ONLINE FIRST

Impact of Smoking on Cognitive Decline in Early Old Age

The Whitehall II Cohort Study

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Context: Smoking is a possible risk factor for dementia, although its impact may have been underestimated in elderly populations because of the shorter life span of smokers.

Objective: To examine the association between smoking history and cognitive decline in the transition from midlife to old age.

Design: Cohort study.

Setting: The Whitehall II study. The first cognitive assessment was in 1997 to 1999, repeated over 2002 to 2004 and 2007 to 2009.

Participants: Data are from 5099 men and 2137 women in the Whitehall II study, mean age 56 years (range, 44-69 years) at the first cognitive assessment.

Main Outcome Measures: The cognitive test battery was composed of tests of memory, vocabulary, executive function (composed of 1 reasoning and 2 fluency tests), and a global cognitive score summarizing performance across all 5 tests. Smoking status was assessed over the entire study period. Linear mixed models were used to assess the association between smoking history and 10-year cognitive decline, expressed as *z* scores.

Results: In men, 10-year cognitive decline in all tests except vocabulary among never smokers ranged from a quarter to a third of the baseline standard deviation. Faster cognitive decline was observed among current smokers compared with never smokers in men (mean difference in 10-year decline in global cognition=–0.09 [95% CI, –0.15 to –0.03] and executive function=–0.11 [95% CI, –0.17 to –0.05]). Recent ex-smokers had greater decline in executive function (–0.08 [95% CI, –0.14 to –0.02]), while the decline in long-term ex-smokers was similar to that among never smokers. In analyses that additionally took dropout and death into account, these differences were 1.2 to 1.5 times larger. In women, cognitive decline did not vary as a function of smoking status.

Conclusions: Compared with never smokers, middle-aged male smokers experienced faster cognitive decline in global cognition and executive function. In ex-smokers with at least a 10-year cessation, there were no adverse effects on cognitive decline.

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THE NUMBER OF DEMENTIA cases worldwide, estimated at 36 million in 2010, is on the rise and projected to double every 20 years.[1] Smoking is increasingly recognized as a risk factor for dementia in elderly individuals.[2-4] There is also evidence to suggest that its impact on adverse cognitive outcomes, including dementia, may have been underestimated owing to selection effects as a result of greater mortality among smokers in midlife.[5,6] The extent to which smoking increases the risk of cognitive decline remains unclear,[2] as few studies have investigated this association[2,7-15] particularly in nonelderly populations.[7,9,10,13] The fact that smokers have greater risks of respiratory and cardiovascular diseases,[16] both linked to cognitive impairment,[17-19] suggests that they may also experience faster cognitive decline.

Public health messages have led many individuals to give up smoking but the extent to which this change in behavior influences subsequent cognitive decline remains unclear.[2] We previously reported smokers compared with nonsmokers to have poorer memory and greater decline in reasoning over 5 years using 2 waves of data.[7] The aim of the present article was to examine the association between smoking history and decline in multiple domains of cognition using 3 waves of cognitive data, for a total follow-up of 10 years. Smoking status was assessed over a 25-

year period, starting 10 years prior to the first cognitive assessment, allowing us to investigate the impact on cognitive decline of persistent smoking, intermittent smoking, and smoking cessation. A key objective was to take into account the potential bias in the estimates of cognitive decline due to selection effects as a result of mortality or dropout over the follow-up. To do this, we used a method that allows joint modeling of cognitive decline, time to dropout, and time to death.[20-22] A final objective was to examine whether age modifies the association between smoking and cognitive decline.

METHODS

STUDY POPULATION

The Whitehall II study is based on employees of the British Civil Service.[23] At study inception (phase 1, 1985-1988), 10 308 participants (67% men) underwent a clinical examination and completed a self-administered questionnaire. Subsequent phases of data collection have alternated between postal questionnaire alone (phases 2 [1988-1990], 4 [1995-1996], 6 [2001], and 8 [2006]) and postal questionnaire accompanied by a clinical examination (phases 3 [1991-1994], 5 [1997-1999], 7 [2002-2004], and 9 [2007-2009]). Cognitive testing was introduced to the study at phase 5 (age range, 44-69 years) and repeated at phases 7 (age range, 50-74 years) and 9 (age range, 55-80 years). All participants provided written consent and the University College London ethics committee approved this study.

SMOKING

Data on cigarette smoking were collected at phases 1, 2, 3, 5, 7, and 9 using questions on smoking status (current, past, or never), age at which the participant started smoking, average number of cigarettes per day, and ounces of tobacco smoked in hand-rolled cigarettes per week. Ex-smokers reported the age at which they had stopped smoking. The measure of smoking history at phase 5 (to coincide with the first measure of cognition) comprised the following categories: current smoker at phase 5, recent ex-smoker (stopped smoking between phases 1 and 5), long-term ex-smoker (those who stopped before phase 1), and never smoker. We also used data on the number of cigarettes smoked per day to calculate pack-years of smoking (the average number of cigarettes smoked per day/20 × number of years of smoking).

We defined smoking status over the follow-up (phases 5, 7, and 9) as persistent smokers (those smoking at phases 5 and 9), intermittent smokers (quitters who started smoking again), and quitters (stopped smoking after phase 5). Participants corresponding to none of these categories were classified using smoking history defined at phase 5, as described earlier.

COGNITION

Cognitive function was assessed using a battery of 5 tests. Short-term verbal memory was assessed with 20 one- or 2-syllable words presented at 2-second intervals that the participants had 2 minutes to recall in writing. Vocabulary was assessed using the Mill Hill Vocabulary Test,[24] in its multiple-choice format, consisting of a list of 33 stimulus words ordered by increasing difficulty and 6 response choices. Executive function was derived from 3 tests: the timed (10 minutes) Alice Heim 4-I test, which assesses reasoning and is composed of a series of 65 verbal and mathematical reasoning items of increasing difficulty,[25] and 2 measures of verbal fluency, phonemic, which is assessed via *S* words, and semantic fluency, which uses the names of animals.[26] One minute was allowed for each test. The mean of the standardized *z* scores of these 3 tests (mean [SD] = 0 [1]) using the mean and standard deviation from phase 5 was used as the executive function score.

A global cognitive score was created using all 5 tests described earlier by first standardizing the raw scores on each test to *z* scores (mean [SD] = 0 [1]) using the mean and standard deviation at phase 5 in the entire cohort for each test. The *z* scores were then averaged to yield the global cognitive score, seen to minimize problems due to measurement error.[27,28]

COVARIATES AT PHASE 5

Sociodemographic variables included were age, sex, marital status (married/cohabiting vs others), and socioeconomic status using 2 measures: occupational position (high [administrative], intermediate [professional or executive], and low [clerical or support]) and education (less than primary school [until age 11 years], lower secondary school [until age 16 years], higher secondary school [until age 18 years], university, and higher university degree).

Health behaviors included alcohol consumption, assessed via questions on the number of alcoholic drinks ("measures" of spirits, "glasses" of wine, and "pints" of beer) consumed in the last 7 days and categorized as none or less than 1 unit/wk (no alcohol), moderate drinkers (1-14 units/wk in women and 1-21 units/wk in men), and heavy drinkers (≥15 units in women and ≥21 units in men); frequency of fruit and vegetable consumption, assessed using the question "How often do you eat fresh fruit or vegetables?" (responses were on an 8-point scale, ranging from seldom or never to 2 or more times a day); and physical activity, categorized as active (≥2.5 h/wk of moderate or ≥1 h/wk of vigorous physical activity), inactive (<1 h/wk of moderate and <1 h/wk of vigorous physical activity), or moderately active (if not active or inactive).[29]

Health measures included resting heart rate, serum cholesterol level, systolic and diastolic blood pressure, and prevalence of coronary heart disease, stroke, and diabetes mellitus. Resting heart rate was measured via electrocardiogram with participants in the supine position and categorized as less than 60, 60 to 80, and more than 80 beats/min.[30] Blood pressure was measured twice with the participant sitting after a 5-minute rest using the Hawksley random-zero sphygmomanometer. The average of 2 readings was taken to be the measured blood pressure. Fasting serum cholesterol level was measured within 72 hours in serum stored at 4°C using enzymatic colorimetric methods. Coronary heart disease prevalence was based on clinically verified events and included myocardial infarction and definite angina.[31] Stroke was assessed using a self-reported measure of physician diagnosis. Diabetes was defined by a fasting glucose level of 126 mg/dL or more (to convert to millimoles per liter, multiply by 0.0555) or a 2-hour postload glucose level of 200 mg/dL or more or reported physician-diagnosed diabetes or use of diabetes medication.[32]

COVARIATES OVER THE FOLLOW-UP

These included coronary heart disease and incident self-reported stroke from phase 5 to phase 9 and lung function from phases 7 and 9[33] measured using a portable flow spirometer (MicroPlus Spirometer; Micro Medical Ltd) used herein as forced expiratory volume in 1 second.[34]

STATISTICAL ANALYSES

We investigated the association between smoking history and global cognition, memory, vocabulary, and executive func-

tion. To allow comparability across tests, all scores were converted to z scores (mean [SD] = 0 [1]). Linear mixed models[35] were used to estimate the association between the smoking history and 10-year cognitive decline. These models use all available data over the follow-up, handle differences in length of follow-up, and take into account the fact that repeated measures on the same individual are correlated. We fitted both the intercept and slope as random effects, allowing individual differences both in cognitive performance at baseline and rate of cognitive decline. Interaction terms suggested sex differences in the association between smoking history and cognitive decline ($P = .03$ for global cognition, $P = .54$ for memory, $P = .15$ for vocabulary, and $P = .02$ for executive function), leading us to stratify the analyses by sex.

The linear mixed model included terms for time (individual follow-up divided by 10 to yield effects of change over 10 years), age at baseline (centered at 55 years), smoking history at baseline, education, occupational position, marital status, and the interaction of each of the covariates with time (model 1) to take into account the fact that all covariates can influence the rate of cognitive decline. The interaction term between smoking history and time provides the mean difference in the 10-year decline among current smokers, long-term ex-smokers, and recent ex-smokers compared with the never smokers. This model was subsequently expanded to include covariates and their interaction with time: first, other health behaviors and health measures at phase 5 (model 2), then stroke and coronary heart disease as time-dependent variables (model 3), and finally the analyses presented in model 2 were repeated with lung function added as a covariate (model 4).

Using models similar to model 1, we investigated dose-response associations between smoking and cognitive decline using pack-years of smoking (at phase 5) and the association between smoking status over the follow-up and concurrent cognitive change. A 3-way interaction term between age, smoking history, and time was used to assess whether the effect of smoking on cognitive decline differed as a function of age. The results of this analysis are presented graphically to make them easily understandable, with estimates of the regression coefficients from model 1 stratified at 55 years, the median age. In the final set of analyses, we examined the impact of missing data (due to death or dropout) on the estimates of cognitive decline using joint modeling,[20,22] which allowed us to take into account the correlation between cognitive decline, time to dropout, and time to death (eAppendix "Methods" section, http://www.archgenpsychiatry.com).

Several sensitivity analyses were conducted. First, interactions of smoking with education ($P > .43$) and apolipoprotein allele ε4 ($P > .24$) were examined; although both variables were associated with cognitive scores at baseline, they did not influence the association of smoking history with cognitive decline. Second, we repeated the analysis among participants with a Mini-Mental State Examination score of 24 or more at phases 7 and 9 to ensure that the results were not being driven by potential cases of dementia.[36] Finally, we restricted the main analysis to individuals with complete data, that is, those who had cognitive data at all 3 waves. All analyses were performed with SAS, version 9.2 (SAS Institute).

RESULTS

SAMPLE DESCRIPTION AND MISSING DATA

Of the 10 308 participants at phase 1 (1985-1988), 306 had died and 752 had dropped out from the study before the start of the cognitive data collection at phase 5 (1997-1999). Of the 9250 remaining individuals, 7495 participated in 1 or more of the 3 cognitive function assessments over 10 years. All analyses are based on 7236 individuals who had complete data on smoking history and other covariates; this group was similar in age (55.8 vs 56.0 years; $P = .09$) to those not included in the analysis but composed of more men (70.5% vs 58.7%; $P < .001$) and persons from the higher occupational group (33.2% vs 20.3%; $P < .001$). Of those included in the analyses, 973 (13.4%) contributed to 1 wave of cognitive data, 1603 (22.2%) to 2 waves, and 4660 (64.4%) to all 3 waves. Of those included in the analysis, 11.8% had less than primary school education, 35.0% had lower secondary school education, 24.8% had finished school, 20.9% had a university degree, and 7.5% had a postgraduate degree.

Table 1 shows characteristics of study participants as a function of smoking history. Ten-year cognitive decline in men aged 55 years (results not shown) was estimated at –0.34 of the baseline standard deviation (95% CI, –0.35 to –0.32) for global cognition, –0.28 (95% CI, –0.31 to –0.25) for memory, and –0.39 (95% CI, –0.41 to –0.37) for executive function. There was a small improvement in vocabulary scores (0.02; 95% CI, 0.00 to 0.03). The corresponding figures for women were –0.30 (95% CI, –0.33 to –0.28) for global cognition, –0.25 (95% CI, –0.30 to –0.20) for memory, –0.37 (95% CI, –0.40 to –0.34) for executive function, and 0.05 (95% CI, 0.02 to 0.07) for vocabulary. Older individuals experienced faster decline; for example, men (women) aged 65 years compared with 55 years at baseline declined –0.10 (–0.11) of the baseline standard deviation more in global cognition, –0.06 (–0.10) in memory, –0.10 (–0.10) in executive function, and –0.06 (–0.04) in vocabulary.

CROSS-SECTIONAL AND LONGITUDINAL ASSOCIATION AS A FUNCTION OF SMOKING HISTORY

Mean raw baseline cognitive scores and 10-year cognitive change for all 5 cognitive tests are presented in eTable 1. The cross-sectional associations between smoking history and cognitive function at phase 5, estimated from the mixed models (model 1), suggested that long-term ex-smokers had better cognitive scores than never smokers on all tests except memory, in both men and women (eTable 2). **Table 2** shows the estimates of subsequent cognitive change over 10 years derived from the same models. In men, compared with never smokers, current smokers had a greater 10-year decline in global cognition (mean difference in decline = –0.09; 95% CI, –0.15 to –0.03) and executive function (–0.11; 95% CI, –0.17 to –0.05). This effect size was similar to the effect of 10 years of age on cognitive decline. Among recent ex-smokers, decline in executive function (–0.08; 95% CI, –0.14 to –0.02) was faster than among never smokers. Smoking history was not associated with cognitive change in women.

In men, the associations between smoking history and decline in global cognition and executive function were not attenuated after adjustment for other health behaviors and health measures (eTable 3). Entering coronary heart disease and stroke events as time-dependent co-

Table 1. Characteristics of the Population as a Function of Smoking History at Phase 5 (1997-1999)

Phase 5 Characteristics by Sex	Current Smoker	Recent Ex-Smoker	Long-term Ex-Smoker	Never Smoker	*P* Value[a]
No. (%)					
Male	468 (9.2)	408 (8.0)	1825 (35.8)	2398 (47.0)	<.001
Female	262 (12.3)	191 (8.9)	507 (23.7)	1177 (55.1)	
Age, y, mean (SD)					
Male	54.5 (5.6)	55.7 (6.1)	56.2 (5.9)	55.3 (6.1)	<.001
Female	56.5 (5.9)	56.8 (5.9)	56.5 (6.1)	56.0 (6.0)	.15
Married/cohabiting, No. (%)					
Male	331 (70.7)	327 (80.2)	1579 (86.5)	2008 (83.7)	.001
Female	145 (55.3)	117 (61.3)	315 (62.1)	704 (59.8)	.32
High occupational position, No. (%)					
Male	155 (33.1)	182 (44.6)	924 (50.6)	1367 (57.0)	<.001
Female	39 (14.9)	32 (16.8)	123 (24.3)	230 (19.5)	.009
University degree or higher, No. (%)					
Male	93 (19.9)	125 (30.6)	494 (27.1)	918 (38.3)	<.001
Female	22 (8.4)	29 (15.2)	110 (21.7)	263 (22.3)	<.001
Heavy alcohol consumption,[b] No. (%)					
Male	181 (38.7)	146 (35.8)	608 (33.3)	516 (21.5)	<.001
Female	61 (23.3)	37 (19.4)	119 (23.5)	147 (12.5)	<.001
Physically active,[c] No. (%)					
Male	230 (49.2)	242 (59.3)	1126 (61.7)	1434 (59.8)	<.001
Female	75 (28.6)	83 (43.5)	219 (43.2)	418 (35.5)	<.001
Daily consumption of fruits and vegetables, No. (%)					
Male	244 (52.1)	282 (69.1)	1329 (72.8)	1747 (72.9)	<.001
Female	114 (56.5)	3154 (80.6)	398 (78.5)	944 (80.2)	<.001
Heart rate >80 beats/min, No. (%)					
Male	72 (15.4)	68 (16.7)	238 (13.0)	313 (13.1)	.05
Female	25 (9.5)	33 (17.3)	85 (16.8)	193 (16.4)	.03
SBP, mm Hg, mean (SD)					
Male	123.1 (15.0)	125.6 (17.0)	125.0 (15.9)	123.1 (15.9)	<.001
Female	119.8 (17.2)	121.8 (17.6)	122.6 (17.2)	122.8 (17.5)	.09
DBP, mm Hg, mean (SD)					
Male	77.4 (9.9)	79.4 (11.4)	79.0 (10.1)	78.5 (10.6)	.01
Female	73.4 (9.6)	74.5 (10.5)	75.7 (9.9)	75.7 (10.2)	.005
Cholesterol level, mg/dL, mean (SD)					
Male	231.7 (42.5)	235.5 (46.3)	231.7 (38.6)	223.9 (38.6)	<.001
Female	235.5 (38.6)	231.7 (38.6)	235.5 (42.5)	231.7 (42.5)	.40
Prevalence of CHD, No. (%)					
Male	24 (6.4)	101 (6.3)	28 (7.8)	24 (6.4)	.15
Female	12 (4.6)	17 (8.9)	19 (3.8)	70 (6.0)	.04
Prevalence of diabetes mellitus, No. (%)					
Male	35 (7.5)	37 (9.1)	106 (5.8)	123 (5.1)	.007
Female	6 (2.3)	16 (8.4)	37 (7.3)	87 (7.4)	.02
Prevalence of stroke, No. (%)					
Male	5 (1.1)	7 (1.7)	16 (0.9)	28 (1.2)	.50
Female	2 (0.8)	2 (1.1)	8 (1.6)	4 (0.3)	.06

Abbreviations: CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.
SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.
[a] *P* for heterogeneity.
[b] Heavy alcohol consumption was defined as 15 units/wk or more in women and 21 units/wk or more in men.
[c] Corresponds to more than 2.5 h/wk of moderate physical activity or more than 1 h/wk of vigorous physical activity.

variates did not change these results (eTable 4). In men with data on lung function (n=4100), adjustment for the mean forced expiratory volume in 1 second over the follow-up (phases 7 and 9) also did not reduce the association (results not shown).

Analysis using pack-years of smoking in men showed that for every 10 pack-years there was greater decline in global cognition (mean 10-year cognitive decline=–0.009; 95% CI, –0.017 to –0.001) and executive function (–0.010; 95% CI, –0.019 to –0.001). No association with pack-years of smoking was observed in women.

SMOKING STATUS OVER THE FOLLOW-UP AND CONCURRENT COGNITIVE CHANGE

In men, compared with never smokers, persistent smokers over the follow-up were more likely to show faster decline in global cognition (–0.12; 95% CI, –0.19 to –0.04), memory (–0.15; 95% CI, –0.29 to –0.01), and executive function (–0.11; 95% CI, –0.20 to –0.03) (**Table 3**). Intermittent smokers also had greater decline in global cognition (–0.10; 95% CI, –0.20 to 0.00). The 168 men who stopped smoking after phase 5 did not show greater cognitive decline than the never smokers

Table 2. Association of Smoking History at Phase 5 (1997-1999) and Cognitive Change Over the Subsequent 10 Years[a]

	Sample Size	Cognitive Change Over 10 Years, Coefficient (95% CI)			
		Global Cognition	Memory	Vocabulary	Executive Function
Men (n = 5099)					
Current smokers	468	−0.09 (−0.15 to −0.03)[b]	−0.05 (−0.16 to 0.06)	−0.04 (−0.09 to 0.01)	−0.11 (−0.17 to −0.05)[b]
Recent ex-smokers	408	−0.04 (−0.09 to 0.02)	0.04 (−0.07 to 0.15)	0.00 (−0.05 to 0.05)	−0.08 (−0.14 to −0.02)[b]
Long-term ex-smokers	1825	0.00 (−0.03 to 0.03)	−0.05 (−0.11 to 0.02)	0.00 (−0.03 to 0.02)	0.02 (−0.02 to 0.05)
Never smokers	2398	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Estimates in never smokers	2398	−0.32 (−0.35 to −0.29)	−0.24 (−0.29 to −0.18)	0.02 (0.00 to 0.05)	−0.37 (−0.41 to −0.34)
Women (n = 2137)					
Current smokers	262	0.03 (−0.05 to 0.12)	0.04 (−0.14 to 0.21)	0.02 (−0.06 to 0.10)	0.03 (−0.06 to 0.12)
Recent ex-smokers	191	0.01 (−0.08 to 0.10)	−0.03 (−0.22 to 0.16)	0.00 (−0.08 to 0.09)	0.04 (−0.07 to 0.14)
Long-term ex-smokers	507	−0.01 (−0.07 to 0.05)	−0.01 (−0.14 to 0.11)	−0.02 (−0.07 to 0.04)	0.00 (−0.07 to 0.07)
Never smokers	1177	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Estimates in never smokers	1177	−0.28 (−0.33 to −0.23)	−0.24 (−0.34 to −0.14)	0.04 (0.00 to 0.09)	−0.35 (−0.40 to −0.30)

[a] Estimates from a mixed model adjusted for educational level (ordinal variable, 5 levels), occupational position (categorical variable, 3 levels), marital status, and age at baseline. A negative value for cognitive change corresponds to a higher decline compared with that in the never smokers.
[b] $P < .05$.

Table 3. Association Between Smoking Status Over the Follow-Up[a] and 10-Year Cognitive Change[b]

	Sample Size	Cognitive Change Over 10 Years, Coefficient (95% CI)			
		Global Cognition	Memory	Vocabulary	Executive Function
Men (n = 4800)					
Persistent smokers	240	−0.12 (−0.19 to −0.04)[c]	−0.15 (−0.29 to −0.01)[c]	−0.04 (−0.10 to 0.03)	−0.11 (−0.20 to −0.03)[c]
Intermittent smokers	106	−0.10 (−0.20 to 0.00)[c]	−0.16 (−0.36 to 0.04)	0.00 (−0.08 to 0.09)	−0.10 (−0.21 to 0.01)
Quitters after phase 5	168	−0.04 (−0.13 to 0.03)	0.08 (−0.08 to 0.24)	0.08 (−0.09 to 0.25)	−0.08 (−0.17 to 0.01)
Never smokers	2242	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Estimates in never smokers	2242	−0.32 (−0.35 to −0.29)	−0.24 (−0.30 to −0.18)	0.02 (−0.01 to 0.04)	−0.38 (−0.41 to −0.35)
Women (n = 1993)					
Persistent smokers	128	0.01 (−0.11 to 0.12)	0.09 (−0.15 to 0.33)	0.03 (−0.08 to 0.14)	−0.03 (−0.15 to 0.09)
Intermittent smokers	16	−0.36 (−0.69 to −0.04)[c]	−0.53 (−1.21 to 0.15)	−0.23 (−0.54 to 0.09)	−0.20 (−0.56 to 0.17)
Quitters after phase 5	100	0.05 (−0.07 to 0.16)	−0.08 (−0.32 to 0.16)	0.00 (−0.11 to 0.10)	0.08 (−0.04 to 0.21)
Never smokers	1104	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Estimates in never smokers	1104	−0.29 (−0.34 to −0.24)	−0.26 (−0.36 to −0.15)	0.04 (0.00 to 0.09)	−0.36 (−0.41 to −0.30)

[a] Smoking status at phase 9 is defined as persistent smokers (smokers at both phases 5 and 9), intermittent smokers (ex-smokers at phase 5 and current smokers at phase 9), and quitters (current smokers at phase 5 and ex-smokers at phase 9). If participants dropped out at phase 7, smoking status at phase 7 was used in the analysis using a similar definition. Participants without information on smoking status at phases 7 or 9 were excluded from this analysis (299 men and 144 women). Results among ex-smokers at both phases 5 and 9 are not shown.
[b] Estimates from a mixed model adjusted for educational level (ordinal variable, 5 levels), occupational position (categorical variable, 3 levels), marital status, and age at baseline.
[c] $P < .05$.

but their decline was not statistically different from that in persistent smokers ($P = .21$ for global cognition, $P = .71$ for memory, $P = .43$ for vocabulary, and $P = .36$ for executive function). In women, there was no evidence of an association.

SMOKING HISTORY AT PHASE 5 AND COGNITIVE DECLINE AS A FUNCTION OF AGE IN MEN

The interaction term between age (continuous variable) at baseline, smoking, and time suggested differences in the effect of smoking for global cognition ($P = .08$) and executive function ($P = .04$) as a function of age. These findings are summarized in **Figure 1**, which shows the analyses reported in Table 2 (differences in cognitive decline between the smoking history categories with the never smokers as the reference group) but stratified by median age (55 years). There was some evidence that the impact of smoking on cognitive decline was weaker in the older group.

JOINT MODELS

These analyses assessed the effect of dropout, due to death or nonparticipation during the follow-up, on the association between smoking history and cognitive decline (eAppendix "Results" section). Joint model estimates of cognitive change were around 10% higher than those using mixed models alone, with larger differences seen in current smokers than in never smokers (**Figure 2**). The relative differences between the estimates from the mixed model and the joint models were more evident in the oldest group (>55 years), with estimates being 100% stronger in the joint models in this age group compared with 17% stronger in the youngest group.

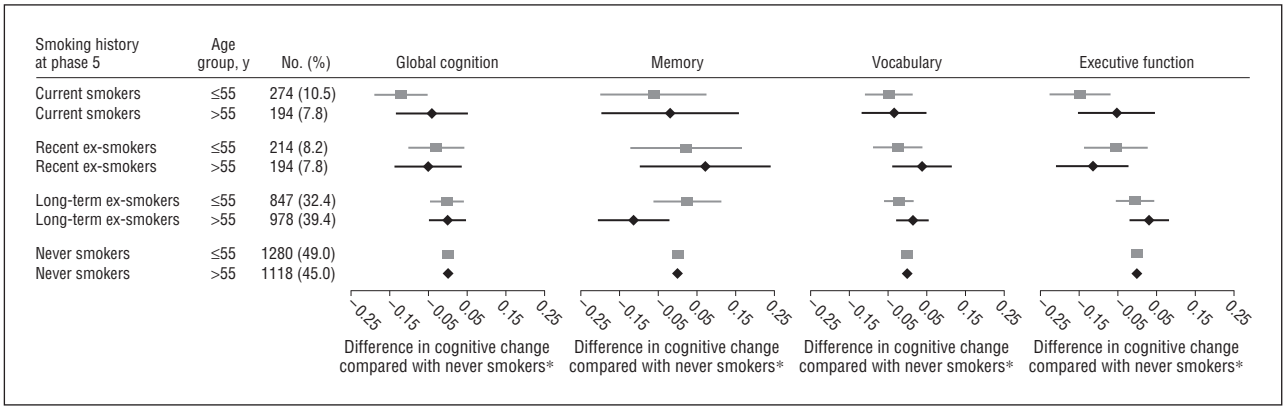

Figure 1. Association between smoking history at phase 5 and cognitive change over the subsequent 10 years in men as a function of age group (reference group: never smokers). *Estimates were obtained from model 1 (results in Table 2) but this time separately in men 55 years or younger (squares) and older than 55 years (diamonds). For example, current smokers 55 years or younger experienced an additional decline in global cognition of –0.12 (95% CI, –0.19 to –0.05) with respect to never smokers in the same age group. The corresponding figure for participants older than 55 years was –0.04 (95% CI, –0.13 to 0.05).

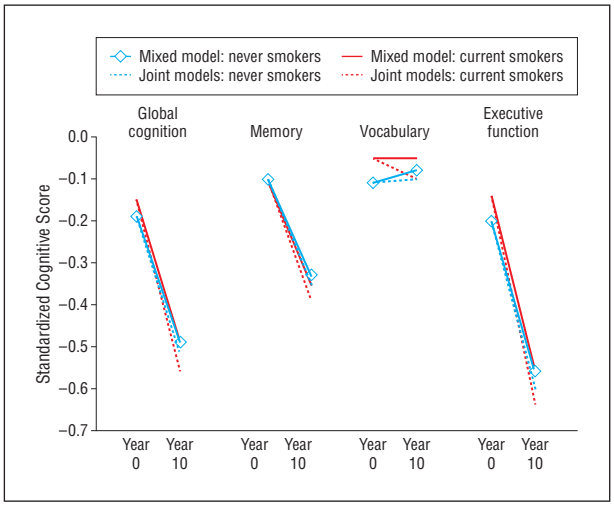

Figure 2. Mixed and joint models showing standardized cognitive scores at baseline and 10-year cognitive decline in current and never smokers at phase 5 (1997-1999).

SENSITIVITY ANALYSES

Analyses restricted to those with a Mini-Mental State Examination score of 24 or more (n=7165) or those with complete data at all 3 waves of cognitive data yielded results similar to that in the main analysis (not shown).

COMMENT

Our analysis of data using 6 assessments of smoking status over 25 years and 3 cognitive assessments over 10 years presents 4 key findings. One, in men, smoking was associated with faster cognitive decline; analyses using pack-years of smoking suggested a dose-response relation. Two, men who continued smoking over the follow-up experienced greater decline in all cognitive tests. Three, men who quit smoking in the 10 years preceding the first cognitive measure were still at risk of greater cognitive decline, particularly in executive function. However, long-term ex-smokers did not show faster cognitive decline. Finally, our results show that the association between smoking and cognition, particularly at older ages, is likely to be underestimated owing to higher risk of death and dropout among smokers.

Our previous article,[7] based on data from the first 2 waves of cognitive assessment, showed smoking in midlife to be associated with poor memory and a 5-year decline in reasoning abilities. We also showed long-term ex-smokers to have better memory and verbal fluency scores than never smokers. In the present article, the third wave of cognitive data allowed us to (1) estimate the association between smoking history and 10-year cognitive decline; (2) cover an age window from 45 to 80 years; and (3) use mixed models with multiple repeated measures rather than analysis of change using 2 waves of data. The third measurement reduces potential biases related to practice effects and regression to the mean, which are particularly encountered in studies with only 2 measurements.[37-39] Thus, the present analyses provide more robust estimates of the impact of smoking on cognitive decline.

COMPARISON WITH OTHER STUDIES

At least 4 previous studies[7,9,10,13] have examined the association between smoking and cognitive decline with cognition first assessed in midlife. In the 1946 British National Birth Cohort study,[13] smoking was associated with a greater decline in memory but not visual search. In the Doetinchem Cohort Study,[10] smokers had faster decline in memory, cognitive flexibility, and global cognition, but not processing speed. Finally, the ARIC MRI Study, the only other study, to our knowledge, with more than 2 waves of cognitive data in a nonelderly population,[9] did not find smoking to influence cognitive decline. One possible explanation for the lack of association in the ARIC MRI Study is that the study population was composed mainly of women (62% of the total population). Our results show no association between smoking and cognitive decline in women, but the underlying reasons remain unclear. Some studies have reported sex differences in this association,[13,40] while others report no differences.[10,15] One explanation for the sex difference we observed might be the greater quantity of tobacco smoked

by men.[40] Indeed, the mean pack-years of smoking (36 vs 31; $P = .05$) as well as the number of cigarettes smoked (19 vs 16; $P = .007$) were higher in men than women. It is also possible that smoking clusters with other risk factors differently in men and women. Alcohol consumption greater than the recommended quantities was seen in 38.7% of male and 23.3% of female smokers; mean alcohol consumption in smokers was considerably higher in men than in women (23.0 vs 9.6 units/wk; $P < .001$). Future research needs to explore possible reasons for these differences.

Few observational studies have distinguished long-term ex-smokers from recent ex-smokers. In the 1946 British National Birth Cohort study,[13] long-term ex-smokers had better memory and slower decline in memory compared with never smokers, but in the Honolulu-Asia Aging study,[41] 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. In the Doetinchem Cohort Study,[10] no difference was found between recent ex-smokers, long-term ex-smokers, and never smokers, although the point estimates of decline increased steadily from never smokers to long-term ex-smokers, then to recent ex-smokers and smokers. Our results show that long-term ex-smokers did not have greater cognitive decline than never smokers while male recent ex-smokers had on average greater decline in executive function than never smokers. These results suggest that residual effects of smoking on cognition might wear off approximately a decade after smoking cessation. A recent nonrandomized trial[42] of smoking cessation on 95 nonsmokers and 228 smokers aged 68 to 88 years found recent quitters (defined as a minimum of 18 smoking-free months over the 24-month period of follow-up) not to have greater cognitive decline than never smokers. The discrepancy with our results might be explained by factors such as the older and smaller study population in the trial as well as the use of a cognitive test battery (the Wechsler Memory Scale Logical Memory test and the Alzheimer's Disease Assessment Scale) designed to assess changes in memory and symptoms of Alzheimer disease.

MECHANISMS

In the present study, the adverse impact of smoking was greater on executive function than memory or vocabulary. *Executive function*, an umbrella term for various complex cognitive processes involved in achieving a particular goal,[43] has been shown to be particularly affected in vascular dementia.[44] We assessed executive function using measures of reasoning and verbal fluency, as these tasks require the combination of different cognitive abilities such as memory, attention, and speed of information processing.[25,26] Smoking is an important risk factor for vascular diseases[45] and could influence executive function via vascular pathways. Nevertheless, the inclusion of heart rate (a marker of cardiovascular fitness),[46] cardiovascular diseases, and cardiovascular risk factors such as blood pressure and cholesterol in the analysis did not attenuate the association with smoking. Although the mechanisms by which smoking affects cognitive decline remain unclear, it has been shown to be associated with periventricular and subcortical white matter lesion progression, themselves associated with greater cognitive decline,[47] independently of other cardiovascular risk factors.

Another mechanism that could underlie the association between smoking and cognitive decline is lung function.[8] Smoking is a risk factor for lung injuries[16] that can increase risk of cognitive impairment and dementia.[17,18] However, the association between smoking and cognitive decline in our study was not explained by lung function, measured by forced expiratory volume in 1 second. Because this measure was introduced only 5 years after the first cognitive assessment, further research is required to examine this potential mechanism in greater detail.

INFLUENCE OF DROPOUT

In longitudinal studies, dropout is common and death is also a cause of sample attrition, particularly in older populations. Dropout is a potential source of bias if it is nonrandom, in that it is associated with either the exposure and/or the outcome under investigation, independently of observed data. Individuals who drop out are more likely to have health problems and experience greater cognitive decline.[48,49] Smoking history in our data was associated with both mortality and dropout during the follow-up, suggesting that cognitive decline may be underestimated among smokers. Our results from the joint models of cognitive decline and dropout are consistent with this possibility; the estimated differences in cognitive change between current smokers and never smokers were 1.2 to 1.5 times larger than those from the mixed models. Furthermore, in older men, mixed models suggested weaker association between smoking and cognitive decline compared with the younger group. These estimates increased by up to 100% when information on dropouts was included in the joint models, thus reducing the apparent difference between the younger and older men in the association between smoking and cognitive decline. These results illustrate the selection biases encountered in studies investigating the association between smoking, a strong risk factor for mortality, and cognitive aging in the elderly population.[5,6] Indeed, such studies have led to speculation as to whether smoking is a risk factor for dementia or whether nicotine has a protective effect on the brain.[5] This confusion stems from the fact that smokers susceptible of dying or developing dementia may already have done so by the age of inclusion in aging studies, and thus, the group of elderly participants free of dementia at baseline in aging studies is depleted of susceptible smokers.[5] Our results on cognitive decline in a nonelderly population might therefore better capture the potential impact of smoking on cognitive function. Further research on elderly populations, possibly even reanalysis of published data, using joint models is needed to understand the impact of smoking on cognitive decline.

LIMITATIONS

Our study has limitations. First, although the sample covered a wide socioeconomic range, with annual full-time

salaries ranging from £4995 to £150 000 (US $7824-$234 954), data are from white-collar civil servants and cannot be assumed to be representative of the general population, particularly the unemployed or blue-collar workers. Second, smoking was self-reported and is likely to have been underreported. Third, we could not ascertain dementia cases, and the extent to which this impacts our results is unclear but our findings regarding stronger relations before age 55 years, when dementia is exceptional, suggest that dementia might not influence the results. The fourth limitation relates to the cognitive tests being dependent on writing speed. Finally, the method we used to model jointly the longitudinal cognitive change, the time to dropout, and the time to death[20] is not yet widely used and makes assumptions that cannot be tested using observed data such as the jointly multivariate gaussian random effects.[50] Other methods to take into account missing data may not produce the same estimate of cognitive decline.[51] The extent to which estimates of cognitive decline vary as a function of the method used to correct for dropout remains unclear. Nevertheless, the differences seen between the estimates from mixed models and the joint models can be reliably used to conclude that nonresponse leads to underestimation of the impact of smoking on cognitive decline.

IMPLICATIONS

Much research on uncovering risk factors for dementia or adverse cognitive aging profiles has been carried out in elderly populations. It is increasingly recognized that age-related cognitive pathologies such as dementia result from long-term processes, perhaps beginning as long as 20 to 30 years before the clinical diagnosis of dementia.[1,52] Our study illustrates the importance of examining risk factors for cognitive decline much earlier in the life course. However, cognitive tests and age-specific norms for detecting "abnormal" cognitive decline do not yet exist. Thus, it is difficult to quantify the clinical significance of our findings. We observe that the effect size associated with smoking is similar to that associated with 10 years of age. The extent to which the steeper cognitive trajectories observed in smokers will lead to dementia later in life cannot yet be addressed using our data and is an important research question.

Our results show that, compared with never smokers, middle-aged male smokers are likely to experience faster 10-year cognitive decline in global cognition and executive function. Intermittent smokers and recent exsmokers also exhibited greater cognitive decline, although no residual adverse effect of smoking on cognitive decline was observable in the group of men who stopped smoking 10 years prior to cognitive testing. Public health messages on smoking should continue to target smokers at all ages.

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REFERENCES

1. World Alzheimer Report 2009. Alzheimer's Disease International Web site. http://www.alz.co.uk/research/world-report. Accessed October 5, 2011.
2. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol*. 2007;166(4):367-378.
3. Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. *BMC Geriatr*. 2008;8:36.
4. Rusanen M, Kivipelto M, Quesenberry CP Jr, Zhou J, Whitmer RA. Heavy smoking in midlife and long-term risk of Alzheimer disease and vascular dementia. *Arch Intern Med*. 2011;171(4):333-339.
5. Hernán MA, Alonso A, Logroscino G. Cigarette smoking and dementia: potential selection bias in the elderly. *Epidemiology*. 2008;19(3):448-450.
6. Elbaz A, Alpérovitch A. Bias in association studies resulting from gene-environment interactions and competing risks. *Am J Epidemiol*. 2002;155(3):265-272.
7. Sabia S, Marmot M, Dufouil C, Singh-Manoux A. Smoking history and cognitive function in middle age from the Whitehall II study. *Arch Intern Med*. 2008;168(11):1165-1173.
8. Collins N, Sachs-Ericsson N, Preacher KJ, Sheffield KM, Markides K. Smoking increases risk for cognitive decline among community-dwelling older Mexican Americans. *Am J Geriatr Psychiatry*. 2009;17(11):934-942.
9. Knopman DS, Mosley TH, Catellier DJ, Coker LH; Atherosclerosis Risk in Communities Study Brain MRI Study. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement*. 2009;5(3):207-214.
10. Nooyens AC, van Gelder BM, Verschuren WM. Smoking and cognitive decline among middle-aged men and women: the Doetinchem Cohort Study. *Am J Public Health*. 2008;98(12):2244-2250.
11. Ott A, Andersen K, Dewey ME, Letenneur L, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A, Launer LJ; EURODEM Incidence Research Group. Effect of smoking on global cognitive function in nondemented elderly. *Neurology*. 2004;62(6):920-924.
12. Reitz C, Luchsinger J, Tang MX, Mayeux R. Effect of smoking and time on cognitive function in the elderly without dementia. *Neurology*. 2005;65(6):870-875.
13. Richards M, Jarvis MJ, Thompson N, Wadsworth ME. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. *Am J Public Health*. 2003;93(6):994-998.

14. Peters R, Beckett N, Geneva M, Tzekova M, Lu FH, Poulter R, Gainsborough N, Williams B, de Vernejoul MC, Fletcher A, Bulpitt C. Sociodemographic and lifestyle risk factors for incident dementia and cognitive decline in the HYVET. *Age Ageing*. 2009;38(5):521-527.
15. Yaffe K, Fiocco AJ, Lindquist K, Vittinghoff E, Simonsick EM, Newman AB, Satterfield S, Rosano C, Rubin SM, Ayonayon HN, Harris TB; Health ABC Study. Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology*. 2009;72(23):2029-2035.
16. The 2004 United States Surgeon General's Report: the health consequences of smoking. *N S W Public Health Bull*. 2004;15(5-6):107.
17. Pathan SS, Gottesman RF, Mosley TH, Knopman DS, Sharrett AR, Alonso A. Association of lung function with cognitive decline and dementia: the Atherosclerosis Risk in Communities (ARIC) Study. *Eur J Neurol*. 2011;18(6):888-898.
18. Singh-Manoux A, Dugravot A, Kauffmann F, Elbaz A, Ankri J, Nabi H, Kivimaki M, Sabia S. Association of lung function with physical, mental and cognitive function in early old age. *Age (Dordr)*. 2011;33(3):385-392.
19. Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, Kelly-Hayes M, Wolf PA. Dementia after stroke: the Framingham Study. *Stroke*. 2004;35(6):1264-1268.
20. Diggle P, Henderson R, Philipson P. Random-effects models for joint analysis of repeated-measurement and time-to-event outcomes. In: Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, eds. *Longitudinal Data Analysis*. London, England: Chapman & Hall/CRC; 2009:349-366.
21. Guo X, Carlin BP. Separate and joint modeling of longitudinal and event time data using standard computer packages. *Am Stat*. 2004;58(1):16-24. doi:10.1198/0003130042854.
22. Henderson R, Diggle P, Dobson A. Joint modelling of longitudinal measurements and event time data. *Biostatistics*. 2000;1(4):465-480.
23. Marmot M, Brunner E. Cohort profile: the Whitehall II study. *Int J Epidemiol*. 2005;34(2):251-256.
24. Raven JC. *Guide to Using the Mill Hill Vocabulary Test With Progressive Matrices*. London, England: HK Lewis; 1965.
25. Heim AW. *AH 4 Group Test of General Intelligence*. Windsor, England: NFER-Nelson Publishing Co Ltd; 1970.
26. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologica*. 1967;5(2):135-140. doi:10.1016/0028-3932(67)90015-2.
27. Wilson RS, Leurgans SE, Boyle PA, Schneider JA, Bennett DA. Neurodegenerative basis of age-related cognitive decline. *Neurology*. 2010;75(12):1070-1078.
28. Arvanitakis Z, Grodstein F, Bienias JL, Schneider JA, Wilson RS, Kelly JF, Evans DA, Bennett DA. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. *Neurology*. 2008;70(23):2219-2225.
29. Stringhini S, Sabia S, Shipley M, Brunner E, Nabi H, Kivimaki M, Singh-Manoux A. Association of socioeconomic position with health behaviors and mortality. *JAMA*. 2010;303(12):1159-1166.
30. Fuster V, Rydén LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, Halperin JL, Kay GN, Klein WW, Lévy S, McNamara RL, Prystowsky EN, Wann LS, Wyse DG, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC, Klein WW, Alonso-Garcia A, Blomström-Lundqvist C, De Backer G, Flather M, Hradec J, Oto A, Parkhomenko A, Silber S, Torbicki A; American College of Cardiology/American Heart Association/European Society of Cardiology Board. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol*. 2001;38(4):1231-1266.
31. Ferrie JE, Langenberg C, Shipley MJ, Marmot MG. Birth weight, components of height and coronary heart disease: evidence from the Whitehall II study. *Int J Epidemiol*. 2006;35(6):1532-1542.
32. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26(suppl 1):S5-S20.
33. Sabia S, Shipley M, Elbaz A, Marmot M, Kivimaki M, Kauffmann F, Singh-Manoux A. Why does lung function predict mortality? results from the Whitehall II Cohort Study. *Am J Epidemiol*. 2010;172(12):1415-1423.
34. Hayes D Jr, Kraman SS. The physiologic basis of spirometry. *Respir Care*. 2009;54(12):1717-1726.
35. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974.
36. Anstey KJ, Burns RA, Birrell CL, Steel D, Kiely KM, Luszcz MA. Estimates of probable dementia prevalence from population-based surveys compared with dementia prevalence estimates based on meta-analyses. *BMC Neurol*. 2010;10:62.
37. Clarke PS. Analysing change based on two measures taken under different conditions. *Stat Med*. 2005;24(22):3401-3415.
38. Dugravot A, Guéguen A, Kivimaki M, Vahtera J, Shipley M, Marmot MG, Singh-Manoux A. Socioeconomic position and cognitive decline using data from two waves: what is the role of the wave 1 cognitive measure? *J Epidemiol Community Health*. 2009;63(8):675-680.
39. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? an example with education and cognitive change. *Am J Epidemiol*. 2005;162(3):267-278.
40. Stewart MC, Deary IJ, Fowkes FG, Price JF. Relationship between lifetime smoking, smoking status at older age and human cognitive function. *Neuroepidemiology*. 2006;26(2):83-92.
41. Galanis DJ, Petrovitch H, Launer LJ, Harris TB, Foley DJ, White LR. Smoking history in middle age and subsequent cognitive performance in elderly Japanese-American men: the Honolulu-Asia Aging Study. *Am J Epidemiol*. 1997;145(6):507-515.
42. Almeida OP, Garrido GJ, Alfonso H, Hulse G, Lautenschlager NT, Hankey GJ, Flicker L. 24-Month effect of smoking cessation on cognitive function and brain structure in later life. *Neuroimage*. 2011;55(4):1480-1489.
43. Elliott R. Executive functions and their disorders. *Br Med Bull*. 2003;65:49-59.
44. Desmond DW. The neuropsychology of vascular cognitive impairment: is there a specific cognitive deficit? *J Neurol Sci*. 2004;226(1-2):3-7.
45. Cardiovascular diseases (CVDs). World Health Organization Web site. http://www.who.int/mediacentre/factsheets/fs317/en/. Published February 2007. Accessed October 5, 2011.
46. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346(11):793-801.
47. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke*. 2008;39(10):2712-2719.
48. Tyas SL, Tate RB, Wooldrage K, Manfreda J, Strain LA. Estimating the incidence of dementia: the impact of adjusting for subject attrition using health care utilization data. *Ann Epidemiol*. 2006;16(6):477-484.
49. Euser SM, Schram MT, Hofman A, Westendorp RG, Breteler MM. Measuring cognitive function with age: the influence of selection by health and survival. *Epidemiology*. 2008;19(3):440-447.
50. Diggle PJ, Sousa I, Chetwynd AG. Joint modelling of repeated measurements and time-to-event outcomes: the fourth Armitage lecture. *Stat Med*. 2008;27(16):2981-2998.
51. Kurland BF, Johnson LL, Egleston BL, Diehr PH. Longitudinal data with follow-up truncated by death: match the analysis method to research aims. *Stat Sci*. 2009;24(2):211.
52. Launer LJ. The epidemiologic study of dementia: a life-long quest? *Neurobiol Aging*. 2005;26(3):335-340.