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Featured Article

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% confidence interval: 1.49–1.92; $P < .00001$; $I^2 = 87\%$). For incident stroke, the pooled risk ratio was 2.18 (95% confidence interval: 1.90–2.50; $P < .00001$; $I^2 = 88\%$). 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.

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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 were 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 the 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 after 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

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meta-analysis of the relationship between stroke and all-cause dementia risk.

2. Methods

We updated the systematic review conducted by Savva et al. [3] and performed study-level random effects meta-analyses after general guidance provided by the Center for Reviews and Dissemination, UK [7].

2.1. Search strategy and selection criteria

Following the methods of the previous systematic review [3] and our predefined 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 (Supplementary Appendix A, Methods, and Fig. A1, A2, A3). We conducted our searches on April 27, 2017 (E.K.), restricting them to studies published after 2008 to avoid overlap with the previous systematic review which searched up to December 31, 2008 [3]. We also conducted backward and forward citation searches (via Web of Science; by the authors E.K. and I.L.) 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, that is, 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 predefined inclusion and exclusion criteria, two reviewers (E.K. and I.L.) independently screened titles, abstracts, and full texts. Discrepancies were resolved by discussion with a third reviewer (D.J.L.).

Key data were extracted by one reviewer (E.K.) and checked by the second (I.L. or S.F.M.). We also contacted corresponding authors of 18 studies for clarification or if relevant data were not fully reported and received additional data or clarification for 13 studies (see Supplementary Appendix A, Methods for details). Two reviewers (E.K. and I.L.) 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 categorized 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 prioritized 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 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 with combined prevalent or incident stroke with transient ischemic attack (TIA). Where results were provided separately on the basis of apolipoprotein E (*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 onset vs. late-onset dementia) or statistical methods used were synthesized 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 the following: (1) study setting (community vs. noncommunity); (2) inclusion of TIA in stroke assessment/diagnosis (yes/no); (3) dementia diagnostic criteria used (Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases, other); (4) stroke assessment based on self-report only (yes/no); (5) adjustment for at least one vascular risk factor (yes/no); (6) mean/median age of participants in years; (7) proportion of male participants (%); (8) year at baseline examination; (9) length of follow-up in years; and (10) 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).

3. Results

Database searches resulted in 11,129 records. After removing duplicates, we screened 6893 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 et al. using data from the Rotterdam Study [14] because of 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 Supplementary 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

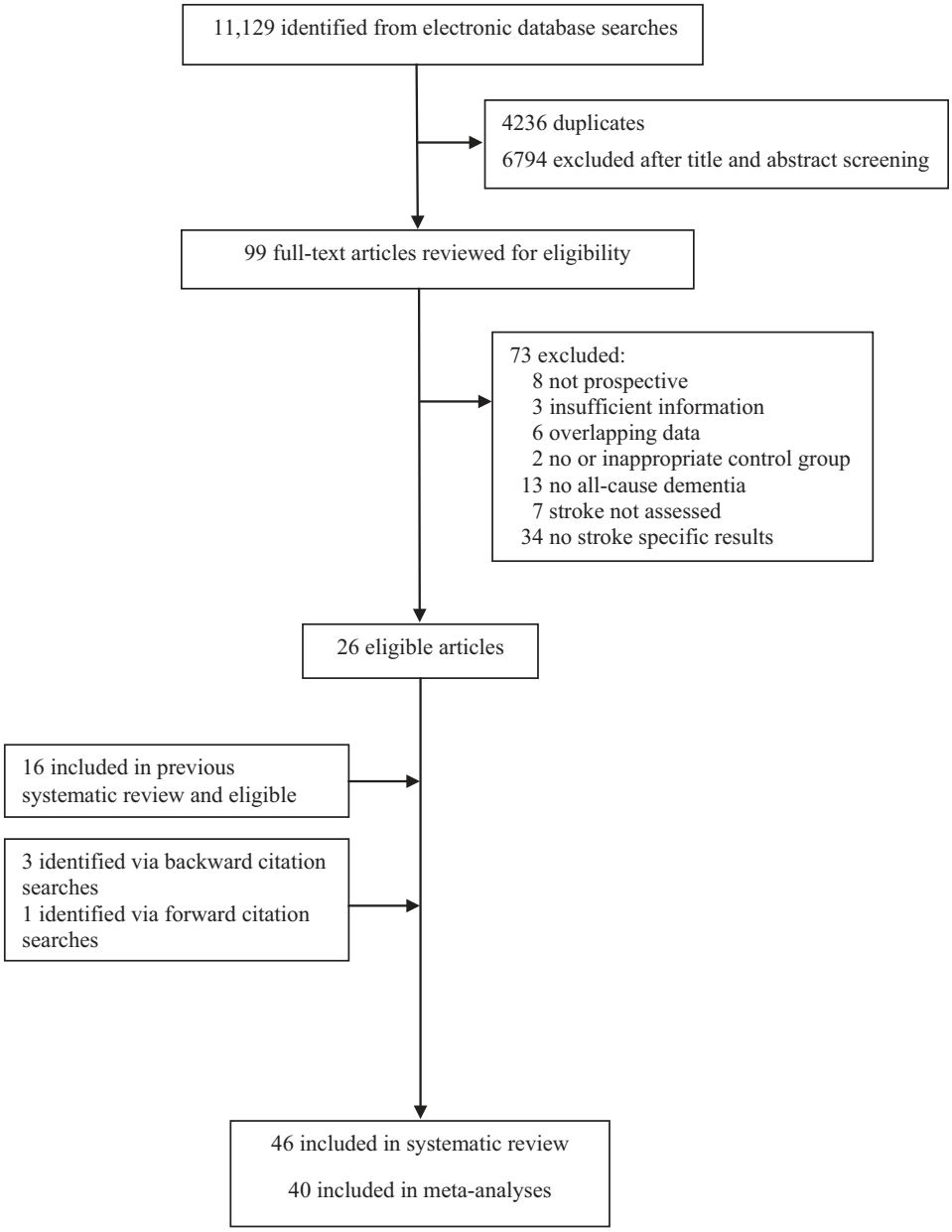

Fig. 1. Flowchart of search results and study retrieval.

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

NOTE. 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 Supplementary 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.

five studies recruited participants with 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-report or informant report, and 15 studies reported adjudicated dementia diagnosis using Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria [16–18]. Five studies assessed both stroke and dementia solely through medical records (Supplementary 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 (Supplementary 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 [53,54] investigated the association between prevalent stroke and incident all-cause dementia (around 1.9 million participants and 240,471 stroke events; Supplementary 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 with those without stroke (pooled HR = 1.69, 95% CI: 1.49–1.92, $P < .00001$, $I^2 = 87\%$, 95% PI: 1.17–2.21; Fig. 2). Visual inspection of the funnel plot indicated no sign of publication bias (Supplementary Appendix B, Fig. B4). In a sensitivity analysis, we excluded results provided by Walters et al. [49] for those aged 80 to 95 years due to correlation with results reported from the same cohort for those aged 60 to 79 years. The pooled HR remained almost unchanged (1.75, 95% CI: 1.55–1.97, $P < .00001$, $I^2 = 78\%$, 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, $P < .001$, $I^2 = 89\%$, 95% PI: 1.17–2.25; and pooled HR = 1.69, 95% CI: 1.46–1.96, $P < .001$, $I^2 = 51\%$, 95% PI: 1.23–2.15, respectively; Supplementary Appendix B, Fig. B5.1, B5.2). Meta-regression analyses showed little evidence of effect modification on the basis of study setting ($P = .82$), inclusion of TIA in stroke assessment/diagnosis ($P = .89$), dementia diagnostic criteria used ($P = .37$), stroke assessment based on self-report only ($P = .59$), adjustment for at least one vascular risk factor ($P = .92$), mean/median age of participants ($P = .48$), year at baseline examination ($P = .47$), length of follow-up ($P = .73$), or study quality ($P = .75$). There was however some evidence for effect modification by sex, indicating that the risk of dementia corresponding to prevalent stroke was higher in men than in women ($P = .04$). Effect modification by sex explained around half of the observed between-study heterogeneity (males: HR = 1.02, 95% CI: 1.00–1.03, $P = .04$; females: HR = 0.98, 95% CI: 0.97–0.99, $P = .04$; adjusted $R^2 = 50.2\%$).

Eight studies [21–23,33,35,46,51,52] reported adjusted ORs instead of HRs (11,336 participants and 1001 stroke events). The pooled estimate indicated increased odds of incident dementia in those with prevalent stroke compared with no prevalent stroke (pooled OR = 1.53, 95% CI: 1.30–1.80, $P < .00001$, $I^2 = 0\%$, 95% PI: 1.22–1.84; Fig. 3). In a sensitivity analysis, we excluded the study by Bruce et al. [22] as it included only participants with diabetes. The estimate remained essentially unchanged (pooled OR = 1.57, 95% CI: 1.29–1.91, $P < .001$, $I^2 = 11\%$, 95% PI: 1.09–2.05).

In a secondary analysis, the pooled estimate for three studies [26,28,42] reporting unadjusted results (2795 participants and 262 stroke events) indicated little evidence of an association between prevalent stroke and

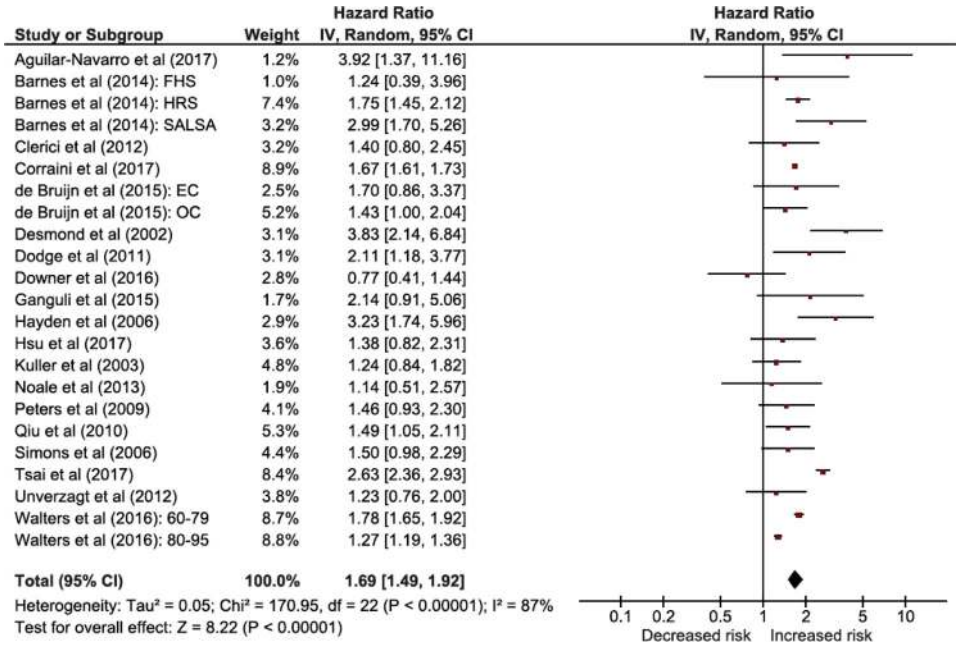

Fig. 2. Meta-analysis of hazard ratios of prevalent stroke compared with no prevalent stroke on incident all-cause dementia. Data are presented as hazard ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases, and total number of participants were not always available in original included studies. Hazard ratio estimate for the study by Hayden et al. [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 Supplementary Appendix shows the corresponding funnel plot. Abbreviations: 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.

incident dementia (pooled RR = 1.22, 95% CI: 0.50–2.99, P = .66, I^2 = 74%, 95% PI: −10.38 to 12.82; Supplementary 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 with absence of stroke (Supplementary 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 standardized 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 et al. [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

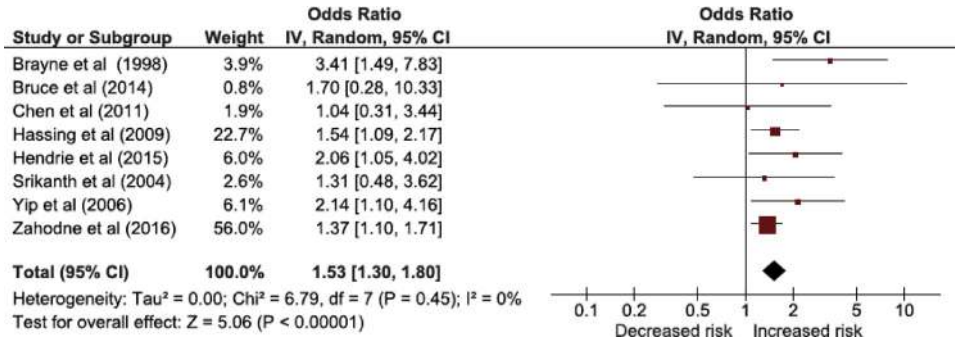

Fig. 3. Meta-analysis of odds ratios of prevalent stroke compared with no prevalent stroke on incident all-cause dementia. Data are presented as odds ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases, and total number of participants were not always available in original included studies. The Supplementary Appendix shows the corresponding funnel plot. Abbreviations: CI, confidence interval; IV, inverse-variance estimation method.

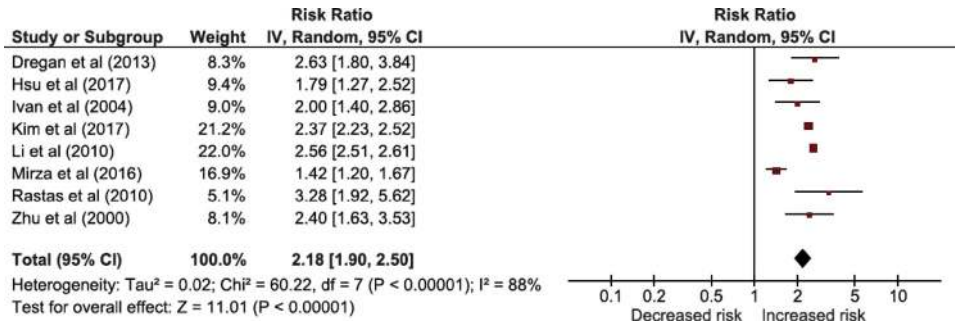

Fig. 4. Meta-analysis of risk ratios of incident stroke compared with no incident stroke on incident all-cause dementia. Data are presented as risk ratios with corresponding weight for each study in the meta-analysis because number of stroke events, dementia cases, and total number of participants were not always available in original included studies. The Supplementary Appendix shows the corresponding funnel plot. Abbreviations: CI, confidence interval; IV, inverse-variance estimation method.

estimate (RR = 2.14, 95% CI: 0.64–7.13; Supplementary 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; Supplementary 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 with no incident stroke (pooled RR = 2.18, 95% CI: 1.90–2.50, $P < .001$, $I^2 = 88\%$, 95% PI: 1.67–2.69; Fig. 4). No obvious sign of publication bias was detected by visual inspection of the funnel plot (Supplementary 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, $P < .001$, $I^2 = 65\%$, 95% PI: 2.09–2.73; Supplementary 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 with no incident stroke (Supplementary Appendix B, Table B4). Meta-regression analyses indicated there was little evidence that inclusion of TIA in stroke assessment/diagnosis ($P = .49$), mean/median age of participants ($P = .16$), year at baseline examination ($P = .37$), length of follow-up ($P = .32$), or study quality ($P = .49$) modified dementia risk.

In a secondary analysis, the pooled estimate for two studies [42,58] reporting unadjusted results (1007 participants and stroke events) indicated that incident stroke almost tripled the risk of dementia compared with no incident stroke (pooled RR = 2.96, 95% CI: 1.81–4.84, $P < .001$, $I^2 = 33\%$; Supplementary Appendix B, Fig. B6.2). A study focusing on early onset dementia in men [61] indicated that incident stroke almost tripled the

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− and stroke−	*APOE* ε4− and stroke+	*APOE* ε4+ and stroke−	*APOE* ε4+ and 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)

Abbreviations: *APOE*, apolipoprotein E; CI, confidence interval; HR, hazard ratio.

risk of developing early onset dementia (HR = 2.96, 95% CI: 2.02–4.35; Supplementary 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 noncarriers in two out of three studies [30,63], and the HR for the nonsignificant 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 HR of the nonsignificant association was again in the same direction [30]. However, there was no consistent difference in the effect sizes observed between *APOE* ε4 carriers and noncarriers 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 noncarriers in both the 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 HR 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 noncarriers for incident stroke.

3.5. *Sex-stratified findings*

Three studies [25,43,57] reported additional results for incident all-cause dementia stratified by sex (Supplementary 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 strokes 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 noncarriers 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-analyses extend the findings of the previous systematic review by Savva et al. [3] 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 strokes in relation to the 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 poststroke dementia are well known and have been previously synthesized [4]; our analysis extends these findings beyond poststroke 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 because it is not possible to randomize participants to stroke events, randomized controlled trials 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 hemorrhagic strokes as predictors of poststroke 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 poststroke 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 gray 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 after 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 strokes 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 we were able to identify studies reporting nonsignificant 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 fluid-attenuated inversion recovery magnetic resonance imaging and ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography [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 period of 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 characterize 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 health-care costs, stroke prevention strategies should be integrated in multimodal health interventions to reduce dementia risk.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.06.3061.

RESEARCH IN CONTEXT

1. Systematic review: To identify studies investigating the association between stroke and incident all-cause dementia, we searched Medline, PsycINFO, and Embase; conducted backward and forward citation; contacted authors for additional data; and combined our findings with those from a 2008 systematic review.
2. Interpretation: Based on data describing more than 370,000 stroke events and over 3 million participants, we found robust evidence to support a significantly increased risk of all-cause dementia in those with a history of stroke. Even stronger associations were also evident for incident stroke, suggesting that it more than doubles the risk of all-cause dementia. Significant heterogeneity was observed, and the association with prevalent stroke appeared stronger in men.
3. Future directions: Our findings highlight the importance of stroke as an independent potentially modifiable risk factor for dementia. These findings were not accounted for by other vascular risk factors, and the stronger association for incident stroke suggests time since stroke may be important. Stroke characteristics and potential effect modifiers such as education and ethnicity warrant further investigation.

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