Smoking History and Cognitive Function in Middle Age From the Whitehall II Study

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Background: Studies about the association between smoking and dementia necessarily involve those who have “survived” smoking. We examine the association between smoking history and cognitive function in middle age and estimate the risk of death and of nonparticipation in cognitive tests among smokers.

Methods: Data are from the Whitehall II study of 10,308 participants aged 35 to 55 years at baseline (phase 1 [1985-1988]). Smoking history was assessed at phase 1 and at phase 5 (1997-1999). Cognitive data (memory, reasoning, vocabulary, and semantic and phonemic fluency) were available for 5,388 participants at phase 5; 4,659 of these were retested 5 years later.

Results: Smokers at phase 1 were at higher risk of death (hazard ratio [HR], 2.00; 95% confidence interval [CI], 1.58-2.52 among men and HR, 2.46; 95% CI, 1.80-3.37 among women) and of nonparticipation in cognitive tests (odds ratio [OR], 1.32; 95% CI, 1.16-1.51 among men and OR, 1.69; 95% CI, 1.41-2.02 among women). At phase 5 in age- and sex-adjusted analyses, smokers compared with those who never smoked were more likely to be in the lowest quintile of cognitive performance. After adjustment for multiple covariates, this risk remained for memory (OR, 1.37; 95% CI, 1.10-1.73). Ex-smokers at phase 1 had a 30% lower risk of poor vocabulary and low verbal fluency. In longitudinal analysis, the evidence for an association between smoking history and cognitive decline was inconsistent. Stopping smoking during the follow-up period was associated with improvement in other health behaviors.

Conclusions: Smoking was associated with greater risk of poor memory. Middle-aged smokers are more likely to be lost to follow-up by death or through nonparticipation in cognitive tests. Ex-smokers had a lower risk of poor cognition, possibly owing to improvement in other health behaviors.

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en). All civil servants aged 35 to 55 years in 20 London-based departments were invited by letter to participate, and 73% agreed. Baseline examination (phase 1) took place from 1985 to 1988 and involved a clinical examination and a self-administered questionnaire containing sections on demographics, health, and lifestyle factors such as smoking habits, work characteristics, social support, and life events. Clinical examination included measures of blood pressure, anthropometry, biochemical variables, neuroendocrine function, and subclinical markers of cardiovascular disease. Subsequent phases of data collection have alternated between postal questionnaire alone (phase 2 [1988-1990], phase 4 [1995-1996], phase 6 [2001], and phase 8 [2006]) and postal questionnaire accompanied by a clinical examination (phase 3 [1991-1994], phase 5 [1997-1999], and phase 7 [2002-2004]). Participants gave written consent to participate in the study, and the University College London ethics committee approved the study.

SMOKING HISTORY

Data on smoking were collected at every phase using questions about smoking status (current, past, or never), age at which the participant started smoking, the mean number of cigarettes smoked per day, the number of cigars or cigarillos smoked, and ounces of tobacco smoked in a pipe or in hand-rolled cigarettes per week (Figure 1). Ex-smokers were asked the age at which they had stopped smoking. The smoking history variable was created with the following categories: never smoker (those who never smoked), current smoker at phase 5, long-term ex-smoker (those who stopped before phase 1), and recent ex-smoker (stopped smoking between phase 1 and phase 5). Among smokers at phase 5, we further used the amount of tobacco smoked in total grams of tobacco per day (1 cigarette equals 1 g, and 1 cigar or cigarillo equals 3 g) to calculate pack-years of smoking (the mean daily number of grams of tobacco divided by 20 and multiplied by the number of years of smoking).

COGNITION

Cognitive function was assessed at phase 5 and at phase 7 using a battery of the following standard tasks:

Memory

Short-term verbal memory was assessed using a 20-word free recall test. Participants were presented a list of 20 words (1 syllable or 2 syllables) at 2-second intervals and were then asked to recall in writing as many of the words in any order and had 2 minutes to do so.

Reasoning

The Alice Heim AH4 Group Test of General Intelligence (AH4-I) is composed of a series of 63 verbal and mathematical reasoning items of increasing difficulty. It tests inductive reasoning, measuring the ability to identify patterns and to infer principles and rules. Participants had 10 minutes to complete this section.

Vocabulary

Vocabulary was assessed using the Mill Hill Vocabulary Test in its multiple format, consisting of a list of 33 stimulus words ordered by increasing difficulty and 6 response choices.

Verbal Fluency

We used 2 measures of verbal fluency—phonemic and semantic. Phonemic fluency was assessed via /s/ words and semantic fluency via animal words. Subjects were asked to recall in writing as many words beginning with /s/ and as many animal names as they could. One minute was allowed for each test.

COVARIATES

Sociodemographic Variables

Sociodemographic variables used were age, sex, marital status (single, widowed, married or cohabiting, or divorced or separated), education achievement (none or lower primary school, lower secondary school, higher secondary school, university, or higher university degree), and socioeconomic position (using the British civil service grades of employment of high [administrative], intermediate [professional or executive], or low [clerical or support]).

Health Behaviors

Health behaviors included the following: (1) alcohol use, assessed via questions about the number of alcoholic drinks (measures of spirits, glasses of wine, and pints of beer) consumed in
the past 7 days converted to the number of units of alcohol (1 U=8 g); (2) frequency of fruit and vegetable consumption, evaluated using the question “How often do you eat fresh fruit or vegetables?” (responses were on an 8-point scale, ranging from seldom or never [1] to 2 times a day [8]); and (3) physical activity, calculated as the sum of the hours of mild, moderate, and vigorous physical activities in response to a 20-item questionnaire on the frequency and duration of participation in walking, cycling, sports, gardening, housework, and home maintenance.

Health Measures

Health measures were drawn from phase 5. Coronary heart disease prevalence was based on clinically verified events and included myocardial infarction and definite angina. Stroke and diabetes mellitus were assessed using self-reports of physician diagnosis. Blood pressure (systolic and diastolic) was measured at the phase 5 clinical examination, twice in the sitting position after 5 minutes’ rest using an automated device (Omron 907; Omron Healthcare Europe, Hoofddorp, the Netherlands). The mean of 2 measurements was taken to be the measured blood pressure. Serum cholesterol level was measured within 72 hours in serum samples stored at 4°C using enzymatic colorimetric methods.

STATISTICAL ANALYSIS

The association between smoking status at phase 1 (never smoker, ex-smoker, and current smoker) and mortality until phase 7 was assessed using Cox proportional hazards regression models. The association between smoking status at phase 1 and nonparticipation in cognitive tests at phase 7 was assessed using logistic regression analyses.

Descriptive analyses as a function of smoking history at phase 5 were performed and tested using χ² analysis for trend for categorical variables and by fitting a linear trend for continuous variables. We first assessed the association between smoking history and continuous measures of cognition using linear mixed-effects models to account for unequal intervals between the 2 clinical examinations (range, 3.9-7.1 years). The independent variables were time, smoking history, time × smoking history since the first cognitive assessment, and other covariates. The dependent variables were the cognitive measures. Next, we examined the association between smoking history and the dichotomized measures of cognition in logistic regression analysis in which the reference group was those who never smoked. Cognitive scores in the lowest sex-specific quintile of cognitive function at phase 5 were considered to represent cognitive deficit, and cognitive scores in the lowest sex-specific quintile of change in cognitive function between phase 5 and phase 7 were considered to represent decline. The interval between the 2 measures of cognition has been adjusted for in the analyses of change using logistic regression. The analyses were adjusted first for age and sex, then for sociodemographic measures (education and age as continuous variables and all others as categorical variables), and finally for health behaviors (all continuous variables) and health measures (all vascular risk factors as continuous variables). Other ways of looking at smoking history (eg, age at starting smoking and time since stopping smoking) were examined in exploratory analyses but are not presented herein (except for analysis using pack-years of smoking for current smokers) because the results are not strikingly different. In addition, we undertook post hoc analysis to examine changes in health behaviors (use of alcohol and consumption of fruits and vegetables) between phase 1 and phase 7 in the smoking history categories. All analyses were performed using commercially available statistical software (SAS, version 8; SAS Institute Inc, Cary, North Carolina).

RESULTS

SAMPLE DESCRIPTION AND MISSING DATA

Of 10 308 participants at phase 1 (1985-1988), 7830 participated in at least 1 part of phase 5 (1997-1999), 2204 were nonresponders, and 274 had died (Figure 1). At phase 5, data on cognitive function, smoking history, and all covariates were available for 5388 respondents. Compared with baseline, this group was younger (55.5 vs 56.1 years) and comprised fewer women (27.6% vs 33.1%) and fewer participants of low socioeconomic status (14.6% vs 22.7%) (P<.001). From this population, calculation of cognitive decline (implying participation in cognitive tests at phase 7) was possible for 4659 participants. Missing data were similarly influenced by age, sex, and socioeconomic position compared with data available for analysis of cognitive deficit (n=5388).

To assess whether the smoking-cognition association is underestimated because of premature mortality among smokers, we examined the association between smoking status at phase 1 and mortality during the mean (SD) 17.1 (2.3) years of follow-up until phase 7 (Table 1). Current smokers at phase 1 had a higher risk of dying during the follow-up period compared with never smokers after adjustment for age, marital status, and socioeconomic position among men (hazard ratio [HR], 2.00; 95% confidence interval [CI], 1.58-2.52) and among women (HR, 2.46; 95% CI, 1.80-3.37). Ex-smokers at phase 1 did not have a higher risk of death during the follow-up period examined (HR, 1.09; 95% CI, 0.84-1.41 among men and HR, 1.23; 95% CI, 0.84-1.79 among women). Among survivors at phase 7 (n=9625), we examined the association between smoking status at phase 1 and nonparticipation in cognitive tests at phase 7. In analyses adjusted for age, marital status, and socioeconomic position, current smokers at phase 1 were more likely to be nonparticipants in cognitive tests among men (odds ratio [OR], 1.32; 95% CI, 1.16-1.51) and among women (OR, 1.69; 95% CI, 1.41-2.02). To examine the persistence of this association, we repeated the analysis with smoking history at phase 5 and with participation in cognitive tests at phase 7 (n=7221). Greater numbers of male smokers (OR, 1.47; 95% CI, 1.20-1.81) and female smokers (OR, 1.81; 95% CI, 1.35-2.43) did not undertake the cognitive tests. Long-term ex-smokers and recent ex-smokers at phase 5 did not differ from never smokers.

Characteristics of individuals included in the analyses on smoking and cognitive deficit at phase 5 are given in Table 2. The test for trend showed that smoking status was associated with education achievement, alcohol use, socioeconomic status, and fruit and vegetable consumption (P<.001). Prevalences of stroke, diabetes mellitus, and coronary heart disease were not associated with smoking history. Among the vascular risk factors, smoking history was associated only with cholesterol level (P<.001). Cognitive scores at phase 5 as a function of health measures are given in Table 3.
SMOKING HISTORY AND COGNITIVE FUNCTION AT PHASE 5

The fully adjusted mixed-effects model showed that smoking history was associated with memory (\(P = .01\)), reasoning (\(P < .001\)), phonemic fluency (\(P < .001\)), and semantic fluency (\(P < .001\)). Table 4 gives results of the logistic regression analysis using binary cognitive outcomes; the sex-specific cutoffs used are also given. In age- and sex-adjusted models, current smokers were more likely to have cognitive deficits on all tests as follows: memory (OR, 1.54; 95% CI, 1.25-1.90), reasoning (OR, 1.53; 95% CI, 1.27-1.85), vocabulary (OR, 1.42; 95% CI, 1.18-1.70), phonemic fluency (OR, 1.32; 95% CI, 1.09-1.60), and semantic fluency (OR, 1.30; 95% CI, 1.08-1.57). In fully adjusted models, the association remained for memory (OR, 1.37; 95% CI, 1.10-1.73). Compared with never smokers, long-term ex-smokers were less likely to have deficits in memory (OR, 0.79; 95% CI, 0.65-0.96), vocabulary (OR, 0.73; 95% CI, 0.60-0.87), phonemic fluency (OR, 0.73; 95% CI, 0.61-0.87), and semantic fluency (OR, 0.75; 95% CI, 0.63-0.89) in fully adjusted models. Recent ex-smokers also had a reduced risk of poor vocabulary score (OR, 0.65; 95% CI, 0.49-0.85) and of poor

Table 1. Association Between Smoking and Mortality and Nonparticipation in Cognitive Tests (2002-2004)

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<tbody>
<tr>
<td>Variable</td>
<td>Hazard Ratio (95% Confidence Interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association with mortality until phase 7</td>
<td>Male 1 [Reference] 1.09 (0.84-1.41)</td>
<td>2.00 (1.58-2.52)</td>
<td></td>
</tr>
<tr>
<td>Association with nonparticipation in cognitive tests at phase 7</td>
<td>Female 1 [Reference] 1.23 (0.84-1.79)</td>
<td>2.46 (1.80-3.37)</td>
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</table>

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<tbody>
<tr>
<td>Variable</td>
<td>Odds Ratio (95% Confidence Interval)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Association with nonparticipation in cognitive tests at phase 7</td>
<td>Male 1 [Reference] 0.95 (0.79-1.15)</td>
<td>1.04 (0.80-1.35)</td>
<td>1.47 (1.20-1.81)</td>
<td></td>
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</table>

Table 2. Characteristics of the Study Population at Phase 5 (1997-1999)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never Smoker</th>
<th>Long-term Ex-Smoker</th>
<th>Recent Ex-Smoker</th>
<th>Current Smoker</th>
<th>(P) Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>55.2 (6.0)</td>
<td>56.1 (6.0)</td>
<td>56.2 (6.0)</td>
<td>55.0 (5.7)</td>
<td>.24</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>826 (32.5)</td>
<td>387 (25.5)</td>
<td>97 (19.0)</td>
<td>177 (21.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High socioeconomic status, No. (%)</td>
<td>932 (36.6)</td>
<td>525 (34.6)</td>
<td>180 (35.2)</td>
<td>231 (28.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>University degree or higher, No. (%)</td>
<td>901 (35.4)</td>
<td>434 (28.6)</td>
<td>132 (25.8)</td>
<td>171 (21.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Married or cohabiting, No. (%)</td>
<td>1908 (75.0)</td>
<td>1217 (80.1)</td>
<td>395 (77.3)</td>
<td>600 (73.6)</td>
<td>.87</td>
</tr>
<tr>
<td>Alcohol use, mean (SD), U/wk</td>
<td>10.5 (11.9)</td>
<td>15.3 (14.5)</td>
<td>17.1 (15.8)</td>
<td>20.6 (22.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical activity, mean (SD), h/wk</td>
<td>21.9 (15.1)</td>
<td>22.7 (15.0)</td>
<td>23.1 (16.0)</td>
<td>21.5 (15.8)</td>
<td>.98</td>
</tr>
<tr>
<td>Daily consumption of fruits and vegetables, No. (%)</td>
<td>1152 (73.0)</td>
<td>373 (73.0)</td>
<td>599 (62.5)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease, No. (%)</td>
<td>143 (5.6)</td>
<td>87 (5.7)</td>
<td>48 (9.4)</td>
<td>48 (9.5)</td>
<td>.18</td>
</tr>
<tr>
<td>Stroke, No. (%)</td>
<td>18 (0.7)</td>
<td>13 (0.9)</td>
<td>3 (0.6)</td>
<td>8 (1.0)</td>
<td>.55</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>60 (2.4)</td>
<td>41 (2.7)</td>
<td>14 (2.7)</td>
<td>12 (1.5)</td>
<td>.30</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td>Systolic 121.9 (16.4)</td>
<td>123.6 (16.6)</td>
<td>124.1 (16.9)</td>
<td>122.0 (15.6)</td>
<td>.24</td>
</tr>
<tr>
<td>Diastolic 77.2 (10.6)</td>
<td>77.8 (10.3)</td>
<td>78.4 (11.2)</td>
<td>76.8 (10.0)</td>
<td>76.8 (10.0)</td>
<td>.91</td>
</tr>
<tr>
<td>Cholesterol level, mean (SD), mg/dL</td>
<td>224 (39)</td>
<td>232 (39)</td>
<td>228 (39)</td>
<td>232 (43)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 4 gives results of the logistic regression analysis using binary cognitive outcomes; the sex-specific cutoffs used are also given.
semantic fluency (OR, 0.72; 95% CI, 0.55-0.94). Among current smokers at phase 5, in fully adjusted models there was no evidence of a dose-response association between pack-years of smoking and cognitive deficit (memory, \(P = .97\); reasoning, \(P = .13\); vocabulary, \(P = .33\); phonemic fluency, \(P = .25\); and semantic fluency, \(P = .97\)).
SMOKING HISTORY AND COGNITIVE DECLINE BETWEEN PHASE 5 AND PHASE 7

The interaction term $\times$ smoking history in the fully adjusted mixed-effects model showed that smoking history was associated with cognitive decline in reasoning ($P < .001$) but not with memory ($P = .64$), vocabulary ($P = .68$), phonemic fluency ($P = .63$), or semantic fluency ($P = .61$); detailed results are available in an appendix from the author. Further analysis regarding decline (Table 5) uses the lowest quintile of change, implying decreases of greater than 1 point for memory and vocabulary, 7 points for reasoning, and 3 points for the fluency measures. In fully adjusted models, current smokers (OR, 1.40; 95% CI, 1.11-1.75) and recent ex-smokers (OR, 1.38; 95% CI, 1.07-1.77) were more likely to show a decline in reasoning. No other association was evident. Further adjustment for health behaviors at phase 7 did not notably change these results. Among current smokers at phase 5, in fully adjusted models there was no dose-response association between pack-years of smoking and cognitive decline (memory, $P = .22$; reasoning, $P = .88$; vocabulary, $P = .54$; phonemic fluency, $P = .30$; and semantic fluency, $P = .94$).

POST HOC ANALYSIS

This analysis was aimed at the exploration of changes in other health behaviors along with change in smoking status (giving up smoking) during the follow-up period. Those who stopped smoking between phase 1 and phase 5 (recent ex-smokers) had the smallest increase in alcohol use between phase 1 and phase 7 (0.82 U/wk of alcohol) compared with the other groups (1.46 U/wk of alcohol among never smokers). In terms of healthy eating, the percentage of participants consuming at least 1 fruit or vegetable per day increased more among recent ex-smokers than among never smokers. Figure 2 shows that recent ex-smokers were at the same level of fruit and vegetable consumption as current smokers at phase 1, but by phase 7 they had reached the same level as long-term ex-smokers and never smokers.

This study presents 4 key findings. First, smoking in middle age is associated with memory deficit and decline in reasoning abilities. Second, long-term ex-smokers are less likely to have cognitive deficits in memory, vocabulary, and verbal fluency. Third, giving up smoking in midlife is accompanied by improvement in other health behaviors. Fourth, our results based on a large prospective cohort study of middle-aged British civil servants suggest that the association between smoking and cognition, even in late midlife, could be underestimated because of higher risk of death and nonparticipation in cognitive tests among smokers.

During the past 20 years, public health messages about smoking have led to changes in smoking behavior.23-25
Therefore, estimation of the association between smoking and any health outcome needs to assess smoking behavior over time, to explore whether change in smoking status is accompanied by other changes, and to examine possible underestimation of the association due to premature mortality or greater loss to follow-up among smokers. Our analyses show all 3 aspects to be important. Exploration of the association between smoking and dementia among older persons is complicated by the fact that assessment can only be among those who have survived long enough to become demented.2,3 The alternative is to examine cognitive deficit and decline at earlier ages. Cognition in midlife is clinically relevant because research suggests that individuals with mild cognitive impairment progress to clinically diagnosed dementia at an accelerated rate.6-8

COMPARISON WITH OTHER STUDIES

Studies using global cognitive tests (eg, the Mini-Mental State Examination) have found smoking to be associated with cognitive impairment,26-30 and with decline.30 Smokers have also been reported to have poorer psychomotor speed,31 visuospatial performance,12,31 memory,12,31,32 reasoning,27 and vocabulary.30 Our results suggest poorer performance on memory and reasoning. Current evidence does not allow conclusions to be drawn about the association between smoking and specific cognitive domains.

Few studies9-15 have examined the association between smoking and cognition in a middle-aged population, and only 2 studies12,31 reported analysis of cognitive decline in this age group. Smoking was found to be associated with decline in memory in one study,12 but no association between the two was found in the other study.13 Our results suggest a greater risk of deficit but not of decline in memory among smokers. Findings from a recent study31 suggest that the effect of smoking on decline in memory is confined to those older than 75 years. Future studies need to replicate these analyses to estimate the age at which smoking-related decline in memory becomes apparent. Our results also show a decline in reasoning abilities among recent ex-smokers and among current smokers.

One could expect survival bias because of premature death of smokers to be limited among middle-aged individuals. Few studies33,34 have measured this bias or the bias introduced by greater loss to follow-up among smokers. In our study, smoking was associated with loss to follow-up by death and through nonparticipation in cognitive tests. Current smokers at phase 1 were twice as likely to die during the follow-up period, and those who were current smokers at phase 1 or at phase 5 were less likely to participate in the cognitive tests. These effects due to death or owing to nonparticipation in cognitive tests were not evident among ex-smokers, and their results on the association between smoking and cognition are likely not to be biased. Therefore, the risk of cognitive deficit and decline among current smokers in our analyses may have been underestimated. It is possible that those who are missing due to death or owing to nonparticipation in cognitive tests had higher risk of cognitive deficit.35

Previous results regarding the association between smoking and cognition in ex-smokers are mixed. In the European Community Concerted Action Epidemiology of Dementia study,30 ex-smokers and never smokers did not differ on cognitive impairment. Other studies26,28 have found the risk of cognitive impairment to be lower among ex-smokers compared with never smokers, although the differences were not significant. Apart from a few studies,12,28,29 most have looked at ex-smoking status without distinguishing between long-term ex-smokers and recent ex-smokers.11,26,27,30,32 In the 1946 British Birth Cohort study,12 long-term ex-smokers had better memory and a slower decline in memory compared with never smokers. In the Honolulu-Asia Aging study,28 long-term ex-smokers did not have a lower risk of cognitive impairment than never smokers, and recent ex-smokers had the same increased risk of impairment as current smokers. Our results show that long-term ex-smokers were consistently less likely to have cognitive deficits in vocabulary and in verbal fluency. Future studies need to delineate the long-term ex-smokers from the recent ex-smokers.

The association between smoking and cognition could be explained by the fact that smoking is a risk factor for atherosclerotic disease,30 which is related to a higher risk of cognitive deficit.37,38 However, we did not find a dose-response association between pack-years of smoking and cognitive deficit or decline. Some studies26,28 have also reported the lack of a dose-response association, while other studies12,30 have found this effect to be inconsistent. It is possible that the loss of the heavy smokers through death and nonparticipation in cognitive tests biases the results using pack-years of smoking. Relative to results among ex-smokers, it has been suggested that some of the differences in cognitive performance between groups defined by their smoking habit may be the consequence of self-selection out of the smoking groups. Therefore, smokers with higher cognitive function scores would be more likely to quit and to become ex-smokers.27 This hypothesis is plausible. However, a com-

Figure 2. Participants consuming at least 1 fruit or vegetable per day at the various phases as a function of smoking history at phase 5. Never smoker indicates those who never smoked; current smoker, those who were smoking at phase 5; long-term ex-smoker, those who stopped smoking before phase 1; and recent ex-smoker, those who stopped smoking between phases 1 and 5.
peting hypothesis is that those who stop smoking also change other health behaviors and possibly other aspects of their life as well. In our population, those who stopped smoking in the 10 years preceding cognitive testing considerably improved their other health behaviors (use of alcohol and consumption of fruits and vegetables) compared with others.

**STRENGTHS**

This study has several strengths. The detailed prospective assessment allowed a precise lifelong smoking history to be established, and several confounders and explanatory variables were included in the analysis. We were able to examine changes in health behaviors longitudinally. Furthermore, the design of the Whitehall II study allowed us to assess the underestimation of the association between smoking and cognition by evaluating the extent of missing data related to death during the follow-up period and related to nonparticipation in cognitive tests.

**LIMITATIONS**

First, although the sample covered a wide socioeconomic range, the data are from white-collar civil servants and cannot be assumed to represent general populations. Second, smoking habits were self-reported and may have been underreported. Third, the requirement to write down answers for tests of verbal fluency may have led to a restriction in response range. Fourth, change between 2 time points is insufficient to examine intra-individual change, and analyses on further waves of data are necessary.

In conclusion, our results show an association between smoking and risk of memory deficit and reasoning decline. These results may have been underreported. Third, the requirement to write down answers for tests of verbal fluency may have led to a restriction in response range. Fourth, change between 2 time points is insufficient to examine intra-individual change, and analyses on further waves of data are necessary.

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**Author Contributions:** Study concept and design: Sabia and Singh-Manoux. Acquisition of data: Marmot and Singh-Manoux. Analysis and interpretation of data: Sabia, Dufouil, and Singh-Manoux. Drafting of the manuscript: Sabia and Singh-Manoux. Critical revision of the manuscript for important intellectual content: Sabia, Marmot, Dufouil, and Singh-Manoux. Statistical analysis: Sabia and Dufouil. Obtained funding: Marmot and Singh-Manoux. Administrative, technical, and material support: Singh-Manoux. Study supervision: Singh-Manoux.

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**REFERENCES**