Cognitive impairment is a major contributor to disability and dependence worldwide. Globally, stroke is the leading cause of long-term disability among adults and the second leading cause of death. The high cumulative risk of dementia or stroke or both conditions has been shown by the Framingham study, and the urgent need to improve knowledge regarding cognition and vascular conditions has been emphasized in a specific meeting providing harmonized standards. Beyond their personal tolls, both of these conditions carry substantial social and economic burdens. These conditions also correlate strongly with increasing age. Given the projected substantial rise in the number of older people around the world, prevalence rates of cognitive impairment and stroke are expected to soar over the next several decades, especially in high-income countries.

Shared pathophysiologic mechanisms seem to exist between cognitive impairment and cerebrovascular disease. Indeed, risk factors for stroke (hypertension, hyperlipidemia, diabetes, obesity and physical inactivity) have been shown to play a role in the onset and progression of cognitive impairment, and it is well established that stroke itself increases the risk of future cognitive impairment. However, whether cognitive impairment increases the risk of future stroke remains unclear. Early identification and regular surveillance for cognitive impairment could potentially enable prompt initiation of treatment aimed at not only potentially limiting further deterioration of cognitive function (if mild), but also possibly reducing the risk of future stroke through timely and optimal control of risk factors.

Several published studies have assessed the association between cognitive impairment and subsequent risk of stroke, but the results have not been consistent. We performed a systematic review and meta-analysis to determine the qualitative and quantitative association between baseline cognitive impairment and risk of future stroke.

**Methods**

**Search strategy**

Our search strategy was based on the recommendations of the Meta-analysis of Observational Studies in Epidemiology group. We searched MEDLINE via PubMed (1966 to November 2013) and conducted a manual search of bibliographies of relevant retrieved articles and reviews. We included cohort studies that reported multivariable adjusted relative risks and 95% confidence intervals or standard errors for stroke with respect to baseline cognitive impairment.

**Results**

We identified 18 cohort studies (total 121,879 participants) and 7,799 stroke events. Pooled analysis of results from all studies showed that stroke risk increased among patients with cognitive impairment at baseline (relative risk [RR] 1.39, 95% confidence interval [CI] 1.24–1.56). The results were similar when we restricted the analysis to studies that used a widely adopted definition of cognitive impairment (i.e., Mini-Mental State Examination score < 25 or nearest equivalent) (RR 1.64, 95% CI 1.46–1.84). Cognitive impairment at baseline was also associated with an increased risk of fatal stroke (RR 1.68, 95% CI 1.21–2.33) and ischemic stroke (RR 1.65, 95% CI 1.41–1.93).

**Interpretation**

Baseline cognitive impairment was associated with a significantly higher risk of future stroke, especially ischemic and fatal stroke.
2013) and Embase (1966 to November 2013) using the following search strategy: stroke OR cerebrovascular disease OR cerebrovascular attack AND cognitive impairment OR memory impairment OR dementia OR Alzheimer disease AND cohort OR follow-up OR prospective OR trial OR incidence OR incident. No language restrictions were applied. Further information was retrieved through a manual search of references from relevant published original studies and reviews.10

**Study selection and quality assessment**

We included studies if they were cohort studies (prospective or retrospective); evaluated cognitive function at baseline; assessed stroke event as an outcome during the follow-up period (e.g., if a person had a stroke before enrolment, the stroke event during follow-up would be recurrent stroke; if a person did not have a stroke before enrolment, the stroke event during follow-up would be first stroke event); had an intended follow-up period of at least 1 year for all participants; and reported quantitative estimates of the multivariable adjusted relative risk (RR) and 95% confidence interval (CI) or standard error for the log RR for future stroke associated with cognitive impairment at baseline. We excluded studies if they had a cross-sectional or case–control design, had a majority of participants with stroke at baseline, reported only unadjusted or age- and sex-adjusted RRs or were duplicate reports.

We extracted the following information from the studies: first author’s name, study name, publication year, study country, number of follow-up years, number of participants (total and number with cognitive impairment), mean age of participants, percentage of women, method used to assess cognitive impairment, stroke outcome (total, fatal, nonfatal, ischemic, hemorrhagic), number of stroke events and adjusted covariates included in the models of analysis. Two of us (M.L. and K.S.H.) independently extracted data from eligible studies. Discrepancies were resolved by discussion with a third investigator (B.O.) and by referencing the original report.

The quality of studies was assessed using criteria modified from a previous meta-analysis,10 with consideration of the following aspects: study design, maintenance of comparable groups, length of follow-up, maximal adjustment for potential confounders, exclusion of participants with baseline stroke, total stroke reported (not just ischemic or fatal stroke) and generalizability to other populations. Studies were graded as high quality if they met at least 5 of the 7 criteria and low quality if they met fewer than 5.

**Data synthesis**

We used multivariable adjusted outcome data (expressed as RRs and 95% CIs or standard errors). When studies provided estimates for cognitive impairment based on more than one assessment method, we used estimates from the Mini-Mental State Examination, if available, for our primary analysis. In each study, we converted these values by using their natural logarithms, and we calculated the standard errors from these logarithmic numbers and their corresponding 95% CIs.

For the statistical analysis, we combined log RRs and standard errors using the inverse variance approach. We used a random-effects model and explored for sources of inconsistency ($I^2$) and heterogeneity. A fixed-effects model was used for comparison with the random-effects model on the overall risk estimate. Reported $p$ values were 2-sided, with significance set at less than 0.05. Heterogeneity was assessed by the $p$ value of $\chi^2$ statistics and by the $I^2$ statistic, which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than to chance.11,12 Based on the suggestion of the Cochrane Collaboration, we regarded heterogeneity as possibly unimportant when the $I^2$ value was less than 40% and high when it was more than 75%.13 We assessed publication bias graphically using a funnel plot and mathematically using an adjusted rank-correlation test, according

**Figure 1: Selection of studies for the meta-analysis.**
Table 1: Characteristics of studies included in a meta-analysis of the association between baseline cognitive impairment and risk of future stroke

| Study                        | Study population | No. of patients (% female) | Stroke at baseline, % | Age, yr, mean | Measures and definition of cognitive impairment | Duration of follow-up, yr | Outcomes                                      | No. of stroke events |
|------------------------------|------------------|-----------------------------|-----------------------|---------------|-------------------------------------------------|--------------------------|-----------------------------------------------|----------------------|
| de Moraes et al.,2003, United States | General          | 11 958 (53)                | 0                     | 57            | DWR; lowest quartile                            | 6.2                      | Ischemic stroke                               | 188                  |
| Chi et al.,2013, Taiwan       | General; propensity score matching | 5 880 (59)                | 0                     | 75            | MMSE score 10–26 and receipt of ACHEI            | 4 ischemic + TIA; 4.2 hemorrhagic | Ischemic stroke + hemorrhagic stroke recorded separately | 606 ischemic + TIA; 84 hemorrhagic |
| Clarke et al.,2011, Canada    | ≥ 65 yr           | 9 451 (58)                 | 0                     | 73.6          | Dementia or CIND at clinical examination        | 10                       | Fatal and nonfatal stroke recorded separately | 172 fatal; 701 nonfatal |
| de Galan et al.,2009, multiple countries | Diabetes, ≥ 55 yr | 11 132 (42)                | 9.2                   | 66            | MMSE score 24–27, < 24                           | 5                        | All stroke                                    | 484                  |
| Ferrucci et al.,1996, United States | ≥ 71 yr          | 5 024 (66)                 | 0                     | 78.5          | SPMSQ score 4–6, 0–3                            | 4.3                      | All stroke                                    | 259                  |
| Gale et al.,1996, United Kingdom | ≥ 65 yr         | 921 (45)                   | NA*                   | 75            | HAMT score 8–9, ≤ 7                             | 20                       | Fatal ischemic stroke                         | 162                  |
| Glymour et al.,2010, United States | ≥ 50 yr          | 19 087 (59)                | 0                     | 66            | Summing recall ≤ 6 (total score 20)             | 8.1                      | All stroke                                    | 1 864                |
| Liebetrat et al.,2008, Sweden | 85 yr            | 401 (70)                   | 0                     | 85            | DSM III criteria                                | 3                        | All stroke                                    | 56                   |
| O'Donnell et al.,2012, multiple countries | High cardiovascular risk | 30 959 (30)                | 21                    | 66.5          | MMSE score 27–29, 24–26, < 24                   | 4.7                      | All stroke                                    | 1 374                |
| Ostir et al.,2003, United States | Hispanic, ≥ 65 yr | 2 682 (59)                 | 0                     | 72            | MMSE score < 21                                 | 7                        | All stroke                                    | 238                  |
| Pettigrew et al.,2000, United States | Asymptomatic carotid atherosclerosis | 1 659 (34)                | 25                    | 67            | MMSE score 25–27, < 25                          | 5                        | Ischemic stroke                               | 138                  |
| Reitz et al.,2008, Netherlands | ≥ 55 yr          | 6 724 (60)                 | 0                     | 69.2          | MMSE score < 26                                 | 7.3                      | All stroke                                    | 713                  |
| Sabayan et al.,2013, Netherlands | 85 yr            | 480 (66)                   | 0                     | 85            | MMSE score 25–27, < 25                          | 5                        | All stroke                                    | 56                   |
| Shipley et al.,2008, United Kingdom | General         | 6 424 (55)                 | NA†                   | Range 18–97  | Slow CRT                                       | 21                       | Fatal stroke                                  | 170                  |
| Skoog et al.,2005, multiple countries | Hypertension, 70–89 yr | 4 937 (64)                | 4                     | 76            | MMSE score 24–28                                 | 3.7                      | All stroke and ischemic stroke                | 204                  |
| Weinstein et al.,2013, United States | General         | 1 679 (53)                 | 0                     | 65.7          | TrB; cognitive Z scores < -1.5                  | 7.4                      | All stroke                                    | 55                   |
| Wiberg et al.,2010, Sweden    | Men, 70 yr       | 930 (0)                    | 0                     | 70            | MMSE score 29, 28, ≤ 27                         | 11.1                     | All stroke + TIA                              | 166                  |
| Zhu et al.,2000, Sweden       | ≥ 75 yr          | 1 551 (76)                 | 0                     | 82            | MMSE score < 24 without dementia; dementia based on DSM III criteria | 2.6                      | All stroke                                    | 110                  |

Note: ACHEI = acetylcholinesterase inhibitors, CIND = cognitive impairment without dementia, CRT = Choice Reaction Time, DSM = Diagnostic and Statistical Manual of Mental Disorders, DWR = Delayed Word Recall test, HAMT = Hodkinson Abbreviated Mental Test, MMSE = Mini-Mental State Examination, NA = not available, SPMSQ = Short Portable Mental Status Questionnaire, TIA = transient ischemic attack, TrB = Trail Making Test, part B (executive function performance). *Random sample from family practitioners’ list of all patients. †Random sample of community-dwelling adults.
to the method of Begg and Mazumdar.14 We used RevMan 5.2 for the meta-analyses.15

The main outcome of interest was the risk of future stroke among patients with cognitive impairment at baseline. Given the various definitions of cognitive impairment across the studies, we took 2 approaches to analyzing the data. First, we combined data from all included studies regardless of the definition used. Second, because one national guideline considers a Mini-Mental State Examination score of 25–30 as normal,16 we analyzed results only from studies that used a widely adopted definition of cognitive impairment (i.e., Mini-Mental State Examination score < 25 or nearest equivalent) and explored the association of this definition with future stroke. To clarify whether a history of cognitive impairment gives a clinician extra information about the risk of a stroke beyond what is captured by traditional risk factors for stroke, we conducted an analysis restricted to studies that used maximal adjustment for potential confounders; the studies included in this analysis provided adjustment of all 7 major potential confounders (age, sex, hypertension or systolic blood pressure or antihypertensive drug use, diabetes mellitus, body mass index or other measure of overweight or obesity, cholesterol concentration or statin use, and smoking).

We performed subgroup analyses for cognitive impairment based on data from all included studies according to cognitive scale score (Mini-Mental State Examination score of 25–29 or nearest equivalent v. < 25 or nearest equivalent), study design (ordinary cohort v. secondary analysis of clinical trials), study location (North America v. Europe v. international or Asian country), follow-up duration (< 5 yr v. ≥ 5 yr), sample size (< 5000 vs. ≥ 5000), method used to determine cognitive impairment (Mini-Mental State Examination v. other methods), exclusion of people with a history of stroke (excluded v. not excluded) and study quality (high-quality v. low-quality score). We conducted further analyses based on stroke outcome (fatal v. nonfatal) and type of stroke (ischemic v. hemorrhagic).

Results

Search results and study characteristics

Of 7518 potentially relevant studies identified through the literature search, 115 were retrieved for detailed assessment. We excluded 87 because

| Table 2: Quality assessment of included studies |
|-----------------------------------------------|
| Study                                      |
| Prospective design | Maintenance of comparable groups | Follow-up ≥ 5 yr | Adjustment for all 7 potential confounders* | Baseline stroke excluded | Total stroke reported† | Generalizability to other populations | Overall quality score |
|---------------------|----------------------------------|------------------|-----------------------------------------|---------------------------|------------------------|-----------------------------------|----------------------|
| de Moraes et al.18  | Yes                              | Yes              | Yes                                     | No                        | Yes                    | No                                | Yes                  | 5                   |
| Chi et al.19        | No                               | Yes              | No                                      | No                        | Yes                    | Yes                               | Yes                  | 4                   |
| Clarke et al.20     | Yes                              | Yes              | Yes                                     | No                        | Yes                    | Yes                               | Yes                  | 6                   |
| de Galan et al.21   | Yes                              | Yes              | Yes                                     | Yes                       | No                     | Yes                               | No                   | 5                   |
| Ferrucci et al.22   | Yes                              | Yes              | No                                      | No                        | Yes                    | Yes                               | Yes                  | 4                   |
| Gale et al.23       | Yes                              | Yes              | Yes                                     | No                        | Yes                    | No                                | Yes                  | 4                   |
| Glymour et al.24    | Yes                              | Yes              | Yes                                     | No                        | Yes                    | Yes                               | Yes                  | 6                   |
| Liebetrau et al.25  | Yes                              | Yes              | No                                      | Yes                       | Yes                    | Yes                               | Yes                  | 5                   |
| O’Donnell et al.26  | Yes                              | Yes              | No                                      | Yes                       | No                     | Yes                               | Yes                  | 4                   |
| Ostir et al.27      | Yes                              | Yes              | Yes                                     | No                        | Yes                    | Yes                               | Yes                  | 6                   |
| Pettigrew et al.28  | Yes                              | Yes              | Yes                                     | No                        | No                     | No                                | No                   | 3                   |
| Reitz et al.29      | Yes                              | Yes              | Yes                                     | No                        | Yes                    | Yes                               | Yes                  | 6                   |
| Sabayan et al.30    | Yes                              | Yes              | Yes                                     | No                        | Yes                    | Yes                               | Yes                  | 5                   |
| Shipley et al.31    | Yes                              | Yes              | Yes                                     | No                        | No                     | No                                | No                   | 4                   |
| Skoog et al.32      | Yes                              | Yes              | No                                      | No                        | No                     | Yes                               | No                   | 3                   |
| Weinstein et al.33  | Yes                              | Yes              | Yes                                     | Yes                       | Yes                    | Yes                               | Yes                  | 6                   |
| Wiberg et al.34     | Yes                              | Yes              | Yes                                     | No                        | Yes                    | Yes                               | No                   | 5                   |
| Zhu et al.35        | Yes                              | Yes              | No                                      | Yes                       | Yes                    | Yes                               | Yes                  | 4                   |

*Age, sex, hypertension or systolic blood pressure or antihypertensive drug use, diabetes mellitus, body mass index or other measure of overweight or obesity, cholesterol concentration or statin use, and smoking.
†Not just ischemic or fatal stroke.
the association of baseline cognitive impairment and future stroke was not reported, 6 because most of the participants had a history of stroke at baseline, 3 because they were duplicate reports and 1 because no adjusted estimate was reported. Our final primary analysis included 18 cohort studies (Figure 1).

Characteristics of the 18 included studies are shown in Table 1. The total number of participants was 121,879, with 7799 reported stroke events. The studies varied with regard to primary outcome: 12 reported total stroke as a primary outcome, 1 reported fatal and nonfatal stroke separately, 1 reported ischemic stroke only, and 1 reported fatal ischemic stroke only. Transient ischemic attacks were included as outcomes in 2 studies. Participants were derived from ordinary cohorts in 14 studies and clinical trials in 4.

Most of the studies were from North American or European countries. One was conducted in Taiwan, and 3 were an international collaboration. The samples ranged from 401 to 30,959 participants, and the follow-up duration ranged

| Study* | Weight, % | Relative risk (95% CI) |
|--------|-----------|------------------------|
| de Moraes et al.18 | 3.0 | 1.50 (1.01–2.23) |
| Chi et al.19 (a) | 4.3 | 1.66 (1.40–1.97) |
| Chi et al.19 (b) | 3.1 | 1.70 (1.16–2.48) |
| Clarke et al.20 (c) | 3.4 | 2.06 (1.50–2.84) |
| Clarke et al.20 (d) | 3.8 | 0.42 (0.32–0.54) |
| de Galan et al.21 (e) | 4.2 | 1.21 (1.00–1.47) |
| de Galan et al.21 (f) | 3.0 | 1.32 (0.89–1.96) |
| Ferrucci et al.22 (e) | 3.9 | 1.20 (0.94–1.54) |
| Ferrucci et al.22 (f) | 2.9 | 2.20 (1.45–3.34) |
| Gale et al.23 (e) | 3.5 | 1.30 (0.96–1.76) |
| Gale et al.23 (f) | 2.6 | 2.80 (1.76–4.46) |
| Glynour et al.24 | 4.5 | 1.26 (1.13–1.40) |
| Liebestrau et al.25 | 2.8 | 1.70 (1.10–2.63) |
| O’Donnell et al.26 (e) | 4.5 | 1.19 (1.05–1.35) |
| O’Donnell et al.26 (e1) | 4.3 | 1.30 (1.11–1.53) |
| O’Donnell et al.26 (f) | 4.2 | 1.44 (1.20–1.73) |
| Ostir et al.27 | 3.6 | 1.85 (1.38–2.48) |
| Pettigrew et al.28 (e) | 3.0 | 1.03 (0.70–1.52) |
| Pettigrew et al.28 (f) | 2.2 | 1.63 (0.92–2.88) |
| Reitz et al.29 | 3.7 | 1.90 (1.43–2.52) |
| Sabayan et al.30 (e) | 2.5 | 1.22 (0.74–2.02) |
| Sabayan et al.30 (f) | 2.6 | 2.14 (1.32–3.46) |
| Shipley et al.31 | 4.5 | 1.28 (1.14–1.44) |
| Skoog et al.32 | 3.9 | 1.20 (0.94–1.54) |
| Weinstein et al.33 | 2.5 | 2.25 (1.37–3.70) |
| Wiberg et al.34 (e) | 3.0 | 1.05 (0.71–1.56) |
| Wiberg et al.34 (e1) | 2.8 | 0.83 (0.53–1.29) |
| Wiberg et al.34 (e2) | 2.6 | 0.62 (0.38–1.00) |
| Zhu et al.35 (e) | 2.7 | 2.00 (1.26–3.17) |
| Zhu et al.35 (f) | 2.5 | 2.60 (1.57–4.30) |

Overall 100.0 1.39 (1.24–1.56)

Heterogeneity: $P = 82$

Figure 2: Association between cognitive impairment at baseline and risk of future stroke. Values greater than 1.0 indicate an increased risk of stroke. *Study subgroups: a = ischemic, b = hemorrhagic, c = fatal and d = nonfatal stroke; e, e1, e2, and f represent different degrees of cognitive impairment reported in a study. CI = confidence interval.
from 2.6 to 21 years. All but one of the studies included both men and women; the remaining study included only men. Ten studies used the Mini-Mental State Examination to assess cognitive function, and 8 studies used other cognitive measures. Participants with a history of stroke were excluded in 12 studies; in the other studies, the proportion of participants with a history of stroke at baseline ranged from 4% to 25%. Seventeen studies used multivariable-adjusted analysis, and 1 study used propensity score matching. On a scale of 7, the overall quality of the studies was good (median score 5, range 3–6) (Table 2).

The funnel plot showed no major asymmetry, and we found no evidence of publication bias using the Begg test ($p = 0.1$) (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140147/-/DC1).

**Primary analysis**

In the primary analysis of pooled data from all of the studies, we found an increased risk of future stroke among patients with cognitive impairment at baseline (relative risk [RR] 1.39, 95% confidence interval [CI] 1.24–1.56; random-effects model) (Figure 2). Heterogeneity was high ($I^2 = 82%$). The estimates were similar between the fixed-effects model (RR 1.31, 95% CI 1.26–1.37) and the random-effects model. In the 3 studies with maximal adjustment for potential confounders, baseline cognitive impairment was associated with increased risk of future stroke (RR 1.28, 95% CI 1.18–1.38; random-effects model); there was no heterogeneity among these studies ($F = 0%$).

When we pooled results from the studies that used a widely adopted definition of cognitive impairment (i.e., Mini-Mental State Examination score < 25 or nearest equivalent), the increased risk of future stroke among patients with cognitive impairment at baseline was still evident (RR 1.64, 95% CI 1.46–1.84; random-effects model) (Figure 3). There was no obvious heterogeneity among these studies ($F = 41%$). Estimates were similar between the fixed-effects model (RR 1.57, 95% CI 1.45–1.71) and the random-effects model. In 2 studies with maximal adjustment for potential confounders, baseline cognitive impairment was associated with increased risk of future stroke (RR 1.35, 95% CI 1.21–1.52; random-effect model); there was no heterogeneity among the studies ($F = 0%$).

A sensitivity analysis of omitting 1 study in each turn did not change the overall results. Another sensitivity analysis, in which we excluded studies that imputed the risk estimates from other stroke outcomes (e.g., ischemic, fatal stroke) if data on total stroke were not available, revealed similar results (RR 1.38, 95% CI 1.21–1.58; 24 reports from 14 studies; $I^2 = 85%$; random-effects model).

**Subgroup analyses**

Baseline cognitive impairment was associated with an increased risk of subsequent stroke in all subgroups when we stratified estimates by cognitive scale score, study design, study location,
follow-up duration, sample size, method used to determine cognitive impairment, exclusion of people with a history of stroke at baseline, and study quality. We observed significant heterogeneity between pooled analyses for cognitive scale score (Mini-Mental State Examination score 25–29 or nearest equivalent v. < 25 or nearest equivalent: RR 1.16, 95% CI 1.06–1.27 v. RR 1.64, 95% CI 1.46–1.84; I² = 95%); there was no substantial heterogeneity within each category of cognitive scale score. No obvious heterogeneity was found between other characteristics of participants (Table 3).

When we conducted further analyses based on stroke outcome (fatal v. nonfatal) and type of stroke (ischemic v. hemorrhagic), we found that baseline cognitive impairment was associated with an increased risk of fatal stroke (RR 1.68, 95% CI 1.21–2.33; 3 studies; I² = 82%; random-effects model) but not with nonfatal stroke (RR 0.71, 95% CI 0.25–2.01; 2 studies; I² = 97%; random-effects model) (Figure 4). When we pooled the data by ischemic or hemorrhagic stroke, we found an association between baseline cognitive impairment and an increased risk of ischemic stroke (RR 1.65, 95% CI 1.41–1.93; 4 studies; I² = 21%; random-effects model) but no increased risk of hemorrhagic stroke (RR 0.57, 95% CI 0.20–1.57; 2 studies; I² = 92%) (Figure 4).

**Interpretation**

In this meta-analysis of 18 cohort studies involving more than 120000 people and almost 8000

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### Table 3: Stratified subgroup analyses for comparison between studies reporting associations between baseline cognitive impairment and risk of future stroke

| Subgroup                        | No. of studies | Relative risk (95% CI) | Heterogeneity within subgroups | Heterogeneity among subgroups |
|---------------------------------|----------------|------------------------|--------------------------------|------------------------------|
| **Cognitive scale score**       |                |                        |                                |                              |
| MMSE 25–29 or nearest equivalent| 6              | 1.16 (1.06–1.27)       | p = 0.8, I² = 0%               |                              |
| MMSE < 25 or nearest equivalent | 8              | 1.64 (1.46–1.84)       | p = 0.08, I² = 41%             |                              |
| **Study design**                |                |                        |                                |                              |
| Ordinary cohorts                | 14             | 1.46 (1.24–1.72)       | p < 0.001, I² = 86%            |                              |
| Analysis of trials              | 4              | 1.26 (1.17–1.35)       | p = 0.6, I² = 0%               |                              |
| **Sample size**                 |                |                        |                                |                              |
| ≥ 5000                          | 9              | 1.34 (1.16–1.55)       | p < 0.001, I² = 87%            |                              |
| < 5000                          | 9              | 1.47 (1.20–1.80)       | p < 0.001, I² = 72%            |                              |
| **Follow-up duration, yr**      |                |                        |                                |                              |
| ≥ 5                             | 12             | 1.32 (1.11–1.57)       | p < 0.001, I² = 86%            |                              |
| < 5                             | 6              | 1.48 (1.31–1.68)       | p = 0.002, I² = 64%            |                              |
| **Assessment tool**             |                |                        |                                |                              |
| MMSE                            | 10             | 1.38 (1.23–1.55)       | p < 0.001, I² = 67%            |                              |
| Other                           | 8              | 1.43 (1.13–1.82)       | p < 0.001, I² = 90%            |                              |
| **Study location**              |                |                        |                                |                              |
| North America                   | 7              | 1.38 (1.02–1.87)       | p < 0.001, I² = 91%            |                              |
| Europe                          | 7              | 1.47 (1.19–1.81)       | p < 0.001, I² = 76%            |                              |
| Multiple countries or Asian country | 4          | 1.34 (1.22–1.48)       | p = 0.07, I² = 47%             |                              |
| **People with prior stroke**    |                |                        |                                |                              |
| Excluded                        | 12             | 1.44 (1.18–1.76)       | p < 0.001, I² = 88%            |                              |
| Not excluded                    | 6              | 1.30 (1.19–1.41)       | p = 0.1, I² = 38%              |                              |
| **Study quality**               |                |                        |                                |                              |
| High, score 5–7                 | 10             | 1.29 (1.03–1.62)       | p < 0.001, I² = 88%            |                              |
| Low, score < 5                  | 8              | 1.45 (1.30–1.62)       | p < 0.001, I² = 65%            |                              |

Note: CI = confidence interval, MMSE = Mini-Mental State Examination.
stroke events, we found that the risk of future stroke was 39% higher among patients with cognitive impairment at baseline than among those with normal cognitive function at baseline. This risk increased to 64% when a broadly adopted definition of cognitive impairment was used. This association was consistent across diverse population subgroups. The size and inclusion of mostly prospectively collected data strengthened the robustness of our findings, because selection bias, recall bias and reverse causality were unlikely. In addition, all of the included studies reported multivariable adjusted RRs, which probably mitigated the possibility of known founders influencing our results.

Differing degrees of cognitive impairment may account for the heterogeneity in the main analysis. In a subgroup analysis, we found a possible dose–response relation between cognitive impairment and stroke: among participants with cognitive impairment, the risk of stroke was significantly greater with a low Mini-Mental State Examination score than with a high score. Heterogeneity was removed by division into strata.

Cognitive impairment may contribute to future stroke through a variety of mechanisms. First, the condition is associated with silent brain infarcts, which increase the risk of subsequent overt stroke. Silent brain infarcts may have been more frequent in the participants with

| Study* | Weight, % | Relative risk (95% CI) |
|--------|-----------|------------------------|
| **Fatal stroke** | | |
| Clarke et al.20 (c) | 24.6 | 2.06 (1.50–2.84) |
| Gale et al.23 (e) | 25.1 | 1.30 (0.96–1.76) |
| Gale et al.23 (f) | 19.4 | 2.80 (1.76–4.46) |
| Shipley et al.31 | 30.9 | 1.28 (1.14–1.44) |
| Overall | 100.0 | 1.68 (1.21–2.33) |
| Heterogeneity: $P = 82\%$ | | |
| **Nonfatal stroke** | | |
| Clarke et al.20 (d) | 50.1 | 0.42 (0.32–0.54) |
| Skoog et al.32 | 49.9 | 1.21 (0.92–1.59) |
| Overall | 100.0 | 0.71 (0.25–2.01) |
| Heterogeneity: $P = 97\%$ | | |
| **Ischemic stroke** | | |
| de Moraes et al.18 | 12.7 | 1.50 (1.01–2.23) |
| Chi et al.19 (a) | 36.8 | 1.66 (1.39–1.98) |
| Gale et al.23 (e) | 19.0 | 1.30 (0.96–1.76) |
| Gale et al.23 (f) | 9.6 | 2.80 (1.76–4.46) |
| Wiberg et al.34 (e) | 6.8 | 1.63 (0.92–2.87) |
| Wiberg et al.34 (e1) | 7.9 | 1.74 (1.03–2.94) |
| Wiberg et al.34 (e2) | 7.3 | 1.69 (0.98–2.92) |
| Overall | 100.0 | 1.65 (1.41–1.93) |
| Heterogeneity: $P = 21\%$ | | |
| **Hemorrhagic stroke** | | |
| Chi et al.19 (b) | 26.4 | 1.70 (1.16–2.48) |
| Wiberg et al.34 (e) | 24.9 | 0.91 (0.49–1.68) |
| Wiberg et al.34 (e1) | 24.4 | 0.24 (0.12–0.48) |
| Wiberg et al.34 (e2) | 24.4 | 0.25 (0.13–0.49) |
| Overall | 100.0 | 0.57 (0.20–1.57) |
| Heterogeneity: $P = 92\%$ | | |

Test for subgroup differences: $\chi^2 = 6.55$, 3 degrees of freedom ($p = 0.09$); $P = 54.2\%$

Figure 4: Association between cognitive impairment at baseline and risk of future stroke, by type of stroke. Values greater than 1.0 indicate an increased risk of stroke. *Study subgroups: a = ischemic, b = hemorrhagic, c = fatal and d = nonfatal stroke; e and f represent different degrees of cognitive impairment reported in a study. CI = confidence interval.
cognitive impairment, but brain imaging was not done at baseline in most of the studies in our meta-analysis. Also, people with cognitive impairment tend to have white-matter hyperintensities, disturbances of cerebrovascular hemodynamics, deposition of amyloid in cerebral vessels and microbleeds, which may in turn increase the risk of future stroke. Most dementias are contributed to by vascular disease, and as such, patients who experience multiple small white-matter infarcts may go on to have dementia without ever having traditional stroke symptoms. The only way to assess these lesions is through magnetic resonance imaging, which was not performed in the studies included in our study. It is thus not inconceivable that dementia may be an epiphenomenon of prior vascular disease, and established vascular disease by itself will beget more strokes. Second, previous studies have shown that several biomarkers of systemic atherosclerosis and inflammation, such as elevated homocysteine and C-reactive protein, are associated with an increased risk of both cognitive impairment and stroke. Also, increased coronary artery calcification is associated with poor memory in midlife and independently increases the risk of future stroke in the general population. Third, cognitive impairment is associated with high within-individual variability in blood pressure, which itself is a risk factor for stroke. Finally, cognitive impairment can be linked to various deleterious factors (e.g., lack of medication compliance, poor diet, physical inactivity, frailty and depression), which increase the risk of stroke.

The impact of stroke on future dementia seems greater than the impact of cognitive impairment on future stroke. A Canadian study suggested that the presence of both stroke and APOE genotype compared with the absence of these 2 factors was associated with a greater risk of dementia (RR 2.57). Screening for cognitive impairment has been recommended in patients with stroke, given results from a recent Canadian study showing that two-thirds of stroke patients have evidence for cognitive impairment. Our findings suggest that identifying people with cognitive impairment may provide an even bigger opportunity to reduce the future burden of stroke through the timely implementation of evidence-based prevention strategies.

Limitations
Our study has limitations. First, meta-analyses may be biased if the literature search fails to identify all relevant studies or the selection criteria for including a study are applied in a subjective manner. To minimize these risks, we carried out thorough searches across different databases using explicit criteria for study selection, data abstraction and data analysis.

Second, we observed a large amount of heterogeneity in the results among all included studies. However, there was no significant heterogeneity among studies that provided information using a widely adopted definition of cognitive impairment.

Third, the sensitivity of the Mini-Mental State Examination to detect cognitive impairment has been found to be moderate compared with the Montreal Cognitive Assessment. Also, different degrees of cognitive impairment may have different effects on the risk of future stroke. Because most of the included studies did not provide a detailed description of the characteristics of the cognitive dysfunction, we were unable to explore this issue further.

Fourth, it would have been better to analyze sex-specific differences in the risk of stroke. However, our study was a study-level meta-analysis, and almost all of the included studies did not provide such data. Pooled analysis of patient-level data from relevant studies is warranted and may provide additional insights.

Finally, the association of cognitive impairment and risk of hemorrhagic stroke was inconclusive, because only 2 studies provided such information, and heterogeneity was high. Because cognitive impairment and intracranial hemorrhage share some pathophysiologic mechanisms, such as cerebral amyloid angiopathy, further studies are warranted to clarify this issue.

Conclusion
We found that the risk of future stroke was increased among patients with cognitive impairment at baseline, particularly among those who met a broadly adopted clinical definition of cognitive impairment. Cognitive impairment should be more broadly recognized as a possible early clinical manifestation of cerebral infarction, so that timely management of vascular risk factors can be instituted to potentially prevent future stroke events and to avoid further deterioration of cognitive health.

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