Stroke and dementia risk: A systematic review and meta-analysis

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Abstract

INTRODUCTION: Stroke is an established risk factor for all-cause dementia, though meta-analyses are needed to quantify this risk.

METHODS: We searched Medline, PsycINFO and Embase for studies assessing prevalent or incident stroke versus a no-stroke comparison group and the risk of all-cause dementia. Random effects meta-analysis was used to pool adjusted estimates across studies and meta-regression was used to investigate potential effect modifiers.

RESULTS: We identified 36 studies of prevalent stroke (1.9 million participants) and 12 studies of incident stroke (1.3 million participants). For prevalent stroke, the pooled hazard ratio for all-cause dementia was 1.69 (95% CI: 1.49-1.92; $p<0.00001$; $I^2 = 87\%$). For incident stroke, the pooled risk ratio was 2.18 (95% CI: 1.90-2.50; $p<0.00001$; $I^2 = 88\%$). Study characteristics did not modify these associations, with the exception of sex which explained 50.2% of between-study heterogeneity for prevalent stroke.

DISCUSSION: Stroke is a strong, independent, and potentially modifiable risk factor for all-cause dementia.

1. Introduction

Stroke is associated with the risk of cognitive impairment and dementia [1-3]. A systematic review [3] of 16 studies conducted in 2008 concluded that both history of and new stroke was associated with risk of developing all-cause dementia, although they were not able to conduct a meta-analysis at the time due to methodological heterogeneity in the included studies. A meta-analysis [4] of 30 studies conducted in 2009 established that dementia prevalence in symptomatic stroke patients increased from 10% before first stroke to 20% soon after first stroke, and more than a third had dementia after recurrent stroke. More recently, a meta-analysis [5] of six studies conducted in 2013 established that stroke is a moderately strong risk factor for Alzheimer's disease (AD) (risk ratio (RR) = 1.59, 95% CI = 1.25 – 2.02). Taken together these studies highlight the central causal role of symptomatic stroke, rather than underlying vascular risk factors. Given the current lack of disease modifying treatments and the complexity of multiple pathologies contributing to dementia, estimating the excess risk of dementia following stroke has the potential to inform preventive strategies to reduce the global burden of dementia. A recent umbrella review identified that no previous meta-analysis of the relationship between stroke and all-cause dementia had been undertaken [6]. A large number of original studies have been published since the systematic review conducted in 2008 [3], our objective was therefore to conduct the first meta-analysis of the relationship between stroke and all-cause dementia risk.

2. Methods

We updated the systematic review conducted by Savva and colleagues [3] and performed study-level random effects meta-analyses following general guidance provided by the Centre for Reviews and Dissemination (CRD, UK) [7].

2.1 Search strategy and selection criteria

Following the methods of the previous systematic review [3] and our pre-defined protocol, we developed search strategies for Medline, PsycINFO and Embase (via OvidSP) including subject headings and free text terms relevant to dementia, stroke and study design (see Appendix A, Methods and Fig. A1, A2, A3). We conducted our searches on 27 April 2017 (EK) restricting them to studies published after 2008 to avoid overlap with the previous systematic review which searched up to 31 December 2008 [3]. We also conducted backward and forward citation searches (via Web of Science; EK, IL) of publications included through our searches and in the previous systematic review [3]. We included prospective studies published in English investigating the association between prevalent or incident stroke and incident all-cause dementia. The population was adults aged 18 years or older, and the comparison group was adults without prevalent or incident stroke. Prevalent stroke was defined as history of previous stroke at baseline and incident stroke as stroke occurrence during follow-up. Studies with outcomes other than all-cause dementia, i.e. dementia subtypes or dementia-related outcomes (e.g. neuroimaging or biomarkers) were excluded. We also excluded studies with no comparison group or comparison group other than no stroke (i.e. stroke subtype), animal studies, case reports, narrative reviews, letters, editorials, opinions, book chapters, conference abstracts and duplicate publications using the same data. Following the pre-defined inclusion and exclusion criteria, two reviewers (EK, IL) independently screened titles and abstracts, and full-texts. Discrepancies were resolved by discussion with a third reviewer (DJL).

Key data were extracted by one reviewer (EK) and checked by the second (IL or SFM). We also contacted corresponding authors of 18 studies for clarification or where relevant data were not fully reported and received additional data or clarification for 13 studies (see Appendix A, Methods for details). Two reviewers (EK, IL) independently assessed the risk of bias of

included studies using the Quality Assessment Tool for Quantitative Studies [8] with discrepancies resolved by discussion. For each included study components of the tool (selection bias, study design, confounders, blinding, data collection methods, and withdrawals and drop-outs) and overall risk of bias were rated as "strong", "moderate" or "weak".

2.2 Data analysis

Studies were categorised by exposure into those investigating either prevalent or incident stroke. Total number of participants and stroke events were reported based on analytic sample size unless otherwise specified. We conducted random effects meta-analyses using the generic inverse-variance method [9] in recognition of the inherent methodological heterogeneity across studies. We used the Review Manager 5.3 software [10] to pool compatible estimates for the associations between prevalent or incident stroke and incident all-cause dementia. We prioritised fully-adjusted estimates of effect and extracted unadjusted results only if adjusted models were not available. When a group of studies entered in meta-analysis reported results as hazard ratios (HRs) and risk ratios (RRs), we presented the pooled estimate as a RR [11]. In separate meta-analyses, we combined results from studies reporting odds ratios (ORs). Adjusted estimates of effect were used for our primary analyses. In secondary analyses, we used summary estimates from unadjusted results. In sensitivity analyses, we excluded studies whose samples were limited to participants with prevalent mild cognitive impairment (MCI) or diabetes at baseline, or combined prevalent or incident stroke with transient ischemic attack (TIA). Where results were provided separately on the basis of APOE genotype (one or more ε4 allele versus none) or sex (male/female), we also present these additional stratified results. We investigated heterogeneity using Cochran's Chi-squared test and the I-squared statistic [12]. Funnel plots were obtained to evaluate the presence of publication bias. Where estimates from three or more studies were pooled, we reported 95% prediction intervals (PIs) which indicate the 95% range of true HRs (RRs or ORs) across settings that are similar to those in the

pooled studies [13]. Studies that could not be included in meta-analyses due to important differences in the outcome (e.g. early- vs. late-onset dementia) or statistical methods used were synthesised narratively.

We used meta-regression to investigate the effects of previously identified potential moderators of the relationship between stroke and dementia [5]. For prevalent stroke, we fitted meta-regression models by regressing the pooled HR of dementia risk on: study setting (community vs. non-community), inclusion of TIA in stroke assessment/diagnosis (yes/no), dementia diagnostic criteria used (DSM/ICD, other), stroke assessment based upon self-report only (yes/no), adjustment for at least one vascular risk factor (yes/no), mean/median age of participants in years, proportion of male participants (%), year at baseline examination, length of follow-up in years, and study quality (strong vs. moderate/weak). For incident stroke, we fitted meta-regression models by regressing the pooled RR of dementia risk on inclusion of TIA in stroke assessment/diagnosis, mean/median age of participants in years, proportion of male participants (%), year at baseline examination, length of follow-up in years, and study quality (strong vs. moderate/weak) (there were an inadequate number of studies to investigate the other potential moderators). Meta-regression analyses were performed using the 'metareg' command in Stata software, version 14.2 (StataCorp, College Station, TX, USA).

3. Results

Database searches resulted in 11,129 records. After removing duplicates, we screened 6,893 titles and abstracts and identified 99 for full-text review. Twenty six studies met our eligibility criteria. We also included 16 out of the 17 studies from the previous systematic review [3] and four studies identified via backward and forward citation searches (Fig. 1). We excluded the study by Reitz and colleagues using data from the Rotterdam Study [14] due to overlap with a

more recent publication from the same cohort [15] which had longer follow-up and a larger sample size.

The characteristics of the 46 included studies are shown in Table 1 and Appendix B, Tables B1 and B2. Nineteen studies were based in America, 16 in Europe, six in Asia, four in Australia and one was multinational. Thirty six studies included dementia-free participants at baseline, five studies reported they included cognitively normal population samples, and five studies recruited participants with mild cognitive impairment (MCI) or other cognitive impairment at baseline. Reporting of follow-up varied between studies (e.g. median, mean or maximum follow-up) and length ranged from nine months to 25 years. Twenty-four studies assessed stroke through self- or informant-report, and 15 studies reported adjudicated dementia diagnosis using DSM or ICD criteria [16-18]. Five studies assessed both stroke and dementia solely through medical records (Appendix B, Tables B3 and B4).

3.1 Risk of bias

Sixteen studies were rated as of overall strong quality, 20 as moderate and ten as weak (Appendix B, Table B5). Of the moderate-quality studies, six showed potential bias in the relevant confounders controlled for in the design or analysis, five showed potential bias in data collection methods and a further five studies were subject to selection bias. The weak-quality studies showed high risk of bias primarily due to a combination of selection bias (n=4), data collection methods (n=5), confounders (n=8) and attrition bias (n=3).

3.2 Prevalent stroke

Thirty four prospective cohort studies [19-52] (including three cohort studies of patients with MCI [19,24,28] and one diabetic cohort [22]) and two observational analyses of cohorts recruited for randomized controlled trials (RCTs) [53,54] investigated the association between prevalent stroke and incident all-cause dementia (around 1.9 million participants and 240,471

stroke events; Appendix B, Table B1). Most studies included older adults with an analytic sample size ranging from 52 [28] to 486,640 [25]. Two studies [26,50] included only women.

Pooled results from 22 cohorts of dementia-free participants at baseline (1,885,536 participants and 237,886 stroke events) indicated a higher adjusted risk of incident dementia in participants with prevalent stroke compared to those without stroke (pooled HR = 1.69, 95% CI: 1.49 – 1.92, p<0.00001, I^2 = 87%; 95% PI: 1.17 – 2.21; Fig. 2). Visual inspection of the funnel plot indicated no sign of publication bias (Appendix B, Fig. B4). In a sensitivity analysis, we excluded results provided by Walters and colleagues [49] for those aged 80 to 95 due to correlation with results reported from the same cohort for those aged 60 to 79. The pooled HR remained almost unchanged (1.75, 95% CI: 1.55 – 1.97, p < 0.00001; I^2 = 78%; 95% PI: 1.33 – 2.17). In further sensitivity analyses, we excluded studies including participants with MCI [19,24,32,40] or combining stroke with TIA [24,30,44,48,49,54]. In both cases, pooled estimates remained essentially unchanged (pooled HR = 1.71, 95% CI: 1.49 – 1.95, p < 0.001; I^2 = 89%; 95% PI: 1.17 – 2.25, and pooled HR = 1.69, 95% CI: 1.46 – 1.96, p < 0.001; I^2 = 51%; 95% PI: 1.23 – 2.15 respectively; Appendix B, Fig. B5.1, B5.2). Meta-regression analyses showed little evidence of effect modification on the basis of study setting (p=0.82), inclusion of TIA in stroke assessment/diagnosis (p=0.89), dementia diagnostic criteria used (p=0.37), stroke assessment based upon self-report only (p=0.59), adjustment for at least one vascular risk factor (p=0.92), mean/median age of participants (p=0.48), year at baseline examination (p=0.47), length of follow-up (p=0.73), or study quality (p=0.75). There was however some evidence for effect modification by sex, indicating that the risk of dementia corresponding to prevalent stroke was higher in men in comparison to women (p=0.04). Effect modification by sex explained around half of the observed between-study heterogeneity (males: HR = 1.02, 95% CI: 1.00 – 1.03, p=0.04; females: HR = 0.98, 95% CI: 0.97 – 0.99, p=0.04; adjusted R^2=50.2%).

Eight studies [21-23,33,35,46,51,52] reported adjusted ORs instead of HRs (11,336 participants and 1,001 stroke events). The pooled estimate indicated increased odds of incident dementia in those with prevalent stroke compared to no prevalent stroke (pooled OR = 1.53, 95% CI: 1.30-1.80, p<0.00001, I^2 = 0%; 95% PI: 1.22 – 1.84; Fig. 3). In a sensitivity analysis, we excluded the study by Bruce and colleagues [22] as it included only participants with diabetes. The estimate remained essentially unchanged (pooled OR = 1.57, 95% CI: 1.29-1.91, p<0.001; I^2= 11%; 95% PI: 1.09 – 2.05).

In a secondary analysis, the pooled estimate for three studies [26,28,42] reporting unadjusted results (2,795 participants and 262 stroke events) indicated little evidence of an association between prevalent stroke and incident dementia (pooled RR = 1.22, 95% CI: 0.50 – 2.99, p=0.66; I^2 = 74%; 95% PI: -10.38 – 12.82; Appendix B, Fig. B5.3). One additional study [47] reported dementia risk according to occurrence of recurrent stroke: both prevalent and recurrent stroke contributed to increased risk of incident dementia compared to absence of stroke (Appendix B, Table B3).

Three additional studies [39,41,50] could not be included in the meta-analyses as they did not fully report their results [41,50] or used standardised morbidity ratio as an effect size which could not be combined with existing estimates [39]. These studies all indicated prevalent stroke was associated with greater risk of incident dementia. We also excluded the study by Hobson and colleagues [36] from the meta-analysis because it was unclear whether it included participants with prevalent dementia at baseline. The authors reported that controlling for baseline dementia, prevalent stroke more than doubled the risk of incident dementia although there was a high degree of uncertainty surrounding their estimate (RR = 2.14, 95% CI: 0.64 – 7.13; Appendix B, Table B3).

3.3 Incident stroke

Twelve prospective cohort studies [15,37,42,55-63] investigated the association between incident stroke and incident all-cause dementia (around 1.3 million participants and 131,217 stroke events; Appendix B, Table B2). The majority of studies included older adults and the analytic sample size ranged from 339 [62] to 799,069 [60]. One study [61] focused on the association with early-onset dementia in men. In one additional study [60] 98% of the participants were men.

When we combined adjusted results from eight studies [15,37,55,57,59,60,62,63] (849,059 participants and 125,947 stroke events), the pooled estimate indicated that incident stroke more than doubled the risk of developing all-cause dementia compared to no incident stroke (pooled RR = 2.18, 95% CI: 1.90 – 2.50, p<0.001; I^2 = 88%; 95% PI: 1.67 – 2.69, Fig. 4). No obvious sign of publication bias was detected by visual inspection of the funnel plot (Appendix B, Fig. B4). None of the studies investigating incident stroke reported including participants with MCI at baseline. In a sensitivity analysis, we excluded three studies [15,62,63] combining stroke with TIA. The pooled estimate was in the same direction though stronger and the degree of heterogeneity between studies was slightly reduced (pooled RR = 2.41, 95% CI: 2.22 – 2.62, p<0.001; I^2 = 65%; 95% PI: 2.09 – 2.73; Appendix B, Fig. B6.1). One study [56] reporting an adjusted OR could not be included in the meta-analyses, although their findings also suggested increased odds of incident dementia in those with incident stroke compared to no incident stroke (Appendix B, Table B4). Meta-regression analyses indicated there was little evidence that inclusion of TIA in stroke assessment/diagnosis (p=0.49), mean/median age of participants (p=0.16), year at baseline examination (p=0.37), length of follow-up (p=0.32), or study quality (p=0.49) modified dementia risk.

In a secondary analysis, the pooled estimate for two studies [42,58] reporting unadjusted results (1,007 participants and stroke events) indicated that incident stroke almost tripled the risk of dementia compared to no incident stroke (pooled RR = 2.96, 95% CI: 1.81 – 4.84, $p<0.001$; I^2 =33%; Appendix B, Fig. B6.2). A study focusing on early-onset dementia in men [61] indicated that incident stroke almost tripled the risk of developing early-onset dementia (HR = 2.96, 95% CI: 2.02 – 4.35; Appendix B, Table B4).

3.4 APOE genotype

Three studies [30,38,63] reported the combined effect of prevalent stroke and APOE ε4 on all-cause dementia risk for combinations of stroke and APOE genotype (Table 2). Prevalent stroke was associated with a significantly increased risk of dementia for APOE ε4 non-carriers in two out of three studies [30,63], and the hazard ratio for the non-significant association was in the same direction [38]. Similarly, two out of three studies of prevalent stroke in APOE ε4 carriers indicated a significantly increased risk of dementia [38,63], and the hazard ratio of the non-significant association was again in the same direction [30]. However, there was no consistent difference in the effect sizes observed between APOE ε4 carriers and non-carriers for prevalent stroke.

Two studies [57,63] reported the combined effect of incident stroke and APOE ε4 on all-cause dementia risk for combinations of stroke and APOE genotype (Table 2). Incident stroke was associated with a significantly increased risk of dementia for APOE ε4 non-carriers in both studies. One out of two studies found that incident stroke was associated with a significantly increased risk of dementia for APOE ε4 carriers [63], though the hazard ratio for the other study was in the same direction [57]. There was no consistent difference in the effect sizes observed between APOE ε4 carriers and non-carriers for incident stroke.

3.5 Sex-stratified findings

Three studies [25,43,57] reported additional results for incident all-cause dementia stratified by sex (Appendix B, Table B6). One large cohort study [25] suggested a stronger association in men whereas two further studies [43,57] did not support a sex difference in the effect size.

4. Discussion

The results of our meta-analyses show that both prevalent and incident stroke are strong independent risk factors for all-cause dementia. However, significant between-study heterogeneity was observed. Associations persisted when excluding studies that included participants with prevalent MCI or combined diagnosis of stroke with TIA. Stratified analyses did not suggest a consistent difference in the effect sizes observed between APOE ε4 carriers and non-carriers for prevalent or incident stroke. Meta-regression analyses suggested that heterogeneity was not explained by a range of demographic factors or study characteristics, with the exception of sex which explained around half of the between-study variance observed for prevalent stroke.

Our meta-analysis extends the findings of the previous systematic review by Savva [3] and colleagues who concluded that stroke approximately doubles the risk of incident dementia in older adults. We included a larger number of prospective studies published since then (46 vs. 17) yielding a sample of nearly 3 million older adults and we were able to provide pooled estimates for both prevalent and incident stroke in relation to risk of all-cause dementia. Our results are also in line with a recent meta-analysis [5] of six studies reporting that participants with a history of stroke had 59% increased risk of developing AD compared with controls. However, the aforementioned study did not include all-cause dementia as an outcome. Associations with increased rates of post-stroke dementia are well known and have been

previously synthesised [4]; our analysis extends these findings beyond post-stroke incidence rates by providing pooled estimates for the risk of developing dementia compared to stroke-free populations.

Significant associations between stroke and higher risk of incident dementia were observed even after included studies adjusted for common modifiable risk factors for stroke such as hypertension, diabetes, myocardial infarction, and heart disease. Current evidence on the excess risk of stroke is based on observational data and since it is not possible to randomize participants to stroke events, RCTs have only indirectly examined the effect of stroke prevention interventions on dementia risk reduction. For example, trials assessing the effect of antihypertensive therapy have reported reduced incidence of all-cause dementia, vascular dementia and AD but results are inconsistent [64,65]. Similarly, prospective studies on anticoagulation for secondary prevention of stroke in older adults with atrial fibrillation have shown variable effects on dementia risk [66,67]. Certain characteristics of stroke may explain the increased risk of dementia in stroke survivors. Studies investigating stroke subtypes have implicated both lacunar and haemorrhagic strokes as predictors of post-stroke dementia [4,68], but evidence is mixed and variation in stroke subtyping methods may explain conflicting findings in the literature. The presence of multiple lesions, the volume of infarcts and the location of stroke (e.g. left hemisphere) have also been identified as risk factors for post-stroke dementia [4]. Neuroimaging studies have highlighted the role of medial temporal lobe atrophy and leukoaraiosis: extensive white matter changes related to subcortical stroke injury may increase the risk of memory decline and contribute to cortical grey matter thinning thereby increasing the risk of cognitive impairment [69]. Moreover, it has been suggested that stroke may trigger a neurodegenerative process by disrupting amyloid clearance [70] or by activating autoimmune responses [71] to brain antigens produced post-stroke. It is also possible that existing AD pathology may predispose to stroke: neuroinflammation and compromised

integrity of arterial walls related to accumulation of amyloid may result in greater risk of cerebrovascular events and increased infarct size [72]. It is therefore plausible that ongoing cerebrovascular injury due to vascular risk factors, immune processes, and pathogenic mechanisms may contribute to dementia risk after stroke.

This is the first meta-analysis to investigate the association of prevalent and incident stroke with incident all-cause dementia. The strengths of this study include the comprehensive search strategy including major electronic databases, backward and forward citation searching, and contacting authors for relevant data. We included publications in which stroke was not the main variable of interest and were able to identify studies reporting non-significant results to counteract potential publication bias. We also performed meta-regression analyses to explore potential moderators that may explain between-study heterogeneity. We provide up to date evidence supporting associations between stroke and increased risk of dementia based on a large number of studies with long follow-up periods and millions of participants.

However, the present results should be considered in light of the limitations of the included original studies. Some studies included selective samples, for example only men or women, volunteers, spouses of participants with stroke and subsamples enrolled in specific projects. Although most studies reported dementia-free participants at baseline, we cannot exclude the possibility that more studies than those already identified in our analysis included populations with MCI and cognitive impairment. These biases may have led to an overestimation of the association between stroke and all-cause dementia. Nonetheless, current results were robust to sensitivity analysis when we excluded studies with known MCI cohorts (i.e. highly similar effect size estimates). In addition, not all studies were specifically designed to investigate the association between prevalent or incident stroke and dementia. This translates into methodological differences in sample selection, stroke assessment and dementia diagnosis criteria, length of follow-up, statistical analysis plans and adjustments to account for potential

confounders. We were not able to incorporate important potential modifiers such as ethnicity and education in our meta-regression analyses due to inconsistent and incomplete reporting in the original studies. Clear and comprehensive reporting of information related to ethnic breakdown and educational level will facilitate harmonization of these potential modifiers across studies and subsequently strengthen future meta-regression analyses. Only three studies used neuroimaging to define stroke status, and it is possible that techniques such as T2-weighted and FLAIR magnetic resonance imaging (MRI), and ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) [73] may help to reduce unexplained between-study variability by improving the quantification of stroke-related pathology which in turn increases dementia risk. Similarly, unassessed variance in participant characteristics and the incidence of dementia unrelated to stroke may also have contributed to between-study variability.

Finally, dementia may develop many years before the diagnosis, and in research studies diagnosis is usually made during assessments at discrete times. Therefore, it is difficult to determine the exact dementia onset and as such the temporality of the association in studies of incident stroke and dementia especially in those with a long duration of follow-up. However, the stronger association observed for incident stroke suggests risk is greater near the time of stroke occurrence. More detailed reporting of the interval between stroke occurrence and dementia diagnosis in future studies will help to better characterise the role of time since stroke in the risk of dementia.

In conclusion, this systematic review and meta-analysis provides evidence that stroke is a strong independent risk factor for dementia. Given the consequences for people with dementia and their families and the significant implications for social and healthcare costs, stroke prevention strategies should be integrated in multimodal health interventions to reduce dementia risk.

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Contributors

DJL conceived and oversaw the study. EK and IL did the literature searches, reviewed all titles and abstracts, selected eligible studies, contacted authors, extracted data, planned and performed analyses and co-wrote the manuscript. SFM assisted with data extraction, DAL contributed substantial edits and OCU contributed to meta-analysis and meta-regression. All authors critically reviewed the final version of the manuscript.

Declaration of interest

We have no conflicts of interest.

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Table 1. Summary of data included in the systematic review*

	Studies, N†	Participants, N	Stroke events, N
All studies	46	3,242,618	371,688
Prevalent stroke	36	1,903,733	240,471
Incident stroke	12	1,338,885	131,217
Settings			
Community	36	1,332,276	225,588
Primary care	2	930,771	59,241
Secondary care	3	422	64
Other‡	5	979,149	86,795

Number of participants is based on analytic sample size and number of stroke events was estimated based on available information if not clearly reported in the original study. * Details of individual studies are shown in Appendix B, Tables B1 to B4. †Two studies reported on both prevalent and incident stroke exposures. ‡Two studies included participants from both primary and secondary care populations, two additional studies included participants from both secondary and community populations, and one study included participants from a military register.

Table 2. Results for the effect of stroke and APOE ε4 on incident all-cause dementia compared with population without stroke and APOE ε4

	APOE ε4- & Stroke-	**APOE ε4- & Stroke+**	**APOE ε4+ & Stroke-**	**APOE ε4+ & Stroke+**
Study	**Effect size (95% CI)**	**Effect size (95% CI)**	**Effect size (95% CI)**	**Effect size (95% CI)**
Prevalent stroke				
Dodge et al. (2011)[30]	Reference	HR = 2.64 (1.27-5.51)	Reference	HR = 1.43 (0.54-3.84)
Jin et al. (2008)[38]	Reference	HR = 1.33 (0.73-2.43)	HR = 2.06 (1.42-2.99)	HR = 2.57 (1.11-5.94)
Zhu et al. (2000)[63]	Reference	HR = 2.7 (1.6-4.8)	HR = 1.7 (1.2-2.4)	HR = 2.7 (1.1-6.8)
Incident stroke				
Ivan et al. (2004)[57]	Reference	HR = 3.4 (2.0-5.8)	Reference	HR = 1.2 (0.4-4.1)
Zhu et al. (2000)[63]	Reference	HR = 2.3 (1.3-4.1)	HR = 1.7 (1.1-2.4)	HR = 4.6 (2.0-10.6)

APOE, Apolipoprotein E; CI, confidence interval; HR, hazard ratio.

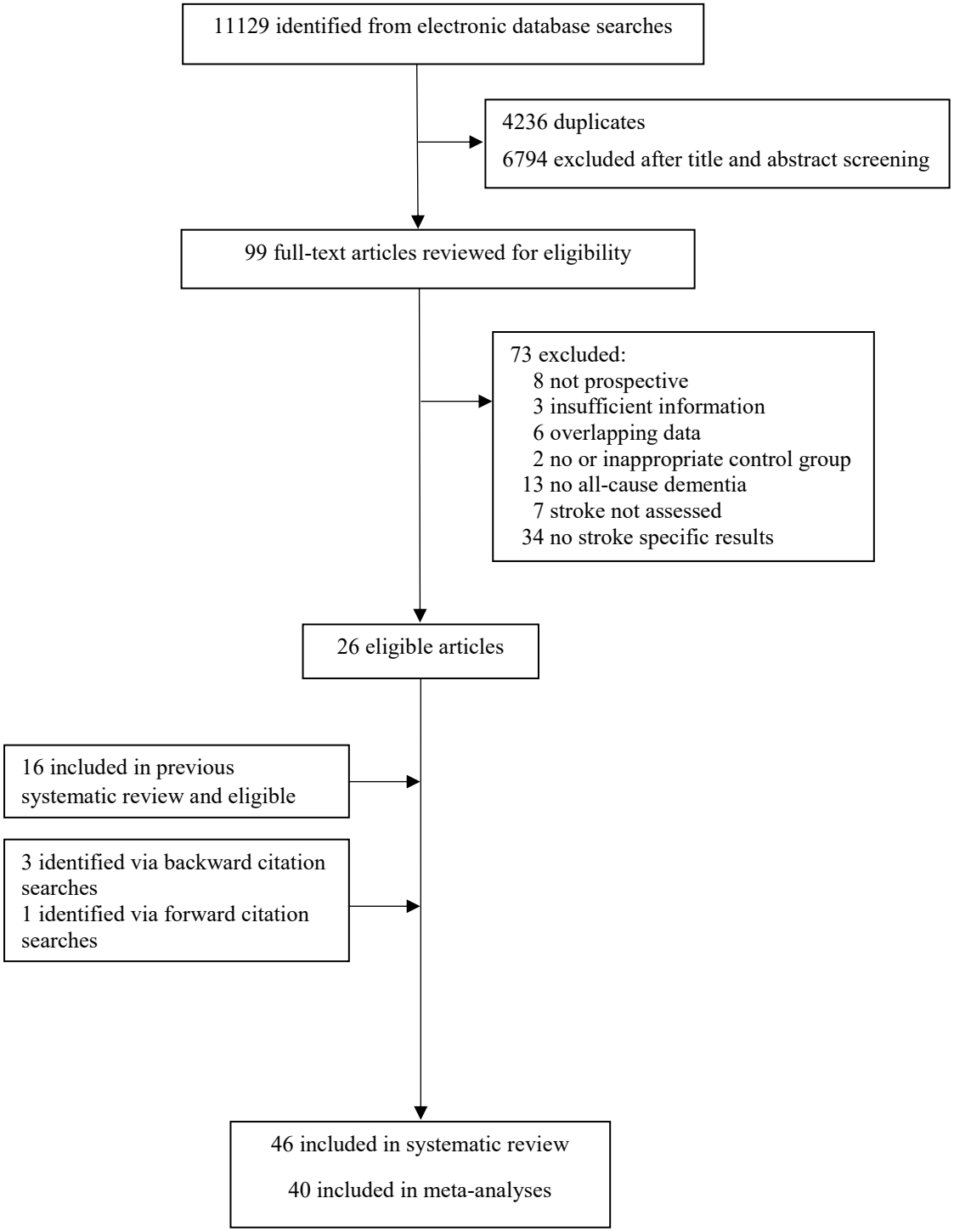
11129 identified from electronic database searches
4236 duplicates
6794 excluded after title and abstract screening
99 full-text articles reviewed for eligibility
73 excluded:
8 not prospective
3 insufficient information
6 overlapping data
2 no or inappropriate control group
13 no all-cause dementia
7 stroke not assessed
34 no stroke specific results
26 eligible articles
16 included in previous systematic review and eligible
3 identified via backward citation searches
1 identified via forward citation searches
46 included in systematic review
40 included in meta-analyses

Figure 1

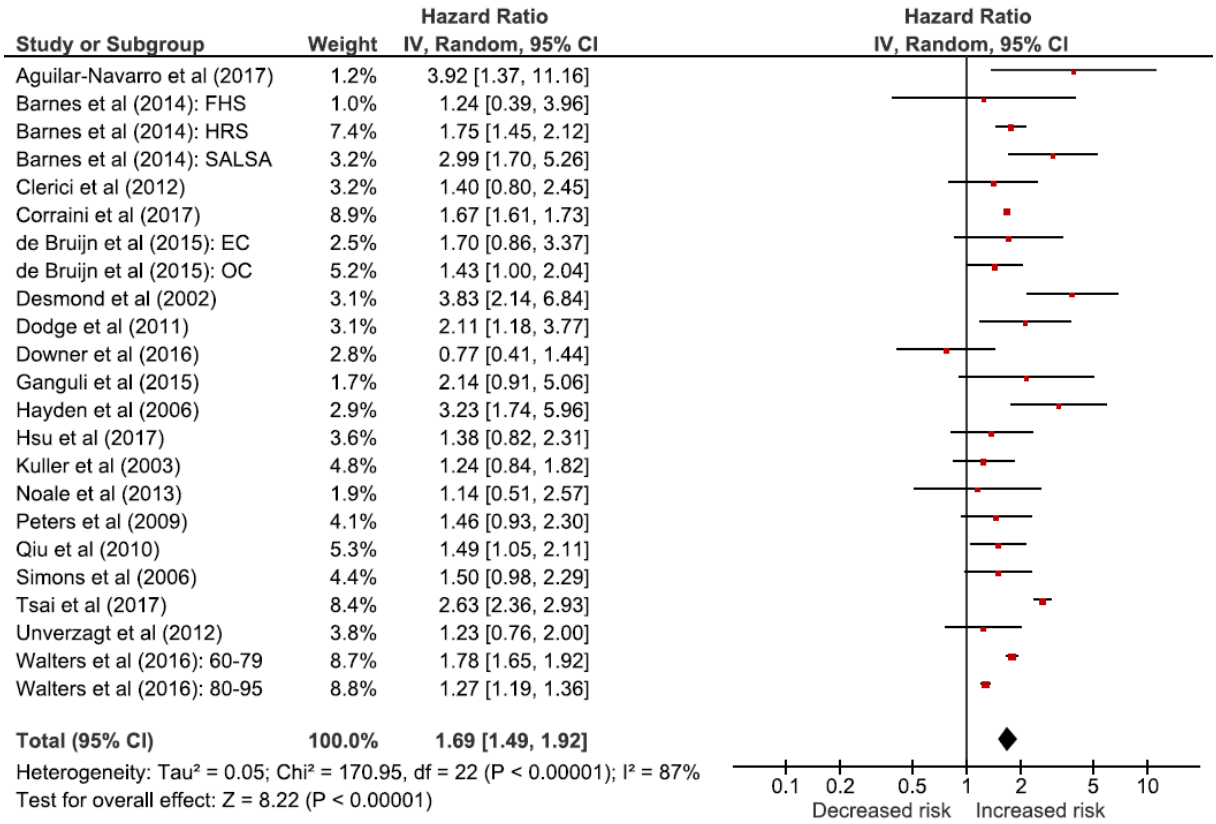
Study or Subgroup
Weight
Hazard Ratio
IV, Random, 95% CI
Hazard Ratio
IV, Random, 95% CI
Aguilar-Navarro et al (2017) 1.2% 3.92 [1.37, 11.16]
Barnes et al (2014): FHS 1.0% 1.24 [0.39, 3.96]
Barnes et al (2014): HRS 7.4% 1.75 [1.45, 2.12]
Barnes et al (2014): SALSA 3.2% 2.99 [1.70, 5.26]
Clerici et al (2012) 3.2% 1.40 [0.80, 2.45]
Corraini et al (2017) 8.9% 1.67 [1.61, 1.73]
de Bruijn et al (2015): EC 2.5% 1.70 [0.86, 3.37]
de Bruijn et al (2015): OC 5.2% 1.43 [1.00, 2.04]
Desmond et al (2002) 3.1% 3.83 [2.14, 6.84]
Dodge et al (2011) 3.1% 2.11 [1.18, 3.77]
Downer et al (2016) 2.8% 0.77 [0.41, 1.44]
Ganguli et al (2015) 1.7% 2.14 [0.91, 5.06]
Hayden et al (2006) 2.9% 3.23 [1.74, 5.96]
Hsu et al (2017) 3.6% 1.38 [0.82, 2.31]
Kuller et al (2003) 4.8% 1.24 [0.84, 1.82]
Noale et al (2013) 1.9% 1.14 [0.51, 2.57]
Peters et al (2009) 4.1% 1.46 [0.93, 2.30]
Qiu et al (2010) 5.3% 1.49 [1.05, 2.11]
Simons et al (2006) 4.4% 1.50 [0.98, 2.29]
Tsai et al (2017) 8.4% 2.63 [2.36, 2.93]
Unverzagt et al (2012) 3.8% 1.23 [0.76, 2.00]
Walters et al (2016): 60-79 8.7% 1.78 [1.65, 1.92]
Walters et al (2016): 80-95 8.8% 1.27 [1.19, 1.36]
Total (95% CI) 100.0% 1.69 [1.49, 1.92]
Heterogeneity: Tau² = 0.05; Chi² = 170.95, df = 22 (P < 0.00001); I² = 87%
Test for overall effect: Z = 8.22 (P < 0.00001)
0.1
0.2
0.5
1
2
5
10
Decreased risk
Increased risk

Figure 2

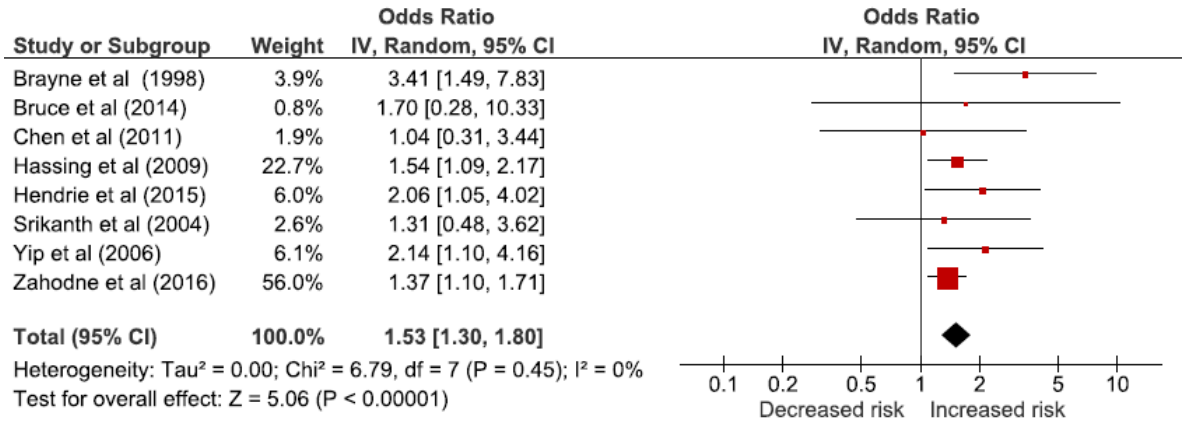

Figure 3

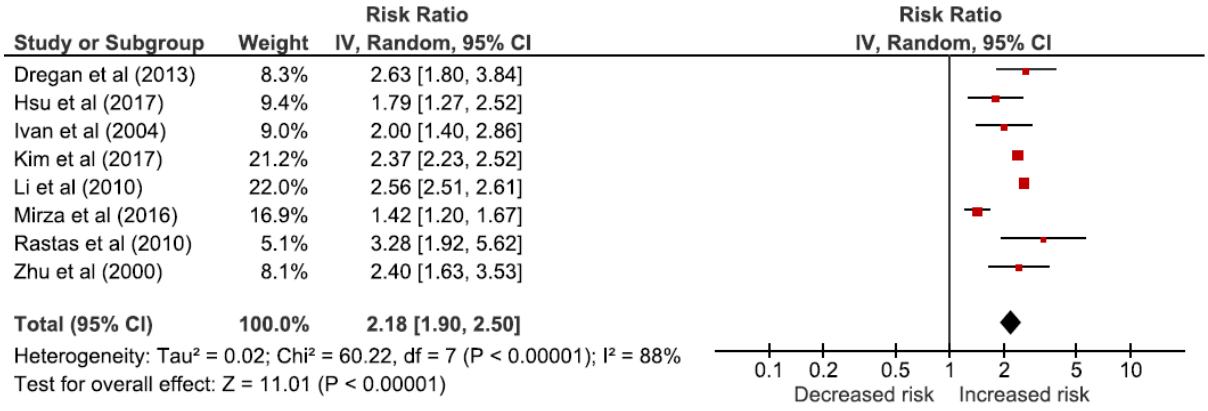

Figure 4

Figure captions

Fig. 1. Flowchart of search results and study retrieval

Fig. 2. Meta-analysis of hazard ratios of prevalent stroke compared to no prevalent stroke on incident all-cause dementia

Data presented as hazard ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. Hazard ratio estimate for the study by Hayden and colleagues [34] was obtained in Review Manager using the generic inverse-variance method and is different from that obtained from a discrete-time survival model reported in the original study (i.e. HR = 3.23, CI = 1.74-5.64). The appendix shows the corresponding funnel plot. IV, inverse-variance estimation method; CI, confidence interval; EC, extended cohort; FHS, Framingham Heart Study; HRS, Health and Retirement Study; OC, original cohort; SALSA, Sacramento Area Latino Study on Aging.

Fig. 3. Meta-analysis of odds ratios of prevalent stroke compared to no prevalent stroke on incident all-cause dementia

Data presented as odds ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. The appendix shows the corresponding funnel plot. IV, inverse-variance estimation method; CI, confidence interval.

Fig. 4. Meta-analysis of risk ratios of incident stroke compared to no incident stroke on incident all-cause dementia

Data presented as risk ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. The appendix shows the corresponding funnel plot. IV, inverse-variance estimation method; CI, confidence interval.

Appendix to:

Stroke and dementia risk: A systematic review and meta-analysis

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Appendix A - Methods

Review Protocol

Review question: Do prospective studies suggest an increased risk of all-cause dementia after stroke?

Population: Adults (≥18 years)

Exposure: Prevalent or incident stroke

Comparators: No stroke

Outcomes: Incident all-cause dementia

Search strategy:

- Searching the following databases: Medline, Embase, PsycINFO (via OvidSP)
- Backward and forward citation searching of included studies via Web of Science

Search terms relevant to stroke: stroke, cerebrovascular accident, cerebral vascular accident, brain infarct*, cerebral infarct*, risk factor

Search terms relevant to dementia: dement*

Study selection criteria:

Inclusion criteria:

- Prospective studies on the association between prevalent or incident stroke and incident all-cause dementia
- Only publications in English

Exclusion criteria:

- Studies with outcomes that are not directly dementia-related (e.g. neuroimaging or biomarkers) or dementia subtypes only
- Studies with no comparison group or comparison group other than no stroke
- Animal studies
- Case reports, narrative reviews, letters, editorials, opinions, book chapters
- Conference abstracts
- Duplicate publications using the same data

Study selection: Titles and abstracts will be independently screened by two reviewers (EK & IL) using the inclusion/exclusion criteria. Full-texts of potentially relevant studies will be also reviewed independently by the same two reviewers. Any discrepancies will be resolved by discussion with involvement of a third reviewer (DJL) where necessary.

Risk of bias assessment: Risk of bias will be assessed independently by two reviewer (EK & IL) using the Quality Assessment Tool for Quantitative Studies [8]. Any discrepancies will be resolved by discussion with involvement of a third reviewer (DJL) where necessary.

Data extraction: Key data including study design, assessment of exposures and outcomes, population, adjusted and unadjusted estimates of the association between exposure and outcome, and sources of data will be extracted by one reviewer (EK) and checked by the second reviewer (IL). Any discrepancies will be resolved by discussion with involvement of a third reviewer (DJL) where necessary.

Evidence synthesis methods: We will synthesize the evidence on the associations between prevalent or incident stroke and all-cause dementia narratively and where appropriate, given consistency between outcome measures, comparator groups and reported statistics, using meta-analytic techniques to estimate the summary measures of effect on relevant outcomes. A meta-analysis will be conducted using random effects models. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the x^2 test for homogeneity and I^2 statistic and, where appropriate, using meta-regression. Small study effects (including publication bias will be visually assessed using funnel plots (if appropriate) and quantified using Egger's statistic.

Contacting corresponding authors

We contacted the corresponding authors of 18 studies [1-18] for clarification or where relevant data was not fully reported. We received additional data or clarification for 13 studies [1-5,8,10,12,13,15-18], no response from four studies [6,9,11,14] and for one study [7] the email delivery was unsuccessful. Eleven [1-11] out of the 18 studies where corresponding authors were contacted, were included in our systematic review. Three studies [12,16,18] were excluded due to data overlapping with other included publications [19,21], two due to insufficient data [14,15] one due to combining stroke with other conditions [13] and one due to no stroke-specific results [17].

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Appendix A - Search strategies

1 exp Stroke/ (107761)

2 stroke.ti,ab. (191763)

3 (poststroke or (post adj stroke)).ti,ab. (10109)

4 (cerebrovascular adj (accident or accidents)).ti,ab. (6037)

5 (cerebral adj vascular adj (accident or accidents)).ti,ab. (1020)

6 ((brain or cerebral) adj infarct*).ti,ab. (18217)

7 (risk adj (factor or factors)).ti,ab. (467918)

8 exp Dementia/ (140757)

9 dement*.ti,ab. (90703)

10 prospective*.ti,ab. (576871)

11 longitudinal.ti,ab. (192206)

12 predict*.ti,ab. (1255001)

13 inciden*.ti,ab. (742390)

14 (determinant or determinants).ti,ab. (200190)

15 (hazard or hazards).ti,ab. (167706)

16 1 or 2 or 3 or 4 or 5 or 6 or 7 (675873)

17 8 or 9 (173398)

18 10 or 11 or 12 or 13 or 14 or 15 (2718880)

19 16 and 17 and 18 (5199)

20 limit 19 to yr="2009 -Current" (2981)

Fig. A1. Search strategy in Medline

1 exp cerebrovascular accident/ (144328)

2 stroke.ti,ab. (280586)

3 (poststroke or (post adj stroke)).ti,ab. (15607)

4 (cerebrovascular adj (accident or accidents)).ti,ab. (8505)

5 (cerebral adj vascular adj (accident or accidents)).ti,ab. (1305)

6 ((brain or cerebral) adj infarct*).ti,ab. (24772)

7 (risk adj (factor or factors)).ti,ab. (637897)

8 exp dementia/ (286468)

9 dement*.ti,ab. (124813)

10 prospective*.ti,ab. (802546)

11 longitudinal.ti,ab. (235360)

12 predict*.ti,ab. (1560352)

13 inciden*.ti,ab. (971263)

14 (determinant or determinants).ti,ab. (229760)

15 (hazard or hazards).ti,ab. (219956)

16 1 or 2 or 3 or 4 or 5 or 6 or 7 (935514)

17 8 or 9 (304436)

18 10 or 11 or 12 or 13 or 14 or 15 (3437070)

19 16 and 17 and 18 (9109)

20 limit 19 to yr="2009 -Current" (6609)

Fig. A2. Search strategy in Embase

1 exp cerebrovascular accidents/ (17865)

2 stroke.ti,ab. (27063)

3 (poststroke or (post adj stroke)).ti,ab. (3735)

4 (cerebrovascular adj (accident or accidents)).ti,ab. (725)

5 (cerebral adj vascular adj (accident or accidents)).ti,ab. (201)

6 ((brain or cerebral) adj infarct*).ti,ab. (1675)

7 (risk adj (factor or factors)).ti,ab. (68704)

8 exp dementia/ (64880)

9 dement*.ti,ab. (55236)

10 prospective*.ti,ab. (56114)

11 longitudinal.ti,ab. (88989)

12 predict*.ti,ab. (373275)

13 inciden*.ti,ab. (68853)

14 (determinant or determinants).ti,ab. (44972)

15 (hazard or hazards).ti,ab. (14483)

16 1 or 2 or 3 or 4 or 5 or 6 or 7 (95865)

17 8 or 9 (79601)

18 10 or 11 or 12 or 13 or 14 or 15 (572422)

19 16 and 17 and 18 (2456)

20 limit 19 to yr="2009 -Current" (1539)

Fig. A3. Search strategy in PsycINFO

Appendix B - Tables B1-B6

Table B1. Key characteristics of included studies investigating the association between prevalent stroke and incident all-cause dementia

Study	Country	Study design	Setting	Follow-up in years	Analytic sample size	No. or % with prevalent stroke	Mean baseline age (SD)	Male, %	Race/ ethnicity	Education
Aguilar-Navarro, 2017 [19]	Mexico	MCI cohort	Secondary care	3.5*	125	25	81.7 (6.9)	43	100% Mexican	9.5 (± 6.1)*
Barnes, 2014 [20]	USA (FHS, HRS, SALSA)	Multiple cohorts	Community	6	FHS: 2,411 HRS: 13,889 SALSA: 1125	FHS: 60 HRS: 946 SALSA: 108	FHS: 72.1 (4.4) HRS: 71.3 (4.2) SALSA: 71.3 (4.0)	FHS: 44.5 HRS: 43.5 SALSA: 42.8	FHS: 100% White HRS: 88% White, 7% Black, 5% Latino SALSA: 100% Latino	FHS: <12 yrs, 13.4% HRS: <12 yrs, 25.8% SALSA: <12 yrs, 71.4%
Brayne, 1998 [21]	United Kingdom	Cohort	Primary care	2.4*	376	44†	77+	36.4	NR	<15 yrs: 69.9%
Bruce, 2014 [22]	Australia (FDS)	Diabetic cohort	Community	14.7*	320	4.7%	57.5 (9.2)	50.3	NR	Educated beyond primary school: 81.9%
Chen, 2011 [23]	China	Cohort	Community	3.9‡	1,307	45	65+	56.5	100% Asian	≥High school: 49.2% Secondary school: 28.2% Primary school: 22.6%
Clerici, 2012[24]	Italy	MCI cohort	Secondary care	2.05‡	245	27	74.1 (6.9)	42	100% White	Low (≤5yrs): 46%, High (>5yrs): 54%

Corraini, 2017 [25]	Denmark (DNPR, DPCR)	Cohort	Secondary care and community	Stroke cohort: 4.17‡ Controls: 5.06‡	486,640	81,107	72‡,§	52.4§	NR	NR
Crooks, 2008 [26]	USA (KPSC Medical Care Program)	Cohort	Community	4	2,249	157	78+	0	89.6% White, 4% Black, 3% Hispanic, 1.5% Asian/Pacific islander, 1.9% Other##	< High school##: 9.9% High school: 26% Some college/trade school: 38.5% College graduate: 25.5%
de Bruijn, 2015 [27]	Netherlands (Rotterdam Study)	Cohort	Community	Original cohort: 8.3* Extended cohort: 8.9*	Original cohort: 7,003 Extended cohort: 2,953	Original cohort: 175 Extended cohort: 94	Original cohort: 69.4 (9.1) Extended cohort: 65.0 (8.3)	Original cohort: 40.2 Extended cohort: 43.8	NR	Original cohort: Low: 54.3%, Intermediate: 37.3% Extended cohort: Low: 33.7%, Intermediate: 49.4%
DeCarli, 2004 [28]	USA	MCI cohort	Secondary care	3.1*	52	12	72.8	71	NR	14.8 (± 2.7)*
Desmond, 2002 [29]	USA	Cohort	Secondary care and community	Stroke cohort: 1.8‡ Controls: 5.2‡	575	334	70.5 (7.1)	43.3	35.3% Black, 23.3% Hispanic, 40.4% White, 1% Other	11.4 (± 4.8)*
Dodge, 2011 [30]	USA (MoVIES)	Cohort	Community	8.0*	822	8.3%	75.8 (4.7)	35.6	NR	High school/ higher education: 63.4%
Downer, 2016 [31]	USA (H-EPESE)	Cohort	Community	10	1,739	88	72.2 (5.7)	42.4	100% Mexican-American	Low (< 4 yrs): 28.9%, High (≥4 yrs): 71.1%
Ganguli, 2015[32]	USA (MYHAT)	Cohort	Community	5	1,701	75	77.4 (7.3)	37.7	94.7% mixed European descent	≥High school: 86.9%

Hassing, 2009 [33]	Sweden (STR, SATSA, OCTO-Twin)	Cohort	Community	40	1,152	17%	52.5 (4.6)	31	NR	7.2 (± 2.3)*
Hayden, 2006 [34]	USA (CCSMHA)	Cohort	Community	3.2*	3,264	109	74.0 (6.4)	41.8	Primarily White	13.4 (± 2.9)*
Hendrie, 2015 [35]	USA (Indianapolis-Ibadan Dementia Project)	Cohort	Community	6.0*	974	122¶	76.6 (4.9)	30.3	100% African Americans	11.6 (± 2.5)*
Hobson, 2010 [36]	United Kingdom	Cohort	Primary and secondary care	4	114	52	72.9 (8.9)#	56.3#	NR	NR
Hsu, 2017 [37]	Taiwan (Elderly NAHSIT)	Cohort	Community	11.0‡	1,436	70	73.2 (5.4)	51.3	100% Asian	4.9 (± 4.9)*
Jin, 2008 [38]	Canada (CSHA)	Cohort	Community	4.6‡	721	72**	65+	35.1††	NR	<8 yrs: 36.2%***
Kokmen, 1996 [39]	USA	Cohort	Community	25	Community comparison 971	971	0-85+	50	NR	NR
Kuller, 2003 [40]	USA (CHS)	Cohort	Community	6 to 7	2,939	151‡‡	65+	40.9‡‡	85% White, 15% Black‡‡	≥17yrs: 38.4%†††, 13-16yrs: 9.6%, 8-12yrs: 47%, <8yrs: 5%
Li, 1991[41]	China	Cohort	Community	3	825	90§§	60+	47.5	~100% Asian	NR
Liebetrau, 2003 [42]	Sweden	Cohort	Community	3	494	93	85+	28.9	NR	High: 25.1%
Noale, 2013 [43]	Italy (ILSA)	Cohort	Community	7.8‡	2,501	130	71.3 (5.3)	43.7	NR	≥3 yrs: 70.7%

Peters, 2009 [53]	International (Hypertension in the Very Elderly Trial)	Observational analysis of RCT cohort	Primary and secondary care	2*	3,336	216	80+	39.6	Multinational	none: 27.4%, primary: 28.2%, secondary: 28.8%, higher: 12.3%, further: 3.3%
Qiu, 2010 [44]	Sweden (Kungsholmen Project)	Cohort	Community	5.1*	1,270	91	81.5 (5.0)	24.9	NR	≥8 yrs: 40.7%
Simons, 2006 [45]	Australia (Dubbo Study)	Cohort	Community	16	2,805	153¶	60+	44.0	NR	NR
Srikanth, 2004[46]	Australia (NEMESIS)	Cohort	Community	9 months	179	88	69.9 (13.4)	58.7	NR	10 (±2.4)*
Srikanth, 2006 [47]	Australia (NEMESIS)	Cohort	Community	21 months	158	80	69.9 (12.4)	60.0	NR	9.8 (±2.4)*
Tsai, 2017 [48]	Taiwan (NHIRD)	Medical records cohort	Community	12	415,576	94,468	68.35 (15.54)	60.4	~100% Asian	NR
Unverzagt, 2012 [54]	USA (ACTIVE)	Observational analysis of RCT cohort	Community	5	2,786	194	73.6 (5.9)	24	73.3% White, 26.7% Black/other	13.6 (±2.7)*
Walters, 2016 [49]	United Kingdom (THIN)	Medical records cohort	Primary care	Aged 60-79: 5‡ Aged 80-95: 3.8‡	Aged 60-79: 800,013 Aged 80-95: 130,382	Aged 60-79: 38,976 Aged 80-95: 20,221	Aged 60-79: 65.6 (6.1) Aged 80-95: 84.8 (3.93)	Aged 60-79: 48.3 Aged 80-95: 34	NR	NR
Yamada, 2009[50]	Japan (AHS)	Cohort	Community	5.9*	1,637	3.5%	70.95 (7.16)	0	100% Asian	Higher education (≥7 yrs): 56.5%

Yip, 2006[51]	United Kingdom (CFAS)	Cohort	Community	7	4,075	307	65+	36.9	NR	< 9 yrs: 8%, 9 yrs: 57.5%, ≥10 yrs: 34.5%
Zahodne, 2016 [52]	USA (WHICAP)	Cohort	Community	6.0*	2,593	184	76.0 (6.2)	31.3	28.6% White, 32.2% African American, 39.2% Hispanic	9.9 (±4.9)*

ACTIVE, Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE); AHS, Adult Health Study; CCSMHA, Cache County Study of Memory Health and Aging; CFAS, Cognitive Function and Ageing Study; CHS, Cardiovascular Health Study; CSHA, Canadian Study of Health and Aging; DNPR, Danish National Patient Registry; DPCR, Danish Psychiatric Central Register; ILSA, Italian Longitudinal Study on Aging; FDS, Fremantale Diabetes Study; FHS, Framingham Heart Study; H_EPESE, Hispanic Established Populations for the Epidemiologic Study of the Elderly; HRS, Health and Retirement Study; KPSC, Kaiser Permanente Southern California; MoVIES, Monongahela Valley Independent Elders Survey; MYHAT, Monongahela-Youghiogheny Healthy Aging Team; NEMESIS, North East Melbourne Stroke Incidence Study; NHIRD, National Health Insurance Research Database; OCTO-Twin, Origins of Variance in the Old-Old; RCT, randomised controlled trial; SALSA, Sacramento Area Latino Study on Aging; SATSA, Swedish Adoption/Twin Study of Aging; SD, standard deviation; STR, Swedish Twin Registry; THIN, The Health Improvement Network; WHICAP, Washington Heights Inwood Columbia Aging Project. *Mean. †Based upon 10% of 340 controls and 28% of 36 dementia cases as seen in table 2 of the original study. ‡Median. §Based upon sample size of 1,290,706. ¶Based upon sample size of 970. #Based upon sample size of 190. **Based upon 10% of sample size of 761 and then analytic sample size of 721. ††Based upon sample size of 949. ‡‡ Based upon sample size of 3,375. §§Based upon the proportion of risk years as seen in table 4 of the original study multiplied by analytic sample size. ¶¶Based upon proportion of stroke events for males and females as seen in table 4 of publication describing characteristics of the Dubbo study (i.e. Simons L, Simons J, McCallum J, Powell I, Friedlander Y, Heller R. Dubbo study of the elderly: sociological and cardiovascular risk factors at entry. Intern Med 1991; 21(5): 701-9). ##Based upon a sample of 2,243 for race/ethnicity, and sample of 2,246 for education. ***Based upon sample of 761. †††Based upon sample of 3,370 for education.

Table B2. Key characteristics of included studies investigating the association between incident stroke and incident all-cause dementia

Study	Country	Study design	Setting	Follow-up in years	Analytic sample size	No. with incident stroke	Mean baseline age (SD)	Male, %	Race/ ethnicity	Education
Dregan, 2013 [55]	United Kingdom (ELSA)	Cohort	Community	10	10,809	516	64.9 (10.3)	45	NR	No qualification: 42%, O-level: 13%, A-level: 21%, Below degree: 11%, Degree level: 11%
Gamaldo, 2006 [56]	USA (BLSA)	Cohort	Community	10.0*	335	36	75.1	60.3	93.7% White, 6% African American, 0.3% Hispanic	16.8 (±2.8)*
Hsu, 2017 [37]	Taiwan (Elderly NAHSIT)	Cohort	Community	11.0†	1,436	232	73.2 (5.4)	51.3	100% Asian	4.9 (±4.9)*
Ivan, 2004 [57]	USA (FHS)	Cohort	Community	10	844	212‡	78.6 (6.7)‡	38.7‡	NR	High school graduate#: 65.2%
Jin, 2006 [58]	Canada (CSHA)	Cohort	Community	5	725	109§	65+	41	NR	NR
Kim, 2017 [59]	South Korea (NHIS-Senior)	Medical records cohort	Community	10	22,792	2,527	60+	45.2	100% Asian	NR
Li, 2010 [60]	USA (US Veteran Affairs)	Medical records cohort	Community	3†	799,069	120,877	74.9 (5.9)	98.2	2% Hispanic white, 0.2% Hispanic black, 0.1% Native American Indian 4% Black, 0.2% Asian, 35% White, 58.5% Unknown	NR

Liebetrau, 2003 [42]	Sweden	Cohort	Community	3	282	39	85+	28.9¶	NR	NR
Mirza, 2016 [15]	Netherlands (Rotterdam Study)	Cohort	Community	9.9*	12,561	1,463	64.7 (9.6)	41.7	NR	Low: 42.2%, Intermediate: 42.5%, High:15.3%
Nordstrom, 2013 [61]	Sweden (Swedish Military Service Conscription Register)	Medical records cohort	Military register	37†	488,484	5,086	18.5 (0.8)	100	NR	Elementary school only: 22.4% Secondary school 2 or 3 yrs: 47.6% University: 26.9%
Rastas, 2010 [62]	Finland (Vantaa 85+)	Cohort	Community	9	339	29	88 (2.6)	21.5	NR	4.2 (±2.9)*
Zhu, 2000 [63]	Sweden (Kungsholmen Project)	Cohort	Community	3.05†	1,209	91	81.8 (4.8)	24.5	NR	<8 yrs: 50%

BLSA, Baltimore Longitudinal Study of Aging; CSHA, Canadian Study of Health and Aging; ELSA, English Longitudinal Study of Ageing; FHS, Framingham Heart Study; NAHSIT, Nutrition and Health Survey in Taiwan; NHIS-Senior, National Health Insurance Service-Senior.
*Mean. †Median. ‡Based upon sample size of 1,272. § Based upon stroke incident rate of 3 per 100 person-years. ¶Based upon sample size of 494. #Based upon sample size of 1,239.

Table B3. Results of included studies for the association between prevalent stroke and incident all-cause dementia

Study	Dementia assessment/diagnosis	Stroke assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Aguilar-Navarro, 2017 [19]	DSM-IV-TR criteria	Stroke in medical records	Age, education, diabetes, MMSE, clock-drawing test, immediate and delayed word recall, semantic fluency	HR = 3.92 (1.37-11.16)	0.010
Barnes, 2014 [20]	Across studies: cognitive impairment in at least 2 domains (decline from prior levels), daily function affected. FHS and SALSA: adjudicated. HRS: brief cognitive battery	NR	Age, education, BMI, diabetes, needs help with money/medications, depressive symptoms	FHS: HR = 1.24 (0.39-3.96) HRS: HR = 1.75 (1.45-2.12) SALSA: HR = 2.99 (1.70-5.26)	NR
Brayne, 1998 [21]	Criteria similar to ICD-10 applied to CAMDEX assessments	Self- or informant-reported stroke history	Age, sex	OR = 3.41 (1.49-7.83)	<.0.05
Bruce, 2014 [22]	Adjudicated based on cognitive assessment and hospital/clinic/other records	Self-reported stroke/TIA or prior hospitalizations for these events	Age, education, current smoking	OR = 1.70 (0.28-10.33)[*]	0.563[a]
Chen, 2011 [23]	GMS-AGECAT, psychiatrist diagnosis or cause of death	Doctor-diagnosed stroke	Age, sex	OR = 1.04 (0.31-3.44)	0.956
Clerici, 2012[24]	DSM-IV criteria	History of stroke or TIA	Age, sex, education, APOE, Cumulative Illness Rating Scale, MMSE, MCI subtype	HR = 1.4 (0.8-2.5)	NR
Corraini, 2017 [25]	ICD-8: 290.10, 290.09, 293.09, 293.19, 094.19, 290.11-290.19, 292.09 and ICD-10: F00, G30, F01, F02-F03, F1x.73 series, G23.1, G31.0, G31.0A, G31.0B, G31.1, G31.8B, G31.8E, G31.85	ICD-8: 433-434, 431, 430, 436 and ICD-10: I63, I61, I60, I64 confirmed by brain imaging	Diabetes, atrial fibrillation, hypertension, smoking, hyperlipidemia/hypercholesterolemia, myocardial infarction/ heart failure/ peripheral vascular disease, traumatic brain injury, depression, substance abuse	HR = 1.67 (1.61-1.73)	NR

Crooks, 2008 [26]	Multistage approach based on TICS-m, TDQ and medical records	Self-reported stroke history	None	HR = 2.32 (1.63-3.29)	NR
de Bruijn, 2015 [27]	Adjudicated, DSM-III-R criteria	Stroke history based on home interviews and medical records	Age, sex, education BMI, hypertension, diabetes, total cholesterol/HDL ratio, lipid-lowering medication, smoking, coronary heart disease, heart failure, atrial fibrillation	Original cohort: HR = 1.43 (1.00-2.04) Extended cohort: HR = 1.70 (0.86-3.37)	NR NR
DeCarli, 2004 [28]	CDR score ≥1	Self- or informant reported stroke history and medical records review	None	HR=0.44 (0.10-1.95)*	0.28*
Desmond, 2002 [29]	DSM-III-R criteria	Diagnosis of ischemic stroke confirmed by brain imaging	Age, sex, education, ethnicity, MMSE	HR = 3.83 (2.14-6.84)†	NR
Dodge, 2011 [30]	Adjudicated based on DSM-III criteria and CERAD	Self-reported history of stroke or TIA	Age, sex, education, recruitment status (random/volunteer)	HR = 2.11 (1.18-3.77)	0.01
Downer, 2016 [31]	Alzheimer's Association and National Institute on Aging Workgroup criteria	Self-reported stroke history	Age, sex, education	HR = 0.77 (0.41-1.44)*	0.41*
Ganguli, 2015[32]	CDR score ≥1	Self-reported stroke history	Age, sex, education	HR = 2.14 (0.91-5.06) Dementia onset age ≤87 y: HR = 3.82 (1.25-11.65) Dementia onset age>87 y: HR = 1.19 (0.28-5.01)	NR <0.05 NR

Hassing, 2009[33]	Adjudicated, DSM-III-R criteria	Self-reported stroke history or review of medical records	Age, sex, education, smoking, alcohol consumption, BMI, hypertension, congestive heart failure, myocardial infarction, diabetes	OR = 1.54 (1.09-2.17)*	0.014*
Hayden, 2006 [34]	Adjudicated, DSM-III-R criteria	Self- or informant reported stroke history	Age, sex, education, APOE, hypertension, high cholesterol, diabetes, obesity, CABG, myocardial infarction	HR = 3.23 (1.74-5.64)	NR
Hendrie, 2015[35]	Adjudicated, ICD-10 and DSM-IV-TR criteria	Self-reported stroke history	Age at diagnosis, sex, education, APOE, statin use at baseline	OR = 2.06 (1.05-4.02)	0.0347*
Hobson, 2010 [36]	DSM-IV criteria	First stroke based on clinical history, clinical examination and neuroimaging	Baseline dementia	RR = 2.14 (0.64-7.13)	NR
Hsu, 2017 [37]	Medical records, ICD-9-CM: 331.0, 290.0-290.4	Self-reported stroke history and stroke during study	Age, sex, education, MCI, BMI, sleep problems, alcohol consumption, DBP, CRP	HR = 1.38 (0.82-2.31)	0.2234
Jin, 2008 [38]	Adjudicated, DSM-III-R criteria	Self- or informant-reported stroke history, medical records or clinical examination	Age, sex, education, SBP, diabetes mellitus	see Table 2‡	see Table 2‡
Kokmen, 1996[39]	Evidence of previous normal functioning, irreversible decline of intellectual/cognitive and social function, memory impairment, impaired functioning and ≥2 of the following: disorientation, personality or behavioural problems, dyscalculia, aphasia, apraxia or agnosia, and impaired judgement or abstract thinking in medical records	Evidence of acute focal neurologic deficit (>24h) and no intracerebral haemorrhage in medical records	Age, sex	SMR = 3.2 (2.8-3.7)	NR
Kuller, 2003[40]	Adjudicated, evidence of progressive or static cognitive impairment in 2 domains affecting activities of daily living	NR	Age, sex, ethnicity, education, 3MSE, APOE, white matter grade, ventricular size, large infarcts, any subclinical disease, diabetes, hypertension, myocardial infarction, angina	HR = 1.2 (0.84-1.82)	NR

	and previous normal intellectual function				
Li, 1991[41]	Modified DSM-III criteria based on clinical/diagnostic evaluation and informant interview in case of death	NR	Age	RR = 5.75 (NR)	<0.05
Liebetrau, 2003[42]	Medical records, DSM-III-R criteria	Self-, informant-reported, medical records (ICD-9: 430-438) or death certificates	None	RR = 0.98 (0.4-2.2)	NR
Noale, 2013 [43]	DSM-III-R criteria	WHO definition. self-reported stroke diagnosis or neurological symptoms or ≥1 positive test of a short neurological evaluation and review of clinical record and/or diagnosis by the study neurologist	Age, sex, education, triglycerides, HDL cholesterol, glycaemia, BMI, heart failure, parkinsonism, depressive symptomatology, family history of dementia	HR = 1.14 (0.51-2.57)*	0.7510*
Peters, 2009 [53]	Adjudicated, DSM-IV criteria	ICD-10: I60-I64	Sex, geographical recruitment area, randomised trial treatment group, BMI, heart failure, diabetes, atrial fibrillation, total cholesterol, HDL, creatinine, glucose, haemoglobin	HR = 1.459 (0.928-2.295)	NR
Qiu, 2010 [44]	DSM-III-R criteria	Medical records, ICD-8,9: 430-438	Age, sex, education, APOE, follow-up survival status, baseline MMSE score, BMI, coronary heart disease, BP lowering drugs, systolic pressure, diastolic pressure, pulse pressure, diabetes/prediabetes, heart failure	HR = 1.49 (1.05-2.11)	NR
Simons, 2006 [45]	Medical records, ICD-9-CM or ICD-10-AM	Self-reported history	Age, sex	HR = 1.50 (0.98-2.29)	NR
Srikanth, 2004 [46]	DSM-IV criteria	WHO definition	Age, baseline S-MMSE	OR = 1.31 (0.48-3.62)	0.59
Srikanth, 2006 [47]	DSM-IV criteria	WHO definition	None	<u>With recurrent stroke:</u> RR = 4.5 (1.9-10.6) <u>Without recurrent stroke:</u>	0.003

				RR = 1.7 (0.7-4.1)	
Tsai, 2017 [48]	Medical records, ICD-9-CM: 290, 294.1, 331.0	Medical records, ICD-9-CM: 430-438	Age, sex, acute kidney injury, diabetes, hypertension, hyperlipidemia, head injury, depression, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atrial fibrillation, cancer, liver disease, chronic infection/inflammation, autoimmune disease, malnutrition	HR = 2.63 (2.36-2.93)	0.20 <.001
Unverzagt, 2012 [54]	Any of the following: memory and reasoning, speed or vocabulary 21.5 SD below the ACTIVE sample baseline mean and functional at or below the 10th percentile of the ACTIVE sample baseline or, first and all subsequent visits' MMSE<22 or are missing. or, self- or proxy-report of diagnosis of dementia or AD during follow-up or, interval self- or proxy-report of institutionalization during follow-up or, deactivation from the study due to family refusing access to subject	Self-reported stroke or TIA history	Age, sex, ethnicity, marital status, training group, alcohol consumption, MMSE, physical function, depressive symptoms, diabetes	HR = 1.23 (0.76-2.00)	0.4
Walters, 2016 [49]	ICD-10 dementia diagnoses including AD, vascular dementia, and unspecified or mixed dementia	ICD-10 diagnosis of stroke/TIA history	Age, age^2, sex, calendar year, deprivation, BMI, BMI^2, current anti-hypertensive use, smoking, alcohol problem history, diabetes history, current depression/use of anti-depressants, atrial fibrillation history, current aspirin	<u>Aged 60-79:</u> HR = 1.78 (1.65-1.92)	NR

			Age, age^2, sex, calendar year, deprivation, BMI, current anti-hypertensive use, systolic BP, lipid ratio, smoking, alcohol problem history, diabetes history, atrial fibrillation history, current depression/use of anti-depressants, current anxiety/use of anxiolytics, current NSAID use, current aspirin use	<u>Aged 80-95:</u> HR = 1.27 (1.19-1.36)	NR
Yamada, 2009[50]	Adjudicated, DSM-IV criteria	NR	Age, age^2, education, grip strength, BMI, smoking, drinking, menopausal age, history of hypertension and diabetes	RR = 1.92 (NR)	NR
Yip, 2006 [51]	Score of 3–5 on the AGECAT diagnostic algorithm	Self-reported stroke history	Age, sex, education, social class	OR = 2.1 (1.1-4.2)	NR
Zahodne, 2016 [52]	Adjudicated	Self-reported stroke history	Age, sex, education, ethnicity, depression, hypertension, diabetes, heart disease, APOE, memory trajectories	OR = 1.37 (1.10-1.71)	<0.05

AD,Alzheimer's disease; AGECAT,Automated Geriatric Examination for Computer Assisted Taxonomy; APOE,Apolipoprotein E; BMI,body-mass index; BP,blood pressure; CABG,coronary artery bypass graft surgery; CAMDEX,Cambridge Examination for Mental Disorders in the Elderly; CDR,Clinical Dementia Rating; CERAD,Consortium to Establish a Registry for Alzheimer's Disease; CI,confidence interval; CRP,C-reactive protein; DBP,diastolic blood pressure; DSM,Diagnostic and Statistical Manual of Mental Disorders; FHS,Framingham Heart Study; GMS-AGECAT,Geriatric Mental State – Automated Geriatric Examination for Computer Assisted Taxonomy; HDL,high-density lipoprotein; HR,hazard ratio; HRS,Health and Retirement Study; ICD,International Classification of Diseases; MCI,mild cognitive impairment; MMSE,Mini-Mental State Examination; NSAID,non-steroidal anti-inflammatory drugs; NR,not reported; OR,odds ratio; RR,risk ratio; SALSA,Sacramento Area Latino Study on Aging; SBP,systolic blood pressure; S-MMSE,Standardized Mini-Mental State Examination; SMR,standardized morbidity ratio; TDQ,Telephone Dementia Questionnaire; TIA, transient ischemic attack; TICS-m,Telephone Interview for Cognitive Status-modified; WHO,World Health Organization; 3MSE,Modified Mini-Mental State Examination. *Additional information provided by the authors. †Results of Cox proportional hazards regression reported as risk ratio. ‡Results reported only for a joint effect of stroke and APOE on incident dementia.

Table B4. Results of included studies for the association between incident stroke and incident all-cause dementia

Study	Dementia assessment/diagnosis	Stroke assessment/diagnosis	Adjustment	Effect size (95% CI)	*P* value
Dregan, 2013 [55]	Self- or informant reported diagnosis	Self-reported diagnosis	Age, sex, education, marital status, social class, diabetes mellitus, hypertension, smoking, depression, physical activity	RR = 2.63 (1.80-3.84)	<0.001
Gamaldo, 2006 [56]	Adjudicated, DSM-III-R criteria	Self- or informant-reported stroke history confirmed by medical records and autopsy in some cases	Age, sex, hypertension, diabetes, coronary artery disease, cholesterol, APOE	OR = 4.34 (1.75-10.83)	<0.05
			Age, sex	Cognitively normal before stroke: OR = 1.1 (0.37-3.34) Cognitive symptoms before stroke, no dementia: OR = 41.0 (5.1-328)	 NR NR
Hsu, 2017 [37]	Medical records, ICD-9-CM: 331.0, 290.0-290.4	Self-reported stroke history and stroke during study	Age, sex, education, MCI, BMI, sleep problems, alcohol consumption, diastolic BP, CRP	HR = 1.79 (1.27-2.52)	0.0008
Ivan, 2004 [57]	Adjudicated, DSM-IV criteria	Acute focal neurological deficit lasting >24 hours	Age, sex, education, second stroke, hypertension, diabetes, atrial fibrillation, current smoking	HR = 2.4 (1.6-3.7)	<0.001
			Sex, education, right/left hemisphere, atherothrombotic brain infarcts, second stroke	Aged <80 HR = 2.6 (1.5-4.5) Aged ≥80 HR = 1.6 (1.0-2.6)	 <0.001 0.075

Jin, 2006 [58]	Adjudicated, DSM-III-R criteria or cause of death by ICD-9 codes (331.0, 331.1, 290, 290.0, 290.2, 290.3, 290.4, 290.8, 290.9, 294.1, 046.1)	Self- or informant-reported or cause of death by ICD-9 codes (431, 434, 434.0, 434.1, 434.9, 436, 437, 437.1, 437.2, 437.9, 997.02)	None	HR = 2.3 (1.3-4.1)	NR
Kim, 2017 [59]	Medical records, ICD-10: F01-F03, G30, G31.1	Medical records, ICD-10: I69.0-I69.9	Age, sex, Charlson Comorbidity Index, residential region, route of admission, income	HR = 2.37 (2.23-2.51)	<0.001
Li, 2010 [60]	Medical records, ICD-9: 291, 294, 331.0	Medical records, ICD-9: 430-434	Age, cardiovascular disease, cardiovascular drugs, diabetes	HR = 2.56 (2.51-2.61)	<0.001
Liebetrau, 2003 [42]	Medical records, DSM-III-R criteria	Self-, informant-reported, medical records (ICD-9: 430-438) or death certificates	None	RR= 3.8 (2.2-6.7)	NR
Mirza, 2016 [15]	Adjudicated, DSM-III-R criteria	Stroke or TIA, medical records, WHO definition	Age, sex, education, study cohort, MMSE, BMI, smoking, total cholesterol, HDL cholesterol, lipid-lowering medication, systolic BP, diastolic BP, BP-lowering medication, diabetes	HR = 1.42 (1.20-1.67)	NR
Nordstrom, 2013 [61]	Medical records, ICD-8 or ICD-10: F00.X, G30.X, 290.X, F01.X, F10.7A, F03.9, F02.3, G31.8A	Medical records, ICD-8 or ICD-10: I63.X, 433, 434	Age, education weight, height, knee strength, BP, baseline cognitive function, parental dementia, annual income, alcohol intoxication, drug intoxication, depression or use of antidepressants, myocardial infarction, neuroleptics, antidiabetics	HR = 2.96 (2.02-4.35)	NR
Rastas, 2010 [62]	Adjudicated, DSM-III-R criteria	TIA or stroke in medical records, focal signs of	Age, sex, education, APOE, HDL cholesterol,	HR = 3.28 (1.92-5.62)	<0.001

		stroke confirmed by a neurologist	LDL cholesterol, triglycerides, homocysteine, diabetes, hypertension, systolic and diastolic BP, baseline stroke		
Zhu, 2000 [63]	DSM-III-R criteria	Medical records, ICD-8: 430-438	Age, sex, education, heart disease, systolic BP, antihypertensive medication	HR = 2.4 (1.6-3.5)*	NR

BMI, body-mass index; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; LDL, low-density lipoprotein; NR, not reported; RR, risk ratio; TIA, transient ischemic attack.
*Results of Cox proportional hazards regression reported as risk ratio.

Table B5. Quality assessment of included studies

Study	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and drop-outs	Global rating
Aguilar-Navarro, 2017 [19]	moderate	moderate	strong	moderate	strong	moderate	strong
Barnes, 2014 [20]	moderate	moderate	strong	moderate	strong	weak	moderate
Brayne, 1998 [21]	moderate	moderate	weak	moderate	strong	weak	weak
Bruce, 2014 [22]	weak	moderate	moderate	moderate	strong	strong	moderate
Chen, 2011 [23]	strong	moderate	weak	moderate	strong	strong	moderate
Clerici, 2012 [24]	moderate	moderate	strong	moderate	strong	strong	strong
Corraini, 2017 [25]	moderate	moderate	moderate	moderate	weak	moderate	moderate
Crooks, 2008 [26]	weak	moderate	weak	moderate	moderate	moderate	weak
de Bruijn, 2015 [27]	moderate	moderate	strong	moderate	strong	strong	strong
DeCarli, 2004 [28]	weak	moderate	weak	moderate	weak	strong	weak
Desmond, 2002 [29]	weak	moderate	moderate	moderate	moderate	strong	moderate
Dodge, 2011 [30]	moderate	moderate	moderate	moderate	strong	weak	moderate
Downer, 2016 [31]	moderate	moderate	weak	moderate	strong	strong	moderate
Dregan, 2013 [55]	moderate	moderate	strong	moderate	weak	moderate	moderate
Gamaldo, 2006 [56]	weak	moderate	strong	moderate	strong	moderate	moderate
Ganguli, 2015 [32]	strong	moderate	weak	moderate	weak	strong	weak
Hassing, 2009 [33]	moderate	moderate	strong	moderate	weak	moderate	moderate
Hayden, 2006 [34]	strong	moderate	strong	moderate	strong	moderate	strong
Hendrie, 2015 [35]	moderate	moderate	strong	moderate	strong	moderate	strong
Hobson, 2010 [36]	moderate	moderate	weak	moderate	strong	weak	weak

Hsu, 2017 [37]	moderate	moderate	strong	moderate	weak	moderate	moderate
Ivan, 2004 [57]	moderate	moderate	strong	moderate	strong	weak	moderate
Jin, 2006 [58]	moderate	moderate	weak	moderate	strong	strong	moderate
Jin, 2008 [38]	moderate	moderate	strong	moderate	strong	strong	strong
Kim, 2017 [59]	moderate	moderate	strong	moderate	weak	moderate	moderate
Kokmen, 1996 [39]	moderate	moderate	weak	moderate	weak	moderate	weak
Kuller, 2003 [40]	moderate	moderate	strong	moderate	strong	strong	strong
Li, 1991 [41]	strong	moderate	weak	moderate	strong	moderate	moderate
Li, 2010 [60]	weak	moderate	moderate	moderate	moderate	weak	weak
Liebetrau, 2003 [42]	moderate	moderate	weak	moderate	weak	moderate	weak
Mirza, 2016 [15]	moderate	moderate	strong	moderate	strong	strong	strong
Noale, 2013 [43]	strong	moderate	strong	moderate	strong	moderate	strong
Nordström, 2013 [61]	weak	moderate	strong	weak	moderate	strong	weak
Peters, 2009 [53]	weak	moderate	strong	moderate	strong	strong	moderate
Qiu, 2010 [44]	moderate	moderate	Strong	moderate	strong	strong	strong
Rastas, 2010 [62]	strong	moderate	strong	moderate	strong	strong	strong
Simons, 2006 [45]	moderate	moderate	weak	moderate	weak	strong	weak
Srikanth, 2004 [46]	moderate	moderate	weak	moderate	strong	strong	moderate
Srikanth, 2006 [47]	moderate	moderate	weak	moderate	strong	strong	moderate
Tsai, 2017 [48]	moderate	moderate	strong	moderate	moderate	moderate	strong
Unverzagt, 2012 [54]	moderate	moderate	strong	moderate	strong	strong	strong
Walters, 2016 [49]	moderate	moderate	strong	moderate	moderate	moderate	strong
Yamada, 2009 [50]	weak	moderate	strong	moderate	strong	strong	moderate

Yip, 2006 [51]	moderate	moderate	moderate	moderate	strong	moderate	strong
Zahodne, 2016 [52]	moderate	moderate	strong	moderate	weak	moderate	moderate
Zhu, 2000 [63]	moderate	moderate	strong	moderate	strong	strong	strong

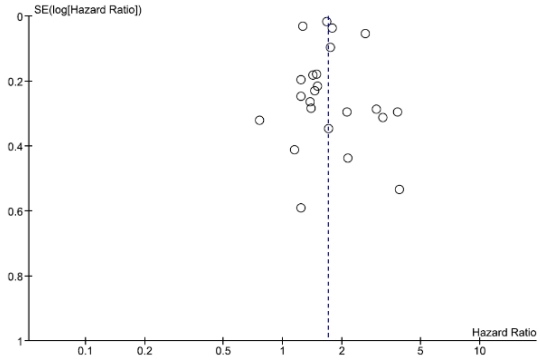
Table B6. Results of included studies for the association between prevalent or incident stroke and incident all-cause dementia stratified by sex

Study (year)	**Male**			**Female**		
	Adjustment	**Effect size (95% CI)**	***P* value**	**Adjustment**	**Effect size (95% CI)**	***P* value**
Prevalent stroke						
Corraini et al (2017)[25]	None	HR = 2.06 (2.00-2.12)	NR	None	HR = 1.61 (1.57-1.66)	NR
Noale et al (2013)[43]	Age, triglycerides, HDL cholesterol, heart failure, parkinsonism, depressive symptomatology, family history of dementia	HR = 1.19 (0.47-3.01)	0.7155	Age, education, BMI, glycaemia, triglycerides, heart failure, parkinsonism, depressive symptomatology	HR = 1.07 (0.31-3.70)	0.9102
Incident stroke						
Ivan et al (2004)[57]	Age, education, right/left hemisphere, atherothrombotic brain infarcts, second stroke	HR = 2.7 (1.4-5.2)	0.002	Age, education, right/left hemisphere, atherothrombotic brain infarcts, second stroke	HR = 1.7 (1.1-2.7)	0.018

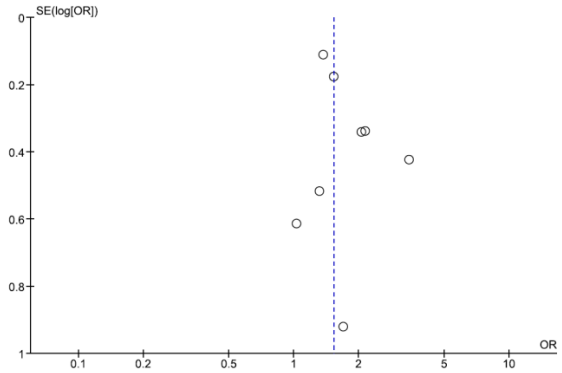
BMI, body-mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; NR, not reported.

Appendix B - Figures

(A)



(B)



(C)

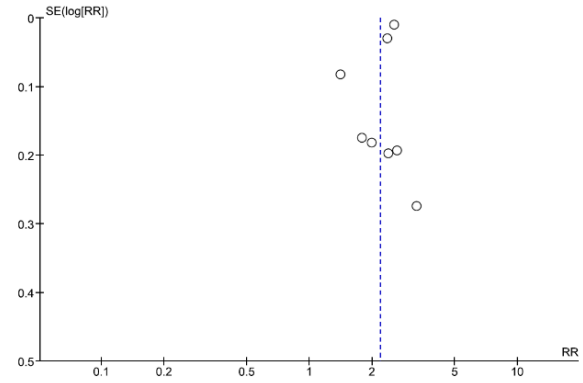


Fig. B4. Funnel plots
The figure shows the funnel plots for the meta-analysis of prevalent stroke combining studies with hazard ratios estimates (A) and odds ratios (B), and the meta-analysis of incident stroke combining studies with risk ratios estimates (C) of incident all-cause dementia.

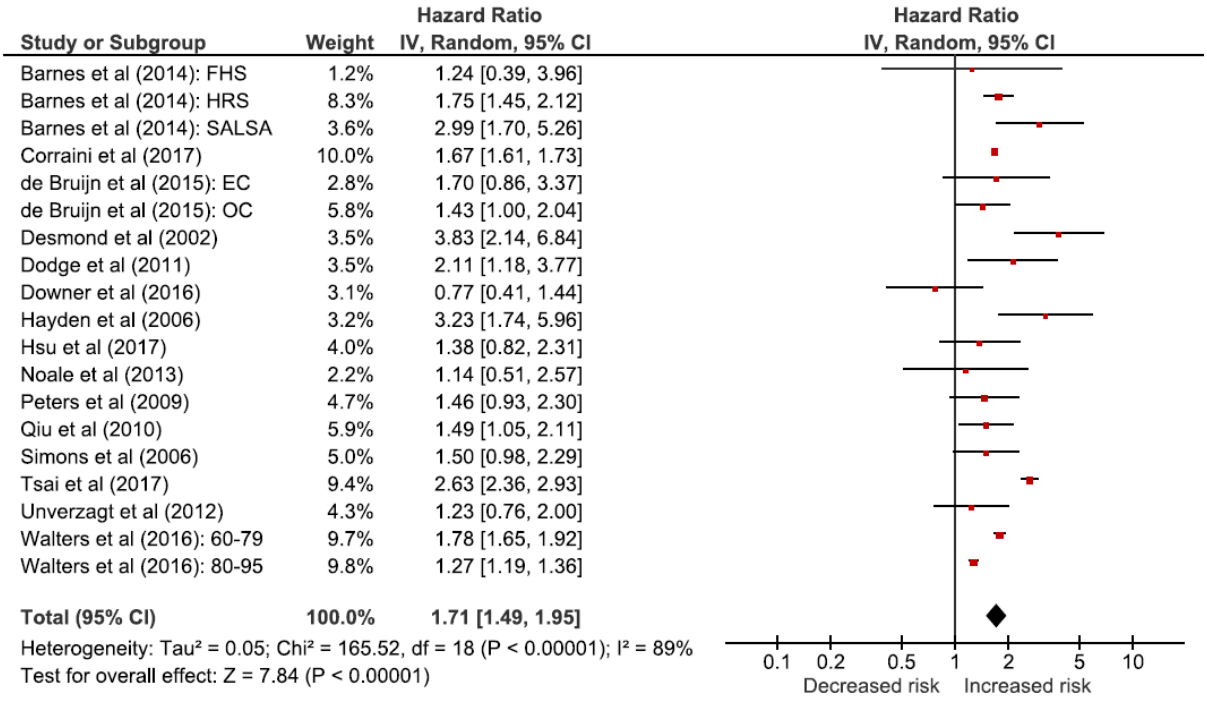


Fig. B5.1 Meta-analysis of hazard ratios of prevalent stroke compared to no prevalent stroke on incident all-cause dementia excluding four studies including subjects with mild cognitive impairment

Data presented as hazard ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. Hazard ratio estimate for the study by Hayden and colleagues [34] was obtained in Review Manager using the generic inverse-variance method and is different from that obtained from a discrete-time survival model reported in the original study (i.e. HR = 3.23, CI = 1.74-5.64). IV, inverse-variance estimation method; CI, confidence interval; EC, extended cohort; FHS, Framingham Heart Study; HRS, Health and Retirement Study; OC, original cohort; SALSA, Sacramento Area Latino Study on Aging.

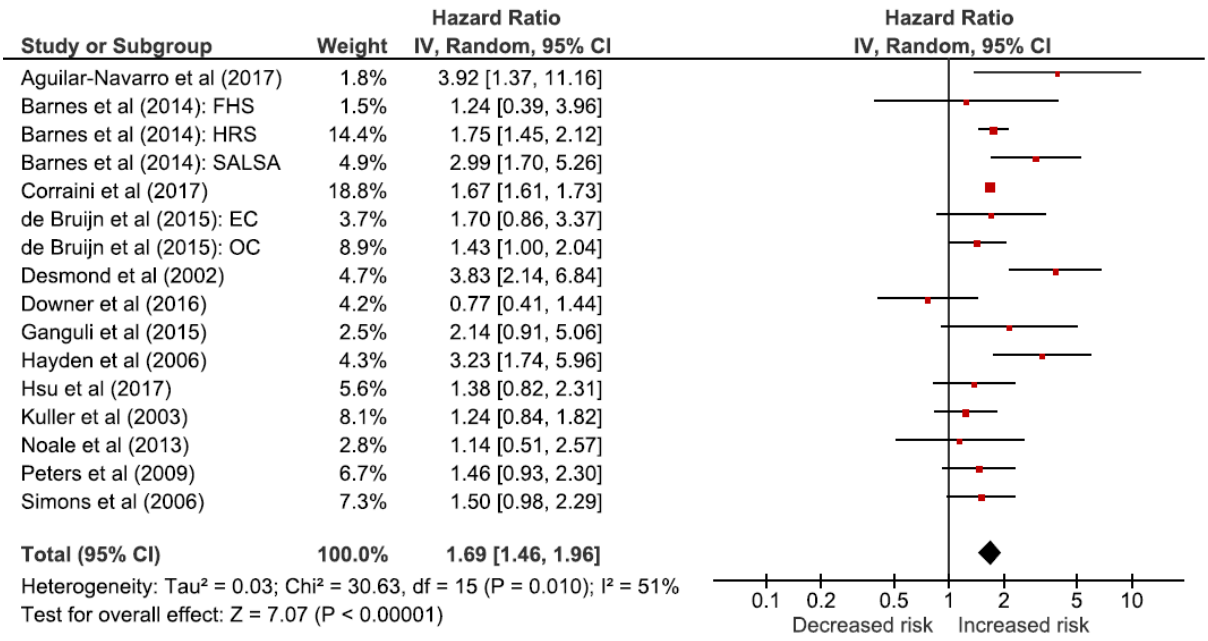


Fig. B5.2 Meta-analysis of hazard ratios of prevalent stroke compared to no prevalent stroke on incident all-cause dementia excluding six studies with transient ischemic attack included in the definition of stroke
Data presented as hazard ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. Hazard ratio estimate for the study by Hayden and colleagues[34] was obtained in Review Manager using the generic inverse-variance method and is different from that obtained from a discrete-time survival model reported in the original study (i.e. HR = 3.23, CI = 1.74-5.64). IV, inverse-variance estimation method; CI, confidence interval; EC, extended cohort; FHS, Framingham Heart Study; HRS, Health and Retirement Study; OC, original cohort; SALSA, Sacramento Area Latino Study on Aging.

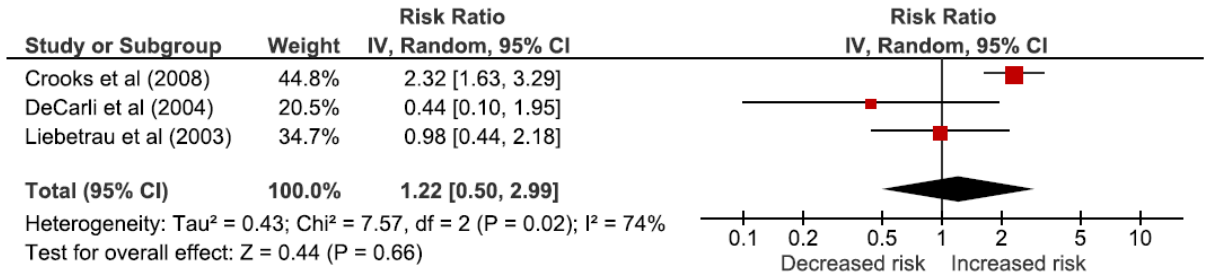


Fig. B5.3 Meta-analysis of unadjusted risk ratios of prevalent stroke compared to no prevalent stroke on incident all-cause dementia
Data presented as risk ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. IV, inverse-variance estimation method; CI, confidence interval.

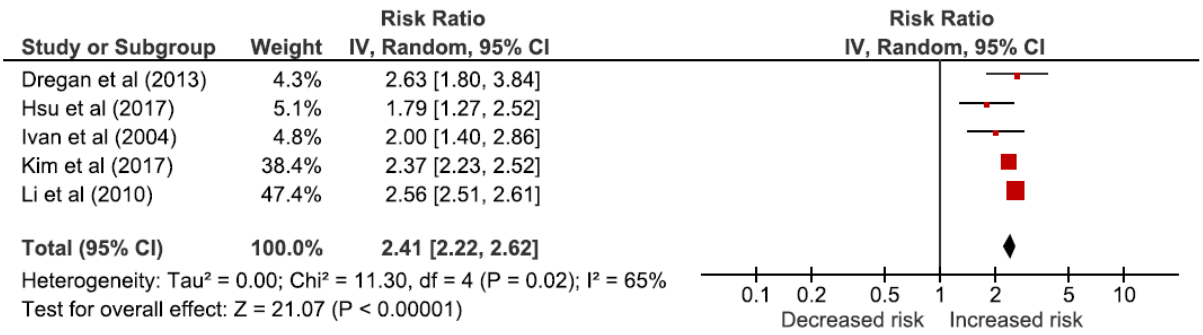


Fig. B6.1 Meta-analysis of adjusted risk ratios of incident stroke compared to no incident stroke on incident all-cause dementia excluding three studies with transient ischemic attack included in the definition of stroke
Data presented as risk ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. IV, inverse-variance estimation method; CI, confidence interval.

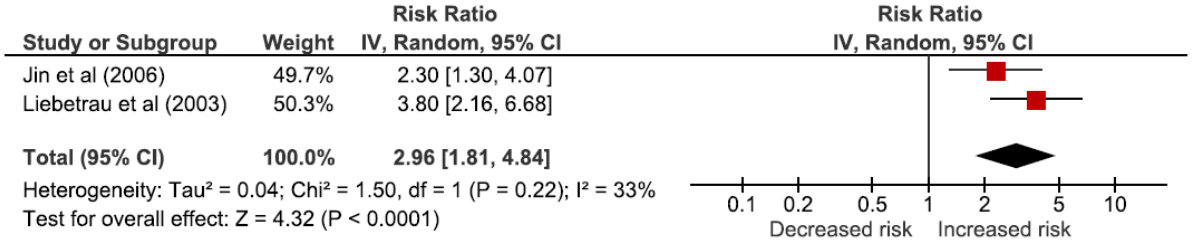


Fig. B6.2 Meta-analysis of unadjusted risk ratios of incident stroke compared to no incident stroke on incident all-cause dementia
Data presented as risk ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases and total number of participants was not always available in original included studies. IV, inverse-variance estimation method; CI, confidence interval.