Smoking and dementia risk: an updated systematic review and meta-analysis of 61 prospective cohort studies and implications for tobacco control

Marie Serve,[a,b,*] Jacob Beard,[c] Sarah Beasley,[d] Tanya Buthanam,[a,e] Claire V. Burley,[a] Elissa Burton,[f,g] Jennifer Doerre,[a] Megan Ghisaidoobe,[a] Zhongyang Guan,[h] Bronwyn Myers,[a,i] Leticia Radin Pereira,[j] Serena Salvatore,[k] Alexandra Seksenyan,[l] Sasha Shetty,[a] Elise Stirling,[a,b] and Blossom C. M. Stephan[a]

[a]Dementia Centre of Excellence, Curtin enAble Institute, Curtin University, Kent Street, Bentley, Western Australia, Australia
[b]Curtin School of Population Health, Faculty of Health Sciences, Curtin University, Bentley, Western Australia, Australia
[c]Centre for Reviews and Dissemination, University of York, York, UK
[d]Cancer Council Western Australia, Perth, Australia
[e]Dementia Australia, Griffith ACT, Australia
[f]Curtin School of Allied Health & enAble Institute, Curtin University, Bentley, Western Australia, Australia
[g]Brightwater Research Centre, Brightwater Care Group, Inglewood, Western Australia, Australia
[h]Nutrition and Health Innovation Research Institute, School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia
[i]Mental Health, Alcohol, Substance Use and Tobacco Research Unit, South African Medical Research Council, Tygerberg, South Africa
[j]Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 3280 Hospital Drive NW, Calgary, AB T2N 4Z6, Canada
[k]Department of Clinical Psychology and Psychobiology, Institute of Neurosciences, University of Barcelona, Barcelona, Spain
[l]Curtin Medical School, Curtin University, Bentley, Western Australia, Australia

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Summary

Background Smoking has been identified as a modifiable dementia risk factor by three Lancet Commissions, yet dementia remains absent from most tobacco control strategies. The magnitude of the association across dementia subtypes, smoking categories, and population characteristics has not been comprehensively synthesised since 2015.

Methods PubMed, Embase, CENTRAL, and PsycINFO were searched from January 2013 to 31 August 2026, updating the 2015 review, which contributed 34 studies. Random-effects meta-analyses (Restricted Maximum Likelihood (REML) with Hartung–Knapp–Sidik–Jonkman adjustment) estimated pooled relative risks (RRs) with 95% confidence intervals (CIs). Subgroup analyses with tests for interaction and meta-regression examined effect modification by baseline age, ethnicity, follow-up duration, and adjustment for sex, education and Apolipoprotein E ε4 (APOE ε4) genotype. Risk of bias was assessed using Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E). Heterogeneity was assessed using Cochran's Q, I^2 and τ^2 and publication bias using funnel plots and Egger's test. Dose–response analysis of smoking and dementia risk was performed. Smoking population attributable fractions (PAF, unweighted and communality-weighted) for the risk of dementia were calculated. This study is registered with PROSPERO, CRD42025644539.

Findings Sixty-one cohort studies (approximately 2.8 million participants) were included. Current smoking was associated with increased risk of all-cause dementia (RR 1.31 [95% CI 1.23–1.39]; number of studies (k) = 39), Alzheimer's disease (1.40 [1.08–1.80]; k = 15), and vascular dementia (1.52 [1.20–1.93]; k = 9). Former smoking was not associated with any outcome, and former smokers had a lower risk of all-cause dementia than current smokers (RR 0.81 [0.75–0.88]). I^2 ranged from 0% to 80%. Egger's test suggested small-study effects only for current smoking and all-cause dementia (P = 0.09). The communality-weighted PAF for smoking and dementia was 2.2% (95% CI 1.7–2.8). Dementia risk increased with smoking intensity as the pooled RR was 1.16 (95% CI 1.09–1.23) at 10 cigarettes per day and rose to 1.34 (95% CI 1.18–1.51) at 20 cigarettes per day.

Interpretation Current smoking is consistently associated with higher risk of all dementia outcomes and increases with smoking intensity. Estimates refer to clinically diagnosed dementia syndromes [Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases (DSM/ICD)] and not to biologically defined disease. Although causality cannot be established from observational data, these findings support considering

*Corresponding author. Curtin University, Perth, Western Australia, Australia.
Email address: marie.serve@curtinmedia.au (M. Serve).

dementia and brain health outcomes in national tobacco control strategies and associated campaigns. Future work using objectively verified smoking histories is needed to clarify how age at cessation and time since quitting influence dementia risk and whether these effects interact with total years of active smoking.

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Keywords: Smoking; Dementia; Risk prediction; Cohort studies

Research in context

Evidence before this study

We searched the PubMed database for systematic reviews and meta-analyses of smoking and dementia published from inception (1946) until January 2025 using the terms "smoking" AND "dementia" AND "meta-analysis". The search retrieved 33 relevant articles and identified the meta-analysis conducted by Zhong et al. (2015) as the most recent and comprehensive. The meta-analysis included 37 prospective cohort studies and reported higher dementia risk in current but not former smokers across all-cause dementia, Alzheimer's disease (AD), and Vascular dementia (VaD), based on studies published up to 2012. Three subsequent Lancet Commissions (2017, 2020, 2024) identified smoking as a modifiable dementia risk factor, yet dementia outcomes remain absent from most national tobacco control strategies.

Added value of this study

This review strengthens the evidence base from the 34 cohort studies of the previous meta-analysis to 61 cohort studies and approximately 2.8 million participants. Pooled estimates for current smoking are similar to those of earlier work and robust to the random-effects estimator, effect-measure type and risk of bias, and former smokers had a lower dementia risk than current smokers. Point estimates were higher for VaD (relative risk (RR) 1.52) than for AD (1.40) and all-cause dementia (1.31) but VaD and AD estimates did not differ significantly within cohorts reporting both outcomes. In addition, differences by baseline age were not statistically significant. Dose–response analysis indicates that dementia risk increases progressively with intensity of smoking.

Implications of all the available evidence

These findings are consistent with smoking being a modifiable risk factor for dementia and with cessation as an important component of prevention strategies. Three Lancet Commissions and the largest meta-analysis to date reach convergent conclusions, supporting consideration of dementia risk reduction within national tobacco control strategies and public health messaging campaigns. Research is needed on how age at quitting, time since cessation and lifetime smoking duration jointly shape dementia risk.

Introduction

Dementia affects over 57 million people worldwide with an estimated global societal cost of US$1.3 trillion in 2019.[1] In the absence of a cure, the identification and modification of risk factors represent the most effective strategy for reducing the population burden of dementia.[2] Three successive Lancet Commissions on Dementia (in 2017,[3] 2020[4] and 2024[5]) identified smoking as a significant and modifiable risk factor for dementia. Notably, the 2024 Commission estimated that smoking accounted for a weighted population attributable fraction (PAF) of 2.3% of dementia cases[5] and a recent meta-analysis of 9 cohort studies indicated a weighted PAF of 4.5%.[6] The Australian 45 and Up Study, a prospective cohort of 178,169 adults reported that current smoking was associated with a 64% increased risk of death from all-cause dementia (HR 1.64, 95% CI 1.14–2.36).[6]

Despite this evidence, dementia and brain health are not recognised as outcomes within national tobacco control strategies (such as the Australian National Tobacco Strategy 2023–2030, which does not reference dementia, Alzheimer's disease, or cognitive impairment).[7] Consequently, neither public health messaging campaigns nor pictorial warnings on cigarette packaging, core components of these strategies, include dementia or brain health as motivators to end tobacco use.[8] These campaigns continue to centre on cancer outcomes and respiratory and cardiovascular diseases (CVD) for which there has been causal evidence since the 1960s and the policy response well established.[9,10] Compared to the large body of evidence linking smoking to cardiovascular disease and cancer, epidemiological evidence linking smoking to risk of dementia has been more limited. A meta-analysis of 37 prospective cohort studies[11–47] completed by Zhong and colleagues in 2015,[48] found that current smokers had a significantly increased risk of all-cause dementia, AD, and vascular dementia (VaD), while former smoking showed no significant association with any outcome. Since then, evidence has expanded and the biological mechanisms that may underpin smoking-dementia

associations are better characterised.[13] For example, chronic exposure to tobacco smoke promotes atherosclerosis, endothelial dysfunction, and microvascular damage, leading to cerebral hypoperfusion and white matter lesions.[14,15] Smoking also induces systemic and cerebral neuroinflammation,[16] increases oxidative stress,[16] disrupts the blood–brain barrier,[17] and accelerates amyloid-β aggregation and tau phosphorylation.[18] The relative contribution of vascular and neurodegenerative pathways to the smoking–dementia association has direct implications for prevention strategy design. Whether the smoking-dementia association differs across dementia subtypes may further inform understanding of the underlying mechanisms. In addition, recent large-scale cohort studies drawing on data from millions of participants represented in national registries and biobanks including the UK Biobank,[19,20] the Korean National Health Insurance Service,[21,22] and a Swedish national register study[23] have contributed to strengthen the evidence. This growth in dementia-related data provides greater statistical power and an opportunity to explore potential differences in the association between smoking and dementia across subtypes.

We therefore conducted an updated systematic review and meta-analysis to quantify the associations between smoking status (ever, current, former vs never) and incidence of all-cause dementia, AD, and VaD, incorporating dose–response analysis by smoking intensity and PAF estimation. We also explored whether these associations are modified by study- and population-level characteristics known to influence dementia risk, including sample size, ethnicity, age at baseline, follow-up duration and adjustment for sex, education and Apolipoprotein E (APOE) ε4 genotype.

Methods

Study design and registration

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[24] and was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42025644539). The review updates and extends the systematic review by Zhong et al.[18]

Search strategy

PubMed, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and PsycINFO were searched from January 2013 to 31 August 2025, and the search was updated to 31 August 2026 during revision. The search strategy combined Medical Subject Headings (MeSH) and free-text terms for dementia ("dementia", "Alzheimer's disease", "cognitive impairment", "cognitive decline", "vascular dementia", "cognition") and smoking exposure ("smoking", "cigarette", "nicotine", "tobacco", "smoke"). Boolean operators and truncation were used to maximise sensitivity. Backward citation searching of all included studies and relevant systematic reviews was performed to identify additional eligible studies. Studies published before 2013 were identified from the previous systematic review by Zhong et al., which systematically searched the literature up to 2012; building on this review preserved continuity with its screening and avoided duplication, while all databases were searched *de novo* for the subsequent period. After review, 34 studies from the Zhong et al.[18] review were considered eligible for inclusion. Three studies[16,17,25] were excluded because of a cross-sectional design. Full search strategies are provided in the Supplementary Appendix.

Eligibility criteria

We included prospective cohort studies investigating the association between smoking and incident dementia (all-cause, AD, or VaD) in community-dwelling adults with a mean baseline age of 50 years or older who were free of dementia at baseline. Studies were required to report risk estimates (RR, hazard ratio [HR], or odds ratio [OR]) with 95% CIs comparing at least one smoking category (ever, current, or former) with never smokers. Studies reporting comparisons only with continuing smokers (e.g., former versus continuing smokers) were retained in the systematic review but excluded from the meta-analysis, as their estimates could not be pooled with those using never smokers as the reference group. Ever smoking refers to individuals who reported any history of smoking, encompassing both current and former smokers. Current smoking denotes individuals who were actively smoking at the time of baseline assessment. Former smoking refers to individuals who had previously smoked but had ceased prior to enrolment. Never smoking refers to individuals who reported no history of smoking and serves as the reference category in all analyses. We excluded cross-sectional studies, randomised controlled trials, case–control studies, case reports, conference abstracts, editorials. Studies conducted in specific patient populations (e.g., those with CVD or psychiatric disorders) were excluded to extend generalisability to community-dwelling populations.

Study selection and data extraction

Records were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) and duplicates removed using the in-built function. Titles and abstracts were independently screened by two reviewers for the primary search (ES, SSh) and update (BCMS, MS), followed by full-text assessment of potentially eligible studies. Data were extracted by a team of up to three reviewers who independently cross-verified data extraction (ES, SSh, MS). Extracted data included first author

name, publication year, study location, sample size, sex distribution, mean age at baseline, ethnicity, smoking exposure categories (alternative classifications such as quitters, reducers, sustainers or increasers were mapped to the ever, current and former categories only when the contrast was referenced to never smokers and estimates referenced to continuing smokers were analysed separately), number of cases and participants, follow-up duration, loss to follow-up, dementia diagnostic criteria, the most fully adjusted risk estimates with 95% CIs, the effect measure (HR, OR or RR), and adjustment factors. Disagreements at any stage were resolved by consensus or consultation with a senior reviewer (MS). Where several publications drew on the same cohort (e.g., UK Biobank, the Korean National Health Insurance Service, the Health Study of Trøndelag (HUNT Study)), the publication with the largest sample size was retained, with the longest follow-up used as a tie-breaker. The exception was the Rotterdam Cardiovascular Risk Factors, Aging and Dementia (CAIDE) and Canadian Study of Health and Aging (CSHA) cohorts, for which both publications were retained in the primary analysis as reporting different types of smoking exposures and dementia outcomes. Overlapping cohorts and the publications-retained sensitivity analysis are listed in Supplementary Tables S1 and S2.

Risk of bias assessment

Risk of bias was assessed using the Risk of Bias In Non-randomised Studies of Exposures (ROBINS-E)[41] tool across seven domains: bias due to confounding (D1), bias arising from measurement of the exposure (D2), bias in selection of participants (D3), bias due to post-exposure interventions (D4), bias due to missing data (D5), bias arising from measurement of the outcome (D6), and bias in selection of the reported result (D7). The assessment was independently conducted by five reviewers (JB, CB, SSa, NG, LRP) and cross-checked by a senior reviewer (MS). Each domain and the overall assessment were rated as low risk, some concerns, high risk, or very high risk.

Statistical analysis

Random-effects meta-analyses using restricted maximum likelihood (REML) estimation of the between-study variance with the Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment were conducted for nine comparisons: ever, current, and former smoking versus never smoking for each of three outcomes (all-cause dementia, AD, VaD). Effect sizes were log-transformed before pooling, and standard errors were derived as $SE = (\ln[\text{upper limit}] - \ln[\text{lower limit}])/3.92$, using the reported 95% confidence limits. HRs and ORs were treated as equivalent to RRs given the relatively low cumulative incidence of dementia in the included cohorts.[42] Because this rare-outcome assumption may not hold in older cohorts with long follow-up, we examined whether pooled estimates differed by effect-measure type. Between-study heterogeneity was quantified using Cochran's Q statistic, the I^2 statistic (with I^2 >50% and >75% considered moderate and high heterogeneity, respectively), and the between-study variance component (τ^2).

Pre-specified subgroup analyses examined potential effect modification by sample size (<1000 vs ≥ 1000 participants), ethnicity, geographic location of the study, mean (or median) age at baseline, maximum follow-up duration (<10 vs ≥ 10 years), loss to follow-up (≤20% vs >20%), diagnostic criteria, adjustment for APOE ε4 genotype, education and sex, publication period, effect measure and overall risk of bias. Differences between subgroups were assessed with a test for interaction (Q-between), and effect modification was inferred only when this test was statistically significant ($P < 0.05$). Random-effects meta-regression (REML with Knapp–Hartung adjustment) was conducted to examine whether study-level characteristics (sample size, mean baseline age, follow-up duration, and loss to follow-up) modified the pooled effect estimates. Meta-regression was performed separately for each smoking comparison (ever, current, former vs never) and each dementia outcome (all-cause dementia, AD, VaD). Publication bias was assessed by visual inspection of funnel plots and Egger's regression test ($P < 0.10$ considered suggestive of asymmetry).

We conducted a two-stage random-effects dose–response meta-analysis. At Stage 1, study-specific log-relative risks (log RRs) across exposure categories were regressed on the category midpoint dose using generalised least squares (GLS), with within-study covariance reconstructed from the reference-category case counts.[43] At Stage 2, study-specific slopes were pooled with the DerSimonian–Laird random-effects estimator. Results are presented as RR per 10 and 20 cigarettes per day, and as RR at 5, 10, 20 and 40 cigarettes per day derived from a restricted cubic spline (RCS). We pooled studies on the original reported metric where possible. Studies that reported pack-years or packs-per-day were converted to cigarettes-per-day at the category midpoint assuming an average smoking duration of 40 years (so 1 pack-year ≈ 0.5 cigarettes per day, and 40 pack-years ≈ 20 cigarettes per day). Open-ended top categories were assigned a midpoint of (lower bound + 5) for cigarettes-per-day bins and (lower bound + 10) for pack-year bins. Non-linearity was assessed using restricted cubic splines with three knots placed at 10, 20 and 30 cigarettes per day. These positions span the densest region of the observed dose distribution (the inter-quartile range across studies), yielding stable spline estimates for the typical exposure range while permitting curvature at higher doses. A Wald test on the cubic basis function tested H_0: the relationship is linear. Inclusion criteria for the dose–response pool were: (i) prospective cohort design;

(ii) two or more categories of exposure with a never-smoker reference, OR a continuous-dose adjusted model that could be linearly back-transformed onto the cigarettes-per-day scale; (iii) all-cause dementia outcome; (iv) reported RR, hazard ratio, or odds ratio with 95% CI. Otuyama 2020 was included on the basis of the adjusted hazard ratio per 1 pack-year, evaluated at the cohort's mean exposure (8.9 pack-years, ≈4.5 cigarettes per day at 40-year duration). Heterogeneity was quantified with Cochran's Q (chi-squared test), τ^2 (DerSimonian–Laird) and I^2. Small-study effects were assessed via Egger's regression test.

The calculation of the population attributable fraction (PAF) for smoking and all-cause dementia followed the methodology adopted by the 2024 Lancet Commission on dementia prevention, intervention and care.[2] The same approach is applied to the pooled relative risk derived from the present meta-analysis, allowing direct comparison with the Commission's published estimate.

The unweighted PAF is the proportion of disease cases in the population that would be prevented if the exposure were eliminated, assuming the relative risk (RR) reflects a causal effect. Levin's formula expresses this as:

$$PAF_unweighted = [Pe \times (RR-1)] / [1 + Pe \times (RR-1)]$$

where P_e is the prevalence of the exposure in the population and RR is the relative risk of disease given exposure. The formula assumes that the RR is approximately invariant across population strata and that the exposure is causally associated with the outcome.

The unweighted PAF is then discounted by this shared portion:

$$PAF_weighted = P_unweighted \times (1 - communality)$$

For smoking, the derived communality is 0.650. The weight applied is therefore:

$$1 - 0.650 = 0.350$$

The 95% confidence interval (CI) of the PAF is obtained by substituting the lower and upper bounds of the RR's 95% CI into the same formula. This is the same approach used by the Lancet Commission.[2]

Post-hoc analysis

Sensitivity analyses repeated the primary analyses with the DerSimonian–Laird estimator and restricted to studies without a high or very high overall risk of bias. Because AD and VaD estimates derive from partly different studies, we compared them within cohorts reporting both outcomes by pooling the within-study ratio of the VaD and AD relative risks. To compare cessation with continued smoking, we pooled within-study ratios of the former-versus-never and current-versus-never estimates from cohorts reporting both.

All analyses were conducted in Python (version 3.12) using NumPy and SciPy. Matplotlib was used for the forest plots and funnel plots.

Ethics

Ethical approval was not required because this study is a systematic review and meta-analysis of published, aggregate data from previously published cohort studies; no individual participant data were accessed.

Role of the funding source

There was no funding source for this study.

Results

Study selection and characteristics

The database search identified 4777 records. After removing 319 duplicates, 4458 records were screened at title and abstract level, of which 43 underwent full-text assessment. Eighteen were excluded after full-text review, with the remaining 25 studies meeting inclusion criteria.[19–43] The updated search (September 2025 to August 2026) identified 896 further records; after removal of 180 duplicates, 716 were screened, six were assessed in full text and two new studies met the inclusion criteria.[8,9] Combined with 34 studies[17–20,23–47] from the previous review,[2] 61 prospective cohort studies[11–13,17–20,23–27,29–43,45–47,49–51] were included in the systematic review and 57[11–13,17–20,23,24,26–29,31–33,35–43,45–47,49–51,53–57,59–61,63–65,67–69,71–73,75–77,79–81,83–85,87,89] were included in the meta-analysis (five studies[25,30,34,44,82] did not report estimates that could be pooled against never smokers). Twelve studies[20,27,28,38,40,45,47,49,53,63,67,69] (14 risk estimates as two studies[28,63] reported associations for men and women) reported data on intensity of smoking and were included in the dose–response analysis (Fig. 1).

The included studies comprised approximately 2·8 million participants, with follow-up periods ranging from 2[41] to 40[43] years. Studies were distributed across regions (some multinational cohorts contributed to more than one region): Africa (n=1),[53] Asia (n = 15),[17,23,24,26–28,31,32,35,37,38,40,45,47,49,50,53,55,57,59,61,63,65,67,69,71,73,75,77,79,81,83,85,87,89] Australia and New Zealand (n = 3),[11,12,39] Europe (n = 16),[13,18,19,25,29,30,33,34,36,41,42,44,46,51,54,60,68,72,76,80,82,84] North America (n = 29)[11,12,14–16,20,21,27,28,38,40,45,47,49,52,53,56,58,62,63,66,70,74,78,83,86,88,90] and South America (1).[48] Sample sizes ranged from 163[37] to 789,532 participants.[40] Among the 57 studies contributing to the meta-analyses, dementia was ascertained with clinical diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders

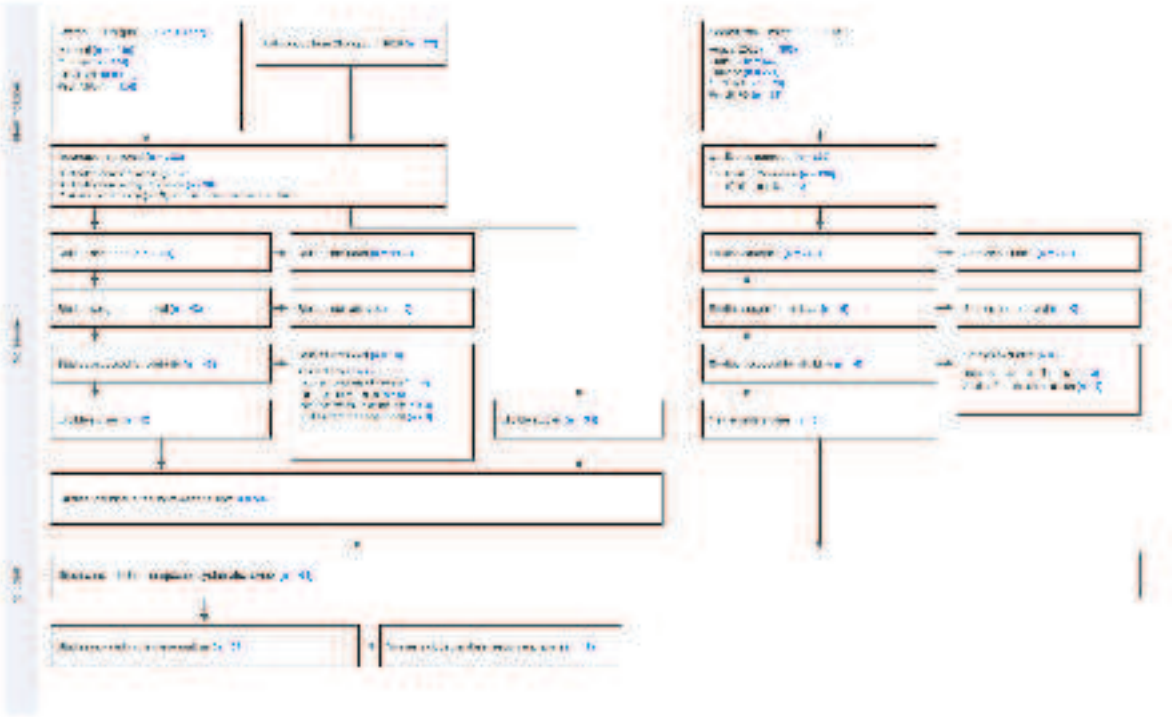


Fig. 1: PRISMA-compliant flow diagram for the updated systematic review. Thirty-four of the 37 studies from the previous systematic review by Zhong et al. (2015) are incorporated into this update. After combining new and previously identified studies, 61 cohort studies were included in the systematic review. The search was updated to 31 August 2026 and two further studies were included.

Association (NINCDS-ADRDA) or consensus panels) in 40, health records or International Classification of Diseases (ICD) codes in 12, algorithms based on cognitive test scores in 4 and unclear methods in 1; none used biomarker- or imaging-confirmed subtyping. Studies published since 2013 relied more often on records or ICD codes (7 of 22 vs 5 of 35 earlier studies) and on cognitive-score algorithms (4 of 22 vs none; Supplementary Tables S3 and S4).

Risk of bias: ROBINS-E assessment was completed for all 61 studies

Overall, no studies were low risk, 24 studies (39%) were classified as having some concerns, 28 (46%) as high risk, and 9 (15%) as very high risk. The most problematic domains were confounding (D1; 21 of 61 studies, 34% high risk), reflecting inadequate adjustment for key confounders such as APOE ε4 genotype and comorbidities, and missing data (D5; 11 of 61 studies, 18% high risk), reflecting high or unreported loss to follow-up in several cohorts. Post-exposure interventions (D4; 60 of 61 studies, 98% low risk) and outcome measurement (D6; 60 of 61 studies, 98% low risk) were generally well addressed. Exposure measurement (D2) was rated as some concern in 56 of 61 studies (92%), reflecting universal reliance on self-reported smoking status (Supplementary Figs. S1 and S2).

All-cause dementia

Ever smoking was associated with a higher risk of all-cause dementia (RR 1.13 (95% CI 1.04–1.22); k = 29; I^2 = 55%), as was current smoking (RR 1.31 (1.23–1.39); k = 39; I^2 = 65%), whereas former smoking was not (RR 1.04 (0.98–1.09); k = 30; I^2 = 53%) (Fig. 2, Table 1). For current smoking, the association differed by region, being weaker in multinational and other cohorts (1.05 (0.96–1.15)) and was stronger in studies adjusting for sex (1.38 vs 1.17; P for interaction<0.0001) or education (1.36 vs 1.21; P for interaction = 0.038) (Supplementary Figs. S3–S5). Point estimates for current smoking decreased with increasing mean baseline age (<65 years: 1.36 (1.30–1.41); 65–74 years: 1.30 (1.15–1.47); >74 years: 1.12 (0.95–1.33)), but the test for interaction was not significant (P = 0.12). For former smoking, estimates differed by baseline age (P for interaction = 0.021), from 1.15 (1.00–1.32) in cohorts aged 65–74 years to 0.87 (0.78–0.98) in cohorts older than 74 years, so the overall null estimate should not be interpreted as uniform across ages. For ever smoking, only publication period modified the association (P for interaction<0.001), with a null estimate in the three studies published since 2013 (0.92 (0.82–1.03)).

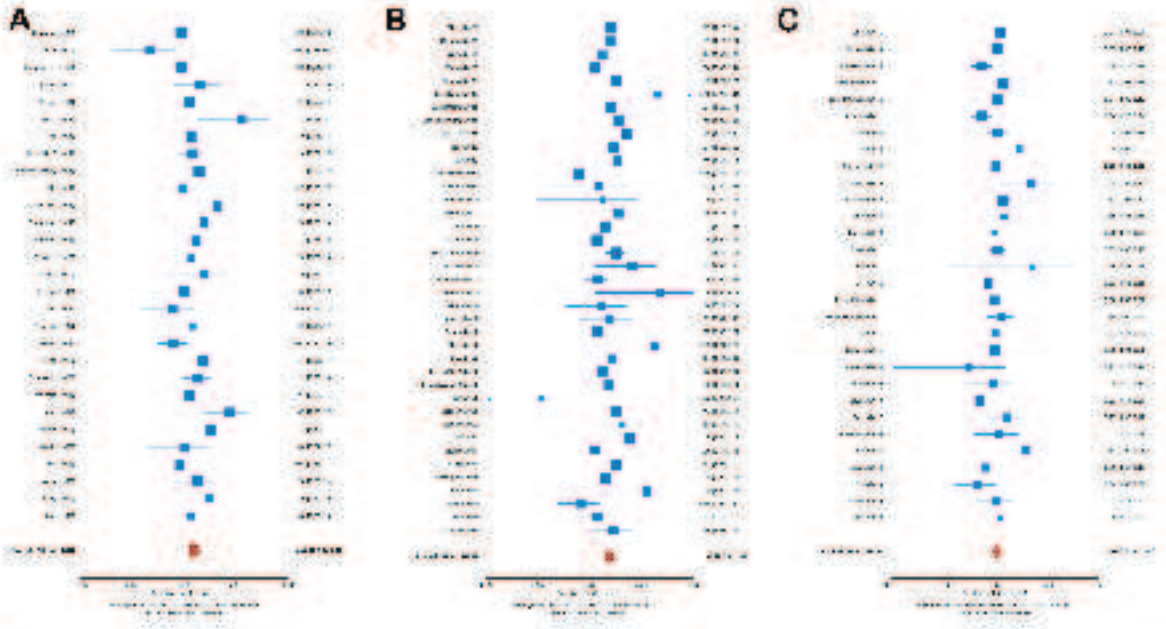


Fig. 2: Smoking and risk of all-cause dementia. Panel A: ever vs never smokers (k = 29). Panel B: current vs never smokers (k = 39). Panel C: former vs never smokers (k = 30). Abbreviations: CI, confidence interval; REML, restricted maximum likelihood; RR, relative risk. Squares show study-specific [RR/HR] and horizontal bars show 95% CIs; square size is proportional to the study weight in the random-effects model. Diamonds show the pooled estimate, with the width of the diamond representing the 95% CI. Pooled estimates were obtained using random-effects meta-analysis with between-study variance (τ^2) estimated by REML. I^2 is the percentage of total variability across studies attributable to heterogeneity rather than chance. τ^2 is the estimated between-study variance. Q is Cochran's Q statistic for heterogeneity, with its P value (P heterogeneity). P (overall effect) is the P value of the test that the pooled effect equals the null (RR = 1).

Alzheimer's disease

Current smoking was associated with a higher risk of AD (RR 1.40 (95% CI 1.08–1.80); k = 15; I^2 = 80%), whereas the association for ever smoking was not statistically significant (1.10 (0.98–1.24); k = 23) and former smoking was not associated with AD (1.02 (0.95–1.09); k = 16) (Fig. 3, Table 1). For current smoking, the association differed by baseline age (P for interaction = 0.029), with the largest estimate in cohorts aged 65–74 years (1.86 (1.27–2.73)); no other characteristic significantly modified the associations with AD (Supplementary Figs. S6–S8).

Outcome	k	Pooled RR (95% CI)	P value	I^2	τ^2	95% prediction interval	Egger P
Ever vs never							
All-cause dementia	29	1.13 (1.04–1.22)	0.004	55%	0.019	0.84–1.52	0.32
Alzheimer's disease	23	1.10 (0.98–1.24)	0.10	67%	0.044	0.70–1.73	0.30
Vascular dementia	10	1.25 (1.07–1.46)	0.01	48%	0.027	0.83–1.89	0.34
Current vs never							
All-cause dementia	39	1.31 (1.23–1.39)	<0.0001	65%	0.018	0.99–1.73	0.09
Alzheimer's disease	15	1.40 (1.08–1.80)	0.01	80%	0.159	0.57–3.43	0.20
Vascular dementia	9	1.52 (1.20–1.93)	0.004	60%	0.046	0.86–2.68	0.92
Former vs never							
All-cause dementia	30	1.04 (0.98–1.09)	0.18	53%	0.007	0.87–1.23	0.73
Alzheimer's disease	16	1.02 (0.95–1.09)	0.51	2%	0.000	0.95–1.09	0.89
Vascular dementia	9	1.06 (0.93–1.20)	0.35	0%	0.005	0.86–1.31	0.39

k = number of study estimates. RR = relative risk. CI = confidence interval. Pooled estimates from random-effects models (Restricted Maximum Likelihood (REML) with Hartung–Knapp–Sidik–Jonkman adjustment). I^2 = proportion of variability due to between-study heterogeneity. 95% prediction interval = range within which the effect in a new comparable study is expected to lie. τ^2 = between-study variance. Egger = P value from Egger's regression test for funnel plot asymmetry. AD = Alzheimer's disease. VaD = vascular dementia.

Table 2: Summary of random-effects meta-analyses of smoking and risk of dementia, Alzheimer's disease, and vascular dementia.

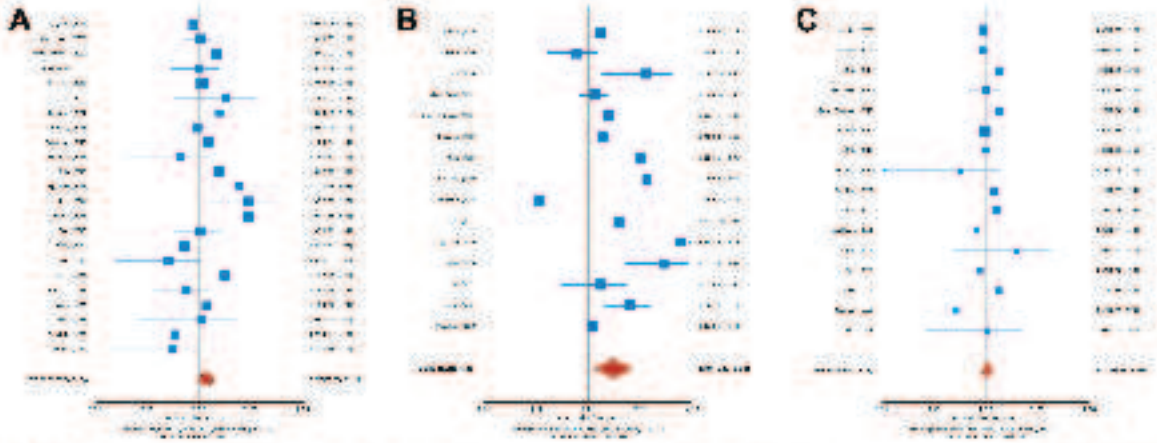


Fig. 3: Smoking and risk of Alzheimer's disease. Panel A: ever vs never smokers (k = 23). Panel B: current vs never smokers (k = 15). Panel C: former vs never smokers (k = 16). Details as for Fig. 2. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood; RR, relative risk. Squares show study-specific [RR/HR] and horizontal bars show 95% CIs; square size is proportional to the study weight in the random-effects model. Diamonds show the pooled estimate, with the width of the diamond representing the 95% CI. Pooled estimates were obtained using random-effects meta-analysis with between-study variance (τ^2) estimated by REML. I^2 is the percentage of total variability across studies attributable to heterogeneity rather than chance. τ^2 is the estimated between-study variance. Q is Cochran's Q statistic for heterogeneity, with its P value (P heterogeneity). P (overall effect) is the P value of the test that the pooled effect equals the null (RR = 1).

Vascular dementia

Ever smoking (RR 1.25 (95% CI 1.07–1.46); k = 10) and current smoking (1.52 (1.20–1.93); k = 9) were associated with a higher risk of VaD, whereas former smoking was not (1.06 (0.93–1.20); k = 9) (Fig. 4, Table 1). For current smoking, estimates differed by publication period, effect measure and overall risk of bias (P for interaction 0.005–0.02), but these comparisons involved very few studies per subgroup (Supplementary Figs. S9–S11).

Comparison of subtypes

Because the AD and VaD estimates derive from partly different sets of cohorts, we compared them within cohorts reporting both outcomes. In the nine cohorts reporting both, the ratio of the VaD to the AD relative risk for current smoking was 1.11 (95% CI 0.88–1.40; P = 0.31); the corresponding ratios were 1.10 (0.96–1.25; k = 10) for ever smoking and 1.01 (0.89–1.14; k = 9) for former smoking (Supplementary Table S5).

Cessation versus continued smoking

Within the 29 cohorts reporting both current and former smoking against never smokers, former smokers had a lower risk of all-cause dementia than current smokers (RR 0.81, 95% CI 0.75–0.88; I^2 = 46%), with similar contrasts for AD (0.77, 0.60–0.98; k = 15) and VaD (0.72, 0.61–0.85; k = 9) (Supplementary Table S6). Studies reporting contrasts against continuing smokers were consistent in the Health and Retirement Study, people who had quit before baseline had a lower dementia risk than current smokers (HR 0.76, 95% CI 0.69–0.83),[91] and two Korean cohorts reported similar findings.[60,79]

Sensitivity analyses

Pooled estimates were almost identical with the DerSimonian–Laird estimator (current smoking and all-cause dementia: RR 1.31, 95% CI 1.23–1.38) and when restricted to studies with some concerns for overall risk of bias (1.30, 1.11–1.53; k = 16) (Supplementary Table S1). Estimates did not differ by effect-measure type for any comparison except current smoking and VaD (P for interaction = 0.005; two studies reporting RRs), and restricting the analysis of current smoking and all-cause dementia to HRs gave 1.30 (1.23–1.38; k = 29). Retaining one publication per cohort for the cohorts that contributed more than one publication to the same comparison gave similar estimates (current smoking and all-cause dementia: 1.31, 1.22–1.40; k = 34; Supplementary Table S1). Diagnostic ascertainment method did not modify any association (all P for interaction ≥0.33).

Publication bias and meta-regression

Funnel plots and Egger's regression tests assessed publication bias across all nine meta-analyses (Supplementary Figs. S12 and S20). Egger's test suggested possible small-study effects for current smoking and all-cause dementia (P = 0.09), although the pooled estimate was unchanged in studies with at least 1000 participants (1.31, 1.23–1.39; k = 35); there was no evidence of asymmetry for the other comparisons (all P ≥ 0.20). Meta-regression analyses (REML with Knapp–Hartung adjustment; Supplementary Table S7) examined whether sample size, baseline age, follow-up duration, or loss to follow-up modified the association between smoking exposure and dementia outcomes.

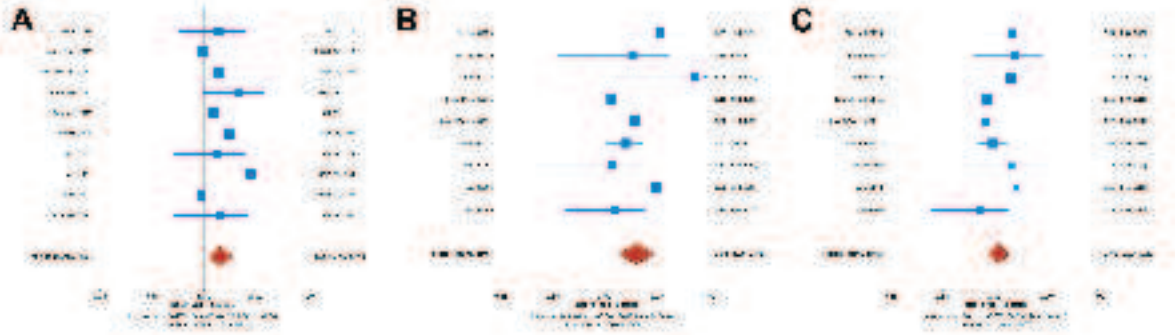


Fig. 4: Smoking and risk of vascular dementia. Panel A: ever vs never smokers (k = 10). Panel B: current vs never smokers (k = 9). Panel C: former vs never smokers (k = 9). Details as for Fig. 2. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood; RR, relative risk. Squares show study-specific [RR/HR] and horizontal bars show 95% CIs; square size is proportional to the study weight in the random-effects model. Diamonds show the pooled estimate, with the width of the diamond representing the 95% CI. Pooled estimates were obtained using random-effects meta-analysis with between-study variance (τ^2) estimated by REML. I^2 is the percentage of total variability across studies attributable to heterogeneity rather than chance. τ^2 is the estimated between-study variance. Q is Cochran's Q statistic for heterogeneity, with its P value (P heterogeneity). P (overall effect) is the P value of the test that the pooled effect equals the null (RR = 1).

Across all smoking-status comparisons (ever, current, and former vs never) for all-cause dementia, AD, and VaD, no moderator was significant (all $P \geq 0.11$); the main sources of heterogeneity identified were region and confounder adjustment in the subgroup analyses.

Dose–response analysis

A two-stage random-effects dose–response meta-analysis across 12 studies (14 estimates; Supplementary Tables S8 and S9) found a pooled linear slope of RR 1.16 (95% CI 1.09–1.23) per 10 cigarettes per day (Supplementary Table S10). Restricted cubic spline analysis showed progressively increasing risk from 1.08 (95% CI 1.06–1.10) at 5 cigarettes to 1.64 (95% CI 1.43–1.89) at 40 cigarettes per day, with no significant departure from linearity ($P = 0.37$) (Fig. 5 and Supplementary Table S11).

PAF calculation

The unweighted PAF of all-cause dementia for current smoking was 6.4% (95% CI 4.8–8.1), based on a global current-smoking prevalence of 22.3% and a pooled relative risk of 1.31 (95% CI 1.23–1.39). The community-weighted PAF was 2.2% (1.7–2.8), consistent with the estimate of the 2024 Lancet Commission (Fig. 6).

Discussion

This systematic review and meta-analysis of 61 cohort studies and approximately 2.8 million participants provides an updated evaluation of the association between smoking and dementia risk. Current smoking is associated with increased risk across all three dementia outcomes, former smoking is not associated with excess risk relative to never smoking and is associated with lower risk than current smoking, and dementia risk increases with smoking intensity. Point estimates were largest in cohorts with a midlife baseline, although the test for interaction was not significant and mean baseline age is an imperfect proxy for the timing of exposure.

Point estimates for current smoking were higher for VaD (52% increased risk) than for AD (40%) and all-cause dementia (31%). However, these pooled estimates derive from partly different sets of cohorts, and within cohorts reporting both subtypes the VaD and AD estimates did not differ significantly. The apparent gradient is therefore descriptive and should not be taken as evidence of a predominant vascular mechanism. Smoking has well-established effects on atherosclerosis,[9] endothelial dysfunction,[8] and cerebral microvascular disease.[10] The association with clinically diagnosed AD suggests that effects are not confined to the vasculature, potentially through direct neurotoxic effects, promotion of amyloid pathology, or mixed vascular–neurodegenerative processes.[11,12] Clinicopathological studies indicate that approximately one-third of people with AD have cerebral infarcts at autopsy and 30–50% have appreciable cerebrovascular pathology alongside Alzheimer-type changes.[13] Vascular pathology contributes to dementia mostly as part of mixed pathology rather than as isolated vascular dementia and is frequently under-recognised clinically.[12] Cohorts incorporating neuroimaging and biomarker measures of cerebrovascular burden (such as white matter hyperintensities, infarcts and microbleeds) alongside amyloid and tau markers could characterise the vascular contribution more completely. Supporting people to quit smoking alongside the management of other vascular risk factors may therefore be a pragmatic prevention strategy.

The dose–response analysis showed a graded increase in dementia risk with smoking intensity. The absence of a threshold or plateau within the observed

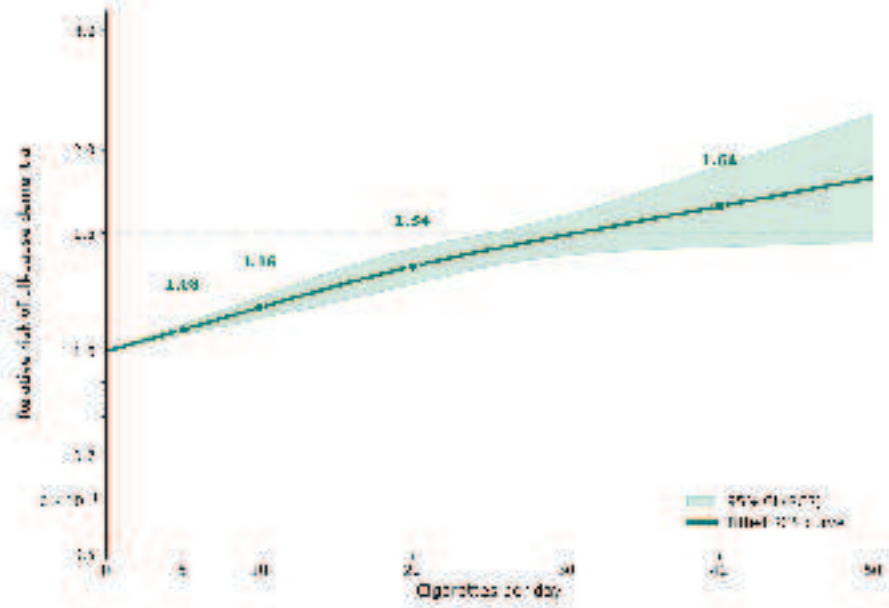


Fig. 5: Pooled restricted cubic spline (RCS) dose–response curve. Three knots placed at 10, 20 and 30 cigarettes per day. Reference is 0 cigarettes per day (never smokers). Shaded band: 95% confidence interval. Predicted relative risks at 5, 10, 20 and 40 cigarettes per day are indicated on the curve. P for non-linearity = 0.37. Analysis was based on 12 studies (14 estimates).

range is consistent with a biological gradient, although dose–response associations in observational data remain susceptible to residual confounding by correlates of heavy smoking. In these observational data, risk estimates were elevated across the range of smoking intensity examined, and we could not identify a level of exposure below which no association was observed.

Former smoking was not associated with dementia relative to never smoking, and within the same cohorts former smokers had a lower risk than current smokers.

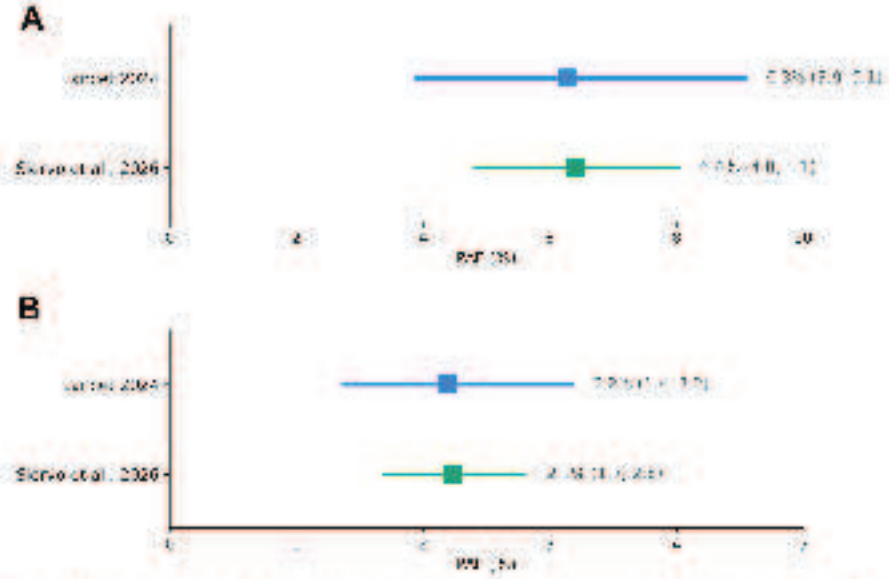


Fig. 6: Population attributable fraction (PAF) of smoking for all-cause dementia and comparison with the 2024 Lancet Commission. Panel A: unweighted PAF. Panel B: communality-weighted PAF, adjusted for the shared variance between smoking and other modifiable dementia risk factors. Both estimates use the same global current-smoking prevalence (22.3%) and the same communality coefficient (0.650). The Sierra et al. estimate uses the pooled relative risk for current smoking and all-cause dementia from the present meta-analysis (RR 1.31 (95% CI 1.23–1.39)). Squares represent point estimates and horizontal bars represent 95% confidence intervals.

These findings are compatible with a benefit of cessation but require cautious interpretation. Pooling all former smokers into one category combines recent and long-term quitters, whose risks may differ; few studies reported time since cessation, although in one recent cohort dementia risk declined with duration of abstinence and approached that of never smokers after approximately 5–7 years.[91] The comparison is also susceptible to competing risk of death, because people who smoke and survive long enough to quit and remain free of dementia may be selected for lower risk, and to reverse causation through 'sick-quitter' effects, whereby emerging illness prompts cessation.[88,92] In addition, estimates for former smoking differed by baseline age, so the overall null estimate should not be read as uniform across ages. Smoking promotes cerebrovascular damage,[93,94] oxidative stress,[5] and neuroinflammation,[9] accelerating amyloid-beta accumulation and tau phosphorylation[95,96] and cessation may partially reverse these processes.[8,110–113] A multinational longitudinal study of 9435 participants across 12 countries found that people who quit smoking during mid-to-late-life experienced significantly slower decline in memory and verbal fluency over six years post-cessation compared with those who continued smoking, regardless of age at quitting.[114] The mechanisms underlying cardiovascular risk reduction after cessation, including restored endothelial function and improved nitric oxide bioavailability, are shared with cerebrovascular pathways implicated in dementia pathogenesis, providing a plausible biological basis for the observation that the risk associated with former smoking approaches that of never smoking.[115,116] Collectively, these data suggest that the brain may retain some capacity for vascular and metabolic recovery following cessation, although this is an inference from the broader literature rather than a direct result of our analysis.

Associations with current smoking tended to be stronger when exposure was assessed in midlife (<65 years) and weaker in late life (>74 years), although the formal test for interaction was not statistically significant. Two mechanisms may account for this pattern. First, a "healthy survivor" effect, whereby individuals who smoke and survive to advanced age represent a biologically resilient subpopulation, not generally representative of people who smoke.[88] Second, reverse causation, whereby prodromal dementia may lead to smoking reduction or cessation prior to clinical diagnosis.[2,88] Both mechanisms would produce systematic underestimation of the true association in studies with older baseline ages. AD- and VaD-specific estimates were largest in the 65–74 years stratum, which may reflect either a longer exposure-disease latency for these subtypes or limited statistical power for subtype-stratified analyses in the youngest age stratum. These patterns support measuring exposure in midlife, well before the prodromal phase, but do not establish midlife as a period of greater susceptibility. Updated pooled estimates for current smoking are similar to those of Zhong et al.[18] (all-cause dementia: RR 1.31 vs 1.30; AD: 1.40 vs 1.40), whereas the VaD estimate is higher (1.52 vs 1.38), reflecting the contribution of recent cohorts with long follow-up. The observation that studies adjusting for sex or education produced stronger associations than less-adjusted studies needs careful interpretation. This pattern may partly reflect survival-related selection arising from the competing risk of death rather than confounding. Specifically, people who die prematurely from cardiovascular disease or cancer before dementia onset are removed from the risk set, which can attenuate the observed smoking–dementia association.[117] Covariate adjustment cannot resolve this as it requires explicit definition of the causal question and analysis of death as a competing event,[91] which few included cohorts undertook. Abner et al.[87] and Rojas-Saunero et al.[88] are examples of studies that used a competing-risk framework. Smoking-related cardiovascular and pulmonary disease may also contribute to dementia directly, and few cohorts characterised clinical or subclinical cerebrovascular disease (for example, with brain MRI) at diagnosis. APOE ε4 may also act as more than a simple confounder in this context: smokers and non-smokers may differ in APOE ε4 distribution, and APOE ε4 may modify rather than confound the smoking-AD association, which complicates direct interpretation of the adjusted estimates. That 61% of included studies were rated as high or very high risk of bias driven primarily by inadequate confounder adjustment and loss to follow-up underscores the importance of this interpretation and indicates that current pooled estimates may remain conservative.

Using the 2024 Lancet Commission framework, the community-weighted PAF for current smoking (2.2%) was consistent with the Commission's estimate, providing independent support for it from a larger evidence base; if the association is causal, roughly one in 45 dementia cases worldwide would be attributable to current smoking. These estimates support including dementia among the outcomes considered in smoking prevention and cessation strategies, alongside cardiovascular disease and cancer.

National tobacco control strategies have not incorporated dementia or brain health in a similar manner to cardiovascular disease or cancer.[1,3] This represents a material gap between the evidence and its translation into policy. The absence of excess risk among former smokers was broadly consistent across outcomes and regions, although estimates varied by baseline age. Studies of cognitive trajectories after cessation suggest that quitting at any age may benefit brain health[114]; this is an inference from the broader literature rather than a direct result of our analysis. Incorporating this message

into campaigns, pictorial warnings and cessation programmes could broaden their reach and motivational appeal, particularly among older adults for whom cardiovascular and cancer messaging may be less salient or perceived as relating to treatable conditions, whereas dementia is widely viewed as untreatable and is among the most feared health outcomes in middle-aged and older populations.[58]

The diagnoses in the included cohorts were clinical-syndromic classifications (DSM-III-R to DSM-5, NINCDS-ADRDA or ICD codes) that predate biomarker-based definitions of AD.[59] AD pathology begins 10–25 years before symptoms[60] and frequently co-occurs with small-vessel disease, cerebral amyloid angiopathy, Lewy body and TDP-43 pathology, particularly in older people,[61,62] and stepwise vascular dementia as defined by earlier criteria is now uncommon. Our subtype estimates should therefore be interpreted as associations with clinically diagnosed syndromes rather than with specific pathologies; a meta-analysis of published cohorts cannot retrospectively apply biomarker criteria. Even the newer cohorts lacked imaging or biomarker confirmation of aetiology, so the evidence base has not advanced since the 2015 review. The long preclinical phase also complicates the exposure–outcome window as smoking measured in late life may already be affected by prodromal changes, whereas exposure measured in midlife, decades before diagnosis, is less susceptible to reverse causation, which may partly explain the larger estimates in midlife cohorts.

Several limitations need consideration. The observational design of all included studies precludes causal inference; the consistency of findings across outcomes, smoking categories and regions is compatible with, but does not establish, a causal relationship. Residual confounding, reverse causation and sick-quitter bias, competing risk of non-dementia death, and heterogeneity in time since cessation may all have influenced the estimates. Smoking status was self-reported in all studies, introducing potential misclassification that would generally attenuate effect estimates. Heterogeneity was substantial for several comparisons, particularly current smoking and AD, indicating variability in effect sizes not fully accounted for by the covariates examined. The limited number of vascular dementia studies (nine to ten per comparison) constrains the power of subgroup analyses for this outcome. Most included studies were conducted in high-income countries with predominantly White or East Asian populations, limiting generalisability to other settings and populations. Few studies reported sex-specific estimates, precluding a meaningful assessment of sex differences, and none distinguished biological sex from social gender. Similarly, race and ethnicity were not consistently reported in the included cohorts and could not be analysed, so we could not assess whether associations differ across racial or ethnic groups. Smoking exposure definitions varied across studies with substantial heterogeneity in the minimum duration or frequency of smoking required to classify a participant as a person who smokes, the recency of cessation used to distinguish current and former smoking, and verification of self-reported smoking status by biochemical measures. These inconsistencies represent a recognised limitation of the literature and may contribute to between-study variability in the pooled estimates. Confounder adjustment was inconsistent, and 61% of included studies were rated as high or very high overall risk of bias. Misclassification of dementia subtypes is a concern not only in registry- and biobank-based cohorts relying on ICD codes, hospital records or death certificates, but also in clinically assessed cohorts using DSM or consensus criteria, as no included study used biomarker- or imaging-confirmed subtyping; newer cohorts relied more often on records and cognitive-score algorithms, although diagnostic method did not modify the pooled associations.

This review shows that current smoking is consistently associated with a higher risk of all-cause dementia, AD and VaD, with risk increasing with smoking intensity, whereas former smoking is associated with risks similar to those of never smokers and lower than those of current smokers. Although observational data cannot establish causality, these findings strengthen the epidemiological evidence supporting consideration of dementia risk reduction within national tobacco control strategies and associated public health campaigns to end tobacco use. Studies with objectively verified smoking histories in diverse populations are needed to determine how dementia risk varies with age at quitting and time since cessation, and whether total years of active smoking modifies these effects.

Contributors

MS and BCMS conceived the study and developed the protocol. MS and CVB performed the literature search. PS, SSh, CVB, and MS conducted title/abstract screening and full-text selection. PS, SS, and MS performed data extraction. JB, CVB, NC, LRP, and SSa conducted the risk of bias assessment. MS performed the statistical analyses. MS and BCMS wrote the first draft of the manuscript. All authors (MS, BCMS, CVB, PS, SSh, SSa, JB, NC, LRP, SB, TB, PB, JD, ZG, BM and ASC) critically reviewed the manuscript, provided intellectual input, and approved the final version for submission. MS and BCMS accessed and verified the underlying data and had full access to all data and had final responsibility for the decision to submit for publication.

Data sharing statement

All data used in this meta-analysis were extracted from published studies. The complete extracted dataset, analysis code, and ROBINS-E assessments are available from the corresponding author upon reasonable request.

Declaration of interests

MS and BCMS are co-directors of NeuroAnalysis. BCMS's Chair in Dementia is funded by Dementia Australia. PB has received grants

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.eclinm.2026.104310.

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