98-1.00)	0.164
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.80 (0.58-1.09)	0.151
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	1.01 (0.99-1.04)	0.361
Log likelihood		*-3601*		*-3600*
BIC [a]		*7320*		*7334*
Women (n=1,566)				
Dose-response by volume				
Per 10 g/week increase	0.95 (0.92-0.99)	0.025	0.96 (0.90-1.02)	0.160
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	1.01 (0.47-2.18)	0.980
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.96 (0.87-1.06)	0.450
Log likelihood		*-988*		*-1698*
BIC [a]		*2078*		*3519*

Model 1 reported the linear dose-response relationship between volume alcohol consumption and T2DM. Model 2 included an interaction term between a continuous measure of volume alcohol consumption and whether participants reported drinking alcohol daily or less than daily over the year preceding interview. All models adjusted for baseline covariates: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five. All models excluded non-current drinkers from the reference level of exposure (0g/week).

7.5.5 Proportionality assumption

In multivariable-adjusted models, the association between categories of average weekly volume of alcohol consumption and the risk of T2DM did not vary overall as a function of time among men (p=0.820). However, among women, non-proportional hazards were present among very light and never drinkers at baseline (p=0.032). As shown in Appendix 7.10, while the risk of T2DM was higher among infrequent and very light drinkers than never drinkers at baseline, the

magnitude of this difference decreased by around 16-17% with every additional year of follow-up.

7.5.6 Drink type

As shown in Table 7.6, when consumption from each drink type was included concurrently within a single multivariable-adjusted model, no difference in linear dose-response was evident among male drinkers, as supported by a Wald test of equality between coefficients (p=0.300). Among women, reductions in risk were close to statistical significance across all drink types, but with the magnitude of reduction per 10 g/week increase in consumption being greatest for beer drinkers (HR 0.86, 95% CI 0.74-1.01). Nevertheless, a Wald test indicated no difference in dose-response by drink type (p=0.460). Results from the imputed dataset were comparable (Appendix 7.11). Non-linear dose-response associations were explored, but none provided an improvement in fit over the linear models.

Table 7.6 Multivariable-adjusted dose-response relationship between categories of average weekly volume of alcohol consumption, drink type and T2DM, stratified by sex. Observed data.

	Men (n=4,869)		Women (n=2,094)	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Drink type				
Beer (per 10 g/week)	0.99 (0.98-1.00)	0.206	0.86 (0.74-1.01)	0.060
Spirits (per 10 g/week)	1.01 (0.99-1.03)	0.252	0.93 (0.86-1.01)	0.080
Wine (per 10 g/week)	1.00 (0.97-1.02)	0.642	0.96 (0.91-1.01)	0.095
Log likelihood		*-4166*		*-1699*
BIC[a]		*8468*		*3521*

Models reported results adjusted for all a priori covariates: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five. Models also included variables representing the volume of each drink type consumed during the week prior to interview. [a]Bayesian information criterion.

7.6 Summary of results

Differences in metabolic risk were evident at baseline according to T2DM diagnosis, with those that developed the condition being older and more likely to have higher values of BMI, lower physical activity, poorer self-reported health, be of a South Asian ethnic background have a family history of T2DM than those who were not diagnosed (Table 7.1). Risk factors for T2DM were also found to be more common among never and non-current drinkers at baseline, who exhibited worse self-reported health, lower physical activity and a greater proportion of South Asian participants and family history of T2DM than current drinking categories (Table 7.2).

In age-adjusted survival analyses, both male and female current drinkers showed statistically significant reductions in the risk of T2DM, relative to never drinkers (Table 7.3). Reductions were of greatest magnitude among women, for whom a positive dose-response relationship was apparent. Following adjustment for confounding factors, reductions in risk were substantially attenuated, with all estimates rendered statistically non-significant (Table 7.3). While point estimates among men were all very close to the null, sizeable if non-significant reductions in risk were still reported among women at volumes in excess of 50 g/week. Among men, sizeable but statistically non-significant elevations in risk were present among non-current drinkers, while female infrequent drinkers exhibited the highest risk relative to never drinkers.

The dose-response relationship between the volume of alcohol consumption and T2DM risk did not appear to differ according to the frequency of consumption, with an interaction term according to daily or non-daily consumption providing no improvement to the fit of any survival model (Table 7.5). Additionally, no evidence was found in support of differences in dose-response according to the type of alcoholic drink consumed, with no drink type exhibiting a statistically significant association with T2DM risk after accounting for the consumption of other types of drink (Table 7.11).

7.7 Limitations

Analyses based on both the observed and imputed datasets were restricted to T2DM-free participants at wave three who had valid T2DM diagnosis data. This necessarily omitted individuals who participated at wave three but were absent at all subsequent waves of follow-up such that their T2DM status could not be ascertained. As indicated in Table 6.5, those who did not participate for ≥4 waves had a worse metabolic risk profile than those that participated across all waves, indicating that the incidence of T2DM was likely to have been underestimated, with analyses applied to a healthier sub-sample of the original cohort.

Additionally, given that participants with unit non-response across ≥4 waves also reported significantly lower volumes of alcohol consumption at wave one than those with complete-case data (men: p=<0.001; women: p=<0.001), models were likely to have under-sampled lighter and potentially less healthy drinkers. Although attempts were made to impute missing alcohol consumption data, the small number of observed never drinkers was such that an imputation model would not successfully converge. Analyses of both the observed and imputed datasets therefore excluded participants with missing alcohol consumption data. Taken together, there was a possibility that the risk of T2DM associated with lower volumes of alcohol may be underestimated.

By using a small, strictly-defined reference category, it was possible that statistical power was low, impairing the ability to detect differences in risk between exposed and unexposed categories. To explore this further, post-hoc power calculations were undertaken for the detection of differences in hazards between never drinkers and participants in the lowest current drinking category (0.1-50 g/week). Sex-specific survival probabilities and sample sizes across the two categories were used to calculate the power to detect a 20% reduction in hazards at a 0.05 level of significance if such a difference were present. Statistical power measured 0.59 among men and 0.39 among women, or a 41% and 61% probability of failing to detect a 20% difference in the hazard ratio. Contrary to expectation, however, the inclusion of non-current drinkers within the abstention reference category was likely to have done little to remedy the issue. Specifically, statistical power fell to 0.56 among male participants and rose to 0.44 among female participants when non-current drinkers were combined with never drinkers. These oppositional changes in power were attributed to sex-specific differences in the survival probabilities of never and non-current drinkers such that, when combined, the male pooled non-drinking survival probability was drawn closer to that of the current drinking comparison group, while the female abstention survival probability was drawn further away. Despite the limited statistical power of categorical comparisons, dose-response relationships could nonetheless be visually examined by referred to point estimates reported across categories of alcohol consumption.

The breadth of consumption categories was limited by the positive skewness of the volume at which alcohol was consumed within the Whitehall II cohort, with the top categories necessarily defined as any consumption >150.0 g/week among men and >100.0 g/week among women. As such, any increased risk of T2DM as commonly seen among heavier drinkers was likely diluted within the top category by a large number of relatively moderate drinkers. This was especially likely among women, where the median consumption within the highest category was just 134.3 g/week (IQR 110.6, 165.9), or a little over one pint of 4% ABV lager per day.[11] Among men, median intake within the top consumption category was 221.2 g/week (IQR 173.8, 292.3). By capturing relatively few heavier drinkers, alcohol consumption data within Whitehall II was likely to have been inadequate for the detection of increases in risk at higher volumes of consumption, as otherwise reported by previous publications. This was further indicated by the lack of improvement to model specification when non-linear associations were tested (Section 7.5.3).

Adding to this issue was the possibility that the volume of alcohol consumption may have been subject to some degree of inaccuracy, with self-reported data limited by various reporting and

recall biases as well as measurement error.[391,392] The issue of recall bias was posited to have been small, with the reliability of recall over seven-day periods found to be better than over longer retrospective episodes.[393] Reporting biases were expected to have been a larger problem, though the magnitude, direction and determinants of any such bias appeared variable and multifaceted,[391] negating any real conclusion as to the degree to which reported results may have been under- or overestimated on average. Nevertheless, in one study that investigated the accuracy of participant self-reports, measures were increasingly reliable within older age categories, with no apparent difference between the sexes.[394] Accordingly, the accuracy of self-reported alcohol consumption data was posited to have improved over time as the constituent sample grew older.

A further issue concerned the reliability of quantity-frequency questionnaires for the estimation of alcohol consumption. Adopted within Whitehall II, such questionnaires have tended to produce lower drinking estimates than alternative graduated frequency questionnaires, which ask participants to estimate the frequency with which they consumed alcohol at pre-specified volumes.[391] In this regard, reported volumes of alcohol consumption may have been underestimated.

7.8 Discussion

Age-adjusted analyses reported in Table 7.3 indicate a statistically significant reduction in the risk of T2DM across nearly all categories of current drinking, relative to never drinkers. Among men, the magnitude of such reductions were roughly equivalent at all levels of consumption, at around 50%, while risks among women declined with each categorical increase in consumption. Consistent with results from the updated meta-analysis (Figure 3.8) and other studies,[395] less pronounced dose-response associations were evident following adjustment for confounding factors (Table 7.3). Although all coefficients were rendered non-significant, it was possible that attenuated risk estimates were of magnitudes no longer sufficient to be detected as significant owing to low statistical power.

Looking instead to the point estimates reported by the multivariable-adjusted models, male and female non-current drinkers showed a greater risk of T2DM than never drinkers (Table 7.3), potentially supporting the case for having excluded former drinkers from any categorical abstention category. These elevated risks were greatest among men, suggesting that male former drinkers may be less healthy and more likely to have previously been heavy drinkers than their female equivalents. Infrequent drinkers exhibited the highest risk of T2DM among women (Table 7.3), calling into question claims that infrequent drinkers may represent a more

appropriate reference group than never drinkers. In keeping with previous research,[96,97,239] such an elevated risk might be expected were such women predominantly episodic heavy drinkers. By contrast, male infrequent drinkers showed little difference in risk, relative to never drinkers.

Among male current drinkers, multivariable-adjusted estimates were close or equal to the null. By contrast, female point estimates indicated an inverse relationship between the volume of alcohol consumption and T2DM risk. That reductions in risk may have been specific to women was in accordance with results from the updated meta-analysis (Figures 3.4 and 3.6), with sex-specific effects and a heightened risk among non-current drinkers both supporting hypotheses laid out at the beginning of the chapter.

As reported in Table 7.5, no difference in dose-response was detected according to whether participants consumed alcohol on a daily or non-daily basis, with effect sizes of negligible magnitude. It was possible that the choice of interaction variable represented a poor parameterisation of consumption pattern, failing to truly reflect episodic heavy drinking occasions. However, even if sufficient data were available as to permit the identification of episodic heavy drinkers, it was possible that the number of such individuals may be insufficient to detect an interaction. While the prevalence and odds of excessive episodic heavy drinking appear greatest within younger men and adults of lower socio-economic status or neighbourhood deprivation,[396,397] Whitehall II predominantly samples middle-aged adults of higher socio-economic status. With an interaction between the volume and frequency of consumption either not present, undetectable or incorrectly specified, analyses in subsequent chapters would forgo any secondary analysis of differences in dose-response according to reported consumption frequency.

The body of current evidence seems to suggest that reductions in risk may be specific to or at least most pronounced among wine drinkers[398] – an effect hypothesised to be conferred through the effect of anti-inflammatory compounds common to fruit-based drinks.[280,281] However, when the average weekly volume of alcohol consumption from each drink type was modelled concurrently, no statistically significant difference in the dose-response relationship was found between drink types for either sex. Of the effect estimates reported, there was a weak indication that beer may be the most strongly associated with a reduction in T2DM risk among women, contrary to other observational studies. While recent publications suggest the beer-specific compound xanthohumol may have an anti-inflammatory effect, preliminary results are currently only available from *in vitro*[399] or *in vivo* animal studies.[400] It was possible that the absence of any significant difference in dose-response by drink type may have been a consequence of having

constrained the models to report linear dose-response associations with T2DM, masking reductions in risk at very low or moderate volumes as a consequence of increases in risk at higher levels of intake. However, as with total volume in Section 7.5.4, transforming consumption from each drink type according to a range of fractional powers provided no improvement in fit relative to a standard linear survival model.

Concordance between the conventional survival analysis and findings from the updated meta-analysis suggest that Whitehall II represents a cohort suitable for further investigating the relationship between alcohol consumption and T2DM. Before constructing survival models capable of accounting for changes to consumption over time, the following chapter first explores the stability of alcohol intake across the life course and whether longitudinal trajectories differ by T2DM diagnosis.

Chapter 8

Trajectories of alcohol consumption

8 Trajectories of alcohol consumption

8.1 Introduction

Having established the suitability of Whitehall II for exploring the relationship between the alcohol consumption and T2DM within a conventional survival framework, this chapter begins by describing whether drinking among men and women within the cohort was constant over time. With survival analyses having almost exclusively modelled T2DM risk according to a single cross-sectional measure of consumption, this chapter goes on to report the longitudinal drinking trajectory as stratified according to categories of baseline alcohol consumption. Such analyses will help to highlight the degree of any potential misclassification error that may be inherent to a conventional survival approach, and thereby the validity of results reported by such analyses.

In conflict with findings from Mendelian randomisation studies,[85] results from the revised meta-analysis of current observational studies (Chapter 3) and a preliminary survival analysis of Whitehall II data (Chapter 7) show a significant and sex-specific dose-response relationship between alcohol consumption and T2DM. Despite observational research indicating reductions in risk among female moderate drinkers and increases in risk at high volumes of consumption among both sexes, little is currently known about how drinking changes over time among those that do and do not develop T2DM. Accordingly, this chapter also reports the longitudinal trajectory of alcohol consumption as stratified by sex and T2DM diagnosis. These results will help shed light upon whether any increases or reductions in risk as reported by current survival analyses were likely to have accrued gradually over the life course as a result of prolonged heavy or moderate consumption, or occurred as a consequence of differences in intake specific to periods of heightened biological sensitivity.[401] For instance, given apparent deteriorations to the alcohol metabolism with increased age,[196,197,198,199] older age may represent a period of the life course in which alcohol consumption may have particularly manifest effects upon T2DM risk.

8.2 Objectives

The objectives of this chapter are thus to:

- Determine whether sex-specific trajectories of the mean weekly volume of alcohol consumption were constant over the captured adult life course.
- Report the longitudinal stability of alcohol consumption within categories defined according to baseline intake.

- Describe the nature of any differences in the longitudinal trajectory alcohol consumption according to whether or not participants develop T2DM.

8.3 Hypotheses

Based on existing research that combined longitudinal measures of alcohol consumption from multiple cohorts,[266] it was expected that the mean volume of alcohol consumption would peak around middle-age before gradually declining thereafter. When stratified according to baseline drinking categories, it was further hypothesised that any decreases in consumption would be most pronounced among heavier baseline drinkers, with non-drinkers representing the most stable baseline category. This supposition was based on results from the Health Professionals Follow-up Study, which reported changes in alcohol consumption over a four-year period.[267] Here, study participants were split into three categories according to their alcohol consumption at baseline, representing non-drinkers (0 g/week), moderate drinkers (<105.0 g/week) and heavier drinkers (>105.0 g/week). Stability was greatest among non-drinkers, among whom 93.4% maintained their abstention over the period. By contrast, stability was lowest among heavier drinkers, with 55.8% having reduced their consumption over time.

Regarding differences in the trajectory of alcohol consumption according to the diagnosis of T2DM, a number of plausible differences were hypothesised:

- Firstly, if the risk of T2DM accumulates over time as a result of chronic heavy drinking, the trajectory of alcohol consumption among those who developed T2DM would have been consistently or else predominantly higher on average than among those that did not develop the condition, as illustrated in Figure 8.1a. Similarly, with reductions in risk apparent at more moderate volumes among women (Chapter 3), it was posited that women without T2DM would exhibit a markedly lower volume of consumption over time.
- Secondly, given evidence indicating deteriorations to the alcohol metabolism with increased age,[196,197,198,199] older age may represent a period during which any deleterious effect of alcohol consumption upon T2DM risk may be particularly pronounced. Under this alternative assumption, and with the incidence of T2DM greatest in older age,[402] there was a possibility that any disparity in drinking between those that do and do not develop the condition may be greatest during a period immediately preceding diagnosis, such as per the example illustrated in Figure 8.1b. Specifically that, regardless of differences in alcohol consumption earlier in the trajectory, the average volume of

alcohol intake would be greatest among those who developed the condition in the few years prior to diagnosis.

- Finally, with a growing number of studies linking the onset of ill-health to a subsequent cessation or attenuation of alcohol consumption,[144,145,146,141] participants who developed T2DM may exhibit a marked decline in their consumption in line with a gradual deterioration in health status prior to diagnosis (Figure 8.1c). Such a downward trajectory may represent either a proactive attempt by participants to improve their health, or else a response to medical advice or pharmaceutical contraindication following a diagnosis of impaired glucose tolerance or other T2DM risk factors such as obesity and high blood pressure.

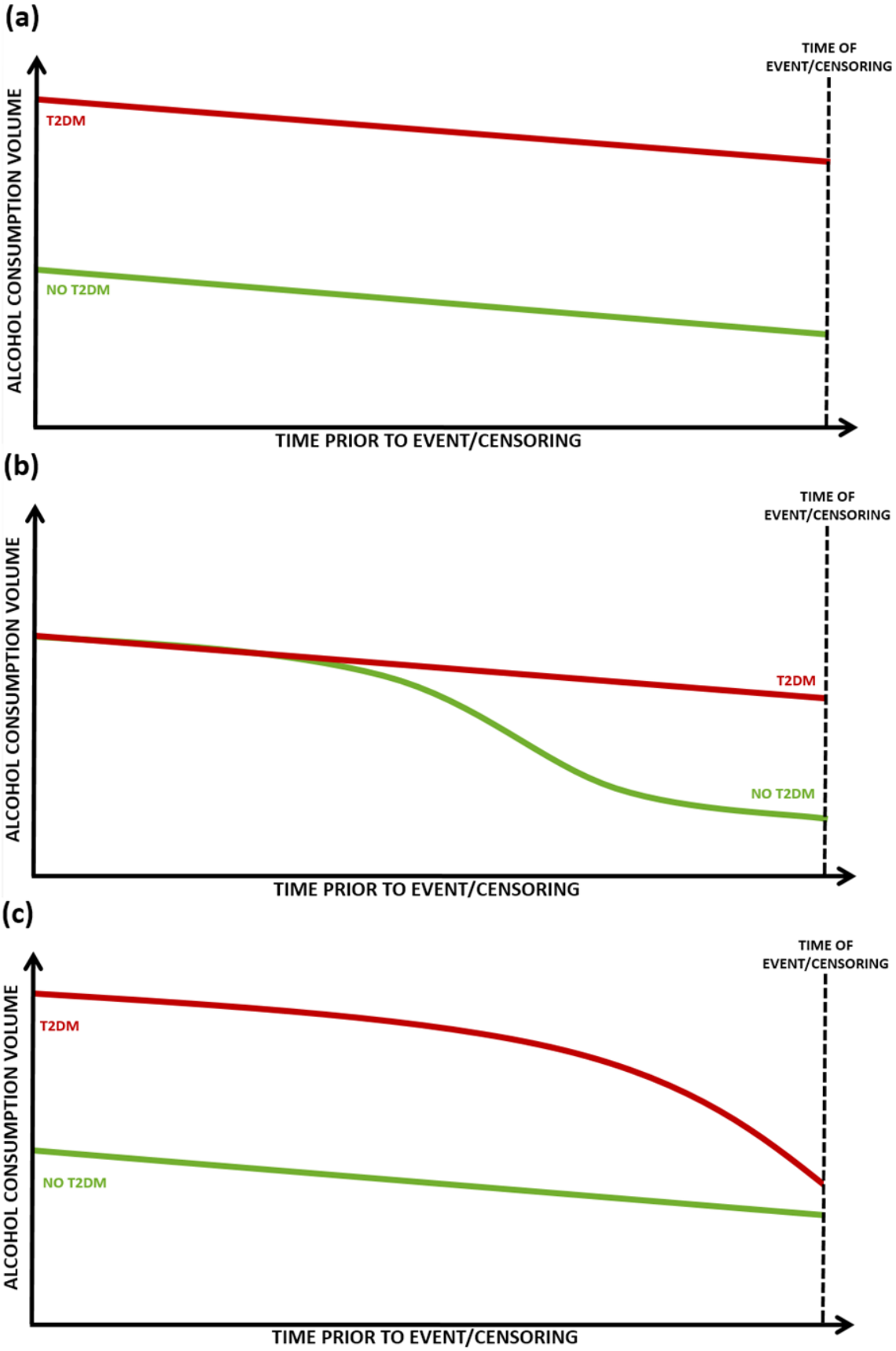


Figure 8.1 Hypothesised differences in average alcohol consumption trajectory according to T2DM diagnosis

8.4 Methods

8.4.1 Sample

8.4.1.1 Prospective trajectories of mean weekly volume of alcohol consumption

To model the mean trajectory of alcohol consumption, the sample was defined as any participant who reported their volume of alcohol consumption in the week prior to interview at any point over the course of study since its inception (wave one). Concerned solely with describing changes to the volume of alcohol consumption with increased age, participants were included irrespective of T2DM diagnosis.

8.4.1.2 Trajectories of mean weekly volume of alcohol consumption by T2DM diagnosis

Exploring differences in the trajectory of alcohol consumption according to the development of T2DM, the sample was defined as any participant free of prevalent T2DM at wave three and who reported their volume of alcohol consumption in the week prior to interview at any point over the course of the study since its inception and also participated in at least one clinical examination after wave three such that their diagnosis status could be established.

8.4.2 Variables

8.4.2.1 Alcohol consumption

Alcohol consumption was captured as described in Section 6.3 and treated as a continuous variable. Participants who consumed 0 g/week in the week prior to interview thus comprised an assortment of never, non-current (former) and infrequent drinkers. No distinction between these groups was made in primary analyses that plotted the mean drinking trajectory. If a sick quitter effect were present within the data, evidenced by a decline in consumption over time, then the exclusion of non-current or infrequent drinkers would risk an underestimation of any downward trajectory.

In secondary analyses that stratified the alcohol consumption trajectory according to drinking categories defined at wave one, the stratification variable was coded as per section 7.4.2.1. Never drinkers and non-current drinkers were combined into a single category owing to the absence of questions sufficient for disaggregating the two non-drinking groups at wave one.

Due to the inherent variation of imputed data, between-imputation differences were present when allocating participants to baseline consumption categories when alcohol consumption data were missing. Accordingly, it was inappropriate to stratify longitudinal alcohol consumption trajectories by baseline consumption category when imputed alcohol data were used. Analyses

of the imputed dataset were thus restricted to participants with observed measures of baseline consumption, with models then capitalising upon imputed repeated measures of volume of alcohol consumption across waves.

8.4.2.2 T2DM

As documented in Section 6.4, cases of T2DM were defined according to any self-reported doctor diagnosis or self-reported use of hypoglycaemic medication, or a positive FPG result following clinical examination. Wave three was the first period of observation for which both subjective and objective measures were available, and thus represented the wave at which prevalent cases were identified and excluded.

8.4.3 Statistical analysis

8.4.3.1 Prospective trajectories of mean weekly volume of alcohol consumption

Seeking to explore how alcohol consumption changed over the life course, age in years was selected as the timescale of interest for this subset of analyses. Age was defined according to the date on which the self-administered questionnaire was completed. In instances where no such date was documented, the date of clinical examination was used. Where both dates were undocumented, the mean wave-specific date of self-administered questionnaire completion was assumed.

8.4.3.1.1 Linear mixed effects models

Although trajectories of alcohol consumption could have been calculated using a standard regression model, this approach treats repeated measures as a series of unique and independent data points, leading to an overestimation of precision.[403] Accordingly, consumption trajectories were calculated using mixed effects models, which nest repeated measures within participants. This inflates standard errors proportionate to the magnitude of correlation between repeated measures, with degrees of freedom calculated according to the number of participants as opposed to the number of data points. The resulting random intercept model is expressed in general terms per Formula 8.1, with the subscript i denoting the participant and the subscript j denoting the repeated measure:

$$y_i(t_{ij}) = (\beta_0 + b_{0i}) + (\beta_1)t_{ij} + \varepsilon_{ij}$$

Formula 8.1 Calculation of a linear random intercept model

The true predicted value of weekly alcohol consumption at the age of the j^{th} measurement for the i^{th} participant is therefore calculated as the estimated mean intercept (β_0) plus a random

effect denoting the participant's predicted deviation from the mean intercept value (b_{0i}), with a fixed slope ($\beta_1(t_{ij})$) that equates to the estimated mean rate of change in alcohol consumption per unit of age. Random error was denoted by ε_{ij}, representing any remaining variation in alcohol consumption not explained by the model. The resulting random intercept model is illustrated in Figure 8.2a.

As shown in Figure 8.2a, although the nesting of repeated measures allows each participant their own intercept value, slopes are constrained and therefore parallel to the mean trajectory. With existing research indicating a variety of slopes,[259] the assumption that any change in alcohol consumption was equal between participants was unlikely to reflect reality.

To capture any underlying differences in slopes between participants, a random slopes model was also constructed, which allowed each participant to exhibit their own rate of change in alcohol consumption per year increase in age. This was achieved by adding a random effects term to the fixed mean slope coefficient, which denotes the predicted deviation of each participant-specific slope from the mean slope ($b_{1i}(t_{ij})$). The resulting random slopes model is expressed per Formula 8.2, and illustrated in Figure 8.2b.

$$y_i(t_{ij})=(\beta_0+b_{0i})+(\beta_1+b_{1i})t_{ij}+\varepsilon_{ij}$$

Formula 8.2 Calculation of a linear random slopes model

An unstructured covariance matrix was specified for the random slopes models, which allowed the within-participant covariance between the intercept and repeated measures to take any form.

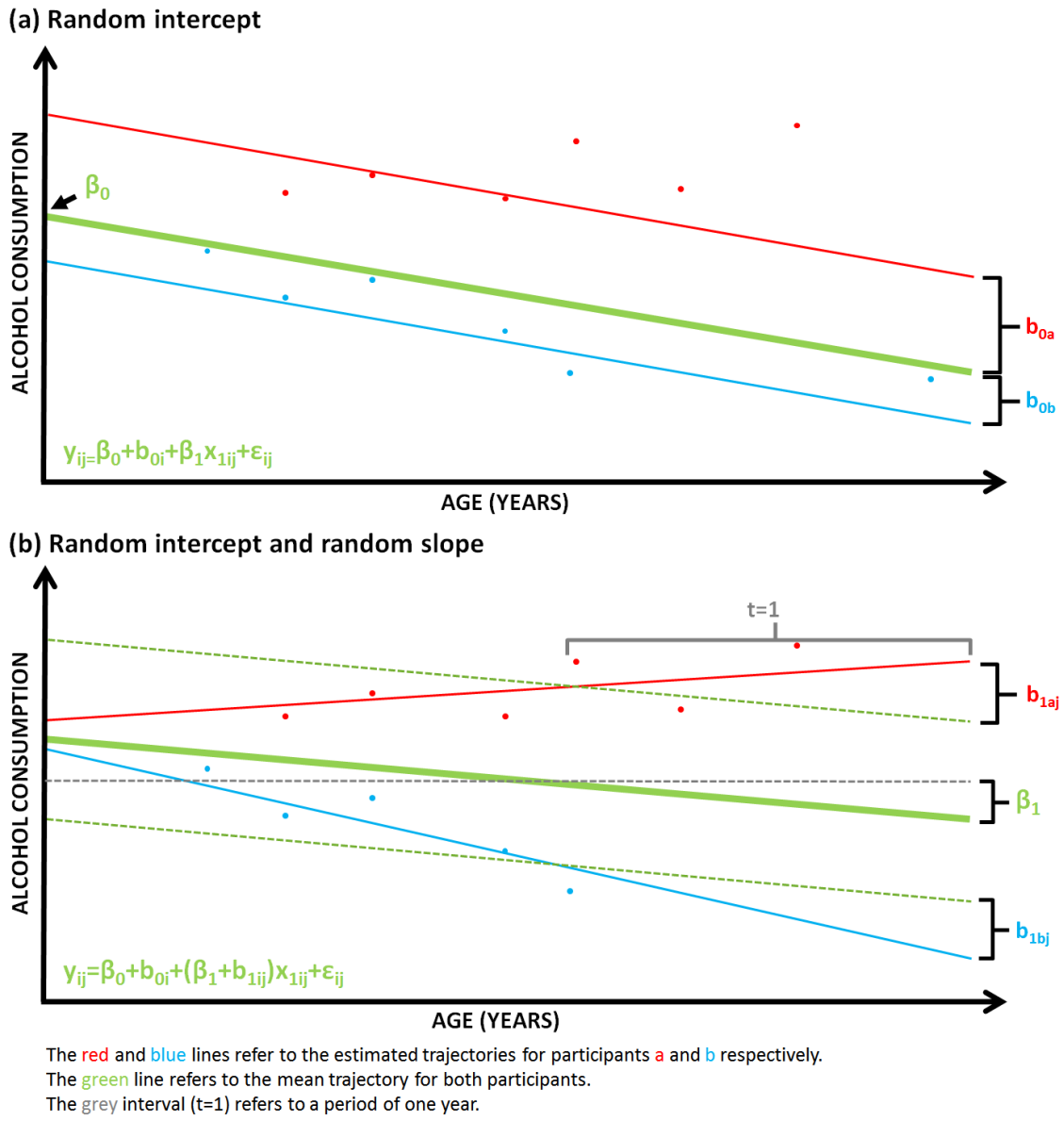


Figure 8.2 An illustration of random intercept and random slopes models

8.4.3.1.2 Non-linear mixed effects models

Although the random slopes model permitted individual-level variation in the rate of change, shifts in alcohol consumption with increased age were assumed to be linear. Owing to the possibility that changes over the life course may have been non-linear, age was subjected to a series of polynomial transformations as per the methods outlined in Section 3.2.4.1. The fit of each non-linear model was then compared against that of the linear model. Where trajectories were better explained by a non-linear slope, the output of any such models were reported.

8.4.3.1.3 Stability of baseline categories

To explore the longitudinal stability of drinking within baseline categories of alcohol consumption, an interaction term was included between the rate of change and the baseline

category of alcohol consumption. Where a significant interaction was identified, trajectories of were stratified according to categories of baseline intake. These analyses were undertaken using fixed slope models due to a lack of variation between repeated measures when nested within baseline categories. This may have been attributable to a real lack of individual-level variation in the rate of change among participants within the same baseline category, or a consequence of stratified sample sizes being too small to achieve numerical integration.

8.4.3.2 Trajectories of mean weekly volume of alcohol consumption by T2DM diagnosis

Participants were separated into two groups according to whether or not they developed T2DM over the course of the study. The period of observation began at the date of diagnosis for those who developed T2DM, or the final date of participation for those who did not, and in each cases coded as year zero. For each participant the volume of alcohol consumption was then traced backwards to the very first reported measure. A time of -15 years thus represented a measure of alcohol consumption that was taken 15 years prior to diagnosis or censoring from the study.

As the number of participants predicted to have developed T2DM over the course of the study varied between imputations, analyses applied to the imputed dataset were restricted to participants with observed T2DM diagnosis data such that the number of participants remained static between imputations.[342]

8.4.3.2.1 Linear mixed effects models

Using methods described in Section 8.4.3.1.1, sex-specific trajectories were first calculated using linear mixed effects models with an interaction between T2DM diagnosis and time. Both fixed and random slopes were estimated, with results reported from the best-fitting model.

8.4.3.2.2 Non-linear mixed effects models

As per section 8.5.1.3, a number of non-linear trajectories were also explored. In this series of comparisons, transformations were restricted to quadratic and cubic exponents due to limitations concerning the range of transformations that can be applied to negative values of time. This was consistent with previous research.[404,405] When calculating fit statistics for each non-linear mixed effects model, fixed slopes were assumed owing to issues of convergence when random slopes were expressed for some transformations. Results from the best-fitting models were reported allowing for random slopes.

8.4.3.2.3 Sick-quitter effects

Secondary analyses were undertaken to calculate the trajectory of alcohol consumption following diagnosis. These models were constructed in a piecewise manner, with models

constructed separately for consumption data prior to and after the date of diagnosis. Non-linear trajectories were explored in each instance as per the methods in section 8.5.1.3.

8.4.3.2.4 Stability of baseline categories

Finally, the longitudinal stability of alcohol consumption within baseline categories was explored per the methods outlined in Section 8.4.3.1.4.

8.4.3.3 Goodness of fit

Goodness of fit was reported according to the log-likelihood and BIC statistics, as described in Section 7.4.3.2. An improvement in fit was defined as any reduction in the BIC greater than or equal to a value of 10.[406]

8.4.3.4 Statistical package

Mixed models were calculated in Stata 13 using the -mixed- package.[407] As per the conventional survival analysis reported in Chapter 7, robust Huber-White standard errors were utilised for the calculation of confidence intervals due to the positive skewness of the alcohol consumption variable in its natural form. Although the volume of intake could have been transformed, this would have complicated interpretation and the communication of results to general audiences.

8.5 Results

8.5.1 Prospective trajectories of mean weekly volume of alcohol consumption

8.5.1.1 Descriptive statistics

The weekly volume of alcohol consumption was measured across 31,342 person-observations among men and 13,765 person-observations among women, as reported by 6,882 and 3,402 participants respectively across a mean 4.6 and 4.0 waves. Within the imputed dataset, alcohol consumption was captured across 39,160 person-observations among men and 19,305 person-observations among women, representing 6,895 and 3,413 women across a mean 5.7 waves. The age of participants ranged from 34.1-83.6 years, capturing almost 50 years of the adult life course over the period of study.

8.5.1.2 Linear trajectories

Random slopes models best described the observed (Table 8.1) and imputed (Appendix 8.1) linear trajectory of alcohol consumption across the captured life course for both men and women. Covariance between the random intercepts and random slopes was negative, indicating a convergence of trajectories with increased age.

Table 8.1 Crude sex-specific linear trajectory of mean weekly volume of alcohol consumption between the ages of 34-84 years: goodness of fit statistics. Observed data.

	Fit statistics	
Linear mixed models	**Log-likelihood**	**BIC[a]**
Men		
Intercept only	-184343	368717
Linear mixed model, fixed slopes	-184318	368678
Linear mixed model, random slopes	-184042	368146
Women		
Intercept only	-72552	145133
Linear mixed model, fixed slopes	-72531	145100
Linear mixed model, random slopes	-72500	145057

[a]Bayesian information criterion.

To confirm the suitability of stratifying drinking trajectories by sex, linear models were run with and without a sex interaction with age. The interaction term provided a statistically significant improvement in model specification (p=<0.001), supporting the case for sex stratification. As reported in Table 8.2, consumption at baseline was estimated as 110.5 g/week (95% CI 107.2-113.8) among men and 48.5 g/week (95% CI 46.0-51.0) among women, falling by an average 2.8 (95% CI 1.8-3.9) g/week and 2.2 (95% CI 1.5-3.0) g/week respectively per 10-year increase in age.

Intercept values were slightly higher within the imputed dataset among both sexes, with a steeper rate of decline reported among men than evident within the observed dataset (Appendix 8.2). Among women, the rate of change was so small as to be rendered statistically insignificant (p=0.352). Plotted linear trajectories from analyses of the observed dataset are shown in Figure 8.3, with trajectories based upon the imputed dataset reported in Appendix 8.3.

Table 8.2 Crude sex-specific linear and non-linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years. Observed data.

Mixed models	g/week (95% CI)	p-value
Men (n=6,882)		
Linear model		
Intercept	110.5 (107.2, 113.8)	<0.001
Age	-2.8 (-3.9, -1.8)	<0.001
Non-linear model		
Intercept	91.8 (90.0, 95.7)	<0.001
Age^1	12.2 (10.1, 14.4)	<0.001
Age^3	-0.9 (-1.0, -0.8)	<0.001
Women (n=3,402)		
Linear model		
Intercept	48.5 (46.0, 51.0)	<0.001
Age	-2.2 (-3.0, -1.5)	<0.001
Non-linear model		
Intercept	45.4 (43.4, 47.4)	<0.001
lnAge	3.5 (1.7, 5.3)	<0.001
Age^3	-0.2 (-0.3, -0.2)	<0.001

Age coefficients refer to the change in the average volume of weekly alcohol consumption per 10-year increase in age.

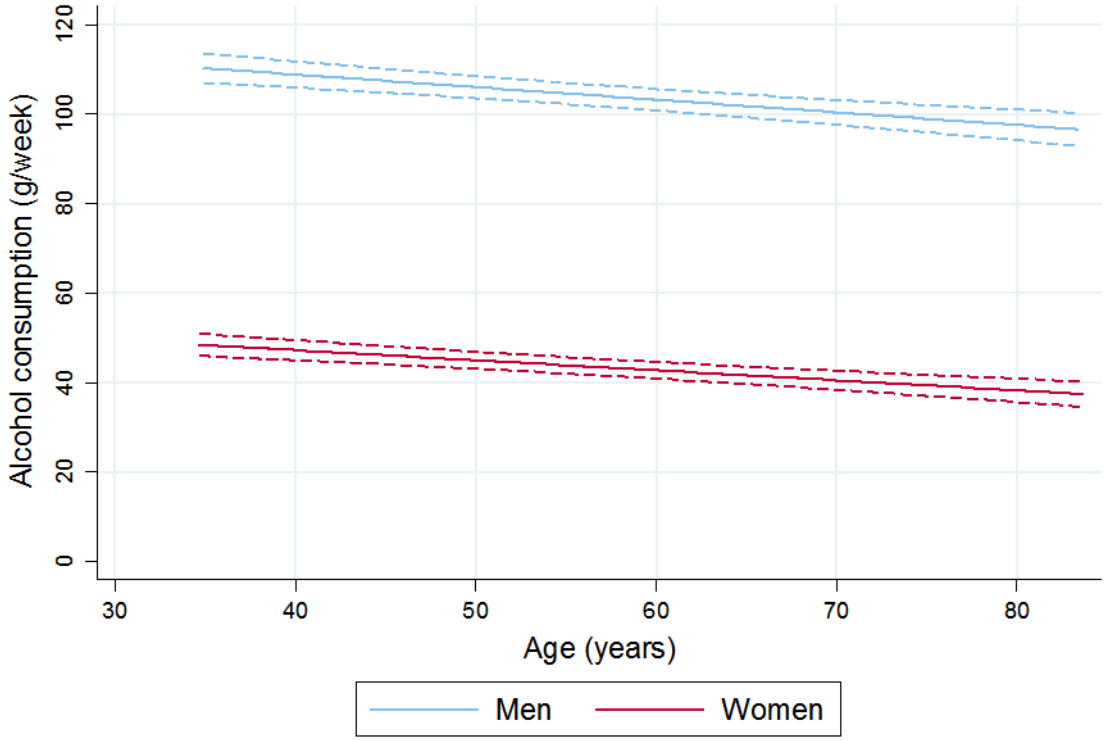


Figure 8.3 Crude sex-specific linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years. Observed data.

8.5.1.3 Non-linear trajectories

A range of non-linear slopes were explored, with fit statistics for each non-linear transformation reported in Appendices 8.4 and 8.5. When applied to both the observed and imputed datasets, non-linear slopes were found to provide a substantial improvement in fit over the linear models. Coefficients from the best-fitting non-linear models are documented in Table 8.2 for the observed dataset and Appendix 8.2 for the imputed dataset, with trajectories plotted in Figure 8.4 and Appendix 8.6 respectively.

Within the observed dataset, the volume of alcohol consumption was consistently highest among men. The mean weekly volume of alcohol consumption increased up to around 56 years of age among men and 51 years of age among women, peaking at 110 g/week (95% CI 107-112) and 46 g/week (95% CI 44-48) respectively (Figure 8.4). Beyond 56 and 51 years of age, the mean volume of alcohol consumption steadily declined, falling to 49 g/week (95% CI 43-55) among men and 23 g/week (95% CI 19-26) among women by the age of 83.5 years (Figure 8.4). Analyses based upon the imputed dataset reported higher volumes of alcohol consumption, measuring a peak of 114 g/week (95% CI 111-117) among men aged 55 years and 52 g/week (95% CI 50-55) among women aged 59 years, before falling to 63 g/week (95% CI 57-68) among men and 28 g/week (95% CI 24-33) among women by the age of 83.5 years (Appendix 8.6).

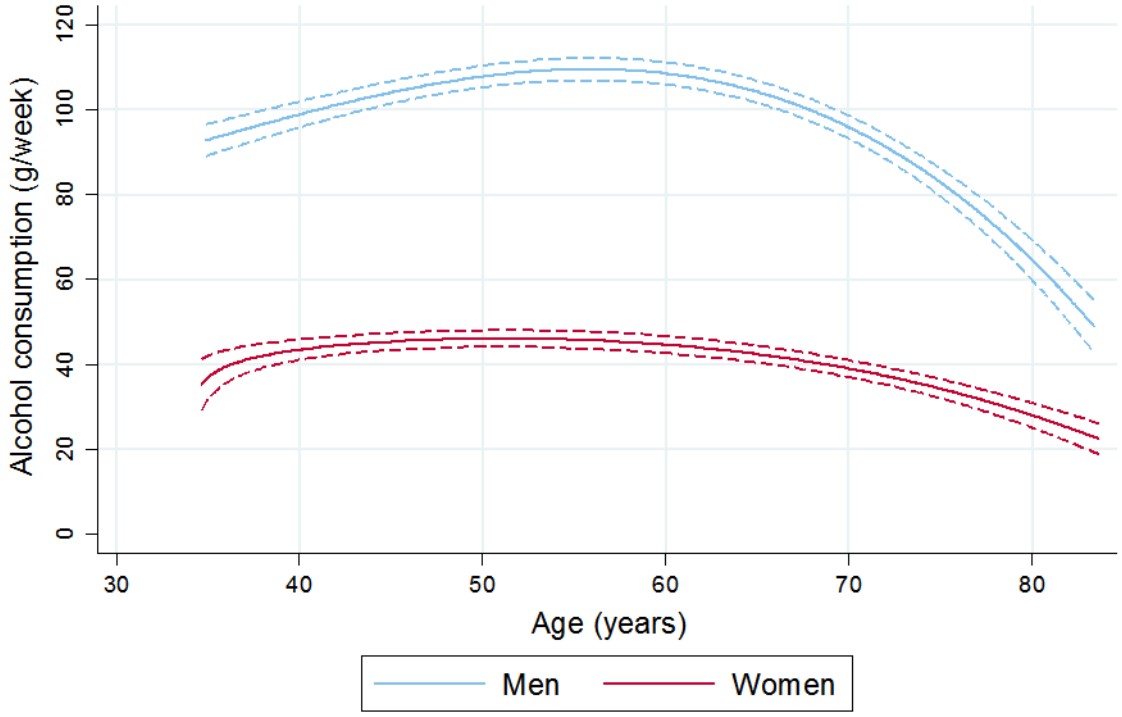


Figure 8.4 Crude sex-specific non-linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years. Observed data.

8.5.1.4 Stability of baseline categories

As reported in Table 8.3 and shown in Figure 8.5, significant differences in the longitudinal slope were identified according to the category of intake at baseline, with similar trends apparent in both sexes. Specifically, slopes between baseline categories tended to converge with increased age, whereby participants in higher categories exhibited downward longitudinal trajectories and those in lower baseline categories exhibited upward or stable slopes over the period, on average.

Among both men and women, changes over the captured life course were most pronounced within the highest baseline category. Relative to the rate of change among non-drinkers, consumption within the highest baseline category fell by an average 29.7 g/week among men and 20.1 g/week among women for every 10 year increase in age. Increases were greatest among infrequent drinkers, whose drinking rose by 8.7 g/week and 3.1 g/week respectively per 10 year increase in age, relative to non-drinkers. However, this rise may have been a consequence of such participants having consumed alcohol more frequently with advancing age such that their drinking was more likely to have been captured by the quantity-frequency questionnaire at each successive wave (Table 6.2). The only stable baseline category was female light drinkers (0.1-50.0 g/week), who showed no statistically significant change in alcohol consumption with increased age, relative to pooled non-drinkers. Although drinking declined

among women defined as more moderate drinkers at baseline (50.1-100.0 g/week), this equated to a mere 2.6 g/week change per decade, relative to non-drinkers. As such, light and moderate baseline consumption categories appeared largely stable over the period of the life course captured by the Whitehall II study.

Results based upon the imputed dataset were similar, with decreasing consumption evident within higher baseline categories and increasing consumption within lower baseline categories (Appendices 8.7 and 8.8). Interestingly, analyses applied to the imputed dataset indicate an increase in alcohol consumption among pooled non-drinkers equal to an average 5.9 g/week (95% CI 4.2-7.6) among men and 5.2 g/week (95% CI 3.8-6.6) among women, suggesting that some former or never drinkers with missing data were predicted to resume or take up drinking alcohol as they aged.

Given that participants varied between 35 and 55 years of age at the time that baseline categories were defined, and with marked differences in alcohol consumption reported by age group in Sections 2.2.1 and 8.5.1.5, there was a possibility that some of the difference in longitudinal trajectories may have been attributable to disparities in the age of participants within each baseline category. A post-hoc sensitivity analyses was thus undertaken which re-ran the mixed effects models with adjustment for differences in age at baseline, parameterised as dates of birth. Adjustment for birth date provided no improvement in the fit of either sex-specific model, and altered intercept and slope coefficients only by fractions of a g/week. The effect of any difference in age at baseline within each category was thus considered negligible.

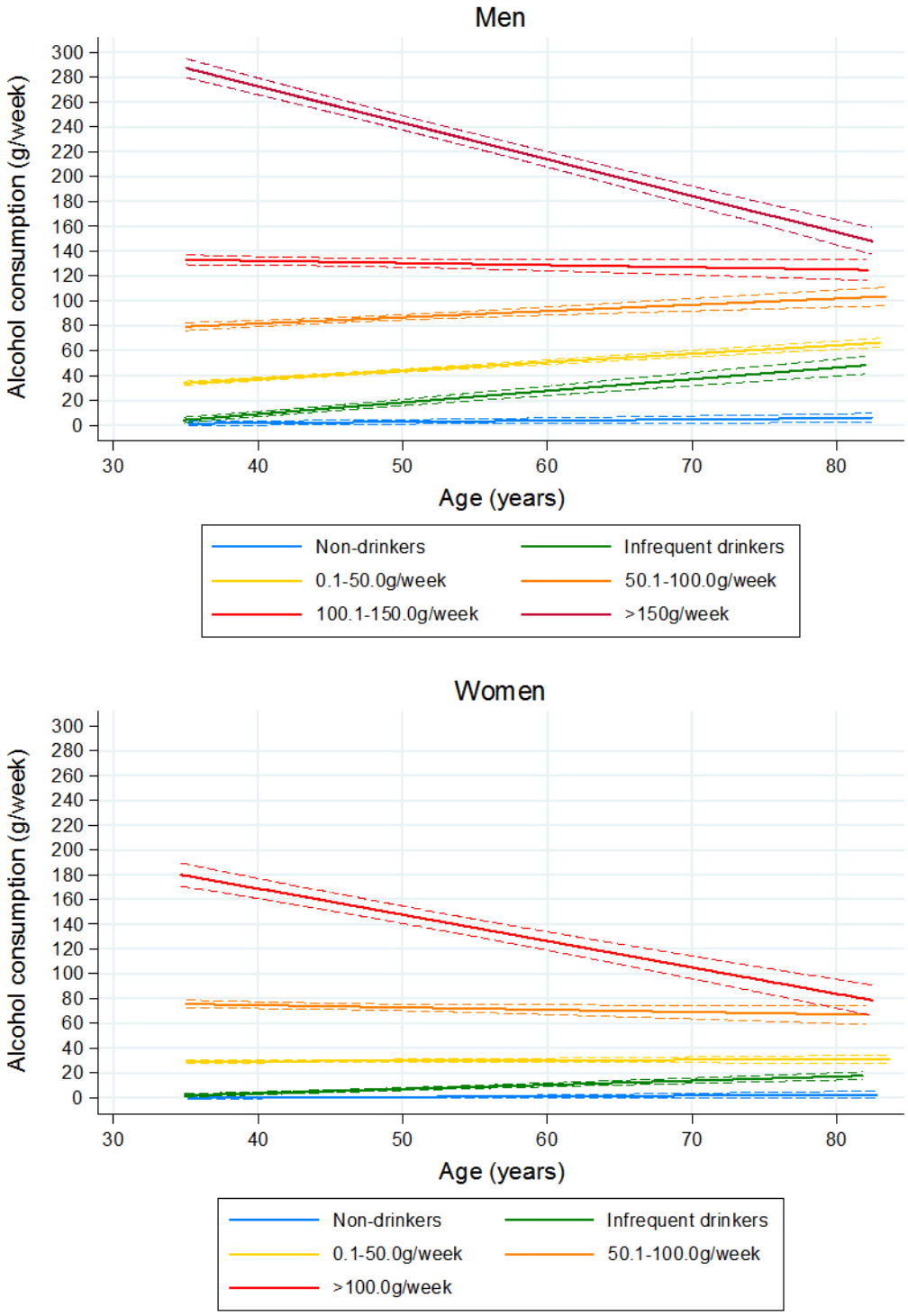


Figure 8.5 Crude sex-specific linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years, stratified by baseline alcohol consumption category. Observed data.

Table 8.3 Crude sex-specific interaction between the trajectory of mean weekly volume of alcohol consumption and baseline alcohol consumption category. Observed data.

Linear mixed models	Sample n	g/week (95% CI)	p-value
Men			
Difference in baseline consumption by drinking category			
Non-drinker	220	Reference	
Infrequent drinker	669	0.7 (-2.4, 3.9)	0.651
0.1-50.0 g/week	2,073	30.3 (27.8, 33.0)	<0.001
50.1-100.0 g/week	1,432	76.5 (72.5, 80.4)	<0.001
100.1-150.0 g/week	881	131.6 (127.3, 125.9)	<0.001
>150.0 g/week	1,563	286.6 (278.5, 294.7)	<0.001
Difference in the rate of change by drinking category			
Non-drinker		Reference	
Infrequent drinker		8.7 (6.8, 10.5)	<0.001
0.1-50.0 g/week		6.2 (4.9, 7.5)	<0.001
50.1-100.0 g/week		4.5 (2.2, 6.8)	<0.001
100.1-150.0 g/week		-2.7 (-5.0, -0.4)	0.020
>150.0 g/week		-29.7 (-32.8, -26.6)	<0.001
Women			
Difference in baseline consumption by drinking category			
Non-drinker	216	Reference	
Infrequent drinker	764	1.0 (-0.7, 2.6)	0.256
0.1-50.0 g/week	1,428	29.3 (27.5, 31.2)	<0.001
50.1-100.0 g/week	542	76.2 (72.7, 79.6)	<0.001
>100.0 g/week	422	176.5 (167.3, 185.7)	<0.001
Difference in the rate of change by drinking category			
Non-drinker		Reference	
Infrequent drinker		3.1 (1.9, 4.2)	<0.001
0.1-50.0 g/week		-0.0 (-1.2, 1.1)	0.936
50.1-100.0 g/week		-2.6 (-4.8, -0.4)	0.019
>100.0 g/week		-20.1 (23.6, 16.6)	<0.001

8.5.2 Trajectories of mean weekly volume of alcohol consumption by T2DM diagnosis

8.5.2.1 Descriptive statistics

Of the 10,308 individuals originally enlisted at baseline, 8,815 participated at wave three. Among these, 250 prevalent cases were documented and thus excluded. A total 5,723 T2DM-free men and 2,570 T2DM-free women survived to and participated in at least one subsequent wave such that incident diagnosis status could be determined. After excluding repeated measures of alcohol consumption recorded after the date of diagnosis, plus one female participants who did not provide a measure of alcohol consumption for at least one wave prior to their date of

censoring or diagnosis, this left an analytic sample of 5,723 men and 2,569 women with 27,711 male person-observations and 11,734 female person-observations over a mean 4.8 waves. Participants were observed over a median 9.5 years for both sexes, up to a maximum of 28.0 years among men and 27.9 years among women. In total, 620 men and 296 women developed T2DM over the period.

Participants who developed T2DM exhibited a worse metabolic profile at wave one than those who did not develop the condition (Table 8.4), with a greater proportion of such participants being physically inactive, of South Asian ethnicity, a lower occupational grade and having a family history of T2DM as well as a higher BMI and more advanced age. In terms of alcohol consumption behaviour, women who developed T2DM reported a lower volume of weekly alcohol consumption at baseline. Imputed descriptive statistics were comparable (Appendix 8.9).

Table 8.4 Baseline characteristics of T2DM-free participants, stratified by T2DM diagnosis. Observed data.

Variables (wave one)	T2DM % (95% CI) n	Censored % (95% CI) n	Difference[a]
Men			
Age			
Mean years	45.0 (44.6, 45.5)[b] 620	44.4 (44.2, 44.6)[b] 5,103	0.013
Alcohol consumption frequency			
None in past year	4.4 (3.0, 6.3) 27	2.6 (2.2, 3.1) 132	0.028
<1/week	21.8 (18.8, 25.3) 135	19.7 (18.6, 20.8) 1,001	
1-3 times/week	40.3 (36.5, 44.2) 249	43.7 (42.3, 45.0) 2,223	
Daily or almost daily	33.5 (29.9, 37.3) 207	34.1 (32.8, 35.4) 1,734	
Alcohol consumption volume			
Median g/week	98.8 (89.8, 107.8)[c] 617	101.5 (98.5, 104.6)[c] 5,067	0.570
BMI			
Mean kg/m^2	26.1 (25.8, 26.3)[b] 619	24.3 (24.2, 24.4)[b] 5,094	<0.001
Ethnicty			
White	84.8 (81.8, 87.5) 526	94.6 (93.9, 95.2) 4,815	<0.001
South Asian	11.8 (9.5, 14.6) 73	3.4 (3.0, 4.0) 175	
Other[d]	3.4 (2.2, 5.1) 21	2.0 (1.6, 2.4) 101	
Family history of T2DM			
Yes	81.1 (77.8, 84.1) 495	91.2 (90.4, 91.9) 4,589	<0.001
No	18.9 (15.9, 22.2) 115	8.8 (8.1, 9.6) 444	
Occupational grade			
Administrative (top)	35.0 (31.3, 38.9) 217	41.3 (39.9, 42.6) 2,106	<0.001
Professional (middle)	54.0 (50.1, 57.9) 335	52.1 (50.7, 53.4) 2,657	
Clerical (bottom)	11.0 (8.7, 13.7) 68	6.7 (6.0, 7.4) 340	
Physical activity[e]			
Inactive	12.4 (10.0, 15.2) 76	8.1 (7.4, 8.9) 410	<0.001
Below guidelines	40.1 (36.2, 44.0) 246	37.4 (36.1, 38.8) 1,892	
Met guidelines	47.6 (43.6, 51.5)	54.5 (53.1, 55.8)	

Smoking			
Never	42.0 (38.1, 45.9) 258	49.8 (48.5, 51.2) 2,525	<0.001
Former	39.3 (35.6, 43.3) 242	36.4 (35.1, 37.7) 1,845	
Current	18.7 (15.8, 22.0) 115	13.8 (12.8, 14.7) 697	
<u>Women</u>			
Age			
Mean years	46.7 (46.0, 47.4)[b] 296	45.3 (45.1, 45.6)[b] 2,274	<0.001
Alcohol consumption frequency			
None in past year	9.5 (6.6, 13.4) 28	5.7 (4.8, 6.7) 128	<0.001
<1/week	51.4 (45.6, 57.0) 152	35.4 (33.4, 37.4) 801	
1-3 times/week	28.7 (23.8, 34.2) 85	36.6 (34.6, 38.6) 829	
Daily or almost daily	10.5 (7.4, 14.5) 31	22.4 (20.7, 24.1) 507	
Alcohol consumption volume			
Median g/week	29.4 (23.3, 35.5)[c] 296	46.9 (44.4, 49.4)[c] 2,247	<0.001
BMI			
Mean kg/m^2	28.0 (27.4, 28.6)[b] 296	24.2 (24.0, 24.3)[b] 2,273	<0.001
Ethnicty			
White	71.2 (65.7, 76.1) 210	89.1 (87.7, 90.3) 2,012	<0.001
South Asian	14.6 (11.0, 19.1) 43	4.6 (3.8, 5.5) 103	
Other[d]	14.2 (10.7, 18.7) 42	6.4 (5.4, 7.5) 144	
Family history of T2DM			
Yes	68.8 (63.1, 73.9) 198	89.2 (87.8, 90.4) 1,989	<0.001
No	31.3 (26.1, 36.9) 90	10.8 (9.6, 12.2) 242	
Occupational grade			
Administrative (top)	4.1 (2.3, 7.0) 12	14.0 (12.7, 15.5) 319	<0.001
Professional (middle)	36.8 (31.5, 42.5) 109	43.0 (41.0, 45.1) 978	
Clerical (bottom)	59.1 (53.4, 64.6) 175	43.0 (40.9, 45.0) 977	

Physical activity[e]			
Inactive	31.9 (26.7, 37.6)	22.6 (20.9, 24.4)	0.002
	91	504	
Below guidelines	34.4 (29.1, 40.1)	40.7 (38.7, 42.8)	
	98	907	
Met guidelines	33.7 (28.4, 39.4)	36.6 (34.6, 38.6)	
	96	815	
Smoking			
Never	59.0 (53.3, 64.6)	54.2 (52.2, 56.3)	0.299
	173	1,227	
Former	22.2 (17.8, 27.3)	24.9 (23.2, 26.8)	
	65	564	
Current	18.8 (14.7, 23.7)	20.8 (19.2, 22.5)	
	55	471	

Sample sizes differed according to item non-response at baseline (wave one). Employment status not listed as all participants were employed at wave one.

[a]To explore differences between non-response groups, one-way ANOVA was used on continuous data, and the chi^2 test on categorical data; [b]Mean and 95% confidence interval; [c]Median and 25th and 75th percentiles; [d]e.g. black Caribbean, African and Arabic; [e]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (not inactive or meeting guidelines).

8.5.2.2 Linear trajectories

For both sexes, random slopes models best described the observed (Table 8.5) and imputed (Appendix 8.10) linear trajectories of alcohol consumption over the period leading up to the development of T2DM or censoring, suggesting marked variability in drinking between repeated measures.

Table 8.5 Sex-specific interaction between the linear trajectory of mean weekly volume of alcohol consumption and T2DM diagnosis: goodness of fit statistics. Observed data

	Men		Women	
Mixed model	**Log-likelihood**	**BIC[a]**	**Log-likelihood**	**BIC[a]**
Crude linear mixed model, fixed slope	-162536	325134	-61948	123953
Crude linear mixed model, random slopes	-162287	324655	-61907	123889

[a]Bayesian information criterion.

Likelihood ratio tests were undertaken to formally establish the suitability of stratifying linear mixed models by sex. The inclusion of sex interactions between time and diagnosis status each improved the goodness of fit (p=<0.001), supporting the case for sex stratification. Sex stratified results are reported in Table 8.6, with corresponding plots shown in Figure 8.6. Men who did not develop T2DM over the course of study showed a gradual decline in their volume of alcohol consumption up to their time of censoring, while men who did develop the condition exhibited a marked increase in consumption up to their time of diagnosis. Based upon the coefficients

reported in Table 8.6, the mean volume of alcohol consumption thirty years prior to diagnosis or censoring was estimated to have been 108.1 g/week (103.6+[1.5*3]) among male non-cases and 75.6 g/week ([103.6+22.4]+[-16.8*3]) among male cases. By the time of diagnosis or censoring, the weekly volume of alcohol consumption was estimated to be an average 103.6 g/week and 126.0 g/week respectively.

By contrast, women who developed T2DM exhibited consistently lower volumes of alcohol consumption throughout the period of observation than those who were censored. By the end of observation, female consumption measured a mean 46.1 g/week among non-cases and 27.7 g/week (46.1-18.4) among cases, or a difference of 18.4 g/week. Results from analyses based upon the imputed dataset were comparable for both sexes, and reported in Appendices 8.11 and 8.12.

Table 8.6 Crude sex-specific interaction between the linear trajectory of mean weekly volume of alcohol consumption and T2DM diagnosis. Observed data.

Crude linear mixed models	g/week (95% CI)	p-value
Men (n=5,723)		
Consumption volume		
Intercept	103.6 (100.5, 106.6)	<0.001
Change per 10 years prior to diagnosis or censoring	-1.5 (-2.7, -0.3)	0.011
Difference in consumption at the time of diagnosis or censoring		
Censored	Reference	
T2DM	22.4 (11.2, 33.7)	<0.001
Difference in the rate of change by diagnosis or censoring		
Censored	Reference	
T2DM	16.8 (10.9, 22.7)	<0.001
Women (n=2,569)		
Consumption volume		
Intercept	46.1 (43.5, 48.6)	<0.001
Change per 10 years prior to diagnosis or censoring	-1.5 (-2.5, -0.6)	0.002
Difference in consumption at the time of diagnosis or censoring		
Censored	Reference	
T2DM	-18.4 (-24.5, -12.3)	<0.001
Difference in the rate of change by diagnosis or censoring		
Censored	Reference	
T2DM	1.3 (-2.7, 5.2)	0.529

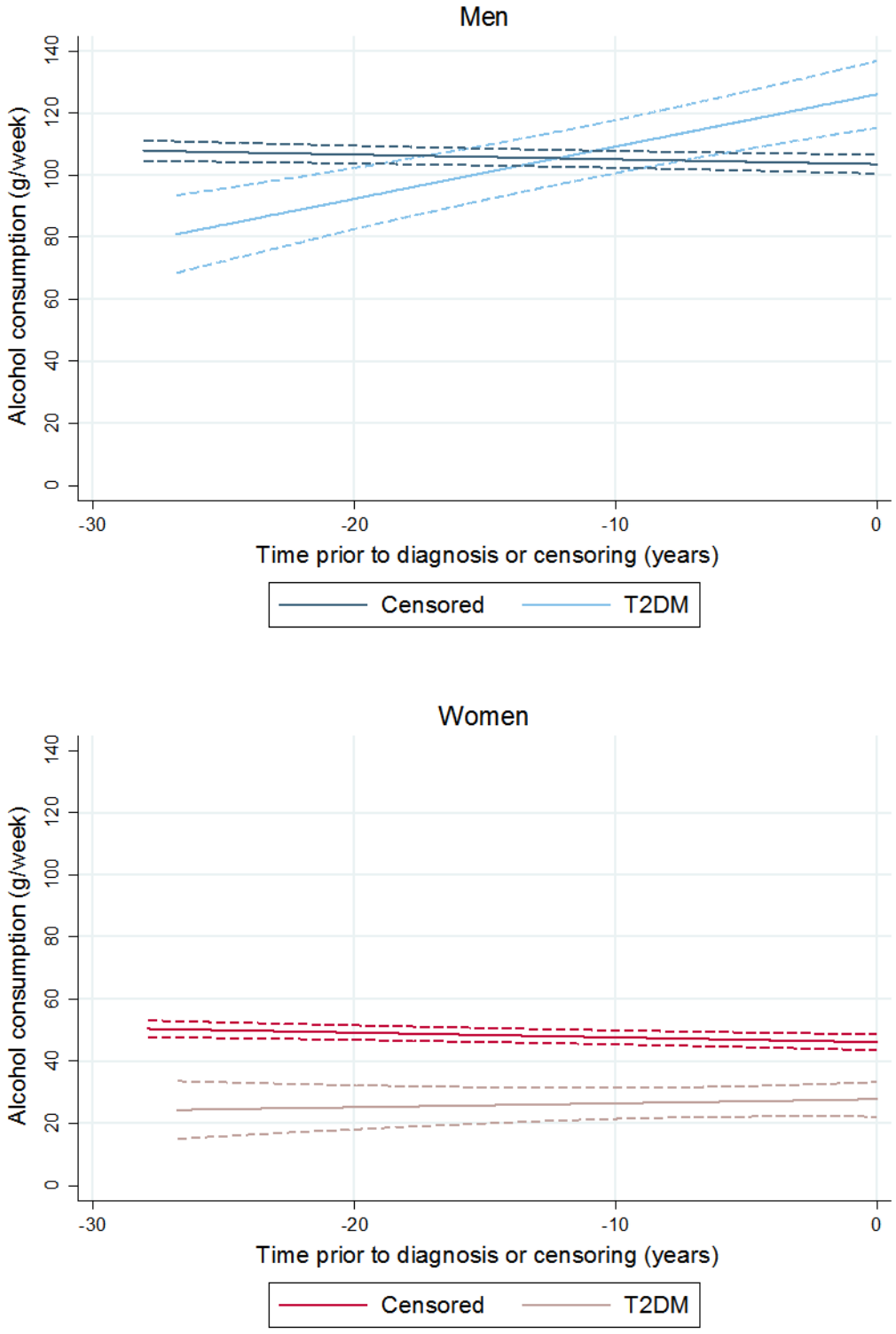


Figure 8.6 Crude sex-specific linear trajectory of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis. Observed data.

8.5.2.3 Non-linear trajectories

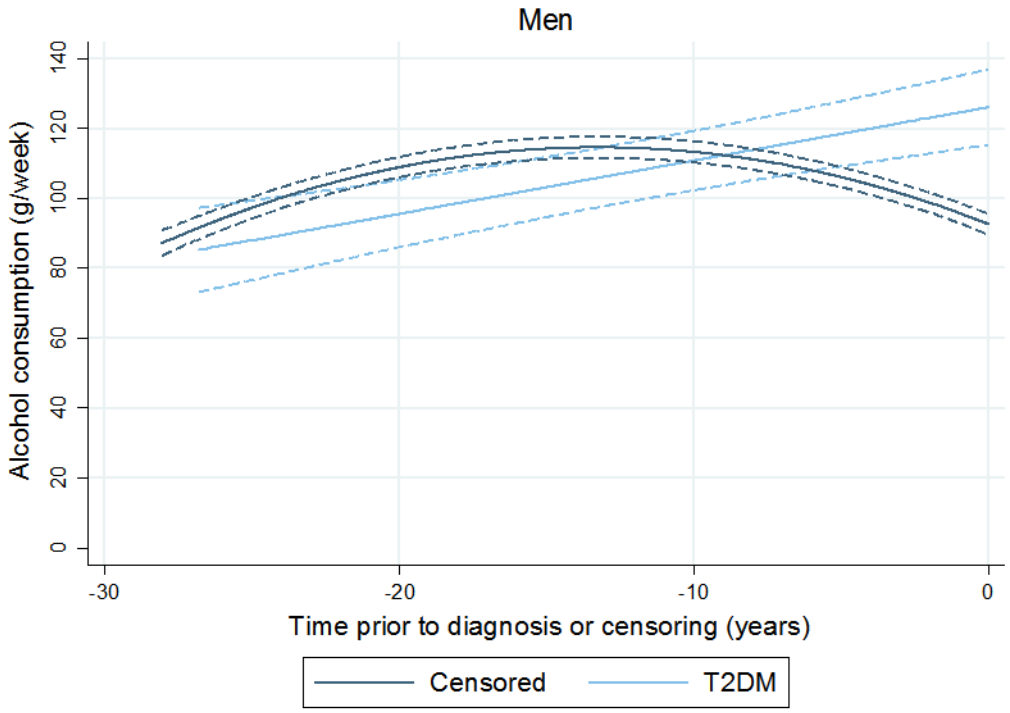
A range of non-linear slopes were explored, with fit statistics reported in Appendices 8.13 and 8.14. Consumption trajectories among men and women who developed T2DM were best described as a linear function of time, with a non-linear trajectories provided the best fit of the underlying data among censored participants (Table 8.7 and Figure 8.7). Results from models applied to the imputed dataset were comparable and reported in Appendices 8.15 and 8.16.

At 30 years prior to date of diagnosis or censoring, alcohol consumption was roughly equivalent among men at around 80.0 g/week regardless of whether they later developed T2DM or were censored. However, by the time of diagnosis or censoring, mean alcohol intake among men who didn't develop T2DM was lower than among men who developed the condition, at 92.6 g/week and 126.0 g/week respectively. This equated to a difference of 33.4 g/week, or around 1.8 pints of 4.0% ABV lager.[11] Among women, consumption remained consistently higher among those that did not develop T2DM. In contrast to men, disparities were most acute at both the beginning and end of the observation period, at just 13.3 g/week at the time of event or censoring, or around 0.7 pints of 4.0% ABV lager.[11]

Table 8.7 Crude, sex-specific and best-fitting trajectory of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis. Observed data.

Crude best-fitting mixed models	g/week (95% CI)	p-value
Men		
T2DM (n=620)		
Intercept	126.0 (115.2, 136.9)	<0.001
Time[1]	15.2 (9.4, 21.0)	<0.001
Censored (n=5,103)		
Intercept	92.6 (89.6, 95.6)	<0.001
Time[1]	-33.2 (-36.6, -29.8)	<0.001
Time[2]	-1.3 (-1.4, -1.1)	<0.001
Women		
T2DM (n=296)		
Intercept	27.8 (22.2, 33.4)	<0.001
Time[1]	-0.2 (-4.1, 3.7)	0.919
Censored (n=2,273)		
Intercept	41.1 (38.6, 43.6)	<0.001
Time[1]	-15.9 (-19.0, -12.7)	<0.001
Time[2]	-0.6 (-0.7, -0.4)	<0.001

Time coefficients refer to the change in the average volume of weekly alcohol consumption per 10 years prior to diagnosis or censoring.



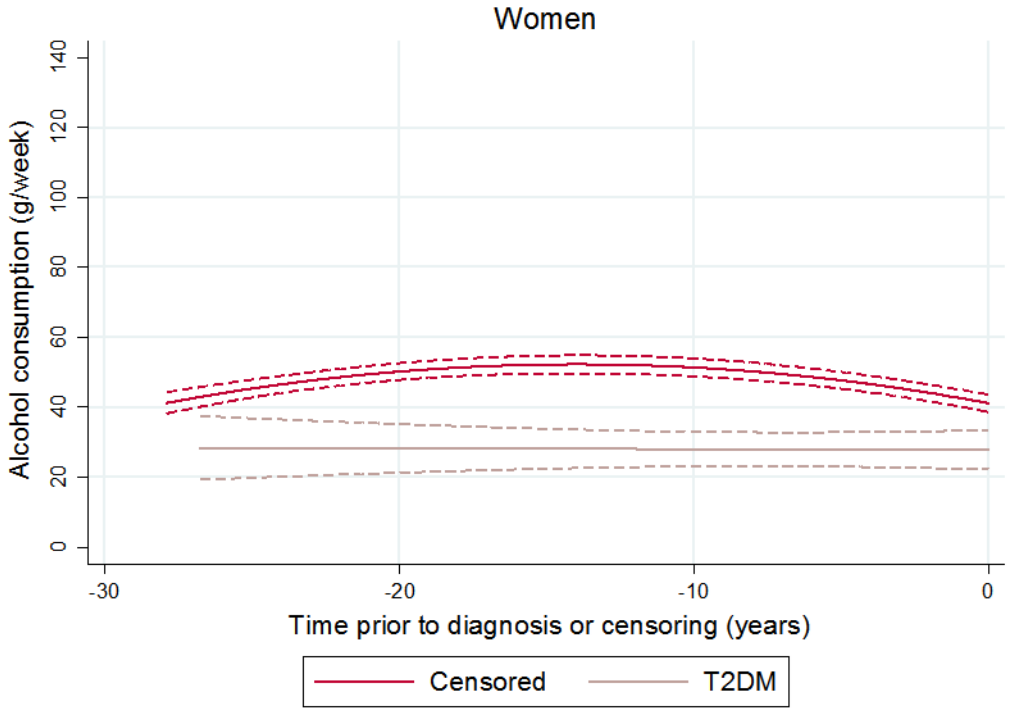


Figure 8.7 Crude sex-specific linear trajectory of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis. Observed data.

8.5.2.4 Sick-quitter effects

Looking specifically at participants who developed T2DM, trajectories were estimated for alcohol consumption beyond the date of diagnosis, with goodness-of-fit statistics for all corresponding models reported in Appendices 8.17 and 8.18. Of the 620 men and 296 women who developed T2DM over the course of the study, alcohol consumption data were observed after the date of diagnosis among 552 and 267 participants respectively. Trajectories of alcohol consumption were estimated based upon a 3,262 person-observations among men and 1,513 person-observations among women.

Table 8.8 Crude trajectories of mean weekly volume of alcohol consumption up to and beyond the date of diagnosis, stratified by sex

	Men		Women	
Piecewise models	**g/week (95% CI)**	**p-value**	**g/week (95% CI)**	**p-value**
Up to diagnosis				
Intercept	126.0 (115.2, 136.9)	<0.001	27.8 (22.2, 33.4)	<0.001
Time[1]	15.2 (9.4, 21.0)	<0.001	-0.2 (-4.1, 3.7)	0.919
After diagnosis				
Intercept	103.1 (91.4, 114.8)	<0.001	21.2 (16.4, 25.9)	<0.001
Time[1]	-21.2 (-32.2, -10.3)	<0.001	-4.5 (-7.9, -1.2)	0.008

Time coefficients refer to the change in the average volume of weekly alcohol consumption per 10 years of follow-up.

As shown in Table 8.8 and Figure 8.8, both sexes showed significant reductions in their consumption following diagnosis, equal to 21.2 g/week per decade among men and 4.5 g/week per decade among women. Trajectories from analyses of the imputed dataset differed little, and are shown in Appendix 8.19.

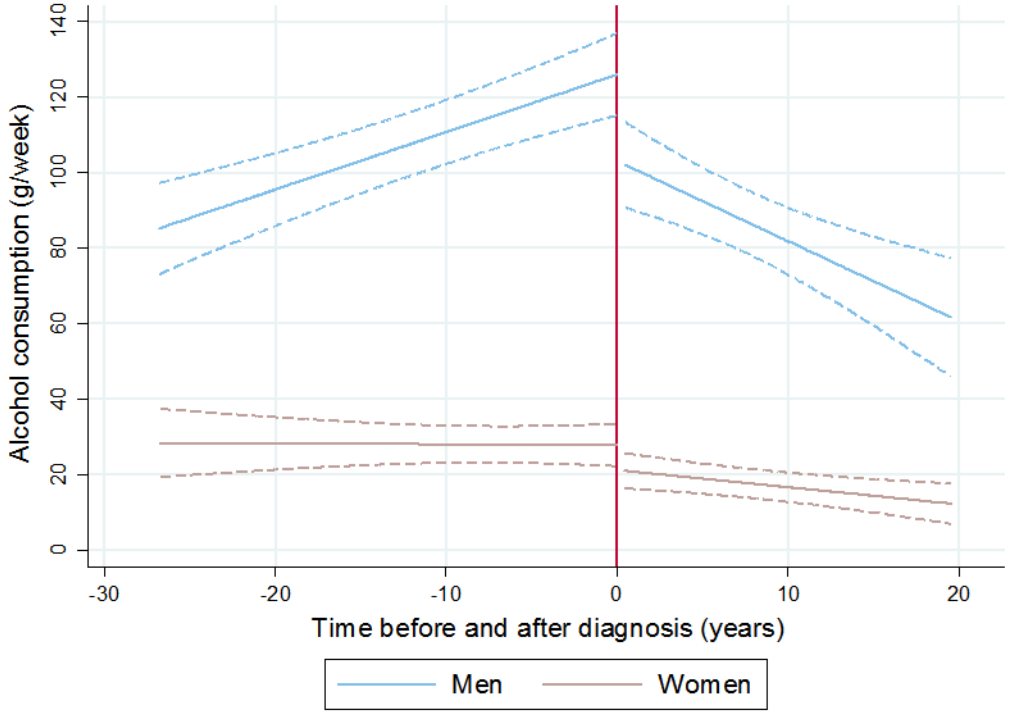


Figure 8.8 Crude trajectories of mean weekly volume of alcohol consumption up to and beyond the date of T2DM diagnosis, stratified by sex

8.5.2.5 Stability of baseline categories

Significant differences in the longitudinal trajectory of alcohol consumption were identified according to categories of intake at baseline, as reported in Table 8.9 and shown for men and women in Figures 8.9 and 8.10 respectively. The length of each plotted trajectory was dependent upon the time between baseline and diagnosis or censoring. No incident cases were observed in the final wave of observation among participants defined as baseline non-drinkers.

Regardless of diagnosis status, male drinking increased on average within all but the highest baseline consumption categories. Within the highest category, alcohol intake was estimated to fall by an average 20.8 g/week per decade among men that developed T2DM, relative to non-drinkers, or 27.2 g/week per decade among those that were censored. Of the upward trajectories apparent within more moderate categories of baseline consumption, increases were shallower among participants that did not develop T2DM.

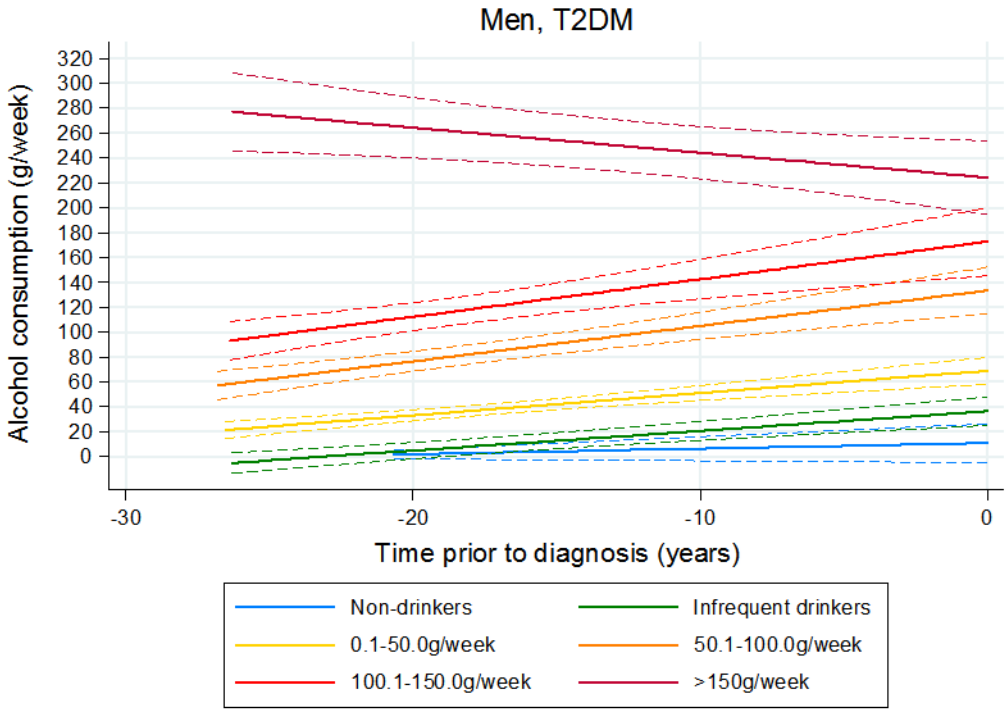
Present within both the highest (>100.0 g/week) and second-highest (50.1-100.0 g/week) categories of baseline consumption, downward trajectories were more apparent among women. These slopes were steepest among those that developed T2DM. For instance, of women who drank 50.1-100.0 g/week at baseline, the mean volume of alcohol consumption fell by 17.0 g/week among those who were diagnosed with T2DM and by just 1.9 g/week among those who

were censored, relative to non-drinkers. Although longitudinal increases in consumption were evident among both censored and diagnosed baseline moderate drinkers, elevations appeared too small to be clinically significant. For example, of women who drank just 0.1-50.0 g/week at baseline, consumption rose by an average 3.0 g/week each decade among those that went on to develop T2DM, and by a statistically insignificant 0.4 g/week among women that were censored, relative to non-drinkers. These same longitudinal trends were observed within the imputed dataset, as reported in Appendices 8.20-8.22.

Table 8.9 Crude sex-specific interaction between the trajectory of mean weekly volume of alcohol consumption and baseline category, stratified by T2DM diagnosis. Observed data.

	T2DM		Censored	
Crude linear mixed models	**g/week (95% CI)**	**p-value**	**g/week (95% CI)**	**p-value**
Men				
Difference in consumption at the time of diagnosis or censoring by baseline consumption category				
Non-drinker	Reference		Reference	
Infrequent drinker	26.2 (6.9, 45.4)	0.008	29.7 (23.5, 36.0)	<0.001
0.1-50.0 g/week	59.1 (40.2, 78.1)	<0.001	51.9 (47.4, 56.4)	<0.001
50.1-100.0 g/week	123.7 (99.5, 148.0)	<0.001	92.4 (85.4, 99.3)	<0.001
100.1-150.0 g/week	162.3 (130.1, 194.5)	<0.001	122.7 (115.3, 130.2)	<0.001
>150.0 g/week	216.1 (182.6, 249.7)	<0.001	188.3 (179.3, 197.2)	<0.001
Difference in the rate of change by baseline consumption category[a]				
Non-drinker	Reference		Reference	
Infrequent drinker	11.7 (3.4, 20.0)	0.006	8.3 (6.2, 10.4)	<0.001
0.1-50.0 g/week	14.7 (6.2, 23.2)	0.001	6.1 (4.5, 7.7)	<0.001
50.1-100.0 g/week	25.9 (14.6, 37.3)	<0.001	4.9 (2.1, 7.8)	0.001
100.1-150.0 g/week	26.0 (11.0, 41.1)	0.001	-1.9 (-4.7, 0.8)	0.173
>150.0 g/week	-20.8 (-39.1, -2.5)	0.026	-27.2 (-30.8, -23.7)	<0.001
Women				
Difference in consumption at the time of diagnosis or censoring by baseline consumption category				
Non-drinker	Reference		Reference	
Infrequent drinker	11.6 (4.8, 18.5)	0.001	14.4 (10.8, 18.0)	<0.001
0.1-50.0 g/week	27.0 (19.7, 34.2)	<0.001	30.9 (27.4, 34.4)	<0.001
50.1-100.0 g/week	39.5 (24.5, 54.6)	<0.001	70.4 (64.3, 76.4)	<0.001
>100.0 g/week	100.7 (68.8, 132.7)	<0.001	109.4 (98.8, 119.9)	<0.001
Difference in the rate of change by baseline consumption category[a]				
Non-drinker	Reference		Reference	
Infrequent drinker	6.8 (2.7, 10.9)	0.001	3.6 (2.1, 5.2)	<0.001
0.1-50.0 g/week	3.0 (-1.1, 7.1)	0.155	0.4 (-1.1, 1.9)	0.609
50.1-100.0 g/week	-17.0 (-24.5, -9.4)	<0.001	-1.9 (-4.4, 0.6)	0.139
>100.0 g/week	-25.0 (-52.2, 2.3)	0.072	-18.3 (-22.6, -14.0)	<0.001

[a]Rate of change per 10 years prior to diagnosis or censoring.



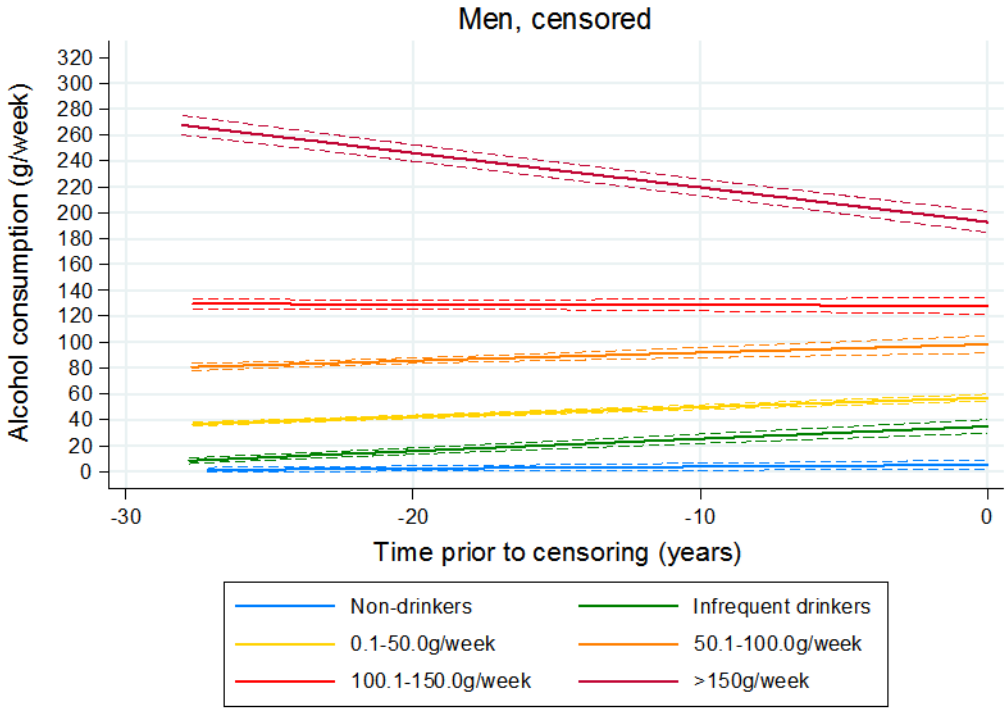
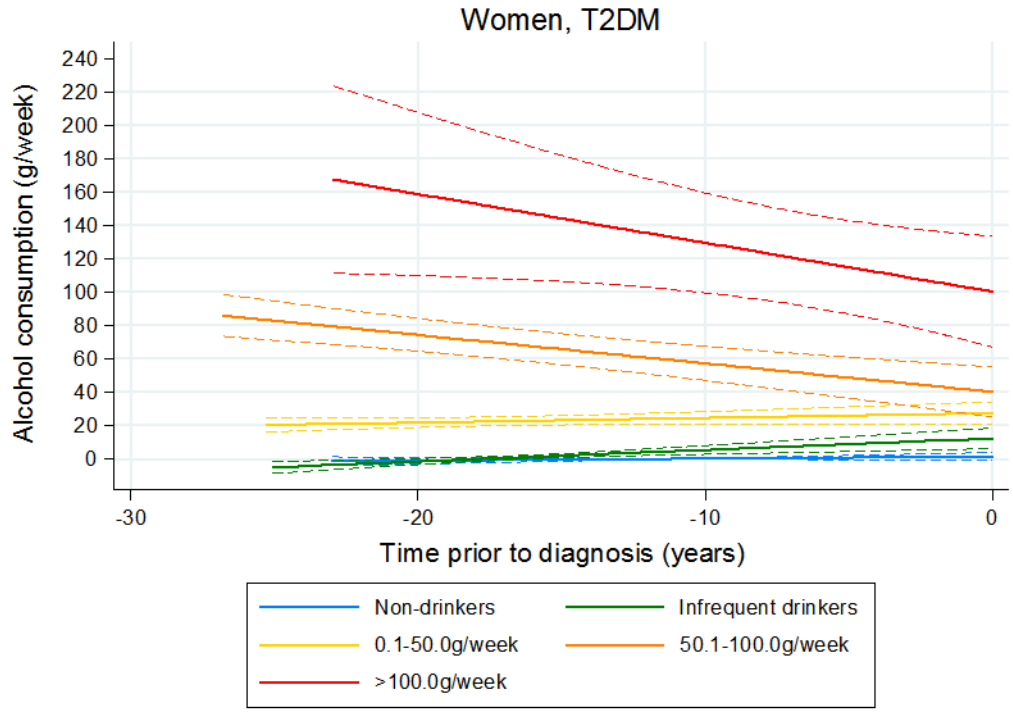


Figure 8.9 Crude male trajectories of mean weekly volume of alcohol consumption, stratified by baseline alcohol consumption category and T2DM diagnosis. Observed data.



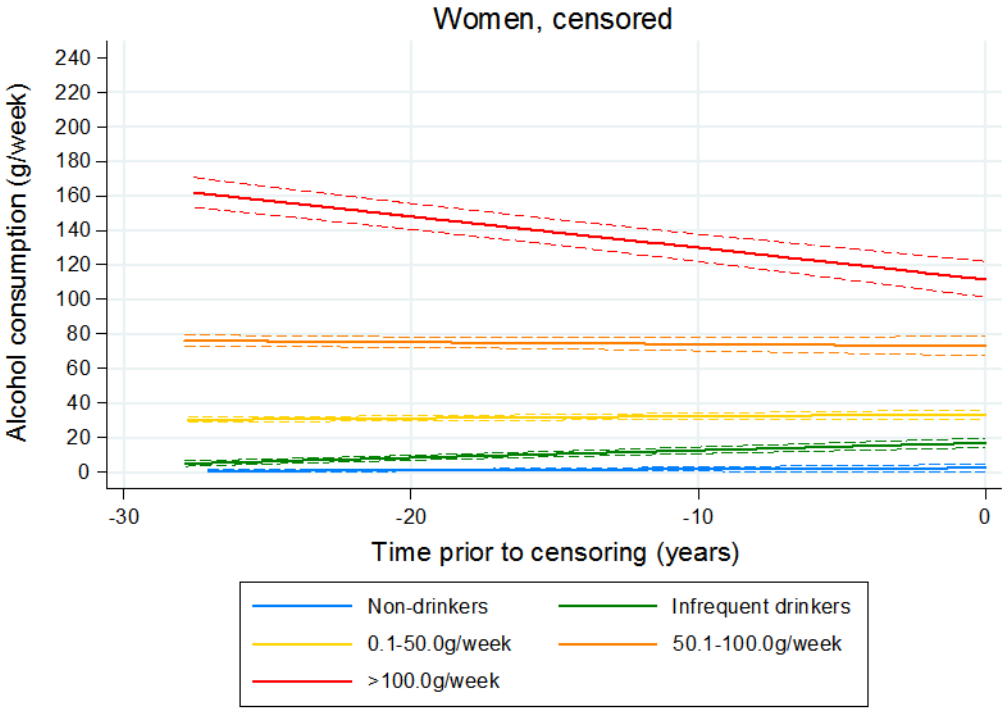


Figure 8.10 Crude female trajectories of mean weekly volume of alcohol consumption, stratified by baseline alcohol consumption category and T2DM diagnosis. Observed data.

8.6 Summary of results

Between the ages of 34 and 84 years, the mean weekly volume of alcohol consumption was markedly higher among men than women. Despite this, the relationship with age was broadly comparable, with volumes increasing up to around 56 years of age among men and 51 years of age among women before decreasing thereafter (Figure 8.4).

When trajectories were stratified by categories of baseline consumption, moderate drinkers were found to remain relatively stable across the adult life course, while heavy drinkers decreased their volume of alcohol consumption and infrequent drinkers increased their intake over the period (Figure 8.5). These changes indicated that, depending upon when in the adult life course a study categorises the alcohol intake of a participant, cross-sectionally defined moderate drinkers may be subject to differential degrees of misclassification error through contamination with heavy and infrequent drinkers.

Stratifying the longitudinal trajectory by T2DM diagnosis revealed that consumption among men and women who did not develop T2DM gradually increased up to around 15 years prior to the time of censoring, before decreasing steadily toward the end of the observation period (Figure 8.7). By contrast, linear increases were evident among men that developed the condition. Thus, by the time of diagnosis or censoring, the mean weekly volume of alcohol consumption among men who didn't develop T2DM was 33.4 g/week lower than among men who developed the condition. A different picture was apparent among women. Here, rather than a similar linear increase among those who developed T2DM, the mean weekly volume of alcohol consumption remained consistently lower than among women who were censored. These differences were most acute at both the beginning and end of the observation period.

Regardless of sex-specific differences in the consumption trajectory prior to developing T2DM, drinking fell among both sexes after the date of diagnosis, at 21.2 g/week among men and 4.5 g/week among women per decade of follow-up (Figure 8.8).

8.7 Limitations

Although Whitehall II captured around 50 years of the adult life course, the dataset was not comprehensive, lacking measures of consumption through early adulthood (18-33 years of age) and advanced old age (≥83 years). Although data concerning these periods were missing, it was expected based on existing research that the unobserved period of early adulthood was likely to have been marked by a trend of increasing consumption, with a decrease in drinking during the unobserved period of advanced old age.[259,266]

As noted in Section 7.6, all analyses of Whitehall II data were dependent upon self-reported measures of alcohol consumption. Consequentially, plotted trajectories were potentially subject to some degree of inaccuracy owing to factors including reporting and recall biases[391] as well as measurement error.[392] In addition, no consideration was given to changes in reported consumption frequency across the life course. This decision was taken after having previously identified no difference in the dose-response relationship according to the frequency of consumption (Table 7.5).

The results reported in this chapter focus on the mean trajectory of sampled participants by age and time. Although some analyses stratified alcohol consumption trajectories according to categories of baseline consumption, providing an indication as to how different drinking groups altered their intake over the life course, all results nonetheless dealt with averages that mask longitudinal changes to the constitution of the mean trajectory. For instance, the declining slopes seen among censored men and women in Figure 8.7 may have been a consequence of either a general decrease in the weekly volume of alcohol consumption to more moderate intakes or the transition of a minority of participants from heavy consumption to non-drinking. To get a rough idea as to the effect of transitions to non-drinking upon plotted trajectories, a post-hoc analysis was undertaken that calculated the best-fitting models in Figure 8.8 when participants with zero consumption (0 g/week) were excluded from each wave. Estimated trajectories are shown in Appendix 8.23. Although little difference was evident among male trajectories beyond an expected elevation in intercept values, both female slopes were shifted upward relative to those reported in Figure 8.7. The degree of change was largest among women who developed T2DM. While results in Table 8.7 indicated a flat trajectory among such participants (-0.2 g/week per decade, p=0.919), the exclusion of non-drinkers resulted in a near-significant upward trajectory equal to an average increase of 5.5 g/week per decade (p=0.103). By contrast, among censored women, the difference in slopes between the two models was closer to just 1.5 g/week per decade. Such differences suggest that both female slopes may have been skewed downward by transitions from drinking to non-drinking up to the time of diagnosis or censoring, with transitions to zero consumption being most pronounced among women who developed T2DM.

A further limitation of the longitudinal mean trajectories was the testing of just two polynomial terms within the non-linear mixed effects models. Although two polynomial terms accommodate a broad family of non-monotonic trajectories,[176] the range and complexity of any resulting slopes is limited to a maximum of one turning point. Plotted non-linear trajectories

may therefore be simplistic and fail to reflect multimodal trajectories present within the underlying data. However, while multiple turning points can be accommodated through the introduction of additional polynomial terms,[176] the added flexibility of such an approach comes at the risk of overfitting the data, producing trajectories that provide a better statistical fit of the observed dataset at the cost of poor generalisability to other cohorts.[175]

As outlined in Section 6.6.1, mortality was likely to have represented a competing risk, with some study participants potentially censored due to mortality before they would otherwise have developed T2DM. Assuming that participants predominantly died due to chronic non-communicable conditions, those who were censored due to death may have exhibited a pronounced downward trajectory in the period leading up to their final wave of participation. In order to investigate the effect of mortality upon the longitudinal trajectories, the best-fitting models were calculated for each sex excluding data from any participant censored due to death. This involved the exclusion of observations from 594 men and 290 women. As shown in Appendix 8.24, the omission of data from participants censored through death had little impact upon plotted trajectories.

8.8 Discussion

8.8.1 Prospective trajectories of mean weekly volume of alcohol consumption

Analyses confirm that drinking varies with advancing age, increasing up to 56 years of age among men and 51 years of age among women before declining thereafter. This finding is consistent with previous research [266] and calls into question the validity of results from analyses that define consumption according to a single baseline measurement.

When consumption trajectories were stratified according to baseline categories of alcohol consumption, mean alcohol intake was found to vary differentially as a function of age (Table 8.3) and in a manner concordant with findings elsewhere.[267] Drinking among both sexes was least stable within the highest baseline categories, where volumes of consumption fell markedly with increasing age. Reasons for such a decline are likely to be complex, as indicated by a study of Whitehall II participants aged 61-85 years at wave 11.[408] Of the 40% of participants who reduced their consumption during the decade preceding wave 11, one of the main reasons given was a decline in opportunities for social drinking (men: 46%; women: 41%), with attenuations also commonly described as a proactive health precaution (men: 45%; women: 34%) or a response to ill-health or pharmaceutical contraindication (men: 20.7%; women: 21.9%). If heavier drinkers were more likely to have reduced their intake owing to ill-health, this may go

some way toward explaining the elevated risks of T2DM evident among non-current drinkers (Chapter 7).

Trajectories stratified according to baseline consumption were found to converge toward moderate volumes with advancing age. There was therefore an indication that the risk of misclassification error may be greatest in studies of older cohorts where cross-sectionally defined moderate drinkers are likely to be contaminated by a greater proportion of infrequent and former heavy drinkers than in younger samples. If infrequent and former heavy drinkers are at greater risk of T2DM than stable moderate drinkers, this longitudinal contamination may help explain why less pronounced reductions in the risk of CHD[409] and all-cause mortality[395] are apparent among older moderate drinkers in conventional survival analyses.

While results from analyses of the imputed dataset showed similar disparities in the longitudinal trajectory by categories baseline consumption, non-drinkers exhibited a more pronounced increase in consumption with advancing age. This suggests either that many former or never drinkers with missing data may have resumed or taken up drinking as they got older, or that the imputation model was poorly specified and did not predict zero values of alcohol consumption effectively.

Whatever the reasons for changes in drinking across the life course, longitudinal variation in the volume of alcohol consumption indicate that the categorisation of study participants according to consumption reported at a single point in time risks introducing misclassification error, with the magnitude of error operating at least in part as a function of participant age.

8.8.2 Trajectories of mean weekly volume of alcohol consumption by T2DM diagnosis

Results from the revised and updated meta-analysis indicate increases in T2DM risk among men from very low volumes of consumption, with reductions in risk specific to moderate female drinkers (Figure 3.4). By examining differences in the trajectory of alcohol consumption by T2DM diagnosis, this chapter aimed to develop a better understanding of whether dose-response relationships reported by conventional survival analyses were the result of harms or benefits having accumulated over time following prolonged exposure to particular volumes of alcohol, or a consequence of acute differences in consumption during periods of the life course in which sensitivity to the effects of alcohol may be especially pronounced.

Among men, alcohol intake was approximately equivalent between groups until just a few years prior to diagnosis, at which point the volume of consumption was greatest among men who developed the condition (Figure 8.7). This finding was most consistent with the second

hypothesis, which contended that sensitivity to the deleterious effects of higher alcohol intakes may be most pronounced later in the life course, with the mean age at diagnosis measuring 61.9 (95% CI 61.4, 62.3) years among men.

While male consumption increased linearly over the period, those who did not develop the condition exhibited a marked decline in their consumption prior to censoring. As noted in the preceding section, the reasons for such a decline were likely to be a combination of factors, including as a response to deteriorating health or as a proactive health precaution.[408] Whatever the predominant motivation, the lack of a similar downward trajectory among men who developed T2DM appeared to be in conflict the third hypothesis outlined in Section 8.3, which posited that declining health prior to diagnosis would elicit a sick quitter effect marked by a reduction in consumption. When trajectories of alcohol consumption were calculated beyond the date of diagnosis, reductions were found to be evident among both sexes after the date of diagnosis (Figure 8.8), suggesting that any deterioration in health prior to the diagnosis of T2DM may have been of insufficient magnitude as to elicit a change in drinking behaviour, with consumption only falling following medical advice.

Neither the first or second hypotheses were supported in women. Here, participants who developed T2DM exhibited an average weekly intake consistently below that of women who did not develop T2DM, with disparities by diagnosis status most pronounced during a period 15 years prior to the date of diagnosis or censoring. Regardless of such a disparity, volumes of alcohol consumption within both female groups were well within the range of intake associated with reductions in the risk of T2DM among women in the updated meta-analysis (Figure 3.4). At least two reasons for this conflict with *a priori* hypotheses were possible. First, the lower volumes consumed by women who developed T2DM may have produced an effect insufficient to offset any increased risk conferred by other factors, with women who developed T2DM having a worse metabolic health profile at wave three than those who were censored (Table 7.1). Secondly, given their worse metabolic health profile, the mean trajectory for women who developed T2DM may have been comprised not primarily of persistent low volume and therefore lower risk drinkers, but of sick quitters who had already attenuated their drinking owing to poor health. Thirdly, it was possible that the absence of distinct female trajectories by diagnosis status may have been attributable to a relatively limited range of alcohol consumption among women within the Whitehall II cohort, with heavier drinkers being few in number. For instance, while estimates from the meta-analysis in Chapter 3 indicate that the risk of T2DM becomes elevated among women at volumes >140 g/week, relative to pooled non-drinkers, just

239 women within the Whitehall II cohort reported consumption anywhere above that level at wave one, falling to just 105 participants by wave 11. A general population cohort with a greater breadth of female consumption similar to that available for men may be better suited to identifying disparities in the mean volume of alcohol consumption among women according to their diagnosis of T2DM.

That the disparity in alcohol intake by diagnosis category was greatest among men in the few years preceding the end of observation suggests that any increased risk conferred by heavy alcohol consumption may occur later in the adult life course and over a relatively acute period of time. Given this indication, survival analyses in Chapter 9 will explore whether the dose-response relationship is better parameterised according to different dimensions of the longitudinal trajectory, providing a clearer picture of differences in dose-response across the life course. Furthermore, while censored participants appeared to reduce their intake during the period leading up to the end of observation, it is unclear whether these downward trajectories represent a proactive attempt to modify negative health behaviours (a 'worried well') or a reaction to deteriorating health ('sick quitters'). Accordingly, survival models reported in Chapter 9 will also be constructed to explore the association between the longitudinal slope and the risk of T2DM independent of the actual volume consumed.

Chapter 9

Longitudinal alcohol consumption and the risk of T2DM

9 Longitudinal alcohol consumption and the risk of T2DM

9.1 Introduction

Having established in Chapter 8 that drinking varies over the life course and differentially within baseline consumption categories, it was possible that estimates derived from conventional survival analyses may fail to adequately capture the complexity of the dose-response relationship between alcohol consumption upon T2DM risk. The primary aim of this chapter was thus to explore the utility of modelling the dose-response relationship according to parameterisations of the longitudinal trajectory other than just the baseline value of consumption. To achieve this, three increasingly complex survival models are considered: an age-varying covariate model, a two-stage model and a shared random effects model.[410,411] Each approach is subject to its own advantages and limitations, and makes differing assumptions concerning the form of the longitudinal process.[412,413,414,415]

Notably, the shared random effects approach offers greater flexibility than the other methods, permitting the calculation of differences in dose-response according to whether drinking is defined according to the intercept value of the longitudinal trajectory or consumption at the time of diagnosis. In modelling these two parameters within a single model, the shared random effects approach will help establish whether these different dimensions of the longitudinal process are each independently associated with T2DM risk. Additionally, with alcohol consumption varying as a function of each, the use of an age timescale within such models will permit an exploration of whether the dose-response relationship changes when alcohol is consumed at different points in the adult life course.

With analyses in Chapter 8 having also identified longitudinal decreases in consumption among heavier drinkers and participants who were not diagnosed with T2DM, the shared random effects approach will also be used to estimate the relationship between the rate of change and T2DM risk after adjustment for the volume of past and current consumption. This final analysis will thus explore the sick quitter hypothesis, establishing whether participants who decreased their consumption tended to be at a higher risk of T2DM than those who did not.

9.2 Objectives

To formally explore the utility of using alternative parameterisations of the longitudinal trajectory, and establish whether downward trajectories are consistent with a sick quitter effect, the objectives of this chapter are thus to:

- Compare dose-response relationships reported according to different parameterisations of the longitudinal trajectory.
- Investigate the effect of adjustment for heterogeneous non-drinking groups upon the sex-specific dose-response relationship.
- Establish whether declining trajectories represent a group of drinkers at elevated risk of T2DM.

9.3 Hypotheses

9.3.1 The primary dose-response relationship

Based on results from the preliminary conventional survival model reported in Chapter 7, it is hypothesised that the dose-response relationship estimated according to the intercept of the longitudinal trajectory would indicate a null or increased risk of T2DM among men and a decreased risk among women at higher volumes of consumption (Table 7.5). By contrast, when parameterised according to intake at the time of diagnosis, it is posited that the so-called 'current value' of consumption would be associated with a heightened risk of T2DM, particularly among men. As indicated in Chapter 8, differences in male drinking were most pronounced in the few years prior to diagnosis or censoring, with volumes markedly higher on average among those who developed T2DM (Figure 8.8). With a mean age of diagnosis around 62 years, there was thus some suggestion that an increased risk of T2DM may be most pronounced when alcohol is consumed in higher volumes at older ages, representing a period in the life course during which the metabolism of alcohol is impaired and sensitivity to its deleterious effects potentially intensified.[196,197,198,199,416,417] Given the possibility that dose-response effects may differ according to a deterioration in the alcohol metabolism with increased age, it was hypothesised that both the intercept and current value parameterisations would have contrasting and independent associations with T2DM risk.

9.3.2 Sick quitter effects

At least as far back as 1988, study participants who reduce their intake over time have been referred to as 'sick quitters' – a group of individuals speculated to attenuate their consumption owing to ill-health.[138] This is a view maintained within the alcohol literature[136] and supported by the heightened risk of T2DM among former drinkers (Table 7.3). Elsewhere, T2DM risk factors[139,140] and poor self-reported health[141,142,143] have been identified as more prevalent among former drinkers than current drinkers, with the onset of ill-health associated with a cessation from alcohol consumption.[144,145,146]

Based on such findings, it is possible that downward trajectories of alcohol consumption may be indicative of an increased risk of T2DM owing to a worse metabolic health. For instance, an analysis of participants from the English Longitudinal Study of Ageing showed that declines in the frequency of alcohol consumption were most rapid among participants who reported a deterioration in self-rated health or otherwise exhibited poor self-rated health across the entire period of follow-up.[418] Similarly, although sub-group sample sizes were small, results from the Health Professionals Follow-Up Study indicate that those who decreased their intake over a four-year period tended to show an elevated if non-significant risk of T2DM regardless of baseline consumption category.[267]

However, a longitudinal decrease in alcohol consumption may not solely occur due to a 'sick quitter' effect. As reported following an analysis of Whitehall II participants aged 61-85 years at wave 11, reasons for a reduction in drinking range from illness, medicinal contraindication, proactive health precaution, a decline in opportunities for social drinking and a history of alcohol misuse.[408] It was therefore likely that individuals with decreasing consumption may not simply represent a homogenous group of 'sick quitters', but a cohort of 'worried well' or socially isolated adults. It was perhaps because of these disparate motivations that analyses stratified by categories of baseline consumption showed decreasing slopes among heavier baseline drinkers irrespective of T2DM diagnosis (Figures 8.10 and 8.11).

If reductions in alcohol consumption were primarily a response to poor metabolic health, a downward trajectory was expected to be associated with an increased risk of T2DM independent of the volume consumed. Alternatively, if reductions in the volume of alcohol consumption were instead a consequence of proactive attempts to improve health or were a result of fewer opportunities for social drinking due to factors unrelated to health status,[408] then a downward slopes is expected to be associated with a decreased or null association with T2DM risk respectively. The precise constitution of any downward trajectory will thus determine the direction of any relationship between the rate of change and T2DM.

9.4 Methods

9.4.1 Sample

The survival models chosen to calculate dose-response according to different parametrisations of the drinking trajectory all handle data in a different manner. For instance, while conventional survival models exclude any participant for whom covariate data are missing at baseline, longitudinal methods are able to include such participants by utilising measures obtained at later

waves. By contrast, while a conventional survival model can estimate dose-response associations for baseline participants based on all observed cases, longitudinal models drop any case diagnosed at a wave on which covariate data are missing. In order that results from each set of analyses were directly comparable, it was necessary to restrict the sample such that the number of participants and incident cases of T2DM were internally consistent.

Given notable if non-significant differences in the risk of T2DM as reported by infrequent and heterogeneous non-drinkers (Table 7.3), the baseline was set as wave three, the first wave at which drinking data were sufficient for disaggregating and thereby adjusting for differences in risk between such groups. The restriction of the sample thus began by including only those individuals who participated at wave three (men: 6,057; women: 2,758) and who were free of prevalent T2DM at wave three (men: 5,898; women: 2,691). Participants were then excluded if they did not provide valid responses to questions concerning the volume and frequency of alcohol consumption (men: 306; women: 169), and did not participate in at least one other wave such that their diagnosis status could not be determined (men: 136; women: 88). Finally, participants were excluded if incident T2DM was documented on a wave for which covariate data were missing (men: 29; women: 0).

In the case of crude models adjusted only for consumption category, this left an analytical sample of 5,427 men and 2,434 women, or 89.2% of wave three participants. A total incident 560 and 268 cases were identified respectively. Longitudinal alcohol consumption data were available across 21,337 and 8,842 person-observations among men and women, with a median follow-up of 20.2 years and 20.0 years. In multivariable-adjusted models, sample sizes were reduced to 4,793 men and 2,053 women, with 451 and 206 incident cases respectively.

9.4.2 Variables

9.4.2.1 Alcohol consumption

The weekly volume of alcohol consumption was captured and defined as described in Section 6.3 and treated as a continuous variable. As robust standard errors could not be calculated within the shared random effects model, the continuous g/week variable was transformed according to the base 2 logarithm owing to positive skewness. Here, any risk estimate is thus interpreted as the change in risk per two-fold increase in the volume consumed.

All models include adjustment for heterogeneous consumption category, defining participants at each wave according to whether they were never drinkers, non-current drinkers, infrequent drinkers or current drinkers. Using the volume and frequency variables described in Section 6.3,

never drinkers were strictly defined at each wave as those who reported never having consumed alcohol at the current and all prior waves. This definition thus excludes any participant who reported 'always being a non-drinker' at given wave yet also reported non-zero consumption at a prior wave. Such individuals were categorised as non-current drinkers, defined as any individual who reported no alcohol consumption in the year prior to interview but who otherwise reported non-zero consumption at a prior wave. Current drinkers were defined at each wave as anyone who reported non-zero consumption in the week prior to interview, while infrequent drinkers were participants who reported consuming alcohol during the year but did not drink alcohol in the week prior to interview.

As a consequence of seeking to explicitly identify different groups of non-drinkers, continuous alcohol consumption data reported prior to wave three were excluded, as questions concerning never drinking were only available from wave three onwards. Additionally, as never drinking could not be imputed among individuals with missing data due to the small number of such participants, alcohol consumption was restricted to observed data only in all models. Representing the largest category at all waves, current drinkers were selected as the reference group.

9.4.2.2 T2DM

As documented in Section 6.4, cases of T2DM were defined according to any self-reported doctor diagnosis or use of hypoglycaemic medication, or a positive FPG result following clinical examination. Analyses focussed upon incident cases of T2DM and so therefore excluded any prevalent diagnoses at baseline.

As the number of participants predicted to have developed T2DM over the course of the study varied between imputations, analyses applied to the imputed dataset were restricted to participants with observed T2DM diagnosis data such that the number of diagnosed participants remained static between imputations.[342]

9.4.2.3 Covariates

Covariates were defined in Section 6.5 and include BMI, ethnicity, employment status, family history of T2DM, occupational grade, physical activity, and smoking status. As described in the statistical analysis section below, age in years was selected as the timescale. As such, it was inappropriate to also adjust for the age of participants at each wave. Instead, adjustment was made for date of birth. Where repeated measures were available, covariates were treated as age-varying within all but the conventional survival analysis where only the baseline values were

used. Given the lack of any indication as to an interaction between the volume and frequency of consumption (Table 7.5), or differences in dose-response according to drink type (Table 7.6), these two factors were not included.

9.4.3 Statistical analysis

9.4.3.1 Time scale

With an interest in testing differences in dose-response according to consumption reported at disparate periods of the adult life course, age in years was selected as the most meaningful timescale. This was contrary to the approach commonly adopted within existing studies, but serves as a conceptual distinction recommended elsewhere over the use of a time-to-event metric due to the incidence of T2DM operating as a function of advancing age as opposed to time since study entry.[419,420,421]

For the conventional survival analyses, which only considered covariate values at baseline, start times were defined as the age of each participant at baseline, with stop times defined according to the age at diagnosis or censoring. For all other analyses, which utilised repeated measures, start times were equal to the age at participation in each wave, and stop times equal to the age at participation in the next wave of study**.** In circumstances where the date of participation in a wave was identical to their date of diagnosis or censoring, a value of 0.001 was arbitrarily added to their stop variable such that covariate data for that final wave could be included. The start and stop variables were scaled according to the minimum age at baseline so that intercept values were equal to consumption at 39.6 years of age.

As Stata does not permit the use of imputed survival data, start and stop data were not imputed for waves of unit non-response. Accordingly, results from analyses applied to the imputed dataset only gave account of item non-response present on included covariates during observed waves of participation.

9.4.3.2 Conventional survival model

A proportional hazards model was constructed as per the method described in Chapter 7, with all covariates fixed according to their values at wave three. This approach is consistent with the method conventionally applied for survival analyses of the alcohol-T2DM relationship. Given the highly significant sex interaction reported in Chapter 7, all survival analyses were stratified by sex.

As the maximisation procedure of the shared random effects model requires that the functional form of the underlying baseline hazard be explicitly defined,[415,422] proportional hazards models were run using parametric Weibull, Gompertz and exponential distributions. The parametric distribution that provided the best fit of the unobserved baseline hazard function was then selected for all subsequent models, defined as the model with the smallest BIC.

9.4.3.3 Age-varying covariates survival model

The age-varying covariates model serves as an extension of the conventional survival model and represents the simplest method for estimating the association between a longitudinally varying exposure and a survival process. As per Formula 9.1, alcohol consumption for the i^{th} participant at the j^{th} measurement is represented at each diagnosis by the last *observed* value (d_{ij}). The association parameter (α) linking alcohol consumption and T2DM thus reports the change in risk for a one-unit increase in the last observed or 'current' volume of alcohol consumption. Additional explanatory variables included in the survival model are represented by $x_i(t)$, with the effect of such covariates captured by their associated regression coefficients (β). Notably, although covariate values are allowed to change as a function of age, the regression effect of each covariate value is treated as proportional and thereby independent of age.

$$h_i(t)=h_0(t)\exp\{\beta x_i(t)+\alpha d_i(t_{ij})\}$$

Formula 9.1 Calculation of a Cox proportional hazard model with time-varying covariates

When obtaining the most probable risk estimates given the observed data, the survival model in Formula 9.1 requires that a complete covariate history is known for all participants.[423] However, in Whitehall II as in other cohorts, longitudinal measures are only captured periodically. The age-varying covariate model thus operates under the assumption that observed values of a covariate remain constant between examinations when drawing on the last known covariate value, as illustrated in Figure 9.1. Although this approach may work well if repeated measures are sufficient in number and frequency as to capture acute changes in consumption, the treatment of the longitudinal trajectory as a step-function is simplistic and can produce a hazard rate unlikely to reflect biological reality.[424]

A further limitation of the age-varying covariates model is that the longitudinal trajectory is assumed to be measured without error. By giving no account of the inherent variability of the observed values and the degree to which they may differ from the true covariate values, noise-attributable regression dilution can lead to an underestimation of the true longitudinal trajectory and thereby the real effect of alcohol consumption upon T2DM risk.[412,413,424]

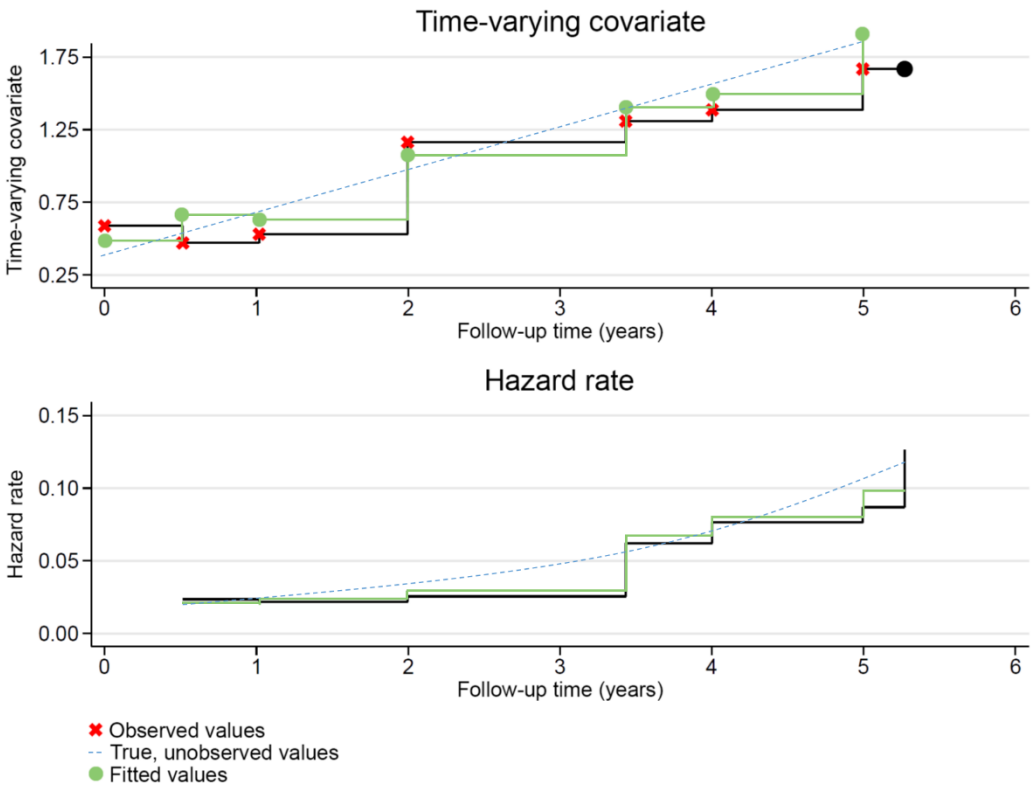


Figure 9.1 Illustration of the longitudinal trajectory and hazard function within age-varying covariate and two-stage survival models

9.4.3.4 Two-stage survival model

The two-stage method provides a better reflection of the inherent uncertainty surrounding the observed values of weekly alcohol consumption. Instead of a survival model that estimates hazards according to the last observed value of alcohol intake, the two-stage approach utilises participant-specific *predictions* of the true volume of alcohol consumption as first estimated via a mixed effects model.[412] By accounting for sampling variability through the inclusion of a random error term, predicted values are closer to the true values of weekly alcohol consumption than the crudely observed data. As such, any underestimation of the association between the weekly volume of alcohol consumption and T2DM tends to be reduced relative to an age-varying covariate model (Figure 9.2).[412]

$$h_i(t)=h_0(t)\exp\{\beta x_i(t_{ij})+\alpha\hat{y}_i(t_{ij})\}$$

$$\hat{y}_i(t_{ij})=(\beta_0+b_{0i})+(\beta_1+b_{1i})t_{ij}+\varepsilon_{ij}$$

Formula 9.2 Calculation of a two-stage survival model

As shown in Formula 9.2, predicted values of weekly volume of alcohol consumption for the i^{th} individual at the j^{th} observation ($\hat{y}_i(t_{ij})$) are calculated within the mixed effects model as the estimated mean intercept (β_0) and the predicted deviation of each participant from the mean

intercept (b_0), plus the estimated mean change in alcohol consumption per unit increase in age ($\beta_1(t_{ij})$) and the predicted participant-specific deviation from the mean slope per year increase in age ($b_1(t_{ij})$), with ε_{ij} representing random error.

Given that the accuracy of a survival model is dependent upon an appropriately specified function of alcohol consumption, linear and non-linear mixed effects models were run on the $\log_2$-transformed volume of alcohol intake according to the restricted range of fractional powers defined in Section 3.2.4.1. Random slopes were assumed in all cases and individual-level predictions from the best-fitting sex-specific models then extracted and added to the parametric survival model.

However, while measurement error is factored in during the calculation of the individual-level predictions, this uncertainty is not carried across into the survival model, which only utilises the fitted values estimated by the mixed model. As a consequence, while a two-stage approach generally provides an improvement in accuracy over age-varying covariate models, producing parameter estimates that are less biased toward the null by random error, resulting coefficients tend to exhibit too great a degree of precision.[412] Additionally, in only using fitted values as predicted for each j^{th} observation, the survival component of the two-stage model still assumes that covariate values are constant between observations (Figure 9.1).

9.4.3.5 Shared random effects survival model

In an attempt to circumvent some of the limitations that carry over into the two-stage method, the dose-response relationship between the volume of alcohol consumption and T2DM risk was also estimated using a shared random effects model. Unlike the two-stage approach, the shared random effects model estimates the longitudinal and survival processes simultaneously within a single model.[415] In doing so, rather than the risk of T2DM being calculated according to the last fitted value available, predictions are instead calculated for all points across the life course ($y_i(t)$), as illustrated in Figure 9.3.[425]

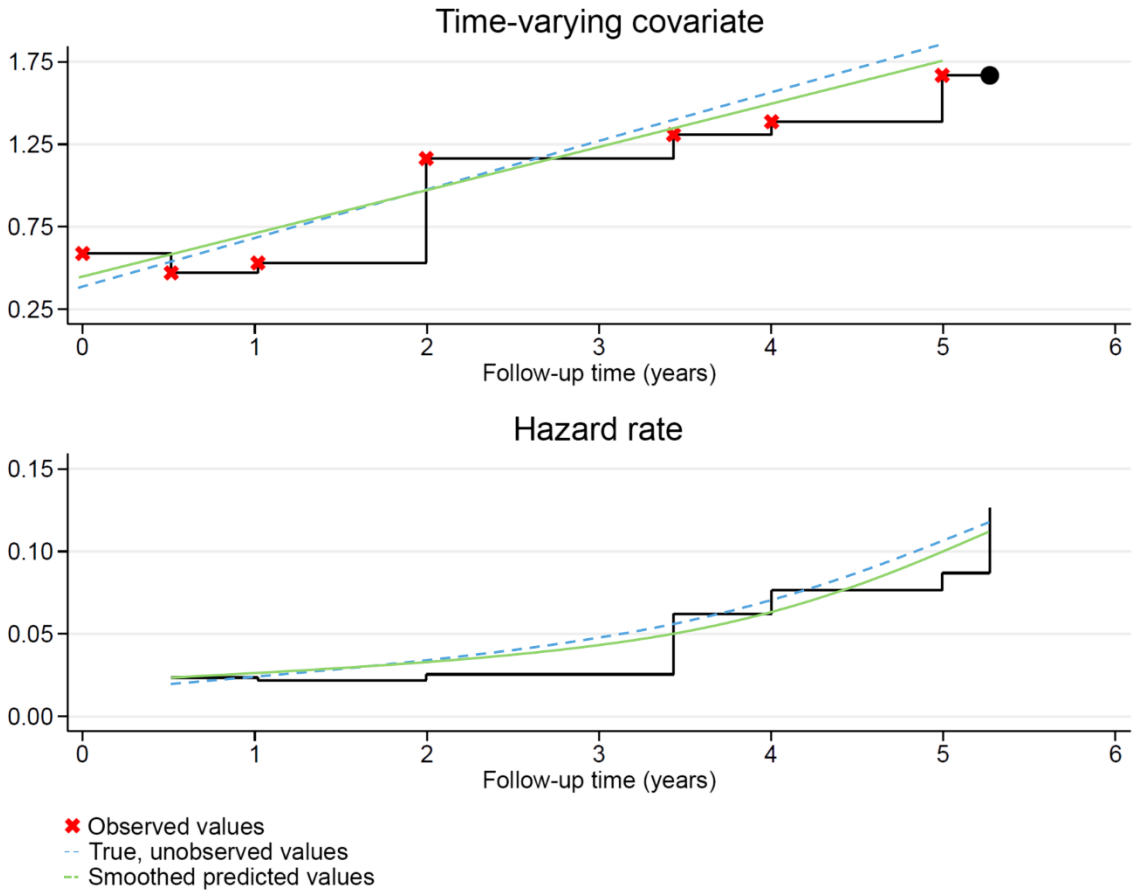


Figure 9.2 Illustration of the longitudinal trajectory and hazard function within a shared random effects survival model

Though computationally intensive, the result is a longitudinal sub-model that better operationalises the unobserved trajectory of alcohol consumption for each participant and allows for the risk of T2DM among surviving participants at each diagnosis to be calculated according to the predicted participant-specific volume of alcohol consumption at the precise age recorded at diagnosis (Formula 9.3).[415,422]

$$h_i(t)=h_0(t)\exp\{\beta x_i(t_{ij})+\alpha y_i(t)\}$$

$$y_i(t)=(\beta_0+b_{0i})+(\beta_1+b_{1ij})t_{ij}+\varepsilon_{ij}$$

Formula 9.3 Calculation of a shared random effects survival model

In simulation studies, these shared random effects models have been found to produce the least biased estimates of any of the three methods considered,[411,412] with hazards closest to the true association under study and the most robust to any misspecification within the mixed effects model.[422,426] Furthermore, by directly accounting for measurement error through the inclusion of random effects within the survival sub-model, parameters estimated by a shared random

effects approach also exhibit a larger and more appropriate degree of precision relative to the two-stage method.[412,425]

9.4.3.5.1 Intercepts versus current values

To explore how the dose-response relationship differs according to consumption at different points in the adult life course, separate models were run that calculated risk according to consumption as predicted at the intercept ((β_0+b_{0i})) or the age at diagnosis ($(\beta_0+b_{0i})+(\beta_1+b_{1ij})t_{ij}$). Then, to ascertain the independent contribution of the two parameters, each was then adjusted for the other via concurrent inclusion within a single model.

9.4.3.5.2 Sick quitter effects

To test whether participants with downward trajectories represented a group of 'sick quitters' at increased risk of T2DM, shared random effects models were constructed that also included a parameter equal to the association between the rate of change and the risk of T2DM (α_3). By holding constant any differences in consumption at the intercept (α_1) and at the age of diagnosis (α_2), these fully adjusted models report the relationship between the slope of the longitudinal trajectory independent of past and current consumption (Formula 9.4).

$$h_i(t)=h_0(t)\exp\{\beta x_i(t_{ij})+\alpha_1 y^a{}_i(t)+\alpha_2 y^b{}_i+\alpha_3 y^c{}_i\}$$

$$y^a{}_i(t)=(\beta_0+b_{0ij})t_{ij}+\varepsilon_{ij}$$

$$y^b{}_i(t)=(\beta_0+b_{0ij})+(\beta_1+b_{1ij})t_{ij}+\varepsilon_{ij}$$

$$y^c{}_i(t)=(\beta_1+b_{1ij})t_{ij}+\varepsilon_{ij}$$

Formula 9.4 Calculation of a shared random effects survival model with an age-dependent slope parameterisation

The resulting slope coefficient is interpreted as the difference in risk per unit increase in the rate of change per year of age (i.e. a slope coefficient equal to one). In order to make this coefficient more meaningful, it was transformed as shown in Formula 9.5 to reflect a 5% increase (HR_{inc}) or decrease (HR_{dec}) in the rate of change per decade increase in age, versus the mean percentage change in weekly alcohol consumption over the period (v).[427] The p-values reported for the each HR are equal, referring to the p-value for the untransformed slope coefficient. To simplify the calculation of the mean rate of change per decade, these shared random effects models were calculated with linear slopes.

$$HR_{inc}=\exp(\alpha_2*((\log(1+5/100))-\log(1+v/100)))$$

$$HR_{dec}=\exp(\alpha_2*((\log(1-5/100))-\log(1+v/100)))$$

Formula 9.5 Calculating the risk of T2DM for a 5% increase or decrease in the rate of change versus the mean percentage change over the period

9.4.3.5.3 Reference category

Finally, to formally explore the effect of providing no adjustment for differences in risk between heterogeneous infrequent, non-current and never drinkers, a sensitivity analyses was run that calculated the intercept and current value dose-response associations without the inclusion of the alcohol consumption indicator variable. Doing so was considered equivalent to running a survival analysis relative to pooled non-drinkers.

9.4.3.6 Goodness of fit

As in Chapter 8, goodness of fit was measured according to the log-likelihood and BIC statistics, with an improvement in fit defined as any reduction in the BIC greater than or equal to a value of 10.[406]

9.4.3.7 Statistical packages

Proportional hazard models were calculated using the -st- package.[390] Where fitted values of weekly alcohol consumption were predicted for inclusion within the two-stage survival model, linear and non-linear predictions were created using the -mixed- package.[407] Shared random effects models were calculated using the -stjm- package.[415] Results from analyses that utilised imputed covariate data were calculated using the -mi- suite of commands.[342] The use of imputed data was not supported by the -stjm- package.

9.5 Results

9.5.1 Conventional survival model

Construction of the conventional survival model began with identifying the best-fitting parametric baseline hazard. Fit statistics from the resulting crude models are reported in Table 9.1. For both men and women, the baseline hazard function was best represented by a Weibull distribution, which was thus selected for all subsequent models in this chapter. The observed and predicted baseline hazard functions are shown in Appendix 9.1.

Table 9.1 Relationship between the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Shared random effects model, goodness of fit statistics, observed data.

Baseline hazard function	Log-likelihood	BIC[a]
Men		
Cox (unspecified)	-4461	8957
Exponential	-1728	3500
Gompertz	-1698	3448
Weibull	-1693	3437
Women		
Cox (unspecified)	-1879	3790
Exponential	-759	1557
Gompertz	-749	1546
Weibull	-747	1542

[a]Bayesian information criterion.

After adjustment for drinking category, a two-fold increase in the weekly volume of alcohol consumption at the intercept was associated with a 4% (HR 1.04, 95% CI 0.98-1.12) increase in the risk of T2DM among men and a statistically significant 26% (HR 0.74, 95% CI 0.65-0.84) decrease in risk among women (Table 9.2).

Multivariable adjustment improved the fit of both male and female conventional survival models. Increases in risk among men were attenuated to the null (HR 0.99, 95% CI 0.92-1.06), and reductions in risk among women reduced to 20% (HR 0.80, 95% CI 0.69-0.93) per two-fold increase in consumption. Results from the imputed dataset, which accounted for missing covariate data, showed comparable results (Appendix 9.2).

Table 9.2 Relationship between the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Conventional survival analysis, observed data.

	Men		Women	
Alcohol consumption (wave	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Model 1				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.04 (0.98, 1.12)	0.211	0.74 (0.65, 0.84)	<0.001
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.25 (0.75, 2.08)	0.385	0.48 (0.24, 0.95)	0.036
Non-current drinker	1.74 (0.83, 3.67)	0.142	0.46 (0.19, 1.11)	0.084
Never drinker	2.39 (1.24, 4.60)	0.009	0.42 (0.18, 0.96)	0.040
Log likelihood		*-1693*		*-747*
BIC[a]		*3437*		*1542*
Model 2				
Cases/non-cases		451/4,342		206/1,847
Consumption volume				
g/week (log_2)	0.99 (0.92, 1.06)	0.679	0.80 (0.69, 0.93)	0.004
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	0.84 (0.48, 1.44)	0.519	0.51 (0.23, 1.12)	0.092
Non-current drinker	1.19 (0.56, 2.55)	0.652	0.44 (0.16, 1.20)	0.109
Never drinker	0.81 (0.38, 1.75)	0.597	0.36 (0.14, 0.95)	0.040
Log likelihood		*-1253*		*-521*
BIC[a]		*2666*		*1188*

Model 1 reported the dose-response relationship between the volume alcohol consumption and T2DM following adjustment for consumption category. Model 2 included additional adjustment for BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status, as defined at baseline. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

9.5.2 Age-varying covariates survival model

Hazard ratios reported according to the current value of alcohol consumption were elevated relative to those associated with consumption at the intercept in Table 9.2. As reported in Table 9.3, doubling of alcohol consumption was associated with an 11% (HR 1.11, 95% CI 1.03-1.19) increase in the risk of T2DM among men and a 16% (HR 0.84, 95% CI 0.74-0.95) reduction in risk among women in crude models. Following multivariable adjustment, risks among men were reduced slightly to a 7% increase in hazards (HR 1.07, 95% CI 0.99-1.15), with an 8% reduction

in hazards reported among women (HR 0.92, 95% CI 0.80-1.06). Hazard ratios estimated using the imputed dataset were comparable (Appendix 9.3).

Table 9.3 Relationship between the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Age-varying covariate survival analysis, observed data.

	Men		Women	
Alcohol consumption	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Model 1				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.11 (1.03, 1.19)	0.004	0.84 (0.74, 0.95)	0.005
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	2.35 (1.37, 4.05)	0.002	0.96 (0.48, 1.91)	0.906
Non-current drinker	2.07 (0.98, 4.37)	0.057	1.15 (0.53, 2.48)	0.722
Never drinker	3.91 (1.95, 7.84)	<0.001	0.67 (0.26, 1.67)	0.387
Log likelihood		*-1673*		*-734*
BIC[a]		*3406*		*1523*
Model 2				
Cases/non-cases		451/4,342		206/1,847
Consumption volume				
g/week (log_2)	1.07 (0.99, 1.15)	0.098	0.92 (0.80, 1.06)	0.241
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.61 (0.90, 2.89)	0.110	1.14 (0.53, 2.45)	0.732
Non-current drinker	1.29 (0.57, 2.95)	0.539	1.26 (0.54, 2.96)	0.594
Never drinker	1.30 (0.58, 2.93)	0.528	0.62 (0.23, 1.71)	0.358
Log likelihood		*-1157*		*-478*
BIC[a]		*2500*		*1124*

Model 1 reported the dose-response relationship between the volume alcohol consumption and T2DM following adjustment for consumption category. Model 2 included additional adjustment for BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five.
[a]Bayesian information criterion.

9.5.3 Two-stage survival model

The best-fitting mixed effects model was determined separately for men and women and plotted in Figure 9.3. These trajectories were consistent with those reported in Chapter 8 (Figure 8.3), with the average volume of consumption increasing up to around 55 years of age before declining thereafter.

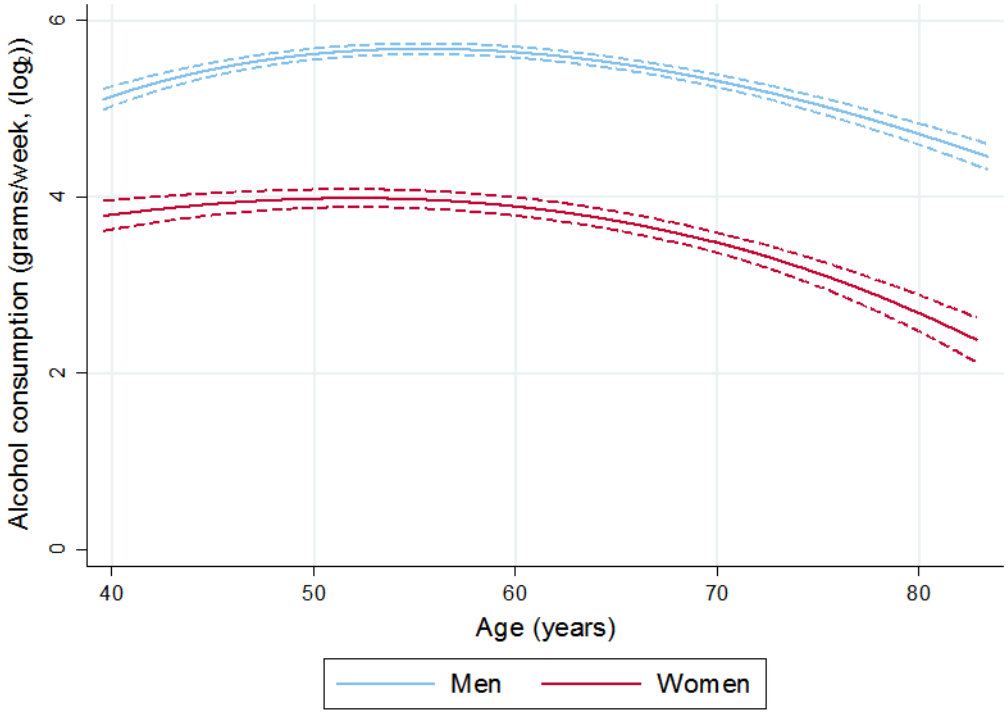


Figure 9.3 Crude, sex-specific and best-fitting trajectories of the mean weekly volume of alcohol consumption (log_2) between the ages of 40-84 years. Observed data.

Multivariable-adjusted risk estimates were closer to the null and no longer statistically significant when calculated based upon predicted values of alcohol consumption. A 4% (HR 1.04, 95% CI 0.97-1.11) increase in T2DM risk was observed per two-fold increase in alcohol intake among men, and an 8% (HR 0.93, 95% CI 0.85-1.02) reduction in risk among women (Table 9.4). Analyses based on the imputed dataset were comparable and are reported in Appendix 9.4.

Table 9.4 Relationship between the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Two-stage survival analysis, observed data.

	Men		Women	
Alcohol consumption	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Model 1				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.05 (0.98, 1.11)	0.151	0.82 (0.76, 0.89)	<0.001
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.41 (1.01, 1.97)	0.045	1.29 (0.91, 1.84)	0.155
Non-current drinker	1.31 (0.66, 2.58)	0.440	1.35 (0.81, 2.25)	0.253
Never drinker	2.52 (1.36, 4.67)	0.003	0.75 (0.36, 1.56)	0.445
Log likelihood		*-1677*		*-730*
BIC[a]		*3413*		*1514*
Model 2				
Cases/non-cases		451/4,342		206/1,847
Consumption volume				
g/week (log_2)	1.04 (0.97, 1.11)	0.262	0.93 (0.85, 1.02)	0.145
Consumption category				
Current drinker	(reference)			
Infrequent drinker	1.23 (0.85, 1.78)	0.279	1.43 (0.95, 2.13)	0.083
Non-current drinker	1.04 (0.49, 2.20)	0.923	1.51 (0.85, 2.67)	0.160
Never drinker	1.06 (0.50, 2.22)	0.880	0.73 (0.33, 1.65)	0.456
Log likelihood		*-1158*		*-478*
BIC[a]		*2502*		*1123*

Model 1 reported the dose-response relationship between the volume alcohol consumption and T2DM following adjustment for consumption category. Model 2 included additional adjustment for BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five.

[a]Bayesian information criterion.

9.5.4 Shared random effects model

9.5.4.1 Intercept versus the current value

Using the same best-fitting trajectories as shown in Figure 9.3, the multivariable-adjusted risk of T2DM per two-fold increase in the intercept and current values of alcohol consumption were estimated in separate models for each sex (Table 9.5). Intake predicted at the age of 39.6 years was associated with little change in the risk of T2DM among men (HR 0.98, 95% CI 0.92-1.05), while a two-fold increase in the current value of alcohol consumption was associated with a non-significant 5% increase in risk (HR 1.05, 95% CI 0.97-1.14). Among women, both the intercept and current values of alcohol consumption were associated with non-significant reductions in risk, though with an effect strongest according to the intercept parameterisation.

Table 9.5 Multivariable-adjusted relationship between intercept and current value parameterisations of average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Shared random effects survival analysis, observed data.

	Men (n=4,793)		Women (n=2,053)	
Parameterisation	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Intercept value				
Consumption volume				
g/week (log_2)	0.98 (0.92, 1.05)	0.628	0.89 (0.79, 1.00)	0.054
Consumption category				
Current drinker	(reference)			
Infrequent drinker	1.03 (0.71, 1.50)	0.868	1.29 (0.83, 1.99)	0.259
Non-current drinker	0.84 (0.43, 1.66)	0.619	1.33 (0.71, 2.50)	0.368
Never drinker	0.82 (0.40, 1.68)	0.588	0.63 (0.26, 1.55)	0.315
Log likelihood		*-38234*		*-15907*
BIC[a]		*76703*		*32026*
Current value				
Consumption volume				
g/week (log_2)	1.05 (0.97, 1.14)	0.189	0.92 (0.81, 1.06)	0.244
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.32 (0.86, 2.02)	0.209	1.37 (0.83, 2.28)	0.217
Non-current drinker	1.14 (0.55, 2.39)	0.725	1.45 (0.73, 2.90)	0.289
Never drinker	1.14 (0.53, 2.44)	0.741	0.69 (0.27, 1.77)	0.443
Log likelihood		*-38233*		*-15908*
BIC[a]		*76701*		*32029*

All models included adjustment for consumption category as well as BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

Table 9.6 reports the same two parameterisations but included concurrently within single sex-specific models. After adjusting for the current value of alcohol consumption, a two-fold increase in the intercept was associated with a statistically significant 20% (HR 0.80, 95% CI 0.69-0.92) reduction in risk among men and a 36% (HR 0.64, 95% CI 0.43-0.97) reduction among women. By contrast, when holding intercept values constant, a two-fold increase in the current value of alcohol intake was associated with a statistically significant 35% increase in risk (HR 1.35, 95% CI 1.12-1.62) among men and a 47% increase in risk among women (HR 1.47, 95% CI 0.94-2.31). No differences in goodness of fit were observed between parameterisations.

After adjustment for the intercept and current values of alcohol consumption, risks were elevated at any age among all heterogeneous non-drinking categories except for female never drinkers, for whom a non-significant reduction in risk was apparent relative to pooled current drinkers (HR 0.82, 95% CI 0.31-2.18).

Table 9.6 Multivariable-adjusted associations between conditional intercept and current value parameterisations of average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Shared random effects survival analysis, observed data.

	Men (n=4,793)		Women (n=2,053)	
Parameterisation	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Intercept value				
Consumption volume				
g/week (log_2)	0.80 (0.69, 0.92)	0.002	0.64 (0.43, 0.97)	0.034
Current value				
g/week (log_2)	1.35 (1.12, 1.62)	0.001	1.47 (0.94, 2.31)	0.091
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.56 (1.00, 2.45)	0.052	1.74 (0.99, 3.06)	0.053
Non-current drinker	1.61 (0.73, 3.55)	0.242	1.87 (0.88, 3.99)	0.104
Never drinker	1.43 (0.63, 3.24)	0.397	0.82 (0.31, 2.18)	0.692
Log likelihood		*-38228*		*-15905*
BIC[a]		*76700*		*32032*

All models included adjustment for consumption category as well as BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

9.5.4.2 Reference category

When the separate survival models reported in Table 9.5 were re-run without adjustment for the differences in risk among heterogeneous non-drinking groups, little change in risk estimates was observed among men, while reductions in risk among women were increased. For instance, compared to a non-significant 8% (HR 0.92, 95% CI 0.81-1.06) reduction in risk per two-fold increase in the current value of alcohol intake after adjustment for consumption category, results in Table 9.7 show a significant 13% (HR 0.87, 95% CI 0.81-0.89) reduction in risk.

Table 9.7 Multivariable-adjusted relationship between intercept and current value parameterisations of average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex and without adjustment for alcohol consumption category. Shared random effects survival analysis, observed data.

	Men (n=4,793)		Women (n=2,053)	
Parameterisation	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Intercept value				
Consumption volume				
g/week (log_2)	0.99 (0.94, 1.04)	0.569	0.86 (0.79, 0.93)	<0.001
Log likelihood		*-38551*		*-16088*
BIC [a]		*77308*		*32361*
Current value				
Consumption volume				
g/week (log_2)	1.02 (0.97, 1.08)	0.358	0.87 (0.81, 0.95)	0.001
Log likelihood		*-38551*		*-16089*
BIC [a]		*77307*		*32364*

All models included adjustment for BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

9.5.4.3 Sick quitter effects

The linear trajectory on the log_2 scale was flat over time among men, falling by 0.2% (p=0.894) per decade. By contrast, female consumption fell by an average 3.1% (p=<0.001) per decade. Table 9.8 reports the multivariable-adjusted association between differences in these rates of change and the risk of T2DM, after adjustment for past and current alcohol consumption.

Among both sexes, a 5% increase in the decennial rate of change was associated with a slight increase in the risk of T2DM (men: HR 1.12, 95% CI 0.59-2.10; women: HR 1.11, 95% CI 1.01-1.62). By contrast, a 5% reduction in the rate of change was associated with a small decrease in

the risk of T2DM among both sexes (men: HR 0.89, 95% CI 0.46-1.73; women: HR 0.97, 95% CI 0.60-0.99).

Table 9.8 Multivariable-adjusted relationship between the rate of change in the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Shared random effects survival analysis, observed data.

	Men (n=4,793)		Women (n=2,053)	
Parameterisation	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Intercept value				
Consumption volume				
g/week (log_2)	0.48 (0.24, 0.93)	0.030	0.54 (0.22, 1.33)	0.179
Current value				
Consumption volume				
g/week (log_2)	2.45 (1.23, 4.88)	0.010	1.80 (0.73, 4.45)	0.202
Slope				
5% increase in the rate of change				
g/week (log_2)	1.12 (0.59, 2.10)	0.733	1.11 (1.01, 1.62)	0.897
5% decrease in rate of change				
g/week (log_2)	0.89 (0.46, 1.73)	0.733	0.97 (0.60, 0.99)	0.897
Log likelihood		*-38282*		*-15917*
BIC[a]		*76808*		*32056*

All models included adjustment for consumption category as well as BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

9.6 Summary of findings

This chapter aimed to investigate the merit of utilising parameterisations of the longitudinal trajectory conventionally overlooked by existing survival analyses, and establish whether participants with downward trajectories of alcohol consumption represent a distinct group of sick quitters at elevated risk of T2DM.

Despite adopting a different timescale, results from the conventional survival models reported in Table 9.2 are consistent with the meta-analysis reported in Chapter 3, whereby consumption predicted at 39.6 years of age was associated with reductions in risk only among women. When the dose-response relationship was instead modelled according to the current value of

consumption, female reductions in risk remained present but were of a smaller magnitude regardless of the method used (Tables 9.3 to 9.5).

In order to establish which of these two different dimensions of the longitudinal trajectory might be the most important for estimating T2DM risk, a shared random effects model was constructed that modelled both parameters concurrently (Table 9.6). After adjusting for differences in the current volume of intake, a two-fold increase in alcohol consumption at the intercept was associated with sizeable reductions in T2DM risk. Conversely, when adjusting for differences in intercept values, higher current values of consumption were associated with a greater risk of T2DM. A sensitivity analysis that excluded adjustment for consumption category indicated more pronounced reductions in risk among women for both parameterisations of alcohol consumption (Table 9.7).

Finally, to determine whether participants who decreased their consumption over time represented a group of 'sick quitters' who may have attenuated their intake owing to having manifested symptoms associated with an elevated risk of T2DM, a shared random effects model was constructed that modelled the effect of differences in rate of change independent of past and current consumption (Table 9.8). Although men and women who decreased their consumption at a faster rate appeared to show slightly lower risks of T2DM, associations were not statistically significant.

9.7 Limitations

The dose-response relationship between the weekly volume of alcohol consumption and the risk of T2DM was estimated by linking longitudinal and survival processes via a range of increasingly complex methods. An alternative approach considered was to jointly model both processes with trajectories of alcohol consumption captured via latent classes.[428,429] Rather than treating participants as a homogenous group by estimating participant-specific slopes constrained according to the same longitudinal function, the joint latent class approach instead treats the population as heterogeneous and thus constituted of multiple disparate trajectory profiles, such as those illustrated in Figure 3.17. Using this approach, participants are divided into a finite number of latent sub-groups, with their membership defined according to a categorical latent variable that can then be included within a survival sub-model.[428] As each latent class represents a specific average trajectory, corresponding risk estimates can be used to ascertain the effect of a particular drinking typologies upon the risk of T2DM, such as a pattern of stable moderate consumption. In this sense, a joint latent class model can offer an interpretive benefit over a shared random effects model.

However, the joint latent class approach is subject to its own limitations.[428] As described elsewhere, the composition of distinct latent classes is in part dependent upon population heterogeneity or, more specifically, the degree of longitudinal variability in a given variable.[259] Thus, if most participants within a cohort exhibit similar consumption trajectories over time, the majority will be categorised into a single latent class with no resulting capacity for exploring differences in risk according to heterogeneous trajectories of clinical interest. This particular shortcoming has been found to apply to the Whitehall II dataset, with heterogeneous non-drinking groups pooled with light drinkers, and heavier drinkers combined with more moderate users of alcohol.[430,431] Such groupings highlight the arbitrary and potentially non-informative nature of statistically-derived latent classes, and indicate that joint latent class models applied to Whitehall II data for the exploration of T2DM risk were likely to insufficiently disaggregate heterogeneous consumption categories, thereby falling foul of the same misclassification errors present in analytic methods conventionally applied in epidemiologic research. In addition, by modelling heterogeneity in longitudinal consumption solely through the derivation of latent categories, it is not possible to explore the relationship between different dimensions of such heterogeneity and T2DM risk, such as the rate of change or deviation from the mean trajectory.[422] It was for these reasons that a shared random effects approach was chosen.

In contrast to the majority of previous studies, which report age-adjusted risk estimates with a time-to-event metric, the analyses reported in this chapter used age as the timescale of interest due to both the incidence of T2DM and volume of alcohol consumption operating as a function of age as opposed to the time and length of participation.[419,420] Results derived from models in this chapter and those reported elsewhere thus may not be directly comparable. To explore how results may have differed according to the choice of timescale, post-hoc sensitivity analyses were run that reproduced the shared random effects models reported in Tables 9.5 and 9.6 but using a conventional time-to-event timescale. With the intercept and current value parameterisations modelled separately, estimates remain of the same direction and approximate magnitude, with reductions in risk continuing to be most pronounced among women (Appendix 9.5). When both parameters were estimated concurrently, as per Table 9.6, both parameterisations remained statistically significant, with the same differential dose-response relationships still reported (Appendix 9.6). These sensitivity analyses affirm that similar conclusions are drawn irrespective of the choice of timescale. Specifically, that conventional approaches may oversimplify the relationship between alcohol and T2DM risk through a failure to consider changes in alcohol consumption across the life course.

Utilising an age-based timescale within a shared random effects framework should permits the calculation of dose-response relationships according to intakes at specific ages that may be of utility to policymakers or clinicians. This is achieved by applying a lag effect to the current value parameter, whereby the risk of T2DM at age t is calculated according to the value of the longitudinal trajectory at t-c, where c is the lag of interest.[422] Unfortunately, the -stjm- package still in the process of being developed, with such functionality is not yet available. As a result, risks reported Chapter 9 were limited to alcohol consumption at the intercept (40 years of age) and the current value (a mean 62 years of age). Although possible to rescale the age variable such that the intercept intersects age at a point in the life course that may be of greater interested to policymakers, such as the minimum legal drinking age, such a model would be required to extrapolate the longitudinal trajectory far beyond the period observed. The validity of any resulting estimates would thus be questionable given that the functional form of the longitudinal trajectory between middle age and later life was unlikely to hold when extended to a period such as young adulthood, which is marked by pronounced elevations in consumption from very low volumes.[259,266]

All reported models assumed a linear dose-response relationship between the volume of alcohol consumption and the risk of T2DM. Such an assumption was not consistent with the non-linear dose-response curve reported in Chapter 3. However, as indicated in Chapter 7, the positive skewness and low average volume of alcohol consumption within the Whitehall II cohort were such that it may not have been possible to detect non-linear dose-response relationships, such as increases in risk at higher intakes. To explore the possibility that a non-linear dose-response relationship may be present between an alternative parameterisation of alcohol consumption and T2DM risk, fitted values from the two-stage models reported in Table 9.4 were transformed according to a restricted range of fractional powers, as detailed in Section 3.2.4.1. No improvements in BIC were identified for any non-linear dose-response association, relative to the linear model. As a result of such a limitation, caution should be applied when interpreting the linear dose-response coefficients and seeking to extrapolate them to higher volumes of drinking. Moreover, from a public health perspective, while higher volumes of alcohol consumption at the intercept appear associated with reductions in T2DM risk among both sexes after adjustment for consumption later in the life course (Table 9.6), it should be borne in mind that drinking may still be associated with a heightened risk of other health conditions even at relatively low volumes.[432]

Although little difference was evident between coefficients reported for models applied to the observed data and those that accounted for item non-response on covariates, all models were restricted to individuals free of missing alcohol consumption and diagnosis data at wave three. As reported in Chapter 6, participants with unit non-response across ≥4 waves of follow-up (Table 6.5) or item non-response at any point during the study (Table 6.7) exhibited a lower volume of alcohol consumption and worse metabolic risk profile at the beginning of the study than those with observed data. There was thus the possibility that risks associated with lower volumes of alcohol may have been underestimated.

9.8 Discussion

Analyses reported in Chapter 3 and Chapter 7 both indicate a disparity in the dose-response relationship between men and women, with reductions in risk specific to female participants. When the dose-response relationship was parameterised according to drinking at the intercept, two-fold increases in the weekly volume of alcohol consumption were associated with a null effect among men and a borderline significant 11% reduction in risk among women (Table 9.5), consistent with earlier findings.

Capitalising upon the flexibility afforded by shared random effects models, the relationship between intake at the intercept and T2DM risk was recalculated with adjustment for the current value of consumption (Table 9.6). Here, two-fold increases in the intercept were associated with significant reductions in risk in both sexes, but with the magnitude of reduction remaining greatest among women (men: 20%; women: 36%). By contrast, when holding the intercept constant, increases in the current volume of consumption were marked by sizeable increases in risk (men: 35%; women: 45%). With this same disparity in effect found to be apparent when shared random effects models were recalculated based on a time-to-event as opposed to an age-based timescale (Appendix 9.6), there was thus an indication that both parameterisations of the longitudinal trajectory exhibit statistically independent and divergent relationships with T2DM risk. Additionally, that conventional survival analyses which adjust for age and rely upon a single measurement of alcohol consumption fail to report important differences in the dose-response relationship across the adult life course.

Given a mean age of 62 years at the time of diagnosis, and a median follow-up of 20 years from the intercept, the results suggest that increases in risk associated with higher volumes of consumption may be specific to intake at older age. Such an effect would be in accordance with studies that report age-related impairments to the alcohol metabolism[196,197,198,199] and consequent increases in length of exposure to higher concentrations of pro-inflammatory

metabolites such as acetaldehyde and acetate.[200,201] Unfortunately, although interventional studies have investigated the relationship between alcohol consumption and a range of inflammatory biomarkers, the number of studies is small, methods are heterogeneous and pooled effects statistically insignificant.[118] While a J-shaped association was estimated between alcohol consumption and CRP in an analysis based on data from 22 Mendelian randomisation studies,[131] estimates were not disaggregated by age group. As such, it was not possible to state conclusively whether alcohol may differentially affect the concentration of inflammatory biomarkers according to the age of participants. Although evidence concerning the inflammatory pathway is currently tenuous, results in Table 9.6 nonetheless allude to the possibility that any advantageous biological effects of alcohol consumption, such as the linear increases in HDL concentration reported by interventional studies,[117,118,119] may be outweighed in later life by heightened inflammatory responses following age-related impairments to the alcohol metabolism.

This hypothesis was further substantiated by a post-hoc analysis, which estimated the effect of differences in the longitudinal trajectory after adjusting solely for drinking at the intercept (Appendix 9.7). Relative to the mean slope, a 5% decrease in the rate of change was associated with significant reductions in the risk of T2DM among both sexes (men: HR 0.42, 95% CI 0.29-0.61; women: HR 0.77, 95% CI 0.63-0.94). These reductions in risk may have been a consequence of participants with faster longitudinal declines in alcohol consumption having consumed alcohol in lower volumes during the sensitive period of old age, relative to those who decreased their intake at the average rate.

Adults who reduce their intake over time are typically posited to represent a group of individuals who attenuate their drinking owing to ill-health,[136,138] with a number of studies linking the onset of poor health to a cessation of drinking[144,145,146] or a reduction in the frequency of consumption.[418] In an effort to isolate the relationship between differences in the rate of change and T2DM risk, analyses were undertaken that reported a slope coefficient following adjustment for past and current intake (Table 9.8). Among both sexes, participants who reduced their alcohol consumption at a faster rate than the mean experienced a lower risk of T2DM, though risk estimates were non-significant. Accordingly, the fully-adjusted model failed to corroborate the presence of a sick quitter effect, whereby participants with a faster rate of decline would instead be expected to report a higher risk of T2DM, independent of the volume consumed.

It was possible that a sick quitter effect was lost as a consequence of the diverse reasons for which study participants appear to attenuate their alcohol consumption. For instance, while

previously published analyses of Whitehall II data indicate that around 21% of men and 22% of women who reduced their intake did so as a direct consequence of illness or pharmaceutical contraindication, a far higher proportion reduced their drinking as a health precaution (men: 45%; women: 34%), with others doing so for reasons as broad as a reduction in opportunities for social drinking, an effort to save money, pressure from family and friends and a history of alcohol misuse.[408] Elsewhere, an analysis of longitudinal data from the Health and Retirement Study reported differences in longitudinal trajectories according to a range of socio-economic factors, with greater affluence and a higher frequency of socialising all associated with increased probabilities of an upward drinking trajectory.[289] Other studies report similar findings, with low incomes[433,434,435] and low education[435] associated with reductions or steeper declines in the volume or frequency of alcohol consumption, suggesting that disposable incomes and social networks may affect drinking behaviours other than just the onset of poor health. Although associations have also been found between drinking trajectories and retirement, effects appear to vary according to differences in occupational drinking cultures.[435] While differences in consumption by these socio-economic factors could feasible be a consequence of correlations between socio-economic status and health,[436] effects were robust to adjustment for illness and self-reported health.[289,433,434,435] Thus, despite evidence linking decreases in alcohol consumption to a decline in health, the determinants of downward trajectories are complex, with health protection, family pressures and socio-economic factors all playing a role in determining longitudinal drinking patterns.

As an alternative explanation for the absence of an increased risk among participants with faster rates of decline, it was possible that selection bias may have been a factor. Specifically, participants who were experiencing a decline in health status owing to issues associated with a heightened risk of T2DM, such as such as obesity or hypertension, may have chosen to withdraw themselves from the study. In doing so, sampled participants with downward trajectories would disproportionately represent those who decreased their consumption due to factors not associated with an increased T2DM risk.

In summary, the results reported in this chapter appear to indicate that conventional survival analyses may provide too simplistic a picture of the relationship between alcohol consumption and the risk of T2DM. When intercept and current values of alcohol intake were estimated concurrently, disparate dose-response associations were identified. With age used as the timescale, there was an indication that reductions in risk associated with alcohol consumption in midlife may be countered by a greater sensitivity to alcohol in older age. In the absence of

more robust evidence concerning the validity of putative pathways by which alcohol may reduce the risk of T2DM, it would be unwise to recommend that non-drinking adults begin consuming alcohol, especially if such individuals abstained owing to ill-health, pharmaceutical contraindication or a history of alcohol misuse. Furthermore, with higher volumes of alcohol consumption associated with an increased risk of T2DM with advancing age, and relatively moderate volumes in midlife associated with reductions in risk, it would be a reasonable precaution to recommend a general attenuation to the volume of consumption among drinkers.

Chapter 10
Discussion

10 Discussion

10.1 Research questions

Previous meta-analyses suggest that moderate alcohol consumption may reduce the risk of T2DM, with the latest publication at the time of commencing this project having reported a J-shaped association and a peak reduction in risk at around 22-24 g/day among both sexes, relative to quasi-never drinkers.[10] When this meta-analysis was updated through the inclusion of 21 studies that were either newly published or provided updated data with longer periods of follow-up or improved confounder adjustment, significant differences in dose-response were found between men and women. As reported in Chapter 3, the most up-to-date observational data suggest that any reduction in risk may actually be specific to women, peaking among those that consume an average 35 g/day (HR 0.66, 95% CI 0.55-0.78).

However, when constituent studies were investigated in more detail, a series of methodological flaws were identified that may undermine the validity of any inference drawn from this result, including a failure to account for differences in risk among heterogeneous non-drinkers and limited consideration as to the effect of longitudinal changes in alcohol consumption upon the dose-response relationship reported.

As a result of such observations, a number of primary aims were formulated:

1. Determine the degree to which categories of alcohol consumption risked being subject to misclassification error as a result of longitudinal changes in alcohol consumption.
2. Describe differences in the mean volume of alcohol consumption over the life course according to T2DM diagnosis.
3. Formally explore the utility of more advanced survival models in developing a better understanding of the relationship between alcohol consumption and T2DM.

Findings from each resulting analysis are summarised in the following section.

10.2 Summary of findings

10.2.1 Misclassification error

Although analyses of the relationship between alcohol consumption and T2DM have conventionally defined intake according to a single measure as reported at baseline, longitudinal data from multiple cohort studies have shown that alcohol consumption varies across the life course.[259] As a consequence of such changes, there was a risk that categories of alcohol

consumption defined in the existing literature may have been subject to misclassification error, complicating interpretations of associated risk estimates. To provide an indication as to how any misclassification error might be distributed across baseline categories, mixed effects models were constructed to plot the mean longitudinal trajectory of alcohol consumption within a series of distinct baseline categories.

When the sex-specific trajectory was stratified in such a manner, marked differences in rates of change were apparent over the adult life course captured by Whitehall II (Figure 8.5). While consumption among moderate baseline drinkers remained little changed over time, male and female participants in the highest categories exhibited a marked decline in drinking with advancing age, with gradual increases in consumption among infrequent drinkers. Accordingly, depending upon the point in the life course at which baseline categories are defined, moderate drinkers may be subject to differential degrees of misclassification error through contamination with heavy and infrequent drinkers. Given the longitudinal convergence of baseline consumption categories toward moderate volumes, misclassification error may be most pronounced in cohorts of older ages. This may go some way toward explaining the less pronounced reductions in the risk of CHD[409] and all-cause mortality[395] reported elsewhere among moderate drinkers in older age groups.

Further stratifying longitudinal trajectories according to the diagnosis of T2DM revealed that the risk of misclassification error appeared greatest among men and women who developed the condition, with greater rates of change as a function of age than those who were censored (Figures 8.10 and 8.11). In particular, consumption among male moderate baseline drinkers increased to such a degree as to be markedly higher than originally classified come the time of diagnosis. As a consequence, conventional survival analyses may risk overestimating the hazardous effects of moderate drinking among men by failing to consider increases to their consumption over time. By contrast, while moderate female drinkers who developed T2DM instead showed little change in consumption over time, they instead risked being increasingly contaminated by infrequent and former heavy drinkers depending upon the point of baseline measurement. As such, studies of women with a shorter time to event may underestimate any advantageous effects of moderate drinking by giving no consideration to the disparate drinking histories of cross-sectionally defined moderate drinkers.

Longitudinal changes to the volume of alcohol consumption as reported in Chapter 8 help draw attention to the risk of misclassification error inherent to conventional survival analyses according to the age of participants at baseline and the time to diagnosis. In so doing, Chapter

8 highlights the possibility that studies may be improved by analyses that give consideration to changes in alcohol consumption across the life course.

10.2.2 Differences in alcohol consumption according to the diagnosis of T2DM

Based on the current literature, a number of hypotheses were proposed concerning how the mean trajectory of alcohol consumption might differ by T2DM status. These included the possibility that the increased risk of T2DM associated with higher volumes of consumption may accumulate over time and therefore be indicated by prolonged or permanently elevated intakes among participants who developed the condition – particularly among men, for whom reductions in risk were not apparent at any level according to the revised and updated meta-analysis reported in Chapter 3. Alternatively, it was possible that increases or decreases in the risk of T2DM might instead be specific to a period of the life course during which sensitivity to the effects of alcohol may be elevated.

While male intake was equivalent around 30 years prior to diagnosis, differences by diagnosis category gradually increased over time. At the point of diagnosis or censoring, consumption among men that developed T2DM was higher than among those who were censored, with a difference equal to around 1.8 pints of 4.0% ABV lager per week on average. With an average age at the time of diagnosis of 62 years, male consumption trajectories were most in keeping with the second hypothesis: that male sensitivity to the deleterious effects of alcohol consumption may be most pronounced later in the life course.

By contrast, neither hypothesis was supported by results from models applied to women. Rather than consumption among those who developed the condition being consistently higher than among censored female participants, or highest specifically during the few years preceding diagnosis, mean consumption was instead consistently below that of women who did not develop T2DM. Such a finding was in conflict with results from the revised meta-analysis in Chapter 3, particularly with mean consumption among both groups of women being permanently within the threshold at which reductions in risk were reported (Chapter 3).

At least two reasons for this incongruity were possible. First, the plotting of mean consumption trajectories may have masked important differences in the constitution of each female trajectory. For instance, the mean trajectory for women who developed T2DM may have been comprised not primarily of persistent low volume and therefore lower risk drinkers, but of both infrequent and former heavy drinkers who may have attenuated their drinking due to poor health prior to study participation. Loosely supporting this, sensitivity analyses that plotted the

same trajectories but excluded zero consumption data indicated that transitions to non-drinking prior to diagnosis or censoring appeared most common among women who developed T2DM, attenuating the difference between the two trajectories (Appendix 8.25). It was therefore plausible that women at risk of T2DM tended to drink alcohol in lower volumes or were more likely to transition to abstention due to adverse health effects from pre-diabetes or its associated risk factors. In this sense, though their volume of drinking was within the range associated with a lower risk of T2DM, this reduction in risk may have been offset by risk factors unaccounted for in the crude analyses. As an alternative explanation, it was also plausible that the absence of trajectories consistent with *a priori* hypotheses may have been attributable to a relatively limited range of alcohol consumption among women, with heavier drinkers being few in number. As such, higher-risk heavier drinkers may have been hidden by a vastly greater proportion of more moderate female drinkers who developed the condition.

10.2.3 Importance of different dimensions of the longitudinal trajectory

10.2.3.1 Intercept versus current consumption

10.2.3.1.1 Primary findings

Despite marked changes to the volume of drinking across the life course, and apparent differences in longitudinal alcohol consumption among men by diagnosis status, survival analyses have conventionally parameterised the dose-response relationship according to just a single cross-sectional measurement obtained at baseline. A final series of analyses was thus undertaken to formally explore the appropriateness of limiting the parameterisation of alcohol consumption in such a fashion.

To achieve this, shared random effects models were constructed that calculated the dose-response relationship according to whether drinking was defined at the intercept (40 years) or the time of diagnosis (mean 62 years of age), with a further analysis undertaken to model both parameters concurrently so as to establish the relationship of each parameter with T2DM after accounting for future or prior drinking. By using age as the timescale, such analyses also permitted some inference to be made as to differences in the dose-response relationship according to the age at which alcohol was consumed. Although the use of age as a timescale is currently rare within the alcohol literature, with only one study selected as part of the revised and updated meta-analysis having adopted such an approach,[245] sensitivity analyses that used the more conventional time-to-event timescale corroborated findings from the primary analyses (Appendices 9.5 and 9.6).

In models that parameterised the longitudinal trajectory according to consumption at the intercept, results were in keeping with those from the revised and updated meta-analyses reported in Chapter 3, whereby reductions in risk were specific to female drinkers (Table 9.5). When the relationship between the weekly volume of alcohol consumption and T2DM risk was instead parameterised according to the current value of alcohol consumption, reductions in risk remained among women but were attenuated in magnitude (Table 9.5). However, when the dose-response relationship was calculated between the intercept and T2DM risk following adjustment for consumption later in the life course, significant reductions in risk were apparent among both sexes, with the magnitude of reduction still greatest among women, at 36% per two-fold increase in consumption versus 20% among men (Table 9.6). By contrast, when the current value of consumption was modelled after holding constant the volume of drinking at the intercept, increased risks of T2DM were evident among both sexes. Such a finding confirms that both parameterisations exhibit statistically independent and divergent relationships with T2DM risk, and thereby suggests that conventional survival analyses fail to capture differences in dose-response across the life course due to their use of a single baseline measure.

That risks associated with higher volumes of consumption appeared more pronounced with advancing age was an effect in accordance with findings from Chapter 8 and consistent with studies that report an age-related deterioration to the alcohol metabolism.[196,197,198,199] While such deterioration may to individuals of a more advanced age experiencing longer periods of exposure to higher concentrations of pro-inflammatory metabolites such as acetaldehyde and acetate,[200,201] insufficient evidence is currently available to substantiate a dose-response effect of alcohol consumption upon inflammatory biomarkers, or how any such effect might operate differentially across the life course.

10.2.3.1.2 Possible explanations for sex-specific dose-response effects

Differential biological pathways

Analyses undertaken in Chapters 3, 7 and 9 all report reductions in the risk of T2DM as being either specific to or most pronounced among women when defined at baseline, even following adjustment for consumption at the time of diagnosis. The reproducibility of this difference lends credence to the possibility that putative biological pathways may operate differently between men and women. However, of the studies available, little evidence of a sex interaction is currently apparent. While there is some suggestion from interventional studies that acute alcohol exposure may elicit a greater increase in insulin sensitivity among women than men, such a disparity was no longer statistically significant following the exclusion of a study that

represented a primary source of between-study heterogeneity.[112] Although studies investigating the effect of alcohol upon HDL concentration are far greater in number, no sex-specific effects have been identified across interventional[118] or Mendelian randomisation studies.[85] Similarly, there is no apparent difference in CRP concentration among men and women sampled across 42 Mendelian randomisation studies,[85] while a meta-analysis of the few interventional studies investigating alcohol and inflammatory markers reported no sex interaction.[118] Though possible that putative biological mechanisms may indeed operate differentially between men and women, robust supporting evidence is lacking.

Differential drink preference

Alternative explanations considered included sex-specific differences in drink preference. While current evidence tends to indicate greater reductions in risk among study participants who consume wine,[238,246,398] no such effect appeared evident within the Whitehall II cohort, with no difference in dose-response found by drink type within preliminary conventional analyses (Table 7.6). Although the magnitude of reductions in risk appeared greatest for beer consumption, current evidence concerning pathways between beer-specific compounds any anti-inflammatory response was only available from a small number of *in vitro*[399] and *in vivo* animal studies.[400] Given its potency, it seems more likely that the inflammatory effects of ethanol may far outweigh any anti-inflammatory effects of drink-specific compounds.[282]

Differential consumption patterns

An alternative hypothesis concerned the possibility that female drinkers within the cohort were more likely to spread their weekly volume of alcohol consumption over a greater number of days, with a larger proportion of men being episodic heavy drinkers. Such an assertion was mooted following research indicating that reductions in the risk of T2DM and other vascular events may be lowest among regular moderate drinkers,[95,97,240,244] with elevated risks most apparent among binge and episodic heavy drinkers,[96 244] even if binge drinkers otherwise consume alcohol at moderate volumes the majority of the time.[268] When continuous weekly alcohol consumption data were modelled in Chapter 7 with an interaction according whether participants consumed alcohol on a daily or non-daily basis, interaction terms were statistically insignificant for both sexes (Table 7.5). It was likely that the absence of a statistically significant interaction was attributable to Whitehall II volume and frequency data being insufficient to explicitly identify episodic heavy drinking – the specific characteristic most strongly associated with heightened risks relative to regular moderate drinking. However, even were such variables available, it was possible that the number of episodic heavy drinkers may have been insufficient

to detect an interaction, with both excessive consumption and binge drinking most prevalent within lower socio-economic groups[396,397] and the Whitehall II being skewed toward higher levels of socio-economic status.

Interaction with sex hormones

A final alternative hypothesis pertains to the possibility that sex hormones may play a role in modifying the effect of alcohol upon T2DM risk. To date, two hormonal biomarkers have been implicated as modifiers of T2DM risk: estradiol, a female sex hormone, and SHBG, a protein involved in the transport of sex hormones. Although results pooled from multiple case-control studies have indicated no difference between men and women in the concentration of estradiol by diagnosis status, women who develop T2DM showed lower concentrations of SHBG while men displayed no difference in concentration by diagnosis status.[273] Unfortunately, in addition a lack of any clear pathway by which factors such as SHBG may modify T2DM risk,[273] research concerning a sex-specific effect of alcohol consumption upon hormone transport activity is lacking and almost entirely cross-sectional.

Summary

Current research is insufficient to draw any firm conclusions as to why female drinkers appear to experience the greatest reduction in the risk of T2DM. In the absence of further and more robust analyses concerning sex differences in the effects of alcohol consumption upon putative biological pathways, disparities in consumption pattern are perhaps the most likely determinant, with data from UK-based studies indicating a greater prevalence[101] and probability[269] of episodic heavy drinking among men.

Whatever the precise reason for differences in dose-response between men and women, it is clear from more advanced survival analyses that the association between alcohol consumption and T2DM risk is likely to be more complex than captured from conventional survival analyses, which fail to consider differences in dose-response across the adult life course.

10.2.3.1.3 Effect of abstention category upon dose-response

Criticism has been levelled at the use of pooled non-drinkers as a reference group, with reductions in risk among current drinkers purported to be artificially increased given its inclusion of former drinkers predisposed to an increased risk of negative health events.[136,137] In response, the revised and updated meta-analysis reported in Chapter 3 included sex-adjusted dose-response curves stratified according to whether selected studies utilised a pooled non-drinking or strictly-defined never drinking abstention category. The dose-response relationship differed

significantly according to the choice of abstention reference category, with reductions in risk most pronounced among studies that calculated risks relative to pooled non-drinkers (Figure 3.5). Such a finding is in keeping with studies of alcohol consumption and all-cause mortality, which report attenuated reductions in risk among current drinkers when former drinkers are excluded from the abstention reference category.[136,147,148]

In Chapter 7 (Appendices 7.7 and 7.8) and Chapter 9 (Tables 9.5 and 9.7), sensitivity analyses were undertaken which calculated the dose-response relationship with and without adjustment for or the inclusion of heterogeneous infrequent and non-drinkers. Results from these analyses are in line with the meta-analysis of conventional survival studies, confirming the importance of disaggregating heterogeneous non-drinkers and accounting for any effect they may have upon the perceived harms or benefits of current drinking. In both chapters, effects were most pronounced among women. This nuance may have been attributable in part to the multivariable-adjusted risks among male infrequent and non-drinkers drinkers being closer to the null than among women (e.g. Table 9.5).

10.2.4 Sick quitter effects

Participants who reduce their intake over course of a study have for a long time been referred to as 'sick quitters' who attenuate their consumption owing to ill-health. [136,138] Such an assertion is supported by studies that report a higher prevalence of T2DM risk factors[139,140] and poor self-reported health[141,142,143] among former drinkers than current drinkers, with the onset of ill-health associated with a subsequent cessation from alcohol consumption.[144,145,146] However, following a piecewise analysis of consumption trajectories prior to and following diagnosis (Figure 8.9), downward trajectories were only apparent after the date of diagnosis, suggesting that the effect of pre-diabetic symptoms may have been insufficient to elicit a change to drinking behaviour. Furthermore, when trajectories were stratified by baseline consumption, downward slopes were specific to heavier drinkers and evident regardless of sex or diagnosis status (Figures 8.10 and 8.11). Such results indicate that any downward trajectories prior to diagnosis may not have been a consequence of declines to health status of a kind associated with a heightened T2DM risk.

To explore this formally, shared random effects models were constructed that reported the effect of differences in the longitudinal rate of change upon the risk of T2DM after adjustment for past and current volume of consumption. As reported in Table 9.8, men and women who reduced their alcohol consumption at a faster rate than the sample average experienced a lower risk of T2DM, though risk estimates were non-significant. Such a finding appeared contrary to

the sick quitter hypothesis. However, it was possible that the presence of a sick quitter effect was lost as a consequence of the diverse reasons for which study participants attenuate their alcohol consumption, including financial constraints and a decline in opportunities for social drinking[408] – factors not necessarily associated with T2DM risk. Thus, while some adults who reduce their consumption may indeed do so as a result of a deteriorating health status, a downward trajectory is not necessarily indicative of a heightened risk of T2DM but may instead be part of normal ageing processes.

10.3 Limitations

Despite a systematic attempt to describe and mitigate the impact of methodological shortcomings within the existing literature, a number of weaknesses remain that may potentially have biased or undermined the validity of reported associations.

Perhaps the primary limitation concerns the variable used to denote the average weekly volume of alcohol consumed. Rather than strictly representing each participant's average weekly intake, the variable was derived from questions that referred to the volume consumed during the week prior to each interview. It was possible that the volume of alcohol intake as documented during the week prior to an interview provided a poor surrogate for true average weekly consumption. For instance, heavy drinking during the week prior to interview may not have been indicative of a participant's average weekly consumption throughout a given year, but instead an uncharacteristic period marked by a special occasion such as a family member's birthday or wedding. Such a situation would thus have reflected an episodic heavy drinking occasion as opposed to a high average weekly volume of alcohol consumption. Unfortunately, episodic heavy drinking occasions, as associated elsewhere with a heightened risk of T2DM,[96,240,245] could not be captured using the volume and frequency variables available within the Whitehall II cohort. It was perhaps because of this that interactions between these two drinking dimensions were not statistically significant, providing a poor parameterisation of the type of consumption pattern most associated with elevated risks of T2DM. The true effect of unobserved episodic heavy consumption upon the relationship between the weekly volume of alcohol consumption and T2DM risk was thus unknown and dependent upon the distribution of such episodes across the volume distribution.

More useful alcohol consumption data may have been obtained from a graduated frequency questionnaire, which ask participants about the frequency with which they typically consume alcohol according to a series of pre-defined volumes. Such methods have been found to yield higher average volumes of estimated alcohol consumption than quantity-frequency

questionnaires,[391] and would help with the identification of episodic heavy consumption. The identification of such episodes is likely to be critical to providing a more accurate assessment of the benefits and risks associated with alcohol consumption.

Although associations identified within the Whitehall II cohort appear consistent with those reported from studies of general population samples, [296] it should nonetheless be noted that the relatively low volume of alcohol consumption was such that power to detect increases in the risk of T2DM at higher levels of the volume distribution was likely to have been impaired. Thus, although the presence of a non-linear dose-response relationship was tested in Chapter 7 as part of a conventional survival analysis, the null result was unlikely to have been a consequence of a true linear reduction in risk at ever-increasing volumes of alcohol consumption but rather an insufficient number of heavier drinkers with which to detect a turning point in the dose-response relationship. For instance, while point estimates from the meta-analysis in Chapter 3 indicate that the risk of T2DM becomes elevated among women at volumes >140 g/week, relative to pooled non-drinkers, just 152 women within the Whitehall II cohort reported consumption anywhere above that level at wave three, with the figure falling to just 105 by wave 11.

Another notable limitation concerned the application of imputed data. Firstly, regarding imputed values of alcohol consumption, it was not possible to predict never drinking among participants with missing alcohol consumption data due to the small number of strictly defined never drinkers within the Whitehall II cohort. As such, analyses inclusive of a categorical alcohol consumption variable were restricted to participants with observed alcohol consumption data only. Given that the median volume of alcohol consumption was lower and the prevalence of metabolic risk factors greater at the commencement of the study among participants with unit (Table 6.5) or item non-response (Table 6.7) than those with complete-case data, restriction of the dataset may have resulted in an underrepresentation of higher-risk light or non-drinkers in survival analyses undertaken for Chapters 7 and 9.

Aside from limitations concerning the use of imputed categories of alcohol consumption, constraints of the statistical software are such that it was not possible to utilise imputed T2DM and time to event data. As noted above, participants with unit non-response tended to have a worse metabolic risk profile at baseline than those with complete-case data. It was therefore likely that the incidence of T2DM among the original cohort was underestimated, with analyses applied to a healthier sub-sample than originally participated. The precise impact of such attrition upon reported dose-response relationships would be dependent upon how unobserved

cases were dispersed across the alcohol consumption distribution. For instance, were attrition more common among heavier drinkers, then any increased risk associated with higher volumes of alcohol intake would have been underestimated. Perhaps as a consequence of the limits concerning the imputed data that could be applied, differences in the primary dose-response relationship between models applied to the observed and imputed datasets were negligible.

10.4 Strengths

A deliberate attempt was made to systematically overcome the limitations inherent to the existing body of epidemiological research in the field, with a view to providing a more accurate and detailed understanding of the dose-response relationship between alcohol consumption and the risk of T2DM.

Firstly, contrary to the vast majority of current studies, participants with zero consumption were disaggregated into heterogeneous infrequent and non-drinking categories, each posited and later confirmed to exhibit disparate and usually elevated risks of T2DM, relative to current drinkers (Table 9.6). Rather than combining these heterogeneous groups into a single reference category, as per convention, risk estimates were instead adjusted for differences in risk between heterogeneous non-drinkers. Such an approach is expected to have helped reduce the extent to which any reductions in risk reported among current drinkers occurred as an artefactual consequence of having compared drinkers against a number of less healthy non-drinkers (Table 7.2). Such an approach is supported by research elsewhere,[136,137,148,437] as well as by results from the meta-analysis in Chapter 3, which showed a greater reduction in risk at moderate volumes of consumption when former drinkers were included within the abstention reference category.

In addition, contrary to the minority of current studies to have also distinguished between different non-drinking groups,[96,219,230,244] never drinkers were not defined according to a single self-report of life-long abstention. With longitudinal research elsewhere having reported that between 52%,[150] 67%[315] and 87%[438] of study participants cross-sectionally defined as never drinkers had previously reported drinking at an earlier wave, never drinkers were instead coded as those who consistently reported being never drinkers and who declared zero consumption at all previous waves, thereby reducing the misclassification of never drinkers.

This project is the first to report differences in the longitudinal trajectory by T2DM diagnosis, highlighting discrepancies in the volume of alcohol consumption and thereby the periods in which increases or decreases in risk may most likely be conferred (Chapter 8). The results reported in Chapter 9 also represent one of the very few instances in which consideration has

ever been given to longitudinal changes in alcohol consumption, with just two previous studies known to have documented the risk of T2DM according to temporal variations in consumption.[153,267] Contrary to the approaches adopted by these two studies, the analyses in reported in Chapter 9 estimated the independent dose-response relationship between different dimensions of the longitudinal trajectory and T2DM, utilising advanced joint modelling techniques that provide more accurate estimates than simpler analytic alternatives.[411,412]

10.5 Further research

Results reported in Chapter 9 indicate that the risks associated with drinking may be especially pronounced in older age, potentially countering any reductions in risk conferred earlier in the life course. Important now are replication studies designed to establish whether the same dose-response associations are present in different cohorts. Such research should focus upon the analysis of longitudinal datasets with repeated measures of sufficient regularity and covering as broad a duration of the adult life course as to model acute fluctuations in dose-response with advancing age. In selecting studies for testing reproducibility, a number of other important characteristics should be considered given the limitations present within Whitehall II.

Firstly, because of the narrow range of weekly alcohol consumption reported by Whitehall II participants, cohorts should be selected with a greater number of heavier drinkers, providing a better capacity for modelling the non-linear associations indicated in Chapter 3. Secondly, with apparent differences in dose-response according to whether or not individuals participate in binge drinking,[94,240,245] and an underestimation of average consumption based on quantity-frequency questionnaires,[391] chosen cohorts should provide more accurate alcohol consumption estimates and sufficient detail for identifying episodic heavy drinking occasions. To achieve this, studies may benefit from the addition of objective transdermal ethanol sensing as a means of monitoring blood alcohol concentrations over extended periods. Such data may prove useful as a means of validating the accuracy of survey-based self-reports, adjusting subjectively reported consumption data as required.[439] Thirdly, to reliably test interactions between the volume of alcohol consumption and factors such as episodic heavy drinking, cohorts should be of a size sufficient to permit tests of sound statistical power. One future possibility is the UK Biobank, which sampled close to 500,000 adults aged 40-69 years by 2010 and is estimated to have statistical power sufficient to detect an odds ratio ≥1.3 after just six years of follow-up for T2DM.[440]

Although reductions in risk appear either specific to or most prominent among female drinkers, research concerning sex-specific differences in the action of putative biological pathways is weak

and inconclusive. Heterogeneous in design and often conflicting in their conclusions, findings are commonly reported by cross-sectional or small-scale interventional studies. Further research is required to better understand the dose-response effects of alcohol consumption upon hypothesised causal intermediates, including insulin sensitivity, HDL concentration and inflammatory response. Such research may benefit from structural equation models designed to quantify both the effect of alcohol upon intermediate factors and the effect of changes to those intermediate factors upon T2DM risk. At present, no analysis has been published that considers the causal pathway in full.

10.6 Policy implications

Since at least 2004,[441] reviews of the evidence base have reported reductions in the risk of T2DM at moderate volumes of regular consumption, with similar findings reported elsewhere for vascular conditions ranging from ischaemic heart disease and stroke.[442] Although recent meta-analyses[10,84] suggest that that peak reductions in the risk of T2DM may be conferred at volumes close to the current recommended limits of 21 units/week among men and 14 units/week among women,[98] T2DM prevention strategies in the UK give no consideration to the role of alcohol, with public health interventions focussing instead upon the impact of other lifestyle factors such as diet and physical activity.[9]

This omission sits contrary to recommendations by some academics that at-risk patients be encouraged to incorporate moderate drinking into their diet,[443,444] and the general public advised that moderate drinking may afford an overall health benefit,[443] even among abstainers.[445] That such recommendations have yet to be adopted by the UK government appears attributable to a lack of consensus amongst epidemiologists regarding the health benefits of drinking.[170] This lack of consensus stems from series of methodological shortcomings, including poor confounder adjustment,[139,446] a lack of established biological mechanisms[446] and the misclassification of drinking categories.[446,136,148]

With the benefits of moderate alcohol consumption reported by existing studies likely to have been overestimated, and insufficient evidence available to substantiate a clear biological mechanism by which alcohol may reduce the risk of T2DM, the appropriateness of using the current literature as grounds for recommending a specific volume of moderate drinking either at the population level or among at-risk sub-groups is questionable. This is especially so when considering the net impact of alcohol consumption, with drinking even at low volumes having been associated with increases in the risk of various cancers.[432] Indeed there are calls from some

quarters that alcohol guidelines should explicitly discourage the drinking of alcohol for perceived health benefits.[447]

Health policy may need to be more nuanced than these two starkly opposed positions, instead advising a general attenuation to the volume of alcohol consumed. Such a position affords two benefits. First, regardless of whether alcohol consumption exhibits J-shaped or linear associations with assorted non-communicable diseases, the net burden of harms associated with alcohol consumption would be lowered through a general reduction in the volume of consumption. Second, by avoiding any suggestion that moderate alcohol consumption may provide a benefit to health, the danger of inadvertently encouraging abstainers to resume consumption would be mitigated. This second point is important given that adults who abstain appear to do so owing to previous alcohol abuse problems, existing ill-health, pregnancy or contraindication with medication.[145,146,408]

Evidence from analyses reported in Chapter 9 suggest that initiatives or policies designed to reduce alcohol consumption may need to pay particular attention to older drinkers. Such a focus is supported by the Royal College of Psychiatrists, which argues that alcoholism and alcohol-related harms within older populations are an under-recognised problem within the UK, with public health policy giving scant consideration to the risks facing drinkers in older age.[448] In response to a perceived oversight by policymakers, the Royal College of Psychiatrists has advised the introduction of age-specific consumption guidelines as a means of communicating at the population level the heightened risks to health experienced by older drinkers, recommending no more than 10.5 units/week for persons aged ≥65.[448] However, although the implementation of an age-specific drinking guidelines for older populations may appear appropriate, such an approach should be balanced against the risk of creating a more complex and less unified health message.[449] With the body of current yet methodologically limited evidence indicating that any cardiovascular benefit from drinking may be limited solely to women aged >55 years who consume volumes below just 5 units/week, and with the risk of non-vascular conditions apparently elevated among both sexes even at low volumes,[99] health messages for older adults should be no different from those for the general population: that current drinkers should aim to reduce the amount they drink, and that non-drinkers should be encouraged to maintain their abstinence.

One notable recommendation from the 2016 Alcohol Guidelines Review was that the alcohol consumption guideline for men should be reduced from 21 units/week to 14 units/week.[99] Such a decision was based on new evidence concerning an increased risk of cancer at low volumes of

consumption and the burden of acute alcohol-related harms that appears to disproportionately befall men, such as drink-related road traffic collisions. Nevertheless, such a recommendation is circumstantially in keeping with results reported throughout this project, which indicate that the risk of T2DM may also be greatest among male drinkers, regardless of the age at which alcohol is consumed. To date, precise reasons underlying this difference are unclear. Of the various possibilities considered, perhaps the most likely factor concerns disparities in drinking pattern by sex, with episodic heavy drinking associated with heightened risks for both T2DM[95,96,97,239,240,244,245] and ischaemic heart disease,[268] and such drinking patterns being most prevalent among men.[101,269] It is therefore reassuring that the 2016 Alcohol Guidelines Review explicitly advises against heavy drinking occasions, with the caveat that adults who continue to binge drink should at the very least aim to reduce the frequency of such behaviour.[99]

While some academics call for the promotion of moderate alcohol consumption among both sexes, observational studies indicative of protective effects at moderate volumes of intake are methodologically weak, with clear causal mechanisms yet to be clearly established. Pending more reliable information concerning the effect of alcohol upon T2DM and a broad range of health conditions, it is inappropriate to recommend that adults take up moderate drinking for a perceived benefit to health, especially given that individuals who abstain from drinking may do so for reasons including a history of addiction, chronic ill-health, pregnancy or pharmaceutical contraindication. Instead, current drinkers should be advised to attenuate both their average weekly consumption and frequency of episodic heavy drinking as a precaution against risks associated with heavy drinking.

Chapter 11
Appendices

Appendix 3.2 The Newcastle-Ottawa quality assessment checklist

NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES

Note: 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 drinker in the community *****
b) somewhat representative of the average current drinker 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, e.g. postal questionnaire
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 a measure of adiposity *****
b) study controls for any additional factor *****

Outcome

1) Assessment of outcome

a) independent blind assessment or objective ascertainment *****
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) <u>Adequacy of follow up of cohorts</u>

a) complete follow up: all subjects accounted for *****
b) subjects lost to follow up unlikely to introduce bias: >5% lost, or description of those lost
c) follow up rate <95% and no description of those lost
d) no statement

11.2 Appendices for Chapter 6

Appendix 6.1 Effect of dietary factors upon the alcohol-T2DM relationship

Men	Sample size[a]		Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Variables of interest	**Participants (n)**	**Incident cases (n)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Alcohol consumption at S3														
Never drinkers[b]	90	16	1.00		1.00		1.00		1.00		1.00		1.00	
Non-current drinkers[c]	587	63	1.08 (0.61-1.92)	0.781	1.11 (0.63-1.97)	0.721	1.10 (0.62-1.95)	0.750	1.11 (0.62-1.97)	0.729	1.08 (0.61-1.92)	0.792	1.10 (0.62-1.95)	0.752
0.1-50.0 g/week	1,429	141	0.96 (0.56-1.66)	0.889	0.99 (0.57-1.70)	0.958	0.97 (0.56-1.68)	0.920	0.98 (0.57-1.70)	0.953	0.96 (0.56-1.65)	0.878	0.98 (0.56-1.69)	0.934
50.1-100.0 g/week	973	103	1.07 (0.61-1.88)	0.802	1.10 (0.63-1.92)	0.744	1.08 (0.62-1.89)	0.784	1.10 (0.63-1.93)	0.744	1.07 (0.61-1.87)	0.813	1.10 (0.62-1.92)	0.751
100.1-150.0 g/week	632	69	1.10 (0.62-1.96)	0.746	1.11 (0.62-1.98)	0.723	1.10 (0.62-1.97)	0.742	1.12 (0.63-2.01)	0.696	1.10 (0.61-1.96)	0.755	1.11 (0.62-1.99)	0.721
>150.0 g/week	1,124	129	1.03 (0.59-1.80)	0.924	1.02 (0.58-1.79)	0.941	1.02 (0.59-1.79)	0.936	1.04 (0.60-1.82)	0.883	1.02 (0.59-1.79)	0.934	1.03 (0.58-1.80)	0.931
BMI														
kg/m^2	4,825	521	1.21 (1.18-1.24)	<0.001	1.20 (1.17-1.23)	<0.001	1.20 (1.18-1.23)	<0.001	1.21 (1.18-1.23)	<0.001	1.21 (1.18-1.24)	<0.001	1.20 (1.18-1.23)	<0.001
Fibre														
g/100g	4825	521	-	-	0.99 (0.98-1.00)	0.020	-	-	-	-	-	-	1.00	
LR test versus BMI						***0.018***							0.98 (0.97-1.00)	0.020
Carbohydrate														
log g/100g	4825	521	-	-	-	-	0.88 (0.68-1.15)	0.359	-	-	-	-	1.27 (0.79-2.05)	0.330
LR test versus BMI								***0.360***						
Polyunsaturated fat														
log g/100g	4825	521	-	-	-	-	-	-	0.92 (0.76-1.12)	0.405	-	-	0.99 (0.78-1.27)	0.943
LR test versus BMI										***0.405***				
Trans fat														
log g/100g	4825	521	-	-	-	-	-	-	-	-	1.03 (0.77-1.37)	0.851	1.02 (0.72-1.43)	0.919
LR test versus BMI												***0.852***		
LR test BMI versus BMI+FFQ														***0.131***

[a]Defined according to those with valid covariate data in Model 6.

[b]Defined as those who reported consuming no alcohol in the last twelve months and having always been a non-drinker.

[c]Defined as those who reported consuming no alcohol in the last twelve months and stated that they had not always been a non-drinker.

Model 1: Adjusted for age (s3), BMI (S3), employment status (S3), ethnicity, family history of T2DM (S3), smoking status (S3), physical activity (S3), occupational grade (S3).

Model 2: As Model 1, plus fibre.

Model 3: As Model 1, plus carbohydrate.

Model 4: As Model 1, plus polyunsaturated fat.

Model 5: As Model 1, plus trans fat.

Model 6: As Model 1, plus fibre, carbohydrate, polyunsaturated fat and trans fat.

Women	Sample size[a]		Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
Variables of interest	**Participants (n)**	**Incident cases (n)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Alcohol consumption at S3														
Never drinkers[b]	104	17	1.00		1.00		1.00		1.00		1.00		1.00	0.467
Non-current drinkers[c]	508	94	1.76 (1.01-3.07)	0.044	1.77 (1.02-3.08)	0.044	1.80 (1.04-3.14)	0.037	1.76 (1.01-3.07)	0.044	1.77 (1.02-3.08)	0.043	1.84 (1.06-3.21)	0.031
0.1-50.0g/week	879	100	1.30 (0.73-2.30)	0.372	1.30 (0.73-2.30)	0.374	1.31 (0.74-2.32)	0.362	1.30 (0.73-2.30)	0.373	1.30 (0.73-2.31)	0.369	1.31 (0.74-2.33)	0.352
50.1-100.0g/week	317	22	1.02 (0.51-2.05)	0.957	1.02 (0.51-2.05)	0.953	1.03 (0.51-2.08)	0.930	1.02 (0.51-2.05)	0.963	1.03 (0.51-2.07)	0.945	1.02 (0.51-2.05)	0.956
>100.0g/week	277	14	0.73 (0.33-1.58)	0.422	0.72 (0.33-1.58)	0.419	0.72 (0.33-1.57)	0.410	0.73 (0.33-1.58)	0.420	0.73 (0.33-1.59)	0.425	0.71 (0.33-1.55)	0.389
BMI														
kg/m^2	1,838	247	1.13 (1.11-1.16)	<0.001			1.13 (1.11-1.16)	<0.001	1.13 (1.11-1.16)	<0.001	1.13 (1.11-1.16)	<0.001	1.13 (1.11-1.16)	<0.001
Fibre														
g/100g	1838	247	-	-	1.00 (0.99-1.01)	0.786	-	-	-	-	-	-	1.01 (0.99-1.02)	0.456
LR test versus BMI						***0.785***								
Carbohydrate														
log g/100g	1838	247	-	-	-	-	0.81 (0.58-1.15)	0.238	-	-	-	-	0.60 (0.34-1.06)	0.078
LR test versus BMI								***0.241***						
Polyunsaturated fat														
log g/100g	1838	247	-	-	-	-	-	-	1.03 (0.79-1.34)	0.836	-	-	1.20 (0.86-1.69)	0.285
LR test versus BMI										***0.836***				
Trans fat														
log g/100g	1838	247	-	-	-	-	-	-	-	-	0.94 (0.59-1.48)	*0.783*	1.10 (0.65-1.85)	0.723
LR test versus BMI												***0.783***		
LR test BMI versus BMI+FFQ														***0.503***

[a]Defined according to those with valid covariate data in Model 6.

[b]Defined as those who reported consuming no alcohol in the last twelve months and having always been a non-drinker.

[c]Defined as those who reported consuming no alcohol in the last twelve months and stated that they had not always been a non-drinker.

Model 1: Adjusted for age (s3), BMI (S3), employment status (S3), ethnicity, family history of T2DM (S3), smoking status (S3), physical activity (S3), occupational grade (S3).

Model 2: As Model 1, plus fibre.

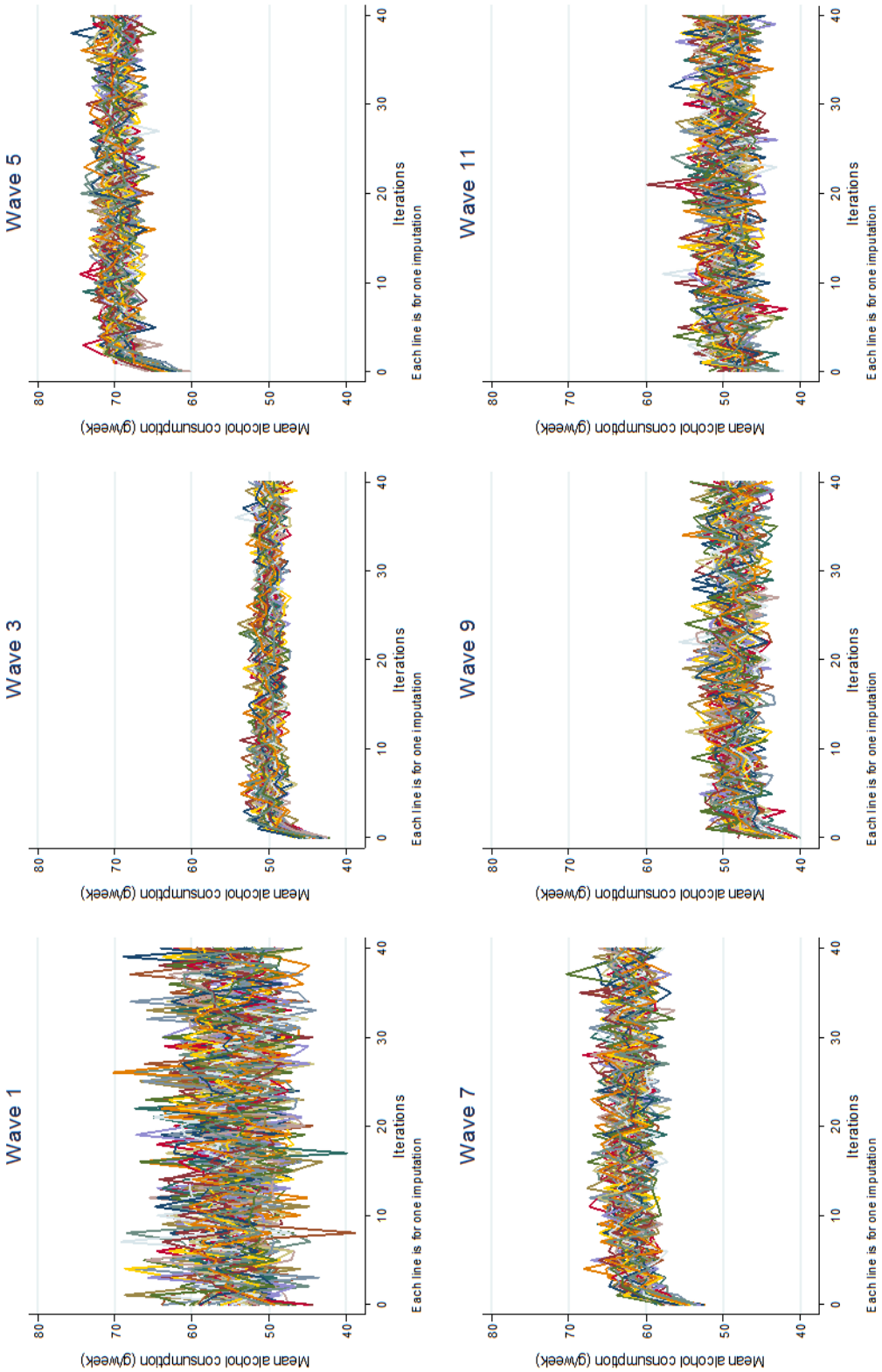
Model 3: As Model 1, plus carbohydrate.

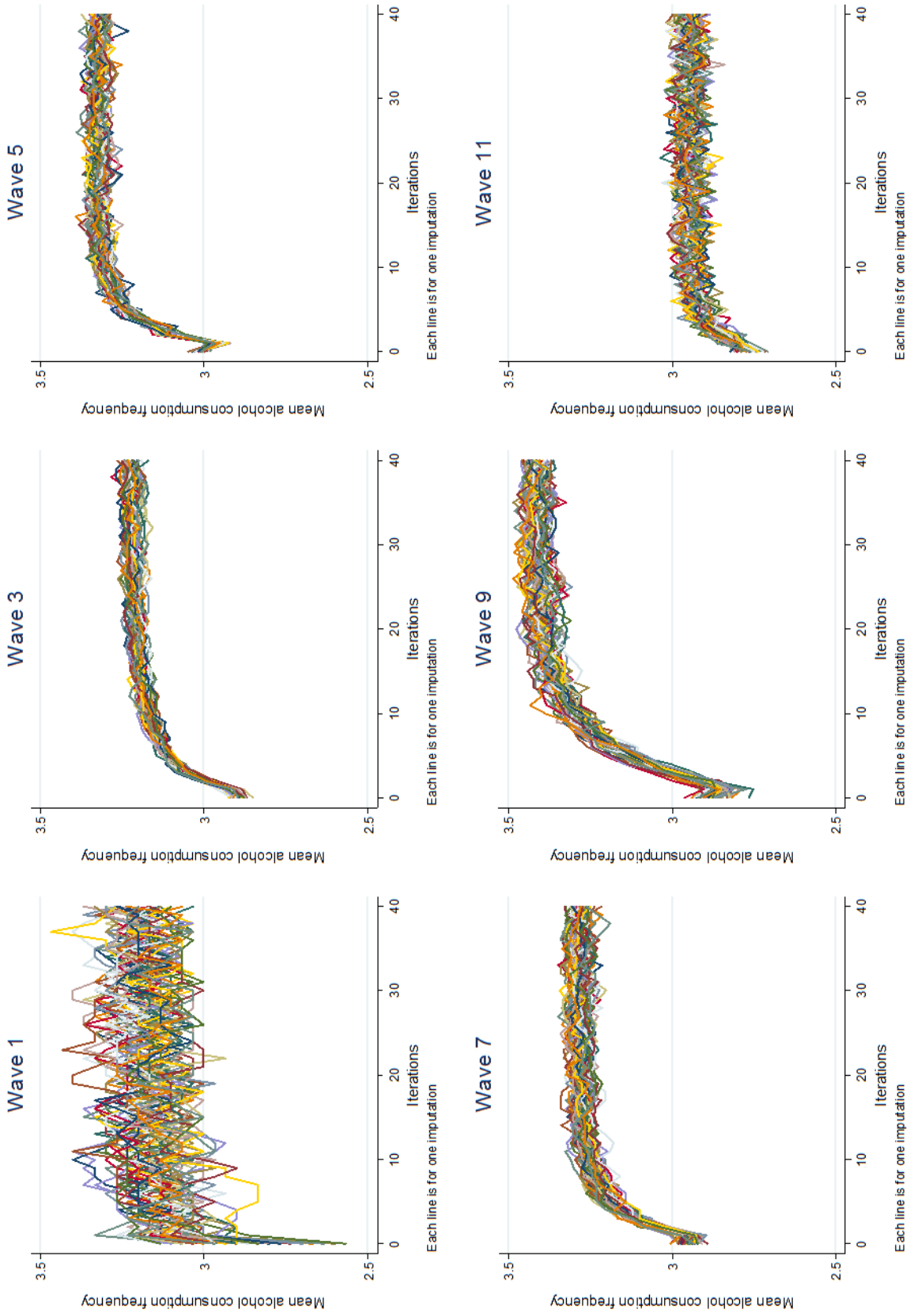
Model 4: As Model 1, plus polyunsaturated fat.

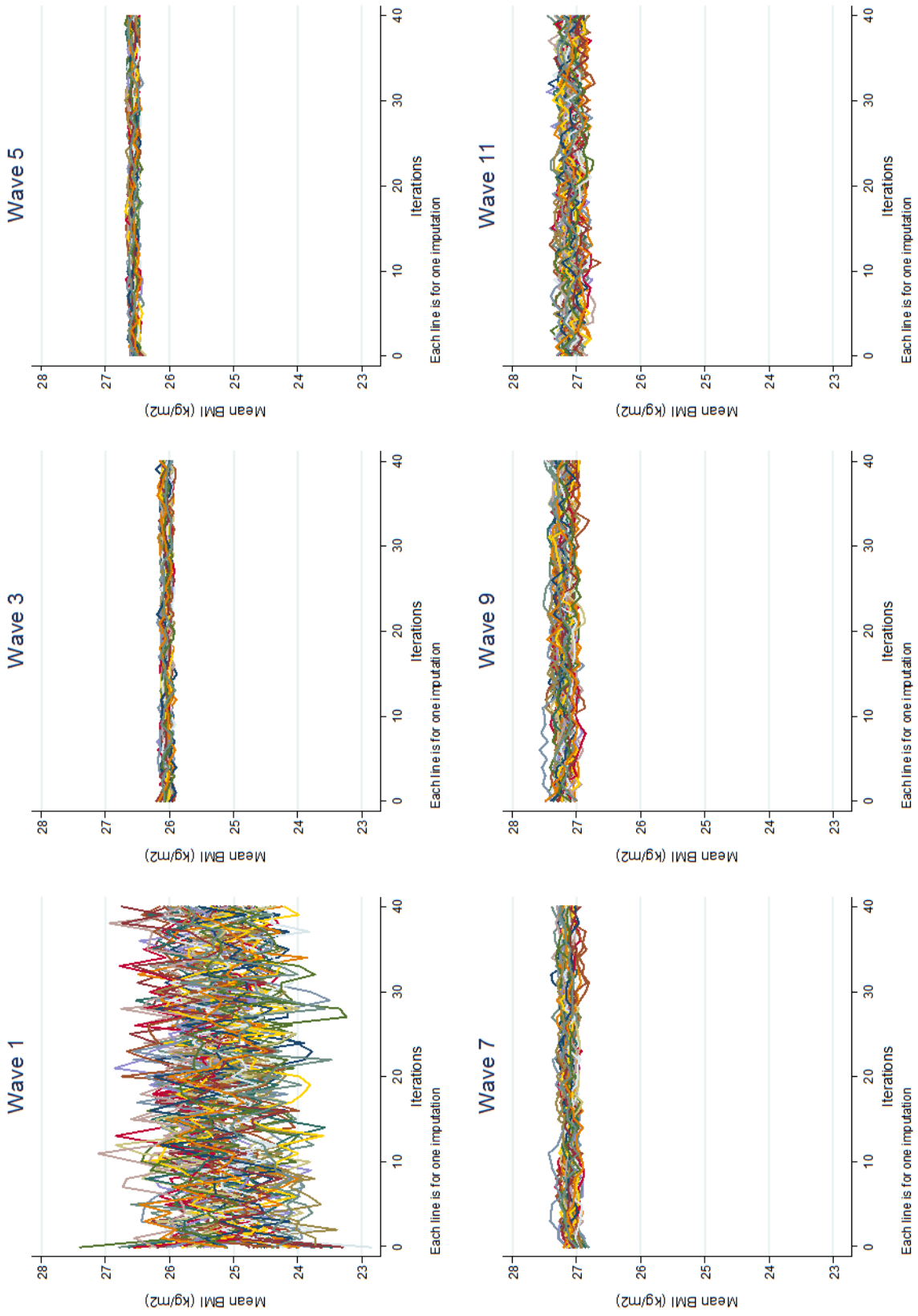
Model 5: As Model 1, plus trans fat.

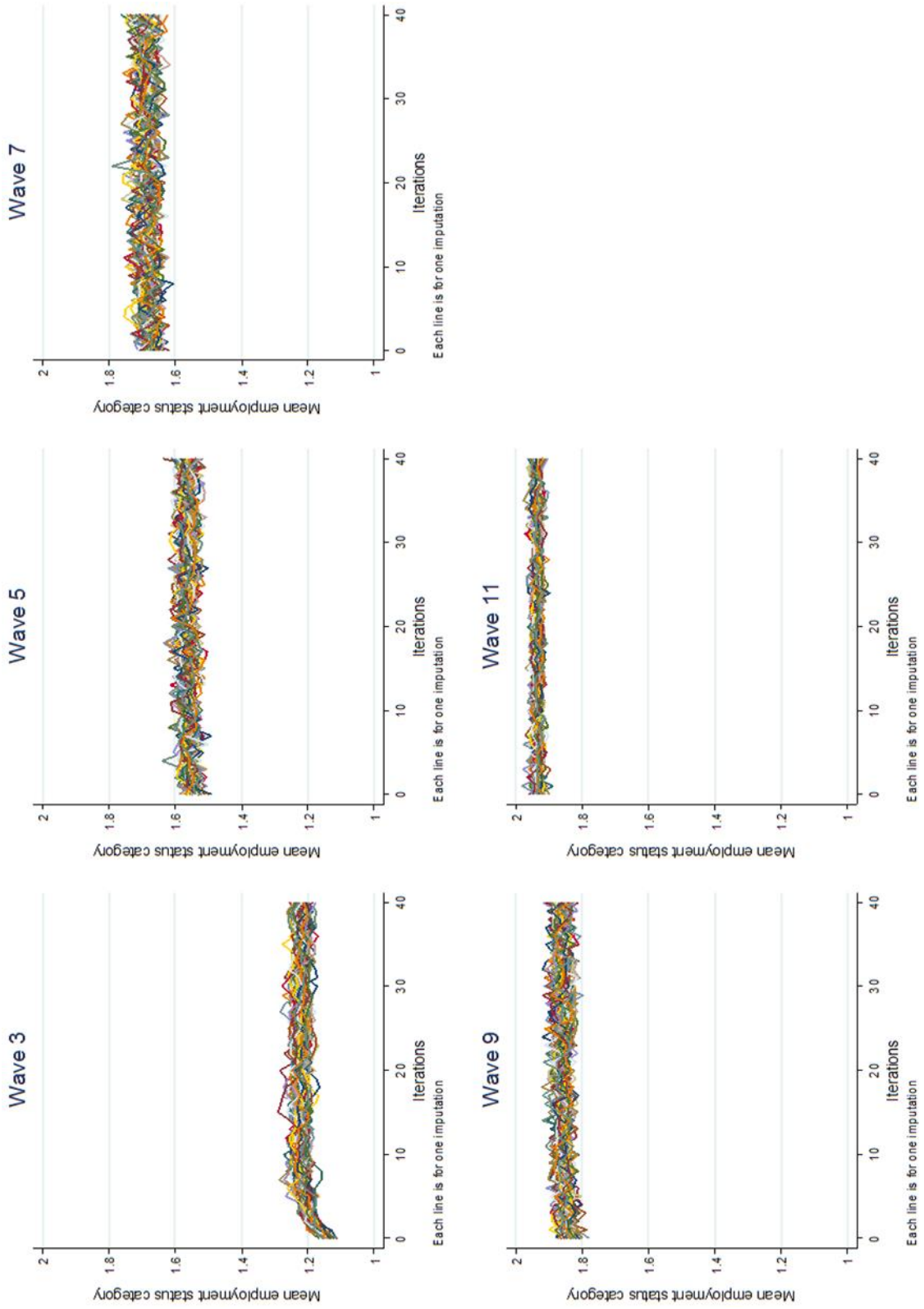
Model 6: As Model 1, plus fibre, carbohydrate, polyunsaturated fat and trans fat.

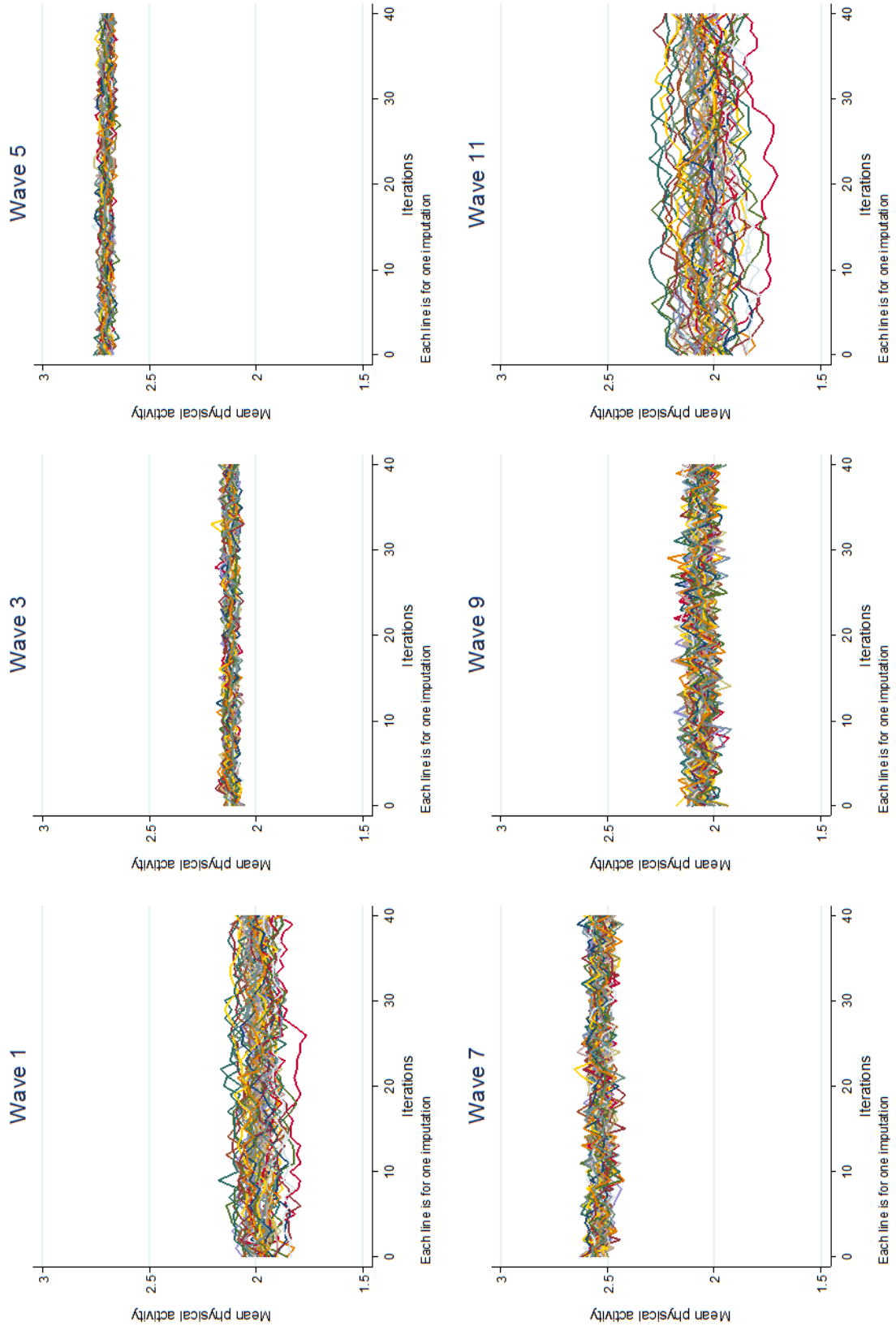
Appendix 6.2 Trace plots illustrating convergence on key variables

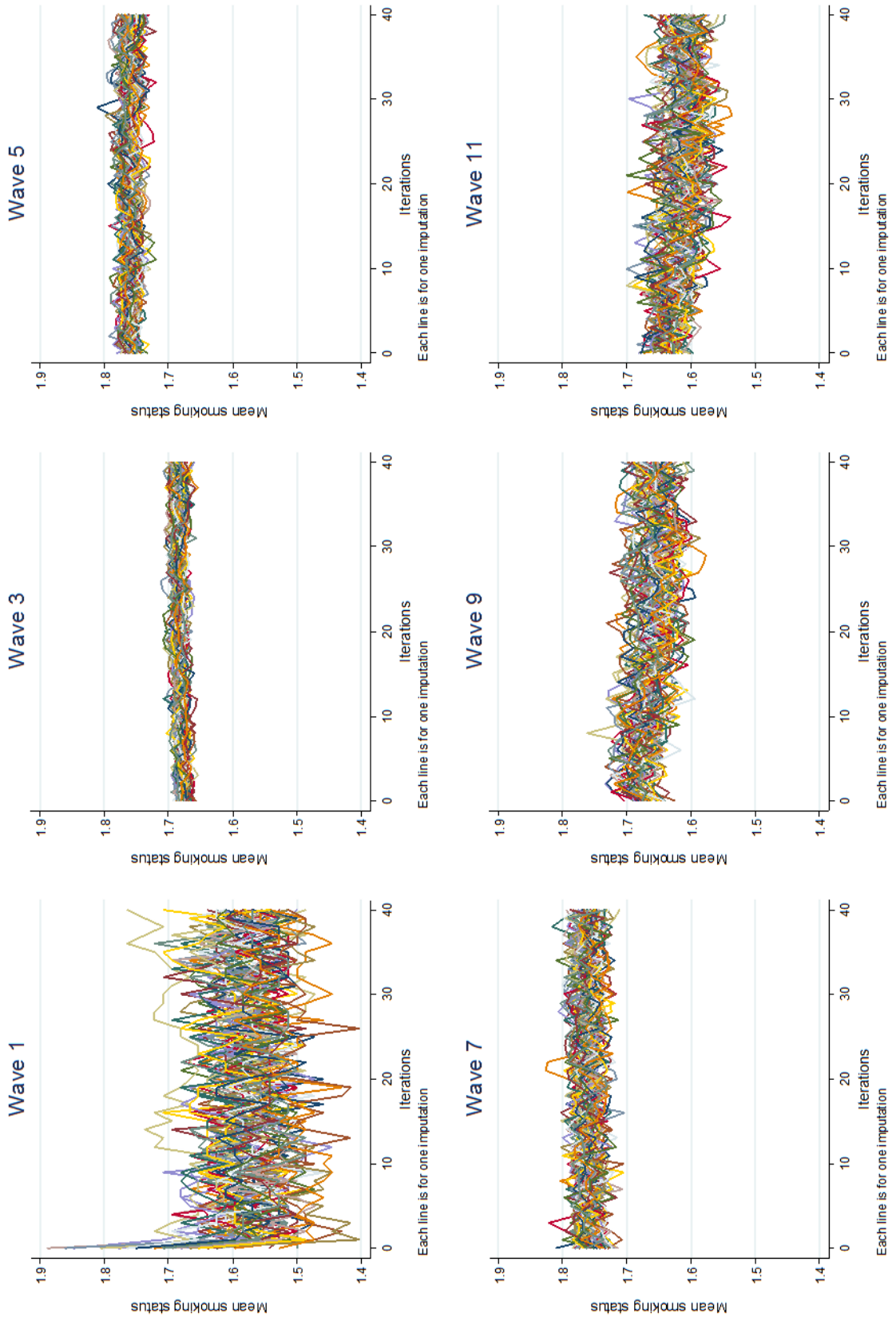



Wave 1
Wave 3
Wave 5
Wave 7
Wave 9
Wave 11
Mean alcohol consumption frequency
Iterations
Each line is for one imputation
2.5
3
3.5
0
10
20
30
40


Wave 1
Wave 3
Wave 5
Wave 7
Wave 9
Wave 11
Mean BMI (kg/m2)
Iterations
Each line is for one imputation

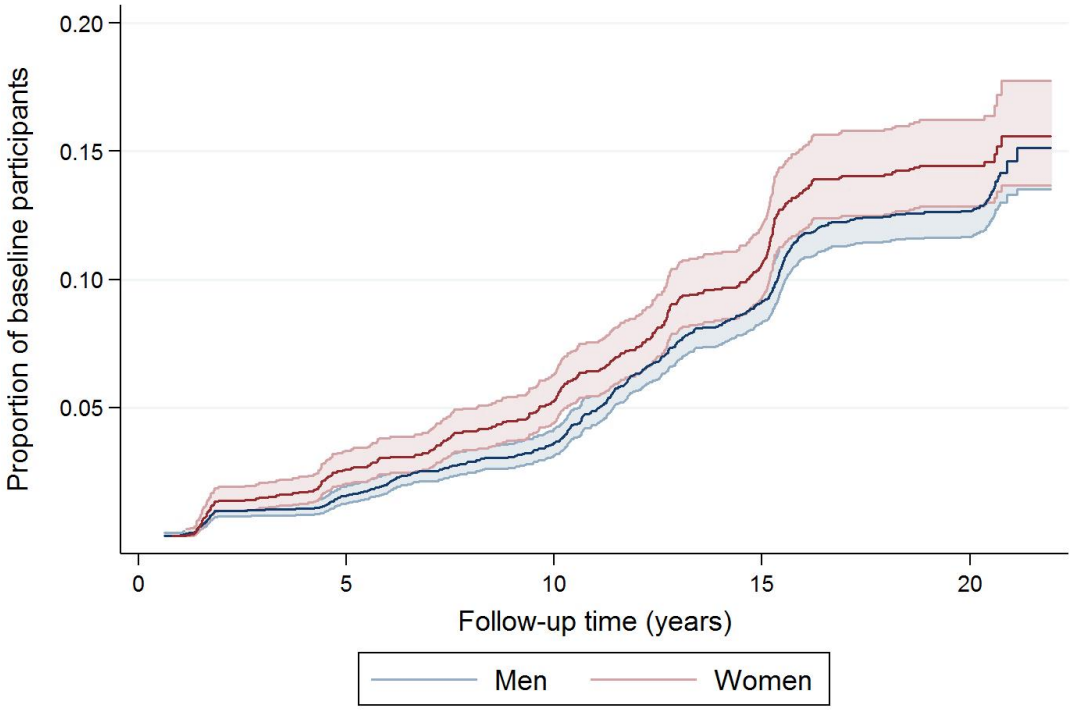

Wave 7
Wave 5
Wave 11
Wave 3
Wave 9
Mean employment status category
Iterations
Each line is for one imputation


Wave 5
Wave 11
Wave 3
Wave 9
Wave 1
Wave 7
Mean physical activity
Iterations
Each line is for one imputation


Wave 5
Wave 11
Wave 3
Wave 9
Wave 1
Wave 7
Mean smoking status
Iterations
Each line is for one imputation

11.3 Appendices for Chapter 7

Appendix 7.1 Crude Nelson-Aalen cumulative hazard estimate, stratified by sex. Observed data.



Appendix 7.2 Baseline characteristics of participants free of T2DM at wave three and with valid follow-up data, stratified by sex. Imputed data.

	Men		Women	
	T2DM	Censored	T2DM	Censored
Variables (wave 3)	**% (95% CI)** **n**	**% (95% CI)** **n**	**% (95% CI)** **n**	**% (95% CI)** **n**
Age				
Mean years	50.4 (49.9-50.9)[a] 620	49.8 (49.6-49.9)[a] 5,103	52.1 (51.3-52.8)[a] 296	50.7 (50.5-51.0)[a] 2,274
Alcohol consumption frequency				
None in past year	4.9 (3.2-6.6) 30	3.1 (2.6-3.6) 158	9.8 (6.4-13.3) 29	6.5 (5.5-7.5) 148
<1/week	19.2 (16.1-22.3) 119	16.3 (15.3-17.3) 832	50.4 (44.6-56.2) 149	32.3 (30.3-34.3) 735
1-3 times/week	34.3 (30.5-38.1) 213	39.7 (38.4-41.1) 2,028	26.6 (21.4-31.7) 79	36.7 (34.6-38.7) 834
Daily or almost daily	41.6 (37.7-27.3) 258	24.9 (24.8-25.0) 2,085	13.2 (9.2-17.2) 39	24.5 (22.7-26.3) 558
BMI				
Mean kg/m^2	27.0 (26.7-27.3)[a] 620	24.9 (24.8-25.0)[a] 5,103	29.5 (28.9-30.2)[a] 296	25.3 (25.1-25.4)[a] 2,274
Employment status				
Employed	90.8 (88.5-93.1) 563	90.9 (90.2-91.7) 4,641	88.5 (84.9-92.2) 262	90.7 (89.5-91.9) 2,062
Retired	6.3 (4.4-8.2) 39	7.5 (6.8-8.2) 382	5.4 (2.8-8.0) 16	5.4 (4.5-6.3) 123
Other[b]	2.9 (1.6-4.2) 18	1.6 (1.2-1.9) 80	6.1 (3.3-8.8) 18	3.9 (3.1-4.7) 89

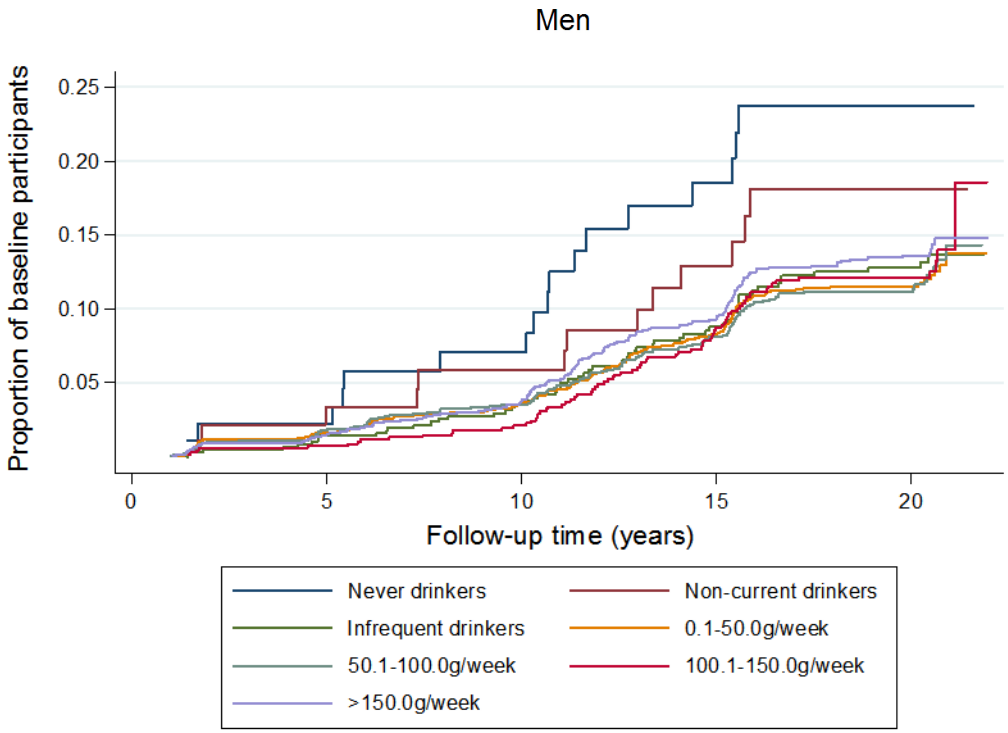
Ethnicity				
White	84.8 (82.0-87.7)	94.6 (94.0-95.2)	71.1 (65.9-76.3)	89.1 (87.8-90.3)
	526	4,826	211	2,025
South Asian	11.8 (9.2-14.3)	3.4 (2.9-3.9)	14.5 (10.5-18.6)	4.6 (3.7-5.4)
	73	175	43	104
Other	3.4 (2.0-4.8)	2.0 (1.6-2.4)	14.3 (10.3-18.4)	6.4 (5.4-7.4)
	21	101	42	145
Family history of T2DM				
No	81.1 (78.0-84.2)	91.2 (90.4-92.0)	68.9 (63.6-74.3)	89.1 (87.8-90.4)
	503	4,653	204	2,026
Yes	18.9 (15.8-22.0)	8.8 (8.0-9.6)	31.1 (25.7-36.3)	10.9 (9.6-12.2)
	117	451	92	248
Occupational class				
Administrative (top)	42.4 (38.5-46.3)	49.9 (48.5-51.3)	5.4 (2.8-8.0)	17.5 (15.9-19.1)
	263	2,546	16	398
Professional (middle)	48.5 (44.6-52.5)	44.3 (43.0-45.7)	42.2 (36.6-47.9)	45.9 (43.8-47.9)
	301	2,263	125	1,043
Clerical (bottom)	9.0 (6.8-11.3)	5.8 (5.1-6.4)	52.4 (46.6-58.1)	36.6 (34.6-38.6)
	56	294	155	833
Physical activity[c]				
Inactive	17.1 (14.1-20.2)	13.6 (12.5-14.5)	41.6 (35.8-47.3)	34.0 (32.0-36.0)
	106	692	123	772
Below guidelines	35.4 (31.5-39.2)	36.6 (35.3-38.0)	34.3 (28.7-39.9)	33.4 (31.4-35.4)
	220	1,869	101	759
Met guidelines	47.5 (43.4-51.5)	49.8 (48.4-51.2)	24.2 (19.1-29.1)	32.7 (30.7-34.6)
	294	2,542	72	743

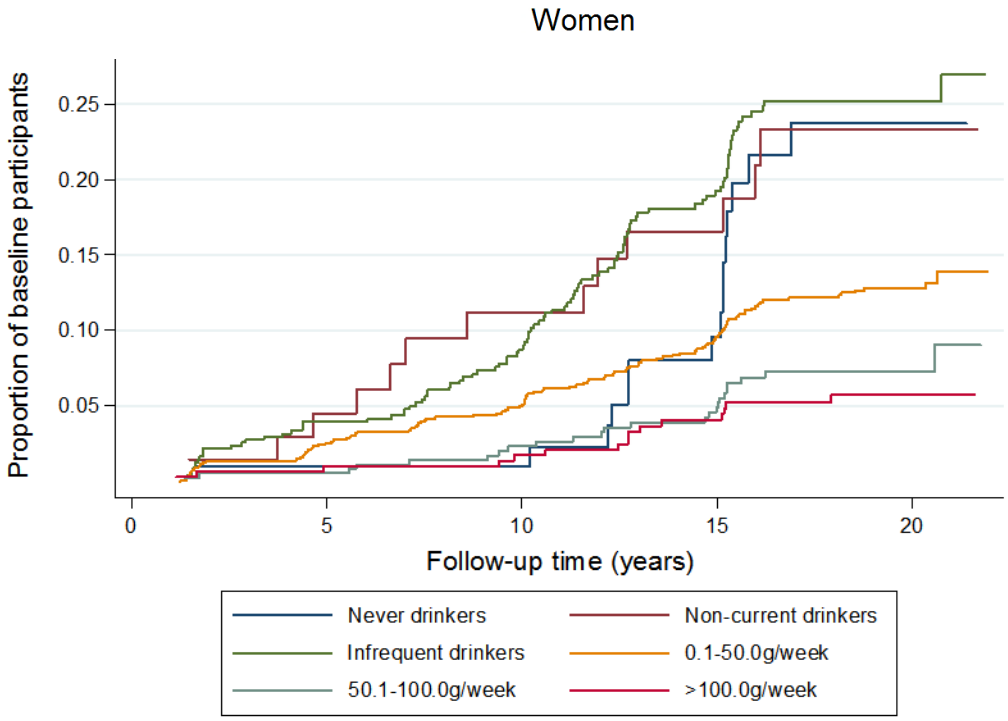
Self-reported general health				
Very good/Excellent	40.7 (36.7-44.6)	53.5 (52.1-54.9)	30.4 (25.1-35.7)	43.5 (41.2-45.4)
	252	2,731	90	985
Good	45.1 (41.1-49.1)	38.0 (36.6-39.3)	44.7 (38.9-50.6)	42.8 (40.7-44.9)
	280	1,939	132	973
Fair/Poor	14.2 (11.4-17.0)	8.5 (7.7-9.3)	24.9 (19.8-29.9)	13.9 (12.4-15.4)
	88	433	74	316
Smoking				
Never	40.9 (37.0-44.8)	48.4 (47.0-49.8)	55.8 (50.1-61.5)	53.1 (51.0-55.1)
	254	2,470	165	1,207
Former	40.8 (36.9-44.7)	39.7 (38.4-41.1)	27.7 (22.5-32.9)	29.5 (27.6-31.4)
	253	2,028	82	671
Current	18.3 (15.2-21.3)	11.8 (10.9-12.7)	16.5 (12.1-20.8)	17.4 (15.8-19.0)
	113	605	49	396

Alcohol consumption volume not listed as it was not possible to impute a categorical volume variable in which never and non-current drinkers were separated.

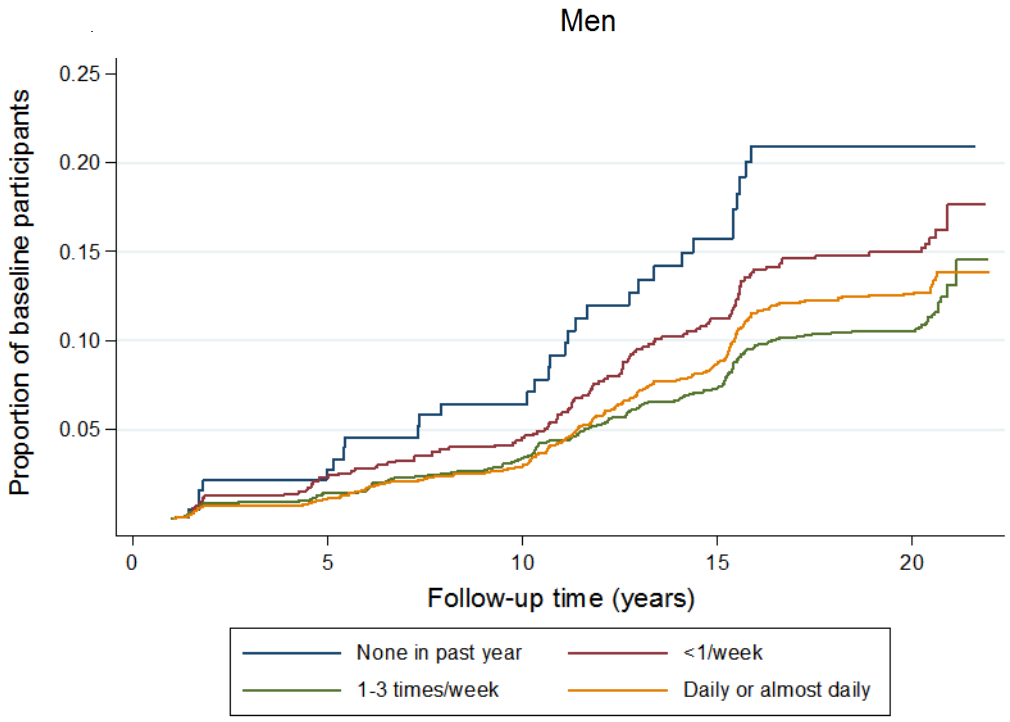
[a]Mean and 95% confidence interval; [b]Redundant, student, long-term sick, long-term carer; [c]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (anyone not inactive or meeting guidelines)

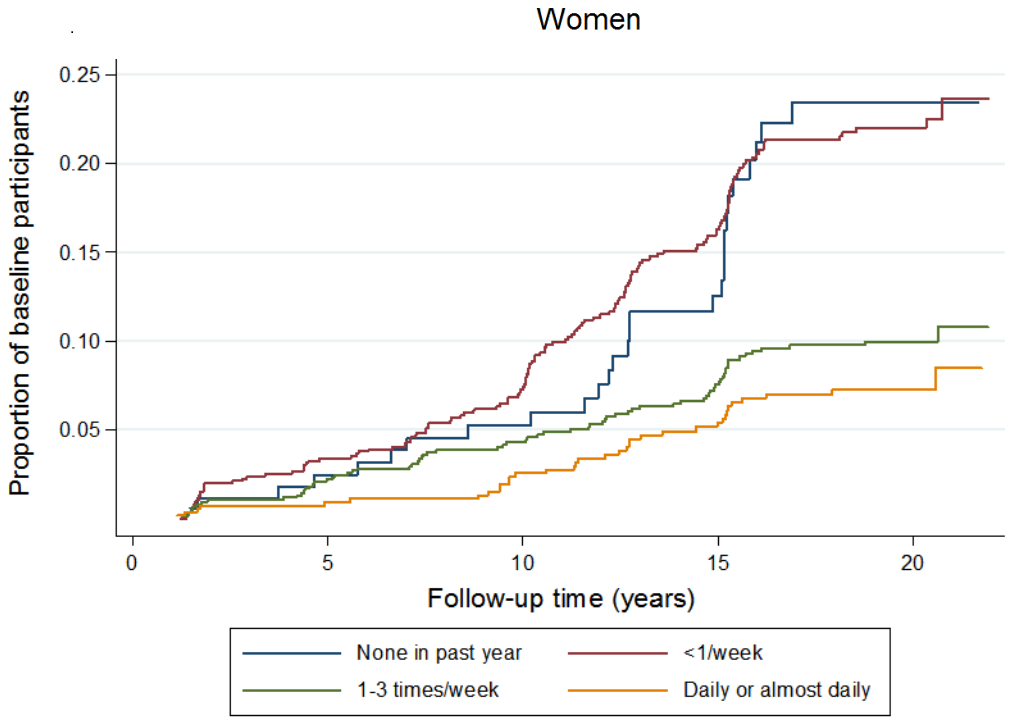
Appendix 7.3 Crude Nelson-Aalen cumulative hazard estimate, stratified by sex and category of average weekly volume of alcohol consumption. Observed data.





Appendix 7.4 Crude Nelson-Aalen cumulative hazard estimate, stratified by sex and frequency of alcohol consumption. Observed data.





Appendix 7.5 Baseline characteristics of participants free of T2DM at wave three and with valid follow-up data, stratified by sex and categories of average weekly volume of alcohol consumption. Imputed data.

	Alcohol consumption category					
	Current		Infrequent		Non-current	Never
Variables (wave 3)	**% (95% CI)**	**n**	**% (95% CI)**	**n**	**% (95% CI)**	**n**
Men						
Age						
Mean years	49.7 (49.5-49.9)[a]	4,678	50.2 (49.7-50.7)[a]	601	50.6 (49.4-51.9)[a] 92	50.1 (48.8-51.4)[a] 93
BMI						
Mean kg/m^2	25.2 (25.1-25.3)[a]	4,678	24.7 (24.4-25.0)[a]	601	24.9 (24.2-25.6)[a] 92	24.3 (23.5-24.9)[a] 93
Employment status						
Employed	90.8 (90.0-91.6)	4,248	87.9 (85.2-90.5)	528	91.3 (85.4-97.2) 84	91.4 (85.6-97.2) 85
Retired	7.5 (6.8-8.3)	353	9.8 (7.4-12.2)	59	6.5 (1.4-11.7) 6	3.2 (-0.4-6.9) 3
Other[b]	1.6 (1.3-2.0)	77	2.3 (1.1-3.5)	14	2.2 (0.0-5.2) 2	5.4 (0.7-10.0) 5
Ethnicity						
White	95.0 (94.4-95.6)	4,444	90.3 (88.0-92.7)	543	53.3 (42.9-63.7) 49	84.9 (77.5-92.4) 79
South Asian	3.3 (2.7-3.8)	152	5.3 (3.5-7.1)	32	38.0 (27.9-48.2) 35	15.1 (7.6-22.5) 14
Other	1.8 (1.4-2.1)	82	4.3 (2.7-6.0)	26	8.7 (2.8-14.6) 8	-

Family history of T2DM				
No	90.5 (89.7-91.3)	88.8 (86.3-91.4)	80.1 (71.7-88.5)	89.2 (82.8-95.7)
	4,234	534	74	83
Yes	9.5 (8.7-10.3)	11.2 (8.6-13.7)	19.9 (11.5-28.3)	10.8 (4.3-17.2)
	445	67	18	10
Incident T2DM				
No	89.3 (88.4-90.2)	89.9 (87.4-92.3)	81.5 (73.4-89.6)	86.0 (78.8-93.2)
	4,179	540	75	80
Yes	10.7 (9.8-11.6)	10.1 (7.7-12.6)	18.5 (10.4-26.6)	14.0 (6.8-21.2)
	499	61	17	13
Occupational class				
Administrative (top)	52.2 (50.8-53.7)	31.3 (27.6-35.0)	27.2 (17.9-36.4)	35.5 (25.6-45.4)
	2,444	188	25	33
Professional (middle)	43.0 (41.6-44.4)	56.9 (52.9-60.9)	52.2 (41.8-62.6)	49.5 (39.1-59.8)
	2,012	342	48	46
Clerical (bottom)	4.7 (4.1-5.4)	11.8 (9.2-14.4)	20.7 (12.2-29.1)	15.1 (7.6-22.5)
	222	71	19	14
Physical activity[c]				
Inactive	12.5 (11.6-13.5)	22.2 (18.8-25.5)	18.5 (10.4-26.6)	23.3 (14.5-32.1)
	585	133	17	22
Below guidelines	36.6 (35.2-38.0)	36.2 (32.3-40.0)	42.4 (32.1-52.7)	35.7 (25.8-45.7)
	1,712	217	39	33
Met guidelines	50.9 (49.5-52.3)	41.7 (37.7-45.6)	39.1 (29.0-49.3)	41.0 (30.8-51.2)
	2,381	251	36	38
Self-reported general health				
Very good/Excellent	53.1 (51.6-54.5)	46.6 (42.6-50.6)	56.5 (46.2-66.8)	43.0 (32.8-53.3)
	2,483	280	52	40
Good	38.9 (37.5-40.3)	38.5 (34.6-42.4)	31.5 (21.8-41.2)	36.8 (26.7-46.8)
	1,821	231	29	34
Fair/Poor	8.0 (7.2-8.8)	14.9 (12.0-17.7)	12.0 (5.2-18.7)	20.2 (11.9-28.6)
	374	89	11	19

Smoking				
Never	46.8 (45.4-48.2) 2,190	52.2 (48.2-56.3) 314	78.8 (70.2-87.4) 72	48.3 (37.9-58.7) 45
Former	41.3 (39.8-42.7) 1,930	33.6 (29.8-37.4) 202	12.5 (5.5-19.5) 12	37.7 (27.7-47.8) 35
Current	11.9 (11.0-12.9) 558	14.2 (11.4-17.0) 85	8.7 (2.8-14.6) 8	14.0 (6.8-21.2) 13
Women				
Age				
Mean years	50.3 (50.0-50.6)[a] 1,713	52.0 (51.5-52.5)[a] 554	50.8 (49.5-52.0)[a] 101	50.7 (49.2-52.1)[a] 69
BMI				
Mean kg/m^2	25.3 (25.0-25.5)[a] 1,713	26.7 (26.2-27.1)[a] 554	26.3 (25.2-27.4)[a] 101	27.1 (25.7-28.4)[a] 69
Employment status				
Employed	91.2 (89.9-92.6) 1,563	86.3 (83.4-89.2) 478	91.1 (85.4-96.7) 92	84.1 (75.2-92.9) 58
Retired	5.7 (4.6-6.8) 98	6.0 (4.0-7.9) 33	4.0 (0.1-7.8) 4	5.8 (0.1-11.5) 4
Other[b]	3.0 (2.2-3.8) 52	7.8 (5.5-10.0) 43	5.0 (0.6-9.3) 5	10.1 (2.8-17.5) 7
Ethnicity				
White	92.3 (91.0-93.5) 1,580	82.2 (78.9-85.4) 455	42.2 (32.3-52.0) 43	59.4 (47.5-71.3) 41
South Asian	2.3 (1.6-3.0) 39	7.8 (5.6-10.1) 43	40.7 (30.9-50.4) 41	20.3 (10.6-30.0) 14
Other	5.5 (4.4-6.5) 94	10.0 (7.5-12.6) 56	17.2 (9.6-24.7) 17	20.3 (10.6-30.0) 14

Family history of T2DM				
No	87.5 (85.9-89.1)	85.8 (82.8-88.7)	83.2 (75.7-90.6)	83.5 (74.4-92.6)
	1,499	475	84	58
Yes	12.5 (10.9-14.1)	14.2 (11.3-17.2)	16.8 (9.4-24.3)	16.5 (7.4-25.6)
	214	79	17	11
Incident T2DM				
No	91.4 (90.0-92.7)	81.2 (78.0-84.5)	85.1 (78.1-92.2)	81.2 (71.7-90.6)
	1,565	450	86	56
Yes	8.6 (7.3-10.0)	18.8 (15.5-22.0)	14.9 (7.8-21.9)	18.8 (9.4-28.3)
	148	104	15	13
Occupational class				
Administrative (top)	21.0 (19.0-22.9)	5.2 (3.4-7.1)	5.0 (0.6-9.3)	5.8 (0.1-11.5)
	359	29	5	4
Professional (middle)	49.2 (46.8-51.6)	42.1 (37.9-46.2)	24.8 (16.2-33.3)	31.9 (20.6-43.2)
	843	233	25	22
Clerical (bottom)	29.8 (27.7-32.0)	52.7 (48.5-56.9)	70.3 (61.2-79.4)	62.3 (50.6-74.1)
	511	292	71	43
Physical activity[c]				
Inactive	29.9 (27.8-32.1)	45.5 (41.3-49.6)	51.5 (41.6-61.4)	46.4 (34.3-58.5)
	513	252	52	32
Below guidelines	35.9 (33.6-38.2)	26.7 (23.0-30.4)	25.7 (17.1-34.4)	31.9 (20.6-43.2)
	615	148	26	22
Met guidelines	34.2 (31.9-36.4)	27.8 (24.1-31.5)	22.8 (14.5-31.1)	21.7 (11.8-31.7)
	585	154	23	15

Self-reported general health				
Very good/Excellent	46.1 (43.8-48.5) 790	35.9 (31.9-39.9) 199	21.8 (13.6-30.0) 22	20.3 (10.6-30.0) 14
Good	42.1 (39.7-44.4) 721	44.4 (40.3-48.6) 246	54.5 (44.6-64.3) 55	37.7 (25.9-49.4) 26
Fair/Poor	11.8 (10.3-13.3) 202	19.7 (16.4-23.0) 109	23.8 (15.3-32.2) 24	42.0 (30.1-54.0) 29
Smoking				
Never	51.0 (48.7-53.4) 874	56.3 (52.1-60.5) 312	88.9 (82.6-95.2) 90	70.8 (59.7-81.8) 49
Former	32.3 (30.1-34.5) 554	25.2 (21.6-28.9) 140	4.2 (0.1-8.2) 4	19.1 (9.5-28.6) 13
Current	16.6 (14.9-18.4) 285	18.5 (15.2-21.7) 102	6.9 (1.9-12.0) 7	10.2 (2.8-17.5) 7

Table excluded consumption frequency owing to colinearity with consumption volume.

[a]Mean and 95% confidence interval; [b]Redundant, student, long-term sick, long-term carer; [c]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (anyone not inactive or meeting guidelines).

Appendix 7.6 Multivariable-adjusted dose response relationship between categories of average weekly volume of alcohol consumption and T2DM, stratified by sex. Imputed data.

	Men (n=5,456)		Women (n=2,434)	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Never drinkers[a]	(reference)		(reference)	
Non-current drinkers[b]	1.26 (0.61-2.64)	0.531	1.12 (0.53-2.39)	0.769
Infrequent drinkers[c]	0.99 (0.57-1.74)	0.981	1.62 (0.92-2.88)	0.098
0.1-50.0g/week	0.97 (0.57-1.64)	0.905	1.06 (0.59-1.91)	0.845
50.1-100.0g/week	1.03 (0.60-1.76)	0.925	0.86 (0.42-1.73)	0.666
100.1-150.0g/week	1.05 (0.60-1.84)	0.866	0.58 (0.27-1.25)	0.163
>150.0g/week[d]	1.01 (0.59-1.73)	0.972	-	-
Log likelihood	*-4733 (-4735, -4731)*		*-1963 (-1964, -1962)*	
BIC[e]	*9630 (9625, 9634)*		*4066 (4064, 4068)*	

Models adjusted for all a priori covariates at baseline: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five.

[a]Participants who reported no consumption in the past week in waves 1 and 3, no consumption in the past year in waves 1 and 3, and stated they had 'always been a non-drinker' in wave 3, the first year the always non-drinker variable was available; [b]Participants who reported no consumption in the last year but had not 'aways been a non-drinker'; [c]Consumed alcohol in the past year but not in the past week; [d]Among women, this category was merged with those who reported consuming 100.1-150.0g/week; [e]Bayesian information criterion. Fit statistics refer to the mean and range of values reported by the first three imputations.

Appendix 7.7 Multivariable-adjusted interaction between a continuous measure of average weekly alcohol volume and consumption frequency, stratified by sex and excluding non-current and infrequent drinkers. Imputed data.

	Model 1		Model 2	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Men (n=4,770)				
Dose-response by volume				
Per 10 g/week increase	1.00 (0.99-1.01)	0.761	1.00 (0.99-1.01)	0.480
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.89 (0.67-1.20)	0.449
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	1.01 (0.98-1.03)	0.653
Log likelihood	*-4074 (-4076, -4072)*		*-4074 (-4075, -4071)*	
BIC [a]	*8267 (8262, 8270)*		*8283 (8278, 8286)*	
Women (n=1,814)				
Dose-response by volume				
Per 10 g/week increase	0.95 (0.92-0.99)	0.021	0.96 (0.91-1.02)	0.156
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	1.06 (0.52-2.17)	0.867
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.95 (0.87-1.05)	0.324
Log likelihood	*-1095 (-1095, -1095)*		*-1094 (-1094, -1094)*	
BIC [a]	*2295 (2295, 2295)*		*2308 (2308, 2309)*	

Model 1 reported the linear dose-response relationship between volume alcohol consumption and T2DM. Model 2 included an interaction term between a continuous measure of volume alcohol consumption and whether participants reported drinking alcohol daily or less than daily over the year preceding interview. All models adjusted for baseline covariates: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five. All models excluded non-current drinkers from the reference level of exposure (0g/week). [a]Bayesian information criterion. Fit statistics refer to the mean and range of values reported by the first three imputations.

Appendix 7.8 Multivariable-adjusted interaction between a continuous measure of average weekly volume of alcohol consumption and drinking frequency, stratified by sex and including non-current and infrequent drinkers. Observed data.

	Model 1		Model 2	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Men (n=4,874)				
Dose-response by volume				
Per 10 g/week increase	1.00 (0.99-1.00)	0.504	0.99 (0.98-1.00)	0.240
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.86 (0.65-1.14)	0.301
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	1.00 (0.98-1.03)	0.621
Log likelihood		*-4177*		*-4177*
BIC[a]		*8473*		*8489*
Women (n=2,094)				
Dose-response by volume				
Per 10 g/week increase	0.94 (0.90-0.97)	0.001	0.93 (0.86-1.00)	0.055
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.78 (0.35-1.72)	0.536
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.97 (0.88-1.08)	0.536
Log likelihood		*-1700*		*-1700*
BIC[a]		*3507*		*3519*

Model 1 reported the linear dose-response relationship between volume alcohol consumption and T2DM. Model 2 included an interaction term between a continuous measure of volume alcohol consumption and whether participants reported drinking alcohol daily or less than daily over the year preceding interview. All models adjusted for baseline covariates: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five. All models included non-current drinkers in the reference level of exposure (0g/week).

[a]Bayesian information criterion.

Appendix 7.9 Multivariable-adjusted interaction between a continuous measure of average weekly volume of alcohol consumption and drinking frequency, stratified by sex and including non-current and infrequent drinkers. Imputed data.

	Model 1		Model 2	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Men (n=5,464)				
Dose-response by volume				
Per 10 g/week increase	1.00 (0.99-1.01)	0.695	1.00 (0.99-1.01)	0.565
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.94 (0.72-1.23)	0.661
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	1.00 (0.98-1.02)	0.910
Log likelihood	*-4734 (-4736, -4731)*		*-4734 (-4735, -4731)*	
BIC[a]	*9588 (9583, 9592)*		*9605 (9600, 9609)*	
Women (n=2,437)				
Dose-response by volume				
Per 10 g/week increase	0.93 (0.90-0.97)	<0.001	0.93 (0.86-1.00)	0.039
Difference in risk by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.81 (0.39-1.67)	0.562
Difference in dose-response by frequency				
Daily	-	-	(reference)	
Non-daily	-	-	0.95 (0.87-1.05)	0.347
Log likelihood	*-1964 (-1965, -1962)*		*-1962 (-1963, -1961)*	
BIC[a]	*4037 (4035, 4039)*		*4048 (4046, 4051)*	

Model 1 reported the linear dose-response relationship between volume alcohol consumption and T2DM. Model 2 included an interaction term between a continuous measure of volume alcohol consumption and whether participants reported drinking alcohol daily or less than daily over the year preceding interview. All models adjusted for baseline covariates: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five. All models included non-current drinkers in the reference level of exposure (0g/week). [a]Bayesian information criterion. Fit statistics refer to the mean and range of values reported by the first three imputations.

Appendix 7.10 Multivariable-adjusted dose response relationship between categories of average weekly volume of alcohol consumption and T2DM, stratified by sex. Hazards were permitted to vary as a function of linear time. Observed data.

	Men (n=4,874)		Women (n=2,094)	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Risk at baseline				
Never drinkers[a]	(reference)		(reference)	
Non-current drinkers[b]	1.83 (0.30-11.24)	0.515	8.41 (0.79-89.64)	0.078
Infrequent drinkers[c]	0.87 (0.20-3.85)	0.856	11.99 (1.59-90.47)	0.016
0.1-50.0g/week	1.13 (0.29-4.40)	0.864	9.48 (1.23-73.25)	0.031
50.1-100.0g/week	1.44 (0.35-5.86)	0.610	4.28 (0.42-43.71)	0.220
100.1-150.0g/week	0.69 (0.15-3.14)	0.631	2.51 (0.20-30.96)	0.472
>150.0g/week[d]	1.34 (0.33-5.50)	0.686	-	-
Risk per year increase in follow-up				
Never drinkers	(reference)			
Non-current drinkers	0.98 (0.83-1.14)	0.772	0.84 (0.69-1.01)	0.064
Infrequent drinkers	1.01 (0.89-1.14)	0.906	0.83 (0.71-0.97)	0.017
0.1-50.0g/week	0.98 (0.88-1.10)	0.776	0.83 (0.71-0.96)	0.016
50.1-100.0g/week	0.97 (0.86-1.09)	0.636	0.87 (0.73-1.03)	0.113
100.1-150.0g/week	1.03 (0.91-1.17)	0.592	0.88 (0.72-1.06)	0.185
>150.0g/week	0.97 (0.87-1.10)	0.674	-	-
Log likelihood		*-4162*		*-1690*
BIC[e]		*8647*		*3657*

Models adjusted for all a priori covariates at baseline: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five.

[a]Participants who reported no consumption in the past week in waves 1 and 3, no consumption in the past year in waves 1 and 3, and stated they had 'always been a non-drinker' in wave 3, the first year the always non-drinker variable was available; [b]Participants who reported no consumption in the last year but had not 'aways been a non-drinker'; [c]Consumed alcohol in the past year but not in the past week; [d]Among women, this category was merged with those who reported consuming 100.1-150.0g/week; [e]Bayesian information criterion.

Appendix 7.11 Multivariable-adjusted dose-response relationship between categories of average weekly volume of alcohol consumption, drink type and T2DM, stratified by sex. Imputed data.

	Men (n=5,083)		Women (n=2,224)	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Drink type				
Beer (per 10 g/week)	0.99 (0.98-1.00)	0.236	0.85 (0.72-0.99)	0.042
Spirits (per 10 g/week)	1.01 (0.99-1.03)	0.343	0.94 (0.87-1.01)	0.113
Wine (per 10 g/week)	1.00 (0.98-1.02)	0.773	0.95 (0.90-1.01)	0.081
Log likelihood	*-4509 (-4574, -4378)*		*-1758 (-1759, -1758)*	
BIC[a]	*8895 (8893, 8897)*		*3640 (3640, 3641)*	

Models reported results adjusted for all a priori covariates: age, BMI, employment status, ethnicity, family history of T2DM, occupational grade, physical activity, smoking status. Ethnicity was derived from responses at waves one and five. Models also included variables representing the volume of each drink type consumed during the week prior to interview.

[a]Bayesian information criterion. Fit statistics refer to the mean and range of values reported by the first three imputations.

11.4 Appendices for Chapter 8

Appendix 8.1 Crude sex-specific linear trajectory of mean weekly volume of alcohol consumption between the ages of 34-84 years: goodness of fit statistics. Imputed data.

	Fit statistics	
Linear mixed models	**Log-likelihood**	**BIC[a]**
Men		
Intercept only	-232502 (-232763,-232191)	465035 (464414-465557)
Linear mixed model, fixed slopes	-232476 (-232731,-232165)	464994 (464371-465504)
Linear mixed model, random slopes	-232361 (-232622,-232023)	464786 (464109-465306)
Women		
Intercept only	-103392 (-103679,-103192)	206814 (206414-207387)
Linear mixed model, fixed slopes	-103390 (-103677,-103191)	206820 (206422-207393)
Linear mixed model, random slopes	-103355 (-103650,-103150)	206756 (206360-207320)

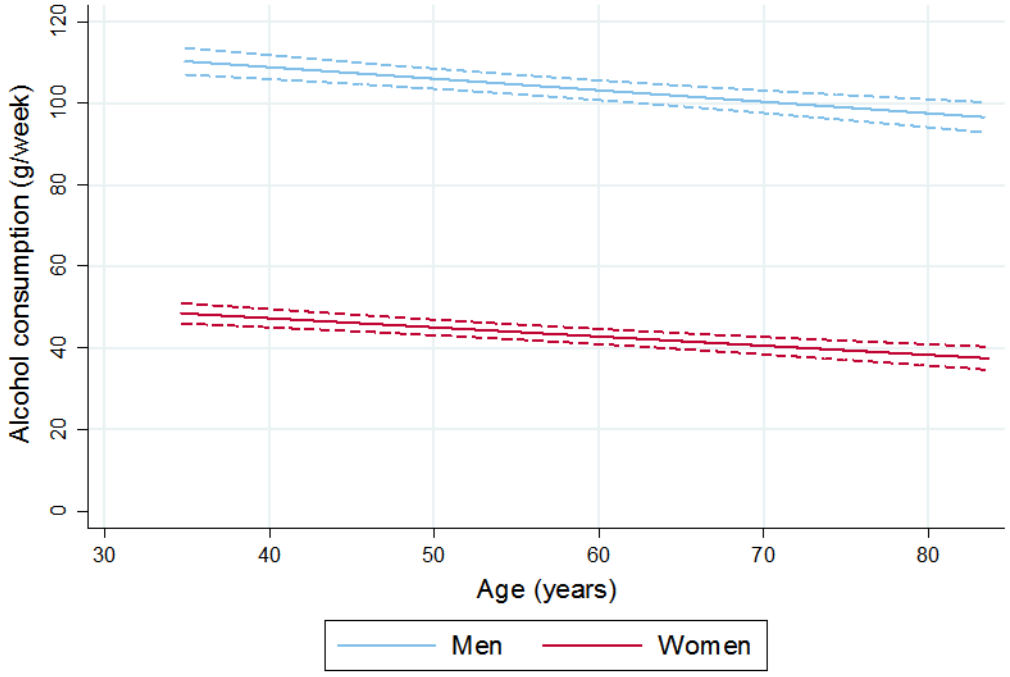
[a]Bayesian information criterion. Values refer to the mean and range of fit statistics as reported from the first three imputations.

Appendix 8.2 Crude sex-specific linear and non-linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years: results. Imputed data.

Mixed models	g/week (95% CI)	p-value
Men (n=6,895)		
Linear model		
Intercept	114.8 (111.3, 118.3)	<0.001
Age	-3.0 (-4.2, -1.9)	<0.001
Non-linear model		
Intercept	88.6 (84.2, 93.0)	<0.001
Age^1	2.5 (2.1, 2.8)	<0.001
Age^2	-6.1 (-6.8, -6.3)	<0.001
Women (n=3,413)		
Linear model		
Intercept	50.5 (47.6, 53.4)	<0.001
Age	-0.5 (-1.4, 0.5)	0.352
Non-linear model		
Intercept	39.4 (36.1, 42.8)	<0.001
Age^1	0.8 (0.6, 1.0)	<0.001
Age^3	-0.4 (-0.5, -0.3)	<0.001

Age coefficients refer to the change in the average volume of weekly alcohol consumption per 10-year increase in age.

Appendix 8.3 Crude sex specific trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years: figure. Imputed data.



Appendix 8.4 Crude sex-specific linear and non-linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years: goodness of fit statistics. Observed data.

	Men		Women	
First-order polynomial models	**Log-likelihood**	**BIC[a]**	**Log-likelihood**	**BIC[a]**
age^{-2}	-184343	368748	-72549	145156
age^{-1}	-184320	368702	-72538	145133
$age^{-0.5}$	-184254	368571	-72520	145098
ln(age)	-184130	368322	-72496	145049
$age^{0.5}$	-184072	368206	-72494	145045
age	-184042	368146	-72500	145057
age^{2}	-184056	368174	-72493	145043
age^{3}	-184098	368259	-72465	144987
Second-order polynomial models	**Log-likelihood**	**BIC[a]**	**Log-likelihood**	**BIC[a]**
age^{-2}+age^{-1}	-184343	368717	-72549	145164
age^{-2}+$age^{-0.5}$	-184342	368757	-72547	145161
age^{-2}+ln(age)	-184337	368747	-72543	145152
age^{-2}+$age^{0.5}$	-184329	368730	-72537	145140
age^{-2}+age	-184315	368702	-72529	145125
age^{-2}+age^{2}	-184284	368641	-72514	145095
age^{-2}+age^{3}	-184261	368552	-72503	145073
age^{-1}+age^{-2}	-184320	368712	-72538	145142
age^{-1}+$age^{-0.5}$	-184313	368699	-72533	145133
age^{-1}+ln(age)	-184304	368680	-72528	145123
age^{-1}+$age^{0.5}$	-184291	368655	-72522	145110
age^{-1}+age	-184276	368624	-72514	145096
age^{-1}+age^{2}	-184246	368564	-72501	145068
age^{-1}+age^{3}	-184225	368523	-72491	145050
$age^{-0.5}$+age^{2}	-184253	368579	-72520	145106
$age^{-0.5}$+age^{-1}	-184247	368565	-72517	145101
$age^{-0.5}$+ln(age)	-184225	368523	-72508	145083
$age^{-0.5}$+$age^{0.5}$	-184207	368487	-72500	145067
$age^{-0.5}$+age	-184190	368452	-72493	145052
$age^{-0.5}$+age^{2}	-184160	368392	-72480	145027
$age^{-0.5}$+age^{3}	-184143	368358	-72472	145011

$ln(age)+age^{-2}$	-184127	368327	-72495	145058
$ln(age)+age^{-1}$	-184117	368306	-72492	145051
$ln(age)+age^{-0.5}$	-184106	368284	-72489	145044
$ln(age)+age^{0.5}$	-184051	368174	-72469	145005
$ln(age)+age$	-184035	368143	-72463	144993
$ln(age)+age^{2}$	-184009	368090	-72452	144971
$ln(age)+age^{3}$	-183997	368067	-72447	144960
$age^{0.5}+age^{-2}$	-184068	368208	-72494	145054
$age^{0.5}+age^{-1}$	-184054	368180	-72490	145047
$age^{0.5}+age^{-0.5}$	-184037	368147	-72485	145037
$age^{0.5}+ln(age)$	-184000	368072	-72473	145013
$age^{0.5}+age$	-183968	368009	-72462	144991
$age^{0.5}+age^{2}$	-183941	367954	-72452	144970
$age^{0.5}+age^{3}$	-183933	367938	-72447	144961
$age+age^{-2}$	-184037	368147	-72500	145066
$age+age^{-1}$	-184022	368116	-72497	145060
$age+age^{-0.5}$	-184003	368079	-72492	145050
$age+ln(age)$	-183968	368009	-72481	145029
$age+age^{0.5}$	-183953	367978	-72476	145019
$age+age^{2}$	-183909	367890	-72461	144988
$age+age^{3}$	-183905	367883	-72458	144983
$age^{2}+age^{-2}$	-184052	368177	-72493	145052
$age^{2}+age^{-1}$	-184037	368147	-72491	145048
$age^{2}+age^{-0.5}$	-184019	368110	-72486	145040
$age^{2}+ln(age)$	-183990	368052	-72479	145024
$age^{2}+age^{0.5}$	-183975	368023	-72475	145016
$age^{2}+age$	-183961	367994	-72470	145008
$age^{2}+age^{3}$	-183953	367978	-72467	145000
$age^{3}+age^{-2}$	-184096	368264	-72465	144996
$age^{3}+age^{-1}$	-184084	368241	-72464	144995
$age^{3}+age^{-0.5}$	-184070	368213	-72461	144989
$age^{3}+ln(age)$	-184050	368172	-72456	144980
$age^{3}+age^{0.5}$	-184041	368155	-72454	144975
$age^{3}+age$	-184034	368141	-72452	144971
$age^{3}+age^{2}$	-184033	368138	-72452	144970

[a]Bayesian information criterion.

Appendix 8.5 Crude sex-specific linear and non-linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years: goodness of fit statistics. Imputed data.

	Men (m=3/50)[a]	
First-order polynomial models	**Log-likelihood**	**BIC[a]**
Men		
age^{-2}	-232501 (-232762, -232191)	465034 (464414, 465556)
age^{-1}	-232501 (-232762, -232191)	465045 (464424, 465567)
$age^{-0.5}$	-232501 (-232762, -232191)	465044 (464423, 465567)
ln(age)	-232501 (-232761, -232191)	465044 (464423, 465564)
$age^{0.5}$	-232492 (-232750, -232181)	465027 (464405, 465542)
age	-232476 (-232731, -232165)	464994 (464371, 465504)
age^{2}	-232436 (-232686, -232126)	464915 (464295, 465415)
age^{3}	-232407 (-232655, -232099)	464857 (464241, 465352)
Women		
age^{-2}	-103392 (-103677, -103192)	206823 (206424, 207394)
age^{-1}	-103389 (-103673, -103190)	206817 (206419, 207385)
$age^{-0.5}$	-103389 (-103673, -103189)	206817 (206418, 207386)
ln(age)	-103391 (-103677, -103191)	206822 (206421, 207393)
$age^{0.5}$	-103392 (-103679, -103192)	206824 (206424, 207397)
age	-103390 (-103677, -103191)	206820 (206422, 207393)
age^{2}	-103380 (-103666, -103184)	206800 (206408, 207372)
age^{3}	-103369 (-103655, -103176)	206778 (206391, 207349)
Second-order polynomial models	**Log-likelihood**	**BIC[a]**
Men		
$age^{-2}+age^{-1}$	-232501 (-232762, -232191)	465034 (464414, 465556)
$age^{-2}+age^{-0.5}$	-232500 (-232762, -232190)	465032 (464412, 465555)
age^{-2}+ln(age)	-232500 (-232761, -232190)	465043 (464423, 465563)
$age^{-2}+age^{0.5}$	-232492 (-232750, -232181)	465026 (464405, 465542)
age^{-2}+age	-232475 (-232730, -232164)	464993 (464371, 465503)
$age^{-2}+age^{2}$	-232436 (-232686, -232126)	464914 (464294, 465414)
$age^{-2}+age^{3}$	-232407 (-232655, -232099)	464856 (464240, 465351)
$age^{-1}+age^{-2}$	-232501 (-232762, -232191)	465045 (464424, 465567)
$age^{-1}+age^{-0.5}$	-232500 (-232762, -232190)	465054 (464433, 465576)
age^{-1}+ln(age)	-232500 (-232761, -232190)	465054 (464433, 465574)
$age^{-1}+age^{0.5}$	-232492 (-232750, -232181)	465037 (464415, 465552)
age^{-1}+age	-232475 (-232730, -232164)	465004 (464381, 465513)
$age^{-1}+age^{2}$	-232436 (-232686, -232126)	464925 (464304, 465425)
$age^{-1}+age^{3}$	-232407 (-232655, -232099)	464867 (464251, 465362)

$age^{-0.5}+age^{2}$	-232500 (-232762, -232190)	465032 (464412, 465555)
$age^{-0.5}+age^{-1}$	-232500 (-232762, -232190)	465054 (464433, 465576)
$age^{-0.5}$+ln(age)	-232466 (-232722, -232152)	464985 (464357, 465498)
$age^{-0.5}+age^{0.5}$	-232444 (-232699, -232131)	464942 (464314, 465450)
$age^{-0.5}$+age	-232422 (-232674, -232109)	464897 (464271, 465401)
$age^{-0.5}+age^{2}$	-232387 (-232635, -232077)	464827 (464206, 465324)
$age^{-0.5}+age^{3}$	-232369 (-232617, -232062)	464791 (464176, 465286)
ln(age)+age^{-2}	-232500 (-232761, -232190)	465043 (464423, 465563)
ln(age)+age^{-1}	-232500 (-232761, -232190)	465054 (464433, 465574)
ln(age)+$age^{-0.5}$	-232466 (-232722, -232152)	464985 (464357, 465498)
ln(age)+$age^{0.5}$	-232419 (-232671, -232105)	464890 (464264, 465394)
ln(age)+age	-232396 (-232646, -232084)	464845 (464222, 465345)
ln(age)+age^{2}	-232367 (-232614, -232058)	464786 (464169, 465281)
ln(age)+age^{3}	-232357 (-232604, -232051)	464766 (464156, 465261)
$age^{0.5}+age^{-2}$	-232492 (-232750, -232181)	465026 (464405, 465542)
$age^{0.5}+age^{-1}$	-232492 (-232750, -232181)	465037 (464415, 465552)
$age^{0.5}+age^{-0.5}$	-232444 (-232699, -232131)	464942 (464314, 465450)
$age^{0.5}$+ln(age)	-232419 (-232671, -232105)	464890 (464264, 465394)
$age^{0.5}$+age	-232374 (-232622, -232064)	464800 (464180, 465296)
$age^{0.5}+age^{2}$	-232353 (-232600, -232047)	464759 (464147, 465252)
$age^{0.5}+age^{3}$	-232352 (-232599, -232048)	464756 (464149, 465250)
age+age^{-2}	-232475 (-232730, -232164)	464993 (464371, 465503)
age+age^{-1}	-232475 (-232730, -232164)	465004 (464381, 465513)
age+$age^{-0.5}$	-232422 (-232674, -232109)	464897 (464271, 465401)
age+ln(age)	-232396 (-232646, -232084)	464845 (464222, 465345)
age+$age^{0.5}$	-232374 (-232622, -232064)	464800 (464180, 465296)
age+age^{2}	-232348 (-232594, -232044)	464748 (464140, 465240)
age+age^{3}	-232353 (-232600, -232051)	464758 (464155, 465253)
$age^{2}+age^{-2}$	-232436 (-232686, -232126)	464914 (464294, 465414)
$age^{2}+age^{-1}$	-232436 (-232686, -232126)	464925 (464304, 465425)
$age^{2}+age^{-0.5}$	-232387 (-232635, -232077)	464827 (464206, 465324)
age^{2}+ln(age)	-232367 (-232614, -232058)	464786 (464169, 465281)
$age^{2}+age^{0.5}$	-232353 (-232600, -232047)	464759 (464147, 465252)
age^{2}+age	-232348 (-232594, -232044)	464748 (464140, 465240)
$age^{2}+age^{3}$	-232362 (-232611, -232062)	464778 (464176, 465275)

age^3+age^{-2}	-232407 (-232655, -232099)	464856 (464240, 465351)
age^3+age^{-1}	-232407 (-232655, -232099)	464867 (464251, 465362)
$age^3+age^{-0.5}$	-232369 (-232617, -232062)	464791 (464176, 465286)
age^3+ln(age)	-232357 (-232604, -232051)	464766 (464156, 465261)
$age^3+age^{0.5}$	-232352 (-232599, -232048)	464756 (464149, 465250)
age^3+age	-232353 (-232600, -232051)	464758 (464155, 465253)
age^3+age^2	-232362 (-232611, -232062)	464778 (464176, 465275)

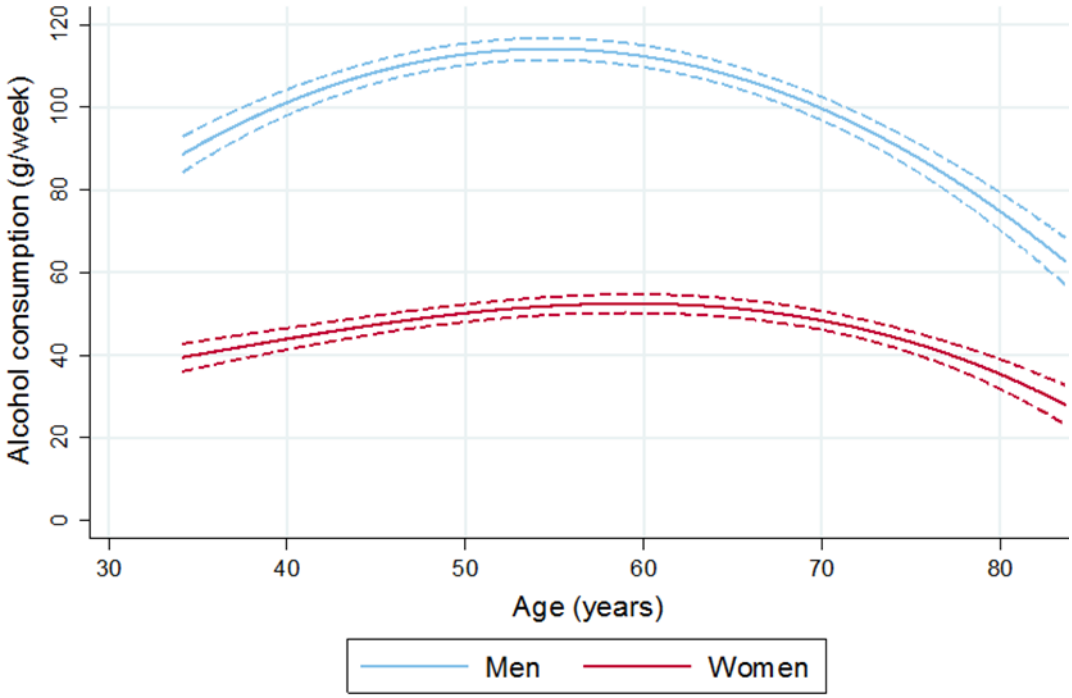
Women

$age^{-2}+age^{-1}$	-103386 (-103670, -103186)	206821 (206421, 207389)
$age^{-2}+age^{-0.5}$	-103388 (-103673, -103188)	206826 (206425, 207395)
age^{-2}+ln(age)	-103391 (-103676, -103191)	206831 (206431, 207402)
$age^{-2}+age^{0.5}$	-103391 (-103677, -103192)	206832 (206434, 207404)
age^{-2}+age	-103389 (-103675, -103191)	206827 (206431, 207398)
$age^{-2}+age^2$	-103378 (-103664, -103184)	206806 (206417, 207376)
$age^{-2}+age^3$	-103368 (-103652, -103176)	206785 (206401, 207353)
$age^{-1}+age^{-2}$	-103386 (-103670, -103186)	206821 (206421, 207389)
$age^{-1}+age^{-0.5}$	-103388 (-103673, -103189)	206826 (206428, 207395)
age^{-1}+ln(age)	-103388 (-103672, -103190)	206825 (206429, 207394)
$age^{-1}+age^{0.5}$	-103385 (-103669, -103189)	206819 (206427, 207387)
age^{-1}+age	-103380 (-103663, -103186)	206809 (206420, 207376)
$age^{-1}+age^2$	-103368 (-103650, -103177)	206785 (206403, 207350)
$age^{-1}+age^3$	-103358 (-103639, -103168)	206765 (206386, 207328)
$age^{-0.5}+age^2$	-103388 (-103673, -103188)	206826 (206425, 207395)
$age^{-0.5}+age^{-1}$	-103388 (-103673, -103189)	206826 (206428, 207395)
$age^{-0.5}$+ln(age)	-103383 (-103666, -103187)	206815 (206423, 207382)
$age^{-0.5}+age^{0.5}$	-103377 (-103660, -103183)	206804 (206416, 207368)
$age^{-0.5}$+age	-103370 (-103652, -103178)	206790 (206405, 207353)
$age^{-0.5}+age^2$	-103357 (-103637, -103168)	206763 (206384, 207324)
$age^{-0.5}+age^3$	-103348 (-103627, -103160)	206745 (206368, 207304)
ln(age)+age^{-2}	-103391 (-103676, -103191)	206831 (206431, 207402)
ln(age)+age^{-1}	-103388 (-103672, -103190)	206825 (206429, 207394)
ln(age)+$age^{-0.5}$	-103383 (-103666, -103187)	206815 (206423, 207382)
ln(age)+$age^{0.5}$	-103367 (-103648, -103175)	206784 (206400, 207345)
ln(age)+age	-103359 (-103639, -103169)	206767 (206386, 207327)
ln(age)+age^2	-103346 (-103624, -103157)	206741 (206364, 207298)
ln(age)+age^3	-103338 (-103617, -103151)	206726 (206351, 207283)

$age^{0.5}+age^{-2}$	-103391 (-103677, -103192)	206832 (206434, 207404)
$age^{0.5}+age^{-1}$	-103385 (-103669, -103189)	206819 (206427, 207387)
$age^{0.5}+age^{-0.5}$	-103377 (-103660, -103183)	206804 (206416, 207368)
$age^{0.5}$+ln(age)	-103367 (-103648, -103175)	206784 (206400, 207345)
$age^{0.5}$+age	-103348 (-103627, -103159)	206746 (206368, 207303)
$age^{0.5}+age^{2}$	-103337 (-103615, -103149)	206724 (206348, 207280)
$age^{0.5}+age^{3}$	-103333 (-103611, -103145)	206715 (206339, 207272)
$age+age^{-2}$	-103389 (-103675, -103191)	206827 (206431, 207398)
$age+age^{-1}$	-103380 (-103663, -103186)	206809 (206420, 207376)
$age+age^{-0.5}$	-103370 (-103652, -103178)	206790 (206405, 207353)
age+ln(age)	-103359 (-103639, -103169)	206767 (206386, 207327)
$age+age^{0.5}$	-103348 (-103627, -103159)	206746 (206368, 207303)
$age+age^{2}$	-103333 (-103611, -103145)	206715 (206338, 207271)
$age+age^{3}$	-103331 (-103610, -103143)	206712 (206335, 207269)
$age^{2}+age^{-2}$	-103378 (-103664, -103184)	206806 (206417, 207376)
$age^{2}+age^{-1}$	-103368 (-103650, -103177)	206785 (206403, 207350)
$age^{2}+age^{-0.5}$	-103357 (-103637, -103168)	206763 (206384, 207324)
age^{2}+ln(age)	-103346 (-103624, -103157)	206741 (206364, 207298)
$age^{2}+age^{0.5}$	-103337 (-103615, -103149)	206724 (206348, 207280)
$age^{2}+age$	-103333 (-103611, -103145)	206715 (206338, 207271)
$age^{2}+age^{3}$	-103333 (-103613, -103144)	206716 (206337, 207276)
$age^{3}+age^{-2}$	-103368 (-103652, -103176)	206785 (206401, 207353)
$age^{3}+age^{-1}$	-103358 (-103639, -103168)	206765 (206386, 207328)
$age^{3}+age^{-0.5}$	-103348 (-103627, -103160)	206745 (206368, 207304)
age^{3}+ln(age)	-103338 (-103617, -103151)	206726 (206351, 207283)
$age^{3}+age^{0.5}$	-103333 (-103611, -103145)	206715 (206339, 207272)
$age^{3}+age$	-103331 (-103610, -103143)	206712 (206335, 207269)
$age^{3}+age^{2}$	-103333 (-103613, -103144)	206716 (206337, 207276)

Fit statistics calculated on fixed effect models due to issues of convergence when some transformations were included as random effects. Values represent the mean and range of fit statistics as reported from the first three imputations. [a]Bayesian information criterion.

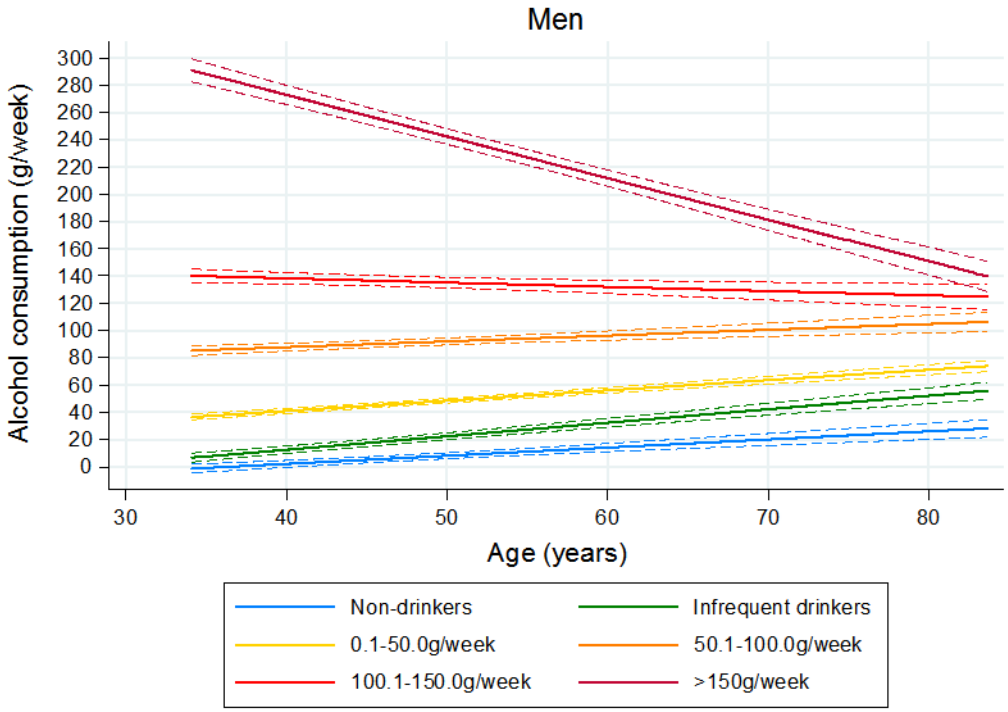
Appendix 8.6 Crude sex-specific non-linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years: figure. Imputed data.

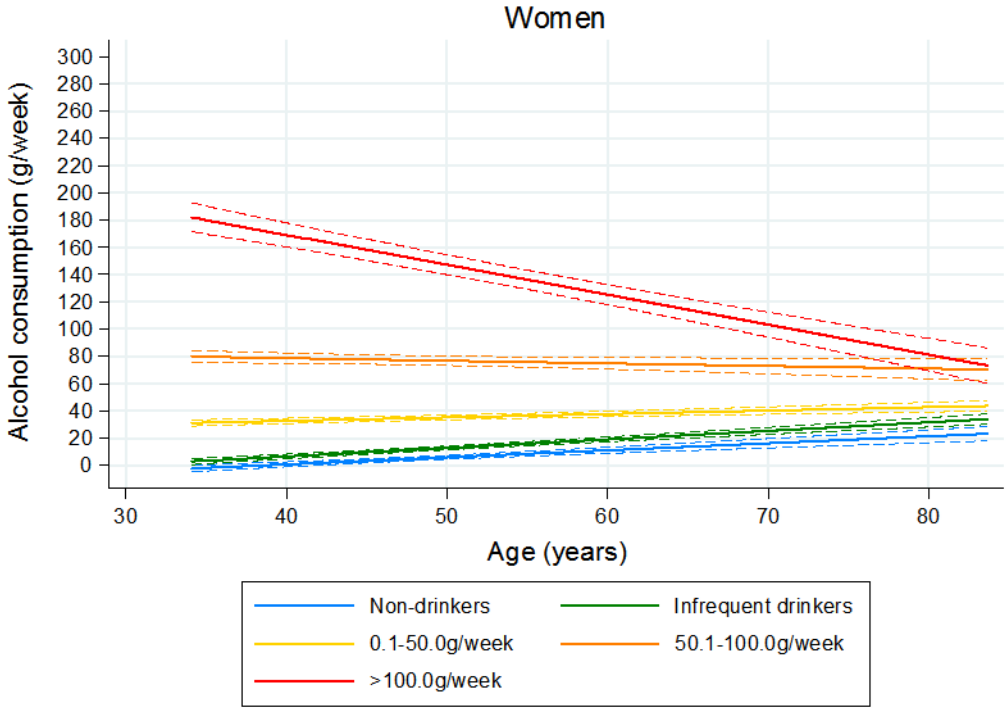


Appendix 8.7 Crude sex-specific interaction between the trajectory of mean weekly volume of alcohol consumption and baseline alcohol consumption category: results. Imputed data.

Linear mixed models	Sample n	g/week (95% CI)	p-value
Men			
Difference in baseline consumption by drinking category			
Non-drinker	220	Reference	
Infrequent drinker	669	7.8 (3.6, 12.0)	<0.001
0.1-50.0 g/week	2,073	37.6 (33.9, 41.3)	<0.001
50.1-100.0 g/week	1,432	85.6 (81.1, 90.1)	<0.001
100.1-150.0 g/week	881	140.8 (135.1, 146.3)	<0.001
>150.0 g/week	1,563	291.9 (283.1, 301.0)	<0.001
Difference in the rate of change by drinking category			
Non-drinker		Reference	
Infrequent drinker		4.0 (1.9, 6.2)	<0.001
0.1-50.0 g/week		1.7 (-0.3, 3.6)	0.092
50.1-100.0 g/week		-1.3 (-3.8, 1.1)	0.276
100.1-150.0 g/week		-8.9 (-11.6, -6.1)	<0.001
>150.0 g/week		-36.4 (-40.0, -32.8)	<0.001
Women			
Difference in baseline consumption by drinking category			
Non-drinker	216	Reference	
Infrequent drinker	764	4.9 (2.0, 7.8)	0.001
0.1-50.0 g/week	1,428	33.4 (30.4, 36.5)	<0.001
50.1-100.0 g/week	542	82.0 (77.1, 86.8)	<0.001
>100.0 g/week	422	184.1 (173.2, 195.0)	<0.001
Difference in the rate of change by drinking category			
Non-drinker		Reference	
Infrequent drinker		1.2 (-0.4, 2.8)	0.143
0.1-50.0 g/week		-2.6 (-4.3, -1.0)	0.002
50.1-100.0 g/week		-7.1 (-9.5, -4.6)	<0.001
>100.0 g/week		-27.1 (-31.2, -23.0)	<0.001

Appendix 8.8 Crude sex-specific linear trajectories of mean weekly volume of alcohol consumption between the ages of 34-84 years, stratified by baseline alcohol consumption category: figure. Imputed data.





Appendix 8.9 Baseline characteristics of T2DM-free participants, stratified by T2DM diagnosis. Imputed data.

Variables (wave one)	T2DM % (95% CI) n	Censored % (95% CI) n
Men		
Age		
Mean years	45.0 (44.6, 45.5)[a] 620	44.4 (44.2, 44.6)[a] 5,103
Alcohol consumption frequency		
None in past year	4.4 (2.8, 6.1) 28	2.6 (2.2, 3.0) 132
<1/week	21.9 (18.6, 25.1) 136	19.6 (18.5, 20.7) 1,002
1-3 times/week	40.2 (36.4, 44.1) 249	43.6 (42.3, 45.0) 2,226
Daily or almost daily	33.5 (29.7, 37.2) 207	34.2 (32.8, 35.5) 1,743
Alcohol consumption volume		
Median g/week	98.8 (89.9, 107.8)[b] 620	101.8 (98.7, 104.9)[b] 5,103
BMI		
Mean kg/m^2	26.1 (25.8, 26.3)[a] 620	24.3 (24.2, 24.4)[a] 5,103
Ethnicty		
White	84.8 (82.0, 87.7) 526	94.6 (94.0, 95.2) 4,826
South Asian	11.8 (9.2, 14.3) 73	3.4 (2.9, 3.9) 175
Other[c]	3.4 (2.0, 4.8) 21	2.0 (1.6, 2.4) 101
Family history of T2DM		
Yes	81.1 (78.0, 84.2) 503	91.2 (90.4, 92.0) 4,652
No	18.9 (15.8, 22.0) 117	8.8 (8.0, 9.6) 451
Occupational grade		
Administrative (top)	35.0 (31.2, 38.8) 217	41.3 (39.9, 42.6) 2.106
Professional (middle)	54.0 (50.1, 58.0) 335	52.1 (50.7, 53.4) 2,657
Clerical (bottom)	11.0 (8.5, 13.4) 68	6.7 (6.0, 7.3) 340

Physical activity[d]		
Inactive	12.4 (9.8, 15.0)	8.3 (7.6, 9.1)
	77	425
Below guidelines	40.0 (36.1, 43.9)	37.4 (36.1, 38.8)
	248	1,911
Met guidelines	47.6 (43.6, 51.5)	54.2 (52.9, 55.6)
	295	2,767
Smoking		
Never	42.4 (38.5, 46.3)	49.9 (48.5, 51.2)
	263	2,545
Former	39.1 (35.2, 42.9)	36.4 (35.0, 37.7)
	242	1,855
Current	18.6 (15.5, 21.6)	13.8 (12.8, 14.7)
	115	703
Women		
Age		
Mean years	46.7 (46.0, 47.4)[a]	45.3 (45.1, 45.6)[a]
	296	2,274
Alcohol consumption frequency		
None in past year	9.5 (6.1, 12.8)	5.7 (4.7, 6.6)
	28	129
<1/week	51.4 (45.6, 57.1)	35.3 (33.4, 37.3)
	152	803
1-3 times/week	28.7 (23.5, 33.9)	36.6 (34.6, 38.5)
	85	831
Daily or almost daily	10.5 (7.0, 14.0)	22.5 (20.7, 24.2)
	31	511
Alcohol consumption volume		
Median g/week	29.4 (23.3, 35.5)[b]	47.0 (44.5, 49.5)[b]
	296	2,274
BMI		
Mean kg/m^2	28.0 (27.4, 28.6)[a]	24.2 (24.0, 24.3)[a]
	296	2,274
Ethnicty		
White	71.1 (65.9, 76.3)	89.1 (87.8, 90.3)
	211	2,025
South Asian	14.5 (10.5, 18.6)	4.6 (3.7, 5.4)
	43	103
Other[c]	14.3 (10.3, 18.4)	6.4 (5.4, 7.4)
	42	145
Family history of T2DM		
Yes	68.9 (63.6, 74.3)	89.1 (87.8, 90.4)
	204	2,026
No	31.1 (25.7, 36.4)	10.9 (9.6, 12.2)
	92	248

Occupational grade		
Administrative (top)	4.1 (1.8, 6.3)	14.0 (12.6, 15.5)
	12	319
Professional (middle)	36.8 (31.3, 42.4)	43.0 (41.0, 45.0)
	109	978
Clerical (bottom)	59.1 (53.5, 64.8)	43.0 (40.9, 45.0)
	175	977
Physical activity[d]		
Inactive	32.8 (27.4, 38.3)	23.0 (21.2, 24.7)
	97	522
Below guidelines	34.2 (28.7, 39.7)	40.3 (38.3, 42.3)
	101	917
Met guidelines	33.0 (27.6, 38.4)	36.7 (34.7, 38.7)
	98	835
Smoking		
Never	59.1 (53.5, 64.7)	54.3 (52.2, 56.3)
	175	1,234
Former	22.2 (17.4, 27.0)	24.9 (23.1, 26.7)
	66	567
Current	18.7 (14.2, 23.1)	20.8 (19.1, 22.5)
	55	473

[a]Mean and 95% confidence interval; [b]Median and 25th and 75th percentiles; [c]e.g. black Caribbean, African and Arabic; [d]Meeting guidelines (≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week); inactive (<60 minutes of moderate and <60 minutes of vigorous activity; below guidelines (not inactive or meeting guidelines).

Appendix 8.10 Sex-specific interaction between the linear trajectory of mean weekly volume of alcohol consumption and T2DM diagnosis: goodness of fit statistics. Imputed data

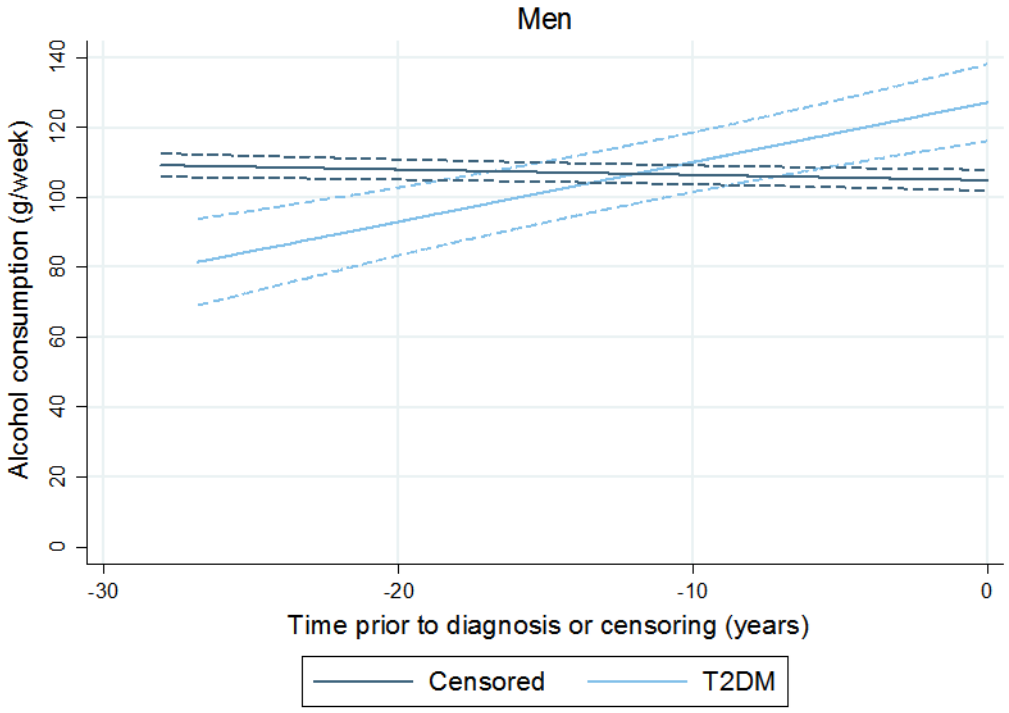
Mixed model	Log-likelihood	BIC[a]
Men		
Crude linear mixed model, fixed slope	-173035 (-173255, -172857)	346132 (345776, 346571)
Crude linear mixed model, random slopes	-172951 (-173171, -172765)	345984 (345613, 346424)
Women		
Crude linear mixed model, fixed slope	-67229 (-67566, -67016)	134514 (134089, 135188)
Crude linear mixed model, random slopes	-67196 (-67546, -66969)	134467 (134014, 135167)

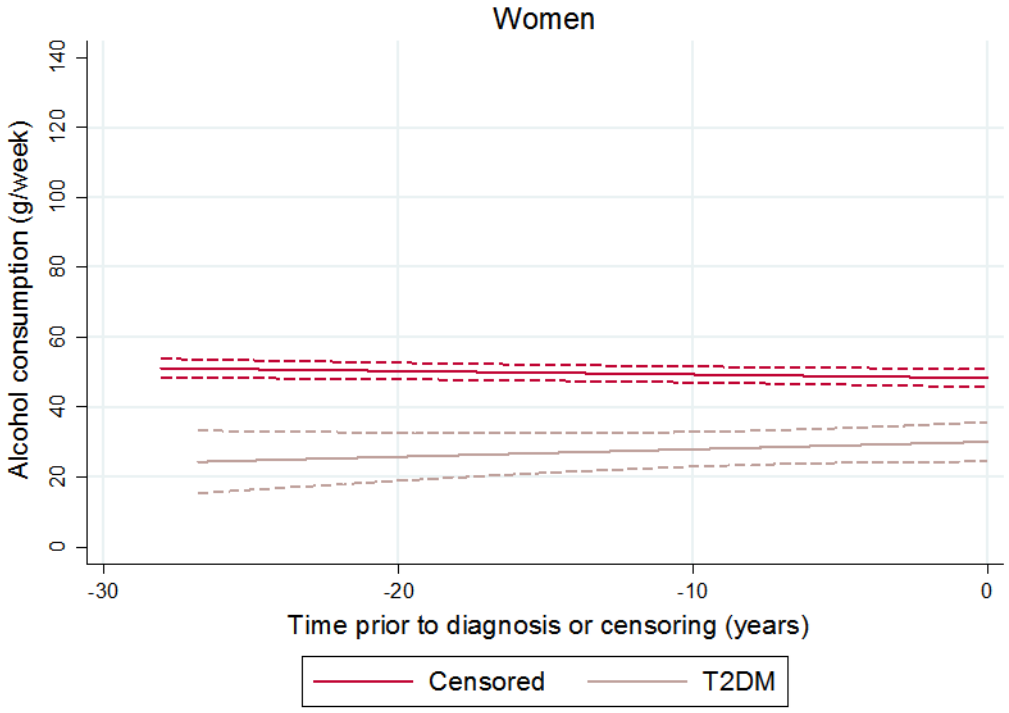
[a]Bayesian information criterion. Values refer to the mean and range of fit statistics as reported by the first three imputations.

Appendix 8.11 Crude sex-specific interaction between the linear trajectory of mean weekly volume of alcohol consumption and T2DM diagnosis: results. Imputed data.

Crude linear mixed models	g/week (95% CI)	p-value
Men (n=5,723)		
Consumption volume		
Intercept	104.9 (101.9, 107.9)	<0.001
Change per 10 years prior to diagnosis or censoring	-1.5 (-2.7, -0.4)	0.009
Difference in consumption at the time of diagnosis or censoring		
Censored	Reference	
T2DM	22.2 (10.8, 33.5)	<0.001
Difference in the rate of change by diagnosis or censoring		
Censored	Reference	
T2DM	17.0 (11.1, 23.0)	<0.001
Women (n=2,570)		
Consumption volume		
Intercept	48.3 (45.7, 50.8)	<0.001
Change per 10 years prior to diagnosis or censoring	-1.0 (-2.0, -0.0)	0.045
Difference in consumption at the time of diagnosis or censoring		
Censored	Reference	
T2DM	-18.2 (-24.4, -12.0)	<0.001
Difference in the rate of change by diagnosis or censoring		
Censored	Reference	
T2DM	2.1 (-1.7, 6.0)	0.279

Appendix 8.12 Crude sex-specific linear trajectory of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis: figure. Imputed data.





Appendix 8.13 Crude sex-specific linear and non-linear trajectories of mean weekly alcohol consumption, stratified by T2DM diagnosis: goodness of fit statistics. Observed data.

	T2DM		No T2DM	
First-order models	**Log-likelihood**	**[a]BIC**	**Log-likelihood**	**[a]BIC**
Men				
$time^{-2}$	-12665	25361	-149882	299804
$time^{-1}$	-12665	25361	-149866	299772
$time^{1}$	-12648	25327	-149877	299794
$time^{2}$	-12647	25324	-149882	299805
$time^{3}$	-12649	25329	-149876	299792
Women				
$time^{-2}$	-4758	9543	-57154	114345
$time^{-1}$	-4758	9543	-57153	114343
$time^{1}$	-4759	9545	-57152	114342
$time^{2}$	-4759	9545	-57159	114355
$time^{3}$	-4759	9545	-57159	114355
Second-order models	**Log-likelihood**	**[a]BIC**	**Log-likelihood**	**[a]BIC**
Men				
$time^{-2}+time^{-1}$	-12665	25368	-149813	299678
$time^{-2}+time$	-12648	25334	-149875	299801
$time^{-2}+time^{2}$	-12647	25332	-149880	299812
$time^{-2}+time^{3}$	-12649	25336	-149874	299799
$time^{-1}+time^{-2}$	-12665	25368	-149813	299678
$time^{-1}+time$	-12648	25334	-149862	299774
$time^{-1}+time^{2}$	-12647	25332	-149864	299778
$time^{-1}+time^{3}$	-12649	25336	-149857	299764
$time+time^{-2}$	-12648	25334	-149875	299801
$time+time^{-1}$	-12648	25334	-149862	299774
$time+time^{2}$	-12647	25332	-149709	299468
$time+time^{3}$	-12647	25333	-149730	299510
$time^{2}+time^{-2}$	-12647	25332	-149880	299812
$time^{2}+time^{-1}$	-12647	25332	-149864	299778
$time^{2}+time$	-12647	25332	-149709	299468
$time^{2}+time^{3}$	-12646	25331	-149779	299609
$time^{3}+time^{-2}$	-12649	25336	-149874	299799
$time^{3}+time^{-1}$	-12649	25336	-149857	299764
$time^{3}+time$	-12647	25333	-149730	299510
$time^{3}+time^{2}$	-12647	25331	-149779	299609

Women				
$time^{-2}+time^{-1}$	-4758	9549	-57152	114351
$time^{-2}+time$	-4758	9550	-57147	114340
$time^{-2}+time^{2}$	-4758	9550	-57154	114354
$time^{-2}+time^{3}$	-4758	9550	-57154	114354
$time^{-1}+time^{-2}$	-4758	9549	-57152	114351
$time^{-1}+time$	-4758	9549	-57146	114339
$time^{-1}+time^{2}$	-4758	9549	-57152	114351
$time^{-1}+time^{3}$	-4758	9549	-57153	114352
$time+time^{-2}$	-4758	9550	-57147	114340
$time+time^{-1}$	-4758	9549	-57146	114339
$time+time^{2}$	-4759	9552	-57103	114252
$time+time^{3}$	-4759	9552	-57111	114268
$time^{2}+time^{-2}$	-4758	9550	-57154	114354
$time^{2}+time^{-1}$	-4758	9549	-57153	114351
$time^{2}+time$	-4759	9552	-57103	114252
$time^{2}+time^{3}$	-4759	9552	-57129	114305
$time^{3}+time^{-2}$	-4758	9550	-57154	114354
$time^{3}+time^{-1}$	-4758	9549	-57153	114352
$time^{3}+time$	-4759	9552	-57111	114268
$time^{3}+time^{2}$	-4759	9552	-57129	114305

Fit statistics calculated on models with fixed slopes and without robust standard errors due to issues of convergence for some transformations when random slopes were expressed.

[a]Bayesian information criterion.

Appendix 8.14 Crude sex-specific linear and non-linear trajectories of mean weekly alcohol consumption, stratified by T2DM diagnosis: goodness of fit statistics. Imputed data.

	T2DM		No T2DM	
First-order models	**Log-likelihood**	**[a]BIC**	**Log-likelihood**	**[a]BIC**
Men				
$time^{-2}$	-13499 (-13501, -13497)	27029 (27024-27032)	-159549 (-159770, -159370)	319139 (318782-319581)
$time^{-1}$	-13499 (-13501, -13497)	27029 (27024-27032)	-159532 (-159754, -159353)	319105 (318747-319549)
$time^{1}$	-13482 (-13483, -13481)	26995 (26992-26997)	-159546 (-159767, -159368)	319133 (318776-319576)
$time^{2}$	-13480 (-13482, -13479)	26992 (26988-26994)	-159549 (-159769, -159370)	319138 (318780-319579)
$time^{3}$	-13482 (-13484, -13480)	26996 (26992-26998)	-159540 (-159760, -159361)	319121 (318763-319562)
Women				
$time^{-2}$	-5140 (-5152, -5132)	10307 (10292-10331)	-62040 (-62367, -61827)	124118 (123691-124772)
$time^{-1}$	-5139 (-5151, -5131)	10306 (10290-10329)	-62039 (-62365, -61825)	124115 (123687-124768)
$time^{1}$	-5140 (-5152, -5132)	10307 (10291-10331)	-62042 (-62369, -61828)	124121 (123694-124775)
$time^{2}$	-5140 (-5152, -5132)	10307 (10291-10331)	-62045 (-62372, -61832)	124128 (123701-124781)
$time^{3}$	-5140 (-5152, -5132)	10307 (10292-10331)	-62044 (-62370, -61830)	124126 (123698-124778)
Second-order models	**Log-likelihood**	**[a]BIC**	**Log-likelihood**	**[a]BIC**
Men				
$time^{-2}$+$time^{-1}$	-13499 (-13501, -13497)	27037 (27032-27040)	-159486 (-159710, -159306)	319023 (318662-319472)
$time^{-2}$+time	-13482 (-13483, -13481)	27002 (27000-27004)	-159544 (-159766, -159366)	319139 (318782-319582)
$time^{-2}$+$time^{2}$	-13480 (-13481, -13479)	26999 (26996-27002)	-159547 (-159767, -159368)	319145 (318787-319586)
$time^{-2}$+$time^{3}$	-13482 (-13484, -13480)	27003 (26999-27006)	-159538 (-159759, -159359)	319128 (318770-319568)
$time^{-1}$+$time^{-2}$	-13499 (-13501, -13497)	27037 (27032-27040)	-159486 (-159710, -159306)	319023 (318662-319472)
$time^{-1}$+time	-13482 (-13483, -13480)	27002 (27000-27005)	-159529 (-159751, -159350)	319109 (318752-319554)
$time^{-1}$+$time^{2}$	-13480 (-13481, -13479)	26999 (26996-27002)	-159529 (-159750, -159349)	319108 (318749-319551)
$time^{-1}$+$time^{3}$	-13482 (-13484, -13480)	27003 (26999-27006)	-159519 (-159741, -159340)	319090 (318731-319532)

time+time^{-2}	-13482 (-13483, -13481)	27002 (27000-27004)	-159544 (-159766, -159366)	319139 (318782-319582)
time+time^{-1}	-13482 (-13483, -13480)	27002 (27000-27005)	-159529 (-159751, -159350)	319109 (318752-319554)
time+time^{2}	-13480 (-13482, -13479)	26999 (26996-27002)	-159366 (-159592, -159193)	318783 (318437-319234)
time+time^{3}	-13481 (-13482, -13479)	27001 (26997-27003)	-159388 (-159615, -159215)	318827 (318482-319280)
time^{2}+time^{-2}	-13480 (-13481, -13479)	26999 (26996-27002)	-159547 (-159767, -159368)	319145 (318787-319586)
time^{2}+time^{-1}	-13480 (-13481, -13479)	26999 (26996-27002)	-159529 (-159750, -159349)	319108 (318749-319551)
time^{2}+time	-13480 (-13482, -13479)	26999 (26996-27002)	-159366 (-159592, -159193)	318783 (318437-319234)
time^{2}+time^{3}	-13480 (-13481, -13478)	26999 (26995-27001)	-159439 (-159666, -159265)	318929 (318581-319382)
time^{3}+time^{-2}	-13482 (-13484, -13480)	27003 (26999-27006)	-159538 (-159759, -159359)	319128 (318770-319568)
time^{3}+time^{-1}	-13482 (-13484, -13480)	27003 (26999-27006)	-159519 (-159741, -159340)	319090 (318731-319532)
time^{3}+time	-13481 (-13482, -13479)	27001 (26997-27003)	-159388 (-159615, -159215)	318827 (318482-319280)
time^{3}+time^{2}	-13480 (-13481, -13478)	26999 (26995-27001)	-159439 (-159666, -159265)	318929 (318581-319382)

Women

time^{-2}+time^{-1}	-5138 (-5149, -5131)	10311 (10297-10333)	-62038 (-62364, -61824)	124122 (123694-124775)
time^{-2}+time	-5140 (-5152, -5132)	10314 (10298-10338)	-62036 (-62364, -61823)	124120 (123692-124775)
time^{-2}+time^{2}	-5140 (-5152, -5132)	10314 (10298-10338)	-62040 (-62367, -61826)	124127 (123700-124781)
time^{-2}+time^{3}	-5140 (-5152, -5132)	10314 (10298-10338)	-62039 (-62365, -61825)	124125 (123697-124778)
time^{-1}+time^{-2}	-5138 (-5149, -5131)	10311 (10297-10333)	-62038 (-62364, -61824)	124122 (123694-124775)
time^{-1}+time	-5139 (-5150, -5131)	10312 (10296-10335)	-62035 (-62363, -61821)	124117 (123690-124772)
time^{-1}+time^{2}	-5139 (-5150, -5131)	10312 (10296-10335)	-62039 (-62365, -61825)	124124 (123696-124777)
time^{-1}+time^{3}	-5139 (-5151, -5131)	10313 (10296-10336)	-62037 (-62363, -61824)	124122 (123694-124774)

time+time^{-2}	-5140 (-5152, -5132)	10314 (10298-10338)	-62036 (-62364, -61823)	124120 (123692-124775)
time+time^{-1}	-5139 (-5150, -5131)	10312 (10296-10335)	-62035 (-62363, -61821)	124117 (123690-124772)
time+time^{2}	-5140 (-5152, -5132)	10314 (10298-10338)	-61987 (-62313, -61776)	124021 (123598-124673)
time+time^{3}	-5140 (-5152, -5132)	10314 (10298-10338)	-61997 (-62324, -61785)	124040 (123617-124694)
time^{2}+time^{-2}	-5140 (-5152, -5132)	10314 (10298-10338)	-62040 (-62367, -61826)	124127 (123700-124781)
time^{2}+time^{-1}	-5139 (-5150, -5131)	10312 (10296-10335)	-62039 (-62365, -61825)	124124 (123696-124777)
time^{2}+time	-5140 (-5152, -5132)	10314 (10298-10338)	-61987 (-62313, -61776)	124021 (123598-124673)
time^{2}+time^{3}	-5140 (-5151, -5132)	10314 (10298-10337)	-62017 (-62344, -61804)	124080 (123654-124735)
time^{3}+time^{-2}	-5140 (-5152, -5132)	10314 (10298-10338)	-62039 (-62365, -61825)	124125 (123697-124778)
time^{3}+time^{-1}	-5139 (-5151, -5131)	10313 (10296-10336)	-62037 (-62363, -61824)	124122 (123694-124774)
time^{3}+time	-5140 (-5152, -5132)	10314 (10298-10338)	-61997 (-62324, -61785)	124040 (123617-124694)
time^{3}+time^{2}	-5140 (-5151, -5132)	10314 (10298-10337)	-62017 (-62344, -61804)	124080 (123654-124735)

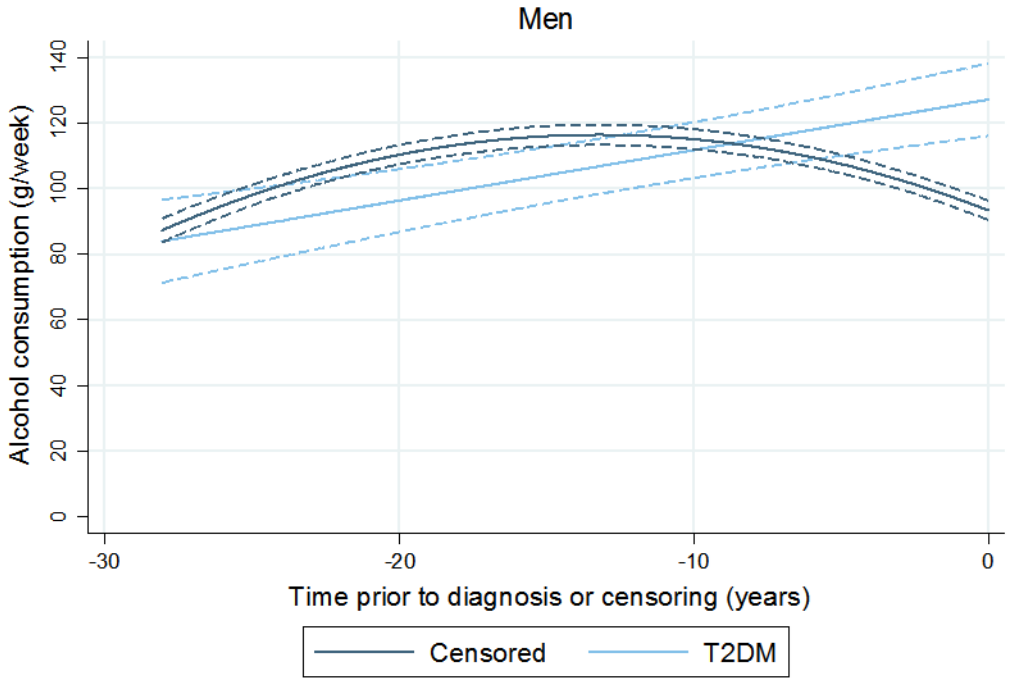
Fit statistics calculated on models with fixed slopes and without robust standard errors due to issues of convergence for some transformations when random slopes were expressed. Values refer to the mean and range of fit statistics as reported by the first three imputations.

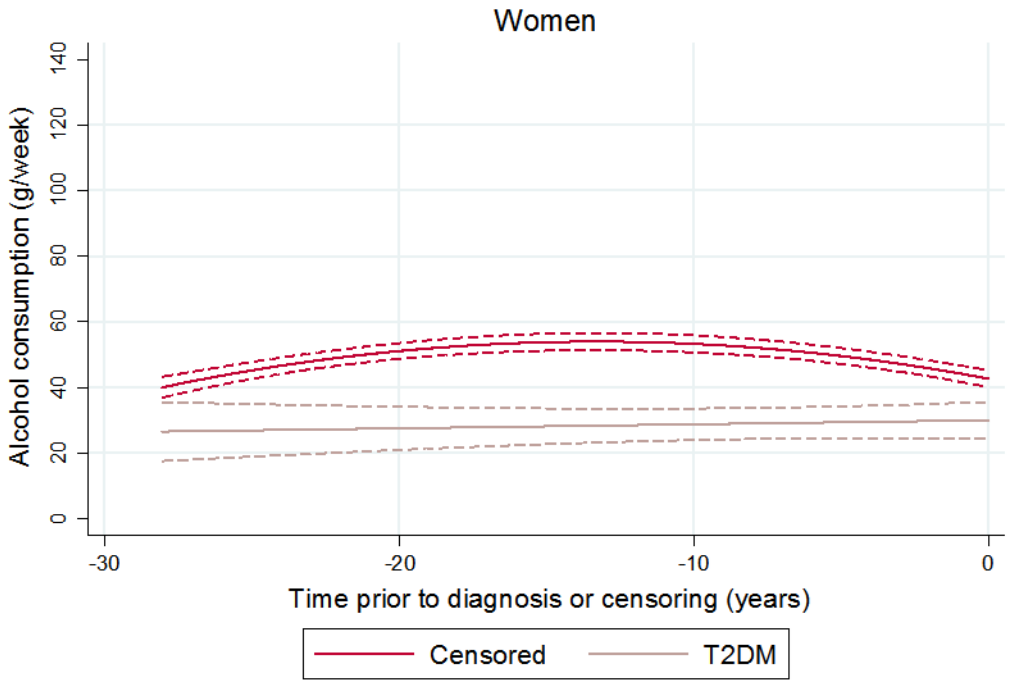
Appendix 8.15 Crude, sex-specific and best-fitting trajectories of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis: results. Imputed data.

Crude best-fitting mixed models	g/week (95% CI)	p-value
Men		
T2DM (n=620)		
Intercept	127.1 (116.0, 138.2)	<0.001
Time[1]	15.4 (9.4, 21.3)	<0.001
Censored (n=5,103)		
Intercept	93.4 (90.4, 96.3)	<0.001
Time[1]	-34.9 (-38.6, -31.1)	<0.001
Time[2]	-1.3 (-1.5, -1.2)	<0.001
Women		
T2DM (n=296)		
Intercept	30.1 (24.5, 35.7)	<0.001
Time[1]	1.2 (-2.5, 5.0)	0.514
Censored (n=2,274)		
Intercept	42.7 (40.1, 45.3)	<0.001
Time[1]	-17.0 (-20.4, -13.6)	<0.001
Time[2]	-0.6 (-0.8, -0.5)	<0.001

Time coefficients refer to the change in the average volume of weekly alcohol consumption per 10 years prior to diagnosis or censoring.

Appendix 8.16 Crude sex-specific best-fitting trajectories of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis: figure. Imputed data.





Appendix 8.17 Crude linear and non-linear trajectories of alcohol consumption up to and beyond the date of diagnosis, stratified by sex: goodness of fit statistics. Observed data.

	Men		Women	
Function	**Log-likelihood**	**[a]BIC**	**Log-likelihood**	**[a]BIC**
Up to diagnosis				
$time^{-2}$	-12665	25361	-4758	9543
$time^{-1}$	-12665	25361	-4758	9543
$time^{1}$	-12648	25327	-4759	9545
$time^{2}$	-12647	25324	-4759	9545
$time^{3}$	-12649	25329	-4759	9545
$time^{-2}$+$time^{-1}$	-12665	25368	-4758	9549
$time^{-2}$+time	-12648	25334	-4758	9550
$time^{-2}$+$time^{2}$	-12647	25332	-4758	9550
$time^{-2}$+$time^{3}$	-12649	25336	-4758	9550
$time^{-1}$+time	-12648	25334	-4758	9549
$time^{-1}$+$time^{2}$	-12647	25332	-4758	9549
$time^{-1}$+$time^{3}$	-12649	25336	-4758	9549
time+$time^{2}$	-12647	25332	-4759	9552
time+$time^{3}$	-12647	25333	-4759	9552
$time^{2}$+$time^{3}$	-12646	25331	-4759	9552
After diagnosis				
$time^{-2}$	-6777	13582	-2721	5468
$time^{-1}$	-6775	13578	-2721	5467
$time^{1}$	-6767	13562	-2719	5463
$time^{2}$	-6766	13561	-2718	5461
$time^{3}$	-6768	13565	-2718	5462
$time^{-2}$+$time^{-1}$	-6769	13573	-2720	5472
$time^{-2}$+time	-6766	13566	-2718	5469
$time^{-2}$+$time^{2}$	-6766	13568	-2718	5468
$time^{-2}$+$time^{3}$	-6768	13571	-2718	5467
$time^{-1}$+time	-6766	13566	-2718	5469
$time^{-1}$+$time^{2}$	-6766	13568	-2718	5468
$time^{-1}$+$time^{3}$	-6768	13571	-2718	5468
time+$time^{2}$	-6766	13567	-2718	5468
time+$time^{3}$	-6766	13568	-2718	5468
$time^{2}$+$time^{3}$	-6766	13567	-2718	5468

Fit statistics calculated on models with fixed slopes and without robust standard errors due to issues of convergence for some transformations when random slopes were expressed. [a]Bayesian information criterion.

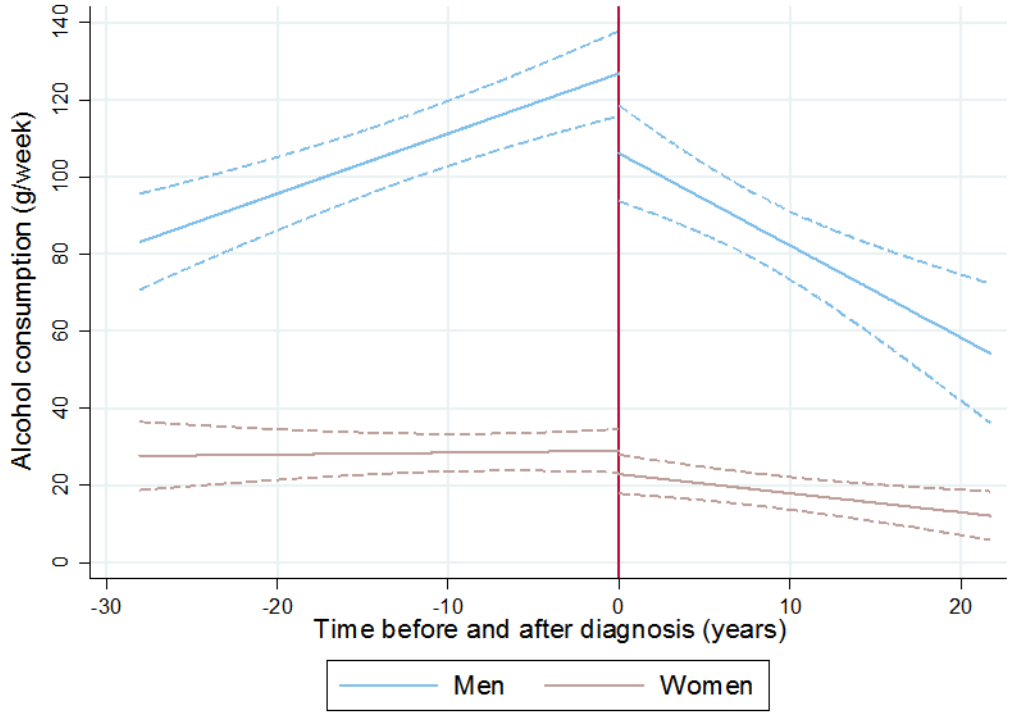
Appendix 8.18 Crude linear and non-linear trajectories of alcohol consumption up to and beyond the date of diagnosis, stratified by sex: goodness of fit statistics. Imputed data.

	Men		Women	
Function	**Log-likelihood**	**[a]BIC**	**Log-likelihood**	**[a]BIC**
Up to diagnosis				
$time^{-2}$	-13499 (-13501, -13497)	27029 (27024, 27032)	-5140 (-5152, -5132)	10307 (10292, 10331)
$time^{-1}$	-13499 (-13501, -13497)	27029 (27024, 27032)	-5139 (-5151, -5131)	10306 (10290, 10329)
$time^{1}$	-13482 (-13483, -13481)	26995 (26992, 26997)	-5140 (-5152, -5132)	10307 (10291, 10331)
$time^{2}$	-13480 (-13482, -13479)	26992 (26988, 26994)	-5140 (-5152, -5132)	10307 (10291, 10331)
$time^{3}$	-13482 (-13484, -13480)	26996 (26992, 26998)	-5140 (-5152, -5132)	10307 (10292, 10331)
$time^{-2}$+$time^{-1}$	-13499 (-13501, -13497)	27037 (27032, 27040)	-5138 (-5149, -5131)	10311 (10297, 10333)
$time^{-2}$+time	-13482 (-13483, -13481)	27002 (27000, 27004)	-5140 (-5152, -5132)	10314 (10298, 10338)
$time^{-2}$+$time^{2}$	-13480 (-13481, -13479)	26999 (26996, 27002)	-5140 (-5152, -5132)	10314 (10298, 10338)
$time^{-2}$+$time^{3}$	-13482 (-13484, -13480)	27003 (26999, 27006)	-5140 (-5152, -5132)	10314 (10298, 10338)
$time^{-1}$+time	-13482 (-13483, -13480)	27002 (27000, 27005)	-5139 (-5150, -5131)	10312 (10296, 10335)
$time^{-1}$+$time^{2}$	-13480 (-13481, -13479)	26999 (26996, 27002)	-5139 (-5150, -5131)	10312 (10296, 10335)
$time^{-1}$+$time^{3}$	-13482 (-13484, -13480)	27003 (26999, 27006)	-5139 (-5151, -5131)	10313 (10296, 10336)
time+$time^{2}$	-13480 (-13482, -13479)	26999 (26996, 27002)	-5140 (-5152, -5132)	10314 (10298, 10338)
time+$time^{3}$	-13481 (-13482, -13479)	27001 (26997, 27003)	-5140 (-5152, -5132)	10314 (10298, 10338)
$time^{2}$+$time^{3}$	-13480 (-13481, -13478)	26999 (26995, 27001)	-5140 (-5151, -5132)	10314 (10298, 10337)

After diagnosis				
$time^{-2}$	-8746 (-8862, -8664)	17521 (17357, 17753)	-3806 (-3880, -3724)	7638 (7474, 7786)
$time^{-1}$	-8744 (-8860, -8662)	17517 (17354, 17749)	-3808 (-3888, -3723)	7643 (7473, 7804)
$time^{1}$	-8736 (-8853, -8657)	17501 (17342, 17735)	-3809 (-3894, -3722)	7645 (7470, 7814)
$time^{2}$	-8736 (-8853, -8657)	17501 (17343, 17735)	-3809 (-3894, -3722)	7645 (7470, 7815)
$time^{3}$	-8738 (-8854, -8659)	17505 (17347, 17738)	-3810 (-3895, -3722)	7646 (7471, 7816)
$time^{-2}$+$time^{-1}$	-8738 (-8856, -8658)	17513 (17352, 17748)	-3799 (-3862, -3723)	7631 (7479, 7757)
$time^{-2}$+time	-8735 (-8853, -8656)	17507 (17348, 17742)	-3804 (-3879, -3722)	7641 (7477, 7790)
$time^{-2}$+$time^{2}$	-8736 (-8853, -8657)	17508 (17351, 17742)	-3804 (-3880, -3721)	7642 (7476, 7793)
$time^{-2}$+$time^{3}$	-8737 (-8854, -8659)	17511 (17353, 17744)	-3804 (-3880, -3721)	7642 (7476, 7793)
$time^{-1}$+time	-8735 (-8852, -8656)	17507 (17348, 17741)	-3807 (-3888, -3722)	7647 (7477, 7809)
$time^{-1}$+$time^{2}$	-8736 (-8853, -8657)	17508 (17350, 17742)	-3807 (-3888, -3721)	7648 (7476, 7810)
$time^{-1}$+$time^{3}$	-8737 (-8854, -8658)	17510 (17353, 17744)	-3807 (-3888, -3721)	7648 (7476, 7810)
time+$time^{2}$	-8735 (-8853, -8656)	17507 (17349, 17742)	-3809 (-3894, -3722)	7651 (7477, 7820)
time+$time^{3}$	-8735 (-8853, -8657)	17507 (17350, 17742)	-3809 (-3894, -3722)	7651 (7477, 7821)
$time^{2}$+$time^{3}$	-8735 (-8852, -8656)	17506 (17348, 17741)	-3809 (-3894, -3722)	7652 (7477, 7822)

Fit statistics calculated on models with fixed slopes and without robust standard errors due to issues of convergence for some transformations when random slopes were expressed. Values refer to the mean and range of fit statistics as reported by the first three imputations. [a]Bayesian information criterion.

Appendix 8.19 Crude trajectories of mean weekly volume of alcohol consumption up to and beyond the date of diagnosis, stratified by sex. Imputed data.

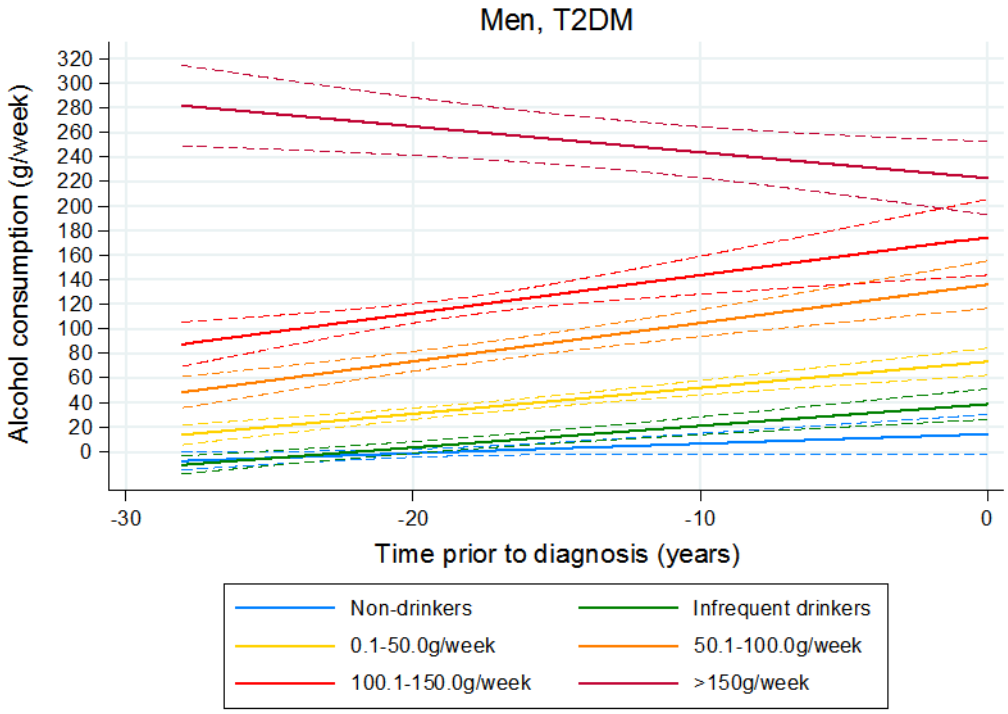


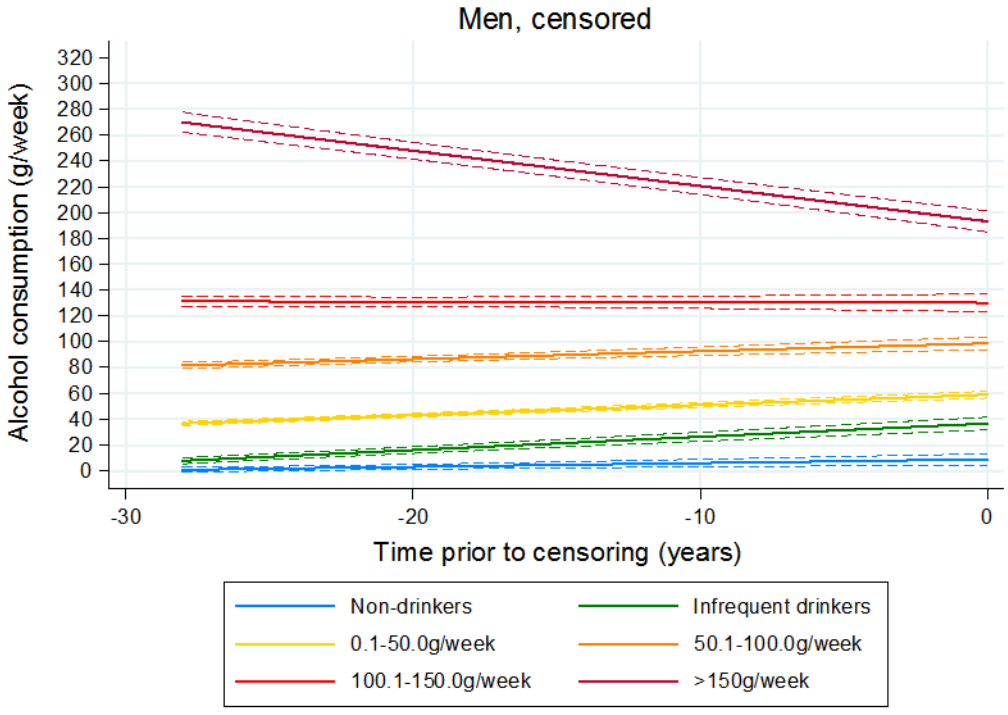
Appendix 8.20 Crude sex-specific interaction between the trajectory of mean weekly volume of alcohol consumption and baseline alcohol consumption category, stratified by T2DM diagnosis: results. Imputed data.

	T2DM		Censored	
Crude linear mixed models	**g/week (95% CI)**	**p-value**	**g/week (95% CI)**	**p-value**
Men				
Difference in consumption at the time of diagnosis or censoring by baseline consumption category				
Non-drinker	Reference		Reference	
Infrequent drinker	24.9 (5.3, 44.5)	0.013	27.7 (21.1, 34.3)	<0.001
0.1-50.0 g/week	59.4 (40.8, 78.1)	<0.001	50.0 (44.9, 55.0)	<0.001
50.1-100.0 g/week	122.3 (97.9, 146.7)	<0.001	89.6 (83.1, 96.2)	<0.001
100.1-150.0 g/week	160.6 (126.2, 195.1)	<0.001	120.9 (112.9, 129.0	<0.001
>150.0 g/week	209.1 (176.0, 242.2)	<0.001	184.2 (175.0, 193.5)	<0.001
Difference in the rate of change by baseline consumption category[a]				
Non-drinker	Reference		Reference	
Infrequent drinker	10.8 (1.4, 20.1)	0.024	7.4 (5.0, 9.8)	<0.001
0.1-50.0 g/week	14.4 (5.1, 23.7)	0.002	5.1 (3.1, 7.0)	<0.001
50.1-100.0 g/week	25.1 (12.9, 37.3)	<0.001	3.3 (0.7, 6.0)	0.012
100.1-150.0 g/week	24.1 (6.0, 42.2)	0.009	-3.3 (-6.4, -0.3)	0.034
>150.0 g/week	-27.5 (-45.8, -9.3)	0.003	-30.0 (-33.9, -26.4)	<0.001
Women				
Difference in consumption at the time of diagnosis or censoring by baseline consumption category				
Non-drinker	Reference		Reference	
Infrequent drinker	14.4 (7.4, 21.4)	<0.001	14.0 (10.0, 18.0)	<0.001
0.1-50.0 g/week	28.5 (21.1, 35.9)	<0.001	29.5 (25.6, 33.4)	<0.001
50.1-100.0 g/week	39.6 (24.4, 54.6)	<0.001	68.8 (62.3, 75.4)	<0.001
>100.0 g/week	102.0 (65.6, 138.5)	<0.001	106.2 (95.5, 116.9)	<0.001
Difference in the rate of change by baseline consumption category[a]				
Non-drinker	Reference		Reference	
Infrequent drinker	8.3 (4.0, 12.7)	<0.001	3.6 (1.8, 5.4)	<0.001
0.1-50.0 g/week	4.1 (-0.2, 8.4)	0.064	-0.2 (-1.9, 1.5)	0.849
50.1-100.0 g/week	-17.4 (-25.0, -9.7)	<0.001	-2.5 (-5.3, 0.2)	0.071
>100.0 g/week	-25.0 (-52.4, 2.4)	0.074	-20.4 (-24.7, 16.1)	<0.001

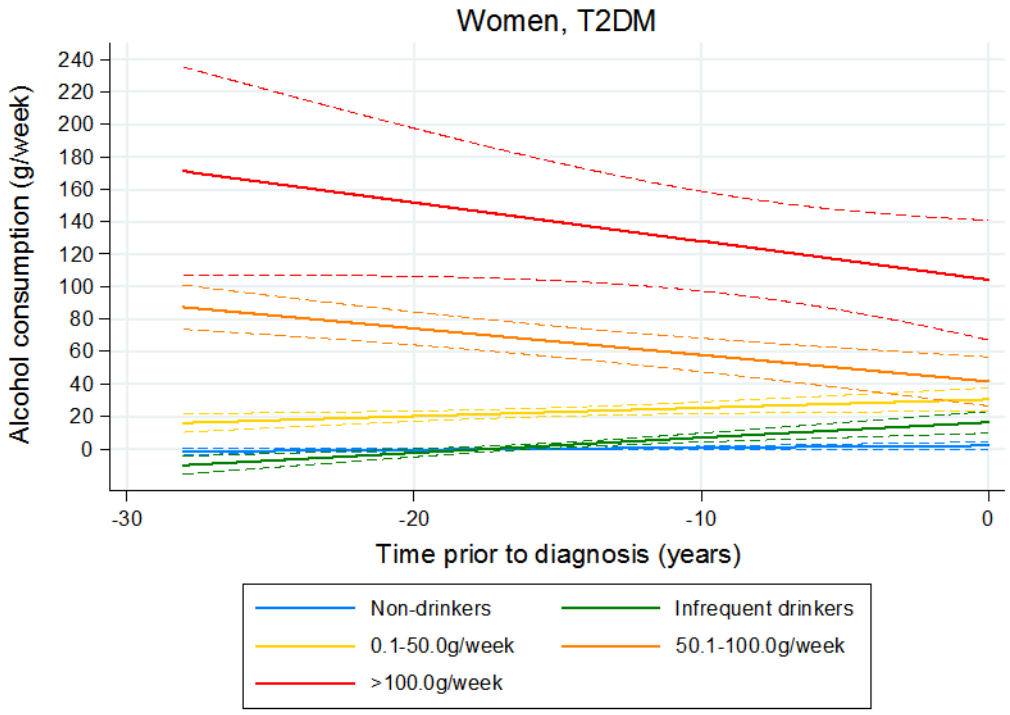
[a]Rate of change per 10 years prior to diagnosis or censoring.

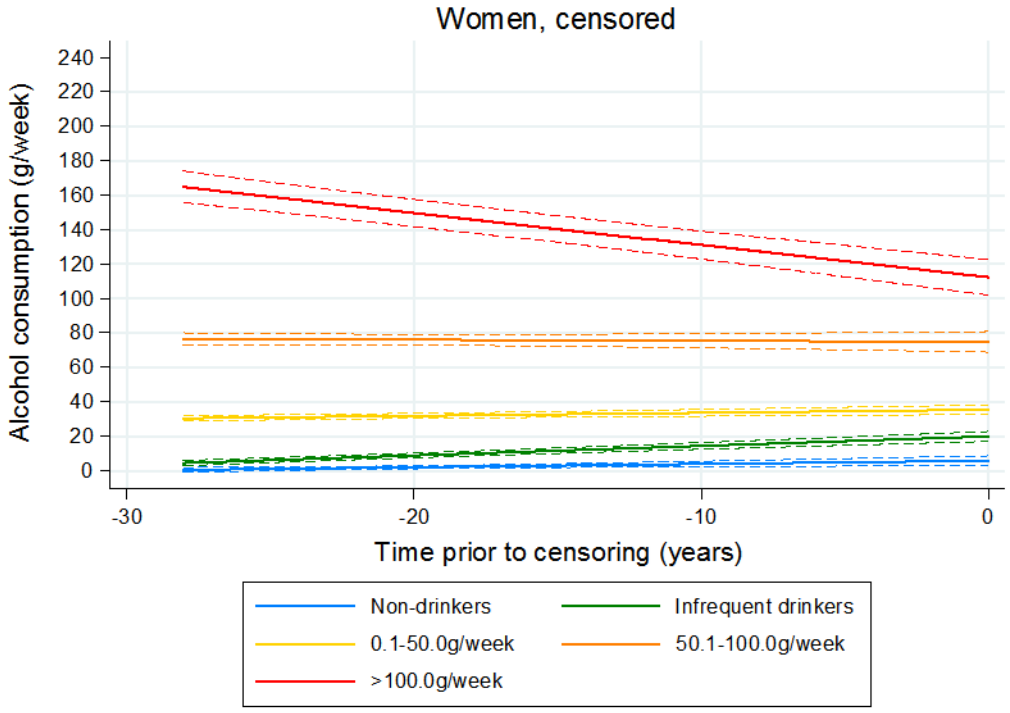
Appendix 8.21 Crude male trajectories of mean weekly volume of alcohol consumption, stratified by baseline alcohol consumption category and T2DM diagnosis: figure. Imputed data.



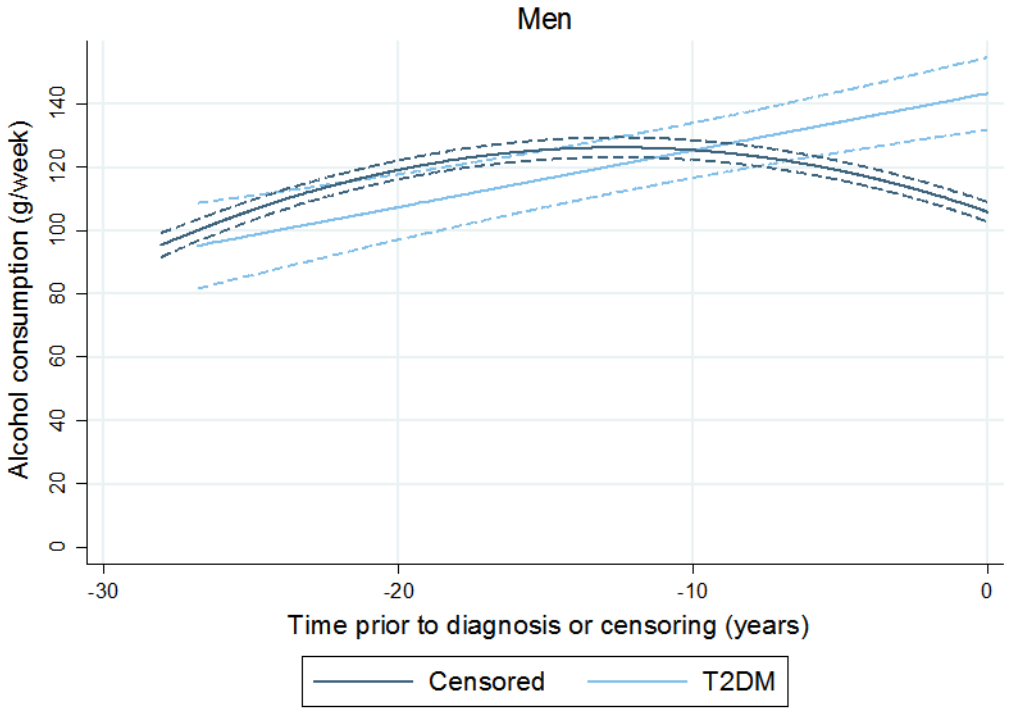


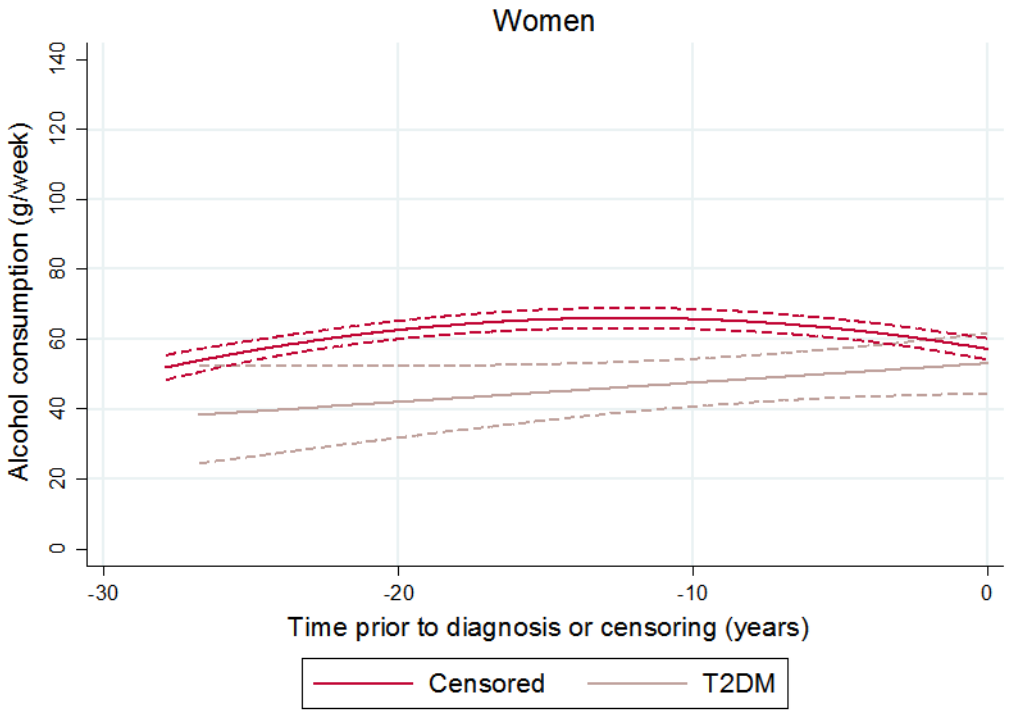
Appendix 8.22 Crude female trajectories of mean weekly volume of alcohol, stratified by baseline alcohol consumption category and T2DM diagnosis: figure. Imputed data.



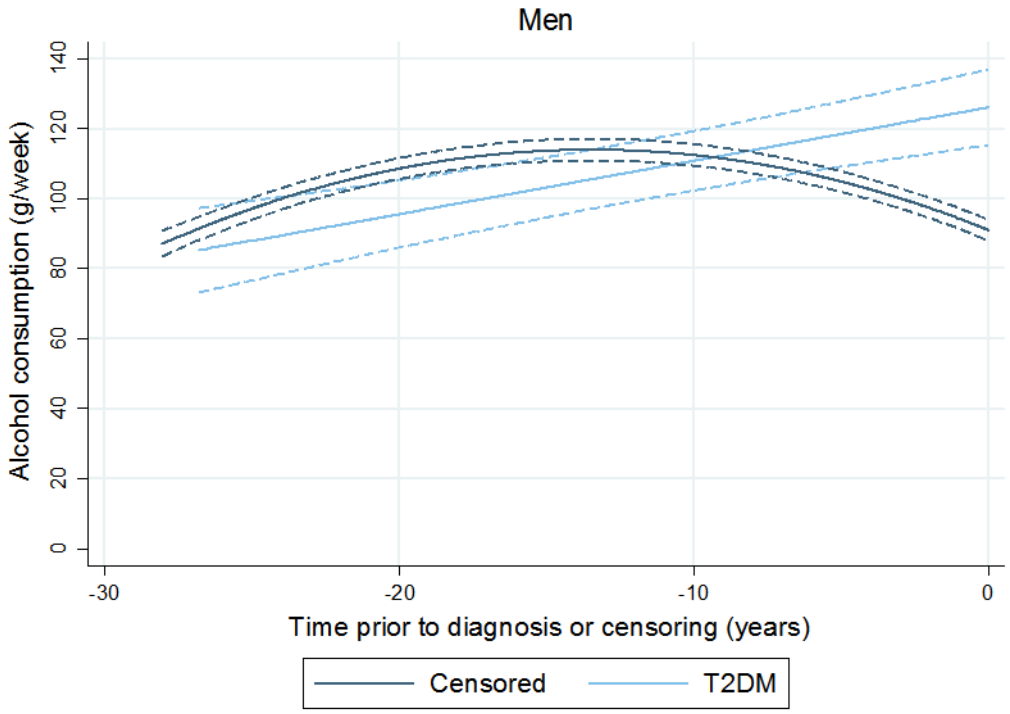


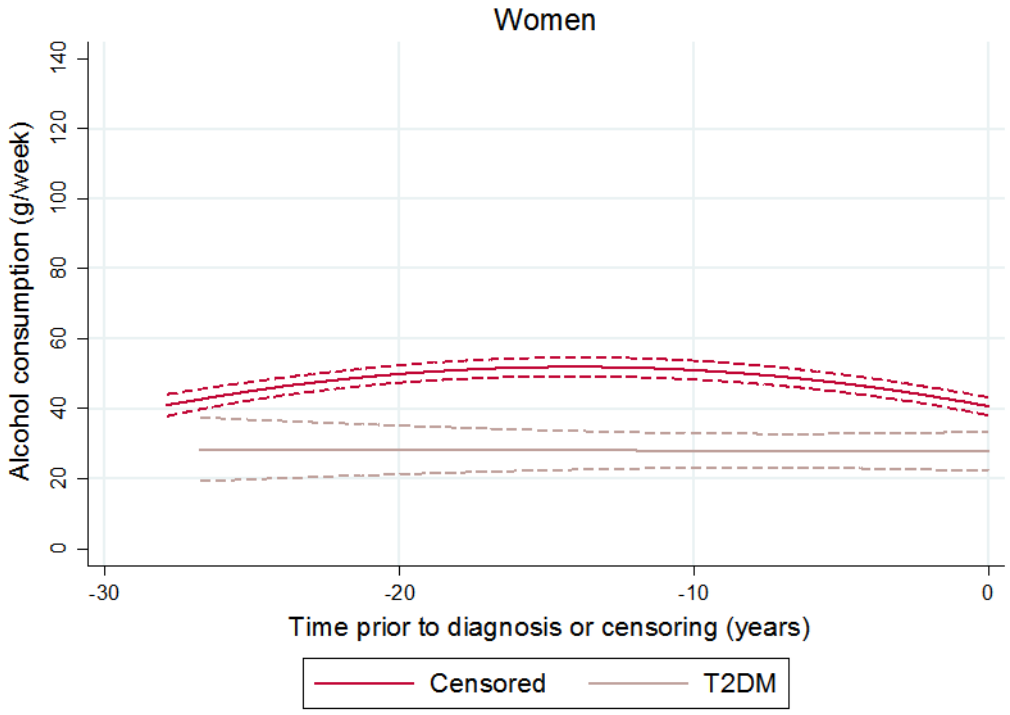
Appendix 8.23 Crude sex-specific best-fitting trajectory of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis and excluding non-drinkers. Observed data.





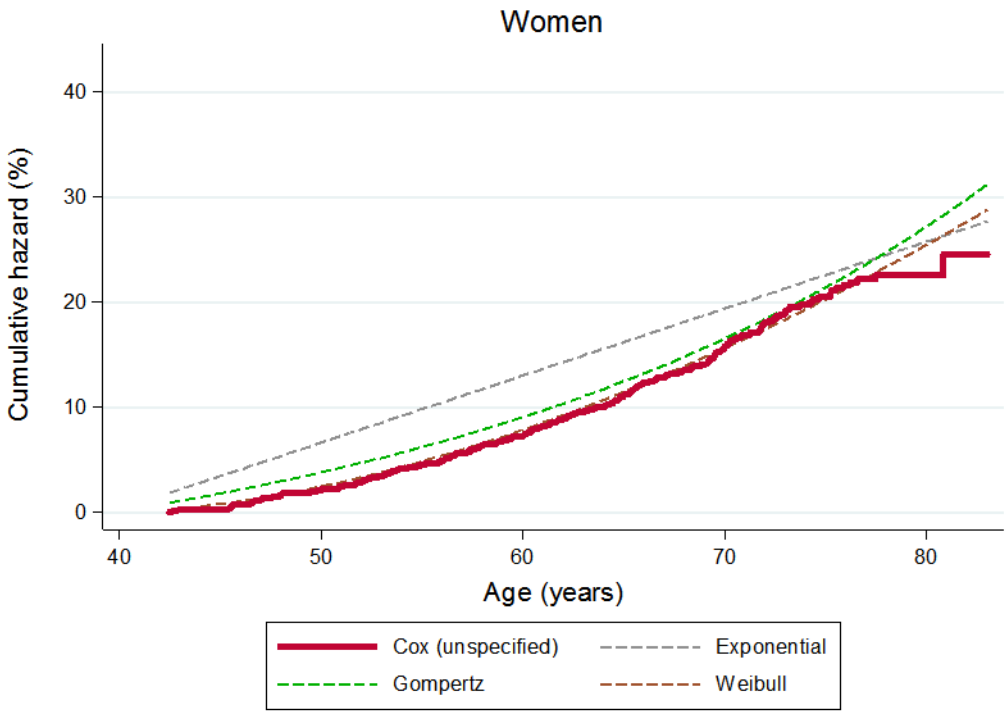
Appendix 8.24 Crude sex-specific and best-fitting trajectory of mean weekly volume of alcohol consumption, stratified by T2DM diagnosis: a competing risk sensitivity analysis. Observed data.

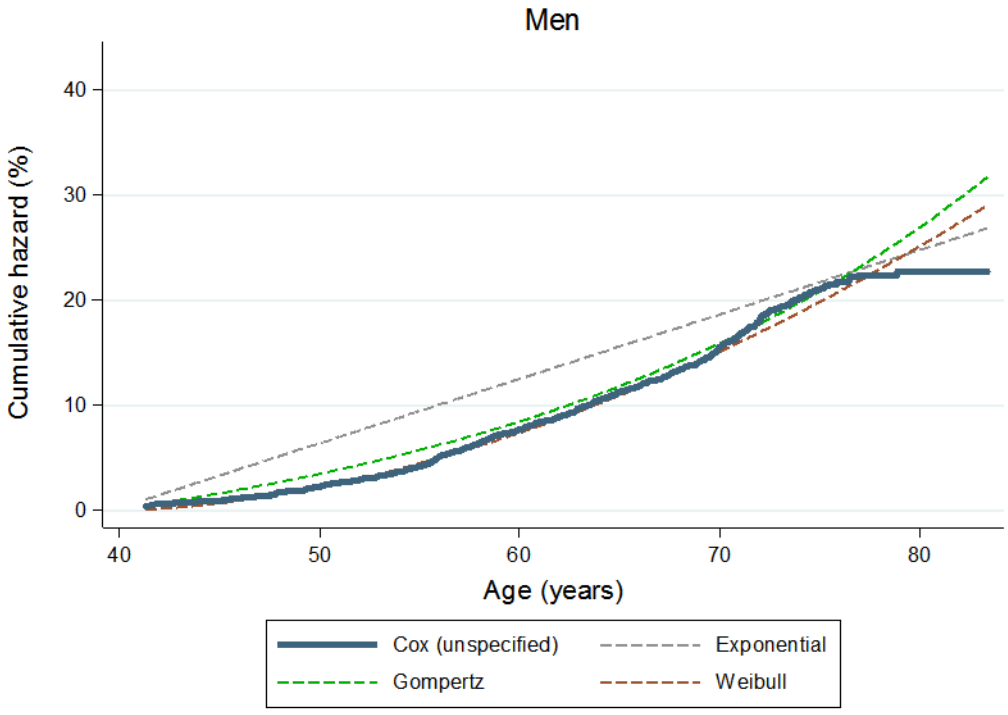




11.5 Appendices for Chapter 9

Appendix 9.1 Alternative distributional functions of the cumulative baseline hazard





Appendix 9.2 Relationship between the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Conventional survival analysis, imputed data.

	Men		Women	
Alcohol consumption (wave 3)	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Model 1				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.04 (0.98, 1.12)	0.211	0.74 (0.65, 0.84)	<0.001
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.25 (0.75, 2.08)	0.385	0.48 (0.24, 0.95)	0.036
Non-current drinker	1.74 (0.83, 3.67)	0.142	0.46 (0.19, 1.11)	0.084
Never drinker	2.39 (1.24, 4.60)	0.009	0.42 (0.18, 0.96)	0.040
Log likelihood	*-1693 (-1693, -1693)*		*-747, (-747, -747)*	
BIC[a]	*3437 (3437, 3437)*		*1542 (1542, 1532)*	
Model 2				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.00 (0.93, 1.06)	0.888	0.81 (0.71, 0.93)	0.003
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	0.94 (0.57, 1.54)	0.805	0.61 (0.30, 1.22)	0.160
Non-current drinker	1.16 (0.57, 2.37)	0.686	0.42 (0.18, 1.00)	0.050
Never drinker	0.96 (0.49, 1.88)	0.911	0.38 (0.16, 0.90)	0.028
Log likelihood	*-1507 (-1508, -1505)*		*-639 (-640, -638)*	
BIC[a]	*3177 (3173, 3180)*		*1427 (1425, 1428)*	

Model 1 reported the dose-response relationship between the volume alcohol consumption and T2DM following adjustment for consumption category. Model 2 included additional adjustment for BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status, as defined at baseline. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion. Fit statistics refer to the mean and range of values reported from the first three imputations.

Appendix 9.3 Relationship between the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Age-varying covariate survival analysis, imputed data.

	Men		Women	
Alcohol consumption	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Model 1				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.11 (1.03, 1.19)	0.004	0.84 (0.74, 0.95)	0.005
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	2.35 (1.37, 4.05)	0.002	0.96 (0.48, 1.91)	0.906
Non-current drinker	2.07 (0.98, 4.37)	0.057	1.15 (0.53, 2.48)	0.722
Never drinker	3.91 (1.95, 7.84)	<0.001	0.67 (0.26, 1.67)	0.387
Log likelihood	*-1673 (-1673, -1673)*		*-734 (-734, -734)*	
BIC [a]	*3406 (3406, 3406)*		*1523 (1523, 1523)*	
Model 2				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.07 (1.00, 1.15)	0.053	0.93 (0.82, 1.05)	0.227
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.68 (0.99, 2.86)	0.054	1.19 (0.60, 2.34)	0.623
Non-current drinker	1.19 (0.56, 2.54)	0.654	1.27 (0.59, 2.72)	0.536
Never drinker	1.67 (0.84, 3.33)	0.146	0.67 (0.28, 1.64)	0.386
Log likelihood	*-1456 (-1456, -1455)*		*-620 (-621, -620)*	
BIC [a]	*3101 (3099, 3102)*		*1414 (1412, 1415)*	

Model 1 reported the dose-response relationship between the volume alcohol consumption and T2DM following adjustment for consumption category. Model 2 included additional adjustment for BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion. Fit statistics refer to the mean and range of values reported from the first three imputations.

Appendix 9.4 Relationship between the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Two-stage survival analysis, imputed data.

	Men		Women	
Alcohol consumption	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Model 1				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.05 (0.98, 1.11)	0.151	0.82 (0.76, 0.89)	<0.001
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.41 (1.01, 1.97)	0.045	1.29 (0.91, 1.84)	0.155
Non-current drinker	1.31 (0.66, 2.58)	0.440	1.35 (0.81, 2.25)	0.253
Never drinker	2.52 (1.36, 4.67)	0.003	0.75 (0.36, 1.56)	0.445
Log likelihood	*-1677 (-1677, -1677)*		*-730 (-730, -730)*	
BIC[a]	*3413 (3413, 3413)*		*1514 (1514, 1514)*	
Model 2				
Cases/non-cases		560/4,867		268/2,155
Consumption volume				
g/week (log_2)	1.04 (0.98, 1.10)	0.209	0.92 (0.85, 1.00)	0.056
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.25 (0.90, 1.74)	0.189	1.38 (0.97, 1.96)	0.073
Non-current drinker	0.93 (0.46, 1.85)	0.831	1.41 (0.84, 2.35)	0.190
Never drinker	1.33 (0.72, 2.45)	0.370	0.74 (0.37, 1.50)	0.404
Log likelihood	*-1457 (-1458, -1456)*		*-620 (-620, -619)*	
BIC[a]	*3103 (3101, 3104)*		*1412 (1411, 1413)*	

Model 1 reported the dose-response relationship between the volume alcohol consumption and T2DM following adjustment for consumption category. Model 2 included additional adjustment for BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion. Fit statistics refer to the mean and range of values reported from the first three imputations.

Appendix 9.5 Multivariable-adjusted relationship between intercept and current value parameterisations of average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Shared random effects survival analysis, time-to-event timescale, observed data.

	Men (n=4,793)		Women (n=2,053)	
Parameterisation	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Intercept value				
Consumption volume				
g/week (log_2)	1.02 (0.95, 1.09)		0.90 (0.80, 1.02)	0.111
Consumption category				
Current drinker	(reference)			
Infrequent drinker	1.14 (0.77, 1.69)		1.31 (0.80, 1.02)	0.250
Non-current drinker	0.96 (0.47, 1.93)		1.35 (0.70, 2.59)	0.369
Never drinker	1.03 (0.49, 2.16)		0.67 (0.27, 1.66)	0.385
Log likelihood		*-38075*		*-15914*
BIC[a]		*76384*		*32039*
Current value				
Consumption volume				
g/week (log_2)	1.05 (0.97, 1.13)	0.258	0.95 (0.83, 1.08)	0.411
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.28 (0.83, 1.97)	0.268	1.47 (0.89, 2.43)	0.135
Non-current drinker	1.10 (0.53, 2.30)	0.796	1.54 (0.77, 3.10)	0.221
Never drinker	1.19 (0.55, 2.55)	0.664	0.77 (0.30, 1.97)	0.584
Log likelihood		*-38074*		*-15915*
BIC[a]		*76383*		*32041*

All models included adjustment for consumption category as well as BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

Appendix 9.6 Multivariable-adjusted associations between conditional intercept and current value parameterisations of average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex. Shared random effects survival analysis, time-to-event timescale, observed data.

	Men (n=4,793)		Women (n=2,053)	
Parameterisation	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Intercept value				
Consumption volume				
g/week (log_2)	0.83 (0.67, 1.02)	0.075	0.32 (0.15, 0.72)	0.005
Current value				
g/week (log_2)	1.28 (1.01, 1.63)	0.042	3.05 (1.33, 6.96)	0.008
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.41 (0.90, 2.20)	0.134	2.06 (1.16, 3.64)	0.013
Non-current drinker	1.26 (0.59, 2.68)	0.553	2.28 (1.06, 4.89)	0.035
Never drinker	3.52 (1.80, 14.64)	0.547	0.97 (0.36, 2.62)	0.957
Log likelihood		*-38073*		*-15909*
BIC[a]		*76389*		*32038*

All models included adjustment for consumption category as well as BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

Appendix 9.7 Multivariable-adjusted relationship between the rate of change in the average weekly volume of alcohol consumption and the risk of T2DM, stratified by sex and adjusted for intake at the intercept. Shared random effects survival analysis, observed data.

	Men (n=4,793)		Women (n=2,053)	
Parameterisation	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Intercept value				
Consumption volume				
g/week (log_2)	1.14 (1.03, 1.26)	0.010	0.96 (0.83, 1.11)	0.581
Consumption category				
Current drinker	(reference)		(reference)	
Infrequent drinker	1.69 (1.08, 2.64)	0.023	1.80 (1.05, 3.10)	0.034
Non-current drinker	1.97 (0.88, 4.42)	0.100	2.00 (0.93, 4.29)	0.077
Never drinker	1.83 (0.76, 4.40)	0.175	0.84 (0.31, 2.29)	0.730
Slope				
5% increase in the rate of change				
g/week (log_2)	2.42 (1.65, 3.56)	<0.001	2.89 (1.28, 6.54)	0.011
5% decrease in rate of change				
g/week (log_2)	0.42 (0.29, 0.61)	<0.001	0.77 (0.63, 0.94)	0.011
Log likelihood		*-38285*		*-15918*
BIC[a]		*76804*		*32048*

All models included adjustment for consumption category as well as BMI, date of birth, employment status, ethnicity, family history of T2DM, occupational grade, physical activity and smoking status. Ethnicity was derived from responses at waves one and five. [a]Bayesian information criterion.

Chapter 12
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12 Reference list

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