Contribution of alcohol use disorders to the burden of dementia in France 2008–13: a nationwide retrospective cohort study

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Summary

Background Dementia is a prevalent condition, affecting 5–7% of people aged 60 years and older, and a leading cause of disability in people aged 60 years and older globally. We aimed to examine the association between alcohol use disorders and dementia risk, with an emphasis on early-onset dementia (<65 years).

Methods We analysed a nationwide retrospective cohort of all adult (≥20 years) patients admitted to hospital in metropolitan France between 2008 and 2013. The primary exposure was alcohol use disorders and the main outcome was dementia, both defined by International Classification of Diseases, tenth revision discharge diagnosis codes. Characteristics of early-onset dementia were studied among prevalent cases in 2008–13. Associations of alcohol use disorders and other risk factors with dementia onset were analysed in multivariate Cox models among patients admitted to hospital in 2011–13 with no record of dementia in 2008–10.

Findings Of 31 624 156 adults discharged from French hospitals between 2008 and 2013, 1 109 343 were diagnosed with dementia and were included in the analyses. Of the 57 353 (5·2%) cases of early-onset dementia, most were either alcohol-related by definition (22 338 [38·9%]) or had an additional diagnosis of alcohol use disorders (10 115 [17·6%]). Alcohol use disorders were the strongest modifiable risk factor for dementia onset, with an adjusted hazard ratio of 3·34 (95% CI 3·28–3·41) for women and 3·36 (3·31–3·41) for men. Alcohol use disorders remained associated with dementia onset for both sexes (adjusted hazard ratios >1·7) in sensitivity analyses on dementia case definition (including Alzheimer's disease) or older study populations. Also, alcohol use disorders were significantly associated with all other risk factors for dementia onset (all p<0·0001).

Interpretation Alcohol use disorders were a major risk factor for onset of all types of dementia, and especially early-onset dementia. Thus, screening for heavy drinking should be part of regular medical care, with intervention or treatment being offered when necessary. Additionally, other alcohol policies should be considered to reduce heavy drinking in the general population.

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See Online for appendix

Background

Dementia is a clinical syndrome caused by brain damage and characterised by progressive deterioration in cognitive ability and capacity for independent living and functioning.[1] It is a common condition, affecting 5–7% of people aged 60 years and older worldwide,[2] and is a leading cause of disability in people aged 60 years and older.[3] Several types of dementia exist; Alzheimer's disease is the most common, followed by vascular dementia and rarer types of dementia, although mixed types of dementia often coexist.

Alcohol use has been associated with changes in cognitive health and dementia (appendix p 3). Briefly, the relationships between alcohol use and cognitive health in general and dementia in particular are complex.[4] Most reviews point to a possible beneficial effect of light-to-moderate drinking on cognitive health. However, moderate drinking has been consistently associated with detrimental effects on brain structure,[5,6] and nearly every review describes methodological problems of underlying studies, such as inconsistent measurement of alcohol use or dementia, or both, and insufficient control of potential confounders.

By contrast, heavy drinking seems detrimentally related to dementia risk, whatever the dementia type. First, ethanol and its metabolite acetaldehyde have a direct neurotoxic effect, leading to permanent structural and functional brain damage. Second, heavy drinking is associated with thiamine deficiency, leading to Wernicke–Korsakoff syndrome. Third, heavy drinking is a risk factor for other conditions that can also damage the brain, such as epilepsy, head injury, and hepatic encephalopathy in patients with cirrhotic liver disease. Fourth, heavy drinking is indirectly associated with vascular dementia because of the associations of heavy drinking with vascular risk factors such as high blood pressure, haemorrhagic stroke, atrial fibrillation, and

Research in context

Evidence before this study

Following the PRISMA guidelines, a systematic search was done using OVID to identify all work published from 2000 to Oct 3, 2017, on MEDLINE, Embase, and PsycINFO. Reviews on the effects of alcohol use on cognitive health were identified using a combination of keywords and Medical Subject Headings terms related to alcohol use, dementia, Alzheimer's disease, brain function, memory, and cognitive health (appendix pp 3–7). 23 relevant systematic reviews were identified. For light-to-moderate drinking, most reviews reported some beneficial relationships, even though alcohol use seemed to be associated with structural brain damage at moderate levels of drinking. For heavy drinking, defined by WHO and the European Medicines Agency as drinking at least 60 g of pure alcohol per day for men and at least 40 g for women, most research pointed towards a detrimental effect of alcohol on cognitive health and an increased risk of dementia. Nearly every review describes methodological problems of underlying studies, such as under-representation of heavy drinkers in population-based cohorts; inconsistent measurement of alcohol use or dementia, or both; insufficient control of potential confounders; and insufficient consideration of sample attrition in patients with alcohol use disorders.

Added value of this study

Using a representative large cohort of all patients admitted to French hospitals between 2008 and 2013, we found a strong association between alcohol use disorders and dementia. Under the age of 65 years, most prevalent cases of dementia were either alcohol related by definition, or patients qualified for a diagnosis of alcohol use disorders. Alcohol use disorders contributed markedly to dementia incidence, and were associated with all types of dementia over the lifetime. Thus, heavy drinking should be considered as one of the major risk factors for this cluster of diseases. Screening, brief interventions for heavy drinking, and treatment for alcohol use disorders should be implemented to reduce the alcohol-attributable burden of dementia.

heart failure. Finally, heavy drinking is associated with tobacco smoking, depression, and low educational attainment, which are possible risk factors for dementia. This combined evidence has led to a discussion about establishing a specific diagnosis of alcohol-related dementia;[7–9] however, alcohol use was not included in the life-course model of risk factors for dementia in the recent *Lancet* Commission on dementia prevention, intervention, and care.[1]

This study explores the effects of alcohol use disorders on dementia onset in France. Alcohol use disorders are defined by the chronic harmful use of alcohol or alcohol dependence.[10] The prevalence of alcohol use disorders in France is close to the European Union mean and markedly higher than global means.[11] We examined the sex-specific effects of alcohol use disorders on early-onset dementia (<65 years),[9,12] and investigated possible effect modification by dementia type.

Methods

Study design

The data source for this study was the French National Hospital Discharge database (Programme de Médicalisation des Systèmes d'Information), which contains all public and private claims for acute inpatient and day-case hospital admissions, post-acute care, and psychiatric care since 2008. The standardised discharge summary includes patient demographics (sex, age at entry, and postal code of residency); primary and associated discharge diagnosis codes according to the WHO International Classification of Diseases, tenth revision (ICD-10); medical procedures received; length of stay; and discharge modes (including in-hospital death). Using unique anonymous identifiers, the hospital trajectory of each patient could be traced from 2008 to 2013.[13]

We included all patients aged 20 years and older residing in metropolitan France who were discharged in the years 2008–13. Following ICD-10 taxonomy, we excluded all patients discharged with diseases that can lead to rare types of dementia (F02): infectious diseases including HIV/AIDS, hereditary metabolic disorders, hereditary neurological disorders including Huntington's disease, other neurological disorders including Parkinson's disease, and systemic connective tissue disorders. We also excluded patients with early-life mental disorders that could increase or confound dementia diagnosis, including cerebral palsy, Down's syndrome and other learning disabilities, and schizophrenia. The full coding dictionary of exclusion criteria, dementia case definitions, and risk factors assessed before dementia onset is provided in the appendix (p 14–18).

The study was approved by the French National Commission for Data Protection (CNIL DE-2015-025), who granted access to the French National Hospital Discharge database for the years 2008 to 2013. The requirement for informed consent was waived because the study used de-identified data.

Procedures

The primary exposure was alcohol use disorders and the main outcome was dementia. Dementia was defined by any primary or associated discharge diagnosis (ICD-10) codes labelling dementia (F00-F03, F05.1, F1x.73, or G30) or related to dementia (other degenerative diseases of the nervous system [G31], progressive vascular leukoencephalopathy [I67.3], or senility [R54]).[14,15]

Dementia onset was defined by the age at first dementia diagnosis recorded from 2008 to 2013; diagnoses made

before age 65 years were classed as early-onset dementia. Dementia onset was separated into three categories: alcohol-related brain damage (F10.73, G31.2); vascular dementia; and other dementia, including Alzheimer's disease. Vascular dementia was broadly defined by any record of vascular dementia, mixed dementia, or progressive vascular leukoencephalopathy as well as any dementia with a history of stroke or transient ischaemic attack.[16]

Alcohol use disorders were identified by two categories of discharge diagnosis (ICD-10) codes: mental and behavioural disorders due to former or current chronic harmful use of alcohol (F10.1–F10.9, Z50.2), including alcohol abstinence (F10.20–F10.23); or chronic diseases attributable to alcohol use disorders (eg, K70 for alcoholic liver disease).[10] Alcohol-related conditions were Wernicke-Korsakoff syndrome, end-stage liver disease and other forms of liver cirrhosis, epilepsy, and head injury.

Vascular risk factors were tobacco smoking, obesity (body-mass index ≥30 kg/m²), high blood pressure, hyperlipidaemia, and diabetes.[1] Cerebrovascular diseases included haemorrhagic stroke, ischaemic stroke, a history of stroke, a history of transient ischaemic attack, and cerebrovascular diseases other than stroke, all assessed before stroke. Other cardiovascular diseases were ischaemic heart disease, peripheral arterial disease, atrial fibrillation, and heart failure.

Educational level is not recorded in the standardised discharge summary. We used 5645 postal codes of residency as a proxy of educational level and for each geographical area compared the proportion of adults with no high school diploma in the fourth (≥67·9%) or third (61·3–67·8%) quartiles with others (Institut National de la Statistique et des Études Économiques, French census on Jan 1, 2011). Other established risk factors for dementia included depression and hearing loss.[1] Additionally, we controlled for possible risk factors for dementia, including visual impairment that might result from retinopathy or glaucoma,[1] sleep apnoea,[1] and other diseases that might lead to rare types of dementia (ie, chronic kidney disease including uraemia, hypothyroidism including myxoedema, and infectious diseases of the CNS including encephalitis).

Statistical analysis

All analyses were stratified by sex because men have shorter life expectancy and higher incidence of almost all risk factors considered. We initially studied prevalent dementia cases in 2008–13 and the distribution of alcohol-related brain damage and other alcohol use disorders by age at dementia onset. Because dementia is often associated with long diagnosis delays and associations of risk factors with dementia could be confounded by reverse causation,[17] we conservatively studied risk factors for incident dementia among patients admitted to hospital from 2011 to 2013 who had no record of dementia from 2008 to 2010.[18] The effects of alcohol use disorders and other risk factors on dementia onset, overall and by type, were estimated in multivariate Cox proportional hazards models without variable selection. Age was used as the timescale to estimate adjusted hazard ratios (HRs) and 95% CIs, with follow-up starting from Jan 1, 2011 (with independent left truncation on Jan 1, 2011) until dementia onset, in-hospital death, or right-censoring at last hospital discharge from 2011 to 2013.[17,19,20] Observed non-proportional hazards were accounted for by including all risk factors as age-varying variables; alcohol use disorders, tobacco smoking, and personal histories of conditions (head injury, stroke, transient ischaemic attack, or myocardial infarction) were considered in the risk set starting from Jan 1, 2011, and other risk factors were conservatively identified at first hospital record.[17] All Cox models were stratified by patient residency area across 21 French administrative regions (Corsica was included in the Provence-Alpes-Côte d'Azur region), having received care in a teaching hospital, and the first year of hospital admission from 2008 to 2013 to account for geographical and temporal variations in alcohol use exposure and dementia diagnosis as well as possible levels of misclassification for all variables.

We did several sensitivity analyses to ascertain the effects of alcohol use disorders on dementia onset. First, we used definitions of dementia restricted to primary discharge diagnosis codes of dementia; ICD-10 codes labelling dementia, overall or by dementia type (vascular dementia, Alzheimer's disease); and severity level (first diagnosis of mild cognitive impairment without or before dementia, first diagnosis of dementia at a severe stage). Second, we considered the full sample, while all exclusion criteria were introduced among previous covariates. Third, we selected study populations at older landmark ages on Jan 1, 2011 (≥45 years, ≥55 years, ≥65 years, ≥75 years, or ≥85 years). Finally, the effects of alcohol abstinence (in people with previous alcohol use disorders) and other uncontrolled alcohol use disorders on the risks for dementia onset and in-hospital death were contrasted over the lifetime by use of a third-order polynomial of age on Jan 1, 2011, in Cox models adjusted for proxy of educational level and vascular risk factors, and stratified by previous variables.

We did a falsification analysis in all Cox multivariate models, which relies on disease controls selected for their unknown and therefore unlikely association with an outcome.[21] If no association is found for the disease controls in a large dataset such as a national hospital discharge database, it supports the validity of the associations found for the risk factors under study. We used cancer as a control, separated into three disease categories in relation to prognosis and possible association with dementia onset: cancer or metastasis of the CNS, other non-melanoma skin cancer assessed before brain metastasis, and non-melanoma skin cancer. All analyses were done in SAS (version 9.4).

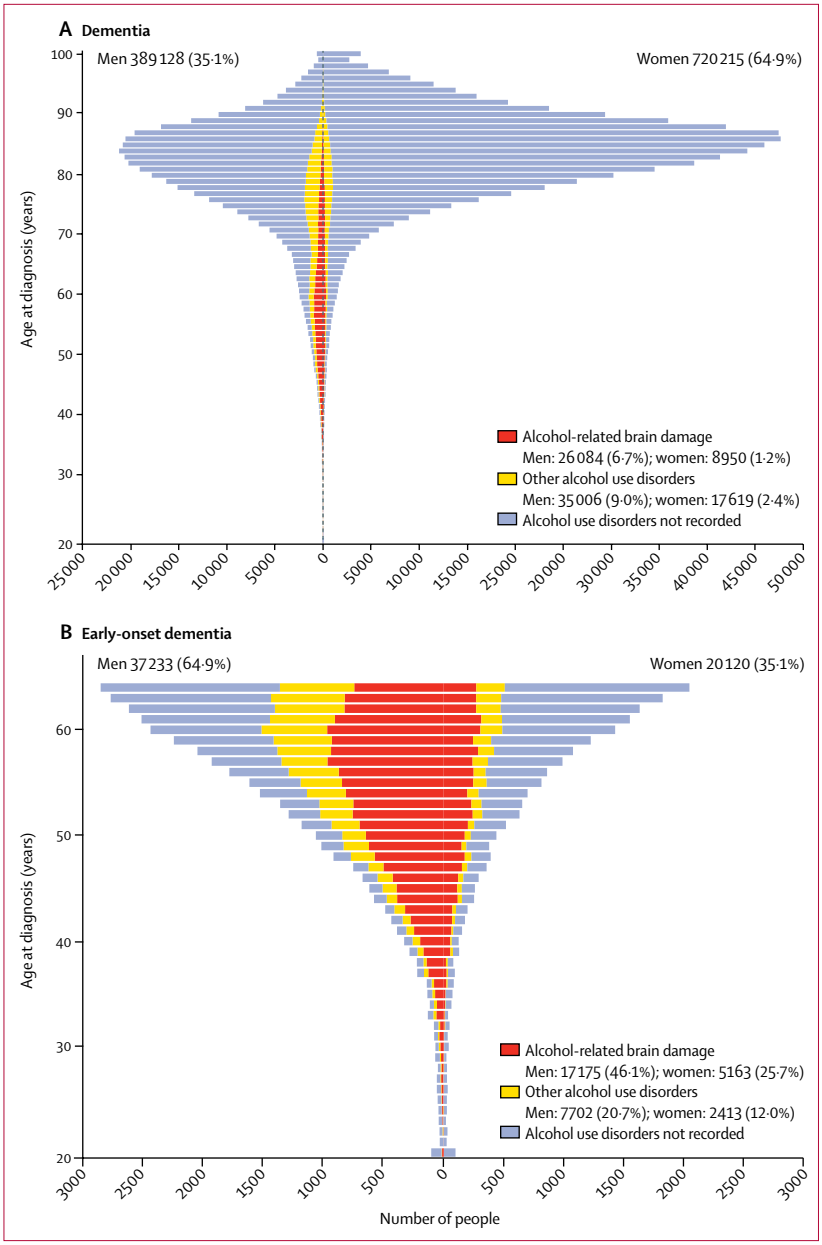

Figure 1: **Population pyramid of dementia (A) and early-onset dementia (B), overall and by alcohol use disorders**
(A) Prevalent cases of dementia (n=1 109 343). (B) Prevalent cases of early-onset dementia (n=57 353).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Of 31 624 156 adults discharged from French hospitals from 2008 to 2013, 1 328 191 (4·2%) were diagnosed with dementia (appendix p 20). We excluded 1 066 019 patients (3·4%) with diseases that can lead to rare types of dementia or with early-life mental disorders that can increase or confound dementia diagnosis (218 848 [20·5%] dementia cases; appendix p 20).

720 215 (64·9%) of the 1 109 343 dementia cases were women (figure 1). The proportion of women increased with age at dementia onset. Conversely, 37 233 (64·9%) of the 57 353 (5·2% of total) early-onset dementia cases were men.

945 512 (3·1%) of 30 558 137 adults were discharged with alcohol use disorders (712 583 [5·5%] of 12 941 788 men and 232 929 [1·3%] of 17 616 349 women), of whom 816 160 (86·3%) qualified for alcohol dependency and 140 312 (14·8%) had at least one period of alcohol abstinence in 2008–13. Alcohol-related brain damage was recorded in 35 034 dementia cases and other alcohol use disorders in 52 625 (figure 1). Both conditions were more frequently recorded in men (26 084 [74·5%] and 35 006 [66·5%], respectively; p<0·0001) and accounted for 32 453 (56·6%) of 57 353 early-onset dementia cases (22 338 [38·9%] and 10 115 [17·6%], respectively).

Of 8 295 081 men discharged from 2011 to 2013, 181 255 (2·2%) were newly diagnosed with dementia at a median age of 82 years (IQR 75–87; table). Alcohol use disorders were recorded in 512 473 (6·2%) men and 29 944 (16·5%) of men with dementia. Alcohol use disorders were associated with an increased risk for dementia onset among men (HR 3·36, 95% CI 3·31–3·41). Alcohol use disorders were the strongest modifiable risk factor for dementia onset in men (figure 2).

Regarding dementia type, 12 435 (6·9%) of 181 255 men with newly diagnosed dementia had alcohol-related brain damage at a median age of 60 years (IQR 53–69; appendix p 23). The strongest association with alcohol-related brain damage was with end-stage liver disease (3593 [28·9%], HR 27·28, 95% CI 26·00–28·61) followed by liver cirrhosis (2491 [20·0%], 23·50, 22·29–24·78). Several risk factors independently contributed to alcohol-related brain damage, in particular all alcohol-related conditions and tobacco smoking (HR >2 for all; appendix p 23).

Compared with alcohol-related brain damage, dementia onset was significantly delayed in other dementia types (p<0·0001). Of 181 255 men with newly diagnosed dementia, 69 700 (38·5%; median age 82 years, IQR 77–87) had vascular dementia (appendix p 24) and 99 120 (54·7%; 83 years, 77–87) had other dementia (appendix p 25). Alcohol use disorders were more frequently recorded in vascular dementia (11·2%) than in other dementia (9·8%; p<0·0001). In multivariate Cox analyses, alcohol use disorders remained associated with an increased risk for each dementia type (vascular dementia HR 2·30, 95% CI 2·24–2·36; other dementia 2·36, 2·31–2·42).

Of 11 474 359 women discharged from 2011 to 2013, 322 261 (2·8%) were newly diagnosed with dementia (table). Incidence of dementia was lower in women than

	Men				Women			
	All (n=8 295 081)	With dementia (n=181 255)	HR (95% CI)	p value	All (n=11 474 359)	With dementia (n=322 261)	HR (95% CI)	p value
Age on Jan 1, 2011, or at dementia onset	55 (40–68)	82 (75–87)	..	..	49 (31–67)	85 (80–89)	..	..
Alcohol use disorders	512 473 (6·2%)	29 944 (16·5%)	3·36 (3·31–3·41)	<0·0001	170 035 (1·5%)	12 730 (4·0%)	3·34 (3·28–3·41)	<0·0001
Alcohol-related conditions								
Wernicke-Korsakoff syndrome	11 196 (0·1%)	1780 (1·0%)	3·94 (3·76–4·14)	<0·0001	5878 (0·1%)	1054 (0·3%)	2·90 (2·72–3·08)	<0·0001
End-stage liver disease	109 836 (1·3%)	5964 (3·3%)	1·42 (1·38–1·46)	<0·0001	57 308 (0·5%)	3033 (0·9%)	1·07 (1·03–1·11)	<0·0001
Liver cirrhosis without end-stage liver disease	72 394 (0·9%)	5088 (2·8%)	2·08 (2·02–2·14)	<0·0001	33 681 (0·3%)	2956 (0·9%)	1·83 (1·76–1·90)	<0·0001
Epilepsy	161 931 (2·0%)	8643 (4·8%)	1·80 (1·75–1·84)	<0·0001	129 061 (1·1%)	8604 (2·7%)	1·59 (1·55–1·62)	<0·0001
Head injury	196 528 (2·4%)	9268 (5·1%)	1·45 (1·42–1·48)	<0·0001	137 684 (1·2%)	13 064 (4·1%)	1·29 (1·27–1·32)	<0·0001
Vascular risk factors								
Tobacco smoking	841 844 (10·1%)	20 162 (11·1%)	1·10 (1·08–1·11)	<0·0001	579 873 (5·1%)	7058 (2·2%)	1·16 (1·13–1·19)	<0·0001
Obesity	718 515 (8·7%)	14 465 (8·0%)	0·78 (0·76–0·79)	<0·0001	1 028 655 (9·0%)	22 484 (7·0%)	0·78 (0·77–0·80)	<0·0001
High blood pressure	2 207 728 (26·6%)	102 072 (56·3%)	1·35 (1·34–1·37)	<0·0001	2 434 589 (21·2%)	188 665 (58·5%)	1·43 (1·42–1·44)	<0·0001
Hyperlipidaemia	1 160 476 (14·0%)	34 472 (19·0%)	0·86 (0·85–0·87)	<0·0001	982 026 (8·6%)	49 190 (15·3%)	0·88 (0·87–0·89)	<0·0001
Diabetes	954 643 (11·5%)	41 571 (22·9%)	1·28 (1·26–1·30)	<0·0001	801 909 (7·0%)	54 289 (16·8%)	1·31 (1·30–1·33)	<0·0001
Cardiovascular diseases								
Haemorrhagic stroke	59 404 (0·7%)	3909 (2·2%)	1·21 (1·17–1·25)	<0·0001	50 622 (0·4%)	4079 (1·3%)	1·08 (1·04–1·11)	<0·0001
Ischaemic stroke	175 031 (2·1%)	12 391 (6·8%)	1·34 (1·32–1·37)	<0·0001	155 633 (1·4%)	16 073 (5·0%)	1·05 (1·04–1·07)	<0·0001
History of stroke	101 024 (1·2%)	11 806 (6·5%)	1·49 (1·47–1·52)	<0·0001	95 079 (0·8%)	14 191 (4·4%)	1·19 (1·17–1·21)	<0·0001
History of transient ischaemic attack	111 732 (1·3%)	6868 (3·8%)	1·02 (0·99–1·05)	0·12	116 078 (1·0%)	9761 (3·0%)	0·94 (0·92–0·96)	<0·0001
Cerebrovascular disease other than stroke	161 217 (1·9%)	7456 (4·1%)	0·91 (0·89–0·94)	<0·0001	105 211 (0·9%)	7052 (2·2%)	0·86 (0·84–0·88)	<0·0001
Ischaemic heart disease	1 137 099 (13·7%)	43 846 (24·2%)	0·83 (0·82–0·84)	<0·0001	611 264 (5·3%)	48 294 (15·0%)	0·85 (0·84–0·86)	<0·0001
Peripheral arterial disease	658 262 (7·9%)	32 398 (17·9%)	1·07 (1·05–1·08)	<0·0001	373 495 (3·3%)	31 056 (9·6%)	0·98 (0·97–1·00)	0·0108
Atrial fibrillation	696 131 (8·4%)	50 846 (28·1%)	1·19 (1·18–1·21)	<0·0001	591 857 (5·2%)	75 384 (23·4%)	1·18 (1·17–1·19)	<0·0001
Heart failure	938 578 (11·3%)	57 447 (31·7%)	1·17 (1·15–1·18)	<0·0001	734 727 (6·4%)	84 363 (26·2%)	1·11 (1·10–1·12)	<0·0001
Other risk factors for dementia								
Residency area with less education, third quartile	2 078 322 (25·1%)	45 493 (25·1%)	1·05 (1·04–1·06)	<0·0001	2 784 136 (24·3%)	77 613 (24·1%)	1·05 (1·04–1·06)	<0·0001
Residency area with less education, fourth quartile	2 143 309 (25·8%)	53 513 (29·5%)	1·07 (1·05–1·08)	<0·0001	2 805 431 (24·4%)	90 694 (28·1%)	1·08 (1·07–1·09)	<0·0001
Depression	416 341 (5·0%)	18 423 (10·2%)	1·52 (1·50–1·54)	<0·0001	845 964 (7·4%)	43 640 (13·5%)	1·27 (1·26–1·28)	<0·0001
Hearing loss	75 656 (0·9%)	7720 (4·3%)	1·74 (1·70–1·78)	<0·0001	94 960 (0·8%)	13 079 (4·1%)	1·53 (1·51–1·56)	<0·0001
Retinopathy	156 768 (1·9%)	5757 (3·2%)	0·97 (0·95–1·00)	0·064	169 418 (1·5%)	11 147 (3·5%)	0·97 (0·96–0·99)	0·0075
Glaucoma	77 205 (0·9%)	3101 (1·7%)	0·97 (0·93–1·00)	0·072	97 835 (0·9%)	5695 (1·8%)	0·90 (0·88–0·93)	<0·0001
Sleep apnoea	359 863 (4·3%)	7487 (4·1%)	0·92 (0·89–0·94)	<0·0001	195 394 (1·7%)	3984 (1·2%)	0·79 (0·76–0·81)	<0·0001
Chronic kidney failure	361 275 (4·4%)	28 401 (15·7%)	1·25 (1·23–1·26)	<0·0001	294 742 (2·6%)	37 501 (11·6%)	1·28 (1·26–1·29)	<0·0001
Hypothyroidism	105 209 (1·3%)	6738 (3·7%)	1·17 (1·15–1·20)	<0·0001	509 446 (4·4%)	31 822 (9·9%)	1·18 (1·17–1·20)	<0·0001
Infectious diseases of the CNS	18 411 (0·2%)	468 (0·3%)	1·42 (1·29–1·55)	<0·0001	19 250 (0·2%)	510 (0·2%)	1·26 (1·16–1·38)	<0·0001
Falsification analysis								
Cancer or metastasis of the CNS	54 477 (0·7%)	998 (0·6%)	0·83 (0·78–0·88)	<0·0001	46 028 (0·4%)	986 (0·3%)	0·79 (0·74–0·84)	<0·0001
Any cancer other than non-melanoma skin cancer	968 534 (11·7%)	26 480 (14·6%)	0·66 (0·65–0·67)	<0·0001	869 614 (7·6%)	23 947 (7·4%)	0·61 (0·60–0·62)	<0·0001
Non-melanoma skin cancer	129 894 (1·6%)	5296 (2·9%)	0·76 (0·74–0·78)	<0·0001	116 811 (1·0%)	5757 (1·8%)	0·70 (0·68–0·72)	<0·0001

Data are median (IQR) or number (%). Table shows adjusted HRs from multivariate Cox regressions for incident dementia (newly diagnosed at hospital in 2011–13 with no recorded dementia in 2008–10). Details of selection of the study population are provided in the appendix (p 20). HR=hazard ratio.

***Table*: Risk factors for dementia onset**

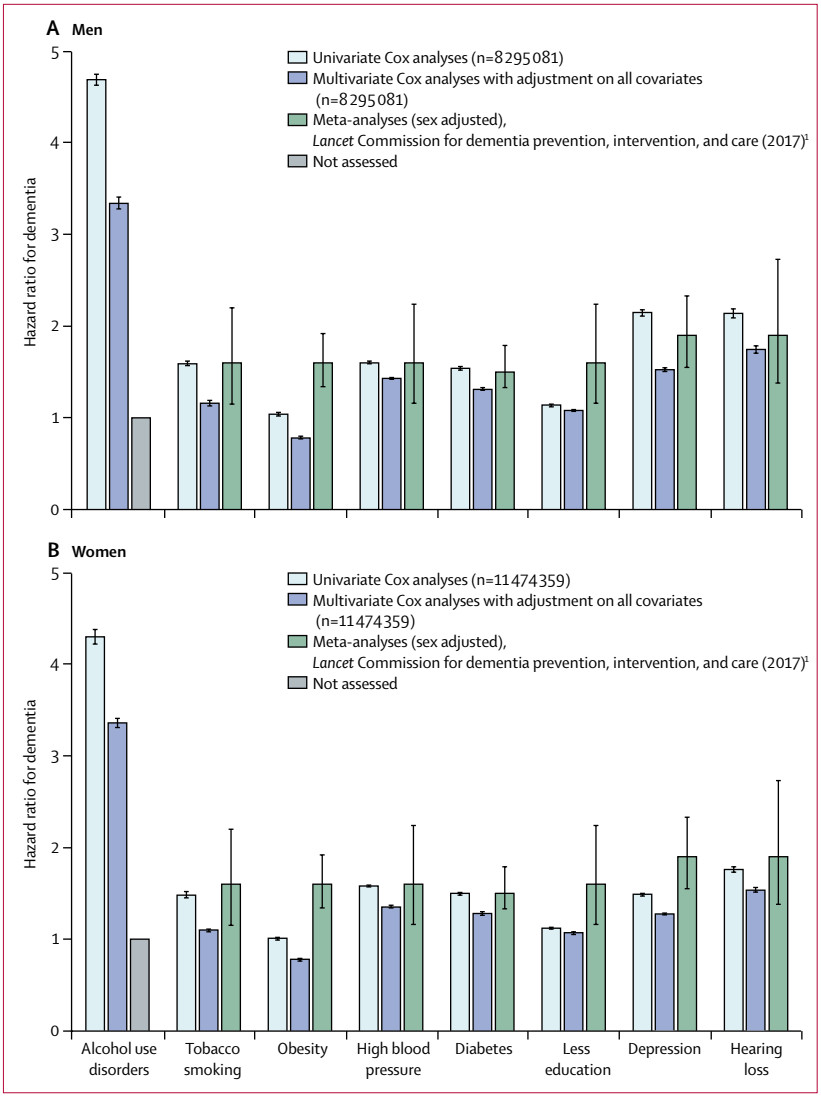

Figure 2: **Potentially modifiable risk factors for dementia among men (A) and women (B)**
Bars are 95% CIs.

men up to age 80 years (appendix p 19). Collectively, the median age at dementia onset was significantly delayed in women compared with men (85 years, IQR 80–89 *vs* 82 years, 75–87; p<0·0001), with significantly fewer reports of alcohol-related brain damage (4281 [1·3%] and 12435 [6·8%], respectively) and vascular dementia (104113 [32·3%] and 69700 [38·5%], respectively; p<0·0001).

Alcohol use disorders in women were similarly associated as in men, with an increased risk for dementia onset (HR 3·34, 95% CI 3·28–3·41) and were the strongest modifiable risk factor for dementia onset in women (figure 2). About the same independent risk factors for dementia onset were identified for both sexes (adjusted HRs >1): all alcohol-related conditions; tobacco smoking, high blood pressure, and diabetes among vascular risk factors; haemorrhagic stroke, ischaemic stroke, a history of stroke, peripheral arterial diseases (in men), atrial fibrillation, and heart failure among cardiovascular diseases; and patient residency area with less education, depression, hearing loss, chronic kidney failure, hypothyroidism, and infectious disease of the CNS among other risk factors (table).

However, except for depression and hypothyroidism, alcohol use disorders and all other independent risk factors for dementia were significantly less frequently recorded in women than in men (appendix p 21). In addition, except for alcohol use disorders, atrial fibrillation, lower education attainment, and hypothyroidism, strengths of association of the risk factors with dementia onset were significantly different between the sexes: higher in men for alcohol-related conditions, stroke, heart failure, depression, hearing loss, and infectious diseases of the CNS; and higher in women for vascular risk factors and chronic kidney failure (table; p<0·05 for all).

The main study results were generally supported by sensitivity and falsification analyses. Alcohol use disorders were strongly associated with dementia onset for any case definition of dementia (figure 3; appendix pp 27–32), and when the full sample was considered with all exclusion criteria introduced among previous covariates (appendix pp 33–34). In other sensitivity analyses in older study populations selected on Jan 1, 2011, alcohol use disorders remained strongly associated with late-onset dementia (appendix pp 35–39). Compared with uncontrolled alcohol use disorders (appendix p 40), alcohol abstinence was significantly associated with lower risks of competing mortality over the lifespan, although no risk reduction was observed for dementia onset (appendix pp 41–44). Finally, regarding the falsification analysis, none of the cancer categories was associated with dementia onset, irrespective of cancer site (table) and prognosis (appendix p 26).

Discussion

In this nationwide study, we found a marked association of alcohol use disorders with all types of dementia, even after controlling for potential confounding risk factors.[1] The overall HR for onset of all types of dementia was above 3·3, and for vascular and other dementia remained above 2·3 for both sexes. The association with alcohol use disorders was especially important in those with early-onset dementia, with most patients having alcohol-related brain damage or an additional diagnosis of alcohol use disorders. This finding corroborates other results, which suggested alcohol is a risk factor for early-onset dementia in men.[12]

The French health-care system provides not only universal, but also liberal access to hospital care with minimal out-of-pocket expenses. Consequently, more than 80% of French adults older than 65 years (50% before that age) were admitted to hospital over the 6-year study period (appendix p 45), supporting a high generalisability

of the study findings to the French population[18] as well as populations with similar exposure to the risk factors in general, and to alcohol use disorders in particular.[11]

However, several potential limitations of our study should be acknowledged, including misclassified and missing variables due to the administrative recording of data. One limitation relates to the assessment of dementia, overall and by type. Although the French claims database is subject to high levels of quality control, all ICD-10 codes of dementia recorded as secondary discharge diagnoses (except senility) would be associated with better hospital reimbursement. Indeed, only 188 841 (37·5%) of 503 516 new dementia cases were identified as the primary discharge diagnosis for both sexes (appendix p 27). However, an opportunistic, up-coding bias seems equivocal because the comparison of incidence by sex and age with the reference cohort study done in the southwest of France showed no clear differences (appendix p 19) and differences are likely to be attributed to unstable estimates caused by the small sample size in the reference cohort study (190 new dementia cases over 5 years).[22]

Diagnosis of dementia type remains probabilistic without brain autopsy, as is the case in most epidemiological studies. Accordingly, we included 122 903 new patients identified with ICD-10 codes related to dementia, because 37 951 (30·9%) were eventually diagnosed with ICD-10 codes labelling dementia in the follow-up.[15] Because of our study aim, we unconventionally prioritised alcohol-related brain damage and vascular dementia over Alzheimer's disease. Accordingly, the proportion of vascular dementia cases recorded of the 503 516 new dementia cases almost doubled from 96 252 (19·1%) with use of ICD-10 codes for vascular dementia, a rate usually reported,[23] to 173 813 (34·5%) with additional use of any record of mixed dementia or dementia with a history of stroke or transient ischaemic attack.[16] However, the main study findings were corroborated in all sensitivity analyses done on dementia case definition.

A second limitation relates to the identification of alcohol use disorders and other risk factors for dementia. Even though alcohol use disorders were identified by several sources of medical information including post-acute rehabilitation over 6 years, alcohol use disorders were most likely underestimated compared with prevalence estimates for France (16·7% for men and 5·4% for women).[11] Alcohol use disorders are highly stigmatised,[24] with low treatment rates of around 10% in Europe;[25] thus, probably only the more severe cases with alcohol dependence were recorded at hospital. However, such a bias would translate into a potential under-estimation of the effect of alcohol use disorders on dementia onset.[26]

Similarly, vascular risk factors were probably underestimated. However, except high blood pressure,[1] the effects of vascular risk factors on dementia onset are probably mediated by cerebrovascular diseases that are measured exhaustively at hospital and were adjusted for in all multivariate analyses. In this regard, we found that obesity and hyperlipidaemia were not independently associated with dementia onset, in agreement with recent reviews.[27,28]

A final limitation concerns the fact that assessments using large-scale administrative databases are typically overpowered to find statistical differences,[21] which is true for the French National Hospital Discharge database. However, we did a falsification analysis by adding cancer controls to all analyses. None of the cancer controls were associated with dementia onset, supporting the main study findings. Additionally, the effect sizes of alcohol

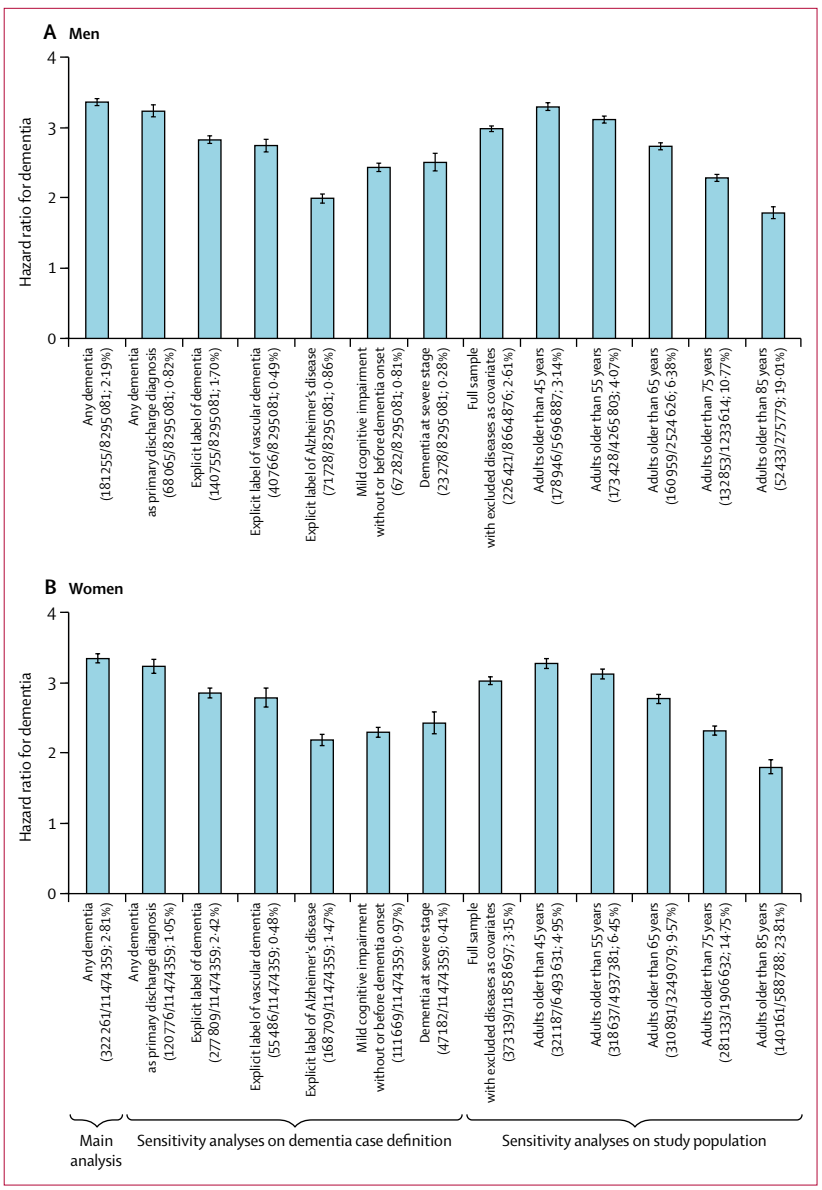

Figure 3: **Association of alcohol use disorders with dementia onset among men (A) and women (B) in sensitivity analyses (multivariate Cox analyses)**
Bars are 95% CIs.

use disorders on dementia onset were substantial and would have probably been significant in epidemiological studies with smaller sample sizes if patients with alcohol use disorders were included and alcohol exposure was assessed. Overall, although misclassification and missing variables might have biased our findings, these biases would have been mainly in the direction of underestimation.

Findings from this nationwide study suggest that the burden of dementia attributable to alcohol is much larger than previously thought. In multivariate analyses, alcohol use disorders were the strongest modifiable risk factor for dementia onset. Additionally, although alcohol abstinence was expectedly associated with a lower risk of competing death compared with uncontrolled alcohol use disorders, the study findings show that the risk for dementia onset remained unchanged after abstinence. This finding corroborates recent results showing that alcohol use directly exerts lifelong brain damage.[5,6] Finally, alcohol use disorders were associated with all other independent risk factors for dementia onset, suggesting that alcohol use disorders contribute in many ways to the risk of dementia.

In summary, our study findings support that alcohol use disorders should be recognised as a major risk factor for all types of dementia. Alcohol-related dementia should be recognised as one of the main causes of early-onset dementia.[7–9] Additionally, clinicians should be better aware of the role of alcohol use disorders in dementia onset over the lifetime, which seems to be a risk factor often omitted.[1] Early detection, brief interventions (ie, short, structured motivational interviews to support individuals to change alcohol-related behaviour), and treatment for alcohol dependence or less severe alcohol use disorders are effective and even cost-effective measures in primary care.[29] Alcohol policy measures, such as reduction of availability, increase of taxation, and ban on advertising and marketing, have also proven to be effective and cost-effective,[30] although these measures have tended not to be popular with governments. For instance, the ban on alcohol advertisements was recently repealed in France.[31] If all these measures are implemented widely, they could not only reduce dementia incidence or delay dementia onset, but also reduce all alcohol-attributable morbidity and mortality.[25]

Contributors

MS conceptualised the study, contributed to the analysis and interpretation of the data, and co-wrote the first draft of the paper. BGP and CD contributed to the clinical and epidemiological implications sections, and helped shape the overall interpretation. OSMH and JR did the systematic search and screened the results for inclusion. JR also contributed to the analysis and interpretation of the data and co-wrote the first draft of the paper.

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Declaration of interests

MS is the founder and CEO of THEN (Paris, France), which received research grants from AbbVie, Gilead, Merck, and Novartis. All other authors declare no competing interests.

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