Prospective Study of Alcohol Consumption and Risk of Dementia in Older Adults

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Dementia imposes a tremendous burden on patients, caregivers, and society. Alzheimer disease alone causes more than 360,000 new cases in the United States annually,1 with a national annual cost of caring for such patients of more than $50 billion.2 This burden has spurred a search for modifiable factors that cause or prevent dementia.

Atherosclerotic vascular disease may be 1 such risk factor for vascular and nonvascular dementia.3 Because moderate alcohol consumption is associated with a lower risk of cardiovascular disease in the elderly,4 such consumption might be expected to lower risk of dementia. However, even moderate alcohol consumption may have effects that increase dementia risk. Blood alcohol levels as low as 0.02% impair driving ability,5 and moderate alcohol use is associated with a greater risk of cerebral hemorrhage.6 In an analysis of subclinical abnormalities of the brain seen on magnetic resonance imaging (MRI) studies among Cardiovascular Health Study (CHS) participants, moderate alcohol consumption was associated with greater brain atrophy but fewer silent infarcts and less white matter disease, associations that might influence risk of dementia in opposite directions.7

Previous studies of alcohol consumption and cognitive decline8-20 or dementia21-25 have reported conflicting results. However, to our knowledge, no previous study has addressed the risk of confirmed dementia in a large cohort of adults with repeated measures of alcohol use.

To address the relationship of alcohol consumption and risk of dementia further, we performed a nested case-control study of alcohol consumption and risk of incident dementia in the CHS, a prospective, population-based study of adults aged 65 years and older in the United States.26,27

METHODS

Study Population and Design

Cardiovascular Health Study participants include 5888 men and women aged 65 years or older who were randomly selected from Medicare-
eligibility lists in 4 communities in the United States (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania). Participants were not institutionalized or wheelchair-dependent, did not require a proxy for consent, were not under treatment for cancer, and were expected to remain in their respective regions for at least 3 years. In 1989 and 1990, 5201 participants were recruited; in 1992 and 1993, an additional 687 black participants were recruited. The institutional review board at each participating center approved the study, and each participant gave informed consent.

The CHS study design and objectives have been published.27 The baseline examination included standardized medical history questionnaires, physical examination, and laboratory examination. Follow-up contact occurred every 6 months, alternating between telephone calls and clinic visits. Cognitive testing included the 30-point Mini-Mental State Examination at baseline and the 100-point Modified Mini-Mental State Examination (3MSE) and the Digital-Symbol Substitution Test in all subsequent years.28,20

**MRI Examination**

A total of 3660 CHS participants completed an MRI examination between 1992 and 1994. Those who completed an MRI examination were generally healthier than those participants who did not,26 and were less likely to abstain from alcohol (48% vs 54%; P < .001).

**Detection of Dementia**

Of the 3660 participants who completed an MRI, 3608 completed a 3MSE at the same clinical visit and were eligible for the CHS cognition study (FIGURE). We determined their subsequent risk of dementia using the CHS Cognition Study protocol.31,32 Investigators performed a multistage screening process on all eligible participants, whether or not they were still alive, beginning in 1999. When a participant died before that time, determination of dementia was made using available medical records, previous CHS testing, and Informant Questionnaire on the Cognitive Decline of the Elderly (IQCODE) questionnaires33 sent to each participant’s personal physician and proxy respondent. Investigators obtained similar information from participants who were alive but did not complete the full screening process.

The first stage of the screening process identified participants at particular risk of dementia for intensive subsequent evaluation. Low-risk participants were alive in 1999 and had no history of stroke or dementia, 3MSE scores of 80 or above throughout 1997-1999, and no decline in 3MSE score from 1992-1994 to 1999 greater than 5 points, consistent with previous studies of cognitive decline in CHS.34 At 3 of the 4 CHS sites (n = 2681), high-risk participants and all black participants (because of their smaller sample size and higher underlying risk)35 then underwent further evaluation in a second stage; low-risk participants (n = 1492) were considered not to have dementia. At the Pittsburgh site, all participants (n = 927), irrespective of risk status, were further evaluated in a second stage.

In the second stage, participants underwent a full neuropsychiatric battery. At the Pittsburgh site, all available participants underwent further neurological testing in a third stage; at the other 3 sites, participants with abnormal tests of memory or of any 2 other domains underwent further evaluation.

In the third stage, neurologists performed detailed neurological examinations, reviewed previously collected information, and classified participants as having no cognitive impairment, mild cognitive impairment, or dementia.31 Neurologists completed the Unified Parkinson’s Disease Rating Scale,36 and the Hachinski Ischemic Scale.37 They diagnosed dementia based on a progressive or static cognitive deficit of...
sufficient severity to affect a participant's activities of daily living, and history of normal intellectual function before the onset of cognitive abnormalities. Participants were required to have impairments in 2 cognitive domains, which did not necessarily include memory.

In the fourth stage, a neurologist with extensive experience in dementia reviewed all subjects diagnosed by local neurologists as free of dementia to ensure that no cases were missed. An adjudication committee of study neurologists or psychiatrists from the 4 CHS clinics then reviewed cases classified as possible dementia in the third and fourth stages, confirmed the diagnoses, and established types of dementia. The classification of dementia type was done after review of the 1992-1994 MRI results although the diagnosis of dementia per se was not affected by the results of the MRI. The adjudication committee based its classifications on criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association, State of California Alzheimer's Disease Diagnostic and Treatment Centers, and National Institute of Neurological Diseases and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences.

Finally, to ensure that all participants with incident dementia were free of dementia at the start of follow-up, we excluded subjects who died within 2 years of undergoing an MRI, had a 3MSE score of less than 80 at the time of their MRI, or had no follow-up testing performed after undergoing an MRI. Based on results from the Pittsburgh site, in which all participants (rather than just high-risk participants) underwent full evaluation, our overall estimates of dementia are approximately 9% lower than if we had fully evaluated all participants.

Alcohol Consumption
At yearly visits, participants were individually asked the usual number of 12-oz cans or bottles of beer, 6-oz glasses of wine, and shots of liquor that they drank at a time and the usual frequency with which they consumed those beverages. In primary analyses, we averaged alcohol consumption from the baseline questionnaire and the questionnaire from the annual clinic visit closest to the date of the MRI examination. In secondary analyses, we used alcohol consumption determined from these 2 assessments individually.

At baseline, participants reported whether they changed their pattern of consumption during the past 5 years and whether they ever regularly consumed 5 or more drinks daily. Participants who reported abstinence at baseline but responded yes to either of these questions were classified as former drinkers. Participants who reported some alcohol consumption at baseline but abstinence at the time of MRI were classified as quitters separate from former drinkers.

As in previous CHS analyses, we categorized participants according to weekly alcohol consumption for primary analyses as follows: none, former, quitter, less than 1 drink, 1 to 6 drinks, 7 to 13 drinks, and 14 or more drinks weekly. For logistic regression analyses, we used abstainers without former use as the reference category, to minimize the inclusion of sick quitters. We performed additional analyses that incorporated alcohol consumption (in drinks per week) as a continuous variable, performing log transformation because of the skewed distribution of alcohol consumption in CHS. When these analyses included nondrinkers, we added 0.01 drinks per week to all observations to allow log transformation.

Other Covariates
We defined diabetes as having a fasting blood sugar level of at least 126 mg/dL (≥6.9 mmol/L) or were receiving medication for diabetes. We dichotomized educational attainment (completion of ≤high school vs ≥vocational school or college), income (<$16000 vs ≥$16000 per year), and marital status (married vs widowed, divorced, separated, or never married). We assessed leisure-time physical activity as a weighted sum of kilocalories expended in specific physical activities. Apolipoprotein E (APOE) genotype testing was performed as previously described, of the 664 participants who agreed to be tested, 171 tested positive for APOE ε4 positive (9 APOE ε4/ε4, 147 ε3/ε4, and 15 ε2/ε4). We assessed depression using the Center for Epidemiological Studies Depression (CES-D) Scale.

We quantified MRI results in a standardized, reliable manner, as previously described. For 3 participants with missing values for body mass index or physical activity, we assigned mean values of these variables; analyses that deleted these individuals gave identical results and are not shown. Unless otherwise noted, covariates were assessed at the onset of follow-up.

Statistical Methods
We used a nested case-control approach to assess the relative odds of incident dementia according to alcohol consumption. We frequency-matched all participants with incident dementia to an equal number of participants without dementia on the basis of age (in 5-year increments), death before the end of follow-up in 1999, and completion of a CHS clinic visit in 1998-1999. We used logistic regression to control for potentially confounding factors and included the matching variables in all models. Other factors included were race, sex, educational attainment, income level, physical activity, diabetes, body mass index, use of hormone replacement therapy, total cholesterol, atrial fibrillation, APOE ε4 status (1 or 2 alleles vs none), former smoking, current smoking, history of congestive heart failure, history of stroke, and history of transient ischemic attack. Because high-density lipoprotein cholesterol (HDL-C), fibrinogen, and MRI results are plausible mediators of the effect of alcohol consumption on vascular disease and dementia, those factors were entered into the model in sensitivity analyses.
To explore possible effect modification, we repeated adjusted analyses within strata of sex, APOE ε4 genotype, and age. Because of the smaller number of participants in stratified analyses, we performed stepwise logistic regression (with entry and stay P values of .20) to generate a more parsimonious model, forcing alcohol consumption, sex, and the matching variables into the model. This model yielded results very similar to the full model when used on the entire cohort and included race, APOE ε4 status, diabetes, and history of stroke. In beverage-specific analyses, we used the full model and simultaneously controlled for use of the other 2 beverages (assessed categorically). For tests of linear trend, we treated the categories of alcohol consumption as continuous variable, excluding former drinkers. For tests of quadratic trend, we squared the linear trend variable after centering it on median consumption. We used SAS statistical software version 8 (SAS Institute Inc, Cary, NC) for all analyses.

**RESULTS**

We have previously reported the characteristics of CHS participants according to alcohol consumption. We documented 373 cases of dementia during follow-up, including 258 with Alzheimer disease alone, 44 with vascular dementia alone, 54 with Alzheimer disease and vascular dementia, and 17 with other types of dementia. TABLE 1 demonstrates characteristics of cases and controls. As expected, lower baseline MMSE scores, previous stroke, diabetes, and a genotype that included an APOE ε4 allele were more common among cases than controls. Median follow-up time was 6.0 years for controls and 6.1 years for cases. Age-adjusted rates of incident dementia were 56 per 1000 among black participants and 36 per 1000 among white participants.

**TABLE 2** demonstrates the association of average alcohol consumption with incident dementia. In logistic regression models adjusting for potential confounders, the lowest odds ratio (OR) for dementia occurred among individuals consuming 1 to 6 drinks per week and the highest OR occurred among those consuming 14 or more drinks per week (P for quadratic term = .001; Table 2). Participants who consumed 1 to 6 drinks per week had a 54% lower odds of experiencing dementia than did abstainers (95% confidence interval [CI], 23%-73%).

**Sensitivity Analyses**

To ensure our findings were robust, we performed several sensitivity analy-
ses. We found similar results in an analysis restricted to the 527 participants whose categorical alcohol consumption was unchanged from the baseline CHS visit to the onset of follow-up for dementia (adjusted OR for consumption of 1 to 6 drinks per week, 0.49; 95% CI, 0.26-0.93; P for quadratic term = 0.005). Analyses using baseline alcohol consumption (determined 5-6 years before the beginning of follow-up) showed a similar relationship, with an OR of 0.68 (95% CI, 0.43-1.08) among participants who consumed 1 to 6 drinks per week (P for quadratic term = 0.06).

As an additional sensitivity analysis, we modeled alcohol as a continuous variable, including linear and squared terms to detect U-shaped relationships. In these models, the P values for the squared terms were 0.08 among all participants other than former drinkers or quitters and 0.09 restricted to current drinkers. In the latter model, the odds of dementia appeared to be lowest at consumption of 1.5 drinks per week, consistent with the categorical results.

In separate models, we controlled for variables that may mediate the association of alcohol consumption with dementia. High-density lipoprotein cholesterol and fibrinogen concentrations together appeared to account for 16% of the lower risk among those who consumed 7 to 13 drinks per week. Controlling for white matter grade and MRI-diagnosed infarcts increased the OR among those who consumed 14 or more drinks to 1.29 (95% CI, 0.62-2.67), while controlling for measures of atrophy decreased the OR among the heaviest drinkers to 1.15 (95% CI, 0.56-2.38).

To minimize the possibility that unrecognized cognitive dysfunction influenced alcohol consumption prior to follow-up, we further adjusted for baseline Mini-Mental State Examination score (on a 30-point scale) or restricted our analyses to the 627 subjects with baseline Mini-Mental State Examination scores of 27 or higher, with similar results. In a model that simultaneously controlled for baseline scores on the Mini-Mental State Examination and Digital-Symbol Substitution Test in addition to other covariates, consumption of 1 to 6 drinks per week was associated with 46% (95% CI, 7%-69%) lower odds of subsequent dementia. Addition of depression scores to our models did not change our results (data not shown).

Alcohol intake had similar relationships with both Alzheimer disease and vascular dementia (Table 2). However, the number of cases of vascular dementia (n=98) was smaller than the number of cases of Alzheimer disease (n=312), precluding firm conclusions about the relationship of alcohol use to vascular dementia.

The overall association of alcohol consumption with odds of dementia differed somewhat between men and women (P interaction=.01) (TABLE 3). Among women, we found a generally inverse relationship, with lower odds among women who consumed 7 or more drinks per week. In contrast, men had a U-shaped relationship between alcohol use and odds of dementia. In both men and women, the OR associated with consumption of 1 to 6 drinks per week was similar to the overall OR of 0.46.

Table 3 also shows that an APOE e4 allele appeared to modify the association of alcohol consumption and odds of dementia, particularly among those who consumed 7 to 13 (P=.05) and 14 or more drinks per week (P=.008). Among participants who tested nega-

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**Table 2. Odds Ratios for Incident Dementia According to Average Weekly Alcohol Consumption Among Participants in the Cardiovascular Health Study**

<table>
<thead>
<tr>
<th>Variables</th>
<th>None</th>
<th>&lt;1</th>
<th>1-6</th>
<th>7-13</th>
<th>≥14</th>
<th>Linear P Value for Trend (Quadratic)</th>
<th>Former</th>
<th>Quitter</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>151</td>
<td>53</td>
<td>33</td>
<td>25</td>
<td>24</td>
<td></td>
<td>35</td>
<td>52</td>
</tr>
<tr>
<td>No. of controls</td>
<td>123</td>
<td>73</td>
<td>72</td>
<td>32</td>
<td>18</td>
<td></td>
<td>22</td>
<td>33</td>
</tr>
<tr>
<td>Matching adjusted, OR (95% CI)*</td>
<td>1.00</td>
<td>0.59 (0.39-0.91)</td>
<td>0.37 (0.23-0.60)</td>
<td>0.64 (0.36-1.13)</td>
<td>1.09 (0.56-2.10)</td>
<td>.06 (&lt;.001)</td>
<td>1.40 (0.77-2.53)</td>
<td>1.31 (0.80-2.16)</td>
</tr>
<tr>
<td>Fully adjusted, OR (95% CI)†</td>
<td>1.00</td>
<td>0.65 (0.41-1.02)</td>
<td>0.46 (0.27-0.77)</td>
<td>0.69 (0.37-1.31)</td>
<td>1.22 (0.60-2.49)</td>
<td>.45 (.001)</td>
<td>1.52 (0.81-2.83)</td>
<td>1.38 (0.81-2.35)</td>
</tr>
<tr>
<td>Alzheimer disease‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>130</td>
<td>44</td>
<td>28</td>
<td>22</td>
<td>19</td>
<td></td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.59 (0.37-0.94)</td>
<td>0.43 (0.25-0.72)</td>
<td>0.65 (0.35-1.23)</td>
<td>0.95 (0.46-1.96)</td>
<td>.08 (.002)</td>
<td>1.47 (0.77-2.82)</td>
<td>1.18 (0.68-2.04)</td>
</tr>
<tr>
<td>Vascular dementia§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>36</td>
<td>17</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td></td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0</td>
<td>0.96 (0.49-1.91)</td>
<td>0.60 (0.26-1.37)</td>
<td>0.79 (0.30-2.10)</td>
<td>0.83 (0.29-3.05)</td>
<td>.46 (.48)</td>
<td>1.36 (0.55-3.40)</td>
<td>1.39 (0.63-3.08)</td>
</tr>
</tbody>
</table>

| Abbreviations: CI, confidence interval; OR, odds ratio. | | | | | | | | |
| *Case and control subjects were frequency-matched on age, vital status at the end of follow-up, and clinic visit status at the end of follow-up. | | | | | | | | |
| †Adjusted for age (as a continuous variable), sex, race, apolipoprotein (APOE) e4 status (yes/no), educational attainment, income level, marital status, estrogen replacement therapy, current smoking, former smoking, diabetes, body mass index, total cholesterol level, atrial fibrillation, history of congestive heart failure, history of stroke, history of transient ischemic attack, and kilocalories expended in daily activities. | | | | | | | | |
| ‡Case subjects whose cause of dementia included Alzheimer disease, adjusted for age, sex, race, diabetes, APOE e4, and history of stroke. The number of controls is the same as that for all-cause dementia. | | | | | | | | |
| §Case subjects whose cause of dementia included vascular dementia, adjusted for age, sex, race, diabetes, APOE e4, and history of stroke. The number of controls is the same as that for all-cause dementia. | | | | | | | | |
Table 3. Adjusted Odds Ratios for Incident Dementia According to Usual Weekly Alcohol Consumption, Stratified by Sex

<table>
<thead>
<tr>
<th>Variables</th>
<th>Weekly No. of Drinks</th>
<th>Linear P Value for Trend (Quadratic)</th>
<th>Former/Quitter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>&lt;1</td>
<td>1-6</td>
</tr>
<tr>
<td>No. of women*</td>
<td>195</td>
<td>81</td>
<td>42</td>
</tr>
<tr>
<td>No. with all-cause dementia</td>
<td>112</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.52 (0.30-0.90)</td>
<td>0.57 (0.28-1.17)</td>
</tr>
<tr>
<td>No. with Alzheimer disease</td>
<td>99</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.51 (0.29-0.90)</td>
<td>0.57 (0.27-1.19)</td>
</tr>
<tr>
<td>No. with vascular dementia</td>
<td>24</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.65 (0.26-1.62)</td>
<td>0.81 (0.26-2.51)</td>
</tr>
<tr>
<td>No. of men*</td>
<td>79</td>
<td>45</td>
<td>63</td>
</tr>
<tr>
<td>No. with all-cause dementia</td>
<td>39</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.82 (0.38-1.78)</td>
<td>0.36 (0.17-0.77)</td>
</tr>
<tr>
<td>No with Alzheimer disease</td>
<td>31</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.78 (0.34-1.80)</td>
<td>0.36 (0.16-0.80)</td>
</tr>
<tr>
<td>No. with vascular dementia</td>
<td>12</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>1.37 (0.44-4.27)</td>
<td>0.47 (0.13-1.75)</td>
</tr>
</tbody>
</table>

**Table 4. Adjusted Odds Ratios for Incident Dementia According to Usual Weekly Alcohol Consumption of Individual Beverage Types**

<table>
<thead>
<tr>
<th>Variable</th>
<th>None</th>
<th>&lt;1</th>
<th>1-6</th>
<th>≥7</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer, OR (95% CI)</td>
<td>1.00</td>
<td>0.84 (0.48-1.47)</td>
<td>0.74 (0.36-1.54)</td>
<td>1.96 (0.71-5.47)</td>
<td>.65 (.08)</td>
</tr>
<tr>
<td>Wine, OR (95% CI)</td>
<td>1.00</td>
<td>0.72 (0.46-1.11)</td>
<td>0.72 (0.39-1.33)</td>
<td>0.62 (0.25-1.50)</td>
<td>.33 (.39)</td>
</tr>
<tr>
<td>Liqueor, OR (95% CI)</td>
<td>1.00</td>
<td>0.84 (0.48-1.45)</td>
<td>1.19 (0.59-2.30)</td>
<td>1.08 (0.55-2.13)</td>
<td>.70 (.30)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for age (as a continuous variable), vital status at the end of follow-up, clinic visit status at the end of follow-up, sex, race, APOE e4 status (yes/no), diabetes, and history of stroke.

Throughout our analyses, we separated long-term abstainers from former drinkers (those who reported prior alcohol consumption at the baseline CHS examination) and quitters (those who quit between the baseline CHS examination and the beginning of follow-up). In all models, former drinkers and quitters had approximately 20% to 60% higher odds of dementia than long-term abstainers, supporting the need to separate these groups.

We tested the associations of beer, wine, or liquor consumption with dementia, controlling for consumption of the other 2 beverages (Table 4). The 3 beverage types did not differ significantly in their relationships with dementia although the CIs for each estimate were wide.

**COMMENT**

In this case-control study nested within a large population-based cohort of older adults, moderate alcohol consumption had an inverse relationship with
risk of dementia, even after multivariate adjustment and exclusion of former drinkers. Abstainers had odds of dementia that were about twice as high as the odds among consumers of between 1 and 6 drinks per week. We found possible differences in the association of alcohol with dementia according to sex and APOE ε4 genotype.

Although several studies have assessed alcohol consumption and cognitive function among older adults, previous work has yielded inconsistent results. However, many of these studies were limited by cross-sectional design, restriction by age or sex, or incomplete ascertainment. Limitations avoided in the design of the CHS Cognition Study. Likewise, few previous studies have had adequate power to address the relationship of alcohol consumption to clinical dementia. A meta-analysis of older case-control studies and 2 small cohort studies reported no association between alcohol use and risk of dementia, but a larger cohort study found a strong, inverse association between wine consumption (up to 4 glasses daily) and risk of dementia in Bordeaux, France. In a younger population with 197 cases of dementia, Rotterdam Study investigators found a U-shaped association between alcohol use and risk of dementia, with the lowest risk among consumers of 1 to 3 drinks per day. Our results are roughly consistent with the findings of the latter 2 studies but suggest a higher risk of dementia with consumption greater than 2 drinks per day.

An important feature of the CHS Cognition Study is serial measurement of alcohol use, including assessment several years before the onset of follow-up. Studies that rely on a single measure of exposure at the beginning of follow-up may be susceptible to bias if patients with unrecognized cognitive dysfunction have already changed their alcohol use by that point. By demonstrating an inverse association of light drinking with dementia even among participants with stable alcohol use over several years prior to follow-up, we minimize—but cannot eliminate—this concern.

Another strength of the CHS Cognition Study is the systematic screening protocol for dementia, which included proxy assessment of unavailable or deceased participants and serial testing of cognitive function. As a result, we detected dementia in some participants who would have been excluded in other studies and tended to identify cases early in the course of clinical dementia. As expected, age-adjusted incidence rates of dementia in the CHS Memory Study are higher than rates from older studies with less extensive ascertainment methods but similar to the higher rates documented more recently.

Alcohol use might be inversely associated with dementia through protective changes in cerebral vasculature. We previously found that light-to-moderate alcohol use is associated with a lower prevalence of MRI-defined white matter lesions and subclinical infarcts (2 abnormalities thought to be of vascular origin), but MRI findings, HDL-C levels, and fibrinogen levels only modestly mediated the association of alcohol use and dementia in this study. Social factors associated with alcohol use could contribute because moderate alcohol use may have psychological benefits and is positively associated with the number of social contacts among older adults. Experimental studies have found that ethanol initially increases hippocampal acetylcholine release, which could conceivably improve memory performance.

The inverse association of alcohol use with dementia was most pronounced among participants without an APOE ε4 allele, who are at lower risk of dementia. Among individuals with an APOE ε4 allele, alcohol use at or above 7 drinks per week appeared to be associated with a substantially higher risk of dementia. These results parallel those of the Epidemiology of Vascular Aging Study, which found that alcohol intake was associated with a lower risk of cognitive deterioration among subjects without an APOE ε4 allele, but a higher risk in APOE ε4 carriers. Surprisingly, the Rotterdam Study found that the lower risk of dementia associated with alcohol use was more consistent among individuals with an APOE ε4 allele, but no significant interaction was detected.

Men and women had somewhat different associations of alcohol and risk of dementia. This was most apparent at higher levels of consumption, which relatively few participants undertook. Our results also differ somewhat from the Rotterdam Study, which found no association of alcohol use and dementia among women. We do not advise women to exceed recommended limits of alcohol intake (≤1 drink per day) on the basis of these results alone.

In this study, participants whose reported consumption was less than 1 drink per week had lower odds of dementia than abstainers. Several factors bear on interpretation of the results for this group. Alcohol use was self-reported, so the actual level of consumption among these participants may have been higher than reported although we believe the rank-ordering of participants was valid. In support of this, after adjusting for age, sex, and race, HDL-C levels, which are directly influenced by alcohol use, were significantly higher among less-than-weekly drinkers (55.8 mg/dL [1.44 mmol/L]) than among abstainers (51.5 mg/dL [1.45 mmol/L]; P = .002). Some older light drinkers may have been moderate drinkers in middle age, because individual alcohol use tends to decline over time, and the apparent benefit of current light drinking may partly reflect effects of previous moderate alcohol use. Finally, we found a borderline significant quadratic term for alcohol use in analyses restricted to current drinkers (P = .09), suggesting a U-shaped association even after excluding abstainers.

The CHS has both strengths and limitations. The CHS participants who underwent MRI examination represent a relatively healthy group of older adults, given CHS eligibility criteria and selective participation in CHS and its MRI component. Thus, our results are most readily generalized to older adults with

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a similar health status. We cannot extrapolate our findings to other populations without further research but have no strong reason to believe our results would differ in other populations.

Even in this prospective analysis, we cannot exclude the possibility that some individuals may have changed their alcohol intake prior to the onset of follow-up because of early evidence of dementia (or illnesses that predispose to it). However, the participants we studied were relatively healthy, we performed analyses using alcohol consumption assessed several years before the onset of follow-up (or restricted to participants with stable consumption), we made a concerted effort to identify participants with mild cognitive impairment at the start of follow-up, and we separated former drinkers from long-term abstainers. Because some heavy drinkers reduce their consumption to moderate levels, rather than to abstinence over time, the lower odds of dementia we found among moderate drinkers may actually be overly conservative. Given the consistently higher odds of dementia among former drinkers than long-term abstainers, however, we emphasize the importance of separating these groups in future analyses.

The associations we describe could also be partly related to differences between drinkers and nondrinkers in factors other than alcohol consumption. Multivariate adjustment attenuated the strength of the reported associations somewhat, although we found similar patterns in unadjusted and adjusted analyses. To have produced the adjusted associations we found, any uncontrolled confounding factors would need to be strongly associated with both alcohol consumption and risk of dementia and generally unrelated to the many sociodemographic and clinical variables for which we controlled.

We relied on self-reported alcohol consumption, which has been validated in other epidemiological investigations but may have introduced some error into our analyses. In a review of errors in assessment of alcohol use in the elderly, Herzog concluded that such errors are no worse in surveys of older adults than in surveys of the general population. Furthermore, among the 744 participants in this study, we found an age-, sex-, and race-adjusted correlation coefficient between average alcohol intake and HDL-C level of 0.24 (P<.001), similar to the magnitude of correlation found in validation studies.

While controlling for possible confounding, we may have overadjusted for some covariates that are actually intermediate in the causal pathway between alcohol consumption and dementia. For example, if moderate alcohol consumption lowers the risk of diabetes, which in turn lowers the risk of dementia, then controlling for diabetes may have caused us to underestimate the actual difference in risk of dementia associated with moderate alcohol consumption. However, given the important concerns about confounding in observational studies of alcohol use, this conservative approach is appropriate.

In conclusion, we found the lowest odds of dementia among older adults who consumed 1 to 6 drinks weekly. Given the many physiological effects associated with alcohol consumption and the observational nature of our study, our findings should be extrapolated to clinical care with great caution. However, our results are consistent with the hypothesis that light-to-moderate drinking has a protective effect on long-term cognitive function.

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