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Smoking, Drinking, and Thinking

The Zutphen Elderly Study

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The authors examine the cross-sectional and longitudinal relation of smoking habits and current alcohol intake to cognitive status and decline over a 3-year period as well as the extent to which these relations are modified by the presence of clinical conditions indicating atherosclerosis (cardiovascular disease(CVD)/diabetes). Data are from the cohort of men followed in the longitudinal Zutphen Elderly Study in 1990 (n = 489) and 1993 (n = 333). Cognitive function was measured in 1990 and 1993 with the 30-point Mini-Mental State Examination (MMSE). After adjustment for age, education, and alcohol intake, current smokers made 20% more errors on the MMSE than never smokers in the cross-sectional analyses. Cognitive decline was greatest in those with CVD/diabetes who currently smoked and never smoked (−1.9 and −1.3 points, respectively). After adjustment for age, education, and smoking status, men with CVD/diabetes and low-to-moderate alcohol intake had a significantly lower risk for poor cognitive function (MMSE ≤ 25) than abstainers (odds ratios of 0.3 for less than one drink and 0.2 for one to two drinks per day). Alcohol intake was not associated with cognitive decline. These findings do not support the hypothesis of a protective effect of smoking on cognitive function; they suggest that smoking may be harmful among those with CVD/diabetes. Alcohol may result in an acute beneficial effect on cognitive function among those with CVD/diabetes. However, selection bias and unmeasured confounding should be of concern when evaluating these results. *Am J Epidemiol* 1996; 143:219–27.

aged; alcohol drinking; cognition; longitudinal studies; smoking

Adequate cognitive functioning is essential to independent living. As the population grows proportionately older, the prevalence of cognitive impairment is expected to increase. This will necessitate studies to identify risk factors that predict its occurrence. Studies point to long-term and acute processes through which both cigarette smoking and alcohol may potentiate changes in the cerebrovascular system that could ultimately affect cognitive function. As both drinking and smoking are potentially modifiable behaviors, it is of interest to examine their relation to cognitive function.

Cigarette smoking may have a negative or positive effect on cognitive function. Long-term negative effects can be mediated via smoking-related events such as thrombosis, atherogenesis, and stroke (1–4). The negative effect of smoking habits could also be short term as smoking cessation reduces the risk for stroke and improves cerebral perfusion (5, 6). In contrast, cigarette smoking has been inversely correlated with the risk for Alzheimer's disease (7, 8). This beneficial effect of smoking may be mediated via nonvascular pathways involving nicotine receptors and neurotransmitter function (9). Indeed, nicotine delivery may improve performance on selected cognitive tests (10).

The effect of alcohol on cognitive function may depend on the amount consumed and the underlying cerebral pathology leading to cognitive impairment. Moderate alcohol intake has been associated with an increased risk for hemorrhagic stroke but a decreased risk for the more prevalent thromboembolic stroke (11). This protective effect may be mediated via acute responses in blood lipids, vasomodulators, and hemostatic factors (12–15). Chronic and heavy use of alcohol has been associated with neurotoxicity leading to the Wernicke-Korsakoff syndrome, which is characterized by severe memory impairment, or possibly to a distinct type of dementia (16, 17).

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Abbreviations: CVA, cerebral vascular accident; CVD, cardiovascular disease; MMSE, Mini-Mental State Examination.

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Although smoking and drinking have been examined in relation to clinical endpoints such as Alzheimer's disease and cardiovascular events (1–3, 6–8, 17–19), few studies have systematically investigated these habits in relation to cognitive function in community samples (20–22). In this study, we examine the cross-sectional and longitudinal relation of smoking and alcohol intake to cognitive status and change as well as the extent to which clinical conditions indicating atherosclerosis modify these relations. Data are from the cohort of men followed in the longitudinal Zutphen Elderly Study.

METHODS

The Zutphen Elderly Study is an extension of the original cohort that formed the Dutch contribution to the Seven Country Study (23, 24). In 1985, 1,266 men were asked to participate, 555 from the original cohort and 711 from a randomly selected sample from all other men living in Zutphen in the same age range (65–84 years). A total of 939 men agreed to participate. In 1990, 560 men (78 percent of the 718 survivors) participated; and in 1993, 390 men (71 percent of the 553 survivors) participated. Follow-up between surveys was complete. The average years of age for the participating cohort members were 71.6 ± 5.4 in 1985, 75.1 ± 4.7 in 1990, and 78.7 ± 4.3 in 1993.

In 1985 and 1990, the interviews, dietary assessments, and medical examinations were conducted at homes and at a study center. In 1993, the interviews took place at home. Factors were measured repeatedly with the same questions or methodology, although cognitive function was tested in 1990 and 1993 only. Data from all three surveys were used to assess possible bias from nonparticipation (due to death and refusal) and behavior change that followed and did not precede cognitive impairment or cardiovascular disease (CVD)/diabetes. Data from 1990 were used to examine the cross-sectional relation of cognitive function to smoking and drinking. Cognitive function measures from 1990 and 1993 were used to examine the relation between 1990 habits and cognitive decline.

Definition of variables

Cognitive function was assessed with the 30-point Mini-Mental State Examination (MMSE) of Folstein et al. (25). This test of orientation, attention, memory, language, and constructional abilities is used extensively in clinical and epidemiologic studies as a general measure of cognitive function (26). From the test of 20 questions, four or fewer missing answers were coded as wrong (27); and for more than four missing answers, the total score was coded as missing.

To assess smoking behavior, respondents were asked about the amount smoked and the ages when they started and stopped smoking. Smoking behavior was categorized as follows: current smokers, never smokers, and former smokers, divided further by the time since they stopped smoking (<10 years or >10 years ago). As only 12 percent of the men smoked more than 10 cigarettes per day, we did not further categorize the current smokers according to the amount smoked. These categories, rather than pack-years, were used to better study the effects of current compared with former and never smokers. Additional analyses did not suggest a consistent dose-response relation between pack-years and the risk for cognitive impairment (cross-sectional analyses) and decline (longitudinal analyses).

Usual alcohol intake in the month preceding the interview was calculated from a validated cross-check dietary history adapted to the Dutch setting (28). The number and type of drink were converted into grams of alcohol and categorized as follows: none, less than one drink (<13.2 g), one to two drinks, and more than three drinks per day.

The following covariate and confounding variables were considered in these analyses: age, education (0–6, 7–12, and ≥13 years), and clinical conditions indicating atherosclerosis. Clinical conditions indicating atherosclerosis included cerebrovascular accident (CVA), transient ischemic attack, myocardial infarction, intermittent claudication, and angina pectoris. These conditions were assessed by a standard medical interview that included questions from the Rose Questionnaire (29). We also included diabetes mellitus because it is strongly related to atherosclerosis (30) and to cognitive function in this cohort (31). Diabetes was ascertained by questionnaire or detected on the basis of a baseline fasting glucose level of >7.8 mmol/liter or a 2-hour postload glucose level of >11.1 mmol/liter. Diagnosis of each reported condition was verified with hospital discharge data and written information from the general practitioners, which was reviewed and uniformly coded by one physician. Records from individuals not reporting medical conditions in the interview were not examined.

Because of their relation to stroke and possibly to cognitive function, we considered the following conditions as potential moderators and mediators: hypertension, high density lipoprotein cholesterol, and fibrinogen. Hypertension was defined as the use of antihypertensive medication, as a systolic blood pressure of >160 mmHg, or as a diastolic blood pressure of >95 mmHg, determined on the basis of the mean of two blood pressure measurements taken with a random mercury sphygmomanometer. Nonfasting blood sam-

ples were used for the determinations of high density lipoprotein cholesterol (32) and fibrinogen (33).

Statistical analyses

The final sample for the cross-sectional analyses included 489 respondents with complete data on all risk factors; the longitudinal analyses included 333 respondents. Univariate relations were tested with chi-square for categorical variables and analysis of variance for continuous outcomes.

To assess bias from nonparticipation, we examined the association of drinking and smoking habits in 1985 to participation in 1990. In this context, we examined the association between 1985 behavior and death due to cardiovascular disease and also the association of participation in 1993 to behavior and cognitive function in 1990.

The cross-sectional relation of the MMSE to smoking behavior was examined in several ways. First, we compared the performance on the MMSE of smokers (current smokers, former smokers who quit <10 years ago, and those who quit >10 years ago) to never smokers. Performance was expressed as the number of errors (30 points-achieved score), which followed a Poisson distribution. Poisson regression was used to calculate the rate ratio of the mean number of erroneous answers in the index versus the reference group. Robust measures of the standard error were estimated to account for extra Poisson variation (34). Univariate analyses and analyses adjusted for age, education, and alcohol intake are shown. We also examined the risk for cognitive impairment in smoking groups compared with never smokers. This was done by dichotomizing the MMSE at <25 points and estimating risk as an odds ratio (95 percent confidence interval) with logistic regression. This cutoff has been used to screen for dementia (35) and is related to the probability of cognitive impairment (36). Both univariate and adjusted analyses are shown, as described above. Finally, we examined whether smoking category was related to change in the MMSE between 1990 and 1993 and whether smokers experienced more decline in the MMSE score than never smokers. Multiple linear regression was used for these analyses; in addition to the variables entered into the cross-sectional models, we also controlled for the 1990 MMSE score.

Analyses on alcohol intake were conducted in a similar manner wherein no reported alcohol intake was used as the reference. All models were adjusted for smoking status (never, former, current), age, and education; the analyses of cognitive decline also included the 1990 MMSE score. These analyses excluded 12 subjects who decreased their intake two or more categories between 1985 and 1990.

To evaluate the role of clinical disease in the relations of interest, two strategies were undertaken. First, factors possibly mediating the relation between the behavior and cognitive function were entered into the multivariate models. Second, we conducted stratified analyses by the presence or absence of CVD/diabetes. We expected that the risk associated with predominately nonvascular mechanisms would be more clearly seen on the one hand in the group without evidence of cardiovascular disease and diabetes, mimicking the situation in which risk is studied in Alzheimer's disease patients (7, 8, 19). On the other hand, the acute effect of smoking and alcohol in those at risk for cerebrovascular damage may be more evident in those with disease. Effect modification of the presence of CVD/diabetes was tested by entering into the adjusted model a term for the presence of disease and an interaction term between disease and smoking category. Similar analyses were conducted by hypertension status, inasmuch as hypertension has been shown to modify the relation of cigarette smoking to stroke (3) and to Alzheimer's disease (19). Analyses were conducted using the SAS statistical package (version 6.09) (37).

RESULTS

Participation and change in reported behavior

There was no selective participation in 1990 by 1985 drinking or smoking habits. However, total mortality was slightly greater among 1985 never smokers compared with former and current smokers and slightly greater among those who abstained from alcohol compared with those who did not (data not shown).

The samples for the cross-sectional and longitudinal samples did not differ in percent from low education (14.7 percent in the cross-sectional and 12.0 percent in the longitudinal sample), with hypertension (39.7 vs. 38.5 percent), with CVD/diabetes (39.7 vs. 35.8 percent), and with CVA (4.1 vs. 3.6 percent). Overall, nonparticipants in 1993 had a lower median 1990 MMSE score (26 vs. 27 for participants) and proportionately included more current smokers ($p < 0.05$) and abstainers from alcohol ($p < 0.07$). Those abstainers who participated in 1993 had a median 1990 MMSE score of 27 compared with 25 for nonparticipants. Otherwise, there was no difference between participants and nonparticipants by category of drinking or smoking status.

Smoking and drinking habits

In 1990, 22.5 percent of the men currently smoked; 43 percent had stopped smoking more than 10 years

ago. The respective durations of smoking (and standard deviations) were as follows: 57.1 (6.3) years among current smokers; 57.7 (7.0) years among those quitting within 10 years; and 31.5 (12.8) years among those quitting over 10 years ago. The average exposures in pack-years (and standard deviations) were 857.3 (454.6), 1,056.9 (753.4), and 486.9 (486.3) for current smokers, those quitting within 10 years, and those quitting more than 10 years ago, respectively. Alcohol intake was low to moderate: 45 percent reported an intake of less than one drink per day, and only 4 percent reported drinking three or more drinks per day.

Disagreement between 1985 and 1990 reports on smoking (i.e., in 1985 the respondent reported currently smoking and in 1990 reported not smoking) or alcohol intake may indicate reporting error or behavior change. Neither poor cognitive function, cognitive change between 1990 and 1993, hypertension, nor CVD/diabetes was associated with disagreement between 1985 and 1990 reports on smoking (data not shown). Disagreement in alcohol intake categories was not associated with any of these factors either. These factors also did not differ among those reporting abstention in 1990 and 1985 ($n = 71$) and those who reported abstention only in 1990 ($n = 54$).

Current smokers were relatively younger and reported drinking more alcohol than the other men. A greater percent of never smokers had CVD, and specifically CVA, compared with former and current smokers (table 1). Similarly, abstainers from alcohol had significantly more CVD/diabetes. In addition, education was associated with an increased intake of alcohol.

Smoking, drinking, and cognitive function

Older age and less education were associated with cognitive impairment and decline. After controlling for these variables, the presence of CVD/diabetes was not related to the rate of making errors or to poor cognitive function (MMSE < 25); however, those with CVD experienced a significantly larger decline in MMSE than those without CVD (−0.90, 95 percent confidence interval −1.41 to −0.39).

Compared with never smokers, current smokers made 20 percent more errors on the MMSE; otherwise, the risk for cognitive impairment did not differ by category of smoking status (table 2). There was no evidence of effect modification in the presence of CVD/diabetes, although those quitting within 10 years and current smokers with CVD/diabetes had slightly lower risks and those without CVD/diabetes, a slightly higher risk for poor cognitive function compared with never smokers. Results were similar when expressed as an error rate ratio (data not shown).

The effect of alcohol intake on cognitive function was modified by the presence of CVD/diabetes (table 3). Those individuals with CVD/diabetes who were moderate drinkers of two or fewer glasses per day had a significantly lower risk for poor cognitive function compared with the abstainers. Moderate drinkers without CVD/diabetes tended to have a higher but nonsignificant risk for poor function compared with abstain-

TABLE 1. Correlates of smoking and drinking habits, the Zutphen Elderly Study of Men

	No.	Cigarette smoking status, 1990						Daily alcohol intake, 1990							
		Never ($n = 91$)		Former ($n = 288$)		Current ($n = 110$)		None ($n = 125$)		<1 drink ($n = 221$)		1–2 drinks ($n = 122$)		≥3 drinks ($n = 21$)	
		Mean	(SD†)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Smoking status (%)															
Never	91							23.2		19.0		14.7		9.5	
Former	288							53.6		58.4		64.6		61.9	
Current	110							23.2		22.6		20.5		28.6	
Age (years)	489	75.7	(5.1)	75.2	(4.6)	74.1	(4.0)*	75 5	(4.7)	75.0	(4.5)	74.8	(4.6)	73.8	(4.0)
Education (years) (%)															
≤6	72	15.4		15.6		11.8		21.6		13.5		11.5		4.6**	
7–12	303	57.1		60.7		69.1		61 6		66.0		56.6		52.3	
≥13	114	27.5		23.6		19.1		16.8		20.4		32.0		42.9	
Hypertension (%)	194	38.0		40.6		38.1		37.6		40.7		39.3		42.8	
CVD†/diabetes‡ (%)	194	41.8		39.6		38.1		50.4		34.8		40.1		23.8***	
CVA† (%)	20	5.5		4.2		2.7		7.2		4.9		0.8		0****	

* $p < 0.05$ by analysis of variance for the relation of age (mean (SD)) to smoking status; ** $p < 0.005$ by chi-square for the relation of education to alcohol intake; *** $p < 0.02$ by chi-square for the relation of CVD to alcohol intake; **** $p < 0.06$ by chi-square for the relation of CVA to alcohol intake.

† SD, standard deviation; CVD, cardiovascular disease; CVA, cerebral vascular accident.

‡ CVD includes CVA, transient ischemic attack, myocardial infarction, intermittent claudication, and angina pectoris.

TABLE 2. Cross-sectional relation of cognitive function to smoking habits, the Zutphen Elderly Study of Men

Cigarette smoking status, 1990	Total sample									Poor cognitive function§							
			Error rate†				Poor cognitive function§			With CVD*,‖/diabetes				Without CVD‖/diabetes			
	No.	Median 1990 MMSE* score	Mean	(SD*)	Error rate ratio‡	95% CI*	<26 MMSE score (%)	OR*,§	95% CI	No.	<26 MMSE score (%)	OR	95% CI	No.	<26 MMSE score (%)	OR	95% CI
Never	91	27	3.8	(2.9)	1.0		34.1	1.0		38	39.5	1.0		53	30.2	1.0	
Former/quit (years ago)																	
≥10	212	27	3.8	(3.1)	1.0	0.87–1.20	30.2	0.9	0.5–1.5	85	34.5	0.9	0.4–2.1	127	27.6	0.9	0.4–1.8
<10	76	27	4.1	(2.9)	1.1	0.9–1.4	34.2	1.1	0.6–2.3	29	34.5	0.9	0.3–3.0	47	34.0	1.3	0.5–3.2
Current	110	26	4.3	(2.9)	1.2	1.0–1.4	33.6	1.1	0.6–2.2	42	33.3	0.8	0.3–2.3	68	33.8	1.4	0.6–3.2

* MMSE, Mini-Mental State Examination; CVD, cardiovascular disease; SD, standard deviation; CI, confidence interval; OR, odds ratio.
† (30 points – achieved score) on the MMSE in 1990.
‡ Ratio of erroneous answers given on the MMSE in the index group vs. the reference group adjusted for age, education, and alcohol intake.
§ MMSE score of <26 in 1990. ORs (adjusted for age, education, and alcohol intake) and 95% CIs are for poor vs. good function.
‖ CVD includes cerebral vascular accident, transient ischemic attack, myocardial infarction, intermittent claudication, and angina pectoris.

TABLE 3. Cross-sectional relation of cognitive function to drinking habits, the Zutphen Elderly Study of Men

Daily alcohol intake, 1990	Total sample†									Poor cognitive function‡							
			Error rate‖				Poor cognitive function‡			With CVD§,#/diabetes				Without CVD#/diabetes			
	No.	Median 1990 MMSE§ score	Mean	(SD§)	Error rate ratio¶	95% CI§	<26 MMSE score (%)	OR§	95% CI	No.	<26 MMSE score (%)	OR	95% CI	No.	<26 MMSE score (%)	OR	95% CI
None	117	26	4.6	(3.7)	1.0		41.0	1.0		57	56.1	1.0		60	26.7	1.0	
Drinks																	
<1	218	27	3.7	(2.5)	0.8	0.7–1.0	33.0	0.8	0.5–1.3	76	31.6	0.3	0.2–0.7	142	33.8	1.8**	0.8–3.8
1–2	122	27	3.6	(2.6)	0.8	0.7–1.0	22.9	0.5	0.3–0.9	49	16.3	0.2	0.1–0.4	73	27.4	1.3**	0.6–3.0
≥3	21	27	3.6	(2.4)	0.9	0.7–1.2	19.0*	0.5	0.2–1.7	5	20.2*	0.2	0.0–2.3	16	18.7	1.2	0.3–5.4

* $p < 0.01$ by chi-square for the relation of alcohol intake to poor cognitive function; ** $p < 0.001$ for the interaction between presence of CVD/diabetes and category of alcohol intake vs. no alcohol intake.
† Excludes 12 people who reported changing their alcohol intake by two categories between the 1985 and 1990 surveys.
‡ MMSE score of <26 in 1990. ORs (adjusted for age, education, and smoking status) and 95% CIs are for poor vs. good function.
§ MMSE, Mini-Mental State Examination; CVD, cardiovascular disease; SD, standard deviation; CI, confidence interval; OR, odds ratio.
‖ (30 points – achieved score) on the MMSE in 1990.
¶ Ratio of erroneous answers given on the MMSE in the index group vs. the reference group adjusted for age, education, and alcohol intake.
# CVD includes cerebral vascular accident, transient ischemic attack, myocardial infarction, intermittent claudication, and angina pectoris.

ers. However, the difference in effect between strata is primarily due to the difference between the abstainers; 56.1 percent of those with CVD/diabetes scored <25 on the MMSE compared with 26.7 percent in the group without disease. Control for hypertension, high density lipoprotein cholesterol, or fibrinogen did not materially change the estimates.

The effect of smoking on cognitive decline was modified by the presence of CVD/diabetes (table 4). In each category of smoking, those with CVD/diabetes had a larger decline in the MMSE than those without CVD; those without CVD/diabetes experienced little change in cognitive function (−0.04-point decline to 0.24-point improvement). Among those with CVD, never smokers experienced a significantly greater decline ($p < 0.05$) in function than former smokers and a similar magnitude of decline as current smokers.

There was no difference in the amount of change in the MMSE score by number of alcohol drinks per day and no evidence that the presence of CVD/diabetes modified this relation (table 4). Only those with CVD/diabetes who reported less than one drink per day experienced a significant decline in the MMSE score.

DISCUSSION

We studied the relation of smoking and drinking habits to cognitive function in a sample of very old men (mean age 75 ± 5 years) participating in the longitudinal Zutphen Elderly Study. The median MMSE score of 27 is similar to that reported for other randomly selected population-based samples of the same age (38, 39). Data on cognitive decline in a population-based sample are scarce. The 3-year decline of −0.30 (2.5 standard deviation) is less than the −1.3 points reported for an older community-based sample (40) and less than the 1-point annual rate of decline reported for clinic populations of Alzheimer's disease patients with an initial score of 25 on the MMSE (41). The magnitude of decline in this study may be somewhat underestimated because the first MMSE was administered in the research center and the second, at home where participants may have felt more at ease.

The relation of smoking and drinking to performance on various cognitive tests has been examined with cohorts living in Framingham (20), East Boston (21, 42), and rural France (22). None of these studies reported consistent relations of cognitive function to smoking or alcohol intake in cross-sectional or longitudinal analyses. These studies did not examine how the relation of alcohol and smoking to cognitive change may be moderated or mediated by the presence of cardiovascular disease and risk factors.

Using data from three visits, we found no selective participation in the 1990 survey according to reported behavior in 1985. However, compared with the 1990 participants, 1993 participants scored better on the 1990 MMSE and included proportionately fewer current smokers and abstainers.

In the cross-sectional analyses, low-to-moderate alcohol intake was moderately protective against poor cognitive function, particularly among those with CVD/diabetes. Cognitive decline was not associated with alcohol intake. The difference between these two analyses could arise for the following reasons. First, alcohol may provide short-term protection against cerebral lesions and consequently cognitive impairment, particularly in those with CVD/diabetes (43). A reduction in intake over the 3 years could reduce this acute alcohol effect. Second, the cross-sectional findings could reflect the effects of relatively poor health status among the abstainers. Between 1985 and 1990, abstainers had a higher rate of mortality; and in 1990, they had more prevalent CVD/diabetes. Furthermore, the effect modification of CVD/diabetes resulted mainly from differences between the abstainers; perhaps the abstainers had more severe disease than those taking alcohol. In addition, abstainers with relatively poor cognitive function did not participate in 1993, which minimizes the differences from those taking alcohol. These findings should be examined in another setting, particularly in light of other issues discussed below, which should be taken into account when interpreting these results.

Similar to the findings with alcohol intake, there was a difference in the results of the cross-sectional and longitudinal analyses of the relation of smoking to cognitive function. There was no significant cross-sectional association between smoking and cognitive function; in the longitudinal analysis, both never smokers and current smokers with CVD/diabetes experienced significant cognitive decline. As with the alcohol abstainers, there was some evidence that never smokers were more ill than those who continued to smoke. The hypothesis that smoking is harmful could explain why there was no difference in cognitive function in the cross-sectional analysis. More illness could also explain why never smokers declined significantly in cognitive function. This finding probably does not represent a protective effect of smoking since the decline was significant only in those with CVD/diabetes and current smokers with CVD/diabetes also experienced significant decline. The finding in current smokers is consistent with the hypothesis that individuals who are susceptible to vascular damage are acutely affected by smoking (5, 6). However, other explanations for these findings should be considered

TABLE 4. Relation of cognitive decline† to smoking and drinking habits, the Zutphen Elderly Study of Men

	Change in cognitive function between 1990 and 1993										
	Crude change			Adjusted change							
				Total		With CVD‡,§/diabetes			Without CVD§/diabetes		
	No	Mean	(SD‡)	Mean	95% CI‡	No.	Mean	95% CI	No.	Mean	95% CI
Total	333	−0.3	(2.5)								
Cigarette smoking status, 1990											
Never	68	−0.9	(2.7)	−0.8¶	−1.3 to −0.2	25	−1.9	−2.9 to −1.0*	43	0.03	−0.6–0.7
Quit ≥10 years ago	152	−0.3	(2.4)	−0.2	−0.5–0.2	53	−1.1	−1.1–0.2**	99	−0.04	−0.5–0.4
Quit <10 years ago	48	0.1	(2.7)	−0.2	−0.8–0.5	18	−0.4	−1.5–0.7**	30	−0.02	−0.8–0.7
Current	65	−0.1	(2.4)	−0.3	−0.8–0.3	24	−1.3	−2.3 to −0.3***	41	0.2	−0.4–0.9
Daily alcohol intake, 1990											
None	71	−0.2	(2.5)	−0.2¶	−0.7–0.4	31	−0.1	−1.1–0.8	40	−0.2	−0.9–0.5
Drinks											
<1	156	−0.4	(2.6)	−0.4	−0.8 to −0.01	51	−1.4	−2.1 to −0.6*,**	105	0.1	−0.3–0.5
1–2	87	−0.3	(2.3)	−0.3	−0.8–0.3	33	−0.8	−1.8–0.1	54	−0.04	−0.6–0.6
≥3	16	0.5	(2.0)	0.3	−0.9–1.6	3	−0.7	−3.8–2.3	13	0.9	−0.4–2.1

* $p < 0.001$ for difference between those with and without CVD/diabetes within category of smoking status or alcohol intake; ** $p < 0.05$ interaction of smoking (drinking) category vs. never smoking (no alcohol intake) among those with and without CVD/diabetes; *** $p < 0.05$ difference between those with and without CVD/diabetes.

† Difference in the Mini-Mental State Examination score between 1990 and 1993.

‡ SD, standard deviation; CI, confidence interval; CVD, cardiovascular disease.

§ CVD includes cerebral vascular accident, transient ischemic attack, myocardial infarction, intermittent claudication, and angina pectoris. Models exclude 12 people who reported changing their alcohol intake by two categories between the 1985 and 1990 surveys.

¶ Adjusted for 1990 Mini-Mental State Examination score, education, and alcohol intake. Models exclude 12 people who reported changing their alcohol intake by two categories between the 1985 and 1990 surveys.

before drawing conclusions regarding the long- and short-term effects of smoking on cognitive function.

Eighteen percent of the men with complete data reported never smoking; most men reported quitting smoking over 10 years ago, and those who continued smoked relatively little. Smoking is related to coronary events and death (24). If the men lost to smoking-related illness were also at risk for cognitive impairment, this would diminish any relation between the two that may have existed (44). Furthermore, never smokers might represent a special group, inasmuch as smoking was probably a norm for this cohort. Characteristics related to survival as well as to the adoption, continuation, and eventual cessation of smoking may represent unmeasured confounders. If these characteristics are associated with atherosclerosis and resulting cognitive impairment, or if they are related to cognitive impairment in some other way, then our estimates would be biased (44). Such unmeasured confounders could also affect the association of alcohol intake to cognitive function. Specific examples of unmeasured putative confounding could include genetic susceptibility (8, 45), disease severity, previous life style, depression (38), and possibly use of some types of medications (46, 47).

Because of the difficulties in measuring smoking behavior, alcohol intake, and cognitive function (12), misclassification may also bias these findings. However, it is unlikely that the measurement error in the exposure differed systematically with the outcome. We showed that a change in reported behavior was not associated with categories of cognitive function. In addition, the factors leading to error in the measurement of cognitive function, such as the time of testing and the interviewer, are not likely to be related to whether the respondent smoked or consumed alcohol. Regression toward the mean may be a problem in the analysis of cognitive decline given that those who participated in 1993 had a higher median MMSE in 1990 than those who did not participate (48). This selection would have led to an overestimate of decline. However, it is not likely that the regression to the mean differentially affected the results across categories of smoking or drinking, as the baseline values were similar. Finally, insensitivity of the MMSE to change in cognitive function at the upper end of performance also may have affected our ability to detect differences in this cohort. However, because only 4.1 percent of the sample scored the maximum 30 points in 1990, this is not likely to have greatly affected our results.

In addition to bias, other factors should be taken into account when interpreting the results. Separating out the various effects of smoking and alcohol on cognitive function is difficult in practice. Both protective and harmful vascular and nonvascular factors that may acutely or chronically affect cognitive function can be postulated. Even if the effect of these behaviors is studied within groups that are more homogeneous regarding risk, such as we attempted in our stratification analysis, comorbidity exists. For instance, Alzheimer's disease patients also have evidence of vascular lesions (49). In addition, cigarette smoke and alcohol may differentially affect various components of the vascular system; damage to each system has a potentially different effect on cognitive function. In the absence of more detailed information on the underlying pathology, studies of cognitive function can provide an estimate of the mean effect of these factors on cognitive function. These effects may differ from sample to sample, depending on the type of morbidity and comorbidity. The age of the sample may also be an important factor moderating the effect of smoking and drinking on cognitive function, inasmuch as the composition of the sample and their habits may change over time.

In conclusion, moderate alcohol intake appears to be inversely associated with poor cognitive function in a cross-sectional analysis. Current and never smokers experienced a larger decline in cognitive function compared with former smokers. The association of these behaviors with cognitive function and decline was strongest in those with CVD/diabetes. These effects may represent the net effect of both putative protective and harmful effects that alcohol and cigarette smoking could have on cognitive function. However, selection bias and unmeasured confounding should be of concern when evaluating these results.

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