

ORIGINAL ARTICLE

Effects of Moderate Alcohol Consumption on Cognitive Function in Women

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ABSTRACT

BACKGROUND

The adverse effects of excess alcohol intake on cognitive function are well established, but the effect of moderate consumption is uncertain.

METHODS

Between 1995 and 2001, we evaluated cognitive function in 12,480 participants in the Nurses' Health Study who were 70 to 81 years old, with follow-up assessments in 11,102 two years later. The level of alcohol consumption was ascertained regularly beginning in 1980. We calculated multivariate-adjusted mean cognitive scores and multivariate-adjusted risks of cognitive impairment (defined as the lowest 10 percent of the scores) and a substantial decline in cognitive function over time (defined as a change that was in the worst 10 percent of the distribution of the decline). We also stratified analyses according to the apolipoprotein E genotype in a subgroup of women.

RESULTS

After multivariate adjustment, moderate drinkers (those who consumed less than 15.0 g of alcohol per day [about one drink]) had better mean cognitive scores than nondrinkers. Among moderate drinkers, as compared with nondrinkers, the relative risk of impairment was 0.77 on our test of general cognition (95 percent confidence interval, 0.67 to 0.88) and 0.81 on the basis of a global cognitive score combining the results of all tests (95 percent confidence interval, 0.70 to 0.93). The results for cognitive decline were similar; for example, on our test of general cognition, the relative risk of a substantial decline in performance over a two-year period was 0.85 (95 percent confidence interval, 0.74 to 0.98) among moderate drinkers, as compared with nondrinkers. There were no significant associations between higher levels of drinking (15.0 to 30.0 g per day) and the risk of cognitive impairment or decline. There were no significant differences in risks according to the beverage (e.g., wine or beer) and no interaction with the apolipoprotein E genotype.

CONCLUSIONS

Our data suggest that in women, up to one drink per day does not impair cognitive function and may actually decrease the risk of cognitive decline.

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HABITUAL EXCESS ALCOHOL INTAKE impairs the brain,¹ but the effect of moderate consumption is unclear. A cognitive benefit from moderate alcohol intake is plausible, given the strong link between moderate alcohol intake and the decreased risk of cardiovascular disease^{2,3}; cognitive impairment and cardiovascular disease share common risk factors.⁴ In addition, Ruitenberg et al. reported that moderate alcohol consumption was related to a decreased risk of both vascular and nonvascular dementia⁵ and proposed that moderate alcohol consumption may increase the release of brain acetylcholine. Most studies,⁶⁻¹⁵ but not all,¹⁶⁻¹⁸ have tended to show that moderate drinkers do better on cognitive tests than nondrinkers; however, few studies have had samples that were large enough to yield statistically significant results or to assess long-term, stable patterns of alcohol intake and very early signs of cognitive decline. Also, many studies have been limited by inadequate control for confounding, and none have examined specific alcoholic beverages. We addressed these issues in the Nurses' Health Study.

METHODS

The Nurses' Health Study began in 1976, when 121,700 female registered nurses, 30 to 55 years of age, completed a mailed questionnaire about their lifestyle and health.¹⁹ Every two years, we mailed follow-up questionnaires, and in 1980 we added a food-frequency questionnaire.

Starting in 1995, we identified participants in the Nurses' Health Study who were 70 years of age or older for a study of cognitive function. Eligible women were community-dwelling participants without a diagnosis of stroke. Of the 21,202 women we contacted, 93 percent completed the telephone cognitive interview, with response rates varying by no more than 2 percent across categories of alcohol intake. With the exclusion of the 3 percent of women who died after the baseline cognitive assessment, we repeated the telephone assessments of cognitive function after an average of 1.8 years (range, 1.3 to 5.5) in 93 percent of the women; 7 percent declined or were lost to follow-up. All aspects of the study were approved by the human research committee at Brigham and Women's Hospital. For the questionnaire information, the return of the completed questionnaire was considered to imply informed consent. For the telephone inter-

view, we obtained oral consent. For the genetic sub-study, we obtained written informed consent.

ASCERTAINMENT OF ALCOHOL CONSUMPTION

We collected information on alcohol use as part of food-frequency questionnaires completed in 1980, 1984, 1986, 1990, 1994, and 1998. Participants were asked how often, on average, they had consumed beer (12 oz), wine (4 oz), or liquor (one standard drink) during the previous year, with the use of nine frequency categories ranging from never to six or more times per day. In 1980, we also asked whether the intake of any of these beverages had greatly changed during the previous 10 years. Starting in 1984, we added separate categories for red and white wine. Total alcohol intake was calculated in grams by adding the intake from each alcoholic-beverage unit: beer, 13.2 g; wine, 10.8 g; and liquor, 15.1 g.

The reproducibility and validity of the assessment of alcohol intake were evaluated among 173 Boston-area participants who completed written one-week dietary records every three months for a year, during which time they weighed or measured all their food and drinks.^{20,21} The correlation of alcohol intake on the questionnaire with alcohol intake on the dietary records was 0.9. Also, significant correlations were noted between alcohol consumption reported in the 1980 and 1984 questionnaires and between reported alcohol intake and serum high-density lipoprotein (HDL) levels.²²

POPULATION FOR ANALYSIS

To avoid bias from the inclusion of former heavy drinkers among the nondrinkers, we excluded women who reported no alcohol intake as of the baseline cognitive assessment but who had reported alcohol intake on previous questionnaires or who reported in 1980 that their alcohol consumption had greatly declined. To limit the analysis to women with stable drinking patterns, we also excluded those who changed their intake by more than one category (with categories of none, less than 5.0 g per day, 5.0 to 14.9 g per day, and 15.0 to 30.0 g per day) between the two questionnaires immediately preceding the baseline cognitive assessment. We also excluded the few women reporting an intake of more than 30.0 g per day. Finally, because the use of antidepressants is strongly related to both alcohol intake and cognition, we excluded the 737 women (6 percent) who reported antidepressant use. Thus, the baseline analyses include 12,480 women who

completed the food-frequency questionnaires, met the eligibility criteria, and completed the baseline cognitive interview. The analyses of change in cognitive function included the 11,102 women who also completed the follow-up assessment.

TESTS OF COGNITIVE FUNCTION

The initial interview consisted of the Telephone Interview for Cognitive Status (TICS),²³ modeled on the Mini-Mental State Examination (MMSE). Scores for the TICS can range from 0 to 41 (perfect), with a score of less than 31 indicating cognitive impairment, and include the score for the immediate recall of a 10-word list. Brandt et al.²³ reported a correlation of 0.94 between TICS and MMSE scores and a high test-retest reliability for the TICS ($r=0.97$).²³

In 1997, we began including additional tests: immediate and delayed recall of the East Boston Memory Test²⁴; delayed recall of the TICS 10-word list to assess verbal memory; a test of verbal fluency, in which women were asked to name as many animals as they could in one minute²⁵; and the digit span backward test to evaluate working memory and attention. In the East Boston Memory Test, each participant is read a brief paragraph and asked to repeat 12 elements immediately and 15 minutes later. Scores can range from 0 to 12, with higher scores indicating better recall. In the digit span backward test, a participant is asked to repeat, in reverse order, increasingly long series of numbers, up to a total of 12. Scores can range from 0 to 12, with higher scores indicating better recall. All women completed the TICS, and 87 percent completed all six tests. Participation rates in the study of cognitive function remained unchanged over time.

We focused our analyses on measures of general cognition and verbal memory. For general cognition, we used the TICS and a global cognitive score calculated by averaging the results of all the tests. The global score was calculated only for the 10,847 women who were administered all tests. Because a point in one test is not equivalent to a point in each of the other tests, we calculated z scores by taking the difference between the participant's score on each test and the mean score and dividing this value by the standard deviation. Because the presence of verbal memory impairment strongly predicts Alzheimer's disease,²⁶ we also calculated a verbal memory score by combining the results of immediate and delayed recall of both the TICS 10-word list and the East Boston Memory Test, using z scores.

Specially trained nurses who were unaware of the study hypothesis and of participants' drinking status completed all telephone assessments. In assessing reliability between interviewers, we found correlations of more than 0.95 between the interviewers' scoring of each test; there was also a high correlation between scores obtained when the TICS was administered twice, 31 days apart, to a subgroup of our participants ($r=0.7$). In a validation study we conducted among women from the Religious Orders Study,²⁷ whose age and level of education were similar to those of the participants in our study, we found a correlation of 0.81 between overall performance in our telephone interview and overall performance in an in-person interview, establishing the high validity of our telephone method. Moreover, the rate of cognitive decline among our subjects was quite similar to that among the participants in the Religious Orders Study, supporting the validity of our telephone assessment for measuring change in cognition.

APOLIPOPROTEIN E GENOTYPE

Several studies^{5,28,29} have suggested an interaction of alcohol with the apolipoprotein E genotype, a strong predictor of Alzheimer's disease and cognitive decline in our study³⁰ and many others. The apolipoprotein E genotype was assessed in a random subgroup of 3036 women included in the baseline analysis.

STATISTICAL ANALYSIS

We analyzed the relation of alcohol consumption (from the most recent questionnaire before the baseline cognitive interview) to cognitive function and cognitive decline. On the basis of the distribution of alcohol intake, we categorized women as nondrinkers (reference category), those who drank 1.0 to 14.9 g of alcohol per day, and those who drank 15.0 to 30.0 g of alcohol per day. We calculated mean scores for the cognitive tests according to alcohol consumption, using linear regression models to adjust for age and other potential confounders (see below).

We also classified cognitive performance as impaired or not impaired. For the TICS, we used an established cutoff score of less than 31 points to define cognitive impairment²³; for the remaining tests, we defined impairment as the lowest 10 percent of the distribution, a commonly used cutoff point for defining impairment in cognitive research,³¹ with high sensitivity and specificity.³² We

used logistic regression with adjustment for age, education, and multiple variables to estimate relative risks of cognitive impairment (calculated from odds ratios) and 95 percent confidence intervals. To assess the effects of individual beverages, we constructed separate regression models for alcohol from beer, white wine, red wine, and spirits and controlled for alcohol from the other sources within each level of total alcohol intake.

In regression models, we considered the following potential confounding variables, possibly related to both cognitive function and alcohol intake: age at the time of the interview (continuous); highest educational degree (registered nurse or associate's degree, bachelor's degree, or graduate degree); a history of hypertension, high cholesterol levels, diabetes, or heart disease (yes vs. no); level of physical activity, measured in metabolic-equivalent hours per week (quintiles); age at menopause; use of postmenopausal hormone therapy (current, past, or never); use of vitamin E supplements (yes vs. no); body-mass index (the weight in kilograms divided by the square of the height in meters [less than 22.0, 22.0 to 24.9, 25.0 to 29.9, or 30.0 or more]); cigarette-smoking status (current, past, or never); aspirin use (once or twice per week, three or more times per week, or none); ibuprofen use (yes vs. no); scores for the mental health index (0 to 79 [low] vs. 80 to 100) and energy-fatigue index (0 to 65 [low] vs. 66 to 100) of the 36-item Medical Outcomes Short Form General Health Survey; and the degree of social integration according to the Berkman-Syme Social Network Index. Information on these variables was obtained from the most recent questionnaire before the baseline cognitive assessment.

For analyses of change in cognitive function, we used logistic regression to estimate adjusted relative risks of a substantial decline (defined as a change that was in the worst 10 percent of the distribution of the decline). In these models, we included the potential confounding variables listed above, as well as the baseline cognitive score. Although the use of adjustment for baseline cognitive performance is controversial, we believe such adjustment is necessary to take into account learning (the effect of familiarity with test questions from the previous administration) and ceiling effects (those with perfect scores cannot improve, and thus, their scores are most likely to decline) and to reduce variability within subjects. The results were similar before and after adjustment for baseline cognitive performance. We previously showed that persons with di-

abetes have an increased risk of cognitive decline³³ and are typically advised to avoid alcohol. In the primary analyses, we adjusted for the presence or absence of diabetes, but we conducted a secondary analysis that excluded women with diabetes. To examine interactions with the apolipoprotein E ϵ 4 allele, we stratified analyses according to those with no ϵ 4 allele and those with any ϵ 4 allele.

RESULTS

In this cohort, 51 percent of the women were nondrinkers, 44 percent drank 1.0 to 14.9 g of alcohol per day (up to about one drink), and 5 percent consumed 15.0 to 30.0 g per day. Health and lifestyle characteristics generally did not vary substantially according to alcohol intake (Table 1).

Women consuming less than 15.0 g of alcohol per day tended to have slightly better mean cognitive scores than nondrinkers (Table 1). After adjustment for potential confounding factors, such women had significantly better mean cognitive scores than nondrinkers on all three primary outcomes (Table 2 and Fig. 1). We found no significant differences in cognitive performance between nondrinkers and those drinking 15.0 to 30.0 g of alcohol per day, although the size of the latter group was small (648 women). For the TICS, each additional year of age was associated with a mean difference of 0.15 point; thus, for participants who were 70 to 81 years of age, drinking 1.0 to 14.9 g of alcohol per day was cognitively equivalent to being approximately a year and a half younger (mean difference, 0.21; range, 0.11 to 0.30).

Women who drank less than 15.0 g of alcohol per day had a risk of cognitive impairment that was approximately 20 percent lower than that among nondrinkers (Table 2), with and without adjustment for confounders, which was statistically significant for all three primary outcomes. For example, for the global cognitive score, women who drank 1.0 to 14.9 g of alcohol per day had an adjusted relative risk of cognitive impairment of 0.81 (95 percent confidence interval, 0.70 to 0.93), as compared with nondrinkers.

Although we measured cognitive decline over a short period (mean, 1.8 years), women who drank 1.0 to 14.9 g of alcohol per day had a lower risk of substantial cognitive decline during this period than did nondrinkers (Table 3). The findings were statistically significant for the TICS score and the verbal memory score.

Table 1. Characteristics of Participants in the Nurses' Health Study According to Alcohol Intake.*

Characteristic	Alcohol Intake		
	None (N=6385)	1.0–14.9 g/day (N=5447)	15.0–30.0 g/day (N=648)
Mean age at interview (yr)	74	74	74
Master's or doctorate degree (%)	5	7	8
Heart disease (%)	6	4	5
High cholesterol (%)	66	64	60
Hypertension (%)	56	50	50
Diabetes (%)	13	5	5
Body-mass index ≥ 30 (%) [†]	21	13	6
Current smoker (%)	6	8	9
Physical activity (mean MET-hr/wk)	15	18	20
Current postmenopausal hormone use (%)	31	35	37
Current vitamin E use (%)	43	48	54
Regular aspirin or ibuprofen use (%)	39	42	46
Low energy level (SF-36 score of 0–65) (%) [‡]	17	10	10
Low mental health index (SF-36 score of 0–79) (%) [‡]	3	2	1
Feeling of social isolation (%) [§]	4	3	5
Scores for cognitive-function tests [¶]			
TICS	33.8 \pm 2.7	34.0 \pm 2.6	34.0 \pm 2.5
East Boston Memory Test — immediate recall	9.4 \pm 1.7	9.5 \pm 1.7	9.5 \pm 1.7
East Boston Memory Test — delayed recall	9.0 \pm 2.0	9.1 \pm 1.9	9.1 \pm 1.9
10-Word list — immediate recall	4.6 \pm 1.7	4.8 \pm 1.7	4.7 \pm 1.6
10-Word list — delayed recall	2.3 \pm 2.0	2.5 \pm 2.0	2.4 \pm 1.8
Verbal fluency	17.1 \pm 4.7	17.1 \pm 4.6	17.2 \pm 4.7
Digit span backward test	6.7 \pm 2.4	6.9 \pm 2.4	6.8 \pm 2.4
TICS score <31 (%)	10.6	7.9	8.0
Lowest 10% for global cognitive score (%)	11.2	8.6	9.0
Lowest 10% for verbal memory score (%)	11.1	8.6	10.0

* Plus-minus values are means \pm SD. Except for cognitive tests, data were obtained from the questionnaire administered before the baseline cognitive assessment.

[†] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[‡] The presence of this characteristic was determined by means of the 36-item Medical Outcomes Study Short Form General Health Survey (SF-36).

[§] The presence of this characteristic was determined by means of the Berkman-Syme Social Network Index.

[¶] Scores for the Telephone Interview for Cognitive Status (TICS) can range from 0 to 41 (perfect), with scores of less than 31 indicating cognitive impairment. Scores for the East Boston Memory Test and digit span backward test can range from 0 to 12, with higher scores indicating better recall. Scores for the 10-word list of the TICS can range from 0 to 10, with higher scores indicating better recall. Scores of verbal fluency reflect the number of animals a participant could name in one minute; thus, higher scores indicate better verbal fluency. The global cognitive score is the average of the results of all cognitive tests. The verbal memory score combines the results of immediate and delayed recall of both the TICS 10-word list and the East Boston Memory Test.

For women who drank 1.0 to 14.9 g of alcohol per day, as compared with nondrinkers, each type of beverage was significantly associated with a lower risk of cognitive impairment, with relative risks according to the global cognitive score ranging from 0.68 for beer to 0.84 for red wine. All the con-

fidence intervals for specific beverages broadly overlapped. When we analyzed the likelihood of a substantial decline in cognitive function, the results were similar to those for baseline analyses, with no marked differences according to the type of beverage.

Table 2. Relative Risks of Cognitive Impairment According to Alcohol Intake.

Measure of Cognitive Impairment*	No. Who Completed Test	Alcohol Intake		
		None†	1.0–14.9 g/day	15.0–30.0 g/day
<i>relative risk (95 percent confidence interval)</i>				
TICS score <31	12,480			
Adjusted for age and level of education		1.00	0.74 (0.65–0.84)	0.77 (0.57–1.04)
Multivariate-adjusted		1.00	0.77 (0.67–0.88)	0.78 (0.57–1.06)
Lowest 10% for verbal memory score	10,856			
Adjusted for age and level of education		1.00	0.76 (0.66–0.87)	0.88 (0.65–1.19)
Multivariate-adjusted		1.00	0.81 (0.70–0.92)	0.93 (0.68–1.26)
Lowest 10% for global cognitive score	10,847			
Adjusted for age and level of education		1.00	0.76 (0.66–0.87)	0.79 (0.58–1.09)
Multivariate-adjusted		1.00	0.81 (0.70–0.93)	0.82 (0.59–1.13)

* TICS denotes the Telephone Interview for Cognitive Status. The verbal memory score combines the results of immediate and delayed recall of both the TICS 10-word list and the East Boston Memory Test. The global cognitive score is the average of the results of all cognitive tests. Multivariate-adjusted relative risks were adjusted for age; level of education; the presence or absence of a history of hypertension, diabetes, high cholesterol levels, and heart disease; level of physical activity; age at menopause; use or nonuse of postmenopausal hormone therapy, aspirin and ibuprofen, and vitamin E supplements; body-mass index; smoking status; scores for the mental health and energy-fatigue indexes on the SF-36; and score for the Berkman-Syme Social Network Index.

† Nondrinkers served as the reference group.

Finally, excluding women with diabetes from the analysis did not change the results. Also, we found no material interactions between alcohol intake and the apolipoprotein E ϵ 4 allele. With respect to the global cognitive score, the relative risk of cognitive impairment among moderate drinkers, as compared with nondrinkers, was 0.84 (95 percent confidence interval, 0.59 to 1.21) among those without the ϵ 4 allele and 0.84 (95 percent confidence interval, 0.46 to 1.53) among those with the allele.

DISCUSSION

We found that older women who consumed up to one drink per day had consistently better cognitive performance than nondrinkers. Overall, as compared with nondrinkers, women who drank 1.0 to 14.9 g of alcohol per day had a decrease in the risk of cognitive impairment of about 20 percent. Moreover, moderate drinkers were less likely to have a substantial decline in cognitive function over a two-year period. We found similar inverse associations for all types of alcoholic beverages.

Our study had several limitations. We could not assess the effect of high levels of alcohol intake, since there were few heavy drinkers in our cohort. Also, cognitive decline was assessed only over a

two-year interval; thus, the association between alcohol consumption and longer-term cognitive decline could not be evaluated. Information on alcohol consumption was self-reported, perhaps leading to some misclassification. However, our assessment of alcohol intake was validated on the basis of dietary records and levels of biochemical markers and has been used to predict several disease outcomes in this cohort.^{34,35}

Our telephone assessment of cognitive function may also have resulted in some misclassification. However, we found that this approach has high rates of reliability and validity in comparison with in-person assessments. Furthermore, using results from the telephone assessment method, we have observed strong associations with established predictors of cognitive function (age, level of education, and apolipoprotein E genotype); the magnitude of these associations is similar to that reported with the use of in-person cognitive interviews,^{27,30} further confirming the validity of our methods. Misclassification of alcohol intake or cognition would tend to result in an underestimate of the associations.

We cannot exclude the possibility that women with poor cognition decreased their alcohol intake (reverse causation). This seems unlikely, however, since we specifically excluded heavier drinkers and

limited our analyses to those with stable patterns of alcohol intake.

Finally, there may be uncontrolled confounding. Moderate drinkers had several favorable health characteristics that may influence cognitive function, such as a decreased incidence of diabetes. However, analyses that excluded women with diabetes yielded similar results. Adjustment for many potential confounders had little effect on the results, suggesting that confounding is unlikely to explain the observed associations. The finding of similar effects for each alcoholic beverage also lends support to a causal interpretation of the association, since patterns of confounding tend to differ according to the type of beverage. Nonetheless, we cannot rule out the possibility of confounding by unmeasured factors.

Our observations are generally similar to those in previous studies of alcohol intake and cognitive function. Such studies were all substantially smaller than ours and often showed nonsignificant inverse relations. Two small studies^{16,17} showed no correlation between the level of alcohol consumption and cognitive function, but four others showed nonsignificant trends toward better cognitive scores among moderate drinkers.⁶⁻⁹ Three large cross-sectional studies of U.S. blacks,¹⁰ French men and women,¹² and Japanese Americans³⁶ all showed

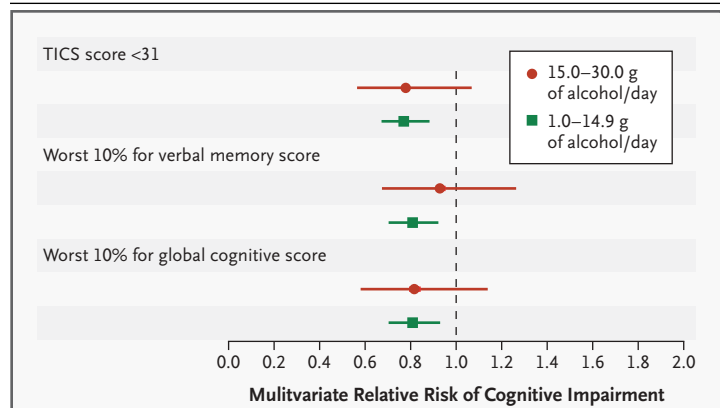


Figure 1. Multivariate Relative Risk of Cognitive Impairment among Women Who Drank 1.0 to 14.9 g of Alcohol per Day or 15.0 to 30.0 g of Alcohol per Day, as Compared with Nondrinkers.

TICS denotes the Telephone Interview for Cognitive Status. The verbal memory score reflects the results of immediate and delayed recall of both the TICS 10-word list and the East Boston Memory Test. The global cognitive score is the average of the results of all cognitive tests.

significantly better cognitive performance among moderate drinkers than among nondrinkers. Similar results were obtained in five prospective studies.^{11,14,15,37,38} In a study of 333 men, Launer et al.¹³ reported that the prevalence of cognitive impairment was significantly lower among men with mod-

Table 3. Relative Risks of a Substantial Decline in Cognitive Function over a Two-Year Period, According to Alcohol Intake.

Measure of Substantial Cognitive Decline*	No. Who Completed Test	Alcohol Intake		
		None†	1.0–14.9 g/day	15.0–30.0 g/day
<i>relative risk (95 percent confidence interval)</i>				
TICS score for worst 10% of distribution of decline				
Adjusted for age and level of education	11,102	1.00	0.82 (0.72–0.95)	1.00 (0.74–1.35)
Multivariate-adjusted		1.00	0.85 (0.74–0.98)	1.04 (0.77–1.41)
Verbal memory score for worst 10% of distribution of decline				
Adjusted for age and level of education	9,670	1.00	0.82 (0.71–0.95)	0.78 (0.55–1.10)
Multivariate-adjusted		1.00	0.83 (0.72–0.97)	0.76 (0.54–1.09)
Global cognitive score for worst 10% of distribution of decline				
Adjusted for age and level of education	9,661	1.00	0.86 (0.74–0.99)	0.81 (0.58–1.13)
Multivariate-adjusted		1.00	0.89 (0.77–1.03)	0.82 (0.58–1.16)

* TICS denotes the Telephone Interview for Cognitive Status. The verbal memory score combines the results of immediate and delayed recall of both the TICS 10-word list and the East Boston Memory Test. The global cognitive score is the average of the results of all cognitive tests. Multivariate-adjusted relative risks were adjusted for age; level of education; the presence or absence of a history of hypertension, diabetes, high cholesterol levels, and heart disease; level of physical activity; age at menopause; use or nonuse of postmenopausal hormone therapy, aspirin and ibuprofen, and vitamin E supplements; body-mass index; smoking status; scores for the mental health and energy-fatigue indexes on the SF-36; score for the Berkman-Syme Social Network Index; and the interval between the most recent interview and the baseline cognitive assessment.

† Nondrinkers served as the reference group.

erate alcohol intake than among nondrinkers, but alcohol intake was not associated with cognitive decline, perhaps owing to the small sample. Several studies showed an apparently stronger association between alcohol intake and cognitive function among women than among men. This difference may reflect a true effect of sex or perhaps less misclassification of moderate alcohol consumption among women.

Several mechanisms have been proposed to explain the association of moderate alcohol consumption with better cognition. The most plausible relates to the consistently lower rates of cardiovascular disease among moderate alcohol drinkers in many studies.^{2,3} This risk reduction has been attributed partly to alcohol-induced elevations in HDL cholesterol and reductions in fibrinogen and other thrombotic factors.³ Thus, moderate intake of alcohol may also help preserve brain vasculature, may prevent subclinical strokes, and could thus result in better cognitive function. In support of this concept, Mukamal et al.³⁹ found that among older persons without cerebrovascular disease, those with moderate alcohol intake had fewer white-matter abnormalities and infarcts on magnetic resonance imaging than nondrinkers. The same authors found

pronounced reductions in the risk of both vascular dementia and Alzheimer's disease among persons consuming one to six drinks per week.⁴⁰

Several studies have assessed whether there is an interaction between alcohol intake and the apolipoprotein E genotype. Ruitenberg et al.⁵ reported a stronger inverse association between the level of alcohol intake and the risk of dementia among persons with the apolipoprotein E ϵ 4 allele than among those without this allele, although the difference between the groups was not significant; Mukamal et al. reported the opposite trend.⁴⁰ Conflicting findings were also reported for cognitive decline.^{28,29} On the basis of these results and our finding of no interaction between alcohol intake and the apolipoprotein E ϵ 4 genotype, any pronounced interaction seems unlikely.

Although the adverse effects of excessive alcohol intake are well known and caution should be exercised in recommending even moderate alcohol intake, our results combined with those of other studies suggest that women who consume up to one drink per day have less cognitive impairment and better cognitive function than nondrinkers.

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REFERENCES

- Chick JD, Smith MA, Engleman HM, et al. Magnetic resonance imaging of the brain in alcoholics: cerebral atrophy, lifetime alcohol consumption, and cognitive deficits. *Alcohol Clin Exp Res* 1989;13:512-8.
- Rimm EB, Stampfer MJ. Alcohol abstinence: a risk factor for coronary heart disease. *Heart Disease Updates* 2000;2:1-9.
- Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;319:1523-8.
- Breteler MM, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology* 1994;44:1246-52.
- Ruitenberg A, van Swieten JC, Witteman JC, et al. Alcohol consumption and risk of dementia: the Rotterdam Study. *Lancet* 2002;359:281-6.
- Cervilla JA, Prince M, Mann A. Smoking, drinking, and incident cognitive impairment: a cohort community based study included in the Gospel Oak project. *J Neurol Neurosurg Psychiatry* 2000;68:622-6.
- Elwood PC, Gallacher JE, Hopkinson CA, et al. Smoking, drinking, and other lifestyle factors and cognitive function in men in the Caerphilly cohort. *J Epidemiol Community Health* 1999;53:9-14.
- Goodwin JS, Sanchez CJ, Thomas P, Hunt C, Garry PJ, Goodwin JM. Alcohol intake in a healthy elderly population. *Am J Public Health* 1987;77:173-7.
- Herbert LE, Scherr PA, Beckett LA, et al. Relation of smoking and low-to-moderate alcohol consumption to change in cognitive function: a longitudinal study in a defined community of older persons. *Am J Epidemiol* 1993;137:881-91.
- Hendrie HC, Gao S, Hall KS, Hui SL, Unverzagt FW. The relationship between alcohol consumption, cognitive performance, and daily functioning in an urban sample of older black Americans. *J Am Geriatr Soc* 1996;44:1158-65.
- Christian JC, Reed T, Carmelli D, Page WF, Norton JA Jr, Breitner JC. Self-reported alcohol intake and cognition in aging twins. *J Stud Alcohol* 1995;56:414-6.
- Dufouil C, Ducimetiere P, Alperovitch A. Sex differences in the association between alcohol consumption and cognitive performance. *Am J Epidemiol* 1997;146:405-12.
- Launer LJ, Feskens EJ, Kalmijn S, Kromhout D. Smoking, drinking, and thinking: the Zutphen Elderly Study. *Am J Epidemiol* 1996;143:219-27.
- Elias PK, Elias MF, D'Agostino RB, Silbershatz H, Wolf PA. Alcohol consumption and cognitive performance in the Framingham Heart Study. *Am J Epidemiol* 1999;150:580-9.
- Galanis DJ, Joseph C, Masaki KH, Petrovitch H, Ross GW, White L. A longitudinal study of drinking and cognitive performance in elderly Japanese American men: the Honolulu-Asia Aging Study. *Am J Public Health* 2000;90:1254-9.
- Dent OF, Sulway MR, Broe GA, et al. Alcohol consumption and cognitive performance in a random sample of Australian soldiers who served in the Second World War. *BMJ* 1997;314:1655-7.
- Broe GA, Creasey H, Jorm AF, et al. Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption. *Aust N Z J Public Health* 1998;22:621-3.
- Edelstein SL, Kritz-Silverstein D, Barrett-Connor E. Prospective association of smoking and alcohol use with cognitive function in an elderly cohort. *J Womens Health* 1998;7:1271-81.

19. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health* 1997;6:49-62.
20. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semi-quantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51-65.
21. Willett WC. *Nutritional epidemiology*. 2nd ed. New York: Oxford University Press, 1998.
22. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol* 1991;133:810-7.
23. Brandt J, Spencer M, Folstein M. The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* 1988;1:111-7.
24. Albert M, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH. Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. *Int J Neurosci* 1991;57:167-78.
25. Morris JC, Edland S, Clark C, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. *Neurology* 1993;43:2457-65.
26. Small BJ, Fratiglioni L, Viitanen M, Windblad B, Backman L. The course of cognitive impairment in preclinical Alzheimer disease: three- and six-year follow-up of a population based sample. *Arch Neurol* 2000;57:839-44.
27. Wilson RS, Schneider JA, Barnes LL, et al. The apolipoprotein E epsilon 4 allele and decline in different cognitive systems during a 6-year period. *Arch Neurol* 2002;59:1154-60.
28. 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;11:280-4.
29. 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.
30. Kang JH, Logroschino G, De Vivo I, Hunter D, Grodstein F. Apolipoprotein E, cardiovascular disease and cognitive function in aging women. *Neurobiol Aging* (in press).
31. Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med* 2001;344:1207-13.
32. Ganguli M, Belle S, Ratcliff G, et al. Sensitivity and specificity for dementia of population-based criteria for cognitive impairment: the MoVIES project. *J Gerontol* 1993;48:M152-M161.
33. Grodstein F, Chen J, Wilson RS, Manson JE. Type 2 diabetes and cognitive function in community-dwelling elderly women. *Diabetes Care* 2001;24:1060-5.
34. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med* 1988;319:267-73.
35. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 1987;316:1174-80.
36. Bond GE, Burr R, McCurry SM, Graves AB, Larson EB. Alcohol, aging, and cognitive performance in a cohort of Japanese Americans aged 65 and older: the Kame Project. *Int Psychogeriatr* 2001;13:207-23.
37. Kalmijn S, van Boxtel MP, Verschuren MW, Jolles J, Launer LJ. Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age. *Am J Epidemiol* 2002;156:936-44.
38. Leroi I, Sheppard JM, Lyketsos CG. Cognitive function after 11.5 years of alcohol use: relation to alcohol use. *Am J Epidemiol* 2002;156:747-52.
39. Mukamal KJ, Longstreth WT Jr, Mittleman MA, Crum RM, Siscovick DS. Alcohol consumption and subclinical findings on magnetic resonance imaging of the brain in older adults: the Cardiovascular Health Study. *Stroke* 2001;32:1939-46.
40. Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr, Mittleman MA, Siscovick DS. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA* 2003;289:1405-13.

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