Smoking History in Middle Age and Subsequent Cognitive Performance in Elderly Japanese-American Men

The Honolulu-Asia Aging Study

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The associations between cigarette smoking history and later cognitive performance were examined among 3,429 Japanese-American participants of the Honolulu Heart Program (HHP) and its extension, the Honolulu-Asia Aging Study (HAAS). Cognitive performance was measured by the Cognitive Abilities Screening Instrument (CASI), administered as part of HAAS (mean age at HAAS exam (standard deviation (SD)): 77.7 (4.6) years). Information on smoking history was collected during the first and third HHP exams (mean age (SD) at Exam III: 58.6 (4.7) years). Compared with never-smokers, those who had smoked continuously between Exams I—III and those who had quit smoking during that period had significantly lower CASI scores, after adjustment for age, education, Japanese acculturation, and Exam III alcohol intake. In multiple logistic regression controlling for the above covariates, a significantly higher risk of cognitive impairment (CASI score <82) was associated with continuous smoking (odds ratio (OR) = 1.36, 95% confidence interval (CI) 1.10–1.69) and quitting between Exams I—III (OR = 1.36, 95% CI 1.03–1.80) compared with never smoking. This excess risk of cognitive impairment among continuous smokers and Exam I—III quitters was slightly diminished by further adjustment for body mass index and several vascular covariates. Additional analyses suggested a reduced risk of cognitive impairment among the longer-term quitters. This study suggests a positive association between smoking during middle age and later risk of cognitive impairment.


Cigarette smoking has been implicated as a risk factor for multiple diseases, including cancers (1–7) and atherosclerosis (8–11). The exact mechanisms by which smoking accelerates risk for these diseases are unclear, although smoking may promote inflammation and increase the risk of coagulation defects (12–14). However, relatively little is known regarding the relation between smoking and cognitive impairment, an important public health problem among the elderly.

The risk of cognitive impairment may be increased or decreased by cigarette smoking. Cigarette smoking could contribute to vascular dementia and cognitive impairment through atherosclerotic and hemodynamic processes (15–18). Conversely, some epidemiologic studies (19–21) have suggested that cigarette smoking may be associated with a lower risk of Alzheimer’s disease in the elderly. Others (22, 23) have pointed out, however, that these findings are subject to a survival bias among older smokers, or may be confounded by genetic influences.

There have been few studies of smoking and cognition in community samples (24–28), and only two of these have included longitudinal study designs (24, 27). Cross-sectional studies are more subject to biases in the measurement of the smoking exposure, and this is of particular concern when the study outcome is cognitive impairment. In this paper, we use longitudinal data from the Honolulu Heart Program (HHP) and its extension, the Honolulu-Asia Aging Study.

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Abbreviations: ABI, index of ankle-to-brachial blood pressure; CASI, Cognitive Abilities Screening Instrument; CI, confidence interval; CVA, cerebral vascular accident; FEV₁, forced expiratory volume in one second; HAAS, Honolulu-Asia Aging Study; HHP, Honolulu Heart Program; OR, odds ratio.

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(HAAS), to determine whether cigarette smoking habit is associated with later cognitive performance in elderly Japanese-American men.

MATERIALS AND METHODS

Study sample

Study participants represent surviving members of the HHP cohort. The HHP began in 1965 as a prospective study of coronary heart disease and stroke among 8,006 men of Japanese ancestry. Sample selection was designed to include all noninstitutionalized Japanese-American male residents of Oahu born between 1900 and 1919. Further details of the study and the selection of the cohort are available elsewhere (29–31). There were three follow-up HHP examinations: Exam II (1968–1970), Exam III (1971–1974), and Exam IV (1991–1993). The Honolulu-Asia Aging Study was added to Exam IV, to investigate determinants of cognitive impairment and dementia in the study sample (32). Data were collected from 3,845 of the 4,161 members of the cohort still alive at the completion of Exam IV.

Measurement of cognitive status

As part of the HAAS, participants completed a Cognitive Abilities Screening Instrument (CASI) exam. Designed for use in cross-cultural studies, the CASI is a composite of the Hasegawa Dementia Screening Scale (33), the Mini-Mental State Examination (MMSE) (34), and the Modified Mini-Mental State Examination (35). These tests are frequently used in epidemiologic and clinical studies of dementia and cognitive impairment involving Japanese as well as Western samples, and have been validated against clinically diagnosed dementia (36, 37). The CASI includes tasks of attention, concentration, orientation, short- and long-term memory, language, visual construction, list-generating fluency, abstraction, and judgment, and has a score range of 0–100 (38).

The CASI was included in the HAAS for two purposes: first, to ascertain overall cognitive performance among cohort members and to identify the determinants of poor cognitive functioning, and second, to screen participants for further follow-up and evaluation for dementia. This study is directed to the first purpose, i.e., examination of the longitudinal correlates of overall cognitive performance, and does not examine the association of smoking and dementia per se. The distribution of CASI scores was highly negatively skewed, with most of the scores on the high end. We therefore used the (CASI)$^3$ transformation for some analyses, which resulted in an approximately normal distribution. However, because the relations between predictor smoking terms and the (CASI)$^3$ score were not materially different from those with the raw CASI scores, we present results from analyses of the untransformed CASI score because these are more interpretable. For other analyses, the CASI was used to define cognitive function as a dichotomous outcome: normal (CASI score ≥82), and poor or impaired (CASI score <82). This cut-point of 82 corresponds to an MMSE score of 25–26 (L. R. White and E. L. Teng, National Institute on Aging, personal communication, 1994), a level that has been used to screen for dementia (39) and is related to the probability of cognitive impairment (36). Dementia was diagnosed among a sample of HHP participants randomly selected within strata of age, education, and CASI score, according to the criteria of the third revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (40). Ninety-seven percent of the dementia cases scored less than 82 points on the CASI. The use of slightly lower CASI scores as criteria for cognitive impairment did not significantly change the results of this study.

Smoking variables

The principal smoking history variables were constructed from HHP Exam I and III information to avoid unreliable recall at the time of the HAAS examination, especially among those with cognitive impairment. At both exams, participants classified themselves as “never,” “former,” or “current” smokers. From these designations, the following four smoking history categories were created: Exam I–III never-smokers (“never” at both exams), Exam I quitters (“former” at both exams), Exam III quitters (“current” at Exam I, “former” at Exam III), and Exam I–III continuing (“current” at both exams). A total of 71 participants indicated “never” ($n = 6$) or “former” ($n = 65$) at Exam I, and “current” smoking status at Exam III. Under the assumption that these responses represented men who were trying to quit smoking, rather than men who had started smoking, this group was included with the Exam III quitter category. In support of this assumption, 73 percent of these men classified themselves as “former” smokers at the HAAS exam. Results from analyses in which these 71 men were classified as continuous smokers were similar to those presented here. Rather than cigarette pack-years, these smoking history categories were used to better study the effects of continuous smoking compared with quitting and never smoking.

Although smoking history from HHP Exams I and III is the primary focus of this paper, we also conducted analyses using smoking information collected at HAAS, at which participants again identified them-
selves as “never,” “former,” or “current” smokers. A total of 256 participants did not provide this information in the HAAS exam. Of these nonrespondents, 198 had low CASI scores, making the nonresponse rate in this group (18 percent) much higher than in men with normal CASI scores (2.5 percent). Also, misclassification rates (participants who were “former” or “current” smokers at Exam I or III or both, but “never” smokers at HAAS exam) were approximately double among those scoring less than 82 on the CASI compared with the other participants. We therefore emphasize the associations with the Exam I–III smoking history categories in this paper.

Exploratory analyses were conducted to assess the relations between years of smoking cessation and risk for cognitive impairment. In these analyses, the never-smokers and the 71 men who had indicated they were “never” or “former” smokers at Exam I, but “current” smokers at Exam III, were excluded, because a clear time of cessation could not be established. Estimated cigarette pack-year consumption at Exam III was also considered as a predictor of cognitive performance. Pack-years were estimated by the formula: years smoked × (usual number of cigarettes smoked/20 cigarettes per pack).

Other covariates

Educational attainment was described by four categories, based on highest level of school completion. To control for levels of acculturation, participants were categorized as Issei (those born in Japan), Nisei (those born outside of Japan, but who returned for at least 5 years of boyhood education), and Kibei (those born outside of Japan, but who did not return for at least 5 years of boyhood education). Self-report of alcohol intake at Exam III was coded into the mutually exclusive categories of no consumption, ≤1 drink per week, ≤1 drink per day, 1–2 drinks per day, and >2 drinks per day. Body mass index at Exam III was computed as weight (kg)/height (m)². Systolic blood pressure was measured three times at Exam III, on the left arm of a seated participant with a sphygmomanometer and a standard cuff, and the average level was used for these analyses. Data on cerebral vascular accident (CVA) were collected continuously through 1988 via a surveillance system established at Exam I (41). Finally, the index of ankle-to-brachial blood pressure (ABI) was used as a measure of subclinical atherosclerosis (42). These data were obtained only at the HAAS exam by measuring blood pressure on the right arm and right ankle in a supine position, using a Doppler stethoscope attached to a standard sphygmomanometer. An ABI of ≤0.9 was considered to indicate subclinical atherosclerosis (43). No data on ABI were available for 169 participants.

Sample attrition and exclusions

Based on Exam I information, HAAS participants were more likely to be never or former smokers than the 794 men who were still alive, but who did not participate in HAAS. HAAS participants also had higher educational attainment and lower systolic blood pressure than nonparticipants.

Of the 3,845 HAAS participants, 3,734 completed the CASI exam. The 111 men who did not complete a CASI exam were significantly older than those who did complete a CASI exam (mean age at Exam I (standard deviation): 54.4 (5.4) vs. 52.7 (4.7)), but the two groups were comparable in Exam I levels of systolic blood pressure, body mass index, alcohol consumption, and educational attainment. The two groups had similar distributions of smoking histories, though rates of smoking cessation at or before Exam I were slightly higher in the group without CASI scores (37 percent) compared with those with CASI scores (28 percent).

Given the hypothesized vascular antecedents of cognitive impairment, the study sample was limited to HAAS participants who were free from clinically diagnosed coronary disease and CVA between Exams I and III. These criteria excluded 138 participants. A further 145 participants were excluded for missing information on covariates, and 23 were excluded because smoking history could not be ascertained, leaving a final sample of 3,429 participants.

Statistical methods

Means and proportions were used to describe the distribution of the outcome and covariates within the four main smoking history categories. The outcome of (CASI)³ was modeled using Proc GLM in SAS (SAS Institute Inc., Cary, North Carolina), and multiple logistic regression analysis was used to model the dichotomous outcome of cognitive impairment. Two models were used in all multivariate analyses. Model 1 controlled for potential confounders of associations between smoking habit and cognitive performance: age at the HAAS exam was entered as a continuous covariate, and indicator terms were used to model educational attainment, acculturation status, and alcohol intake at Exam III. In addition to model 1 covariates, model 2 included adjustment for Exam III levels of body mass index and systolic blood pressure (44), occurrence of CVA after Exam III, and low ABI at the HAAS exam. These last parameters could either confound or partially mediate the relation between smoking and cognitive performance. Indicator terms for coronary disease that occurred after Exam III (assessed by the same surveillance system used for de-
tection of CVA cases) and diabetes diagnosed between Exam I and III were not retained, since these were not significantly associated \((p > 0.30)\) with the cognitive outcomes, and did not affect the associations between smoking history and cognition. Forced expiratory volume in one second (FEV\(_1\)), an indicator of pulmonary function recently reported to be predictive of CASI scores in this cohort (45), was not available for 203 of the Exam III participants, and was therefore not included in these analyses. However, additional analyses indicated that control for this variable did not appreciably affect the associations between the smoking history terms and cognitive performance.

Indicator terms for smoking history were entered last into each statistical model, with the never-smokers serving as the reference. In analyses among the continuous smokers and quitters, the continuous smoker group was the reference, and four categorical terms were entered for years of smoking cessation before Exam III: 0–5 years, 6–10 years, 11–20 years, and >20 years previous to Exam III. For Exam III cigarette-pack years, indicator terms were constructed to represent categories of 1–25, 26–50, and >50 pack-years, with never-smokers as the reference category. All data analyses were carried out using SAS software.

**RESULTS**

Characteristics of the study sample are summarized in table 1, both as a total and within the Exam I–III smoking history categories. There were no significant differences across the smoking history categories in unadjusted mean CASI scores. Approximately one-third of the study sample (1,086 men) was classified as cognitively impaired, using the CASI cut-point of <82. Never-smokers and Exam I quitters had the lowest proportion of poor CASI scores, with slightly higher rates in the other two categories. Never-smokers had higher educational attainment, and this category included proportionately more nondrinkers and fewer heavy drinkers than the other categories. Exam I–III continuous smokers were the heaviest

<table>
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<tr>
<th>Table 1. Socio-demographic and health-related characteristics, according to smoking history: Honolulu Heart Program/Honolulu-Asia Aging Study (HAAS), 1965–1993</th>
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<tbody>
<tr>
<td><strong>Total sample ((n = 3,429))</strong></td>
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<tr>
<td><strong>Exam I never-smokers ((n = 1,374))</strong></td>
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<tr>
<td><strong>Exam III quitters ((n = 386))</strong></td>
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<tr>
<td>CASI score (mean (SD)) 82.5 (16.1)()a</td>
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<tr>
<td>Low CASI score (%)</td>
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<tr>
<td>Age (years) at HAAS exam (mean (SD))</td>
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<tr>
<td>Education category (%)</td>
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<tr>
<td>None/primary</td>
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<tr>
<td>Secondary</td>
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<td>High school</td>
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<td>University/technical</td>
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<td>Generation (%)</td>
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<td>Kibel</td>
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<td>Alcohol intake (oz/month) (%)</td>
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<td>Nondrinker</td>
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<td>1–4</td>
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<td>31–60</td>
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<tr>
<td>BMI () (kg/m(^2)) at Exam III (mean (SD))</td>
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<tr>
<td>Systolic BP () (mmHg) at Exam III (mean (SD))</td>
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<tr>
<td>CVA () after Exam III (%)</td>
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<tr>
<td>ABI () &lt;0.9 (%)</td>
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</tbody>
</table>

* Smoking history categories with different letters are significantly different \((p < 0.05); t test for continuous variables, chi-square tests for proportions).

\(\dagger\) CASI, Cognitive Abilities Screening Instrument; SD, standard deviation; BMI, body mass index; BP, blood pressure; CVA, cerebral vascular accident; ABI, ankle-brachial blood pressure index.

\(\ddagger\) Percent of total sample.

\(\S\) Percent within each smoking history category.

\# Sample sizes for analyses with ABI variable: total sample, \(n = 3,260\); never-smokers, \(n = 1,115\); Exam I quitters, \(n = 896\); Exam III quitters, \(n = 371\); Exam I–III smokers, \(n = 878\).

\(\dagger\) 1 ounce = 29.6 ml.
drinkers, as expected. Continuous smokers also had an elevated incidence of CVA and subclinical atherosclerosis, as indicated by ABI <0.9. The distribution of the acculturation term was similar across all smoking history groups, and there were no clear trends in body mass index or systolic blood pressure across the groups.

Continuous smoking between Exams I–III and shorter-term (Exam III) quitting were independently associated with a significant decrease in CASI score, compared with never smoking (table 2, model 1). Addition of the model 2 covariates reduced the parameter estimates associated with continuous smoking by 66 percent, and that associated with shorter-term quitting by 48 percent.

Relative to never-smokers, continuous smokers and Exam III quitters had elevated rates of poor CASI performance after statistical adjustment for the other covariates (table 3). Exam I quitters had slightly lower odds for poor CASI performance, although these were not significantly different from rates among never-smokers. The elevated odds of poor CASI performance among Exam III quitters and continuous smokers persisted after adjustment for the model 2 covariates (table 3, model 2).

When HAAS smoking status (never, former, current) was used in place of the Exam I–III smoking history terms in these models, the risk of low CASI score among current smokers was of borderline statistical significance (p = 0.08) compared with never-smokers (odds ratio (OR) = 1.36, 95 percent confidence interval (CI) 0.96–1.92, after adjustment for model 1 covariates). In these cross-sectional analyses, the risk of low CASI was not significantly different between the never- and former smokers (not shown in tables).

The Exam I–III continuous smoker group (n = 921) was further split into men who reported continued smoking at the HAAS exam (n = 202), and those who had quit between Exam III and HAAS (n = 626). A total of 93 men were excluded from these analyses due to missing (n = 74) or incongruent (n = 19) smoking data at the HAAS exam. Compared with the never-smokers, the Exam I-HAAS continuous smokers had a slightly higher risk of poor cognitive performance (OR = 1.32, 95 percent CI 0.92–1.91, after adjustment for model 1 covariates) than did men who had quit between Exam III and HAAS (OR = 1.15, 95 percent CI 0.90–1.47).

There was no clear relation between Exam III cigarette pack-years and CASI outcome after adjustment for model 1 covariates (not shown in tables). Participants in the 1–25 and >50 pack-year categories were not at increased risk of cognitive impairment compared with never-smokers. The highest risk was found among those in the 26–50 pack-years category (OR = 1.22, 95 percent CI 0.99–1.48).

Compared with Exam I–III continuous smokers, those who quit more than 5 years prior to Exam III had about half the risk of poor cognitive performance later in life (table 4). In this reduced sample of quitters and continuous smokers, we also modeled years since quitting as a continuous term, along with its square, because the protective association with smoking cessation appeared to be a threshold function. Both terms were significantly associated with the cognitive performance outcome in both models (p < 0.05), with risk for poor cognitive performance being inversely related to time since quitting (not shown in tables).

**DISCUSSION**

As the populations of industrialized societies grow older, the prevalence of cognitive impairment is expected to increase. It is therefore important to identify risk factors for cognitive decline, especially those that

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<th>Smoking history category</th>
<th>Model 1†</th>
<th>Model 2†</th>
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<tr>
<td></td>
<td>Beta coefficient</td>
<td>Standard error</td>
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<tr>
<td>Exam I quitters (n = 948)</td>
<td>0.06</td>
<td>0.64</td>
</tr>
<tr>
<td>Exam III quitters (n = 386)</td>
<td>-2.27</td>
<td>0.85</td>
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<tr>
<td>Exam I–III continuous smokers (n = 921)</td>
<td>-2.28</td>
<td>0.66</td>
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</table>

*Cognitive Abilities Screening Instrument.
† Model 1 adjusted for age, education category, acculturation status, and Exam III alcohol consumption category.
‡ Model 2 adjusted for model 1 covariates, plus Exam III levels of body mass index and systolic blood pressure, cerebral vascular accident occurring after Exam III, and prevalence of low ankle-brachial blood pressure index at HAAS exam (n = 3,260).
are potentially modifiable. Results presented in this paper indicate that continuous smoking during a period of middle age is predictive of poorer cognitive performance later in the lives of these Japanese-American men. Also, those who had quit for the shortest amount of time had elevated rates of poor cognitive performance compared with never-smokers and former smokers who had quit for longer periods of time.

The major strength of this study is the well-documented assessment of smoking history, which was collected well before the CASI exam. Long-term retrospective recall of smoking behavior may be subject to errors of memory, and use of concurrent smoking history to examine cognitive performance may result in spurious associations. Moreover, the cognitive status of the participant may also bias smoking history recall in cross-sectional studies. In the present study, we found that cognitively impaired participants were more likely to not provide smoking information, or to provide incorrect information, at the HAAS exam compared with those with normal CASI scores. Additional strengths of this study include the large sample size and the availability of objective measures of vascular conditions which could potentially confound the associations between smoking history and cognitive performance.

We are aware of only a few existing reports on smoking behavior and cognitive performance in community study samples (24–28), and none of these reports has demonstrated consistent associations between these domains. Cross-sectional studies among the Framingham (26) and East Boston (25) cohorts found few significant associations between smoking and the components of neuropsychological test batteries. Smoking history was not independently related to cognitive impairment, as determined by dichotomous MMSE outcomes, in the Zutphen Elderly Study (24),...
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or among 3,770 French study participants (28). Longitudinal change in cognitive function was measured in East Boston (27) and Zutphen (24), but smoking status was not significantly predictive of cognitive change among the total cohort of either study. Given this brief review of available literature, the results of the present study appear to provide the first suggestion of an increased risk of poor cognitive performance associated with long-term smoking.

Our analyses indicate that the risks associated with continuous smoking and shorter-term (Exam III) quitting remained marginally associated with poor cognitive performance, independent of the hypothesized intermediary variables included in model 2, the presence of coronary disease or diabetes, and Exam III levels of FEV1. These observations indicate that smoking may be positively related not only to vascular dementia, but may also contribute to dementia due to Alzheimer's disease. This suggestion conflicts with the results from case-control studies, which taken as a whole indicate a protective effect of smoking regarding Alzheimer's disease (19–21). The available evidence regarding smoking and Alzheimer's disease is inconclusive, however, and interpretation is further complicated by methodological issues. It has been hypothesized (22), for example, that smokers who survive to an age associated with a higher incidence of Alzheimer's disease may represent a genetically select group. However, we recognize that the covariates we included in this study provided only partial statistical representation of general vascular conditions. In addition to this potential residual confounding, these vascular covariates are not indicative of small artery disease, which may influence cognitive functioning. Case-ascertainment of dementia by subtype has recently been completed in this cohort, and future analyses can directly address the relation between smoking and outcomes of Alzheimer's disease and vascular dementia among HAAS participants.

The analytic outcomes of the present study are based on a single cognitive examination. While this strategy is commonly employed in large epidemiologic studies, it would have been informative to examine associations between smoking history and change in cognitive status as measured by an additional CASI exam. Other limitations of the present findings include the small odds ratios associated with shorter-term quitting and continuous smoking, and the lack of congruent findings between smoking indicators (smoking history vs. pack-years) and risk of cognitive impairment. Regarding the former limitation, it has been pointed out that for the analogous relation between smoking and Alzheimer's disease, differential survivorship between smokers and nonsmokers may bias the observed risks (24). Thus, any positive relation between smoking and cognitive failure would be diminished by participants who are lost to smoking-related illness. Smoking has been shown to be significantly predictive of mortality in this cohort (46), and we found current smokers at Exam I to be less likely to survive to and participate in HAAS. With respect to lack of congruence between smoking indicators, we feel analyses conducted with the smoking history variables may be more reliable than analyses that use pack-year consumption variables, because the latter incorporate estimations of both duration and amount of smoking. Analyses from the Epidemiologic Followup Study to the First National Health and Nutrition Examination Survey (NHANES I) demonstrated that smoking history (current, never, former) may be better recalled than pack-year history (47). Nevertheless, our analyses using pack-year estimates did not provide any support for a protective effect of smoking, but gave some suggestion of increased risk of poor cognitive performance at higher levels of smoking intensity. We were not able to demonstrate a dose-response relationship between cognitive performance and either smoking history or duration of quitting, because only men who had quit more than 5 years before Exam III had lower rates of poor cognitive performance. However, we do not have information on smoking behavior between Exam III and the HAAS exam, and it is possible that shorter-term quitters were more likely to resume smoking during that period. The findings from this study among Japanese-American men may not be generalizable to populations of European ancestry, since the relative frequencies of the two major subtypes of dementia tend to differ between these two populations, with proportionally higher estimates of Alzheimer's disease among European populations (32, 48). Finally, there remain many possible unmeasured confounders of the relation between smoking and cognition, including gender, genetic susceptibility (49), comorbidities, behavioral habits, social adjustment, and other psychological conditions (50) which could not be addressed in this study.

Cigarette smoking is one of the most common exposures in population studies and the risks associated with smoking have been demonstrated for a variety of health outcomes. In a large sample, we have used smoking history collected many years previously to examine the risk of cognitive impairment in old age. Based on the results of the present study, we conclude that continuous smoking in middle age is associated with increased risk of cognitive impairment later in life among these men. Among smokers, there appears to be a cognitive benefit associated with the long-term cessation of smoking. Combined with the well-
documented relations between cigarette smoking and cancer and cardiovascular disease, these results further underscore the negative health consequences associated with smoking.

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