

Risk factors for cognitive impairment and dementia after stroke: a systematic review and meta-analysis

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Summary

Background Cognitive impairment and dementia are highly prevalent among stroke survivors and represent a major burden for patients, carers, and health-care systems. We studied the risk factors for post-stroke cognitive impairment (PSCI) and dementia (PSD) beyond the well established risk factors of age and stroke severity.

Methods In this systematic review and meta-analysis we conducted a systematic literature search from database inception until Sept 15, 2023. We selected prospective and retrospective cohort studies, post-hoc analyses from randomised controlled trials, and nested case-control studies of patients with acute stroke (ischaemic, haemorrhagic, and transient ischaemic attack), exploring associations between risk factors at baseline and PSCI or PSD over a follow-up period of at least 3 months. Study quality was assessed using the Newcastle-Ottawa quality assessment scale. We calculated pooled relative risks (RRs) with random-effects meta-analyses and performed subgroup, meta-regression, and sensitivity analyses. This study was preregistered with PROSPERO, CRD42020164959.

Findings We identified 162 eligible articles for our systematic review, of which 113 articles (89 studies, 160 783 patients) were eligible for meta-analysis. Baseline cognitive impairment was the strongest risk factor for PSCI (RR 2.00, 95% CI 1.66–2.40) and PSD (3.10, 2.77–3.47). We identified diabetes (1.29, 1.14–1.45), presence or history of atrial fibrillation (1.29, 1.04–1.60), presence of moderate or severe white matter hyperintensities (WMH; 1.51, 1.20–1.91), and WMH severity (1.30, 1.10–1.55, per SD increase) as treatable risk factors for PSCI, independent of age and stroke severity. For PSD, we identified diabetes (1.38, 1.10–1.72), presence of moderate or severe WMH (1.55, 1.01–2.38), and WMH severity (1.61, 1.20–2.14, per SD increase) as treatable risk factors. Additional risk factors included lower educational attainment, previous stroke, left hemisphere stroke, presence of three or more lacunes, brain atrophy, and low baseline functional status. Associations of risk factors with PSD were weaker in studies conducted and published more recently. We found substantial interstudy heterogeneity and evidence of reporting bias.

Interpretation Our results highlight the importance of cognitive impairment in the acute phase after stroke for long-term prediction of PSCI and PSD. Treatable risk factors include diabetes, atrial fibrillation, and markers of cerebral small vessel disease (ie, white matter hyperintensities and lacunes). Future trials should explore these risk factors as potential targets for prevention of PSCI and PSD.

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Introduction

The growing proportion of stroke survivors worldwide has shifted attention to the long-term consequences of stroke. Prevalence and incidence rates of cognitive deficits vary depending on the outcome definition and assessment timepoint.¹ Post-stroke cognitive impairment (PSCI) has been observed in up to 80%² of stroke survivors at 4 years after stroke, and post-stroke dementia (PSD) in up to 40%¹ of stroke survivors 1 year after stroke, thus posing a major burden to patients, caregivers, and health-care systems. A more detailed understanding of the factors predisposing individuals to PSCI and PSD is required to counsel patients and families and to inform prevention trials.

Established risk factors for PSCI and PSD, as determined by meta-analyses and population-based

studies, include older age and more severe strokes. Less robust evidence exists for lower educational attainment, history of atrial fibrillation and diabetes, and previous stroke, as well as presence of neuroimaging markers of cerebral small vessel disease (cSVD), including white matter hyperintensities (WMH).^{1,3–5}

Risk factors for PSCI and PSD can be categorised into those that are non-modifiable (eg, age, stroke severity, and educational attainment) and those that are treatable after stroke, such as atrial fibrillation^{6,7} or diabetes, which have, to date, received less attention. Recent data further suggest that WMH, which might be modified by antihypertensive treatment,⁸ could regress after stroke.^{9,10} Robust information on risk factors is important for more accurate risk prediction and the development of strategies for prevention.¹¹

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Research in context

Evidence before this study

The first large-scale meta-analysis reporting on predictors for post-stroke dementia (PSD) was published in 2009. Since then, research on risk factors for PSD has gained momentum and has also been extended to encompass milder forms of cognitive impairment, commonly referred to as post-stroke cognitive impairment (PSCI). Systematic reviews and meta-analyses that comprehensively evaluate all risk factors investigated in individual studies are scarce. There is also a lack of pooled estimates for PSCI independent of well established risk factors, such as age and stroke severity. We systematically searched MEDLINE, Cochrane, and reference lists for articles on risk factors for cognitive deficits after stroke published in English up to Sept 15, 2023, using search terms including “predictor(s)”, “risk factor(s)”, “longitudinal”, “prospective”, “stroke”, “post-stroke”, “dementia”, and “cognitive”. Observational studies and post-hoc analyses from randomised controlled trials on patients with ischaemic stroke or haemorrhagic stroke, or patients with transient ischaemic attack for whom risk factors were recorded at baseline and who had cognitive follow-up of at least 3 months were included.

Added value of this study

Our systematic review and meta-analysis includes data from more than 160 000 stroke patients from 89 individual studies that assessed risk factors for PSCI and PSD. Applying rigorous criteria for study selection, we show a strong correlation of pooled estimates from studies on PSD only with those from studies on severity of PSCI, including dementia. Of all the predictors studied, cognitive impairment in the acute phase after stroke showed the strongest association with both PSCI

and PSD. Among cardiovascular risk factors, diabetes was the strongest predictor of both PSCI and PSD. Evidence on the role of atrial fibrillation remains more inconclusive regarding its role in the development of PSD. Additional predictors for PSCI and PSD beyond age and stroke severity include lower educational attainment, previous stroke, presence and increasing severity of cerebral small vessel disease-related neuroimaging markers (ie, white matter hyperintensities [WMH] and lacunes), atrophy, medial temporal lobe atrophy, left hemisphere stroke, lower cognitive performance and functional status at baseline, and urinary incontinence. We provide new evidence on temporal trends in risk prediction. The strength of the associations of stroke severity, educational attainment, WMH severity, and atrial fibrillation with PSD was weaker in studies that were conducted and published later in time.

Implications of all the available evidence

Risk factors for dementia and for milder forms of cognitive impairment after stroke largely overlap, with similar effect sizes. Testing for cognitive impairment in the acute phase after stroke could help identify patients at higher risk for long-term PSCI and PSD. Treatable risk factors, such as diabetes, atrial fibrillation, and markers of cerebral small vessel disease, particularly WMH, should be explored as targets in the secondary prevention of adverse cognitive outcomes after stroke. The contribution of treatable risk factors to PSD risk has declined over the past four decades, possibly mirroring improvements in treatable risk factor management and decreasing trends in dementia incidence in general. Risk prediction tools should be regularly updated to accurately reflect the significance of various risk factors for PSCI and PSD.

A wealth of recent studies has explored a growing number of candidate risk factors but, for the majority, there is still uncertainty as to whether these factors contribute to PSCI or PSD risk independently of age and stroke severity. Studies are characterised by heterogeneity in study design, follow-up period, method, diagnostic tools, and outcome definition for PSCI and PSD.¹² Previous meta-analyses have examined only a few risk factors,^{5,13–19} did not account for heterogeneity between studies,¹³ did not extend analyses to the clinically relevant endpoint of PSCI,^{1,20,21} and did not stratify by studies adjusting for age and stroke severity.^{4,13,16} This uncertainty regarding the risk factor profiles of PSCI and PSD hampers efforts for the development of risk-stratification tools and prevention strategies.

To address this gap, we performed a systematic review and meta-analysis to assess the risk factor profiles for both PSCI and PSD beyond age and stroke severity, placing a particular focus on treatable risk factors. We further examined temporal trends in the strength of associations between predictors and PSCI and PSD and

evaluated the quality of available evidence as well as sources of heterogeneity between studies.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was registered in advance (appendix pp 56–61) and conducted in accordance with PRISMA²² and the MOOSE guidelines²³ (appendix pp 51–53). It includes publicly available effect estimates. Ethical approval and informed consent were obtained by each study included in this meta-analysis.

From database inception until Aug 4, 2022, one investigator (JF) conducted the systematic literature search with no language restriction in MEDLINE and Cochrane using a predefined search strategy (appendix p 3). Reference lists of previous relevant systematic reviews and eligible articles were also screened manually by the same investigator. After screening titles and abstracts, full texts were examined based on our predefined eligibility criteria. In case of uncertainty, a consensus was reached with a second author (MKG). If multiple publications were available from the same study

See Online for appendix

population, we selected the article that adjusted for stroke severity in addition to age, had the highest number of additional model covariables, or had the largest sample size. The systematic literature search was updated to include publications until Sept 15, 2023.

We included prospective and retrospective cohort studies investigating the association between risk factors assessed at baseline and dementia or global cognitive impairment after stroke. For inclusion in our systematic review, articles had to report summary estimates for binary outcomes (PSD or PSCI, yes or no) based on predefined diagnostic criteria, or cutoffs in neuropsychological tests, or both (appendix p 9); include at least 30 patients aged 18 years or older; and assess risk factors within the first 90 days after stroke and cognitive outcomes at least 3 months after stroke onset. We included studies of patients with ischaemic or haemorrhagic stroke (WHO criteria) or with transient ischaemic attack (TIA), but studies including more than 50% of patients with TIA were excluded. Nested case-control studies and post-hoc analyses from randomised controlled trials (RCTs) were included if they met the eligibility criteria and did not randomly assign participants on the basis of presence of the risk factor under study.

Exclusion criteria were: animal studies; RCTs with randomisation based on risk factor presence or absence; cross-sectional studies; studies examining specific subgroups of stroke patients based on affected brain areas; predominantly subjective, self-reported, or proxy-reported stroke, PSD, or PSCI; cohorts consisting only of patients with a pre-stroke diagnosis of dementia, cognitive impairment, or diseases that might interfere with cognitive function; cohorts with genetic diseases predisposing to stroke; studies with stroke-free controls; and studies with a follow-up of less than 90 days. In addition, we excluded studies focused solely on continuous cognitive outcomes, trajectories of cognitive performance (recovery or decline), or domain-specific performance or impairment. We excluded studies from the meta-analysis that did not adjust their models for age or stroke severity.

Data analysis

The data extraction process is detailed in the appendix (p 4). We assessed study quality using a modified version of the Newcastle-Ottawa quality assessment scale (NOS) for cohort studies,²⁴ excluding criterion 3 (exposure ascertainment), which resulted in a possible range of 0–8 points. This modification was necessary, as we were interested in multiple exposure variables, rather than a single exposure variable. A detailed description of the quality assessment process is given in the appendix (p 5).

To obtain pooled estimates from studies with different effect measures for binary endpoints, we converted odds ratios and hazard ratios to relative risks (RRs) using

established approaches^{25–27} (appendix p 6). For many risk factors, articles used different units or scales when describing the relationship between exposure and PSCI or PSD. To achieve comparability between differently coded variables, the effect measures were harmonised (appendix p 7). We pooled estimates for an individual risk factor if at least two studies reported harmonisable results on the same outcome (either PSCI or PSD). Due to the heterogeneous definitions and measurement methods of most risk factors, we used random-effects meta-analyses with the inverse variance method to pool RRs (95% CI). Knapp-Hartung adjustments²⁸ were used to calculate confidence intervals around the pooled effects. Between-study heterogeneity was estimated with I^2 , Cochran Q, and τ^2 using the DerSimonian-Laird estimator. Spearman's correlation was applied to compare pooled estimates for PSCI and PSD across risk factors. The relationship between logarithmised pooled RRs for PSCI and PSD was further described using a linear regression model. For binary risk factors that were significant in the main analysis we calculated the pooled population attributable fraction (PAF) via random-effects meta-analysis as described above. The study was preregistered on PROSPERO (CRD42020164959).

We conducted sensitivity and subgroup analyses for risk factors studied in ten or more studies. In sensitivity analyses, we removed outliers and influential studies (appendix p 8) and restricted analyses to studies with 6 or more points on the NOS. The specific subgroup analyses are detailed in the appendix (pp 41–42). We did meta-regression analyses to explore how predefined parameters, including mean age, sex ratio, mean educational attainment, NOS score, publication date, and follow-up time might modify the associations found in the main analysis. If more than one variable reached a p value of less than 0.1 in the univariable meta-regression, all respective variables were entered into a multivariable regression analysis if they were not subject to multicollinearity.

We assessed reporting bias using Egger's test for funnel plot asymmetry and corrected the pooled effect estimates from the main analysis and sensitivity analysis using the trim and fill approach²⁹ to account for potential reporting bias.

We applied the Benjamini-Hochberg procedure³⁰ for post-hoc false discovery rate correction of the individual p values from the main analysis. We used R, version 4.2.1, for all statistical analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The titles and abstracts of 13127 unique articles were screened for eligibility (figure 1). We identified 162 eligible

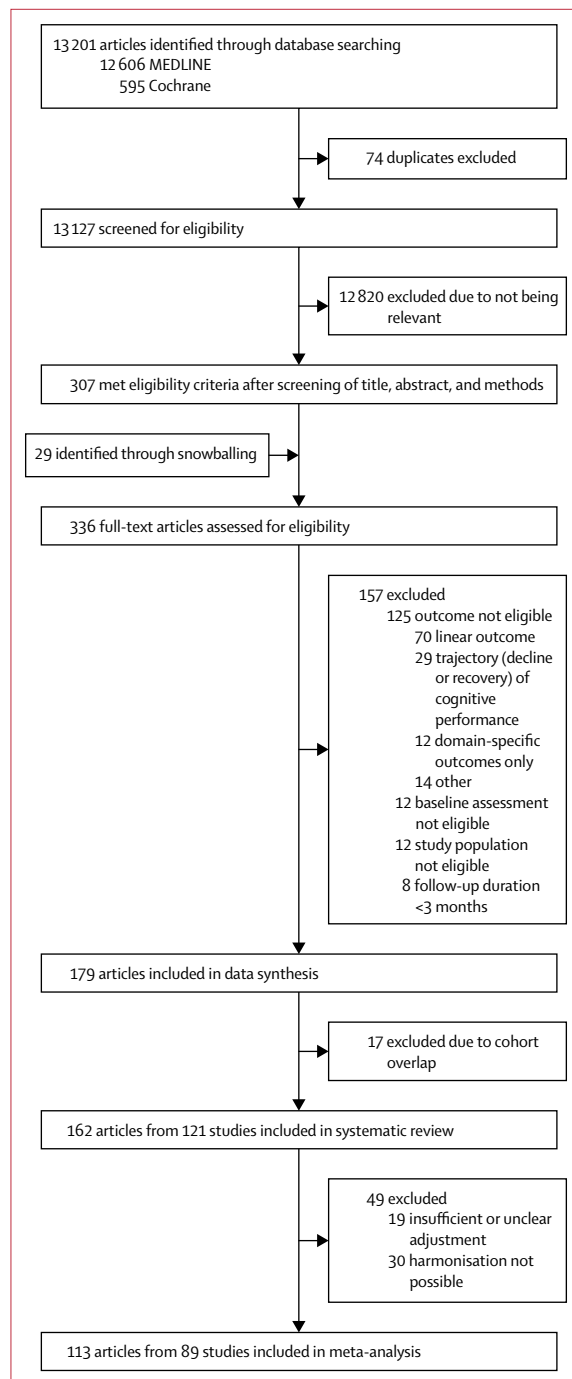


Figure 1: Flow chart for study selection

articles for our systematic review, of which 113 reporting results from 89 studies were included in the meta-analysis. More details are given in the appendix (pp 10–12).

Study characteristics, and demographic and clinical data from all eligible studies are summarised in the appendix (pp 13–32). The meta-analysis included 160 783 stroke patients (median $n=301$, range 47–63 959)

from 66 prospective cohort studies, three post-hoc analyses from RCTs, and 20 retrospective studies. Most studies (number of studies [k]=73, number of participants [n]=29 341) were hospital-based, while fewer were population-based ($k=8$, $n=23\,077$), or registry-based ($k=8$, $n=108\,365$). The median NOS score was 5 (IQR 4–5, range 2–7; appendix pp 33–35). The cumulative number of studies meeting each quality criterion out of all studies included in this meta-analysis is illustrated in the appendix (p 62).

The table presents the pooled effect estimates and heterogeneity estimates for individual predictors. Figure 2 depicts the pooled estimates for PSCI plotted against those for PSD, while accounting for overlap between studies on PSCI and PSD. Overall, the effect estimates for PSCI were highly correlated with those for PSD ($r=0.90$, $p<0.0001$). The beta regression coefficient (β_1) for the relationship between $\log(\text{RR for PSCI})$ and $\log(\text{RR for PSD})$ was 0.69 (95% CI 0.43–0.95), suggesting proportionally larger effect sizes for PSD than for PSCI and reflecting a dose–response relationship.

Figures 3 and 4 depict forest plots of significant predictors for PSCI and PSD, respectively, from the main analysis. The strongest risk factor for PSCI was cognitive impairment at baseline (RR 2.00, 95% 1.66–2.40). Treatable baseline factors associated with PSCI were presence or history of diabetes (1.29, 1.14–1.45), presence or history of atrial fibrillation (1.29, 1.04–1.60), presence of moderate or severe WMH (1.51, 1.20–1.91), and WMH severity (1.30, 1.10–1.55, per SD increase). Further significant risk factors were age (1.03, 1.01–1.04, per year increase), stroke severity (1.07, 1.01–1.12, per point increase on the National Institutes of Health Stroke Scale [NIHSS]), educational attainment (0.92, 0.88–0.97, per year increase), previous stroke (1.76, 1.32–2.34), presence of brain atrophy (1.52, 1.10–2.09), left hemisphere stroke (1.56, 1.27–1.92), baseline Montreal Cognitive Assessment score (0.8, 0.71–0.91, per point increase), baseline modified Rankin scale (mRS; 1.18, 1.10–1.26, per point increase), baseline functional status assessed by varying tools (1.17, 1.01–1.35, per SD increase), and urinary incontinence (2.34, 1.42–3.83). Following adjustment for multiple comparisons, the associations between PSCI and diabetes, WMH severity, age, educational attainment, history of stroke, left hemisphere stroke, cognitive impairment at baseline, and baseline mRS remained significant.

Likewise, the strongest risk factor for PSD was cognitive impairment at baseline (RR 3.10, 95% CI 2.77–3.47). Treatable baseline factors associated with PSD were presence or history of diabetes (1.38, 1.10–1.72), presence of moderate or severe WMH (1.55, 1.01–2.38), and WMH severity (1.61, 1.20–2.14, per SD increase). Also, we detected age (1.08, 1.05–1.11, per year increase), stroke severity (1.13, 1.04–1.23, per point increase on NIHSS), educational attainment (0.93, 0.88–0.97, per year increase), history of stroke (1.64, 1.16–2.32), pre-stroke

	Post-stroke cognitive impairment							Post-stroke dementia						
	k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value (RR)	I ²	p value (I ²)	k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value (RR)	I ²	p value (I ²)
Demographic and socioeconomic predictors														
Age (years)	45	8174*/27254*	3.3 (3.0–12.0)*	1.03 (1.01–1.04)	0.00036†‡	89.8	<0.0001	17	1483/7186	3.0 (3.0–36.5)*	1.08 (1.05–1.11)	<0.0001†‡	67.9	<0.0001
Female sex	26	3436*/9496	5.6 (3.0–11.6)*	1.20 (1.00–1.44)	0.055	85.4	<0.0001	9	5648/33721	33.2 (6.25–63.0)*	0.94 (0.79–1.13)	0.47	44.0	0.07
Educational attainment (yes)	26	3014*/8851	3.0 (3.0–7.1)*	0.92 (0.88–0.97)	0.0042†‡	90.7	<0.0001	11	1111/5602	3.0 (3.0–20.9)*	0.93 (0.88–0.97)	0.0048†	28.8	0.17
Unemployment	3	325/647	24.0 (18.0–36.0)	1.28 (0.81–2.03)	0.16	82.6	0.003	0	..	..	..	..	..	..
Manual work	2	262/877	13.5 (8.25–18.8)	1.67 (0.08–36.87)	0.28	22.9	0.26	1	..	..	..	..	..	..
Black ethnicity	0	..	..	..	..	..	..	2	4757/45927	21.1 (12.0–30.1)	1.57 (0.12–20.99)	0.27	67.8	0.08
Cardiovascular risk factors														
Diabetes	16	2495*/11439	5.1 (3.0–11.9)*	1.29 (1.14–1.45)	0.0004†‡	73.6	<0.0001	11	5667/33953	16.0 (3.0–39.6)*	1.38 (1.10–1.72)	0.010†	64.9	0.001
Hypertension	14	4963*/16234	3.0 (3.0–3.3)*	1.19 (0.91–1.56)	0.19	86.9	<0.0001	5	4982/30929	28.9 (15.9–48.0)*	1.07 (0.97–1.18)	0.14	0.0	0.76
Atrial fibrillation	10	1294*/4249	3.0 (3.0–4.65)*	1.29 (1.04–1.60)	0.027†	54.3	0.02	7	4838/25382	15.9 (3.0–45)*	1.27 (0.86–1.90)	0.19	78.0	0.0001
Hyperlipidaemia or dyslipidaemia	7	3544/11271	3.0 (3.0–3.15)*	0.83 (0.63–1.09)	0.14	27.8	0.22	5	5290/32523	50.4 (39.6–58.8)*	0.96 (0.90–1.02)	0.16	0.0	0.93
Smoking (ever or current)	9	1551/4582	3.0 (3.0–5.15)*	0.81 (0.55–1.18)	0.23	81.7	<0.0001	5	4639/23864	28.9 (16.0–50.4)	1.07 (0.91–1.25)	0.32	0.0	0.52
Alcohol	5	1030*/3116	3.0 (3.5–15)*	1.23 (0.75–2.01)	0.31	84.3	<0.0001	1	..	..	..	..	..	..
BMI (kg/m ²)	6	571*/2358	3.0 (3.0–11.6)*	0.99 (0.93–1.05)	0.56	48.2	0.09	1	..	..	..	..	..	..
Cardiovascular diseases														
Previous stroke	10	886*/3067	3.0 (3.0–9.35)*	1.76 (1.32–2.34)	0.0015*†‡	70.1	0.0004	7	915/4822	3.0 (3.0–12.8)*	1.64 (1.16–2.32)	0.013†	67.0	0.006
Previous TIA	1	..	..	..	..	..	..	2	579/3073	39.6 (34.3–45.0)	1.03 (0.85–1.25)	0.33	0.0	0.90
Heart disease	5	3255/10616	3.0 (3.0–3.0)*	1.07 (0.82–1.40)	0.50	55.8	0.06	5	12436/95489	50.4 (46.8–58.8)*	1.04 (0.99–1.10)	0.07	0.0	0.95
Kidney disease	0	..	..	..	..	..	..	3	1176/10522	26.7 (14.8–38.5)*	1.30 (0.37–4.54)	0.46	84.0	0.002
Peripheral artery disease	1	..	..	..	..	..	..	3	7848/66525	43.2 (23.1–46.8)	1.11 (0.98–1.26)	0.06	0.0	0.85
Other pre-stroke risk factors														
Pre-stroke cognitive impairment	1	..	..	..	..	..	..	5	270/1168	3.0 (3.0–3.0)*	1.96 (1.12–3.42)	0.029†	92.4	<0.0001
Pre-stroke cognitive function (IQCODE score)	4	187/601	3.0 (3.0–3.0)*	2.66 (0.82–8.59)	0.08	94.7	<0.0001	3	139/568	3.0 (3.0–3.0)*	2.18 (0.23–20.72)	0.28	96.0	<0.0001
Pre-stroke functional impairment	1	..	..	..	..	..	..	2	4331/22281	58.8 (54.6–63.0)	1.19 (0.05–26.06)	0.60	89.1	0.002

(Table continues on next page)

	Post-stroke cognitive impairment							Post-stroke dementia						
	k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value (RR)	I ²	p value (I ²)	k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value (RR)	I ²	p value (I ²)
(Continued from previous page)														
Neuroimaging parameters: SVD related														
Global SVD burden (score)	4	293*/1518	11.6 (8.8–13.3)*	1.13 (0.96–1.32)	0.09	29.9	0.23	1	..	..	..	..	..	..
WMH (moderate or severe)	5	645*/1985	3.0 (3.0–7.3)*	1.51 (1.20–1.91)	0.0079†	52.4	0.08	6	790/4163	3.0 (3.0–31.2)*	1.55 (1.01–2.38)	0.045	70.7	0.004
WMH severity (SD)	12	1234*/3628	10.2 (7.8–17.2)*	1.30 (1.10–1.55)	0.0062†‡	75.1	<0.0001	5	238/1542	38.2 (27.1–55.1)*	1.61 (1.20–2.14)	0.010†	17.7	0.30
Lacune presence	2	142*/1019	13.3 (12.4–14.2)	1.35 (0.43–4.22)	0.18	0.0	0.44	3	291*/901	16.0 (11.0–31.1)	1.67 (0.56–5.00)	0.18	80.4	0.006
Lacune count	3	325*/1213	29.6 (20.6–38.5)*	1.40 (0.54–3.68)	0.27	85.7	0.0009	0	..	..	..	..	..	..
Lacunes (≥3)	0	..	..	..	..	..	..	2	66/1096	104.0 (104.0–104.0)*	2.42 (1.27–4.61)	0.037†	0.0	0.85
Microbleeds	2	142*/1019	13.3 (12.4–14.2)	1.20 (0.16–9.25)	0.46	25.9	0.24	0	..	..	..	..	..	..
Microbleeds (count)	2	29*/719	11.6 (11.6–11.6)*	1.01 (0.77–1.31)	0.79	0.0	0.40	0	..	..	..	..	..	..
Enlarged perivascular spaces (SD)	2	166/502	NA	1.09 (0.77–1.54)	0.20	0.0	0.52	0	..	..	..	..	..	..
Disseminated superficial siderosis	0	..	..	..	..	..	..	2	277/830	59.1 (52.7–65.6)	3.75 (0.003–4418.4)	0.25	80.7	0.023
Neuroimaging parameters: other														
Atrophy	5	491/1093	7.1 (5.05–9.58)*	1.52 (1.10–2.09)	0.023†	67.3	0.016	1	..	..	..	..	..	..
Atrophy severity (SD)	4	356/1172	3.3 (3.15–13.7)*	1.25 (0.97–1.61)	0.06	21.0	0.28	2	78/268	47.5 (35.2–59.8)*	2.51 (0.05–138.55)	0.21	61.6	0.11
Medial temporal lobe atrophy	2	226/460	7.5 (5.25–9.75)	1.35 (0.92–1.99)	0.06	0.0	0.66	3	219/1473	7.5 (5.25–9.75)*	1.67 (1.10–2.55)	0.034†	0.0	0.39
Silent infarcts	1	..	..	..	..	..	..	2	96/359	NA	1.61 (0.08–30.66)	0.29	0.0	0.40
Infarct volume (SD)	4	318*/1539	8.8 (5.25–14.7)	1.07 (0.95–1.20)	0.16	56.1	0.08	2	101/330	9.5 (6.25–12.8)	1.13 (0.31–4.09)	0.45	73.3	0.053
Stroke features and acute phase deficits														
Stroke severity (NIHSS)	27	3128*/8434	3.0 (3.0–10.2)*	1.07 (1.01–1.12)	0.014†	87.0	<0.0001	7	4543/23359	3.0 (3.0–58.8)	1.13 (1.04–1.23)	0.010†	79.2	<0.0001
Lobar ICH	1	..	..	..	..	..	..	2	160/475	59.7 (53.5–65.8)	1.75 (0.07–43.13)	0.27	3.9	0.31
Left hemisphere	10	684*/2027	3.0 (3.0–9.75)*	1.56 (1.27–1.92)	0.0008†‡	65.2	0.002	5	237/1117	3.0 (3.0–6.25)*	2.51 (1.25–5.01)	0.021†	70.1	0.01
Cortical lesions	2	300/805	5.95 (4.47–7.43)	1.52 (0.31–7.37)	0.18	47.7	0.17	1	..	..	..	..	..	..
Multiple lesions	2	107/338	30.6 (21.3–39.9)	2.14 (0.01–807.7)	0.35	82.1	0.018	3	471*/2530	33.2 (24.6–41.8)*	1.30 (0.71–2.38)	0.20	24.4	0.27
Strategic infarct	2	171/328	3.0 (3.0–3.0)*	1.57 (0.02–149.73)	0.43	89.3	0.002	1	..	..	..	..	..	..
(Table continues on next page)														

Post-stroke cognitive impairment								Post-stroke dementia						
	k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value (RR)	I ²	p value (I ²)	k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value (RR)	I ²	p value (I ²)
(Continued from previous page)														
ASPECTS (score)	2	171/316	3.0 (3.0–3.0)	1.27 (0.07–21.93)	0.48	93.9	<0.0001	0	..	..	..	..	..	..
Posterior circulation stroke	2	637/934	6.0 (6.0–6.0)*	1.14 (0.35–3.74)	0.39	97.0	<0.0001	0	..	..	..	..	..	..
Baseline cognitive impairment	4	259*/1112	11.5 (8.8–18.6)*	2.00 (1.66–2.40)	0.0012†‡	87.7	<0.0001	5	576/2953	25.7 (21.1–50.4)	3.10 (2.77–3.47)	<0.0001†‡	0.0	0.95
Baseline cognitive function (MoCA)	3	273/707	8.4 (8.4–8.4)*	0.80 (0.71–0.91)	0.017†	36.9	0.20	1	..	..	..	..	..	..
Baseline cognitive function (SD)	0	..	..	..	..	..	..	2	149/470	38.2 (38.2–38.2)*	0.42 (0.01–19.38)	0.21	71.1	0.06
Functional status (mRS)	6	867*/1745	3.0 (3.0–3.6)*	1.18 (1.10–1.26)	0.0015†‡	11.3	0.34	3	4089/20900	35.1 (19.1–51.2)*	1.33 (0.51–3.48)	0.33	83.8	0.002
Functional status (SD)	6	1147/3801	29.8 (20.9–38.6)*	1.17 (1.01–1.35)	0.044†	23.1	0.26	2	4067/20799	35.1 (19.1–51.2)	1.11 (0.81–1.52)	0.14	0.0	0.58
Urinary incontinence	2	287/824	3.0 (3.0–3.0)	2.34 (1.42–3.83)	0.029†	0.0	0.60	0	..	..	..	..	..	..
Dysphasia	2	376/1042	3.0 (3.0–3.0)	1.65 (0.08–33.66)	0.28	78.1	0.032	2	520/2483	26.7 (14.8–38.5)	2.31 (0.06–90.65)	0.21	87.6	0.005
Delirium	1	..	..	..	..	..	..	2	59/161	13.0 (8.0–18.0)	1.98 (0.60–6.56)	0.09	0.0	0.57
Blood and genetic parameters														
Homocysteine (μmol/L)	5	462*/4654	3.0 (3.0–13.5)*	1.01 (0.97–1.05)	0.49	73.9	0.004	0	..	..	..	..	..	..
APOE ε4 (any number of alleles)	2	123/501	18.7 (16.1–21.4)	1.34 (0.05–38.11)	0.46	67.1	0.08	3	471/2577	47.4 (47.4–47.4)*	1.45 (0.51–4.10)	0.26	77.4	0.012
Neutrophil-lymphocyte ratio	2	158/712	3.0 (3.0–3.0)	1.24 (0.24–6.52)	0.34	79.3	0.028	0	..	..	..	..	..	..
Uric acid (μmol/L)	2	296/768	3.0 (3.0–3.0)*	1.00 (0.99–1.01)	0.53	18.2	0.27	0	..	..	..	..	..	..
Cystatin C (mg/L)	2	472/863	3.0 (3.0–3.0)	0.89 (0.00–3640.45)	0.89	79.2	0.028	0	..	..	..	..	..	..
Trimethylamine-N-oxide	2	407/873	7.5 (5.25–9.75)	1.07 (0.38–3.04)	0.55	88.8	0.003	0	..	..	..	..	..	..
Fasting blood glucose (SD)	2	202/728	3.0 (3.0–3.0)*	1.25 (0.07–22.90)	0.51	93.3	0.0001	1	..	..	..	..	..	..
LDL (mmol/L)	2	132*/1055	11.6 (11.6–11.6)*	0.99 (0.29–3.63)	0.92	48.1	0.16	0	..	..	..	..	..	..
HDL (mmol/L)	2	87*/4047	13.5 (8.25–18.8)	1.02 (0.38–2.73)	0.86	10.1	0.29	0	..	..	..	..	..	..
Stroke cause														
Small vessel occlusion	3	378/730	4.5 (3.75–5.25)*	0.78 (0.23–2.69)	0.48	72.5	0.026	0	..	..	..	..	..	..
Large artery atherosclerosis	3	801/1406	3.0 (3.0–3.0)*	1.23 (0.63–2.40)	0.31	74.6	0.02	0	..	..	..	..	..	..
Cardioembolism	2	580/1053	3.0 (3.0–3.0)*	1.19 (0.13–11.30)	0.50	38.2	0.20	0	..	..	..	..	..	..

(Table continues on next page)

Post-stroke cognitive impairment					Post-stroke dementia								
k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value	I ²	p value (I ²)	k	Cases/N	Median follow-up (IQR)	Pooled RR (95% CI)	p value (RR)	I ²	p value (I ²)
(Continued from previous page)													
Undetermined	3	708/1279	4.5 (3.75–5.25)*	1.13 (0.49–2.64)	0.59	62.0	0	..	..	..	..	..	..
Other determined	2	580/1053	3.0 (3.0–3.0)*	0.91 (0.52–1.60)	0.29	0.0	0	..	..	..	..	..	..
Carotid artery stenosis	4	471/1206	6.45 (6.22–6.68)*	1.30 (0.94–1.80)	0.08	84.6	1	..	..	..	..	..	..
Carotid plaques	2	243/544	3.0 (3.0–3.0)*	1.66 (0.08–33.58)	0.28	73.1	0	..	..	..	..	..	..
Neuropsychiatric disorders													
Depression	3	402/1042	4.5 (3.75–5.25)*	1.31 (0.64–2.67)	0.25	86.9	1	..	..	..	..	..	..
Depressive symptoms (SD)	2	96/582	4.5 (3.75–5.25)	1.18 (0.47–2.96)	0.25	0.0	0	..	..	..	..	..	..
Heart disease includes CAD, IHD, and CHF. Among the studies on kidney disease, two investigated CKD and one the history of any nephropathy. Median follow-up time is given in months. CAD=coronary artery disease. CHF=chronic heart failure. CKD=chronic kidney disease. ICH=intracerebral haemorrhage. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IHD=ischemic heart disease. k=number of studies. MoCA=Montreal Cognitive Assessment. mRS=modified Rankin scale. NA=not applicable. NIHSS=National Institutes of Health Stroke Scale. RR=relative risk. SVD=small vessel disease. TIA=transient ischaemic attack. WMH=white matter hyperintensities. *Incomplete N, number of men, cases, or follow-up times, which occurred when studies were included in the analysis that did not provide the respective numbers. †Statistically significant. ‡p value remained significant after false discovery rate correction.													
Table: Pooled relative risks of predictors for post-stroke cognitive impairment and post-stroke dementia													

Table: Pooled relative risks of predictors for post-stroke cognitive impairment and post-stroke dementia

cognitive impairment (1.96, 1.12–3.42), presence of three or more lacunes (2.42, 1.27–4.61), medial temporal lobe atrophy (1.67, 1.10–2.55), and left hemisphere stroke (2.51, 1.25–5.01) as significant risk factors for PSD. Following adjustment for multiple comparisons, age and cognitive impairment at baseline remained significant.

Meta-analyses of PAFs (appendix p 36) indicated that, among the binary risk factors, baseline cognitive impairment had the highest attributable risk for PSCI and PSD with an estimated 36.6% and 21.3%, respectively. Pooled PAFs of treatable risk factors (diabetes, atrial fibrillation, and WMH) ranged from 3% to 13%.

The Egger's test indicated reporting bias for the associations between PSCI and age, educational attainment, and stroke severity (appendix p 38). After excluding outliers identified in a sensitivity analysis (appendix pp 39–40), the test for reporting bias remained significant only for the association between stroke severity and PSCI. Funnel plots for visual assessment of reporting bias are available in the appendix (pp 63–64).

Significant heterogeneity ($I^2 > 50\%$) was present in 58 of the 97 main analyses (table). After excluding a median of two outlying studies (range 1–5) in sensitivity analyses, the heterogeneity was reduced for most analyses, but not for the associations between PSCI and age, sex, educational attainment, and stroke severity, as well as between PSD and stroke severity and presence of moderate or severe WMH (appendix pp 39–40).

Figures 3 and 4 show the change in effect estimates when restricting the analysis to studies with NOS of 6 or more or when adjusting for publication bias and excluding outliers. Confidence intervals widened when restricting the analysis to studies with NOS of 6 or more, but the effect sizes of significant predictors remained generally consistent. Overall, adjusting for publication bias after excluding outliers did not change the effect sizes.

Subgroup analyses per predictor and outcome are summarised in the appendix (pp 41–44). Subgroup differences were frequent in analyses that stratified by overall study quality, assessment of dementia or cognitive impairment (use of a neuropsychological test battery vs a cognitive screening tool), publication year (before vs after 2009), and study setting.¹ Studies on the treatable risk factors diabetes and atrial fibrillation often reported larger effect sizes for PSD when they were published before 2009, had a hospital-based study setting, and used a neuropsychological test battery instead of a cognitive screening test to assess dementia.

Meta-regression analyses (appendix pp 45–50) revealed that later mean recruitment date attenuated the association of NIHSS score, educational attainment, and WMH severity with PSD (appendix pp 65–66). Later publication date attenuated the association of NIHSS score, educational attainment, and atrial fibrillation with PSD (appendix pp 65–66). Further significant meta-regression results are illustrated in the appendix (pp 67–70).

Discussion

By analysing data from 89 studies and 160783 patients with stroke or TIA, we have established a number of risk factors for PSCI and PSD beyond the well known predictors of age and stroke severity. Baseline cognitive impairment showed the strongest association with both PSCI and PSD. Our analyses further highlight diabetes, atrial fibrillation, presence of moderate or severe WMH, and WMH severity as treatable risk factors. Additionally, we found that lower educational attainment, previous stroke, left hemisphere stroke, and lower baseline mRS are predictors of PSCI and PSD. The results are consistent across studies on any severity of PSCI, including dementia, and studies on PSD only. Although our meta-analysis identifies significant interstudy heterogeneity, evidence of publication bias, and methodological shortcomings among the included studies, it provides insight for risk prediction, patient counselling, and preventive strategies.

We identified baseline cognitive impairment as a strong predictor for both PSCI and PSD, a finding that was not picked up by previous meta-analyses and reviews.¹⁴ A potential clinical implication of the present meta-analysis is that cognitive testing in the acute phase after stroke should be considered to identify patients at high risk for PSCI who might benefit from intensified monitoring and care. The data available for the current meta-analysis did not allow for the assessment of a possible interaction between baseline cognitive impairment and stroke severity with respect to risk for PSCI and PSD. Future studies should investigate this possible interaction. As was previously shown, cognitive recovery primarily occurs within the first 2–6 months after stroke.³¹ Considering our findings, future clinical trials should investigate whether targeted interventions to improve cognitive recovery during this critical period can reduce the risk for PSCI and PSD.

Lower functional status at baseline was significantly associated with PSCI, but not PSD, possibly due to many studies adjusting for stroke severity, a strong predictor of functional status.³² Two studies on PSCI reported large effect estimates for urinary incontinence, also a correlate of functional status,³³ while only partially adjusting for stroke severity. More research is needed to confirm an independent relationship between acute phase urinary incontinence and PSCI.

We found diabetes to be one of the strongest treatable risk factors for PSCI. As expected from the correlation between the observed effect estimates for PSCI and PSD, this finding is consistent with a previous meta-analysis on PSD¹ and a population-based cohort study³ that identified diabetes as the only significant vascular risk factor for PSD. Most studies included in our analysis did not account for diabetes type or management status. Future studies should do analyses stratified by these factors. Diabetes is an established risk factor for all-cause dementia³⁴ and cognitive impairment,³⁵ independent of

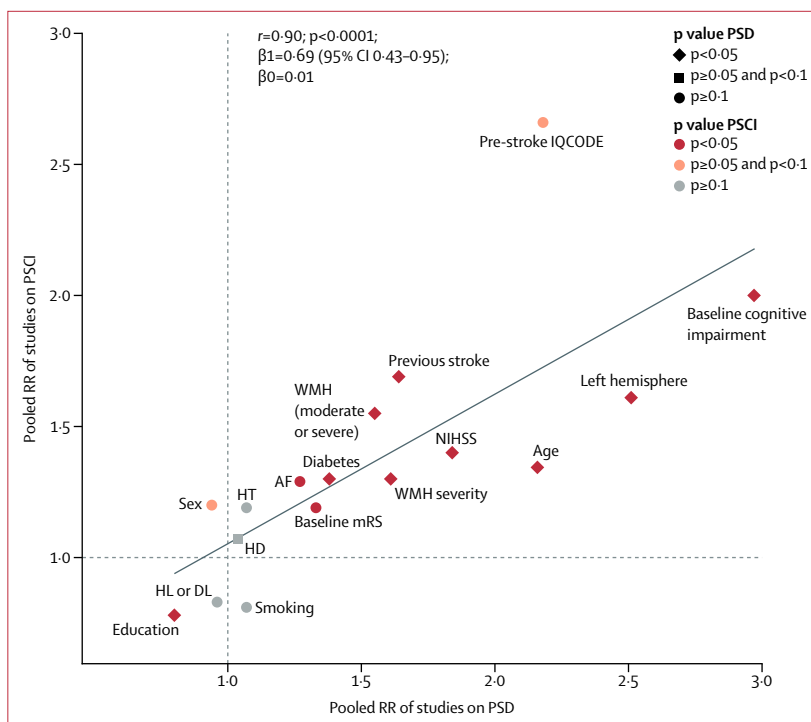


Figure 2: Correlation of pooled RRs from studies on PSCI versus from studies on PSD for which data were available

If a study reported on both outcomes, we included it only as part of the pooled estimate for PSD. The dots show the pooled effect for an individual risk factor and are coded by shape and colour to indicate level of statistical significance of the p value for PSD and for PSCI, respectively. For the continuous variables, RRs are provided per 10-year increase in age, 5-point increase on NIHSS, 1-point increase on mRS and IQCODE, 3-year increase in educational attainment, and 1 SD increase in WMH severity. Female sex represents the effect group. Spearman's correlation coefficient (r) is displayed in the top left alongside the beta regression coefficient (β_1) and intercept (β_0) of a regression line modelling the regression equation $\log(\text{RR}_{\text{psci}}) = \beta_0 + \beta_1 * \log(\text{RR}_{\text{psd}}) + \epsilon$. AF=atrial fibrillation. DL=dyslipidaemia. HD=heart disease. HL=hyperlipidaemia. HT=hypertension. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. mRS=modified Rankin scale. NIHSS=National Institute of Health Stroke Scale. PSCI=post-stroke cognitive impairment. PSD=post-stroke dementia. RR=relative risk. WMH=white matter hyperintensities.

stroke. Pathophysiological pathways through which diabetes could impact cognitive outcomes include cSVD and neurodegeneration.^{36–39} Another contributing factor might be stroke recurrence, which is more frequent in patients with diabetes and metabolic syndrome compared with those without these exposures.^{40,41} The potential mediating role of these factors for PSCI deserves further investigation. A 2017 Cochrane review of RCTs in stroke-free people with diabetes found no conclusive evidence of the superiority of a particular antidiabetic treatment in preventing adverse cognitive endpoints.⁴² Given the scarcity of evidence on antidiabetic treatments for the prevention of PSCI and PSD, more studies are needed.

Although hypertension is a similarly well researched risk factor for stroke,⁴³ recurrent stroke,⁴⁴ and dementia,⁴⁵ our results suggest that a history or presence of hypertension does not independently contribute to the risk of PSCI or PSD, aligning with previous research.¹³ One explanation for the lack of significance in these results could be attributed to a substantial portion of patients in the included studies with well managed hypertension.

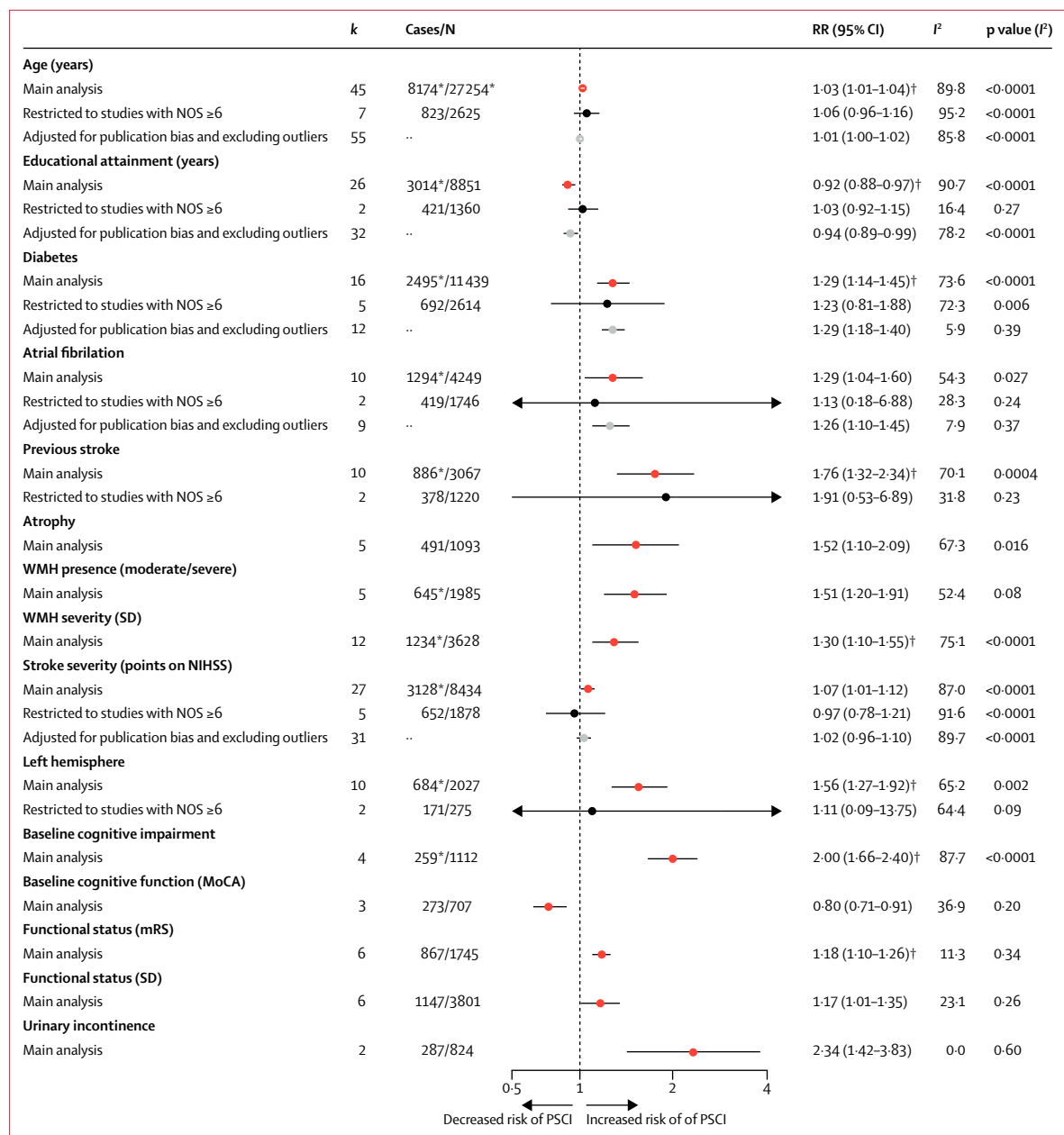


Figure 3: Forest plot of pooled RRs for PSCI

Results for significant predictors of PSCI in the main analysis (red), when restricting the analysis to studies rated with 6 or more points on the NOS (black), and when adjusting the analysis for publication bias while excluding outlying study effect estimates (grey). Pooled effect estimates are plotted when more than one study could be included in the analysis. k=number of studies. MoCA=Montreal Cognitive Assessment. mRS=modified Rankin scale. NIHSS=National Institutes of Health Stroke Scale. NOS=Newcastle-Ottawa quality assessment scale. PSCI=post-stroke cognitive impairment. RR=relative risk. WMH=white matter hyperintensities. *Incomplete N or case count, which occurred when studies were included in the analysis that did not provide the respective numbers. †p value remained significant after false discovery rate correction.

We found the presence of moderate or severe WMH, as well as WMH severity, to be related to a higher risk of PSCI and PSD. Mechanisms underlying these associations remain poorly understood, but might involve manifestations of cSVD as a known risk factor for PSCI,⁴⁶ a larger stroke volume in patients with increasing WMH severity, and interference with neuronal networks

for cognitive reserve.⁵ Although data for other imaging markers of cSVD are scarce (Wang et al;¹⁶ table) and associations with PSCI and PSD were mostly unadjusted,^{14–16} our meta-analysis revealed a relationship between the presence of three or more lacunes with PSD, bearing in mind that only two studies could be included in this analysis. We could not detect an association

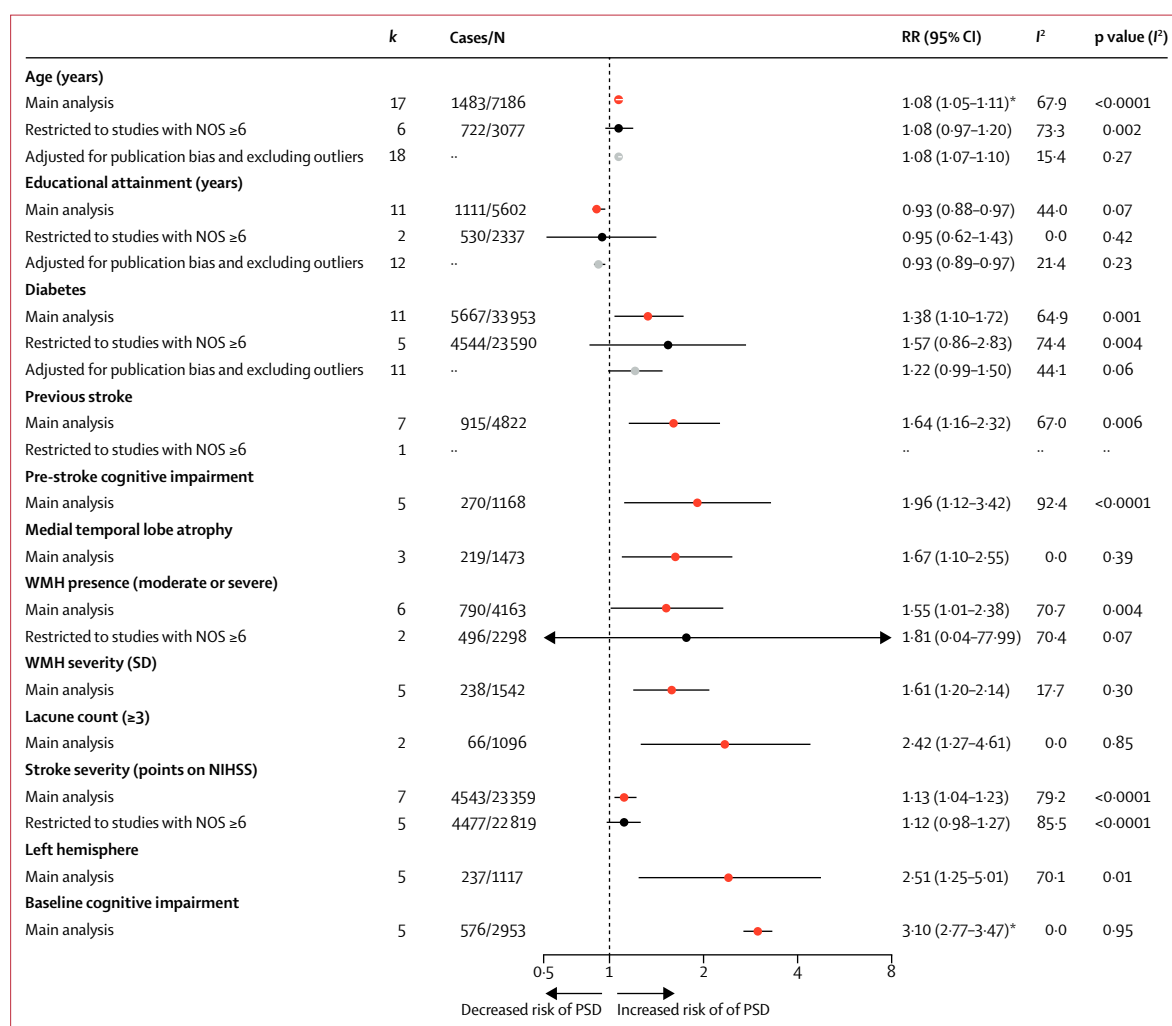


Figure 4: Forest plot of pooled RRs for PSD

Results for significant predictors of PSD in the main analysis (red), when restricting the analysis to studies rated with 6 or more points on the NOS (black), and when adjusting the analysis for publication bias while excluding outlying study effect estimates (grey). Pooled effect estimates are plotted when more than one study could be included in the analysis. k=number of studies. NIHSS=National Institutes of Health Stroke Scale. NOS=Newcastle-Ottawa quality assessment scale. PSD=post-stroke dementia. RR=relative risk. WMH=white matter hyperintensities. *p value remained significant after false discovery rate correction.

between lacunes and PSCI. However, a recent multicentre cohort study with standardised brain imaging found both a global cSVD score and individual cSVD markers, including lacune count, to be associated with PSCI.⁴⁶ WMH can regress, making WMH severity a potential therapeutic and preventive target.^{9,10} Notably, the SPRINT MIND trial showed a positive effect of intensive blood pressure reduction on WMH progression in hypertensive adults without a history of diabetes or stroke.⁴⁷ Whether slowing the progression of cSVD with intensive blood pressure reduction after stroke reduces cognitive endpoints remains to be determined.

Meta-regression analyses revealed that the strength of the associations of mean NIHSS score, educational attainment, WMH severity, and atrial fibrillation with PSD has decreased over the last four decades, possibly reflecting advancements in acute stroke therapy and

secondary stroke prevention, improved access to treatment,^{48,49} and the decreased dementia incidence.^{50,51} In particular, the attenuation of the association between admission NIHSS score and PSD might reflect recent improvements in acute stroke care. The weakening of the association of WMH severity and atrial fibrillation with PSD might mirror improvements in secondary stroke prevention and overall risk factor management, including blood pressure control and implementation of newer anticoagulant therapies,^{47,52} which are probably also contributing to overall decreasing trends in dementia incidence.⁵³ Although these temporal trends could also relate to other factors, such as the decline in reporting bias, our findings highlight the need for contemporary risk prediction modelling to inform decision making. The predictive value of risk factors and risk prediction scores can change over time, which has implications for

patient counselling, secondary stroke prevention, and future clinical trial design.

Our study has limitations. First, between-study heterogeneity and publication bias could impede the explanatory power of our findings. The heterogeneity could, however, be partly explained by study quality and outliers. Second, more than two-thirds of the included studies obtained less than 6 points on the NOS, most frequently due to non-representativeness of the general population, inflated loss to follow-up rates, and insufficient follow-up length. More findings from high-quality, long-term population-based studies are needed. Although widely applied, the NOS's validity is argued.⁵⁴ To enhance comprehensibility and validity, we predefined the individual quality criteria. Our analyses were reliant on aggregated data and study-level characteristics, as opposed to individual patient data (IPD), which limited our ability to conduct more in-depth analyses, such as exploring the relationship between varying degrees of stroke severity and PSCI or PSD across different follow-up durations. The literature search was primarily conducted by one investigator and limited to two main databases and a comprehensive hand-search of reference lists. The quantitative analysis included studies that were published from database inception until Aug 4, 2022. However, we have updated the literature search to account for all studies published up until Sept 15, 2023 (appendix pp 53–55). Further, we could not account for all methodological differences between the included studies. Specifically, the use of varying diagnostic tools and criteria for PSCI limited comparability of the available research. Not all predictors were investigated in each of the included studies, reducing the power of the analysis for rarer risk factors. Conversion of the original effect measures (odds ratios or hazard ratios) to RR and conversion of exposure units introduced some uncertainty. However, this uncertainty is still estimated lower than the bias that would have resulted from completely excluding studies from the quantitative analysis. Although our meta-analysis included different stroke subtypes and TIA, it is important to note that the risk factors for PSCI and PSD might differ across these subtypes. Future studies should enable a more nuanced understanding of risk factors for each stroke subtype—eg, by stratifying analyses. We cannot eliminate the possibility of confounding in the association between left hemisphere stroke and PSCI due to language impairment, given that only 60% of studies excluded or controlled for aphasia. However, a recent IPD meta-analysis indicated a higher risk of PSCI in patients with left-hemispheric lesions, even in cases without significant language impairment.⁵⁵ Our analysis revealed a lack of evidence from South America, Africa, and Oceania, which in turn restricts the generalisability of our findings. Similarly, the included patients tended to have had mild strokes, potentially impacting the applicability of our findings to cases of more severe strokes.

Our study has several strengths. Previous systematic reviews and meta-analyses on predictors for binary cognitive endpoints after stroke predominantly concentrated on PSD, probably due to the more solid and standardised criteria for its diagnosis. By including PSCI, our study significantly extends the evidence beyond PSD. This updated meta-analysis illustrates the change of associations between risk factors and PSD over time, probably reflecting changes and advancements in both clinical and research practices. We used extensive methods to synthesise as many individual study results as possible. Particularly, we harmonised outcome measures and exposure units to increase statistical power. To our knowledge, this is the first study to exclude analysis results that were not adjusted for age. We conducted comprehensive subgroup, sensitivity, meta-regression, and publication bias analyses to elucidate the detected interstudy heterogeneity. Finally, we screened more than 13 000 articles for eligibility and included 89 studies on more than 160 000 total participants in the meta-analysis, increasing the robustness of our results.

In conclusion, this systematic review and meta-analysis provides a comprehensive overview of the risk factor profiles of PSCI and PSD, accounting for recent improvements in acute stroke management and secondary prevention. Our findings highlight the critical role of baseline cognitive impairment in individual risk prediction for long-term cognitive impairment and in patient selection for clinical trials. Future studies should explore treatable risk factors such as diabetes, atrial fibrillation, and WMH as potential targets for prevention of adverse cognitive outcomes after stroke. We further identified decreasing time trends in the associations between several risk factors and PSD, thus emphasising the need for up-to-date risk prediction.

Contributors

JF conducted the systematic literature search, reviewed all titles and abstracts, selected eligible articles, extracted the data from individual articles, planned and performed the statistical analyses, verified the data, and drafted and co-wrote the Article. MKG conceived the study, contributed to reviewing the articles for eligibility, verified the data, and planned and contributed to the analyses, the interpretation of the results, and drafting of the Article. MD conceived the study, evaluated the results, and co-wrote the Article. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data extracted from original articles and analytic code are available upon reasonable request to be used for meta-analyses of summary statistics or umbrella reviews. Proposals should be directed to martin.dichgans@med.uni-muenchen.de.

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