Association between alcohol use disorders and dementia in 262,703 dementia-free Finnish adults: Is cardiovascular disease a mediator?

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Abstract

Background: The possible mediating role of cardiovascular disease (CVD) in the relationship between alcohol use disorders (AUD) and the risk of early- (<age 65) and late-onset (≥age 65) dementia lacks formal investigation.

Methods: Using linked Finnish national register data, a population-based cohort study of 262,703 dementia-free Finnish men and women aged 40+ at baseline (December 31, 1999) was established. AUD and CVD in 1988-2014, and incident dementia in 2000-2014 were identified from Finnish Hospital Discharge Register and/or Drug Reimbursement Register. Causal association and mediation were assessed using mediational g-formula.

Results: AUD was associated with a substantial increase in the risk of early-onset dementia in both men (hazard ratio: 5.67, 95% confidence interval: 4.37-7.46) and women (6.13, 4.20-8.94) after adjustments for confounding; but the elevated risk for late-onset dementia was smaller (men: 2.01, 1.80-2.25; women: 2.03, 1.71-2.40). Mediational g-formula results showed that these associations were causal in men with no mediation by CVD as virtually identical total effect of AUD (early-onset: 5.26, 3.48-7.48; late-onset: 2.01, 1.41-2.87) and direct effect of AUD (early-onset: 5.24, 3.38-7.64; late-onset: 2.19, 1.61-2.96) were found with no indirect effect via CVD. In women, the results were similar for late-onset dementia (total effect: 2.80, 1.70-4.31; direct effect: 2.92, 1.86-4.62) but underpowered for early-onset dementia.

Conclusions: AUD increased dementia risk, particularly the risk of early-onset dementia. This elevated risk of dementia associated with AUD was not mediated by CVD. Clinicians should consider the increased risk of dementia in management of middle-aged and older adults with a history and/or current AUD.

Key words: alcohol use disorders, dementia, cardiovascular disease, causal mediation, g-formula

Introduction

Alcohol use disorders (AUD) – alcohol dependence and alcohol abuse or harmful use – are one of the most common mental disorders in high-income countries that contribute markedly to the burden of disease (1, 2). With over 100 million estimated cases, AUD were the most common substance use disorders worldwide in 2016 (3). Of the 99.2 million disability-adjusted life-years (DALYs) attributable to alcohol use (4.2% of all DALYs), 16.4% of them were attributable to AUD (3). Mild AUD often diminish without treatment, but more severe AUD are under-detected and undertreated (2), which is more problematic for older adults as AUD are often masked by comorbid physical or psychiatric conditions (4). In 2015, approximately 47 million people were living with dementia globally, and the number is forecasted to reach 132 million by 2050 (5). Dementia mostly affects older populations; along with the rapid population ageing, dementia is deemed as one of the greatest global challenges for health and social care in this century (6).

AUD and its relation to dementia has been overlooked (7). A recent nationwide retrospective cohort study using inpatient data from the French National Hospital Discharge register found that AUD was the strongest risk factor for all types of subsequent dementia (8). This finding however may not be generalizable to the general population (6, 7). Based on only three longitudinal studies, the 2020 Report of the *Lancet* Commission on Dementia Prevention, Intervention, and Care (9) concluded that excessive alcohol consumption (>21 units/week) is a risk factor for dementia. On the contrary, a meta-analysis of 15 prospective cohort studies with 2-8 years of follow-up (10) and an overview of three systematic reviews (11) both reported no association between heavy drinking and dementia. A recent Mendelian randomization (MR) study, which is not influenced by confounding and overcomes the main bias in observational epidemiology by design (12), also showed no causal association between AUD and dementia (13). This MR study nevertheless may suffer from the violation of the exclusion restriction assumption that threats the validity of the results (14, 15). Hence, more

evidence that uses other advanced causal inference methods, such as parametric g-formula, is needed.

The detrimental role of chronic heavy alcohol drinking in dementia has been attributed to the permanent structural and functional brain damage related to ethanol and its metabolite acetaldehyde, thiamine deficiency, and other conditions which can lead to brain damage such as hepatic encephalopathy, epilepsy, and head injury (8, 16). In the hypothesised heart-brain connection, Qiu and Fratiglioni (17) further linked cardiovascular risk factors (e.g. lifestyle, obesity, diabetes, hypertension) in young adulthood, subclinical atherosclerosis/arteriosclerosis at middle age, and heart disease at age 60-74 to brain lesions (e.g. white matter lesions and neurodegeneration), cognitive decline and dementia at age 75+. Given the accumulating evidence on the causal association between alcohol consumption and cardiovascular disease (CVD) (18, 19) and on the shared physiopathology and risk factors between CVD and dementia (17, 20), some of the detrimental effects of AUD on dementia may not be directly caused by AUD but through triggering CVD (i.e. CVD is a mediator). To our best knowledge, no study formally tested this pathway.

In the present study, we used longitudinal Finnish population register data which was linked with individual-level healthcare data in 1988-2014 to investigate the causal association between AUD in 1988-2014 and incident dementia in 2000-2014 as well as the mediating role of CVD using the g-formula approach.

Methods

Study design

We established a population-based cohort study, using longitudinal register data in 1988-2014 on an 11% random sample of the population residing in Finland at the end of 1987-2007 drawn from the population register by Statistics Finland. Data from Finnish Drug Reimbursement Register (DRR,

1995-2014; anti-dementia medication available since 2000) and Hospital Discharge Register (HDR, 1988-2014) were linked to the sample via unique individual IDs. Each hospitalisation record in the HDR can have up to three diagnoses, and we used all available diagnoses. The use of the data for research purposes has been approved by the ethical committees of Statistics Finland (permission 'TK-53-1519-09') and the National Institute for Health and Welfare of Finland (permission 'THL/231/5.05.00/2016').

Our cohort included 262,703 dementia-free men and women aged 40 and over on December 31, 1999 (i.e. baseline) whose dementia incidence was followed between 2000 and 2014. Individuals were excluded if they: 1) did not reside in Finland in 2000-2014; 2) did not live in private households at baseline (e.g. living in social care facilities for demented individuals); 3) were hospitalised in 1988-1999 for diseases that may lead to a rare type of dementia or for early-life mental disorders that may increase or confound dementia diagnosis(8) (i.e. exclusion conditions; Supplementary Table 1); 4) were hospitalised for dementia in 1988-1999 including delirium superimposed on dementia (International Classification of Diseases [ICD]-10 code: F05.1); 5) were entitled to special reimbursement for medication expenses for Alzheimer's disease (AD) in 1999; or 6) were hospitalised for alcohol-induced persisting dementia (ICD-9: 291.2, ICD-10: F10.27) or residual and late-onset psychotic dementia due to alcohol use (ICD-10: F10.73) in 1988-1999 (Supplementary Figure 1). Supplementary Figure 2 illustrates the study design of our cohort study.

Alcohol use disorders

AUD in 1988-2014 was identified from HDR. The measure of AUD consisted of acute alcohol intoxication and poisoning, mental and behavioural disorders due to chronic harmful use of alcohol, and diseases due to harmful use of alcohol, as well as contact with health services for alcohol use and alcohol abuse counselling and surveillance (Supplementary Table 1).

Dementia

Both DRR and HDR were used to identify incident dementia in 2000-2014. Dementia ascertained from DRR came from 1) entitlement for medication expense reimbursement for AD (disease category 307) with the starting year and month (date set to the 15th); and 2) purchase of any anti-dementia medication (Anatomical Therapeutic Chemical code: N06D) with the date of purchase. Hospital care for dementia was derived from HDR with the date of hospital admission and up to three diagnoses with ICD-9 (1988-1995) or ICD-10 (1996-2014) codes (Supplementary Table 1) (21). The date of incident dementia was the earliest entry in these data sources.

CVD and CVD risk factors

CVD and CVD risk factors (hypertension, hyperlipidaemia, and diabetes) in 1988-2014 were assessed using both DDR and HDR (Supplementary Table 2). CVD covered ischemic heart disease, cerebrovascular disease including transient cerebral ischemic attack, peripheral arterial disease, atrial fibrillation, and heart failure (8).

Socio-demographic factors

All socio-demographic factors were measured prior to the measurement window of AUD, CVD, and dementia to ensure the temporality. We used educational attainment, quintiles of household income adjusted by consumption units in the household (22), labour-force status, and last held occupational social class to reflect participants' socioeconomic status (SES). The former three SES markers, living arrangements, and region of residence were measured at the end of 1987, while the last SES marker was updated at the end of 1985.

Statistical analysis

According to a simulation study on dementia, if the time-to-onset of disease is known exactly and death is a competing event, standard cause-specific hazards models can be applied and estimated (23). Since we have information on the exact date when dementia was diagnosed, Cox proportional hazards regression was used to analyse the relationship between AUD in 1988-2014 and incident dementia in 2000-2014. Age in years was specified as the time scale. Participants were censored if they were hospitalised for exclusion conditions, did not live in private households, or died. Three models were estimated controlling for calendar year (Model 1), additionally for socio-demographic factors (Model 2), CVD risk factors (Model 3), and CVD (Model 4). All time-varying variables were included as time-varying regressors in the Cox regression models. The difference in the hazard ratios of AUD between Models 3 and 4 could be interpreted as the indirect effect of AUD via CVD – the traditional difference method of mediation analysis (24).

To explore the causal relationship between AUD and dementia and to quantify the mediation by CVD, we used the mediational g-formula based on the counterfactual causal inference framework, which allows us to model complex longitudinal data with time-varying exposures, mediators, confounders, and outcomes (25-27). In the counterfactual causal inference framework, causal inferences can be drawn by comparing the observed outcome when individuals are exposed to a risk factor or receive an intervention and the counterfactual outcome that would have observed had individuals not been exposed to risk factor or received the intervention (28). Similar to previous causal mediation analyses (26, 29), we also assumed a single-year cross-lagged causal structure in which CVD risk factors, CVD, and dementia in year *t* were modelled with logistic regression using CVD risk factors and CVD in year *t-1* as time-varying covariates, age in 5-year categories (deterministically time-varying), as well as socio-demographic factors as time-invariant covariates (Figure 1). These models were fitted for a 'healthy' cohort of 92,973 men and 108,437 women without AUD, CVD, and dementia at baseline to ensure a clear temporality of disease progression.

Mediation was then assessed using a synthetic cohort approach: we took healthy 40-year-olds and used Monte Carlo integration to simulate their disease progression of CVD, dementia, and other time-varying covariates up to age 100 (*natural course scenario*) while preventing the onset of AUD. This was then performed another two times in which all participants were set to have AUD at all ages, while CVD and other time-varying covariates progressed as expected among individuals with AUD (*counterfactual total effect scenario*) and progressed as expected among those without AUD (*counterfactual no-mediation scenario*), respectively. These scenarios are illustrated in Supplementary Figure 3. The difference in dementia between Scenarios 1 and 2 and between Scenarios 1 and 3 provided the total effect and direct effect of AUD, respectively (30). The indirect effect via CVD was the relative difference between the total effect and the direct effect. Effects were estimated using Cox regression with scenario indicators on the Monte Carlo generated data (27), and standard errors were calculated by bootstrap.

Sensitivity analysis on the association between AUD in 1988-2014 and incident AD in 2000-2014 was conducted, using competing-risks regression (other types of dementia as the competing event) with the Fine and Gray's approach (31). Another set of sensitivity analysis moved the baseline to December 31, 2002 to account for the possible misclassification as anti-dementia medication only became available since 2000. All Cox regression and competing-risks regression were performed using Stata 15 (StataCorp, 2017, College Station, TX), and the g-formula analyses were undertaken using *R* version 3.6.2 (R Core Team, 2019, Vienna, Austria). All analyses were performed separately by sex and by current age to distinguish early- (<65) and late-onset (≥65) dementia.

Results

In 2000-2014, 345 (0.4%) men and 347 (0.4%) women developed early-onset dementia, while 7,248 (9.6%) and 13,293 (13.9%) men and women, respectively, developed late-onset dementia (Table 1). The median time to develop dementia was 13.04 years (95% confidence interval [CI]: 12.98, 13.12) and 12.73 (95% CI: 12.70-12.79) years for men and women, separately (Table 2). Having been

hospitalised for AUD was more prevalent among those who developed dementia before age 65 (Table 1, men: 27.0%, women: 10.1%) compared to their dementia-free counterparts (men: 7.9%, women: 2.4%). At age 65 and beyond, this difference was negligible. The incidence rate of both early- and late-onset dementia was higher among participants who had been hospitalised for AUD than those who had not.

In the full sample, approximately 50% of participants obtained only compulsory education and lived with their partner and children (Table 2). The majority were employed at baseline; about a half of women were white-collar employees, while manual workers formed the largest occupational social class among men. Participants with early- and late-onset dementia tended to have lower SES compared to the full sample.

In Model 1 (Table 3) adjusting for calendar year, AUD was associated with a large increase in the risk of early-onset dementia in both men (hazard ratio [HR]: 6.78, 95% CI: 5.33-8.61) and women (6.91, 4.86-9.83). CVD risk factors and CVD were not associated with early-onset dementia, except for CVD in men and diabetes in women (Model 1). Further adjustment for socio-demographic factors (Model 2) attenuated the association between AUD and early-onset dementia by 18% in men and by 14% in women. The association in general did not change when CVD risk factors were further controlled for (Model 3).

The crude association between AUD and late-onset dementia was smaller but nevertheless evident (Model 1, men: 2.11, 95%CI: 1.88-2.35; women: 2.08, 1.76-2.46). For both sexes, a higher hazard of late-onset dementia was associated with diabetes and CVD. The excess hazard of late-onset dementia associated with AUD reduced by 7% and 4% in men and women, respectively, after controlling for socio-demographic factors. The increased hazard also did not change with further adjustment of CVD risk factors. The results in the pooled sample of men and women are shown in Supplementary Table 3.

Using the g-formula approach, highly similar total effect of AUD (Table 4, HR for early-onset: 5.26, 95%CI: 3.48-7.48; HR for late-onset: 2.01, 1.41-2.87) and direct effect of AUD (early-onset: 5.24, 3.38-7.64; late-onset: 2.19, 1.61-2.96) were found in men with no indication of indirect effect via CVD (early-onset: 1.00, 0.95-1.06; late-onset: 0.92, 0.79-1.00), suggesting a causal association between AUD and early- and late-onset dementia but no mediation by CVD in men. Similar findings were found in women for late-onset dementia (total effect: 2.80, 95%CI: 1.70-4.31; direct effect: 2.92, 1.86-4.62, indirect effect: 0.96, 0.83-1.00), but not for early-onset dementia because this result was underpowered (only 16 out of 320 women with early-onset dementia also had AUD) and thus unreliable. The results remained unchanged when pooling men and women together and adjusting for sex (Supplementary Table 4). Using the traditional difference method, the excess hazards related to AUD attenuated only by 1-4% after further adjustment for CVD (Model 4 vs. Model 3), indicating no clear mediation by CVD as well. However, interaction between AUD and CVD was found for late-onset dementia (P<0.01). Stratifying by CVD, the association between AUD and dementia was larger among those with no CVD than among those with CVD (Supplementary Table 5).

The pattern of the association between AUD and AD was largely the same but weaker as with all dementia (Supplementary Table 6). Moving baseline to December 31, 2002, the association between AUD and early-onset dementia attenuated to some extent but remained large, whereas it generally did not change for late-onset dementia (Supplementary Table 7).

Discussion

In this population-based cohort study of 262,703 dementia-free individuals aged 40 and over with 15 years of follow-up, we found over five-fold and two-fold increase in the risk of early- and late-onset dementia associated with AUD, respectively, in both sexes. Mediational g-formula results supported a causal association between AUD and dementia and no mediation by CVD.

Our findings in general echoed with those from the French hospital cohort study (8), but the considerably smaller associations we found restrain us to reach the same conclusion that AUD is among the strongest risk factors for dementia. The discrepancy could arise from the richer individual-level data that we were able to link from different national registers, the longer follow-up, and the clearer temporality. The French study examined the association between AUD in 2008-2013 and incident dementia in 2011-2013 among inpatients who were not hospitalised for dementia in 2008-2010. This study design only allowed the assessment of a short-term association, and it complicated the interpretation – since dementia takes decades to gradually develop (32), the physiopathological brain changes of dementia may have started and progressed long time before AUD was measured. This nevertheless affects our findings to a lesser degree as we had the information on AUD for 12 years before the baseline. In addition, as dementia risk is closely related to the education an individual receives (6), lacking such data and other important individual-level socio-demographic characteristics in the French study could result in inadequate adjustment for confounding. Our findings of a heightened risk of early-onset dementia associated with AUD were comparable in magnitude to those of a study investigating the relationship between alcohol intoxication and early-onset dementia using Swedish registry data of Swedish men conscripted for mandatory military service with a median follow-up of 37 years (33).

Contradicting to the previous MR study (13), our g-formula results supported a causal association between AUD and dementia. This inconsistency may relate to the different definitions of AUD – we used the formal medical diagnosis from the hospital records, whereas in the MR study AUD was assessed using the Alcohol Use Disorder Identification Test (AUDIT). The lack of statistical power and plausible biological pleiotropy (i.e. the same genetic variant affect multiple health outcomes via various biological pathways) which violates the exclusion restriction assumption in the MR study (14, 15) may also contribute to their null findings of causal associations of alcohol dependence (assessed using clinician rating or semi-structured interviews in accordance with DSM-IV criteria) and AUD with dementia. The consistency assumption of the g-formula method (34) posits a single effect of AUD on

dementia, but different versions of AUD (e.g. more or less severe with short or long durations) with potentially different magnitudes of effect on dementia can exist. Our findings thus represent the population-average causal effect of AUD on dementia.

The link between excessive alcohol consumption and cardiovascular risk has been well established (35-38). A recent study from the U.S. demonstrated that increasing number of CVD risk factors in mid-life – high body mass index, current smoking, hypertension, diabetes, and high total cholesterol – was associated with an elevated level of amyloid in the brain (39). All the evidence together with the hypothesised heart-brain connection (17) posits CVD to be a possible mediator linking AUD and dementia. However, our findings using the traditional difference method and the advanced g-formula approach both did not support such pathway; and this is reinforced by the lack of associations between CVD risk factors and dementia onset except for diabetes that we observed.

In contrast to Whitehall II cohort study in which the association between AUD and dementia attenuated by 41% after taking health behaviours (physical activity, smoking status, and fruit and vegetable consumption), CVD risk factors, and CVD into account (40), the association remained largely unchanged following adjustment for diabetes, hypertension, and hyperlipidaemia in our study, suggesting that these CVD risk factors may not be confounders. The greater association between AUD and late-onset dementia found in participants with no CVD than in those with CVD does not imply that CVD is beneficial. First, our results from the crude model indicated that CVD was adversely associated with late-onset dementia. Second, this negative interaction is likely due to mortality selection that older adults with CVD are more likely to die before reaching the age when late-onset dementia starts to occur.

Our study has several strengths and limitations. We used a large nationally representative sample of adults aged 40 and beyond with a long follow-up. The exposure of AUD was based on hospital records with a clear medical diagnosis from 1988 to 2014, which enabled us to evaluate the long-term effect of AUD on dementia. The dementia diagnosis was optimised by using data from various

national registers which were shown to have a very good accuracy of identifying dementia cases (21). The use of national register data also made our study not suffer from attrition during follow-up. However, given that early-onset dementia was rare, we may lack statistical power in examining its relation with AUD. Dementia incidence could be underestimated using national registers (21). Although a previous study that reviewed validation studies of the Finnish HDR found that the register's completeness and accuracy ranged from satisfactory to very good (41), the incidence of AUD identified using the HDR could also be underestimated, leading to a biased estimation of the association between AUD and dementia. In addition, the causality is debatable for individuals who had a short time window between having had AUD and dementia onset. However, since we identified AUD using hospital records, it is likely that those individuals have been engaged in harmful drinking for a long time, which in turn reduces the bias. Because of the data restrictions, we were not able to incorporate other factors such as smoking, obesity, physical inactivity, and psychosocial factors. These factors, similar to CVD, could be confounders, moderators, or mediators. Future research is needed to advance our understanding of the biological, behavioural, and psychosocial pathways between AUD and dementia.

Since the mediational g-formula method approximates the joint distribution through parametric models (42), if the underlying models were wrongly specified, estimates generated by such models will be less valid. The single-year cross-lagged assumption increased our certainty about the direction of causality, but it will be violated if there are anticipation effects (43) although they are unlikely to exist as this would require individuals to develop AUD because they anticipate dementia. Aforementioned factors that could affect AUD, CVD, and dementia were unmeasured and thus may bias coefficients in the underlying models, and thereby the estimated total and mediated effects (44).

Although AUD decreases at older ages (4), older adults could be more vulnerable to harmful effects of alcohol consumption due to their ageing-related biological changes (45, 46) and negative

interactions between alcohol and medications (47, 48). Clinicians therefore should pay more attention to middle-aged and older individuals with a history and/or current excessive alcohol use to reduce their risk of developing dementia, particularly in light of the substantially elevated risk of early-onset dementia caused by AUD. Because of the under-detection and misdiagnosis of AUD in older populations, general practitioners and geriatricians should be more aware of the elevated dementia risk in older adults with possible excessive alcohol drinking and AUD, which are often masked by their comorbid physical or psychiatric conditions (4). Evidence from in vivo magnetic resonance studies demonstrated that some structural brain changes are reversible with prolonged abstinence from alcohol (49). Early detection, diagnosis, intervention, and treatment of AUD and prolonged abstinence from alcohol therefore could be very effective approaches to lower dementia risk, especially the risk of early-onset dementia, however this needs further investigations.

Funding

The research leading to this publication has been supported by the Max Planck Society within the framework of the project "On the edge of societies: New vulnerable populations, emerging challenges for social policies and future demands for social innovation. The experience of the Baltic Sea States" (2016-2021). PM was supported by the Academy of Finland (#308247, # 345219), the European Research Council under the European Union's Horizon 2020 Research and Innovation Programme (grant agreement No.101019329), and the Max Planck – University of Helsinki Center for Social Inequalities in Population Health. The funders played no role in study design, collection, analysis, interpretation of data, writing of the report, or in the decision to submit the paper for publication.

Conflicts of Interest

None declared.

Acknowledgement

The authors would like to thank Statistics Finland, the National Institute for Health and Welfare of Finland, and Social Insurance Institution of Finland for providing the data.

Author Contributions

Y.H. conceived the study, conducted the scientific literature search, prepared the data for analysis, and prepared the first and final drafts of the manuscript. Y.H., P.L., and M.J.B. analysed the data. K.K., P.M., and M.J.B. made substantial contribution in study design and interpretation of the results. All authors critically reviewed the first and final drafts of the manuscript for important intellectual content.

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Table 1. Alcohol use disorders in 1988-2014 among participants with and without dementia, by current age in 2000-2014

	Men			Women		
	Dementia-free (N, %)	Dementia (N, %)	Dementia rate (1,000 person years, 95% CI)	Dementia-free (N, %)	Dementia (N, %)	Dementia rate (1,000 person years, 95% CI)
Currently aged <65						
AUD						
No	82,878 (92.1)	252 (73.0)	0.27 (0.24, 0.31)	88,102 (97.6)	312 (89.9)	0.32 (0.29, 0.36)
Yes	7,073 (7.9)	93 (27.0)	1.85 (1.51, 2.27)	2,140 (2.4)	35 (10.1)	2.24 (1.61, 3.12)
Total	89,915	345	0.36 (0.32, 0.39)	90,242	347	0.35 (0.31, 0.39)
Currently aged ≥65						
AUD						
No	64,141 (94.5)	6,874 (94.8)	12.65 (12.35, 12.95)	81,436 (98.5)	13,126 (98.7)	16.94 (16.65, 17.23)
Yes	3,734 (5.5)	374 (5.2)	19.49 (17.61, 21.57)	1,237 (1.5)	167 (1.3)	23.12 (19.87, 26.91)
Total	67,875	7,248	12.88 (12.59, 13.18)	82,673	13,293	16.99 (16.71, 17.29)

AUD: alcohol use disorders; CI: confidence interval

Table 2. Distribution of cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus and sociodemographic characteristics

	Full sample (at baseline)		**Early-onset dementia (at time of diagnosis)**		**Late-onset dementia (at time of diagnosis)**	
	Men (N=122,634)	**Women** (N=140,069)	**Men** (N=345)	**Women** (N=347)	**Men** (N=7,248)	**Women** (N=13,293)
Time to dementia onset						
Median (95% CI)	13.04 (12.98-13.12)	12.73 (12.70-12.79)	11.13 (10.79-12.19)	11.20 (10.62-11.96)	13.12 (13.04-13.14)	12.77 (12.71,12.79)
Age						
Mean (SD)	56.7 (11.5)	59.4 (13.0)	59.7 (4.5)	59.8 (4.2)	80.0 (6.4)	82.2 (6.5)
CVD[†] (%)	21.5	21.8	37.4	27.7	72.2	70.4
CVD risk factors (%)						
Hypertension (%)	31.5	37.9	49.3	49.0	76.8	81.6
Hyperlipidaemia (%)	8.5	7.5	27.0	28.8	41.6	39.1
Diabetes (%)	6.1	5.7	15.4	12.1	22.3	19.1
Sociodemographic characteristics at the end of 1985/7						
Place of residence (%)						
South	47.4	48.7	49.3	50.9	44.4	45.7
North	11.9	11.2	9.4	10.8	12.1	11.5
West	26.4	26.3	24.9	24.9	27.5	27.1
East	14.3	13.9	16.4	13.5	16.1	15.8
Education (%)						
Compulsory only	47.5	52.0	44.4	47.6	68.8	75.8
Upper secondary	30.1	28.6	37.4	34.9	15.5	15.3
Tertiary	22.3	19.4	18.3	17.6	15.8	8.9
Household income quintile (%)						
Lowest	20.1	20.1	19.1	19.3	18.9	19.7
2	20.0	20.0	23.6	19.6	20.2	20.2
3	20.0	20.0	19.1	21.6	20.6	20.3
4	20.0	20.0	19.4	21.1	19.6	20.3
Highest	20.0	20.0	18.8	18.4	20.7	19.5
Occupation class (%)						
White collar	33.1	50.7	28.5	52.6	28.5	37.1
Manual worker	48.1	33.6	58.7	33.8	45.9	42.4
Farmer	9.4	8.2	4.4	3.8	16.3	13.8

	Full sample (at baseline)		Early-onset dementia (at time of diagnosis)		Late-onset dementia (at time of diagnosis)	
	Men (N=122,634)	**Women** (N=140,069)	**Men** (N=345)	**Women** (N=347)	**Men** (N=7,248)	**Women** (N=13,293)
Self-employed	6.9	4.6	6.4	6.9	8.5	5.0
Other	2.5	3.0	2.0	2.9	0.8	1.7
Labour force status (%)						
Employed	80.9	69.2	87.4	84.5	49.6	33.9
Unemployed	1.4	1.1	3.2	1.2	1.0	0.6
Pensioners	15.8	22.9	5.3	6.7	48.1	61.0
Other	1.9	6.9	4.1	7.6	1.3	4.5
Living arrangement (%)						
Living only with partner	22.6	22.1	12.3	13.4	46.1	38.7
Living with partner and children	56.1	49.5	55.7	64.0	37.8	20.2
Living alone	9.8	15.1	13.2	8.2	9.5	27.8
Other	11.5	13.3	18.8	14.3	6.5	13.3

SD: standard deviation

[†] CVD includes ischemic heart disease, cerebrovascular disease (including transient cerebral ischemic attack), peripheral arterial disease, atrial fibrillation and heart failure

Table 3. Cox regression results on the association between alcohol use disorder in 1988-2014 and incident dementia in 2000-2014

	Early-onset dementia (HR, 95% CI)				Late-onset dementia (HR, 95% CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Men								
AUD	6.78 (5.33, 8.61)	5.74 (4.44, 7.43)	5.67 (4.37, 7.36)	5.49 (4.23, 7.13)	2.11 (1.88, 2.35)	2.03 (1.81, 2.27)	2.01 (1.80, 2.25)	1.98 (1.77, 2.21)
CVD risk factors								
Diabetes	1.34 (0.99, 1.79)		1.18 (0.86, 1.62)	1.18 (0.86, 1.62)	1.25 (1.18, 1.32)		1.24 (1.17, 1.32)	1.24 (1.17, 1.31)
Hypertension	1.12 (0.90, 1.38)		1.00 (0.79, 1.27)	0.91 (0.71, 1.16)	1.02 (0.97, 1.08)		0.98 (0.92, 1.04)	0.89 (0.84, 0.95)
Hyperlipidaemia	0.90 (0.71, 1.15)		0.91 (0.69, 1.20)	0.84 (0.63, 1.11)	1.00 (0.96, 1.06)		0.97 (0.92, 1.02)	0.92 (0.87, 0.97)
CVD	1.53 (1.22, 1.91)			1.43 (1.12, 1.83)	1.28 (1.22, 1.35)			1.32 (1.24, 1.40)
Women								
AUD	6.91 (4.86, 9.83)	6.09 (4.19, 8.86)	6.13 (4.20, 8.94)	6.08 (4.15, 8.89)	2.08 (1.76, 2.46)	2.04 (1.72, 2.41)	2.03 (1.71, 2.40)	2.01 (1.70, 2.38)
CVD risk factors								
Diabetes	1.59 (1.15, 2.19)		1.35 (0.95, 1.91)	1.34 (0.95, 1.90)	1.14 (1.09, 1.19)		1.12 (1.07, 1.18)	1.11 (1.06, 1.16)
Hypertension	1.02 (0.83, 1.26)		0.85 (0.68, 1.07)	0.84 (0.67, 1.05)	1.01 (0.97, 1.06)		0.97 (0.93, 1.02)	1.00 (0.87, 0.96)
Hyperlipidaemia	1.25 (0.98, 1.58)		1.19 (0.92, 1.54)	1.17 (0.91, 1.52)	1.02 (0.98, 1.06)		1.00 (0.96, 1.04)	0.97 (0.93, 1.01)
CVD	1.24 (0.97, 1.58)			1.11 (0.87, 1.43)	1.20 (1.15, 1.25)			1.20 (1.15, 1.25)

AUD: alcohol use disorders; CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio

Model 1: calendar year dummies, separately for AUD, each CVD risk factor, and CVD in relation to incident dementia

Model 2: Model 1 + time invariant region, education, household income, labour-force status, living arrangement, and occupational social class

Model 3: Model 2 + time-varying hypertension, hyperlipidaemia, and diabetes

Model 4: Model 3 + time-varying CVD

Table 4. Mediational g-formula results of mediation by cardiovascular disease on the association between alcohol use disorders and incident dementia

	Men (HR, 95% CI)		Women (HR, 95% CI)	
	Early-onset dementia	**Late-onset dementia**	**Early-onset dementia**	**Late-onset dementia**
Total effect	5.26 (3.48, 7.48)	2.01 (1.41, 2.87)	1.39 (0.35, 4.84)	2.80 (1.70, 4.31)
Direct effect	5.24 (3.38, 7.64)	2.19 (1.61, 2.96)	1.46 (0.40, 4.86)	2.92 (1.86, 4.62)
Indirect effect via CVD	1.00 (0.95, 1.06)	0.92 (0.79, 1.00)	0.95 (0.79, 1.13)	0.96 (0.83, 1.00)

HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease

Figure 1