PREDICTORS FOR COGNITIVE IMPAIRMENT AND DEMENTIA AFTER STROKE

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To my loved ones

Für meine Lieben

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1. SUMMARY

Stroke is one of the leading causes of death and disability worldwide. A large proportion of stroke survivors suffer from subsequent cognitive decline, with dementia representing its most severe form. In the absence of widely available disease-modifying therapies, it is essential to understand the risk factors that predispose patients to post-stroke cognitive impairment (PSCI) and dementia (PSD) to improve individual risk prediction and to develop preventive strategies. However, these risk factors remain insufficiently understood, especially over the long term. Existing observational and clinical studies are constrained by methodological heterogeneity, short follow-up periods, and a limited focus on milder outcomes, such as mild cognitive impairment (MCI), which is included in PSCI. While factors such as older age and greater stroke severity have consistently been linked to PSCI and PSD, the role of other potential predictors is less certain. Moreover, robust evidence for modifiable risk factors remains scarce.

Thus, the overarching aim of this thesis was to improve the understanding of the associations between factors present before or at the time of stroke with PSCI and PSD, thereby aiding tailored risk stratification and secondary prevention efforts. Given the heterogeneity of previous studies, the first study synthesized existing evidence in a systematic review and meta-analysis. Eligible studies were required to use validated cognitive assessment tools, have a longitudinal design, and adjust effect estimates for the well-established risk factors age and stroke severity. Pooling data from 89 studies including more than 160,000 stroke patients, we found that acute-phase cognitive impairment, assessed with brief screening tools shortly after stroke, was the strongest predictor of both PSCI and PSD. Among modifiable risk factors, diabetes mellitus and atrial fibrillation (AF) were the most consistent cardiovascular risk factors, although the role of AF remained less clear for the PSD endpoint. Additional robust predictors included lower educational attainment, prior stroke, markers of cerebral small vessel disease (SVD) – particularly white matter hyperintensities and lacunes – cerebral atrophy, left-hemispheric lesions, and acute-phase functional deficits. Notably, the strength of associations for some risk factors, such as stroke severity and AF, appeared weaker in more recent studies, possibly reflecting improvements in acute stroke care and vascular risk factor management.

Second, building on these findings, I analyzed longitudinal data from the prospective multicenter DEMDAS (DZNE mechanisms of dementia after stroke) study, which enrolled 736 patients (33% female, mean age 68 years) at the time of stroke. Over a median follow-up of 5.0 years (2899 person-years), 55 patients developed dementia. We identified metabolic syndrome (MetS) – particularly its components hyperglycemia (prediabetes or diabetes) and reduced high-density lipoprotein cholesterol (HDL-C) – as a novel risk factor for PSD and a potential target for secondary prevention. Consistent with the first study, additional key predictors included older age, greater stroke severity, lower educational attainment, acute-phase cognitive and functional impairment, AF, and imaging markers of SVD. PSD risk was also elevated in patients with recurrent stroke, whereas acute reperfusion therapy

was associated with a substantially reduced risk. Risk factor profiles for PSCI largely mirrored those for PSD. Importantly, our analyses revealed distinct risk profiles for early-onset PSD (dementia diagnosed within 3–6 months post-stroke) versus delayed-onset PSD (>6 months): early-onset PSD was more strongly linked to factors related to the acute stroke and pre-stroke brain health, while MetS and stroke recurrence were more prominent predictors for delayed-onset PSD. The association between cardiometabolic risk factors and PSD persisted even after adjusting for recurrent stroke, suggesting additional underlying mechanisms beyond recurrent cerebrovascular events.

In conclusion, this thesis strengthens the evidence for the multifactorial nature of PSCI and PSD by combining a systematic synthesis of prior studies with longitudinal data from a deeply phenotyped stroke cohort. The most important risk factor categories identified in this thesis include i) pre-stroke brain health and reserve, ii) acute stroke-related severity and deficits, and iii) cardiovascular and metabolic risk factors. MetS and reduced HDL-C emerged as novel cardiometabolic risk factors and potential targets for secondary prevention. These findings can inform individualized risk prediction and guide the design of clinical trials aimed at preventing cognitive decline after stroke. More broadly, they underscore the need for future observational and interventional studies to prioritize modifiable risk factors and to establish cognitive endpoints as central outcomes in secondary prevention trials.

2. LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AF	atrial fibrillation
ARIC	Atherosclerosis Risk in Communities
BMI	body mass index
CAA	cerebral amyloid angiopathy
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CETP	cholesteryl-ester transfer protein
CMB	cerebral microbleed
DEMDAS	DZNE (Deutsches Zentrum für Neurodegenerative Erkrankungen) Mechanisms of Dementia After Stroke
DALYs	disability-adjusted life years
DLB	dementia with Lewy bodies
FTD	frontotemporal dementia
HDL-C	high-density lipoprotein cholesterol
HS	hemorrhagic stroke
ICH	intracerebral hemorrhage
IHD	ischemic heart disease
IQCODE	Informant Questionnaire for Cognitive Decline in the Elderly
IS	ischemic stroke
LBD	Lewy body disease
LDL	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
MCI	mild cognitive impairment
MetS	metabolic syndrome
MTLA	medial temporal lobe atrophy
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment

NIHSS	National Institutes of Health Stroke Scale
NOACs	non-vitamin K antagonist oral anticoagulants
OCS	Oxford Cognitive Screen
PET	positron emission tomography
PSCI	post-stroke cognitive impairment
PSCIND	post-stroke cognitive impairment no dementia
PSD	post-stroke dementia
PSMCI	post-stroke mild cognitive impairment
SAH	subarachnoid hemorrhage
SVD	cerebral small vessel disease
TCI	transient cognitive impairment
TIA	transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VaD	vascular dementia
WMH	white matter hyperintensities

3. INTRODUCTION

3.1 Stroke: epidemiology, global burden, and sequelae

Stroke is the second leading cause of death and the third leading cause of combined death and disability.[1,2] Stroke is generally defined as an acute neurological deficit resulting from a focal vascular injury to the central nervous system (brain, spinal cord, or retina), diagnosed on the basis of clinical symptoms and/or pathological, imaging, or other objective evidence.[3] The two primary subtypes are ischemic stroke (IS) and hemorrhagic stroke (HS).[4] IS accounts for approximately 65% of incident strokes globally and is caused by a disruption of cerebral blood flow due to blockage of a vessel, leading to tissue death and functional loss.[1,5] IS can be further classified based on etiology using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[6] HS results from the rupture of a cerebral artery or vascular malformation, causing bleeding into the brain parenchyma (intracerebral hemorrhage, ICH) or the space surrounding the brain (subarachnoid hemorrhage, SAH). ICH and SAH comprise 29% and 6% of strokes, respectively.[1,5] In high-income countries, IS often accounts for more than 90% of stroke cases.[7] Key risk factors for stroke include hypertension, high body mass index (BMI), diabetes, smoking, and high low-density lipoprotein (LDL) cholesterol.[7,8] The INTERSTROKE study found that ten modifiable risk factors contribute to 90% of stroke cases,[9] making stroke and its consequences highly preventable.

However, despite these insights into modifiable risk factors and significant improvements in acute stroke care,[10] the global stroke burden continues to grow. The number of incident cases increased from 7 million in 1990 to 12 million in 2021, projected to exceed 21 million by 2050 (**Figure 1**).[8,11] Stroke-related deaths followed a similar trajectory, rising from 5 million to 7 million, with an expected increase to 12 million by 2050. While the absolute numbers of stroke and its consequences are increasing, age-adjusted incidence and mortality rates are declining, with projected reductions of 7% and 28%, respectively, from 2021 to 2050. This decline in stroke-related mortality is especially pronounced in high-income countries.[12] One of the major challenges that remains is stroke-related disability. In 2021, 94 million people were living with the chronic sequelae of stroke. These numbers are expected to reach 159 million by 2050, despite only a 4% decline in age-adjusted prevalence rates.[1,11] The economic impact is equally significant, with global stroke costs exceeding USD 890 billion annually, a figure projected to nearly double by 2050.[13] These trends underscore the urgent need for improved prevention, treatment, rehabilitation, and secondary prevention strategies.

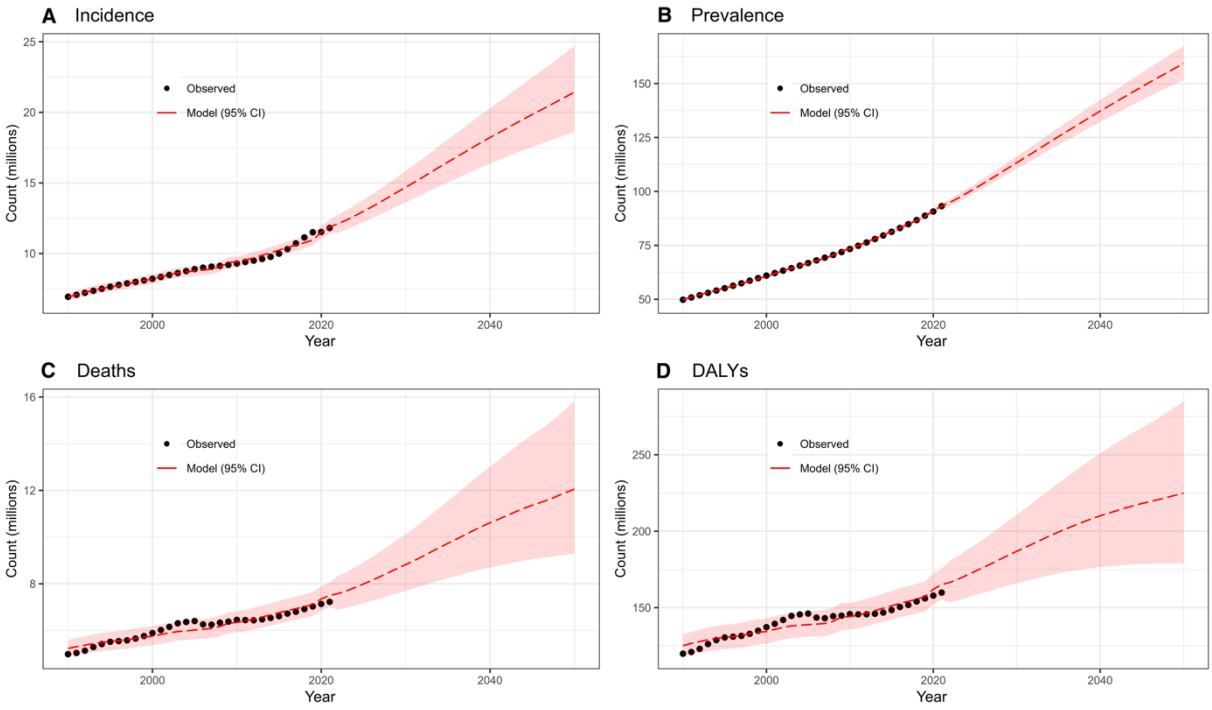

Figure 1. The historical trends and future projections of global stroke from 1990 to 2050: incidence (A), prevalence (B), deaths (C), and disability-adjusted life years (DALYs) (D). Figure taken from Cheng et al. (2024).[11]

The growing proportion of stroke survivors has shifted focus to the long-term consequences of stroke,[14] which can significantly impact both patients and their families. Common post-stroke deficits include neurological and motor impairments such as hemiparesis, speech and vision difficulties, increased susceptibility to infections, and neuropsychiatric symptoms.[15] These often lead to reduced functional independence and diminished quality of life. Another critical long-term consequence after stroke is cognitive impairment, which can range from transient mild cognitive deficits to clinically diagnosed dementia.[16-18]

3.2 Cognitive impairment after stroke

In recent decades, there has been growing research interest in the prevalence, predictors, and underlying mechanisms of post-stroke cognitive outcomes. Stroke can profoundly impact cognition, leading to immediate and often long-term changes in cognitive function.[19] Many stroke survivors experience acute cognitive decline early after the event, followed by heterogeneous and sometimes fluctuating trajectories. While some individuals recover substantially, others remain cognitively stable or experience progressive decline, which in some cases advances to dementia.[20-26]

The term post-stroke cognitive impairment (PSCI) encompasses any cognitive impairment following a stroke, regardless of stroke etiology and severity of cognitive problems.[27,28] More than half of stroke

survivors experience PSCI within the first few months, with prevalence rates varying by study setting, sample characteristics, diagnostic criteria, timepoint of assessment, and assessment methods.[29,30] On average, approximately two-thirds of PSCI cases present with mild and one-third with severe cognitive impairment, i.e., dementia,[29] which will be introduced in detail in the next section. Although the affected cognitive domains can depend on the infarct or bleeding location,[31] impairments in attention, processing speed, executive function, and memory have been most frequently reported,[31-35] most of which have been more closely related to vascular cognitive impairment.[17,28]

Few studies have examined the long-term prevalence of PSCI. However, available evidence indicates persistently high rates: 59% at 7 years post-stroke in a Norwegian cohort (N=109),[36] 22% at annual follow-ups up to 14 years in an extensive study from the UK (N=4,212),[37] and over 80% at 4 years post-stroke in the ARCOS-IV study from New Zealand (N=257).[24]

3.2.1 Dementia

Dementia is defined by a decline in at least two cognitive domains severe enough to interfere with daily activities, typically resulting from neurodegenerative disease or injury.[38] Patients may struggle with acquiring and recalling information, experience difficulties with speaking, reading, writing, or managing complex tasks, and exhibit behavioral or personality changes.[38] These challenges can be utterly distressing, placing a significant emotional and financial burden on the individuals and their families. Most dementia cases follow a progressive course, sometimes leading to a rapid decline in cognitive and functional abilities, necessitating institutionalization in many instances.[39] A large population-based study (N=13,004) from the UK reported median survival times from dementia onset to death of 4.1 years for men and 4.6 years for women, with longer survival times observed in individuals who were younger at the time of diagnosis.[40] In 2021, dementia ranked as the 7th leading cause of death worldwide and the 4th leading cause in high-income countries.[41]

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most frequent cause of dementia, contributing to approximately 60-80% of dementia cases.[42] Other dementia forms include vascular dementia (VaD), dementia with Lewy bodies (DLB), or frontotemporal dementia (FTD). Postmortem evidence revealed that most individuals with dementia have mixed pathology – typically a combination of Alzheimer's disease pathology and vascular contributions (e.g., infarcts).[43-45] Yet, differentiating the specific contributions to dementia in living patients remains challenging, mainly due to the limited disease specificity of current biomarkers.

Like for stroke, the global prevalence and incidence rates of dementia are on the rise, along with the increase in life expectancy.[46] In 2019, approximately 57 million individuals were living with dementia, and projections suggest that this figure will increase to 153 million by 2050.[47] The number of new dementia diagnoses has surged from 2.9 million in 1990 to 7.2 million in 2019.[48] Meanwhile, the age-

standardized incidence rates are declining in several, mostly high-income countries,[48] indicating potential for prevention strategies.[49,50]

3.2.1.1 Stroke and dementia risk

Despite significant advancements in the field, broadly available and effective disease-modifying therapies for dementia are lacking. Consequently, there is a significant focus on understanding and targeting the modifiable risk factors for dementia. In 2024, Lancet Standing Commission stated that nearly half of all dementia cases could be prevented or delayed by modifying 14 key risk factors: lower education, head injury, physical inactivity, smoking, heavy alcohol consumption, hypertension, obesity, diabetes, hearing loss, depression, limited social contact, air pollution, vision loss, and high cholesterol.[51] Many of these risk factors are also important contributors to stroke, which is now often regarded not only as a major risk factor for dementia but also as a potential cause, particularly of VaD.[51,52]

Stroke survivors have more than twice the risk of developing dementia compared to individuals without stroke,[52] with the risk increasing with greater stroke severity.[53] Findings from the Framingham Heart Study indicated that the excess risk of dementia following stroke has declined between 1977 and 2008, dropping from a 9-fold increase in the first observation period to less than a 2-fold increase in the last.[54] This reduction may be attributed to improvements in stroke treatment and diagnostic procedures.[54] Despite this, the growing number of new strokes and individuals living with its chronic sequelae make stroke an important contributor to the simultaneously growing incidence of dementia.[11,47] Hence, without significant advances in prevention and treatment, the burden of dementia and its consequences on patients, caregivers, and healthcare systems will continue to increase.[55]

The relationship between cerebrovascular disease and dementia is complex, with multiple potential and likely interrelated mechanisms that could accumulate or interact, though they remain poorly understood.[56] Cerebral infarcts or hemorrhages can increase dementia risk by causing direct injury to critical brain regions, disrupting structural and functional connections, triggering secondary neurodegeneration, or inducing global brain dysfunction driven by inflammation and metabolic changes.[17,28] Evidence of elevated dementia and cognitive impairment rates both before and after stroke indicates a shared predisposition of stroke and dementia,[16,57-59] which could in part be attributable to sociodemographic, lifestyle,[60] or genetic factors.[61] Many traditional cardiovascular risk factors for stroke, like hypertension, diabetes, and smoking, also contribute to dementia risk.[62-65] Additionally, stroke may exacerbate underlying AD pathology, e.g., by accelerating amyloid-beta or tau tangle accumulation, leading to earlier cognitive decline and dementia onset.[66-68]

3.2.1.2 Post-stroke dementia

Post-stroke dementia (PSD) is classified as a subtype of vascular dementia and represents the most severe stage of PSCI.[17] According to guidelines by the Vascular Impairment of Cognition Classification Consensus Study (VICCCS), PSD is defined by the onset of progressive cognitive decline within six months after stroke, regardless of prior mild cognitive impairment.[69] However, PSD is often more broadly defined as any new-onset dementia following a stroke, without necessarily requiring cognitive decline to begin within the first six months.[16,28,57] The cumulative incidence rate of PSD is highest within the first year after stroke.[57] Meta-analyses have found heterogeneous incidence rates reported for PSD within the first year, which ranged from 7.4% (95% CI 4.8-10.0) in population-based studies of first-ever stroke patients without pre-stroke dementia to 41.3% (95% CI 29.6-53.1) in hospital-based studies, which did not exclude prior stroke or dementia.[16,57] Estimates for long-term PSD incidence are comparably scarce, especially after hemorrhagic stroke.[28] The Oxford Vascular Study (OxVasc), a large-scale population-based study from the UK, reported a 5-year PSD incidence rate of 33.1% (95% CI 31.7-34.5).[57] A Minnesota population-based study of patients with ischemic stroke between 1960 and 1984 reported a 25-year PSD cumulative incidence rate of 48%.[70] In a registry-based study from Denmark, the 30-year absolute risk of PSD was 11.5% (95% CI 11.2-11.7).[71] Cumulative incidence rates of PSD depend on various study population characteristics such as the inclusion or exclusion of pre-stroke dementia and prior strokes, as well as mean age and stroke severity.[53,57,70,71]

In recent years, researchers have further differentiated PSD into early-onset and delayed-onset PSD.[72-75] Although a universally accepted definition is lacking – partly due to the arbitrary nature of applied cut-offs – early-onset PSD is most commonly defined as dementia occurring within 3 to 6 months after stroke.[72,73] However, some sources extended this timeframe to within 1 year.[76] Regardless of the definition, early- and delayed-onset PSD are thought to be driven by distinct mechanisms, which will be outlined in more detail in section 3.3. The incidence rate for early-onset PSD is higher than that of delayed-onset PSD. However, direct comparisons across studies are challenging due to differences in study populations, follow-up durations, and definition criteria. Previously reported incidence rates for delayed-onset PSD range from 1.6 to 8.5 new cases per 100 person-years.[74,77-80] In comparison, the incidence rate of early-onset PSD is approximately 25 per 100 person-years within the first year.[57]

3.2.2 Mild cognitive impairment

PSCI that does not fulfill the criteria for dementia is typically referred to as post-stroke mild cognitive impairment (PSMCI) or post-stroke cognitive impairment no dementia (PSCIND). A key distinction between PSMCI due to vascular pathology and dementia is that PSMCI can sometimes improve or even fully resolve.[81] However, patients experiencing transient cognitive impairment (TCI) in the acute phase of stroke have been shown to have an almost fivefold higher risk of developing PSD within 5 years compared to those without TCI.[18] Early PSMCI is generally a strong predictor of poorer long-term

outcomes, including PSD, dependency, depression, and mortality.[16,57,82-87] This highlights the importance of identifying and monitoring patients with MCI at any stage following a stroke to assess and reassess individual risk and implement potential preventive strategies.

Results from meta-analyses suggest that PSMCI affects about 35-40% of individuals within the first year following stroke.[29,88] Meanwhile, the prevalence of PSMCI beyond the first year has been vastly understudied.[29,88] Many studies reporting on long-term cognitive outcomes post stroke focus on PSD or any PSCI, which includes PSMCI and PSD.[14,16,37,57,89] Two small hospital-based studies from Madrid, Spain,[90] and Dijon, France,[91] reported MCI prevalence rates of 36.6% (N=142) at two years and 79.1% (N=43) at three years post-stroke, respectively.

3.3 Baseline risk factors for dementia and cognitive impairment after stroke

As described above, dementia and stroke share several risk factors. However, the risk profile for PSCI appears to be more complex and distinct from that of either stroke or dementia alone. Overall, PSCI risk is assumed to result from a complex interplay of multiple factors, including cardiovascular risk, prior brain health, and severity of the acute stroke injury (**Figure 2**). In the following sections, these risk factors will be categorized as modifiable and non-modifiable at the time of stroke,[28] acknowledging that the modifiability of specific risk factors may be debatable. For instance, pre-stroke and stroke-related factors, such as prior cerebrovascular events or lesion location, will be classified as non-modifiable, since they can no longer be altered once the stroke has occurred. As another example, the history of educational attainment and pre-stroke cerebral reserve will be considered non-modifiable factors at the time of stroke, even though cognitive function after stroke may be modifiable.

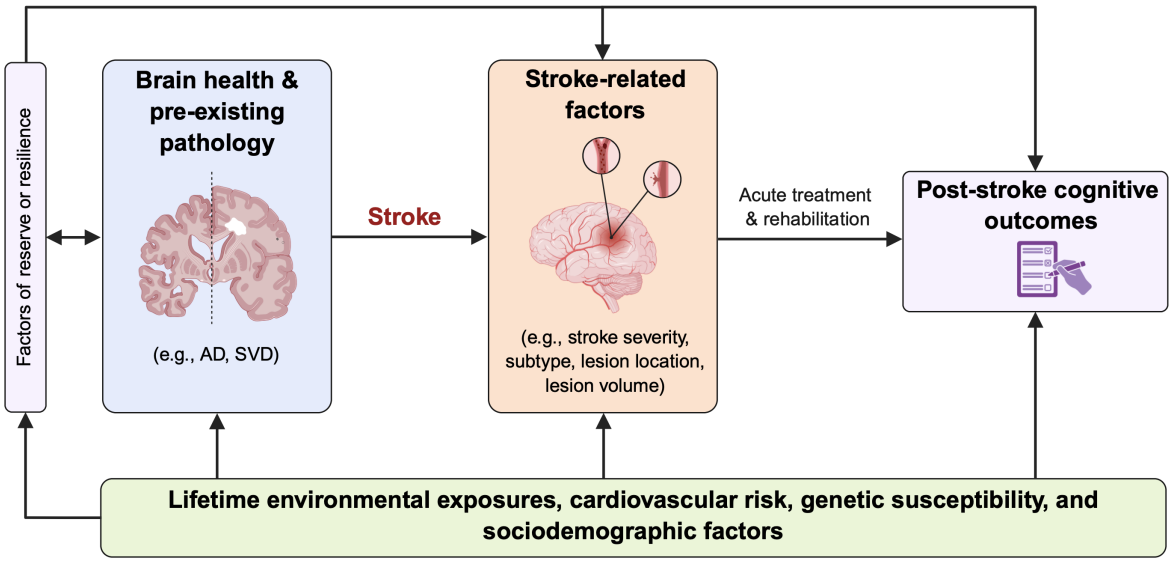

Figure 2. Factors contributing to post-stroke cognitive impairment and dementia. Figure created by the author of this thesis using BioRender.com.[57,92,93] AD, Alzheimer's disease. SVD, cerebral small vessel disease.

3.3.1 Non-modifiable risk factors

3.3.1.1 Sociodemographic factors

The two most well-established sociodemographic risk factors for PSCI are advanced age and lower educational attainment.[16,29,37,57,72,94-96] Evidence from a recent long-term registry-based study conducted in South Korea indicates that for every 10-year increase in age at the time of stroke, the risk of PSD within the first ten years following the stroke nearly doubles.[97] Furthermore, older patients tend to experience faster cognitive decline after stroke, which may be attributed to the aging brain's reduced capacity to recover from vascular injuries or may reflect an acceleration of cognitive decline that has already initiated before the stroke.[25,98]

Higher educational attainment is an important protective factor against cognitive decline and dementia. The number of years of lower and higher education can also serve as a proxy for pre-stroke cognitive reserve. Another measure of cognitive reserve is pre-stroke cognitive function, which is often evaluated through tools such as the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE).[99] Several studies have documented cognitive decline that initiated before stroke,[16,19,57,59,100,101] which supports the assumption of a shared susceptibility to both stroke and dementia. Pre-stroke cognitive decline has been consistently associated with an increased risk of PSD in several studies,[16,96] which could relate to underlying vascular and/or neurodegenerative pathology. In the Nor-COAST study, pre-stroke cognitive impairment was associated with neuroimaging markers of vascular mixed pathology and neurodegeneration, but not with markers of neurodegeneration in the absence of vascular pathology.[102] However, more research is needed to disentangle the contribution of vascular and neurodegenerative pathology underlying pre-stroke and post-stroke cognitive impairment.

In addition to educational attainment and cognitive reserve, other aspects reflecting socioeconomic status, such as income and employment, may also affect the risk of cognitive impairment and dementia.[103] Yet, these factors have been insufficiently investigated within stroke populations. A recent study utilising Danish register data from 2010 to 2020 reported a 2.8 times higher PSD incidence rate during a follow-up period of 4.2 years among stroke survivors with low income compared to those with high income, and a 1.4 times higher rate associated with unemployment compared to employment.[104] Another study from the London Stroke Register found a higher 3-month prevalence of PSCI among individuals in manual compared to non-manual jobs.[37] The association between lower socioeconomic status and PSCI is likely influenced by a complex interplay of economic, social, environmental, and psychosocial factors affecting health outcomes,[105] but requires further investigation.

The relationship between sex and gender with PSCI risk remains ambiguous and is presumably complex. Some studies suggest that females may be at a higher risk for PSCI than males,[16,106] while others report no significant differences.[57,107] In the REGARDS study, males exhibited a faster post-stroke cognitive decline than females,[94] and recent findings from a cohort of over 2,000 ischemic stroke

survivors imply that the risk of domain-specific cognitive impairment may differ between sexes.[107] Nevertheless, it is essential to interpret all sex-specific findings with caution due to potential survival bias: women typically live longer but often face greater dependency and multimorbidity.[108,109] Additionally, it is still unclear how socioeconomic status, cardiovascular risks, and biological factors may influence these associations.

Emerging evidence suggests a potential link between ethnicity and PSCI. In the REGARDS study,[94] Black stroke survivors experienced faster cognitive decline early after stroke compared to their white counterparts. Another recent study from South Carolina reported a 1.5-fold higher risk for all-cause PSD for African Americans compared to whites in a cohort of almost 69,000 stroke survivors. Two long-term registry-based studies further corroborate these findings, showing a substantially higher risk among Black stroke survivors.[37,106] Again, the mechanisms underlying these associations remain poorly understood, especially regarding the potential confounding effects of socioeconomic and cardiovascular risk factors.

The relationship of sociodemographic variables – including sex, socioeconomic status, and ethnicity – with PSCI and PSD is intricate and multifactorial. These factors often intersect with one another and with elements such as health literacy, behavior, and access to medical care, calling for further studies to improve their understanding.

3.3.1.2 Pre-existing brain health

Indicators of pre-stroke brain health, often referred to as "brain resilience," include brain volume, cerebral small vessel disease (SVD), and prior cerebrovascular events. Age and cognitive reserve, which have been established in the previous section, can also contribute to brain resilience. However, the following section will focus specifically on markers that can be detected via neuroimaging or clinical diagnosis.

Cerebral small vessel disease

SVD is an umbrella term for pathological changes of the microvasculature in the brain leading to damage of the brain parenchyma, visible on neuroimaging.[110] SVD increases the brain's vulnerability to vascular events and cognitive decline.[111] The most common form is hypertensive SVD, which is associated with cardiovascular risk factors, especially hypertension. Other forms are cerebral amyloid angiopathy (CAA) and rare monogenic forms of SVD, e.g., CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).[112] SVD is a strong independent risk factor for stroke, cognitive impairment, and dementia, and is estimated to contribute to about half of all dementias globally.[110,113-115] Conventional SVD MRI markers include white matter hyperintensities (WMHs), lacunes, cerebral microbleeds (CMBs), enlarged perivascular spaces, cerebral atrophy, superficial siderosis, and microinfarcts (**Figure 3**).[112,116]

Associations between some of these markers, particularly WMHs, and PSCI have been reported.[16,57,96,115,117-119] WMH volume is a strong predictor of cognitive outcomes after stroke, and recent findings indicate that not only the volume, but also the locations of WMHs in strategic white matter tracts, are of importance.[120,121] However, the existing evidence on several other SVD markers is conflicting, especially in relation to milder forms of PSCI.[118,122] Furthermore, it remains unclear if and to what extent a progression of SVD after stroke may accelerate cognitive decline or the onset of PSD.

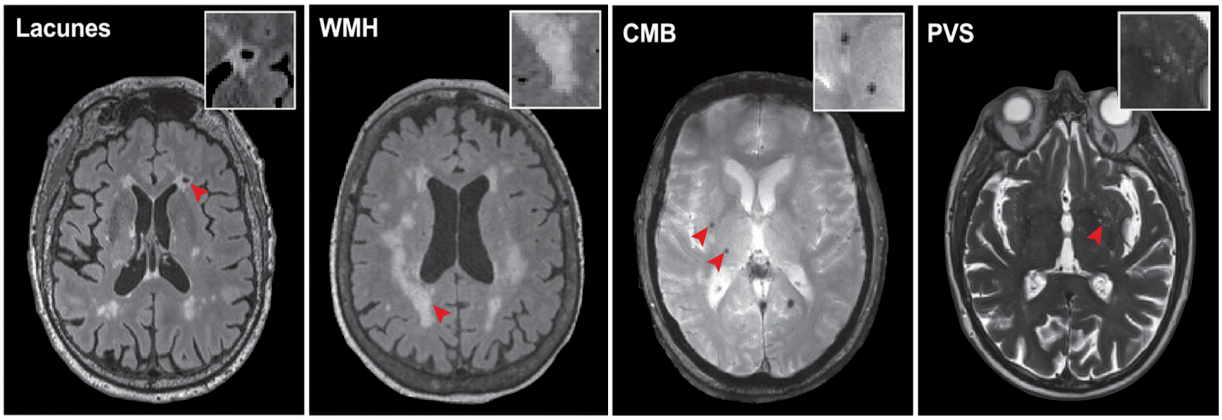

Figure 3. Exemplary images of SVD lesions. CMB, cerebral microbleeds. PVS, perivascular space. WMH, white matter hyperintensities. Figure adapted from Georgakis, Fang et al. (2023)[117] with permission from John Wiley and Sons.

Cerebral atrophy and neurodegenerative co-pathologies

PSCI and PSD risk are frequently associated with global cerebral atrophy and medial temporal lobe atrophy (MTLA).[16,96,118,122-124] Cerebral atrophy is common in SVD as well as in many neurodegenerative diseases.[121,125] MTLA, a hallmark of AD, has been proposed as a useful imaging marker for distinguishing AD dementia from other subtypes, such as DLB or VaD.[126] These associations suggest that AD pathology may contribute to cognitive decline and dementia following stroke.[73,127]

However, the evidence linking other AD-related markers to PSD and PSCI is heterogeneous. For example, Pendlebury et al. (2020) reported a 3.6-fold increased risk of PSD among patients with APOE-ε4 homozygosity, a well-known risk factor for sporadic AD.[76] Earlier studies, which were often limited by smaller sample sizes, had yielded inconsistent findings regarding the association between APOE-ε4 carrier status and post-stroke cognitive outcomes. However, a growing body of evidence does support a potential link between APOE-ε4 status and a higher PSD risk.[75,128-132] One reason for this might be that APOE-ε4 is not only a risk factor for AD, but also for CAA, an amyloidogenic type of SVD leading to intracerebral hemorrhage.[133]

Similarly, studies using amyloid positron emission tomography (PET) to assess amyloid plaque deposition and infer AD pathology in PSCI and PSD have reported heterogeneous results.[75,134] In a neuropathological study of 50 stroke survivors, only two of the 23 individuals who developed dementia

before death exhibited substantial AD pathology, while over 75% met criteria for VaD.[80] Reflecting on these and other findings, a 2017 review concluded that AD pathology likely plays a greater role in early-onset PSD (estimated 30–50%) than in delayed-onset PSD (<20%).[73] Taken together, current evidence suggests a contributory role of AD pathology in PSCI and PSD, though the extent of this contribution remains unclear and likely varies between individuals. Moreover, the potential involvement of other neurodegenerative pathologies, such as Lewy body disease (LBD), is yet to be thoroughly investigated.

History of prior cerebrovascular events

The risk of cognitive decline and dementia after stroke is higher in individuals who have already experienced one or more strokes in the past.[96,135,136] Similarly, several longitudinal observational studies of stroke survivors have found a significant increase in risk of PSD in individuals who experienced a new stroke during follow-up,[53,57,96,106] while studies regarding the association with milder forms of PSCI are lacking. Nonetheless, the magnitude of this effect is unclear, since some studies have found no association between stroke recurrence and PSD, especially in the long term.[74] Growing evidence suggests that even individuals with a transient ischemic attack (TIA), commonly known as "mini-stroke", have a higher risk for dementia than the age-matched general population.[57,137] However, studies investigating whether stroke patients with a history of TIA have a higher risk for PSCI remain limited.[57]

3.3.1.3 Stroke-related factors

Stroke severity and lesion volume

PSCI risk compounds not only with every additional stroke but also with greater severity of each event.[53,57,95,96,136] In the ARIC study,[53] compared to stroke-free individuals, the risk for PSD ranged from 1.73 (95% CI 1.49-2.00) in those who experienced one stroke with a National Institutes of Health Stroke Scale (NIHSS) score of ≤10 to 6.68 (95% CI 3.77-11.83) in those with ≥2 strokes, with at least one with NIHSS >10. A similar stepwise association between index stroke severity and dementia risk (**Figure 4**) was observed in the OxVasc study, where even transient ischemic attack (TIA) was associated with an elevated risk.[57] In OxVasc, dementia risk was only modestly increased after TIA or mild stroke (dementia brought forward by 2 and 4 years, respectively), and substantially greater after severe stroke (NIHSS >10, dementia onset accelerated by 25 years), when compared to the age- and sex-matched general population.

Stroke severity strongly correlates with infarct or hemorrhage volume,[138] which has also been linked to PSCI and PSD.[16,119,139,140] However, findings have been inconsistent,[141] possibly due to the limited predictive value of lesion volume in milder strokes.

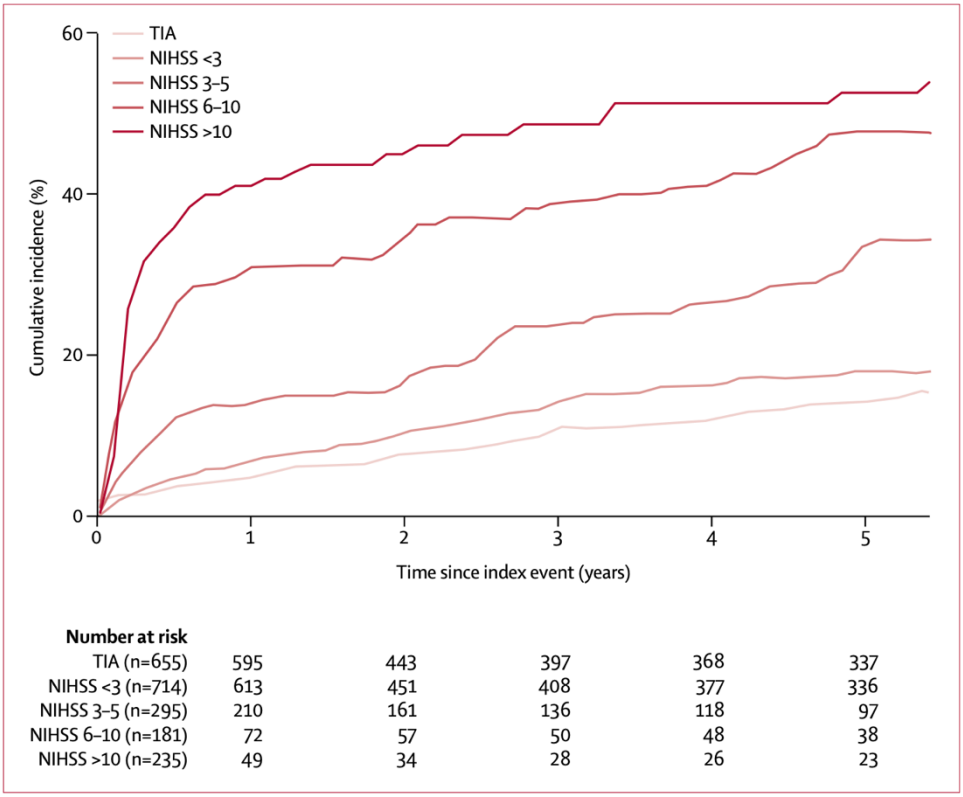

Figure 4. Kaplan-Meier curves of cumulative incidence of post-event dementia in the Oxford Vascular Study up to 5 years follow-up, stratified by event severity. NIHSS, National Institutes of Health Stroke Scale. TIA, Transient Ischemic Attack. Figure taken from Pendlebury et al. (2019).[57] For rights and permissions licensing information, please see https://creativecommons.org/licenses/by/4.0/

Lesion location

In addition to lesion volume, lesion location has also been implicated in cognitive outcomes. For instance, strokes affecting the left hemisphere have been associated with a higher risk of PSD and PSCI.[16,57,142] The Meta-VCI Map consortium recently conducted a pooled lesion symptom mapping analysis of individual patient data from 12 stroke cohorts (N=2950) to identify infarct locations most predictive of PSCI.[143] They identified strong associations between PSCI and lesions in the left frontotemporal lobes, right parietal lobe, and left thalamus, confirming and extending results from an earlier and smaller (N=267) study on performance on MoCA three months after stroke.[144] Global PSCI 3 to 6 months after stroke has been linked to lesions in the left angular gyrus, left basal ganglia structures, and the white matter around the left basal ganglia in the CU-STRIDE cohort.[145] While these results offer valuable insights into early PSCI risk, their applicability to PSD or long-term PSCI remains uncertain, as most cognitive outcome assessments were conducted between 2 and 6 months post-stroke. In addition, large strokes involving multiple brain areas complicate the study of lesion-specific associations with PSCI. Aphasia, which is common in left middle cerebral artery strokes, can interfere with language-dependent cognitive assessments, often resulting in an overestimation of PSCI rates among individuals with left-hemisphere lesions and aphasia.[16,93] Among survivors of hemorrhagic stroke, lobar ICH has been associated with a higher risk of PSD compared to non-lobar ICH.[96,119]

Presumably, this observation at least partly reflects underlying CAA, which is strongly linked to the risk of lobar ICH.[146] Overall, advances in neuroimaging have fueled increasing research efforts to improve the prediction of PSCI based on lesion location. Emerging evidence suggests that combining traditional lesion-symptom mapping with analyses of lesion-induced network disruptions (lesion network mapping) could improve prediction.[147] Moreover, specific infarct locations have been linked to stroke severity.[148,149] However, the mechanisms linking lesion locations to PSCI risk remain poorly understood.

Stroke subtype

Previous evidence further suggests that the risk of PSCI and PSD may vary by stroke type. An extensive nationwide registry study from Denmark found a higher dementia risk after hemorrhagic stroke than after ischemic stroke, compared to the general population.[71] Hemorrhagic strokes are typically associated with more severe brain injury, greater disability, and higher mortality, while treatment options remain more limited, and they often require invasive hematoma evacuation.[150] These factors may partly explain the higher dementia risk after hemorrhagic stroke observed in the Danish study and an earlier meta-analysis.[16] Supporting this, the OxVasc study reported that the association between PSD and hemorrhagic versus ischemic stroke was attenuated, but remained significant, when adjusting for stroke severity.[57] On the contrary, a recent analysis pooling data from four US cohorts showed no differences in cognitive decline between ischemic and hemorrhagic stroke patients.[151]

Among patients with ischemic stroke, current evidence does not indicate significant differences in the risk of PSCI,[152] PSD,[153] or post-stroke cognitive decline[151] across TOAST subtypes, which include small vessel (lacunar), large artery atherosclerotic, cardioembolic, and cryptogenic stroke, as well as stroke of other determined etiology.[6] This implies that although small vessel strokes are typically smaller and associated with less disability and mortality than other subtypes, the risk of cognitive impairment remains elevated, likely due to the underlying burden of SVD.[153]

Stroke-related deficits and complications

Low scores on brief cognitive screening tests (e.g., the Montreal Cognitive Assessment [MoCA] or the Mini-Mental State Examination [MMSE]) administered in the acute phase after stroke may reflect both pre-existing cognitive reserve and stroke-related deficits, such as delirium. Although early deficits are not always permanent and many patients recover from acute-phase cognitive impairment in the first few months,[37] it is still one of the strongest predictors of PSD and PSCI.[16,17,57,73,80,117,154] For instance, in the OxVasc study, an acute phase MMSE score of <24 was associated with a more than 3-fold increase in the five-year risk of dementia following stroke.[57]

Finally, the risk for poor cognitive outcomes may also be influenced by specific stroke-related complications, such as aphasia, delirium, leg paralysis, and infections.[95,155,156] Among these, the most consistent evidence exists for delirium. For other complications, the evidence remains limited. Studying

them may be challenging due to their close correlation with stroke severity, older age, and other baseline characteristics, making it difficult to disentangle independent effects.

In conclusion, this section has introduced and discussed risk factors considered non-modifiable in this thesis and previously,[28] as most of them are largely unchangeable during or shortly after the acute phase of a stroke. Nonetheless, it is important to note that parameters such as stroke severity, infarct volume, and stroke-related complications can sometimes be prevented or alleviated in the acute phase. Reperfusion therapy can help reduce final infarct volume and neurological deficits.[157,158] However, whether such interventions also decrease the risk of PSCI and PSD remains uncertain. That is likely partly due to the relatively recent implementation of endovascular thrombectomy as a standard clinical intervention, which began around 2015 in most Western countries.[159] Results from more recent long-term observational studies, including Study II of this thesis, will hopefully provide further insights into this question.

3.3.2 Modifiable risk factors

Identifying risk factors for PSCI and PSD is essential for two key objectives: enhancing individual risk prediction and identifying potentially modifiable factors that may serve as targets for prevention strategies. Despite increasing research interest,[51] robust evidence regarding modifiable risk factors remains limited.

Among traditional modifiable cardiovascular risk factors, diabetes mellitus has emerged as the most consistently associated with an elevated risk of post-stroke cognitive decline, PSCI, and PSD.[16,57,95,160-163] Growing evidence suggests cerebral microvascular dysfunction as a key mechanism underlying the relationship of diabetes with both stroke and cognitive impairment, which is assumed to be primarily driven by hyperglycemia, insulin resistance, obesity, and hypertension.[164] These pathophysiological processes may already begin during the prediabetic stage,[165-167] highlighting the importance of early detection and rigorous management of elevated blood glucose levels. However, previous findings from studies investigating the association of prediabetes with post-stroke cognitive performance and dementia have been inconclusive.[160,162,168,169]

Atrial fibrillation (AF) has frequently been reported as a potential risk factor for PSCI and PSD, although findings across studies remain inconsistent. Several investigations have linked AF to worse cognitive outcomes following stroke,[170,171] potentially due to its associations with silent cerebral infarctions,[172,173] cerebral atrophy,[174,175] chronic cerebral hypoperfusion,[176-178] systemic inflammation,[178] and greater stroke severity.[177,179] However, other studies have not detected a clear association.[16,57] This heterogeneity may reflect differences in AF detection methods, follow-up durations, or sample characteristics, underscoring the need for further research using standardized protocols and long-term follow-up.

Other vascular risk factors – such as hypertension, hyperlipidemia, smoking, obesity, and physical inactivity – have not shown independent associations with post-stroke cognitive outcomes,[16,57,94] despite being well-established contributors to stroke risk.[180]

To date, the impact of vascular risk factors on PSCI and PSD is generally considered to be indirect, primarily mediated through increased risks of stroke recurrence and the progression of SVD.[57,179,181-183] However, empirical studies that attempt to quantify these mediation effects – particularly the extent to which recurrent stroke or SVD burden explains the association between vascular risk factors and cognitive decline – remain scarce and are methodologically challenging to conduct.

As detailed in section 3.3.1.2 ("Pre-existing brain health"), SVD is considered an important risk factor for PSCI and PSD. Recent research increasingly suggests that SVD is a cerebrovascular pathology that could be modified by the reduction or rigorous management of cardiovascular risk factors.[184] The strongest evidence to date comes from the SPRINT-MIND trial, which demonstrated that intensive blood pressure control was associated with a slower progression of WMH and reduced risk of cognitive impairment.[185,186] However, it remains uncertain whether SVD progression can mainly be slowed or stabilized, or whether regression is also possible, and not biased by poor spatial resolution of MRI or changes in scanning protocols.[187] In light of this, the present thesis considers SVD a potentially modifiable risk factor for post-stroke cognitive outcomes.

While diabetes mellitus, SVD, and to a lesser extent atrial fibrillation have emerged as potentially modifiable risk factors for PSCI and PSD, the mechanisms underlying these associations and their implications for secondary prevention are yet to be clarified. Given the growing research interest, it also remains uncertain whether additional modifiable risk factors exist that have thus far received limited attention, which will be a focus of Study II.

4. THESIS AIMS

Understanding the risk factors that predispose stroke survivors to subsequent cognitive impairment and dementia is essential for improving risk prediction and identifying targets for secondary prevention. Therefore, the primary aims of this thesis were: (1) to systematically review and meta-analyze the existing literature on risk factors for PSD and PSCI, and (2) to investigate predictors of PSD and PSCI risk in a deeply phenotyped cohort of more than 700 stroke survivors followed for up to five years after stroke.

Specifically, **Study I** aimed to identify key baseline risk factors beyond the well-established predictors of age and stroke severity, employing rigorous inclusion criteria and methodology for the systematic review and meta-analysis. **Study II** aimed to build on the evidence synthesized in Study I by examining the long-term cognitive risk associated with both established and previously unreported baseline risk factors, most of which can be routinely assessed in clinical practice.

As important sub-aims, this thesis sought to: (i) disentangle the role of cardiovascular risk factors, (ii) identify novel modifiable risk factors, and (iii) elucidate time-dependent associations between risk factors and PSD risk. Collectively, these investigations aim to enhance understanding of the factors contributing to PSD and PSCI, potentially improving individual risk prediction, identifying secondary prevention targets, and informing patient selection for clinical post-stroke trials.

5. RESEARCH ARTICLES

Due to their size, the supplementary materials of the presented original research articles are included in the Appendix at the end of the thesis.

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

5.1.1 Summary

In this first study, a systematic review and meta-analysis, we synthesized all previously published evidence on the risk factors for PSCI and PSD. The design of this meta-analysis distinguished itself from previously published ones in the following key ways: (i) its comprehensive scope – analyzing not only studies on PSD but also on PSCI, which includes milder forms of cognitive impairment, (ii) its focus on effect estimates that were adjusted for the well-established factors age and stroke severity, and (iii) its inclusion of only longitudinal studies that assessed risk factors within the first 90 days and cognitive outcomes at least 3 months post-stroke. We synthesized evidence from 89 studies encompassing over 160,000 stroke survivors and reported the results for any risk factors investigated in at least two studies. We employed extensive harmonization methods of exposure and outcome variables to enable the synthesis of the largest possible number of individual study results, including harmonizing exposure and outcome measures to enhance the statistical power of the analyses.

As a main result, we identified baseline cognitive impairment as the strongest predictor for all cognitive outcomes – a finding that has not been emphasized in previous studies or reviews. Our results highlighted risk factors such as diabetes, AF, and markers of SVD, particularly WMHs, as critical treatable risk factors contributing to PSCI and PSD. Other strong predictors were lower educational attainment, previous stroke, left hemisphere stroke, and reduced baseline functional independence. Furthermore, sensitivity analyses revealed that the strength of associations between certain risk factors and PSD reported by individual studies has decreased over time, suggesting improvements in stroke care and risk factor management. The findings of this study underscore the clinical importance of early cognitive testing after stroke for risk stratification and highlight modifiable cardiovascular and cerebrovascular factors as potential targets for secondary prevention strategies aimed at mitigating long-term cognitive problems.

5.1.2 Reference

The paper was published in *The Lancet Healthy Longevity*[188] under the following reference:

Filler J*, Georgakis MK*, Dichgans M. Risk factors for cognitive impairment and dementia after stroke: a systematic review and meta-analysis. Lancet Healthy Longev. 2024 Jan;5(1):e31-e44. doi: 10.1016/S2666-7568(23)00217-9. Epub 2023 Dec 12. PMID: 38101426. *contributed equally

Please refer to the Appendix for the entire supplementary materials

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

Jule Filler, Marios K Georgakis*, Martin Dichgans*

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]

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.

See Online for appendix

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 PRISMA[22] and the MOOSE guidelines[23] (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

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 adjustments[28] 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 approach[29] to account for potential reporting bias.

We applied the Benjamini-Hochberg procedure[30] 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 13 127 unique articles were screened for eligibility (figure 1). We identified 162 eligible

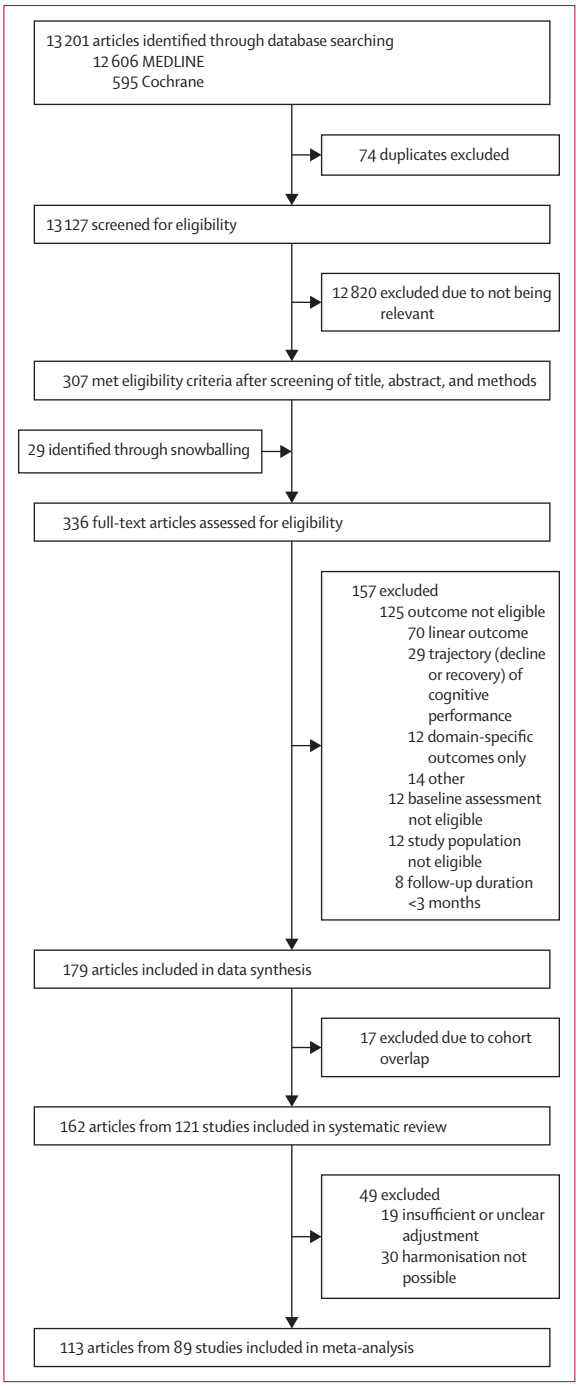

Figure 1: **Flow chart for study selection**

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 (β1) for the relationship between log(RR for PSCI) and log(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*/27 254*	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	5648/33 721	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	4757/45 927	21·1 (12·0–30·1)	1·57 (0·12–20·99)	0·27	67·8	0·08
Cardiovascular risk factors														
Diabetes	16	2495*/11 439	5·1 (3·0–11·9)*	1·29 (1·14–1·45)	0·0004†‡	73·6	<0·0001	11	5667/33 953	16·0 (3·0–39·6)*	1·38 (1·10–1·72)	0·010†	64·9	0·001
Hypertension	14	4963*/16 234	3·0 (3·0–3·3)*	1·19 (0·91–1·56)	0·19	86·9	<0·0001	5	4982/30 929	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	4838/25 382	15·9 (3·0–45)*	1·27 (0·86–1·90)	0·19	78·0	0·0001
Hyperlipidaemia or dyslipidaemia	7	3544/11 271	3·0 (3·0–3·15)*	0·83 (0·63–1·09)	0·14	27·8	0·22	5	5290/32 523	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	4639/23 864	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	3255/10 616	3·0 (3·0–3·0)*	1·07 (0·82–1·40)	0·50	55·8	0·06	5	12 436/95 489	50·4 (46·8–58·8)*	1·04 (0·99–1·10)	0·07	0·0	0·95
Kidney disease	0	..	..	..	..	..	..	3	1176/10 522	26·7 (14·8–38·5)*	1·30 (0·37–4·54)	0·46	84·0	0·002
Peripheral artery disease	1	..		..	..	..	..	3	7848/66 525	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	4331/22 281	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	..	..	..	..	..	..

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	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 (3·0–36·3)*	1·18 (1·10–1·26)	0·0015†‡	11·3	0·34	3	4089/20 900	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	4067/20 799	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
Neutrohil–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	..	..	..	..	..	..

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	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)														
Undetermined	3	708/1279	4·5 (3·75–5·25)*	1·13 (0·49–2·64)	0·59	62·0	0·07	0	..	..	..	..	..	..
Other determined	2	580/1053	3·0 (3·0–3·0)*	0·91 (0·52–1·60)	0·29	0·0	0·33	0	..	..	..	..	..	..
Carotid artery stenosis	4	471/1206	6·45 (6·22–6·68)*	1·30 (0·94–1·80)	0·08	84·6	0·0002	1	..	..	..	..	..	..
Carotid plaques	2	243/544	3·0 (3·0–3·0)*	1·66 (0·08–33·58)	0·28	73·1	0·054	0	..	..	..	..	..	..
Neuropsychiatric disorders														
Depression	3	402/1042	4·5 (3·75–5·25)*	1·31 (0·64–2·67)	0·25	86·9	0·0005	1	..	..	..	..	..	..
Depressive symptoms (SD)	2	96/582	4·5 (3·75–5·25)	1·18 (0·47–2·96)	0·25	0·0	0·43	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=ischaemic 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**

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 160 783 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.[1,4] 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 PSD[1] and a population-based cohort study[3] 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 dementia[34] and cognitive impairment,[35] independent of 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.[1,3] 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.

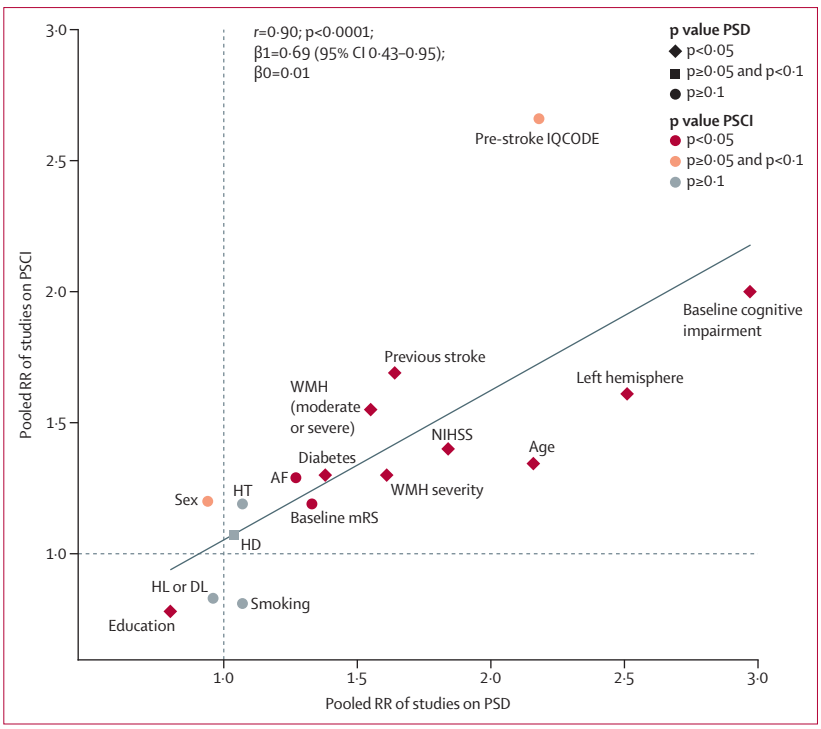

Figure 2: **Correlation of pooled RRs from studies on PSCI versus from studies on PSD for which data were available**

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 (β1) and intercept (β0) of a regression line modelling the regression equation $\log(RR\_psci)=\beta0+\beta1*\log(RR\_psd)+\varepsilon$. 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.

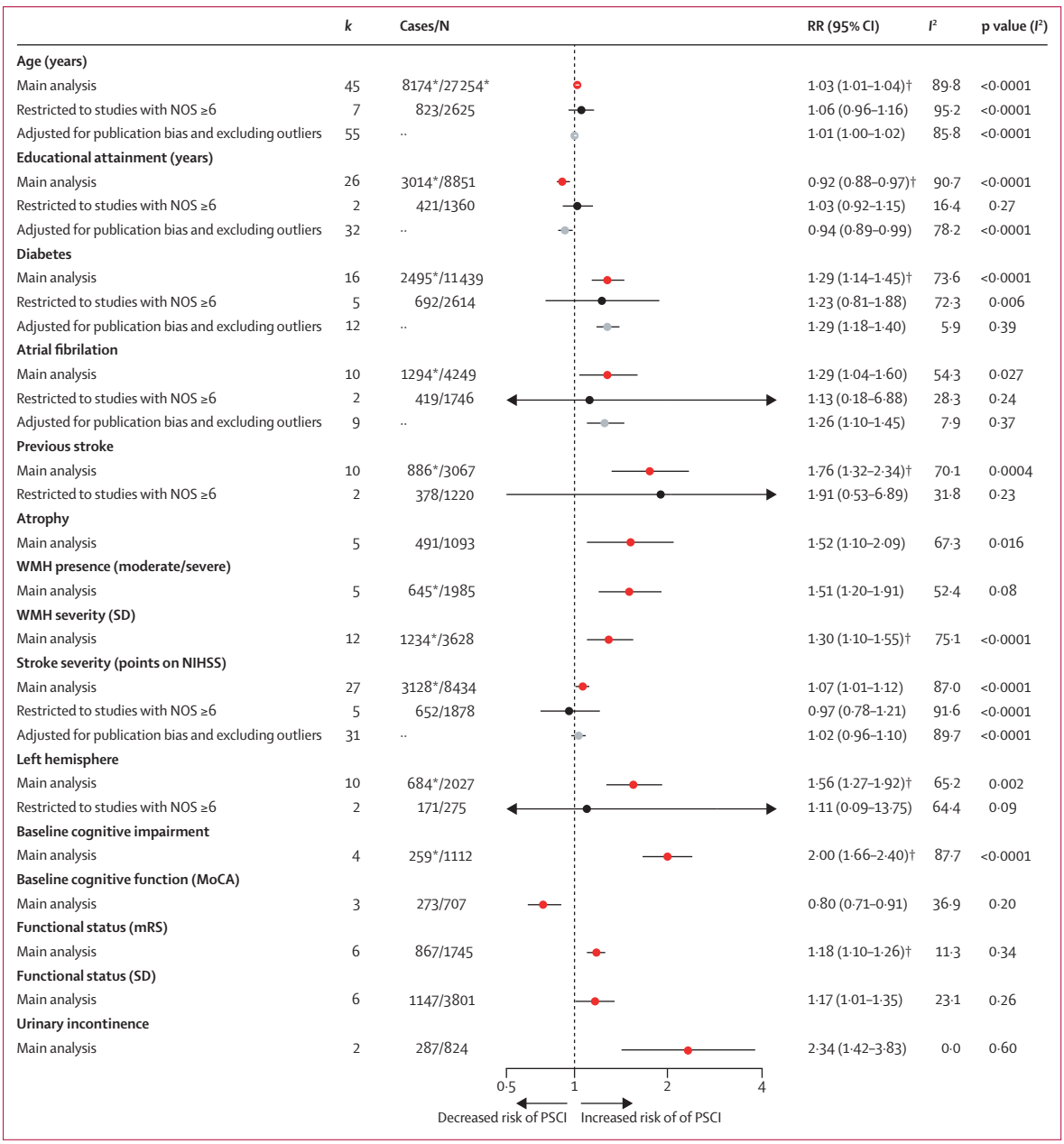

Figure 3: **Forest plot of pooled RRs for PSCI**
Results for significant predictors of PSCI in the main analysis (red), when restricting the analysis to studies rated with 6 or more points on the NOS (black), and when adjusting the analysis for publication bias while excluding outlying study effect estimates (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

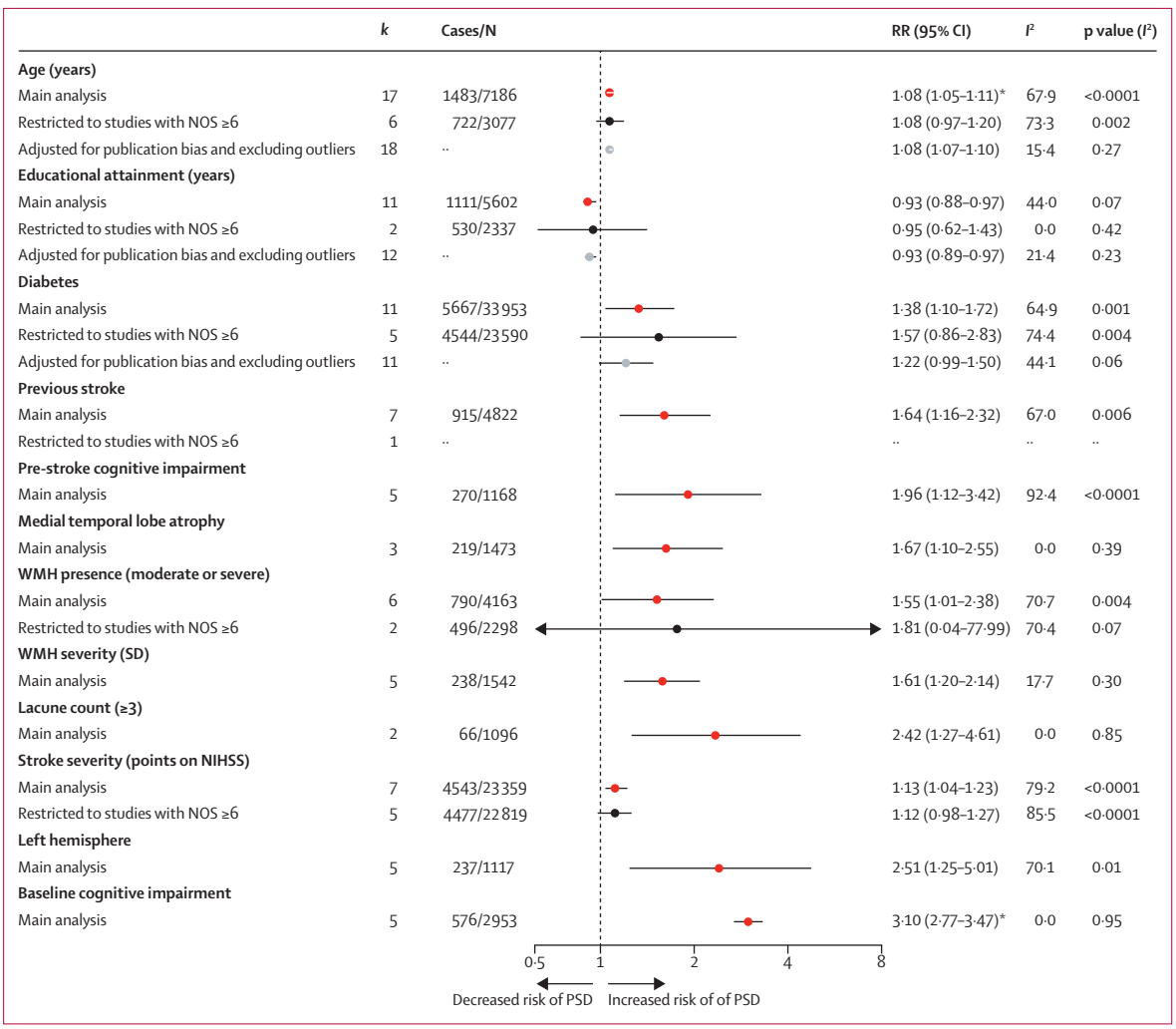

Figure 4: **Forest plot of pooled RRs for PSD**

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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5.2 Risk factors for dementia and cognitive impairment during 5 years after stroke: a prospective multicenter cohort study

5.2.1 Summary

Building on the findings from Study I, Study II investigated clinically accessible risk factors for PSCI and PSD over five years after stroke in the DEMDAS (German Center for Neurodegenerative Diseases (DZNE) mechanisms of dementia after stroke) study, a multicenter prospective cohort study of 736 stroke patients recruited at six German tertiary stroke centers. A particular focus was placed on identifying modifiable risk factors. Comprehensive clinical, imaging, and cognitive assessments were conducted at baseline and regular follow-ups. The primary outcome was the 5-year risk of PSD. Additionally, we assessed the following secondary outcomes: early-onset PSD (dementia occurring between 3-6 months post-stroke), delayed-onset PSD (dementia >6 months), and PSCI (MCI or dementia within five years). All statistical models were adjusted for age, sex, education, and admission stroke severity.

The cumulative 5-year incidence of PSD was 8.8% (55 new cases of dementia over 2899 person-years), with 21 (38%) of these with an onset between 3-6 months post-stroke. Key risk factors for PSD identified in this study included older age, lower education, higher NIHSS, reduced baseline cognitive and functional scores, AF, diabetes, and metabolic syndrome (MetS) – particularly its components reduced high-density lipoprotein cholesterol (HDL-C) and elevated blood glucose. Neuroimaging markers, including lower brain volume and SVD markers (specifically, WMHs, lacunes, CMBs, and skeletonized mean diffusivity), and stroke recurrence during follow-up, were also associated with increased risk. Acute reperfusion therapy was linked to a reduced PSD risk.

Risk profiles differed by dementia onset timing: early-onset PSD was more strongly associated with factors related to the acute stroke and its severity, whereas metabolic syndrome emerged as a prominent risk factor for delayed-onset PSD, potentially accounting for over half of the delayed-onset cases. Sensitivity analyses adjusting for recurrent stroke confirmed the robustness of results, and associations with PSCI generally mirrored those for PSD.

Overall, the findings from this study underscore the multifactorial nature of PSD risk and highlight metabolic syndrome, particularly its component reduced HDL-C, as a novel and modifiable contributor, which could be a relevant target for preventing PSD, especially delayed-onset PSD. While acute stroke care remains essential for reducing the risk of early-onset PSD, our results emphasize the importance of sustained efforts to monitor and manage cardiometabolic risk factors to mitigate long-term cognitive risk, independent of preventing recurrent strokes. These findings may inform the development of prediction tools for long-term PSD risk and inform future prevention trials targeting vascular and metabolic risk factors.

5.2.2 Reference

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Please refer to the Appendix for the entire supplementary materials.

Risk factors for dementia and cognitive impairment within 5 years after stroke: a prospective multicentre cohort study

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Summary

Background Stroke survivors frequently experience subsequent cognitive impairment or dementia. We aimed to identify risk factors for post-stroke dementia (PSD) and cognitive impairment (PSCI) within 5 years after stroke.

Methods The DEMDAS (German Center for Neurological Diseases (DZNE) mechanisms of dementia after stroke) study is a prospective cohort of stroke patients admitted to six German tertiary stroke centres between May 1, 2011 and January 31, 2019. Eligible dementia-free patients with ischaemic or haemorrhagic stroke underwent baseline examinations and regular clinical, neuropsychological, and neuroimaging follow-ups over 5 years, with the last follow-ups completed in January 2024. PSD was the primary outcome, determined by comprehensive cognitive testing, patient and informant interviews, and review of medical records. The secondary outcomes were early-onset PSD (3–6 months), delayed-onset PSD (>6 months), and PSCI. Associations between baseline risk factors and PSD were assessed using Cox regression models adjusted for age, sex, education, and stroke severity.

Findings Of 736 patients (245 [33%] female, mean age 68·0 years [SD 11·2], median admission National Institutes of Health Stroke Scale (NIHSS) 3 [IQR 1–5]), 557 (76%) were followed up until death or the end of the study, and 706 (96%) contributed to the PSD analysis. During a median of 5·0 years [IQR 3·3–5·1] of follow-up, 55 new dementia cases were diagnosed (6-month incidence: 3·1% [1·8–4·5], 5-year incidence: 8·8% [6·5–11·1]), of which 21 (38%) were classified as early-onset PSD. The 5-year risk of PSD was associated with older age (HR 1·13 [95% CI 1·08–1·18] per

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[x]The members of DEMDAS Investigators are listed in the Supplementary Materials section.
Translation: For the German translation of the abstract see Supplementary Materials section.

year), higher stroke severity (1·08 [1·03–1·13] per point on NIHSS), lower educational attainment (1·16 [1·05–1·28] per year), acute phase cognitive impairment (5·86 [2·21–15·58]), lower Barthel Index (1·10 [1·05–1·16] per 5 points less), atrial fibrillation (1·91 [1·10–3·30]), metabolic syndrome (MetS, 2·05 [1·15–3·64]), particularly reduced high-density lipoprotein cholesterol (HDL-C, 2·61 [1·50–4·52]) and pre-/diabetes mellitus (2·13 [1·13–4·00]), imaging markers of small vessel disease, and stroke recurrence during follow-up (2·36 [1·16–4·83]). Patients who received acute reperfusion treatment had a 65% lower risk of PSD than those who did not (0·35 [0·16–0·77]). While factors related to the severity of the index stroke were more strongly associated with early-onset PSD, MetS showed a stronger association with delayed-onset PSD. The association between MetS and PSD was independent of stroke recurrence and consistent across age subgroups, with 5-year cumulative incidence ranging from 1·7% (0·0–4·0) in patients ≤65 years without MetS to 24·5% (14·3–33·4) in patients ≥74 years with MetS.

Interpretation The risk of dementia after stroke is multifactorial, with differing risk profiles for early-onset and delayed-onset PSD. Metabolic syndrome, including reduced HDL-C, emerged as a novel risk factor and potential target for PSD prevention.

Funding German Center for Neurodegenerative Diseases (DZNE).

Keywords: Stroke; Brain ischaemia; Risk factors; Stroke outcomes; Stroke epidemiology; Dementia; Vascular dementia; Dementia epidemiology; Post-stroke dementia; Post-stroke cognitive impairment; Cognitive decline; Diabetes; Metabolic syndrome; Small vessel disease

Introduction

Over the past three decades, global stroke mortality rates have steadily declined,[1] shifting focus towards long-term outcomes following stroke.[2–4] Cognitive impairment and dementia are among the most serious consequences, affecting patients, their families, and healthcare systems. Five to 40% of stroke survivors develop post-stroke dementia (PSD) within the first year, and 8–80% within 5 years, depending on risk profiles.[3,5] A better understanding of the factors that predispose stroke patients to cognitive decline and dementia is needed to identify high-risk individuals, develop effective prevention and monitoring strategies, and counsel patients and caregivers.

A large-scale population-based study has shown that PSD incidence rates vary substantially with risk factors such as age, stroke severity, prior stroke, or APOE-ε4 genotype.[3,6] Hospital-based prospective studies allow recruitment of well-characterised patient subgroups, deep risk factor profiling, detailed acute phase assessment, identification of novel risk factors, and standardised follow-up with comprehensive cognitive assessments. However, reliable results from studies with long-term follow-up remain limited.[4,7]

There is particular interest in risk factors that could be modified and explored in clinical trials. Currently, diabetes mellitus and atrial fibrillation are the most established modifiable risk factors for PSD, although their role in the development of cognitive impairment remains insufficiently understood.[3,5,7,8] Many patients with diabetes also have a cluster of cardiometabolic risk factors, known as metabolic syndrome (MetS).[9,10] MetS is diagnosed when three out of five markers are present: abdominal obesity, elevated triglycerides, reduced HDL-C, hypertension, and hyperglycaemia.[9] MetS has been associated with higher risks of cardiovascular disease[10] and dementia in population-based studies,[11–13] but its role in PSD remains unexplored. With novel available treatments against metabolic dysfunction, such as obesity and diabetes, investigating how MetS components affect PSD risk could inform new preventive strategies for stroke survivors.

Dementia diagnosed between 3 and 6 months after stroke, termed early-onset PSD, has been primarily related to the severity of the vascular insult and reduced reserve or resilience (including factors such as age, cognitive reserve, atrophy, cerebral small vessel disease (SVD) burden, or previous brain injuries).[14] However, even in patients who do not develop dementia in the first 6 months after stroke, a significant risk of delayed-onset PSD persists.[14] Few studies have explored risk factors for delayed-onset PSD after excluding early-onset cases.[6,14–18] These studies suggest delayed-onset PSD is mainly associated with imaging markers of SVD burden, while the role of stroke recurrence, other vascular factors, and contributing pathologies remains unclear.[14–18] Patients at higher risk of delayed-onset PSD could particularly benefit from targeted preventive interventions,[14] underscoring the importance of identifying the modifiable risk factors for delayed-onset PSD.

Here, we report the main results of the prospective hospital-based German Center for Neurological Diseases (DZNE) mechanisms of dementia after stroke (DEMDAS) study, which was designed to determine the

Research in context

Evidence before this study

We updated our previous systematic review on risk factors for post-stroke dementia (PSD) and cognitive impairment (PSCI), which originally searched MEDLINE and the Cochrane Library from database inception to Sept 15, 2023. The updated search added Embase and extended coverage to Dec 10, 2024. Eligible English-language articles reported associations between baseline risk factors and longitudinal PSD or PSCI risk. Search terms included "prospective", "longitudinal", "risk factors", "stroke", "dementia", and "cognitive impairment". While few baseline risk factors have been consistently identified in large, prospective cohort studies, robust evidence existed for older age, greater stroke severity, prior stroke, lower educational attainment, acute phase cognitive impairment, APOE-ε4 carrier status, lacunes, and white matter hyperintensities. Diabetes mellitus and atrial fibrillation were the most established vascular risk factors, but evidence for other modifiable factors remained inconclusive. The most robust evidence came from few population-based studies, which provide results that are more generalisable to the general stroke patient population. In contrast, reports from hospital-based studies, which allow for deeper phenotyping and identifying novel risk factors, were limited in quality and follow-up length. PSD incidence was highest early post-stroke, but data on risk factors for delayed-onset PSD (>6 months) were particularly limited, despite indications of differing mechanisms underlying early- and delayed-onset PSD.

Added value of this study

In this 5-year multicentre prospective hospital-based cohort of well-characterised patients with minor or major stroke, we used a standardised methodology for baseline and follow-up examinations, allowing precise evaluation of cognitive decline and dementia onset. Risk for PSD or PSCI varied substantially across sociodemographic, clinical, cardiometabolic, and neuroimaging factors. We identified a previously unrecognised association between PSD and metabolic syndrome, specifically its components diabetes and reduced HDL-C, independent of stroke recurrence. Patients who received acute reperfusion treatment had a significantly lower risk of PSD. The PSD incidence rate was 4·2 times higher in the early phase (3–6 months, 5·86/100 person-years) compared to the later phase (>6 months, 1·39/100 person-years). Early-onset PSD was predominantly linked to factors related to the stroke itself and prior brain health, while delayed-onset PSD was more strongly associated with cardiometabolic risk and stroke recurrence.

Implications of all the available evidence

The risk of post-stroke dementia and cognitive impairment is significantly influenced by factors related to poor pre-stroke brain health, greater stroke severity, vascular and metabolic risk, recurrent stroke, and cerebral small vessel disease. While the risk of PSD is highest early after stroke, a substantial risk persists over the long term. The importance of individual risk factors varies for early-onset PSD and delayed-onset PSD. Identifying these risk factors for PSD in the short- and long-term is essential for predicting individual risk, providing tailored counselling to patients and their families, and guiding the selection of participants for clinical trials. Cardiometabolic risk factors are associated with PSD regardless of stroke recurrence. These findings underscore the importance of focussing research efforts on modifiable risk factors and of prioritising dementia as a key outcome in clinical trials of secondary prevention in stroke patients.

risk factors for PSD and identify possible new targets for PSD prevention. We further sought to investigate the different risk factors for early-onset and delayed-onset PSD and to examine the prevalence and predictors of post-stroke cognitive impairment.

Methods

Study design

The DZNE Mechanisms of Dementia After Stroke study (DEMDAS) is a prospective, multicentre, hospital-based cohort study aimed at understanding the determinants and mechanisms of dementia after stroke. Initially launched as a pilot study at LMU Munich, Germany (recruiting 136 participants between May 2011 and November 2013), the study was expanded to include an additional 600 patients across six tertiary stroke centres in Munich, Berlin, Bonn, Göttingen, and Magdeburg, Germany (Table S1). Participants were recruited from January 2014 to January 2019 and followed up for 5 years after stroke. The study was conducted in accordance with the Declaration of Helsinki, and ethics approval was obtained at each participating site prior to the start of the study (ethics committee of the medical faculty, LMU Munich [035–11 and 201–13], ethics committee of the medical faculty, Rhenish Friedrich-Wilhelms-University, Bonn [116/13], ethics committee of the university medicine Göttingen [21/1/12], ethics committee of the Technical University Munich [93/14 S], ethics committee of the Otto-Von-Guericke-University at the medical faculty and the university hospital Magdeburg [66,13]; the site at Charité university medicine Berlin participated in the study with the ethics vote of the LMU Munich, according to the Professional Code of Conduct of the Berlin Medical Association of September 2009, Section 15 [2]). The DEMDAS study is registered at http://www.clinicaltrials.gov (NCT01334749) and the detailed methodologies have been previously described.[4,19,20]

Participants

Participants aged 18 years or older were included if hospitalised at any of the participating study centres for an acute ischaemic or haemorrhagic stroke, defined as a focal neurological deficit with symptom onset within the last five days before admission combined with an acute ischaemic infarct as documented by either a diffusion-weighted imaging positive lesion on cranial magnetic resonance imaging (MRI) or a new lesion on a delayed computed tomography (CT) scan; or an intracerebral haemorrhage as documented on CT or MRI. Participants were required to have an available informant. Exclusion criteria included pre-stroke dementia or significant cognitive decline (Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE] score >64),[21] malignant disease with a life expectancy <3 years, MRI contraindications, cerebral venous thrombosis, traumatic haemorrhage, haemorrhage from vascular malformations, or isolated meningeal or intraventricular haemorrhage. Participants and their informants were re-examined in person at 6, 12, 36, and 60 months post-stroke by trained study nurses and clinicians. Written informed consent was obtained from all patients or their legal guardians before study entry.

Procedures

At baseline, participants underwent standardised evaluations by a study clinician and a study nurse shortly after hospitalisation. These included interviews, clinical and cognitive assessments, laboratory tests, and neuroimaging.[4,19,20] The data collected covered sociodemographic information, medical and family history, medication use, and physiological measurements (e.g., blood pressure, BMI). Sex was self-reported as male or female. Genetic ancestry was analysed by comparing participant genotype data against the 1000 Genomes Project (1kG) Phase 3 reference panel (Supplementary Methods). Acute-phase neurological, functional, and cognitive status were assessed using clinical scales (National Institutes of Health Stroke Scale [NIHSS], modified Rankin Scale [mRS], Barthel Index, Delirium Rating Scale) and cognitive screening tests (Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA]). Metabolic syndrome was defined as the presence of three or more predefined criteria (Supplementary Methods).[9] As part of the study protocol, cranial 3-T MRIs were conducted within 3–5 days post-stroke in all patients whenever feasible, enabling the assessment of multiple neuroimaging variables, including brain volume, infarct volume, conventional SVD markers (lacunes, white matter hyperintensities, cerebral microbleeds, and perivascular spaces), and mean skeletonised mean diffusivity (MSMD, details in Supplementary Methods and as reported previously[4]).

To minimise attrition and bias related to dementia outcome assessment, follow-up visits were conducted at 6, 12, 36, and 60 months via in-person visits at the study centres, home visits, or, if needed, telephone or mail. Additional telephone interviews were performed at 3, 24, and 48 months. In-person follow-ups included comprehensive cognitive and functional evaluations, which are described in detail in the Supplementary Methods.

The primary outcome, post-stroke dementia (PSD), was defined according to the DSM-5 criteria for major neurocognitive disorder, encompassing all incident dementia regardless of cause or time of onset, as detailed in the Supplementary Methods. Cognitive outcomes at each follow-up were evaluated by a committee of neurologists and memory clinic physicians using a tiered protocol (Supplementary Methods). Dementia diagnosis dates were determined after reviewing all medical records, cognitive and functional test results, and reports from patients and/or informants. The secondary outcomes were early-onset PSD (diagnosed 3–6 months post-stroke), delayed-onset PSD (>6 months), and post-stroke cognitive impairment (PSCI). The distinction between early- and delayed-onset PSD was not part of the original study protocol,[19] but was included following work published in 2016 by Mok and colleagues.[14,15,18] Most cognitive recovery occurs within the first 6 months post-stroke, though improvement can continue up to 12 months and beyond.[22] The 6-month cut-off reflects this clinically relevant early recovery window, but given the absence of a universally accepted threshold, we conducted a sensitivity analysis using a 12-month cut-off for early-onset PSD. PSCI was defined as the combined endpoint of dementia and mild cognitive impairment.[23]

Statistical analysis

Baseline characteristics were compared between patients with and without PSD using two-tailed t-tests for normally distributed continuous variables, Wilcoxon-rank-sum tests for non-normally distributed continuous variables, or χ^2 tests for categorical variables. We calculated the cumulative PSD incidence rates and 95% CIs using a Kaplan–Meier estimator accounting for the competing risk of death for the total sample and stratified by risk factors. To improve interpretability, age, education, and NIHSS score were categorised for these analyses (Supplementary Methods), and cumulative incidence rates were compared using Gray's test. Patients were censored at the last follow-up examination before they were lost to follow-up. The exact onset of dementia symptoms between follow-up visits was often unknown. Hence, we imputed onset dates using the mean interval between visits and conducted a sensitivity analysis with multiple imputation. We used standard and competing-risk Cox regression models to calculate cause-specific and subdistribution hazard ratios, respectively, evaluating the relationships between baseline factors and the 5-year risk of incident PSD.[24]

Models were adjusted for age, sex, education, and stroke severity,[3,5] with death as the competing risk. The proportional hazards assumption was tested using the Grambsch and Therneau test.[25] In case of violation ($p < 0{\cdot}05$), we employed flexible parametric survival models with natural splines to model non-proportional hazards and time-varying effects (Table S19).[26] For analysing associations with the secondary outcomes early-onset and delayed-onset PSD, we split follow-up into an early (≤6 months) and a later period (>6 months; Supplementary Methods). Patients with early-onset PSD were excluded from the analysis of delayed-onset PSD. Population attributable fractions (PAFs) for early- and delayed-onset PSD, along with their CIs, were estimated using bootstrap resampling (10,000 iterations, Supplementary Methods). Differences in PAFs between early- and delayed-onset PSD were calculated for each bootstrap iteration with 95% CIs derived from the 2·5th and 97·5th percentiles of the bootstrap distribution of PAF differences. Predictors for PSCI across the 5-year study period were assessed using generalised estimating equations (GEE) logistic regression models. All PSCI models were adjusted for age, sex, education, and stroke severity. We performed subgroup analyses of the PSD analysis stratified by sex. A priori and post-hoc power calculations are detailed in the Supplementary Methods. Sensitivity analyses included adjustments for acute stroke treatment, stroke

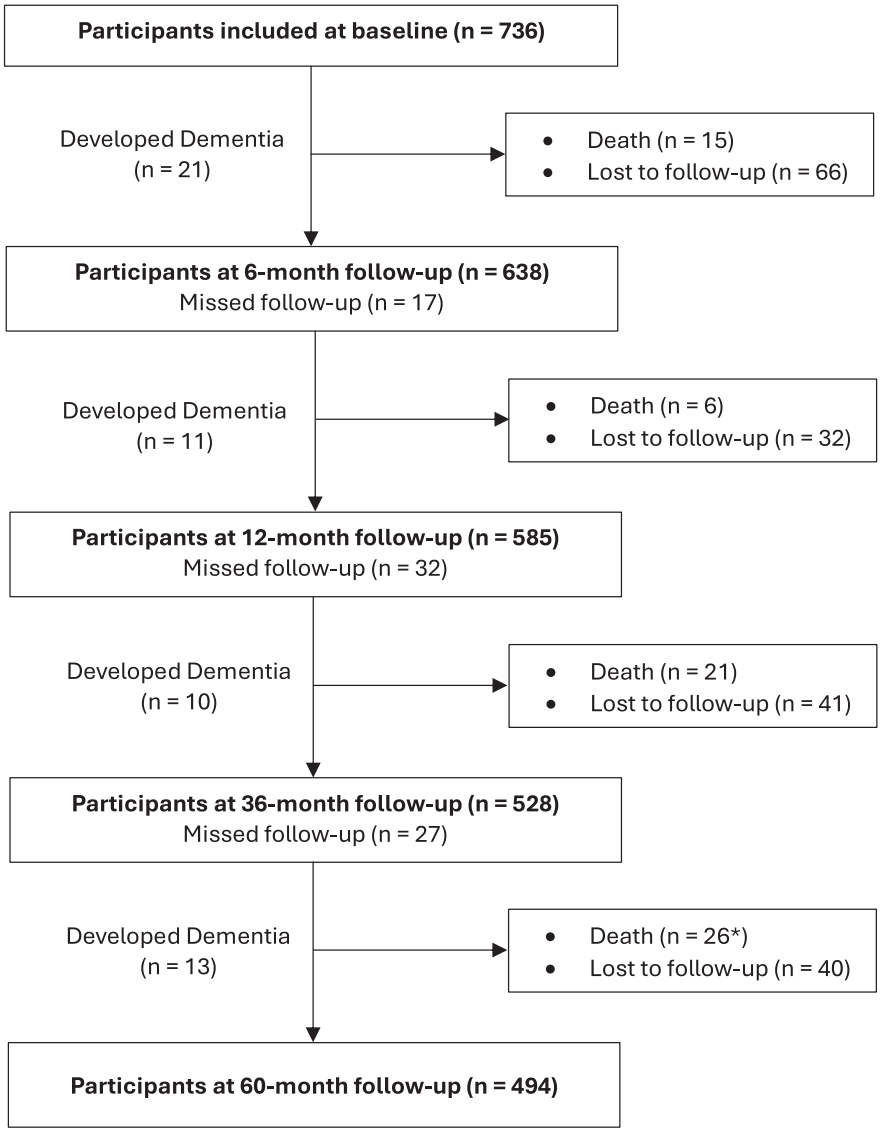

Fig. 1: **Participant flow chart for the 5-year follow-up period.** Follow-ups via telephone at 3, 24, and 48 months exist but are not shown here. *Five deaths were recorded after participants were lost to follow-up.

	No PSD (n = 681)	PSD (n = 55)	p value
Sociodemographic variables			
Age (years)	67·3 ± 11·0	76·5 ± 9·3	<0·0001
Age ≥74 years	223 (32·7%)	38 (69·1%)	<0·0001
Female[a]	226 (33·2%)	19 (34·5%)	0·95
Male[a]	455 (66·8%)	36 (65·5%)	0·95
Education (years)	13 (12–16)	12 (11–13)	0·005
Education ≤12 years	262 (38·5%)	30 (54·5%)	0·03
Genetic ancestry[b]			1·00
European	552/554 (99·6%)	45/45 (100%)	
Ad mixed American	1 (0·2%)	0 (0·0%)	
East Asian	1 (0·2%)	0 (0·0%)	
Clinical/cognitive acute phase deficits			
Admission NIHSS score	2 (1–5)	4 (3–7)	0·001
Admission NIHSS ≥3	345 (50·7%)	42 (76·4%)	0·0004
Barthel index score	100 (85–100)	75 (55–90)	<0·0001
Delirium rating scale score	0 (0–1)	0 (0–1)	0·15
Acute phase MoCA score	25 (23–28)	21 (19–24)	<0·0001
Acute phase cognitive impairment[c]	338/660 (51·2%)	44/49 (89·8%)	<0·0001
Cardiovascular risk factors			
Hypertension	523 (76·8%)	48 (87·3%)	0·10
Diabetes mellitus	129 (18·9%)	21 (38·2%)	0·001
Dyslipidaemia	204 (30·0%)	25 (45·5%)	0·03
Current smoking	165 (24·2%)	6 (10·9%)	0·04
Regular alcohol consumption	517 (72·7%)	40 (71·4%)	0·71
Atrial fibrillation	126 (18·5%)	22 (40·0%)	0·0002
Prior history of stroke	68 (10·0%)	11 (20·0%)	0·04
Ischaemic heart disease	69 (10·0%)	12 (21·8%)	0·01
BMI (kg/m^2)	27·1 ± 4·3	26·4 ± 4·2	0·23
Systolic blood pressure (mmHg)	139 (129–150)	146 (130–152)	0·17
Diastolic blood pressure (mmHg)	80 (71–86)	79 (73–85)	0·55
HbA_{1c} (%)	5·7 (5·4–6·1)	5·8 (5·5–6·7)	0·03
LDL cholesterol (mg/dL)	127 (104–153)	113 (89–154)	0·13
HDL cholesterol (mg/dL)	48 (40–58)	43 (36–58)	0·03
Triglycerides (mg/dL)	121 (91–167)	108 (88–207)	0·95
Criteria for metabolic syndrome[d]			
Abdominal obesity	363/641 (56·7%)	28/48 (58·3%)	0·94
Elevated triglycerides	215/640 (33·6%)	18/52 (34·6%)	1·00
Reduced HDL cholesterol	204/658 (31·0%)	27/52 (51·9%)	0·003
Elevated blood pressure	603/680 (88·7%)	50/55 (90·9%)	0·78
Prediabetes/diabetes mellitus	347/643 (54·0%)	39/53 (73·6%)	0·009
Metabolic syndrome (≥3 of the above components present)	329 (48·2%)	36 (65·5%)	0·02
Index stroke classification			
Ischaemic stroke	664 (97·5%)	51 (92·7%)	0·10
TOAST classification of acute ischaemic stroke subtype			0·03
Large artery atherosclerosis	154 (22·6%)	12 (21·8%)	–
Cardioembolism	144 (21·1%)	20 (36·4%)	–
Small artery occlusion	84 (12·3%)	2 (3·6%)	–
Other determined aetiology	28 (4·1%)	1 (1·8%)	–
Undetermined aetiology	254 (37·3%)	16 (29·1%)	–
Haemorrhagic stroke	17 (2·5%)	4 (7·3%)	0·10
Acute stroke treatment			
Intravenous thrombolysis (IVT)	178 (26·1%)	10 (18·2%)	0·30
Endovascular thrombectomy (EVT)	71 (10·4%)	7 (14·6%)	0·80
Any reperfusion therapy (IVT and/or EVT)	198 (29·1%)	11 (20·0%)	0·20

(Table 1 continues on next page)

recurrence, and acute phase cognitive impairment. p-values of <0·05 were considered statistically significant and we accounted for multiple comparisons using the false discovery rate (FDR) method for p-values derived from the main analyses. All statistical analyses were conducted in RStudio (version 2023·06·1).

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

Of 736 stroke patients recruited (mean age 68·0 [SD 11·2], 245 [33·3%] female), 706 (95·9%) underwent at least one follow-up examination and were included in the primary outcome analysis. A total of 557 (75·7%) patients were followed until death or end of study. Patient flow is detailed in Fig. 1, and baseline characteristics are presented in Table S1 (total sample) and in Table S2 (by sex). Missing values for baseline variables ranged from 0% (most clinical characteristics) to 19% (APOE genotype; Table S1). The median admission NIHSS score was 3 (IQR 1–5). 79 (10·7%) patients had a history of prior stroke, and 363 (49·3%) met the criteria for metabolic syndrome (MetS).

Patients were followed for a total of 2899 person-years (median 5·0 [IQR 3·3–5·1]), during which 68 (9·2%) died and 179 (24·3%) were lost to follow-up. Table S3 presents the number of patients who were lost to follow-up or died, broken down by study centre and follow-up period. Reasons for death or loss to follow-up are detailed in Table S4. Retained participants were younger, more educated, less dependent, had lower rates of hypertension and atrial fibrillation, better pre-stroke and acute phase cognitive performance, higher HDL-C, lower SVD burden, and greater brain volume than participants who died or were lost to follow-up (Table S5). The in-person follow-up visits occurred at median times of 6·2, 12·2, 36·3, and 60·5 months (Figure S1).

During follow-up, 55 participants developed incident dementia (6-month incidence: 3·2% [1·8–4·5], 5-year incidence: 8·8% [95% CI 6·5–11·1]; Figures S3 and S4). Table 1 details baseline characteristics stratified by patients who did and did not develop PSD. Twenty patients with diagnosed dementia died before reaching the 5-year follow-up. Fig. 2 presents the 5-year cumulative incidence of PSD, stratified by key baseline categorical risk factors. PSD incidence was higher in the oldest age tertile (≥74 years; 19·5% [13·2–25·4]) than in the middle (66–73 years; 5·8% [2·5–9·0], p < 0·0001) and lowest tertiles (<66 years; 3·7% [1·1–6·1], p < 0·0001); among patients with admission NIHSS ≥3 compared to those with NIHSS <3 (13·2% [9·3–16·9] vs 4·2% [1·8–6·4], p = 0·0001); among patients with ≤12 years of

educational attainment compared to those with more than 12 years (13·2% [8·7–17·6] vs 6·1% [3·6–8·5], p = 0·01); and among those with acute phase cognitive impairment (MoCA < 26 or MMSE < 27) compared to those without (14·1% [10·0–18·0] vs 1·7% [0·2–3·3], p < 0·0001). There were no significant differences in the unadjusted cumulative PSD incidence rates between female and male participants (8·9% [4·8–12·7] vs 8·8% [6·0–11·6], p = 0·99) and between those who did and did not receive acute reperfusion therapy (6·2% [2·6–9·7] vs 10·0% [7·0–12·8], p = 0·15). When stratified by stroke aetiology, patients with haemorrhagic stroke had the highest PSD incidence (23·5% [0·04–41·4]), followed by those with cardioembolic (14·9% [8·4–20·9]), large artery (8·7% [3·8–13·3]), undetermined (6·7% [3·4–10·0]), other aetiology (3·7% [0·0–10·6]), and small vessel stroke (3·3% [0·0–7·6], p = 0·006).

Among cardiovascular risk factors, PSD incidence was higher in patients with atrial fibrillation than in those without (19·4% [11·7–26·5] vs 6·4% [4·2–8·6], p < 0·0001) and in patients with diabetes mellitus (18·0% [10·5–25·0]) than in those with prediabetes (9·3% [5·1–13·3], p = 0·02) and no diabetes (5·0% [2·3–7·6], p < 0·0001). Also, patients with signs of small vessel disease on MRI (SVD score ≥ 1) had a higher incidence of PSD than those without (12·6% [8·9–16·2] vs 3·5% [1·1–5·9], p = 0·0001).

Patients with MetS had a higher 5-year incidence of PSD compared to those without MetS (12·7% [8·7–16·5] vs 5·3% [2·8–7·7], p = 0·004; Fig. 3). This difference was maintained when further stratifying by age tertiles, sex, educational attainment, stroke severity, acute phase cognitive impairment, and acute reperfusion treatment (Fig. 4). Among the five MetS markers, the 5-year cumulative PSD incidence was significantly higher in patients with reduced HDL-C (15·0% [9·6–20·1] vs 6·0% [3·6–8·3], p = 0·0008) and prediabetes or diabetes mellitus (12·4% [8·6–16·1] vs 4·9% [2·3–7·6], p = 0·002), but did not differ significantly when stratifying by the remaining three MetS components (Fig. 3).

In Cox regression models (Table 2), older age and lower educational attainment were important sociodemographic risk factors for PSD. Further, patients with higher admission NIHSS scores, lower Barthel Index scores, lower MoCA scores, or acute phase cognitive impairment were at an increased PSD risk. Major vascular and metabolic risk factors included diabetes mellitus, atrial fibrillation, prior stroke, higher triglycerides, and MetS (≥3 components, per additional component, reduced HDL-C, and prediabetes or diabetes mellitus). Acute reperfusion therapy was associated with a lower PSD risk. Significant neuroimaging markers included lower normalised brain volume, higher lacune and cerebral microbleed count, greater normalised white matter hyperintensity volume, and higher mean skeletonised mean diffusivity. PSD risk was further related to APOE-ε4 homozygosity and recurrent stroke during follow-up. Results for PSCI aligned with those for PSD, with additional risk factors including lower HDL-C, higher infarct volume, and perivascular space grade (Table 2).

	No PSD (n = 681)	PSD (n = 55)	p value
(Continued from previous page)			
Neuroimaging parameters			
Normalised brain volume (%)	68·0 (64·6–71·8)	63·6 (61·4–66·3)	<0·0001
Infarct volume (mm^3)	2248 (8520–11760)	2488 (600–14632)	0·68
Normalised stroke lesion volume (%)	0·15 (0·03–0·76)	0·17 (0·04–0·96)	0·63
Small vessel disease score			0·001
0	251/615 (40·8%)	8/51 (15·7%)	–
1	179/615 (29·1%)	22/51 (43·1%)	–
2	125/615 (20·3%)	11/51 (21·6%)	–
3	48/615 (7·8%)	6/51 (11·8%)	–
4	12/615 (1·9%)	4/51 (7·8%)	–
Lacune count	0 (0–0)	0 (0–0)	0·01
≥3 lacunes	7/618 (1·1%)	5/53 (9·4%)	0·0001
Normalised white matter hyperintensity volume (%)	0·21 (0·07–0·50)	0·43 (0·23–1·36)	<0·0001
Cerebral microbleed count	0 (0–0)	0 (0–0)	0·10
Perivascular space grade	1 (1–2)	2 (1–3)	0·004
Mean skeletonised mean diffusivity (z-score)	−0·19 (−0·78–0·51)	0·86 (−0·01–1·97)	<0·0001
Genetic risk factors			
APOE genotype			0·18
0 ε4 allele	431/551 (78·2%)	31/43 (72·1%)	–
1 ε4 allele	112/511 (20·3%)	10/43 (23·3%)	–
2 ε4 alleles	7/511 (1·3%)	2/43 (4·6%)	–
Pre-stroke clinical/cognitive function			
mRS before stroke	0 (0–0)	0 (0–0)	0·36
IQCODE score	48 (48–49)	49 (48–51)	0·002

Data are n (%), median (IQR), mean (SD), or n/N (%). APOE = apolipoprotein E. BMI = body-mass index. EVT = Endovascular thrombectomy. HbA_{1c} = glycated haemoglobin. HDL = high-density lipoprotein. IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly. IVT = Intravenous thrombolysis. LDL = low-density lipoprotein. MoCA = Montreal Cognitive Assessment. mRS = Modified Rankin Scale. NIHSS = National Institutes of Health Stroke Scale. TOAST = Trial of Org 10172 in Acute Stroke Treatment. [a]Sex was self-reported as male or female. [b]Genetic ancestry was analysed comparing participant genotype data against the 1000 Genomes Project (1kG) Phase 3 reference panel (Supplementary Methods). [c]MoCA <26 or mini-mental state examination <27 when MoCA was not available (n = 73). [d]Defined according to Alberti et al.[2]

Table 1: **Baseline characteristics of stroke survivors who did and did not develop post-stroke dementia.**

Of the 55 incident dementia cases, 34 (61·8%) were classified as delayed-onset PSD. At baseline, patients who developed delayed-onset PSD had significantly higher MoCA scores compared to those with early-onset PSD (Table S6). Associations of baseline risk factors with early-onset and delayed-onset PSD are presented in Table S7. Risk factors significantly associated with early-onset PSD that did not reach statistical significance for delayed-onset PSD included atrial fibrillation, prior stroke, higher Delirium Rating Scale score, lower brain volume, and higher infarct volume (Table S7). Conversely, risk factors significantly associated with delayed-onset PSD that did not reach statistical significance for early-onset PSD included lower educational attainment, MetS, reduced HDL-C, higher triglyceride

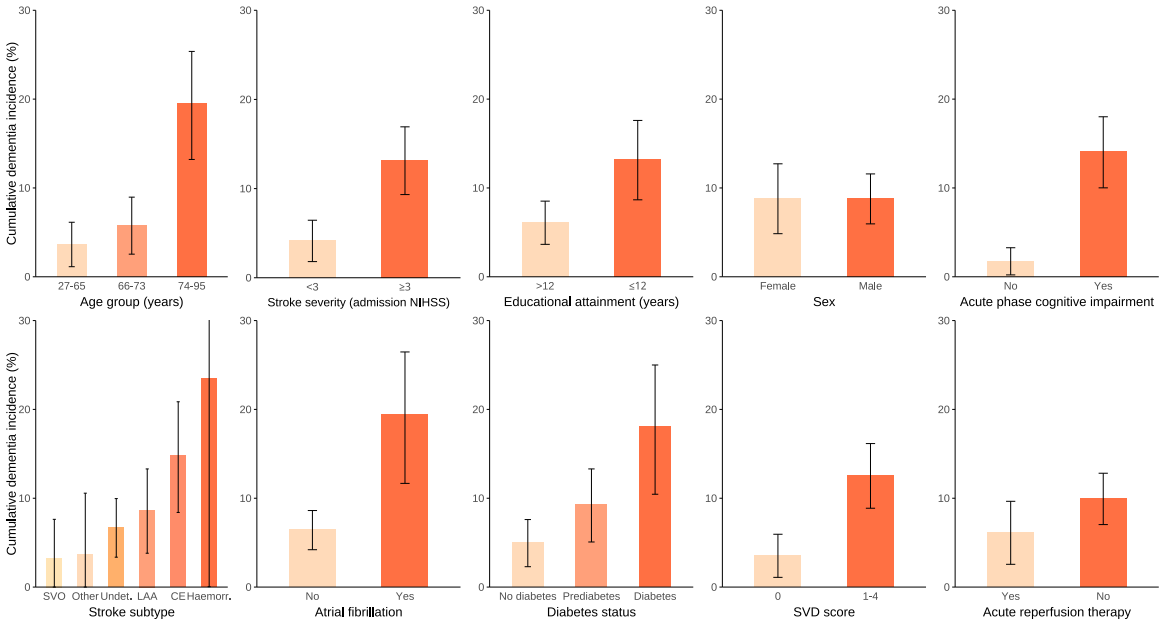

***Fig. 2:* Cumulative post-stroke dementia incidence stratified by different categorical baseline characteristics.** Acute phase cognitive impairment was defined as MoCA <26 or MMSE <27. Prediabetes was defined as HbA_{1c} ≥5·7 and <6·5. Diabetes mellitus was defined as HbA_{1c} ≥6·5 or treatment with antidiabetic medication. Acute reperfusion therapy indicates intravenous thrombolysis and/or endovascular thrombectomy. Error bars represent the 95% confidence interval for the Kaplan–Meier estimated cumulative incidence. Cumulative incidence rates were compared using Grey's test. CE = cardioembolism. Haemorr. = haemorrhagic stroke. LAA = large artery atherosclerosis. NIHSS = National Institutes of Health Stroke Scale. SVD = cerebral small vessel disease. SVO = small vessel occlusion. TOAST = Trial of Org 10172 in Acute Stroke Treatment. Undet. = stroke of undetermined aetiology.

levels, acute reperfusion therapy, and greater WMH volume (Table S7). Flexible parametric survival models revealed time-varying relationships of Delirium Rating scale score and MetS (Figure S7 and Table S19), in line with the analyses stratifying by early and delayed onset.

Main contributors to early-onset PSD were age ≥74 years, acute phase cognitive impairment, admission NIHSS ≥3, and atrial fibrillation, while the main contributors to delayed-onset PSD were age ≥74 years, acute phase cognitive impairment, MetS, and admission NIHSS ≥3 (Fig. 5). Bootstrapped CIs were wide but indicated a stronger contribution of MetS to delayed-onset PSD compared to early-onset PSD.

Female participants were older, had fewer years of education, less frequently had acute phase cognitive impairment, and more frequently had abdominal obesity and cardioembolic stroke (Table S2). Sex-stratified analyses of PSD risk (Table S8) revealed overall similar trends but were likely underpowered, especially for women. Among men, age ≥74 was associated with a 6·4-fold increased risk of PSD, compared to a 3-fold increase in women. Diabetes mellitus, prior ischaemic heart disease, admission NIHSS ≥3, and educational attainment ≤12 years were strong predictors for PSD in men, but not women, whereas atrial fibrillation and pre-stroke IQCODE were strong predictors of PSD in women but not in men.

During follow-up, 56 (7·6%) patients experienced at least one recurrent stroke (Figure S5, Table S8); 10 (17·9%) developed dementia afterwards, while three (5·4%) had developed dementia before recurrence. Recurrent stroke before dementia diagnosis was associated with higher 5-year and delayed-onset PSD risk (HR 2·36 [1·16–4·83] and 3·94 [1·76–8·82], respectively; Table S9). Sensitivity analyses confirmed overall consistent associations between baseline variables and PSD risk, even after adjusting for acute reperfusion treatment, recurrent stroke, or acute phase cognitive impairment (Tables S10–S15) and when using 12 months as the cut-off for early- vs delayed-onset PSD (Table S16), as well as after multiple imputation for dementia onset date (Table S17). After adjusting for acute treatment, admission NIHSS emerged as a strong predictor for both early- and delayed-onset PSD. The associations of PSD with atrial fibrillation, prediabetes/diabetes, and MetS were also strengthened, while the associations with prior stroke and APOE-ε4 homozygosity were attenuated.

Discussion

This study not only provides estimates of the association between reported risk factors and 5-year PSD risk, but also highlights a previously unrecognised

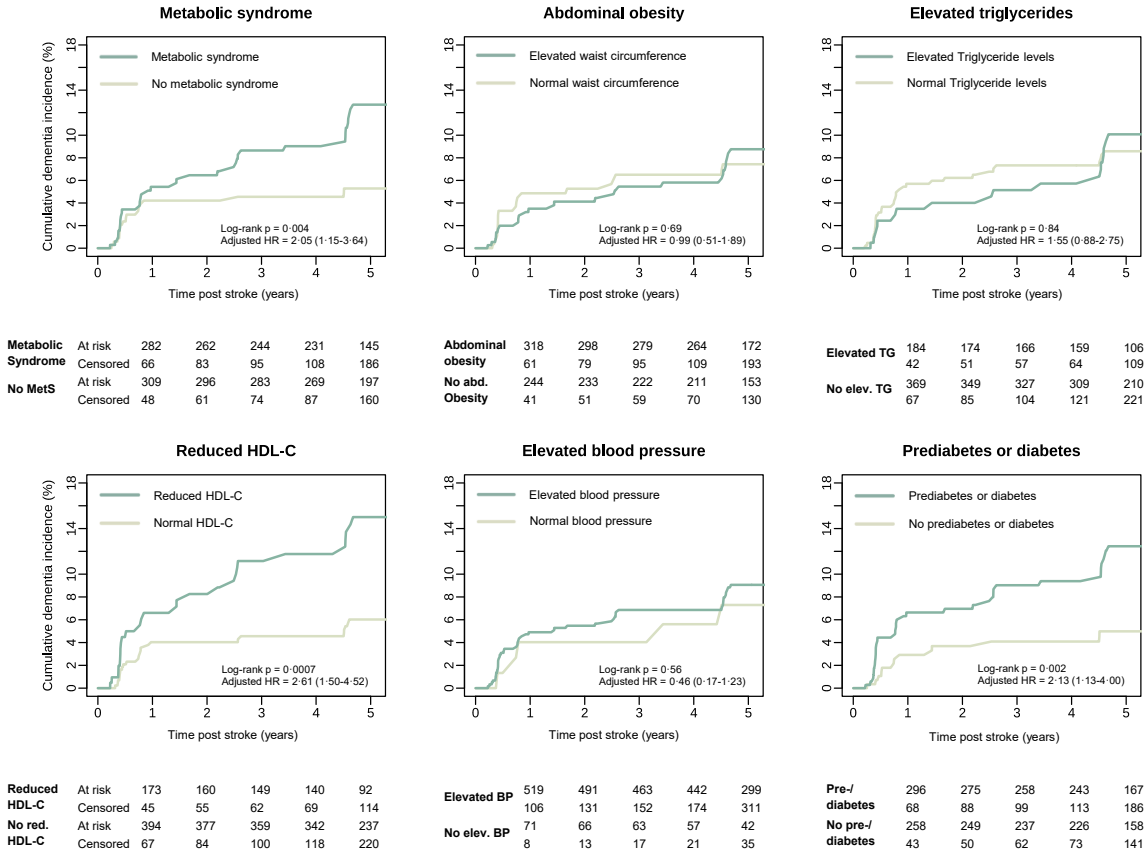

***Fig. 3*: Cumulative incidence curves for post-stroke dementia stratified by the presence of metabolic syndrome (top left panel) and individual metabolic syndrome components (top middle to bottom right panel).** Metabolic Syndrome was defined as the presence of three or more of the five criteria (Supplementary Methods).[9] BP = Blood pressure. HDL-C = high-density lipoprotein cholesterol. MetS = Metabolic Syndrome. NIHSS = National Institutes of Health Stroke Scale. TG = Triglycerides.

association with metabolic syndrome (MetS), particularly its components reduced HDL-C and pre-/diabetes. MetS was a risk factor for delayed-onset PSD (>6 months), but not for early-onset PSD (≤6 months). Conversely, early-onset PSD was more strongly associated with older age, factors related to the stroke and its severity, and atrial fibrillation than delayed-onset PSD. Collectively, our findings highlight the multifactorial nature of PSD risk and emphasise time-dependent differences in the importance of individual risk factors.

We identified a set of binary risk factors, each of which was strongly associated with an increased PSD risk (HRs >2): age ≥74 years, admission NIHSS ≥3, acute phase cognitive impairment, diabetes mellitus, MetS, reduced HDL-C, presence of ≥3 lacunes, and stroke recurrence. Additionally, acute stroke treatment was associated with a 65% lower risk of PSD. These findings could inform both the development of prediction tools for long-term PSD risk and the selection of patients for PSD prevention trials. Overall, our results emphasise poor prior brain health, greater stroke severity, cardiometabolic risk factors, recurrent stroke, and SVD as the key contributors to PSD risk, which is largely consistent with previous findings.[3,5,7] Modifiable risk factors are particularly relevant for designing secondary prevention trials and were therefore a focus in our analysis.

Baseline MetS was associated with a twofold increase in the risk of 5-year PSD and a 3·5-fold increase in the risk of delayed-onset PSD. This effect was independent of stroke recurrence and consistent across subgroups of age, with 5-year cumulative incidence rates ranging from 1·7% in younger patients (≤65 years) without MetS to 24·5% in older patients (≥74 years) with MetS. Reduced HDL-C and diabetes mellitus were the two most important individual MetS components contributing to this association. However, we also found a 30% increase in PSD risk with each additional MetS component, suggesting a potential dose-dependent relationship that extends beyond the effects of these two factors. To the best of our knowledge, the relationship between MetS and dementia has

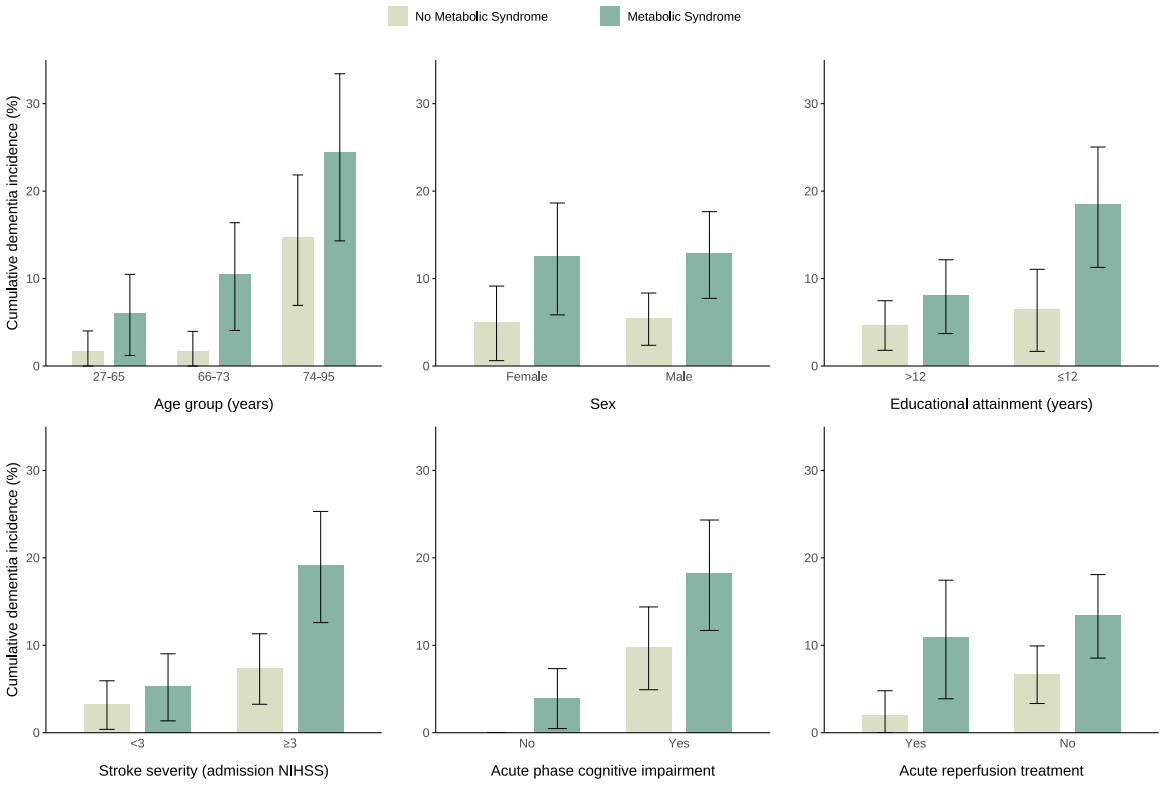

Fig. 4: **Cumulative incidence rates for post-stroke dementia stratified by metabolic syndrome and other relevant baseline factors.** Error bars represent the 95% confidence interval for the Kaplan–Meier estimated cumulative incidence. Formal interaction tests showed no significant interactions (all p > 0·05). NIHSS = National Institutes of Health Stroke Scale.

not been studied in the post-stroke setting, although MetS has been recognised as a potentially modifiable risk factor for all-cause dementia,[11,13,27,28] vascular dementia,[27,28] and Alzheimer's disease.[27,28] The prevalence of MetS in our cohort (49·3%) was about twice as high as that in the European general population,[29] but comparable to other stroke cohorts of similar age.[30,31]

Diabetes mellitus is an established modifiable risk factor for PSD,[3,5,7,14,15,17,18] that contributes primarily by exacerbating vascular complications.[8] Although it remains uncertain whether diabetes management reduces dementia risk, a recent study that combined RCT data and Danish nationwide registry data suggested a beneficial effect of glucagon-like peptide-1 (GLP-1) on dementia risk in patients with type 2 diabetes.[32] This approach should also be investigated in stroke patients with diabetes. Considering recent findings,[33] it is further worth exploring whether GLP-1 or dual GIP/GLP-1 receptor agonists could prevent dementia in stroke patients with prediabetes and obesity by preventing the progression to diabetes. Given the high prevalence of MetS in our and other stroke cohorts, such therapeutic strategies could hold potential for PSD prevention, particularly if future studies confirm the role of cardiometabolic risk factors in long-term cognitive decline.

We found that the relationships between cardiometabolic risk factors and PSD remained robust with minimal changes in effect sizes after adjusting for recurrent stroke. While most secondary prevention trials use stroke recurrence as the single neurological endpoint,[34] our findings suggest that the relationship between PSD and modifiable factors like diabetes mellitus and MetS is largely independent of stroke recurrence. This highlights the importance of including dementia as a primary outcome in secondary prevention trials for stroke patients.

Compared to previous studies, the incidence and prevalence of PSD in our cohort were substantially lower.[3,35] For example, the 1-year cumulative incidence was approximately 5% in our study versus 17% in OxVasc.[3] Several differences in study design and sample characteristics likely explain this discrepancy. First, OxVasc included all acute vascular events in Oxfordshire, capturing patients with severe strokes who may not have reached tertiary care or were managed in community settings. By contrast, DEMDAS enrolled only patients referred to tertiary stroke

Risk factors	Post-stroke dementia				Post-stroke cognitive impairment		
	Cases/N	Adjusted hazard ratio (95% CI)	p value	FDR-p	Adjusted odds ratio (95% CI)	p value	FDR-p
Sociodemographic factors							
Age (per year)	55/706	1·13 (1·08–1·18)	<0·0001	<0·0001	1·03 (1·02–1·04)	<0·0001	<0·0001
Age ≥ 74	55/706	4·76 (2·65–8·55)	<0·0001	<0·0001	2·08 (1·69–2·60)	<0·0001	<0·0001
Female sex	55/706	0·47 (0·24–0·91)	0·02	0·05	0·99 (0·79–1·23)	0·91	0·91
Education (per year)	55/706	0·86 (0·78–0·95)	0·003	0·009	0·92 (0·89–0·96)	<0·0001	<0·0001
Education ≤ 12	55/706	1·89 (1·05–3·40)	0·03	0·06	1·83 (1·48–2·26)	<0·0001	<0·0001
Clinical/cognitive acute phase deficits							
Stroke severity (per point on admission NIHSS)	55/706	1·08 (1·03–1·13)	0·002	0·008	1·04 (1·02–1·06)	0·0008	0·002
Admission NIHSS ≥ 3	55/706	2·68 (1·44–4·97)	0·002	0·007	1·40 (1·14–1·71)	0·001	0·003
Barthel index (per 5 points)	55/704	0·90 (0·85–0·95)	<0·0001	0·0005	0·98 (0·97–0·98)	<0·0001	<0·0001
Delirious symptoms (per point on DRS)	55/706	1·17 (1·02–1·34)	0·03	0·05	1·06 (0·99–1·14)	0·09	0·12
Acute phase cognitive function (per point on MoCA)	41/625	0·83 (0·76–0·90)	<0·0001	0·0001	0·80 (0·77–0·83)	<0·0001	<0·0001
Acute phase cognitive impairment[a]	49/683	5·86 (2·21–15·58)	0·0004	0·002	3·17 (2·73–3·67)	<0·0001	<0·0001
Vascular risk factors							
Hypertension	55/706	1·05 (0·45–2·44)	0·92	0·95	0·92 (0·71–1·18)	0·49	0·52
Diabetes mellitus	55/706	2·28 (1·33–3·91)	0·003	0·009	1·62 (1·28–2·06)	<0·0001	0·0002
Dyslipidaemia	55/706	1·35 (0·77–2·34)	0·29	0·38	1·09 (0·88–1·34)	0·43	0·47
Current smoking	55/706	0·85 (0·36–1·97)	0·70	0·80	1·12 (0·87–1·44)	0·39	0·44
Regular alcohol consumption	55/706	0·73 (0·40–1·33)	0·30	0·38	0·89 (0·70–1·13)	0·33	0·38
Atrial fibrillation	55/706	1·91 (1·10–3·30)	0·02	0·04	1·60 (1·24–2·08)	0·0004	0·0009
Prior history of stroke	55/706	2·05 (1·08–3·88)	0·03	0·05	1·46 (1·08–1·97)	0·01	0·03
Ischaemic heart disease	55/706	1·98 (1·04–3·76)	0·04	0·06	1·81 (1·34–2·43)	<0·0001	0·0003
BMI (per 5 units [kg/m^2])	55/706	0·98 (0·63–1·52)	0·93	0·95	1·01 (0·99–1·04)	0·31	0·36
Systolic blood pressure (per 10 mmHg)	55/701	1·01 (0·88–1·17)	0·84	0·94	0·92 (0·88–0·97)	0·003	0·005
Diastolic blood pressure (per 10 mmHg)	55/701	1·05 (0·86–1·28)	0·63	0·74	0·89 (0·85–0·94)	<0·0001	<0·0001
HbA_{1c} (per %)	52/658	1·06 (0·99–1·14)	0·09	0·15	1·04 (1·00–1·10)	0·08	0·11
LDL cholesterol (per 10 mg/dL)	53/684	1·01 (0·93–1·08)	0·88	0·94	1·00 (1·00–1·00)	0·11	0·15
HDL cholesterol (per 10 mg/dL)	52/679	0·81 (0·62–1·05)	0·11	0·17	0·89 (0·84–0·95)	0·01	0·03
Triglycerides (per 10 mg/dL)	52/663	1·03 (1·01–1·06)	0·02	0·04	1·01 (1·00–1·02)	0·07	0·11
Metabolic syndrome components[b]							
Abdominal obesity	48/666	0·99 (0·51–1·89)	0·97	0·97	1·17 (0·94–1·46)	0·15	0·20
Elevated triglycerides	52/663	1·55 (0·88–2·75)	0·13	0·19	1·22 (0·97–1·53)	0·09	0·12
Reduced HDL cholesterol	52/679	2·61 (1·50–4·52)	0·0006	0·003	1·25 (1·00–1·55)	0·05	0·08
Elevated blood pressure	55/705	0·46 (0·17–1·23)	0·12	0·18	0·67 (0·49–0·92)	0·01	0·03
Prediabetes or diabetes mellitus	53/666	2·13 (1·13–4·00)	0·02	0·04	1·27 (1·02–1·57)	0·03	0·05
Metabolic syndrome (≥3 of the above components present)	55/706	2·05 (1·15–3·64)	0·01	0·04	1·13 (0·92–1·38)	0·25	0·30
Per count of components increase	55/706	1·30 (1·04–1·63)	0·02	0·04	1·05 (0·97–1·14)	0·23	0·29
Index stroke classification							
Ischaemic stroke	55/706	1	0·06	0·09		0·72	0·74
Haemorrhagic stroke	55/706	2·69 (0·97–7·43)	–	–	1·11 (0·63–1·94)	–	–
Acute stroke treatment							
Any reperfusion therapy (IVT and/or EVT)	55/706	0·35 (0·16–0·77)	0·009	0·03	0·50 (0·37–0·67)	<0·0001	<0·0001
Neuroimaging parameters							
Normalised brain volume (per SD)	50/634	0·60 (0·41–0·89)	0·01	0·03	0·65 (0·56–0·75)	<0·0001	<0·0001
Normalised infarct volume (per SD)	50/634	1·19 (0·93–1·51)	0·16	0·22	1·12 (1·02–1·23)	0·02	0·04
Total small vessel disease score (per SD)	51/642	1·25 (0·90–1·73)	0·18	0·24	1·27 (1·13–1·42)	<0·0001	0·0002
Lacune count (per SD)	53/647	1·36 (1·26–1·47)	<0·0001	<0·0001	1·38 (1·20–1·60)	<0·0001	<0·0001
Presence of ≥3 lacunes	53/647	11·00 (4·92–24·60)	<0·0001	<0·0001	8·20 (3·36–20·01)	<0·0001	<0·0001
Normalised WMH volume (per SD)	48/633	1·42 (1·19–1·68)	<0·0001	0·0005	1·50 (1·32–1·70)	<0·0001	<0·0001
Cerebral microbleed count (per SD)	51/642	1·17 (1·07–1·27)	0·0008	0·004	1·03 (0·95–1·13)	0·44	0·47
Perivascular space grade (per SD)	53/646	1·23 (0·93–163)	0·14	0·20	1·15 (1·02–1·28)	0·02	0·03
Mean skeletonised mean diffusivity (per SD)	45/606	1·94 (1·39–2·70)	<0·0001	0·0006	1·76 (1·55–2·00)	<0·0001	<0·0001
APOE genotype							
0 ε4 alleles	43/563	1	–	–	1	–	–
1 ε4 allele	43/576	1·11 (0·52–2·36)	0·78	0·87	0·90 (0·76–1·06)	0·21	0·26
2 ε4 alleles	43/576	4·94 (1·36–11·79)	0·01	0·04	2·81 (1·74–4·54)	<0·0001	<0·0001

(Table 2 continues on next page)

Risk factors	Post-stroke dementia				Post-stroke cognitive impairment		
	Cases/N	Adjusted hazard ratio (95% CI)	p value	FDR-p	Adjusted odds ratio (95% CI)	p value	FDR-p
(Continued from previous page)							
Pre-stroke clinical/cognitive function							
Modified Rankin Scale score before stroke	55/706	1·10 (0·75–1·62)	0·62	0·74	1·15 (0·98–1·36)	0·09	0·12
IQCODE score	49/655	1·07 (0·88–1·31)	0·48	0·58	1·07 (1·00–1·14)	0·04	0·06
Recurrent events							
Stroke recurrence	55/757	2·36 (1·16–4·83)	0·02	0·04	–	–	–

Associations with PSD were calculated using cox proportional hazards models with death as a competing risk. Associations with PSCI across the 6-, 12-, 36-, and 60-month follow-ups were calculated with logistic regression models using generalised estimating equations (GEE). Hazard ratios and odds ratios were adjusted for age, sex, education, and admission NIHSS score. At the 6-, 12-, 36-, and 60-month follow-ups, 180 (24·4%), 132 (17·9%), 102 (13·9%), and 112 (15·2%) participants had PSCI, respectively. The analysis for stroke recurrence could only be performed for the PSD endpoint and included only cases that were dementia-free at the time of the recurrent stroke. APOE = apolipoprotein E. BMI = body-mass index. DRS = Delirium Rating Scale. EVT = Endovascular thrombectomy. HbA_{1c} = glycated haemoglobin. HDL = high-density lipoprotein. IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly. IVT = Intravenous thrombolysis. LDL = low-density lipoprotein. MoCA = Montreal Cognitive Assessment. NIHSS = National Institutes of Health Stroke Scale. [a]MoCA <26 or mini-mental state examination <27 when MoCA was not available (n = 73). [b]Defined according to Alberti et al.[9]

Table 2: **Baseline factors associated with 5-year risk of incident post-stroke dementia (PSD) and post-stroke cognitive impairment (PSCI).**

centres, likely underrepresenting such cases. Second, nearly 30% of our participants received acute reperfusion therapy, including thrombolysis and thrombectomy, which became standard practice in the early to mid-2000s and after 2015, respectively, and were infrequently used in earlier cohorts. In our study, patients who received reperfusion therapy had a 65% lower risk of PSD than those who did not. Although observational, this finding suggests that timely treatment may lower long-term dementia risk. Third, our cohort also had a younger median age (68 vs 73 years in the general European stroke population[36]) and lower NIHSS scores at admission, both known predictors of PSD, which may further explain the lower observed incidence and reflect selection effects inherent to our study population.

Our findings suggest sex-specific differences in the risk profile for PSD. Although women in our sample were older and had lower educational attainment, they had a lower overall risk of PSD compared to men. This may reflect weaker associations of age, education, stroke severity, and vascular risk factors, particularly diabetes and ischaemic heart disease, with PSD in women. Conversely, atrial fibrillation was more strongly associated with PSD in women, possibly due to their higher rate of cardioembolic stroke, which has been reported previously.[37] A similar sex difference was found in a study from the U.S. National Alzheimer's Coordinating Center (NACC) cohort.[38] These results underscore the importance of considering sex differences for individual risk prediction and clinical trial design.

In our study, dementia incidence was higher in the early compared to the late phase post-stroke, but more than 60% of PSD cases manifested with a delayed onset. The low prevalence of severe strokes in our sample likely contributed to the smaller proportion of early-onset PSD.[3,14] Importantly, PSD risk remained elevated beyond the early phase after stroke, across all stroke severity levels, as was also apparent in 5-year data from the OxVasc study.[3] Overall, these findings emphasise a persistent PSD risk beyond the acute phase, underscoring the need to understand long-term cognitive trajectories.

Our results imply a difference in the importance of baseline risk factors for early- compared to delayed-onset PSD. In keeping with previous findings,[3,5,7,14,17] we found early-onset PSD to show stronger associations with acute stroke-related deficits and parameters related to prior reserve or resilience. In contrast, delayed-onset PSD was more strongly associated with MetS, reduced HDL-C, diabetes mellitus, acute phase cognitive impairment, and lower educational attainment. Results from our PAF analyses indicated that MetS contributed to 53% of delayed-onset PSD cases, exceeding the PAF for age ≥74 years. Whether post-stroke interventions targeting MetS or its components reduces long-term PSD remains unknown, but identifying high-risk patients opens opportunities for targeted interventions. Recurrent stroke was associated with delayed-onset, but not with early-onset PSD, which aligns with some, but not all, previous studies.[14–16,18] Discrepancies may be partly explained by a slightly higher incidence of recurrent stroke in our cohort than in others.[16,18]

Atrial fibrillation was associated only with early-onset PSD in our study, with a stronger overall association observed in women, consistent with recent findings from the NACC.[38] While previous reports on the association between atrial fibrillation and PSD have been inconsistent,[7] our results suggest that its role may be more pronounced early after stroke and potentially modulated by sex-specific factors. Hypertension, a risk factor for recurrent stroke,[1] was not associated with a higher PSD risk in our cohort, consistent with previous meta-analyses.[5,7] This may reflect good baseline blood pressure control among the participants.

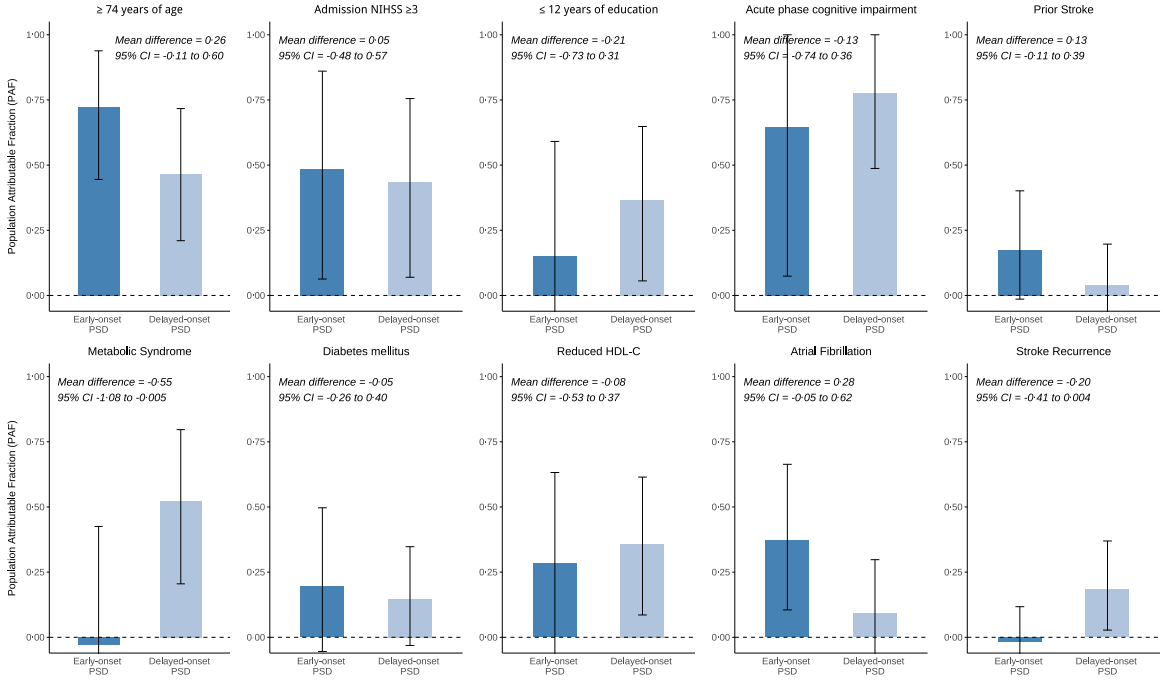

Fig. 5: **Population attributable fractions (PAF) for different risk factors for early- and delayed-onset post-stroke dementia, defined as dementia that occurred between 3 and 6 or after 6 months, respectively.** Acute phase cognitive impairment was defined as MoCA <26 or MMSE <27, and metabolic syndrome as presence of three or more commonly used criteria (Supplementary Methods and Alberti et al.[9]). Error bars represent 95% confidence intervals, derived from 10,000 bootstrap iterations. HDL-C = high-density lipoprotein cholesterol. NIHSS = National Institutes of Health Stroke Scale.

The association between lower HDL-C and PSD became apparent only when using sex-specific cut-offs for HDL-C (<40 mg/dL for males, <50 mg/dL for females) related to MetS. Low HDL-C has been identified as a risk factor for Alzheimer's Disease in Mendelian randomisation meta-analyses and the Framingham Heart Study.[39,40] Possible mechanisms linking HDL-C to dementia include its vascular-protective, anti-inflammatory, and cholesterol efflux-enhancing properties,[8,41] which could support post-stroke recovery and mitigate chronic vascular injury, such as SVD.[42] Future studies should investigate whether the relationship between low HDL-C and PSD is mediated by progressive SVD burden.

Our results emphasise the importance of SVD as a predictor of both early- and delayed-onset PSD.[4,14,15,43] The relationship was evident for both conventional SVD markers (lacune count, WMH volume, and CMB count) and MSMD, a marker sensitive to early microvascular injury. Of twelve patients who presented with ≥3 lacunes on baseline MRI, five developed PSD, corresponding to an 11·3 times higher PSD risk compared to patients with 0–2 lacunes. Clinical trials are needed to assess if targeting SVD progression improves post-stroke cognitive outcomes.[44] Our findings further suggest that even mild delirium symptoms are associated with PSCI and early-onset PSD, reinforcing the role of acute phase impairments in early-onset PSD.[14] The weaker overall association may be due to the mild symptom burden in our cohort and the limited number of patients meeting criteria (DRS ≥ 10, n = 4) for a clinical diagnosis of delirium, which has previously been linked to cognitive decline.[45]

Strengths of this study include its prospective, multicentre design with regular follow-ups across five years, the large sample size, standardised clinical and imaging protocols, central monitoring, and rigorous procedures maintained for baseline, follow-up, and end-point assessments. This study also has limitations. First, due to the demanding study protocol, which included serial MRI scanning, detailed cognitive testing, and the requirement of an informant, patients with milder strokes were overrepresented. However, this also reflects a population that is most likely to benefit from interventions targeting long-term outcomes. Our findings are limited to a highly selected hospital-based study cohort and require replication in larger, more inclusive, population-based, and ethnically more diverse cohorts to achieve generalisability. Second, the attrition rate was comparably high, which may have introduced bias. At baseline, patients lost to follow-up had poorer brain health, greater acute phase

impairment, and more cardiovascular comorbidity, potentially limiting the generalisability of our findings to healthier stroke survivors. Third, as cognitive, health, and mortality data could not be obtained for many patients who revoked consent, PSD incidence, PSCI prevalence, and mortality may have been underestimated. Fourth, we were unable to perform subgroup analyses by dementia subtype. Although initially planned, difficulties in obtaining definitive diagnoses for dementia subtypes and the limited statistical power due to the low number of dementia cases led us to exclude these analyses. Additionally, we chose to discontinue amyloid-β positron emission tomography (PET) imaging after an interim analysis on 56 patients.[46] Fifth, female participants were underrepresented, which mirrors a broader issue in stroke studies.[47] This imbalance may have been influenced by factors such as greater disability and lower likelihood of having an informant among women, which could limit generalisability of the findings across sexes. Lastly, PAF estimates should be interpreted cautiously due to the observational nature of the study and uncertain causality.

Altogether, our findings suggest that while acute stroke care is critical for mitigating early-onset dementia risk, sustained efforts to monitor and manage cardiometabolic risk factors are needed to lower PSD risk in the long run. Cardiometabolic risk factors may contribute to delayed-onset PSD through mechanisms beyond recurrent vascular events, highlighting the importance of including PSD as a key outcome for clinical post-stroke trials. Further studies should explore whether targeting metabolic dysfunction reduces long-term PSD risk.

Contributors

JF contributed to data preparation and interpretation, performed the statistical analysis, and drafted the manuscript. MKG critically reviewed and edited the manuscript; contributed to data interpretation; provided advice on the analyses; and was part of the endpoint committee for ascertaining dementia cases. DJ ascertained dementia cases as part of the endpoint committee. MDu conceptualised the neuroimaging protocol and established the central imaging platform. RF contributed significantly to data preparation. AD contributed to data preparation, description of MRI methods, and provided advice on the analysis of the MRI data. MKG, FB, SS, CK, PH, CHN, TGL, KB, and BI contributed to data acquisition as study physicians. LK managed the on-site study coordination. MW contributed to conceptualisation of the neuropsychological test battery. AS administered the clinical research platform of DZNE. KW coordinated the study and contributed to data collection, cleaning, preparation, and quality control. GP, IZ, ME, SW, and MG contributed to the conception, design, and funding acquisition for the DEMDAS study, as well as to data collection. MDi contributed to data interpretation; co-wrote the manuscript; was part of the endpoint committee; and initiated, designed, obtained funding for, and coordinated the DEDEMAS-DEMDAS study. All authors had full access to all the data in the study, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication. JF, MKG, and MDi take full responsibility for the reported results, having verified the data and ensured the integrity of the data and the accuracy of the analyses.

Data sharing statement

Upon publication, de-identified participant data and software code will be made available to researchers upon reasonable request to martin.dichgans@med.uni-muenchen.de.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2025.101428.

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6. DISCUSSION

6.1 Summary of the key findings

In this thesis, I leveraged evidence from 89 studies, including over 160,000 stroke patients, and from a 5-year prospective multicenter cohort study, to identify baseline risk factors for PSCI and PSD. The two studies provide evidence on both novel and previously reported predictors with the potential to enhance individual risk stratification and serve as targets for secondary prevention.

Study I, the meta-analysis, identified acute-phase cognitive impairment as the strongest predictor of PSCI and PSD. Diabetes mellitus was the most consistent modifiable risk factor, while the role of AF was less clear. Furthermore, SVD – particularly WMHs and lacunes – was strongly associated with cognitive outcomes, representing a cerebrovascular pathology whose course may be modifiable through intensive cardiovascular risk factor management. Additional predictors included lower educational attainment, previous stroke, left hemisphere stroke, brain atrophy, and reduced functional independence at baseline. Notably, the strength of association for some risk factors, such as AF and stroke severity, appeared weaker in more recent studies, potentially reflecting improvements in stroke care and risk factor management. Overall, the findings from this first study highlight the prognostic value of early cognitive assessment and reinforce the importance of targeting cardiovascular and cerebrovascular health to reduce long-term cognitive decline after stroke.

Study II, the prospective cohort study, confirmed the multifactorial nature of PSD risk and identified MetS – particularly its components reduced HDL-C and hyperglycemia – as novel, modifiable risk factors. While early-onset PSD was mainly linked to factors related to the acute stroke and pre-stroke brain health, delayed-onset PSD was more strongly associated with cardiometabolic risk and stroke recurrence. Acute reperfusion therapy was associated with a markedly lower risk of PSD, and associations for PSCI largely mirrored those for PSD. These findings underscore the need for both optimal acute stroke care and long-term monitoring and management of vascular and metabolic health to reduce the risk of cognitive decline and dementia, while pointing to new potential targets for secondary prevention strategies.

6.2 Relevance of cardiometabolic risk factors for cognitive outcomes after stroke

Given their importance for developing secondary prevention strategies, modifiable risk factors were a central focus of this thesis. Both studies identified a history of diabetes mellitus and AF as key modifiable cardiovascular risk factors, and SVD as a potentially modifiable cerebrovascular pathology predicting both PSCI and PSD. One of the major findings of Study I, the strong association between diabetes mellitus and poorer cognitive outcomes, raised the question of whether other, or earlier, indicators of metabolic dysfunction might also contribute to post-stroke cognitive decline and dementia.

6.2.1 Prediabetes and diabetes

While Study I only found a clear association between diabetes and post-stroke cognitive outcomes, Study II provides additional evidence that the risk may already be elevated in individuals with prediabetes. However, due to limited statistical power when restricting the analysis to individuals with prediabetes, and potential confounding from other indicators of impaired cardiometabolic health,[190] we could not establish an independent association between prediabetes and PSD and PSCI. Previous studies on this relationship have reported inconsistent findings,[162,168,169,191,192] likely due to differences in follow-up duration, timing of baseline assessments, outcome measures, and criteria for diagnosing prediabetes.

In the general population, prediabetes has been associated with an increased risk of all-cause dementia, VaD, and AD.[193,194] However, large epidemiological studies such as the Atherosclerosis Risk in Communities (ARIC) study have suggested that the subsequent progression to overt diabetes largely mediates this association.[195] This emphasizes the need to account for risk factor and disease progression in future longitudinal studies. Nonetheless, pathophysiological mechanisms implicated in the association between diabetes and cognitive decline, such as cerebrovascular lesions, insulin resistance, inflammation, and endothelial dysfunction,[196] may already be active in prediabetic stages, albeit to a lesser degree. In support of this, prediabetes has been linked to greater WMH volumes, a higher prevalence of lacunar infarcts, and smaller white matter volumes in the population-based Maastricht study.[167] Similarly, elevated fasting glucose has been associated with accelerated cortical atrophy over 12 years.[197] Furthermore, cognitive impairment associated with diabetes mellitus has been proposed to begin during the prediabetic stage and progress gradually over time, rather than accelerating rapidly after a formal diabetes diagnosis.[194] This underscores the importance of early identification and intervention to mitigate long-term cognitive consequences.

Taken together, individuals with prediabetes represent a vulnerable group of stroke survivors who may already exhibit early cerebrovascular pathological alterations and face an elevated risk of both cognitive decline and progression to diabetes. Even if the cognitive risk in this group is not yet firmly established, they warrant close monitoring and rigorous cardiometabolic risk management.

6.2.2 Metabolic syndrome and reduced HDL-cholesterol

Study II revealed that both elevated blood glucose, indicative of prediabetes or diabetes, and reduced HDL-C, two of the five defining components of MetS, were significantly associated with an increased risk of PSD, particularly delayed-onset PSD. In addition, the overall presence of clinically diagnosable MetS (i.e., ≥3 components) was linked to a higher PSD risk. A recent meta-analysis reported an increased risk of cognitive impairment, all-cause dementia, and pure VaD among individuals with MetS in samples from the general population, while the evidence regarding AD remains conflicting.[198] These results suggest that MetS and its components may play a particularly important role in cognitive health within populations with a high vascular risk burden – such as stroke cohorts like DEMDAS – where the prevalence of MetS is notably higher than in the general population.[199-201] The relationship between

MetS and cognitive impairment is likely underpinned by a range of complex, often multifactorial pathophysiological mechanisms. Central among these is insulin resistance-related impairment in cerebrovascular reactivity, alongside contributions from systemic and neuroinflammation, oxidative stress, and disturbed brain lipid metabolism, all of which may act synergistically to exacerbate cerebrovascular injury, neurodegeneration, and cognitive decline.[202-204] Although insulin resistance, which is commonly present in individuals with diabetes mellitus, is considered a key driver of this association, our findings from Study II on the independent relationship of the component reduced HDL-C with PSD and PSCI risk suggest that additional mechanisms warrant consideration and further investigation.

Reduced HDL-C was associated with a two- to threefold risk of PSD and delayed-onset PSD, which represents a novel and central finding of this thesis. Importantly, this association was only detectable when applying the sex-specific, MetS-related cut-offs for HDL-C. When HDL-C was analyzed as a continuous variable, we only observed an association with PSCI but not with PSD outcomes. To date, neither continuous nor categorical HDL-C levels have been linked to PSCI or PSD, although evidence from observational studies from the general population has been growing. These studies have yielded inconclusive findings, with both low and very high HDL-C levels associated with an increased risk of all-cause dementia, AD, and MCI, suggesting a potential U-shaped relationship.[205-211] However, the predictive value of HDL-C for cognitive outcomes after stroke remains poorly understood. A 2015 Turkish stroke registry study reported an association between lower HDL-C and a higher risk of a combined endpoint of PSMCI and PSD over five years.[212] However, the definition of low HDL-C was unclear, and the use of Cox regression models for a partially reversible cognitive endpoint such as MCI is debatable. More recently, a smaller Chinese cohort study (N=227) found that a higher triglyceride to HDL-C (TG/HDL-C) ratio was associated with 3-month PSCI measured by the MoCA.[213] The TG/HDL-C ratio is considered a surrogate marker for insulin resistance and has been associated with increased risk of cardiovascular disease,[214] potentially offering predictive value for cardiovascular outcomes comparable to a MetS diagnosis.[215] Although not explored in Study II, the TG/HDL-C ratio may warrant further investigation in future analyses.

We found that each additional MetS component was associated with a 30% higher risk of PSD and a 46% higher risk of delayed-onset PSD, suggesting a cumulative effect that may be independent of which specific components are present at baseline. This finding aligns with a study by Allan and colleagues (2011), which reported a dose-dependent increase in delayed-onset PSD risk with a higher number of coexisting cardiovascular risk factors, including prior stroke, ischemic heart disease, hypertension, AF, diabetes, hypercholesterolemia, and smoking.[80] Similarly, population-based studies have shown that a greater overall cardiovascular risk burden is associated with an increased risk of dementia.[216,217]

While our findings support a cumulative association, it remains unclear whether the effect of multiple cardiometabolic risk factors is merely additive or potentially supra-additive – i.e., whether the interaction of overlapping pathophysiological mechanisms results in a disproportionately greater risk of

PSD. This possibility has been proposed previously,[202,203,218] but warrants further investigation in future mechanistic and longitudinal studies. Although our study suggests a role of hyperglycemia and reduced HDL-C, it remains uncertain which combinations of MetS components predict the highest risk, and whether targeted control of these factors could meaningfully reduce PSCI and PSD incidence.

6.2.3 Atrial fibrillation

The findings from this thesis can help to clarify the previously inconclusive relationship between AF and post-stroke cognitive outcomes. In Study I, our meta-analysis found a 1.3-fold increased risk of PSCI in patients with AF by pooling ten studies. In contrast, no significant association was observed with PSD based on seven studies. Notably, the strength of the association between AF and PSD appeared to attenuate with more recent publication dates, possibly reflecting advances in AF management, such as broader use of newer anticoagulation therapies.[219,220]

In Study II (DEMDAS), AF was associated with a twofold increased risk of PSD and a 1.6-fold risk of PSCI over the 5-year follow-up. Subsequent sensitivity and subgroup analyses revealed two noteworthy aspects: the relationship between AF and PSD was (i) more pronounced in the early phase after stroke (i.e., early-onset PSD) and (ii) stronger among female participants. The studies included in our meta-analysis (Study I) differed markedly in median follow-up duration: 3 months for PSCI versus 16 months for PSD. If the contribution of AF to post-stroke cognitive outcomes is largest in the acute and subacute phase following stroke, this may explain why longer-term studies report weaker or non-significant associations.

Like diabetes, AF has been linked to SVD and other structural brain changes, which may impair brain health and increase vulnerability to cognitive decline after stroke.[172,175,221] However, the most likely explanation for the strong association with early-onset PSD may be AF's influence on acute stroke characteristics, including stroke severity, infarct number, and location.[73,222]

The observed sex differences in the association between AF and PSD warrant further investigation. Women with AF may be at a higher general risk of cognitive decline and dementia than men,[223,224] especially at older ages.[225] They also tend to have more comorbidities and higher rates of cardioembolic stroke, which is often AF-related, and they may experience poorer outcomes – potentially resulting from sex-specific disparities in AF treatment and care.[226-228] Future studies are needed to better understand the mechanisms underlying these sex-specific vulnerabilities and to evaluate whether tailored prevention strategies are warranted.

6.2.4 Other cardiovascular risk factors

At baseline, nearly 90% of patients included in Study II met the criteria for elevated blood pressure, defined as the use of antihypertensive medication and/or elevated blood pressure levels.[229] Interestingly, higher blood pressure was associated with a lower risk of PSCI, a lower risk of PSD in men, and a lower risk of delayed-onset PSD, although the latter became non-significant after adjusting for acute-phase

cognitive impairment. This counterintuitive association is consistent with findings from the REGARDS study, where stroke patients without hypertension experienced faster cognitive decline than those with hypertension.[94]

Evidence from longitudinal population-based studies investigating the trajectories of blood pressure levels in the decades preceding a dementia diagnosis points towards an elevated risk in patients with lower blood pressure levels following an earlier period of elevated blood pressure.[230-232] Similarly, other studies have reported that while elevated mid-life blood pressure predicts increased dementia risk, lower blood pressure in late life is also associated with a higher dementia risk, possibly due to mechanisms such as cerebral hypoperfusion or increased vascular stiffness.[233-235]

Nevertheless, the findings from our study and the REGARDS cohort should be interpreted with caution, as they may be biased by several factors related to the study design and sample. First, the proportion of stroke patients without elevated blood pressure was small – only 11.2% (n = 82) in DEMDAS – which may limit statistical power to detect associations. Second, the relatively low median systolic and diastolic blood pressure levels observed at baseline suggest that most patients were under effective blood pressure control at the time of recruitment into the study, and potentially even before the index stroke. Third, it has been shown that single blood pressure measurements may have limited prognostic utility, especially in contexts like that of an acute stroke.[236] Finally, elevated blood pressure at baseline may reflect either previously undiagnosed hypertension or a transient hypertensive crisis. In either case, nearly all stroke patients undergo intensive blood pressure management following the event,[237] complicating the interpretation of baseline blood pressure measurements in relation to long-term cognitive outcomes.

The findings from both studies in this thesis indicate that the relationship between ischemic heart disease (IHD) and post-stroke cognitive outcomes remains inconclusive. In Study I, we found no significant association between heart disease and either PSCI or PSD, though there was a trend toward an increased risk of PSD, broadly aligning with previous reports.[16,57,136] In contrast, Study II revealed a significant association between IHD and PSCI, but not PSD, after correction for multiple testing. Notably, sex-stratified analyses suggested that the association between IHD and PSD may be limited to male participants. However, the overall prevalence of IHD in our cohort was relatively low (12.4% in men and 7.8% in women), likely limiting statistical power, particularly in subgroup analyses. Given that IHD frequently co-occurs with other cardiovascular risk factors that increase the likelihood of both stroke and vascular cognitive impairment,[238] it is supposedly not an independent risk factor for post-stroke cognitive decline. Nonetheless, a history of IHD may still serve as a clinical marker of elevated vascular risk, helping to identify patients who warrant closer monitoring for cognitive outcomes.

Other cardiovascular risk factors, including smoking, hyper- or dyslipidemia, alcohol consumption, BMI, obesity, kidney disease, or peripheral artery disease, were not identified as risk factors for PSCI

or PSD in either of the two studies in this thesis, although several of them are considered traditional modifiable risk factors for dementia and cognitive dysfunction.[8]

6.2.5 Stroke recurrence

Stroke recurrence emerged as a strong risk factor for PSD, particularly delayed-onset PSD, in Study II. This finding aligns with prior evidence showing a stepwise increase in PSD risk with each additional stroke and greater stroke severity,[53,57] and it further supports proposed mechanisms underlying delayed-onset PSD.[72-74] Nevertheless, the relatively small proportion of recurrent strokes among delayed-onset PSD cases suggests that recurrence is only one of multiple contributing pathways – perhaps representing the most severe manifestation within a broader continuum of cerebrovascular pathology that can drive especially vascular dementia and cognitive impairment. Preventing recurrent events remains a cornerstone of post-stroke care and a key strategy for reducing the risk of cognitive decline and dementia, which is primarily achieved through rigorous vascular risk factor management.[239]

Stroke recurrence was the only vascular risk factor occurring during follow-up that we incorporated into our analyses. The examination of changes in, or the incidence of, other vascular or metabolic risk factors during follow-up was beyond the scope of the current analyses. However, this is planned to be addressed in the future. Recent studies suggest that markers of disease progression and dynamic changes in risk factor levels may improve the prediction of cognitive outcomes. For example, in a previous publication from the DEMDAS cohort, Fang et al. reported that new ischemic lesions detected on MRI six months after the index stroke were associated with lower cognitive scores, worse functional outcomes, and an increased risk of stroke recurrence over three years of follow-up.[240] In terms of cardiovascular risk factors, an individual participant data meta-analysis demonstrated that higher cumulative mean blood glucose levels after stroke were associated with more rapid cognitive decline over a median follow-up of 4.7 years, whereas post-stroke blood pressure and LDL-C levels were not.[241] Whether the association between cardiovascular risk factors – present before, at the time of, or after stroke – and cognitive outcomes is mediated by SVD remains unclear, largely due to the lack of longitudinal neuroimaging in most studies. Cohorts like DEMDAS, Nor-COAST,[242] or the ongoing DISCOVERY[92] and FIND Stroke Recovery studies,[243] which include imaging during follow-up, offer valuable opportunities to investigate these mechanisms in detail.

6.3 Implications for clinical practice and secondary prevention

The findings from this thesis may inform routine clinical practice after stroke and inform the design of future secondary prevention trials.

6.3.1 Cardiometabolic risk factors and stroke recurrence

In Study II, the associations between cardiometabolic risk factors and PSD remained robust after accounting for stroke recurrence. This finding is pivotal, as stroke recurrence has traditionally been considered the principal pathway through which these risk factors influence the risk of post-stroke cognitive decline.[181,244] Consequently, stroke recurrence and major adverse cardiovascular events (MACE), along with functional outcomes, have been the primary outcomes in most secondary prevention trials after stroke.[93,245-248] Cognitive endpoints, however, have been largely overlooked, despite their substantial impact at both the individual and population levels.[93] Expanding on earlier hypotheses,[80] this thesis provides new and compelling evidence that cardiometabolic risk factors contribute to PSD and PSCI through mechanisms beyond stroke recurrence. Together with growing evidence,[80,249] these findings strongly support the inclusion of cognitive outcomes as crucial stand-alone endpoints in future secondary prevention trials after stroke.

6.3.2 Secondary prevention of cognitive decline after stroke

Currently, disease-modifying treatments for dementia are limited, making the prevention and mitigation of risk through management of established modifiable factors a critical priority.[47,51] Although there is substantial evidence from observational studies linking modifiable vascular and cardiometabolic risk factors to PSCI and PSD, evidence from RCTs supporting the effectiveness of interventions targeting these factors to reduce the incidence of post-stroke cognitive problems remains limited.[17,27,247] The following section will discuss the potential of different preventive interventions based on existing evidence from stroke-free and stroke-specific studies.

Cardiovascular and cardiometabolic risk factors can be prevented and managed using pharmacological, lifestyle, or combined strategies. Naturally, these factors should be controlled as early and consistently as possible during the lifespan, and to avoid cerebrovascular events in the first place. But especially after a stroke, rigorous risk factor management is key for preventing any adverse outcomes, including cognitive decline and dementia, as has been demonstrated in both epidemiological and clinical studies. For example, an observational study from the London Stroke Registry showed that appropriate pharmacological management of vascular risk factors after stroke was associated with a lower risk of PSCI during 10 years of follow-up in patients with ischemic stroke and without a history of AF.[250] Patients prescribed a combination of antihypertensive, lipid-lowering, and antithrombotic therapy had an almost 50% reduced risk of PSCI. While these findings are limited by factors inherent to observational studies, they highlight the importance of secondary prevention strategies targeting

modifiable risk factors. However, causal treatment effects can only be established in well-designed RCTs.

6.3.2.1 Pharmacological management of cardiovascular risk factors

Glycemic control

This thesis highlights the importance of elevated blood sugar as a potential preventive target for adverse cognitive outcomes after stroke. In individuals with diabetes, it remains uncertain whether effective diabetes treatment alone can fully mitigate the risk of dementia, as the need for multiple or high doses of oral medications or insulin may itself reflect more severe diabetes.[51] In the general population, intensive glycemic control strategies have not consistently demonstrated a reduction in dementia risk compared to standard treatment.[65,251] However, newer evidence suggests that some classes of antidiabetic medications, particularly SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors, are associated with a lower risk of dementia.[252] For metformin, the evidence remains inconclusive, while the use of sulfonylureas has been linked to an increased dementia risk.[252,253]

Blood pressure management

Hypertension was not identified as a risk factor for PSCI or PSD in either of the studies in this thesis. However, blood pressure lowering with antihypertensive agents has been significantly associated with a reduced risk of incident dementia and cognitive impairment in the general population, although the ideal blood pressure range for cognitive prevention remains unknown.[254,255] In the SPRINT MIND trial, intensive (aiming for <120 mm Hg systolic blood pressure) versus standard blood pressure control (<140 mm Hg) resulted in a significant reduction of the risk of MCI and the combined endpoint MCI and probable dementia, but not in the primary outcome, probable dementia, alone.[186]

Nevertheless, trials specifically conducted in the post-stroke setting have not demonstrated substantial or consistent benefits of blood pressure lowering for cognitive outcomes.[247,256-261] Several factors may account for these inconclusive results, including advanced pre-existing brain injury in stroke survivors, competing contributors to cognitive decline, and the often limited follow-up duration of post-stroke trials.[236]

Taken together, although evidence from RCTs and epidemiological studies from the general population suggests a benefit, it remains unclear whether blood pressure lowering independently decreases the risk of PSCI and PSD, and, if so, what the optimal antihypertensive treatment regimen would be for stroke survivors.[262]

Lipid control

In Study II, reduced HDL-C emerged as a novel predictor and possible target for secondary prevention of PSCI and PSD. To date, few trials have reported independent benefits of lipid control to prevent cognitive decline. Evidence from observational studies suggests that sustained statin use may be related to a reduced risk of all-cause dementia and AD in individuals with hypercholesterolemia.[263,264] However,

a Cochrane Review of three randomized controlled trials found no protective effect of statins on cognitive outcomes in older adults at vascular risk.[265] A Japanese RCT from 2015 did not find significant differences in secondary cognitive outcomes after stroke between a pravastatin and a control group,[266] while a meta-analysis and a recent registry-based study from Korea found a lower risk of PSD and PSCI associated with post-stroke statin use.[97,267] Because statins are now routinely prescribed for secondary stroke prevention, long-term RCTs comparing statin use with non-use are no longer feasible. However, future trials should include cognitive outcomes to evaluate the potential benefits of specific agents or treatment regimens.

Whether specifically targeting HDL-C can reduce the risk of post-stroke cognitive decline remains unknown. Notably, a Mendelian randomization analysis by Georgakis et al. (2019) found that HDL-C–raising genetic variants in the cholesteryl-ester transfer protein (CETP) locus were associated with a lower risk of small-vessel stroke and reduced WMH volume, albeit also with a higher risk of bleeding.[268] Thus, raising HDL-C represents a potential, but still unproven, avenue for secondary prevention that warrants further investigation.

Anticoagulation in atrial fibrillation

The markedly increased risk of PSCI and PSD in patients with AF underscores the need for rigorous secondary prevention strategies in this high-risk group. Anticoagulant therapy is well-established to reduce the risk of cognitive impairment and dementia in individuals with AF, irrespective of prior stroke history.[220,269,270] However, it remains uncertain whether newer non-vitamin K antagonist oral anticoagulants (NOACs) offer greater cognitive protection compared to traditional vitamin K antagonists like warfarin.[219,220,271,272] Robust evidence from RCTs is lacking,[270,273] and findings from observational studies on cognitive outcomes after stroke remain limited and conflicting.[97,161,274-276] While we were unable to directly assess the relationship of oral anticoagulant use with PSCI and PSD in this thesis, the observed attenuation of the association between AF and PSD over time in Study I may partly reflect improvements in secondary prevention strategies. Future trials are warranted to determine whether, and which, anticoagulants can help reduce the risk of cognitive decline and dementia after stroke.

Targeting cerebral small vessel disease

Controlling cardiovascular risk factors remains one of the most promising strategies for the primary and secondary prevention of SVD. Yet, few trials have been conducted, and even less evidence supports a beneficial effect on cognitive outcomes.[184,277-279] As outlined in the Introduction of this thesis, intensive blood pressure control currently shows the greatest potential, with evidence suggesting it could help slow WMH progression and prevent or delay cognitive decline.[185,186] In the TREAT-SVDs trial, short-term treatment with different antihypertensive classes (amlodipine, losartan, atenolol) showed no differential effects on cerebrovascular reactivity in sporadic SVD, but class-specific effects were

observed in CADASIL, suggesting that the impact of antihypertensive drug classes on clinical outcomes in SVD warrants further investigation.[279] In secondary prevention, the SPS3 trial, which included patients with a recent lacunar stroke, found no improvement in cognitive outcomes with dual antiplatelet therapy over aspirin alone, nor with intensive blood pressure reduction during a median follow-up of 3 years.[258] More recently, the LACI-2 trial reported a lower risk of cognitive impairment in lacunar stroke patients treated with isosorbide mononitrate alone or in combination with cilostazol, two agents that may enhance vascular endothelial function.[280] However, the trial did not result in a treatment effect for a composite endpoint including adverse vascular, functional, and cognitive outcomes, highlighting the need for larger phase-3 trials.[280]

Apart from the various pharmacological strategies discussed here, results from ongoing trials might help elucidate possible other pharmacological treatments or secondary prevention avenues, e.g. involving agents with anti-inflammatory,[281] vasoactive,[282] or neuroprotective properties.[283]

6.3.2.2 Non-pharmacological strategies: physical activity and cognitive training

Although not addressed in either of the studies in this thesis, previous evidence supports the beneficial role of physical activity and exercise in maintaining cognitive health and preventing dementia across the lifespan, with extreme sedentariness linked to the highest risk of developing dementia.[51] In the context of stroke, physical activity-based interventions have been proposed as promising strategies to support cognitive recovery, particularly during the early post-stroke period when neuroplasticity and recovery are most pronounced.[26,284]

However, evidence from RCTs in both general and stroke populations has been mixed. Most studies report no or only modest cognitive benefits of exercise-based interventions,[284-289] and such interventions may be more effective when combined with other approaches.[290] A more recent RCT demonstrated cognitive improvements in patients whose most recent stroke occurred a median of 5.5 years prior, suggesting that exercise may offer protective effects even beyond the early recovery phase.[291] Lifestyle interventions have also been applied in specific high-risk groups. For instance, the Look AHEAD trial, which involved a 10-year lifestyle intervention targeting weight loss in overweight patients with type 2 diabetes through improving diet and exercise habits, showed no associations with cognitive function despite improvements in diabetes management.[292]

In summary, despite somewhat encouraging signals, most available studies are limited by small sample sizes, short intervention and follow-up durations, and large heterogeneity.[284,287,288] Importantly, there is a lack of RCTs investigating the impact of exercise interventions on clinically relevant binary outcomes such as PSCI or PSD. Further large-scale, long-term trials are needed to determine the true effectiveness of exercise-based interventions for cognitive prevention in stroke survivors.

Several trials have examined the effectiveness of cognitive training for improving cognitive function after stroke, but have generally reported small or no benefits, and were often limited by methodological

shortcomings and short follow-up periods.[27,293-298] These findings are broadly consistent with evidence from stroke-free samples, where cognitive training for individuals with MCI, AD, or VaD has shown similarly modest effects.[299-301] Systematic reviews and meta-analyses have synthesized results from trials on computer-based cognitive training and combined approaches, such as cognitive training with repetitive transcranial magnetic stimulation – both potentially promising avenues – but current evidence is insufficient, and larger, high-quality studies are needed to establish their efficacy.[284,302,303] Importantly, the lack of trials assessing whether cognitive training can prevent or delay PSCI or PSD further limits its current clinical applicability.

Few other non-pharmacological interventions beyond physical activity and cognitive training to prevent cognitive decline or improve cognition after stroke have been reviewed, but the evidence is insufficiently conclusive and robust.[27,284,304]

6.3.2.3 Multi-domain interventions

Among the most promising strategies for cognitive prevention after stroke are multi-domain or multi-component interventions that combine several non-pharmacological and/or pharmacological interventions. Importantly, two large and one smaller RCT have demonstrated the effectiveness of multi-domain interventions for improving cognitive performance and lowering dementia risk in at-risk individuals from the general population.[305-307]

Ten years ago, the FINGER trial was the first to demonstrate the effectiveness of a 2-year multi-domain intervention for improving cognitive performance in at-risk individuals from Finland.[306] Recently, more results from RCTs have been published that confirm and expand on these findings.[305,307] Of these, particularly the multi-domain lifestyle intervention "Maintain Your Brain", which was administered entirely online in a large-scale (n > 6,000) RCT from Australia, yielded considerable effect sizes over 3 years and could represent a promising approach that is accessible to the general population.[305]
Previously, two reviews had reported inconclusive findings,[308,309] and a recent RCT from Japan, which included >500 individuals with MCI, also demonstrated no efficacy of a multi-domain intervention for the prevention of cognitive decline.[310]

While evidence from the general population offers grounds for optimism, existing post-stroke trials have reported no, or only minimal, beneficial effects of multi-domain interventions on cognitive outcomes.[298,311,312] This may reflect limitations such as short follow-up durations, selective attrition, and the practical challenges of conducting complex interventions in stroke survivors. More research is needed into how post-stroke cardiovascular risk factor management can be better tailored to individual patients to optimize both adherence and effectiveness for cognitive secondary prevention. Although the impact of combined interventions aimed at improving cardiovascular health and health behaviors on cognitive outcomes post stroke remains unclear, their implementation may still be justified given their broader benefits for vascular risk reduction, overall physical health, and psychological well-being.

6.3.2.4 *Acute reperfusion therapy*

To our knowledge, Study II is the first to report a substantial reduction in long-term PSCI and PSD risk among patients receiving acute reperfusion therapy (IVT and/or EVT) compared with otherwise similar patients who did not. Here, reperfusion therapy was associated with a 65% lower risk of PSD and a 50% lower risk of PSCI. Importantly, given the observational nature of the study, we cannot infer a causal treatment effect. The potential cognitive benefits of EVT in particular have been investigated in only a few studies, likely due to its relatively recent adoption as routine care after 2015.[159] A retrospective population-based cohort study reported a 21% lower 5-year dementia incidence among patients treated with IVT, but did not assess EVT or combined IVT + EVT treatment.[313] In contrast, a large registry-based study from Korea found no association between reperfusion therapy and PSD risk, possibly in part due to the low proportion of patients receiving EVT.[97] More recently, a meta-analysis including three RCTs and one observational study (follow-up: 3–12 months) found better cognitive performance associated with EVT.[314] In one of the RCTs, combined EVT + IVT treatment was associated with higher cognitive scores at 6 months than IVT alone.[315] However, none of these studies assessed long-term binary outcomes such as PSCI or PSD.

Taken together, the findings from this thesis and previous studies suggest a potential effect of reperfusion therapy, particularly when IVT and EVT are combined, on cognitive outcomes after stroke. However, definitive evidence from trials assessing long-term outcomes, including dementia, is still lacking. These observations underscore the importance of incorporating cognitive endpoints into future clinical trials of acute stroke treatments.

6.3.2.5 *Further considerations for secondary prevention*

Despite emerging strategies aimed at preventing or delaying cognitive decline and dementia after stroke, the effectiveness of managing risk factors that may have been present or accumulated over decades remains uncertain. The contribution of vascular risk factors is assumed to be age-dependent, with both the age at and duration of exposure being critical. Prior research has emphasized the lifelong influence of vascular risk factors, particularly the critical role of midlife exposure, in relation to brain health and the risk of cognitive decline and dementia in later life.[195,233,316-322] Along similar lines, population-based studies have found a decrease in the strength of associations between several cardiovascular risk factors and dementia with increasing age, suggesting a lower contribution of these risk factors to dementia in older ages.[323,324] Moreover, a recent study using data from the Korean National Health Insurance Database demonstrated that a longer duration of type 2 diabetes mellitus was significantly associated with an increased risk of PSD among individuals with a history of stroke and no prior diagnosis of dementia.[169] Specifically, individuals with a diabetes duration of five years or more exhibited a 47% higher risk of PSD, while those with a duration of less than five years had a 27% increased risk, when compared to individuals without diabetes. These findings align with observations from large population-

based studies. Among more than 10,000 individuals in the Whitehall II study, younger age at diabetes onset and longer disease duration were associated with a higher dementia risk.[322]

Similarly, for SVD, early detection and timely intervention are essential, as SVD-related brain changes can be widespread, progressive, and may precede cognitive symptoms by years or even decades.[110] Many stroke patients already present with substantial SVD burden at baseline,[57,112,116] and findings from the OxVasc study suggest that long-term mean blood pressure levels prior to stroke or TIA are more strongly associated with SVD burden at the time of the event than baseline levels or a history of hypertension.[236] Thus, it is still unclear whether addressing the modifiable risk factors underlying SVD after stroke can meaningfully alter outcomes or whether SVD mainly reflects and predicts disease burden and progression.

Apart from improving individual risk stratification, the age- and duration-dependent contributions of vascular and cerebrovascular factors to dementia have important implications for research and clinical trial design. Trials could, for example, stratify participants by both age and duration of exposure to specific risk factors, which may help uncover differential treatment effects and inform enrichment strategies. Observational and interventional studies should also aim to capture retrospective cardiovascular risk histories, even though such data may be affected by recall bias if they are solely self-reported.[325] Moreover, as cardiometabolic risk factors appear more strongly linked to delayed-onset PSD, prevention trials targeting these factors should incorporate extended follow-up periods beyond the typical 6–12 months to capture these cases adequately.

It is noteworthy that while research efforts toward precision medicine and individual risk reduction remain essential, secondary prevention after stroke also has important implications at the population level. Evidence from primary cardiovascular disease prevention highlights the "prevention paradox," whereby population-wide strategies to lower risk factors can achieve a greater overall impact than interventions limited to high-risk individuals.[326,327] Applied to secondary prevention after stroke, this suggests that focusing solely on high-risk patients may be insufficient to meaningfully reduce the overall burden of PSCI and PSD. Instead, complementary population-wide approaches for improving vascular and metabolic health – even if benefits for any given individual are modest – could translate into substantial gains for population-level outcomes in stroke survivors.

In conclusion, pharmacological, non-pharmacological, and multi-domain interventions aimed at improving cognitive function or preventing cognitive decline and dementia after stroke have, to date, yielded limited results. Several methodological limitations hamper the ability to detect meaningful intervention effects. Notably, cognition and dementia are often assessed only as secondary outcomes in post-stroke secondary prevention RCTs, particularly in trials evaluating pharmacological management of cardiovascular risk factors.[254,258,328] Moreover, many studies lack the statistical power to detect preventive effects on dementia, which requires large sample sizes and long-term follow-up due to its relatively lower incidence and often delayed onset.[254,266] These challenges are further compounded by

higher attrition and lower treatment adherence rates among stroke survivors who already show cognitive decline.[329] Both the age at and duration of exposure to cardiovascular risk factors, as well as the timing of interventions after stroke, may be crucial for their effectiveness. Nevertheless, despite these challenges, the growing burden of stroke and dementia highlights the urgent need to intensify research into both primary and secondary prevention strategies. Future trials may benefit from insights gained from the general population, where preventive interventions have shown promising results,[305,306] and from applying enrichment strategies informed by epidemiological studies that identify high-risk individuals. Such approaches could enhance trial efficiency and increase the potential for detecting clinically meaningful cognitive benefits.

6.3.3 Importance of early cognitive testing

The findings from this thesis offer important insights for individual risk prediction. Both studies underscore the value of early cognitive screening after stroke as an accessible and powerful tool for identifying patients at particularly high risk of cognitive decline. While the association between acute-phase cognitive impairment and long-term cognitive outcomes has been described before,[16,57] our work places emphasis on its potential for robust risk stratification. Across both studies, patients with acute-phase cognitive impairment had a substantially higher risk – specifically, 2- to 6-fold – of developing PSCI and PSD. As such, acute-phase cognitive impairment alone may be more predictive than other clinical risk factors, like, e.g., stroke severity.[330] Regardless of the exact mechanisms underlying acute-phase cognitive impairment, incorporating early cognitive testing into routine stroke care could improve risk communication with patients and caregivers, guide personalized follow-up strategies, and inform further diagnostic and therapeutic decision-making. Its relevance extends beyond cognitive prognostication: early PSCI has also been linked to an increased risk of stroke recurrence and poorer functional outcomes.[87,331] Given these multiple implications, future secondary prevention trials should consider systematically including patients with early PSCI as an enrichment strategy to enhance trial efficiency and target those most likely to benefit.[332] Moreover, implementing stroke-appropriate, cognitive domain-specific screening tools for acute-phase cognitive impairment in both clinical practice and research could help minimize confounding from language or attentional deficits and enhance prognostic accuracy in stroke patients.[333,334]

6.4 Methodological considerations and limitations

In Study I, synthesizing the available evidence on post-stroke cognitive outcomes proved challenging. Despite extensive efforts to harmonize exposure and outcome measures to achieve comparability across studies, the included studies applied varying criteria for defining PSCI or PSD, leading to substantial heterogeneity and limited comparability, particularly for risk factors that were only investigated in a few smaller studies. The absence of standardized diagnostic tools and uniform definition criteria is an important conceptual limitation of research on the prevalence, incidence, and predictors of PSCI.[17,88,335] The resulting heterogeneity is particularly pronounced for PSCI and PSMCI, whereas there is generally a broader consensus on the definition of PSD.[17] Furthermore, many studies included in Study I relied on brief cognitive screening tools, such as the MoCA or the MMSE, but applied heterogeneous cut-offs to define the PSCI outcome.[29] The MoCA has greater sensitivity for detecting probable PSMCI, particularly in the early post-stroke phase, while the MMSE is recommended primarily for PSD assessment.[336-338] This may take away from the reliability of those studies that defined PSCI solely based on the MMSE. Although screening tools like the MoCA are more practical for clinical use and have proven reasonable validity, they primarily identify more severe cognitive impairment and provide limited insight into domain-specific deficits. When feasible, comprehensive neuropsychological test batteries are considered preferential due to their higher sensitivity and reliability when the goal is to make a definitive diagnosis,[17] while a universally accepted diagnostic framework for PSCI remains lacking.[339] Hence, the repeated use of a cognitive test battery that allowed for capturing global and domain-specific performance is one of the key strengths of the DEMDAS study (Study II).

How stroke survivors perform on cognitive tests can be confounded by psychological factors or other stroke-related impairments, e.g., of the motor and language abilities, especially early after stroke. This represents a methodological limitation concerning both studies in this thesis, since it can lead to the exclusion of more severely affected patients. This selection bias was present in the DEMDAS cohort and was discussed in Study II. In Study I, we could observe a similar tendency towards lower stroke severities, while 49 of the 113 included articles did not report summary statistics of any stroke severity measure. More severely affected patients are also more likely to be lost to follow-up, as could be observed in DEMDAS, despite a pre-designed multimodal follow-up procedure. Consequently, some patients who developed PSD might have been lost before a diagnosis, resulting in attrition bias. Future studies should employ tools such as the Oxford Cognitive Screen (OCS), which has been developed for use in stroke settings, as it allows for the cognitive screening of patients with aphasia and the detection of neglect and apraxia.[334] Additionally, for the design of future studies, studies that achieved comparably low attrition rates, as was the case in the OxVasc study,[57] should be taken as an example.

Several factors may limit the generalizability of the present findings. First, hospital-based studies are more prone to selection bias than population-based studies.[16,340] In this thesis, most studies included in Study I (73 [82%]) and Study II were hospital-based. Nevertheless, hospital-based settings offer

important advantages, including detailed phenotyping, early and specific assessments after stroke, and standardized follow-up protocols. Second, most studies in Study I were conducted in Asia, Europe, or North America, and DEMDAS mainly included patients of European ancestry, restricting generalizability to other ethnic groups. Third, both DEMDAS and most studies in the meta-analysis recruited a higher proportion of men than women, which is a common issue in stroke research, likely reflecting a combination of factors such as greater stroke severity, more comorbidities, and a lower likelihood of women to meet eligibility criteria.[341-344] Future studies should therefore strive for more balanced, or even female-enriched, recruitment to address this disparity and strengthen the evidence base.

The low dementia incidence observed in Study II brings on statistical limitations for the PSD endpoint by limiting the power of many subgroup analyses. Thus, especially the analyses of exposures with a low prevalence rate, such as APOE-ε4 carrier status, lack power and robustness. Additionally, because Study II was conducted across multiple centers, some with few dementia cases, standard Cox regression without center stratification may have introduced variability. While we adjusted for major confounders, low event numbers per site limited formal assessment of clustering or center-specific differences. Notably, sensitivity analyses using random-effects and GEE models with exchangeable correlation structures, which account for potential within-center correlations and yield more robust, population-averaged estimates,[345] yielded similar results as the standard Cox models.

As mentioned above, sex-specific subgroup analyses were likely underpowered. Furthermore, the generalizability of our results to patients with hemorrhagic stroke is hampered. In both studies, it was not statistically feasible to stratify by stroke subtype – neither ischemic versus hemorrhagic nor by specific etiologies. In Study I, this was due to the small number of studies focusing specifically on HS, and the lack of stratified analyses in studies that included both ischemic and hemorrhagic stroke patients. In Study II, the very low proportion of individuals with HS (2.8%) precluded meaningful subgroup analyses. More broadly, the representation of HS patients in stroke research is often limited, possibly reflecting both its lower prevalence in high-income countries and the lower likelihood that the often more severely affected HS patients are recruited into studies with demanding, time-intensive protocols.[8,93] Although stratification by stroke subtype would have been of interest, it was technically beyond the scope of this thesis and not part of the predefined analyses. Importantly, other factors, such as stroke severity and lesion location, may exert a far stronger association with post-stroke cognitive outcomes than stroke etiology per se.[57,151-153] Nevertheless, further studies are warranted to clarify whether stroke etiology may contribute unique mechanisms underlying the development of PSCI and PSD.

Another important conceptual limitation of Study II was the lack of subtyping of the dementia cases (i.e., predominant vascular, AD, or mixed pathology). Although this was part of the original pre-specified analysis plan in the study protocol,[346] the study design did not account for the consistent and comprehensive diagnostic procedures required for accurate subtype classification. More specifically,

invasive assessments such as lumbar puncture or PET imaging – which at the time were the only methods enabling definitive diagnostic classification based on CSF or imaging biomarkers – were not included in the protocol, as these procedures are not recommended in otherwise healthy patients without a clear clinical indication. Looking ahead, however, recent advances in blood-based biomarkers for AD (e.g., plasma phospho-tau217) may offer less invasive and scalable alternatives, potentially enabling reliable dementia subtype classification even in large epidemiological studies.[347,348]

The findings from this thesis do not allow definitive conclusions regarding milder forms of PSCI. In Study I, most included studies focused on PSD or on the composite outcome PSCI, which combines PSD and PSMCI. Study II likewise centered on PSD, as its main purpose was to report the results of the primary 5-year endpoint of the DEMDAS study. Our results, nevertheless, suggest that milder forms of PSCI and dementia likely share similar risk factor profiles, as they may represent different stages along a continuum of post-stroke cognitive decline.[17,83] Moving on, we plan to conduct more fine-grained analyses examining outcomes such as PSMCI, progression from MCI to dementia, as well as domain-specific and continuous cognitive measures.

Finally, certain risk factors or entire categories of risk factors were not investigated in this thesis, due to the insufficient and/or inconclusive evidence base. For instance, Study II did not examine indicators of inflammation, physical activity, socioeconomic status, or psychological well-being, as well as environmental factors, all of which may contribute to cognitive decline and dementia.[51,349] These factors may deserve further investigation in future studies.

6.5 Conclusions and future directions

In light of the rising global stroke burden and declining stroke-related mortality, strategies to prevent the long-term consequences of stroke are urgently needed. Among these, dementia and cognitive impairment remain major causes of disability, placing heavy demands on patients, families, and society. Effective aftercare and prevention of cognitive decline require both the identification of individuals at highest risk to optimize counselling, monitoring, and care, as well as a deeper understanding of the pathological mechanisms and modifiable risk factors that could serve as targets for secondary prevention. Because vascular contributions to PSCI and PSD are often substantial, cardiovascular risk factor management holds promise for delaying or preventing cognitive decline in many patients. Yet, previous evidence on predictors, especially modifiable risk factors, has been limited by heterogeneous study designs, inconsistent outcome definitions, short follow-up periods, and often poor methodological quality. This thesis sought to address these gaps by providing robust evidence on the risk factor profile for PSCI and PSD, with a particular focus on modifiable factors, through a large-scale meta-analysis and a 5-year multicenter observational study of a deeply phenotyped stroke cohort.

The findings from this thesis highlight the multifactorial nature of PSCI and PSD (**Figure 5**) and provide compelling evidence for the role of cardiovascular and cardiometabolic risk factors in the development of dementia after stroke.

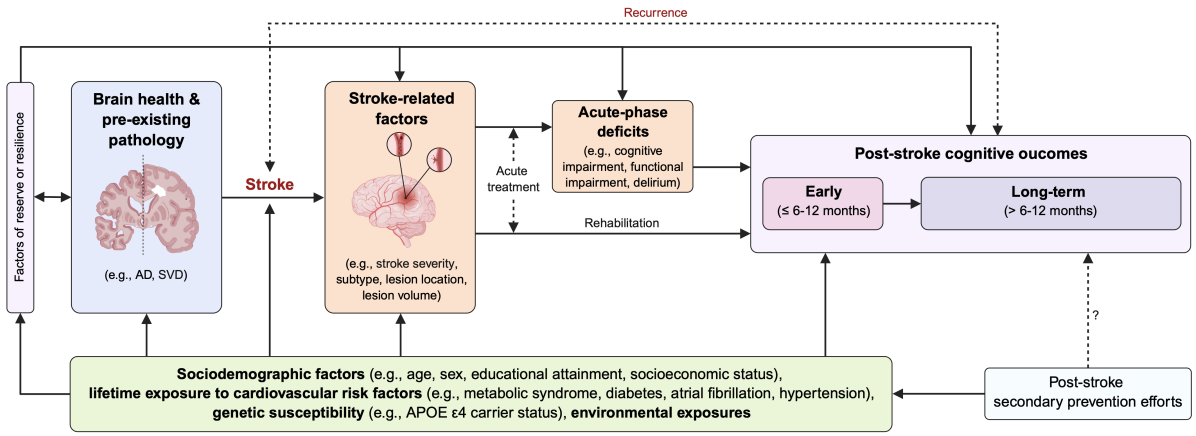

Figure 5. Extended framework depicting the factors contributing to post-stroke cognitive impairment and dementia, including insights gained in this thesis**.** Figure created by the author of this thesis using BioRender.com.[57,92,93] AD, Alzheimer's disease. APOE, apolipoprotein E. SVD, cerebral small vessel disease.

Key predictors identified in this thesis include factors related to and markers of pre-stroke brain health (older age, greater SVD burden, cerebral atrophy), pre-stroke cognitive reserve (lower education, lower pre-stroke cognition), stroke-related factors (greater severity, acute-phase cognitive and functional impairment, delirium), and cardiovascular/metabolic risk factors (atrial fibrillation, metabolic syndrome – particularly diabetes/prediabetes and reduced HDL-C – prior stroke, and recurrent stroke). In contrast, acute reperfusion therapy was associated with significantly lower dementia risk. These findings can

support the development of risk prediction tools and inform clinical trial design, with metabolic syndrome and HDL-C emerging as novel potential targets for secondary prevention.

Importantly, this thesis shows that cardiometabolic risk factors contribute to PSD through mechanisms beyond recurrent stroke, emphasizing the need to include cognitive outcomes as primary endpoints in post-stroke prevention trials. Future work should disentangle the possible additional underlying pathways – such as SVD, inflammation, and neurodegeneration – that may mediate these associations.

Finally, the results extend previous evidence for distinct risk profiles of early- and delayed-onset PSD. While early-onset PSD appears more strongly driven by atrial fibrillation, stroke-related factors, and brain vulnerability at the time of stroke, delayed-onset PSD is more closely linked to cardiometabolic risk factors and recurrent stroke. Further long-term studies are needed to refine these distinctions.

Overall, prioritizing modifiable risk factors and clarifying the contribution of and interplay between cerebrovascular and neurodegenerative (particularly AD-related) pathology will be essential for developing tailored preventive strategies.

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Content Author	Sarah T Pendlebury, Peter M Rothwell

Use of AI

This thesis was written in accordance with the "Rules for the use of artificial intelligence (AI) tools for examination-relevant activities" by the Graduate School of Systemic Neurosciences. Sections 1, 3, 4, 5.1.1, 5.2.1, and 6 were corrected and optimized with the aid of ChatGPT and Grammarly.

10. APPENDIX – SUPPLEMENTARY MATERIAL

Supplementary Material of the included studies, as published in the original papers.

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

Study II: Risk factors for dementia and cognitive impairment during 5 years after stroke: a prospective multicenter cohort study

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Filler J, Georgakis MK, Dichgans M. Risk factors for cognitive impairment and dementia after stroke: a systematic review and meta-analysis. *Lancet Healthy Longev* 2023; published online Dec 12. https://doi.org/10.1016/S2666-7568(23)00217-9.

Supplementary Material

Supplement 1: Search strategy

PubMed

1. (((Predict* OR longitudinal OR prospective OR “risk factor*”)
2. AND (stroke OR post-stroke OR poststroke)
3. AND (dementia OR cognit* OR neuropsych*))
4. NOT(“Animals”[Mesh]NOT (“Animals”[Mesh] AND “Humans”[Mesh]))

Cochrane

1. (Predict*):ti,ab,kw OR (longitudinal):ti,ab,kw OR (risk NEXT factor):ti,ab,kw
2. AND ((stroke):ti,ab,kw OR (post-stroke):ti,ab,kw OR (poststroke):ti,ab,kw)
3. AND ((dementia):ti,ab,kw OR (cognit*):ti,ab,kw OR (neuropsych*):ti,ab,kw)
4. NOT ((MeSH descriptor: [Animals] explode all trees))
5. NOT ((MeSH descriptor: [Animals] explode all trees) AND (MeSH descriptor: [Humans] explode all trees))

Supplement 2: Data extraction

The following data were extracted from each study and entered into a pre-defined data extraction sheet:

- study characteristics (country, city, recruitment period, study design, setting, exclusion of dementia or cognitive impairment before stroke, follow-up period, loss to follow-up-rate, definition of pre-stroke cognitive impairment if applicable),
- population characteristics (sample size, demographic characteristics, stroke characteristics, prevalence of cardiovascular risk factors, prevalence of pre-stroke cognitive impairment),
- outcome-related information (examined outcome(s), definition, method of ascertainment, overall outcome prevalence, outcome prevalence among the unexposed for categorical variables),
- predictor-related information (examined predictor(s), method of ascertainment, definition, summary statistics for continuous variables, proportion of exposed for categorical variables, reference group/interval for effect measure),
- and statistical data (type of effect measure (OR, HR, RR), effect size and 95% confidence intervals, model covariables, sample size included in the analysis). Statistical analysis data were only extracted from studies that provided multivariable regression analysis results.

Supplement 3: Newcastle-Ottawa quality assessment scale for cohort studies

Selection

1) Representativeness of the exposed cohort: a point was awarded if the study was population-based or based on a registry that represents the population.
2) Selection of the non-exposed cohort: a point was assigned if the patients with different levels of exposure to the risk factor stemmed from the same hospital or population.
3) Demonstration that outcome of interest was not present at start of study:
    a. Studies that do not exclude or adjust for pre-stroke dementia or cognitive impairment = 0 points
    b. studies that exclude or adjust for pre-stroke dementia or cognitive impairment = 1 point

Comparability

1) Comparability of cohorts on basis of the design or analysis:
    a. No adjustment for age or stroke severity = 0 points
    b. Adjustment for age or stroke severity = 1 point
    c. Adjustment for age & stroke severity (and more) = 2 points

Outcome

1) Assessment of outcome:
    a. Outcome assessed based on registries/medical records = 0 points
    b. Active cognitive testing is part of the study design = 1 point
2) Was follow-up long enough for outcome to occur:
    a. Mean/median FU < 12 months = 0 points
    b. Mean/median FU ≥ 12 months = 1 point
3) Adequacy of follow-up cohorts: how high was the loss to follow-up (LTFU)?
    a. ≥ 5% average annual LTFU = 0 points
    b. < 5 % average annual LTFU = 1 point

Supplement 4: Outcome harmonization

We converted original-scale odds ratios (OR) and hazard ratios (HR) to relative risks (RR), applying different methods based on data reported by the original publications. For categorical variables we transformed OR to RR based on the outcome prevalence among the unexposed (p_0), if provided.[1] If p_0 was not provided and in case of continuous variables, we applied the same formula using the overall reported prevalence p. If even p was not provided, we transformed OR to RR using a square root transformation method proposed by VanderWeele in 2017[2] for PSCI and PSD, assuming the true prevalence to lay in a normally distributed interval between 0.2 and 0.8 (PSCI) and between 0.2 and 0.45 (PSD).[3,4] For the conversion of HR to RR we applied a respective formula proposed by VanderWeele,[5] assuming the outcome probabilities to lay in the same intervals as above. When using the VanderWeele approaches, the confidence bounds for the new, approximated RR required adjustment by a factor that accounts for the so-called maximum bias ratio, relative to the interval width of outcome probabilities. For ORs, this factor was 1.25 for PSCI and 1.12 for PSD. For HRs, this factor was 1.13 for PSCI and 1.07 for PSD. This means, using the example for PSCI, that the approximated RR will be biased by maximally 25% when converted from OR and 13% when converted from HR. While some uncertainty is introduced by this approach, it is still drastically less than that of interpreting OR or HR as RR without transformation. In this case the bias can be inflated up to 400% and 80%, respectively.[2]

Supplement 5: Exposure harmonization

- Continuous predictors of the same unit but of differently sized intervals (e.g., effect per 10-year increase in age) were transformed to be comparable where necessary
- Binary predictors were transformed to have the same reference group (e.g., sex)
- To make categorical variables (≥ 2 levels) comparable to continuous variables of the same predictor, an approach by Hamling[6] was applied for which the number of exposed/unexposed cases/controls, the effect estimate + confidence bounds, and the (approximate) dose level per category is required -> yields an estimated trend RR based on the entered dose
- If a study did not provide the 2x2 table information, but the OR and the total number of exposed/unexposed and total number of cases/controls, the 2x2 content could be derived by solving for a:
  *OR = (a * (total_unexposed – total_cases + a)) / ((total_exposed – a) * (total_cases – a))*
  and then the remaining cells
- For stroke severity, as many results as possible were harmonized to fit the scale per 1 point increase on NIHSS – some scales could be converted to NIHSS (per 1 point increase):
  - SSS (Scandinavian Stroke Scale) -> exponentiation by 2.326 & inversion of effect size[7]
  - CNS (Canadian Neurological Scale) -> exponentiation by ½ & inversion of effect size[8]
- If provided units were not interconvertible, but the mean and SD (or median and IQR) were available, a transformation to "per SD increase" was possible[9]

Supplement 6: Detection of outliers and influential studies

Studies were excluded as outliers or influential studies from sensitivity analyses detected by the methods[10] summarized below:

- **Basic outlier detection:** confidence interval of the individual study effect estimate does not overlap with the confidence interval of the pooled effect estimate
- **Influence analysis**[11]**:** detection of studies that exert a high impact on the pooled effect size (regardless of whether the study is also an outlier → influential studies can but don't have to be outliers and vice versa)
    - Baujat plot: plotting a study's influence on the pooled result and its contribution to overall heterogeneity (Cochran's Q)
    - Influence diagnostics: plots that display different influence diagnostics that indicate the studies that do and do not fit well in the applied meta-analysis model: 1. Externally Standardized Residuals, 2. DFFITS Value, 3. Cooks Distance, 4. Covariance Ratio, 5. Leave-One-Out τ^2 and Q Values, and 6. Hat Value and Study Weight
    - Leave-One-Out Meta-Analysis based on I^2
- **Graphic Display of Heterogeneity (GOSH-) plot analysis:** the same meta-analysis model is fitted to all possible subsets of the included studies (2^{k-1} possible study combinations)

Supplemental Table S1: criteria and tools for the diagnosis of cognitive impairment and dementia after stroke

Outcome: Post-stroke cognitive impairment

A) Screening test	Cut-off	References
MMSE	< 21	12
	< 24	13-20
	< 25	21-24
	< 26	25-29
	< 27	30-37
	< 28	38
MoCA	< 22	39-41
	< 23	27,42,43
	< 24	44,45
	< 25	28,46,47
	< 26	22,26,30,31,48-62
	< 27	63,64
CDR/CDR-SB	> 0	65,66
CAMCOG	< 80	67
ACE-R	< 82	68
AMT	< 8	69
TICS-m	< 14	70
	< 32	71,72
SIS	< 5	73
CASI	< 68	74
Abbreviated Mental Test	< 8	16
B) Diagnostic criterion	***Petersen criteria***	75-78
	O'Brien criteria	75
	Winblad criteria	79
	Gauthier criteria	80
	Criteria of the Canadian study of health and aging	81
	DSM-4	82
	NINDS-SCSN VCDIHS	83
	< - 1 SD on ≥ 2 tests in ≥ 1 domain	84
	impairment in ≥ 1 domain	30,85,86
	< 10^{th} percentile in > 2 tests in ≥ 1 domain	87
	< - 1.5 SD in ≥ 1 domain	31,88,89
	< - 1.5 in > 50% of tests in ≥ 1 domain	82,90
	< - 2 SD in ≥ 1 domain	91,92

Outcome: Post-stroke dementia

A) Screening test	Cut-off	References
MMSE	< 20	93
	< 22	74
	< 24	94,95
MoCA	< 21	96
	< 24	96
	< 26	97
CDR	> 0	98
R-CAMCOG	< 34	98
TICS-m	< 20	99
IQCODE	> 103	100,101
B) Diagnostic criterion	***DSM-3/DSM-3R***	93,102-109
	DSM-4/DSM-4-TR	31,67,75,76,80,84,87,95,101,104,110-117
	DSM-5	22,24,63,85,94,96,118,119
	NINDS-AIREN	25,75,81,83,100,104,105,110,114,120-123
	NINCDS-ADRDA	100,122
	ICD-9	99,124
	ICD-10	100,118,120,125,126
	NIA criteria for all-cause dementia	127
	< - 1.5 SD in ≥ 2 domains (of K-VCIHS-NP)	128

Supplemental Table S2: Articles excluded from the systematic review and reasons for exclusion

Excluded articles (references)	Reasons for exclusion
[129-198]	Continuous cognitive performance
[199-227]	Trajectories (decline or recovery) of cognitive performance
[177,228-238]	Domain-specific outcome/s
[239-250]	Baseline assessment not eligible
[251-261]	Study population not eligible
[246,262-268]	Follow-up duration < 3 months
[269-283]	Other

Supplemental Table S3: Articles excluded from the quantitative analysis and reasons for exclusion

Excluded articles (references)	Reason for exclusion
[12,22,43,63,67,74,88,93,103,109,110,113,114,118,121,284-298]	Unadjusted analysis/not adjusted for age or stroke severity/adjustment not clear
[29,35,46,51,59,60,66,112,299-309]	Only study on a specific predictor/none of the results could be included in pooled analysis

Supplemental Table S4: Articles excluded from the quantitative analysis and overlap with other eligible study

Excluded article (reference)	Overlap with article (reference)	Fully excluded	Full exclusion only due to overlap* (k = 17)	If partly included, in analysis/analyses of
Zietemann, 2018[310]	Georgakis, 2022[89]	☆	☆	
MacIntosh, 2021[311]	Ouk, 2020[312]	☆	☆	
Krawczyk, 2019[313]	Ouk, 202[312]	☆	☆	
Molad, 2019[314]	Ben Assayag, 2017[76]	·	·	WMH volume, infarct volume, lobar microbleeds, age, education, stroke severity, APOE E4 with PSCI
Hallevi, 2020[315]	Ben Assayag, 2017[76]	·	·	Working status with PSCI
Tene, 2018[290]	Ben Assayag, 2017[76]	☆	·	
Molad, 2017[291]	Ben Assayag, 2017[76]	☆	·	
Ben Assayag, 2017[309]	Ben Assayag, 2017[76]	☆	·	
Auriel, 2016[316]	Ben Assayag, 2017[76]	·	·	Depression with PSCI
Ben Assayag, 2015[317]	Ben Assayag, 2017[76]	☆	☆	
Wang, 2021[318]	Dong, 2021[39]	·	·	Carotid artery stenosis with PSCI and PSD
Ding, 2019[319]	Dong, 2021[39]	·	·	Diabetes with PSCI
Pasi, 2021[320]	Biffi, 2016[99]	·	·	Lacunes, deep CMBs, disseminated superficial siderosis with PSD
Desmond, 2002[321]	Desmond, 2000[105]	·	·	Baseline cognitive impairment with PSD
Moroney, 1997[322]	Desmond, 2000[105]	☆	☆	
Tatemichi, 1993[323]	Desmond, 2000[105]	·	·	Lacunar stroke with PSD
Ojagbemi, 2021[324]	Ojagbemi, 2021[123]	·	·	Pre-stroke cognitive impairment, age, diabetes with PSD
Lee, 2021[325]	Lee, 2021[92]	☆	☆	
Lee, 2021[326]	Lee, 2021[92]	☆	☆	
Lim, 2017[327]	Lim, 2018[91]	·	·	Education, pre-stroke cognitive impairment with PSD
Yatawara, 2020[328]	Chander, 2017[28]	·	·	Chronic lacunes with PSD
Chander, 2017[329]	Chander, 2017[28]	☆	☆	
Kandiah, 2016[27]	Chander, 2017[28]	☆	·	
Kandiah, 2011[330]	Chander, 2017[28]	·	·	Periventricular WMH, deep WMH with PSCI
Saini, 2014[331]	Zhao, 2021[82]	·	·	WMH severity, atrophy with PSCI
Dong, 2012[332]	Zhao, 2021[82]	☆	☆	
Yatawara, 2020[333]	Yang, 2015[115]	·	·	Deep microbleeds with PSD
Wong, 2016[334]	Yang, 2015[115]	☆	☆	
Mok, 2016[335]	Yang, 2015[115]	·	·	WMH, lacunes, APOE E4 with PSD
Shiekh, 2020[336]	Yang, 2020[126]	·	·	Ethnicity with PSD
Liu, 2020[292]	Gong, 2021[40]	☆	·	
Zhu, 2021[301]	Ge, 2020[46]	☆	·	
Zhong, 2021[337]	Ge, 2020[46]	·	·	TMAO with PSCI
Qian, 2020[302]	Ge, 2020[46]	☆	·	
Zhong, 2018[303]	Ge, 2020[46]	☆	·	
Zhu, 2019[304]	Ge, 2020[46]	☆	·	
Zhu, 2022[305]	Ge, 2020[46]	☆	·	
Sagnier, 2017[293]	Coutureau, 2021[56]	☆	·	
Munsch, 2016[306]	Coutureau, 2021[56]	☆	·	
Geng, 2017[307]	He, 2018[61]	☆	·	
Makin, 2015[294]	Makin, 2018[68]	☆	·	
Douiri, 2013[338]	Douiri, 2013[16]	☆	☆	

Patel, 2002[339]	Douiri, 2013[16]	·	·	Sex, socioeconomic status, smoking, alcohol, hypertension, diabetes, prior TIA, atrial fibrillation, IHD, urinary incontinence, dysphasia with PSCI
Ojala-Oksala, 2012[340]	Sibolt, 2013[108]	·	☆	Education with PSCI
Melkas, 2012[295]	Sibolt, 2013[108]	☆	·	
Allan, 2011[299]	Firbank, 2012[107]	☆	·	
Morris, 2011[308]	Firbank, 2012[107]	☆	·	
Pendlebury, 2011[296]	Pendlebury, 2019[95]	☆	·	
Kelly, 2022[341]	Pendlebury, 2019[95]	·	·	Chronic kidney disease with PSD
Pendlebury, 2020[342]	Pendlebury, 2019[95]	·	·	APOE E4 with PSD
Yang, 2007[343]	Zhou, 2004[117]	☆	☆	
Serrano, 2007[344]	Barba, 2000[104]	☆	☆	
Cordonnier, 2007[345]	Hénon, 2001[100]	☆	☆	
Cordoliani-Mackowiak, 2003[346]	Hénon, 2001[100]	☆	☆	
Pasquier, 2000[297]	Hénon, 2001[100]	☆	·	
Baum, 2007[347]	Tang, 2004[111]	·	·	Age, stroke severity, with PSCI
Tang, 2006[348]	Tang, 2004[111]	·	·	Sex, urinary incontinence, education, atrial fibrillation, cerebral atrophy, IQCODE with PSCI
Klimkowicz-Mrowiec, 2006[349]	Klimkowicz, 2005[101]	☆	☆	
Treves, 1997[288]	Bornstein, 1996[102]	☆	·	
Gur, 1994[289]	Bornstein, 1996[102]	☆	·	

Stars indicate full exclusion from the analysis.
* Articles not marked with a star in this column were also excluded from the meta-analysis because of other reasons, which can be taken from Table S3.

Supplemental Table S5: Characteristics of all 89 studies meeting inclusion criteria and included in the quantitative analysis.

	Geographical region	Population	Study type	Recruitment	Follow-up (months)*	Sample Size	Outcome
Bornstein et al (1996)[102]	Asia	IS, IE, no prior CI	HB, PC	1988-1990	up to 60	175	PSD
Kokmen et al (1996)[350]	North America	IS,IE, no prior dementia	HB, PC, PB	1960-1984	up to 300	971	PSD
Barba et al (2000)[104]	Europe	IS, HS	HB, PC	1994-1995	3	327	PSD
Desmond et al (2000)[105]	North America	IS	HB, PC	1988-1997	3	585	PSD
Hénon et al (2001)[100]	Europe	IS, HS, IE, no prior dementia	HB, PC	1995-1996	up to 36	202	PSD
Yamamoto et al (2002)[106]	Asia	LS, IE, no prior dementia	HB, PC	1987-1991	104.4	209	PSD
Lin et al (2003)[120]	Asia	IS, no prior dementia	HB, PC	1995-1999	3	352	PSD
Mok et al (2004)[65]	Asia	IS	HB, PC	2002	3	75	PSCI
Rasquin et al (2004)[77]	Europe	IS, no prior dementia	HB, PC	2000-2001	12.1	176	PSD, PSCI
Talelli et al (2004)[13]	Europe	IS, IE, no prior CI	HB, PC	NA	up to 12	208	PSCI
Tang et al (2004)[111]	Asia	IS, HS, no prior dementia	HB, PC	NA	3	280	PSD
Zhou et al (2005)[14]	Asia	IS, no prior dementia	HB, PC	1999-2000	3	546	PSD, PSCI
Klimkowicz et al (2005)[101]	Europe	IS, no prior dementia	HB, PC	2000-2001	3	114	PSD
Srikanth et al (2006)[84]	Australia & Oceania	IS, HS, IE	HB, PC	1998-1999	25.7	99	PSD, PSCI
Newman et al (2007)[38]	International	IS, fasting tHcy level > 25th percentile	HB, RCT post-hoc analysis	1996-2003	20.3	3680	PSCI
Saxena et al (2008)[69]	Asia	IS, HS	HB, PC	2002	6	200	PSCI
Delgado et al (2010)[351]	South America	IS, HS	HB, PC	2005-2006	up to 12	164	PSD, PSCI
Wagle et al (2010)[78]	Europe	IS, HS	HB, PC	2005-2006	13.4	152	PSCI
Liman et al (2011)[15]	Europe	IS, HS, IE, no prior dementia	PB, PC	1998-2006	up to 36	1379	PSCI
van Rijsbergen et al (2011)[98]	Europe	IS, HS, no prior CI	PB, nested case-control	NA	23	122	PSD
Brucki et al (2012)[25]	South America	IS, TIA	HB, PC	NA	up to 12	172	PSD, PSCI
Firbank et al (2012)[107]	Europe	IS, HS, no prior dementia	HB, PC	2000-2001	median 38.2	355	PSD
Zhang et al (2012)[30]	Asia	IS, HS, IE, no prior CI	HB, PC	2009-2010	3	577	PSCI
Bocti et al (2013)[26]	North America	IS, TIA, no prior dementia	HB, PC	2007-2011	3	451	PSCI
Douiri et al (2013)[16]	Europe	IS, HS, IE	PB/RB, PC	1995-2010	up to 180	2007	PSCI
Sibolt et al (2013)[108]	Europe	IS	HB, PC	1993-1995	3	486	PSD
Salvadori et al (2013)[80]	Europe	IS, HS	HB, PC	2009-2010	8.4	137	PSD, PSCI
Yu et al (2013)[87]	Asia	IS	RB, PC	2007-2008	3	620	PSD, PSCI
Chaudhari et al (2014)[81]	Asia	IS, HS, no prior dementia	HB, PC	2011-2013	up to 6	106	PSD, PSCI
Jacquin et al (2014)[31]	Europe	IS, HS, IE, no prior CI	HB, PC	2010-2014	3	271	PSD, PSCI
Lim et al (2014)[128]	Asia	IS, no prior CI	HB, retrospective nested case-control	2007-2011	16	104	PSD
Pavlovic et al (2014)[83]	Europe	LS, IE, no prior CI	HB, PC	2000-2007	47.5	294	PSD, PSCI
Tveiten et al (2014)[44]	Europe	HS, IE	HB, PC	2005-2009	median 45.6	50	PSCI
Huang et al (2015)[71]	Asia	IS, IE	HB, RC	2006-2010	69.6	446	PSCI
Kumral et al (2015)[75]	Asia	IS, HS, TIA	HB, PC	1998-2009	up to 60	9522	PSD, PSCI
Mellon et al (2015)[48]	Europe	IS	HB, PC	2011-2012	6	226	PSCI
Ursin et al (2015)[79]	Europe	IS, IE, no prior CI	HB, PC	2007-2008	up to 12	180	PSCI
Yang et al (2015)[115]	Asia	IS, HS, TIA, no prior dementia	HB, PC	2009-2010	up to 6	1013	PSD
Alexandrova et al (2016)[17]	Europe	IS, no prior dementia	HB, PC	2006-2009	up to 12	47	PSCI
Biffi et al (2016)[99]	North America	HS, no prior dementia	HB, PC	2006-2013	median 47.4	738	PSD
Caratozzolo et al (2016)[94]	Europe	IS, HS, no prior CI	HB, RC	2011	up to 12	105	PSD
Chen et al (2016)[90]	Asia	IS, no prior CI	HB, RC	2013	7.1	56	PSCI
Moulin et al (2016)[127]	Europe	HS, no prior dementia	HB, PC	2004-2009	median 72	264	PSD

Portegies et al (2016)[122]	Europe	stroke patients, no prior dementia	PB, PC	1990-2012	median 28.9	1237	PSD
Yamamoto et al (2016)[18]	Asia	IS, IE, no prior CI	HB, PC	2006-2008	49.2	249	PSCI
Arba et al (2017)[32]	International	IS, HS, IE, no prior dementia	RB, RC	NA	up to 36	5435	PSCI
Ben Assayag et al (2017)[76]	Asia	IS, TIA, IE, no prior CI	HB, PC	2008-2014	24	507	PSD, PSCI
Chander et al (2017)[28]	Asia	IS, no prior CI	HB, RC	2010-2014	3.3	445	PSCI
Li et al (2017)[19]	Asia	IS, IE, no prior CI	HB, RC	2013-2014	up to 12	382	PSCI
Mahon et al (2017)[49]	Australia & Oceania	IS, HS	PB, PC	2011-2012	48	499	PSCI
Nijsse et al (2017)[50]	Europe	IS, HS, no prior CI	HB, PC	2011-2013	up to 6	395	PSCI
You et al (2017)[21]	International	HS	HB, RCT post-hoc analysis	2005-2007	3	231	PSCI
Guo et al (2018)[73]	Asia	IS, no prior CI	HB, PC	2008-2012	up to 6	1371	PSCI
He et al (2018)[61]	Asia	IS, IE, no prior dementia	HB, PC	2013-2014	3	796	PSCI
Makin et al (2018)[68]	Europe	IS	PB, PC	2010-2012	up to 12	208	PSCI
Surawan et al (2018)[20]	Asia	IS, TIA, no prior dementia	HB, PC	2017	5.6	401	PSCI
Baccaro et al (2019)[70]	South America	IS, HS	HB, PC	2006-2014	up to 24	100	PSCI
Li et al (2019)[116]	Asia	IS, HS, TIA, no prior dementia	PB, RC	2000-2005	up to 120	8236	PSD
Liang et al (2019)[33]	Asia	IS, IE, no prior dementia	HB, RC	2010-2015	15	573	PSCI
Liu et al (2019)[24]	Asia	IS, no prior dementia	HB, PC	2013-2015	3	161	PSCI
Lu et al (2019)[52]	Asia	IS, IE, no prior CI	HB, PC	2018	up to 6	232	PSCI
Pendlebury et al (2019)[95]	Europe	IS, HS, TIA, IE	PB, PC	2002-2012	50.4	2305	PSD
Weng et al (2019)[45]	Asia	IS, no prior dementia	HB, PC	2017-2018	3	499	PSCI
Droś et al (2020)[96]	Europe	IS, HS, TIA, no prior dementia	HB, PC	NA	up to 12	691	PSD
Ettelt et al (2020)[53]	Europe	IS	RB,RC	NA	3	166	PSCI
Ge et al (2020)[46]	Asia	IS	HB, RCT post-hoc analysis	2009-2012	3	660	PSCI
Jia et al (2020)[34]	Asia	IS, IE, no prior CI	HB, RC	2013-2018	3	1019	PSCI
Ling et al (2020)[54]	Asia	IS, no prior dementia	HB, PC	2019	3	93	PSCI
Ouk et al (2020)[312]	North America	IS, IE, no prior dementia	RB, RC	2003-2013	67.2	23579	PSD
Prodjohardjono et al (2020)[97]	Asia	IS, IE, no prior CI	HB, PC	2018-2019	3	83	PSD
Wu et al (2020)[353]	Asia	IS	HB, PC	2014-2016	up to 36	487	PSCI
Yang et al (2020)[126]	Europe	IS, HS, no prior dementia	RB, RC	2006-2017	43.2	63959	PSD
Zhu et al (2020)[37]	Asia	IS, IE, no prior CI	RB, RC	2017	12	256	PSCI
Coutureau et al (2021)[56]	Europe	IS, no prior dementia	HB, PC	2012-2015	3	348	PSCI
Dong et al (2021)[39]	Asia	IS, no prior CI	HB, RC	2017-2018	up to 6	383	PSCI
Esmael et al (2021)[57]	Africa	IS, IE, no prior CI	HB, PC	2017-2019	3	150	PSCI
Gong et al (2021)[40]	Asia	IS, no prior CI	HB, PC	2017-2018	up to 12	269	PSCI
Lee et al (2021)[92]	Asia	IS, no prior dementia	HB, RC	2010-2015	3	345	PSCI
Ojagbemi et al (2021)[123]	Africa	IS, HS	HB, PC	2017-2019	up to 12	150	PSD
Wang et al (2021)[62]	Asia	IS, no prior CI	HB, PC	2017-2019	3	1694	PSCI
Zha et al (2021)[36]	Asia	IS, IE, no prior dementia	HB, PC	2012-2017	3	367	PSCI
Zhao et al (2021)[82]	Asia	Stroke patients	HB, PC	NA	up to 72	284	PSCI
Zhong et al (2021)[85]	Asia	IS, no prior CI	HB, PC	2018-2019	3	129	PSD, PSCI
Georgakis et al (2023)[89]	Europe	IS, HS, no prior dementia	HB, PC	2011-2019	11.6	666	PSCI
Munthe-Kaas et al (2022)[119]	Europe	Stroke patients	HB, PC	2015-2017	3	815	PSD, PSCI
Vlachos et al (2022)[86]	Europe	IS, HS, IE, no prior CI	HB, PC	2014-2016	12	127	PSCI
Yan et al (2022)[64]	Asia	IS, no prior CI	HB, PC	2019-2020	3	308	PSCI
Zhang et al (2022)[41]	Asia	IS, no prior CI	HB, PC	2018-2020	3	187	PSCI
Zhang et al (2022)[47]	Asia	IS, no prior CI	HB, PC	2020-2021	3	198	PSCI

*Follow-up time is given as arithmetic mean unless otherwise indicated. CI=cognitive impairment. HB=hospital-based. HS=hemorrhagic stroke. IE=index event. IS=ischemic stroke. NA=not applicable. PB=population-based. PC=prospective cohort. PSCI=post-stroke cognitive impairment. PSD=post-stroke dementia. RC=retrospective cohort. RCT=randomised controlled trial. tHcy=total homocysteine. TIA=transient ischemic attack.

Supplemental Table S6: Detailed characteristics of eligible studies included in the systematic review

	Demographic and clinical characteristics							Study characteristics				
Study (First author, year, reference)	**Country, recruitment period**	**Mean age (y)**	**Female (%)**	**Educational attainment (y)**	**baseline NIHSS**	**Patient characteristics**	**N**	**Setting, design**	**Mean follow-up (months)**	**Post-stroke outcome(s)**	**Outcome definition**	**Outcome ascertainment**	**Included in meta-analysis**
Ebrahim, 1985[12]	UK, NA	NA	NA	NA	NA	Stroke patients with or without pre-stroke cognitive impairment	463	Hospital-based, prospective cohort	6+	Cognitive impairment	MMSE < 21	screening	·
Loeb, 1992[109]	Italy, 1979-1984	65.1	17.6	NA	NA	First-ever lacunar stroke patients without pre-existing dementia	108	Hospital-based, prospective cohort	55.8	Dementia	DSM-3R	battery	·
Miyao, 1992[93]	Japan, 1984-1990	68.1	35.3	NA	NA	First-ever lacunar stroke patients without pre-existing dementia	215	Hospital-based, prospective cohort	27.2	Dementia	DSM-3R, MMSE < 20	screening	·
Bornstein, 1996[102]	Israel, 1988-1990	72.3	45.2	NA	NA	First-ever ischemic stroke patients without any cognitive impairment before stroke	175	Hospital-based, prospective cohort	60+	Dementia	DSM-3R	screening	☆
Kokmen, 1996[350]	USA, 1960-1984	NA	49.9	NA	NA	First-ever non-hemorrhagic stroke patients without pre-existing dementia	971	Hospital-based, prospective population-based	300+	Dementia	decline of intellectual and/or cognitive and social function that was irreversible with medical or psychiatric treatment; evidence of memory impairment; and dementia sufficiently important to impair age-, education-, and occupation-appropriate lifestyle	registry	☆

de Koning, 1998[103]	Netherlands, 1993-1996	69.2	40.1	8.7	NA	First-ever or recurrent stroke or TIA patients with or without pre-stroke cognitive impairment	284	Hospital-based, prospective cohort	9+	Dementia	DSM-3R	battery	·
Barba, 2000[104]	Spain, 1994-1995	69	47	NA	7 (CNS)	First-ever or recurrent ischemic or hemorrhagic stroke patients; exclusion of TIA, SAH, and stroke associated with other primary brain lesions (eg., tumors and trauma)	327	Hospital-based, prospective cohort	3	Dementia	DSM-4, NINDS-AIREN, DSM-3R	battery/proxies	☆
Desmond, 2000[105]	USA, 1988-1997	72	52.5	NA	6.6 (SSS)	First-ever or recurrent ischemic stroke patients	585	Hospital-based, prospective cohort	3	Dementia	DSM-3R, NINDS-AIREN	battery	☆
Hénon, 2001 (Lille stroke/ dementia study)[100]	France, 1995-1996	NA	NA	NA	NA	First-ever stroke patients without pre-existing dementia	202	Hospital-based, prospective cohort	36+	Dementia	ICD-10, IQCODE ≥ 104, NINCDS-ADRDA, NINDS-AIREN	battery/screening/proxies	☆
Madureira, 2001[110]	Portugal, 1995-1997	59	45.1	4.7	NA	Ischemic or hemorrhagic stroke patients without pre-existing dementia	237	Hospital-based, prospective cohort	3	Dementia	DSM-4, NINDS-AIREN	battery	·
Yamamoto, 2002[106]	Japan, 1987-1991	69.1	37.9	NA	NA	First-ever lacunar stroke patients without pre-existing dementia	209	Hospital-based, prospective cohort	104.4	Dementia	DSM-3R	battery/screening via telephone	☆
Lin, 2003[120]	Taiwan, 1995-1999	64.4	33.6	NA	3.6	First-ever or recurrent ischemic stroke patients without pre-existing dementia	352	Hospital-based, prospective cohort	3	Dementia	ICD-10, NINDS-AIREN	battery	☆
Mok, 2004[65]	China, 2002	70.7	48	4.9	4.9	First-ever or recurrent ischemic stroke patients	75	Hospital-based, prospective cohort	3	Cognitive impairment	CDR ≥ 1	screening	☆

Rasquin, 2004 (CODAS)[77]	Netherlands, 2000-2001	67.9	42.7	NA	NA	Ischemic stroke patients without pre-existing dementia	176	Hospital-based, prospective cohort	12.1	Dementia, cognitive impairment	amplified Petersen criteria	battery	☆
Talelli, 2004[13]	Greece, NA	66.2	40.9	79.5 % < 12 y	NA	First-ever ischemic stroke patients without any cognitive impairment before stroke	208	Hospital-based, prospective cohort	12+	Cognitive impairment	MMSE < 24	screening	☆
Tang, 2004[111]	China, NA	70.9	45.4	4.3	6.7	First-ever or recurrent ischemic or hemorrhagic stroke patients without pre-existing dementia; exclusion of TIA, subdural hematoma, SAH, history of central nervous system disease	280	Hospital-based, prospective cohort	3	Dementia	DSM-4 for vascular dementia	screening	☆
Zhou, 2005 (Chongquing stroke study)[14]	China, 1999-2000	67.6	47.2	NA	4.9	First-ever or recurrent ischemic stroke patients without pre-existing dementia	546	Hospital-based, prospective cohort	3	Dementia, Cognitive impairment	DSM-4; MMSE < 24	screening	☆
Klimkowicz, 2005[101]	Poland, 2000-2001	65.6	44.7	NA	48.9 (SSS)	Ischemic stroke patients without pre-existing dementia	114	Hospital-based, prospective cohort	3	Dementia	DSM-4, IQCODE ≥ 104	battery/proxies	☆
Martin-Ruiz, 2006 (MRC-COGFAST)[112]	UK, NA	80.4	45.1	NA	NA	Stroke patients without pre-existing dementia	195	Hospital-based, prospective cohort	24+	Dementia	DSM-4	screening	·
Srikanth, 2006 (NEMESIS)[84]	Australia, 1998-1999	66.9	NA	NA	NA	First-ever stroke patients	99	Hospital-based, prospective cohort	25.7	Dementia, cognitive impairment	DSM-4; > - 1 SD on ≥ 2 tests in ≥ 1 domain	battery	☆
Newman, 2007 (VISP)[38]	International, 1996-2003	66.3	37.5	NA	1.7	Ischemic stroke patients with a fasting tHcy level > 25th percentile	3680	Hospital-based, post-hoc analysis from RCT	20.3	Cognitive impairment	MMSE ≤ 27	screening	☆

Rowan, 2007[67]	UK, NA	79.4*	44.7	NA	NA	Ischemic or hemorrhagic stroke or TIA patients	170	Hospital-based, prospective cohort	27+	Dementia, cognitive impairment	DSM-4, CAMCOG < 80	screening	·
Saxena, 2008[69]	Singapore, 2002	71.5	46	NA	NA	First-ever or recurrent ischemic or hemorrhagic stroke patients	200	Hospital-based, prospective cohort	6	Cognitive impairment	AMT ≤ 7	screening	☆
Khedr, 2009[74]	Egypt, NA	57.7	33.3	NA	41.4 (SSS)	Ischemic or hemorrhagic stroke patients without any cognitive impairment before stroke	81	Hospital-based, prospective cohort	3	Dementia	DSM-4, MMSE ≤ 21, CASI ≤ 67	battery	·
Narasimhalu, 2009 (ESPRIT)[113]	Singapore, 1999-005	60	30	NA	NA	First-ever or recurrent ischemic stroke or TIA patients	362	Hospital-based, post-hoc analyisis from RCT	38.4	Dementia	DSM-4	battery	·
Delgado, 2010[351]	Chile, 2005-2006	72.2	42	9.2	5.7	First-ever or recurrent ischemic or hemorrhagic stroke patients; exclusion of TIA, SAH, juxtadural hematoma, other central nervous system disorders	164	Hospital-based, prospective cohort	12+	Dementia, cognitive impairment	NA	battery	☆
Gur, 2010[114]	International, NA	73.6	36.7	NA	12	First-ever ischemic stroke patients without any cognitive impairment before stroke	30	Hospital-based, prospective cohort	4.5	Dementia	DSM-4, NINDS-AIREN	screening	·
Wagle, 2010[78]	Norway, 2005-2006	75.9	46.2	11	4.5	First-ever or recurrent ischemic or hemorrhagic stroke patients	152	Hospital-based, prospective cohort	13.4	Cognitive impairment	Petersen criteria	battery	☆
Liman, 2011 (ESPro)[15]	Germany, 1998-2006	70.2	51.4	NA	NA	First-ever ischemic or hemorrhagic stroke patients without pre-existing dementia	1379	Population-based, prospective	36+	Cognitive impairment	MMSE < 24	screening	☆

Racić, 2011[121]	Bosnia and Herzegovina, NA	NA	NA	NA	NA	Ischemic or hemorrhagic stroke patients without pre-existing dementia	463	Hospital-based, prospective cohort	3	Dementia	NINDS-AIREN	battery	·
van Rijsbergen, 2011[98]	Netherlands, NA	75.1	42	4.6	6.1*	Ischemic or hemorrhagic stroke patients without any cognitive impairment before stroke	122	Hospital-based, nested case-control	23	Dementia	CDR ≥ 1, R-CAMCOG ≤ 33	battery	☆
Brucki, 2012[25]	Brazil, NA	67.8	47.1	3.5	NA	Ischemic stroke or TIA patients	172	Hospital-based, prospective cohort	12+	Dementia, cognitive impairment	NINDS-AIREN, MMSE < 26	screening	☆
Firbank, 2012[107]	UK, 2000-2001	79.8	53.8	NA	NA	First-ever stroke patients without pre-existing dementia	355	Hospital-based, prospective cohort	38.2*	Dementia	DSM-3R	battery	☆
Zhang, 2012[30]	China, 2009-2010	63.1	31.7	NA	NA	First-ever ischemic or hemorrhagic stroke patients without any cognitive impairment before stroke; exclusion of TIA and SAH	577	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 26 or MMSE < 27, confirmation by neuropsychological battery, impairment in ≥ 1 domain	battery	☆
Bocti, 2013[26]	Canada, 2007-2011	69.6	47.5	57.9 % < 12 y	NA	First-ever or recurrent ischemic stroke or TIA patients without pre-existing dementia	451	Hospital-based, prospective cohort	3	Cognitive impairment	MMSE < 26 and MoCA < 26	screening	☆
Douiri, 2013[16]	UK, 1995-2010	68.9	46.7	NA	NA	First-ever ischemic or hemorrhagic stroke patients, including SAH (3.3%)	2007	Prospective registry/ population-based	180+	Cognitive impairment	MMSE < 24 or abbreviated mental test < 8	screening	☆
Sibolt, 2013 (SAM)[108]	Finnland, 1993-1995	72*	49.4	NA	NA	Ischemic stroke patients	486	Hospital-based, prospective cohort	3	Dementia	DSM-3	battery	☆

Salvadori, 2013[80]	Italy, 2009-2010	68.2	33	9.2	3.6	First-ever or recurrent ischemic or hemorrhagic stroke patients	137	Hospital-based, prospective cohort	8.4	Dementia, cognitive impairment	DSM-4, Gauthier criteria	battery	☆
Yu, 2013 (KSR)[87]	South Korea, 2007-2008	64	38.7	NA	4.2	First-ever or recurrent ischemic stroke patients	620	Registry-based, prospective cohort	3	Dementia, cognitive impairment	DSM-4, score < 10th percentile in > 2 tests in ≥ 1 domain	battery	☆
Chaudhari, 2014[81]	India, 2011-2013	59.4	26.5	8*	5.9*	First-ever or recurrent ischemic or hemorrhagic stroke patients without pre-existing dementia; exclusion of SAH	106	Hospital-based, prospective cohort	6+	Dementia, cognitive impairment	NINDS-AIREN, criteria of the Canadian Study of Health and Aging	battery	☆
Jacquin, 2014[31]	France, 2010-2012	66.1	44.1	NA	3*	First-ever ischemic or hemorrhagic stroke patients without any cognitive impairment before stroke; exclusion of SAH	271	Hospital-based, prospective cohort	3	Dementia, cognitive impairment	DSM-4, MMSE ≤ 26 and MoCA < 26, in case of discordance confirmation by neuropsychological battery (< - 1.5 SD in ≥ 1 domain)	battery/screening	☆
Lim, 2014[128]	South Korea, 2007-2011	69.1	38.5	9.2	2.7	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	104	Hospital-based, retrospective nested case-control	16	Dementia	< - 1.5 SD in ≥ 2 domains of K-VCIHS-NP, K-IADL ≥ 0.43	battery	☆
Pavlovic, 2014[83]	Serbia, 2000-2007	62.2	53.7	11.8	NA	First-ever lacunar stroke patients without any cognitive impairment before stroke	294	Hospital-based, prospective cohort	47.5	Dementia, cognitive impairment	NINDS-AIREN, NINDS-SCSN VCDIHS	battery	☆
Tveiten, 2014[44]	Norway, 2005-2009	70.8	52	NA	NA	First-ever hemorrhagic stroke patients; exclusion of ICH related to trauma, tumour, ruptured aneurysm, or thrombolytic treatment, and isolated intraventricular hemorrhage	50	Hospital-based, prospective cohort	45.6*	Cognitive impairment	MoCA < 24	screening	☆

Huang, 2015[71]	China, 2006-2010	41.2	30.3	10.7	5.9	First-ever ischemic stroke patients	446	Hospital-based, retrospective cohort	69.6	Cognitive impairment	TICS-m < 32	screening via telephone	☆
Kumral, 2015[75]	Turkey, 1998-2009	66.2	43.4	NA	NA	Ischemic or hemorrhagic stroke or TIA patients	9522	Hospital-based, prospective cohort	60+	Dementia, cognitive impairment	DSM-4 & NINDS-AIREN, Petersen & O'Brien citeria	battery	☆
Mellon, 2015 (ASPIRE-S)[48]	Ireland, 2011-2012	68.1	41.1	NA	53.2* (SSS)	First-ever or recurrent ischemic stroke patients	226	Hospital-based, prospective cohort	6	Cognitive impairment	MoCA < 26	screening	☆
Renjen, 2015[298]	India, NA	61.8	36	NA	NA	Ischemic or hemorrhagic stroke patients	50	Hospital-based, prospective cohort	12+	Dementia, cognitive impairment	DSM, PGI BBD > 30; PGI BBD 18-29	battery	·
Ursin, 2015[79]	Norway, 2007-2008	72.1	48.1	NA	4.3	First-ever stroke patients without any cognitive impairment before stroke	180	Hospital-based, prospective cohort	12+	Mild cognitive impairment	criteria defined by Winblad, 2004[352]	battery	☆
Yang, 2015 (STRIDE)[115]	China, 2009-2010	69.2	44.3	5.6	NA	First-ever or recurrent ischemic or hemorrhagic stroke or TIA patients without pre-existing dementia	1013	Hospital-based, prospective cohort	6+	Dementia	DSM-4	battery	☆
Alexandrova, 2016[17]	Bulgaria, 2006-2009	63*	44.7	NA	5*	First-ever or recurrent ischemic stroke patients without pre-existing dementia	47	Hospital-based, prospective cohort	12+	Cognitive impairment	MMSE < 24	screening	☆
Biffi, 2016[99]	USA, 2006-2013	74.3	48	NA	NA	First-ever or recurrent hemorrhagic stroke patients without pre-existing dementia; exclusion of ICH related to trauma, conversion of an ischemic infarct, rupture of a vascular malformation or aneurysm, or tumour	738	Hospital-based, prospective cohort	47.4*	Dementia	ICD-9, TICS-m < 20	screening/registry	☆

Caratozzolo, 2016[94]	Italy, 2011	67.7	37.1	7.7	5.8	First-ever or recurrent ischemic or hemorrhagic stroke patients without any cognitive impairment before stroke	105	Hospital-based, retrospective cohort	12+	Dementia	DSM-5, Itel-MMSE < 24, ADL > 1 decrease	screening	☆
Chen, 2016[90]	China, 2013	63.8	37.5	9.2	3.9	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	56	Hospital-based, retrospective cohort	7.1	Cognitive impairment	< -1.5 in more than 50% of tests in ≥ 1 domain	battery	☆
Moulin, 2016 (PITCH)[127]	France, 2004-2009	67.5*	45.9	NA	7.9	First-ever or recurrent hemorrhagic stroke patients without pre-existing dementia; exclusion of pure intraventricular hemorrhage, ICH resulting from intracranial vascular malformation, intracranial venous thrombosis, trauma, tumour, or hemorrhagic transformation within an infarct	264	Hospital-based, prospective cohort	72*	Dementia	National Institute on Aging - Alzheimer's Association criteria for all-cause dementia	battery	☆
Portegies, 2016 (Rotterdam Study)[122]	Netherlands, 1990-2012	79.9*	60.4	NA	NA	Stroke patients without pre-existing dementia	1237	Population-based, prospective cohort	28.9*	Dementia	NINDS-AIREN, NINCDS-ADRDA	registry	☆
Yamamoto, 2016[18]	Japan, 2006-2008	73.3	34.9	NA	NA	First-ever ischemic stroke patients without any cognitive impairment before stroke	249	Hospital-based, prospective cohort	49.2	Cognitive impairment	MMSE < 24	screening	☆
Arba, 2017 (VISTA)[32]	International, NA	62.6	36	NA	NA	First-ever ischemic or hemorrhagic stroke or TIA patients without pre-existing dementia; exclusion of SAH	5435	Registry-based, retrospective cohort	36+	Cognitive impairment	MMSE ≤ 26	screening/registry	☆

Ben Assayag, 2017 (TABASCO)[76]	Israel, 2008-2014	67.4	40.6	13.1	1.9*	First-ever ischemic stroke or TIA patients without any cognitive impairment before stroke	507	Hospital-based, prospective cohort	24	Dementia, cognitive impairment	DSM-4-TR, modified Petersen criteria: ≤ - 1.5 SD in ≥ 1 domain on MoCA	battery	☆
Chander, 2017 (SISCO)[28]	Singapore, 2010-2014	61.3	33.7	6.1	NA	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	445	Hospital-based, retrospective cohort	3.3	Cognitive impairment	MMSE < 26 or MoCA < 25	screening	☆
Li, 2017[19]	China, 2013-2014	65.2	49	NA	NA	First-ever ischemic stroke patients without any cognitive impairment before stroke	382	Hospital-based, retrospective cohort	12+	Cognitive impairment	MMSE < 24	screening	☆
Mahon, 2017 (ARCOS-IV)[49]	New Zealand, 2011-2012	67.9	47.1	NA	NA	First-ever or recurrent ischemic or hemorrhagic stroke patients; including SAH (7%)	499	Population-based, prospective cohort	48	Cognitive impairment	MoCA < 26	screening/registry	☆
Nijsse, 2017 (Restore4Stroke)[50]	Netherlands, 2011-2013	66.5	36.7	NA	2.5	First-ever or recurrent ischemic or hemorrhagic stroke patients without any cognitive impairment before stroke	395	Hospital-based, prospective cohort	6+	Cognitive impairment	MoCA < 26	screening	☆
Shih, 2017[124]	Taiwan, 2000-2004	66.5	43.2	NA	NA	First-ever ischemic or hemorrhagic stroke patients	11220	Registry-based, retrospective cohort	120+	Dementia	ICD-9	registry	·
You, 2017 (INTERACT1)[21]	International, 2005-2007	62.3	35.5	NA	8*	First-ever or recurrent hemorrhagic stroke patients; exclusion of ICH secondary to a structural cerebral abnormality (e.g., arteriovenous malformation, intracranial aneurysm, or tumour)	231	Hospital-based, post-hoc analysis from RCT	3	Cognitive impairment	MMSE ≤ 24	screening	☆

Guo, 2018[73]	China, 2008-2012	63.6	43.5	10.7	6.8	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	1371	Hospital-based, prospective cohort	6+	Cognitive impairment	SIS ≤ 4	screening	☆
He, 2018[61]	China, 2013-2014	63.2	46.2	NA	11.5	First-ever ischemic stroke patients without pre-existing dementia	796	Hospital-based, prospective cohort	3+	Cognitive impairment	MoCA < 26	screening	☆
Lim, 2018[91]	South Korea, 2006-2015	63	35.3	11.2	2*	Ischemic stroke patients without any cognitive impairment before stroke	354	Registry-based, retrospective cohort	3	Cognitive impairment	K-VCIHS-NP < -2 SD in ≥ 1 domain	battery	·
Makin, 2018[68]	UK, 2010-2012	65.7*	38.4	10.8*	1.9*	Ischemic stroke patients	208	Population-based, prospective cohort	12+	Cognitive impairment	ACE-R < 82	screening/medical records	☆
Oh, 2018[285]	SouthKorea, 2015-2017	64.8	17.3	NA	NA	First-ever or recurrent ischemic or hemorrhagic stroke patients	52	Hospital-based, prospective cohort	NA	Mild cognitive impairment	MCVI assessment tool < 23	screening	·
Salihović, 2018[118]	Bosnia and Herzegovina, 2011-2012	65.5	37.5	NA	NA	Stroke patients without any cognitive impairment before stroke	275	Hospital-based, prospective cohort	12+	Dementia	DSM-5, ICD-10	battery	·
Surawan, 2018[20]	Thailand, 2017	64.2	46.1	NA	2.1*	First-ever or recurrent ischemic stroke or TIA patients without pre-existing dementia	401	Hospital-based, prospective cohort	5.6	Cognitive impairment	MMSE ≤ 23	screening	☆
Baccaro, 2019 (EMMA)[70]	Brazil, 2006-2014	62	43	NA	NA	First-ever or recurrent ischemic or hemorrhagic stroke patients; exclusion of lesion in both hemispheres, TIA, SAH, Parkinson's disease, tumour, subdural hematoma, and multiple sclerosis	100	Hospital-based, prospective cohort	24+	Cognitive impairment	TICS-m < 14	screening via telephone	☆

Chaurasia, 2019[22]	India, 2015-2017	64.2	26.5	NA	NA	Ischemic or hemorrhagic stroke patients	200	Hospital-/registry-based, prospective cohort	6	Cognitive impairment	DSM-5, MMSE ≤ 24, MoCA < 26	screening	·
Gong, 2019[23]	China, 2016-2018	57.3	30.4	NA	12.5* (GCS)	Ischemic stroke patients without pre-existing dementia	92	Hospital-based, retrospective cohort	3	Cognitive impairment	MMSE ≤ 24	screening	·
Hou, 2019[51]	China, 2018-2019	66.4	46.4	59.8 % < 12 y	5*	First-ever ischemic stroke patients without pre-existing dementia	285	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 26	screening	·
Li, 2019[116]	Taiwan, 2000-2005	66.5	43	NA	NA	Ischemic or hemorrhagic stroke or TIA patients without pre-existing dementia; exclusion of trauma and tumour	8236	Population-based, retrospective cohort	120+	Dementia	DSM-4	registry	☆
Liang, 2019[33]	China, 2010-2015	66	44.1	6*	3*	First-ever ischemic stroke patients without pre-existing dementia	573	Hospital-based, retrospective cohort	15	Cognitive impairment	MMSE ≤ 26	screening	☆
Liu, 2019[24]	China, 2013-2015	60.7	33.6	4.7*	2.3*	First-ever or recurrent ischemic stroke patients without pre-existing dementia	161	Hospital-based, prospective cohort	3	Cognitive impairment	DSM-5, MMSE ≤ 24	screening	☆
Lu, 2019[52]	China, 2018	65.4	35.2	9	3.6	First-ever ischemic stroke patients without any cognitive impairment before stroke	232	Hospital-based, prospective cohort	6+	Cognitive impairment	MoCA < 26	screening	☆
Pendlebury, 2019[95]	UK, 2002-2012	74.4	51	67.1 % < 12 y	3.2	First-ever or recurrent ischemic or hemorrhagic stroke or TIA patients	2305	Population-based, prospective	50.4	Dementia	MMSE < 24 & remained for other FU visits, DSM-4	screening/medical records/registry	☆

Weng, 2019[45]	China, 2017-2018	67.8*	37.8	NA	2*	Ischemic stroke patients without pre-existing dementia	499	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 24	screening	☆
Broersen, 2020 (PROSCIS-B)[72]	Germany, NA	67	38	NA	3.4*	Ischemic stroke patients without pre-existing dementia	555	Hospital-based, prospective cohort	12+	Cognitive impairment	TICS-m < 32	screening via telephone	·
Droś, 2020 (PROPOLIS)[96]	Poland, NA	68*	49.7	12*	4*	First-ever or recurrent ischemic or hemorrhagic stroke or TIA patients without pre-existing dementia	691	Hospital-based, prospective cohort	12+	Dementia	DSM-5; MoCA ≤ 20 at 3 month FU; MoCA ≤ 23 at 12 month FU; IQCODE ≥ 4.0 through proxies if MoCA not possible	battery/screening	☆
Ettelt, 2020 (GSR-ET)[53]	Germany, NA	67.8	43.4	NA	11.2	Ischemic stroke patients	166	Registry-based, retrospective cohort	3	Cognitive impairment	MoCA < 26	screening/registry	☆
Ge, 2020 (CATIS)[46]	China, 2009-2012	59.9	30.8	6.9	4*	Ischemic stroke patients	660	Hospital-based, post-hoc analyisis from RCT	3	Cognitive impairment	MoCA < 25	screening	☆
Jia, 2020[34]	China, 2013-2018	64	47.9	3.9*	2.5*	First-ever ischemic stroke patients without any cognitive impairment before stroke	1019	Hospital-based, retrospective cohort	3	Cognitive impairment	MMSE ≤ 26	screening	☆
Ling, 2020[54]	China, 2019	69.5	33.3	NA	2.1*	First-ever or recurrent ischemic stroke patients without pre-existing dementia	93	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 26	screening	☆

Mao, 2020[55]	China, 2016-2018	69.4	44.1	NA	5.9	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	195	Hospital-based, prospective cohort	12+	Cognitive impairment	MoCA < 26	screening	·
Meng, 2020[29]	China, 2013-2015	62.8	34	6*	2*	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	920	Hospital-based, prospective cohort	54	Cognitive impairment	MMSE < 26, confirmation by CDR & ADAS-cog	battery	·
Myint, 2020[125]	UK, 2003-2015	75.9	49.8	NA	NA	First-ever or recurrent ischemic or hemorrhagic stroke patients without pre-existing dementia	7454	Hospital-based, prospective cohort	44.4	Dementia	ICD-10	registry	·
Ouk, 2020[312]	Canada, 2003-2013	70.6	46.5	NA	8.2 (CNS)	First-ever ischemic stroke patients without pre-existing dementia	23579	Registry-based, retrospective cohort	67.2	Dementia	algorithm, registry-based	registry	☆
Prodjohardjono, 2020[97]	Indonesia, 2018-2019	60.5	37.5	12*	NA	First-ever ischemic stroke patients without any cognitive impairment before stroke	83	Hospital-based, prospective cohort	3	Dementia	MoCA-INA < 26	screening	☆
Wu, 2020[353]	China, 2014-2016	71.5	50.5	NA	NA	First-ever or recurrent ischemic stroke patients	487	Hospital-based, prospective cohort	36+	Cognitive impairment	NA	screening	☆
Yang, 2020[126]	UK, 2006-2017	75*	49.2	NA	NA	First-ever ischemic or hemorrhagic stroke patients without pre-existing dementia	63959	Registry-based, retrospective cohort	43.2	Dementia	ICD-10	registry	☆

Zhu, 2020[37]	China, 2017	67.1	45.7	9.4	5.3*	First-ever ischemic stroke patients without any cognitive impairment before stroke	256	Registry-based, retrospective cohort	12	Cognitive impairment	MMSE ≤ 26	screening	☆
Coutureau, 2021 (Brain before Stroke)[56]	France, 2012-2015	67.5	36.5	NA	4*	Ischemic stroke patients without pre-existing dementia	348	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 26	screening	☆
Cova, 2021[354]	Italy, 2018-2019	76.2	51.4	8.6	7.1	Ischemic or hemorrhagic stroke patients	251	Hospital-based, prospective cohort	12.8	Cognitive impairment	[354]	screening	·
Dong, 2021[39]	China, 2017-2018	63*	24.5	NA	11*	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	383	Hospital-based, retrospective cohort	6+	Cognitive impairment	MoCA < 22	screening	☆
Esmael, 2021[57]	Egypt, 2017-2019	60.7	47.3	NA	14.1	First-ever ischemic stroke patients without any cognitive impairment before stroke	150	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 26	screening	☆
Gong, 2021[40]	China, 2017-2018	62.2	28.9	7	1.9	Ischemic stroke patients without any cognitive impairment before stroke	269	Hospital-based, prospective cohort	12+	Cognitive impairment	MoCA < 22	screening	☆
Lee, 2021[92]	South Korea, 2010-2015	63	35.7	11.4	2*	Ischemic stroke patients without pre-existing dementia	345	Hospital-based, retrospective cohort	3	Cognitive impairment	z-score of < -2 in ≥ 1 domain	battery/registry	☆
Li, 2021[58]	China, 2014-2016	65.3	53.1	NA	NA	Stroke patients	322	Hospital-based, retrospective cohort	34	Cognitive impairment	MoCA < 26	screening/medical records	·

Li, 2021 (ICONS)[42]	China, 2015-2018	61	26.7	NA	1.6	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	1070	Hospital-based, prospective cohort	12+	Cognitive impairment	MoCA < 23	screening	·
Ojagbemi, 2021[123]	Nigeria, 2017-2019	60.2	40.7	9.1	8.1 (SLS)	First-ever or recurrent ischemic or hemorrhagic stroke patients	150	Hospital-based, prospective cohort	12+	Dementia	NINDS-AIREN	battery	☆
Shan, 2021[35]	China, 2020-2021	66.5	45.3	63 % < 12 y	5*	First-ever ischemic stroke patients without any cognitive impairment before stroke	276	Hospital-based, prospective cohort	3	Cognitive impairment	MMSE ≤ 26	screening	·
Wang, 2021[59]	China, 2018-2020	64.6	40.4	9.5	6*	First-ever ischemic stroke patients without any cognitive impairment before stroke	416	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 26	screening	·
Wang, 2021[62]	China, 2017-2019	64*	47.3	NA	4*	Ischemic stroke patients without any cognitive impairment before stroke	1694	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 26	screening	☆
Yuan, 2021[63]	China, 2016-2019	66.1	48.2	8.1	NA	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	376	Hospital-based, prospective cohort	12+	Cognitive impairment	DSM-5, development of symptoms within 3-6 months, lasting for at least 6 months, MoCA ≤ 26 points	screening	·
Zha, 2021[36]	China, 2012-2017	61.8	38.3	NA	2.8	First-ever ischemic stroke patients without pre-existing dementia	367	Hospital-based, prospective cohort	3	Cognitive impairment	MMSE ≤ 26	screening	☆

Zhao, 2021[82]	Singapore, NA	60.9	29.1	7.8	1.4	First-ever or recurrent stroke patients	284	Hospital-based, prospective cohort	72+	Cognitive impairment	DSM-4, < -1.5 SD in at least 50% of tests in ≥ 1 domain	battery	☆
Zhong, 2021[85]	China, 2018-2019	57.2	33	NA	2*	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	129	Hospital-based, prospective cohort	3	Dementia, cognitive impairment	DSM-5, PSCI-ND, impairment in ≥ 1 domain; independence in I-ADL	battery	☆
Gao, 2022[60]	China, NA	65.5	65.5	10.2	13	Hemorrhagic stroke patients without pre-existing dementia	353	Hospital-based, retrospective cohort	3	Cognitive impairment	MoCA < 26	screening	·
Georgakis, 2023 (DEDEMAS/ DEMDAS)[89]	Germany, 2011-2019	67.9	33.3	13*	2*	First-ever or recurrent ischemic or hemorrhagic stroke patients without pre-existing dementia; exclusion of patients with venous thrombosis, traumatic cerebral hemorrhage, ICH because of a vascular malformation, or purely meningeal or intraventricular hemorrhage	666	Hospital-based, prospective cohort	11.6	Cognitive impairment	z-score of < -1.5 in ≥ 1 cognitive domain	battery	☆
Huang, 2022[66]	Taiwan, 2015-2018	58.8	28.7	NA	3.3*	First-ever ischemic stroke patients without any cognitive impairment before stroke	173	Hospital-based, prospective cohort	12	Cognitive impairment	CDR-SB > 0	screening	·
Li, 2022[43]	China, 2019-2020	65.1	50	NA	NA	Ischemic stroke patients without any cognitive impairment before stroke	80	Hospital-based, retrospective cohort	3	Cognitive impairment	MoCA < 23	screening	·
Munthe-Kaas, 2022 (Nor-COAST)[119]	Norway, 2015-2017	71.6	43	12.5	3	Stroke patients	815	Hospital-based, prospective cohort	3	Dementia, cognitive impairment	DSM-5, ≥ 1.5 SD below normative mean in ≥ 1 domain	battery	☆

Vlachos, 2022[86]	Norway, 2014-2016	55.7	22.8	15.3	0*	First-ever ischemic or hemorrhagic stroke patients without any cognitive impairment before stroke	127	Hospital-based, prospective cohort	12	Cognitive impairment	impairment (1-2 SD below norms) in ≥ 1 domain	battery	☆
Yan, 2022[64]	China, 2019-2020	60.4	31	8.2	1.9*	Ischemic stroke patients without any cognitive impairment before stroke	308	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA ≤ 26	screening	☆
Zhang, 2022[41]	China, 2018-2020	56*	20.9	7.4*	2*	First-ever or recurrent ischemic stroke patients without any cognitive impairment before stroke	187	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 22	screening	☆
Zhang, 2022[47]	China, 2020-2021	65.7	41.9	NA	5*	First-ever ischemic stroke patients without any cognitive impairment before stroke	198	Hospital-based, prospective cohort	3	Cognitive impairment	MoCA < 25	screening	☆

Values are by default provided as the arithmetic mean
*, median; $^{+}$, maximum follow-up
Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; ADL, Activities of Daily Living; ADRDA, Alzheimer's Disease and Related Disorders Association; AIREN, Association Internationale pour la Recherche et l'Enseignement en Neurosciences; CAMCOG, Cambridge Cognition Examination; CASI, Cognitive Abilities Screening Instrument; CDR, Clinical Dementia Rating Scale; CNS, Canadian Neurological Scale; DEDEMAS/DEMDAS, Determinants of Dementia After Stroke Study; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; K-VCIHS-NP, Korean version of the Vacular Cognitive Impairment Harmonization Standards neuropsychological; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NINCDS, National Institute of Neurological and Communicative Disorders Association; NINDS, National Institute of the Neurological Disorders and Stroke; Nor-COAST, Norwegian Cognitive Impairment After Stroke Study; PGI-BBD, PGI Battery of Brain Dysfunction; SAH, subarachnoid hemorrhage; SD, standard deviation; TIA, transient ischemic attack; TICS-m, modified Telephone Interview for Cognitive Function

Supplemental Table S7: Quality ratings for studies included in the quantitative analysis using a modified 8-pt. version of the Newcastle Ottawa Scale

Study	Selection			Comparability		Outcome			Total
	Representative-ness of exposed cohort	Representative-ness of unexposed cohort	Outcome not present at beginning of study	Analysis adjusted for age	Analysis adjusted for stroke severity	Outcome assessment	Follow-up length	Adequacy of follow-up	
Bornstein, 1996[102]	·	☆	☆	☆	·	☆	☆	·	6
Kokmen, 1996[350]	☆	☆	☆	☆	·	·	☆	·	5
Barba, 2000[104]	·	☆	☆	☆	☆	☆	·	☆	6
Desmond, 2000[105]	·	☆	·	☆	·	☆	·	·	3
Hénon, 2001[100]	·	☆	☆	☆	☆	☆	☆	☆	7
Yamamoto, 2002[106]	·	☆	☆	☆	·	☆	☆	·	5
Lin, 2003[120]	·	☆	☆	☆	☆	☆	·	·	5
Mok, 2004[65]	·	☆	☆	☆*	☆	☆	·	☆	5
Rasquin, 2004[77]	·	☆	☆	☆	·	☆	☆	·	5
Talelli, 2004[13]	·	☆	☆	☆	·	☆	☆	·	5
Tang, 2004[111]	·	☆	☆	☆	☆	☆	·	·	5
Zhou, 2005[14]	·	☆	☆	☆	·	☆	·	·	4
Klimkowicz, 2005[101]	·	☆	☆	☆	☆	☆	·	☆	6
Srikanth, 2006[84]	☆	☆	·	☆	·	☆	☆	·	5
Newman, 2007[38]	·	☆	·	☆	·	☆	☆	☆	5
Saxena, 2008[69]	·	☆	·	☆	·	☆	·	·	3
Delgado, 2010[351]	·	☆	☆	☆	·	☆	☆	·	5
Wagle, 2010[78]	·	☆	☆	☆	☆	☆	☆	·	6
Liman, 2011[15]	☆	☆	☆	☆	☆	☆	☆	·	7
van Rijsbergen, 2011[98]	·	☆	☆	☆	·	☆	☆	·	5
Brucki, 2012[25]	·	☆	·	☆*	☆	☆	·	·	3
Firbank, 2012[107]	·	☆	☆	☆	·	☆	☆	·	5
Zhang, 2012[30]	·	☆	☆	☆	·	☆	·	·	4
Bocti, 2013[26]	·	☆	☆	☆	☆	☆	·	·	5
Douiri, 2013[16]	☆	☆	·	☆	·	☆	☆	·	5
Sibolt, 2013[108]	☆	☆	☆	☆	·	☆	·	·	5
Salvadori, 2013[80]	·	☆	☆	☆	☆	☆	·	·	5
Yu, 2013[87]	·	☆	·	☆	☆	☆	·	·	4
Chaudhari, 2014[81]	·	☆	☆	☆*	☆	☆	·	☆	5
Jacquin, 2014[31]	·	☆	☆	☆	·	☆	·	·	4
Lim, 2014[128]	·	☆	☆	☆	·	☆	☆	·	5
Pavlovic, 2014[83]	·	☆	☆	☆	·	☆	☆	·	5
Tveiten, 2014[44]	·	☆	·	☆	·	☆	☆	☆	5
Huang, 2015[71]	·	☆	·	☆	·	☆	☆	☆	5
Kumral, 2015[75]	·	☆	·	☆	☆	☆	☆	·	5
Mellon, 2015[48]	·	☆	·	☆	☆	☆	·	·	4

Ursin, 2015[79]	·	☆	☆	☆	☆	☆	☆	☆	7
Yang, 2015[115]	·	☆	☆	☆	·	☆	·	·	4
Alexandrova, 2016[17]	·	☆	☆	☆	·	☆	☆	·	5
Biffi, 2016[99]	·	☆	☆	☆	·	☆	☆	☆	6
Caratozzolo, 2016[94]	·	☆	☆	☆	·	☆	☆	·	5
Chen, 2016[90]	·	☆	☆	☆	·	☆	·	·	4
Moulin, 2016[127]	·	☆	☆	☆	☆	☆	☆	☆	7
Portegies, 2016[122]	☆	☆	☆	☆	·	☆	☆	·	6
Yamamoto, 2016[18]	·	☆	☆	☆	·	☆	☆	·	5
Arba, 2017[32]	·	☆	☆	☆	·	☆	☆	·	5
Ben Assayag, 2017[76]	·	☆	☆	☆	☆	☆	☆	·	6
Chander, 2017[28]	·	☆	☆	☆	·	☆	·	·	4
Li, 2017[19]	·	☆	☆	☆	·	☆	☆	·	5
Mahon, 2017[49]	☆	☆	·	☆	·	·	☆	☆	5
Nijsse, 2017[50]	·	☆	☆	☆	☆	☆	·	·	5
You, 2017[21]	·	☆	·	☆	☆	☆	·	·	4
Guo, 2018[73]	·	☆	☆	☆	☆	☆	·	☆	6
He, 2018[61]	·	☆	☆	☆	☆	☆	·	☆	6
Makin, 2018[68]	☆	☆	·	☆	·	☆	☆	·	5
Surawan, 2018[20]	·	☆	☆	☆	☆	☆	·	·	5
Baccaro, 2019[70]	·	☆	·	☆	·	☆	☆	·	4
Li, 2019[116]	☆	☆	☆	☆	·	·	☆	·	5
Liang, 2019[33]	·	☆	☆	☆	·	☆	☆	·	5
Liu, 2019[24]	·	☆	☆	☆	☆	☆	·	·	5
Lu, 2019[52]	·	☆	☆	☆	·	☆	·	☆	5
Pendlebury, 2019[95]	☆	☆	·	☆	☆	☆	☆	☆	7
Weng, 2019[45]	·	☆	☆	☆	☆	☆	·	·	5
Droś, 2020[96]	·	☆	☆	☆	☆	☆	·	·	5
Ettelt, 2020[53]	·	☆	·	☆	☆	·	·	·	3
Ge, 2020[46]	·	☆	·	☆	☆	☆	·	☆	5
Jia, 2020[34]	·	☆	☆	☆	☆	☆	·	·	5
Ling, 2020[54]	·	☆	☆	☆	☆	☆	·	·	5
Ouk, 2020[312]	☆	☆	☆	☆	☆	·	☆	·	6
Prodjohardjono, 2020[97]	·	☆	☆	☆	☆	☆	·	·	5
Wu, 2020[353]	·	☆	·	☆	·	☆	☆	·	4
Yang, 2020[126]	☆	☆	☆	☆	·	·	☆	·	5
Zhu, 2021[301]	·	☆	☆	☆	☆	☆	☆	·	6
Coutureau, 2021[56]	·	☆	☆	☆	☆	☆	·	·	5
Dong, 2021[39]	·	☆	☆	☆	☆	☆	·	·	5
Esmael, 2021[57]	·	☆	☆	☆	☆	☆	·	·	5
Gong, 2021[40]	·	☆	☆	☆	·	☆	·	·	4
Lee, 2021[92]	·	☆	☆	☆	☆	☆	·	·	5
Ojagbemi, 2021[123]	·	☆	☆	☆	☆	☆	·	·	6
Wang, 2021[62]	·	☆	☆	☆	☆	☆	·	·	5

Zha, 2021[36]	·	☆	☆	☆	☆	☆	·	·	5
Zhao, 2021[82]	·	☆	☆	☆	☆	☆	·	☆	6
Zhong, 2021[85]	·	☆	☆	☆	·	☆	·	·	4
Georgakis, 2022[89]	·	☆	☆	☆	☆	☆	·	·	5
Munthe-Kaas, 2022[119]	·	☆	·	☆	☆	☆	·	·	4
Vlachos, 2022[86]	·	☆	☆	☆	·	☆	☆	☆	6
Yan, 2022[64]	·	☆	☆	☆	·	☆	·	☆	5
Zhang, 2022[41]	·	☆	☆	☆	☆	☆	·	·	5
Zhang, 2022[47]	·	☆	☆	☆	☆	☆	·	·	5

Four (4%) of 89 studies scored 3, fifteen (17%) scored 4, fifty-two (58%) scored 5, thirteen (15%) scored 6, and five (6%) scored 7 points on the NOS. Supplement 2 includes the detailed rules for decision-making on each of the criteria.
* indicate studies that excluded age from the final multivariable model due to stepwise regression modelling and non-significance in a univariate regression analysis.

Supplemental Table S8: Meta-analysis of population attributable fractions

Risk factors for PSCI	***k***	**PAF**	**95% CI**	**I^2**	**P (I^2)**
Diabetes	14	4.9%	(1.6, 8.2)	75.0	< 0.0001
Atrial fibrillation	9	3.1%	(0.1, 6.0)	39.0	0.1078
Prior stroke	9	5.6%	(-1.0, 12.1)	58.5	0.0134
Atrophy	5	10.8%	(0.3, 21.3)	23.4	0.2651
WMH presence (moderate/severe)	3	6.6%	(1.9, 11.2)	44.9	0.1629
Left hemisphere	10	11.0%	(2.9, 19.1)	43.8	0.0667
Baseline cognitive impairment	2	36.6%	(-0.9, 74.2)	0.0	0.9018
Urinary incontinence	2	24.9%	(9.8, 39.9)	0.0	0.8142
Risk factors for PSD	***k***	**PAF**	**95% CI**	**I^2**	**P (I^2)**
Diabetes	9	4.3%	(1.3, 7.3)	90.0	< 0.0001
Prior stroke	6	7.1%	(1.5, 12.7)	55.0	0.0493
Pre-stroke cognitive impairment	4	14.0%	(3.0, 25.0)	0.0	0.8763
MTLA	3	16.8%	(4.3, 29.3)	44.1	0.1671
WMH presence (moderate/severe)	3	13.0%	(9.2, 16.9)	0.0	0.5913
Lacune count ≥ 3	1	27.1%	(1.8, 52.5)	NA	NA
Left hemisphere	5	19.8%	(6.7, 32.8)	0.0	0.9831
Baseline cognitive impairment	3	21.3%	(10.4, 32.3)	8.1	0.3367

Pooled PAFs for binary risk factors that were significant in the main analysis. k, number of studies included in the analysis; PAF, population attributable fraction.

Supplemental Table S9: Summary statistics of the included studies

Study/sample characteristic	k, n, %, or median of average/median
Setting	
Hospital-based	k = 73 (82%, n = 29,341)
Population-based	k = 8 (9%, n = 23,077)
Registry-based	k = 8 (9%, n = 108,365)
Follow-up period	Range: 3 months to 25 years
3 months	k = 31 (35%, n = 12,933)
3-12 months	k = 27 (30%, n = 8,452)
≥ 12 months	k = 31 (35%, n = 139,397)
Age (y)	66.5 (IQR 63-70)
Females	42.8% (IQR 34.5%-47%)
Geographical region	
Asia	k = 43 (48%, n = 36,593)
Europe	k = 31 (35%, n = 87,186)
North America	k = 5 (6%, n = 26,324)
South America	k = 3 (3%, n = 436)
Africa	k = 2 (2%, n = 300)
Australia and Oceania	k = 2 (2%, n = 598)
Multi-continent	k = 3 (3%, n = 9,346)
Stroke type	
Ischemic stroke only	k= 50 (56%, n = 46,424)
Hemorrhagic stroke only	k = 4 (4%, n = 1283)
Mixed stroke population	k = 35 (38%, n = 113,149)
Median proportion ischemic : hemorrhagic in mixed populations	87.2% (IQR 82.5%-91.5%) : 11.6% (IQR 7.65%-13.8%)
TIA included	k = 10 (11%, n = 28,733)
Median proportion of TIA when included	16.3% (IQR 6.48%-29.2%)
NIHSS score	3 (IQR 2-5.3, range 0-14)

Summery statistics of the design, setting, and sample characteristics of studies included in the quantitative analysis. IQR=interquartile range, k=number of studies, n=number of participants included in the studies.

Supplemental Table S10: Egger's test results and adjustment for reporting bias

		Egger's test			Main analysis		Adjusted for publ. bias*			Adjusted for publ. bias + excluding outliers*		
Out-come	**Risk factor**	**k**	**Regression intercept [95% CI bounds]**	**p-value**	**Pooled RR (95% CI)**	**p-value**	**k**	**RR (95% CI), +*k* added**	**p-value**	**k**	**RR (95% CI), +*k* added**	**p-value**
Post-stroke cognitive impairment	Age	**45**	**3.22 [1.95, 4.50]**	**< 0.0001**	**1.03 (1.01-1.05)**	**0.0004**	**61**	1.01 (0.99-1.03), + 16	0.208	**54**	**1.01 (1.00-1.02), + 13**	**0.012**
	Sex	26	–0.85 [–2.49, 0.80]	0.32	1.20 (1.00-1.44)	0.055	**28**	**1.25 (1.03-1.52), + 2**	**0.025**	**22**	**1.20 (1.06-1.37), + 0**	**0.006**
	Educational attainment	**26**	**–3.14 [–4.18, –2.10]**	**< 0.0001**	**0.92 (0.88-0.97)**	**0.004**	37	0.99 (0.92-1.05), + 11	0.643	**32**	**0.94 (0.89-0.99), + 7**	**0.031**
	Stroke severity	**27**	**2.38 [1.18, 3.58]**	**0.0006**	**1.07 (1.01-1.12)**	**0.014**	37	1.02 (0.96-1.08), + 10	0.534	31	1.02 (0.96-1.10), + 10	0.467
	Diabetes	16	1.44 [0.00, 2.88]	0.07	**1.30 (1.15-1.47)**	**0.0004**	21	1.14 (0.99-1.32), + 5	0.066	**12**	**1.29 (1.18-1.40), + 0**	**< 0.0001**
	Hypertension	14	1.28 [–0.16, 2.72]	1.08	1.19 (0.91-1.56)	0.186	15	1.03 (0.72-1.49), + 2	0.849	12	1.09 (0.96-1.25), + 3	0.16
	Atrial Fibrillation	10	1.54 [–0.72, 3.79]	0.22	**1.29 (1.04-1.60)**	**0.027**	12	1.21 (0.94-1.55), + 2	0.12	**9**	**1.26 (1.10-1.45), + 2**	**0.004**
	Prior stroke	10	–1.86 [–4.50, 0.78]	0.20	**1.76 (1.32-2.34)**	**0.0015**	**12**	**1.96 (1.42-2.71), + 2**	**0.0008**	**8**	**1.79 (1.45-2.21), + 1**	**0.0003**
Post-stroke dementia	Age	17	0.39 [–1.32, 2.10]	0.66	**1.08 (1.05-1.11)**	**< 0.0001**	**18**	**1.08 (1.05-1.11), + 0**	**< 0.0001**	**18**	**1.09 (1.07-1.11), + 3**	**< 0.0001**
	Educational attainment	11	–1.02 [–2.52, 0.80]	0.34	**0.93 (0.88-0.97)**	**0.005**	**12**	**0.93 (0.88-0.98), + 1**	**0.013**	**10**	**0.93 (0.89-0.97), + 0**	**0.002**
	Diabetes	**11**	**3.59 [1.03; 3.52]**	**0.006**	**1.38 (1.10-1.72)**	**0.01**	17	1.09 (0.83-1.42), + 6	0.525	**11**	**1.20 (1.01-1.41), +3**	**0.037**

Assessment of reporting bias with the Egger's test for analyses on associations between predictors and post-stroke cognitive outcomes. Analyses were performed only for analyses with a power of k ≥ 10 studies in the main analysis. A p-value of < 0.05 indicates potential reporting bias. The analysis excluding outliers is based on the subset from sensitivity analyses (Supplemental Table S8).

* Adjustment for funnel plot asymmetry using the trim and fill method for random effects models[355]

Abbreviations: RR, Relative Risk; k, number of studies included in the analysis; TIA, transient ischemic attack

Supplemental Table S11: Sensitivity analysis of main effects by removing outliers based on influence analysis

		Main analysis				Analysis after removal of outlying studies			
	Risk factor	Pooled RR (95% CI)	p-value	I^2 (95% CI)	p-value	Pooled RR (95% CI)	p-value	I^2 (95% CI)	p-value
Post-stroke cognitive impairment	Age[1]	**1.03 (1.01-1.05)**	**0.0004**	89.8 (87.3-91.9)	< 0.0001	**1.02 (1.01-1.03)**	**< 0.0001**	81.8 (76.1-86.2)	< 0.0001
	Sex[2]	**1.20 (1.00-1.44)**	**0.055**	85.4 (79.8-89.5)	< 0.0001	**1.20 (1.06-1.37)**	**0.006**	62.1 (39.9-76.1)	< 0.0001
	Educational attainment[3]	**0.92 (0.88-0.97)**	**0.004**	90.7 (87.7-93.1)	< 0.0001	**0.92 (0.88-0.97)**	**0.001**	76.1 (65.0-83.7)	< 0.0001
	Stroke severity[4]	**1.07 (1.01-1.12)**	**0.014**	87.0 (82.2-90.5)	< 0.0001	**1.06 (1.01-1.12)**	**0.028**	82.2 (74.3-87.7)	< 0.0001
	Diabetes[5]	**1.30 (1.15-1.47)**	**0.0004**	73.6 (56.7-83.9)	< 0.0001	**1.29 (1.18-1.40)**	**< 0.0001**	5.9 (0.0-60.8)	0.388
	Hypertension[6]	1.19 (0.91-1.56)	0.186	86.9 (79.7-91.5)	< 0.0001	1.05 (0.95-1.17)	0.267	9.4 (0.0-68.1)	0.357
	Atrial fibrillation[7]	**1.29 (1.04-1.60)**	**0.027**	54.3 (6.7-77.6)	0.02	**1.31 (1.13-1.52)**	**0.004**	0.0 (0.0-70.8)	0.437
	Hyper-/Dyslipidemia[8]	0.83 (0.63-1.09)	0.138	27.8 (0.0-68.8)	0.216	0.89 (0.78-1.01)	0.064	0.0 (0.0-74.6)	0.812
	Smoking[9]	0.81 (0.55-1.18)	0.231	81.7 (0.05-90.0)	< 0.0001	0.91 (0.69-1.21)	0.468	43.7 (0.0-76.3)	0.10
	Prior stroke[10]	**1.76 (1.32-2.34)**	**0.0015**	70.1 (42.7-84.4)	< 0.0004	**1.76 (1.45-2.14)**	**0.0004**	28.5 (0.0-69.2)	0.211
	WMH presence[11]	**1.51 (1.20-1.91)**	**0.008**	52.4 (0.0-82.5)	0.078	**1.41 (1.37-1.45)**	**< 0.0001**	0.0 (0.0-84.7)	0.994
	WMH severity[12]	**1.30 (1.10-1.55)**	**0.006**	75.1 (56.2-85.9)	< 0.0001	**1.28 (1.18-1.40)**	**0.0001**	46.4 (0.0-74.2)	0.052
	Left hemisphere[13]	**1.56 (1.27-1.92)**	**0.0008**	65.2 (31.7-82.3)	0.002	**1.88 (1.55-2.29)**	**0.0004**	17.3 (0.0-62.1)	0.301
Post-stroke dementia	Age[14]	**1.08 (1.05-1.11)**	**< 0.0001**	67.9 (46.8-80.6)	< 0.0001	**1.08 (1.07-1.10)**	**< 0.0001**	31.1 (0.0-62.9)	0.120
	Sex[15]	0.94 (0.79-1.13)	0.473	44.0 (0.0-74.1.1)	0.074	0.99 (0.87-1.13)	0.909	16.8 (0.0-59.8)	0.297
	Educational attainment[16]	**0.93 (0.88-0.97)**	**0.005**	28.8 (0.0-64.9)	0.171	**0.93 (0.89-0.97)**	**0.002**	12.5 (0.0-53.6)	0.328
	Stroke severity[17]	**1.13 (1.04-1.23)**	**0.01**	79.2 (57.3-89.9)	< 0.0001	**1.16 (1.07-1.25)**	**0.0045**	67.0 (21.3-86.1)	0.01
	Diabetes[18]	**1.38 (1.10-1.72)**	**0.01**	64.9 (33.3-81.6)	0.001	**1.28 (1.11-1.48)**	**0.004**	14.0 (0.0-56.8)	0.320
	Atrial fibrillation[19]	1.27 (0.86-1.90)	0.187	78.0 (54.5-89.4)	0.0001	1.15 (0.78-1.71)	0.398	66.5 (20.1-86.0)	0.011
	Prior stroke[20]	**1.64 (1.16-2.32)**	**0.013**	67.0 (26.5-85.2)	0.006	**1.62 (1.03-2.53)**	**0.041**	53.6 (0.0-82.9)	0.072
	WMH presence[21]	**1.55 (1.01-2.38)**	**0.045**	70.7 (31.6-87.4)	0.004	**1.72 (1.04-2.83)**	**0.040**	63.0 (2.2-86.0)	0.029

Analyses for $k \geq 7$ studies were included. Outliers and influential studies were removed based on visual and statistical methods including basic outlier removal, influence analysis (baujat plot, influence diagnostics, leave-one-out-analysis), and GOSH plot analysis.

[1]4 removed: Zhou, Guo, Esmael, Mahon

[2]4 removed: Tang, Jia, Prodjohardjono, Zha

[3]1 removed: Guo

[4]4 removed: Nijsse, Esmael, Ettelt, Zha

[5]4 removed: Newman, Jacquin, Guo, Ding

[6]4 removed: Guo, Lu, Esmael, Wu

[7]3 removed: Tang, Guo, Ettelt

[8]1 removed: Lee

[9]2 removed: Wu, Jia

[10]3 removed: Mok, Zhou, Nijsse

[11]1 removed: Wu

[12]2 removed: Pavlovic, Arba

[13]1 removed: Schellhorn

[14]2 removed: Klimkowicz, Sibolt

[15]1 removed: Kokmen

[16]1 removed: Rasquin

[17]1 removed: Ouk

[18]3 removed: Hénon, Klimkowicz, Li

[19]1 removed: Zhou

[20]2 removed: Lim, Pendlebury

[21]1 removed: Arba

Abbreviations: RR, Relative Risk; GOSH, Graphic Display of Heterogeneity

Supplemental Table S12: Overview of subgroup analysis results: PSCI

	predictor																	
subgroup analysis	**age**	**female sex**	**educational attainment**	**diabetes**	**hypertension**	**atrial fibrillation**	**hyperlipidemia**	**smoking**	**BMI**	**prior stroke**	**heart disease**	**pre-stroke cogn. performance**	**moderate or severe WMH**	**WMH severity**	**atrophy presence**	**atrophy severity**	**stroke severity**	**left hemisphere involvement**
NOS ≥/< 5	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	☆	·	·
NOS ≥/< 6	·	★	★	·	·	·	·	·	·	·	·	·	·	·	·	·	·	☆
NOS points	·	☆	☆	·	·	·	·	·	·	·	☆	·	·	·	·	☆	☆	☆
population- vs. hospital-based	·	★	☆	·	★	·	·	·	·	·	·	·	·	·	·	·	·	·
adjustment for/exclusion of pre-stroke dementia/cognitive impairment	·	·	·	★	·	·	·	·	·	·	·	·	☆	·	·	·	·	★
adjustment for age vs. age & stroke severity	·	·	·	·	·	·	·	·	☆	☆	·	☆	·	·	·	☆	·	·
mean FU ≥/< 12 months	·		·	·	·	·	·	★	☆	·	★	·	☆	·	·	·	·	·
LTFU </≥ 5%	·	★	·	★	·	·	·	·	·	·	·	·	·	·	·	·	·	·
neuropsychological test battery vs. cognitive screening	·	·	·	·	·	★	·	·	★	·	·	·	·	·	★	·	·	·
> 50% ischemic vs. ≥ 50% hemorrhagic stroke patients	·	·	·	·	·	·	·	·	·	☆	·	·	·	·	·	·	·	★
in-/exclusion of TIA patients	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
mean age ≥/< 65 years	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	☆	·	·
mean NIHSS 0-2 vs. 2-5 vs. >5	·	·	·	☆	·	·	·	·	·	☆	·	☆	·	·	·	·	·	☆
published before vs. after 2009	·	·	·	★	★	·	·	·	·	·	·	·	·	·	☆	·	·	·
prospective vs. retrospective study design	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·	☆	·	·
geographic location Asia vs. Europe	·	·	·	·	·	·	·	·	★	·	·	·	·	·	☆	·	·	★

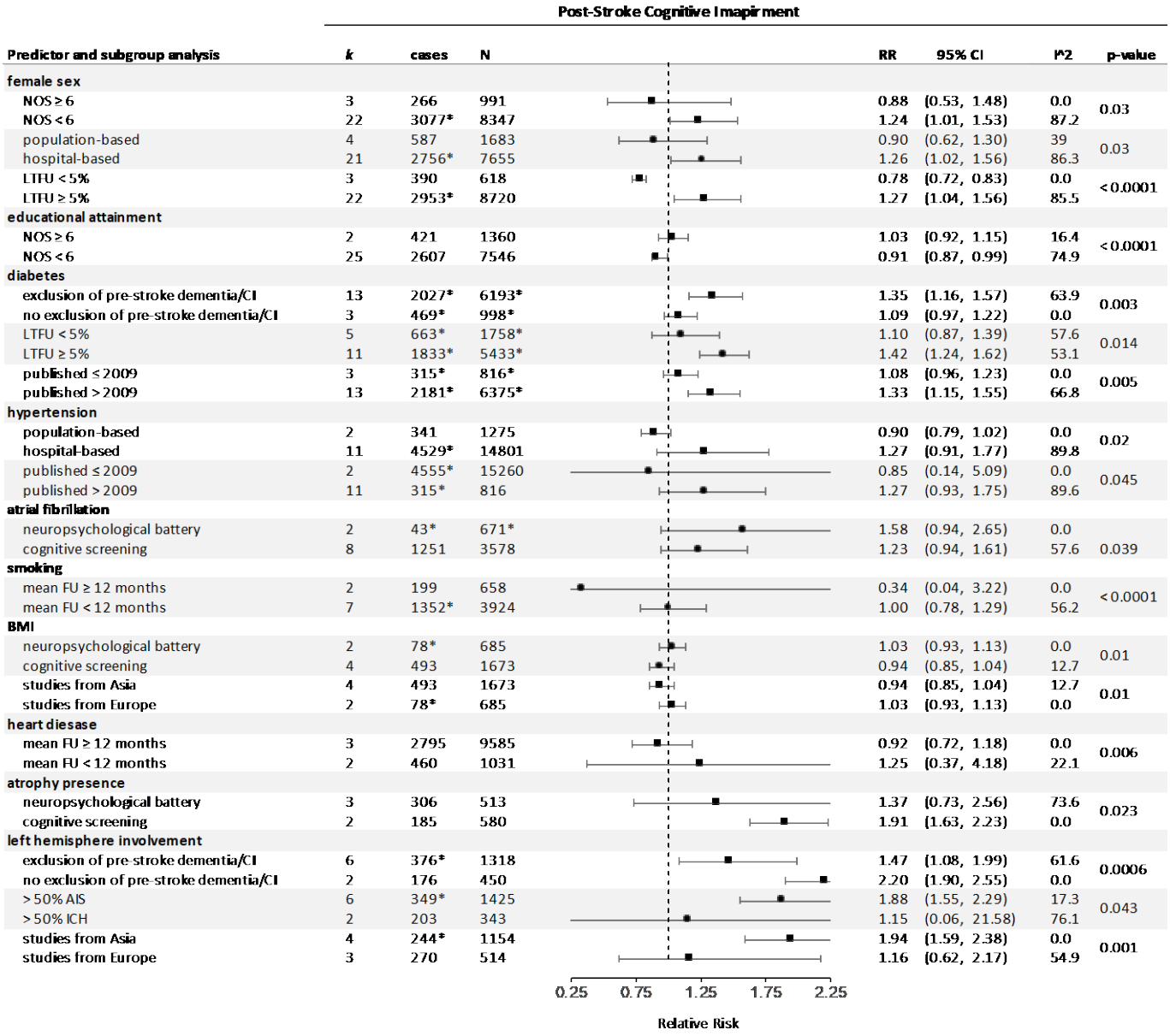
Dots indicate subgroup analyses that either yielded no significant subgroup difference or where there was an insufficient number of studies to perform a subgroup comparison. Stars indicate significant subgroup differences (assessed with Chochran's Q) per predictor. Empty stars indicate analyses where only one study was included in at least one subgroup.
Abbreviations: NOS, Newcastle Ottawa Scale; FU, follow-up; LTFU, loss to follow-up; NIHSS, National Institute of Health Stroke Scale; WMH, white matter hyperintensity; BMI, body mass index

Supplemental Table S13: Overview of subgroup analysis results: PSD

	predictors																
subgroup analysis	**age**	**female sex**	**educational attainment**	**diabetes**	**hypertension**	**atrial fibrillation**	**hyperlipidemia**	**smoking**	**prior stroke**	**heart disease**	**pre-stroke CI**	**moderate or severe WMH**	**WMH severity**	**stroke severity**	**MTLA**	**left hemisphere involvement**	**baseline cognitive impairment**
NOS ≥/< 5	★	·	·	·	·	·	·	·	·	★	·	·	☆	·	·	★	·
NOS ≥/< 6	·	·	·	·	·	·	·	★	·	·	☆	·	·	·	·	·	·
NOS points	☆	·	·	·	·	·	·	☆	·	☆	☆	·	☆	★	·	★	·
population- vs. hospital-based	·	·	·	★	·	★	·	·	★	★	☆	·	·	·	·	·	·
adjustment for/exclusion of pre-stroke dementia/cognitive impairment	·	★	·	·	·	·	·	·	·	·	·	·	·	·	·	·	·
adjustment for age vs. age & stroke severity	·	·	·	·	·	·	·	·	·	·	★	·	·	·	·	☆	·
mean FU ≥/< 12 months	·	·	·	·	·	★	·	·	·	★	★	·	☆	★	·	·	·
LTFU </≥ 5%	·	·	·	★	·	·	·	·	·	·	☆	·	·	·	·	·	★
neuropsychological test battery vs. cognitive screening	·	·	·	★	·	★	·	★	·	·	·	·	·	·	·	·	·
> 50% ischemic vs. ≥ 50% hemorrhagic stroke patients	·	·	·	·	·	·	·	·	·	·	☆	★	★	·	·	☆	·
in-/exclusion of TIA patients	·	·	·	·	★	·	·	·	·	·	·	·	★	·	★	·	·
mean age ≥/< 65 years	·	·	·	·	·	·	·	·	·	·	★	·	·	·	·	·	·
mean NIHSS 0-2 vs. 2-5 vs. >5	☆	·	·	☆	·	☆	·	·	·	·	·	·	·	·	·	·	·
published before vs. after 2009	·	·	★	★	·	★	·	·	·	·	☆	·	·	★	·	·	·
prospective vs. retrospective study design	·	·	·	★	·	·	·	·	☆	·	·	☆	·	☆	·	·	·
geographic location Asia vs. Europe	·	·	·	·	·	·	·	·	★	·	·	·	☆	·	☆	·	·

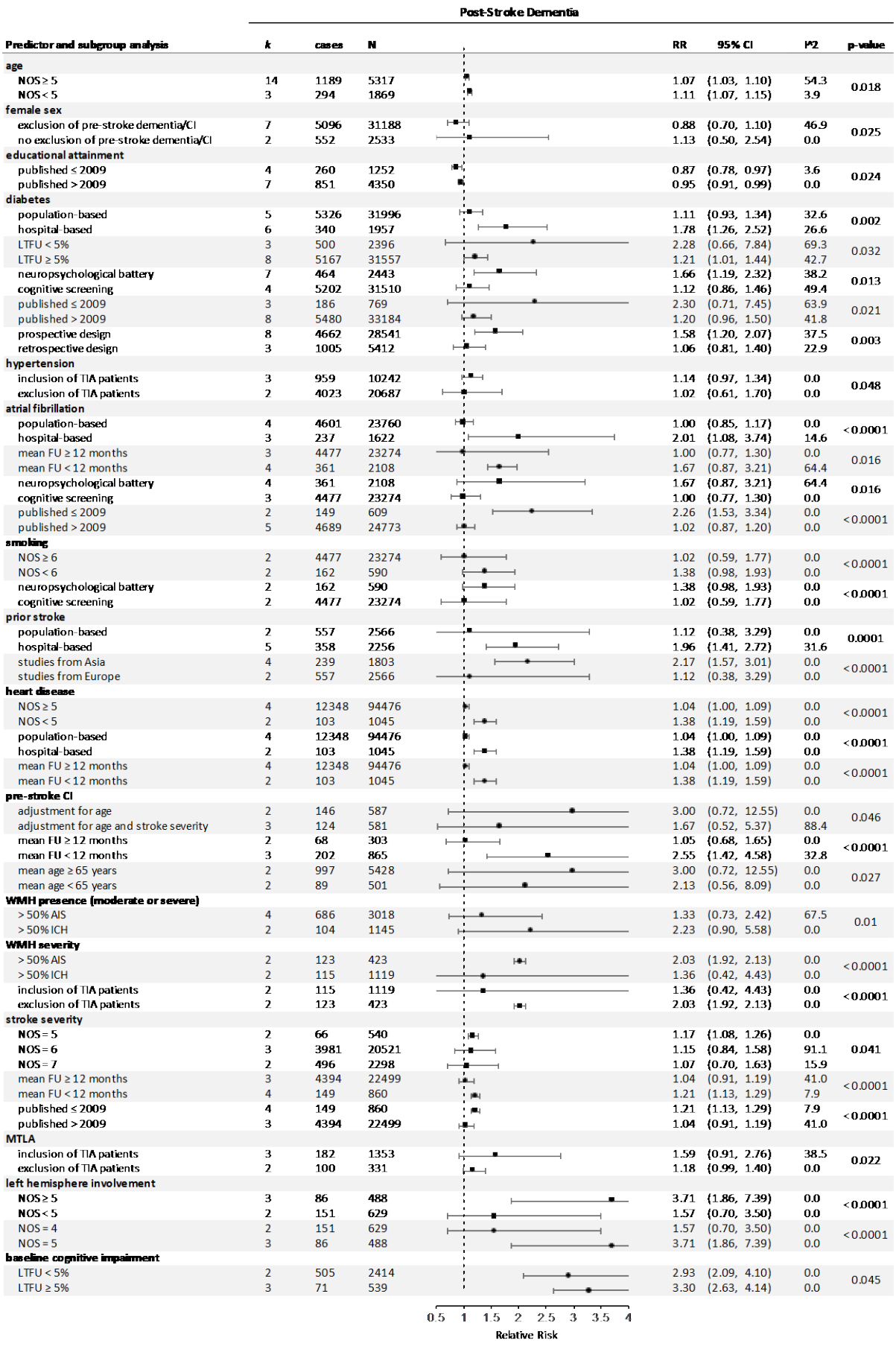
Dots indicate subgroup analyses that either yielded no significant subgroup difference or where there was an insufficient number of studies to perform a subgroup comparison. Stars indicate significant subgroup differences (assessed with Chochran's Q) per predictor. Empty stars indicate analyses where only one study was included in at least one subgroup.
Abbreviations: NOS, Newcastle Ottawa Scale; FU, follow-up; LTFU, loss to follow-up; NIHSS, National Institute of Health Stroke Scale; WMH, white matter hyperintensity; MTLA, medial temporal lobe atrophy

Supplemental Table S14: Detailed subgroup analysis results: PSCI



Detailed overview of the significant subgroup differences for the outcome PSCI, grouped by predictor. Asterisks indicate incomplete N or cases count, which occurred when studies were included in the analysis that did not provide the respective numbers.

Supplemental Table S15: Detailed subgroup analysis results: PSD



Detailed overview of the significant subgroup differences for the outcome PSD, grouped by predictor.

Supplemental Table S16: Meta-regression analysis results

		Post-stroke cognitive impairment						Post-stroke dementia					
		univariable meta-regression			multivariable meta-regression			univariable meta-regression			multivariable meta-regression		
	Variable	k	Exponentiated coefficient (95% CI)	p	k	Exponentiated coefficient (95% CI)	p	k	Exponentiated coefficient (95% CI)	p	k	Exponentiated coefficient (95% CI)	p
age	Age (y)	45	1.00 (0.99-1.00)	0.29				15	1.00 (0.99-1.00)	0.20			
	Females (%)	44	1.00 (1.00-1.00)	0.10				15	1.00 (0.99-1.00)	0.55			
	Educational attainment (y)	14	1.00 (0.98-1.03)	0.63				3	0.99 (0.96-1.01)	0.21			
	Diabetes (%)	39	1.00 (1.00-1.00)	0.62				14	1.00 (1.00-1.00)	0.65			
	NOS points	45	1.01 (0.98-1.03)	0.58				17	0.99 (0.97-1.00)	0.14			
	NIHSS points	**29**	**1.01 (1.00-1.03)**	**0.01**				**6**	**0.99 (0.97-1.00)**	**0.04**			
	Recruitment period (y)	38	1.00 (1.00-1.00)	0.88				17	1.00 (1.00-1.00)	0.77			
	Publication date (y)	45	1.00 (1.00-1.00)	1.00				17	1.00 (1.00-1.00)	0.21			
	Follow-up time (m)	31	1.00 (1.00-1.00)	0.38				11	1.00 (1.00-1.00)	0.20			
sex	Age (y)	27	1.02 (0.98-1.07)	0.33				9	1.01 (0.98-1.05)	0.39			
	Females (%)	27	1.00 (0.97-1.02)	0.76				10	1.00 (0.97-1.03)	0.82			
	Educational attainment (y)	11	0.96 (0.86-1.07)	0.48				3	0.87 (0.55-1.36)	0.53			
	Diabetes (%)	23	1.01 (0.99-1.02)	0.46				9	1.00 (0.99-1.02)	0.56			
	NOS points	27	0.89 (0.72-1.10)	0.29				9	1.01 (0.88-1.14)	0.93			
	NIHSS points	*18*	*1.13 (0.99-1.30)*	*0.07*				2	..	..			
	Recruitment period (y)	21	1.00 (0.97-1.03)	0.87				**9**	**1.01 (1.00-1.02)**	**0.02**			
	Publication date (y)	27	0.98 (0.96-1.01)	0.21				*9*	*1.01 (1.00-1.02)*	*0.08*			
	Follow-up time (m)	18	0.99 (0.97-1.01)	0.34				6	1.00 (0.99-1.00)	0.59			
educ. attainment	Age (y)	29	1.00 (0.99-1.00)	0.41				11	1.00 (0.99-1.01)	0.68			
	Females (%)	29	1.00 (0.99-1.00)	0.23				11	0.99 (0.98-1.00)	0.08			
	Educational attainment (y)	**18**	**1.02 (1.01-1.04)**	**0.005**				4	1.02 (0.98-1.06)	0.30			
	Diabetes (%)	25	1.00 (1.00-1.00)	0.73				10	1.00 (0.99-1.00)	0.67			
	NOS points	29	1.03 (1.00-1.06)	0.12				11	1.01 (0.98-1.05)	0.52			
	NIHSS points	20	1.00 (0.98-1.02)	0.99				6	1.00 (0.96-1.03)	0.84			
	Recruitment period (y)	24	1.00 (1.00-1.01)	0.75				**10**	**1.00 (1.00-1.01)**	**0.04**			
	Publication date (y)	**29**	**1.01 (1.00-1.01)**	**0.004**	18	1.00 (1.00-1.01)	0.16	**11**	**1.01 (1.00-1.01)**	**0.03**	MC		
	Follow-up time (m)	**18**	**1.01 (1.00-1.02)**	**0.01**		**1.01 (1.00-1.02)**	**0.02**	8	1.00 (1.00-1.00)	0.37			
diabetes	Age (y)	16	1.01 (0.98-1.05)	0.45				10	0.99 (0.95-1.03)	0.59			
	Females (%)	16	1.00 (0.98-1.02)	0.92				10	1.00 (0.96-1.03)	0.52			
	Educational attainment (y)	7	1.03 (0.98-1.09)	0.22				2	..	..			
	Diabetes (%)	15	0.99 (0.98-1.01)	0.31				10	1.00 (0.97-1.03)	0.83			
	NOS points	16	0.96 (0.84-1.10)	0.58				11	1.03 (0.86-1.23)	0.75			
	NIHSS points	11	0.96 (0.88-1.05)	0.38				3	0.73 (0.54-1.00)	0.45			
	Recruitment period (y)	12	1.01 (0.99-1.03)	0.31				11	1.00 (0.97-1.03)	0.85			
	Publication date (y)	16	1.00 (0.99-1.02)	0.63				**11**	**0.97 (0.95-1.00)**	**0.03**	7	0.98 (0.94-1.03)	0.40
	Follow-up time (m)	10	1.00 (0.98-1.01)	0.71				*7*	*1.00 (0.99-1.00)*	*0.09*		1.00 (0.99-1.01)	0.94

hypertension	Age (y)	14	1.01 (0.94-1.08)	0.86				5	0.99 (0.95-1.02)	0.52			
	Females (%)	14	1.02 (0.98-1.06)	0.39				5	0.99 (0.96-1.02)	0.56			
	Educational attainment (y)	5	0.94 (0.81-1.09)	0.40				1	..	..			
	Diabetes (%)	**12**	**1.03 (1.01-1.06)**	**0.01**									
	NOS points	14	0.83 (0.64-1.07)	0.15				5	0.93 (0.77-1.11)	0.41			
	NIHSS points	7	1.04 (0.97-1.12)	0.23				0	..	..			
	Recruitment period (y)	**10**	**1.05 (1.01-1.09)**	**0.006**				5	1.00 (0.98-1.03)	0.80			
	Publication date (y)	14	1.04 (0.99-1.08)	0.10				5	1.00 (0.95-1.06)	0.90			
	Follow-up time (m)	5	0.94 (0.87-1.02)	0.15				3	1.00 (1.00-1.01)	0.64			
atrial fibrillation	Age (y)	10	1.01 (0.96-1.05)	0.82				**7**	**0.92 (0.86-0.98)**	**0.009**		0.96 (0.92-1.01)	0.12
	Females (%)	10	0.99 (0.96-1.02)	0.44				7	0.95 (0.89-1.01)	0.10			
	Educational attainment (y)	4	0.94 (0.82-1.07)	0.33				1	..	..			
	Diabetes (%)	9	1.01 (0.99-1.03)	0.27				7	1.00 (0.96-1.05)	0.94	7		
	NOS points	10	1.05 (0.89-1.25)	0.53				7	0.85 (0.64-1.13)	0.27			
	NIHSS points	6	0.95 (0.86-1.05)	0.33				3	1.05 (0.85-1.30)	0.66			
	Recruitment period (y)	6	1.00 (0.97-1.02)	0.92				7	0.98 (0.93-1.03)	0.42			
	Publication date (y)	10	0.99 (0.96-1.02)	0.43				**7**	**0.96 (0.94-0.97)**	**< 0.0001**		**0.96 (0.94-0.98)**	**0.0002**
	Follow-up time (m)	7	1.00 (0.92-1.10)	0.96				6	0.99 (0.98-1.00)	0.15			
stroke severity	Age (y)	**25**	**0.99 (0.98-1.00)**	**0.009**		**0.99 (0.97-1.00)**	**0.03**	7	0.99 (0.97-1.01)	0.49			
	Females (%)	25	1.00 (1.00-1.01)	0.33				7	1.00 (0.98-1.01)	0.610			
	Educational attainment (y)	12	0.99 (0.98-1.01)	0.49				1	..	..			
	Diabetes (%)	22	1.00 (0.99-1.01)	0.70				7	1.00 (0.99-1.01)	0.62			
	NOS points	25	1.02 (0.95-1.09)	0.57	18			7	0.95 (0.87-1.04)	0.31			
	NIHSS points	24	1.01 (0.99-1.03)	0.50				4	0.99 (0.95-1.03)	0.58			
	Recruitment period (y)	20	1.01 (0.99-1.02)	0.36				**6**	**0.99 (0.98-0.99)**	**< 0.0001**			
	Publication date (y)	25	1.00 (0.99-1.01)	0.98				**7**	**0.99 (0.97-0.99)**	**< 0.0001**	MC		
	Follow-up time (m)	*18*	*1.00 (1.00-1.01)*	*0.06*		1.00 (1.00-1.01)	0.59	**7**	**1.00 (1.00-1.00)**	**< 0.0001**			
WMH severity	Age (y)	12	1.00 (0.96-1.04)	0.79				5	1.03 (0.94-1.13)	0.57			
	Females (%)	12	1.02 (0.99-1.04)	0.12				5	1.02 (0.94-1.11)	0.64			
	Educational attainment (y)	*10*	*1.03 (1.00-1.06)*	*0.06*		0.95 (0.80-1.14)	0.61	3	1.09 (0.97-1.24)	0.15			
	Diabetes (%)	9	0.99 (0.97-1.02)	0.66				**4**	**0.98 (0.96-1.00)**	**0.04**			
	NOS points	12	1.13 (0.88-1.46)	0.32				*5*	*1.16 (0.98-1.37)*	*0.08*	NA		
	NIHSS points	9	1.05 (0.98-1.12)	0.19	6			3	1.07 (0.90-1.26)	0.46			
	Recruitment period (y)	**9**	**0.96 (0.92-0.99)**	**0.02**		0.93 (0.82-1.05)	0.26	**5**	**0.91 (0.84-1.00)**	**0.04**			
	Publication date (y)	*12*	*0.97 (0.94-1.00)*	*0.09*				5	0.96 (0.85-1.08)	0.48			
	Follow-up time (m)	**8**	**1.03 (1.01-1.06)**	**0.004**		*1.04 (0.99-1.09)*	*0.09*	3	1.01 (0.99-1.02)	0.44			
prior stroke	Age (y)	10	1.04 (0.98-1.09)	0.18				**7**	**0.90 (0.86-0.95)**	**0.0003**			
	Females (%)	**10**	**1.04 (1.01-1.07)**	**0.009**				**7**	**0.95 (0.92-0.99)**	**0.01**	NA		
	Educational attainment (y)	**5**	**0.86 (0.78-0.96)**	**0.008**				**5**	**0.86 (0.78-0.96)**	**0.008**			
	Diabetes (%)	8	1.00 (0.99-1.01)	0.92				7	1.01 (0.98-1.05)	0.55			
	NOS points	10	1.00 (0.72-1.38)	1.00	NA			7	0.92 (0.73-1.17)	0.51			
	NIHSS points	10	1.09 (0.97-1.22)	0.15				4	0.88 (0.41-1.88)	0.74			
	Recruitment period (y)	**9**	**0.97 (0.94-1.00)**	**0.04**				7	1.01 (0.97-1.06)	0.60			
	Publication date (y)	**10**	**0.96 (0.94-0.98)**	**0.001**				7	0.98 (0.94-1.02)	0.38			
	Follow-up time (m)	7	0.98 (0.92-1.04)	0.49				6	0.99 (0.97-1.01)	0.48			

smoking	Age (y)	9	0.94 (0.85-1.04)	0.26	5	0.99 (0.94-1.05)	0.80
	Females (%)	9	0.98 (0.93-1.03)	0.50	5	0.99 (0.96-1.03)	0.70
	Educational attainment (y)	5	1.03 (0.93-1.14)	0.55	1	..	..
	Diabetes (%)	**8**	**0.97 (0.95-0.98)**	**0.00**	4	0.99 (0.96-1.02)	0.57
	NOS points	9	1.18 (0.86-1.63)	0.31	5	0.89 (0.70-1.14)	0.36
	NIHSS points	5	0.97 (0.93-1.01)	0.10	0	..	..
	Recruitment period (y)	4	0.98 (0.89-1.07)	0.63	4	0.98 (0.95-1.01)	0.19
	Publication date (y)	9	1.01 (0.96-1.06)	0.81	5	0.96 (0.91-1.01)	0.12
	Follow-up time (m)	4	1.02 (0.96-1.08)	0.60	5	1.00 (0.99-1.00)	0.12

Variables with a $p < 0.1$ in the univariable analysis were introduced in the multivariable meta-regression models for each predictor of PSCI/PSD.

Supplemental Table S17: Meta-regression analysis results excluding outliers

		Post-stroke cognitive impairment						Post-stroke dementia					
		univariable meta-regression			multivariable meta-regression			univariable meta-regression			multivariable meta-regression		
	Variable	k	Exponentiated coefficient (95% CI)	p	k	Exponentiated coefficient (95% CI)	p	k	Exponentiated coefficient (95% CI)	p	k	Exponentiated coefficient (95% CI)	p
age	Age (y)	41	1.00 (1.00-1.00)	0.99				13	1.00 (0.99-1.00)	0.73			
	Females (%)	40	1.00 (1.00-1.00)	0.20				13	1.00 (1.00-1.00)	0.94			
	Educational attainment (y)	13	1.00 (0.99-1.00)	0.17				3	0.99 (0.96-1.01)	0.21			
	Diabetes (%)	35	1.00 (1.00-1.00)	0.62				12	1.00 (1.00-1.00)	0.51			
	NOS points	41	1.00 (0.99-1.01)	0.84				**15**	**0.98 (0.97-1.00)**	**0.006**			
	NIHSS points	26	1.00 (1.00-1.00)	0.99				**6**	**0.99 (0.97-1.00)**	**0.04**	NA		
	Recruitment period (y)	34	1.00 (1.00-1.00)	0.36				15	1.00 (1.00-1.00)	0.53			
	Publication date (y)	41	1.00 (1.00-1.00)	0.19				15	1.00 (1.00-1.00)	0.43			
	Follow-up time (m)	28	1.00 (1.00-1.00)	0.88				*9*	*1.00 (1.00-1.00)*	*0.08*			
sex	Age (y)	22	0.99 (0.96-1.02)	0.38				9	1.01 (0.98-1.05)	0.39			
	Females (%)	22	0.99 (0.98-1.01)	0.40				9	1.01 (0.99-1.04)	0.29			
	Educational attainment (y)	8	0.95 (0.85-1.05)	0.29				3	0.99 (0.96-1.01)	0.21			
	Diabetes (%)	19	1.00 (0.99-1.02)	0.50				9	1.00 (0.99-1.02)	0.56			
	NOS points	22	0.90 (0.79-1.03)	0.12				9	1.00 (0.92-1.10)	0.98			
	NIHSS points	14	1.06 (0.97-1.16)	0.21				2	..	..			
	Recruitment period (y)	18	1.01 (0.98-1.03)	0.54				8	1.00 (0.99-1.02)	0.65			
	Publication date (y)	22	1.01 (0.99-1.03)	0.62				9	1.00 (0.98-1.02)	0.86			
	Follow-up time (m)	**13**	**0.99 (0.98-1.00)**	**0.04**				6	1.00 (0.99-1.00)	0.59			
educ. attainment	Age (y)	28	1.00 (0.99-1.00)	0.40				10	1.00 (0.98-1.01)	0.58			
	Females (%)	28	1.00 (0.99-1.00)	0.27				*10*	*0.99 (0.98-1.00)*	*0.06*			
	Educational attainment (y)	**18**	**1.02 (1.01-1.04)**	**0.005**		1.01 (0.98-1.04)	0.60	4	1.02 (0.98-1.06)	0.30			
	Diabetes (%)	25	1.00 (1.00-1.00)	0.73				9	1.00 (1.00-1.01)	0.80			
	NOS points	28	1.03 (0.99-1.06)	0.12				10	1.01 (0.98-1.05)	0.50			
	NIHSS points	19	1.00 (0.98-1.02)	0.93	11			6	1.00 (0.96-1.03)	0.84			
	Recruitment period (y)	23	1.00 (1.00-1.01)	0.83				**9**	**1.00 (1.00-1.01)**	**0.04**			
	Publication date (y)	**28**	**1.01 (1.00-1.01)**	**0.006**		0.99 (0.98-1.01)	0.59	**10**	**1.01 (1.00-1.01)**	**0.04**			
	Follow-up time (m)	**18**	**1.01 (1.00-1.02)**	**0.01**		**1.03 (1.01-1.05)**	**0.01**	7	1.00 (1.00-1.00)	0.37			
diabetes	Age (y)	12	1.01 (0.99-1.03)	0.34				8	0.99 (0.95-1.03)	0.56			
	Females (%)	12	1.00 (0.99-1.02)	0.61				8	1.00 (0.97-1.02)	0.75			
	Educational attainment (y)	*6*	*1.03 (1.00-1.06)*	*0.07*				2	..	..			
	Diabetes (%)	*11*	*0.99 (0.98-1.00)*	*0.07*				8	1.00 (0.98-1.02)	0.92			
	NOS points	*12*	*1.09 (0.99-1.20)*	*0.07*				8	0.94 (0.84-1.05)	0.28			
	NIHSS points	7	0.96 (0.89-1.05)	0.37				2	..	..			
	Recruitment period (y)	8	1.00 (0.98-1.02)	0.97				8	1.00 (0.98-1.02)	0.83			
	Publication date (y)	12	1.00 (0.99-1.02)	0.70				8	0.99 (0.97-1.01)	0.35			
	Follow-up time (m)	**7**	**1.02 (1.00-1.04)**	**0.04**				6	1.00 (0.99-1.00)	0.19			

hypertension	Age (y)	10	1.03 (0.94-1.14)	0.51				5	0.99 (0.95-1.02)	0.52			
	Females (%)	10	1.02 (0.98-1.08)	0.31				5	0.99 (0.96-1.02)	0.56			
	Educational attainment (y)	2	..	..				1	..	..			
	Diabetes (%)	**9**	**1.04 (1.01-1.07)**	**0.01**				5	1.00 (0.97-1.02)	0.86			
	NOS points	10	0.87 (0.66-1.14)	0.30				5	0.93 (0.77-1.11)	0.41			
	NIHSS points	4	1.05 (0.86-1.29)	0.65				0	..	..			
	Recruitment period (y)	**8**	**1.05 (1.01-1.10)**	**0.02**				5	1.00 (0.98-1.03)	0.80			
	Publication date (y)	10	1.03 (0.98-1.09)	0.26				5	1.00 (0.95-1.06)	0.90			
	Follow-up time (m)	3	0.96 (0.90-1.03)	0.22				3	1.00 (1.00-1.01)	0.64			
atrial fibrillation	Age (y)	7	0.98 (0.95-1.02)	0.34				*6*	*0.93 (0.87-1.00)*	*0.05*		0.96 (0.91-1.01)	0.15
	Females (%)	7	0.99 (0.97-1.01)	0.44				6	0.97 (0.90-1.01)	0.13			
	Educational attainment (y)	2	..	..				1	..	..			
	Diabetes (%)	6	1.01 (0.99-1.02)	0.35				6	1.01 (0.97-1.06)	0.54	6		
	NOS points	7	1.06 (0.89-1.26)	0.51				6	0.95 (0.66-1.35)	0.76			
	NIHSS points	2	..	..				1	..	..			
	Recruitment period (y)	5	1.00 (0.98-1.03)	0.94				6	0.98 (0.94-1.04)	0.55			
	Publication date (y)	7	1.01 (0.98-1.03)	0.62				**6**	**0.96 (0.94-0.99)**	**0.001**		**0.97 (0.94-0.99)**	**0.01**
	Follow-up time (m)	5	1.00 (0.95-1.06)	0.89				5	0.99 (0.98-1.01)	0.40			
stroke severity	Age (y)	**23**	**0.98 (0.97-0.99)**	**0.003**				6	1.00 (0.97-1.02)	0.63			
	Females (%)	23	1.00 (0.99-1.01)	0.99				6	1.00 (0.98-1.01)	0.67			
	Educational attainment (y)	10	1.00 (0.98-1.02)	0.92				1	..	..			
	Diabetes (%)	19	1.00 (0.99-1.01)	0.68				6	1.00 (0.99-1.01)	0.11			
	NOS points	23	0.96 (0.87-1.05)	0.33				6	0.95 (0.89-1.02)	0.19			
	NIHSS points	21	1.01 (0.98-1.03)	0.53				4	0.99 (0.95-1.03)	0.58			
	Recruitment period (y)	17	1.00 (0.99-1.01)	0.73				**5**	**0.99 (0.98-0.99)**	**0.0003**			
	Publication date (y)	23	1.00 (0.99—1.02)	0.75				**6**	**0.99 (0.99-1.00)**	**0.001**	MC		
	Follow-up time (m)	14	1.01 (1.00-1.01)	0.10				**6**	**1.00 (1.00-1.00)**	**0.001**			
WMH severity	Age (y)	9	1.01 (0.97-1.04)	0.77				5	1.03 (0.94-1.13)	0.57			
	Females (%)	9	1.00 (0.98-1.01)	0.84				5	1.02 (0.94-1.11)	0.64			
	Educational attainment (y)	**8**	**1.05 (1.01-1.09)**	**0.01**		**1.03 (1.01-1.05)**	**0.01**	3	1.09 (0.97-1.24)	0.15			
	Diabetes (%)	7	1.00 (0.98-1.01)	0.74				**4**	**0.98 (0.96-1.00)**	**0.04**			
	NOS points	9	1.14 (0.95-1.37)	0.15				*5*	*1.16 (0.98-1.37)*	*0.08*			
	NIHSS points	8	1.05 (0.97-1.13)	0.27	**8**			3	1.07 (0.90-1.26)	0.46	MC		
	Recruitment period (y)	8	0.98 (0.95-1.01)	0.24				**5**	**0.91 (0.84-1.00)**	**0.04**			
	Publication date (y)	*10*	*0.98 (0.95-1.00)*	*0.05*		**0.97 (0.95-0.99)**	**0.003**	5	0.96 (0.85-1.08)	0.48			
	Follow-up time (m)	6	1.00 (0.98-1.02)	0.84				3	1.01 (0.99-1.02)	0.44			
prior stroke	Age (y)	7	1.02 (1.00-1.04)	0.13				**5**	**0.90 (0.82-0.97)**	**0.01**			
	Females (%)	7	1.02 (1.00-1.04)	0.10				5	0.96 (0.91-1.02)	0.20			
	Educational attainment (y)	4	0.89 (0.75-1.06)	0.18				1	..	..			
	Diabetes (%)	6	1.00 (0.99-1.01)	0.70				5	1.00 (0.96-1.05)	0.90			
	NOS points	7	1.05 (0.88-1.25)	0.58				5	0.97 (0.60-1.57)	0.90			
	NIHSS points	7	1.03 (0.95-1.11)	0.45				2	..	..			
	Recruitment period (y)	6	0.99 (0.96-1.01)	0.28				5	1.01 (0.96-1.07)	0.65			
	Publication date (y)	**7**	**0.97 (0.94-1.00)**	**0.03**				5	0.97 (0.92-1.03)	0.34			
	Follow-up time (m)	5	1.01 (0.95-1.08)	0.73				..	..	..			

smoking	Age (y)	7	1.02 (0.95-1.10)	0.52		5	0.99 (0.94-1.05)	0.80
	Females (%)	7	1.00 (0.97-1.03)	0.96		5	0.99 (0.96-1.03)	0.70
	Educational attainment (y)	**4**	**1.13 (1.03-1.24)**	**0.01**	N	1	..	..
	Diabetes (%)	**6**	**0.98 (0.95-1.00)**	**0.04**	A	4	0.99 (0.96-1.02)	0.57
	NOS points	7	1.07 (0.91-1.26)	0.42		5	0.89 (0.70-1.14)	0.36
	NIHSS points	4	0.99 (0.93-1.05)	0.65		0	..	..
	Recruitment period (y)	2	..	..		4	0.98 (0.95-1.01)	0.19
	Publication date (y)	7	1.00 (0.98-1.03)	0.77		5	0.96 (0.91-1.01)	0.12
	Follow-up time (m)	3	1.03 (0.98-1.08)	0.22		5	1.00 (0.99-1.00)	0.12

Outlier removal based on sensitivity analysis (Supplementary Table S8). Variables with a $p < 0.1$ in the univariable analysis were introduced in the multivariable meta-regression models for each predictor of PSCI/PSD.

Supplemental Table S18: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	p.1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.2
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	pp.5-6
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	pp.6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.6, Supplement 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.6, Supplement 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.7, Supplement 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p.7, Supplement 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p.7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p.7, Supplement 4, Supplement 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p.7, Supplement 4, Supplement 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	pp.7-8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	pp.7-8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p.8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p.8

Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.9, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Tables S2-S4
Study characteristics	17	Cite each included study and present its characteristics.	p.9, Table S5-S6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1, Table S8-S9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	pp.9-11, Table 1
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	pp.11-12, Tables S11-S17, Figures S5-S7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p.10, Table S11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p.11, Table S10, Figures S2-S3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pp.12-16
	23b	Discuss any limitations of the evidence included in the review.	pp.14-15
	23c	Discuss any limitations of the review processes used.	pp.14-15
	23d	Discuss implications of the results for practice, policy, and future research.	pp.12-16
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p.7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p.7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplement 7
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p.2, p.8, p.17
Competing interests	26	Declare any competing interests of review authors.	p.17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p.17

Supplemental Table S19: MOOSE Guidelines for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	5
2	Hypothesis statement	5
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6
8	Search strategy, including time period included in the synthesis and key words	6, Suppl. 1
9	Effort to include all available studies, including contact with authors	-
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	-
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	Tables S2-S4
14	Method of addressing articles published in languages other than English	7
15	Method of handling abstracts and unpublished studies	-
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-7
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7, Suppl. 5, Suppl. 6
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	7, Suppl. 5, Suppl. 6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	-
21	Assessment of study quality, including blinding of quality assessors, stratification, or regression on possible predictors of study results	7, Suppl. 4
22	Assessment of heterogeneity	7-8
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7-8
24	Provision of appropriate tables and graphics	7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 3-4
26	Table giving descriptive information for each study included	Table S5-S6
27	Results of sensitivity testing (eg, subgroup analysis)	11-12, Tables S11-S15
28	Indication of statistical uncertainty of findings	11

Supplemental Table S20: Update of the literature search

Risk factor	Outcome	Studies reporting significantly higher risk	Studies reporting significantly lower risk	Studies reporting no significant association
Age	PSCI	[356-364]		[365]
Age	PSD	[366]		
Amyloid A	PSCI	[356]		
ApoA1	PSCI			[356]
APTT (Activated partial thromboplastin time)	PSCI			[356]
Baseline cognitive performance	PSCI		[363]	
Baseline mRS	PSCI	[362]		
BMI	PSCI			[367]
Central obesity	PSCI	[367]		
Cerebral infarction	PSCI	[360]		[365]
Coronary heart disease	PSCI			[365]
cSVD score: 4	PSCI	[359]		
Cystatin C	PSCI	[356]		
Diabetes	PSCI	[356]		[361,10]
Dyslipidemia	PSCI			[361]
Education (higher vs. lower)	PSCI		[357,358,361,365]	[356, 363]
Education (lower)	PSD	[366]		
Epilepsy	PSCI			[361]
Fibrinogen	PSCI	[359]		
Frailty	PSCI	[363]		
Glasgow Coma Scale score	PSCI	[362]		
HDL	PSCI			[365]
Hematoma volume	PSCI	[357]		
Hemoglobin	PSCI		[357]	
Hemorrhage in the dominant hemisphere	PSCI	[357]		
Homocysteine	PSCI	[360]		[365]
Hypertension	PSCI	[360-362]	[361,365]	
Intracranial calcium score (high)	PSCI	[364]		
Large artery atherosclerosis or cardioembolism	PSD			[366]
LDL	PSCI			[357,365]

Left hemisphere stroke	PSCI	[358]		
Lobar hemorrhage	PSCI			[357]
Mean corpuscular volume	PSCI	[357]		
Microbleeds	PSCI			[365]
Occupation (manual work)	PSCI	[361]		
Plasma neuropeptide Y	PSCI		[368]	
Prior stroke	PSD	[359]		[366]
Red cell distribution width	PSCI	[357]		
S100B protein	PSCI	[360]		
Sex (male)	PSCI		[359,362]	[361,363,365]
Sleep fragmentation before stroke	PSCI	[369]		
Sleep quality	PSCI	[369]		
Stroke severity (NIHSS score)	PSCI	[364]		[359,362,363]
Structural disconnection score	PSCI	[370]		
Systemic immune inflation index	PSCI	[371]		
TIA	PSCI			[365]
Total cholesterol	PSCI			[365]
Triglycerides	PSCI			[365]
Transient cognitive impairment	PSD			[372]
White blood count	PSCI	[356]		
White matter hyperintensities	PSCI	[359]		[357]
WMH (deep)	PSCI	[359]		
WMH severity	PSCI	[365,373]		[364]

Overview of evidence that has been published since the last update of our search.

Supplement 7: PROSPERO protocol

This systematic review and meta-analysis was pre-registered on PROSPERO. The protocol can be found on the following pages.

Deviation of the final meta-analysis from the original protocol: After an initial search period, we realized that the inclusion of continuous and domain-specific endpoints would have inflated the content of the review to an unmanageable degree, if we accounted for all literature published until today. We therefore decided to concentrate the systematic review and meta-analysis on the binary outcomes PSD and PSCI.

NIHR | National Institute for Health Research

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

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation

Caroline Schmidt, Marios Georgakis, Martin Dichgans. Risk factors for dementia, cognitive impairment, and cognitive decline after stroke: a systematic review and meta-analysis. PROSPERO 2020 CRD42020164959 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020164959

Review question

The aim of this systematic review and meta-analysis is to explore potential risk factors in dementia, cognitive impairment, and cognitive decline after stroke.

Searches

The search strategy we applied consisted of a search using a combination of specific keywords and relevant terms. There were no restrictions made by publication year or language, the sole exclusion being studies that focused on animal models. An in-depth search of the following bibliographic databases will be carried out: PubMed, the Cochrane Library (for existing reviews), and Scopus. The databases will be searched from inception through to June 2020. In addition to the database searches, the reference lists of included articles and reviews will also be searched for additional potentially relevant studies ("snowball" procedure). Eligible studies will be further screened for potential population overlap. The studies will then undergo a full text screening based on the inclusion and exclusion criteria by two independent reviewers (CMS and MKG). A flow diagram (from PRISMA guidelines) will be completed to show the progression of the study selection via the agreed upon inclusion and exclusion criteria.

Types of study to be included

Prospective and retrospective cohort studies. Secondary analyses from randomized controlled trials (if they had cognitive measurements as a major outcome) will be considered, as long as the randomization was not performed on the basis of the presence or absence of the risk factors under study.

Condition or domain being studied

Risk factors that may predict Post-Stroke Dementia (PSD), Post-Stroke Cognitive Impairment (PSCI), and/or cognitive decline.

Post-Stroke Dementia (PSD) is defined as a diagnosis of major vascular neurocognitive disorder that results in severe cognitive impairment following stroke. Dementia itself is diagnosed when all diagnostic criteria such as: validated dementia-related scores on clinically approved neuropsychiatric batteries, adherence to the guidelines set forth in the DSM-V, ICD-10, and NINDS-AIREN criteria are met to satisfaction.

Post-Stroke Cognitive Impairment (PSCI) is defined as cognitive impairment following a stroke that is not severe enough to fulfill diagnostic criteria for dementia, or the diagnostic criteria used to detect dementia was not implemented. PSCI is

diagnosed via a series of approved neuropsychiatric batteries in the post-stroke phase.

Cognitive decline is defined as a progressive decline of cognitive functioning detected primarily through clinically approved neuropsychiatric batteries such as those used to diagnose PSD and PCSI.

Participants/population

Inclusion Criteria:

- Must have a dedicated stroke cohort (index, not chronic)

- Limited to patients with ischemic or hemorrhagic stroke with clinical signs of neurological dysfunction documented as present at the time of diagnosis. Transient Ischemic Attacks only acceptable where cases account for < 50% of the total cohort

- Adult humans (18+ years of age)

- Cohort studies including ≥ 30 patients

- Participants recruited prospectively (recruited after stroke, but before PSCI or PSD diagnosis) or retrospectively (recruited after diagnosis with PSCI and/or PSD, but within 3 months of acute stroke)

- Studies should assess PSD, PSCI, or cognitive decline as primary or secondary outcomes

- Outcomes should be assessed at least 90 days after stroke onset

Exclusion Criteria:

- Animal and Autopsy studies

- Case-control, cross-sectional studies, or randomized clinical trials, unless cognitive outcomes were a major focal point

- Cohorts with specific, regional, or restricted forms of stroke events

- Studies that classify stroke, PSD, or PSCI via subjective assessment, self-report, or by proxy

- Cohorts with previous diagnosis of dementia, cognitive impairment, or diseases that might interfere with cognitive function

- Cohorts with genetic forms or genetic predisposition for stroke

- Studies that have no follow-up or follow-up does not exceed 90 days

Intervention(s), exposure(s)

Any risk factors explored by individual studies regarding associations with PSD, PSCI, or cognitive decline after stroke.

Risk Factors:

- Any risk factors explored by individual studies will be taken into consideration without pre-defined criteria, including previously identified risk factors for PSD and PSCI

- Risk factors should be assessed at baseline (within 90 days after stroke onset). However, any blood samples must be initially taken between hospital admission through the first 90 days post-stroke

- All follow-up periods for studies focusing on cognitive decline must occur post-90 days to account for the settling of acute symptoms and the resolution of any post-stroke delirium

Comparator(s)/control

Controls could be considered either: healthy/non-event, absence of predictor of interest or risk factors, or absence of predicted outcome with addition of the potential risk factor(s)/predictor of interest.

For binary risk factors (e.g. history of a disease), we will compare individuals with presence vs. absence of the risk factor under study. Continuous risk factors (e.g. biomarkers) will either be explored in their entire range through linear analyses, or individuals will be classified in > 2 categories depending on the levels of the risk factor under study.

Context

Studies that have recruited adult participants who have suffered clinically verified, WHO defined, stroke (i.e. not studies that accept self-reported stroke). Accepted studies must include some accepted form of reported cognitive assessment directly of the patient (i.e. no self-reported measures and includes measures that may accept, but must go beyond, certain subjective assessments such as IQCODE).

Main outcome(s)

The following primary outcome will be examined:

- Post-Stroke Dementia (PSD) as defined by established diagnostic criteria (i.e. DSM or NINDS-AIREN), not subjective, self-report, or by proxy report (such as through questionnaires like IQCODE) and assessed by various neuropsychiatric batteries or other clinically defined and accepted diagnostic tests.

Measures of effect

PSD should be assessed over a follow-up period extending at least up to 90 days after index stroke.

Additional outcome(s)

The following secondary outcomes will be examined:

- Post-Stroke Cognitive Impairment (PSCI) assessed by various neuropsychiatric batteries or other screening tests of global executive function (i.e. MoCA, MMSE, CAMCOG, etc.), using validated cut-off scores

- Cognitive performance (single assessment) and cognitive decline (≥ 2 assessments on follow-up), as validated by neuropsychological tests. The neuropsychological tests will be catagorized based on previous literature in the following cognitive domains:

-- Global cognitive performance

-- Executive function

-- Learning and memory

-- Visual-spatial ability

-- Processing speed and attention

-- Language

- Any and all impacts that potential risk factors may or may not have on the trajectory of the development or mitigation of PSD and PSCI.

Measures of effect

Post-stroke cognitive impairment should be assessed over a follow-up period extending at least up to 90 days after index stroke. Cognitive performance should be assessed with a single assessment at a time point at least 90 days after index stroke. Cognitive decline should be assessed with at least two assessments with the same neuropsychological test, with the last assessment carried out at least 90 days after index stroke.

Data extraction (selection and coding)

Following the literature search, the selected studies will be thoroughly screened and the duplicates removed. Where studies report on the same population, the largest, or most generally inclusive, study will be chosen to avoid multiple single participant data. Data will then be extracted from the studies selected for inclusion.

Extracted information will include:

- Publication details: First author and publication year

- Study details: sample size, study design, geographical location, number of participating/recruiting centers, type of participating center (hospital or population-based), recruitment period(s), study dates

- Study population: inclusion and exclusion criteria, demographics, presence of vascular risk factors (hypertension, diabetes, BMI, smoking status, atrial fibrillation, history of cardiovascular disease, etc.)

- Details about index stroke event: proportion of stroke subtypes (ischemic, hemorrhagic, and by etiological subtype), stroke severity (based on NIHSS guidelines), proportion of TIAs included in the study, imaging method used for confirmation of diagnosis (e.g. CT, MRI), and treatment course

- Control information: definition of stroke-free cases, definition of outcome-free cases

- Details of stroke: duration after index stroke for dementia assessment, duration after assessment that dementia was diagnosed, cognitive impairment was diagnosed, or cognitive decline was noted, type (ischemic, intracerebral hemorrhage, TIA), causal factor if known (subtype), severity (NIHSS score), treatment course, volume, and location

- Details of risk factors under study: examined risk factors and method of assessment, definition (in case of binary risk factors), and scale of assessment (in case of continuous risk factors)

- Assessment of outcomes: method of assessment of dementia and/or cognitive impairment, diagnostic criteria used for dementia assessment, tests used for the assessment of cognitive impairment, cognitive decline, and cognitive performance, and all relevant cut-off scores used

- Follow-up information

- Details of statistical analysis: risk ratios for binary outcomes and beta coefficients for continuous outcomes (cognitive performance and decline) by risk factor along with their 95% confidence intervals.

Risk of bias (quality) assessment

The risk of bias of the included studies will be assessed using the cohort subscale of the standardized appraisal tool for observational, non-randomized studies, the Newcastle-Ottawa scale. For every item on the scale, one point will be awarded.

- Representativeness: Only included patients with acute stroke of any subtype or severity

- Selection of non-exposed cohort: Control population is selected from the same source as the exposed

- Ascertainment of exposure: Only used objective assessments

- Outcome of interest was not present at the start of the study: Excluded all patients with pre-stroke dementia or cognitive impairment and cases of chronic stroke

- Comparability of cohorts: Adjusted for age. An additional point if also adjusted for baseline stroke severity

- Assessment of outcome: PSD/PSCI and cognitive decline are diagnosed/assessed via established criteria and based on a battery of neuropsychological tests. No point if PSD/PSCI was assessed solely based on a test of global cognitive function, via registry-based data, or telephone follow-up interview

- Length of follow-up: Cognitive outcomes assessed ±1 year after index stroke event

- Adequacy of follow-up: Attrition rates are ≤10%. No comment on follow-up completion, or missing key information that was assessed at baseline, but not at follow-up, equals zero points.

Strategy for data synthesis

A descriptive analysis of the included studies will be performed and the findings will be presented in tables or figures where appropriate. For every outcome either the maximally adjusted effect estimates (risk ratios for binary outcomes and beta coefficients for continuous outcomes), along with 95% confidence intervals, will be extracted or crude estimates will be calculated.

We aim to use random-effects models, due to the several levels of heterogeneity across studies that we anticipate we will find. Heterogeneity will be quantified with the I^2 and the Cochran Q statistics. Publication bias will be visually explored in funnel plots, and small study effects will be quantified via the Egger Test, in meta-analyses including ≥10 study arms. In case of significant small study effects ($p<0.10$), we will adjust for publication bias with the “trim and fill” method.

We anticipate the data to vary widely, but after quality assessment and publication bias have been taken into consideration, and the nature of the available quantitative data has been determined to satisfaction, then the meta-analysis will be performed using STATA software and/or R software.

Analysis of subgroups or subsets

It is difficult to explicitly define all specific subgroups in advance of data extraction. Though, if studies have used methods and variables that are sufficiently compatible to allow comparisons to be made, then subgroup analyses will be performed based on points such as: cognitive outcome, domain-specific impairment, risk ratios for dementia, risk ratios for cognitive impairment, known predictors of PSD and PSCI, and timescale between stroke onset and PSD/PSCI assessment and/or diagnosis, beta coefficients for continuous outcomes such as cognitive performance and cognitive decline, among others to be determined.

Specific, pre-determined subgroup analyses if possible:

- Ischemic vs. hemorrhagic stroke

- Population-based vs. hospital-based studies

- Retrospective vs. prospective cohort studies

- Sensitivity analyses restricted to studies fulfilling each of the abovementioned quality criteria, determined by the Newcastle-Ottawa Scale

- Sensitivity analyses by level of adjustment (e.g. studies that adjusted for demographics, stroke severity, vascular risk factors, etc.)

- Sensitivity analyses of studies not including any TIAs

- Subgroup analyses by mean stroke severity at baseline (defined by NIHSS)

- Male vs. female (if possible)

- >75 vs. <75 years of age

Additional sensitivity/subgroup analyses may additionally be considered depending on availability of data in the individual studies.

Contact details for further information

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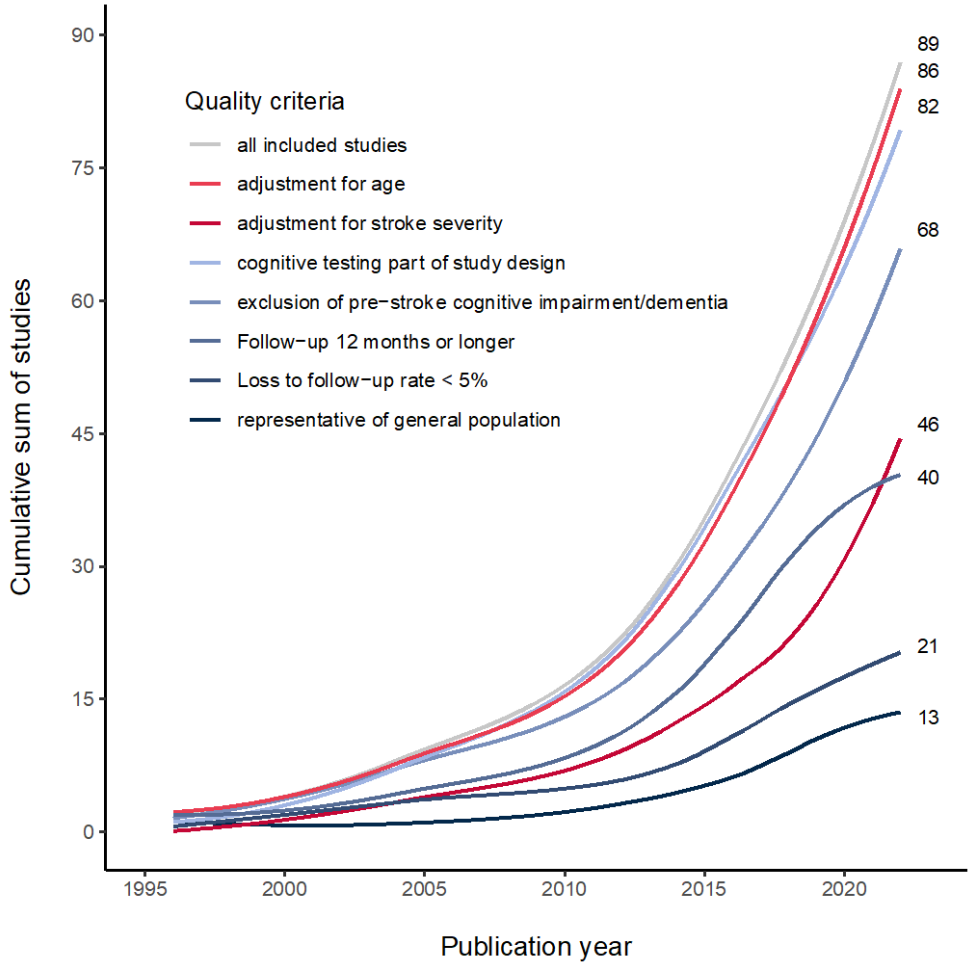
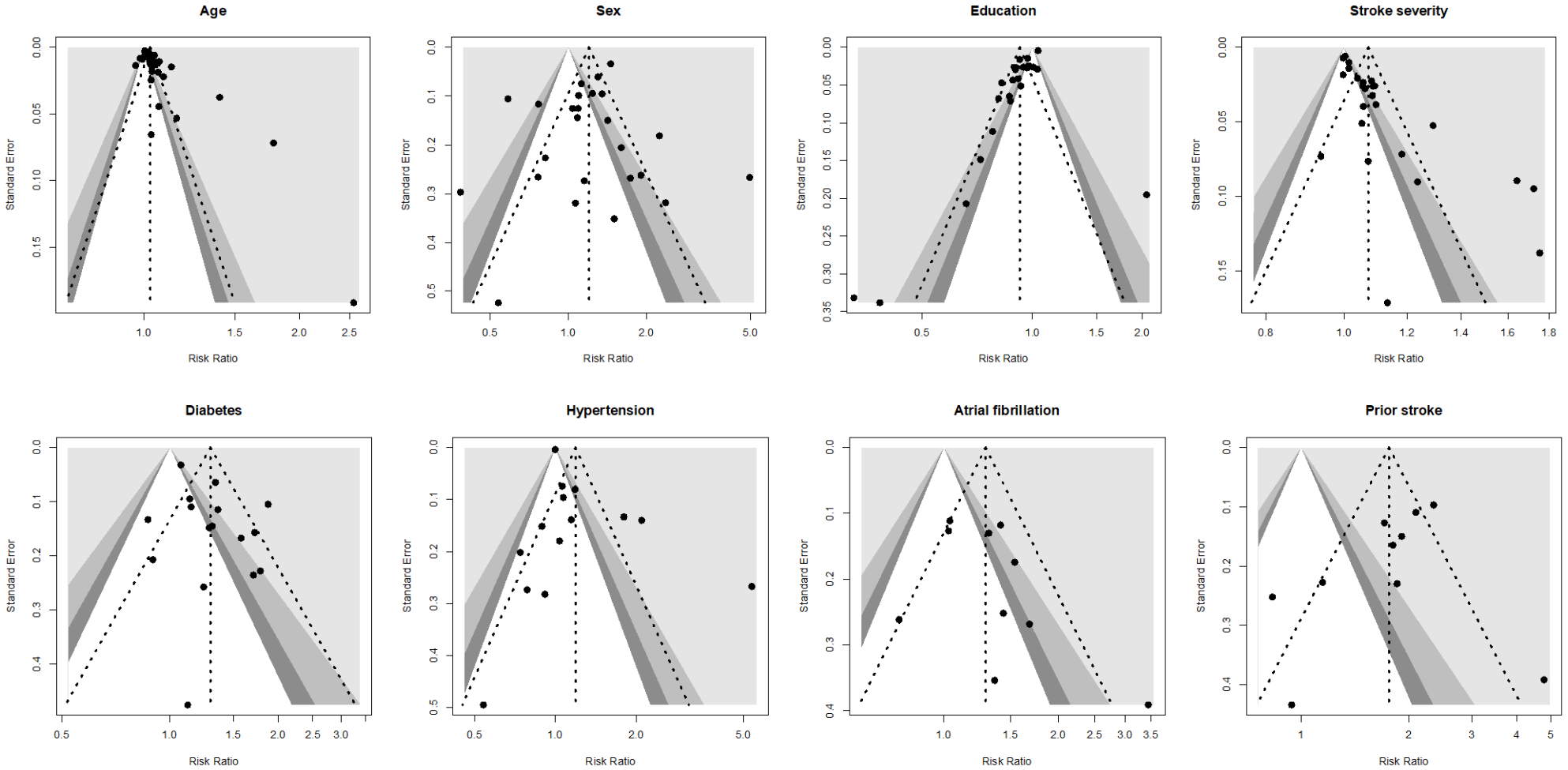
Supplemental Figure S1: Cumulative number of studies that met the individual quality criteria (Newcastle Ottawa Scale) over time



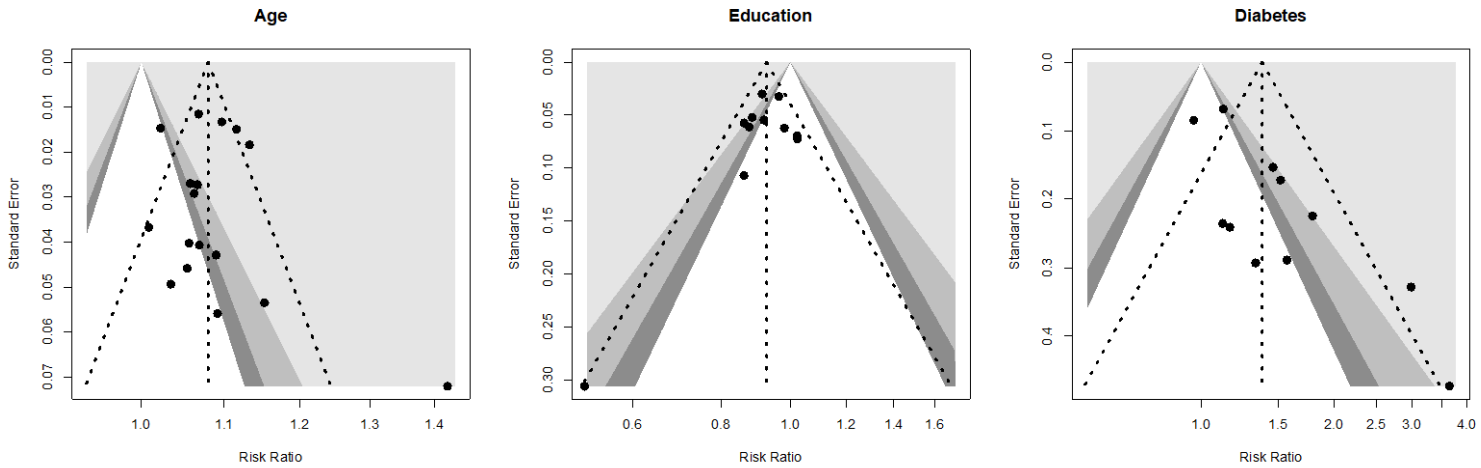
The top grey line indicates the total cumulative number of studies that were included in this meta-analysis up to each year. Numbers on the right indicate the total cumulative number of studies that fulfilled each quality criterion.

Supplemental Figure S2: Contour-enhanced funnel plots for the associations of predictors with post-stroke cognitive impairment



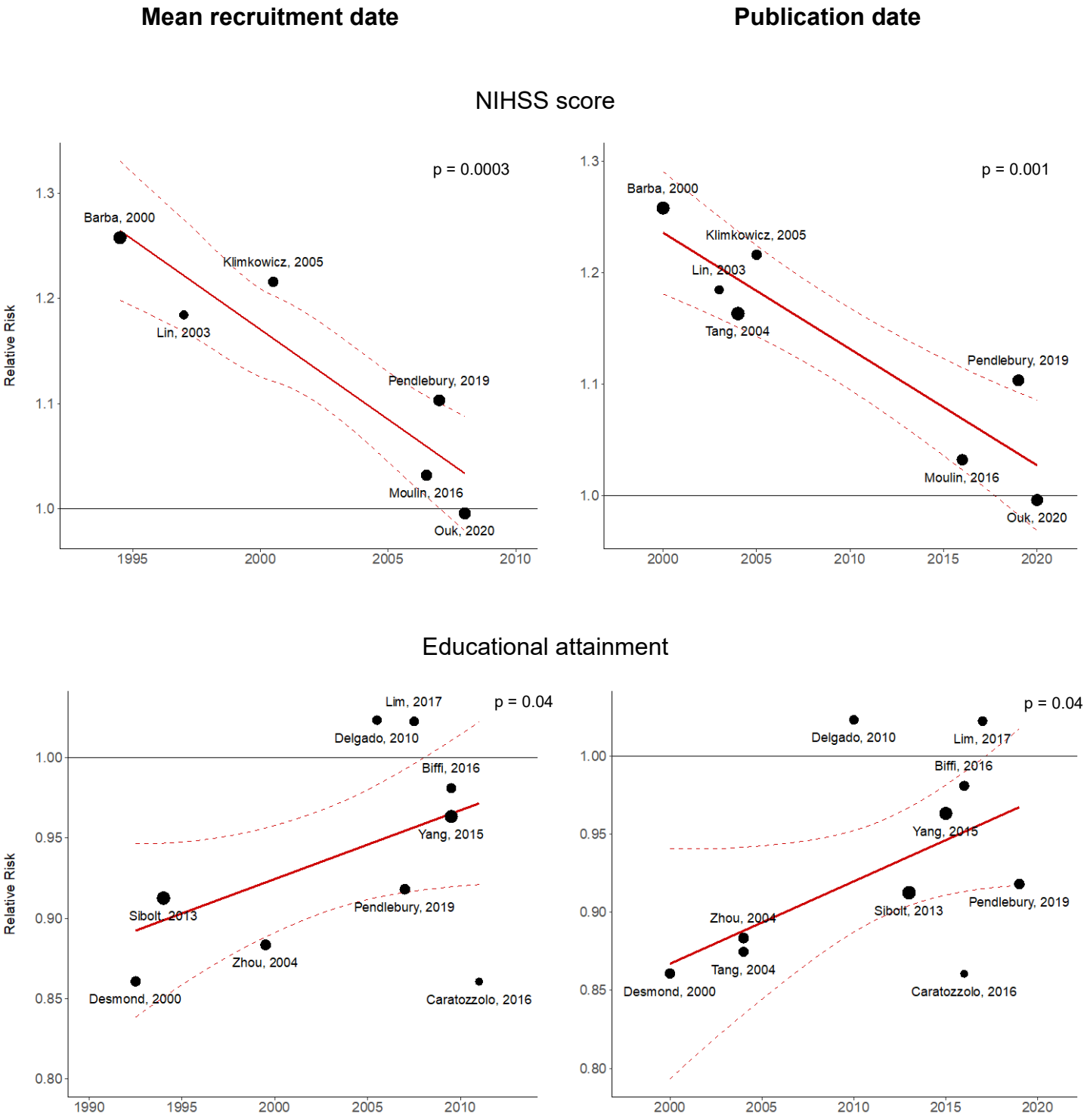
Dark, middle, and light grey areas indicate whether the effect estimate of an individual study has a p-value of < 0.1, < 0.05, or < 0.01, respectively.

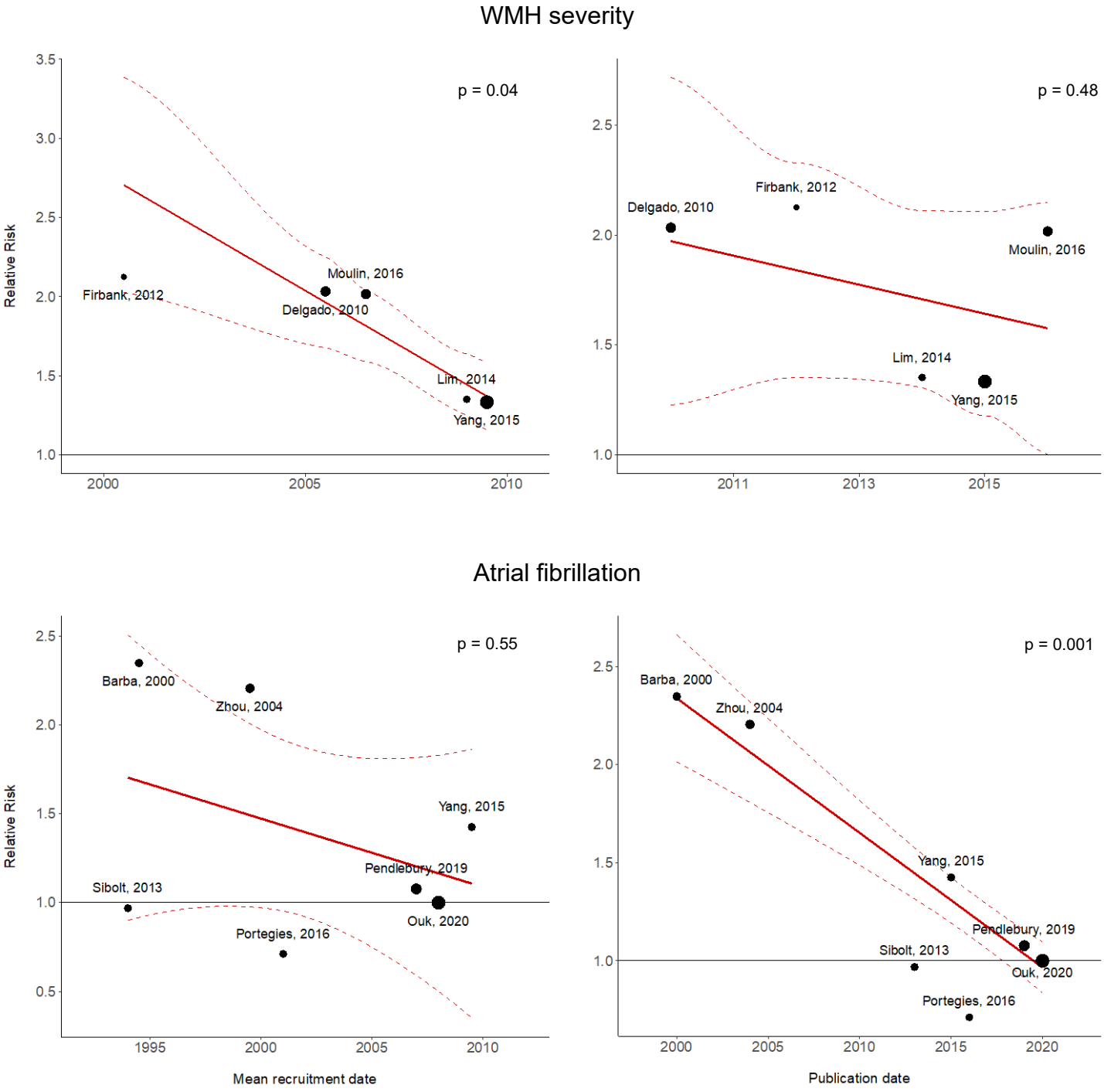
Supplemental Figure S3: Contour-enhanced funnel plots for the associations of predictors with post-stroke dementia



Dark, middle, and light grey areas indicate whether the effect estimate of an individual study has a p-value of < 0.1, < 0.05, or < 0.01, respectively.

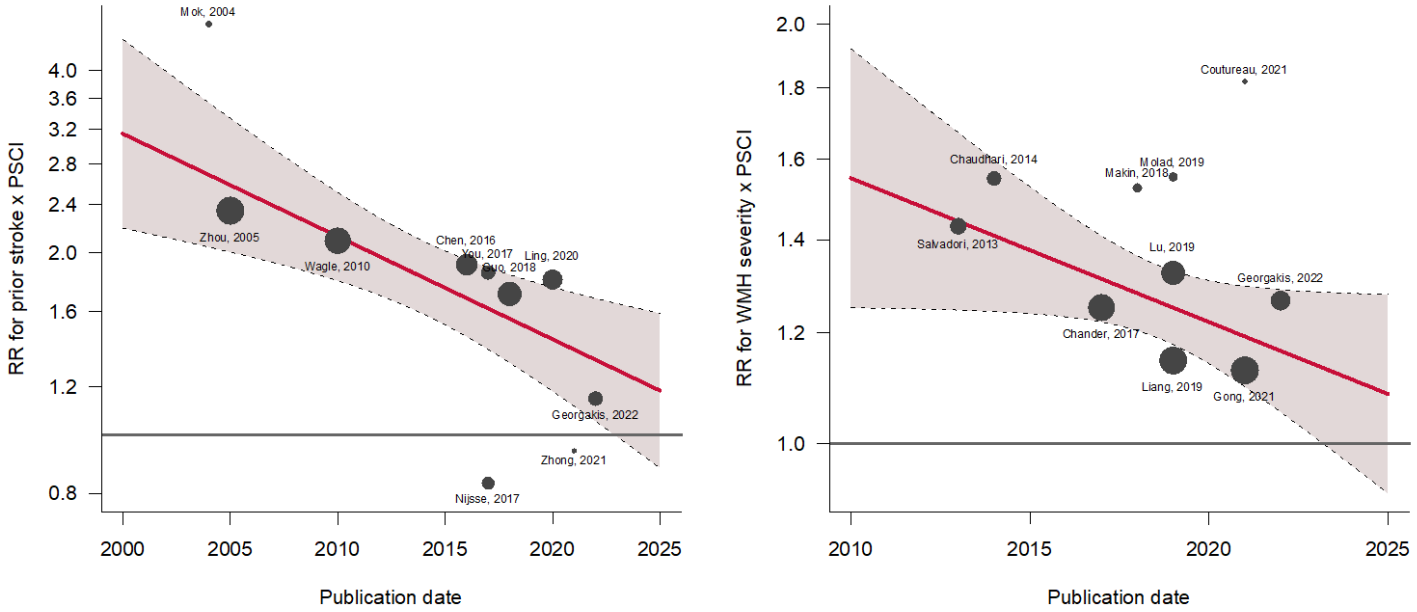
Supplemental Figure S4: Bubble plots of associations with PSD moderated by recruitment date and publication year





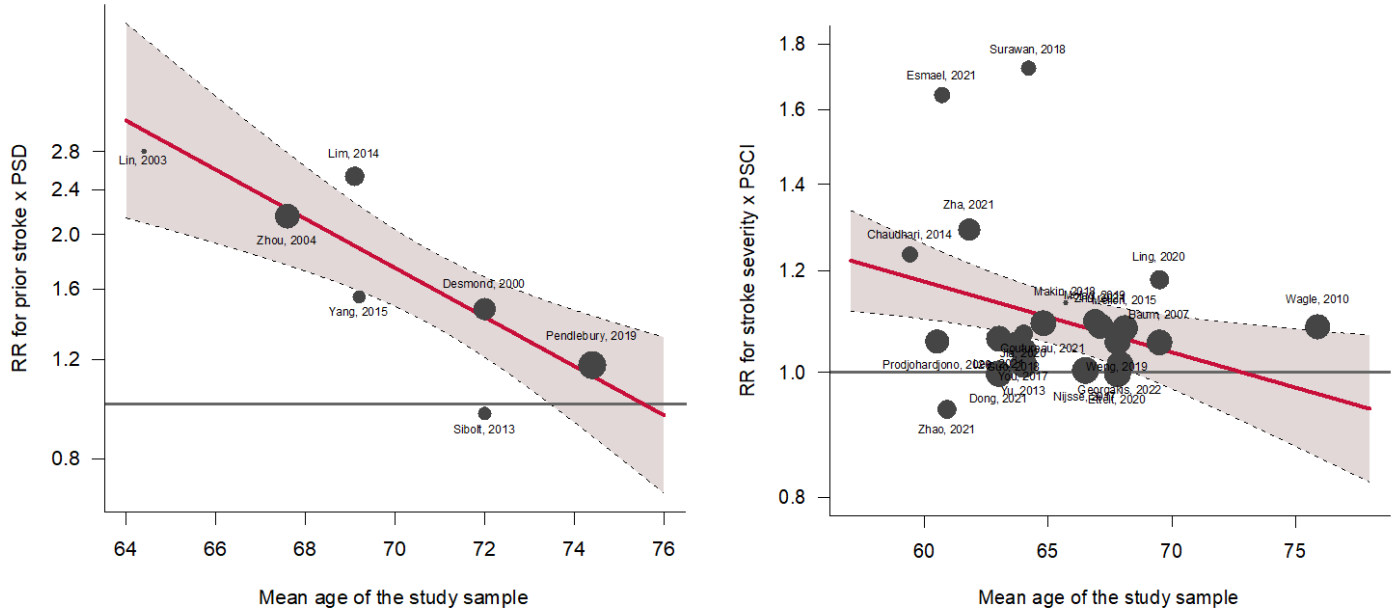
Bubble plots of study-specific effect sizes for the associations of NIHSS score, educational attainment, WMH severity, and atrial fibrillation with PSD, plotted by mean recruitment year (left column), and publication year (right column). Shown are the regression line (red) and confidence interval bands. PSD, Post-stroke Dementia; RR, Relative Risk; WMH, White Matter Hyperintensity

Supplemental Figure S5: Bubble plots of associations with PSCI moderated by publication year



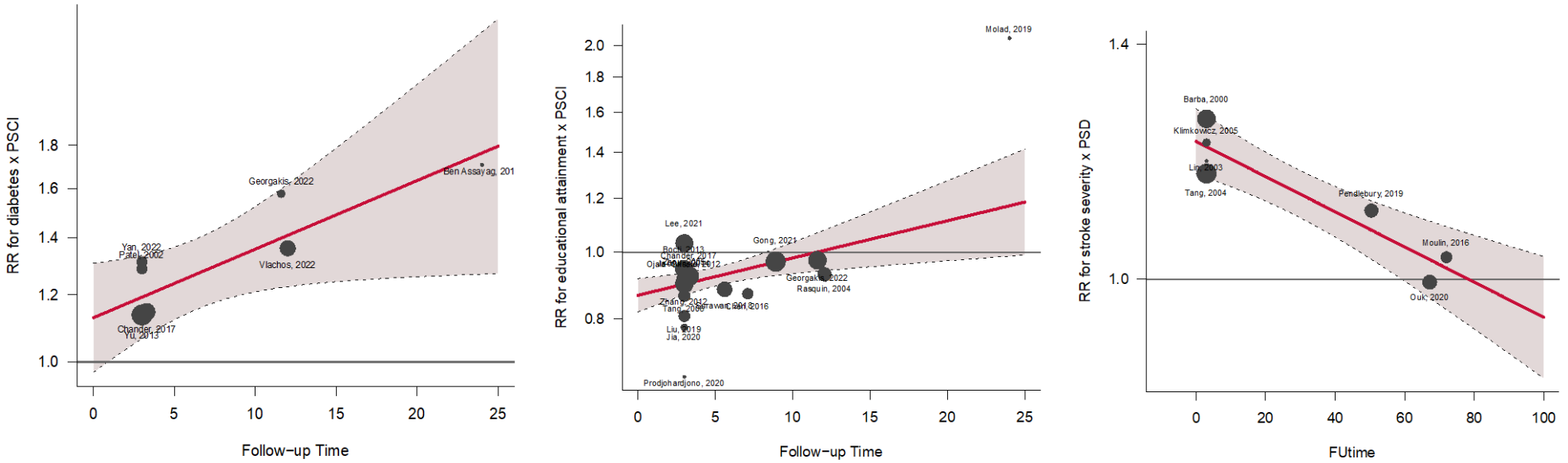
Bubble plots of individual study effect sizes for the associations between prior stroke and PSCI (left) and WMH severity and PSCI (right) plotted by publication date. Shown are the regression line (red) and confidence interval bands. PSCI, Post-stroke Cognitive Impairment; RR, Relative Risk; WMH, White Matter Hyperintensity

Supplemental Figure S6: Bubble plots of associations moderated by mean age of the study sample



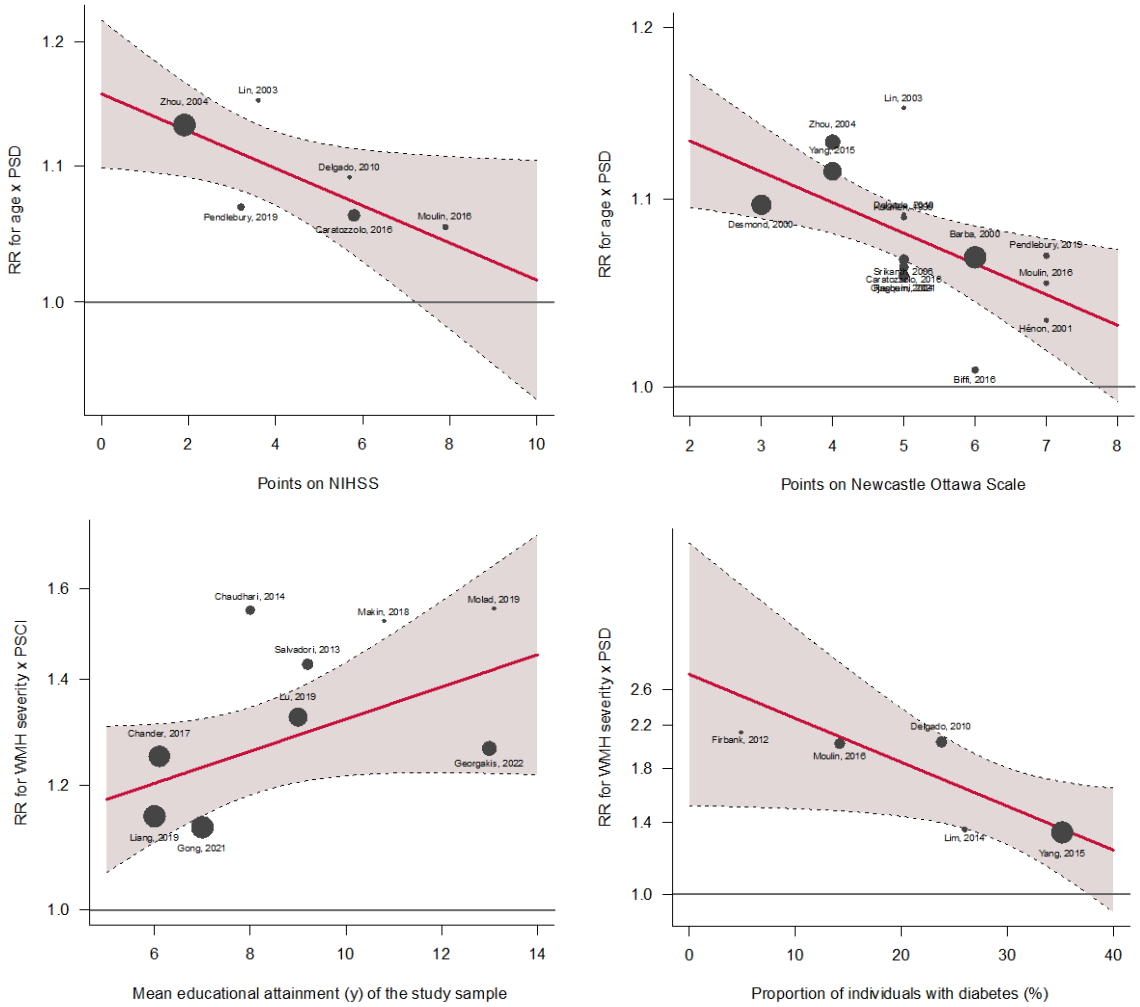
Bubble plots of individual study effect sizes for the associations between prior stroke and PSD (left) and stroke severity and PSCI (right) plotted by mean age of the study sample. Shown are the regression line (red) and confidence interval bands. PSD, Post-stroke Dementia; PSCI, Post-stroke Cognitive Impairment; RR, Relative Risk

Supplemental Figure S7: Bubble plots of associations moderated by follow-up time



Bubble plots of individual study effect sizes for the associations between diabetes and PSCI (left), educational attainment and PSCI (middle), and stroke severity and PSD (middle) plotted by mean follow-up time. Shown are the regression line (red) and confidence interval bands. NOS, Newcastle Ottawa Scale; PSD, Post-stroke Dementia; PSCI, Post-stroke Cognitive Impairment; RR, Relative Risk

Supplemental Figure S8: Bubble plots of associations moderated by NIHSS score, NOS score, mean educational attainment of the study sample, and proportion of individuals with diabetes



Bubble plots of individual study effect sizes for the associations between age and PSD (top left and top right) plotted by points on NIHSS and points on NOS as well as the associations between WMH severity and PSCI (bottom left) and WMH severity and PSD (bottom right) plotted by mean educational attainment of the study sample and proportion of individuals with diabetes, respectively. Shown are the regression line (red) and confidence interval bands. NOS, Newcastle Ottawa Scale; PSD, Post-stroke Dementia; PSCI, Post-stroke Cognitive Impairment; RR, Relative Risk; WMH, White Matter Hyperintensity

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Supplementary Material

Risk factors for dementia and cognitive impairment within 5 years after stroke: a prospective multicentre cohort study

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Supplementary Methods

DEMDAS study centres
DEMDAS was conducted at seven tertiary stroke centres located in major German cities: the interdisciplinary stroke center including the Institute for Stroke and Dementia Research (coordinating institution) and the Department of Neurology, University Hospital, LMU Munich; the Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich; the Division of Vascular Neurology, Department of Neurology, University Hospital Bonn; the University Medical Center, the Department of Neurology, Göttingen; and the Department of Neurology and Institute of Cognitive Neurology and Dementia Research, Otto von Guericke University Magdeburg; the Center for Stroke Research Berlin and the Department of Neurology of the Charité - Universitätsmedizin Berlin. These centres operate within larger regional networks of stroke care and typically serve a diverse mix of patients, including both direct admissions and transfers requiring advanced treatment.

Pathways of patient admission to the centres

- **Direct presentation**: Some patients self-presented to emergency departments.
- **EMS referral**: Others were transported directly by emergency medical services based on regional triage protocols, treatment indication, and hospital capacities.
- **Inter-hospital transfers**: Patients initially admitted to smaller or non-specialized hospitals were often transferred to tertiary centers when specialized treatment such as mechanical thrombectomy was indicated.

The proportion of patients entering through each pathway varied by location. For example, the Magdeburg site, being the only comprehensive stroke centre in a large catchment area, admitted patients from a wider geographic range. In contrast, metropolitan areas like Berlin, Munich, or Bonn have multiple tertiary centres, which may lead to a more diverse mix of local and referred patients, including both nearby residents and patients transferred from outside the immediate city due to the centres' specialized expertise or capacity.
Regardless of referral pathway, all participants were treated in dedicated stroke units within the participating hospitals, ensuring standardized acute management and study enrollment procedures.

Baseline assessments
At enrolment, a comprehensive interview and assessments were conducted using standardised protocols. Data collection included sociodemographic information, family history, medical history of previous diagnoses, medication use, and vascular risk factors. Participants were counted as having a cardiovascular risk factor (hypertension, dyslipidaemia, diabetes mellitus, atrial fibrillation, prior stroke, or ischaemic heart disease) when they had ever received a respective diagnosis (before or at the time of hospitalisation for the stroke after which they were recruited into DEDEMAS/DEMDAS), representing a history of or currently having that risk factor. Diabetes mellitus included both type 1 and type 2 diabetes. Clinical evaluations included physiological measurements (e.g. blood pressure and BMI measurement) and scales such as the National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Glasgow Coma Scale (GCS). For cognitive testing, the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were applied. Peripheral blood samples were collected from all patients and biochemical assessments were performed as part of the clinical routine. Ischaemic stroke subtyping was performed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[1] classification by trained neurologists at each of the participating centres.

Biochemical assessments and biobanking
Peripheral blood assessments included complete blood count, LDL-, HDL-, and total cholesterol, triglycerides, fasting glucose, glycated haemoglobin A1c, electrolytes, transaminases, creatinine, high-sensitivity C-reactive protein, fibrinogen, procalcitonin, homocysteine, thyroid hormones, vitamin B12, folate, total and MB-creatinine kinase, troponin T, and routine coagulation markers. Additional blood samples were collected for biobanking (serum, plasma, DNA, and miRNA) at baseline and follow-ups according to standard operating procedures. All samples were centralised in the coordinating centre in Munich, where they were double-pseudonymised and managed via a secure data integration system (DIS) developed by the Munich Biotech Cluster m4 with maintenance and support by Bitcare GmbH. Data integrity was ensured by independent verification by two blinded data managers.

Genetic ancestry analysis
To confirm the continental-level genetic ancestry of the study cohort and perform quality control, participant genotype data (genome build hg19) was compared against the 1000 Genomes Project (1kG) Phase 3 reference panel (N=2504 samples, hg19). All analyses were conducted using PLINK (v1.9) and R (v4.4.3]).

Prior to merging, both the study cohort data and the 1kG reference panel underwent quality control using PLINK. Filters included removal of non-autosomal SNPs, SNPs with minor allele frequency < 0.01, SNP call rate < 95%, sample call rate < 95%, and SNPs significantly deviating from Hardy-Weinberg equilibrium ($p < 1x10^{-6}$). The QC'd datasets were then harmonized based on genomic position (hg19). Allele consistency (A1/A2) and potential strand issues were checked during merging with PLINK; SNPs with irresolvable mismatches were excluded. The harmonized and merged dataset was subsequently LD-pruned using PLINK (--indep-pairwise 50 5 0.2), removing SNPs in high linkage disequilibrium ($r^2 > 0.2$) within a 50kb window, stepping 5 SNPs at a time. Principal Component Analysis (PCA) was performed on the final merged, QC'd, and pruned dataset using the --pca function in PLINK, calculating the top 20 principal components (PCs). The first two PCs were visualized using ggplot2 in R (Figure S2), with samples colored by their 1kG super-population label (AFR, AMR, EAS, EUR, SAS) or study cohort membership, allowing for visual inspection of ancestry clustering.
To quantitatively assess ancestry, a Random Forest classifier was built using the randomForest R package. The model was trained using the first 10 PCs of the 1kG reference samples as predictor variables and their known super-population labels as the outcome. This trained model was then applied to the principal components of the study cohort samples to predict their probabilities of belonging to each of the five 1kG super-populations. The results were used to confirm the expected European ancestry of the study cohort.

Definition of criteria for metabolic syndrome
Metabolic syndrome was defined as the presence of 3 or more of the following 5 criteria at baseline, as defined by Alberti et al.[2]

1. *Elevated waist circumference:* ≥102 cm in males or ≥88 cm in females
2. *Elevated triglyceride levels:* ≥150 mg/dL or current pharmacotherapeutic treatment for elevated triglycerides
3. *Reduced HDL-C levels:* <40 in males or <50 in females or current pharmacotherapeutic treatment for low HDL-C
4. *Elevated blood pressure:* Systolic ≥130 and/or diastolic ≥85 mm Hg or current pharmacotherapeutic treatment for hypertension
5. *Elevated blood glucose:* HbA_{1c} ≥5·7 or current pharmacotherapeutic treatment for elevated glucose

Brain MRI acquisition
Patients underwent cranial MRI examinations at baseline within three days (DEDEMAS) or five days (DEMDAS) of stroke onset. All examinations were scanned on 3-Tesla systems (Siemens Healthineers, Erlangen, Germany). The following imaging sequences were acquired: 3D T1- weighted (T1w) magnetisation prepared rapid gradient echo (MPRAGE), 3D fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) with multiple diffusion directions, T2-weighted (T2w) turbo spin echo, and T2*-weighted (T2*w) fast low angle shot (FLASH) gradient echo. The protocols used per sequence have been described in detail previously.[3] There were differences between the imaging protocols used for the run-in phase study (DEDEMAS) and the multicentre DEMDAS study. These differences are minor (not relevant for analyses) due to differences in scanner hardware and software across sites with the exception of the first 18 patients that were recruited in DEDEMAS, who were scanned with a different protocol.[3] There were no major imaging protocol deviations, which led to an exclusion of one or more image series.

Brain volume and primary infarct volume
Normalised brain volume was defined as (brain volume + infarct volume) / total intracranial volume. Normalised infarct volume was defined as infarct volume / total intracranial volume.[3]

Assessment of small vessel disease markers
Conventional SVD markers on baseline MRI were assessed semi-quantitatively using widely accepted consensus criteria.[4,5] The following individual SVD markers were assessed: lacunes, white matter hyperintensities, cerebral microbleeds, and perivascular spaces. In earlier work, the assessment of these markers has been described in detail.[3] Normalised WMH volume was defined as WMH volume / total intracranial volume.

Assessment of diffusion MRI data
Microstructural tissue integrity was assessed using mean skeletonised mean diffusivity (MSMD) based on a single-shell diffusion-weighted imaging sequence. Diffusion MRI data were visually assessed and preprocessed including denoising, Gibbs artefact removal, and correction for head motion and eddy current-induced distortions. This was done using tools from MRtrix3 (mrtrix.org/, 'dwidenoise', 'mrdegibbs') and the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; version 5.0.11, 'eddy_correct'). To compute MSMD, we then employed a tract-based spatial statistics pipeline on DTI maps and a custom white matter skeleton mask, as done previously.[6,7]

Follow-up assessments
Participants and their informants were invited for in-person follow-up visits at 6, 12, 36, and 60 months post-stroke, during which they underwent comprehensive cognitive and functional assessments conducted by trained neuropsychologists, study nurses, and physicians. Additionally, telephone interviews were conducted at 3, 24, and 48 months post-stroke to collect clinical and cognitive data. A detailed battery of neuropsychological tests, covering five cognitive domains (executive function, memory, language, attention, and visuospatial function), and functional tests, including the modified Rankin Scale (mRS), Barthel Index (BI), and Instrumental Activities of Daily Living (IADL), were administered during in-person follow-ups. Standardised questionnaires were used to document new clinical events, medical treatments, and cardiovascular risk factors at the follow-ups.
To minimize attrition and missing data, a standardised protocol was followed to contact participants or their informants for follow-ups.[3] Initially, a trained study nurse contacted participants by telephone prior to each follow-up timepoint to schedule an in-person visit. If participants could not be reached by telephone, the nurse called their informants. In cases where neither the participant nor the informant could be reached, an invitation for an in-person visit was sent by mail. If there was still no response, the data manager contacted the local registration office to confirm whether the participant was alive or had changed addresses. If a new address was obtained, the steps were repeated to establish contact.
For participants who could be reached but were unable or unwilling to attend in-person visits, two alternative options were provided: first, they were offered the opportunity to complete portions of the study questionnaires via telephone interviews with study nurses. If this was not feasible, they were mailed the questionnaires with a request to complete and return them to the study site.

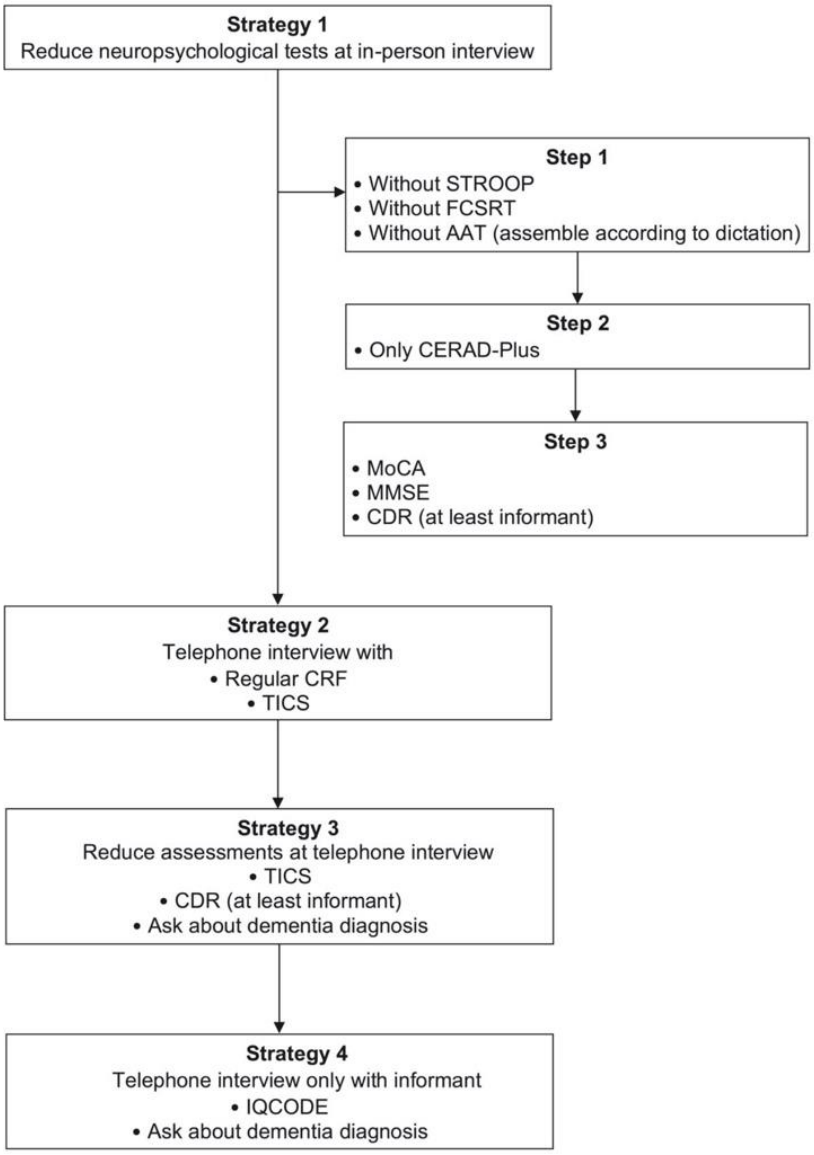
Cognitive follow-up assessments
At the in-person follow-up visits at 6, 12, 36, and 60 months post-stroke cognitive performance was assessed in five domains via a detailed neuropsychological test battery:

1. *Executive function*
   - "Trail Making Test Part B" from the "Consortium to Establish a Registry for Alzheimer's Disease Plus (CERAD-Plus)[8]" battery
   - "Stroop Colour-Word-Interference Test"[9]
2. *Memory*
   - "Word List Learning/Recall and Recognition" and "Figure Recall" from CERAD-Plus[8]
   - immediate and delayed recall of the "Rey-Osterrieth Complex Figure (ROCF)"[10]
3. *Language*
   - "Semantic and Phonemic Fluency" and "Boston Naming Test" from CERAD-Plus[8]
4. *Attention*
   - "Trail Making Test Part A" from CERAD-Plus[8]
   - "Digit-Symbol-Substitution Test of the Wechsler Intelligence Scale"[11]
5. *Visuospatial function*
   - "Figure Drawing Test" from CERAD-Plus[8]
   - copy test of ROCF[10]

We calculated test-specific z-scores based on published norms: (1) Z-scores of the CERAD test battery were based on published norms using a standardised program.[12] (2) Z-scores of Rey-Osterrieth complex figure-copy, immediate and delayed recall were calculated based on published norms corrected for age, sex, and education.[13] (3) Z-scores of the Stroop test were calculated based on published norms corrected for age, sex, and education.[14] (4) Z-scores of the number symbol test were calculated based on normative scores of the Wechsler Adult Intelligence Scale, Third Edition (WAID-III).[15]

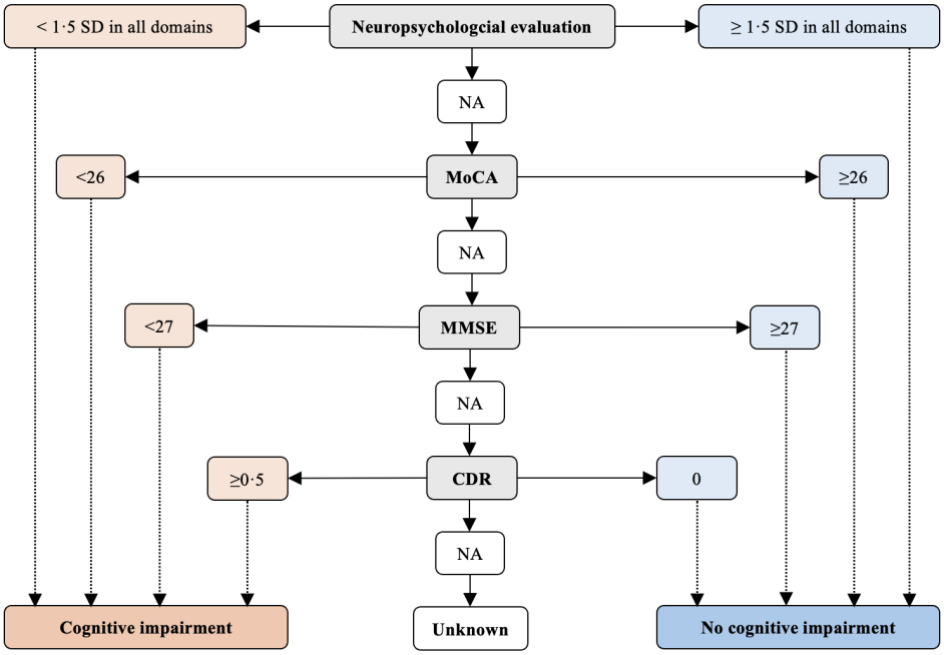
Furthermore, the "Clinical Dementia Rating Scale (CDR)[16]" was completed by both the study participant and their informant to assess dementia severity at each in-person follow-up visit. Short screening tests (Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA)) were repeatedly applied at baseline and in-person follow-up visits. The modified German version of the "Telephone Interview for Cognitive Status" (TICS) and a telephone version of the MoCA[17] were applied at the telephone interviews at 3, 24, and 48 months. All tests were performed and rated by centrally trained investigators.

If patients were unable or not willing to undergo the comprehensive neuropsychological test battery, the following hierarchical procedure to reduce the volume of cognitive testing was applied to minimize attrition and missing data:

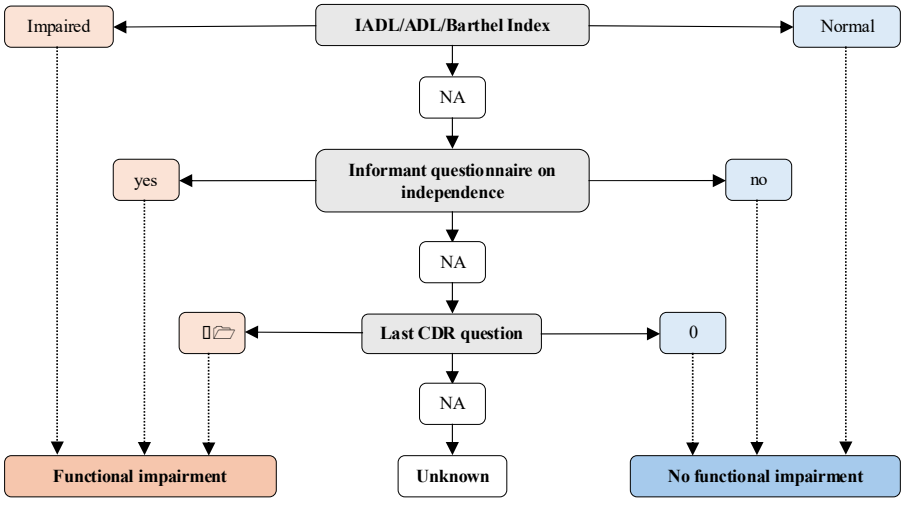

Strategy 1
Reduce neuropsychological tests at in-person interview
Step 1
• Without STROOP
• Without FCSRT
• Without AAT (assemble according to dictation)
Step 2
• Only CERAD-Plus
Step 3
• MoCA
• MMSE
• CDR (at least informant)
Strategy 2
Telephone interview with
• Regular CRF
• TICS
Strategy 3
Reduce assessments at telephone interview
• TICS
• CDR (at least informant)
• Ask about dementia diagnosis
Strategy 4
Telephone interview only with informant
• IQCODE
• Ask about dementia diagnosis

Step-by-step process of endpoint assessment

1. Identification of patients with cognitive impairment



2. Screening for functional impairment → isolated MCI or MCI + functional impairment



3. Consensus committee meeting assessing the DSM-V criteria → final differential diagnosis: MCI vs. dementia
    - Ruling out depression (in psychiatric assessment or CES-D ≥ 16) and delirium (physical examination or DRS > 15)
    - Determination if functional impairment is the result of cognitive decline
    - Definition of date of dementia diagnosis
    - Screening of medical notes of patients that had only home visits
    - Screening of medical files of all patients who died or were lost to follow-up

Loss to follow-up
Participants were considered lost to follow-up if they revoked consent to participate in the study or could not be contacted after multiple attempts via telephone, mail, or their informant. At study entry, participants provided consent for the investigators to access medical records and retrieve mortality data from the resident registration office. However, if consent was later revoked, obtaining this information was legally prohibited.

Data management and quality control
Demographic, clinical, and neuropsychological data from both baseline and follow-up visits, as well as telephone interviews, were initially collected by participating study sites using Case Report Forms (CRFs) specifically designed for this study. Completed CRFs were then sent to the coordinating center at the Institute for Stroke and Dementia Research (ISD), LMU Munich. Trained data managers conducted comprehensive quality control procedures. As a first step, each CRF was manually reviewed for completeness and screened for potential outliers and implausible values. Any discrepancies or missing data were resolved by contacting the study nurses at the respective sites. Data from the CRFs were subsequently digitised into a central database using TeleForm (Electric Paper GmBH, Lüneburg, Germany). Centralised plausibility checks were performed regularly using standardised algorithms to identify outliers or implausible entries. Whenever issues were detected, study nurses at the corresponding sites were consulted to verify and correct the data. Data management and central quality control were conducted using SAS version 9·4 (SAS Institute Inc., Cary, NC). Details of MRI image quality control have been reported previously.[3]

Supplementary statistical methods
Handling of quantitative variables

	Sociodemographic variables	**Clinical/cognitive acute phase deficits**	**Vascular and metabolic risk factors**	**Neuroimaging parameters**	**Pre-stroke cognition/function**
Continuous variables	age, educational attainment	NIHSS score, Barthel Index, Delirium Rating Scale score, MoCA score	BMI, systolic blood pressure, diastolic blood pressure, HbA_{1c}, LDL-C, HDL-C, triglycerides, count of metabolic syndrome components	normalised brain volume, normalised infarct volume, SVD score, lacune count, normalised WMH volume, CMB count, perivascular space grade, mean diffusivity	Modified Rankin Scale score, IQCODE score
Categorical variables	age: (a) tertiles [≤65 *vs* 66-73 *vs* ≥74], (b) dichotomous [<74 *vs* ≥74], educational attainment: dichotomous [≤12 *vs* >12]	NIHSS score: dichotomous [0-2 *vs* ≥3], acute phase cognitive impairment: dichotomous [MoCA <26 or MMSE <27 *vs* MoCA ≥26 or MMSE ≥27		lacune count: dichotomous [<3 *vs* ≥3]	

Age tertiles were determined based on the study sample. Age ≥74 represents the highest age tertile in our sample and is similar to previously used categorisation.[18] Educational attainment was categorised using a pre-defined and previously reported cut-off.[18-20] The admission NIHSS score cut-off was identified within the study sample using the maxstat.test function from the "maxstat" package in R, which determines the optimal cut point for separating groups based on the survival outcome.[21] An admission NIHSS ≥3, identified as the optimal cut-off, aligns with the "major stroke" definition used in the OxVasc study.[18] The lacune count cut-off was selected based on earlier reports.[22-24]

Primary outcome
Post-stroke dementia
Since death is a competing risk for PSD, we calculated the 5-year cumulative incidence of PSD using a Kaplan-Meier-estimator, adjusted for the competing risk of death.[25] Differences in cumulative incidence between subgroups of risk factors were evaluated using Gray's test.[26] Associations between baseline risk factors and 5-year PSD risk were assessed using cause-specific and Fine-Gray subdistribution Cox proportional hazard models, accounting for the competing risk of death.[27] The proportional hazards (PH) assumption was tested using the Grambsch and Therneau test based on Schoenfeld residuals and reported in Table S18. In cases where the PH assumption was violated, we used flexible parametric survival models with natural splines.[28] Risk factors were

selected based on previous (conflicting) evidence regarding their association with PSD and PSCI[18,20,29-32] or with dementia in non-stroke populations.[33,34]All multivariate Cox regression models included the covariables age, sex, education, and admission NIHSS score, based on previous evidence on the importance of these risk factors.[18,20]

Secondary outcomes

Early-onset and delayed-onset PSD

To explore the relationships between baseline risk factors and early-onset PSD (dementia diagnosed 3-6 months post-stroke) and delayed-onset PSD (diagnosis >6 months post-stroke), we used the "survSplit" function in R's "survival" package to divide the follow-up period into two discrete intervals: an early phase (≤6 months) and a later phase (>6 months).[25,32] The first part of the model assessed the relationship between baseline risk factors and early-onset PSD, while the second part evaluated their association with delayed-onset PSD. For the second part, individuals with early-onset PSD or those censored before 6 months post-stroke were excluded.[22,23] This effectively reset the 6-months mark as an arbitrary "new" T0, disregarding events that occurred prior.
We set the cut-point at 195 days (approximately 6·4 months) to account for the fact that most individuals completed their 6-month follow-up slightly later (median 6·2 [IQR 5·9-6·7]) than the exact 183-day mark. Sensitivity analyses applying earlier or later cut points yielded consistent results. Overall, 706 patients contributed to the analysis for early-onset PSD, and 617 of these also contributed to the analysis for delayed-onset PSD.

Following the Cox regression analysis, we calculated population attributable fractions (PAFs) for relevant binary risk factors for early-onset and delayed-onset PSD. PAFs represent the proportion of dementia cases in our study population that could theoretically have been prevented if the specified risk factor had been absent or eliminated. For each binary risk factor, PAFs and their 95% confidence intervals were calculated for 10,000 bootstrap resamples using the baseline prevalence of the risk factor in the respective subsample (706 and 617 patients for early- and delayed-onset PSD, respectively) and the adjusted HRs derived from multivariable Cox proportional hazards models adjusted for age, sex, education, admission NIHSS, and stroke recurrence. The difference in PAFs between the two periods was computed for each bootstrap iteration. The 2.5th and 97.5th percentiles of the bootstrap distribution of PAF differences were used to derive the 95% confidence interval.

Post-stroke cognitive impairment

Associations between baseline risk factors and post-stroke cognitive impairment (PSCI) were assessed over 60 months post-stroke as a combination of mild-cognitive impairment and dementia at the 6-, 12-, 36-, and 60-month follow-ups. To account for repeated measurements within individuals, we employed generalised estimating equations (GEEs) with a first-order autoregressive working correlation structure and robust SEs. GEE models were adjusted for age, sex, education, and admission NIHSS score.

False Discovery Rate (FDR) Correction

To account for multiple comparisons in the main analyses, we applied FDR correction using the Benjamini-Hochberg procedure across all tested risk factors for each outcome (PSD and PSCI). Specifically, we corrected for 48 statistical comparisons for PSD and 47 for PSCI, including cases where a single risk factor was represented as both a continuous and categorical variable.

Sensitivity and subgroup analyses

Subgroup analyses stratified the Cox regression models examining baseline risk factors for PSD by sex.
Sensitivity analyses extended the Cox models for 5-year PSD risk, early-onset, and delayed-onset PSD by including the additional covariates acute stroke treatment, recurrent stroke, and acute phase cognitive impairment. Recurrent stroke introduces a time-dependent risk for PSD, as it constitutes a separate time-to-event outcome. Therefore, for sensitivity analyses incorporating recurrent stroke, we divided the follow-up period for patients who experienced a recurrent stroke without a prior dementia diagnosis into two phases: pre-recurrence and post-recurrence.[25] This approach accounted for different PSD risk before and after the recurrence, resulting in a larger sample size for the sensitivity analysis. Additionally, the analysis for early- versus delayed-onset PSD was conducted with a 12-month instead of the original 6-moth cut-off.

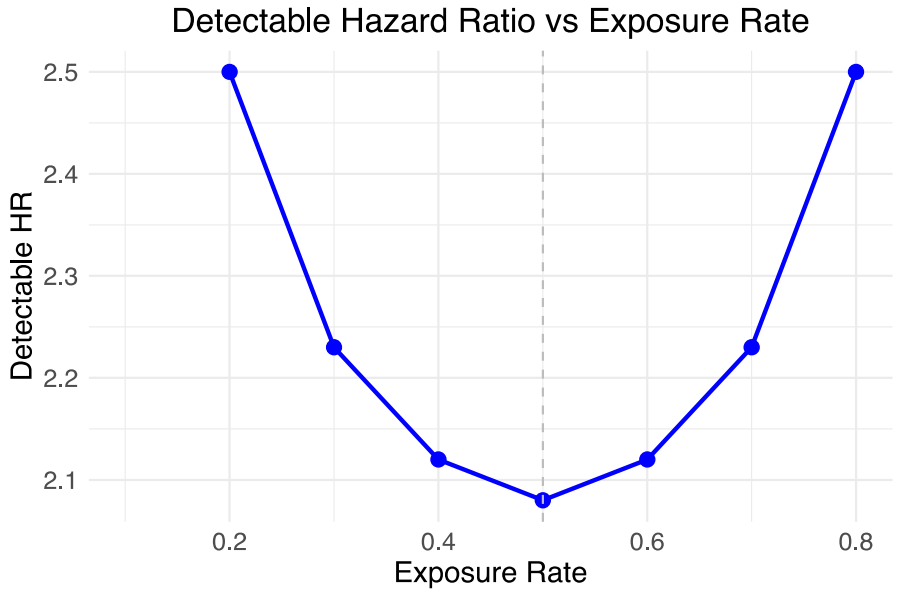
Missing data

Baseline variables generally had missing value rates below 10%, except for acute phase MoCA score, normalised brain volume, normalised infarct volume, normalised WMH volume, and APOE genotype (**Table S1**). Data for the model covariates age, sex, education, and admission NIHSS score were complete. Missingness was assumed to be at random, and the main analyses were conducted after excluding patients with missing values for the main independent variable.

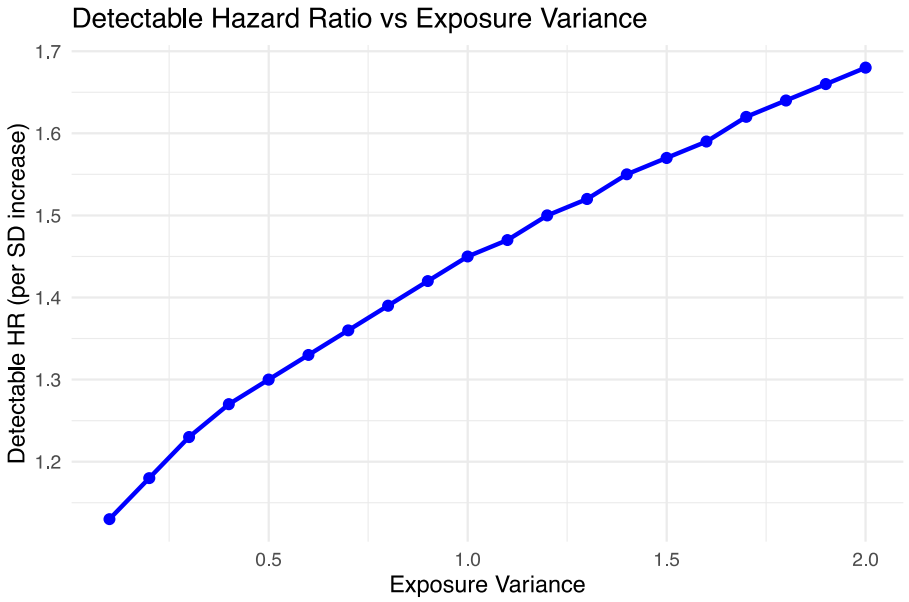
Power calculation

A priori power calculations for survival analysis estimated that a sample size of 600 would enable us to detect associations between risk factors (10% exposure rate) and PSD with a HR of 2·0 with a power of 91%.[19]

Post-hoc, we calculated the minimum detectable effect size (HR) for different risk factor prevalence rates for binary variables and for different variances for continuous variables (per SD), respectively. The graphs and tables below illustrate the effect sizes detectable with 80% power and a 5% significance level, given the final sample size of 706 patients contributing to survival analysis and the cumulative 5-year PSD incidence of 8·3%. This observed incidence was lower than initially anticipated in the a priori power calculation.

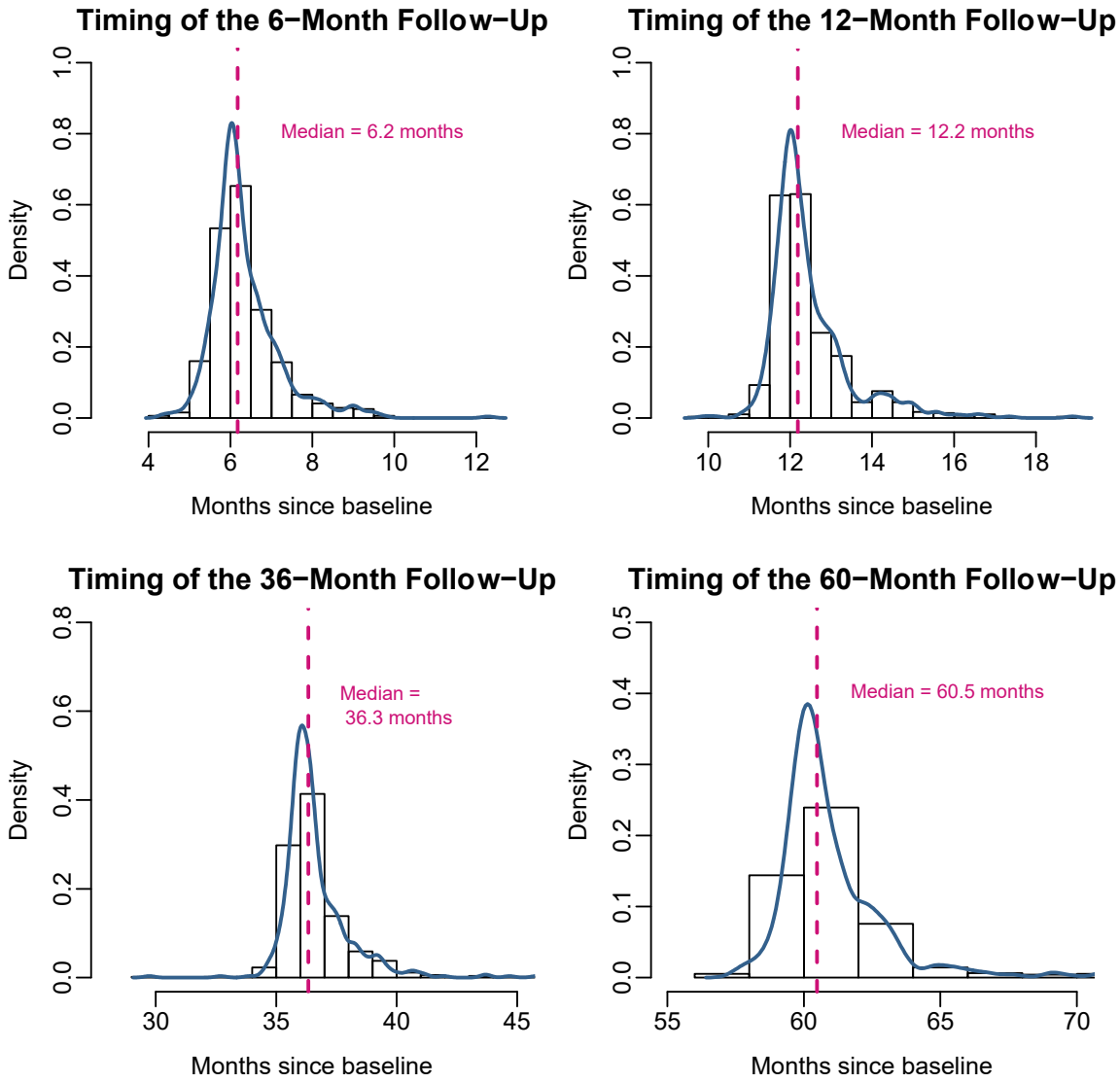


Risk factor prevalence	10%	20%	30%	40%	50%	60%	70%	80%
Detectable hazard ratio	NA	2·50	2·23	2·12	2·08	2·12	2·23	2·50



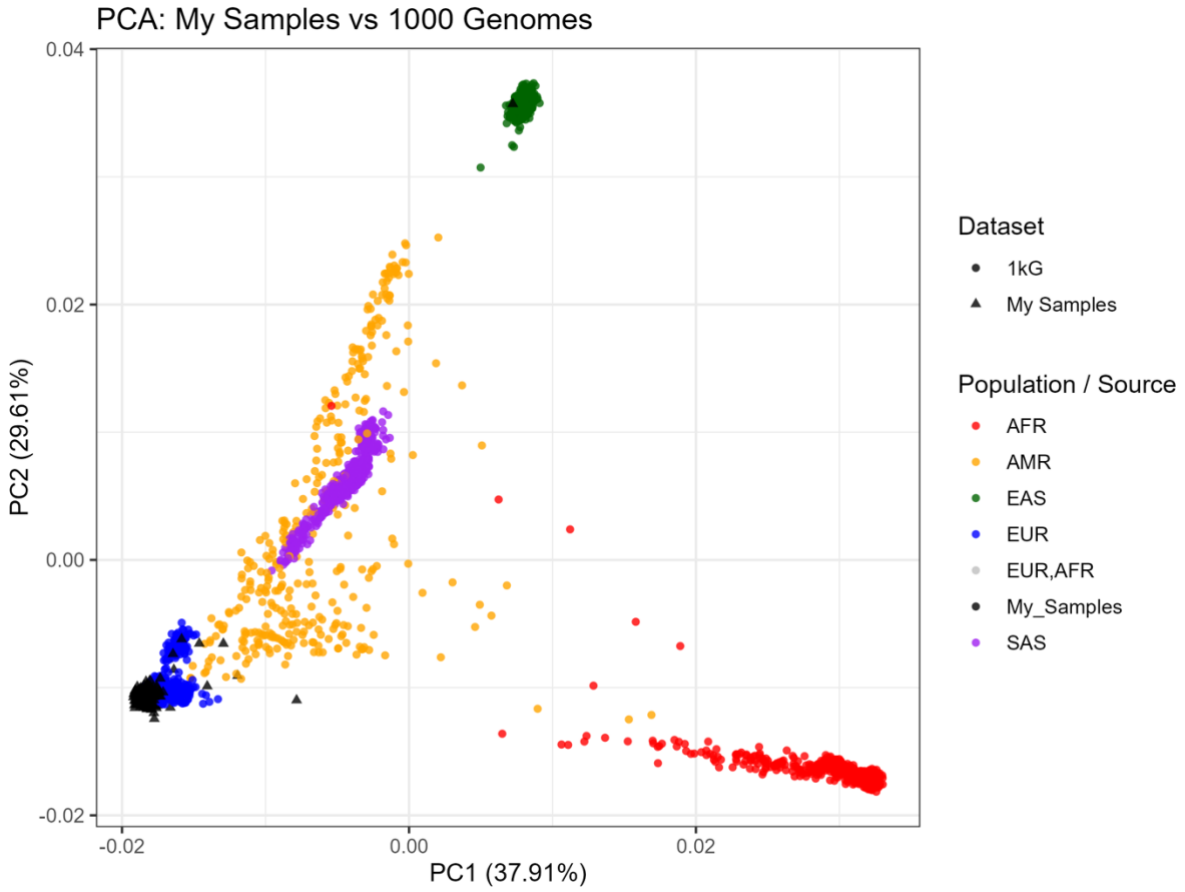
Risk factor variance	0·25	0·5	0·75	1·0	1·25	1·5	1·75	2·0
Detectable hazard ratio (per SD increase)	1·21	1·30	1·38	1·45	1·51	1·57	1·63	1·68

Figure S1: Distribution of time since stroke for each follow-up time point



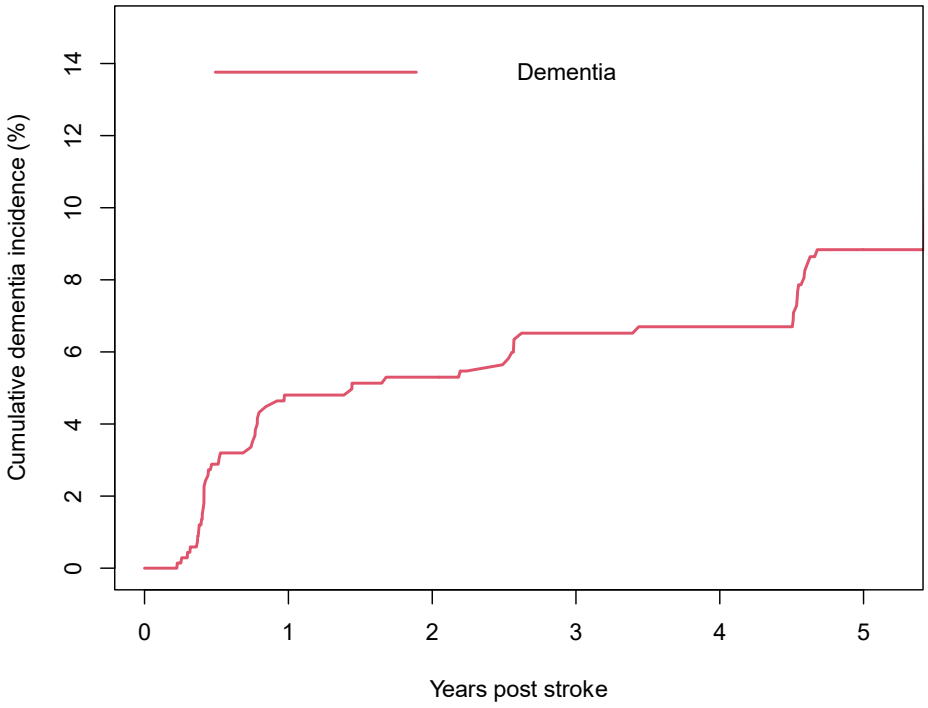
Distribution and density curve of time since baseline for each of the distinct in-person follow-up time points including the respective study sample medians (vertical dashed lines). Exact data on time since stroke were available for 637 participants at 6 months, for 584 at 12 months, for 527 at 36 months, and for 489 at 60 months.

Figure S2: Genetic ancestry of the study cohort confirmed by PCA with 1000 genomes



Principal Component Analysis (PCA) of the DEDEMAS/DEMDAS study cohort (n=599) and 1000 Genomes Project (1kG) Phase 3 reference panel (N=2,504) to assess continental-level ancestry. PCA was performed using pruned, quality-controlled genotype data (hg19) with the top two PCs plotted. Each point represents an individual from either the 1kG panel (colored by super-population) or the study cohort (black triangles). The study samples cluster closely with the European (EUR) reference group, confirming the cohort's expected genetic ancestry. PCA was conducted in PLINK v1.9 and visualized in R v4.4.3 using ggplot2.

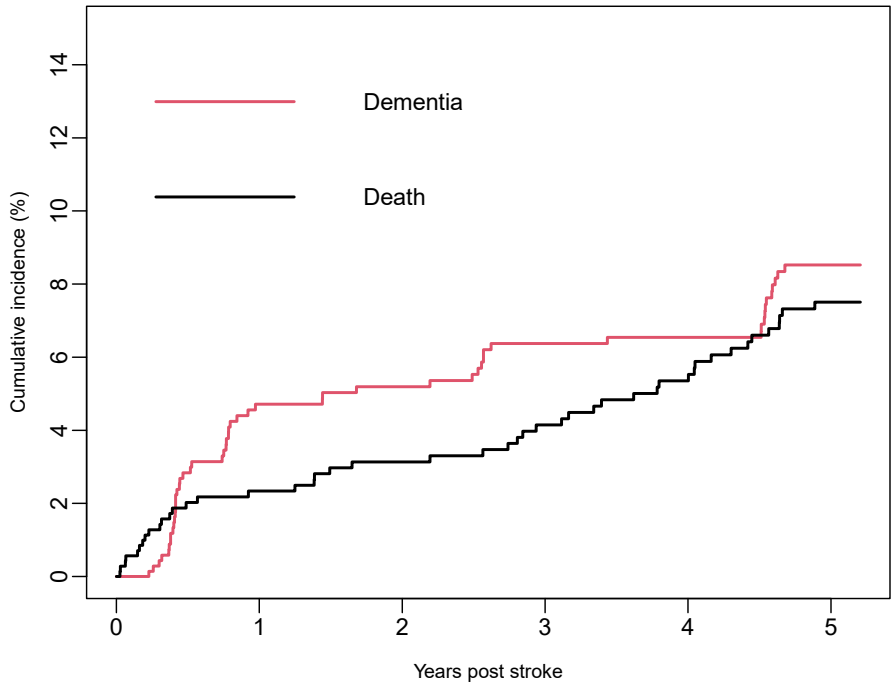
Figure S3: Cumulative incidence curve for dementia over 5 years post stroke



Number at risk	706	591	558	527	500	342

Cumulative Kaplan-Meier curve of dementia incidence during five years after stroke in the total DEDEMAS-DEMDAS cohort (N=706).

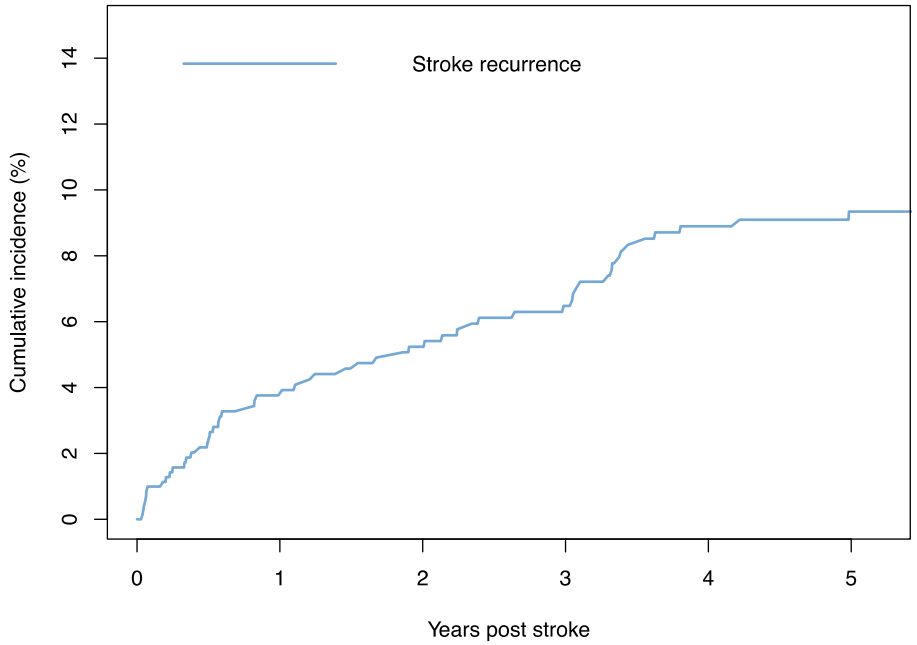
Figure S4: Cumulative incidence for dementia and death over 5 years post stroke



Number at risk	706	591	558	527	501	343

Competing risks cumulative incidence for dementia and death during five years after stroke.

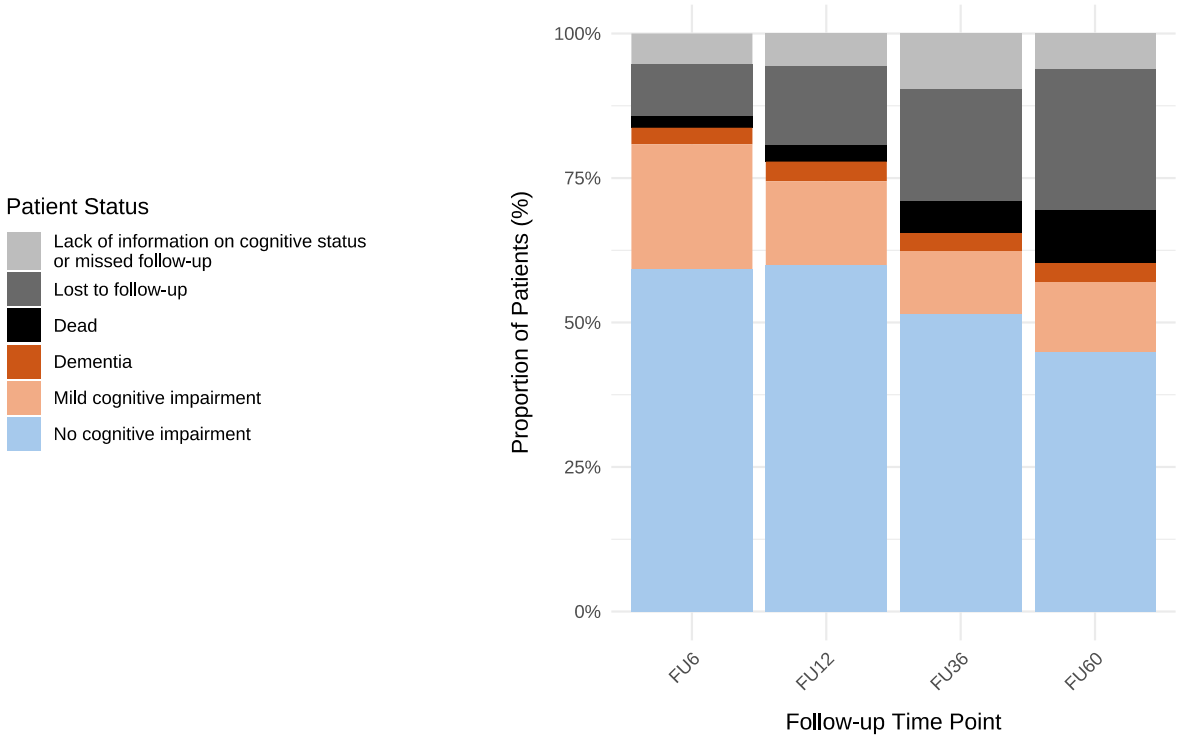
Figure S5: Cumulative incidence curve for stroke recurrence over 5 years post stroke



Number at risk	706	595	548	515	484	370

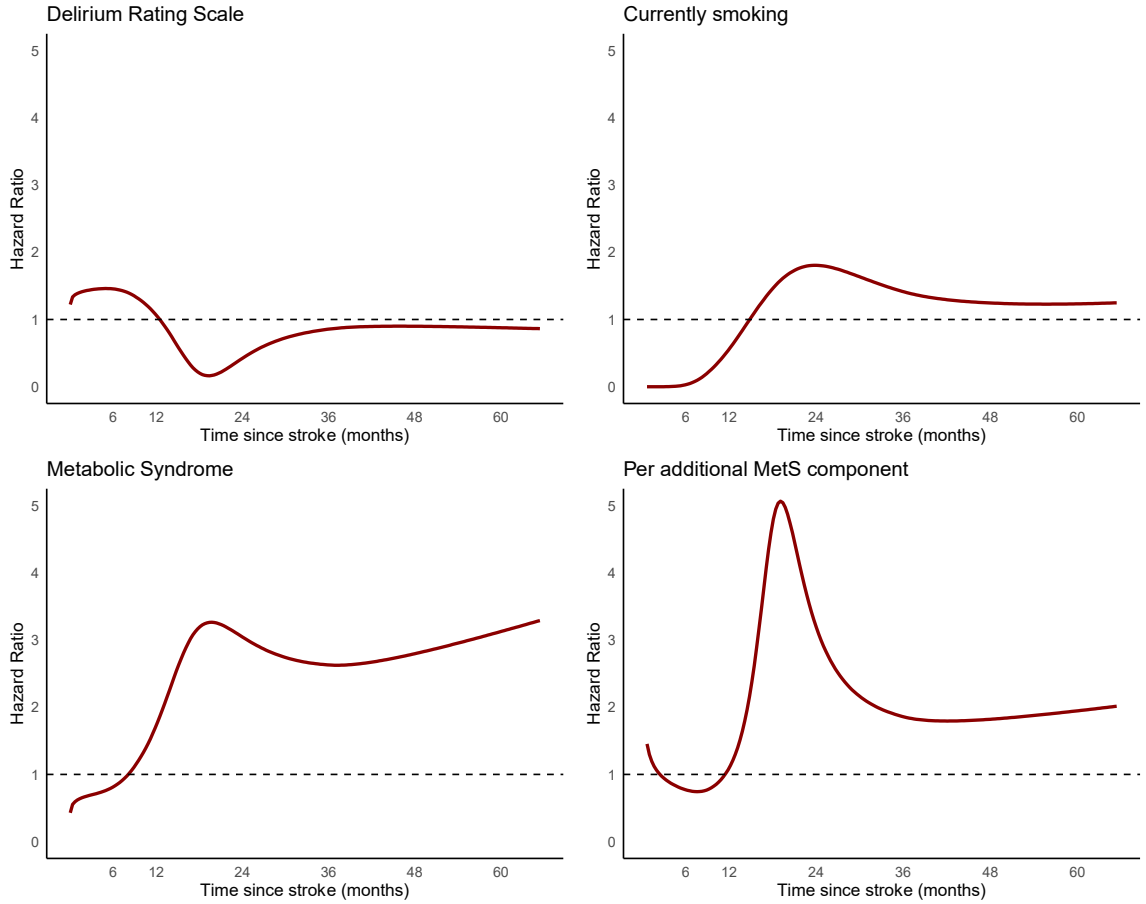
Kaplan-Meier cumulative incidence curve for stroke recurrence during five years after stroke.

Figure S6: Proportion of endpoints per follow-up time point



Proportion of the initial 736 patients at each in-person follow-up who had no cognitive impairment, mild cognitive impairment, or dementia; who were dead or lost to follow-up; or for who information was missing because they missed follow-up assessment or information on cognitive status were insufficient. At the 6-, 12-, 36-, and 60-month follow-up, 638, 585, 528, and 494 patients were assessed, respectively.

Figure S7: Time-varying associations with PSD risk



Time-varying hazard ratios for post-stroke dementia (PSD) by Delirium Rating Scale score (top left), currently smoking at the time of stroke (top right), Metabolic Syndrome (bottom left), and per additional MetS component (bottom right). Each panel displays the estimated hazard ratio (HR, solid line) over time since stroke, with 95% confidence intervals (shaded area), based on flexible parametric survival models[28] allowing for time-varying effects (detailed in **Table S19**). While Delirium Rating Scale score, Metabolic Syndrome, and count of MetS components show significant time-dependent associations with PSD risk, smoking showed no significant association at any time point. Models were adjusted for age, sex, education, and admission NIHSS. MetS=Metabolic Syndrome. NIHSS=National Institutes of Health Stroke Scale.

Table S1: Baseline characteristics of the entire DEDEMAS-DEMDAS study sample

	Total sample (N = 736)	Missing data
Study		
DEDEMAS[a]	136 (18·5%)	··
DEMDAS	600 (81·5%)	··
Munich-LMU[a]	219 (29·7%)	··
Munich-TUM[b]	69 (9·4%)	··
Berlin-1[c]	33 (4·5%)	··
Berlin-2[d]	38 (5·2%)	··
Bonn[e]	105 (14·3%)	··
Göttingen[f]	81 (11·0%)	··
Magdeburg[g]	55 (7·5%)	··
Sociodemographic factors		
Age (years)	68·0 (11·2)	0 (0%)
Age ≥ 74 years	261 (35·5%)	0 (0%)
Female sex	245 (33·3%)	0 (0%)
Education (years)	13 (12-16)	0 (0%)
Education ≤ 12 years	292 (39·7%)	0 (0%)
Pre-stroke employment status		5 (0·7%)
Working full-time	185 (25·3%)	··
Working part-time	53 (7·2%)	··
On sick leave	4 (0·5%)	··
Retired	479 (65·5%)	··
Unemployed (seeking employment)	10 (1·4%)	··
Pre-stroke living situation*[1]		0 (0%)
Private household, living alone	191 (25·9%)	··
Private household, with spouse/life partner	522 (70·9%)	··
Private household, with children	56 (7·6%)	··
Private household, with other person/s	6 (0·8%)	··
Retirement home	2 (0·3%)	··
Genetic ancestry		137 (18·6%)
European	597 (99·7%)	··
Ad Mixed American	1 (0·2%)	··
East Asian	1 (0·2%)	··
Clinical/cognitive acute phase deficits		
Admission NIHSS score	3 (1-5)	0 (0%)
Admission NIHSS ≥3	387 (52·6%)	0 (0%)
Barthel Index score	100 (80-100)	4 (0·5%)
Delirium Rating Scale score	0 (0-1)	0 (0%)
Acute phase MoCA score	25 (23-28)	89 (12·1%)
Acute phase cognitive impairment*[2]	382/709 (53·9%)	27 (3·7%)
Cardiovascular risk factors		
Hypertension	571 (77·6%)	0 (0%)
Diabetes mellitus	150 (20·4%)	0 (0%)
Dyslipidaemia	229 (31·1%)	0 (0%)
Current smoking	171 (23·2%)	0 (0%)
Regular alcohol consumption	557 (75·7%)	0 (0%)
Atrial fibrillation	148 (20·1%)	0 (0%)
Prior history of stroke	79 (10·7%)	0 (0%)
Ischaemic heart disease	80 (10·9%)	0 (0%)
BMI (kg/m^2)	27·0 (4·3)	1 (0·1%)
Systolic blood pressure (mmHg)	139 (129-150)	5 (0·7%)
Diastolic blood pressure (mmHg)	80 (71-86)	5 (0·7%)
HbA_{1c} (%)	5·7 (5·4-6·1)	50 (6·8%)
LDL cholesterol (mg/dL)	126 (103-154)	22 (3·0%)
HDL cholesterol (mg/dL)	48 (40-58)	27 (3·7%)
Triglycerides (mg/dL)	121 (91-170)	44 (6·0%)
Metabolic syndrome components*[3]		
Abdominal obesity	391/689 (56·7%)	47 (6·4%)
Elevated triglycerides	233/692 (33·7%)	44 (6·0%)

Reduced HDL cholesterol	231/709 (32·6%)	27 (3·7%)
Elevated blood pressure	653/735 (88·8%)	1 (0·1%)
Prediabetes or diabetes mellitus	386/686 (56·3%)	50 (6·8%)
Metabolic syndrome (≥ 3 of the above components present)	365 (49·3%)	0 (0%)
Index stroke classification		
Ischaemic stroke	715 (97·1%)	0 (0%)
TOAST classification of acute ischaemic stroke subtype		0 (0%)
Large artery atherosclerosis	166 (22·6%)	··
Cardioembolism	164 (22·3%)	··
Small artery occlusion	86 (11·7%)	··
Other determined aetiology	29 (3·9%)	··
Undetermined aetiology	270 (36·7%)	··
Haemorrhagic stroke	21 (2·8%)	··
Acute stroke treatment		
Intravenous thrombolysis (IVT)	188 (25·5%)	0 (0%)
Endovascular thrombectomy (EVT)	78 (10·6%)	0 (0%)
IVT + EVT	57 (7·7%)	0 (0%)
Any reperfusion therapy (IVT and/or EVT)	209 (28·4%)	0 (0%)
Neuroimaging parameters		
Normalised brain volume (%)	67·8 (64·1-71·6)	79 (10·7%)
Stroke lesion volume (mm^3)	2288 (526-12408)	72 (9·8%)
Normalised infarct volume (%)	0·15 (0·03-0·78)	78 (10·6%)
Small vessel disease score		70 (9·5%)
0	259/666 (38·9%)	··
1	201/666 (30·2%)	··
2	136/666 (20·4%)	··
3	54/666 (8·1%)	··
4	16/666 (2·4%)	··
Lacune count	0 (0-0)	65 (8·8%)
≥3 lacunes	12 (1·8%)	65 (8·8%)
Normalised white matter hyperintensity volume (%)	0·22 (0·08-0·52)	78 (10·6%)
Cerebral microbleed count	0 (0-0)	70 (9·5%)
Perivascular space grade	1 (1-2)	66 (9·0%)
Mean skeletonised mean diffusivity (z-score)	-0·12 (-0·69-0·63)	108 (14·7%)
Genetic risk factors		
APOE genotype		142 (19·3%)
0 ε4 allele	463/594 (77·9%)	··
1 ε4 allele	122/594 (20·5%)	··
2 ε4 alleles	9/594 (1·5%)	··
Pre-stroke clinical/cognitive function		
Modified Rankin Scale score before stroke	0 (0-0)	0 (0%)
IQCODE score	48 (48-49)	60 (8·1%)

Data are n (%), median (IQR), mean (SD), or n/N (%). DEDEMAS (Determinants of Dementia After Stroke) represents the pilot phase of the DEMDAS study. APOE=apolipoprotein E. BMI=body-mass index. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL=low-density lipoprotein. MoCA=Montreal Cognitive Assessment. NIHSS=National Institutes of Health Stroke Scale. TOAST=Trial of Org 10172 in Acute Stroke Treatment.

*[1] More than one can apply

*[2] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).

*[3] Defined according to Alberti et al.[2]

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[b]Klinik für Neurologie, Klinikum rechts der Isar, Technische Universität München

[c]Center for Stroke Research Berlin, Department of Neuroloy – Campus Charité Mitte, Charité – Universitätsmedizin Berlin

[d]Center for Stroke Research Berlin, Department of Neurology – Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin

[e]Klinik und Poliklinik für Neurologie, Universitätsklinikum Bonn

[f]Klinik für Neurologie, University Medical Center Göttingen

[g]Universitätsklinikum Magdeburg

Table S2: Baseline characteristics of DEDEMAS-DEMDAS stratified by sex

	Male (n = 491)	Female (n = 245)	P-value
Sociodemographic variables			
Age (years)	67·2±10·8	69·6±11·7	0·007
Age ≥74 years	159 (32·4%)	102 (41·6%)	0·02
Education (years)	14 (12-17)	12 (11-14)	<0·0001
Education ≤12 years	162 (33·0%)	130 (53·1%)	<0·0001
Clinical/cognitive acute phase deficits			
Admission NIHSS score	3 (1-5)	3 (1-5)	0·43
Admission NIHSS ≥3	252 (51·3%)	135 (55·1%)	0·37
Barthel Index score	100 (85-100)	100 (80-100)	0·30
Delirium rating scale score	0 (0-1)	0 (0-1)	0·70
Acute phase MoCA score	25 (22-27)	26 (23-28)	0·04
Acute phase cognitive impairment*[1]	273/476 (57·4%)	109/233 (46·8%)	0·01
Cardiovascular risk factors			
Hypertension	375 (76·4%)	196 (80·0%)	0·30
Diabetes mellitus	105 (21·4%)	45 (18·4%)	0·40
Dyslipidaemia	152 (31·0%)	77 (31·4%)	1·00
Current smoking	119 (24·2%)	52 (21·2%)	0·40
Regular alcohol consumption	396 (80·7%)	161 (65·7%)	< 0·0001
Atrial fibrillation	91 (18·5%)	57 (23·3%)	0·20
Prior history of stroke	52 (10·6%)	27 (11·0%)	1·00
Ischaemic heart disease	61 (12·4%)	19 (7·8%)	0·07
BMI (kg/m^2)	27·1±4·0	26·7±4·8	0·30
Systolic blood pressure (mmHg)	140 (129-151)	138 (128-150)	0·20
Diastolic blood pressure (mmHg)	80 (73-88)	78 (70-84)	0·0002
HbA_{1c} (%)	5·7 (5·4-6·2)	5·7 (5·4-6·1)	0·30
LDL cholesterol (mg/dL)	124 (102-150)	132 (104-156)	0·02
HDL cholesterol (mg/dL)	45 (38-52)	56 (46·4-64·5)	<0·0001
Triglycerides (mg/dL)	122 (91-177)	120 (91-151)	0·20
Criteria for Metabolic syndrome*[2]			
Abdominal obesity	225/457 (49·2%)	166/232 (71·6%)	<0·0001
Elevated triglycerides	168/463 (36·3%)	65/229 (28·4%)	0·05
Reduced HDL cholesterol	150/475 (31·6%)	81/235 (34·5%)	0·50
Elevated blood pressure	432/490 (88·2%)	221/245 (90·2%)	0·48
Prediabetes/Diabetes mellitus	263/462 (56·9%)	123/233 (52·8%)	0·34
Metabolic syndrome (≥3 of the above components present)	237 (48·3%)	128 (52·2%)	0·35
Index stroke classification			
Ischaemic stroke	475 (96·7%)	240 (98·0%)	0·48
TOAST classification of acute ischaemic stroke subtype			0·03
Large artery atherosclerosis	117 (23·8%)	49 (20·0%)	··
Cardioembolism	97 (19·8%)	67 (27·3%)	··
Small artery occlusion	55 (11·2%)	31 (12·7%)	··
Other determined aetiology	25 (5·1%)	4 (1·6%)	··
Undetermined aetiology	181 (36·9%)	89 (36·3%)	··
Haemorrhagic stroke	16 (3·3%)	5 (2·0%)	0·48
Acute stroke treatment			
Any reperfusion therapy (IVT and/or EVT)	139 (28·3%)	70 (28·6%)	1·00
Neuroimaging parameters			
Normalised brain volume (%)	67·8 (64·4-71·6)	67·6 (63·9-71·6)	0·74
Infarct volume (mm^3)	2352 (528-14960)	2168 (520-7256)	0·03
Normalised stroke lesion volume (%)	0·16 (0·03-0·97)	0·15 (0·03-0·54)	0·12
Small vessel disease score			0·17
0	180/444 (40·5%)	79/222 (35·6%)	··
1	126/444 (28·4%)	75/222 (33·8%)	··
2	85/444 (19·1%)	51/222 (23·0%)	··
3	42/444 (8·5%)	12/222 (5·4%)	··
4	11/444 (2·5%)	5/222 (2·2%)	··
Lacune count	0 (0-0)	0 (0-0)	0·01
≥3 lacunes	10/446 (2·2%)	2/225 (0·9%)	0·30

Normalised white matter hyperintensity volume (%)	0·20 (0·06-0·50)	0·24 (0·10-0·60)	0·01
Cerebral microbleed count	0 (0-0)	0 (0-0)	0·23
Perivascular space grade	1 (1-2)	1 (1-2)	0·50
Mean skeletonised mean diffusivity (z-score)	-0·22 (-0·81-0·48)	-0·05 (-0·63-0·77)	0·009
Genetic risk factors			
APOE genotype			0·36
0 ε4 allele	307/400 (76·7%)	156/194 (80·4%)	··
1 ε4 allele	88/400 (22·0%)	34/194 (17·5%)	··
2 ε4 alleles	5/400 (1·2%)	4/194 (2·1%)	··
Pre-stroke clinical/cognitive function			
mRS before stroke	0 (0-0)	0 (0-0)	0·71
IQCODE score	48 (48-49)	48 (48-49)	0·68

Data are n (%), median (IQR), mean (SD), or n/N (%). APOE=apolipoprotein E. BMI=body-mass index. EVT=endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=intravenous thrombolysis. LDL=low-density lipoprotein. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. TOAST=Trial of Org 10172 in Acute Stroke Treatment.
*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).
*[2] Defined according to Alberti et al.[2]

Table S3: Loss to follow-up and death by study centre

	Loss to follow-up (N = 179)					
Study centre	**Initial N**	**Between BL and FU6**	**Between FU6 and FU12**	**Between FU12 and FU36**	**Between FU36 and FU60**	**Total lost**
DEDEMAS	136	4	7	3	10	24 (17·6%)
DEMDAS	600					
Munich-LMU	219	19	6	18	12	55 (25·1%)
Munich-TUM	69	11	3	3	2	19 (27·5%)
Berlin-1	33	0	2	0	1	3 (9·1%)
Berlin-2	38	5	0	2	0	7 (18·4%)
Bonn	105	10	8	5	6	29 (27·6%)
Göttingen	81	8	3	3	8	22 (27·2%)
Magdeburg	55	9	3	7	1	20 (36·4%)
Total	736	66	32	41	40	179 (24·3%)

	Death (before LTFU, N = 63)					
Study centre	**Initial N**	**Between BL and FU6**	**Between FU6 and FU12**	**Between FU12 and FU36**	**Between FU36 and FU60**	**Total died**
DEDEMAS	136	3	1	9	2	15 (11·0%)
DEMDAS	600					
Munich-LMU	219	9	2	7	10	28 (13·2%)
Munich-TUM	69	1	2	··	1	4 (5·8%)
Berlin-1	33	··	1	1	2	4 (12·1%)
Berlin-2	38	··	··	··	4	4 (10·5%)
Bonn	105	··	··	1	1	2 (1·9%)
Göttingen	81	1	··	2	··	3 (3·7%)
Magdeburg	55	1	··	1	1	3 (5·4%)
Total	736	15	6	21	21	63 (8·6%)

Breakdown of patients lost to follow-up (top) and who died (bottom) during the 5-year study period, by centre and follow-up period. Deaths do not include 5 deaths which occurred after the patients were lost to follow-up.

Table S4: Reasons for death and loss to follow-up during 5 years of follow-up

Reason for drop-out	**Cause/Reason**	**n (%)**
Death (n = 68) *	Brain haemorrhage	3 (4·4)
	Cardiac failure/arrest	4 (5·9)
	Consequences of SARS-CoV2 infection	1 (1·5)
	Infections	3 (4·4)
	Malignant neoplasms	13 (19·1)
	Myocardial infarction	4 (5·9)
	Pulmonary fibrosis	1 (1·5)
	Recurrent infarct	1 (1·5)
	Sepsis/multiorgan failure	10 (14·7)
	Stroke-related complications	2 (2·9)
	Unknown	26 (38·2)
Loss to Follow-up (n = 179)	Failed attempt to get in contact	21 (11·7)
	Moved/distance too long	8 (4·5)
	Other disease	5 (2·8)
	Other/Unknown	5 (2·8)
	Poor general condition	36 (20·1)
	Psychiatric disorder	2 (1·1)
	Revocation of consent	102 (57·0)

*Five deaths were recorded after the patients were lost to follow-up, three due to multiorgan failure, the other two due to an unknown cause

Table S5: Baseline characteristics of stroke survivors who dropped out of the study due to death or loss to follow-up and those who did not

	Followed up until the end of the study (n = 494)	Dropped out early (death or LTFU, n = 242)	P-value
Sociodemographic variables			
Age (years)	66·4±10·8	71·4±11·1	< 0·0001
Age ≥74 years	148 (30·0%)	113 (46·7%)	< 0·0001
Female sex	173 (35·0%)	72 (29·8%)	0·18
Education (years)	13 (12-17)	13 (11-15)	0·02
Education ≤12 years	187 (37·9%)	105 (43·4%)	0·17
Clinical/cognitive acute phase deficits			
Admission NIHSS score	3 (1-5)	3 (1-5)	0·57
Admission NIHSS ≥3	250 (50·6%)	137 (56·6%)	0·15
Barthel Index score	100 (85-100)	95 (72-100)	0·0003
Delirium rating scale score	0 (0-1)	0 (0-1)	0·31
Acute phase MoCA score	26 (23-28)	24 (22-26)	< 0·0001
Acute phase cognitive impairment*[1]	225 (46·3%)	157 (70·4%)	< 0·0001
Cardiovascular risk factors			
Hypertension	372 (75·3%)	199 (82·2%)	0·04
Diabetes mellitus	90 (18·2%)	60 (24·8%)	0·05
Dyslipidaemia	147 (29·8%)	82 (33·9%)	0·29
Current smoking	1110 (22·3%)	61 (25·2%)	0·43
Regular alcohol consumption	377 (76·3%)	180 (74·4%)	0·63
Atrial fibrillation	84 (17·0%)	64 (26·4%)	0·004
Prior history of stroke	45 (9·1%)	34 (14·0%)	0·06
Ischaemic heart disease	51 (10·3%)	29 (12·0%)	0·58
BMI (kg/m^2)	27·1±4·2	26·9±4·4	0·48
Systolic blood pressure (mmHg)	138 (128-150)	142 (130-152)	0·03
Diastolic blood pressure (mmHg)	80 (70-86)	80 (73-88)	0·30
HbA_{1c} (%)	5·7 (5·4-6·1)	5·8 (5·5-6·2)	0·04
LDL cholesterol (mg/dL)	124 (103-152)	129 (103-156)	0·47
HDL cholesterol (mg/dL)	49 (40-59)	45 (38-5)	0·01
Triglycerides (mg/dL)	122 (91-172)	118 (90-163)	0·52
Criteria for Metabolic syndrome*[2]			
Abdominal obesity	266/469 (56·7%)	125/220 (56·8%)	1·00
Elevated triglycerides	158/462 (34·2%)	75/230 (32·6%)	0·74
Reduced HDL cholesterol	144/476 (30·3%)	87/233 (37·4%)	0·07
Elevated blood pressure	434/493 (88·0%)	219/242 (90·5%)	0·38
Prediabetes/Diabetes mellitus	247/463 (53·3%)	139/232 (59·9%)	0·12
Metabolic syndrome (≥3 of the above components present)	233 (47·2%)	132 (54·5%)	0·07
Index stroke classification			
Ischaemic stroke	480 (97·2%)	235 (97·1%)	0·83
TOAST classification of acute ischaemic stroke subtype			0·40
Large artery atherosclerosis	113 (22·9%)	53 (21·9%)	··
Cardioembolism	98 (20·0%)	65 (26·9%)	··
Small artery occlusion	57 (11·5%)	29 (12·0%)	··
Other determined aetiology	20 (4·0%)	9 (3·7%)	··
Undetermined aetiology	191 (38·7%)	79 (32·6%)	··
Haemorrhagic stroke	14 (2·8%)	7 (2·9%)	0·83
Acute stroke treatment			
Any reperfusion therapy (IVT and/or EVT)	152 (30·8%)	57 (23·6%)	0.05
Neuroimaging parameters			
Normalised brain volume (%)	68·6 (65·1-72·3)	66·0 (62·5-69·9)	< 0·0001
Infarct volume (mm^3)	2484 (512-13122)	2088 (546-9830)	0·57
Normalised stroke lesion volume (%)	0·16 (0·03-0·81)	0·14 (0·04-0·62)	0·59
Small vessel disease score			0·002
0	194/456 (42·5%)	65/210 (31·0%)	··
1	141/456 (30·9%)	60/210 (28·6%)	··
2	84/456 (18·4%)	52/210 (24·8%)	··
3	30/456 (6·6%)	24/210 (11·4%)	··
4	7/456 (1·5%)	9/210 (4·3%)	··
Lacune count	0 (0-0)	0 (0-0)	0·003
≥3 lacunes	4/457 (0·9%)	8/214 (3·7%)	0·02
Normalised white matter hyperintensity volume (%)	0·20 (0·06-0·43)	0·33 (0·11-0·81)	< 0·0001
Cerebral microbleed count	0 (0-0)	0 (0-0)	0·47
Perivascular space grade	1 (1-2)	1 (1-2)	0·0002
Mean skeletonised mean diffusivity (z-score)	-0·26 (-0·88-0·43)	0·19 (-0·45-1·02)	< 0·0001
Genetic risk factors			
APOE genotype			0·06
0 ε4 allele	324/406 (79·8%)	139/188 (73·9%)	··
1 ε4 allele	74/406 (18·2%)	48/188 (25·5%)	··
2 ε4 alleles	8/406 (2·0%)	1/188 (0·53%)	··
Pre-stroke clinical/cognitive function			

mRS before stroke	0 (0-0)	0 (0-0)	0·12
IQCODE score	48 (48-49)	48 (48-50)	0·03

Data are n (%), median (IQR), mean (SD), or n/N (%). APOE=apolipoprotein E. BMI=body-mass index. EVT=endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=intravenous thrombolysis. LDL=low-density lipoprotein. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. TOAST=Trial of Org 10172 in Acute Stroke Treatment.
*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).
*[2] Defined according to Alberti et al.[2]

Table S6: Baseline characteristics of stroke survivors with early- versus delayed-onset PSD

	Early-onset PSD (n = 21)	Delayed-onset PSD (n = 34)	P-value
Sociodemographic variables			
Age (years)	79·4 (8·6)	74·7 (9·4)	0·07
Age ≥74 years	17 (81·0%)	21 (61·8%)	0·20
Female sex	7 (33·3%)	12 (35·3%)	1·00
Education (years)	13 (11-14)	12 (11-13)	0·70
Education ≤12 years	10 (58·8%)	20 (47·6%)	0·60
Clinical/cognitive acute phase deficits			
Admission NIHSS score	4 (3-9)	3 (3-6)	0·14
Admission NIHSS ≥3	16 (76·2%)	26 (76·5%)	1·00
Barthel Index score	65 (55-75)	85 (60-95)	0·05
Delirium rating scale score	0 (0-1)	0 (0-4)	0·20
Acute phase MoCA score	19 (17-22)	23 (20-25)	0·04
Acute phase cognitive impairment*[1]	16/20 (90·0%)	26/29 (89·7%)	1·00
Cardiovascular risk factors			
Hypertension	18 (85·7%)	30 (88·2%)	0·10
Diabetes mellitus	9 (42·9%)	12 (35·5%)	0·80
Dyslipidaemia	8 (38·1%)	17 (50·0%)	0·60
Current smoking	0 (0·0%)	6 (17·6%)	0·10
Atrial fibrillation	12 (57·1%)	10 (29·4%)	0·08
Prior history of stroke	6 (28·6%)	5 (14·7%)	0·40
Ischaemic heart disease	5 (23·8%)	7 (20·6%)	1·00
BMI (kg/m^2)	26·3 (4·0)	26·4 (4·5)	0·90
Systolic blood pressure (mmHg)	149 (136-155)	144 (126-150)	0·10
Diastolic blood pressure (mmHg)	79 (75-85)	80 (72-85)	0·80
HbA_{1c} (%)	5·9 (5·6-6·8)	5·7 (5·6-6·8)	0·60
LDL cholesterol (mg/dL)	101 (86-129)	125 (92-166)	0·10
HDL cholesterol (mg/dL)	42 (36-54)	43 (36-58)	0·90
Triglycerides (mg/dL)	103 (74-148)	118 (95-219)	0·30
Metabolic syndrome components*[2]			
Abdominal obesity	7/16 (43·8%)	21/32 (65·6%)	0·30
Elevated triglycerides	5/20 (25·0%)	13/32 (40·6%)	0·40
Reduced HDL cholesterol	10/20 (50·0%)	17/32 (53·1%)	1·00
Elevated blood pressure	20/21 (95·2%)	30/34 (88·2%)	0·70
Prediabetes/Diabetes mellitus	15/20 (75·0%)	24/33 (72·7%)	1·00
Metabolic syndrome (≥3 of the above components present)	11 (52·4%)	25 (73·5%)	0·20
Index stroke classification			
Ischaemic stroke	20 (95·2%)	31 (91·2%)	1·00
TOAST classification of acute ischaemic stroke subtype			0·28
Large artery atherosclerosis	6 (28·6%)	6 (17·6%)	··
Cardioembolism	9 (42·9%)	11 (32·4%)	··
Small artery occlusion	0 (0·0%)	2 (5·9%)	··
Other determined aetiology	1 (4·8%)	0 (0·0%)	··
Undetermined aetiology	4 (19·0%)	12 (35·3%)	··
Haemorrhagic stroke	1 (4·8%)	3 (8·8%)	1·00
Acute stroke treatment			
Any reperfusion therapy (IVT and/or EVT)	5 (23·8%)	6 (17·6%)	0·83
Neuroimaging parameters			
Normalised brain volume (%)	62·4 (61·3-64·9)	64·3 (61·5-66·7)	0·30
Infarct volume (mm^3)	3752 (1092-29020)	1720 (460-7140)	0·20
Normalised stroke lesion volume (%)	0·28 (0·07-1·83)	0·13 (0·03-0·47)	0·10
Small vessel disease score			0·20
0	4/20 (20·0%)	4/31(12·9%)	··
1	5/20 (25·0%)	17/31(54·8%)	··
2	5/20 (25·0%)	6/31(19·4%)	··
3	3/20 (15·0%)	3/31(9·7%)	··
4	3/20 (15·0%)	1/3 (3·2%)	··
Lacune count	0 (0-0)	0 (0-1)	0·06
≥3 lacunes	2/21 (9·5%)	3/32 (9·4%)	1·00
Normalised white matter hyperintensity volume (%)	0·59 (0·24-1·53)	0·39 (0·23-1·25)	0·70
Cerebral microbleed count	0 (0-0)	0 (0-0)	0·50
Perivascular space grade	2 (1-3)	1 (1-2)	0·20
Mean skeletonised mean diffusivity (z-score)	1·03 (0·25-2·24)	0·46 (-0·18-1·79)	0·20
Genetic risk factors			
APOE genotype			0·60
0 ε4 allele	10/16 (62·5%)	21/27 (77·8%)	··
1 ε4 allele	5/16 (31·3%)	5/27 (18·5%)	··
2 ε4 alleles	1/16 (6·3%)	1/27 (3·7%)	··
Pre-stroke clinical/cognitive function			
mRS before stroke	0 (0-0)	0 (0-0)	0·80

IQCODE score	50 (48-52)	48 (48-51)	0·60

Data are n (%), median (IQR), mean (SD), or n/N (%). APOE=apolipoprotein E. BMI=body-mass index. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. LDL=low-density lipoprotein. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. TOAST=Trial of Org 10172 in Acute Stroke Treatment.

*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).

*[2] Defined according to Alberti et al.[2]

Table S7: Risk factors for post-stroke dementia diagnosed before and after 6 months

	Early-onset dementia risk (3-6 months)			*Delayed-onset dementia risk (>6 months)*		
Baseline risk factor	**Cases/N**	**HR (95% CI)**	**P-value**	**Cases/N**	**HR (95% CI)**	**P-value**
Age (per year)	21/706	1·18 (1·11-1·26)	< 0·0001	34/617	1·10 (1·06- 1·15)	< 0·0001
Age ≥ 74	21/706	8·19 (2·75-24·42)	0·0002	34/617	3·63 (1·80-7·31)	0·0003
Female sex	21/706	0·49 (0·19-1·28)	0·15	34/617	0·46 (0·21-0·99)	0·05
Education (per year)	21/706	0·89 (0·78-1·02)	0·11	34/617	0·84 (0·75-0·95)	0·005
Education ≤ 12	21/706	1·40 (0·58-3·34)	0·45	34/617	2·27 (1·12-4·61)	0·02
Clinical/cognitive acute phase deficits						
Stroke severity (per point on admission NIHSS)	21/706	1·09 (1·01-1·18)	0·02	34/617	1·07 (1·00-1·14)	0·05
Admission NIHSS ≥3	21/706	2·70 (0·99-7·38)	0·05	34/617	2·65 (1·19-5·89)	0·02
Barthel Index (per point)	21/704	0·97 (0·96-0·99)	0·0002	34/615	0·98 (0·97-1·00)	0·01
Delirious symptoms (per point on DRS)	21/706	1·29 (1·13-1·46)	< 0·0001	34/617	1·00 (0·80-1·26)	0·96
Acute phase cognitive function (per point on MoCA)	15/625	0·79 (0·70-0·89)	< 0·0001	26/552	0·85 (0·78-0·94)	0·0009
Acute phase cognitive impairment*[1]	20/683	5·02 (1·15-21·92)	0·03	29/599	6·51 (1·95-21·75)	0·002
Cardiovascular risk factors						
Hypertension	21/706	0·85 (0·25-2·91)	0·79	34/617	1·20 (0·42-3·46)	0·73
Diabetes mellitus	21/706	2·44 (1·02-5·83)	0·04	34/617	2·18 (1·07-4·43)	0·03
Dyslipidaemia	21/706	0·97 (0·40-2·34)	0·95	34/617	1·64 (0·83-3·23)	0·15
Current smoking	21/706	0·00 (0·00-Inf)	0·99	34/617	1·52 (0·61-3·79)	0·37
Regular alcohol consumption	21/706	0·36 (0·15-0·86)	0·02	34/617	1·30 (0·53-3·18)	0·56
Atrial fibrillation	21/706	3·71 (1·56-8·83)	0·003	34/617	1·20 (0·57-2·53)	0·63
Prior history of stroke	21/706	2·86 (1·11-7·41)	0·03	34/617	1·54 (0·59-4·01)	0·38
Ischaemic heart disease	21/706	2·09 (0·76-5·74)	0·15	34/617	1·90 (0·82-4·38)	0·13
BMI (kg/m^2)	21/706	1·00 (0·89-1·13)	0.97	34/617	0·99 (0·90-1·09)	0·87
Systolic blood pressure (mmHg)	21/701	1·02 (0·99-1·04)	0·19	34/612	0·99 (0·97-1·01)	0·43
Diastolic blood pressure (mmHg)	21/701	1·00 (0·97-1·04)	0·76	34/612	1·00 (0·98-1·03)	0·74
HbA_{1c} (%)	20/658	1·06 (0·90-1·25)	0·47	32/573	1·06 (0·93-1·21)	0·37
LDL cholesterol (mg/dL)	20/684	0·99 (0·98-1·00)	0·19	33/598	1·00 (1·00-1·01)	0·27
HDL cholesterol (mg/dL)	20/679	0·98 (0·94-1·01)	0·18	32/593	0·98 (0·95-1·01)	0·14
Triglycerides (mg/dL)	20/663	1·00 (0·99-1·01)	0·92	32/578	1·00 (1·00-1·01)	0·01
Metabolic syndrome components*[2]						
Abdominal obesity	16/666	0·57 (0·21-1·55)	0·27	32/587	1·33 (0·62-2·84)	0·46
Elevated triglycerides	20/663	0·92 (0·33-2·54)	0·88	32/578	2·11 (1·02-4·35)	0·04
Reduced HDL cholesterol	20/679	2·30 (0·94-5·59)	0·07	32/593	2·82 (1·38-5·76)	0·004
Elevated blood pressure	21/705	1·02 (0·13-7·65)	0·99	34/616	0·32 (0·11-0·95)	0·04
Prediabetes/Diabetes mellitus	20/666	2·05 (0·74-5·56)	0·16	33/580	2·17 (0·98-4·80)	0·06
Metabolic syndrome (≥3 of the above components present)	21/706	1·04 (0·44-2·46)	0·93	34/617	3·46 (1·52-7·85)	0·003
Per count of components increase	21/706	1·08 (0·75-1·56)	0·67	34/617	1·46 (1·10-1·94)	0·009
Index stroke classification						
Haemorrhagic stroke	21/706	1·46 (0·19-10·94)	0·71	34/617	3·72 (1·12-12·41)	0·03
Acute stroke treatment						

Any reperfusion therapy (IVT and/or EVT)	21/706	0·47 (0·16-1·37)	0·17	34/617	0·28 (0·11-0·74	0·01
Neuroimaging parameters						
Normalised brain volume (per SD)	19/634	0·52 (0·29-0·92)	0·02	31/559	0·66 (0·42-1·04)	0·07
Normalised infarct volume (per SD)	19/634	1·38 (1·04-1·84)	0·03	31/559	1·00 (0·66-1·51)	0·98
Total SVD score (per SD)	20/643	1·50 (0·96-2·33)	0·07	31/567	1·09 (0·74-1·61)	0·65
Lacune count (per SD)	21/647	1·32 (1·13-1·55)	0·0005	32/570	1·49 (1·19-1·85)	0·0004
Presence of ≥3 lacunes	21/647	6·93 (1·60-30·07)	0·01	32/570	17·43 (5·08-59·76)	< 0·0001
Normalised WMH volume (per SD)	19/633	1·31 (0·97-1·76)	0·08	29/558	1·51 (1·19-1·92)	0·0008
Cerebral microbleed count (per SD)	20/642	1·10 (0·83-1·48)	0·50	31/566	1·21 (1·00-1·46)	0·06
Perivascular space grade (per SD)	21/646	1·41 (0·96-2·05)	0·08	32/569	1·12 (0·81-1·57)	0·49
Mean skeletonised mean diffusivity (per SD)	17/606	1·89 (1·21-2·93)	0·005	28/536	1·97 (1·33-2·94)	0·0008
Genetic risk factors						
APOE genotype						
0 ε4 alleles	ref	ref	..	ref	ref	..
1 ε4 allele	16/576	1·79 (0·61-5·30)	0·29	27/508	0·79 (0·29-2·15)	0·64
2 ε4 alleles	16/576	8·94 (1·13-70·73)	0·04	27/508	3·37 (0·45-25·54)	0·24
Pre-stroke clinical/cognitive function						
mRS before stroke	21/706	1·04 (0·61-1·77)	0·89	34/617	1·15 (0·74-1·79)	0·52
IQCODE score	19/655	1·04 (0·91-1·18)	0·56	30/575	1·10 (0·98-1·24)	0·10
Recurrent events						
Stroke recurrence	21/757	0·62 (0·08-4·67)	0·68	34/650	3·94 (1·76-8·82)	0·0009

Cox proportional hazards regression models for the association between risk factors and early-onset (left) and delayed-onset PSD (right). Recurrent stroke was included as a time-dependent variable as described in the **Supplementary Methods**.

APOE=apolipoprotein E. BMI=body-mass index. DRS=Delirious rating scale. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL=low-density lipoprotein. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. WMH=white matter hyperintensity.

*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).

*[2] Defined according to Alberti et al.[2]

Table S8: Subgroup analysis stratifying the main analyses by sex

	Male			*Female*		
Risk Factor	**Cases/N**	**HR (95% CI)**	**P-Value**	**Cases/N**	**HR (95% CI)**	**P-Value**
Sociodemographic factors						
Age (per year)	36/491	1·15 (1·09-1·20)	<0·0001	19/245	1·11 (1·04-1·18)	0·001
Age ≥74	36/491	6·38 (3·08-13·24)	<0·0001	19/245	2·95 (1·10-7·94)	0·03
Education (per year)	36/491	0·82 (0·73-0·93)	0·002	19/245	0·92 (0·79-1·07)	0·28
Education ≤12	36/491	2·87 (1·46-5·62)	0·002	19/245	0·92 (0·36-2·34)	0·85
Clinical/cognitive acute phase deficits						
Stroke severity (per point on admission NHSS)	36/491	1·10 (1·02-1·17)	0·009	19/245	1·06 (0·99-1·14)	0·10
Admission NIHSS ≥3	36/491	3·08 (1·42-6·70)	0·004	19/245	1·40 (0·52-3·77)	0·51
Barthel Index (per point)	36/488	0·97 (0·96-0·99)	<0·0001	19/244	0·99 (0·97-1·01)	0·36
Delirious symptoms (per point on DRS)	36/491	1·11 (0·96-1·28)	0·15	19/245	1·39 (1·12-1·74)	0·003
Acute phase cognitive function (per point on MoCA)	26/436	0·85 (0·78-0·93)	0·0005	15/211	0·78 (0·69-0·89)	0·0003
Acute phase cognitive impairment*[1]	32/476	7·61 (1·78-32·52)	0·006	17/233	5·06 (1·41-18·14)	0·01
Vascular risk factors						
Hypertension	36/491	0·92 (0·38-2·22)	0·84	19/245	2·02 (0·26-15·99)	0·51
Diabetes mellitus	36/491	3·56 (1·83-6·94)	0·0002	19/245	0·72 (0·21-2·53)	0·61
Dyslipidaemia	36/491	1·88 (0·98-3·63)	0·06	19/245	0·78 (0·30-2·02)	0·61
Current smoking	36/491	0·53 (0·16-1·76)	0·30	19/245	1·85 (0·50-6·88)	0·36
Regular alcohol consumption	36/491	0·97 (0·40-2·36)	0·95	19/245	0·48 (0·19-1·19)	0·11
Atrial fibrillation	36/491	1·45 (0·72-2·91)	0·29	19/245	3·19 (1·25-8·15)	0·02
Prior stroke	36/491	2·21 (0·96-5·12)	0·06	19/245	2·03 (0·66-6·26)	0·22
Ischaemic heart disease	36/491	2·80 (1·37-5·75)	0·005	19/245	0·59 (0·08-4·46)	0·61
BMI (kg/m^2)	36/490	1·07 (0·97-1·17)	0·19	19/245	0·89 (0·78-1·03)	0·12
SBP (mmHg)	36/488	1·01 (0·99-1·03)	0·32	19/243	0·99 (0·96-1·01)	0·36
DBP (mmHg)	36/488	1·00 (0·97-1·03)	0·90	19/243	1·02 (0·98-1·05)	0·38
HbA1c (%)	35/456	1·07 (0·97-1·18)	0·16	17/230	0·85 (0·42-1·70)	0·64
LDL-C (mg/dL)	35/476	1·00 (0·99-1·01)	0·62	18/238	1·01 (0·99-1·02)	0·33
HDL-C (mg/dL)	35/474	0·96 (0·93-0·99)	0·01	17/235	0·99 (0·97-1·02)	0·72
Triglycerides (mg/dL)	35/463	1·00 (1·00-1·01)	0·17	17/229	1·01 (1·00-1·01)	0·02
Metabolic syndrome components*[2]						
Abdominal obesity	31/457	1·18 (0·58-2·41)	0·65	17/232	0·71 (0·25-2·07)	0·53
Elevated triglycerides	35/463	1·48 (0·74-2·96)	0·26	17/229	2·03 (0·68-6·07)	0·21
Reduced HDL-C	35/474	2·75 (1·39-5·45)	0·004	17/235	2·53 (0·92-6·95)	0·07
Elevated blood pressure	36/490	0·22 (0·08-0·61)	0·004	19/245	27302244·33 (0·00-Inf)	1·00
Prediabetes or diabetes mellitus	36/462	2·42 (1·10-5·33)	0·03	17/233	1·82 (0·59-5·63)	0·30
Metabolic syndrome (≥3 of the above components present)	36/491	2·09 (1·05-4·18)	0·04	19/245	2·22 (0·75-6·58)	0·15
Per count of components increase	36/491	1·36 (1·04-1·78)	0·02	19/245	1·23 (0·80-1·89)	0·34
Index stroke classification						
Haemorrhagic stroke	36/491	2·98 (1·04-8·52)	0·04	19/245	0·00 (0·00-Inf)	1·00
Acute stroke treatment						
Any reperfusion therapy (IVT and/or EVT)	36/491	0·24 (0·08-0·69)	0·008	19/245	0.36 (0.09-1.39)	0.14

Neuroimaging parameters						
Normalised brain volume (per SD)	33/438	0·59 (0·37-0·94)	0·03	17/219	0·68 (0·35-1·34)	0·26
Normalised infarct volume (per SD)	33/439	1·13 (0·85-1·50)	0·40	17/219	1·85 (1·00-3·41)	0·05
Total SVD score (per SD)	34/444	1·36 (0·96-1·91)	0·08	17/222	1·08 (0·59-1·96)	0·81
Lacune count (per SD)	35/446	1·38 (1·21-1·58)	<0·0001	18/225	1·30 (0·84-2·01)	0·24
Presence of ≥3 lacunes	35/446	10·30 (3·52-30·10)	<0·0001	18/225	19·76 (2·32-168·44)	0·006
Normalised WMH volume (per SD)	32/438	1·57 (1·28-1·92)	<0·0001	16/219	1·10 (0·72-1·66)	0·66
CMB count (per SD)	34/444	1·26 (1·01-1·57)	0·04	17/222	1·14 (0·89-1·46)	0·31
PVS grade (per SD)	35/446	1·39 (1·01-1·92)	0·04	18/224	1·03 (0·65-1·61)	0·91
Mean skeletonised mean diffusivity (per SD)	29/414	1·85 (1·28-2·67)	0·001	16/214	2·29 (1·27-4·14)	0·006
APOE genotype						
1 ε4 allele	30/400	1·37 (0·57-3·28)	0·48	13/194	0·87 (0·22-3·54)	0·85
2 ε4 alleles	30/400	2·74 (0·36-21·04)	0·33	13/194	12·48 (1·27-122·94)	0·03
Pre-stroke clinical/cognitive function						
mRS before stroke	36/491	1·15 (0·74-1·79)	0·54	19/245	1·10 (0·61-2·00)	0·74
IQCODE score	35/452	0·96 (0·90-1·04)	0·32	14/224	1·34 (1·18-1·52)	<0·0001
Recurrent events						
Stroke recurrence	36/527	2·25 (0·98-5·17)	0·06	19/260	3·22 (0·69-15·12)	0·14

Cox proportional hazards regression models for the association between risk factors and PSD in males (left) and females (right), adjusted for age, education, and admission NIHSS. Recurrent stroke was included as a time-dependent variable as described in the **Supplementary Methods**.

APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.

*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).

*[2] Defined according to Alberti et al.[2]

Table S9: Stroke recurrence during 5 years of follow-up

	One recurrent stroke (n=51)	Two recurrent strokes (n=5)
Developed dementia during follow-up		
No	27	5
Before recurrence	4	··
After recurrence	9	··
LTFU without dementia diagnosis	11	··
Type of first recurrent stroke		
Ischaemic	30*	4
Haemorrhagic	4	··
Unknown	17	1
Type of second recurrent stroke		
Ischaemic	··	4
Haemorrhagic	··	··
Unknown	··	1

Number of patients who experienced one or two recurrent strokes by dementia status and stroke subtype.
*one with haemorrhagic transformation

Table S10: Sensitivity analysis additionally adjusting the main analyses for acute stroke treatment

Baseline risk factor	Cases/N	HR (95% CI)	P-value
Sociodemographic variables			
Age (per year)	55/706	1·13 (1·09-1·17)	<0·0001
Age ≥ 74	55/706	4·33 (2·41-7·79)	<0·0001
Female sex	55/706	0·40 (0·21-0·77)	0·006
Education (per year)	55/706	0·86 (0·78-0·94)	0·001
Education ≤ 12	55/706	1·85 (1·06-3·23)	0·03
Clinical/cognitive acute phase deficits			
Stroke severity (per point on admission NIHSS)	55/706	1·12 (1·06-1·18)	<0·0001
Admission NIHSS ≥3	55/706	3·44 (1·80-6·57)	0·0002
Barthel Index (per point)	55/704	0·98 (0·97-0·99)	<0·0001
Delirious symptoms (per point on DRS)	55/706	1·15 (1·03-1·29)	0·01
Acute phase cognitive function (per point on MoCA)	41/625	0·84 (0·78-0·90)	<0·0001
Acute phase cognitive impairment*[1]	49/683	16·36 (4·36-61·39)	<0·0001
Vascular risk factors			
Hypertension	55/706	1·02 (0·45-2·28)	0·97
Diabetes mellitus	55/706	2·33 (1·34-4·05)	0·003
Dyslipidaemia	55/706	1·31 (0·76-2·25)	0·32
Current smoking	55/706	0·79 (0·33-1·89)	0·59
Regular alcohol consumption	55/706	0·83 (0·45-1·52)	0·54
Atrial fibrillation	55/706	2·07 (1·19-3·59)	0·01
Prior stroke	55/706	1·82 (0·91-3·63)	0·09
Ischaemic heart disease	55/706	1·86 (0·96-3·57)	0·06
BMI (kg/m^2)	55/706	1·01 (0·94-1·09)	0·79
SBP (mmHg)	55/701	1·00 (0·98-1·02)	0·97
DBP (mmHg)	55/701	1·00 (0·98-1·03)	0·80
HbA1c (%)	52/658	1·05 (0·94-1·16)	0·39
LDL-C (mg/dL)	53/684	1·00 (0·99-1·01)	0·97
HDL-C (mg/dL)	52/679	0·98 (0·96-1·00)	0·06
Triglycerides (mg/dL)	52/662	1·00 (1·00-1·01)	0·07
Metabolic syndrome components*[2]			
Abdominal obesity	48/666	1·17 (0·63-2·16)	0·62
Elevated triglycerides	52/662	1·49 (0·83-2·68)	0·18
Reduced HDL-C	52/679	2·68 (1·51-4·75)	0·0007
Elevated blood pressure	55/705	0·37 (0·14-0·98)	0·05
Prediabetes or diabetes	53/666	2·32 (1·23-4·38)	0·009
Metabolic syndrome (≥3 of the above components present)	55/706	2·18 (1·22-3·90)	0·008
Per count of components increase	55/706	1·33 (1·06-1·66)	0·01
Index stroke classification			
Haemorrhagic stroke	55/706	2·02 (0·71-5·77)	0·19
Neuroimaging parameters			
Normalised brain volume (per SD)	50/634	0·61 (0·42-0·90)	0·01
Normalised infarct volume (per SD)	50/634	1·19 (0·93-1·52)	0·17
Total SVD score (per SD)	51/642	1·17 (0·87-1·57)	0·31
Lacune count (per SD)	53/647	1·38 (1·21-1·57)	<0·0001
Presence of ≥3 lacunes	53/647	10·38 (3·94-27·33)	<0·0001
Normalised WMH volume (per SD)	48/633	1·37 (1·14-1·66)	0·001
CMB count (per SD)	51/642	1·15 (0·97-1·36)	0·10
PVS grade (per SD)	53/646	1·19 (0·92-1·54)	0·19
Mean skeletonised mean diffusivity (per SD)	45/606	1·88 (1·39-2·54)	<0·0001
APOE genotype			
1 ε4 allele	43/575	1·00 (0·47-2·13)	1·00
2 ε4 alleles	43/575	4·05 (0·93-17·57)	0·06
Pre-stroke clinical/cognitive function			
mRS before stroke	55/706	1·09 (0·77-1·55)	0·62
IQCODE score	49/655	1·07 (0·98-1·18)	0·13
Recurrent events			

Stroke recurrence	55/757	2·86 (1·37-5·93)	0·005

Cox proportional hazards regression models for the association between risk factors and post-stroke dementia, adjusted for age, sex, education, admission NIHSS, and acute stroke treatment (IVT and/or EVT). Recurrent stroke was included as a time-dependent covariable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.
*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).
*[2] Defined according to Alberti et al.[2]

Table S11: Sensitivity analysis additionally adjusting the analysis split by post-stroke time period for age, sex, education, NIHSS, and acute stroke treatment

	Early-onset dementia risk (3-6 months)			*Delayed-onset dementia risk (>6 months)*		
Baseline risk factor	**Cases/N**	**HR (95% CI)**	**P-value**	**Cases/N**	**HR (95% CI)**	**P-value**
Age (per year)	21/706	1·18 (1·11-1·26)	< 0·0001	34/617	1·10 (1·05- 1·15)	< 0·0001
Age ≥ 74	21/706	7·46 (2·50-22·29)	0·0003	34/617	3·31 (1·63-6·70)	0·0009
Female sex	21/706	0·44 (0·17-1·14)	0·09	34/617	0·38 (0·17-0·85)	0·02
Education (per year)	21/706	0·89 (0·77-1·02)	0·09	34/617	0·84 (0·74-0·94)	0·004
Education ≤ 12	21/706	1·38 (0·58-3·29)	0·47	34/617	2·23 (1·10-4·52)	0·03
Clinical/cognitive acute phase deficits						
Stroke severity (per point on admission NIHSS)	21/706	1·14 (1·05-1·23)	0·0009	34/617	1·11 (1·04-1·19)	0·002
Admission NIHSS ≥3	21/706	3·40 (1·23-9·39)	0·02	34/617	3·47 (1·53-7·84)	0·003
Barthel Index (per point)	21/704	0·97 (0·96-0·99)	0·0001	34/615	0·98 (0·97-1·00)	0·01
Delirious symptoms (per point on DRS)	21/706	1·30 (1·14-1·48)	< 0·0001	34/617	0·98 (0·77-1·24)	0·85
Acute phase cognitive function (per point on MoCA)	15/625	0·80 (0·70-0·92)	0·001	26/552	0·86 (0·79-0·94)	0·001
Acute phase cognitive impairment*[1]	20/683	23·10 (3·83-139·19)	0·0006	29/599	8·14 (0·84-79·03)	0·07
Cardiovascular risk factors						
Hypertension	21/706	0·68 (0·19-2·41)	0·55	34/617	1·25 (0·43-3·60)	0·68
Diabetes mellitus	21/706	2·36 (0·97-5·71)	0·06	34/617	2·16 (1·06-4·41)	0·03
Dyslipidaemia	21/706	0·89 (0·37-2·18)	0·80	34/617	1·70 (0·86-3·39)	0·13
Current smoking	21/706	0·00 (0·00-Inf)	1·00	34/617	1·29 (0·51-3·26)	0·60
Regular alcohol consumption	21/706	0·37 (0·15-0·93)	0·03	34/617	1·58 (0·63-3·93)	0·33
Atrial fibrillation	21/706	3·73 (1·56-8·92)	0·003	34/617	1·40 (0·66-2·99)	0·38
Prior history of stroke	21/706	2·61 (0·98-6·94)	0·05	34/617	1·27 (0·47-3·43)	0·64
Ischaemic heart disease	21/706	1·87 (0·67-5·22)	0·23	34/617	1·77 (0·75-4·18)	0·19
BMI (kg/m^2)	21/706	1·03 (0·91-1·16)	0.62	34/617	0·99 (0·90-1·09)	0·83
Systolic blood pressure (mmHg)	21/701	1·02 (0·99-1·04)	0·22	34/612	0·99 (0·97-1·01)	0·37
Diastolic blood pressure (mmHg)	21/701	1·01 (0·97-1·04)	0·60	34/612	1·00 (0·97-1·03)	0·94
HbA_{1c} (%)	20/658	1·08 (0·90-1·28)	0·41	32/573	1·03 (0·90-1·17)	0·69
LDL cholesterol (mg/dL)	20/684	0·99 (0·98-1·00)	0·27	33/598	1·00 (0·99-1·01)	0·37
HDL cholesterol (mg/dL)	20/679	0·98 (0·94-1·01)	0·21	32/593	0·98 (0·95-1·01)	0·22
Triglycerides (mg/dL)	20/663	1·00 (0·99-1·01)	0·90	32/578	1·00 (1·00-1·01)	0·05
Metabolic syndrome components*[2]						
Abdominal obesity	16/666	0·45 (0·15-1·34)	0·15	32/587	1·76 (0·81-3·81)	0·15
Elevated triglycerides	20/663	0·91 (0·33-2·51)	0·85	32/578	1·93 (0·92-4·03)	0·08
Reduced HDL cholesterol	20/679	2·33 (0·91-5·98)	0·08	32/593	2·81 (1·36-5·80)	0·005
Elevated blood pressure	21/705	0·78 (0·10-6·04)	0·81	34/616	0·28 (0·09-0·86)	0·03
Prediabetes/Diabetes mellitus	20/666	2·36 (0·84-6·65)	0·10	33/580	2·19 (0·98-4·88)	0·05
Metabolic syndrome (≥3 of the above components present)	21/706	1·05 (0·44-2·54)	0·90	34/617	3·49 (1·54-7·92)	0·003
Per count of components increase	21/706	1·09 (0·74-1·59)	0·66	34/617	1·46 (1·10-1·94)	0·009
Index stroke classification						
Haemorrhagic stroke	21/706	1·16 (0·15-9·14)	0·89	34/617	2·82 (0·83-9·56)	0·09
Neuroimaging parameters						

Normalised brain volume (per SD)	19/634	0·67 (0·36-1·27)	0·22	31/559	0·59 (0·37-0·94)	0·03
Normalised infarct volume (per SD)	19/634	1·43 (1·03-1·97)	0·03	31/559	0·97 (0·64-1·47)	0·89
Total SVD score (per SD)	20/643	1·34 (0·83-2·17)	0·23	31/567	1·06 (0·71-1·56)	0·79
Lacune count (per SD)	21/647	1·37 (1·15-1·63)	0·0005	32/570	1·48 (1·17-1·85)	0·0008
Presence of ≥3 lacunes	21/647	7·27 (1·61-32·70)	0·01	32/570	15·20 (4·16-55·23)	< 0·0001
Normalised WMH volume (per SD)	19/633	1·24 (0·89-1·73)	0·21	29/558	1·48 (1·16-1·87)	0·001
Cerebral microbleed count (per SD)	20/642	1·07 (0·78-1·46)	0·67	31/566	1·17 (0·97-1·42)	0·10
Perivascular space grade (per SD)	21/646	1·30 (0·87-1·95)	0·20	32/569	1·12 (0·79-1·58)	0·52
Mean skeletonised mean diffusivity (per SD)	17/606	1·62 (0·97-2·70)	0·06	28/536	2·01 (1·37-2·96)	0·0004
Genetic risk factors						
APOE genotype						
0 ε4 alleles	ref	ref	..	ref	ref	..
1 ε4 allele	16/576	1·61 (0·54-4·82)	0·39	27/508	0·71 (0·25-1·98)	0·51
2 ε4 alleles	16/576	7·47 (0·94-59·61)	0·06	27/508	2·75 (0·36-21·07)	0·33
Pre-stroke clinical/cognitive function						
mRS before stroke	21/706	0·92 (0·53-1·59)	0·77	34/617	1·19 (0·76-1·88)	0·44
IQCODE score	19/655	1·05 (0·94-1·16)	0·36	30/575	1·11 (0·99-1·25)	0·08
Recurrent events						
Stroke recurrence	21/757	0·69 (0·09-5·17)	0·72	34/650	4·70 (2·08-10·62)	0·0002

Cox proportional hazards regression models for the association between risk factors and early-onset (left) and delayed-onset PSD (right), adjusting for age, sex, education, admission NIHSS, and acute stroke treatment (IVT and/or EVT). Recurrent stroke was included as a time-dependent variable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=intravenous thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.

*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).

*[2] Defined according to Alberti et al.[2]

Table S12: Sensitivity analysis additionally adjusting the main analyses for stroke recurrence

Baseline risk factor	Cases/N	HR (95% CI)	P-value
Sociodemographic factors			
Age (per year)	55/757	1·13 (1·09-1·18)	<0·0001
Age ≥74	55/757	4·70 (2·64-8·38)	<0·0001
Female sex	55/757	0·52 (0·28-0·98)	0·04
Education (per year)	55/757	0·86 (0·79-0·95)	0·002
Education ≤12	55/757	1·91 (1·09-3·36)	0·02
Clinical acute phase deficits			
Stroke severity (per point on **admission** NHSS)	55/757	1·08 (1·02-1·13)	0·004
Admission NIHSS ≥3	55/757	2·49 (1·33-4·67)	0·01
Barthel Index (per point)	55/755	0·98 (0·97-0·99)	<0·0001
Delirious symptoms (per point on DRS)	55/757	1·18 (1·05-1·32)	0·004
Acute phase cognitive function (per point on MoCA)	41/669	0·84 (0·78-0·90)	<0·0001
Acute phase cognitive impairment*[1]	49/733	6·38 (2·50-16·30)	0·0001
Cardiovascular risk factors			
Hypertension	55/757	0·95 (0·42-2·15)	0·91
Diabetes mellitus	55/757	2·06 (1·18-3·61)	0·01
Dyslipidaemia	55/757	1·23 (0·72-2·12)	0·45
Current smoking	55/757	1·01 (0·41-2·46)	0·98
Regular alcohol consumption	55/757	0·81 (0·44-1·50)	0·51
Atrial fibrillation	55/757	2·10 (1·21-3·65)	0·008
Prior stroke	55/757	1·85 (0·94-3·66)	0·07
Ischaemic heart disease	55/757	1·63 (0·84-3·18)	0·15
BMI (kg/m^2)	55/757	1·00 (0·92-1·08)	0·92
SBP (mmHg)	55/752	1·00 (0·99-1·02)	0·80
DBP (mmHg)	55/752	1·00 (0·98-1·03)	0·67
HbA_{1c} (%)	52/703	1·06 (0·96-1·18)	0·24
LDL-C (mg/dL)	53/731	1·00 (0·99-1·01)	0·66
HDL-C (mg/dL)	52/726	0·98 (0·96-1·00)	0·08
Triglycerides (mg/dL)	52/709	1·00 (1·00-1·01)	0·03
Metabolic syndrome components*[2]			
Abdominal obesity	48/716	0·95 (0·51-1·74)	0·86
Elevated triglycerides	52/709	1·50 (0·83-2·68)	0·18
Reduced HDL-C	52/726	2·56 (1·45-4·53)	0·001
Elevated blood pressure	55/756	0·43 (0·17-1·12)	0·08
Prediabetes or diabetes mellitus	53/712	2·14 (1·14-4·01)	0·02
Metabolic syndrome (≥3 of the above components present)	55/757	1·96 (1·09-3·50)	0·02
Per count of components increase	55/757	1·28 (1·02-1·60)	0·03
Index stroke classification			
Haemorrhagic stroke	55/757	3·04 (1·08-8·57)	0·03
Acute stroke treatment			
Any reperfusion therapy (IVT and/or EVT)	55/757	0·31 (0·14-0·66)	0·003
Neuroimaging parameters			
Normalised brain volume (per SD)	50/677	0·62 (0·43-0·91)	0·01
Normalised infarct volume (per SD)	50/677	1·21 (0·95-1·55)	0·13
Total SVD score (per SD)	51/686	1·23 (0·95-1·70)	0·10
Lacune count (per SD)	53/691	1·34 (1·17-1·53)	<0·0001
Presence of ≥3 lacunes	53/691	7·61 (2·71-21·33)	0·0001
Normalised WMH volume (per SD)	48/675	1·41 (1·16-1·71)	0·0006
CMB count (per SD)	51/686	1·17 (1·00-1·38)	0·05
PVS grade (per SD)	53/690	1·28 (0·99-1·66)	0·06
Mean skeletonised mean diffusivity (per SD)	45/647	1·91 (1·42-2·59)	<0·0001
APOE genotype			
1 ε4 allele	43/621	1·15 (0·55-2·42)	0·71
2 ε4 alleles	43/621	5·06 (1·19-21·50)	0·03
Pre-stroke clinical/cognitive function			
mRS before stroke	55/757	1·14 (0·81-1·62)	0·45
IQCODE score	49/704	1·08 (0·98-1·18)	0·13

Cox proportional hazards regression models for the association between risk factors and post-stroke dementia, adjusted for age, sex, education, admission NIHSS, and stroke recurrence. Recurrent stroke was included as a time-dependent covariable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.
*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).
*[2] Defined according to Alberti et al.[2]

Table S13: Sensitivity analysis adjusting the analysis split by post-stroke time period for age, sex, education, NIHSS, and stroke recurrence

	Dementia risk 3-6 months			*Dementia risk >6 months*		
Baseline risk factor	**Cases/N**	**HR (95% CI)**	**P-value**	**Cases/N**	**HR (95% CI)**	**P-value**
Age (per year)	21/757	1·19 (1·12-1·27)	<0·0001	34/650	1·10 (1·05-1·15)	<0·0001
Age ≥74	21/757	8·13 (2·73-24·20)	0·0002	34/650	3·59 (1·78-7·22)	0·0003
Female sex	21/757	0·56 (0·22-1·45)	0·23	34/650	0·50 (0·23-1·08)	0·08
Education (per year)	21/757	0·90 (0·79-1·02)	0·11	34/650	0·84 (0·75-0·95)	0·004
Education ≤12	21/757	1·42 (0·59-3·41)	0·43	34/650	2·31 (1·14-4·70)	0·02
Clinical acute phase deficits						
Stroke severity (per point on admissionNIHSS)	21/757	1·09 (1·01-1·18)	0·03	34/650	1·07 (1·00-1·14)	0·05
Admission NIHSS ≥3	21/757	2·50 (0·91-6·83)	0·07	34/650	2·49 (1·12-5·53)	0·02
Barthel Index (per point)	21/755	0·97 (0·96-0·98)	<0·0001	34/648	0·98 (0·97-1·00)	0·009
Delirious symptoms (per point on DRS)	21/757	1·30 (1·14-1·48)	<0·0001	34/650	1·01 (0·80-1·27)	0·95
Acute phase cognitive function (per point on MoCA)	15/669	0·80 (0·71-0·90)	0·0002	26/581	0·86 (0·78-0·94)	0·001
Acute phase cognitive impairment*[1]	20/733	5·38 (1·24-23·43)	0·02	29/632	7·07 (2·12-23·56)	0·001
Cardiovascular risk factors						
Hypertension	21/757	0·77 (0·22-2·65)	0·67	34/650	1·09 (0·38-3·16)	0·87
Diabetes mellitus	21/757	2·16 (0·90-5·17)	0·08	34/650	2·00 (0·98-4·10)	0·06
Current smoking	21/757	0·00 (0·00-Inf)	0·99	34/650	1·80 (0·71-4·53)	0·21
Dyslipidaemia	21/757	0·86 (0·35-2·09)	0·78	34/650	1·53 (0·77-3·04)	0·22
Atrial fibrillation	21/757	4·01 (1·68-9·59)	0·002	34/650	1·34 (0·63-2·84)	0·45
Prior history of stroke	21/757	2·45 (0·93-6·43)	0·07	34/650	1·46 (0·56-3·82)	0·44
Ischaemic heart disease	21/757	1·67 (0·60-4·65)	0·32	34/650	1·60 (0·68-3·76)	0·28
BMI, kg/m2	21/757	1·00 (0·89-1·13)	0·97	34/650	0·99 (0·90-1·09)	0·88
SBP, mmHg	21/752	1·02 (0·99-1·04)	0·18	34/645	0·99 (0·97-1·01)	0·48
DBP, mmHg	21/752	1·00 (0·97-1·04)	0·80	34/645	1·00 (0·98-1·03)	0·73
HbA_{1c}, %	20/703	1·07 (0·90-1·27)	0·47	32/602	1·06 (0·93-1·22)	0·35
LDL-C, mg/dL	20/731	0·99 (0·98-1·00)	0·28	33/627	1·01 (1·00-1·01)	0·16
HDL-C, mg/dL	20/726	0·98 (0·94-1·01)	0·23	32/622	0·98 (0·97-1·01)	0·17
Triglycerides, mg/dL	20/708	1·00 (0·99-1·01)	0·88	32/605	1·00 (1·00-1·01)	0·01
Metabolic syndrome components*[2]						
Abdominal obesity	16/716	0·56 (0·20-1·53)	0·26	32/620	1·26 (0·58-2·69)	0·56
Elevated triglycerides	20/708	0·90 (0·33-2·48)	0·84	32/605	2·01 (0·97-4·16)	0·06
Reduced HDL-C	20/726	2·20 (0·90-5·38)	0·08	32/622	2·81 (1·37-5·76)	0·005
Elevated blood pressure	21/756	0·92 (0·12-6·97)	0·94	34/649	0·31 (0·10-0·90)	0·03
Prediabetes/Diabetes mellitus	20/712	2·02 (0·73-5·57)	0·17	33/610	2·21 (1·00-4·91)	0·05
≥ 3 of the above criteria present	21/757	0·97 (0·41-2·31)	0·95	34/650	3·33 (1·46- 7·57)	0·004
Per count of components increase	21/757	1·06 (0·74-1·52)	0·76	34/650	1·43 (1·08-1·90)	0·01
Index stroke classification						
Haemorrhagic stroke	21/757	1·59 (0·21-11·95)	0·65	34/650	4·35 (1·30-14·59)	0·02
Acute stroke treatment						
Any reperfusion therapy (IVT and/or EVT)	21/757	0·41 (0·14-1·20)	0·10	34/650	0·25 (0·10-0·67)	0·006

Neuroimaging parameters						
Normalised brain volume (per SD)	19/677	0·54 (0·30-0·96)	0·04	31/587	0·67 (0·43-1·06)	0·09
Normalised stroke lesion volume (per SD)	19/677	1·42 (1·06-1·90)	0·02	31/587	1·01 (0·66-1·54)	0·98
Total SVD score (per SD)	20/686	1·51 (0·99-2·31)	0·06	31/595	1·12 (0·76-1·64)	0·57
Lacune count (per SD)	21/691	1·30 (1·10-1·54)	0·002	32/599	1·44 (1·14-1·81)	0·002
Presence of ≥3 lacunes	21/691	5·07 (1·11-23·09)	0·04	32/599	11·24 (3·08-41·09)	0·0002
Normalised WMH volume (per SD)	19/675	1·30 (0·96-1·76)	0·09	29/585	1·50 (1·17-1·91)	0·001
CMB count (per SD)	20/686	1·11 (0·82-1·49)	0·50	31/595	1·22 (1·00-1·48)	0·04
PVS grade (per SD)	21/690	1·46 (1·00-2·14)	0·05	32/598	1·16 (0·83-1·62)	0·39
Mean skeletonised mean diffusivity (per SD)	17/647	1·84 (1·20-2·83)	0·005	28/563	1·98 (1·33-2·95)	0·0008
Genetic risk factors						
APOE genotype						
1 ε4 allele	16/621	1·94 (0·65-5·74)	0·23	27/536	0·80 (0·29-2·19)	0·66
2 ε4 alleles	16/621	9·33 (1·18-73·67)	0·03	27/536	3·43 (0·46-25·86)	0·23
Pre-stroke clinical/cognitive function						
mRS before stroke	21/757	1·10 (0·64-1·86)	0·76	34/650	1·19 (0·76-1·85)	0·45
IQCODE score	19/704	1·04 (0·91-1·20)	0·54	30/606	1·10 (0·98-1·25)	0·11

Cox proportional hazards regression models for the association between risk factors and early-onset (left) and delayed-onset PSD (right), adjusting for age, sex, education, admission NIHSS, and stroke recurrence. Recurrent stroke was included as a time-dependent variable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=intravenous thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.

*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).

*[2] Defined according to Alberti et al.[2]

Table S14: Sensitivity analysis additionally adjusting the 5-year PSD analyses for acute phase cognitive impairment

	Cases/N	HR (95% CI)	P-value
Sociodemographic factors			
Age (per year)	49/683	1·11 (1·07-1·15)	<0·0001
Age ≥74 years	49/683	3·62 (1·97-6·65)	<0·0001
Female sex	49/683	0·65 (0·33-1·27)	0·20
Education (per year)	49/683	0·90 (0·81-0·99)	0·03
Education ≤12 years	49/683	1·56 (0·85-2·87)	0·15
Clinical acute phase deficits			
Stroke severity (per point on admission NHSS)	49/683	1·07 (1·02-1·13)	0·006
Admission NIHSS ≥3	49/683	2·43 (1·28-4·62)	0·007
Barthel Index (per point)	49/682	0·98 (0·97-0·99)	0·002
Delirious symptoms (per point on DRS)	49/683	1·14 (1·01-1·28)	0·03
Cardiovascular risk factors			
Hypertension	49/683	1·06 (0·44-2·54)	0·90
Diabetes mellitus	49/683	2·71 (1·52-4·85)	0·0007
Dyslipidaemia	49/683	1·24 (0·70-2·22)	0·46
Current smoking	49/683	0·87 (0·36-2·14)	0·77
Regular alcohol consumption	49/683	0·70 (0·37-1·32)	0·27
Atrial fibrillation	49/683	2·22 (1·24-3·96)	0·007
Prior stroke	49/683	1·95 (0·98-3·289)	0·06
Ischaemic heart disease	49/683	1·65 (0·83-3·25)	0·15
BMI (kg/m^2)	49/683	1·02 (0·94-1·10)	0·71
SBP (mmHg)	49/678	1·00 (0·98-1·02)	0·99
DBP (mmHg)	49/678	1·01 (0·99-1·03)	0·43
HbA_{1c} (%)	46/635	1·09 (0·98-1·20)	0·12
LDL-C (mg/dL)	47/661	1·00 (0·99-1·01)	0·53
HDL-C (mg/dL)	46/656	0·97 (0·95-1·00)	0·02
Triglycerides (mg/dL)	46/639	1·00 (1·00-1·01)	0·06
Metabolic syndrome components*			
Abdominal obesity	42/646	0·87 (0·46-1·66)	0·67
Elevated triglycerides	46/639	1·55 (0·82-2·95)	0·18
Reduced HDL-C	46/656	2·50 (1·38-4·56)	0·003
Elevated blood pressure	49/682	0·76 (0·27-2·16)	0·60
Prediabetes or diabetes mellitus	47/643	2·82 (1·37-5·84)	0·005
Metabolic syndrome (≥3 of the above components present)	49/683	2·14 (1·16-3·96)	0·02
Per count of components increase	49/683	1·34 (1·05-1·71)	0·02
Index stroke classification			
Haemorrhagic stroke	49/683	2·34 (0·83-6·60)	0·11
Acute stroke treatment			
Any acute reperfusion treatment (IVT and/or EVT)	49/683	0·49 (0·23-1·06)	0·07
Neuroimaging parameters			
Normalised brain volume (per SD)	45/613	0·61 (0·41-0·93)	0·02
Normalised infarct volume (per SD)	45/613	1·09 (0·82-1·45)	0·54
Total SVD score (per SD)	46/621	1·27 (0·94-1·72)	0·12
Lacune count (per SD)	48/626	1·32 (1·16-1·50)	<0·0001
Presence of ≥3 lacunes	48/626	10·33 (3·90-27·40)	<0·0001
Normalised WMH volume (per SD)	43/613	1·45 (1·20-1·76)	<0·0001
CMB count (per SD)	46/621	1·12 (0·95-1·32)	0·17
PVS grade (per SD)	48/625	1·23 (0·94-1·60)	0·13
Mean skeletonised mean diffusivity (per SD)	41/587	1·95 (1·43-2·67)	<0·0001
Genetic risk factors			
APOE genotype			
0 ε4 alleles	40/557	ref	ref
1 ε4 allele	40/557	0·91 (0·42-2·00)	0·82
2 ε4 alleles	40/557	9·51 (1·08-84·04)	0·04
Pre-stroke clinical/cognitive function			
mRS before stroke	49/683	0·88 (0·58-1·33)	0·55
IQCODE score	43/633	1·05 (0·96-1·16)	0·29
Recurrent events			

Stroke recurrence	49/732	3·19 (1·54-6·64)	0·002

Cox proportional hazards regression models for the association between risk factors and post-stroke dementia, adjusted for age, sex, education, admission NIHSS, and acute phase cognitive impairment (MoCA <26 or MMSE <27 [n=73]). Recurrent stroke was included as a time-dependent covariable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.
* Defined according to Alberti et al.[2]

Table S15: Sensitivity analysis adjusting the analysis split by post-stroke time period for age, sex, education, NIHSS, and acute phase cognitive impairment

	Dementia risk 3-6 months			*Dementia risk > 6 months*		
Risk factors	**Cases/N**	**HR (95% CI)**	**P-value**	**Cases/N**	**HR (95% CI)**	**P-value**
Sociodemographic factors						
Age (per year)	20/683	1·17 (1·09- 1·25)	<0·0001	29/599	1·08 (1·03-1·13)	0·002
Age ≥74 years	20/683	6·50 (2·16-19·53)	<0·0001	29/599	2·61 (1·23-5·52)	0·01
Female sex	20/683	0·76 (0·29-2·00)	0·58	29/599	0·58 (0·25-1·34)	0·20
Education (per year)	20/683	0·91 (0·79-1·04)	0·18	29/599	0·88 (0·78-1·00)	0·06
Education ≤12 years	20/683	1·42 (0·58-3·52)	0·44	29/599	1·66 (0·76-3·63)	0·20
Clinical acute phase deficits						
Stroke severity (per point on admission NIHSS)	20/683	1·09 (1·01-1·18)	0·03	29/599	1·06 (0·99-1·14)	0·08
Admission NIHSS ≥3	20/683	2·74 (0·99-7·58)	0·05	29/599	2·23 (0·98-5·09)	0·06
Barthel Index (per point)	20/682	0·97 (0·96-0·99)	0·001	29/598	0·99 (0·98-1·00)	0·22
Delirious symptoms (per point on DRS)	20/683	1·28 (1·12-1·46)	0·0003	29/599	0·94 (0·72-1·23)	0·66
Vascular risk factors						
Hypertension	20/683	0·65 (0·18-2·35)	0·51	29/599	1·44 (0·42-4·89)	0·56
Diabetes mellitus	20/683	2·70 (1·10-6·63)	0·03	29/599	2·49 (1·16-5·38)	0·02
Dyslipidaemia	20/683	0·78 (0·31-1·96)	0·60	29/599	1·877 (0·83-3·77)	0·14
Current smoking	20/683	0·00 (0·00-Inf)	1·00	29/599	1·47 (0·56-3·86)	0·43
Regular alcohol consumption	20/683	0·41 (0·16-1·04)	0·06	29/599	1·15 (0·45-2·89)	0·77
Atrial fibrillation	20/683	3·42 (1·40-8·35)	0·007	29/599	1·62 (0·72-3·60)	0·24
Prior history of stroke	20/683	2·40 (0·90-6·39)	0·08	29/599	1·57 (0·58-4·20)	0·37
Ischaemic heart disease	20/683	1·33 (0·44-4·39)	0·61	29/599	1·84 (0·78-4·38)	0·17
BMI, kg/m2	20/683	1·03 (0·91-1·17)	0·65	29/599	1·00 (0·90-1·10)	0·97
SBP, mmHg	20/678	1·01 (0·99-1·04)	0·34	29/594	0·99 (0·97-1·01)	0·44
DBP, mmHg	20/678	1·01 (0·97-1·05)	0·57	29/594	1·01 (0·98-1·04)	0·59
HbA_{1c}, %	19/635	1·11 (0·94-1·32)	0·22	27/555	1·07 (0·92-1·24)	0·36
LDL-C, mg/dL	19/661	0·99 (0·98-1·01)	0·31	28/580	1·01 (1·00-1·02)	0·12
HDL-C, mg/dL	19/656	0·97 (0·93-1·00)	0·08	27/575	0·98 (0·95-1·01)	0·16
Triglycerides, mg/dL	19/639	1·00 (1·00-1·01)	0·50	27/559	1·00 (1·00-1·01)	0·10
Metabolic syndrome components*						
Abdominal obesity	15/646	0·50 (0·17-1·48)	0·21	27/571	1·08 (0·49-2·44)	0·85
Elevated triglycerides	19/639	1·22 (0·43-3·47)	0·70	27/559	1·71 (0·75-3·89)	0·20
Reduced HDL-C	19/656	2·973 (1·05-7·14)	0·04	27/575	2·42 (1·12-5·24)	0·02
Elevated blood pressure	20/682	1·17 (0·15-8·93)	0·88	29/598	0·65 (0·19-2·24)	0·49
Prediabetes/Diabetes mellitus	19/643	2·64 (0·86-8·17)	0·09	28/562	2·82 (1·10-7·20)	0·03
Metabolic syndrome (≥ 3 of the above components present)	20/683	1·18 (0·49-2·88)	0·71	29/599	3·32 (1·37-8·07)	0·008
Per count of components increase	20/683	1·20 (0·81-1·78)	0·36	29/599	1·41 (1·03-1·93)	0·03
Index stroke classification						
Haemorrhagic stroke	20/683	1·33 (0·17-10·20)	0·78	29/599	3·25 (0·96-10·98)	0·06
Acute stroke treatment						
Any reperfusion therapy (IVT and/or EVT)	20/683	0·61 (0·19-2·01)	0·42	29/599	0·41 (0·15-1·15)	0·09

Neuroimaging parameters						
Normalised brain volume (per SD)	18/613	0·72 (0·37-1·341)	0·34	27/542	0·58 (0·35-0·97)	0·04
Normalised infarct volume (per SD)	18/613	1·39 (0·99-1·93)	0·06	27/542	0·74 (0·39-1·40)	0·36
Total SVD score (per SD)	19/621	1·42 (0·89-2·78)	0·14	27/549	1·15 (0·76-1·74)	0·51
Lacune count (per SD)	20/626	1·33 (1·12-1·58)	0·001	28/553	1·43 (1·14-1·78)	0·002
Presence of ≥3 lacunes	20/626	6·81 (1·52-30·52)	0·01	28/553	17·70 (4·77-66·06)	<0·0001
Normalised WMH volume (per SD)	19/613	1·31 (0·95-1·80)	0·09	27/542	1·59 (1·24-2·03)	0·0002
CMB count (per SD)	18/621	1·03 (0·76-1·41)	0·83	28/549	1·15 (0·96-1·38)	0·14
PVS grade (per SD)	20/625	1·30 (0·87-1·95)	0·20	28/552	1·17 (0·81-1·68)	0·41
Mean skeletonised mean diffusivity (per SD)	16/587	1·71 (1·01-2·89)	0·05	25/521	2·08 (1·40-3·11)	0·0003
APOE genotype						
1 ε4 allele	15/557	1·65 (0·54-5·00)	0·38	25/494	0·59 (0·20-1·73)	0·37
2 ε4 alleles	15/557	32·70 (3·46-309·76)	0·002	25/494	0·00 (0·00-Inf)	1·00
Pre-stroke clinical/cognitive function						
mRS before stroke	20/683	0·71 (0·37-1·36)	0·30	29/599	1·01 (0·60-1·70)	0·97
IQCODE score	18/633	1·05 (0·95-1·16)	0·37	25/558	1·08 (0·94-1·23)	0·27
Recurrent events						
Stroke recurrence	20/732	0·69 (0·09-5·18)	0·72	29/631	5·78 (2·52-13·26)	<0·0001

Cox proportional hazards regression models for the association between risk factors and early-onset (left) and delayed-onset PSD (right), adjusted for age, sex, education, admission NIHSS, and acute phase cognitive impairment (MoCA <26 or MMSE <27 [n=73]). Recurrent stroke was included as a time-dependent covariable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.
* Defined according to Alberti et al.[2]

Table S16: Sensitivity analysis using the cut-off of 12 months for early- vs. delayed-onset dementia

	Early-onset dementia risk (3-12 months)			*Delayed-onset dementia risk (>12 months)*		
Baseline risk factor	**Cases/N**	**HR (95% CI)**	**P-value**	**Cases/N**	**HR (95% CI)**	**P-value**
Age (per year)	31/706	1·17 (1·11-1·23)	< 0·0001	24/589	1·09 (1·04- 1·15)	0·0006
Age ≥ 74	31/706	6·68 (2·87-15·56)	< 0·0001	24/589	3·30 (1·45-7·50)	0·004
Female sex	31/706	0·34 (0·14-0·79)	0·01	24/589	0·69 (0·29-1·64)	0·40
Education (per year)	31/706	0·92 (0·82-1·03)	0·13	24/589	0·78 (0·67-0·90)	0·001
Education ≤ 12	31/706	1·43 (0·69-2·96)	0·33	24/589	2·70(1·16-6·30)	0·02
Clinical/cognitive acute phase deficits						
Stroke severity (per point on admission NIHSS)	31/706	1·07 (1·00-1·14)	0·05	24/589	1·08 (1·01-1·16)	0·02
Admission NIHSS ≥3	31/706	2·86 (1·23-6·65)	0·01	24/589	2·45 (0·96-6·21)	0·06
Barthel Index (per point)	31/704	0·97 (0·96-0·99)	< 0·0001	24/587	0·99 (0·97-1·00)	0·12
Delirious symptoms (per point on DRS)	31/706	1·25 (1·11-1·41)	0·0002	24/589	0·92 (0·65-1·30)	0·64
Acute phase cognitive function (per point on MoCA)	24/625	0·82 (0·74-0·90)	< 0·0001	17/527	0·84 (0·75-0·94)	0·003
Acute phase cognitive impairment*[1]	30/683	4·44 (1·31-15·07)	0·02	19/572	8·37 (1·89-36·94)	0·005
Cardiovascular risk factors						
Hypertension	31/706	0·70 (0·26-1·89)	0·49	24/589	1·84 (0·42-8·02)	0·42
Diabetes mellitus	31/706	2·02 (0·97-4·20)	0·06	24/589	2·48 (1·08-5·72)	0·03
Dyslipidaemia	31/706	1·32 (0·65-2·70)	0·44	24/589	1·42 (0·63-3·23)	0·40
Current smoking	31/706	0·24 (0·03-1·83)	0·17	24/589	1·76 (0·61-5·13)	0·30
Regular alcohol consumption	31/706	0·54 (0·25-1·16)	0·11	24/589	1·29 (0·47-3·54)	0·62
Atrial fibrillation	31/706	2·56 (1·26-5·20)	0·009	24/589	1·32 (0·53-3·27)	0·54
Prior history of stroke	31/706	2·29 (0·98-5·35)	0·06	24/589	1·64 (0·55-4·89)	0·37
Ischaemic heart disease	31/706	2·21 (0·98-5·02)	0·06	24/589	1·52 (0·51-4·53)	0·45
BMI (kg/m^2)	31/706	0·99 (0·89-1·10)	0.86	24/589	0·99 (0·88-1·11)	0·86
Systolic blood pressure (mmHg)	31/701	1·01 (0·99-1·03)	0·18	24/584	0·99 (0·96-1·01)	0·22
Diastolic blood pressure (mmHg)	31/701	1·01 (0·98-1·04)	0·36	24/584	0·99 (0·96-1·03)	0·70
HbA_{1c} (%)	30/658	1·05 (0·87-1·27)	0·60	22/546	1·07 (0·94-1·21)	0·32
LDL cholesterol (mg/dL)	30/684	1·00 (0·99-1·01)	0·89	23/570	1·00 (0·99-1·01)	0·68
HDL cholesterol (mg/dL)	30/679	0·99 (0·96-1·02)	0·52	22/565	0·96 (0·93-1·00)	0·05
Triglycerides (mg/dL)	30/662	1·00 (0·99-1·00)	0·81	22/551	1·00 (1·00-1·01)	0·004
Metabolic syndrome components*[2]						
Abdominal obesity	25/666	0·60 (0·26-1·40)	0·24	23/560	1·70 (0·66-4·35)	0·27
Elevated triglycerides	30/662	0·84 (0·36-1·96)	0·69	22/551	3·25 (1·34-7·88)	0·009
Reduced HDL cholesterol	30/679	1·77 (0·83-3·78)	0·14	22/565	4·22 (1·71-10·42)	0·002
Elevated blood pressure	31/705	0·42 (0·12-1·43)	0·16	24/588	0·58 (0·13-2·57)	0·47
Prediabetes/Diabetes mellitus	30/666	1·94 (0·86-4·38)	0·11	23/552	2·26 (0·84-6·05)	0·10
Metabolic syndrome (≥3 of the above components present)	31/706	1·17 (0·57-2·40)	0·67	24/589	5·13 (1·70-15·50)	0·004
Per count of components increase	31/706	1·03 (0·76-1·41)	0·83	24/589	1·67 (1·19-2·35)	0·003
Index stroke classification						
Haemorrhagic stroke	31/706	1·80 (0·42-7·66)	0·42	24/589	4·71 (1·08-20·59)	0·04
Acute stroke treatment						
Any reperfusion therapy (IVT and/or EVT)	31/706	0·34 (0·12-0·99)	0·05	24/589	0·35 (0·11-1·09)	0·07

Neuroimaging parameters						
Normalised brain volume (per SD)	27/634	0·68 (0·40-1·15)	0·15	24/534	0·54 (0·32-0·92)	0·02
Normalised infarct volume (per SD)	27/634	1·25 (0·92-1·71)	0·16	24/534	1·04 (0·68-1·57)	0·87
Total SVD score (per SD)	29/642	1·36 (0·92-2·01)	0·12	22/541	1·06 (0·65-1·71)	0·82
Lacune count (per SD)	30/647	1·35 (1·16-1·57)	< 0·0001	23/544	1·61 (1·18-2·19)	0·002
Presence of ≥3 lacunes	30/647	9·31 (2·72-31·85)	0·0004	23/544	16·32 (3·47-76·67)	0·0004
Normalised WMH volume (per SD)	27/633	1·45 (1·14-1·84)	0·002	21/534	1·38 (0·96-1·98)	0·08
Cerebral microbleed count (per SD)	29/642	1·12 (0·89-1·42)	0·33	22/541	1·20 (0·96-1·50)	0·11
Perivascular space grade (per SD)	30/646	1·36 (0·97-1·90)	0·07	23/543	1·07 (0·70-1·64)	0·74
Mean skeletonised mean diffusivity (per SD)	25/606	1·87 (1·24-2·82)	0·003	20/512	1·98 (1·22-3·21)	0·006
Genetic risk factors						
APOE genotype						
0 ε4 alleles	ref	ref	..	ref	ref	..
1 ε4 allele	25/576	1·34 (0·54-3·30)	0·53	18/482	0·60 (0·16-2·22)	0·44
2 ε4 alleles	25/576	4·21 (0·55-32·36)	0·16	18/482	3·88 (0·49-30·55)	0·20
Pre-stroke clinical/cognitive function						
mRS before stroke	31/706	0·90 (0·56-1·45)	0·67	24/589	1·31 (0·81-2·13)	0·27
IQCODE score	29/655	1·04 (0·95-1·15)	0·12	20/548	1·16 (1·01-1·34)	0·03
Recurrent events						
Stroke recurrence	31/757	1·84 (0·64-5·31)	0·26	24/615	3·41 (1·25-9·27)	0·02

Cox proportional hazards regression models for the association between risk factors and early-onset (left) and delayed-onset PSD (right), when setting the cut-off at 1 year instead of 6 months post stroke. Recurrent stroke was included as a time-dependent variable as described in the **Supplementary Methods**.

APOE=apolipoprotein E. BMI=body-mass index. DRS=Delirious rating scale. EVT=Endovascular thrombectomy. HbA_{1c}=glycated haemoglobin. HDL=high-density lipoprotein. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous thrombolysis. LDL=low-density lipoprotein. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. WMH=white matter hyperintensity.

*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).

*[2] Defined according to Alberti et al.[2]

Table S17: Sensitivity analysis with multiple imputation of the dementia onset date

Risk Factor	Cases/N	HR (95% CI)	P-Value
Sociodemographic factors			
Age (per year)	55/706	1·13 (1·09-1·18)	<0·0001
Age ≥74	55/706	4·74 (2·66-8·47)	<0·0001
Female sex	55/706	0·49 (0·26-0·92)	0·03
Education (per year)	55/706	0·87 (0·79-0·95)	0·004
Education ≤12	55/706	1·83 (1·05-3·21)	0·04
Clinical acute phase deficits			
Stroke severity (per point on admission NHSS)	55/706	1·07 (1·02-1·13)	0·005
Admission NIHSS ≥3	55/706	2·72 (1·45-5·10)	0·003
Barthel Index (per point)	55/704	0·98 (0·97-0·99)	0·0001
Delirious symptoms (per point on DRS)	55/706	1·17 (1·04-1·30)	0·009
Acute phase cognitive function (per point on MoCA)	41/625	0·83 (0·77-0·90)	<0·0001
Acute phase cognitive impairment*[1]	49/683	5·89 (2·30-15·10)	0·0006
Vascular risk factors			
Hypertension	55/706	1·05 (0·47-2·35)	0·91
Diabetes mellitus	55/706	2·26 (1·30-3·92)	0·006
Dyslipidaemia	55/706	1·35 (0·79-2·31)	0·28
Current smoking	55/706	0·84 (0·35-2·01)	0·69
Regular alcohol consumption	55/706	0·73 (0·40-1·34)	0·31
Atrial fibrillation	55/706	1·86 (1·08-3·22)	0·03
Prior stroke	55/706	2·00 (1·03-3·91)	0·05
Ischaemic heart disease	55/706	1·96 (1·03-3·75)	0·05
BMI (kg/m^2)	55/706	0·99 (0·92-1·08)	0·92
SBP (mmHg)	55/701	1·00 (0·99-1·02)	0·88
DBP (mmHg)	55/701	1·00 (0·98-1·03)	0·76
HbA1c (%)	52/658	1·06 (0·96-1·18)	0·26
LDL-C (mg/dL)	53/684	1·00 (0·99-1·01)	0·86
HDL-C (mg/dL)	52/679	0·98 (0·96-1·00)	0·08
Triglycerides (mg/dL)	52/662	1·00 (1·00-1·01)	0·04
Metabolic syndrome components*[2]			
Abdominal obesity	48/666	0·98 (0·53-1·81)	0·96
Elevated triglycerides	52/662	1·54 (0·86-2·75)	0·15
Reduced HDL-C	52/679	2·56 (1·46-4·51)	0·002
Elevated blood pressure	55/705	0·47 (0·18-1·22)	0·13
Prediabetes or diabetes mellitus	53/666	2·05 (1·10-3·82)	0·03
Metabolic syndrome (≥3 of the above components present)	55/706	1·99 (1·12-3·54)	0·02
Per count of components increase	55/706	1·30 (1·04-1·62)	0·02
Index stroke classification			
Haemorrhagic stroke	55/706	2·69 (0·96-7·55)	0·07
Acute stroke treatment			
Any acute reperfusion therapy (IVT and/or EVT)	55/706	0·35 (0·16-0·74)	0·009
Neuroimaging parameters			
Normalised brain volume (per SD)	50/634	0·60 (0·41-0·87)	0·01
Normalised infarct volume (per SD)	50/634	1·19 (0·93-1·51)	0·17
Total SVD score (per SD)	51/642	1·24 (0·92-1·66)	0·16
Lacune count (per SD)	53/647	1·36 (1·20-1·55)	<0·0001
Presence of ≥3 lacunes	53/647	11·15 (4·8-29·04)	0·001
Normalised WMH volume (per SD)	48/633	1·40 (1·16-1·70)	0·002
CMB count (per SD)	51/642	1·15 (0·98-1·36)	0·09
PVS grade (per SD)	53/646	1·19 (0·92-1·54)	0·19
Mean skeletonised mean diffusivity (per SD)	45/606	1·89 (1·39-2·57)	0·0002
APOE genotype			
1 ε4 allele	43/576	1·15 (0·55-2·40)	0·72
2 ε4 alleles	43/576	5·34 (1·25-22·91)	0·003
Pre-stroke clinical/cognitive function			
mRS before stroke	55/706	1·09 (0·78-1·54)	0·61
IQCODE score	49/655	1·07 (0·98-1·18)	0·15

Pooled results of the association between baseline risk factors and post-stroke dementia, based on 20 datasets, derived using multiple imputation for the date of dementia onset. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.
*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).
*[2] Defined according to Alberti et al.[2]

Table S18: Comparison of subdistribution and cause-specific hazard ratios for 5-year PSD risk

	Cases/N	Subdistribution HR (95% CI)	P-Value	P-Value PH Test	Cause-specific HR (95% CI)	P-Value	P-Value PH Test
Sociodemographic factors							
Age (per year)	55/706	1·13 (1·08-1·18)	<0·0001	0·21	1·13 (1·09-1·17)	<0·0001	0·09
Age ≥74	55/706	4·76 (2·65-8·55)	<0·0001	0·47	4·75 (2·66-8·49)	<0·0001	0·28
Female sex	55/706	0·40 (0·20-0·80)	0·009	0·82	0·40 (0·21-0·77)	0·006	0·75
Education (per year)	55/706	0·86 (0·77-0·95)	0·002	0·52	0·86 (0·78-0·94)	0·001	0·65
Education ≤12	55/706	1·89 (1·05-3·40)	0·03	0·63	1·88 (1·07-3·29)	0·03	0·58
Clinical/cognitive acute phase deficits							
Stroke severity (per point on admission NHSS)	55/706	1·12 (1·06-1·19)	0·0001	0·36	1·12 (1·06-1·18)	<0·0001	0·59
Admission NIHSS ≥3	55/706	2·68 (1·44-4·97)	0·002	0·93	2·67 (1·43-5·00)	0·002	0·93
Barthel Index (per point)	55/704	0·98 (0·97-0·99)	<0·0001	0·14	0·98 (0·97-0·99)	<0·0001	0·20
Delirious symptoms (per point on DRS)	55/706	1·15 (0·99-1·34)	0·07	0·05	1·15 (1·03-1·29)	0·01	0·03
Acute phase cognitive function (per point on MoCA)	41/625	0·84 (0·77-0·92)	<0·0001	0·26	0·84 (0·78-0·90)	<0·0001	0·29
Acute phase cognitive impairment*[1]	49/683	5·86 (2·21-15·58)	0·0004	0·90	5·91 (2·30-15·13)	0·0002	0·76
Vascular risk factors							
Hypertension	55/706	1·01 (0·44-2·35)	0·98	0·31	1·02 (0·45-2·28)	0·97	0·21
Diabetes mellitus	55/706	2·33 (1·38-3·94)	0·001	0·60	2·33 (1·34-4·05)	0·003	0·61
Dyslipidaemia	55/706	1·32 (0·75-2·30)	0·34	0·46	1·31 (0·76-2·25)	0·32	0·44
Current smoking	55/706	0·79 (0·34-1·82)	0·58	0·06	0·79 (0·33-1·89)	0·59	0·03
Regular alcohol consumption	55/706	0·82 (0·44-1·55)	0·55	0·10	0·83 (0·45-1·52)	0·54	0·06
Atrial fibrillation	55/706	2·07 (1·19-3·61)	0·01	0·07	2·07 (1·19-3·59)	0·01	0·05
Prior stroke	55/706	1·82 (0·91-3·65)	0·09	0·11	1·82 (0·91-3·63)	0·09	0·15
Ischaemic heart disease	55/706	1·86 (0·91-3·81)	0·09	0·26	1·86 (0·96-3·57)	0·06	0·42
BMI (per unit [kg/m^2])	55/706	1·01 (0·93-1·10)	0·81	0·60	1·01 (0·94-1·09)	0·79	0·57
SBP (per mmHg)	55/701	1·00 (0·99-1·02)	0·97	0·06	1·00 (0·98-1·02)	0·97	0·08
DBP (per mmHg)	55/701	1·00 (0·98-1·02)	0·79	0·48	1·00 (0·98-1·03)	0·80	0·64
HbA_{1c} (%)	52/658	1·05 (0·97-1·12)	0·22	0·65	1·05 (0·94-1·16)	0·39	0·72
LDL-C (per 10 mg/dL)	53/684	1·00 (0·99-1·01)	0·98	0·15	1·00 (0·99-1·01)	0·97	0·11
HDL-C (per 10 mg/dL)	52/679	0·98 (0·95-1·00)	0·11	0·29	0·98 (0·96-1·00)	0·06	0·67
Triglycerides (mg/dL)	52/663	1·00 (1·00-1·01)	0·03	0·06	1·00 (1·00-1·01)	0·07	0·05
Metabolic syndrome components*[2]							
Abdominal obesity	48/666	1·17 (0·59-2·33)	0·66	0·06	1·17 (0·63-2·16)	0·62	0·06
Elevated triglycerides	52/663	1·49 (0·86-2·60)	0·16	0·02	1·49 (0·83-2·68)	0·18	0·03
Reduced HDL-C	52/679	2·69 (1·55-4·66)	0·0004	0·61	2·68 (1·51-4·75)	0·0007	0·52
Elevated blood pressure	55/705	0·37 (0·14-0·98)	0·04	0·57	0·37 (0·14-0·98)	0·05	0·63
Prediabetes or diabetes mellitus	53/666	2·33 (1·24-4·38)	0·009	0·64	2·32 (1·23-4·38)	0·009	0·71
Metabolic syndrome (≥3 of the above components present)	55/706	2·18 (1·23-3·86)	0·008	0·07	2·18 (1·22-3·90)	0·008	0·03
Per count of components increase	55/706	1·33 (1·07-1·65)	0·01	0·06	1·33 (1·06-1·66)	0·01	0·05

Index stroke classification							
Haemorrhagic stroke	55/706	2·02 (0·76-5·43)	0·16	0·60	2·02 (0·71-5·77)	0·19	0·48
Acute stroke treatment							
Any reperfusion therapy (IVT and/or EVT)	55/706	0·35 (0·16-0·77)	0·009	0·41	0·35 (0·16-0·75)	0·007	0·52
Neuroimaging parameters							
Normalised brain volume (per SD)	50/634	0·61 (0·41-0·91)	0·02	0·31	0·61 (0·42-0·90)	0·01	0·32
Normalised infarct volume (per SD)	50/634	1·19 (0·93-1·52)	0·16	0·41	1·19 (0·93-1·52)	0·17	0·32
Total SVD score (per SD)	51/642	1·17 (0·84-1·62)	0·35	0·22	1·17 (0·87-1·57)	0·31	0·24
Lacune count (per SD)	53/647	1·38 (1·27-1·50)	<0·0001	0·14	1·38 (1·21-1·57)	<0·0001	0·12
Presence of ≥3 lacunes	53/647	10·39 (5·16-20·92)	<0·0001	0·10	10·38 (3·94-27·33)	<0·0001	0·07
Normalised WMH volume (per SD)	48/633	1·37 (1·17-1·61)	0·0001	0·68	1·37 (1·14-1·66)	0·001	0·90
CMB count (per SD)	51/642	1·15 (1·04-1·27)	0·007	0·88	1·15 (0·97-1·36)	0·10	0·95
PVS grade (per SD)	53/646	1·19 (0·90-1·57)	0·22	0·22	1·19 (0·92-1·54)	0·19	0·22
Mean skeletonised mean diffusivity (per SD)	45/606	1·88 (1·37-2·58)	<0·0001	0·29	1·88 (1·39-2·54)	<0·0001	0·50
APOE genotype				0·93			0·86
1 ε4 allele	43/576	1·11 (0·52-2·36)	0·78		1·11 (0·53-2·32)	0·78	
2 ε4 alleles	43/576	4·94 (1·36-17·90)	0·01		4·93 (1·15-21·04)	0·03	
Pre-stroke clinical/cognitive function							
mRS before stroke	55/706	1·09 (0·74-1·61)	0·66	0·78	1·09 (0·77-1·55)	0·62	0·89
IQCODE score	49/655	1·07 (0·89-1·30)	0·47	0·92	1·07 (0·98-1·18)	0·13	0·53
Recurrent events							
Stroke recurrence	55/757	2·36 (1·16-4·83)	0·02	0·18	2·47 (1·20-5·11)	0·01	0·15

Associations between risk factors and post-stroke dementia derived by competing risk (left) and standard Cox proportional hazards models. Death was included as a competing risk. Cox proportional hazards regression models for the association between risk factors and post-stroke dementia, adjusted for age, sex, education, and admission NIHSS. The proportional hazards assumption was tested using the Grambsch and Therneau test based on Schoenfeld residuals (p-values < 0.05 suggest a potential violation). Recurrent stroke was included as a time-dependent covariable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. EVT=Endovascular Thrombectomy. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. IVT=Intravenous Thrombolysis. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PH=Proportional Hazards. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.
*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).
*[2] Defined according to Alberti et al.[2]

Table S19: Time-dependent hazard ratios for PSD for selected risk factors

			HR (95% CI)						
Variable	**Time-varying**	**P (TVC)**	**3 months**	**6 months**	**1 year**	**2 years**	**3 years**	**4 years**	**5 years**
Delirium Rating Scale	Yes	0.003	1.45 (1.25-1.68)	1.45 (1.21-1.73)	1.00 (0.72-1.39)	0.47 (0.10-2.15)	0.87 (0.70-1.07)	0.90 (0.75-1.08)	0.88 (0.72-1.06)
Currently smoking	Yes	0.02	0.00 (0.00–32.19)	0.04 (0.00–4.91)	0.63 (0.09–4.33)	1.80 (0.54–6.00)	1.39 (0.55–3.53)	1.24 (0.40–3.86)	1.23 (0.30–5.01)
Atrial fibrillation	No	0.23	..	..	..	..	..	..	..
Triglycerides	No	0.07	..	..	..	..	..	..	..
Abdominal obesity	No	0.29	..	..	..	..	..	..	..
Elevated Triglycerides	No	0.16	..	..	..	..	..	..	..
Metabolic Syndrome (≥ 3 components present)	Yes	0.01	0.70 (0.23–2.16)	0.84 (0.40–1.76)	1.86 (0.88–3.90)	3.00 (1.50–6.00)	2.62 (1.48–4.65)	2.83 (1.58–5.06)	3.14 (1.71–5.76)
Per additional MetS component	Yes	0.006	0.92 (0.55–1.55)	0.76 (0.52–1.12)	1.20 (0.63–2.27)	3.01 (1.16–7.78)	1.84 (1.38–2.44)	1.83 (1.39–2.42)	1.95 (1.45–2.63)

Associations between selected variables and PSD using flexible parametric survival models[28] to assess potential time-varying effects. Variables were selected based on evidence of a potential violation of the proportional hazards assumption (**Table S18**). For each variable, hazard ratios and 95% confidence intervals are presented at 3 months, 6 months, and 1, 2, 3, 4, and 5 years after stroke. Time-varying effects were modelled using natural splines (df = 4 for baseline hazard; df = 2 for TVC) and adjusted for age, sex, education, and admission NIHSS. The global p-value for the time-varying effect was derived from a likelihood ratio test comparing models with and without time-varying covariate terms. The time-varying HRs for Delirium Rating Scale, smoking, Metabolic Syndrome, and per additional MetS component have been plotted and are presented in **Figure S6**. MetS=Metabolic Syndrome. NIHSS=National Institutes of Health Stroke Scale. TVC=time-varying coefficient.

Table S20: Risk factors associated with PSD and PSCI showing unadjusted hazard ratios and odds ratios

		Post-stroke dementia		Post-stoke cognitive impairment	
Risk Factor	**Cases/N**	**HR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Sociodemographic factors					
Age (per year)	55/706	1·12 (1·08-1·16)	<0·0001	1·03 (1·01-1·05)	<0·0001
Age ≥74	55/706	4·74 (2·67-8·40)	<0·0001	2·15 (1·71-2·69)	<0·0001
Female sex	55/706	1·00 (0·57-1·75)	1·00	1·22 (1·03-1·44)	0·02
Education (per year)	55/706	0·87 (0·80-0·95)	0·002	0·91 (0·89-0·94)	<0·0001
Education ≤12	55/706	1·98 (1·16-3·36)	0·01	2·02 (1·69-2·41)	<0·0001
Clinical/cognitive acute phase deficits					
Stroke severity (per point on admission NHSS)	55/706	1·05 (1·00-1·11)	0·07	1·03 (1·02-1·05)	0·0003
Admission NIHSS ≥3	55/706	2·65 (1·48-4·75)	0·001	0·98 (0·97-0·98)	<0·0001
Barthel Index (per point)	55/704	0·97 (0·96-0·98)	<0·0001	1·07 (1·01-1·14)	0·02
Delirious symptoms (per point on DRS)	55/706	1·21 (1·08-1·36)	0·001	0·80 (0·78-0·81)	<0·0001
Acute phase cognitive function (per point on MoCA)	41/625	0·78 (0·73-0·83)	<0·0001	0·98 (0·97-0·98)	<0·0001
Acute phase cognitive impairment*[1]	49/683	9·70 (3·83-24·54)	<0·0001	3·45 (2·91-4·08)	<0·0001
Vascular risk factors					
Hypertension	55/706	2·16 (0·98-4·77)	0·06	1·22 (0·92-1·62)	0·16
Diabetes mellitus	55/706	2·76 (1·60-4·75)	0·0003	1·74 (1·47-2·06)	<0·0001
Dyslipidaemia	55/706	1·83 (1·08-3·12)	0·03	1·22 (1·10-1·36)	0·0002
Current smoking	55/706	0·42 (0·18-0·99)	0·05	0·96 (0·75-1·21)	0·71
Regular alcohol consumption	55/706	0·84 (0·46-1·51)	0·55	0·87 (0·71-1·05)	0·15
Atrial fibrillation	55/706	3·22 (1·88-5·53)	<0·0001	1·99 (1·63-2·43)	<0·0001
Prior stroke	55/706	2·24 (1·16-4·35)	0·02	1·61 (1·23-2·12)	0·0006
Ischaemic heart disease	55/706	2·44 (1·29-4·64)	0·006	1·87 (1·50-2·34)	<0·0001
BMI (kg/m^2)	55/706	0·96 (0·90-1·03)	0·25	1·01 (0·98-1·03)	0·59
SBP (mmHg)	55/701	1·01 (0·99-1·02)	0·30	1·00 (0·99-1·00)	0·15
DBP (mmHg)	55/701	0·99 (0·97-1·01)	0·36	0·98 (0·98-0·99)	<0·0001
HbA1c (%)	52/658	1·03 (0·94-1·12)	0·55	1·04 (1·00-1·09)	0·04
LDL-C (mg/dL)	53/684	1·00 (0·99-1·00)	0·50	1·00 (1·00-1·00)	0·14
HDL-C (mg/dL)	52/679	0·98 (0·96-1·00)	0·12	1·00 (0·99-1·00)	0·14
Triglycerides (mg/dL)	52/662	1·00 (1·00-1·00)	0·80	1·00 (1·00-1·00)	0·70
Metabolic syndrome components*[2]					
Abdominal obesity	48/666	1·12 (0·63-1·99)	0·70	1·27 (1·04-1·56)	0·02
Elevated triglycerides	52/662	1·06 (0·60-1·88)	0·84	1·04 (0·87-1·24)	0·64
Reduced HDL-C	52/679	2·48 (1·44-4·27)	0·001	1·25 (1·04-1·49)	0·01
Elevated blood pressure	55/705	1·31 (0·52-3·29)	0·57	0·94 (0·69-1·27)	0·67
Prediabetes or diabetes mellitus	53/666	2·51 (1·36-4·64)	0·003	1·49 (1·26-1·76)	<0·0001
Metabolic syndrome (≥3 of the above components present)	55/706	2·22 (1·27-3·91)	0·005	1·24 (1·09-1·41)	0·0008
Per count of components increase	55/706	1·30 (1·06-1·59)	0·01	1·09 (1·02-1·16)	0·010
Index stroke classification					
Haemorrhagic stroke	55/706	2·95 (1·06-8·17)	0·04	1·18 (0·87-1·61)	0·28
Acute stroke treatment					
Any reperfusion therapy (IVT and/or EVT)	55/706	0·62 (0·32-1·20)	0·15	0·79 (0·68-0·17)	0·002
Neuroimaging parameters				0·65 (0·59-0·73)	<0·0001
Normalised brain volume (per SD)	50/634	0·40 (0·29-0·53)	<0·0001	1·12 (1·06-1·19)	<0·0001
Normalised infarct volume (per SD)	50/634	1·11 (0·90-1·37)	0·31	1·36 (1·22-1·51)	<0·0001
Total SVD score (per SD)	51/642	1·61 (1·26-2·05)	0·0002	1·43 (1·31-1·55)	<0·0001
Lacune count (per SD)	53/647	1·34 (1·20-1·51)	<0·0001	8·85 (4·38-17·92)	<0·0001
Presence of ≥3 lacunes	53/647	8·50 (3·36-21·51)	<0·0001	1·58 (1·38-1·81)	<0·0001
Normalised WMH volume (per SD)	48/633	1·64 (1·40-1·93)	<0·0001	1·03 (0·96-1·11)	0·40
CMB count (per SD)	51/642	1·13 (0·98-1·31)	0·09	1·24 (1·18-1·31)	<0·0001
PVS grade (per SD)	53/646	1·56 (1·24-1·96)	0·0001	1·85 (1·61-2·11)	<0·0001
Mean skeletonised mean diffusivity (per SD)	45/606	2·47 (1·92-3·18)	<0·0001	0·65 (0·59-0·73)	<0·0001
APOE genotype					
1 ε4 allele	43/594	1·29 (0·63-2·64)	0·48	0·96 (0·81-1·12)	0·59
2 ε4 alleles	43/594	3·58 (0·85-14·97)	0·08	2·58 (1·57-4·24)	0·0002
Pre-stroke clinical/cognitive function					
mRS before stroke	55/706	1·42 (1·03-1·97)	0·03	1·23 (1·10-1·37)	0·0004

IQCODE score	49/655	1·15 (1·05-1·25)	0·002	1·10 (1·00-1·21)	0·05
Recurrent events					
Stroke recurrence	55/757	2·55 (1·25-5·22)	0·01	··	··

Associations between risk factors and post-stroke dementia (PSD, left) and post-stroke cognitive impairment (PSCI, right). Shown are the unadjusted hazard ratios and odds ratios, derived from univariable Cox proportional hazards and GEE models, respectively. Recurrent stroke was included as a time-dependent covariable as described in the **Supplementary Methods**. APOE=apolipoprotein E. BMI=body-mass index. CMB = cerebral microbleed. DBP = diastolic blood pressure. HbA_{1c}=glycated haemoglobin. HDL-C=high-density lipoprotein cholesterol. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. LDL-C=low-density lipoprotein cholesterol. MoCA=Montreal Cognitive Assessment. mRS=Modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. PVS = perivascular space. SBP = systolic blood pressure. SD = standard deviation. SVD = small vessel disease. WMH = white matter hyperintensity.
*[1] MoCA <26 or mini-mental state examination <27 when MoCA was not available (n=73).
*[2] Defined according to Alberti et al.[2]

Table S21: STROBE checklist for the reporting of observational studies in epidemiology

	Item No	Recommendation	Page/Location
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p.1, p.3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	pp.7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	p.8
Methods			
Study design	4	Present key elements of study design early in the paper	p.9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	pp.9-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	pp.9-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	pp.9-10, Suppl. methods
Bias	9	Describe any efforts to address potential sources of bias	p.10
Study size	10	Explain how the study size was arrived at	p.11, Suppl. methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Suppl. methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	pp.10-11, Suppl. methods
		(*b*) Describe any methods used to examine subgroups and interactions	p.11
		(*c*) Explain how missing data were addressed	p.11, Suppl. methods
		(*d*) If applicable, explain how loss to follow-up was addressed	Suppl. methods
		(*e*) Describe any sensitivity analyses	pp.10-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p.13, Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1, Table S6
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p.13, Table 1, Table S1
		(b) Indicate number of participants with missing data for each variable of interest	Table S1
		(c) Summarise follow-up time (eg, average and total amount)	p.13
Outcome data	15*	Report numbers of outcome events or summary measures over time	pp.13-14, Figures S1, S3, S4, S5, and S6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	pp.13-14, Table 2, Suppl. Methods, Table S7, Table S20
		(*b*) Report category boundaries when continuous variables were categorised	pp.13-14, Table 2, Suppl. methods, Table S7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p.15, Table S8, Tables S10-S17
Discussion			
Key results	18	Summarise key results with reference to study objectives	p.16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	pp.19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	pp.16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	pp.19-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.21

Table S22: The banner list of DEMDAS investigators

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Risikofaktoren für Demenz und kognitive Störungen innerhalb von 5 Jahren nach Schlaganfall: eine prospektive multizentrische Kohortenstudie

Zusammenfassung

Hintergrund: Kognitive Störungen gehören zu den häufigsten Langzeitfolgen eines Schlaganfalls. Ziel dieser Studie war es, Risikofaktoren für Demenz und kognitive Störungen innerhalb von fünf Jahren nach Schlaganfall zu identifizieren.

Methoden: Die DEMDAS (“Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE) mechanisms of dementia after stroke”) Studie ist eine prospektive Kohortenstudie von Schlaganfallpatient*innen, die zwischen dem 1. Mai 2011 und dem 31. Januar 2019 in eines von sechs tertiären Schlaganfallzentren in Deutschland eingewiesen wurden. Eingeschlossen wurden Patient*innen mit ischämischem oder hämorrhagischem Schlaganfall ohne vorbestehende Demenz. Sie erhielten eine Baseline-Untersuchung sowie regelmäßige klinische, neuropsychologische und bildgebende Follow-up-Untersuchungen über bis zu fünf Jahre. Die letzten Follow-ups wurden im Januar 2024 abgeschlossen. Der primäre Endpunkt war das Auftreten einer Demenz, bestimmt anhand ausführlicher kognitiver Testungen, Befragungen der Patient*innen und Angehörigen sowie Sichtung aller medizinischen Unterlagen. Sekundäre Endpunkte waren i) früh einsetzende Demenz (3-6 Monate nach Schlaganfall), ii) später einsetzende Demenz (>6 Monate) und iii) jegliche kognitive Störung (leichte kognitive Störung enschließlich Demenz). Assoziationen zwischen Baseline-Risikofaktoren und Demenz wurden mit Cox-Regressionsmodellen untersucht, adjustiert für Alter, Geschlecht, Bildungsgrad und Schlaganfallschwere.

Ergebnisse: Von 736 eingeschlossenen Patient*innen (33 % weiblich; mittleres Alter 68,0 Jahre [SD 11,2]; medianer National Institutes of Health Stroke Scale (NIHSS) Score bei Aufnahme 3 [IQR 1–5]) konnten 557 (76 %) bis zum Tod oder Studienende nachverfolgt werden. 706 (96 %) hatten mindestens ein Follow-up und gingen in die Demenzanalyse ein. Über einen medianen Follow-up-Zeitraum von 5,0 Jahren (IQR 3,3–5,1) wurden 55 neue Demenzfälle diagnostiziert (6-Monats-Inzidenz: 3,1 % [1,8–4,5]; 5-Jahres-Inzidenz: 8,8 % [6,5–11,1]); davon 21 (38 %) zwischen 3 und 6 Monaten nach dem Schlaganfall. Ein erhöhtes 5-Jahres-Demenzrisiko war assoziiert mit höherem Alter (HR 1,13 [95 %-KI 1,08–1,18] pro Jahr), größerer Schlaganfallschwere (1,08 [1,03–1,13] pro NIHSS-Punkt), geringerer Bildung (1,16 [1,05–1,28] pro Jahr weniger), kognitiver Beeinträchtigung in der Akutphase (5,86 [2,21–15,58]), niedrigerem Barthel-Index (1,10 [1,05-1,16] pro 5 Punkte weniger), Vorhofflimmern

(1,91 [1,10–3,30]), metabolischem Syndrom (2,05 [1,15–3,64]) – insbesondere niedrigem HDL-Cholesterin (2,61 [1,50–4,52]) und Prä-/Diabetes mellitus (2,13 [1,13–4,00]) – Bildgebungsmarkern für Small Vessel Disease sowie mit erneuten Schlaganfällen während des Follow-ups (2,36 [1,16–4,83]). Patientinnen, die eine akute Reperfusionstherapie erhielten, hatten ein um 65 % niedrigeres Demenzrisiko als solche ohne (0,35 [0,16–0,77]). Während Faktoren der Akutschwere des Schlaganfalls vor allem mit früh einsetzender Demenz assoziiert waren, war das metabolische Syndrom ein starker Risikofaktor für später einsetzende Demenz. Der Zusammenhang zwischen metabolischem Syndrom und Demenz blieb unabhängig von erneuten Schlaganfällen und über Altersgruppen hinweg bestehen: Die kumulative 5-Jahres-Inzidenz reichte von 1,7 % (0,0–4,0) bei ≤65-Jährigen ohne metabolisches Syndrom bis 24,5 % (14,3–33,4) bei ≥74-Jährigen mit metabolischem Syndrom.

Interpretation: Das Demenzrisiko nach Schlaganfall ist multifaktoriell, und die Risikoprofile für früh und später einsetzende Demenz unterscheiden sich. Das metabolische Syndrom und dessen Komponente niedriges HDL-Cholesterin stellen neu identifizierte Risikofaktoren und potenzielle Ziele für die Prävention kognitiver Verschlechterung und Demenz nach Schlaganfall dar.

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11. LIST OF PUBLICATIONS

Accepted for publication/published

Filler J, Georgakis MK, Janowitz D, Duering M, Fang R, Dewenter A, Bode FJ, Stoesser S, Kindler C, Hermann P, Nolte CH, Liman TG, Kerti L, Bernkopf K, Ikenberg B, Glanz W, Wagner M, Spottke A, Waegemann K, Goertler M, Wunderlich S, Endres M, Zerr I, Petzold GC, Dichgans M. Risk factors for dementia and cognitive impairment during 5 years after stroke: a prospective multicenter cohort study. Lancet Reg Health Eur. 2025 Sep; 56:101428.doi: 10.1016/j.lanepe.2025.101428. Epub 2025 Aug 19.

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Vlegels N*, Knuth NL*, Steiner KA, Zhang L, Vix AL, Moumin D, Mirzen I, Khalifeh N, Forster C, Gesierich B, Müller F, Lohse P, **Filler J**, Fang R, Klein M, Dimitriadis K, Franzmeier N, Thomas Liebig T, Endres M, Goertler M, Petzold GC, Wunderlich S, Zerr I, Field TS, Pham M, Swartz RH, Poli S, Berrouschot J, Zafar A, Schneider H, Shankar JJ, Aamodt AH, Minnerup J, Mandzia J, Reimann G, Psychogios M, Mundiyanapurath S, Reich A, Yeo LL, Duering M, Reidler P, Tymianski MGM, D. Hill MD, Dichgans M, Tiedt S. Brain-derived Tau for Monitoring Brain Injury in Acute Ischemic Stroke.

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12. DECLARATION OF AUTHOR CONTRIBUTIONS

Study I: "Risk factors for cognitive impairment and dementia after stroke: a systematic review and meta-analysis" (Filler, Georgakis, & Dichgans, 2024, The Lancet Healthy Longevity)

Authors: Jule Filler*, Marios K Georgakis*, and Martin Dichgans

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Contribution of co-authors: 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.

My specific contributions to this publication: Together with MKG, I contributed to the design of the meta-analysis. I performed the literature search, assessed all the articles for eligibility, extracted the data from the original articles, and planned and performed all statistical analyses. Following the analyses, I interpreted the results, drafted, and revised the manuscript.

Study II: "Risk factors for dementia and cognitive impairment during 5 years after stroke: a prospective multicenter cohort study" (Filler et al., 2025, The Lancet Regional Health – Europe)

Authors: Jule Filler, Marios K Georgakis, Daniel Janowitz, Marco Duering, Rong Fang, Anna Dewenter, Felix J Bode, Sebastian Stoesser, Christine Kindler, Peter Hermann, Christian H Nolte, Thomas G Liman, Lucia Kerti, Kathleen Bernkopf, Benno Ikenberg, Wenzel Glanz, Michael Wagner, Annika Spottke, Karin Waegemann, Michael Goertler, Silke Wunderlich, Matthias Endres, Inga Zerr, Gabor C Petzold, and Martin Dichgans, on behalf of the DEMDAS investigators

Contribution of co-authors: JF contributed to data preparation and interpretation, performed the statistical analysis, and drafted the manuscript. MKG critically reviewed and edited the manuscript; contributed to data interpretation; provided advice on the analyses; and was part of the endpoint committee for ascertaining dementia cases. DJ ascertained dementia cases as part of the endpoint committee. MDu conceptualised the neuroimaging protocol and established the central imaging platform. RF contributed significantly to data preparation. AD contributed to data preparation, description of MRI methods, and provided advice on the analysis of the MRI data. MKG, FB, SS, CK, PH, CHN, TGL, KB, and BI contributed to data acquisition as study physicians. LK managed the on-site study coordination. MW contributed to conceptualization of the neuropsychological test battery. AS administered the clinical research platform of DZNE. KW coordinated the study and contributed to data collection, cleaning, preparation, and quality control. GP, IZ, ME, SW, and MG contributed to the conception, design, and funding acquisition for the DEMDAS study, as well as to data collection. MDi contributed to data interpretation; co-wrote the manuscript; was part of the endpoint committee; and initiated, designed, obtained funding for, and coordinated the DEDEMAS-DEMDAS study. All authors had full access to all the data in the study, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication. JF, MKG, and MDi take full responsibility for the reported results, having verified the data and ensured the integrity of the data and the accuracy of the analyses.

My specific contributions to this publication: I contributed to data preparation and performed all statistical analyses. I interpreted the results, drafted, and revised the manuscript.