Heavy Smoking in Midlife and Long-term Risk of Alzheimer Disease and Vascular Dementia

Minna Rusanen, MD; Miia Kivipelto, MD, PhD; Charles P. Quesenberry Jr, PhD; Jufen Zhou, MS; Rachel A. Whitmer, PhD

Background: Smoking is a risk factor for several life-threatening diseases, but its long-term association with dementia is controversial and somewhat understudied. Our objective was to investigate the long-term association of amount of smoking in middle age on the risk of dementia, Alzheimer disease (AD), and vascular dementia (VaD) several decades later in a large, diverse population.

Methods: We analyzed prospective data from a multi-ethnic population-based cohort of 21 123 members of a health care system who participated in a survey between 1978 and 1985. Diagnoses of dementia, AD, and VaD made in internal medicine, neurology, and neuropsychology were collected from January 1, 1994, to July 31, 2008. Multivariate Cox proportional hazards models were used to investigate the association between midlife smoking and risk of dementia, AD, and VaD.

Results: A total of 5367 people (25.4%) were diagnosed as having dementia (including 1136 cases of AD and 416 cases of VaD) during a mean follow-up period of 23 years. Results were adjusted for age, sex, education, race, marital status, hypertension, hyperlipidemia, body mass index, diabetes, heart disease, stroke, and alcohol use. Compared with nonsmokers, those smoking more than 2 packs a day had an elevated risk of dementia (adjusted hazard ratio [HR], 2.14; 95% CI, 1.65-2.78), AD (adjusted HR, 2.57; 95% CI, 1.63-4.03), and VaD (adjusted HR, 2.72; 95% CI, 1.20-6.18).

Conclusions: In this large cohort, heavy smoking in midlife was associated with a greater than 100% increase in risk of dementia, AD, and VaD more than 2 decades later. These results suggest that the brain is not immune to long-term consequences of heavy smoking.

Arch Intern Med. 2011;171(4):333-339.
Published online October 25, 2010.
doi:10.1001/archinternmed.2010.393

ALTHOUGH IT IS WELL established that smoking increases the risk of several diseases, there has unfortunately been a recent increase in smoking among young adults in some developed countries.[1] Current estimates suggest there are several million deaths attributable to smoking and markedly increased cardiovascular- and cancer-associated

See Invited Commentary at end of article

mortality rates.[2] Although smoking increases risk of most diseases and death, some studies suggest that it is associated with a lower risk of certain neurodegenerative diseases such as Parkinson disease.[3] The link between smoking and risk of Alzheimer disease (AD), the most common subtype of dementia, has been somewhat controversial, with some studies suggesting that smoking reduces the risk of cognitive impairment.[4]

Because of the long preclinical phase of AD, it is important to identify exposure to putative risk factors in middle age, before pathologic features of AD have started to develop in the brain.[5-7] However, there are relatively few large population-based cohort studies that have studied the relationship between smoking in early life and development of dementia later in life. Most smoking and dementia studies were conducted in elderly cohorts with a relatively short follow-up time (2 to 7 years).[8-14] The few studies that have examined midlife smoking have been conducted in relatively homogenous populations. One study that specifically focused on the amount of midlife smoking found that the risk of AD increased along with the level of smoking,[15] while another study found that smoking status in midlife was associated with increased risk of dementia and AD especially among apolipoprotein E (APOE) ε4 carriers.[16] A third study found a nonsignificant positive association between smoking in midlife and risk of hospitalization for dementia.[17] Yet, both smoking and AD rates vary by race, and some studies suggest that the

Author Affiliations:
Departments of Neurology, University of Eastern Finland (Drs Rusanen and Kivipelto) and Kuopio University Hospital (Dr Rusanen), Kuopio, Finland; Karolinksa Aging Research Center, Stockholm, Sweden (Dr Kivipelto); and Kaiser Permanente Division of Research, Oakland, California (Drs Quesenberry and Whitmer and Ms Zhou).

prevalence of dementia, as well as smoking, is higher in African American populations.[18,19] Thus, further evaluation of smoking and risk of dementia is warranted in large, ethnically diverse populations.

The association between smoking and different subtypes of dementia beyond AD is also a less investigated issue. Smoking is known to increase the risk of stroke,[20] and consequently, may also predispose to VaD. However, few previous longitudinal studies have investigated this association. To date, only 1 study, to our knowledge, has evaluated the long-term association of midlife smoking on risk of VaD.[15] Other studies that have shown a positive association have had elderly cohorts with short follow-up times (approximately 2 years).[9,14]

The goal of this study was to investigate the association between the amount of midlife smoking and long-term risk of all-cause dementia, AD, and VaD 2 to 3 decades later in a large multiethnic cohort of health plan members.

METHODS

SOURCE POPULATION AND ANALYTIC COHORT

The study cohort includes members of the Kaiser Permanente Medical Care Program of Northern California, who participated in a voluntary health examination called the Multiphasic Health Checkup (MHC) in San Francisco and Oakland during 1978 through 1985, when they were 50 to 60 years old (N=33 108). Kaiser Permanente of Northern California is a nonprofit, integrated health maintenance organization that covers more than one-fourth of the population in the geographic areas served. The members are representative of the sociodemographics of the local population.[21] The MHC was given as part of routine medical care at all San Francisco and Oakland medical clinics. Our analytic cohort comprises 21 123 people who were still alive and members of the health plan in 1994, when electronic medical record diagnoses of dementia became available. People who had missing data on the smoking questionnaire (n=1045) were excluded.

DATA COLLECTION

The purpose of the MHC was to collect a large amount of data on health habits and medical conditions of the participants, and it was given as part of routine medical care. It included a detailed interview on health behavior (including smoking), health status, and medical as well as family history. Participants were asked if they were never, former, or current smokers. For current smokers, amount smoked per day was asked with the following categories: smoking less than 0.5 pack per day, 0.5 to 1 pack per day, 1 to 2 packs per day, and more than 2 packs per day. In addition, several clinical measurements, including height, weight, and systolic and diastolic blood pressure (BP) of the participants, were carried out, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. A blood sample was drawn for determining the serum cholesterol level. High cholesterol was defined as a total serum cholesterol level of 240 mg/dL or greater (to convert cholesterol to millimoles per liter, multiply by 0.0259). The participants were considered to have hypertension if they had 1 of the following: self-report of physician-diagnosed hypertension, use of antihypertensive medication, systolic BP of 140 mm Hg or higher, or diastolic BP of 90 mm Hg or higher. Diabetes was defined by self-report of physician-diagnosed diabetes, use of insulin or oral hypoglycemic agents, a fasting (last food eaten in ≥8 hours) glucose level of 140 mg/dL or higher, or a nonfasting (last food eaten in ≤4 hours) glucose level of 200 mg/dL or higher (to convert glucose to millimoles per liter, multiply by 0.0555). Stroke and cardiovascular disease were recorded from hospital discharge diagnoses (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes for ischemic stroke, 433-438; hemorrhagic stroke, 430-432; and cardiovascular disease 410, 411, 413, 414, 428, 440, 443, and V717) from 1978 through the end of the study. Final multivariate models were adjusted for both stroke during dementia follow-up (stroke from 1994 to 2008) or intercurrent stroke (stroke between baseline and the start of dementia ascertainment from 1978 to end of 1993). The study was approved by the internal review board of Kaiser Permanente.

DEMENTIA DIAGNOSES

The dementia diagnoses were derived from electronic health records. The diagnoses considered in this study include both AD (n=1136) (*ICD-9, Clinical Modification* [*ICD-9-CM*] code 331.0) and VaD (n=416) (*ICD-9-CM* code 290.4), which were made by a neurologist or neuropsychologist. General dementia diagnoses (n=5367), which additionally includes diagnosis of unspecified dementia (*ICD-9-CM* code 290.0), were made by an internal medicine physician. The diagnoses were ascertained from January 1, 1994, to July 31, 2008. The mean (SD) age in 1994, at the onset of dementia follow-up was 71.6 (5.8) years.

STATISTICAL ANALYSES

All statistical analyses were carried out using SAS version 9.1 software (SAS Institute, Inc, Cary, North Carolina). The sociodemographic and clinical characteristics of the participants were compared using the χ^2 test for categorical variables and analysis of variance for continuous variables. The Cox proportional hazards model with age as a time scale was used to investigate the relationship between midlife smoking and dementia, AD, and VaD. Participants were censored according to age at dementia diagnosis, age at date of death, age at date of end of Kaiser membership (as defined by a lag in health plan membership of ≥90 days), or age at end of follow-up (July 31, 2008). Individuals with a dementia diagnosis other than the one under investigation were excluded from the analyses regarding AD or VaD separately (AD models n=17 360 and VaD models n=16 294). For cases, the calculated person-years in this study included age (as a time scale) in January 1, 1994, until the age at diagnosis of dementia, AD, or VaD and, for controls, until age at death, age at lag in health plan membership, or age at end of follow-up (July 31, 2008). Incidence rates were determined specifically for smoking categories. Age-adjusted incidence rates were calculated using the whole cohort as the standard population with 4 age groups including younger than 77 years, 77 to 81 years, 81 to 85 years, and older than 85 years.

For the Cox proportional hazard model analyses, smoking was defined as a categorical variable with the following 6 levels: never smokers, former smokers, and current smokers who smoke less than 0.5 pack per day, 0.5 to 1 pack per day, 1 to 2 packs per day, and more than 2 packs per day. In the Cox models, the never smokers were used as a reference group. The models were first adjusted for the potential sociodemographic confounders age (as a time scale), sex, education (categorized as high school, trade school, college 1-2 years, college 3-4 years, and postgraduate, with grade school as a reference), race (entered as white, Asian, and other, with African American as a reference group), and marital status (classified as never married and divorced/widowed/separated, with married as a reference group). Second, the models were also adjusted for midlife BMI, hyperlipidemia, diabetes, hypertension, heart disease, and stroke (yes/no) during the follow-up. Finally, the analyses were additionally adjusted for midlife alcohol drinking (classified as former, occasionally, 1-2 drinks per day, and >3 drinks per day, with never drinkers as a reference group). To examine whether the association between smok-

Table 1. Sociodemographic and Clinical Characteristics of the Participants

Characteristic	Dementia (n=5367)	Nondementia (n=15 756)	All (N=21 123)	P Value, χ^2 Test
Age at baseline, y[a]	60.07 (5.32)	57.31 (5.28)	58.01 (5.42)	<.001
Age at dementia diagnosis, y[a]	81.45 (5.85)	NA	81.45 (5.85)	NA
Follow-up time from baseline to the end of study (censor date)[a]	21.37 (4.27)	23.72 (5.26)	23.12 (5.13)	<.001
Age at January 1, 1994, start of dementia ascertainment, y[a]	73.95 (5.51)	70.81 (5.69)	71.61 (5.81)	<.001
Age at censor date, y[a]	81.45 (5.85)	81.03 (6.3)	81.14 (6.2)	<.001
Male sex[b]	2131 (39.71)	6961 (44.18)	9092 (43.04)	<.001
Race				
Missing	8 (0.15)	21 (0.13)	29 (0.14)	
African American	1427 (26.59)	3485 (22.12)	4912 (23.25)	
White	3411 (63.56)	9956 (63.19)	13 367 (63.28)	<.001
Asian	321 (5.98)	1569 (9.96)	1890 (8.95)	
Other	200 (3.73)	725 (4.6)	925 (4.38)	
Education[b]				
Missing	65 (1.21)	120 (0.76)	185 (0.88)	
Elementary or grade school	603 (11.24)	1413 (8.97)	2016 (9.54)	
High school	1642 (30.59)	4554 (28.9)	6196 (29.33)	
Trade/business school	520 (9.69)	1460 (9.27)	1980 (9.37)	
College, y				<.001
1-2	1130 (21.05)	3524 (22.37)	4654 (22.03)	
3-4	575 (10.71)	2017 (12.8)	2592 (12.27)	
Postgraduate	832 (15.5)	2668 (16.93)	3500 (16.57)	
Marriage[b]				
Missing	11 (0.2)	31 (0.2)	42 (0.2)	
Married	3833 (71.42)	11 557 (73.35)	15 390 (72.86)	
Never married	218 (4.06)	718 (4.56)	936 (4.43)	.002
Divorced or widowed or separated	1305 (24.32)	3450 (21.9)	4755 (22.51)	
Baseline alcohol consumption[b]				
Missing	90 (1.68)	227 (1.44)	317 (1.5)	
Never	896 (16.69)	2287 (14.52)	3183 (15.07)	
Former	197 (3.67)	633 (4.02)	830 (3.93)	
Occasionally	2778 (51.76)	8088 (51.33)	10 866 (51.44)	<.001
Drinks/d				
1-2	1051 (19.58)	3235 (20.53)	4286 (20.29)	
≥3	355 (6.61)	1286 (8.16)	1641 (7.77)	
Comorbidity				
Baseline BMI, mean (SD)[a]	26.24 (4.5)	25.94 (4.4)	26.02 (4.5)	<.001
Baseline hypertension[b]	2276 (42.4)	5798 (36.8)	8074 (38.2)	<.001
Baseline hyperlipidemia[b]	3092 (57.6)	8180 (51.9)	11272 (53.3)	<.001
Diabetes[b]	428 (7.9)	1010 (6.4)	1438 (6.8)	<.001
Heart disease[b]	371 (6.9)	950 (6.03)	1321 (6.2)	.02
Stroke from 1994-2008[b]	55 (1.0)	119 (0.7)	174 (0.8)	.06
Stroke from 1978-1993[b]	293 (5.4)	522 (3.3)	815	<.001
Smoking[b]				
Never	2724 (50.7)	7481 (47.4)	10205 (48.3)	
Former	1628 (30.3)	4913 (31.1)	6541 (30.9)	
Current, packs/d				
<0.5	234 (4.3)	745 (4.7)	979 (4.6)	
0.5-1	435 (8.1)	1352 (8.5)	1787 (8.4)	<.001
1-2	283 (5.27)	1067 (6.77)	1350 (6.39)	
≥2	63 (1.1)	198 (1.2)	261 (1.2)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.
[a] Mean (SD) for continuous variables.
[b] Number (percentage) for categorical variables.

ing and dementia, AD, or VaD was modified by sex or race, interaction terms were added to the Cox models.

RESULTS

SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

A total of 5367 people (25.4%) were diagnosed as having dementia (including 1136 AD cases and 416 VaD cases) during a mean follow-up period of 23 years. Sociodemographic and clinical characteristics of the study population are given in **Table 1**. As expected, those who were diagnosed as having dementia were older, had fewer years of education, and were more likely to be women than the individuals without dementia. There were differences in the occurrence of dementia between race groups: compared with whites, African Americans were more likely to have a dementia diagnosis, while Asians were less likely. In addition, a higher percentage of divorced, widowed, or

Table 2. Age-Adjusted Incidence Rates and Crude Proportional Hazards of Dementia, Alzheimer Disease (AD), and Vascular Dementia (VaD) Risk by Midlife Smoking Status[a]

Smoking Status	No. of Dementia Cases	AIR, per 10 000 Person-Years (95% CI)	Dementia, HR (95% CI)	No. of AD Cases	AD, HR (95% CI)	No. of VaD Cases	VaD, HR (95% CI)
Never	2724	409.03 (392.02-426.03)	1 [Reference]	590	1 [Reference]	210	1 [Reference]
Former	1628	403.08 (381.05-425.11)	0.99 (0.93-1.06)	351	0.99 (0.89-1.11)	124	0.96 (0.79-1.16)
Current, packs/d							
<0.5	234	398.19 (337.64-458.75)	1.08 (0.94-1.23)	39	0.85 (0.65-1.11)	17	1.10 (0.73-1.66)
0.5-1	435	483.59 (425.64-541.54)	1.34 (1.21-1.48)	89	1.09 (0.89-1.33)	31	1.16 (0.83-1.62)
1-2	283	489.14 (410.44-567.85)	1.37 (1.21-1.55)	50	1.17 (0.92-1.48)	29	1.44 (1.00-2.08)
≥2	63	786.42 (481.23-1091.61)	2.01 (1.57-2.58)	17	2.36 (1.54-3.61)	5	2.02 (0.99-4.55)

Abbreviations: AIR, age-adjusted incidence rate; CI, confidence interval; HR, hazard ratio.
[a] Cox proportional hazards models using age as the time scale.
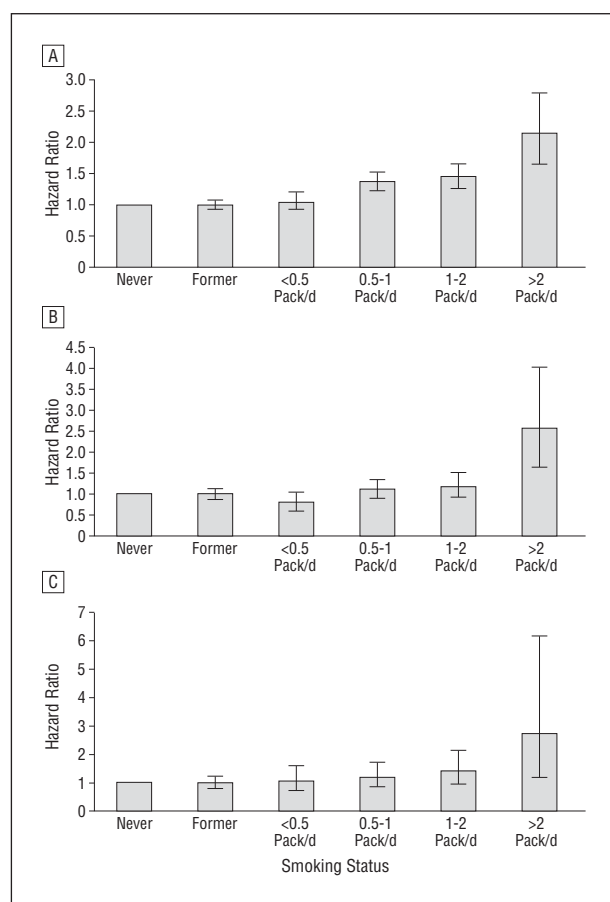

Figure. The risk of dementia (A), Alzheimer disease (B), and vascular dementia (C) according to smoking amount in midlife. Values are hazard ratios from Cox proportional hazards model adjusted for age, sex, education, race, marital status, hypertension, high cholesterol, body mass index, diabetes, heart disease, stroke, and alcohol drinking. Error bars indicate 95% confidence intervals.

separated persons and a higher percentage of never drinkers were found among those with a dementia diagnosis. Dementia was also associated with a greater likelihood of a higher mean midlife BMI and all comorbidities.

MIDLIFE SMOKING AND THE RISK OF DEMENTIA

Although both the incidence rates and age-adjusted incidence rates did not increase in a linear fashion by smoking levels, a dramatic increase in the incidence of dementia was found for those individuals who reported smoking 2 or more packs per day at midlife (**Table 2**). The calculated incidence rate of dementia for those persons was 312.21 (95% confidence interval [CI], 235.11-389.30), and the age-adjusted incidence rate was 786.42 (95% CI, 481.23-1091.61) per 10 000 person-years.

Smoking more than 2 packs daily in midlife increased the later risk of dementia (hazard ratio [HR], 2.01; 95% CI, 1.57-2.58) in the unadjusted Cox proportional hazards model (adjusted for age as a time scale, Table 2). In the fully adjusted multivariate model (adjusted for age as a time scale, sex, education, race, marital status, hypertension, high cholesterol level, BMI, diabetes, heart disease, stroke, and alcohol drinking), using the nonsmokers as a reference group, the HR (95% CI) was 2.14 (1.65-2.78) for those smoking more than 2 packs per day, 1.44 (1.26-1.64) for 1 to 2 packs per day, and 1.37 (1.23-1.52) for 0.5 to 1 packs per day. Former smoking (HR, 1.00; 95% CI, 0.94-1.07) or smoking less than 0.5 pack (HR, 1.04; 95% CI, 0.91-1.20) per day did not have an effect on dementia risk (**Figure**, A). Those who previously smoked or who smoked less than 0.5 pack per day had a dementia risk similar to nonsmokers. An additional fully adjusted multivariate model was conducted to control only for stroke that occurred between baseline and the start of dementia assessment (intercurrent stroke) to consider the potential confounding or mediating effects of stroke, which occurred prior to dementia, on the smoking-dementia association. These results were not markedly different than the prior model: compared with never smokers the HR (95% CI) was 2.12 (1.64-2.75) for those smoking more than 2 packs per day, 1.43 (1.26-1.63) for 1 to 2 packs per day, and 1.36 (1.22-1.51) for 0.5 to 1 pack per day. Former smoking (HR, 1.00; 95% CI, 0.94-1.07) or smoking less than 0.5 pack (HR, 1.05; 95% CI, 0.91-1.20) was not associated with risk of dementia.

MIDLIFE SMOKING AND THE RISK OF AD

There was an increased risk of AD also observed for those smoking more than 2 packs daily in midlife (crude model HR, 2.36; 95% CI, 1.54-3.61; Table 2) compared with those not smoking. In the fully adjusted Cox model, the association remained the same (HR, 2.57; 95% CI, 1.63-

4.03; Figure, B). For those smoking 1 to 2 packs (HR, 1.18; 95% CI, 0.92-1.52) or 0.5 to 1 pack (HR, 1.11; 95% CI, 0.90-1.36) per day, there was an increase in risk, although nonsignificant, whereas former smoking (HR, 1.00; 95% CI, 0.89-1.13) or smoking less than 0.5 pack (HR, 0.80; 95% CI, 0.61-1.06) per day was not associated with a risk of AD compared with nonsmokers.

MIDLIFE SMOKING AND THE RISK OF VaD

Despite the smaller number of cases, an increased risk of VaD later in life was also detected among midlife smokers (crude model for smoking >2 packs daily, HR, 2.02; 95% CI, 0.90-4.55;Table 2). Even after controlling for various potential vascular confounding factors, in the fully adjusted Cox model, those smoking more than 2 packs per day in midlife were almost 3 times (HR, 2.72; 95% CI, 1.20-6.18) more likely to develop VaD later in life than the nonsmoking individuals (Figure, C). The observed risk increase was borderline significant for those smoking 1 to 2 packs (HR, 1.42; 95% CI, 0.95-2.13) per day. Former smoking (HR, 0.99; 95% CI, 0.80-1.22), smoking less than 0.5 (HR, 1.05; 95% CI, 0.69-1.61) or 0.5 to 1 packs (HR, 1.20; 95% CI, 0.84-1.70) per day in midlife did not increase the later risk of VaD compared with nonsmokers.

INTERACTION BETWEEN SMOKING AND RACE OR SEX

There were no significant interaction terms of smoking × sex or smoking × race (P > .05). Post hoc stratified analyses did not reveal any trends that showed differences in the association between smoking and dementia by race or sex.

SENSITIVITY ANALYSES BY STROKE STATUS

Stroke was both highly associated with smoking (χ^2 test, P < .001) and dementia risk (P < .001), although it did not significantly interact with smoking on risk of dementia, AD, or VaD (P > .05 for all interaction term models of smoking × stroke on risk). Although stroke (whether intercurrent or during follow-up) did not confound or attenuate the association between smoking and dementia risk, we wanted to examine the association between smoking and dementia risk separately for those with and without a stroke because stroke is a robust predictor of dementia and highly associated with smoking. Heavy smoking is a risk factor for dementia, AD, and VaD even among those without a stroke or without an intercurrent stroke (**Table 3**). These post hoc subgroup analyses should be interpreted with caution, since there were no statistically significant interaction terms of stroke times smoking on dementia risk.

COMMENT

To our knowledge, this is the first study to investigate the long-term association between the amount of smoking in midlife and the risk of dementia, AD, and VaD later in life in a large, multiethnic cohort. The risk of dementia, AD, and VaD was dose dependent in that the risk increased with the increasing amount of smoked ciga-

Table 3. Cox Proportional Hazard Models of Smoking and Dementia Risk Stratified by Stroke Status and Intercurrent Stroke Status

Status	Dementia HR (95% CI)
Stroke[a]	
Among those without a stroke	
Never smoker	1 [Reference]
Former smoker	1.01 (0.94-1.1)
Current, packs/d	
<0.5	0.97 (0.81-1.16)
0.5-1	1.38 (1.2-1.57)
1-2	1.44 (1.23-1.69)
≥2	2.19 (1.61-2.97)
Among those with a stroke	
Never smoker	1 [Reference]
Former smoker	0.93 (0.85-1.03)
Current, packs/d	
<0.5	1.29 (1.05-1.57)
0.5	1.22 (1.04-1.42)
1-2	1.26 (1.03-1.53)
≥2	1.83 (1.18-2.81)
Intercurrent Stroke[b]	
Among those without a stroke	
Never smoker	1 [Reference]
Former smoker	0.99 (0.93-1.06)
Current, packs/d	
<0.5	1.07 (0.94-1.23)
0.5-1	1.32 (1.19-1.47)
1-2	1.35 (1.19-1.54)
≥2	1.99 (1.54-2.59)
Among those with a stroke	
Never smoker	1 [Reference]
Former smoker	0.89 (0.68-1.17)
Current, packs/d	
<0.5	1.33 (0.72-2.47)
0.5-1	1.24 (0.85-1.82)
1-2	1.33 (0.84-2.1)
≥2	1.77 (0.72-4.37)

Abbreviations: CI, confidence interval, HR, hazard ratio.
[a] Stroke between 1994 and 2008. "Never smoker" was the reference group.
[b] Stroke between 1978 and 1993. "Never smoker" was the reference group.

rettes. Indeed, very heavy smokers (those who reported smoking >2 packs per day in middle age) were at the greatest risk of dementia even decades later in life.

The association between smoking specifically in middle age and the long-term subsequent risk of dementia later in life has been addressed previously in only 3 cohort studies with smaller sample sizes of predominantly white participants.[15-17]

The majority of previous studies on smoking and dementia have evaluated the association between smoking and short-term risk of dementia, though most of these studies calculated pack-years for smoking.[9,13,14] Our findings are consistent with the studies indicating that heavier smoking is associated with a greater dementia risk,[9,13-15] although some studies found no association.[12]

Evaluation of smoking in middle age is important, since it is possible that subclinical dementia or cognitive impairment can affect behavior or induce bias owing to falsely recalled information. This can be of particular importance if smoking information is collected among an elderly population. In the present study, the participants had a mean age of 58 years at the time of the base-

line examination, so it is highly unlikely that subclinical dementia would have biased our results. In addition, the baseline examination conducted in midlife and the long follow-up time enables us to evaluate smoking habits before neuropathologic changes have likely commenced in the brain, and thereby, to investigate smoking more specifically as a true long-term "risk factor," rather than a "risk predictor," for dementia.

In this study, midlife smoking was associated with an increased risk of both AD and VaD. The relationship between smoking and VaD has not been as widely investigated as the relationship with AD. Smoking is a well-established risk factor for stroke,[20] and consequently, it can also predispose to multi-infarct dementia. Interestingly, in the present study the association between smoking and VaD remained significant after controlling for various potential vascular confounding factors (including stroke); thus, smoking seems to also have some independent effect on VaD, beyond acceleration of cerebrovascular disease. These mechanisms, as well as the mechanisms through which smoking makes one susceptible to AD, need to be further clarified in future studies. It is well recognized that smoking augments oxidative stress and inflammation, which are also believed to be important pathophysiologic mechanisms in AD.[22] It is possible that smoking affects the development of dementia via vascular and neurodegenerative pathways.

In this large and diverse cohort with several ethnic groups, as well as both sexes, no interaction between smoking and sex or between smoking and race was found. This is an important finding because, despite that the incidence of dementia is suggested to vary by race,[18] previous studies of putative risk factors for dementia have mainly been conducted within white cohorts. The present study is generalizable to elderly populations at risk for dementia. Based on the present results, we can postulate that the deleterious effects of smoking on risk of dementia seem to be the same for both sexes and across different ethnic groups.

One obvious limitation of this study is the definition of dementia diagnoses, which were obtained from medical records. Although the diagnoses were not systematically and clinically determined according to a strict protocol, the dementia subtypes (AD and VaD) were diagnosed by a neurologist or neuropsychologist in a memory clinic according to common clinical practice. The diagnoses of VaD in this study refers to multi-infarct dementia, which is more straightforward to diagnose than AD or mixed dementia. Therefore, the diagnoses of VaD may be considered reliable, while the AD group may also include people with mixed dementia, since AD is more likely to be diagnosed in a person having memory impairment as a leading symptom. Furthermore, there might be some subjects with undiagnosed dementia in the cohort and, in addition, some AD and VaD cases might have been missed in participants who had died prior to the onset of the ascertainment in 1994. Thus, some selective survival effect cannot be ruled out regarding the present results. Yet, smoking is associated with increased mortality,[23] and accordingly, if it is assumed that among the deceased there were more smokers and that the deceased were also more likely to have dementia, then the present results would not overestimate but rather underestimate the true effects of smoking on the risk of dementia later in life. Another limitation is that the smoking data were collected at midlife only, and thus the present study cannot evaluate whether smoking cessation is associated with reduced dementia risk.

To our knowledge, this is the first study evaluating the amount of midlife smoking on long-term risk of dementia and dementia subtypes in a large multiethnic cohort. Our study suggests that heavy smoking in middle age increases the risk of both AD and VaD for men and women across different race groups. The large detrimental impact that smoking already has on public health has the potential to become even greater as the population worldwide ages and dementia prevalence increases.

REFERENCES

1. Bartecchi CE, MacKenzie TD, Schrier RW. The human costs of tobacco use (1). *N Engl J Med*. 1994;330(13):907-912.
2. Mucha L, Stephenson J, Morandi N, Dirani R. Meta-analysis of disease risk associated with smoking, by gender and intensity of smoking. *Gend Med*. 2006; 3(4):279-291.
3. Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernández-Crehuet Navajas R. Smoking and Parkinson's disease: systematic review of prospective studies. *Mov Disord*. 2004;19(6):614-621.
4. Wang CC, Lu TH, Liao WC, et al. Cigarette smoking and cognitive impairment: a 10-year cohort study in Taiwan. *Arch Gerontol Geriatr*. 2010;51(2):143-148.
5. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol*. 2006;5(9):735-741.
6. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ*. 2005;330(7504):1360.

7. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64(2):277-281.

8. Wang HX, Fratiglioni L, Frisoni GB, Viitanen M, Winblad B. Smoking and the occurrence of Alzheimer's disease: cross-sectional and longitudinal data in a population-based study. *Am J Epidemiol*. 1999;149(7):640-644.

9. Ott A, Slooter AJ, Hofman A, et al. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet*. 1998;351(9119):1840-1843.

10. Launer LJ, Andersen K, Dewey ME, et al; EURODEM Incidence Research Group and Work Group, European Studies of Dementia. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. *Neurology*. 1999;52(1):78-84.

11. Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. The influence of smoking on the risk of Alzheimer's disease. *Neurology*. 1999;52(7):1408-1412.

12. Aggarwal NT, Bienias JL, Bennett DA, et al. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. *Neuroepidemiology*. 2006;26(3):140-146.

13. Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MM. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. *Neurology*. 2007;69(10):998-1005.

14. Juan D, Zhou DH, Li J, Wang JY, Gao C, Chen M. A 2-year follow-up study of cigarette smoking and risk of dementia. *Eur J Neurol*. 2004;11(4):277-282.

15. Tyas SL, White LR, Petrovitch H, et al. Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging*. 2003;24(4):589-596.

16. Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. *J Cell Mol Med*. 2008;12 (6B):2762-2771.

17. Rosengren A, Skoog I, Gustafson D, Wilhelmsen L. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. *Arch Intern Med*. 2005; 165(3):321-326.

18. Gurland BJ, Wilder DE, Lantigua R, et al. Rates of dementia in three ethnoracial groups. *Int J Geriatr Psychiatry*. 1999;14(6):481-493.

19. Zang EA, Wynder EL. Smoking trends in the United States between 1969 and 1995 based on patients hospitalized with non-smoking-related diseases. *Prev Med*. 1998;27(6):854-861.

20. Gorelick PB, Sacco RL, Smith DB, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA*. 1999;281(12):1112-1120.

21. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82(5):703-710.

22. Markesbery WR, Carney JM. Oxidative alterations in Alzheimer's disease. *Brain Pathol*. 1999;9(1):133-146.

23. de Groot LC, Verheijden MW, de Henauw S, Schroll M, van Staveren WA; SENECA Investigators. Lifestyle, nutritional status, health, and mortality in elderly people across Europe: a review of the longitudinal results of the SENECA study. *J Gerontol A Biol Sci Med Sci*. 2004;59(12):1277-1284.

INVITED COMMENTARY

Preclinical Alzheimer Disease

Prevention Holy Grail or Pandora's Box?

By 2050, the number of people with AD and other forms of dementia in the United States and other countries is expected to triple.[1] Given this anticipated dramatic increase in the incidence and prevalence of dementia, the identification of successful prevention and treatment strategies is critical. However, current pharmaceutical treatment of dementia can only modestly improve symptoms, has little benefit regarding the underlying pathophysiologic symptoms of the disease, and has no clear role in primary or secondary prevention, to our knowledge. As a result, current prevention strategies will rely on risk factor identification and modification until disease-modifying agents prove efficacious.

Many recent developments have provided hope for the improved diagnosis, treatment, and prevention of AD. First, several potential risk factor modification strategies for dementia prevention have emerged. If the onset of AD could be delayed by 5 years, the expected prevalence would decrease by greater than 1 000 000 cases.[2] The most promising avenues for prevention include cardiovascular risk reduction, physical and cognitive activity, and depression identification and treatment.[3] Most of these risk factors have been characterized in well-conducted prospective observational studies, and many are being tested in randomized clinical trials, including multidomain trials involving several interventions.

In this issue of the *Archives*, Rusanen et al add to the prevention possibilities in their report that heavy smoking in midlife (ie, mean age of 58 years) is associated with greater risk of dementia diagnoses in late life. The investigators studied a group of Kaiser Permanente Medical Care Program of Northern California members who participated in a midlife health questionnaire and who were still part of the Kaiser Permanente system in late life. Participants with midlife heavy smoking (defined as >2 packs per day) had a nearly 2-fold greater risk of being diagnosed with all-cause dementia, AD, and vascular dementia according to *International Classification of Diseases, Ninth Revision* (*ICD-9*) diagnostic criteria. Importantly, those who described themselves as former smokers at the time of the midlife questionnaire did not have an increased risk of dementia. This finding is consistent with that of a recent study of elderly individuals who have maintained cognitive function throughout late life; cognitive maintainers were more likely to be nonsmokers.[4] In summary, the findings suggest that midlife smoking may increase the risk of developing dementia and imply that quitting may reduce that risk.

Against this backdrop of several biologically plausible and fairly well-studied modifiable risk factors for cognitive decline and dementia comes a controversial consensus report from the recent National Institutes of Health–sponsored State-of-the-Science (SOS) Conference on Preventing Alzheimer's Disease and Cognitive Decline, which concluded that the quality of the evidence for prevention was low.[5] This report reminds us that the field of AD and cognitive decline prevention is just beginning; however, it minimizes the tremendous accomplishments that have occurred, especially in the past decade. The SOS statement recommended several important next steps, most of which will require significant resources from the National Institutes of Health or other committed groups such as the Alzheimer's Association. These suggestions include studying cognition throughout the life course, using