

# Alcohol consumption and risk of dementia: the Rotterdam Study

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## Summary

**Background** Light-to-moderate alcohol consumption reduces the risk of coronary heart disease and stroke. Because vascular disease is associated with cognitive impairment and dementia, we hypothesised that alcohol consumption might also affect the risk of dementia.

**Methods** We examined the relation between alcohol consumption and risk of dementia in individuals taking part in the Rotterdam Study—a prospective population-based study of 7983 individuals aged 55 years and older. We studied all participants who did not have dementia at baseline (1990–93) and who had complete data on alcohol consumption (n=5395). Through follow-up examinations in 1993–94 and 1997–99 and an extensive monitoring system, we obtained nearly complete follow-up (99·7%) until the end of 1999. We used proportional hazards regression analysis, adjusted for age, sex, systolic blood pressure, education, smoking, and body-mass index, to compare the risk of developing dementia between individuals who regularly consumed alcohol and individuals who did not consume alcohol.

**Findings** The average follow-up was 6·0 years. During this period, 197 individuals developed dementia (146 Alzheimer's disease, 29 vascular dementia, 22 other dementia). The median alcohol consumption was 0·29 drinks per day. Light-to-moderate drinking (one to three drinks per day) was significantly associated with a lower risk of any dementia (hazard ratio 0·58 [95% CI 0·38–0·90]) and vascular dementia (hazard ratio 0·29 [0·09–0·93]). We found no evidence that the relation between alcohol and dementia varied by type of alcoholic beverage.

**Interpretation** These findings suggest that light-to-moderate alcohol consumption is associated with a reduced risk of dementia in individuals aged 55 years or older. The effect seems to be unchanged by the source of alcohol.

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## Introduction

Light-to-moderate alcohol consumption is associated with lower risks of coronary heart disease, ischaemic stroke, and total mortality in elderly men and women.<sup>1–3</sup> Since evidence is increasing that vascular disease is associated with cognitive impairment and dementia,<sup>4,5</sup> light-to-moderate alcohol intake might also reduce the risk of dementia and Alzheimer's disease. Conversely, several studies suggested a neurotoxic effect of high amounts of alcohol intake.<sup>6–8</sup> Previously, a population-based prospective study in Bordeaux, France, reported an inverse association between wine consumption and the risk of dementia.<sup>9</sup> We hypothesised that light-to-moderate alcohol intake was associated with a lower risk of dementia, and aimed to quantify the relation between alcohol consumption and the risk of dementia and subtypes of dementia; specifically, we examined whether the effect varied by type of alcoholic beverage.

## Methods

### Study population

This study was done as part of the Rotterdam Study—a population-based prospective cohort study for which residents aged 55 years and older of a suburb of Rotterdam, Netherlands, including those living in institutions, were asked to participate.<sup>10</sup> The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre Rotterdam. Participants gave written informed consent and permission to retrieve information from treating physicians.

During the baseline examination (1990–93), participants were interviewed at home by a trained research assistant. Information was obtained on current and past health, medication, lifestyle, and risk indicators for chronic diseases. The participants subsequently visited the study centre twice for clinical examinations. A food-frequency questionnaire was given to participants who attended the second visit at the study centre (n=7006). The questionnaire was not administered during the pilot phase of the Rotterdam Study (n=273) nor to nursing-home residents (n=492). Furthermore, 477 participants did not receive a dietary questionnaire because of logistical reasons, and, since people with dementia can provide unreliable answers regarding their food patterns, the questionnaire was either not administered to such individuals or was excluded from analysis afterwards (n=97). For the same reason, we excluded individuals (n=60) who were screen-positive for low cognitive function (mini mental-state examination [MMSE] score <26, or geriatric mental state [GMS] score >0) and who scored less than 80 points on the cognitive part of the Cambridge examination for mental disorders of the elderly (CAMCOG),<sup>11</sup> which is the neuropsychological test used in the case-finding procedure for dementia. Because of logical inconsistencies in the dietary interviews, 212 additional respondents were excluded

later, resulting in 5395 completed reliable questionnaires. Follow-up examinations took place in 1993–94 and 1997–99.

#### *Alcohol intake*

Before the baseline centre visits, participants received a checklist on which they indicated all foods and drinks they had consumed at least once during the preceding year. The completed checklist formed the basis of an interview at the study centre by a trained dietician. An extensive, validated semiquantitative food-frequency questionnaire was used.<sup>12,13</sup> The questionnaire comprised 170 food items and all relevant beverages, including tea, coffee, and alcohol.<sup>13</sup>

First, we asked participants whether they ever drank alcohol. If the answer was affirmative, we asked about the frequency of drinking. People who reported that they drank alcohol at least twice a month were further asked about the average amounts of specific beverages (wine, beer, liquor, and fortified wine [eg, sherry, port]) that they drank. Participants were furthermore asked if they had changed their pattern of alcohol consumption during the preceding 5 years (less than they used to drink, more than they used to drink) and if they had consumed more than six alcoholic beverages on one day during the last year (binge drinking). Average daily dietary nutrient intake was calculated by multiplication of the frequency and amount consumed for each food item by its nutrient content listed in an automated version of the Dutch Food Composition Table.<sup>14</sup>

#### *Diagnosis of dementia*

Dementia screening and diagnosis during baseline and follow-up examinations followed a three-step protocol, as described in detail elsewhere.<sup>15</sup> Briefly, all participants were screened with a short test of cognition (MMSE and GMS, organic level). Screen-positives underwent further cognitive testing, and an informant was interviewed on daily functioning of the participant. People who were suspected of having dementia were examined by a neurologist, and underwent neuropsychological testing, and, if possible, magnetic resonance imaging of the brain. Additionally, the total cohort was continuously monitored for incident dementia cases via linkage between the study database and computerised medical records from general practitioners and from the Regional Institute for Outpatient Mental Health Care (RIAGG).<sup>15</sup>

Surveillance of the population through the general practitioner and RIAGG reports continued up to Dec 31, 1999. Follow-up was virtually complete (99.7%: complete information during the first follow-up period, 18 people lost to follow-up during the second follow-up period). Of the individuals screened in person and those monitored through general practitioners and RIAGG, the study diagnosis of dementia was made according to established criteria (NINCDS-ADRDA, NINDS-AIREN, DSM-III-R) by a panel that reviewed all existing information.<sup>15–18</sup> Briefly, for the distinction between Alzheimer's disease and vascular dementia, review of the data focused on cerebrovascular disorders as determined by neurological examination or on magnetic resonance imaging; their association with the onset of dementia; the acuteness of onset and pattern of disease progression; and the distribution of cognitive deficits over the distinct domains of cognition. A cerebrovascular event that occurred less than 3 months before the onset of dementia strongly suggested a diagnosis of vascular dementia. However, the presence

of cerebrovascular disorders did not prohibit a diagnosis of Alzheimer's disease. In individuals with the clinical presentation of Alzheimer's disease, a history of stroke was regarded as not directly causally related to dementia if the stroke had occurred long before or after the onset of dementia.

#### *Other baseline measurements*

The following baseline variables were used as possible confounders: age; sex; diabetes (defined according to WHO criteria as the use of medication for diabetes or a random or post-load serum glucose concentration >11 mmol/L); systolic blood pressure (measured in sitting position at the right upper arm with a random-zero sphygmomanometer); education (dichotomised into primary education or less, and more than primary education); smoking (categorised as never, past, or current smoking); and body-mass index (weight [kg]/height [m<sup>2</sup>]). A history of stroke was assessed at baseline and afterwards through our monitoring system and verified with medical records by a neurologist. A history of myocardial infarction was assessed by direct questioning and through the monitoring system, and was verified by electrocardiography and by the patient's general practitioner or cardiologist.

Apolipoprotein E (*APOE*) genotyping was done on coded DNA samples without knowledge of the diagnosis. The PCR product was digested with the restriction enzyme *HhaI*, and fragments were separated by electrophoresis.<sup>19</sup> Homozygotes and heterozygotes for the *APOE\*4* allele were combined and designated as the *APOE\*4* category.

During the home interview, participants were asked to report and show all medication used during the week preceding the interview. Subsequently, all drugs were classified according to their corresponding anatomical-therapeutical-chemical (ATC) code.

#### *Statistical analysis*

We estimated the risk of dementia associated with alcohol consumption with Cox's proportional hazards regression analysis. We assessed alcohol as a categorical and as a continuous (number of glasses per day) variable. Since heavy alcohol consumption has neurotoxic effects and is reportedly associated with an increased risk of dementia,<sup>6–8</sup> we created a category for heavy drinking (four or more glasses per day) and categorised the rest into about equally-sized groups (no alcohol intake; less than one glass per week; one or more glasses per week but less than one per day; one to three glasses per day). No alcohol intake was used as reference category. Because of the putative different effect of high levels of alcohol intake, we repeated the analyses with alcohol as a continuous variable, excluding people who drank four or more glasses per day. All analyses were controlled for age (continuously per year) and sex.

To check whether associations could be attributed to confounding, analyses were repeated with possible confounders added to the models (education, smoking, body-mass index, diabetes, and systolic blood pressure). All analyses were repeated with dementia subtypes (Alzheimer's disease, vascular dementia) as the outcome. We checked the proportional hazards assumptions by plotting Kaplan-Meier curves and by plotting log minus log curves. To examine whether the overall effect of alcohol consumption on dementia was significant, we compared the log likelihood for the models excluding alcohol to the corresponding models including alcohol.

	Alcohol consumption				
	None*	<1 drink per week	≥1 drink per week but <1 per day	1–3 drinks per day	≥4 drinks per day
Number of individuals (number with dementia)	1113 (62)	1156 (44)	1518 (48)	1443 (38)	165 (5)
Mean (SD) age (years)	69.2 (8.1)	68.4 (7.8)	67.2 (7.7)	66.9 (7.4)	65.2 (6.4)
Number of women	836 (75%)	884 (77%)	889 (59%)	552 (38%)	22 (13%)
Mean (SD) blood pressure (mm Hg)					
Systolic	140.0 (22.8)	139.6 (21.9)	137.4 (22.2)	137.4 (21.2)	142.4 (20.8)
Diastolic	73.0 (11.2)	73.8 (11.0)	73.4 (11.2)	73.9 (11.2)	77.4 (10.7)
Smoking status					
Never	522 (47%)	554 (48%)	511 (34%)	211 (15%)	10 (6%)
Past	368 (33%)	402 (35%)	680 (45%)	787 (55%)	68 (41%)
Current	219 (20%)	196 (17%)	323 (21%)	432 (30%)	87 (53%)
Mean (SD) body-mass index (kg/m <sup>2</sup> )	26.6 (4.2)	26.6 (3.9)	26.6 (3.5)	26.0 (3.2)	26.1 (3.6)
Number with diabetes†	159 (15%)	88 (8%)	95 (6%)	134 (10%)	24 (15%)
Number with primary education or less†	509 (46%)	436 (38%)	467 (31%)	395 (28%)	47 (29%)
Number with APOE*4 allele present†	317 (30%)	283 (26%)	394 (27%)	397 (29%)	35 (22%)

\*Including 28 participants who reported using alcohol less than twice a month. These individuals did not differ from non-drinkers with respect to age, sex, smoking status, or educational level.

†Proportion calculated based on actual number of individuals with data on this variable.

Table 1: Baseline characteristics of participants in the Rotterdam Study

We examined possible effect modification by sex, age, smoking, education, or APOE genotype, through stratified analyses. Furthermore, we tested for statistical interaction by adding interaction terms to the regression models: sex×alcohol intake category; age (continuously)×alcohol intake category; smoking (categorical)×alcohol intake category; education (categorical)×alcohol intake category; APOE (categorical: APOE\*4 present or absent)×alcohol intake category.

The risk of dementia and dementia subtypes associated with specific types of alcoholic beverages was analysed as follows. For each individual, we expressed the amount of intake of wine, beer, liquor, and fortified wine as a percentage of that individual's total alcohol intake. Next, we added these alcohol-type-specific variables to the model that already contained amount of alcohol intake in categories as described above. The change in likelihood between the model with total amount of alcohol and the model with total amount as well as type of alcohol reflects whether the risk of dementia was dependent on specific alcoholic beverages beyond any effect of alcohol itself. The risk of dementia associated with intake of specific types of beverages (beer, liquor, and fortified wine) was expressed relative to the risk associated with wine drinking.

To check whether any observed relation between alcohol intake and risk of dementia was due to selection bias in the reference group (no alcohol intake), we repeated the analyses excluding those who reported use of medication in which alcohol intake was contraindicated (anxiolytics, antidepressants, and hypnotics). Additionally, we excluded participants with a history of alcoholism (n=4) and those with alcohol consumption less than twice a month (n=28). Cardiovascular disease might make people change their alcohol intake, and hence we also repeated the analyses excluding those with diagnosed myocardial infarction or stroke at baseline (n=715) and those who used antihypertensive medication at baseline (n=1646).

Finally, we repeated the analyses excluding participants who reported a change in their pattern of alcohol consumption in the past 5 years, since reported intake over the past year might not accurately reflect habitual intake over a longer period.

#### Role of the funding source

The study sponsors had no involvement in study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

## Results

During 32 341 person-years of follow-up (mean follow-up 6.0 years), 197 participants developed dementia (incidence rate 6.1/1000 person-years). Alzheimer's disease was diagnosed in 146 (74%) patients (134 without and 12 with cerebrovascular disease), vascular dementia was diagnosed in 29 (15%) patients, and 22 (11%) were diagnosed with other types of dementia (including eight with Parkinson's disease dementia).

Table 1 shows the baseline characteristics of the study population according to categories of alcohol consumption. Median alcohol consumption was 0.29 glasses per day (IQR 0.01–1.24), and was higher for men (0.87, 0.15–2.24) than for women (0.11, 0.00–0.73). With increasing alcohol intake, the proportion of never smokers and less-educated individuals sharply decreased. Table 2 shows the distribution of consumption of alcoholic beverages in the study population. Beer and liquor were mainly consumed by men. Fortified wine was mainly consumed by women.

Alcohol consumption was associated with a lower risk of dementia. The deviance for a model including alcohol was 4.08 when alcohol was analysed as a continuous variable (p=0.04) and 6.48 when it was analysed as a categorical variable (p=0.166), compared with a model excluding alcohol. The overall effect of alcohol consumption in categories on the risk of dementia is

	Beer		Wine		Liquor		Fortified wine	
	Number of individuals	Median (IQR) drinks/day	Number of individuals	Median (IQR) drinks/day	Number of individuals	Median (IQR) drinks/day	Number of individuals	Median (IQR) drinks/day
Total	1132 (21%)	0.31 (0.09–0.95)	1994 (37%)	0.14 (0.05–0.47)	1886 (35%)	0.90 (0.18–2.49)	1745 (32%)	0.22 (0.06–0.87)
Men	980 (44%)	0.34 (0.10–1.10)	655 (30%)	0.24 (0.06–0.59)	1338 (61%)	1.25 (0.36–2.49)	395 (18%)	0.26 (0.07–0.87)
Women	152 (5%)	0.14 (0.07–0.38)	1339 (42%)	0.12 (0.04–0.44)	548 (17%)	0.41 (0.08–1.30)	1350 (42%)	0.17 (0.04–0.75)

Table 2: Distribution of alcohol intake over subtypes of alcoholic beverage in the Rotterdam Study

Dementia subtype	Hazard ratio (95% CI)				
	No alcohol	<1 drink per week	≥1 drink per week but <1 per day	1–3 drinks per day	≥4 drinks per day
<b>All dementia* (n=197)</b>					
Total	1.00	0.82 (0.56–1.22)	0.75 (0.51–1.11)	0.58 (0.38–0.90)	1.00 (0.39–2.59)
Men	1.00	0.60 (0.27–1.34)	0.53 (0.28–1.00)	0.40 (0.21–0.74)	0.88 (0.32–2.44)
Women	1.00	0.91 (0.58–1.44)	0.91 (0.55–1.49)	0.85 (0.47–1.57)	..‡
<b>Alzheimer's disease* (n=146)</b>					
Total	1.00	0.91 (0.58–1.44)	0.91 (0.58–1.44)	0.72 (0.43–1.20)	1.17 (0.35–3.55)
Men	1.00	0.40 (0.11–1.50)	0.81 (0.35–1.86)	0.52 (0.22–1.20)	1.16 (0.30–4.47)
Women	1.00	1.05 (0.64–1.72)	0.92 (0.53–1.62)	0.96 (0.49–1.85)	..‡
<b>Vascular dementia† (n=29)</b>					
Total	1.00	0.79 (0.30–2.08)	0.36 (0.12–1.08)	0.30 (0.10–0.92)	1.53 (0.31–7.56)
Men	1.00	1.19 (0.30–4.80)	0.33 (0.07–1.46)	0.29 (0.07–1.18)	1.71 (0.31–9.51)
Women	1.00	0.54 (0.13–2.16)	0.46 (0.09–2.29)	0.40 (0.05–3.34)	..‡
<b>Other dementia† (n=22)</b>					
Total	1.00	0.39 (0.10–1.46)	0.49 (0.17–1.46)	0.37 (0.11–1.18)	..‡
Men	1.00	0.42 (0.08–2.18)	0.17 (0.03–0.88)	0.25 (0.07–0.92)	..‡
Women	1.00	0.34 (0.04–3.27)	1.57 (0.35–7.15)	0.68 (0.07–6.64)	..‡

\*Adjusted for age, sex, body-mass index, systolic blood pressure, diabetes, smoking, and education. †Adjusted for age and sex only. The fully adjusted models, though over-fitted, yielded nearly identical results. ‡None of the individuals in these groups had dementia at follow up.

Table 3: Hazard ratios of dementia and subtypes of dementia according to alcohol consumption

shown in table 3. Compared with no alcohol consumption, light-to-moderate drinking (one to three drinks per day) was associated with a significantly lower risk of dementia. The effect of light-to-moderate drinking seemed most prominent among men (age-adjusted hazard ratio 0.39 [0.21–0.72]) for men, 0.80 [0.45–1.45] for women), yet the statistical interaction between sex and alcohol consumption was far from significant ( $p=0.49$ ). We also found no significant interactions with age ( $p=0.09$ ), smoking ( $p=0.71$ ), or level of education ( $p=0.14$ ).

For vascular dementia and other dementia, we had a limited number of cases and hence only adjusted for age and sex in order not to over-fit our models. However, the hazard ratios from the fully adjusted models were nearly identical to those from the models we only adjusted for age and sex. Analyses related to subtypes of dementia showed that the effect of alcohol was mainly present for vascular dementia (table 3). When alcohol was analysed as a continuous variable, the hazard ratio adjusted for education, smoking, body-mass index, diabetes, and systolic blood pressure was 0.86 (0.73–1.00) per glass of alcohol per day when we included the entire range of alcohol consumption (men 0.86 [0.71–1.04], women 0.90 [0.67–1.19]), and 0.79 (0.65–0.96) per glass of alcohol per day when we excluded heavy drinkers who consumed four or more glasses per day (men 0.75 [0.58–0.96], women 0.91 [0.68–1.23]).

Table 4 shows the relation between light-to-moderate alcohol consumption and risk of dementia according to

absence or presence of an *APOE\*4* allele. Light-to-moderate alcohol consumption seemed to be associated with a lower risk of vascular dementia in the absence and presence of the *APOE\*4* allele; however the confidence intervals were wide owing to the small sample size. The association with alcohol seen for overall dementia and for Alzheimer's disease was achieved with lower amounts of alcohol intake in carriers of the *APOE\*4* allele. However, the interaction term was not significant (overall dementia  $p=0.23$ ).

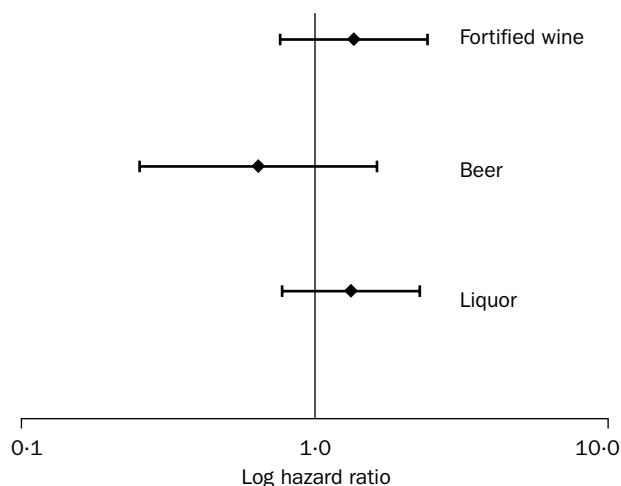
We found no support for the hypothesis that the risk of dementia or subtypes of dementia varied according to the type of alcoholic beverage consumed. A model in which we included specific types of alcoholic beverages (wine, beer, liquor, and fortified wine) as well as different amounts of alcohol was not significantly better than a model without specific types of alcoholic beverages ( $p=0.40$ ). This finding is also reflected in the figure, which shows the hazard of dementia associated with drinking beer, liquor, or fortified wine relative to that associated with wine drinking, controlling for total amount of alcohol intake.

Only 346 (6%) participants reported a change in drinking pattern during the previous 5 years. A higher proportion of people with changed drinking patterns reported drinking less (5%) than drinking more (1%). The results essentially did not change with iterative exclusion of participants with changed drinking patterns, those with a history of alcoholism (0.1%), those who drank less than twice a month (0.5%), or those who were

Dementia subtype	Hazard ratio (95% CI)*†			
	No alcohol	<1 drink per week	≥1 drink per week but <1 per day	1–3 drinks per day‡
<b>All dementia</b>				
<i>APOE*4</i> absent (n=99)	1.00	1.03 (0.60–1.78)	1.07 (0.62–1.85)	0.53 (0.27–1.02)
<i>APOE*4</i> present (n=89)	1.00	0.71 (0.40–1.25)	0.46 (0.25–0.84)	0.56 (0.32–1.00)
<b>Alzheimer's disease</b>				
<i>APOE*4</i> absent (n=75)	1.00	1.26 (0.67–2.37)	1.39 (0.73–2.64)	0.67 (0.31–1.46)
<i>APOE*4</i> present (n=65)	1.00	0.69 (0.35–1.34)	0.46 (0.23–0.94)	0.60 (0.30–1.21)
<b>Vascular dementia§</b>				
<i>APOE*4</i> absent (n=13)	1.00	0.91 (0.24–3.43)	0.55 (0.13–2.42)	0.17 (0.02–1.55)
<i>APOE*4</i> present (n=13)	1.00	0.78 (0.19–3.27)	0.26 (0.05–1.37)	0.26 (0.06–1.17)

\*Adjusted for age, sex, body-mass index, systolic blood pressure, diabetes, smoking, and education. †*APOE* status was not determined in 226 individuals (four with dementia). ‡Because only five people with incident dementia consumed four or more drinks per day, we could not obtain reliable estimates for this category. §Adjusted for age and sex only. The fully adjusted models, though over-fitted, yielded nearly identical results.

Table 4: Hazard ratios of dementia and subtypes of dementia according to alcohol consumption, stratified for *APOE\*4* status



#### Hazard of dementia associated with drinking beer, liquor, or fortified wine relative to that associated with wine drinking

binge drinkers (6.2%). The hazard ratio for light-to-moderate drinking after exclusion of participants with changed drinking patterns was 0.57 (95% CI 0.36–0.89), and after exclusion of binge drinkers was 0.56 (0.36–0.88).

The hazard ratio did not change much after exclusion of people with prevalent stroke or myocardial infarction at baseline (hazard ratio light-to-moderate drinking 0.55 [0.33–0.92]), but slightly decreased after exclusion of participants who used antihypertensive medication (0.48 [0.27–0.86]). Use of medications that contraindicated alcohol consumption (anxiolytics, hypnotics, and antidepressants) was reported by 691 (13%) participants. Again, exclusion of these individuals did not alter the results appreciably (0.60 [0.37–0.98]).

#### Discussion

We found that, in this population of individuals aged 55 years or older, those who consumed up to three glasses of alcohol per day had a lower risk of dementia and vascular dementia than those who never drank alcohol.

Some limitations of this study have to be considered. Alcohol consumption was based on a semiquantitative food-frequency questionnaire. Although assessment of alcohol intake embedded in a food-frequency questionnaire shows high reproducibility,<sup>20,21</sup> under-reporting and over-reporting are possible. Several studies report that errors are, in general, linearly related to intake.<sup>22</sup> If under-reporting is indeed linearly related to the level of intake, serious bias in estimates of health risk can occur, but ranking of individuals according to their alcohol intake is still possible. Because of this under-reporting, the amounts of alcohol consumption associated with certain health risks might in fact be higher than those indicated.

An important feature of the Rotterdam Study is that alcohol intake was assessed at baseline, before the onset of dementia. To obtain reliable data, we administered our food-frequency questionnaire only to people who were living independently and had good cognitive function. This practice resulted in a relatively healthy cohort of older individuals, which was reflected in a lower incidence of dementia than in the cohort as a whole.<sup>23</sup> Therefore, cognitive impairment is unlikely to have influenced alcohol intake at baseline. Since we had

nearly complete follow-up, selection bias did not play a part in our findings.

Several mechanisms could be responsible for the inverse relation between consumption of up to three alcoholic drinks a day and dementia. One possibility is that alcohol might act through reduction of cardiovascular risk factors,<sup>1–3</sup> either through an inhibitory effect of ethanol on platelet aggregation,<sup>24</sup> or through alteration of the serum lipid profile.<sup>25</sup> Our finding that the lower risk was seen mainly for vascular dementia is in agreement with this hypothesis. A second possibility is that alcohol might have a direct effect on cognition through release of acetylcholine in the hippocampus. There is substantial evidence that acetylcholine facilitates learning and memory.<sup>26</sup> The effect of alcohol on acetylcholine release in the hippocampus is thought to be biphasic: in rats, a low concentration of alcohol (0.8 g/kg) stimulated acetylcholine release, whereas higher alcohol concentrations (2.4 g/kg) were inhibitory.<sup>27</sup> This mechanism might explain our finding that alcohol intake of up to three glasses a day was associated with a lower risk of dementia, whereas higher intake was not.

The analyses stratified by *APOE* genotype suggested an interaction between this variable and alcohol consumption. The fact that the interaction was not significant might either reflect low power or real absence of interaction. Evidence for a mediating effect of apolipoprotein E in the relation between alcohol and cognitive function has been suggested in one study,<sup>28</sup> but was not confirmed in another.<sup>29</sup> Oxidation of apolipoprotein E allows it to bind  $\beta$  amyloid, which is thought to increase plaque formation among carriers of the *APOE\*4* allele.<sup>30</sup> The antioxidative effect of alcohol could suppress this binding.<sup>31</sup> Alternatively, since *APOE\*4* is associated with lower concentrations of HDL cholesterol and higher concentrations of LDL cholesterol, light-to-moderate alcohol consumption might protect against dementia by improving the lipid profile of *APOE\*4* carriers.<sup>32</sup> Further studies are needed to clarify the relation between apolipoprotein E and alcohol consumption.

Previously, the PAQUID study in Bordeaux, France,<sup>9</sup> reported that wine consumption is associated with a lower risk of dementia, but our data did not suggest a different effect of specific types of alcoholic beverages beyond the effect of alcohol itself. However, wine was the only source of alcohol reported by more than 95% of the regular drinkers in the PAQUID study. Therefore, it was unable to distinguish between sources of alcohol intake. The detailed food frequency questionnaire in our study enabled us to examine various amounts and different sources of alcohol intake. Our observations are consistent with recent findings of the Canadian Study of Health and Aging<sup>33</sup> and with findings from several studies on coronary heart disease.<sup>1,34</sup>

#### Contributors

Annemieke Ruitenberg examined participants for presence of dementia, analysed data, and wrote the initial draft of the paper. Kala Mehta contributed to data analysis and drafting of the paper. John van Swieten was the study neurologist and supervised the team that diagnosed dementia. Jacqueline Witteman, Cornelia van Duijn, Albert Hofman, and Monique Breteler are principal investigators of, respectively, cardiovascular, genetic, overall, and neurological research in the Rotterdam Study, and contributed to hypothesis generation and study design. Monique Breteler supervised the study. All authors contributed to data interpretation and the final version of the paper.

#### Conflict of interest statement

None declared.

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**References**

- Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? *BMJ* 1996; **312**: 731-36.
- Berger K, Ajani UA, Kase CS, et al. Light-to-moderate alcohol consumption and risk of stroke among US male physicians. *N Engl J Med* 1999; **341**: 1557-64.
- Doll R, Peto R, Hall E, Wheatley K, Gray R. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *BMJ* 1994; **309**: 911-18.
- Skoog I. Status of risk factors for vascular dementia. *Neuroepidemiology* 1998; **17**: 2-9.
- Breteler MMB, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. *BMJ* 1994; **308**: 1604-08.
- Saunders PA, Copeland JR, Dewey ME, et al. Heavy drinking as a risk factor for depression and dementia in elderly men: findings from the Liverpool longitudinal community study. *Br J Psychiatry* 1991; **159**: 213-16.
- Joyce EM. Aetiology of alcoholic brain damage: alcoholic neurotoxicity or thiamine malnutrition? *Br Med Bull* 1994; **50**: 99-114.
- Fratiglioni L, Ahlborn A, Viitanen M, Winblad B. Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. *Ann Neurol* 1993; **33**: 258-66.
- Orgogozo JM, Dartigues JF, Lafont S, et al. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. *Rev Neurol (Paris)* 1997; **153**: 185-92.
- Hofman A, Grobbee DE, de Jong PTVM, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991; **7**: 403-22.
- Roth M, Tym E, Mountjoy CQ, et al. CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry* 1986; **149**: 698-709.
- Goldbohm RA, van den Brandt PA, Brants HA, et al. Validation of a dietary questionnaire used in a large-scale prospective cohort study on diet and cancer. *Eur J Clin Nutr* 1994; **48**: 253-65.
- Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, et al. Dietary assessment in the elderly: validation of a semiquantitative food frequency questionnaire. *Eur J Clin Nutr* 1998; **52**: 588-96.
- NEVO-table. Dutch food composition table, 1993. The Hague: Voorlichtingsbureau voor de Voeding, 1993.
- Ott A, Breteler MMB, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia: the Rotterdam Study. *Am J Epidemiol* 1998; **147**: 574-80.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd edn. Washington, DC: American Psychiatric Association, 1987.
- Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; **43**: 250-60.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34**: 939-44.
- Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. *Lancet* 1991; **337**: 1158-59.
- Byers T, Marshall J, Anthony E, Fiedler R, Zielezny M. The reliability of dietary history from the distant past. *Am J Epidemiol* 1987; **125**: 999-1011.
- Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985; **122**: 51-65.
- Feunekes GI, van't Veer P, van Staveren WA, Kok FJ. Alcohol intake assessment: the sober facts. *Am J Epidemiol* 1999; **150**: 105-12.
- Ruitenbergh A, Ott A, Swieten van JC, Hofman A, Breteler MMB. Incidence of dementia: does gender make a difference? *Neurobiol Aging* (in press).
- Fenn CG, Littleton JM. Inhibition of platelet aggregation by ethanol in vitro shows specificity for aggregating agent used and is influenced by platelet lipid composition. *Thromb Haemost* 1982; **48**: 49-53.
- Miller NE, Bolton CH, Hayes TM, et al. Associations of alcohol consumption with plasma high density lipoprotein cholesterol and its major subfractions: the Caerphilly and Speedwell Collaborative Heart Disease Studies. *J Epidemiol Commun Health* 1988; **42**: 220-25.
- Perry E, Walker M, Grace J, Perry R. Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends Neurosci* 1999; **22**: 273-80.
- Henn C, Loffelholz K, Klein J. Stimulatory and inhibitory effects of ethanol on hippocampal acetylcholine release. *Arch Pharmacol* 1998; **357**: 640-47.
- Carmelli D, Swan GE, Reed T, Schellenberg GD, Christian JC. The effect of apolipoprotein E epsilon4 in the relationships of smoking and drinking to cognitive function. *Neuroepidemiology* 1999; **18**: 125-33.
- Dufouil C, Tzourio C, Brayne C, Berr C, Amouyel P, Alperovitch A. Influence of apolipoprotein E genotype on the risk of cognitive deterioration in moderate drinkers and smokers. *Epidemiology* 2000; **11**: 280-84.
- Strittmatter WJ, Weisgraber KH, Huang DY, et al. Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. *Proc Natl Acad Sci USA* 1993; **90**: 8098-102.
- Goldberg DM, Hahn SE, Parkes JG. Beyond alcohol: beverage consumption and cardiovascular mortality. *Clin Chim Acta* 1995; **237**: 155-87.
- Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis* 1988; **8**: 1-21.
- Hebert R, Lindsay J, Verreault R, Rockwood K, Hill G, Dubois MF. Vascular dementia: incidence and risk factors in the Canadian Study of Health and Aging. *Stroke* 2000; **31**: 1487-93.
- Klatsky AL, Friedman GD, Armstrong MA. The relationships between alcoholic beverage use and other traits to blood pressure: a new Kaiser Permanente study. *Circulation* 1986; **73**: 628-36.