Alcohol consumption, mild cognitive impairment, and progression to dementia

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ABSTRACT Objective: To estimate the impact of alcohol consumption on the incidence of mild cognitive impairment and its progression to dementia. **Methods:** We evaluated the incidence of mild cognitive impairment in 1,445 non–cognitively impaired individuals and its progression to dementia in 121 patients with mild cognitive impairment, aged 65 to 84 years, participating in the Italian Longitudinal Study on Aging, with a 3.5-year follow-up. The level of alcohol consumption was ascertained in the year before the survey. Dementia and mild cognitive impairment were classified using current clinical criteria. **Results:** Patients with mild cognitive impairment who were moderate drinkers, i.e., those who consumed less than 1 drink/day (approximately 15 g of alcohol), had a lower rate of progression to dementia than abstainers (hazard ratio [HR] 0.15; 95% CI 0.03 to 0.78). Furthermore, moderate drinkers with mild cognitive impairment who consumed less than 1 drink/day of wine showed a significantly lower rate of progression to dementia than abstainers (HR 0.15; 95% CI 0.03 to 0.77). Finally, there was no significant association between higher levels of drinking (≥1 drink/day) and rate of progression to dementia in patients with mild cognitive impairment vs abstainers. No significant associations were found between any levels of drinking and the incidence of mild cognitive impairment in non–cognitively impaired individuals vs abstainers. **Conclusions:** In patients with mild cognitive impairment, up to 1 drink/day of alcohol or wine may decrease the rate of progression to dementia.
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The Italian Longitudinal Study on Aging (ILSA) found that vascular risk factors influenced incident mild cognitive impairment (MCI) and the rate of progression to dementia.[1,2] Actually, many risk factors for cerebrovascular disease and vascular dementia (VaD), including serum total cholesterol (TC), hypertension, atherosclerosis, and APOE genotype, have also been shown to increase the risk of Alzheimer disease (AD).[2,3] Among the vascular-related factors, the impact of diet has been the subject of recent interest.[4] In fact, findings from the ILSA demonstrated that although dietary fatty acid intake was not associated with the incidence of MCI, specifically high polyunsaturated fatty acid intake seemed to show a trend toward protection from the development of MCI.[5]

Many studies have assessed alcohol consumption and cognitive function in the elderly, but with inconsistent results.[6-8] Furthermore, epidemiologic studies have reported an association between wine consumption and the incidence of AD[9] and between alcohol consumption and the risk of dementia.[10-14] Some reports have suggested that there is a J- or U-shaped relationship between alcohol consumption and cognitive impairment.[7,9,10] This implies that light-to-moderate alcohol consumption might have a protective effect vs total abstention or heavy consumption. In particular, a recent study showed that midlife alcohol consumption was related to the risk of MCI in old age in a U-shaped manner, with both nondrinkers and frequent drinkers having a higher risk than occasional drinkers.[15] Finally, another report found that moderate alcohol intake was associated with an approximately 50% reduced risk of combined probable dementia and MCI.[16] In the present study, we sought to estimate the

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possible impact of alcohol consumption on the incidence of MCI and its progression to dementia in a large Italian population-based sample.

METHODS

Participants. The subjects of this study were enrolled in a larger study, the ILSA, promoted by the Italian National Research Council–CNR-Targeted Project on Aging. The methods of the ILSA data collection have been described in detail elsewhere.[2] A sample of 5,632 subjects aged 65 to 84 years, independent or institutionalized, was randomly selected from the electoral rolls of eight Italian municipalities, after stratification for age and gender. Informed consent was obtained from all subjects according to local institutional guidelines. Data were obtained from the first prevalence survey study between March 1992 and June 1993 (prevalence day: March 1, 1992) and from the second prevalence survey study between September 1995 and October 1996 (prevalence day: September 1, 1995).

Clinical, demographic, and laboratory examination. Cases of coronary artery disease (CAD; myocardial infarction and angina pectoris), hypertension, type 2 diabetes mellitus, and stroke were identified with a two-phase procedure.[2] In Phase 1, a screening questionnaire, a series of brief screening tests to identify suspect cases for further investigation, and a clinical evaluation were administered to each subject; in Phase 2, suspected cases were confirmed with a standardized clinical examination by a certified geriatrician, neurologist, or internist. Details of the diagnostic criteria used to define the prevalence rates of the investigated conditions have been presented elsewhere.[2] The screening questionnaire included information on demographic characteristics, body weight and weight history, smoking habits, and current use of medications (including inspection of the drugs by the interviewer).

Blood samples were obtained after a 13-hour overnight fast; serum TC concentration was determined as reported in detail elsewhere.[17] Based on self-reports, smoking habits were categorized as "ever" or "never," and the variable "cigarette pack-years" [years smoked * usual number of cigarettes smoked/20 cigarettes per pack] was generated to represent the total smoking exposure.

Neuropsychological and functional variables. The Mini-Mental State Examination (MMSE)[18] was used to evaluate global cognitive function (orientation, attention, immediate and delayed verbal memory, constructional praxis, and language). Episodic memory was tested with the Babcock Story Recall Test (BSRT).[19] This test measures immediate and delayed recall, using a 21-unit story. For the purpose of scoring, an event-weighted, hierarchical system was used, based on the degree of organization of the recollection provided by the subject. Functional status was assessed with the Activities of Daily Living scale (scores ranging from 6 [all functions preserved] to 18 [all functions lost]), which determines the level of independence in six activities: bathing, dressing, toileting, transferring from bed to chair, continence, and feeding.[20] Ability in home management was assessed by the Instrumental Activities of Daily Living scale (scores ranging from 8 [all functions preserved] to 31 [all functions lost]), which determines the level of independence in executing tasks such as using the telephone, shopping for personal items, preparing meals, doing light housework (e.g., washing dishes), managing money or drugs, and so forth.[21]

Classification of dementia and MCI. The case finding strategy for the diagnosis of dementia consisted of a two-phase procedure as reported in detail elsewhere.[2] An extensive risk factor interview and a screening test battery were administered to all participants; those who screened positive underwent a clinical evaluation by a trained neurologist, and those with a confirmed diagnosis of dementia were excluded. The main screening criteria for cognitive impairment or dementia were the MMSE with a cutoff score of 23 or a previous diagnosis reported by the respondent proxy. The structured clinical assessment performed by a neurologist consisted of a review of clinical records, a neurologic examination, Sections B and H of the Cambridge Mental Disorders Examination,[22] the Pfeffer Functional activities questionnaire,[23] and the Hamilton Depression Rating Scale.[24] The diagnosis was based on the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd revised edition criteria for dementia syndrome[25]; the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease andRelated Disorders Association criteria for possible and probable AD[26]; and the *International Classification of Diseases*, 10th revision criteria for VaD and other dementing diseases.[27]

We generally adhered to the diagnostic criteria for MCI as defined by Petersen et al.,[28] we did not require subjective memory impairment, and we allowed for the presence of noncognitive disabilities and comorbid illnesses. Details of the diagnostic criteria for MCI have been presented elsewhere.[1-3]

Assessment of alcohol consumption. We collected information on alcohol consumption with food frequency questionnaires completed in 1992. Participants were asked how much beer or wine they had consumed per day in the previous year. The amount consumed was quantified according to three categories: 1) "two fingers" to half a glass (equal to 0.125 L), 2) two glasses (equal to 0.25 L), or 3) four glasses (equal to 0.50 L). Data on superalcoholic beverage consumption was collected by asking the participants how often they had consumed "shots" of spirits (equal to one standard drink) in the previous year, according to three frequency categories: 1) number of times/day, 2) number of times/month, and 3) number of times/year. Furthermore, participants were asked when they had begun to drink and how much beer or wine per day they had consumed ever since to evaluate among drinkers who never interrupted their drinking habits, who interrupted their drinking habits during the preceding 5 years (current), and who interrupted their drinking habits before the preceding 5 years (former). In particular, among "formers," we also included the subjects who reported no alcohol intake at the baseline cognitive assessment but who had reported alcohol intake on their recall and who changed their alcohol intake during their lifetime by more than one category. Then, liters were transformed into US ounces (1 L = 33.81 fluid ounces). The dose of alcohol was calculated by multiplying the volume of an alcoholic beverage by the percentage of alcohol as volume. This average-sized dose of alcohol is equal to 0.5 ounces of absolute alcohol, which we called a "drink equivalent." One fluid ounce (US) of alcohol equals approximately 30 mL, and one drink equals approximately 15 g. In particular, it was assumed that 12 ounces of beer that is 4% alcohol by volume, 5 ounces of wine that is approximately 10% alcohol by volume, and 1 ounce of superalcoholic beverage that is approximately 40% alcohol by volume should have the same dose of alcohol, i.e., approximately 0.5 ounces of alcohol. In our data, the amount of alcohol deriving specifically from red or white wines could not be measured.

Of 704 elderly subjects enrolled in the Casamassima cohort, one of eight ILSA centers, 297 subjects also completed a semiquantitative food frequency questionnaire (other than the food frequency questionnaire purposed in the ILSA protocol) evaluating macronutrient energy intakes. Among these 297 subjects, 278 subjects represented the study population of many reports, published by our group elsewhere,[4,5] whereas 18 subjects were excluded because they did not meet criteria for those studies and they were classified as affected by MCI (one subject did not match the two assessments). The reproducibility and validity of the assessment of alcohol intake were evaluated among 278 cognitively healthy elderly subjects and 18 patients with MCI who completed the semiquantitative food frequency questionnaire. These subjects indicated how often during the previous year, on average, they had eaten a certain food, choosing among the pictures of three different serving sizes or natural units. The correlation of alcohol intake on the questionnaire with alcohol intake on the dietary records was 0.82 ($p < 0.01$) for non–cognitively impaired (NCI) individuals and 0.59 ($p < 0.04$) for patients with MCI.

Statistical analysis. We estimated the rate of incidence of MCI and its progression to dementia associated with alcohol consumption with Cox proportional hazards regression analysis. We assessed alcohol as a continuous (number of drinks per day) and as a categorical variable (no alcohol intake, ≤1 drink/day, 1 or more drinks but ≤2 drinks/day, >2 drinks/day). "No alcohol intake" was used as the reference. All analyses were controlled for age (coded 0 for 65- to 74-year-old and 1 for 75- to 84-year-old subjects) and gender (coded 0 for women and 1 for men). Analyses were adjusted for possible confounders: education (coded 0 for ≤3 years and 1 for >3 years; 3 years of education was the first quartile of the sample for MCI incidence and the median value of the sample for progression to dementia), cigarette pack-years (coded 0 for cigarette pack-years = 0 [never smoking] and 1 for cigarette pack-years ≥ 0.5), CAD, type 2 diabetes, hypertension, stroke, and TC (in the sample for the incidence of MCI, coded as quartile 1 if ≤193 mg/dL [≤5.0 mmol/l], 2 if 194 to 219 mg/dL [5.0 to 5.7 mmol/l], 3 if 220 to 246 mg/dL [5.7 to 6.4 mmol/l], and 4 if ≥247 mg/dL [≥6.4 mmol/l]; in the sample for the progression to dementia, coded as quartile 1 if ≤175 mg/dL [≤4.5 mmol/l], 2 if 176 to 199 mg/dL [4.6 to 5.2 mmol/l], 3 if 200 to 229 mg/dL [5.2 to 6.0 mmol/l], and 4 if ≥230 mg/dL [≥6.0 mmol/l]).

We checked the proportional hazards assumptions by plotting log-minus-log curves. The rate of MCI in NCI individuals and the progression to dementia in patients with MCI associated with specific classes of alcoholic beverage were analyzed in separate regression models. For each individual, we expressed the amount of alcohol intake deriving from wine, beer, and superalcoholic beverages in the number of drinks, controlled for alcohol deriving from other sources within each category of total alcohol intake as described above. The rate of progression to dementia in patients with MCI associated with the intake of beer and superalcoholic beverages was expressed relatively to the rate associated with "only" wine consumption, given that the effects of beer and superalcoholic beverages after adjusting for alcohol deriving from other sources were collinear within each category of total alcohol intake. Moreover, a possible linear relationship was evaluated between total alcohol intake, wine and beer beverages (considered as continuous variables) and rate of MCI in NCI individuals and rate of progression to dementia in patients with MCI who reported in the questionnaires to be current or former drinkers (linear models). Finally, a possible quadratic relationship was evaluated between each type of alcoholic beverage and rate of incident MCI in NCI subjects and rate of progression to dementia in patients with MCI, squaring each type of alcoholic beverage variable (X, linear term) after centering it on median consumption (X^2, quadratic term) by a polynomial model. In these two last models, in controlling for alcohol deriving from other sources within each category of total alcohol intake, we excluded superalcoholic sources, because in the previous 5 years it was not mentioned in the dietary questionnaire as for wine and beer consumption. We used SAS statistical software version 9.1 (SAS Institute Inc, Cary, NC) for all analyses.

RESULTS Of the 5,632 elderly subjects enrolled in the cohort in 1992, 4,521 agreed to participate. The attrition according to the criteria for MCI excluded 1,558 of 4.521 participants (demented at baseline: 226; refusal to perform MMSE or BSRT or both neuropsychological tests: 1,171; education level unknown or doubtful: 161), and MCI was diagnosed in 139 of 2,963 subjects (3.2%). Differences in age (73.4 ± 5.6 vs 75.2 ± 5.7, $p < 0.01$ evaluated by separate variance t test) and gender (Pearson $\chi^2 = 34.16$, $p < 0.01$) were observed between participants and nonparticipants (2,963 participants: 1,589 men [56.4%] and 1,374 women [48.8%]; 2,669 nonparticipants: 1,227 men [43.6%] and 1,442 [51.2%] women). To evaluate risk factors predicting the incidence of MCI, 1,445 of 2,963 elderly subjects completed the follow-up assessment, whereas to evaluate risk factors predicting progression to dementia, 121 of 139 patients with MCI completed the follow-up assessment, as detailed elsewhere.[4]

Alcohol consumption and incidence of MCI. During 15,341 person-years of follow-up (median follow-up 3.5 years), 105 subjects developed MCI. Table 1 shows the baseline characteristics of NCI participants according to categories of alcohol consumption. Participants who reported drinking more than one form of alcohol were counted more than one time. The amount of alcohol intake deriving from wine was 75.9%, that from beer was 2.0%, and that from superalcoholic beverages was 22.1%. Among the NCI individuals, median alcohol consumption was 0.88 drinks/day (interquartile range [IQR] 0.85 to 1.80) and was higher for men (1.69, IQR 0.85 to 3.38) than for women (0.85, IQR 0.00 to 0.88). With increasing alcohol intake, the proportion of never smokers sharply decreased. Table 2 shows the distribution of the consumption of alcoholic beverages in NCI participants. Beer, wine, and superalcoholic beverages were consumed more by men than by women. The overall effect of alcohol consumption in categories on the rate of MCI, adjusted for age, gender, education, CAD, hypertension, diabetes, stroke, smoking, and TC is shown in table E-1 on the *Neurology* Web site at

Table 1 Baseline characteristics of non-cognitively impaired participants according to categories of alcohol consumption per day in the previous year, the Italian Longitudinal Study on Aging (1992 to 1996)

	Alcohol consumption			
	None	<1 drink/day	1 or 2 drinks/day	>2 drinks/day
Number of individuals (number of patients with incident MCI)	242 (20)	538 (38)	367 (25)	298 (22)
Age, mean ± SD, years	71.09 ± 4.94	72.12 ± 5.06	71.90 ± 5.06	71.67 ± 4.80
gender (men), n (%)	53 (24.9)	215 (38.8)	263 (71.5)	284 (91.6)
Education, mean ± SD, years	7.78 ± 5.15	6.54 ± 4.53	7.48 ± 4.80	7.12 ± 4.64
Hypertension (yes), n (%)	147 (69.0)	381 (68.8)	265 (72.0)	204 (65.8)
Stroke (yes), n (%)	19 (8.9)	26 (4.7)	23 (6.3)	14 (4.5)
Smoking status, median (IQR), pack-years	0 (0–6)	0 (0–19)	8.3 (0–31.25)	25 (2–48.2)
Type 2 diabetes (yes), n (%)	25 (11.7)	50 (9.0)	39 (10.6)	26 (8.4)
Coronary artery disease (yes), n (%)	36 (16.9)	95 (17.1)	66 (17.9)	52 (16.8)
Total cholesterol, mean ± SD, mg/dL	224.81 ± 42.30	222.22 ± 41.15	217.12 ± 39.83	220.90 ± 40.40
Mean ± SD, mmol/L	5.82 ± 1.10	5.76 ± 1.07	5.62 ± 1.03	5.72 ± 1.05
Anxiolytics (yes), n (%)	29 (13.6)	66 (11.9)	29 (7.9)	19 (6.1)
Antidepressants (yes), n (%)	6 (2.8)	16 (2.9)	3 (0.8)	1 (0.3)
Hypnotics (yes), n (%)	3 (1.2)	4 (0.7)	3 (0.8)	4 (1.3)

MCI = mild cognitive impairment; IQR = interquartile range.

www.neurology.org. There was no association between alcohol intake and risk of MCI (table E-1). Compared with no alcohol consumption, we found no significant interaction effect between gender and overall alcohol consumption on the rate of the incidence of MCI (data no shown), as well as in the analyses estimating the effect of the amount of intake of alcohol deriving from wine or beer or superalcoholic beverages and controlled for alcohol deriving from the other sources within each category of total alcohol intake (table E-1). Finally, there was no linear and quadratic relationship between total alcohol, wine, beer, and superalcoholic beverages (considered as continuous variables) and the rate of MCI in NCI individuals who reported in the questionnaires that they were current or former drinkers (table E-1).

Alcohol consumption and progression of MCI to dementia. During 8,241 person-years of follow-up (median follow-up 3.5 years), 14 subjects developed dementia. Table 3 shows the baseline characteristics of the patients with MCI according to categories of alcohol consumption. The amount of alcohol intake deriving from wine was 85.0%, that from beer was 0.4%, and that from superalcoholic beverages was 14.6%. Among the patients with MCI, median alcohol consumption was 0.85 drinks/day (IQR 0.85 to 1.69) and was higher for men (1.69, IQR 0.85 to 1.80) than for women (0.85, IQR 0.00 to 0.85). With increasing alcohol intake, the proportion of never smokers sharply decreased. Table 2 shows the distribution of consumption of alcoholic beverages in patients with MCI. Participants who reported

Table 2 Distribution of alcohol intake per day in the previous year over subtypes of alcoholic beverages in NCI participants (n = 1,445) and in patients with MCI (n = 121) at baseline, the Italian Longitudinal Study on Aging (1992 to 1996)

	Beer		Wine		Superalcoholic beverages	
	Number of NCI individuals (%)	Median (IQR) drinks/day	Number of NCI individuals (%)	Median (IQR) drinks/day	Number of NCI individuals (%)	Median (IQR) drinks/day
Total	76 (5.3)	0.35 (0.35–0.70)	1,131 (78.3)	1.69 (0.85–1.69)	585 (40.5)	0.14 (0.04–1.08)
Men	56 (6.9)	0.35 (0.35–0.70)	721 (88.5)	1.69 (0.85–3.38)	416 (51)	0.14 (0.04–1.08)
Women	20 (3.2)	0.35 (0.35–0.70)	410 (65.1)	0.85 (0.85–0.85)	169 (26.8)	0.07 (0.01–0.14)
	Number of patients with MCI (%)	Median (IQR) drinks/day	Number of patients with MCI (%)	Median (IQR) drinks/day	Number of patients with MCI (%)	Median (IQR) drinks/day
Total	2 (1.7)	0.35 (—)	97 (80.2)	0.85 (0.85–1.69)	40 (33.1)	0.04 (0.01–0.22)
Men	1 (1.7)	0.35 (—)	57 (95.0)	1.69 (0.85–2.54)	28 (46.7)	0.07 (0.01–0.76)
Women	1 (1.6)	0.35 (—)	40 (65.6)	0.85 (0.85–0.85)	12 (19.7)	0.03 (0.01–0.04)

NCI = non-cognitively impaired; MCI = mild cognitive impairment; IQR = interquartile range.

Table 3 Baseline characteristics of patients with MCI according to categories of alcohol consumption per day in the previous year, the Italian Longitudinal Study on Aging (1992 to 1996)

	Alcohol consumption			
	None	<1 drink/day	1 or 2 drinks/day	>2 drinks/day
Number of individuals (number of patients with incident MCI)	23 (6)	55 (3)	22 (3)	21 (2)
Age, mean ± SD, years	80.25 ± 2.44	80.7 ± 22.59	81.13 ± 2.40	80.5 ± 2.43
gender (men), n (%)	1 (6.3)	21 (35)	17 (73.9)	21 (95.5)
Education, mean ± SD, years	2.19 ± 1.22	2.13 ± 1.31	2.22 ± 1.28	2.32 ± 1.32
Hypertension (yes), n (%)	14 (87.5)	41 (68.3)	14 (60.9)	13 (59.1)
Stroke (yes), n (%)	3 (18.8)	6 (10)	2 (8.7)	0 (0)
Smoking status, median (IQR), pack-years	0 (0–0)	0 (0–0.25)	8.7 (0–31)	11.38 (4–54.3)
Diabetes (yes), n (%)	3 (18.8)	8 (13.3)	1 (4.3)	3 (13.6)
CAD (yes), n (%)	1 (6.3)	11 (18.3)	3 (13.0)	1 (4.5)
Total cholesterol, mean ± SD, mg/dL	211.38 ± 48.82	210.65 ± 50.37	191.70 ± 35.73	197.5 ± 34.84
Mean ± SD, mmol/L	5.47 ± 1.26	5.46 ± 1.30	4.97 ± 0.93	5.12 ± 0.90
Anxiolytics (yes), n (%)	1 (6.3)	8 (13.3)	1 (4.4)	3 (13.6)
Antidepressants (yes), n (%)	1 (6.3)	2 (3.3)	1 (4.3)	1 (4.5)
Hypnotics (yes), n (%)	2 (12.5)	0 (0)	1 (4.3)	0 (0)

MCI = mild cognitive impairment; IQR = interquartile range; CAD = coronary artery disease.

drinking more than one form of alcohol were counted more than one time. Beer, wine, and superalcoholic beverages were consumed more by men than by women. The overall effect of alcohol consumption in categories on the rate of dementia, adjusted for age, gender, education, hypertension, stroke, CAD, Type 2 diabetes, smoking, and TC is shown in table 4. Compared with no alcohol consumption, light drinking (from 0.1 to 1 drink/day) was associated with a significantly lower rate of progression to dementia (hazard ratio [HR] 0.18, 95% CI 0.04 to 0.81 in the partially adjusted model and HR 0.15, 95% CI 0.03 to 0.78 in fully adjusted model; table 4). The amount of alcohol intake deriving from wine, controlled for alcohol deriving from other sources within each category of total alcohol intake, was also associated with a significantly lower rate of progression to dementia (HR 0.18, 95% CI 0.04 to 0.81 in the partially adjusted model and HR 0.15, 95% CI 0.03 to 0.77 in fully adjusted model; table 4). Furthermore, there was no significant association between higher levels of drinking (≥1 drink/day) and rate of progression to dementia in patients with MCI vs abstainers (table 4). Given that only 14 patients with MCI at baseline progressed to dementia, we did not estimate the interaction effect between alcohol consumption and gender on the rate of progression to dementia (data not shown). We note, however, that the fully adjusted models, though overfitted, yielded comparable results. Finally, there was no linear and quadratic relationship between total alcohol, wine, beer, and superalcoholic beverages (considered as continuous variables) and rate of progression to dementia in patients with MCI who reported in the questionnaires to be current or former drinkers (table 4).

Sensitivity analysis. Only 93 NCI individuals (6.4%) and 8 patients with MCI (6.7%) reported a change in their drinking pattern during the preceding 5 years. All NCI individuals and patients with MCI with changed drinking patterns reported drinking less than in the preceding 5 years. In particular, they interrupted their drinking habits and they did not go back to drinking (included in "former" in table E-1 and table 4). To avoid biases due to the inclusion of former heavy drinkers among nondrinkers, we excluded from the analyses ("current" in table E-1 and table 4) the subjects who reported no alcohol intake at the baseline cognitive assessment but who had reported alcohol intake on their recall (included in "former" in table E-1 and table 4). In particular, we also excluded from the analyses ("current" in table E-1 and table 4) the 59 NCI participants (<4.1%) and 7 patients with MCI (5.7%) who changed their alcohol intake during their lifetime by more than one category (included in "former" in table E-1 and table 4). Finally, because the use of antidepressants (2.6% for NCI and 4.1% for patients with MCI), anxiolytics (9.9% for NCI and 10.7% for patients with MCI), and hypnotics (<1% for NCI and 2.5%

Table 4 Hazard ratios for dementia according alcohol consumption per day in the previous year in patients with MCI, the Italian Longitudinal Study on Aging (1992 to 1996)

	Category (drink/day), current				Linear model, current	Polynomial (quadratic) model, current		Linear model, former	Polynomial (quadratic) model, former	
	None	<1	1 or 2	>2		HR for centered linear (X) term (95% CI)	HR for centered quadratic (X^2) term (95% CI)		HR for centered linear (X) term (95% CI)	HR for centered quadratic (X^2) term (95% CI)
	HR (95% CI)				HR (95% CI)			HR (95% CI)		
No. of patients with MCI at baseline	23	55	22	21						
No. of patients with MCI progressed to dementia	6	3	3	2						
Total alcohol consumption										
Partially adjusted model, HR (95% CI)	1.00	0.18 (0.04–0.81)	0.56 (0.09–3.56)	0.37 (0.04–3.16)	0.65 (0.32–1.34)	0.61 (0.23–1.57)	1.04 (0.77–1.40)	0.54 (0.25–1.18)	0.45 (0.18–1.12)	1.11 (0.86–1.44)
Fully adjusted model, HR (95% CI)	1.00	0.15 (0.03–0.78)	0.47 (0.08–2.73)	0.44 (0.05–4.06)	0.93 (0.43–1.97)	0.91 (0.32–2.59)	1.0 (0.74–1.37)	0.73 (0.32–1.66)	0.60 (0.22–1.63)	1.10 (0.85–1.41)
Wine										
Partially adjusted model, HR (95% CI)	1.00	0.18 (0.04–0.81)	0.54 (0.08–3.46)	0.31 (0.03–3.23)	0.52 (0.22–1.25)	0.54 (0.19–1.50)	0.97 (0.65–1.46)	0.38 (0.14–1.02)	0.37 (0.13–1.02)	1.04 (0.70–1.54)
Fully adjusted model, HR (95% CI)	1.00	0.15 (0.03–0.77)	0.44 (0.07–2.64)	0.36 (0.03–4.26)	0.76 (0.30–1.91)	0.80 (0.26–2.45)	0.96 (0.64–1.45)	0.51 (0.18–1.49)	0.49 (0.16–1.47)	1.05 (0.72–1.54)

The partially adjusted coefficients were adjusted for gender (0 for men and 1 for women), age (in ordered quartiles), and education (coded 0 for ≤3 years and 1 for >3 years). The fully adjusted coefficients were adjusted for gender (0 for men and 1 for women), age (coded 0 for 65- to 74-year-old and 1 for 75- to 84-year-old subjects), education (coded 0 for ≤3 years and 1 for >3 years), cigarette pack-years (coded 0 for cigarette pack-years = 0 [never smoking] and 1 for ever smoking), coronary artery disease (coded 0 if not affected and 1 if affected), stroke (coded 0 if not affected and 1 if affected), Type 2 diabetes (coded 0 if not affected and 1 if affected), hypertension (coded 0 if not affected and 1 if affected), total cholesterol (in ordered quartiles), and anxiolytics (coded 0 if not used and 1 if used).

Abstainers served as the reference group.

MCI = mild cognitive impairment; former = drinkers who interrupted their drinking habits and did not go back to drinking during the preceding 5 years; HR = hazard ratio.

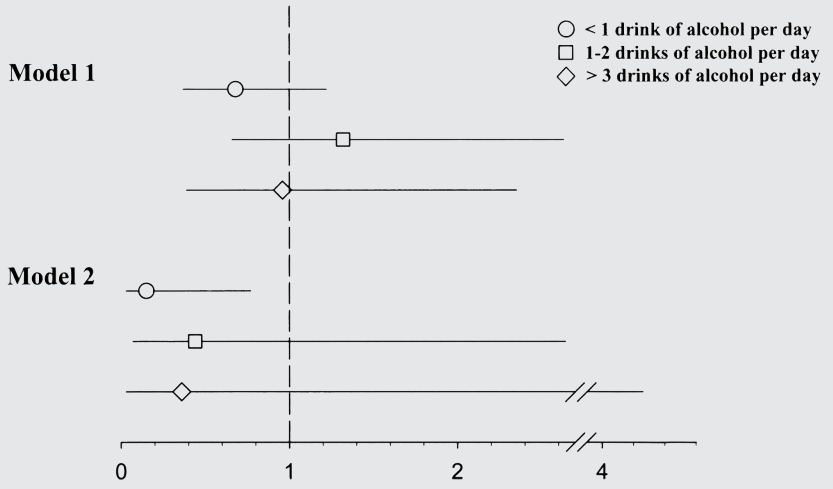
for patients with MCI) is strongly associated with both alcohol intake and cognition, we repeated the analyses, excluding those who reported use of these three medications and adjusting only for those who reported use of anxiolytics. For those who were excluded, the results essentially did not change with respect to those reported in table E-1 and table 4 (data not shown).

As an additional sensitivity analysis, we modeled alcohol as a continuous variable, including linear and squared terms to detect U-shaped relationships. In this model, no U-shaped significant effect on the rate of MCI or progression to dementia was found among all subjects as well as in interaction between alcohol consumption and gender (table E-1 and table 4). We found no support for the hypothesis that the rate of progression to dementia varied according to the type of alcoholic beverage consumed. A model in which we included specific types of alcoholic beverages (wine, beer, and superalcoholic beverages) as well as different amounts of alcohol was not significantly better than a model without specific types of alcoholic beverages. These findings are also reflected in the figure, which shows the multivariate HRs of incident MCI (Model 1) and progression to dementia (Model 2) associated with the amount of alcohol intake in the fully adjusted models.

DISCUSSION Patients with MCI who consumed up to 1 drink/day had a reduction in the rate of progression to dementia in comparison with patients with MCI who never consumed alcohol. Overall, vs nondrinkers, patients with MCI who consumed 1.0 to 14.9 g of alcohol/day, derived mostly from wine, had a decrease in the rate of progression to dementia of approximately 85%. Moderate intake of alcohol deriving from wine, in drinks controlled for the intake of alcohol deriving from other sources within each level of total intake, was also associated with a significantly lower rate of progression to dementia.

Many studies have assessed the possible role of alcohol consumption on cognitive function among older adults,[6-8] but with inconsistent results. How-

Figure Multivariate hazard ratios of incident MCI among non–cognitively impaired subjects and progression to dementia among patients with MCI



Multivariate hazard ratios of incident mild cognitive impairment (MCI) among non–cognitively impaired subjects (Model 1) and progression to dementia among patients with MCI (Model 2) who drank <1 alcoholic drinks/day (circle with solid line) or 1 to 2 alcoholic drinks/day (square with solid line) or >2 alcoholic drinks/day (rhomb with solid line) vs abstainers.

ever, many of these reports were limited by a cross-sectional design, restrictions in age or gender, or incomplete assessment. In the present study, no significant associations between levels of alcohol consumption and incidence of MCI were found. Compared with no alcohol consumption, there was no significant interaction between gender and overall alcohol consumption on the risk of MCI and, in the same analysis, for beverage type beyond any effect of the alcohol itself. To the best of our knowledge, only two other studies have examined the effect of alcohol consumption on the risk for the incidence of MCI.[15,16] After an average follow-up of 23 years, nondrinkers and frequent drinkers were both more than twice as likely to have MCI in old age than occasional drinkers.[15] However, the APOE genotype seemed to modify the relationship, such that the risk of old age dementia increased with increasing midlife alcohol consumption only among carriers of the APOE ε4 allele.[15] In the present report, we did not confirm these findings, but we note that the alcohol consumption reported was a midlife determination.[15] Probably, a follow-up period longer than 3.5 years would have revealed that a moderate alcohol consumption might influence the incidence of MCI. However, our findings are consistent with those obtained in the Women's Health Initiative Memory Study with a 4.2-year follow-up, which found that moderate alcohol intake was associated with an approximately 50% reduced risk of combined probable dementia and MCI.[16] However, after adjusting for demographic and socioeconomic factors and baseline Modified Mini-Mental State Examination, the significance disappeared.[16]

Currently, ours is the first study in which alcohol consumption was associated with the rate of progression of MCI to dementia. In this respect, our findings are consistent with those of the Rotterdam Study, with an average follow-up of 6 years, in which light-to-moderate alcohol consumption was associated with a reduced risk of dementia (AD, VaD, or other dementias) in individuals aged 55 years or older, with this effect seemingly independent of the source of alcohol.[11] Our estimates closely parallel those of a nested case–control study of 373 cases with dementia, 65 years and older, who participated in the Cardiovascular Health Study (CHS), where relative (compared with those for abstainers) odds of 0.65 (<1 drink/week), 0.46 (1 to 6 drinks/week), 0.69 (7 to 13 drinks/week), and 1.22 (≥14 drinks/week) of dementia were observed.[13] Finally, a recent community-based study involving 2,258 nondemented individuals in New York reported that adherence to a diet similar to a traditional Mediterranean diet, one of whose hallmarks is a moderate consumption of alcohol, was associated with a significant reduction in the risk of AD.[29]

In the present study, moderate intake of alcohol deriving from wine was also associated with a significantly lower rate of progression to dementia. Red wine, one of the typical components of the Mediterranean diet, was investigated in the PAQUID study in France, in which individuals 65 years and older a moderate wine consumption (3 or 4 glasses/day) was associated with a lower risk of AD and overall dementia, whereas mild consumption (1 or 2 glasses/day) was associated with a lower risk of AD but not dementia.[9] The Canadian Study of Health and Aging also reported a lower risk of AD with the consumption of wine but not other alcoholic beverages.[7] The Copenhagen City Heart Study recently reported that monthly and weekly intake of wine was associated with a decreased risk of dementia in individuals aged 65 years and older, whereas the intake of alcohol was not protective against dementia. Actually, an increased risk for dementia was observed among monthly, weekly, and daily drinkers of beer and spirits.[12] Finally, in the Washington Heights Inwood-Columbia Aging Project, with 908 subjects aged 65 years and older, consumption of up to 3 servings/day of wine was associated with a lower risk of AD in elderly individuals without the APOE ε4 allele.[14]

The mechanism by which low alcohol intake could be protective against the progression of MCI to dementia is, at present, unknown. Alcohol consumption might protect from dementia by effects on the cerebral vasculature, supporting the observation that moderate alcohol intake might be protective against ischemic stroke.[30] In the Rotterdam study, the protective effect of alcohol consumption was

found mainly for VaD, and the authors suggested that moderate alcohol intake might protect against dementia via a reduction in vascular risk factors.[11] In fact, light-to-moderate alcohol use is associated with a lower prevalence of MRI-defined white matter lesions and subclinical infarcts,[31] although MRI abnormalities, high-density lipoprotein (HDL) cholesterol levels, and fibrinogen levels only marginally influenced the association of alcohol consumption and dementia in the CHS.[13] Furthermore, light-to-moderate alcohol intake has been reported to be associated with a lower prevalence of vascular brain findings and, in APOE ε4 carriers, with hippocampal and amygdalar atrophy as assessed by MRI.[31] Experimental studies found than ethanol initially increases hippocampal acetylcholine release, which could conceivably improve memory performance.[32] Moderate doses of alcohol may increase prostacyclin concentrations, reduce the generation of thromboxane A2, and inhibit platelet function.[33,34] They may increase plasma levels of endogenous tissue-type plasminogen activator, a serine protease that regulates intravascular fibrinolysis,[35] and fibrinolytic activity while decreasing plasma fibrinogen levels.[36] It is also known that alcohol is associated with increased levels of HDL cholesterol, its subfractions HDL2 and HDL3, and its associated apolipoproteins A-I and A-II.[37,38] The association with HDL cholesterol is deemed to account for up to half of the reduction in coronary events associated with moderate alcohol consumption.[39] Wine consumption may exert a protective effect, through alcohol intake itself, through the antioxidant effects of polyphenols richly represented in red wine,[40,41] or through both. The latter effects, of course, are independent of alcohol and, in fact, have also been associated with alcohol-free red wine.[42] Processes that originate, modulate, or precipitate the deposition of amyloid beta in the brain, such as oxidative stress, rather than vascular processes, may better explain the development of AD, and the vascular effects of the alcohol component of alcoholic beverages may not be enough to explain the protective effects of the moderate intake of alcohol from dementia. The presence in wine of nonalcoholic components, such as particular antioxidants, could explain a differential effect of wine on the progression to dementia. In fact, liquor has been shown to have less antioxidant activity than wine.[43] It is also possible that moderate lifestyles in general, which obviously vary according to different cultural environments, protect from cognitive impairment. Thus, it may not be the direct effect of alcohol or specific substances in alcoholic drinks that provide the protection, but moderate alcohol drinking may be an indicator of a complex set of favorable social and lifestyle factors. 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 and overall health status.

Some limitations in this study must be considered. It is of concern that self-reported alcohol intake is fallible and that the reliability of self-reports are affected by the level of cognition. Data on alcohol consumption were validated on a semiquantitative food frequency questionnaire, which was not a gold standard in the field and, perhaps, led to some misclassification. However, our assessment of alcohol intake was validated on the basis of dietary levels and has been used to predict mortality in this cohort.[44] Our alcohol assessment in the past for each subject may have been affected by a recall bias, in particular in patients with MCI. However, as for NCI individuals, a significant correlation was observed between alcohol consumption reported in the dietary records and in the semiquantitative food frequency questionnaire. However, we cannot rule out the possibility that other confounders, which have not been evaluated or are suboptimally measured, might have played a role. Nonetheless, adjustment for many potential confounders had little effect on the results, suggesting that confounding is unlikely to explain the observed associations. Finally, a longer follow-up period would have resulted in a greater number of incidents of MCI or progressors to dementia, but it would have reduced the relevance of alcohol habits as assessed at enrollment. Moreover, this approach would have been complicated by uncertainty relative to the latency of alcohol influences on the rate of the incidence of MCI or its progression to dementia. Finally, in the present study, we did not study the possible risk of MCI and its progression to dementia linked to the APOE genotype. In fact, in many studies, the effect of alcohol consumption on cognitive decline and dementia was associated with the presence of the APOE ε4 allele,[9,11-13] suggesting that genetic susceptibility is likely to modify the effect of alcohol consumption on the risk of dementia.

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APPENDIX

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Alcohol consumption, mild cognitive impairment, and progression to dementia

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