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Cigarette Smoking and Alcohol Consumption in Relation to Cognitive Performance in Middle Age

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In the elderly, cigarette smoking has been related to reduced cognitive performance and moderate alcohol consumption to increased cognitive performance. It is not clear whether these associations also exist in middle age. The authors examined these relations in a population-based cohort study of 1,927 randomly selected, predominantly middle-aged subjects aged 45–70 years at the time of cognitive testing and living in the Netherlands. From 1995 until 2000, an extensive cognitive battery was administered, and compound scores were calculated. Risk factors had been assessed approximately 5 years previously. Multiple linear regression analyses (in which one unit of the cognitive score = one standard deviation) showed that, after the authors adjusted for age, sex, education, alcohol consumption, and cardiovascular risk factors, current smokers had reduced psychomotor speed (beta = –0.159, 95% confidence interval: –0.071, –0.244; $p = 0.0003$) and reduced cognitive flexibility (beta = –0.133, 95% confidence interval: –0.035, –0.230; $p = 0.008$) compared with never smokers. This effect was similar to that of being approximately 4 years older. Alcohol consumption was related to increased speed and better flexibility, especially among women who drank 1–4 alcoholic beverages a day. In conclusion, among middle-aged subjects, current smoking was inversely and alcohol consumption positively related to psychomotor speed and cognitive flexibility. This finding suggests that actions to prevent cognitive decline can be taken in middle age.

age factors; age groups; alcohol drinking; cognition; cohort studies; middle age; psychomotor performance; smoking

Abbreviations: HDL, high density lipoprotein; MORGEN, Monitoring Project on Cardiovascular Disease Risk Factors.

Few studies have examined risk factors for cognitive decline in middle-aged subjects. A recent report showed that a preclinical or subclinical phase of reduced cognitive function precedes the appearance of diagnosed Alzheimer's disease by at least 10 years (1). To postpone or prevent cognitive decline and even dementia in old age, intervention during middle age may be required. Lifestyle factors, such as cigarette smoking and alcohol drinking, are suitable for interventions targeted to the individual or the community.

There are a number of cross-sectional and longitudinal epidemiologic studies on smoking, drinking, and cognitive function in the elderly (2–18). In the majority of the most recent ones, current smoking was associated with reduced cognitive function, whereas moderate alcohol consumption seemed to be related to better cognitive function. Information on these associations in middle age is scarce, however (19). Furthermore, it is still unclear whether the association between alcohol consumption and cognition is different for men and women (14, 18) and whether the protective effect is

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limited to subjects with atherosclerosis or cardiovascular disease (9). In addition, most previous studies used rather crude instruments for measuring cognitive function.

In the current study, we examined cigarette smoking and alcohol consumption in relation to several different cognitive domains in a population-based sample of men and women, the majority of whom were middle-aged, who participated in a longitudinal population-based study. The cognitive tests used have been developed specifically for use in healthy middle-aged and elderly subjects (20, 21).

MATERIALS AND METHODS

Study population

Data were derived from the Monitoring Project on Cardiovascular Disease Risk Factors (MORGEN) study, a prospective study of Dutch adults aged 20–60 years living in Amsterdam, Maastricht, and Doetinchem (22). The current study was limited to subjects aged 45 years or older living in one of these study areas, Doetinchem, a small town of approximately 40,000 inhabitants located in a rural eastern area of the Netherlands. The MORGEN study was designed to monitor levels of and trends in major cardiovascular risk factors and lifestyle factors and their relation to chronic diseases. The MORGEN study's baseline examinations took place between 1987 and 1991. Each year, a new random sample was drawn from the civil registry stratified by age (5-year age classes) and sex. In Doetinchem, 12,668 subjects participated, and the overall response rate was 62 percent (68 percent for those older than age 45 years). A substantial proportion of the nonresponse in this study (about 10 percent) may have been due to errors in the civil registry and to the fact that people had moved away from the area since the address data had been obtained. Response rates were higher for women than for men and were also higher for respondents in the older age categories. There was no substantial selection by educational level (23).

From 1993 until 1997, a 6-year follow-up examination of participants who were seen between 1987 and 1991 was conducted in Doetinchem. The response rate at follow-up for subjects aged 45 years or older, that is, those who were eligible for cognitive testing, was 71 percent. Measurements were similar to those obtained at the baseline examinations. Again, from 1998 onward, a second follow-up examination was begun, identical to the first follow-up. Cognitive function was measured once in each participant from 1995 until 2000, so cognitive testing was spread over several rounds of follow-up. Risk factors assessed approximately 5 years prior to cognitive testing were used.

The study was approved by the Medical Ethics Committee of the Organization for Applied Scientific Research-Zeist. All participants signed an informed consent.

Assessment of exposure

For all examinations, participants received a self-administered questionnaire at home and were invited to come to a research center for medical examinations. The questionnaire contained items on demographic variables, lifestyle factors, (family) history of diseases, and medication use and was checked at the research center by trained personnel. Smoking status was assessed with a standard questionnaire asking about the average number of cigarettes smoked and the duration of smoking. Cigarette smoking at baseline (i.e., approximately 5 years prior to cognitive testing) was classified as current, former, or never. The number of pack-years was calculated as the average daily number of cigarettes smoked divided by 20 and multiplied by the number of years of smoking. Alcohol consumption was measured with a standardized questionnaire as the number of drinks (equivalent to a glass of wine) per day of beer, wine, fortified wine types (i.e., port, sherry), or spirits. To allow for a possible nonlinear relation between alcohol and cognitive function, alcohol consumption was grouped into six categories according to those used by Elias et al.: nondrinkers, drinking ≤1 drink/day, >1 to ≤2 drinks/day, >2 to ≤4 drinks/day, >4 to ≤8 drinks/day, and >8 drinks/day (18).

Assessment of cognitive function

Cognitive function was assessed in subjects aged 45–70 years at the time of cognitive testing (85.5 percent were aged <65 years) by using a neuropsychological test battery that measures specific cognitive domains, including memory function, speed of cognitive processing, cognitive flexibility (the time needed for higher order information processing), and global cognitive function (21, 24). Included were the (Visual) Verbal Learning Test, the Concept Shifting Task, an abbreviated Stroop Color Word Test consisting of three subtasks, the Letter Digit Substitution Test, and a Word Fluency Test, in which as many animals as possible had to be named in 60 seconds. The Stroop Color Word Test consisted of three cards: I, color names; II, colored patches; and III, color names printed in incongruously colored ink. The amount of time needed to read (card I and III) or to name (card II) colors was recorded. In the Concept Shifting Task, 16 small circles were grouped in a larger circle on each test sheet. In the smaller circles, the test items (1, 2, 3, . . . ; A, B, C, . . . ; and 1, A, 2, B, 3, C, . . .) appeared in a fixed, random order. Subjects were requested to cross out the items in the correct order. The time needed to complete the tasks was recorded. A detailed description of these tests can be found elsewhere (20, 21). These tests are sensitive to calendar age, including the middle age range, and have no ceiling effect. In addition, they are robust in detecting age-related impairment, even at middle age, and are sensitive to subcortical dysfunction (25). They have also been used in other large-scale studies on cognitive function (24, 26).

Cognitive tests were carried out by trained investigators and took about 20 minutes to complete. We measured cognitive function from November 1995 until May 2000 (because of a lack of time, the Concept Shifting Task was deleted from the battery from January 2000 onward). In total, 1,927 subjects performed the cognitive tests (1,667 subjects completed the Concept Shifting Task).

The timed tests (Stroop Color Word Test and Concept Shifting Task) were log transformed first, because they were not normally distributed. Raw data were made comparable

by transforming them into a standardized z score (the difference between each test score and the average score, divided by the standard deviation of that score). We calculated compound scores for psychomotor speed by averaging the z scores of the 0, A (numbers), and B (letters) versions of the Concept Shifting Task and subtask I of the Stroop Color Word Test (complete data were available for 1,639 subjects) (21). To calculate a compound score for memory function, the z scores of the total, maximal, and delayed recall scores of the Verbal Learning Test were averaged (n = 1,906). For cognitive flexibility or complex speed, the average of the z scores of the C-version (alternating numbers and letters) of the Concept Shifting Task and subtask III of the Stroop Color Word Test was calculated (n = 1,635). As a reflection of global cognitive function, the average of the z scores of subtask III of the Stroop Color Word Test, the Letter Digit Substitution Test, the Word Fluency Test, and the total and the delayed recall score of the Verbal Learning Test was calculated (n = 1,886).

In case of problems in assessing cognition, a code was given for a subject's lack of motivation in completing the questionnaire, presence of physical or cognitive limitations, illiteracy, and deviation from the instructions and for technical problems. The most frequent problem encountered was the presence of physical or cognitive limitations (including dyslexia). The percentages of complete and reliable tests ranged from 95.9 percent for the Concept Shifting Task to 98.8 percent for the Word Fluency Test. Exclusion of subjects for whom problems were found during assessment of the cognitive tests did not alter the results, so it was decided to retain these subjects for analysis.

Other measurements

Education was assessed as the highest level achieved and was classified into five categories: primary school, junior (vocational) education, secondary (vocational) education, vocational college, and university. Self-reported history of myocardial infarction, cerebrovascular accident, and diabetes was recorded at the time of cognitive testing. Physical activity of at least a moderate level (hours/week) was also assessed during cognitive testing with an extended version of a validated physical activity questionnaire (27). All other possible confounders were assessed at baseline (5 years prior to cognitive testing). Height and weight were measured during a physical examination at the research center. Body mass index was calculated as weight (kg) divided by height (m) squared. Blood pressure was measured twice at the left arm with a random-zero sphygmomanometer while the subject was seated. For the analyses, the average of the two blood pressure measurements was taken.

Nonfasting blood samples were obtained by using a standardized protocol. Plasma total and high density lipoprotein (HDL) cholesterol and glucose were determined at the Clinical Chemistry Laboratory of the University Hospital "Dijkzigt" in Rotterdam, which is the Lipid Reference Laboratory for standardized cholesterol determinations in the Netherlands. Total cholesterol was determined enzymatically by using a Boehringer test kit (28). HDLs were determined after precipitation of apolipoprotein-B–containing lipoproteins with magnesium phosphotungstate (29). Random glucose levels were measured by using the hexokinase method.

Statistical analysis

To calculate age- and education-adjusted average test scores for all cognitive tests by smoking status, analysis of covariance was used. The average of Stroop Color Word Test subtasks I and II and of Concept Shifting Task versions A and B was taken. We performed multiple linear regression analyses in which each regression coefficient represented the difference in the standardized cognitive score (z score) for the five alcohol consumption groups relative to the abstainers and for former and current smokers relative to never smokers. In addition, subjects who smoked for >0–20 pack-years and >20 pack-years were compared with never smokers by including two dummy variables in the regression model. Confounders that were taken into account were age (continuous), sex, education (four dummy categories), body mass index, total cholesterol level, and systolic blood pressure. In addition, the alcohol analyses were adjusted for cigarette smoking, and vice versa. In a subanalysis, we also adjusted for HDL cholesterol, random glucose levels, and physical activity. To test for a linear trend, the alcohol categories were entered into the model as a linear term. To examine nonlinearity, the quadratic term of daily alcohol consumption was entered into the model. Furthermore, we checked whether age (dichotomized at 65 years), sex, or a history of cardiovascular disease modified the associations by adding interaction terms in the models and by stratification. We repeated the analyses after excluding alcohol abstainers and using the lightest drinking group as reference, to investigate whether former heavy drinkers influenced the results. The SAS computer package was used for all statistical analyses (version 8.1; SAS Institute, Inc., Cary, North Carolina).

RESULTS

Thirty percent of the men and 26 percent of the women were current smokers (table 1). Smokers were younger and more often had only a primary school education. The average numbers of pack-years of smoking were 22.3 (standard deviation, 13.5) for current smokers and 14.0 years (standard deviation, 14.5) for former smokers. Twenty-two percent of the men and 48 percent of the women were alcohol abstainers. Men were more often categorized in the moderate and heavy drinking groups, whereas women were more frequent in the lightest drinking group. All means of the compound scores for the different cognitive domains were, by definition, zero.

Cigarette smoking

Table 2 shows the age- and education-adjusted mean scores for the separate variables of the cognitive tests by smoking status. Current smokers scored significantly worse on the Verbal Learning Test and on the Stroop Color Word Test. Test scores of subjects who formerly smoked seemed

TABLE 1. Baseline characteristics of men and women studied regarding the relation of cigarette smoking and alcohol consumption to cognitive performance in middle age, Monitoring Project on Cardiovascular Disease Risk Factors, the Netherlands, 1995–2000

	Men (n = 905)	Women (n = 989)
Mean age (years) (SD*)†	56.6 (7.1)	56.2 (7.1)
Education (% primary school only)	9.8	13.0
Smoking status (%)		
Never smoker	22.7	41.8
Former smoker	47.6	31.9
Current smoker	29.7	26.4
Alcohol consumption (glasses/day) (%)		
0	21.6	47.9
≤1	24.5	29.2
>1 to ≤2	22.1	15.3
>2 to ≤4	23.2	6.4
>4 to ≤8	7.9	1.2
>8	0.8	0
Body mass index (kg/m^2) (SD)	26.0 (3.0)	25.6 (4.0)
Total cholesterol (mmol/liter) (SD)	5.80 (1.01)	5.81 (1.05)
Systolic blood pressure (mmHg) (SD)	128.7 (16.2)	122.6 (17.0)
History of vascular disease (%)†	5.8	3.4

* SD, standard deviation.
† At the time of cognitive testing.

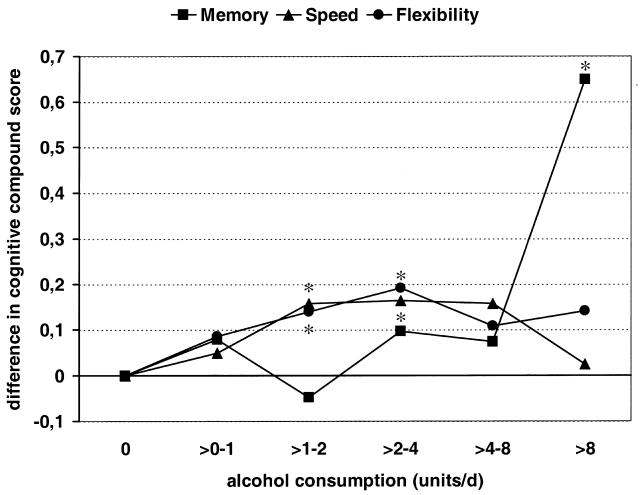

FIGURE 1. Adjusted beta coefficients reflecting the difference in the standardized scores (one unit of the cognitive score = one standard deviation) for different cognitive domains according to alcohol consumption categories, Monitoring Project on Cardiovascular Disease Risk Factors, the Netherlands, 1995–2000. Beta coefficients were adjusted for age, sex, education, body mass index, total cholesterol, systolic blood pressure, and cigarette smoking. d, day.

to be in between those of smokers and never smokers. Multiple linear regression analyses showed that current smokers had reduced psychomotor speed (beta = –0.159, p = 0.0003) and reduced cognitive flexibility (beta = –0.133, p = 0.008) compared with never smokers (table 3), which was similar to the effect of being 3.5–4.5 years older. We found no interaction between sex and smoking status in relation to cognitive function. Additional adjustment for a history of cardiovascular disease did not attenuate the associations. A dose-response relation seemed to be present as well; for those subjects who smoked for ≤20 pack-years, the difference in the psychomotor speed score compared with never smokers was –0.078 (p = 0.06), whereas for those who smoked for >20 pack-years, the difference was –0.141 (p = 0.004). For the association with flexibility, these differences were –0.053 (p = 0.25) and –0.133 (p = 0.02), respectively. The relation between pack-years and speed and flexibility was similar among current and former smokers.

Alcohol consumption

The association between alcohol consumption and the timed tasks—psychomotor speed and flexibility—was slightly U-shaped, with significant p values for the quadratic term (p = 0.001 and p = 0.01, respectively) (figure 1). Subjects who drank between 1–2 and 2–4 alcoholic beverages per day performed significantly better on these tests. Surprisingly, subjects who drank >8 glasses of alcohol per day performed better on the memory subtasks compared with abstainers. However, this group was very small (n = 7) and consisted of men only. Average alcohol consumption in this group was 10 drinks/day, with a maximum of 12.9 drinks/day. Alcohol consumption was not associated with overall cognition. There was a significant interaction between sex and alcohol consumption in relation to speed (p = 0.008), indicating that, for women, the association between alcohol consumption and psychomotor speed was positive and linear (p-trend < 0.001), whereas for men it was absent (table 4). The association with cognitive flexibility was stronger among women as well, although the interaction term was not significant. When we excluded the abstainers and used the lightest alcohol consumption group as the reference, results were not altered.

Additional adjustment for other possible confounders or for cardiovascular disease as a mediating factor did not change the results. No interaction with age or cardiovascular disease was found, suggesting that the associations were similar in those younger and those older than age 65 years at the time of the cognitive tests and in those with and those without a history of cardiovascular disease. Finally, we conducted the analyses again after excluding subjects who scored in the lowest 5 percent of the overall cognitive index and of the memory subscale, which did not alter the results.

TABLE 2. Adjusted† mean scores on the cognitive tests, by smoking status, Monitoring Project on Cardiovascular Disease Risk Factors, the Netherlands, 1995–2000

	Never smokers (n = 618)		Former smokers (n = 746)		Current smokers (n = 530)	
	Mean	95% CI‡	Mean	95% CI	Mean	95% CI
Verbal Learning Test						
Best trial (no. of words)	10.4	10.2, 10.5	10.1	9.9, 10.2*	10.1	9.9, 10.3*
Delayed recall (no. of words)	8.2	8.0, 8.4	7.9	7.7, 8.1	7.9	7.7, 8.2
Concept Shifting Task						
A + B version (average in seconds)§	18.4	17.8, 18.9	18.8	18.3, 19.3	18.9	18.3, 19.4
C version (seconds)§	30.5	29.4, 31.5	30.7	29.6, 31.7	30.7	29.6, 31.9
Stroop Color Word Test						
Subtasks I and II: reading and naming (average in seconds)	18.8	18.5, 19.0	19.1	18.9, 19.4	19.5	19.2, 19.8*
Subtask III: interference (seconds)	44.2	43.0, 45.4	45.5	44.4, 46.6	46.5	45.2, 47.7*
Letter Digit Substitution Test (no. of letters/minute)	32.3	31.8, 32.8	32.1	31.6, 32.5	31.7	31.2, 32.2
Word Fluency Test (no. of animals/minute)	23.7	23.3, 24.1	23.4	23.0, 23.8	23.8	23.4, 24.3

* $p < 0.05$ for difference with never smokers.
† Adjusted for age and education.
‡ CI, confidence interval.
§ Minus the no. of seconds needed for the zero version of the Concept Shifting Task.

DISCUSSION

This population-based study of mostly middle-aged subjects showed that current smoking and number of pack-years of smoking were related to reduced performance on tests of psychomotor speed and cognitive flexibility assessed approximately 5 years later. The association between past alcohol consumption and speed and flexibility appeared to be slightly U-shaped, with the best performance among those who drank between one and four glasses of alcohol per day, and the association was stronger for women than for men. Observed relations were independent of differences in age, education, and several cardiovascular risk factors.

Methodological considerations

The strength of our study was the use of a cognitive battery that included tests sensitive to small cognitive changes even in middle age. We decided to investigate cognitive function as a continuous instead of a binary measure (cognitive impairment vs. normal cognition), since clinically significant cognitive deficits are less frequent among the middle-aged and because analyzing the cognitive scores continuously yielded more power. In middle age, cognitive function is still relatively well preserved. Therefore, it is not very likely that exposure assessment was influenced by reduced cognitive function. The possibility does exist that subjects with cognitive impairment were already cognitively impaired 5 years previously and, as a result, changed their smoking and drinking habits. However, when we excluded subjects whose cognitive scores were in the lowest 5 percent, the results were essentially the same.

A limitation of our study is that cognitive function was measured only once. It would have been more informative to have data on change in cognitive function after smoking and drinking were assessed. Furthermore, response rates were moderate, but there was no evidence of selective participation. Nevertheless, one can imagine that heavy drinkers and subjects with severe cognitive impairment were underrepresented, possibly resulting in underestimation of the association between heavy drinking and cognitive impairment. Finally, we had no information on drinking history. Abstainers may have included formerly heavy drinkers and subjects who quit drinking because of an illness. Their risk of cognitive impairment will be different from that of lifetime abstainers. When we excluded the abstainers and used the lightest drinking group as the reference, though, the results were essentially the same.

Previous studies

Most previous studies investigating the association between smoking and cognitive function focused on older subjects and were cross-sectional. The majority found that current smoking was related to reduced cognitive function (2–7), and a dose-response relation with amount smoked has been observed (8). There are a number of longitudinal studies on this topic. They also showed that smoking increased the risk of cognitive decline or cognitive impairment (6, 9–11), although, in the East Boston, Massachusetts, study, no consistent association was observed between smoking and cognitive decline (13).

Cross-sectional studies on alcohol consumption and cognitive impairment among the elderly have demonstrated an inverse association (4, 8, 14, 15), an inverted U-shaped association (16), or no clear association (2). In the Epidemiology of Vascular Aging (EVA) Study, an inverse association

TABLE 3. Adjusted beta coefficients reflecting the difference in the standardized score† for several cognitive domains, according to smoking status, Monitoring Project on Cardiovascular Disease Risk Factors, the Netherlands, 1995–2000

	Model I‡		Model II§	
	Beta coefficient	95% CI¶	Beta coefficient	95% CI
Cognitive index (range, –1.9 to 1.6)				
Former vs. never smokers	–0.019	–0.071, 0.034	–0.017	–0.070, 0.035
Current vs. never smokers	–0.005	–0.063, 0.052	–0.003	–0.060, 0.055
Memory (range, –3.0 to 2.5)				
Former vs. never smokers	–0.012	0.085, –0.108	–0.009	0.085, –0.103
Current vs. never smokers	–0.040	0.062, –0.143	–0.035	0.067, –0.138
Speed (range, –2.0 to 4.8)				
Former vs. never smokers	–0.059	0.021, –0.139	–0.058	0.023, –0.138
Current vs. never smokers	–0.159*	–0.071, –0.244	–0.157*	–0.070, –0.244
Flexibility (range, –3.0 to 4.0)				
Former vs. never smokers	–0.041	0.048, –0.131	–0.040	0.050, –0.103
Current vs. never smokers	–0.133*	–0.035, –0.230	–0.130*	–0.032, –0.227

* $p < 0.05$.
† One unit of the cognitive score = one standard deviation.
‡ Adjusted for age, sex, education, body mass index, total cholesterol, systolic blood pressure, and alcohol consumption.
§ Additional adjustment for a history of cardiovascular diseases (myocardial infarction, stroke, or diabetes).
¶ CI, confidence interval.

between alcohol consumption and cognitive impairment was primarily present among female participants, which is in agreement with our results (14). Past alcohol consumption was associated with either an increased (5) or a decreased (17, 18) risk of cognitive impairment several years later. Results from longitudinal studies that included two assessments of cognitive function were inconsistent. Some found no relation between alcohol consumption and cognitive

TABLE 4. Adjusted† beta coefficients reflecting the difference in the standardized score‡ for several cognitive domains, according to alcohol drinking categories,§ among men and women, Monitoring Project on Cardiovascular Disease Risk Factors, the Netherlands, 1995–2000

	Category (no. of drinks/day)										*p*-trend	*p*-quadratic
	≤1		1 to ≤2		2 to ≤4		4 to ≤8		>8			
	Beta coefficient	95% CI¶	Beta coefficient	95% CI	Beta coefficient	95% CI	Beta coefficient	95% CI	Beta coefficient	95% CI		
Cognitive index												
Men	0.030	–0.061, 0.121	–0.062	–0.156, 0.032	0.026	–0.068, 0.120	0.028	–0.105, 0.161	0.241	–0.120, 0.600	0.66	0.47
Women	0.026	–0.043, 0.095	–0.004	–0.093, 0.085	0.154*	0.027, 0.281	0.133	–0.135, 0.401			0.08	0.84
Memory												
Men	0.084	–0.077, 0.245	–0.101	–0.267, 0.065	0.058	–0.109, 0.225	0.080	–0.155, 0.315	0.672*	0.032, 1.312	0.48	0.25
Women	0.054	–0.071, 0.179	–0.015	–0.176, 0.146	0.190	–0.040, 0.420	0.107	–0.379, 0.593			0.28	0.94
Speed												
Men	–0.045	–0.190, 0.101	0.097	–0.050, 0.244	0.055	–0.092, 0.203	0.039	–0.166, 0.245	–0.041	–0.613, 0.532	0.28	0.13
Women	0.125*	0.024, 0.226	0.216*	0.086, 0.346	0.347*	0.160, 0.534	0.461*	0.096, 0.826			<0.001	0.08
Flexibility												
Men	0.024	–0.134, 0.182	0.120	–0.040, 0.280	0.156	–0.005, 0.317	0.102	–0.122, 0.326	0.097	–0.523, 0.717	0.05	0.04
Women	0.143*	0.026, 0.260	0.163*	0.013, 0.313	0.277*	0.060, 0.494	0.034	–0.389, 0.457			0.006	0.10

* $p < 0.05$.
† Adjusted for age, sex, education, body mass index, total cholesterol, systolic blood pressure, and cigarette smoking.
‡ One unit of the cognitive score = one standard deviation.
§ Reference, no alcohol consumption.
¶ CI, confidence interval.

decline (9, 11, 13), whereas one found that abstinence from alcohol was a baseline predictor of poor cognitive outcome (12).

Very few studies have been conducted among middle-aged subjects. The Atherosclerosis Risk in Communities (ARIC) study investigated the cross-sectional relation between smoking, drinking, and cognitive function among subjects aged 45–69 years (19). Current smokers performed worse on the Digit Symbol Substitution Subtest and the Delayed Word Recall. Furthermore, a positive association was found between alcohol drinking and the Word Fluency Test, and an inverted U-shaped relation was found with the Digit Symbol Substitution Subtest and the Delayed Word Recall. These results are comparable to those from our study. In a cross-sectional study among subjects aged 24–81 years, no association between smoking, alcohol consumption, and similar measures of cognitive function could be identified (30).

Possible mechanisms

In our study, the cognitive domains affected—psychomotor speed and cognitive flexibility—may suggest subcortical dysfunction, which can be the result of subcortical small-vessel lesions. Speed of mental processing in particular has been related to white matter changes (24, 31). Thus, a vascular mechanism for the observed associations seems likely. Smoking is a risk factor for stroke and has also been associated with vascular dementia (32, 33). Cerebral vasodilatation and vasoconstriction response and cerebral blood flow was lower in the cerebral vessels of smokers (34), which could be improved by quitting smoking (35). These changes could lead to large and small infarcts, resulting in reduced cognitive function. Cerebral blood flow has also been directly related to cognitive performance (36).

The relation between alcohol consumption and cognitive function appeared to be slightly U-shaped, which is similar to the shape of the observed association of alcohol consumption with cardiovascular disease and atherosclerosis (37–39). This association may be mediated by beneficial effects of alcohol on lipid levels (38, 40), lipoprotein(a) levels (41), insulin sensitivity (42), plasma concentration of endogenous tissue-type plasminogen activator (43), plasminogen activator inhibitor type 1 (44), prostacyclin levels (45), and fibrinogen levels and fibrinolytic activity (46). The positive effect could also be mediated by flavonoids in red wine, which has antioxidant properties (47). In addition, alcohol consumption leads to increased cerebral blood flow (48), which is associated with better cognitive performance (36). In contradiction to the more acute effects of alcohol on cerebral blood flow, subjects with chronic alcoholism were found to have reduced cerebral blood flow and consequently reduced cognitive function (49, 50). Adjustment for a history of cardiovascular disease or diabetes did not attenuate the associations between alcohol consumption, cigarette smoking, and cognition. However, these diseases do not fully reflect subclinical atherosclerosis and small-vessel disease in the brain, which may be a stronger intermediate factor. Unfortunately, we were not able to adjust for more direct indicators of these vascular conditions.

Chronic and heavy alcohol consumption is neurotoxic and may lead to the Wernicke-Korsakoff syndrome, which is characterized by severe memory impairment. In our study, we did not find an adverse relation between the highest drinking group and cognitive function, but drinking levels in this group were not extremely high. In addition, subjects in the highest drinking group were slightly younger and were relatively highly educated. Adjustment for these risk factors did not alter the results. A previous study also found that patients with chronic alcoholism had normal cognitive performance, whereas patients with Korsakoff's syndrome had performance deficits on several cognitive domains (51).

Among women compared with men, we observed a stronger relation between moderate alcohol consumption and some aspects of cognition, as was also found in some other studies (2, 5, 14, 18). Alcohol consumption levels are different for men and women, that is, there were no women in the highest alcohol consumption group, but the same categories were used for both sexes. Furthermore, women who drink alcohol may have different risk factor behavior and may have a higher socioeconomic status than men who drink alcohol. Moderate alcohol consumption may be regarded as a proxy for outgoing and social behavior, which could be related to better cognitive function. We adjusted for many potentially confounding factors, but perhaps some residual confounding remained. The divergent results may also be due to sex differences in alcohol metabolism (52). The effects of alcohol on HDL cholesterol, blood pressure, and peripheral artery disease, for example, seem to be different in men and women (53–56). In general, women are more vulnerable to the adverse effects of alcohol (57). Therefore, the presence of a predominant protective effect of moderate alcohol consumption on cognition among women is unexpected. However, it may be that women are more susceptible to not only the adverse effects but also the protective effects of alcohol.

Conclusion

This study showed that common risk factors that have been associated with cognitive decline in old age already lead to a subtle reduction in cognitive function in middle age. The effects of cigarette smoking and alcohol consumption on cognition found in this study were small and, for most people, probably not even noticeable, but they were comparable to the effects of being approximately 4 years older. We expect that, at later ages, the cognitive disturbances among those who continue to smoke will become more pronounced and clinically important. Therefore, community interventions regarding these common risk factors in middle age may have a large impact on cognitive decline in old age.

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