Alcohol intake in relation to brain magnetic resonance imaging findings in older persons without dementia[1–3]

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ABSTRACT

Background: Consumers of light-to-moderate amounts of alcohol have a lower risk of dementia and, possibly, Alzheimer disease than do abstainers. Because vascular disease may contribute to symptoms of Alzheimer disease, reduction of cerebrovascular disease in consumers of light amounts of alcohol could account for that observation. However, a low concentration of alcohol may also have direct effects on the hippocampus, a brain structure highly affected by Alzheimer disease.

Objective: We investigated alcohol intake in relation to brain magnetic resonance imaging (MRI) findings of presumed vascular origin (ie, white matter lesions and infarcts) and findings more specifically found in early Alzheimer disease (ie, hippocampal and amygdalar atrophy).

Design: In a population-based sample of 1074 older persons without dementia (aged 60–90 y), we made brain MRIs from which we rated white matter lesions and brain infarcts. In a subset of 509 people, hippocampal and amygdalar volumes on MRI were measured. Alcohol intake was assessed by using a structured questionnaire. We categorized alcohol intake as lifetime abstention and very light (<1 drink/wk), light (≥1 drink/wk to <1 drink/d), moderate (≥1 drink/d to <4 drinks/d), and heavy (≥4 drinks/d) intakes.

Results: Persons whose alcohol consumption was light to moderate had less severe white matter lesions and brain infarcts on MRI than did abstainers or heavy drinkers. Abstainers and very light drinkers had smaller hippocampal and amygdalar volumes on MRI than did light-to-moderate drinkers, but only if the former carried an apolipoprotein (*APOE*) ε4 allele.

Conclusion: Light-to-moderate alcohol intake is associated with a lower prevalence of vascular brain findings and, in *APOE* ε4 carriers, hippocampal and amygdalar atrophy on MRI. *Am J Clin Nutr* 2004;80:992–7.

KEY WORDS Alcohol, Alzheimer disease, brain, hippocampus, amygdala, magnetic resonance imaging

INTRODUCTION

Several prospective, population-based studies have shown that persons with light-to-moderate consumption of alcohol have a lower risk of dementia than do persons who abstain or have heavy alcohol use (1–4). Most studies find a relation with vascular dementia (2, 4, 5) that is consistent with the known beneficial effects of light-to-moderate alcohol consumption on vascular risk profile (6) and risk of stroke (7). Vascular disease likely contributes to the clinical syndrome in a large proportion of elderly Alzheimer patients (8, 9). A plausible explanation for the associations that are seen between alcohol consumption and overall dementia or Alzheimer disease (3, 4, 10) is that they have to do with an effect on vascular disease. Alternatively, alcohol in low amounts could have stimulatory effects on the release of acetylcholine in the hippocampus (11), and other nonvascular mechanisms might play a role (12). A nonvascular relation between alcohol intake and Alzheimer disease was indeed suggested by our observation in the Rotterdam Study that alcohol intake seemed to be associated with Alzheimer disease only in carriers of the apolipoprotein (*APOE*) ε4 allele (2), which is the risk allele for Alzheimer disease (13).

To further investigate what could underlie the relation between alcohol intake and risk of dementia, we decided to focus on the relation between alcohol intake and structural brain findings on magnetic resonance imaging (MRI) of older persons without dementia. We hypothesized that, if the effect of alcohol on dementia risk purely had to do with an effect on vascular disease, we would see a relation between alcohol intake and markers of cerebrovascular disease [eg, brain infarcts and white matter lesions (9, 14–16)], but not between alcohol intake and putative presymptomatic MRI markers of Alzheimer disease [eg, hippocampal and amygdalar atrophy (17–22)]. We investigated this hypothesis in the population-based Rotterdam Scan Study.

SUBJECTS AND METHODS

Study sample

This study was based on data collected in the Rotterdam Scan Study, a population-based cohort study designed to investigate the determinants of age-related brain changes as seen on MRI and their consequences (23). The study protocol has been described in detail elsewhere (24). The study's baseline examinations were

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conducted in1995 and 1996. At that time, we made a random selection in strata of age (5 y) and sex of 1904 persons aged 60–90 y originating from 2 population cohort studies. We excluded from this sample persons with dementia, according to the protocol of the Rotterdam Study (25) for detecting dementia. Briefly, this stepwise protocol started with a cognitive screen with the Mini-Mental State Examination and Geriatric Mental Schedule organic part A. Persons who were positive on screening underwent further neuropsychological testing and, if indicated, were examined by a neurologist. After the exclusion of persons with dementia or contraindications to MRI [eg, claustrophobia or the presence of implanted metal clips (for cerebral aneurysms) or a pacemaker], 1717 persons were eligible, of whom 1077 participated and gave written informed consent (participation rate: 63%; mean age: 72.2 y; proportion of women: 52%). All 1077 persons underwent MRI sequences for assessment of white matter lesions and brain infarcts. In a subset of 563 of these 1077, the MRI was done with the use of a unit (Siemens, Erlangen, Germany) that allowed us to include a 3-dimensional (3-D) MRI sequence needed for the assessment of hippocampal and amygdalar volumes. The Medical Ethics Committee of Erasmus Medical Center approved the study protocol.

Alcohol intake

A physician used a structured questionnaire to evaluate the alcohol intake of each participant at baseline. Alcohol intake was coded as lifetime abstention, former drinking, and current drinking (defined as having consumed alcohol during the past 12 mo). Current and former drinkers were asked about the amount of their alcohol consumption. The amount assessed with this questionnaire correlated well with the information obtained from a food-frequency questionnaire administered in part of the sample 5 y earlier (Pearson's $r = 0.72$, $P < 0.01$; 26). We categorized current alcohol drinkers as very light (<1 drink/wk), light (≥ 1 drink/wk to <1 drink/d), moderate (≥ 1 drink/d to <4 drinks/d), and heavy (≥ 4 drinks/d) drinkers, as in our previous report on dementia (2). One alcoholic drink (a glass of beer, wine, fortified wine, or spirits) was considered to contain ≈ 13 g alcohol. Binge drinking was defined as drinking ≥ 6 glasses in 1 d during the 6 mo before the interview. For 3 participants, information on alcohol intake was missing.

MRI acquisition

All 1077 participants underwent axial T1-, T2-, and proton density–weighted brain MRI scanning with a 1.5-Tesla unit (Philips, Best, Netherlands, or Siemens) at baseline (24). Only the Siemens MRI unit, in which 563 participants had their MRI scan, allowed us also to include a custom-made 3-D MRI sequence (half-Fourier Acquisition Single-Shot Turbo-Spin Echo; 27) needed for volumetric assessment of the hippocampus and amygdala. Fifty-two of the 563 participants experienced claustrophobia during the MRI scan, and 2 others provided no information on alcohol intake, which left 509 participants with information on alcohol intake and hippocampal and amygdalar volumes.

Cerebrovascular disease on MRI

MRI measurements were performed by investigators who were blinded to clinical information of the participants (24, 28). White matter lesions were considered present if visible as hyperintense on proton-density–and T2-weighted images, without prominent hypointensity on T1-weighted scans. Periventricular white matter lesions were scored semiquantitatively from 0 to 9, and subcortical white matter lesions were counted in different size categories to approximate a total lesion volume (in mL; 24). We defined infarcts as focal hyperintensities on T2-weighted images. Infarcts in the white matter also were required to have corresponding hypointensities on T1-weighted images to distinguish them from white matter lesions. Infarcts on MRI were classified as silent or symptomatic (28).

Hippocampal and amygdalar volumes on MRI

We constructed a series of coronal brain slices (contiguous 1.5-mm slice thickness) from the 3-D MRI, which were aligned to be perpendicular to the long axis of the hippocampus. We manually traced the boundaries of the hippocampus and amygdala on both sides on each slice by using a mouse-driven cursor (27). The summed surface areas were multiplied by slice thickness to yield estimates of the hippocampal and amygdalar volumes (mL). The left- and right-sided volumes were summed to yield the total hippocampal and amygdalar volumes. As a proxy for head size, we measured on the middle sagittal MRI slice the intracranial cross-sectional area (27). We corrected for head size differences among subjects by dividing the uncorrected volumes by the subject's calculated head size area and subsequently multiplying this ratio by the average head size area (separately for men and women; 29, 30).

Covariates

The following covariates were assessed at baseline by interview and physical examination: pack-years of cigarette smoking, educational level, body mass index (BMI; in kg/m^2), diabetes mellitus, and hypertension (28). *APOE* genotype testing was performed (31) and available for 969 participants in the total sample and 436 participants in the subset with hippocampal and amygdalar volume assessment; testing was not performed in the rest of the subjects, mainly because no blood from them was available. Participants were classified as carriers or noncarriers of an *APOE* $\epsilon 4$ allele; those with genotype *APOE* $\epsilon 2\epsilon 4$ ($n = 22$ in the total sample and 9 in the subsample) were excluded from analyses considering *APOE* genotype.

Statistical analysis

The analyses of alcohol intake and white matter lesions and infarcts were based on 1074 persons, and the analyses of alcohol intake and hippocampal and amygdalar volumes were based on the subset of 509 persons. We used multivariable linear regression to quantify the association between alcohol-intake categories and white matter lesions and hippocampal and amygdalar volumes. With logistic regression, we calculated the adjusted odds ratio (95% CI) of brain infarcts across alcohol-intake categories by using abstainers as the reference category. For tests of linear trend, we treated the categories of alcohol intake as the continuous variable. For tests of quadratic trend, we squared the linear trend variable. We included age, sex, and pack-years of cigarette smoking as covariates. In addition, we adjusted for educational level, BMI, diabetes, and hypertension. We evaluated whether the effects of alcohol differed by sex or *APOE*

TABLE 1
Characteristics of the total study sample and of the subsample with assessment of hippocampal and amygdalar volumes on 3-dimensional (3-D) magnetic resonance imaging (MRI)

	Total sample (n = 1074)	Subsample with 3-D MRI (n = 509)
Age (y)	72 ± 7[1]	73 ± 8
Women (%)	52	49
Current alcohol intake (drinks/d)	1.2 ± 1.3	1.2 ± 1.4
Former alcohol users (%)	8	8
Pack-years of cigarette smoking (y)	19 ± 24	20 ± 25
Primary education (%)	35	31
BMI (kg/m^2)	27 ± 4	26 ± 4
Presence of diabetes (%)	7	6
Presence of hypertension (%)	52	53
Presence of *APOE* ε4 allele (%)[2]	28	27
Presence of symptomatic infarct on MRI (%)	4	6

[1] $\bar{x}$ ± SD (all such values). No significant differences were observed between the samples.
[2] Available in 969 out of the total sample and in 436 out of the subsample.

genotype (carrier or noncarrier of the *APOE* ϵ4 allele) by performing stratified analyses and including interaction terms in the model. Statistical analyses were performed by using SPSS statistical software for WINDOWS (version 11.5; SPSS Inc, Chicago).

RESULTS

There were no differences in baseline characteristics between the total sample and the subsample in which hippocampal and amygdalar volumes on MRI were evaluated (**Table 1**). Characteristics according to alcohol intake categories are given for the total sample in **Table 2**. Former drinkers (n = 86 in the total sample and n = 42 in the subsample) had hypertension and diabetes mellitus more frequently than did the current drinkers, which supports our presumption that former drinkers might have stopped drinking because of illness. Therefore, former drinkers were excluded from analyses of alcohol intake and brain MRI findings.

Light alcohol drinkers had the smallest amount of periventricular white matter lesions on MRI [adjusted difference from abstainers: 0.69 (95% CI: 0.25, 1.13; P = 0.002); adjusted difference from heavy drinkers: 0.79 (95% CI: 0.17, 1.41; P = 0.01)], as shown in **Table 3**. The light alcohol drinkers also tended to have fewer subcortical white matter lesions than did the heavy drinkers, but the difference did not reach significance [adjusted difference from abstainers: 0.57 (95% CI: −0.05, 1.20; P = 0.07); adjusted difference from heavy drinkers: 0.35 (95% CI: −0.54, 1.24; P = 0.44)]. Brain infarcts on MRI tended to be found less frequently in very light and light drinkers, but none of the odds ratios reached statistical significance (Table 3). When we excluded persons with symptomatic infarcts on MRI (n = 42)—because they could have changed their alcohol intake after the stroke—the results remained similar. The associations did not change after additional adjustments for educational level, BMI, diabetes, and hypertension, and they were similar in men and women and in *APOE* ϵ4 carriers and noncarriers.

Overall, there was no association between alcohol intake and hippocampal or amygdalar volumes on MRI, as shown in **Table 4**. However, the effect of alcohol intake on volumes differed by *APOE* genotype (P for interaction = 0.02 for hippocampal volume and = 0.07 for amygdalar volume). In carriers of the ϵ4 allele, alcohol intake was positively associated with hippocampal and amygdalar volumes, whereas, in ϵ4 noncarriers, there was no association (**Figure 1**). The associations between alcohol intake and hippocampal or amygdalar volumes did not change after additional adjustment for educational level, BMI, diabetes, and hypertension, and they were similar in men and women.

In the total sample, there were 111 persons who fulfilled the criteria for binge drinking (≥6 alcoholic drinks in1 d). Of this group, 56 were also in the subset with hippocampal and amygdalar data, and excluding them did not change the results.

TABLE 2
Characteristics according to current alcohol intake in the total sample[1]

	Alcohol intake						
	None (n = 114)	Very light (<1 drink/wk) (n = 195)	Light (≥1 drink/wk to <1 drink/d) (n = 247)	Moderate (≥1 drink/d to <4 drinks/d) (n = 386)	Heavy (≥4 drinks/d) (n = 46)	Former consumption (n = 86)	P[2]
Age (y)	72 ± 8[3]	73 ± 8	72 ± 8	72 ± 7	70 ± 7	74 ± 7	0.09
Women (%)	78	69	50	38	26	55	<0.001
Pack-years of cigarette smoking (y)	7 ± 16	14 ± 22	18 ± 22	23 ± 24	37 ± 33	21 ± 25	<0.001
Primary education (%)	45	38	34	28	39	45	0.003
BMI (kg/m^2)	27 ± 4	27 ± 4	27 ± 4	26 ± 3	26 ± 3	26 ± 4	0.20
Presence of diabetes (%)	10	7	5	5	4	17	0.001
Presence of hypertension (%)	56	56	51	47	54	59	0.18
Presence of *APOE* ε4 allele (%)	31	23	23	28	30	39	0.10
Presence of symptomatic infarct on MRI (%)	6	3	2	5	4	2	0.42

[1] MRI, magnetic resonance imaging.
[2] ANOVA (continuous variables) or chi-square test (categorical variables).
[3] $\bar{x}$ ± SD (all such values).

TABLE 3
Vascular brain magnetic resonance imaging (MRI) findings according to alcohol intake in the total sample

	Alcohol intake					*P* for trend	
	None (n = 114)	Very light (<1 drink/wk) (n = 195)	Light (≥1 drink/wk to <1 drink/d) (n = 247)	Moderate (≥1 drink/d to <4 drinks/d) (n = 386)	Heavy (≥4 drinks/d) (n = 46)	Linear	Quadratic[1]
White matter lesions							
Periventricular, grade[2]	2.73 ± 0.19[3]	2.51 ± 0.14	2.04 ± 0.12	2.37 ± 0.10	2.83 ± 0.29	0.001	0.001
Subcortical, volume (mL)[2]	1.58 ± 0.27	1.60 ± 0.20	1.01 ± 0.18	1.49 ± 0.14	1.36 ± 0.42	0.31	0.36
Brain infarcts							
[n (%)]	34 (30)	43 (22)	52 (21)	94 (24)	9 (20)		
Odds ratio (95% CI)[4]	1.00 (reference)	0.63 (0.36, 1.09)	0.65 (0.38, 1.12)	0.86 (0.52, 1.43)	0.80 (0.33, 1.96)	0.14	0.11

[1] Calculated from multiple linear regression models with alcohol intake in categories and its squared term.
[2] Adjusted for age, sex, and pack-years of cigarette smoking; analysis of covariance was used for calculating adjusted means in groups.
[3] $\bar{x}$ ± SE (all such values).
[4] Adjusted for age, sex, and pack-years of cigarette smoking; logistic regression was used to calculate adjusted odds ratios.

DISCUSSION

In this population-based study in older persons, we found that drinkers of light-to-moderate amounts of alcohol had fewer cerebral white matter lesions and brain infarcts on MRI than did abstainers and heavy drinkers. In *APOE* ε4 carriers, but not in ε4 noncarriers, we found a positive association between alcohol intake and hippocampal and amygdalar volumes on MRI.

Some aspects of the methods used in this study should be discussed. First, there could be error in the MRI measures, particularly in the semiquantitative assessments. However, given that MRI assessments were done with the investigators blinded to the subjects' alcohol intake, this is random error that only leads to weaker associations between alcohol and MRI measures. Second, we relied on self-reported alcohol intake, which may have led to underreporting or overreporting. Although we may have misclassified absolute amounts of alcohol intake, the ranking of subjects according to their alcohol intake most likely was adequate (32). If persons who actually drink heavily underreported their alcohol consumption, we will have underestimated the difference in risk between those who drink moderately and abstainers. Third, we assessed average alcohol intake over a 1-y period before MRI examinations, but it might be better to have information on the average alcohol intake over the lifetime. Moreover, we lacked detailed information on drinking patterns, which may be important in estimating the effects of alcohol. Fourth, we had no information on the type of alcoholic drink consumed. Previous studies showed that beer, spirits, and wine—consumed in moderation—are equally associated with a reduced risk of dementia (2, 4), although the Copenhagen City Heart Study found the association only for moderate wine consumption (10). Drinking patterns in the older Dutch population studied here were reported before (2); they show that, among alcohol consumers, 35% drink wine, 35% drink spirits, 30% drink fortified wine, and 20% drink beer. Finally, given that our study is observational and that alcohol intake may be associated with several unmeasured confounders, we cannot infer causality of the associations.

Light-to-moderate alcohol drinking is associated with a lower risk of cognitive impairment and dementia than is lifetime abstention (1–4, 10, 33, 34). In line with the beneficial effects of alcohol on the lipid profile, hemostatic factors (6), and atherosclerosis (35), most investigators found a reduced risk of vascular dementia in consumers of light-to-moderate amounts of alcohol (2, 4, 5). We found that, consistent with these vascular effects of alcohol and with observations in the Cardiovascular Health Study (36), consumers of light-to-moderate amounts of alcohol had fewer cerebral white matter lesions—in particular, those in the periventricular region—and infarcts on MRI. Different pathophysiologic events may lead to the development of either periventricular or subcortical white matter lesions (14). The periventricular white matter, in particular, is vulnerable to ischemia, and severe periventricular white matter lesions are related to carotid atherosclerosis (37). The Atherosclerosis Risk in Communities study of middle-aged subjects did not show an effect of alcohol intake on cerebrovascular disease on MRI, but those

TABLE 4
Hippocampal and amygdalar volume on magnetic resonance imaging (MRI) according to alcohol intake in the subsample[1]

	Alcohol intake					*P* for trend	
	None (n = 38)	Very light (<1 drink/wk) (n = 97)	Light (≥1 drink/wk to <1 drink/d) (n = 103)	Moderate (≥1 drink/d to <4 drinks/d) (n = 209)	Heavy (≥4 drinks/d) (n = 20)	Linear	Quadratic[2]
Hippocampal volume (mL)[3]	6.33 ± 0.14	6.41 ± 0.09	6.47 ± 0.08	6.38 ± 0.06	6.28 ± 0.20	0.30	0.25
Amygdalar volume (mL)[3]	4.56 ± 0.11	4.49 ± 0.07	4.63 ± 0.07	4.62 ± 0.05	4.62 ± 0.16	0.66	0.90

[1] All values are $\bar{x}$ ± SE.
[2] Calculated from multiple linear regression models with alcohol intake in categories and its squared term.
[3] Adjusted for age, sex, and pack-years of cigarette smoking; analysis of covariance was used for calculating adjusted means in groups.

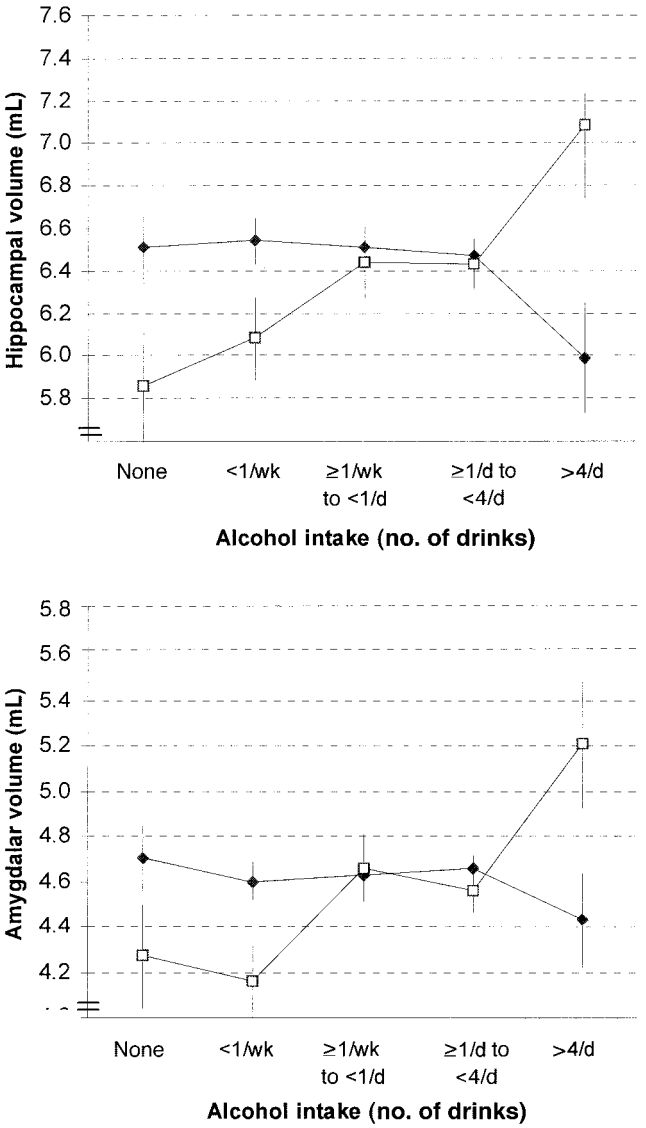

FIGURE 1. Hippocampal and amygdalar volumes on magnetic resonance imaging according to alcohol intake by strata of *APOE* genotype (ϵ4 noncarriers: $n = 288$, ◆; ϵ4 carriers: $n = 101$, □). Volumes were adjusted for age, sex, and pack-years of cigarette smoking and normalized to average head size. Error bars indicate SEM. For the analyses of hippocampal volumes, the *P* value for linear trend in *APOE* ϵ4 noncarriers was 0.15 and that in ϵ4 carriers was 0.009. For the analyses of amygdalar volumes, the *P* value for linear trend in *APOE* ϵ4 noncarriers was 0.84 and that in ϵ4 carriers was 0.02. The *P* value of the interaction term between *APOE* genotype and alcohol intake was 0.02 for hippocampal volume and 0.07 for amygdalar volume.

investigators combined moderate and heavy alcohol intake into one category, which may have diluted any beneficial effect (38). Light-to-moderate alcohol drinking has also been associated with a reduced risk of Alzheimer disease in several (1, 3, 4, 10, 39), but not all (40, 41) studies. Besides reducing cerebrovascular disease that contributes to the development of symptoms of Alzheimer disease (8, 9, 25), alcohol in moderate amounts may also increase the release of acetylcholine of the hippocampus (11) and induce the release of potentially beneficial prostaglandins (12). In traditional Alzheimer disease, amyloid plaques and neurofibrillary tangles accumulate in the brain, with a high predilection for the medial temporal lobe (42). This may lead to neuronal loss and atrophy in vivo that are detectable on MRI even in persons who have not yet developed clinical symptoms of dementia (17–22). *APOE* ϵ4 carriers are at increased risk of Alzheimer disease-related neurologic disorders (43), atrophy of structures in the medial temporal lobe (44), and clinical Alzheimer disease (13). Observations in the Rotterdam Study suggested that light-to-moderate alcohol consumption is associated with a reduced risk of Alzheimer disease only in *APOE* ϵ4 carriers (2). Carmelli et al (45) also reported a stronger association of light drinking and better cognitive performance in *APOE* ϵ4 carriers than in noncarriers. In the current study, we found that *APOE* ϵ4 carriers who were consumers of light-to-moderate amounts of alcohol had less hippocampal and amygdalar atrophy than did abstainers. Although not all persons with hippocampal or amygdalar atrophy will develop Alzheimer disease, such persons are at increased risk of clinical symptoms of Alzheimer disease (18), and, thus, our findings support the hypothesis that there could be a reduced risk of Alzheimer disease for consumers of light-to-moderate amounts of alcohol who have the *APOE* ϵ4 allele. It is currently unclear which biological mechanisms could be involved in the associations between alcohol and Alzheimer disease. We speculate that a putative antioxidative effect of alcohol (46) might suppress the highly sensitive peroxidation of *APOE* ϵ4 (47) and thereby reduce amyloid plaque formation in the medial temporal lobe (48, 49) or neurotoxicity of the β-amyloid (50). Unlike the current study, the Cardiovascular Health Study found a lower risk of dementia in alcohol consumers to be more consistent among persons without the *APOE* ϵ4 allele (4). It is possible that the youth of the population studied in the Rotterdam Study compared with the age of the Cardiovascular Health Study population led to these discrepancies, because the *APOE* ϵ4 allele is a stronger risk factor for Alzheimer disease at younger ages (13). The Epidemiology of Vascular Aging study also found a reduced risk of cognitive deterioration with alcohol intake in ϵ4 noncarriers, but, in that study, the *APOE* ϵ4 allele itself was not a risk factor for cognitive decline (51).

In conclusion, our findings suggest that light-to-moderate alcohol intake is associated with brain MRI findings that are related to cerebrovascular disease and—in *APOE* ϵ4 carriers—with hippocampal and amygdalar atrophy on MRI. These findings are in line with recent observations that light-to-moderate alcohol consumption is associated with a reduced risk of dementia.

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