OPEN ACCESS

Alcohol use and risk of dementia in diverse populations: evidence from cohort, case–control and Mendelian randomisation approaches

Anya Topiwala ,[1] Daniel F Levey,[2,3] Hang Zhou,[2,3] Joseph D Deak,[2,3] Keyrun Adhikari,[2,3] Klaus P Ebmeier ,[4] Steven Bell,[5] Stephen Burgess ,[6] Thomas E Nichols ,[4,7] Michael Gaziano,[8,9] Murray Stein,[10] Joel Gelernter[3,11]

10.1136/bmjebm-2025-113913

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjebm-2025-113913).

For numbered affiliations see end of article.

Correspondence to:
Dr Anya Topiwala; anya.topiwala@bdi.ox.ac.uk

To cite: Topiwala A, Levey DF, Zhou H, *et al*. *BMJ Evidence-Based Medicine* 2026;**31**:13–22.

Abstract

Objectives To investigate the relationship between alcohol consumption and dementia.

Design Prospective cohort and case–control analyses combined with linear and non-linear Mendelian randomisation.

Setting Two large-scale population-based cohorts: the US Million Veteran Programme and the UK Biobank. Genetic analyses used summary statistics from genome-wide association studies (GWAS).

Participants 559 559 adults aged 56–72 years at baseline were included in observational analyses (mean follow-up: 4 years in the US cohort; 12 years in the UK cohort). Genetic analyses used summary data from multiple large GWAS consortia (2.4 million participants).

Main outcome measures Incident all-cause dementia, determined through health record linkage, and genetic proxies.

Results During follow-up, 14 540 participants developed dementia and 48 034 died. Observational phenotype-only analyses revealed U-shaped associations between alcohol and dementia risk: higher risk was observed among non-drinkers, heavy drinkers (>40 drinks per week; HR 1.41, 95% CI 1.15 to 1.74), and those with alcohol use disorder (AUD) (HR 1.51, 95% CI 1.42 to 1.60) compared with light drinkers. In contrast, Mendelian randomisation genetic analysis identified a monotonic increase in dementia risk with greater alcohol consumption. A 1 SD increase in log-transformed drinks per week was associated with a 15% dementia increase (inverse-variance weighted (IVW) OR 1.15, 95% CI 1.03 to 1.27). A twofold increase in AUD prevalence was associated with a 16% increase in dementia risk (IVW OR 1.16, 95% CI 1.03 to 1.30). Alcohol intake increased dementia, but individuals who developed dementia also experienced a decline in alcohol intake over time, suggesting reverse causation—where early cognitive decline leads to reduced alcohol consumption—underlies the supposed protective alcohol effects in observational studies.

Conclusions These findings provide evidence for a relationship between all types of alcohol use and increased dementia risk. While correlational observational data suggested a protective effect of light drinking, this could be in part attributable to reduced drinking seen in early dementia; genetic analyses did not support any protective effect, suggesting that any level of alcohol consumption may contribute to dementia risk. Public health

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous observational studies have reported a J-shaped association between alcohol consumption and dementia, suggesting that light-to-moderate drinking may be protective. However, these findings may reflect ascertainment of state rather than trait alcohol use phenotypes, residual confounding or reverse causation, rather than a causal effect.

WHAT THIS STUDY ADDS

⇒ In the largest combined observational and genetic study to date, light alcohol consumption was associated with the lowest dementia risk observationally, but genetic analyses showed a monotonic increasing dementia risk with increased alcohol intake. Mendelian randomisation suggests a causal role of alcohol consumption in increasing dementia risk, with no evidence supporting a protective effect at any consumption level.

HOW MIGHT THIS STUDY AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings challenge the notion that low levels of alcohol are neuroprotective and suggest that public health efforts to reduce alcohol use disorder could significantly lower dementia incidence. Halving the population prevalence of alcohol use disorder may reduce dementia cases by up to 16%, highlighting alcohol reduction as a potential strategy in dementia prevention policies.

strategies that reduce the prevalence of alcohol use disorder could potentially lower the incidence of dementia by up to 16%.

Introduction

Alcohol consumption is widespread, modifiable and associated with many medical harms, but its causal relationship with dementia remains contentious. While heavy drinking has been associated with increased dementia risk in some cohorts, findings are inconsistent across different studies and designs.[1] The situation is even more ambiguous among moderate drinkers, with some research purporting protective effects of moderate alcohol consumption.[2] However, recent neuroimaging studies have uncovered adverse associations with dementia endophenotypes, even at low levels of alcohol consumption.[3] These findings highlight the complexity of alcohol's impact on cognitive health and underscore the urgent need to clarify the true effects of alcohol on dementia risk. This is of critical importance for public health, as it can guide risk awareness, inform preventative strategies and influence health guidelines for individuals.

It has been proposed that the effects of alcohol on brain health may be non-linear, with an 'optimal' dose for health greater than zero. However, methodological differences across studies may explain the contradictory findings in the existing literature.[4] Most studies have had limited inclusion of heavy or dependent drinkers, which restricts their power to detect the full range of alcohol's effects.[4] Additionally, many studies have involved elderly participants, where cognitive decline may influence drinking patterns rather than the opposite—that is, reverse causation.[5] The inclusion of non-drinking reference groups likely consisted of former heavy drinkers who are now abstinent,[6] which introduces confounding (because such subjects are susceptible to long-term health effects of alcohol from prior heavy use), complicating efforts to draw definitive conclusions about causality. Additionally, phenotypic assessment has often focused on current rather than lifetime drinking, counting recovering dependent individuals in the same category as lifetime never-drinkers, leaving analyses unable to account for the effects of prior use. As a result, we are currently unable to infer confidently a causal relationship between alcohol consumption and cognitive decline.[7] Practical and ethical issues preclude randomised controlled trials on alcohol use and dementia risk. However, Mendelian randomisation (MR), a quasi-experimental approach leveraging genetic data, offers an opportunity to estimate causal effects.[8] In this design, genomic risk for a trait essentially stands in analytically for the trait itself. Five MR studies have investigated the linear relationship between alcohol consumption and late-onset Alzheimer's disease in European ancestry-only populations, all reporting null findings.[9 10] These studies were limited by statistical power, and in the context of alcohol's broader impact on dementia, non-Alzheimer dementia aetiologies may be more relevant.[11] Moreover, previous studies, with one lower powered exception in white British individuals,[12] did not examine the crucial question of non-linear relationships with alcohol, precluded by relying on summary data from existing Alzheimer's genome-wide association studies (GWAS). The absence of large-scale data on both alcohol use and diverse dementia phenotypes has hindered progress in answering a key question: Is there an optimal non-zero weekly alcohol intake for brain health? Additionally, if it is the case that even low or moderate alcohol intake is harmful to brain health, earlier research suggesting the contrary may have led individuals to intentionally increase alcohol intake to take advantage of its purported health benefits. More and better data are needed to optimise public health advice.

In this study, we employed observational phenotypic-only and then genetic methods to estimate the role of alcohol use in dementia risk across the entire dose range, including in the moderate drinking range. To achieve this, we used two large and diverse biobanks: the Million Veteran Programme (MVP)[13] in the USA and the UK Biobank (UKB).[14] Given the current uncertainty about which specific subtypes of dementia alcohol could impact, we included a broad range of dementia phenotypes, rather than restricting our focus to Alzheimer's disease, as has been done in prior studies. The primary data for the genetic analyses were generated through a novel bi-ancestry GWAS of all-cause dementia in MVP, allowing for a crucial examination of non-linear relationships between alcohol consumption and dementia risk at the largest scale to date. Our study also benefited from extensive longitudinal phenotype data, capturing how alcohol consumption patterns evolve in ageing individuals, allowing us to explore the potential role of reverse causation between alcohol and dementia. To strengthen causal inference, we triangulated traditional observational methods with genetic analyses, exploring a range of alcohol-related traits across different genetic ancestries and examining how these factors interact with the ageing process.

Methods

Study populations

The observational study utilised data from two large, diverse cohorts (figure 1): MVP and UKB. MVP includes US veterans who were recruited from 2011 to the present.[13] UKB recruited volunteers aged 40–69 years from 2006 to 2010.[14] Participants were followed up from recruitment until either their first dementia diagnosis, death or the date of last follow-up (December 2019 for MVP and January 2022 for UKB). Participants in both cohorts provided written informed consent, and the studies had approval from their respective institutional and ethics review boards. All individuals in analyses were unrelated and stratified by genetic ancestry to allow for analyses across diverse populations.

The genetic analyses included a total of 2.4 million participants from 45 GWAS cohorts (online supplemental table S18). These genetic cohorts facilitated the MR analyses.

Alcohol measurement

Alcohol intake was assessed using self-reported drinks per week (DPW), which were derived from participant questionnaires in MVP and UKB, and additionally the AUDIT-C clinical screening tool in MVP. The AUDIT-C is a widely used three-item version of the Alcohol Use Disorders Identification Test (AUDIT) that screens for hazardous drinking patterns. The AUDIT-C score ranges from 0 to 12, with the items assessing the frequency of alcohol consumption, the number of standard drinks consumed on a typical drinking day, and the frequency of binge drinking (>6 drinks on one occasion). In the MVP, DPW was calculated by multiplying the midpoints of drinking frequency and the number of drinks consumed per day. One standard drink is defined as approximately ~14 g of ethanol. In UKB, participants reported their average weekly or monthly alcohol intake in glasses, which were converted to DPW. To limit potential reverse causation, the earliest recorded alcohol intake was prioritised for analyses, whenever possible, except where explicitly testing for the impact of exposure measurement timing on association with dementia. For the latter, we compared alcohol use as assessed at enrolment surveys. For clinical identification, the AUDIT-C scores can be categorised

	Observational analyses	Genetic analyses	
		1. Linear	2. Nonlinear
Cohorts (N)	Million Veteran Program (247,136) UK Biobank (312,423)	Multiple GWAS studies (2.4 million)	Million Veteran Program (204,356)
Exposures	Self-reported: 1. Alcoholic drinks per week 2. AUDIT-C scores 3. Alcohol Use Disorder	Genetically predicted: 1. Alcoholic drinks per week 2. Problematic Alcohol Use 3. Alcohol Use Disorder	Genetically predicted Alcoholic drinks per week
Outcome	Incident all-cause dementia	Genetically predicted All-cause dementia	Genetically predicted All-cause dementia
Analyses	Cox proportional hazards regression	Two sample linear MR	One sample nonlinear MR

Figure 1 Analyses overview. GWAS, genome-wide association studies; MR, Mendelian randomisation.

into three risk groups: non- or occasional drinker (0, 1), low risk (2–3), high risk (>4).[15 16] Never and former drinkers were distinguished where possible. However, this phenotype usually reflects current, that is, state use of alcohol, rather than lifetime, that is trait, use. Alcohol use disorder (AUD) cases were identified using diagnostic codes in the linked electronic health record (EHR).

For the genetic analyses, we looked at both how much people drink (quantity-frequency traits) and problematic alcohol use (PAU), which reflect somewhat different underlying genetic risks and biology.[17] For example, PAU, but not the amount people drink, is linked to several psychiatric disorders.[18 19] PAU was defined through a meta-analysis that combined data from alcohol use disorder and the AUDIT-P (Alcohol Use Disorders Identification Test – Problem Consumption).[18] AUDIT-P is a subset of the AUDIT tool that focuses on alcohol-related problems and behaviours.

Outcome measurement

Given the uncertainty regarding whether specific dementia subtypes are differentially impacted by alcohol consumption, our primary outcome was all-cause dementia. Dementia cases were identified using EHR data and International Classification of Diseases (ICD) codes (online supplemental table S19). To minimise the risk of reverse causation, prevalent cases (those diagnosed with dementia at the time of enrolment) were excluded from observational analyses. However, for genetic analyses, both incident (new cases) and prevalent cases were included, as reverse causation is less of a concern in this context.

Covariates

Potential confounders were identified based on the existing literature. Baseline information on demographic factors, lifestyle behaviours, and physical and psychiatric health was collected using self-administered questionnaires. Educational qualifications and household income were treated as categorical variables. Smoking was classified as daily, occasionally or non-smoker. Body mass index was calculated using self-reported height and weight at enrolment. A history of head injury and post-traumatic stress disorder was recorded as binary variables. Substance use disorders were defined by a lifetime history of opioid or cannabis dependence as indicated by ICD codes in the EHR. Diabetes mellitus was recorded at enrolment survey or in EHR. Mean systolic and diastolic blood pressure was calculated across multiple measurements recorded in the EHR. Higher order age terms (age^2 and age^3 and age-by-sex interactions) were included in the models to account for the non-linear, exponential increase in dementia risk with age and to allow for potential sex-specific age effects.

Genotyping in MVP

Genotyping and imputation for MVP participants has been described previously.[13] We used genetic data from release 4. Briefly, participants were genotyped using a custom Affymetrix Axiom Array. Missing genotype data were imputed using Minimac4, along with a reference panel from the African Genome Resources panel by the Sanger Institute. Insertions, deletions and more complex genetic changes were imputed independently using data from the 1000 Genomes Project and combined in an approach similar to that employed by the UK Biobank. Participants' broad ancestry groups were determined using their genetic data to reference panels from the 1000 Genomes Project.

Genetic variants

Genetic variants linked to three separate alcohol use traits—DPW, PAU and AUD—were selected from the largest available GWAS studies. A critical difference from phenotype (state) data is that genetic instruments reflect lifetime risk or exposure, that is, trait rather than state. Only variants with strong evidence ($p<5\times10^{-8}$) were chosen (online supplemental table S7–S10 and S18). When possible, variants were identified from analyses that included multiple ancestries, but ancestry-specific betas and standard errors were used for accuracy. As a result, some instruments had higher p values and lower F statistics. Post hoc choice of instruments, genetic models or data based on measured F-statistics can introduce bias. Notably, the widely cited rule that F>10 avoids bias in instrumental variable analysis is misleading.[20] We included

variants with multiple alleles since all datasets clearly reported them, facilitating comparison across studies. All studies were adjusted for the same covariate set (age, sex and ancestry principal components). Where the availability of strong variants was limited, a less stringent p value threshold ($p<5\times10^{-5}$) was used. To ensure variants were independent, ancestry-specific linkage disequilibrium (LD) clumping was conducted using PLINK v2.0, using data from the 1000 Genomes Project (10 000 kb window and LD $r^2=0.001$).

Dementia phenotype definition determines interpretation of MR estimates.[21] We used genetic associations with all-cause dementia calculated de novo in our primary genetic analyses, given uncertainty about which dementia subtypes alcohol impacts. When outcome data were unavailable, we sought proxies.

Statistical analyses

Analyses were performed in R (v4.1.2), unless otherwise stated.

Observational associations between alcohol and dementia

To estimate the associations between alcohol and incident dementia, Cox proportional hazards models were used. The time at risk was calculated from baseline (when covariates were measured) to either the date of dementia diagnosis or censoring. Influential observations were identified by plotting deviance residuals. The proportional hazards assumption was visually assessed using Schoenfeld residuals and formally with time interactions. For covariates not of primary interest (eg, age and body mass index), which violated the proportional hazards assumption, stratified models were fitted without the constraint of non-proportionality. Separate baseline hazard functions were fitted for each stratum. The Aalen-Johansen estimator[22] was used to assess if death was a competing risk. Competing risk of death was accounted for using the subdistribution method.[23] The reference group for alcohol intake was light drinkers, as some current non-drinkers had reduced alcohol intake due to health concerns ('sick quitters'). Random effects meta-analysis was performed to generate pooled effect sizes across MVP and UKB cohorts (with comparable ancestries).

Longitudinal trajectories of alcohol preceding dementia

In MVP, participants had multiple available AUDIT-C scores, which allowed for the examination of changes in drinking behaviours before dementia diagnosis, relevant to reverse causation. Binomial regression models were used, including the following fixed effects: time (from diagnosis/study-end to date of alcohol measurement), dementia status (case/control), enrolment age, sex, education and income, a two-way interaction term between time and dementia status, and a three-way interaction term between time, dementia status and AUDIT-C category (non-drinker, low-risk, high-risk). Wald tests were conducted to estimate the overall effect of interactions between dementia status and time. These tests evaluated whether AUDIT-C trajectory differed by dementia diagnosis. Random effects for participant identification were included. The resulting models were visualised with graphs showing predicted longitudinal trends in AUDIT-C scores for a typical participant.

Genome-wide association study of all-cause dementia

Dementia cases were defined by the presence of a relevant ICD 9/10 code in their linked EHRs. Controls were individuals without such codes. To avoid relatedness bias, closely related individuals were excluded (>0.088 Kinship coefficient). Ancestry-specific logistic regression was performed in PLINK 2.0 with adjustment for age, sex and genetic background (measured by 10 principal components). To assign ancestry groups, we compared each participant's genetic data to five reference groups from the 1000 Genomes Project and assigned to the nearest reference ancestry. A second round of principal component analysis within each assigned ancestral group was performed, and outliers with principal component scores >6 SD from the mean were identified. We also excluded genetic variants that were missing data in more than 20% of participants or if they were very rare (<0.1%). After filtering, the final sample included 25 473 cases and 425 844 controls of European ancestry, and 5706 cases and 108 532 controls of African ancestry. The Latin American ancestry group did not have sufficient power for analysis. Heritability for common variants mapped to HapMap3 was calculated using LD score regression. Additionally, genetic correlation between alcohol and dementia phenotypes was estimated.

Mendelian randomisation

Both linear and non-linear MR analyses were conducted. The primary analyses used to evaluate if alcohol use traits affect dementia was the inverse variance weighted (IVW) method, with several other methods employed as sensitivity analyses. To test whether dementia affects alcohol use, reverse MR was also conducted. Additionally, other factors that might influence the relationship between alcohol and dementia were adjusted for using multivariable MR.

For the non-linear analysis, European participants from the MVP—313 873 individuals including 16 932 with dementia—were divided into five groups created using individual-level data from these subjects (n=313 873, including 16 932 dementia cases), which provided greater power than UKB for non-linear analyses. To identify how dementia risk varies with quantity of alcohol drinks, a genetic risk score for DPW was calculated for each individual by multiplying the number of alcohol-increasing alleles the individual carries by the effect size of the allele, adding up 641 such variants at $p<5\times10^{-8}$. A statistical method called fractional polynomials was used to explore how genetically predicted alcohol intake relates to dementia in a non-linear way. The five groups were made using a method that ranks participants by genetic risk—the doubly-ranked method.[24] Five groups were chosen to balance assessment of the relationship shape and statistical power. For each group, the localised average causal effect (LACE) was calculated—which reflects the strength of the association between alcohol and dementia—by comparing how strongly the genetic score relates to dementia versus how it relates to alcohol use. These associations were adjusted for age, age^2, sex and ancestry differences (top 10 ancestry principal components). Analysing how these effects varied across the five groups provided insight into whether the relationship between alcohol and dementia is linear or non-linear. Non-linearity was tested by comparing the non-linear model to a linear model and assessing the trend in LACE estimates. All statistical analyses were conducted using the SUMnlmr package. Negative control analyses of age and sex were performed to rule out bias from confounding.[19]

Patient and public involvement statement

Patients and the public were involved in the wider design of our research through a specially convened focus group to identify important priorities for our research. No patients or public were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the patient community.

Results

Observational analyses

Population characteristics

Across the two cohorts, 559 559 participants were included in observational analyses (figure 1), of whom 10 564 developed incident all-cause

dementia over follow-up in MVP (mean=4.3 years, median=4.4 years, maximum=9.0 years), and 3976 in UKB (mean=12.4 years, median=12.7 years, maximum=15.0 years) (total=14,540), consistent with a lower mean age in UKB (table 1); 28 738 died during follow-up in MVP and 19 296 in UKB (total=48,034). Over 90% of participants in both cohorts reported consuming alcohol at first measurement. Compared with drinkers, current non-drinker groups were older, with a higher proportion of females and lower educational qualifications. Similar patterns were observed in African (AFR) and Latin American (AMR) ancestry groups (online supplemental table S1).

Observational associations between alcohol use and dementia risk

Conventional observational analyses—that is, using no genetic data—found a U-shaped relationship between self-reported alcohol intake and incident dementia in both MVP and UKB participants of European (EUR) ancestry (figure 2)—that is, lowest dementia risk in low-moderate drinkers, rather than non-drinkers. Non-drinkers (irrespective of subdivision into never and former drinkers), heavy (>40 DPW) and dependent drinkers (HR 1.51, 95% CI 1.42 to 1.60) had a higher incidence of all-cause dementia compared with light drinkers (<7 DPW). In UKB, but not MVP, moderate drinkers (7–14 DPW) had a significantly lower dementia incidence than light drinkers. Accounting for the competing risk of death had little impact on the associations (online supplemental table S2 and S3).

A key strength of the MVP cohort is its ancestral diversity, allowing analyses of non-European ancestry populations, previously neglected in alcohol research. Individuals with a history of AUD had elevated dementia incidence across both AFR (HR 1.44, 95% CI 1.25 to 1.67) and AMR (HR 1.58, 95% CI 1.24 to 2.01]) ancestries (online supplemental table S4).

Alcohol drinking trajectories before dementia diagnosis

Observational associations between alcohol intake and dementia could be explained by a causal impact of alcohol—alcohol causing dementia—or changes in drinking pattern in prodromal disease—altered, generally decreased, alcohol intake as part of the dementia prodrome (reverse causation). To explore this, we leveraged the longitudinal EHR in MVP to explore how alcohol consumption behaviours (using AUDIT-C)[25] changed the preceding diagnosis of dementia. Non-drinkers were consistent in their abstinence (figure 3). Among all drinkers, consumption declined over time. However, this decline was faster among those who went on to develop dementia than for controls (dementia*time β=0.05, SE=0.02, p=0.0003). Furthermore, the accelerated drop in drinking was magnified for those with higher historical drinking (first recorded AUDIT-C >4 dementia status*time β=0.09, SE=0.02, p<0.001) (figure 3). Relatedly, associations of alcohol with dementia diagnosis varied with the temporal proximity of the two (online supplemental figure S1). We compared associations with dementia according to when alcohol intake was measured: (1) the first recorded alcohol record (an average of 9 years before dementia diagnosis), and (2) at study enrolment (an average of 4 years before dementia diagnosis). When alcohol was measured closer to diagnosis, observed harmful risks of heavy drinking were attenuated, and moderate drinking was associated with an apparent protective effect (7–14 DPW HR 0.87, 95% CI 0.78 to 0.97).

Genetic analyses

Bi-ancestry GWAS of all-cause dementia

For the genetic analyses, we required powerful GWAS data for all traits studied. To increase power for all-cause dementia in older adults, we conducted a de novo GWAS in MVP to generate necessary data for our analyses. We found four genetic variants linked to dementia in individuals of EUR ancestry— these are in *PICALM, APOE, BCAM/NECTIN2, BIN1/NIFKP9* (online supplemental table S5 and figure S2). In individuals of AFR ancestry, only one variant (in the *APOE* gene) showed a strong link (online supplemental figure S3). The strongest association in EUR was with a variant called rs429358 ($p=1.14\times10^{-314}$), in the *APOE* gene. The overall genetic contribution to dementia risk was low (heritability=0.01 on the liability scale). There were significant genetic correlations between three examined alcohol phenotypes and all-cause dementia (online supplemental table S6). These were strongest for AUD (R_g=0.45 (0.10–0.80)) and weakest for DPW (R_g=0.19 (0.01–0.36)).

Genetic associations between alcohol use and dementia

Three genetic measures related to alcohol use were used as exposures, to study the impact of both alcohol drinking quantity, as well as problematic and dependent drinking, on dementia risk. These exposures were: (1) DPW, instrumented using 641 independent genetic variants; (2) PAU, with 80 genetic variants; and (3) AUD, with 66 genetic variants (online supplemental table S7–10). Higher genetic risk for alcohol consumption, as well as problematic and dependent drinking, was associated with an increased risk of all-cause dementia in European ancestry participants (figure 4). For example, an increase from one to three DPW (or five to 16 DPW) was associated with a 15% increased risk of dementia risk (IVW OR 1.15, 95% CI 1.03 to 1.27). Additionally, a twofold increase in genetic risk for AUD was associated with a 16% increase in dementia risk (IVW OR 1.16, 95% CI 1.03 to 1.30).[26] To assess the strength of causal evidence, we conducted several sensitivity analyses (online supplemental table S11–14). These included: correcting for data from overlapping samples, removing outliers and testing if dementia might cause alcohol use instead, which did not undermine the key findings. In contrast, some heterogeneity across SNP estimates and pleiotropy (for DPW) was observed. We also adjusted for other factors such as socioeconomic status, smoking and post-traumatic stress disorder. After adjusting for post-traumatic stress disorder, the link between alcohol use disorder and dementia was attenuated, but still significant when controlling for smoking or cannabis use. For individuals of African ancestry, the link was weaker, probably due to lower statistical power of analyses (online supplemental table S11).

Next, we tested whether the relationship between alcohol and dementia changes at different drinking levels (non-linear analyses), which cannot be examined using linear MR. Non-linear MR necessitates individual level genetic data and was performed in MVP, which had a large number of dementia cases and thus power to detect effects. Unlike in the observational analyses, no U-shaped association was found between alcohol intake and dementia, and no protective effects of low levels of alcohol intake were observed (figure 4, online supplemental table S15). Instead, dementia risk steadily increased with more genetically predicted drinking. For example, people averaging 12 DPW showed an increased risk of dementia (OR 1.09, 95% CI 1.04 to 1.15) (online supplemental table S15). To validate the genetic instruments used for alcohol, we tested whether they were related to age and sex (which should not be affected by alcohol) in a negative control analysis.[27] No significant associations were found, supporting that our results reflect effects rather than confounding (online supplemental tables S16, S17).

Discussion

Conventional observational analyses showed a U-shaped association between alcohol consumption and dementia (as has been seen in previous studies), seeming to support the proposal that low or moderate alcohol use is associated with lower dementia risk than no alcohol at all. However, less-confounded genetic analyses provided evidence

Table 1 Participant characteristics

	Million Veteran Programme						UK Biobank						
Drinking status	Non-drinker	<7 DPW	7–<14 DPW	14–<22 DPW	22–<40 DPW	>40 DPW	Never	Former	<7 DPW	7–<14 DPW	14–<22 DPW	22–<40 DPW	>40 DPW
No. (%)	76 636 (37.5)	109 495 (53.6)	12 525 (6.1)	3216 (1.6)	1136 (0.6)	1358 (0.7)	13 986 (4.5)	12 647 (4.0)	126 447 (40.5)	83 300 (13.7)	42 786 (26.7)	26 775 (8.6)	6482 (2.1)
Age, mean years (SD)	67.5 (10.6)	66.8 (12.1)	64.1 (11.1)	62.8 (10.2)	59.3 (11.4)	57.5 (10.3)	56.7 (8.6)	56.7 (7.9)	56.2 (8.1)	56.1 (8.0)	56.2 (7.9)	56.2 (7.9)	55.7 (7.7)
Sex, No. (%)													
Female	4457 (5.8)	6360 (5.8)	322 (2.6)	96 (3.0)	37 (3.3)	47 (3.5)	9742 (69.7)	6685 (52.9)	81 525 (64.5)	38 447 (46.2)	13 241 (30.9)	4788 (17.9)	741 (11.4)
Smoking status, No. (%)													
Regular	12 705 (16.6)	15 875 (14.5)	2961 (2.4)	1139 (3.5)	463 (4.1)	703 (5.2)	881 (6.3)	1886 (14.9)	8978 (7.1)	7657 (9.2)	5593 (13.1)	5101 (19.1)	1924 (29.7)
Never	59 626 (77.8)	85 084 (77.7)	8285 (66.1)	1763 (54.8)	563 (49.6)	511 (37.6)	11 409 (81.6)	5568 (44.0)	79 090 (62.5)	42 488 (51.0)	17 642 (41.2)	8715 (32.5)	1644 (25.4)
Household income, No. (%)†													
<$10 000	4122 (5.4)	3952 (3.6)	683 (5.5)	322 (10.0)	160 (14.1)	270 (19.9)	5839 (41.7)	5191 (41.0)	26 715 (21.1)	13 384 (16.1)	6611 (15.5)	4770 (17.8)	1602 (24.7)
>$150 000	789 (1.0)	2864 (2.6)	295 (2.4)	49 (1.5)	6 (0.5)	9 (0.7)	330 (2.4)	356 (2.8)	6288 (5.0)	6121 (7.3)	3610 (8.4)	1991 (7.4)	370 (5.7)
Educational qualifications, No. (%)‡													
Less than high school	4565 (6.0)	3150 (2.9)	384 (3.1)	163 (5.1)	53 (4.7)	67 (4.9)	3196 (22.9)	2976 (23.5)	16 336 (12.9)	9981 (12.0)	5318 (12.4)	3894 (14.5)	1202 (18.5)
Professional/ doctoral degree	1839 (2.4)	3720 (3.4)	287 (2.3)	43 (1.3)	11 (1.0)	15 (1.1)	4071 (29.1)	3617 (28.6)	46 569 (36.8)	32 835 (39.4)	16 305 (38.1)	8937 (33.4)	1811 (27.9)
Mean time at risk, days (SD)	4.5 (2.3)	4.5 (2.3)	4.4 (2.3)	4.4 (2.2)	4.5 (2.2)	4.4 (2.2)	12.4 (1.9)	12.1 (2.3)	12.4 (1.6)	12.6 (1.7)	12.5 (1.8)	12.4 (2.0)	12.2 (2.4)

*Defined as daily smoker in Million Veteran and current smoker in UK Biobank.

†The equivalent categories of household income in UK Biobank were <£18 000 and >£100 000. Highest and lowest categories only displayed.

‡In UK Biobank the lowest educational category was no formal qualifications. Highest and lowest categories only displayed.

DPW, drinks per week; ICD, International Classification of Diseases; No., number.

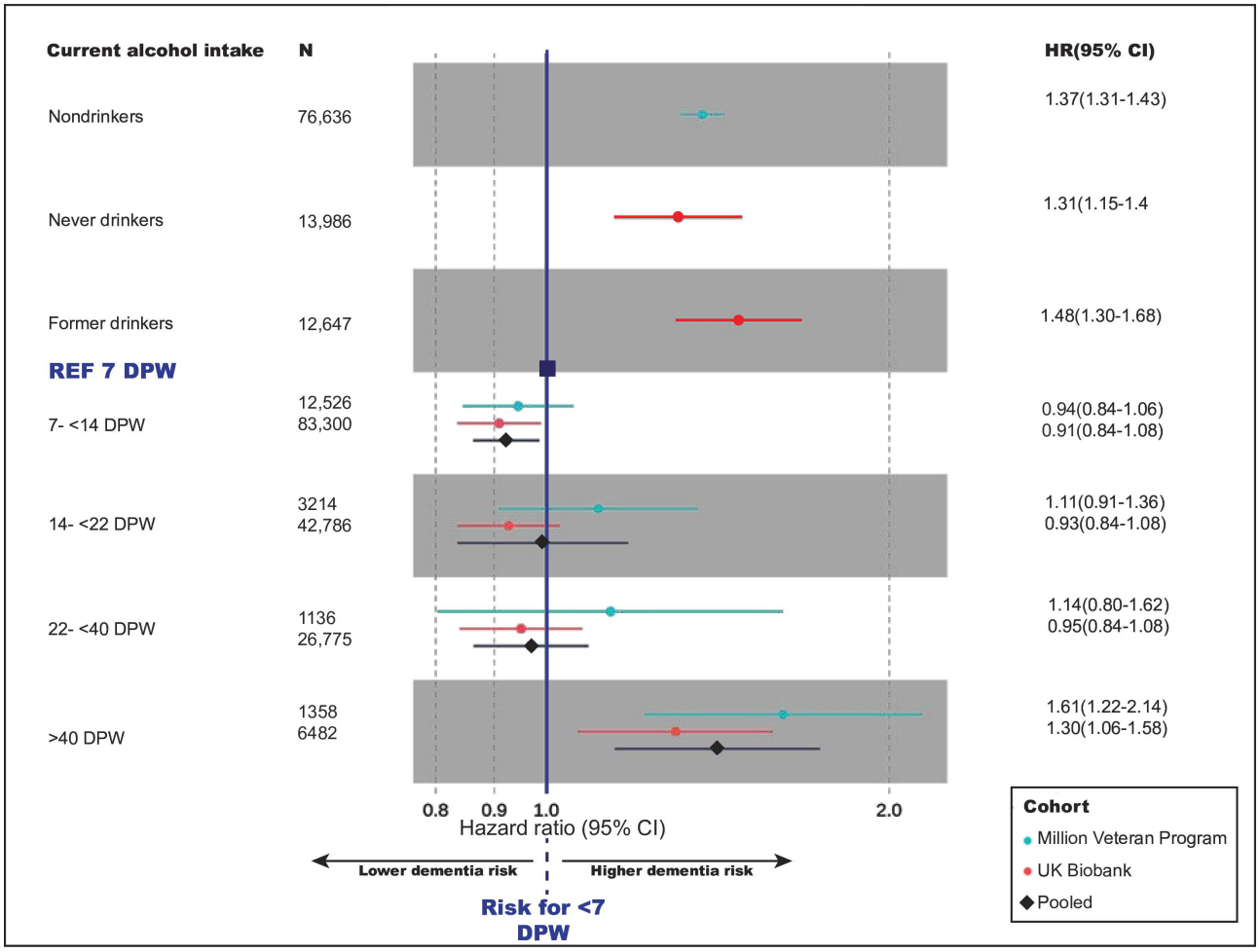

Figure 2 Observational associations between alcohol intake and incident dementia. HRs (dots or diamonds) and 95% CI (lines) of all-cause incident dementia according to current alcohol intake, as compared to reference group (solid black line) of individuals consuming <7 drinks per week (DPW). Choice of light drinkers as a reference group is motivated by concerns about current non-drinkers including individuals who previously drank heavily but have reduced their alcohol intake in response to a health concern. Dementia cases were identified by relevant codes in the electronic health record (online supplemental table S19). Alcohol intake was ascertained at first recording, from the AUDIT-C (Alcohol Use Disorders Identification Test) screening questionnaire in the Million Veteran Program, and the baseline questionnaire in the UK Biobank. Individuals classed as current non-drinkers in the Million Veteran Program were those with an AUDIT-C score of zero. Never and former drinkers could not be distinguished within this group based on the AUDIT-C questions, whereas in UK Biobank, never and former drinkers were identifiable from questionnaire answers. Estimates were generated from Cox proportional hazards models, using unrelated European individuals, and adjusted for age, sex, income, education, smoking, body mass index; and additionally in the Million Veteran Program: head injury, post-traumatic stress disorder and substance use. Estimates for other ancestry groups are given in online supplemental table S4. Pooled estimates across the two cohorts (black diamonds) were generated using random effects meta-analysis.

that alcohol consumption in general, as well as problematic drinking, increases dementia risk. A monotonically increasing risk of alcohol consumption on all-cause dementia was observed, contradicting the interpretation that one can drink alcohol to decrease dementia risk. Furthermore, drinkers who went on to develop dementia typically reduced their alcohol consumption in the years preceding diagnosis, suggesting that the apparent protective effects of moderate drinking may be a consequence of reverse causation. The observational analysis was also susceptible to being influenced by the current, as opposed to lifetime, nature of the trait as ascertained. The genetics analyses, in contrast, considered lifetime genetically predicted risk, a prediction that is quite stable especially in large samples such as those we studied.

The reduction in alcohol use before dementia onset aligns with findings from studies of other putative dementia risk factors, including body mass index.[28] This has important general implications for study design and for the interpretation of prior studies. Reverse causation is further supported by our finding of a higher incidence of dementia among non-drinkers, in line with previous studies.[5] These groups may include 'sick quitters'—individuals with prior heavy use[13] —often with earlier deaths, which may explain their higher dementia risk. Additionally, non-drinkers tended to have lower socioeconomic status and education levels, both of which are associated with poorer pre-morbid cognitive function and increased vulnerability to dementia. Imperfect control means that even though these factors were accounted for statistically, measurement errors mean residual confounding could still underlie apparent observational associations with dementia. In line with many,[1 4] but not all,[5] prior studies, heavy alcohol use was associated with an increased dementia risk. Variability in alcohol phenotypes, timing of alcohol self-report (especially between mid-life and late-life),[5] and differing methods for adjusting for confounding factors are likely to contribute to these discrepancies. Ethnic diversity in alcohol use and dementia risk has been understudied, but our analyses across European, African and Latin American ancestry populations observed similar risks associated with alcohol use disorder.[5]

Importantly, MR, which has a lower risk of both residual confounding and reverse causation, supported a potential causal role of alcohol use, including DWP, and problematic and dependent use, in increasing dementia risk. We suggest two explanations

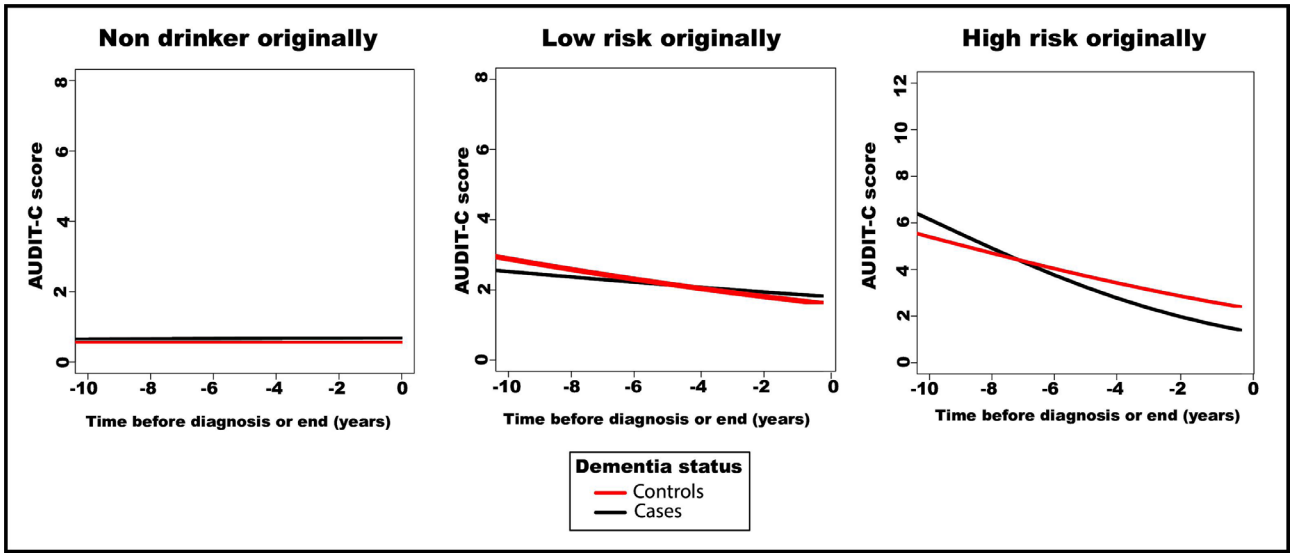

Figure 3 Trends in longitudinal alcohol use in people without dementia (black) and those who developed dementia (red), stratified by risk of alcohol abuse. Alcohol use is defined using the AUDIT-C (Alcohol Use Disorders Identification Test) screening questionnaire which was administered and documented at multiple time points in the electronic health record. Dementia status was ascertained by the presence of a relevant clinical code in the electronic health record. The plots show predictions of how drinking behaviour changes over time for individuals who develop dementia (cases) and those who remain dementia-free (controls) for: (A) individuals who were non- or occasional drinkers at first record (AUDIT-C <1, n=108 544); (B) individuals who were low-risk drinkers at first record (AUDIT-C 2–<4, n=51 443); (C) individuals who were high-risk drinkers at first record (AUDIT-C >4, n=16 881). Time 0 is the time of diagnosis for cases or last follow-up for controls. Predictions are based on mixed effects models adjusted for age, sex, body mass index, smoking, educational qualification and household income. Graphs show predictions for a male participant of average age, body mass index, education and income.

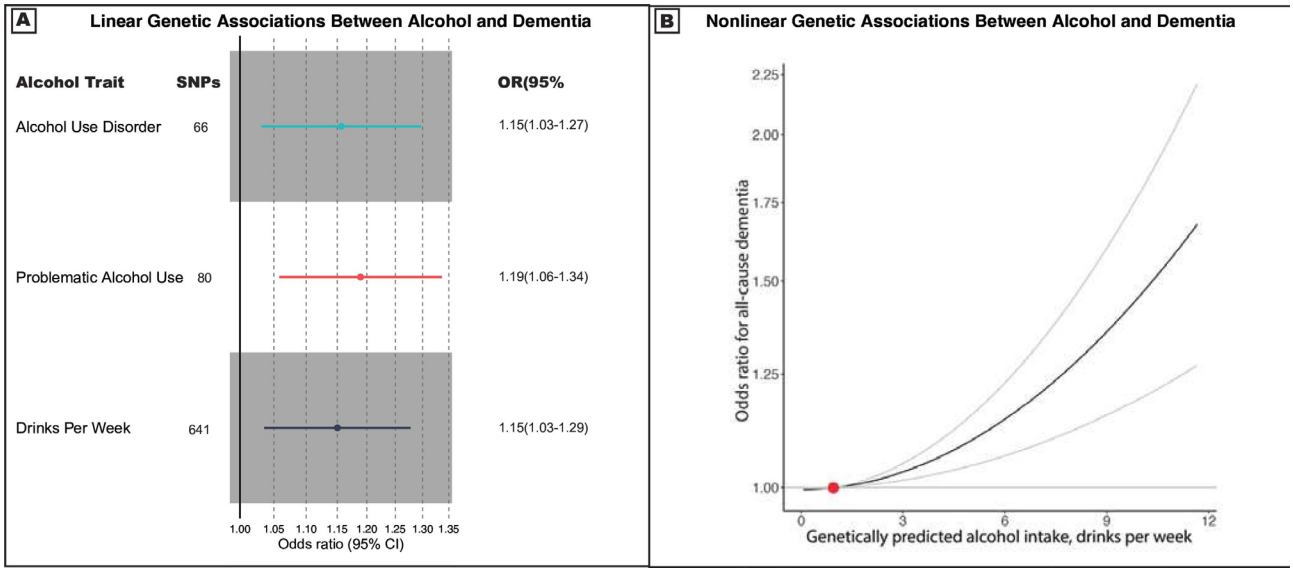

Figure 4 Linear and non-linear genetic associations between alcohol use and dementia. (A) Forest plot shows causal odds ratios for all-cause dementia for either a 1 SD increase in log-drinks per week or a twofold increase in prevalence of problematic alcohol use or alcohol use disorder. A stringent ($p<5x10^{-8}$) threshold was used to select genetic instruments from genome-wide association analyses. Alcohol use is characterised by three phenotypes: a clinical diagnosis of alcohol use disorder in the electronic health record, problematic use (meta-analysing alcohol use disorder and AUDIT-P, a screening tool for problematic drinking), and number of drinks per week. All-cause dementia was determined by any clinical dementia diagnosis in the electronic health record. Estimates were generated from one- and two-sample inverse variance weighted Mendelian randomisation from a combined sample size across source genome-wide association studies of over 2.4 million individuals (online supplemental table S18). (B) Non-linear Mendelian randomisation was performed using the doubly-ranked method, in unrelated European ancestry Million Veteran Program participants (n=313 873, 16 932 dementia cases). The x-axis shows the alcohol intake in drinks per week at enrolment. The y-axis shows the odds ratio for the respective all-cause dementia risk. The gradient at each point of the curve is the localised average causal effect. Values are based on mean intake in five strata of exposure (quintiles). Grey lines represent the 95% CI. The reference value (in red) for alcohol intake was taken as one drink per week. P value for linearity: 0.8 (a non-significant result indicates that the best fitting quadratic model is not strongly preferred over the linear model); p value for trend: 0.5 (a non-significant result indicates no strong evidence for trend in the estimates calculated in different strata).

for discrepancies between our MR results and previous null result studies.[14] Earlier studies considered a narrow range of alcohol phenotypes and focused on late-onset Alzheimer's disease, with one exception,[29] whereas we included a broader range of alcohol and neurodegenerative pathologies. Second, our study had greater statistical power. Furthermore, our non-linear analyses did not support the previously hypothesised protective effects of low alcohol consumption on dementia and instead showed a monotonically increasing risk with alcohol dose. These results are consistent with a lower powered one-sample MR study in current drinkers of white British ancestry,[12] as well as neuroimaging findings.[3 30 31]

This finding has key public health implications, as it challenges the longstanding notion that moderate alcohol intake might have a protective effect on the brain. Several important sensitivity analyses strengthened our findings, including use of age and sex as negative controls to rule out potential biases. Additionally, the consistency of these findings across multiple alcohol phenotypes enhances the robustness of our conclusions.

Despite the strengths of our study—a large sample size, cross-ancestry analyses and triangulation of observational and genetically informed approaches using both quantity-frequency and use disorder alcohol phenotypes—there are limitations. Most notably, analyses had the greatest power to detect effects in EUR groups, and dementia diagnoses from EHR may be subject to ascertainment bias, though this would likely bias associations toward the null. MR methods rely on unverifiable assumptions, and the estimates we derived reflect the accumulated effect of alcohol over a lifetime and do not necessarily translate into potential consequences resulting from an adult life intervention. Heterogeneity in estimates between genetic variants may plausibly be due to alcohol acting via different pathways and organs to damage the brain, or failure of the homogeneity or linearity assumptions.[32] The latter were tested and held. Non-linear MR estimates at the lower alcohol doses have less precision than those at higher doses, with potential implications for detecting J-shaped relationships; however, negative controls for age and sex did not indicate bias across strata.[27]

In summary, our study findings support a detrimental effect of all types of alcohol consumption on dementia risk, with no evidence supporting the previously suggested protective effect of moderate drinking. The pattern of reduced alcohol use before dementia diagnosis observed in our study underscores the complexity of inferring causality from observational data, especially in ageing populations. Our findings highlight the importance of considering reverse causation and residual confounding in studies of alcohol and dementia, and they suggest that reducing alcohol consumption may be an important strategy for dementia prevention.

Author affiliations
[1]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[2]Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA
[3]Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, USA
[4]Department of Psychiatry, University of Oxford, Oxford, UK
[5]Department of Oncology & Cancer Reserach UK Cambridge Centre, University of Cambridge, Cambridge, UK
[6]MRC Biostatistics Unit & Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[7]Oxford Centre for Integrative Neuroimaging, Oxford, UK
[8]Department of Medicine, Harvard University, Cambridge, Massachusetts, USA
[9]Million Veteran Program, VA Boston Healthcare System, Boston, MA, USA
[10]Department of Psychiatry and School of Public Health, University of California, La Jolla, California, USA
[11]Yale University, New Haven, Connecticut, USA

Acknowledgements We wish to thank Maria Christodoulou and the University of Oxford Statistics Consulting service for providing advice on the survival model analyses.

Contributors AT conceived the study design, accessed the data, performed statistical analyses and wrote the first draft of the manuscript. AT is the guarantor. DL accessed the data and performed analyses. KA performed analysis. HZ and JD advised on statistical analyses. MS, MG, KPE and TN advised on study design. JG supervised the project. All authors helped to write the paper and had final responsibility for the decision to submit for publication.

Funding This research used data from the Million Veteran Program and was supported by funding from the Department of Veterans Affairs Office of Research and Development, Million Veteran Program Grant #I01CX001849, and the VA Cooperative Studies Program (CSP) study #575B, and MVP025. This publication does not represent the views of the Department of Veterans Affairs or the United States Government. AT is supported by the Wellcome Trust (216462/Z/19/Z). SBu is supported by the Wellcome Trust (225790/Z/22/Z) and the United Kingdom Research and Innovation Medical Research Council (MC_UU_00002/7). This research was supported by the National Institute for Health Research Cambridge Biomedical Research Centre (NIHR203312). The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Competing interests MBS has in the past 3 years received consulting income from Acadia Pharmaceuticals, Aptinyx, atai Life Sciences, BigHealth, Biogen, Bionomics, BioXcel Therapeutics, Boehringer Ingelheim, Clexio, Delix Therapeutics, Eisai, EmpowerPharm, Engrail Therapeutics, Janssen, Jazz Pharmaceuticals, NeuroTrauma Sciences, PureTech Health, Sage Therapeutics, Sumitomo Pharma, and Roche/Genentech. Dr Stein has stock options in Oxeia Biopharmaceuticals and EpiVario. He has been paid for his editorial work on Depression and Anxiety (Editor-in-Chief), Biological Psychiatry (Deputy Editor), and UpToDate (Co-Editor-in-Chief for Psychiatry). He has also received research support from NIH, Department of Veterans Affairs, and the Department of Defense. He is on the scientific advisory board for the Brain and Behavior Research Foundation and the Anxiety and Depression Association of America. JG is paid for editorial work on the journal Complex Psychiatry.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. Ethical approval for this work was obtained from the VA Central Institutional Review Board (IRB) (MVP 029). All research procedures complied with the ethical standards of the VA Office of Research and Development. UK Biobank has obtained ethical approval for data collection from the North-West Multi-centre Research Ethics Committee (21/NW/0157). No separate ethical approval was required. The study was conducted in accordance with the principles of the Declaration of Helsinki. Participants

gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Access to UK Biobank data is available following a successful application. Access to Million Veteran Program summary statistics is available via dbGAP.

ORCID iDs
Anya Topiwala https://orcid.org/0000-0002-8408-0372
Klaus P Ebmeier https://orcid.org/0000-0002-5190-7038
Stephen Burgess https://orcid.org/0000-0001-5365-8760
Thomas E Nichols https://orcid.org/0000-0002-4516-5103

References

1 **Schwarzinger M**, Pollock BG, Hasan OSM, *et al*. Contribution of alcohol use disorders to the burden of dementia in France 2008-13: a nationwide retrospective cohort study. *Lancet Public Health* 2018;3:e124–32.
2 **Mukamal KJ**, Kuller LH, Fitzpatrick AL, *et al*. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA* 2003;289:1405–13.
3 **Topiwala A**, Ebmeier KP, Maullin-Sapey T, *et al*. Alcohol consumption and MRI markers of brain structure and function: cohort study of 25,378 UK Biobank participants. *Neuroimage Clin* 2022;35:103066.
4 **Rehm J**, Hasan OSM, Black SE, *et al*. Alcohol use and dementia: a systematic scoping review. *Alz Res Therapy* 2019;11:1–11.
5 **Mewton L**, Visontay R, Hoy N, *et al*. The relationship between alcohol use and dementia in adults aged more than 60 years: a combined analysis of prospective, individual-participant data from 15 international studies. *Addiction* 2023;118:412–24.
6 **Fillmore KM**, Kerr WC, Stockwell T, *et al*. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies. *Addict Res Theory* 2006;14:101–32.
7 **Anstey KJ**, Peters R. Alcohol and dementia - risk or protective factor? *Nat Rev Neurol* 2018;14:635–6.
8 **Sanderson E**, Glymour MM, Holmes MV, *et al*. Mendelian randomization. *Nat Rev Methods Primers* 2022;2:6.
9 **Andrews SJ**, Goate A, Anstey KJ. Association between alcohol consumption and Alzheimer's disease: a Mendelian randomization study. *Alzheimer Dementia* 2020;16:345–53.
10 **Campbell KA**, Fu M, MacDonald E, *et al*. Relationship between alcohol consumption and dementia with Mendelian randomization approaches among older adults in the United States. *Alz Dem Diag Ass Dis Mo* 2024;16:e12598.
11 **Topiwala A**, Wang C, Ebmeier KP, *et al*. Associations between moderate alcohol consumption, brain iron, and cognition in UK Biobank participants: observational and Mendelian randomization analyses. *PLoS Med* 2022;19:e1004039.
12 **Zheng L**, Liao W, Luo S, *et al*. Association between alcohol consumption and incidence of dementia in current drinkers: linear and non-linear Mendelian randomization analysis. *EClin Med* 2024;76:102810.
13 **Gaziano JM**, Concato J, Brophy M, *et al*. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol* 2016;70:214–23.
14 **Sudlow C**, Gallacher J, Allen N, *et al*. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;12:e1001779.
15 **Foster JH**, Martin CR, Davis JP. Alcohol Consumption during the COVID-19 Lockdown Period: Predictors of At-Risk Drinking at Different AUDIT-C Cut-Off Thresholds. *Int J Environ Res Public Health* 2021;18:13042.
16 **Reinert DF**, Allen JP. The alcohol use disorders identification test: an update of research findings. *Alcohol Clin Exp Res* 2007;31:185–99.
17 **Zhou H**, Gelernter J. Human genetics and epigenetics of alcohol use disorder. *J Clin Invest* 2024;134:e172885.
18 **Zhou H**, Kember RL, Deak JD, *et al*. Multi-ancestry study of the genetics of problematic alcohol use in over 1 million individuals. *Nat Med* 2023;29:3184–92.
19 **Kranzler HR**, Zhou H, Kember RL, *et al*. Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nat Commun* 2019;10:1499.
20 **Burgess S**, Thompson SG, **CRP CHD Genetics Collaboration**. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol* 2011;40:755–64.
21 **Escott-Price V**, Hardy J. Genome-wide association studies for Alzheimer's disease: bigger is not always better. *Brain Commun* 2022;4:fcac125.
22 **Aalen OO**, Johansen S. An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scand J Stat* 1978;141–50.
23 **Fine JP**, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* 1999;94:496–509.
24 **Tian H**, Mason AM, Liu C, *et al*. Relaxing parametric assumptions for non-linear Mendelian randomization using a doubly-ranked stratification method. *PLoS Genet* 2023;19:e1010823.
25 **Bush K**. The AUDIT Alcohol Consumption Questions (AUDIT-C) An Effective Brief Screening Test for Problem Drinking. *Arch Intern Med* 1998;158:1789.
26 **Burgess S**, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. *Eur J Epidemiol* 2018;33:947–52.
27 **Hamilton FW**, Hughes DA, Spiller W, *et al*. Non-linear Mendelian randomization: evaluation of biases using negative controls with a focus on BMI and vitamin D. *medRxiv* 2023.
28 **Singh-Manoux A**, Dugravot A, Shipley M, *et al*. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. *Alzheimers Dement* 2018;14:178–86.
29 **Desai R**, John A, Saunders R, *et al*. Examining the Lancet Commission risk factors for dementia using Mendelian randomisation. *BMJ Ment Health* 2023;26:e300555.
30 **Topiwala A**, Allan CL, Valkanova V, *et al*. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ* 2017;357:j2353.
31 **Daviet R**, Aydogan G, Jagannathan K, *et al*. Associations between alcohol consumption and gray and white matter volumes in the UK Biobank. *Nat Commun* 2022;13:1175.
32 **Burgess S**, Bowden J, Fall T, *et al*. Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants. *Epidemiology (Sunnyvale)* 2017;28:30–42.