

Association between Reported Alcohol Intake and Cognition: Results from the Women's Health Initiative Memory Study

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Some, but not all, observational studies have suggested that moderate levels of alcohol intake may be associated with improved cognitive function and reduced risk of cognitive decline and dementia. The authors of this 1996–2002 study used data from the Women's Health Initiative Memory Study of postmenopausal combination hormone therapy to assess cross-sectional and prospective associations of self-reported alcohol intake with cognitive function. Across 39 US academic medical centers, 4,461 community-dwelling women aged 65–79 years were followed an average of 4.2 years with annual Modified Mini-Mental State Examinations and standardized protocols for detecting mild cognitive impairment and probable dementia. Compared with no intake, intake of ≥ 1 drink per day was associated with higher baseline Modified Mini-Mental State Examination scores ($p < 0.001$) and a covariate-adjusted odds ratio of 0.40 (95% confidence interval: 0.28, 0.99) for significant declines in cognitive function. Associations with incident probable dementia and mild cognitive impairment were of similar magnitude but were not statistically significant after covariate adjustment. Associations with intakes of < 1 drink per day were intermediate. Moderate levels of alcohol intake may be associated with better cognition and reduced risk of significant cognitive decline; however, confounding associations with unmeasured factors cannot be ruled out.

cognition; dementia; ethanol; women's health

Abbreviations: *APOE4*, apolipoprotein E epsilon-4 genotype; CI, confidence interval; E + P, conjugated equine estrogens plus medroxyprogesterone acetate; HDL, high density lipoprotein; SE, standard error; 3MSE, Modified Mini-Mental State Examination; WHIMS, Women's Health Initiative Memory Study.

Recent longitudinal community cohort studies suggest that moderate alcohol intake may benefit cognition. For example, the Epidemiology of Vascular Aging Study (participants aged 59–71 years; 59 percent female) found that mean scores on the Mini-Mental State Examination (1), a measure of global cognitive function, were higher among women reporting moderate levels of alcohol intake compared with no intake (2). The Atherosclerosis Risk in Communities Study (subjects aged 45–69 years; 55 percent female) found

that current drinkers, most of whom drank lightly to moderately, had higher cognitive scores than nondrinkers on three cognitive tests, with a clear dose-response association on a word fluency test and an inverted U-shaped response on delayed word recall and digit symbol substitution tests (3). These findings generally agree with those from other cohorts of women (4–6).

Evidence is growing that moderate levels of alcohol intake are associated with a reduced risk of dementia. A case-

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control study conducted within the Cardiovascular Health Study (participants aged 65–97 years; 60 percent female) found that the odds ratio for incident dementia was 0.37 (95 percent confidence interval (CI): 0.23, 0.60) for subjects reporting consumption of 1–6 drinks per week compared with nondrinkers; for those reporting 7–13 drinks per week, the odds ratio was 0.64 (95 percent CI: 0.36, 1.13) (7). Similarly, the Rotterdam Study (participants aged 60–90 years; 52 percent female) reported hazard ratios for dementia (relative to nondrinkers) of 0.82 (95 percent CI: 0.56, 1.22) for <1 drink per week, 0.75 (95 percent CI: 0.51, 1.11) for 1–6 drinks per week, and 0.58 (95 percent CI: 0.38, 0.90) for 1–3 drinks per day (8). A positive relation has not been detected consistently, however (9–12). For example, the Established Populations for Epidemiologic Studies of the Elderly program (subjects aged ≥65 years; 56 percent female) reported an odds ratio of 1.1 (95 percent CI: 0.8, 1.5) for Alzheimer's disease comparing consumption of 1 ounce (28.3 g) of alcohol per day with no consumption (9).

We used data from a large, randomized clinical trial of postmenopausal combination estrogen and progestin therapy, which involved annual assessment of cognition and dementia status over an average of 4.2 years of follow-up, to address several goals. We examined associations of cross-sectional global cognitive function with clinically significant decreases in global cognitive function and with the incidence of probable dementia and mild cognitive impairment. In this paper, results from analyses with and without control for demographic/socioeconomic factors and cardiovascular risk factors are presented. Because both alcohol intake and hormone therapy may influence cognition by altering levels of lipoproteins and/or coagulation and have been reported to interact with respect to their association with cognitive function (13), we also assessed whether the influence of combination hormone therapy on cognition varied according to alcohol intake.

MATERIALS AND METHODS

The Women's Health Initiative Memory Study (WHIMS) (14) is an ancillary study to the Women's Health Initiative trials of hormone therapy (15), two large, randomized, double-blind, placebo-controlled, clinical trials of hormone-related outcomes. WHIMS was conducted to assess the relative effect of 0.625 mg/day of conjugated equine estrogen alone or in combination with 2.5 mg/day of continuous medroxyprogesterone acetate on the incidence of dementia and global cognitive functioning in postmenopausal women. Following discovery of an unfavorable risk-to-benefit ratio of its noncognitive endpoints (16), administration of study drugs in the Women's Health Initiative conjugated equine estrogens plus medroxyprogesterone acetate (E + P) trial was discontinued (July 2002). This decision also ended the E + P trial of WHIMS, which subsequently reported an adverse association between E + P and both dementia and cognitive function (17, 18). We analyzed data from this trial.

The study design, eligibility criteria, and recruitment procedures of the Women's Health Initiative E + P trial have been described elsewhere (15). Beginning in 1996, women aged 50–79 years were enrolled if they had an intact uterus

and were postmenopausal. Women were excluded if there were concerns about competing risks, safety, or adherence/retention (including an assessment of alcoholism by staff). Women were assigned randomly with equal probability to take one daily tablet that contained either 0.625 mg of conjugated equine estrogen with 2.5 mg of medroxyprogesterone acetate (PREMPRO; Wyeth Pharmaceuticals, Collegeville, Pennsylvania) or a matching placebo.

Participants in the WHIMS E + P trial were recruited between May 1996 and December 1999 from women in the Women's Health Initiative E + P trial who were at least 65 years of age and free of dementia, as ascertained by the WHIMS protocol (14). Written informed consent was obtained. The National Institutes of Health (Bethesda, Maryland) and institutional review boards approved the protocol and consent forms.

Baseline alcohol intake was assessed by using the Women's Health Initiative food frequency questionnaire (19), which queried intake (beer, wine, and liquor separately) over the past 3 months. Alcohol intakes were grouped as none, <1 drink per day, and ≥1 drink per day. Self-reported alcohol intake has correlations with other measures of alcohol intake of about $r = 0.6$ – 0.7 (20). The correlation of self-reported intake with the underlying "true" intake may be roughly estimated as the square root of this correlation, for example, approximately $r = 0.80$ (21). In a separate questionnaire, women who reported no current intake and responded "yes" to the question, "During your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?" were asked whether intake was stopped for "health problems" or "nonhealth problems." No information was collected to estimate the extent of lifetime intake.

Global cognitive function was measured with the Modified Mini-Mental State Examination (3MSE) (22) at baseline and annually for up to 6 years. The average time between the first and last examinations (4.2 years) was similar across reported alcohol intakes ($p = 0.24$). The 3MSE consists of 15 items that sum to 0–100; higher scores reflect better cognitive functioning. Test items measure temporal and spatial orientation, immediate and delayed recall, executive function (control and management of other cognitive processes), naming, verbal fluency, abstract reasoning, praxis, writing, and visuo-constructional abilities. The 3MSE has good reliability, sensitivity, and specificity for detecting cognitive impairment and dementia (23). In our analyses, we assessed associations with baseline 3MSE and with the occurrence, at any time during follow-up, of a decline from baseline of 8 units (2 standard errors (SEs)), which corresponds to a clinically significant decline (18).

3MSE assessments were administered by trained and certified technicians who were masked to other outcomes. Participants who scored below preestablished cutpoints were scheduled for a more extensive neurocognitive assessment and neuropsychiatric examination to determine the presence or absence of probable dementia and mild cognitive impairment, which was centrally adjudicated (14). Regardless of adjudicated dementia status, women continued to be scheduled for their annual 3MSE assessments.

Baseline demographic and clinical factors were collected via self-report and standardized assessments. Factors

TABLE 1. Demographic, socioeconomic status, and lifestyle characteristics of participants in the Women's Health Initiative Memory Study, by level of alcohol intake, United States, 1996–2002

Variable	No alcohol intake (n = 1,345)		<1 drink per day (n = 2,500)		≥1 drink per day (n = 616)		p value*
	Frequency	%	Frequency	%	Frequency	%	
Age (years)							
65–69	603	28.9	1,196	57.4	286	13.7	0.47
70–74	488	30.9	871	55.1	222	14.0	
≥75	254	32.0	433	54.5	108	13.6	
No. of years since menopause							
10–14	199	30.3	372	56.6	86	13.1	0.06
15–24	727	28.7	1,442	56.9	364	14.4	
≥25	304	34.0	475	53.1	116	13.0	
Education							
<High school	150	52.4	126	44.1	10	3.5	<0.001
High school/General Educational Development test certificate	312	33.6	529	56.9	88	9.5	
>High school but <4 years of college	532	30.5	969	55.6	243	13.9	
≥4 years of college	346	23.3	865	58.3	272	18.3	
Ethnicity							
American Indian/Alaskan Native	4	40.0	5	50.0	1	10.0	<0.001
Asian/Pacific Islander	59	66.3	25	28.1	5	5.6	
Black/African American	106	51.0	98	47.1	4	1.9	
Hispanic/Latino	48	49.5	43	44.3	6	6.2	
White, non-Hispanic	1,102	27.6	2,296	57.6	590	14.8	
Other	25	41.7	29	48.3	6	10.0	
Family income (\$/year)							
<19,999	406	42.2	478	49.7	77	8.0	<0.001
20,000–34,999	419	32.2	735	56.4	148	11.4	
35,000–49,999	230	25.2	538	59.0	144	15.8	
50,000–74,999	148	23.0	362	56.1	135	20.9	
≥75,000	98	20.0	298	60.8	94	19.2	
Smoking status							
Never	877	38.0	1,240	53.7	194	19.1	<0.001
Former	394	22.1	1,049	58.8	341	19.2	
Current	60	19.7	176	57.9	68	22.4	

* Results from chi-square tests.

included in our analyses were those found to be significantly related to the 3MSE (18, 24) and that were expected to be associated with alcohol intake: age; years since menopause; education; ethnicity; family income; use of tobacco; body mass index; history of hypertension, cardiovascular disease, or diabetes; use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statin therapy) or aspirin; prior use of hormone therapy; and intervention assignment.

Differences in baseline demographic and clinical factors among women grouped by alcohol intake were assessed by using chi-square tests and analyses of variance. Cross-sectional analyses associations between the 3MSE and alcohol intake were examined by using analyses of variance and covariance. Women were grouped according to whether

they were measured to have had a drop of 8 or more 3MSE units from baseline at any time during follow-up; logistic regression (in which treatment assignment was included as a covariate) was used to examine the relation between this occurrence and baseline alcohol intake, with and without adjustment for demographic/socioeconomic, lifestyle, and clinical factors.

Associations between alcohol intake and incidence of probable dementia and combined probable dementia/mild cognitive impairment were examined with proportional hazards regression and Kaplan-Meier plots. In these analyses, women were censored when they were lost to follow-up or at the trial's termination.

TABLE 2. Association of alcohol intake with clinical characteristics and therapy among participants in the Women's Health Initiative Memory Study, by level of alcohol intake, United States, 1996–2002

Variable	No alcohol intake (n = 1,345)		<1 drink per day (n = 2,500)		≥1 drink per day (n = 616)		p value*
	Frequency	%	Frequency	%	Frequency	%	
Body mass index (kg/m ²)							
<25	410	28.4	760	52.7	271	18.8	<0.001
25–29	440	27.8	925	58.4	219	13.8	
30–34	287	31.1	542	58.7	95	10.3	
≥35	201	41.4	258	53.1	27	5.6	
Hypertension status							
None	642	27.2	1,372	58.2	342	14.5	<0.001
Current/controlled†	241	36.5	343	51.9	77	11.7	
Current/uncontrolled	462	32.0	785	54.4	197	13.6	
Prior cardiovascular disease							
No	1,190	29.3	2,293	56.5	577	14.2	0.001
History of stroke	25	38.5	35	53.8	5	7.7	
History of other cardiovascular disease‡	130	38.7	172	51.2	34	10.1	
Diabetes							
No	1,193	28.7	2,360	56.8	604	14.5	<0.001
Yes	151	50.5	137	45.8	11	3.7	
Use of HMG-CoA§ reductase inhibitors							
No	1,186	29.6	2,248	56.2	569	14.2	0.03
Yes	167	34.2	270	55.2	52	10.7	
Regular use of aspirin							
No	968	30.6	1,774	56.0	423	13.4	0.33
Yes	377	29.1	724	55.9	193	14.9	
Prior use of hormone therapy							
No	1,072	30.8	1,957	56.3	446	12.8	0.001
Yes	273	27.7	543	55.1	170	17.2	
Intervention assignment							
E + P§	664	30.2	1,238	56.3	297	13.5	0.84
Placebo	681	30.1	1,262	55.8	319	14.1	

* Results from chi-square tests.

† Measured as <140/90 mmHg.

‡ Other cardiovascular disease defined as myocardial infarction, angina, percutaneous coronary transluminal angioplasty, or coronary artery bypass graft.

§ HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; E + P, conjugated equine estrogens plus medroxyprogesterone acetate.

RESULTS

At baseline, of the 4,461 women in the study, 1,345 (30.2 percent) reported no alcohol intake, 2,500 (56.0 percent) reported intake of <1 drink per day, and 616 (13.8 percent) reported intake of ≥1 drink per day. Of the women reporting no current alcohol intake, 758 (56.4 percent) reported drinking at least 12 drinks in the past, 111 (8.3 percent) reported having quit drinking because of health problems, and 84 (6.2 percent) reported quitting because of nonhealth problems. Within the group of women reporting ≥1 drink per day, consumption was distributed as 394 (64.0 percent) at 1 per day, 186 (30.2 percent) at 2–3 per day, 21 (3.4 percent)

at 4–5 per day, and 15 (2.4 percent) at ≥6 per day. Tables 1 and 2 summarize the distributions of several demographic/socioeconomic, lifestyle, and clinical characteristics of women grouped by level of alcohol intake. Greater alcohol intake was reported by women who were more educated, Caucasian, or currently smoking and those with a higher family income; lower body mass index; no history of hypertension, cardiovascular disease, or diabetes; or no current use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. Women reporting intake of ≥1 drink per day were more likely to have used hormone therapy in the past.

As displayed in table 3, the proportion of nondrinkers scoring below the WHIMS cutpoints for dementia screening

TABLE 3. Relation between level of alcohol intake and baseline 3MSE* score for participants in the Women's Health Initiative Memory Study, United States, 1996–2002

Variable	No alcohol intake	<1 drink per day	≥1 drink per day	p value
Baseline 3MSE level (frequency (%))				
95–100	834 (62.2)	1,805 (72.3)	493 (80.2)	<0.001†
Above the cutpoint‡ to 94	390 (29.1)	569 (22.8)	102 (16.6)	
Cutpoint or below	117 (8.7)	123 (4.9)	20 (3.2)	
3MSE total score at enrollment in the Women's Health Initiative (mean (standard error))	94.65 (0.11)	95.78 (0.08)	96.55 (0.16)	<0.001§
Adjusting for socioeconomic status/lifestyle¶ (mean (standard error))	95.24 (0.10)	95.64 (0.07)	96.03 (0.15)	<0.001§
Adjusting for clinical characteristics# (mean (standard error))	94.73 (0.11)	95.76 (0.08)	96.50 (0.16)	<0.001§
Adjusting for all covariates (mean (standard error))	95.28 (0.10)	95.63 (0.07)	96.00 (0.15)	<0.001§

* 3MSE, Modified Mini-Mental State Examination.

† Results from a chi-square test.

‡ Screening cutpoint is ≤80 for women with 0–8 years of formal education and ≤88 for women with ≥9 years of formal education.

§ Results from analysis of covariance.

¶ Age, no. of years since menopause, education, ethnicity, family income, and smoking status.

Body mass index, hypertension status, prior cardiovascular disease, diabetes, prior hormone therapy, statin use, and aspirin use.

at baseline (8.7 percent) was more than double that of women reporting ≥1 drink per day (3.2 percent), with the proportion of occasional drinkers in between (4.9 percent): overall $p < 0.001$. Baseline mean 3MSE score increased across the three levels of alcohol intake in a graded fashion: for women reporting no alcohol intake, 94.65 (SE, 0.11); for women reporting intake of <1 drink per day, 95.78 (SE, 0.08); and for women reporting ≥1 drink per day, 96.55 (SE, 0.16). These differences remained statistically significant after adjustment for demographic, socioeconomic, lifestyle, and clinical characteristics ($p < 0.001$). The magnitudes of these differences were attenuated, but remained highly significant, in the full covariate model.

For women reporting no current intake, mean 3MSE scores at baseline were similar for those reporting no prior use compared with prior use: 94.86 (SE, 0.19) versus 94.50

(SE, 0.16), $p = 0.49$. This difference remained nonsignificant in the full covariate model.

Clinically significant declines in 3MSE scores from baseline occurred for 5.7 percent of women reporting no alcohol intake, 3.3 percent of women reporting <1 drink per day, and 2.3 percent of women reporting ≥1 drink per day. These results are based on the 4,372 (98.0 percent) women who returned for at least one follow-up visit; follow-up was similar among women grouped by baseline alcohol intake ($p = 0.30$). The numbers of women seen at annual visits 1–6 were 4,282, 4,109, 4,079, 3,683, 1,732, and 84, respectively.

As shown in table 4, relative to those for women reporting no intake, the odds ratios for these declines were 0.56 (95 percent CI: 0.41, 0.77) for women reporting <1 drink per day and 0.40 (95 percent CI: 0.22, 0.72) for women reporting ≥1 drink per day. Full covariate adjustment attenuated these

TABLE 4. Odds ratios for occurrence of clinically significant declines of 8 or more units in 3MSE* score from baseline, after adjustment for hormone therapy assignment, for several models, Women's Health Initiative Memory Study, United States, 1996–2002

Variable	Relative to no alcohol intake				p value (all pairwise differences)†
	<1 drink per day		≥1 drink per day		
	Odds ratio	95% CI*	Odds ratio	95% CI	
No additional covariates	0.56	0.41, 0.77	0.40	0.22, 0.72	<0.001
Adjusting for socioeconomic status/lifestyle‡	0.67	0.48, 0.95	0.51	0.27, 0.94	0.025
Adjusting for clinical characteristics§	0.58	0.42, 0.80	0.41	0.23, 0.74	<0.001
Adjusting for all covariates	0.69	0.49, 0.97	0.53	0.28, 0.99	0.042

* 3MSE, Modified Mini-Mental State Examination; CI, confidence interval.

† Results from analysis of covariance.

‡ Age, no. of years since menopause, education, ethnicity, family income, and smoking status.

§ Body mass index, hypertension status, prior cardiovascular disease, diabetes, prior hormone therapy, statin use, and aspirin use.

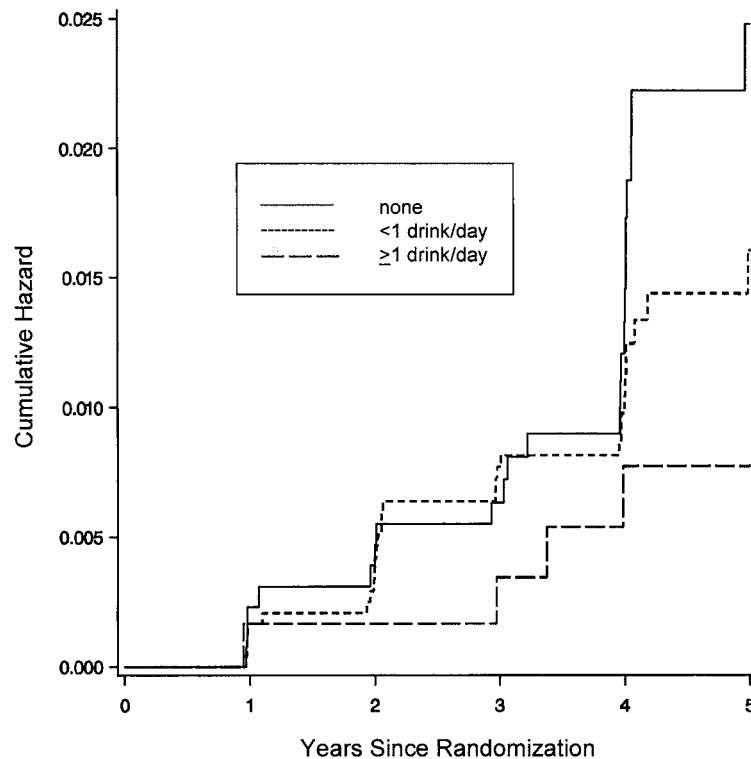


FIGURE 1. Time from randomization until classification of probable dementia by self-reported alcohol intake, Women's Health Initiative Memory Study, United States, 1996–2002.

odds ratios to 0.69 (95 percent CI: 0.49, 0.97) and 0.53 (95 percent CI: 0.28, 0.99), respectively; however, the overall differences remained statistically significant ($p = 0.042$).

Figure 1 depicts the distribution of time from randomization until incidence of probable dementia ($n = 61$) according to the WHIMS adjudication criteria. The incidence of dementia was inversely ordered according to reported alcohol intake; however, differences among the three groups did not reach statistical significance (table 5: $p = 0.09$). The fitted hazard ratio for probable dementia, relative to nondrinkers, was 0.64 (SE, 0.17) for women reporting <1 drink per day and 0.41 (SE, 0.20) for women reporting ≥ 1 drink per day. Differences of marginal statistical significance remained after adjustment for both socioeconomic status/lifestyle and clinical characteristics. Including baseline 3MSE score as a covariate essentially eliminated these differences ($p = 0.75$).

Figure 2 portrays the time to development of either probable dementia or mild cognitive impairment (whichever appeared first, $n = 170$). The incidence of this combined endpoint was inversely (and significantly) ordered with respect to alcohol intake ($p < 0.001$). The relative hazards for the pooled endpoint of mild cognitive impairment or probable dementia were of similar magnitude to those of probable dementia alone: 0.54 (SE, 0.09) for women reporting <1 drink per day and 0.47 (SE, 0.07) for women reporting ≥ 1 drink per day. Differences were moderated with adjustment for socioeconomic status/lifestyle characteristics ($p = 0.13$)

and were essentially eliminated with adjustment for baseline 3MSE score ($p = 0.81$).

Alcohol intake did not seem to materially influence the negative effect of E + P on global cognition and probable dementia. The mean difference between 3MSE scores among women assigned to E + P versus placebo, adjusted for baseline 3MSE score, was -0.40 (SE, 0.15) for nondrinkers, -0.22 (SE, 0.11) for women reporting <1 drink per day, and -0.00 (SE, 0.21) for women reporting ≥ 1 drink per day (interaction $p = 0.29$). The relative hazard ratios for probable dementia (comparing E + P with placebo assignment) among these groups were 1.70 (SE, 0.70), 2.22 (SE, 0.85), and 4.34 (SE, 4.85), respectively ($p = 0.65$).

DISCUSSION

Cross-sectional associations

WHIMS results are in agreement with other reports of a salutatory effect of moderate alcohol intake on cognition and the risk of dementia. Self-report of moderate alcohol intake was associated with better global cognitive function at baseline. Nondrinkers were more than twice as likely as women reporting ≥ 1 drink per day to score below the age-adjusted cutpoint for 3MSE screening. Mean baseline 3MSE scores increased in a graded fashion across the three levels of alcohol intake, and differences in these groups remained statistically significant after adjustment for demographic and socioeconomic factors, smoking, and clinical characteristics.

TABLE 5. Relative hazard ratios for probable dementia by baseline alcohol intake, compared with no intake, for several models after adjustment for hormone therapy assignment, Women's Health Initiative Memory Study, United States, 1996–2002

Variable	Relative to no alcohol intake				<i>p</i> value (all pairwise differences)
	<1 drink per day		≥1 drink per day		
	Hazard ratio	95% CI*	Hazard ratio	95% CI	
Probable dementia					
No additional covariates	0.64	0.38, 1.08	0.41	0.16, 1.06	0.09
Adjusting for socioeconomic status†	0.78	0.43, 1.42	0.30	0.08, 1.04	0.10
Adjusting for clinical characteristics‡	0.65	0.38, 1.10	0.39	0.15, 1.02	0.08
Adjusting for all covariates	0.76	0.41, 1.40	0.28	0.08, 0.99	0.08
Adjusting for baseline 3MSE* score	1.14	0.65, 2.01	0.81	0.30, 2.18	0.75
Mild cognitive impairment or probable dementia					
No additional covariates	0.54	0.39, 0.74	0.47	0.28, 0.79	<0.001
Adjusting for socioeconomic status†	0.76	0.53, 1.08	0.57	0.32, 1.07	0.13
Adjusting for clinical characteristics‡	0.59	0.43, 0.81	0.44	0.26, 0.78	0.001
Adjusting for all covariates	0.81	0.56, 1.16	0.57	0.31, 1.09	0.18
Adjusting for baseline 3MSE score	0.89	0.64, 1.25	0.92	0.53, 1.59	0.81

* CI, confidence interval; 3MSE, Modified Mini-Mental State Examination.

† Age, no. of years since menopause, education, ethnicity, family income, and smoking status.

‡ Body mass index, hypertension status, prior cardiovascular disease, diabetes, statin use, aspirin use, and prior hormone therapy.

The Epidemiology of Vascular Aging Study found a twofold increased odds ratio for high cognitive performance on the Mini-Mental State Examination for women who consumed ≥2 drinks per day compared with nondrinkers (2). Positive associations between moderate levels of alcohol intake and measures of global cognition among women have been reported in other studies (3–5, 25–27); however, no relation has been found in some (12, 28, 29), and at least one has reported a negative association (30).

Associations with changes in global cognition

Clinically significant declines in global cognition over an average of 4.2 years of follow-up were less common among women who reported alcohol intake at baseline. These differences persisted after statistical adjustment for both demographic/social and clinical factors.

Our findings align with those from other reports. Galanis et al. (31) described a U-shaped relation between alcohol intake and subsequent cognitive decline, with reduced risk for alcohol consumption of ≤2 ounces (56.6 g) per day. Similar U-shaped associations between alcohol intake and subsequent cognition among men were reported by others (4, 9, 32). Leroi et al. (33) found that alcohol intake was associated with less decline among women, but not men. Such findings have not been universal, however. Launer et al. (34) found no protective relation between intake and cognitive decline after adjustment for socioeconomic status and clinical factors, and Edelstein et al. (10) found that alcohol intake was associated with a significant decline in several

measures of cognitive function. Peele and Brodsky (35) provide a comprehensive review of research in this area.

Associations with incident dementia and mild cognitive impairment

We found that moderate alcohol intake was associated with an approximately 50 percent reduced risk of combined probable dementia and/or mild cognitive impairment ($p < 0.001$). The estimated risk of probable dementia alone was also reduced by about 50 percent; however, this relation did not reach statistical significance ($p = 0.11$). Differences appeared to emerge 2–3 years following baseline. Similar to our results for cross-sectional cognition and cognitive decline, the association with the combined endpoint could not be accounted for by differences between drinkers and nondrinkers with respect to clinical characteristics. However, it was moderated (and no longer reached statistical significance) after adjustment for demographic and socioeconomic factors. Adjustment for baseline 3MSE score almost completely eliminated this association.

Our estimates closely parallel those of the Cardiovascular Health Study, which reported relative odds of dementia (compared with those for nondrinkers) of 0.65 (<1 drink per week), 0.46 (1–6 drinks per week), 0.69 (7–13 drinks per week), and 1.22 (≥14 drinks per week) (7). Similarly, Ruitenberg et al. (8) found a J-shaped relation between alcohol consumption and risk of dementia. Truelsen et al. (36) reported no overall protective effect of alcohol intake on risk of dementia but found that wine intake (relative to no

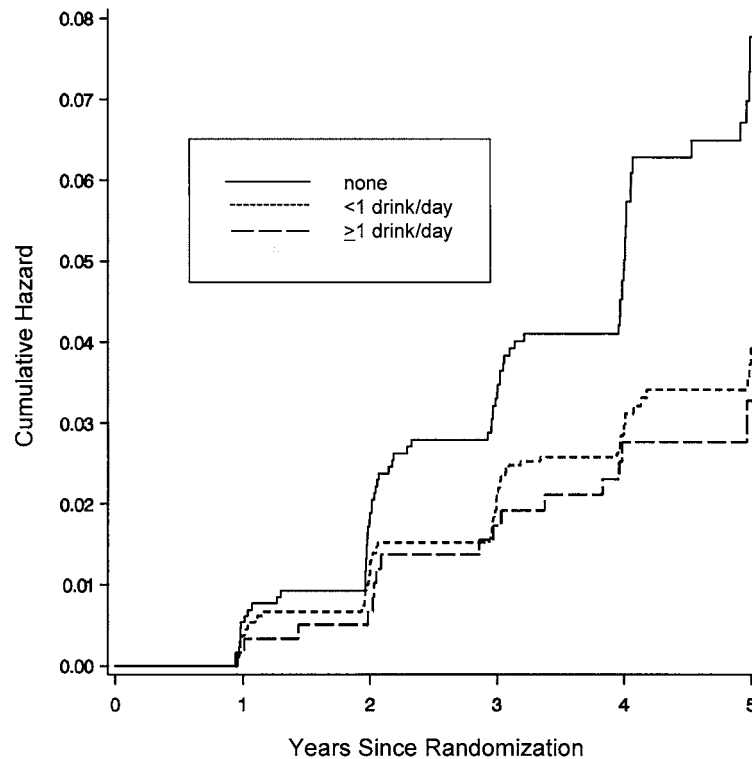


FIGURE 2. Time until classification of probable dementia or mild cognitive impairment by self-reported alcohol intake, Women's Health Initiative Memory Study, United States, 1996–2002.

wine intake) was associated with reduced odds of dementia by factors of 0.43 (monthly), 0.33 (weekly), and 0.57 (daily). Earlier meta-analyses found no association between alcohol intake and risk of Alzheimer's disease (37). Hebert et al. (38) found a slight, but nonsignificant, increase in incident Alzheimer's disease associated with moderate alcohol consumption.

Interaction between E + P therapy and alcohol intake

Tivis et al. (13) reported a benefit of combined hormone therapy on visuo-spatial processing in postmenopausal women (average age: 56 years). This benefit was limited to women who reported low- to mid-moderate alcohol intake (0.01–0.49 ounces (0.28–13.87 g) per day) and apparently reversed among those whose intakes were higher (interaction $p = 0.02$). We found no evidence of an interaction between assignment to hormone therapy and alcohol intake on global cognition or on the incidence of mild cognitive impairment and dementia.

Influence of errors in self-report and measurement

It is of concern that self-reported alcohol intake is fallible and that reporting errors may vary by underlying level of cognition. We cannot rule out the possibility that our findings derived from a tendency for women with lower cognitive function to underreport drinking; however, two features

of our data argue against this interpretation. We found an association between self-reported alcohol intake and global cognitive function for women who scored above our at-risk screening cutpoints (and thus had little evidence of impairment): of the 1,061 women scoring between the screening cutpoint and 94, 63.2 percent reported alcohol intake compared with 73.4 percent of the 3,132 women scoring 95 or higher ($p < 0.001$ without covariate adjustment; $p = 0.01$ with full covariate adjustment). In addition, the magnitude of the associations we described would require unreasonably high levels of underreporting to be spurious. At baseline, odds of alcohol intake decreased by a factor of 0.69 (95 percent CI: 0.64, 0.75) for every 5-unit difference in 3MSE score. Thus, to account fully for this relation, an approximately 30 percent underreporting of any intake for every 5-unit difference would be required, that is, a very large, unidirectional, and systematic difference.

Potential mechanisms

Moderate alcohol intake may be inversely related to ischemic stroke (39, 40) and to white matter disease and infarcts (41), which may explain decreased rates of vascular dementia (8). A positive association of moderate alcohol drinking with cognitive function may be mediated through vascular factors since the effects of alcohol are stronger on vascular dementia than on Alzheimer's disease (8). Moderate doses of alcohol may increase prostacyclin

concentrations, reduce generation of thromboxane A₂, and inhibit platelet function (42–44). They may increase plasma levels of endogenous tissue-type plasminogen activator, a serine protease that regulates intravascular fibrinolysis (45), and fibrinolytic activity while decreasing plasma fibrinogen levels (46). Alcohol is related to increased levels of high density lipoprotein (HDL) cholesterol, its subfractions HDL₂ and HDL₃, and its associated apolipoproteins A-I and A-II (47–51). The association with HDL cholesterol may account for half of the reduction in coronary events associated with moderate alcohol consumption (52).

In carriers of the apolipoprotein E epsilon-4 genotype (*APOE4*), plaque formation is increased because of oxidation of apolipoprotein E and binding to beta-amyloid (53). Alcohol may suppress this binding because of its antioxidant effects. *APOE4* is associated with lower HDL and higher low density lipoprotein cholesterol; therefore, moderate alcohol consumption may protect cognitive function through its lipid effects in *APOE4* carriers. The National Heart, Blood, and Lung Institute twin study found that the protective effect of light alcohol drinking was stronger for *APOE4* carriers (54). However, the Epidemiology of Vascular Aging Study found that alcohol drinking was associated with a decreased risk of cognitive decline in those without *APOE4*, and an opposite association was found in *APOE4* carriers (55). The Cardiovascular Health Study found a similar relation for dementia (7).

Alcohol may affect cognition through a release of acetylcholine in the hippocampus. Deficits in the cholinergic system have been linked to problems with attention, learning, and memory (56). Low doses of alcohol may cause a delayed stimulation of hippocampal acetylcholine release in rats (57).

A protective effect of alcohol on cognitive function in moderate drinkers may be due to a relatively poor health status among abstainers or because cognitive status influences alcohol consumption.

Limitations

Our study has several potential weaknesses. Frank differences exist between women grouped by reported alcohol intake, which may be associated with social status and access to health care. Including socioeconomic status markers as covariates in our analyses could not account for associations with global cognition but did weaken associations with dementia and mild cognitive impairment, which became not statistically significant: it is possible that other unmeasured socioeconomic status and clinical factors may more fully account for these differences. It is also possible that a woman's cognitive state may affect whether she chooses to drink; women with lower levels of cognitive function may choose to consume less alcohol, reversing the causal pathway. The compressed range of cognition levels in our cohort may have hampered our description of associations.

The associations we have described bear some resemblance to the reported beneficial effects of hormone therapy on cardiovascular disease and dementia prior to clinical trials. Use of hormone therapy was also known to vary among women according to social class, access to care, and

overall health status. Although such factors may not fully account for the associations we have described, we cannot dismiss this possibility; recent reinterpretation of effects attributed to hormone therapy from observational studies heightens the caution with which we interpret our findings. The converse also cannot be dismissed: alcohol intake may have confounded some of the benefits ascribed to hormone therapy. It may be that only a randomized clinical trial will clarify whether moderate alcohol intake truly is protective against cognitive decline.

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