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Meta-Analysis

Smoking as a Risk Factor for Dementia and Cognitive Decline: A Meta-Analysis of Prospective Studies

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The authors assessed the association of smoking with dementia and cognitive decline in a meta-analysis of 19 prospective studies with at least 12 months of follow-up. Studies included a total of 26,374 participants followed for dementia for 2–30 years and 17,023 participants followed up for 2–7 years to assess cognitive decline. Mean study age was 74 years. Current smokers at baseline, relative to never smokers, had risks of 1.79 (95% confidence interval (CI): 1.43, 2.23) for incident Alzheimer's disease, 1.78 (95% CI: 1.28, 2.47) for incident vascular dementia, and 1.27 (95% CI: 1.02, 1.60) for any dementia. Compared with those who never smoked, current smokers at baseline also showed greater yearly declines in Mini-Mental State Examination scores over the follow-up period (effect size (β) = −0.13, 95% CI: −0.18, −0.08). Compared with former smokers, current smokers at baseline showed an increased risk of Alzheimer's disease (relative risk = 1.70, 95% CI: 1.25, 2.31) and an increased decline in cognitive abilities (effect size (β) = −0.07, 95% CI: −0.11, −0.03), but the groups were not different regarding risk of vascular dementia or any dementia. The authors concluded that elderly smokers have increased risks of dementia and cognitive decline.

Alzheimer disease; cognition; dementia, vascular; meta-analysis; smoking

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; RR, relative risk.

The association between smoking and risk of dementia, including Alzheimer's disease, remains unclear. Early research found that nicotine improves short-term cognitive performance (1) and inhibits amyloid formation (2). This finding suggested that smoking may be protective against dementia and that nicotine may be cognitively enhancing. More recently, this evidence has been questioned and claims made that the known negative effect of smoking on cardiovascular disease means that it is likely to be a risk factor for vascular dementia (3). Because of the increasing prevalence of dementia and the high associated burden of disease, morbidity, and disability (1), there is an urgent need to clearly identify modifiable risk factors, such as smoking, for cognitive decline and dementia.

In 2002, a systematic review of 21 case-control and eight cohort studies examining smoking as a risk factor for Alzheimer's disease found conflicting results regarding the direction of the association (4). Case-control studies suggested that smoking is protective (odds ratio = 0.74, 95 percent confidence interval (CI): 0.66, 0.84), whereas the pooled effect for the cohort studies showed an opposite effect (relative risk (RR) = 1.10, 95 percent CI: 0.94, 1.29), with a strong significant association between smoking and increased risk of Alzheimer's disease for participants who were smokers at baseline and had developed Alzheimer's disease at follow-up (RR = 1.99, 95 percent CI: 1.33, 2.98). The latter finding was based on only two studies that used true prospective cohort designs examining incidence of dementia. In addition, the review examined a diagnosis of Alzheimer's disease as the single outcome despite the putative connection between smoking and vascular dementia.

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TABLE 1. Definitions of outcomes for inclusion in the meta-analysis of smoking as a risk factor for dementia and cognitive decline

Outcome	Example criteria used in studies*
Alzheimer's disease	NINCDS-ADRDA† (50) and DSM-III-R† (51) criteria. Probable Alzheimer's disease is diagnosed if there is a progressive dementing disorder in middle or late adulthood, usually with insidious onset, and other systemic or brain diseases have been excluded. A medical history; neurological, psychiatric, and clinical examination; and neuropsychological and laboratory tests are used to make the diagnosis. (12–14)
Vascular dementia	NINDS-AIREN† criteria (52). Dementia must be reasonably related to cerebrovascular disease, with evidence demonstrated by history, clinical examination, or neuroimaging. (13, 15)
Any dementia	Dementia defined by DSM-III-R criteria (51), including Alzheimer's disease, vascular dementia, dementia with Lewy bodies (53), frontotemporal dementia (54), Pick's disease, alcohol-related dementia, and mixed (55) and other dementias. (15)
Cognitive performance at follow-up	Cognitive performance at follow-up must be adjusted for cognitive performance at baseline. (37)
Cognitive performance change	Difference in cognitive performance between baseline and follow-up. (15, 27, 29)
Cognitive decline	Sample dichotomized into cognitive decliners and nondecliners according to change in cognitive performance between baseline and follow-up. (23, 26, 29)
Cognitive impairment	Sample dichotomized into cognitively impaired and cognitively intact at follow-up according to a cognitive performance cutoff point. Cases of cognitive impairment at baseline must be excluded. (22, 25, 28)

* Parenthetical number(s) at the end of each row, sample reference(s) for more information.

† NINCDS-ADRDA; National Institute of Neurological and Communication Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; DSM-III-R; *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; NINDS-AIREN, National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences [International Association for Research and Education in Neuroscience].

To date, there has been no known systematic review of longitudinal studies of smoking as a risk factor for the range of cognitive decline and dementias that occur in aging. When such studies associate exposure at baseline with incident dementia, and cognitive decline at follow-up, they provide information at much lower risk of bias compared with case-control studies and historical cohort studies. The growing number of reports from large-scale longitudinal studies of cognitive function and dementia now offer the opportunity to conduct such a review and to provide a stronger quantitative assessment of the effect of smoking on dementia and cognitive decline. The aim of this review was to quantitatively evaluate the association of self-reported smoking with incident dementia and cognitive decline.

MATERIALS AND METHODS

Literature search

Electronic databases including PubMed (National Library of Medicine, Bethesda, Maryland; 1950 to June 2005), PsycINFO (American Psychological Association, Washington, DC; 1872 to June 2005), and Cochrane CENTRAL (John Wiley & Sons, Inc., Hoboken, New Jersey; 1800 to June 2005) were searched. The search used a combination of keywords for smoking (smoking, tobacco, nicotine) and cognition (cognit*, memory, attention, reaction time, processing speed, crystalli#ed ability, crystalli#ed intelligence, fluid ability, fluid intelligence, general mental ability OR GMA, intelligence, executive function, neuropsychological test*, mini mental state examination OR MMSE, dementia, mild cognitive impairment OR MCI), where * indicates truncation and # indicates wild card. The search was limited to English language and human studies only. Reference lists of selected publications were also hand searched for any other relevant articles.

Inclusion and exclusion criteria

To be included, studies had to have at least two occasions of measurement and report outcomes for either dementia (Alzheimer's disease, vascular dementia, or dementia; table 1) or cognitive decline. For analysis of dementia outcomes, studies were included only if they screened for dementia at baseline and had a follow-up of at least 12 months. For analysis of cognitive outcomes, data on cognitive performance had to be obtained at baseline plus at least one follow-up of at least 12 months' duration. No relevant randomized controlled trials were identified in the literature.

For both dementia and cognitive outcomes, studies had to measure exposure to smoking at baseline and analyze the association between smoking and dementia or cognitive decline to be included. Studies were excluded if they had a clinical sample (e.g., Parkinson's disease, head injury, human immunodeficiency virus) or a sample size of less than 50.

Multiple publications from a single study

Multiple publications using the same sample or study (e.g., The Rotterdam Study) were included if they examined 1) different smoking measures (e.g., one article may examine packs of cigarettes smoked per day multiplied by years of smoking (pack-years) while another may examine smoking status); 2) different cognitive outcomes (e.g., one article may examine dementia while another examined Alzheimer's disease); or 3) smoking or cognitive outcomes measures in different forms (e.g., one article examined a continuous

outcome while another analyzed a categorical outcome). When there were multiple publications from a single study with the same smoking measures and outcome measures, decision rules were established for choosing one out of multiple publications. Priority was given to studies in which smoking was the key independent variable and then to more recent studies. However, it was found that for each study, only one publication provided sufficient data for inclusion in the review, except for the Washington Heights Inwood Columbia Aging Project study. For example, from the Epidemiology of Vascular Aging Study, an earlier report (5) was selected over a later study (6) because of the availability of relevant data in the former compared with the latter. For the Washington Heights Inwood Columbia Aging Project study, a more recent publication was chosen to replace an earlier study on recommendation of the authors (7, 8). Relevant publications were selected independently by two of the authors (K. A. and C. vS.), and disagreements were resolved through discussion.

Outcomes

There were seven potential study outcomes, including three for dementia and four based on cognitive measures, described in table 1. Outcomes for dementia included Alzheimer's disease, vascular dementia, or any dementia. Several studies reported results for only Alzheimer's disease as an outcome (7, 9–11), whereas others reported results for subtype(s) of dementia as well as for any dementia (12–16). Cognitive outcomes were categorized as cognitive performance at follow-up, cognitive performance change, cognitive decline, and cognitive impairment.

Data extraction

Articles were de-identified (blinded title, author(s), year of publication, and journal name) before data extraction. The following information was extracted from each article by C. vS. and was cross-checked by a second researcher: length of follow-up, description of smoking measure, description of cognitive measures, average age, percentage of males, average years of education, and, where relevant, total number of cases and noncases, measure of association (odds ratio, hazard ratio, relative risk) with its 95 percent confidence interval, and variables adjusted for in the analyses. Results from both unadjusted and adjusted analyses were extracted.

Data compilation for analysis

Authors were contacted via e-mail for any missing information. Studies used different types of comparisons within smoking status measures (including ever vs. never, current vs. former or never, current vs. never, current vs. former, former vs. never), and some studies reported smoking in pack-years defined as years of smoking the equivalent of one pack of cigarettes per day. Current smokers in these studies were defined as participants who reported they were smokers when data were collected at baseline.

When results for more than one follow-up period were reported for the same study, the estimate from the longest follow-up was selected. For studies reporting multiple statistical models with different covariates, the result with the smallest standard error of estimates was selected because it represents the most precise effect estimate from the study. For example, for the outcome of Alzheimer's disease, Moffat et al. (11) investigated three models that included smoking but differed regarding the final covariate, which was either free testosterone index, total testosterone, or sex hormone-binding globulin. The estimate for smoking was selected from the model including free testosterone index, which had the smallest standard error. For all studies, preference was given to the results adjusted for the most covariates.

Types of comparisons

Meta-analysis was conducted when more than one study was compatible in terms of the smoking measure and the outcome measure. Studies were grouped according to type of comparison and were subgrouped according to type of outcome. Studies with sufficient statistical data for analysis (obtained from articles or from successful contact with authors) were examined for compatible measures of smoking and cognitive outcomes. There were enough data to conduct comparisons of 1) current smokers versus never smokers for risk of Alzheimer's disease, vascular dementia, any dementia, and change in cognitive performance; 2) ever smokers versus never smokers for Alzheimer's disease, any dementia, and cognitive impairment; 3) former smokers versus never smokers for Alzheimer's disease, vascular dementia, any dementia, and change in cognitive performance; 4) current smokers versus former smokers for Alzheimer's disease, vascular dementia, any dementia, and change in cognitive performance; and 5) current smokers versus former or never smokers for Alzheimer's disease and cognitive decline. The only cognitive measure for which there were enough compatible data within a comparison group to analyze cognitive performance change (defined in table 1) was the Mini-Mental State Examination.

Statistical analysis

Studies with dichotomous outcomes reported effect size measures in the form of relative risks, hazard ratios, or odds ratios. A hazard ratio is the ratio of the probability of an outcome in the exposed group compared with the nonexposed group. For our review, relative risks, hazard ratios, and odds ratios were treated the same and are referred to as relative risks. This combining step is based on the assumption that dementia is a relatively rare event and that the three different measures are therefore valid estimates of relative risk (17), and that it has been used previously (18).

The data points for the meta-analysis of binary outcomes were the logarithms of the relative risks and their standard errors. The standard errors of the relative risks are typically estimated from the 95 percent confidence interval of the log relative risk by dividing the width of the interval by 3.92 (which is twice the 97.5th percentile of the standard normal

distribution). Studies that examined three smoking statuses (current, former, and never) provided data for only current-versus-never and former-versus-never comparisons. Thus, conservative estimates for the current-versus-former comparison were mathematically derived from results reported for current versus never and former versus never. For continuous outcomes, the effect size was defined as the mean difference in rate of change in the outcome between two groups, typically represented by the linear regression coefficient (β) of the smoking variable after adjusting for other covariates.

Heterogeneity among studies was examined by using standard χ^2 tests (19). To improve sensitivity of detecting heterogeneity among studies, a p value of 10 percent was used (19). Fixed-effect meta-analysis (inverse variance method) was utilized to pool estimates if there was no evidence of heterogeneity. If heterogeneity was present, the DerSimonian and Laird random-effects method was used to pool effect sizes (20, 21). Both types of pooled effect are weighted such that the weight is inversely proportional to the standard error of the estimate of each study. Therefore, sample size is accounted for in the pooled effects since typically larger studies produce estimates with lower standard errors (higher precision) and hence are given larger weight.

The small number of studies (range, 2–5) within each group of studies with compatible measures precluded investigation of heterogeneity via meta-regression, subgroup analysis, or assessment of publication bias.

RESULTS

Of 6,455 abstracts identified in the database search, data were available for 30 reports from prospective cohort studies. Only 19 reports included data suitable for inclusion in meta-analyses (7, 9–16, 22–31). Consequently, 11 studies with data, or for which data were supplied by authors, could not be included in the meta-analysis because of a lack of compatibility with any other study (5, 32–41). Figure 1 shows the stages in identifying studies for inclusion in our review. No relevant clinical trials meeting study criteria were identified. Characteristics of the 19 studies included in meta-analyses are shown in table 2.

A total of 13,786 participants were included in the 10 studies on smoking and Alzheimer's disease. Length of follow-up ranged from 2 to 30 years. A total of 4,888 participants from two studies were included in analyses of smoking and vascular dementia. A total of 3,767 participants from five studies were included in analyses of smoking and any dementia. Although the Atherosclerosis Risk in Communities study (37) reported cognitive performance at follow-up, it could not be included in the meta-analysis because of the lack of compatible studies with which results from this study could be pooled. Therefore, the outcome of cognitive performance at follow-up was not included in the meta-analyses. Regarding the other cognitive outcomes, there were three compatible studies including 7,872 participants for cognitive performance change, three compatible studies including 766 participants for cognitive decline, and three compatible studies including 8,385 participants for cognitive impairment.

Current smokers versus never smokers

The relative risk estimates from the individual studies and the pooled estimates for current smokers versus nonsmokers regarding the dementia outcomes and the effect size for the yearly cognitive change outcome are shown in table 3. Compared with never smoking, current smoking was a significant risk factor for all outcomes analyzed. Compared with never smokers, current smokers had 1.79 times (95 percent CI: 1.43, 2.23) the risk of incident Alzheimer's disease, 1.78 times (95 percent CI: 1.28, 2.47) the risk of incident vascular dementia, and 1.27 times (95 percent CI: 1.02, 1.60) the risk of any dementia. Current smokers also showed a significantly larger yearly decline in Mini-Mental State Examination scores compared with never smokers over the follow-up period ($\beta = -0.13$, 95 percent CI: -0.18, -0.08).

Ever smokers versus never smokers

The individual study and pooled relative risks for ever smokers versus never smokers for Alzheimer's disease, any dementia, and cognitive impairment are shown in table 4. The pooled results showed that, compared with never smokers, those who reported ever having smoked were not at increased risk of Alzheimer's disease, any dementia, or cognitive impairment.

Former smokers versus never smokers

The individual and pooled relative risks results for former smokers versus never smokers regarding Alzheimer's disease, vascular dementia, and any dementia and the effect size for the yearly cognitive change outcome are shown in table 5. The pooled results indicate that for the dementia outcomes, former smokers were not at increased risk compared with never smokers. There was, however, evidence of a higher rate of cognitive decline for former smokers compared with never smokers ($\beta = -0.07$, 95 percent CI: -0.11, -0.03).

Current smokers versus former smokers

Individual study and pooled relative risks for current smokers versus former smokers regarding all dementia outcomes and the effect size for the yearly cognitive change outcome are shown in table 6. Compared with former smoking, current smoking was a significant risk factor for Alzheimer's disease (RR = 1.70, 95 percent CI: 1.25, 2.31) but not for vascular dementia (RR = 1.26, 95 percent CI: 0.60, 2.63) or any dementia (RR = 1.30, 95 percent CI: 0.96, 1.77). There was also evidence that, compared with former smokers, current smokers showed a greater yearly cognitive decline in the follow-up period ($\beta = -0.07$, 95 percent CI: -0.13, -0.02).

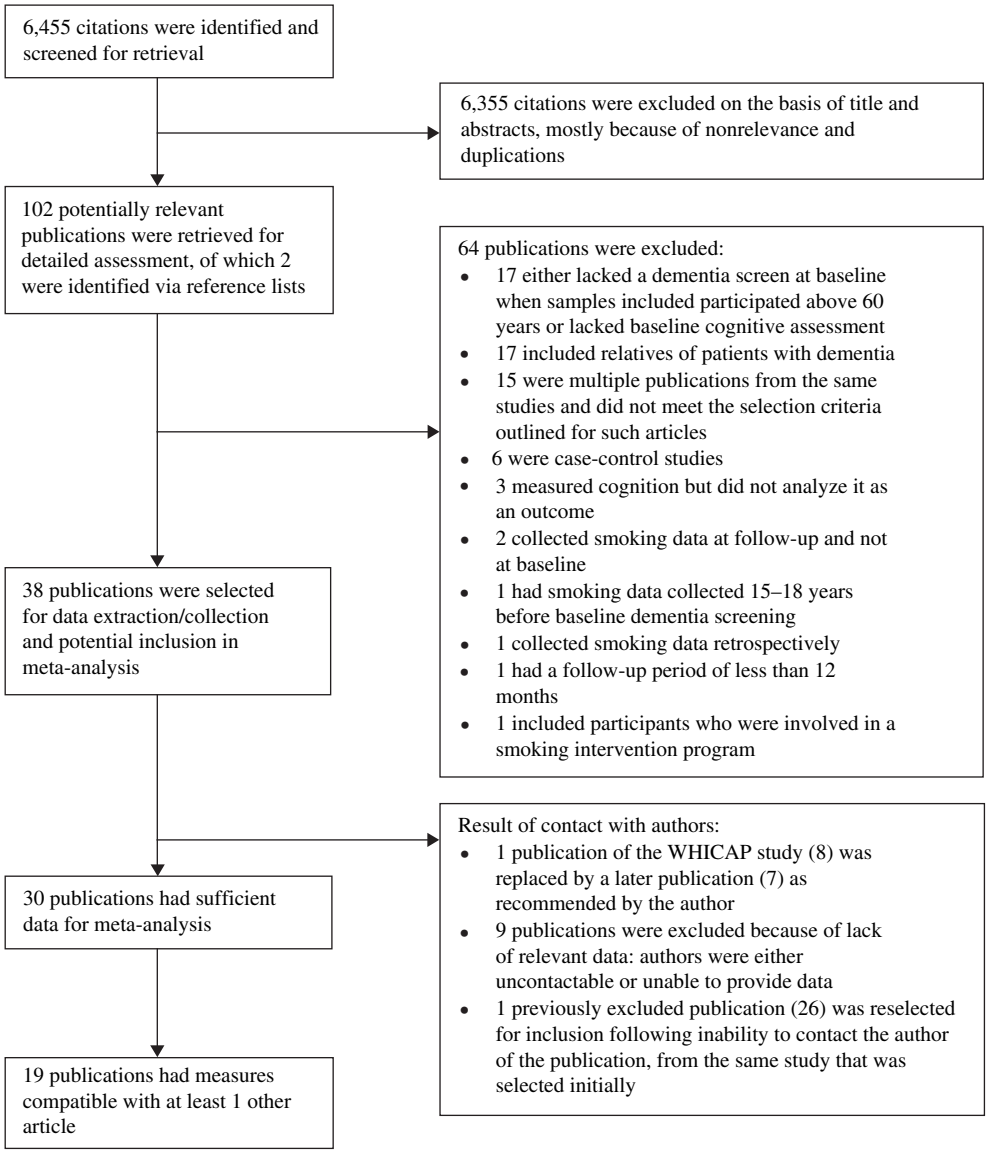

FIGURE 1. Process for identifying studies for inclusion in the review. WHICAP, Washington Heights Inwood Columbia Aging Project.

Current smokers versus former and never smokers

The individual study and pooled relative risks for current smokers versus former/never smokers regarding Alzheimer's disease and cognitive decline are shown in table 7. Pooled estimates suggested an increased risk for current smokers for cognitive decline (RR = 1.41, 95 percent CI: 1.61, 1.71) but not Alzheimer's disease (RR = 1.25, 95 percent CI: 0.49, 3.17).

DISCUSSION

The results of this study clearly show that, when compared with people who have never smoked, current smokers have an increased risk of dementia and cognitive decline ranging from 40 percent to 80 percent, depending on the outcome examined. However, our analyses did not reveal an increased risk of dementia or cognitive decline for ever smoking compared with never smoking. The ''ever smoker'' category includes current with previous smokers, which complicates interpretation of these results. When former smokers were compared with never smokers, they were not found to have an increased risk of dementia but did show an increased risk of yearly decline in the Mini-Mental State Examination. Compared with former smokers, current smokers had an increased risk of Alzheimer's disease and a yearly decline in the Mini-Mental State Examination, but there was no difference in their risk of vascular dementia or

TABLE 2. Characteristics of studies included in the review of smoking as a risk factor for dementia and cognitive decline

Study: first author, year (reference no.) (no. of subjects)	Study name	Length of follow-up in years	Source	Smoking status	Outcome (no. of events for dichotomous outcomes)	Outcome(s) measure	Mean age in years (SD*)	Male %	Mean education in years (SD)
Broe, 1998† (12) ($N = 327$)	SOPS*	Fixed‡: 3	Community dwelling sampled from lists from the Department of Veterans Affairs or ABS*	Current, former, never smokers	Alzheimer's disease ($n = 31$) and dementia ($n = 45$)	DSM-IV,* NINCDS-ADRDA*	80.2 (3.5)	50.5	10.1 (1.9)
Ford, 1996 (22) ($N = 529$)	Cleveland Study of the Elderly	Fixed: 4	Medicare lists of city of Cleveland (Ohio) residents	Ever smoker	Cognitive impairment ($n = 51$)	SPMSQ*	Range, 74–101	33.6	NA*
Graves, 1999 (23) ($N = 544$)	The Kame Project	Fixed: 2	Census of Japanese Americans	Current smoker	Cognitive decline ($n = 131$)	CASI*	71.5 (5.3)	44.2	13.1 (2.9)
Juan, 2004 (13) ($N = 2,729$)		Varied§: followed for 2 years	Random selection from 6 neighborhoods	Current, former, never smokers	Alzheimer's disease ($n = NA$) and vascular dementia ($n = NA$)	DSM-III-R,* NINCDS-ADRDA, NINDS-AIREN*	66.9 (8.4)	NA	10.9 (0.1)
Launer, 1996 (24) ($N = 268$)	Zutphen Elderly Study	Fixed: 3	Men living in Zutphen (the Netherlands)	Current, former, never smokers	Cognitive performance change	MMSE*	75.1 (4.7)	100	NA
Launer, 1999 (14) ($N = 651$)	EURODEM*: Odense (Denmark), Paquid,* Rotterdam (the Netherlands), MRC Alpha*	Varied: 2.24 (NA)	Odense (persons living within the municipality); Paquid (electoral roles); Rotterdam (persons living in the district of municipality, Ommoord); MRC Alpha (general practitioner registry in the municipality of Liverpool)	Current, former, never smokers	Alzheimer's disease ($n = 277$) and dementia ($n = 400$)	DSM-III-R; NINDS-ADRDA	NA		NA
Laurin, 2003 (25) ($N = 163$)	CSHA*	Fixed: 5	Population-based listings	Ever smoker	CIND* ($n = 22$) and dementia ($n = 21$)	CIND: modified version of Zaudig's criteria; dementia: DSM-III,* NINCDS-ADRDA, ICD-10-R*; other	76.9 (5.9)	34.2	9.2 (4.0)
Laurin, 2004¶ (15) ($N = 2,341$)	HAAS*	Varied: 30.3 (1.6)	Community based	Current, former, never smokers	Alzheimer's disease ($n = 134$), vascular dementia ($n = 40$), and dementia ($n = 222$)	DSM-III; NINCDS-ADRDA; CADDTC*	77.4 (4.0)	100	10.8 (3.1)
Lindsay, 2002 (9) ($N = 3,973$)	CSHA	Fixed: 5	Population-based listings	Ever smoker	Alzheimer's disease ($n = 182$)	NINCDS-ADRDA	73.3 (6.4)	42.0	11.0 (3.7)
Luchsinger, 2005 (7) ($N = 1,138$)	WHICAP*	Varied: 5.5 (3.2)	Medicare recipients residing in northern Manhattan, New York	Current smoker	Alzheimer's disease ($n = 422$)	NINCDS-ADRDA	76.2 (5.9)	30.2	8.2 (4.6)
Lui, 2003 (26) ($N = 4,462$)	SOF*	Fixed: 4	Population-based listings in four areas of the United States	Current smoker	Cognitive decline ($n = 696$)	MMSE	75.9 (4.2)	0.0	12.9 (2.7)

Merchant, 1999 (10) ($N = 1,204$)	WHICAP	Varied: 2.0 (1.7)	Medicare recipients in three contiguous zip codes	Current, former, never smokers	Alzheimer's disease ($n = 142$)	DSM-IV, NINCDS-ADRDA, CDR*	75.4 (6.1)	31.3	8.8 (4.4)
Moffat, 2004 (11) ($N = 572$)	BLSA*	Varied: 19.1 (NA)	Volunteers, community dwelling	Ever smoker	Alzheimer's disease ($n = 54$)	DSM-III-R, NINDS-ADRDA	66.3 (10.3)	100	17.1 (2.9)
Ott, 2004 (27) ($N = 7,172$)	EURODEM: Odense, Paquid, Rotterdam, MRC Alpha	Varied: 2.3 (0.7)	Odense (persons living within the municipality); Paquid (electoral roles); Rotterdam (persons living in district of municipality, Ommoord); MRC Alpha (general practitioner registry in the municipality of Liverpool)	Current, former, never smokers	Cognitive performance change	MMSE	73.9 (6.28)	44.0	NA
Paleologos, 1998 (28) ($N = 121$)	SITE*	Fixed: 4	Group of retirement villages	Ever smoker	Cognitive impairment ($n =$ NA)	MMSE	78.37 (4.0)	24.8	NA
Wang, 1999 (16) ($N = 343$)	Kungsholmen Project	Varied: 2.2 (1.0)	Registered residents in a district	Ever smoker	Alzheimer's disease ($n = 34$) and dementia ($n = 46$)	DSM-III-R (modified)	84.0 (5.2)	18.7	9.0 (2.7)
Weisskopf, 2004 (29) ($N = 432$)	VA* Normative Aging Study	Varied: 3.5 (1.1)	Community-dwelling men	Current, former, never smokers	Cognitive performance change	MMSE	67.4 (6.63)	100	14.5 (2.9)
Whittington, 1997# (30) (female, $N = 2,083$; male, $N = 1,296$)	Health and Lifestyle Survey	Fixed: 7	Electoral registrars for England, Scotland, and Wales	Current smoker	Cognitive decline (female, $n = 546$; male, $n = 316$)	Incidental memory, visuospatial reasoning, reaction time tasks	Male: 39.9 (14.8); female: 44.1 (15.8)		Male: 11.2 (1.3); female: 11.5 (1.2)
Yoshitake, 1995 (31) ($N = 765$)	The Hisayama Study	Varied: followed for 7 years	Residents of a subrural community	Current smoker	Alzheimer's disease ($n =$ NA)	DSM-III; NINCDS-ADRDA; NINDS-AIREN	73.6 (5.9)	40.3	NA

* SD, standard deviation; SOPS, Sydney Older Persons Study; ABS, Australian Bureau of Statistics; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; SPMSQ, Short Portable Mental Status Questionnaire; NA, not available from article or not provided by contacted author; CASI, Cognitive Abilities Screening Instrument; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences [International Association for Research and Education in Neuroscience]; MMSE, Mini-Mental State Examination; EURODEM, European Community Concerted Action Epidemiology of Dementia; MRC Alpha, Medical Research Council: Ageing in Liverpool Project–Health Aspects; Paquid, Personnes Agées Quid; CSHA, Canadian Study of Health and Aging; CIND, cognitive impairment–no dementia; DSM-III, *Diagnostic and Statistical Manual of Mental Disorder*s, Third Edition; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision; HAAS, Honolulu-Asia Aging Study; CADDTC, California Alzheimer's Disease Diagnostic and Treatment Centers criteria; WHICAP, Washington Heights Inwood Columbia Aging Project; SOF, Study of Osteoporotic Fractures; CDR, Clinical Dementia Rating; BLSA, Baltimore Longitudinal Study of Aging; SITE, Western Sydney Stroke in Elderly; VA, Veterans Administration.

† For this study, only results from the former-versus-never comparison were included in analysis because asymptotic logistic regression results for the current category were based on 0 observed cases of Alzheimer's disease and 1 observed case of dementia.

‡ Fixed, fixed follow-up time points.

§ Varied, follow-up period varied for participants; hence, mean (standard deviation) was reported.

¶ The Laurin results differ from those in another publication using the same study (56) because they report on different subsamples, but this latter study did not meet selection criteria for the present review.

Data for males and females were reported separately because this study investigated these samples separately. Results for cognitive decline as measured by incidental memory were selected for analysis.

TABLE 3. Relative risks of dementia and cognitive decline for current smokers versus never smokers

Outcome	Test for heterogeneity		Test for overall effect		Study: first author, year (reference no.)	Weight (%)	Relative risk (fixed)	95% confidence interval
	χ^2	*p* value	*z* score	*p* value				
Alzheimer's disease	3 df: 2.35	0.50	5.11	<0.001	Juan, 2004 (13)*	13.74	2.72	1.49, 4.96
					Merchant, 1999 (10)†	22.72	1.70	1.07, 2.71
					Laurin, 2004 (15)‡	25.88	1.55	1.00, 2.40
					Launer, 1999 (14)§	37.66	1.74	1.21, 2.50
					Pooled	100	1.79	1.43, 2.23
Vascular dementia	1 df: 2.15	0.14	3.46	<0.001	Laurin, 2004 (15)¶	15.65	1.01	0.44, 2.31
					Juan, 2004 (13)*	84.35	1.98	1.39, 2.83
					Pooled	100	1.78	1.28, 2.47
Any dementia	1 df: 0.72	0.40	2.09	0.04	Laurin, 2004 (15)‡	43.84	1.14	0.81, 1.61
					Launer, 1999 (14)§	56.16	1.39	1.03, 1.88
					Pooled	100	1.27	1.02, 1.60
Yearly cognitive performance change (MMSE)	2 df: 4.00	0.14	5.04	<0.001	Weisskopf, 2004 (29)#	10.36	0.01	−0.15, 0.16
					Launer, 1996 (24)**	18.89	−0.10	−0.22, 0.02
					Ott, 2004 (27)††	70.75	−0.16	−0.22, −0.10
					Pooled	100	−0.13	−0.18, −0.08

* Estimates were adjusted for age, sex, education, blood pressure, and alcohol intake.
† Estimates were adjusted for education and ethnicity.
‡ Estimates were adjusted for age, education, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, apolipoprotein-e4, and vitamin E.
§ Estimates were adjusted for age, age squared, study, sex, and education.
¶ Estimates were adjusted for age, education, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, apolipoprotein-e4, and beta-carotene.
# Estimates were adjusted for age, education, alcohol intake, years between Mini-Mental State Examination (MMSE) tests, computer experience, English as the first language, and patella lead exposure.
** Estimates were adjusted for age, education, alcohol intake, and baseline MMSE.
†† Estimates were adjusted for age, age squared, sex, education, type of residence, myocardial infarction, stroke, and baseline MMSE.

TABLE 4. Relative risks of dementia and cognitive impairment for ever smokers versus never smokers

Outcome	Test for heterogeneity		Test for overall effect		First author, year (reference no.)	Weight (%)	Relative risk (fixed)	95% confidence interval
	χ^2	*p* value	*z* score	*p* value				
Alzheimer's disease	2 df: 12.19	0.01	0.61	0.54	Wang, 1999 (16)*	24.83	1.10	0.50, 2.41
					Lindsay, 2002 (9)*	36.77	0.82	0.57, 1.17
					Moffat, 2004 (11)†	38.41	1.86	1.39, 2.49
					Pooled	100.00	1.21	0.66, 2.22
Any dementia	1 df: 0.74	0.39	0.66	0.51	Wang, 1999 (16)*	38.88	1.40	0.76, 2.57
					Laurin, 2003 (15)‡	61.12	1.00	0.61, 1.62
					Pooled	100.00	1.14	0.78, 1.66
Cognitive impairment	2 df: 7.04	0.03	0.36	0.72	Paleologos, 1998 (28)§	12.69	0.07	0.01, 0.63
					Ford, 1996 (22)¶	41.51	1.03	0.54, 1.98
					Laurin, 2003 (15)‡	45.79	1.43	0.87, 2.33
					Pooled	100.00	0.85	0.35, 2.09

* Estimates were adjusted for age, sex, and education.
† Estimates were adjusted for age, education, body mass index, diabetes, cancer, hormone supplementation, and free testosterone index.
‡ Unadjusted: estimates calculated from number of subjects.
§ Estimates were adjusted for age and sex.
¶ Estimates were adjusted for age, sex, and income.

TABLE 5. Relative risks of dementia and cognitive decline for former smokers versus never smokers

Outcome	Test for heterogeneity		Test for overall effect		First author, year (reference no.)	Weight (%)	Relative risk (fixed)	95% confidence interval
	χ^2	*p* value	*z* score	*p* value				
Alzheimer's disease	4 df: 5.27	0.26	0.09	0.93	Juan, 2004 (13)*	5.48	1.53	0.65, 3.60
					Broe, 1998 (12)†	5.81	1.03	0.45, 2.37
					Laurin, 2004 (15)‡	23.03	1.03	0.68, 1.56
					Merchant, 1999 (10)§	25.86	0.70	0.47, 1.04
					Launer, 1999 (14)¶	39.81	1.19	0.87, 1.63
					Pooled	100	1.01	0.83, 1.23
Vascular dementia	1 df: 0.40	0.52	0.23	0.81	Juan, 2004 (13)*	45.33	1.33	0.55, 3.24
					Laurin, 2004 (15)#	54.67	0.90	0.40, 2.02
					Pooled	100	1.07	0.59, 1.95
Any dementia	2 df: 0.35	0.84	0.09	0.93	Broe, 1998 (12)†	7.61	1.08	0.53, 2.20
					Laurin, 2004 (15)‡	37.46	0.92	0.67, 1.27
					Launer, 1999 (14)¶	54.93	1.03	0.79, 1.34
					Pooled	100	0.99	0.81, 1.21
Yearly cognitive performance change (MMSE)	2 df: 0.28	0.87	3.13	<0.01	Launer, 1996 (24)**	17.29	−0.07	−0.17, 0.03
					Weisskopf, 2004 (29)††	23.09	−0.09	−0.18, 0.00
					Ott, 2004 (27)‡‡	59.63	−0.06	−0.11, −0.01
					Pooled	100	−0.07	−0.11, −0.03

* Estimates were adjusted for age, sex, education, blood pressure, and alcohol intake.
† Estimates were adjusted for age (at follow-up), sex, and education.
‡ Estimates were adjusted for age, education, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, apolipoprotein-e4, and vitamin E.
§ Estimates were adjusted for education and ethnicity.
¶ Estimates were adjusted for age, age squared, study, sex, and education.
# Estimates were adjusted for age, education, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, apolipoprotein-e4, and beta-carotene.
** Estimates were adjusted for age, education, alcohol intake, and baseline Mini-Mental State Examination (MMSE).
†† Estimates were adjusted for age, education, alcohol intake, years between MMSE tests, computer experience, English as the first language, and patella lead exposure.
‡‡ Estimates were adjusted for age, age squared, sex, education, type of residence, myocardial infarction, stroke, and baseline MMSE.

any dementia. Finally, current smokers had an increased risk of cognitive decline compared with ''former and never'' smokers.

The results of these analyses must be interpreted in the context of the strengths and limitations of the available data. The categories of ''former'' and ''ever'' smoker are nonspecific and could equate persons who smoked for a short period very early in life with persons who smoked heavily for decades. The strongest comparisons are clearly between ''current'' smokers and ''never'' smokers. Most weight should be placed on the results comparing these groups. The fact that consistent findings occurred in analyses of small numbers of studies implies that stronger results may be observed if more studies were available for inclusion in a meta-analysis. Therefore, the results strongly supported the finding that current smoking is a risk factor for cognitive decline and dementia among older adults.

Former smokers were at significantly lower risk than current smokers of Alzheimer's disease and yearly cognitive decline but were no different from current smokers regarding their risk of vascular dementia and any dementia. Smoking cessation is associated with reduced risk of lung cancer (42), cardiovascular risk (43), and cancer (44). It is therefore possible that the effects of smoking on cognition are not evident in a proportion of former smokers who may have ''recovered'' from the detrimental effects of smoking on the brain and cognitive function. A reduction in inflammatory markers such as C-reactive protein is evidenced after smoking cessation (45). Similar mechanisms of reduced inflammation or oxidative stress (46) may lead to a reduction in risk of cognitive decline and dementia among former smokers, but further research is required to test this hypothesis and determine the time period after which risk begins to decline. It is also possible that consistent differences between ever smokers and never smokers were not found because the category of ever smoker included such a broad range of possible smoking duration.

The studies selected for this review had baseline samples of subjects aged mostly in their mid-seventies and so the

TABLE 6. Relative risks of dementia and cognitive decline for current smokers versus former smokers

Outcome	Test for heterogeneity		Test for overall effect		First author, year (reference no.)	Weight (%)	Relative risk (fixed)	95% confidence interval
	χ^2	*p* value	*z* score	*p* value				
Alzheimer's disease	3 df: 1.85	0.60	3.39	<0.001	Juan, 2004 (13)*	8.63	1.78	0.62, 5.06
					Merchant, 1999 (10)†	25.28	2.43	1.32, 4.48
					Laurin, 2004 (15)‡	25.77	1.50	0.82, 2.76
					Launer, 1999 (14)§	40.33	1.46	0.90, 2.37
					Pooled	100	1.70	1.25, 2.31
Vascular dementia	1 df: 0.06	0.80	0.61	0.54	Laurin, 2004 (15)¶	40.54	1.12	0.35, 3.58
					Juan, 2004 (13)*	59.46	1.36	0.52, 3.55
					Pooled	100	1.26	0.60, 2.63
Any dementia	1 df: 0.07	0.79	1.69	0.09	Laurin, 2004 (15)‡	42.96	1.24	0.78, 1.98
					Launer, 1999 (14)§	57.04	1.35	0.90, 2.02
					Pooled	100	1.30	0.96, 1.77
Yearly cognitive performance change (MMSE)	2 df: 4.24	0.12	2.71	<0.01	Weisskopf, 2004 (29)#	8.78	0.09	−0.09, 0.28
					Launer, 1996 (24)**	12.17	−0.03	−0.19, 0.12
					Ott, 2004 (27)††	79.05	−0.10	−0.16, −0.04
					Pooled	100	−0.07	−0.13, −0.02

* Estimates were adjusted for age, sex, education, blood pressure, and alcohol intake.
† Estimates were adjusted for education and ethnicity.
‡ Estimates were adjusted for age, education, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, apolipoprotein-e4, and vitamin E.
§ Estimates were adjusted for age, age squared, study, sex, and education.
¶ Estimates were adjusted for age, education, alcohol intake, body mass index, physical activity, systolic and diastolic blood pressures, year of birth, total energy intake, cholesterol concentration, history of cardiovascular disease, supplemental vitamin intake, apolipoprotein-e4, and beta-carotene.
# Estimates were adjusted for age, education, alcohol intake, years between Mini-Mental State Examination (MMSE) tests, computer experience, English as the first language, and patella lead exposure.
** Estimates were adjusted for age, education, alcohol intake, and baseline MMSE.
†† Estimates were adjusted for age, age squared, sex, education, type of residence, myocardial infarction, stroke, and baseline MMSE.

TABLE 7. Relative risks of dementia and cognitive decline for current smokers versus formers and never smokers

Outcome	Test for heterogeneity		Test for overall effect		First author, year (reference no.)	Weight (%)	Relative risk (fixed)	95% confidence interval
	χ^2	*p* value	*z* score	*p* value				
Alzheimer's disease	1 df: 4.90	0.03	0.47	0.64	Yoshitake, 1995 (31)*	43.56	0.73	0.34, 1.57
					Luchsinger, 2005 (7)†	56.44	1.90	1.32, 2.73
					Pooled	100	1.25	0.49, 3.17
Cognitive decline	3 df: 1.38	0.71	3.50	<0.001	Whittington, 1997 (males) (30)‡	3.28	2.55	0.88, 7.39
					Whittington, 1997 (females) (30)‡	4.21	1.58	0.62, 4.04
					Graves, 1999 (23)§	38.25	1.42	1.04, 1.94
					Lui, 2003 (26)¶	54.26	1.34	1.03, 1.75
					Pooled	100	1.41	1.16, 1.71

* Estimates were adjusted for age.
† Estimates were adjusted for age, sex, education, apolipoprotein-e4, diabetes, hypertension, and heart disease.
‡ Estimates were adjusted for age, education, baseline memory score, respiratory function, and change in respiratory function.
§ Estimates were adjusted for age, sex, education, baseline Cognitive Abilities Screening Instrument score, and follow-up period.
¶ Unadjusted: estimates calculated from number of subjects.

results can be confidently generalized to this age group only. It is likely that smokers in late adulthood have a lifetime history of smoking so that the observed association between current and never smokers reflects the accumulated effect of smoking over decades. There were insufficient data to evaluate the relation between duration of smoking and dementia risk. Too few studies reported data on pack-years to enable analysis of this relation.

The present review was limited by the small number of comparable studies in any one category, such that we were unable to investigate sources of heterogeneity or test for publication bias. The fact that seven studies did not focus on smoking but reported results incidentally (11, 15, 23, 25, 26, 28, 29), with data obtained from authors, reduced potential publication bias. It is possible that an initial screening of potentially relevant articles on the basis of title and abstract alone was insufficient to detect the presence of data relevant to dementia or cognitive decline within the body of an article. Manually searching all prospective studies of dementia or cognitive decline for data on smoking exposure would overcome this problem.

Because our review is based on observational studies, it is possible that other health and lifestyle factors associated with smoking explain the associations between smoking and dementia and smoking and cognitive decline. For example, smokers may have poorer nutrition, have poorer general health, be more likely to drink harmful levels of alcohol, or undertake less physical activity. Although many studies adjusted for demographic and health factors that may influence the observed associations, there was inconsistency among studies in the choice of covariates.

Smoking may also affect dementia risk via its effect on other medical conditions such as coronary events (47), and it may interact with other cardiovascular risk factors in a synergistic or additive manner (7). It may also interact with genetic factors such as apolipoprotein E genotype (*APOE*) to increase the risk of dementia (48). Two studies included in our review reported data on *APOE* as a covariate (7, 15), but neither reported interactions between smoking and *APOE* genotype specifically. However, a report from the Rotterdam Study found that *APOE* $\epsilon 4$ carriers who were smokers had no increased risk of dementia, whereas *APOE* $\epsilon 4$ noncarriers who were smokers had double the risk of dementia and Alzheimer's disease (49).

The strengths of this review include its strict selection criteria, ensuring that only high-quality studies were included; inclusion of publications in which smoking was not the main variable of interest to counteract publication bias; and the fact that a number of studies had large sample sizes and long follow-ups.

We conclude that elderly current smokers are at increased risk of dementia and cognitive decline compared with those who have never smoked but that there remains insufficient data to determine how past smoking affects risk of both cognitive decline and dementia. Cognitive outcomes should be measured in clinical trials of smoking cessation. Public health information about smoking should include warnings that it may increase the risk of dementia.

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