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Original Contribution

Is There an Association Between Low-to-Moderate Alcohol Consumption and Risk of Cognitive Decline?

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The authors evaluated the association of low-to-moderate alcohol consumption with risk of cognitive decline in a census-based cohort study of men and women aged ≥55 years conducted in Zaragoza, Spain (1994–1999). Participants free of dementia at baseline ($N = 3,888$) were examined after 2.5 and 4.5 years of follow-up. Information on alcohol intake was collected with the EURODEM Risk Factors Questionnaire and the History and Aetiology Schedule. The study endpoint was severe cognitive decline, defined as loss of ≥1 point/year on the Mini-Mental State Examination or a diagnosis of incident dementia (*Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*, Text Revision criteria). Compared with those for abstainers, the multivariate-adjusted odds ratios for severe cognitive decline for male drinkers of <12 g alcohol/day, drinkers of 12–24 g alcohol/day, and former drinkers were 0.61 (95% confidence interval (CI): 0.31, 1.20), 1.19 (95% CI: 0.61, 2.32), and 1.03 (95% CI: 0.59, 1.82), respectively. The corresponding odds ratios for women were 0.88 (95% CI: 0.45, 1.72), 2.38 (95% CI: 0.98, 5.77), and 1.03 (95% CI: 0.48, 2.23). This study did not support the hypothesis that low-to-moderate alcohol consumption prevents cognitive decline. The inverse association between low-to-moderate alcohol intake and cognitive decline observed in other studies may have been due to inclusion of former drinkers in the abstainers reference category.

aged; alcohol drinking; cognition; dementia; follow-up studies; risk

Abbreviations: AGECAT, Automated Geriatric Examination for Computer Assisted Taxonomy; CI, confidence interval; GMS-B, Geriatric Mental State B; HAS, History and Aetiology Schedule; MMSE, Mini-Mental State Examination.

Heavy alcohol consumption impairs cognitive performance (1–3) and is related to clinical dementia (4). However, low-to-moderate alcohol intake may protect against dementia (5–9) and cognitive deterioration (10–13). A number of biologic mechanisms have been proposed to explain this potential beneficial effect of moderate alcohol consumption on the brain, including the antioxidant properties of wine flavonoids (14) and alcohol-related prevention of ischemia or stroke (15). A recent systematic review also suggested that limited alcohol intake in early adult life may protect against incident dementia, although these findings were difficult to interpret because of high between-study heterogeneity (16).

The protective effect of moderate alcohol consumption is still controversial, however, and some studies have reported harmful effects of moderate alcohol intake (17). Indeed, the evidence for a protective effect may have been overestimated because of inclusion of former drinkers in the nondrinkers comparator group in most studies. For example, Ganguli et al. (18) reported that mild-to-moderate drinking, compared with no drinking, was associated with a lower average decline in cognitive domains. Much of this difference was explained by lower declines among current drinkers when compared with former drinkers, whereas lifelong abstainers did not differ from current moderate drinkers. Other potential methodological issues in studies of moderate alcohol intake and cognitive decline include lack of standardization in the definition of alcohol drinking categories (19), problems related to missing observations

and dropouts in longitudinal data (20), and the possibility of publication bias.

In this article, we report the association between alcohol intake and risk of incident cognitive decline in the ZARADEMP Project, a prospective, population-based study of adults 55 years of age or older living in Zaragoza, Spain. The ZARADEMP Project used carefully standardized methods to collect alcohol intake and cognitive function data over 4.5 years of follow-up.

MATERIALS AND METHODS

Study design and sample

The ZARADEMP Project (21) is a longitudinal, community-based study carried out in Zaragoza, the fifth largest city in Spain, to examine the incidence and risk factors for dementia. In 1994, a stratified random sample of individuals 55 years of age or older drawn from census lists was invited to participate in the baseline examination. Sample allocation was proportional by age and sex. The study included 4,803 participants, with an overall participation rate of 79.5%. Residents in nursing homes and institutionalized subjects (2.2%) were also included in the sample. For this analysis, we excluded 173 subjects with incomplete data on alcohol intake at baseline and 742 subjects considered to be cases or subcases of dementia at baseline (refer to the definitions below), for a remaining sample size of 3,888 participants.

The ZARADEMP Study participants underwent 2 follow-up visits, in 1997 and 1999, the average length of follow-up being 4.5 years. The numbers of participants interviewed in the 1997 and 1999 follow-up visits were 3,096 and 2,290, with participation rates of 92.1% and 91.1%, respectively. The ethics committee of the Zaragoza University Hospital approved this study, and all individuals provided written informed consent.

Data collection

Several standard tools, previously validated in Spain, were incorporated in the ZARADEMP interview (21). The mental state of study participants was assessed by using the Geriatric Mental State B (GMS-B) (22), a semistructured, standardized clinical interview that may be used by lay interviewers. GMS-B includes cognitive and neuropsychological items and provides a threshold global score that discriminates between dementia cases and noncases. A computerized dementia diagnostic program, AGECAT (Automated Geriatric Examination for Computer Assisted Taxonomy) (23, 24), was applied to the GMS-B to classify individuals as noncases (level 0), subcases (level 1), or dementia or depression cases (level 2 or higher). Psychiatric history was taken by using the History and Aetiology Schedule (HAS) (25), a standardized method accompanying the GMS-B that collects psychiatric history data from a caregiver or directly from the respondent when he or she is judged reliable. The HAS includes a section exploring alcohol drinking habits. Cognitive function was also evaluated by using the validated Spanish version of the Mini-Mental State Examination (MMSE) (26, 27).

Table 1. Baseline Characteristics According to Incident Severe Cognitive Decline in the ZARADEMP Study, Zaragoza, Spain, 1994–1999

	Severe Cognitive Decline		*P* Value[a]
	No (n = 2,684)	Yes (n = 412)	
Women, %	54.9	63.6	<0.01
Mean age in years (SD)	70.5 (8.2)	78.4 (9)	<0.01
Mean MMSE score (SD)	27.5 (2.3)	26.7 (2.4)	<0.01
No. of years of education (SD)	8.36 (3.9)	7.29 (3.0)	<0.01
Marital status, %			
Single/separated	10.5	8.7	<0.01
Widow	22.9	42.7	
Smoking status, %			
Current smoker	14.3	8.7	<0.01
Former smoker	22.2	18.0	
Psychotropic medication use, %	19.1	27.2	<0.01
Hypertension,[b] %	69.5	71.2	0.50
Depression, %	10.8	12.1	0.40
Disability, %	3.2	14.3	<0.01

Abbreviations: MMSE, Mini-Mental State Examination; SD, standard deviation.

[a] Used were the chi-square test for categorical data and the Mann-Whitney U test for continuous data.

[b] Use of antihypertensive medication and/or systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg.

Information on medical conditions and potential risk factors for dementia was collected by using the EURODEM Risk Factors Questionnaire (28), which also includes items related to alcohol consumption. The Lawton and Brody scale (29, 30) and the Katz Index (31, 32) were used to assess instrumental activities of daily living (ability to use the telephone, shopping, etc.) and basic activities of daily living (dressing, bathing, toileting, etc.), respectively.

Assessment of alcohol consumption

Usual daily alcohol intake was estimated from the Risk Factors Questionnaire. Subjects were questioned about present and past consumption, type (wine, beer, and spirits), and quantity of alcoholic beverages. Questions in the HAS interview were used to corroborate this information. If discrepancies were detected, the information was clarified in the same interview, and the Risk Factors Questionnaire scores were corrected when appropriate. Quantities were then converted into number of beverages per day, and total daily intake was estimated as grams of alcohol according to the average number of grams for each type of beverage, as described by Gual et al. (33) for Spanish populations.

Alcohol intake habits differed between men and women. Therefore, study participants were categorized as abstainers, which included very occasional consumers of very small quantities of alcohol; former drinkers; and drinkers of <12 g/day, 12–24 g/day, and/or >24 g/day for women; and as

Table 2. Differences in Baseline Characteristics, According to Alcohol Consumption, of Men in the ZARADEMP Study, Zaragoza, Spain, 1994–1999

	Alcohol Intake, g/day						*P* Value[a]	
	Abstainers (n = 462, n_i = 48)	<12 (n = 231, n_i = 23)	12–24 (n = 156, n_i = 19)	>24–40 (n = 141, n_i = 8)	>40 (n = 87, n_i = 8)	Former Drinkers (n = 284, n_i = 44)	(1)[b]	(2)[c]
Mean age in years (SD)	70.9 (8.6)	72.3 (8.9)	70.8 (9.2)	68.7 (7.9)	68.1 (6.5)	73.4 (9.2)	<0.01	<0.01
Mean MMSE score (SD)	27.8 (1.8)	27.6 (2.5)	27.8 (2.8)	27.7 (2.2)	27.8 (3.3)	27.2 (2.1)	<0.01	<0.01
No. of years of education (SD)	8.8 (4.4)	8.6 (4.7)	8.6 (4.2)	9.0 (4.7)	8.5 (4.2)	7.4 (3.6)	<0.01	<0.01
Marital status, %								
Single/separated	8.5	4.3	7.1	7.1	4.6	8.1	0.03	0.05
Widower	10.6	12.6	10.3	4.3	9.2	15.9		
Smoking status, %								
Current smoker	23.6	22.5	39.1	34.0	54.0	17.6	<0.01	<0.01
Former smoker	37.9	48.5	35.9	47.5	36.8	58.1		
Psychotropic medication use, %	11.3	12.1	14.7	9.9	13.8	13.0	0.73	0.74
Hypertension,[d] %	64.9	64.5	63.9	61.7	68.3	68.4	0.79	0.24
Depression, %	4.1	2.2	6.4	5.7	2.3	5.3	0.27	0.29
Disability, %	2.8	2.2	3.8	2.1	0	7.7	<0.01	<0.01

Abbreviations: MMSE, Mini-Mental State Examination; n_i, number of subjects with severe cognitive decline; SD, standard deviation.
[a] Chi-square and Kruskal-Wallis tests.
[b] Global.
[c] Comparison between former drinkers and the remaining categories.
[d] Use of antihypertensive medication and/or systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg.

abstainers; former drinkers; and drinkers of <12 g/day, 12–24 g/day, >24–40 g/day, and >40 g/day for men.

Other variables

Information on age, marital status, education, and smoking was collected by interview at the baseline visit. Physical examination included anthropometric measurements (height and weight) and measurement of blood pressure following World Health Organization recommendations. Hypertension was defined as the use of antihypertensive medication and/or, following World Health Organization criteria, as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg (34). Depression was assessed by using the GMS-B–AGECAT system, and cases of depression were defined according to AGECAT diagnostic criteria.

Study outcomes

An epidemiologic case-finding process for dementia was implemented at each visit. Well-trained and regularly supervised lay interviewers conducted the 25–90-minute ZARADEMP interview at the subjects' own home or place of residence. Medical reports, laboratory data, and prescriptions, which people commonly have available at home in Spain, were consulted to complete the data. Dementia cases considered to be questionable according to predetermined criteria (inconsistent information) were reassessed in the participants' home by supervising trained research psychiatrists using the same interview. In previous reports, we have shown the validity of dementia diagnosis based on the AGECAT system (27). Baseline cases and subcases of dementia (defined by AGECAT criteria) were excluded from this analysis.

In the 1997 and 1999 follow-up visits, research psychiatrists also interviewed all probable dementia cases identified on the basis of GMS-B threshold global scores and/or MMSE standard cutoff points. The psychiatrists performed a neurologic examination, and medical reports were used, when available, to help in the diagnostic process. Informants were interviewed when a participant was considered unreliable (in cases of dementia and approximately 10% of subcases of dementia). All probable incident cases of dementia identified by the psychiatrists were then presented to a panel of psychiatrists, who examined all available documentation to confirm the diagnosis of incident dementia based on *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*, Text Revision criteria. Interviewers for the 1997 and 1999 follow-up visits were unaware of the results of the baseline interview.

Changes in cognitive performance were quantified as the difference in MMSE scores between the first and last assessments available. Annual change was calculated by dividing the difference by the time between the 2 assessments. Subjects were classified as having severe cognitive decline if they had lost 1 point or more per year in MMSE scores or if they had been diagnosed as incident dementia cases.

Statistical analyses

Logistic and linear regression models were used to study the association of alcohol intake level with development

Table 3. Differences in Baseline Characteristics, According to Alcohol Consumption, of Women in the ZARADEMP Study, Zaragoza, Spain, 1994–1999

	Alcohol Intake, g/day				*P* Value[a]	
	Abstainers (n = 1,494, n_i = 224)	<12 (n = 113, n_i = 16)	12–24 (n = 43, n_i = 9)	Former Drinkers (n = 73, n_i = 12)	(1)[b]	(2)[c]
Mean age in years (SD)	71.7 (8.7)	71.8 (9.2)	70.8 (8.3)	73.2 (8.0)	0.50	0.09
Mean MMSE score (SD)	27.1 (2.3)	27.4 (2.5)	27.2 (2.2)	26.8 (2.5)	0.42	0.23
No. of years of education (SD)	7.8 (3.4)	8.6 (3.8)	9.3 (3.6)	7.5 (2.9)	<0.01	0.09
Marital status, %						
Single/separated	11.9	15.9	16.3	16.4	0.07	0.29
Widow	36.6	35.4	32.6	41.1		
Smoking status, %						
Current smoker	2.5	6.2	11.6	1.4	<0.01	0.69
Former smoker	2.8	9.7	14.0	4.1		
Psychotropic medication use, %	26.2	29.2	16.3	35.6	0.09	0.07
Hypertension,[d] %	74.9	63.4	53.5	76.8	<0.01	0.54
Depression, %	16.5	14.2	14.0	13.7	0.82	0.55
Disability, %	5.6	4.5	7.0	2.7	0.36	0.30

Abbreviations: MMSE, Mini-Mental State Examination; n_i, number of subjects with severe cognitive decline; SD, standard deviation.

[a] Chi-square and Kruskal-Wallis tests.

[b] Global.

[c] Comparison between former drinkers and the remaining categories.

[d] Use of antihypertensive medication and/or systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg.

of cognitive decline and with rate of change in MMSE scores. All analyses were performed separately for men and women. The following covariates were selected on the basis of their association with the outcome variable and the main variable of interest or because of known clinical importance: age, marital status (married/single-separated/widow-widower), years of education, smoking (never/former smoker/current smoker), hypertension, depression, use of psychotropic medication (obtained from the HAS), and disability (assessed by the Lawton and Brody scale and the Katz Index). For this study, the scores were dichotomized following previous project criteria, distinguishing between disability (positive scores on at least one domain in both instruments) and no disability (35). Effect modification by age and education was also examined by adding the products of these variables with alcohol intake to the models.

To assess potential selection bias, we performed a sensitivity analysis by including as study outcomes all subcases of dementia prevalent at baseline. The subcases were excluded from the main analysis. Statistics were calculated by using SPSS version 14.0 software (SPSS, Inc., Chicago, Illinois). All *P* values were 2 sided.

RESULTS

At follow-up, 425 participants had died, 367 had dropped out of the study, and 1,361 men and 1,735 women were interviewed. Among men, the proportions of abstainers, current drinkers, and former drinkers were 33.9%, 45.2%, and 20.9%, respectively. Among women, the corresponding proportions were 86.1%, 9.7%, and 4.2%. Two hundred and twenty-eight men (16.7%), but only 12 women (0.7%), reported consumption of ≥24 g of alcohol per day. This category of women consumers was removed from the analyses because of the small number.

A total of 412 subjects (13.3%) were classified as having an incident case of severe cognitive decline. Compared with noncases, severe cognitive decline cases were more likely to be older, female, widowed, disabled, and users of psychotropic medication at baseline (Table 1). Cases were also less likely to be highly educated and to be current or former smokers.

Among men, former drinkers were of the highest average age and included the highest proportion of participants with hypertension and a disability; former smokers had the lowest average MMSE baseline score and included the lowest proportion of participants of a high educational status and who smoked (Table 2). Among women, former drinkers were of the highest average age and included the highest proportion of participants who used psychotropic medication and had hypertension, had the lowest average MMSE baseline score, and included the lowest proportion of participants with a high educational status, with a disability, and who smoked (Table 3). Current drinkers included the highest proportion of both smokers and former smokers.

Table 4. Odds Ratios and 95% Confidence Intervals for Incident Severe Cognitive Decline, by Alcohol Consumption Category, in the ZARADEMP Study, Zaragoza, Spain, 1994–1999

	No.	Alcohol Intake, g/day												
		Abstainer		<12		12–24		>24–40		>40		*P* Value[a]	Former Drinker		*P* Value[b]
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		OR	95% CI	
Men															
Crude	1,361	1.00	Ref	0.95	0.56, 1.61	1.19	0.68, 2.10	0.52	0.24, 1.12	0.87	0.39, 1.91	0.39	1.58	1.02, 2.45	0.04
Adjusted[c]	1,149	1.00	Ref	0.61	0.31, 1.20	1.19	0.61, 2.32	0.69	0.27, 1.75	1.27	0.52, 3.12	0.91	1.03	0.59, 1.82	0.80
Sensitivity analysis[d]	1,232	1.00	Ref	0.73	0.42, 1.27	1.10	0.62, 1.95	0.46	0.20, 1.06	0.85	0.36, 2.02	0.21	1.06	0.67, 1.69	0.79
Women															
Crude	1,735	1.00	Ref	0.93	0.54, 1.62	1.50	0.71, 3.17					0.58	1.11	0.59, 2.10	0.74
Adjusted[c]	1,429	1.00	Ref	0.88	0.45, 1.72	2.38	0.98, 5.77					0.31	1.03	0.48, 2.23	0.93
Sensitivity analysis[d]	1,632	1.00	Ref	0.87	0.48, 1.57	2.27	1.05, 4.91					0.21	1.20	0.66, 2.20	0.56

Abbreviations: CI, confidence interval; OR, odds ratio; Ref, referent.

[a] Comparison of alcohol intake categories (excluding former drinkers).

[b] Comparison of former drinkers with the remaining categories.

[c] Adjusted for age, years of education, Mini-Mental State Examination (MMSE) score at baseline, marital status, smoking status, hypertension, depression, psychotropic medication use, and disability.

[d] Dependent variable includes as cases those subcases at baseline excluded for follow-up; adjusted for age, years of education, MMSE score at baseline, marital status, smoking status, hypertension, depression, psychotropic medication use, and disability.

Although crude analysis showed that male former drinkers were at a higher risk of severe cognitive decline, the association was no longer significant after adjustment for covariates (odds ratio compared with abstainers = 1.03, 95% confidence interval (CI): 0.59, 1.82) (Table 4). There was also no clear pattern of increasing or decreasing risk of severe cognitive decline with increasing alcohol intake for men or for women. For men, and compared with abstainers, the multivariate-adjusted odds ratios for severe cognitive decline for drinkers of <12 and of 12–24 g of alcohol/day were 0.61 (95% CI: 0.31, 1.20) and 1.19 (95% CI: 0.61, 2.32), respectively. The corresponding odds ratios for women were 0.88 (95% CI: 0.45, 1.72) and 2.38 (95% CI: 0.98, 5.77). Since ''disability'' was included in the model but was highly correlated with the outcome (Table 4), the results might attenuate toward the null. However, very similar results were observed when the model did not include disability. For men, the odds ratios were 1.10 (95% CI: 0.66, 1.83) for former drinkers, 0.74 (95% CI: 0.41, 1.34) for drinkers of <12 g/day, 1.24 (95% CI: 0.66, 2.32) for drinkers of 12–24 g/day, 0.68 (95% CI: 0.28, 1.61) for drinkers of >24–40 g/day, and 1.30 (95% CI: 0.56, 3.04) for drinkers of >40 g/day. For women, the odds ratios were 0.99 (95% CI: 0.50, 1.95) for former drinkers, 0.92 (95% CI: 0.51, 1.65) for drinkers of <12 g/day, and 1.95 (95% CI: 0.86, 4.40) for drinkers of 12–24 g/day. Results of sensitivity analyses to assess the possible influence of selection bias did not appreciably modify the results.

The mean loss in MMSE score was 0.22 (standard deviation, 1.22) points per year for men and 0.31 (standard deviation, 1.25) points per year for women. Table 5 presents the results of the associations between baseline alcohol consumption and annual cognitive decline. For both genders, crude and multivariable analysis did not reveal any significant difference between alcohol intake category at baseline and change in cognitive performance over time.

DISCUSSION

In this study, we found no evidence of an association between alcohol consumption and cognitive decline over 4.5 years of follow-up. Specifically, consumption of less than 40 g/day by men and less than 24 g/day by women was not associated with a decreased risk of cognitive decline or dementia. These thresholds of alcohol intake are recommended for low-to-moderate alcohol consumption by national organizations in Spain (36) and are in accordance with World Health Organization criteria for comparative research purposes (37).

Several community-based cohorts identified J-shaped or U-shaped associations between alcohol consumption and cognitive function, such that light-to-moderate drinking in mid-to-late life is associated with better cognitive performance and lesser cognitive decline than either no drinking or heavy drinking (9, 17, 18, 38, 39). However, operational definitions of low or moderate drinking vary greatly across studies (18), and the concept of moderate drinker is very imprecise, comprising a wide range of measures that may include those drinking less than one drink a day (40). While most studies have used semiquantitative measures such as

Table 5. Annual Difference Scores and 95% Confidence Intervals on the MMSE Between the Baseline and Last Assessments, by Alcohol Consumption Category, in the ZARADEMP Study, Zaragoza, Spain, 1994–1999

	Alcohol Intake, g/day											
	Abstainer		<12		12–24		>24–40		>40		Former Drinker	
	Difference	95% CI	Difference	95% CI	Difference	95% CI	Difference	95% CI	Difference	95% CI	Difference	95% CI
Men ($N = 1,352$)												
Crude	0.00	Ref	−0.02	−0.17, 0.13	0.13	−0.04, 0.30	−0.15	−0.33, 0.02	−0.09	−0.31, 0.12	0.09	−0.40, 0.24
Adjusted[a]	0.00	Ref	−0.09	−0.23, 0.05	0.09	−0.07, 0.25	−0.06	−0.23, 0.11	−0.01	−0.21, 0.20	0.04	−0.09, 0.18
Women ($N = 1,720$)												
Crude	0.00	Ref	−0.14	−0.33, 0.05	0.22	−0.08, 0.53					0.06	−0.18, 0.29
Adjusted[a]	0.00	Ref	−0.55	−0.25, 0.14	0.29	−0.02, 0.61					−0.06	−0.30, 0.19

Abbreviations: CI, confidence interval; MMSE, Mini-Mental State Examination; Ref, referent.
[a] Adjusted for age, years of education, and MMSE score at baseline.

drinks or units per day or week (10, 41, 42), others have classified drinkers qualitatively into light/moderate/heavy, frequent/infrequent, or never/ever (43–45). In our study, we attempted to obtain standardized measures of daily intake of alcohol in grams according to usual patterns of alcohol consumption and usual amount of alcohol per drink in Spain (33). This method has some potential advantages since the concept of a standard drink can vary by country (16, 19), and studies using unspecified measures (40, 46) or semiquantitative measures (10, 42) of alcohol consumption may be subject to increased measurement error.

Furthermore, most studies included former drinkers in the reference group of abstainers (8, 47–49). Potential biases associated with this approach have been identified by several authors (19, 50). For instance, Ganguli et al. (18) noted that much of the difference in cognitive decline between current drinkers and nondrinkers might be explained by lesser declines among current drinkers when compared with former drinkers rather than when compared with lifelong abstainers. In our study, an ad hoc analysis comparing moderate drinkers (24–40 g/day) with abstainers and former drinkers combined as the reference category resulted in an odds ratio for severe cognitive decline of 0.43 (95% CI: 0.20, 0.90). Indeed, former drinkers tend to be less healthy than moderate drinkers (51), and the ''sick quitter'' phenomenon is well known in the alcohol-related literature (52). This may also be the case in our sample, since former drinkers had significantly higher disability levels when compared with moderate drinkers or lifetime abstainers.

While it is recommended that lifetime abstainers be considered the comparison group in these types of studies, using reported lifetime abstainers as the comparison group might produce substantial measurement error, especially if reporting is based on a single measurement (50). Using a single question about frequency of alcohol consumption with several response options in their initial assessment, Rehm et al. (50) showed that those reporting lifetime abstention often reported drinking at some time in their life in earlier assessments. In our study, we used a similar question but in combination with the HAS interview in an attempt to minimize measurement errors. The HAS is a fully validated psychiatric interview that carefully assesses psychiatric history in a standardized way, including history of alcohol use (25). Furthermore, we included in the nondrinker category individuals who drank in the past only very sporadically and very small quantities of alcohol, an approach close to Rehm et al.'s recommendation to include irregular lifetime light drinkers with lifetime abstainers in the comparison group.

The data from the Cardiovascular Health Study are relevant in this context, since this US study did not include former drinkers in the nondrinkers comparison group (9). In this study, 1–6 drinks weekly (considered moderate consumption) was associated with a lower risk of dementia among older adults (odds ratio = 0.36, 95% CI: 0.17, 0.77). This category of intake is approximately equivalent to our <12 g/day group, which was not associated with reduced risk of severe cognitive decline in our study (odds ratio = 0.79, 95% CI: 0.45, 1.39). The Cardiovascular

Health Study recruited participants from Medicare eligibility lists and excluded institutionalized or dependent individuals, whereas our study included a representative population sample in which we controlled for disability, and the main outcome measure in the Cardiovascular Health Study was incident dementia, a more restrictive outcome than in our study (9). Furthermore, a secondary analysis in our study with incident dementia as the only outcome did not modify our results in an important way. It might be argued that null findings in our study might be due to inadequate power to detect associations. Nevertheless, we reran the model with pooled categories of alcohol consumption to increase the number of subjects in each category, and no important modifications were observed in the results. Moreover, specific power calculations provided no evidence to reject the null hypothesis of a lack of association of alcohol consumption with incident severe cognitive decline.

Many arguments favor performing stratified analysis by gender when studying alcohol consumption, as we did in this study. First, patterns of alcohol consumption are very different in men and women (33, 53). Second, vulnerability to alcohol effects may differ in men and women, evidenced by different consumption thresholds for elevated risk in men and women recommended by international organizations (37). Finally, previous reports have suggested sex differences in the association between alcohol consumption and cognitive performance (9, 54).

Several factors add strength to our findings, including the use of a representative population sample, the high rate of follow-up, and the use of detailed methods to identify alcohol consumption and cognitive decline. The criterion of loss of one or more points per year in MMSE score supports the idea that the cognitive decline identified is severe enough and has clinical significance. Moreover, the adequacy of including both loss in MMSE scores and incident dementia in the outcome variable ''severe cognitive decline'' is supported by the finding that both criteria are not equivalent, since only a proportion of those cases of documented cognitive decline fulfilled the diagnosis of dementia, which was carefully assessed with the GMS-B–AGECAT system.

Some limitations, however, also need to be considered. We did not perform separate analyses for type of alcohol consumed by our participants because wine was the most common alcoholic beverage in this sample (96.1% of the drinkers), and the literature does not suggest that the effects of alcohol on cognitive function depend on type of beverage (39, 49). Although we controlled for possible confounding, we did not adjust for social and lifestyle factors coassociated with drinking habit, such as physical activity or social contacts, which might influence cognitive function in a way uncontrolled for in this study (17, 44, 54).

In conclusion, our study conducted in a southern European city did not support the hypothesis that low-to-moderate alcohol consumption prevents cognitive decline and/or dementia. Our findings further imply that detailed reporting of alcohol intake patterns, including separate reporting for former drinkers and lifetime abstainers, may be needed to evaluate the association between alcohol intake and cognitive decline or dementia.

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