



# Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis

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## Summary

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**Background** Reliable data on the prevalence and predictors of post-stroke dementia are needed to inform patients and carers, plan services and clinical trials, ascertain the overall burden of stroke, and understand its causes. However, published data on the prevalence and risk factors for pre-stroke and post-stroke dementia are conflicting. We undertook this systematic review to assess the heterogeneity in the reported rates and to identify risk factors for pre-stroke and post-stroke dementia.

**Methods** Studies published between 1950 and May 1, 2009, were identified from bibliographic databases, reference lists, and journal contents pages. Studies were included if they were on patients with symptomatic stroke, were published in English, reported on a series of consecutive eligible patients or volunteers in prospective cohort studies, included all stroke or all ischaemic stroke, measured dementia by standard criteria, and followed up patients for at least 3 months after stroke. Pooled rates of dementia were stratified by study setting, inclusion or exclusion of pre-stroke dementia, and by first, any, or recurrent stroke. Pooled odds ratios were calculated for factors associated with pre-stroke and post-stroke dementia.

**Findings** We identified 22 hospital-based and eight population-based eligible cohorts (7511 patients) described in 73 papers. The pooled prevalence of pre-stroke dementia was higher (14.4%, 95% CI 12.0–16.8) in hospital-based studies than in population-based studies (9.1%, 6.9–11.3). Although post-stroke ( $\leq 1$  year) dementia rates were heterogeneous overall, 93% of the variance was explained by study methods and case mix; the rates ranged from 7.4% (4.8–10.0) in population-based studies of first-ever stroke in which pre-stroke dementia was excluded to 41.3% (29.6–53.1) in hospital-based studies of recurrent stroke in which pre-stroke dementia was included. The cumulative incidence of dementia after the first year was little greater (3.0%, 1.3–4.7) per year in hospital-based studies than expected on the basis of recurrent stroke alone. Medial temporal lobe atrophy, female sex, and a family history of dementia were strongly associated with pre-stroke dementia, whereas the characteristics and complications of the stroke and the presence of multiple lesions in time and place were more strongly associated with post-stroke dementia.

**Interpretation** After study methods and case mix are taken into account, reported estimates of the prevalence of dementia are consistent: 10% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and more than a third had dementia after recurrent stroke. The strong association of post-stroke dementia with multiple strokes and the prognostic value of other stroke characteristics highlight the central causal role of stroke itself as opposed to the underlying vascular risk factors and, thus, the likely effect of optimum acute stroke care and secondary prevention in reducing the burden of dementia.

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## Introduction

Although there is broad consensus that stroke is associated with an increased risk of subsequent dementia, the results of previous studies on the prevalence of post-stroke dementia are conflicting: the 3-month post-stroke rates of dementia vary from 6%<sup>1</sup> to more than 30%,<sup>2</sup> and the findings in relation to risk factors are inconsistent. Reported rates of pre-stroke dementia are similarly discordant. Therefore, more reliable estimates of the risks of post-stroke dementia and its predictors are needed to inform patients and carers, plan clinical services, design clinical trials, and ascertain the overall burden of stroke.

We did a quantitative systematic review of the prevalence of pre-stroke dementia and the prevalence and incidence of post-stroke dementia and their associated risk factors. Although it has been suggested that much of the variation in the reported rates of pre-stroke and post-stroke dementia is caused by differences in the method of diagnosis,<sup>3,4</sup> we hypothesised that the heterogeneity might be better explained by differences in the study design, with lower rates expected in population-based studies (which would include patients with minor strokes), in studies of post-stroke dementia that excluded pre-stroke dementia, and in studies restricted to first-ever stroke. Also, to better

understand the probable causes of post-stroke dementia, we aimed to identify the risk factors for dementia and whether there were any differences in the risk factors associated with pre-stroke and post-stroke dementia. Specifically, we aimed to ascertain the importance of the characteristics of the stroke itself (eg, lesion volume, multiple lesions, and acute complications) versus the underlying vascular risk factors in the causes of post-stroke dementia.

## Methods

### Procedures

This systematic review was done according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria.<sup>5</sup> Ovid Medline (1950 to April, 2009) and Embase (1980 to April, 2009) were searched (last on May 1, 2009) by one researcher (STP) with the exploded medical subject headings (MESH) “dementia” or “vascular dementia” or “multi-infarct dementia” and “stroke”. The bibliographies of relevant review articles on post-stroke dementia and the contents pages of the four journals that contained the greatest number of relevant papers in the electronic search were searched by hand.

Studies were included if they: were on patients with symptomatic stroke; were published in English; reported on a series of consecutive eligible patients (with an inclusion rate of at least 50%, allowing for exclusions owing to aphasia, visual or hearing impairment, language barriers, and early mortality) or volunteers in prospective cohort studies; included all stroke or all ischaemic stroke (studies restricted to other particular stroke subtypes were excluded); and gave dementia measured by standard criteria, such as diagnostic and statistical manual of mental disorders IV (DSM IV), international classification of disease-10 (ICD-10), or a mini-mental state examination (MMSE) score of less than 24 as an outcome. Additionally, to avoid diagnostic difficulties owing to delirium in the acute phase after stroke, only those studies of post-stroke dementia with a follow-up of at least 3 months after stroke onset were eligible for inclusion. Two types of population-based study were eligible: those in which all patients with stroke in a defined population were ascertained; and those in which cohorts of normal volunteers were recruited and followed prospectively, and data were reported on those who had a stroke during follow-up. To ascertain the factors associated with pre-stroke and post-stroke dementia, we included studies with an eligibility rate of less than 50% because estimation of risk factors would probably be less susceptible to bias owing to low inclusion rates than would the estimation of the absolute rate of dementia. Where there was uncertainty about the methods used for patient recruitment for a cohort, the authors were contacted and asked for clarification.

The abstracts of all papers identified from the initial searches were reviewed by one author (STP), and both authors reviewed the full text of all eligible studies that

reported rates or risk factors for pre-stroke or post-stroke dementia. Where there was more than one publication on a cohort of patients or volunteers, data on the incidence and prevalence of dementia were taken from those publications that described the total population rather than those that described a subset (eg, those who had brain imaging). Where data from later cohorts was added to those from earlier cohorts, from which data had already been published, the numbers in the combined cohort were used in the analysis (eg, studies from the Columbia University group<sup>6,7</sup>). In cases of disagreement between authors about the eligibility of studies or data extraction, consensus was reached through joint reassessment.

### Statistical analysis

Pooled estimates of the prevalence of pre-stroke and post-stroke dementia were obtained by the Mantel-Haenszel method. The 95% CIs of the pooled risk estimates were calculated to allow for extra-binomial variation,<sup>8</sup> because standard methods of calculating 95% CIs produce artificially narrow intervals if there is heterogeneity of risk between different studies. Analyses of the heterogeneity of prevalence across studies were done with  $\chi^2$  tests.

Rates of pre-stroke and post-stroke dementia were stratified by study setting (hospital based *vs* population based) and by the mean age of the patients. Studies that used the MMSE as the outcome measure were analysed separately from those in which dementia was measured with standard criteria (eg, DSM-III or ICD-10). The prevalence of pre-stroke dementia was analysed according to study setting and whether pre-stroke dementia was measured at the time of stroke in all patients or in only those patients who survived to a designated follow-up time, some months later.

The pooled prevalence of post-stroke dementia measured with standard criteria was calculated by combining the data from all studies that reported the rates from 3 months to 1 year after stroke. Studies were stratified by study setting, by the inclusion or exclusion of patients with pre-stroke dementia, and by whether only first-ever, first-ever or recurrent, or only recurrent strokes were reported. The proportion of the overall heterogeneity of the prevalence of pre-stroke and post-stroke dementia across all studies that could be accounted for by the above sub-categorisations was ascertained by an inverse-variance weighted regression of  $\log(\text{risk})$  against study type. The degree of variance in the prevalence of post-stroke dementia that was explained by the method of dementia diagnosis (ie, DSM or ICD-10) was also assessed in studies of post-stroke dementia.

The cumulative incidence of dementia after stroke, excluding pre-stroke dementia, was calculated with data extrapolated from longitudinal studies, by logistic regression. To allow for differences in the inclusion or exclusion of pre-stroke dementia among studies, or for the exclusion of all patients with dementia at 3 or 6 months

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for studies of delayed post-stroke dementia, data were adjusted by use of the pooled estimates of pre-stroke and post-stroke dementia where necessary (webappendix).

To identify the factors associated with pre-stroke and post-stroke dementia, pooled odds ratios for demographic variables, vascular risk factors, and stroke characteristics were calculated for patients with and without dementia with a fixed effects analysis unless there was evidence of heterogeneity ( $p \leq 0.1$ ), in which case random effects analysis was used. Heterogeneity was also quantified using  $I^2$  values. Hospital-based and population-based studies were combined for the calculation of the pooled odds ratios. Where measurement methods for a given variable differed between studies, data were dichotomised as follows: high or low education (primary education only or less than 6–8 years of education) and the presence or absence of leukoaraiosis or cerebral atrophy. For some factors (eg, education or atrophy), data could not be dichotomised for all studies; in such cases, the non-dichotomised data are shown in the webappendix.

## Results

The search of the electronic published work produced 6197 references (including 326 duplicates), of which

64 articles were eligible for inclusion (figure 1). A further 24 original research articles were identified by hand-searching the four journals that contained the highest number of relevant publications from the electronic search (*Stroke*; *Journal of Neurology*, *Neurosurgery and Psychiatry*; *Neurology*; and *Dementia and Geriatric Cognitive Disorders*) and reference lists. Nine of these 24 articles were eligible, making a total of 73 eligible articles.

Non-eligible studies of post-stroke dementia included non-consecutive patient series,<sup>9–11</sup> subsets of volunteer cohorts,<sup>12</sup> cross-sectional studies done long after the stroke,<sup>13</sup> studies of stroke subtypes or syndromes,<sup>14,15</sup> studies in which the time after stroke was variable or not specified,<sup>16–19</sup> studies in which the reported rates included mild cognitive impairment,<sup>20,21</sup> and a study that used clinical judgment alone to diagnose dementia.<sup>22</sup> Ineligible studies of post-stroke MMSE included those in which the numbers of patients with MMSE below a predefined cut-off score were not given,<sup>23–26</sup> one study that was done on a population that was mostly illiterate,<sup>27</sup> and one that was restricted to young patients.<sup>28</sup>

Several studies included in the systematic review and used to calculate the relative odds for pre-stroke and post-stroke dementia were not included in the pooled estimates of the prevalences of pre-stroke or post-stroke dementia. One study was restricted to patients with atrial fibrillation,<sup>29</sup> three studies included less than 50% of eligible patients<sup>1,30,31</sup> or excluded dependent patients,<sup>1,32</sup> and one included only patients with an MMSE score of at least 15 at the initial post-stroke assessment.<sup>33</sup>

Tables 1, 2, and 3 show the demographic details, study design, and methods used to measure dementia in all the publications that were relevant to the eligible hospital-based and population-based cohorts. All hospital-based studies of post-stroke dementia prospectively ascertained consecutive eligible patients.<sup>1–4,6,7,29–81</sup> Two of the population-based studies collected data on all patients who had incident strokes during a defined period (one retrospectively<sup>82</sup> and one prospectively<sup>87–89</sup>) and three collected data prospectively on cohorts of volunteers who were unaffected by stroke or dementia at the time of recruitment but in which a proportion had stroke during follow-up.<sup>83–86</sup> All four studies (one hospital-based<sup>90</sup> and three population-based<sup>91–93,97</sup>) of post-stroke MMSE scores were prospective studies of patients with stroke.

21 hospital-based cohorts of consecutive patients with stroke (5097 patients [mean age range 59–80 years]) and six population-based cohorts (2414 patients [mean age range 69–79 years]) reported data on pre-stroke or post-stroke dementia (tables 1, 2, and 3). Post-stroke MMSE data only were reported in a further 189 patients in one hospital-based study and in 1005 patients in three population-based cohorts (table 3).

All the population-based studies looked at first-ever stroke only compared with three of 21 hospital-based studies of dementia (tables 1 and 2).<sup>33,44,46,48,81</sup> Similarly, all

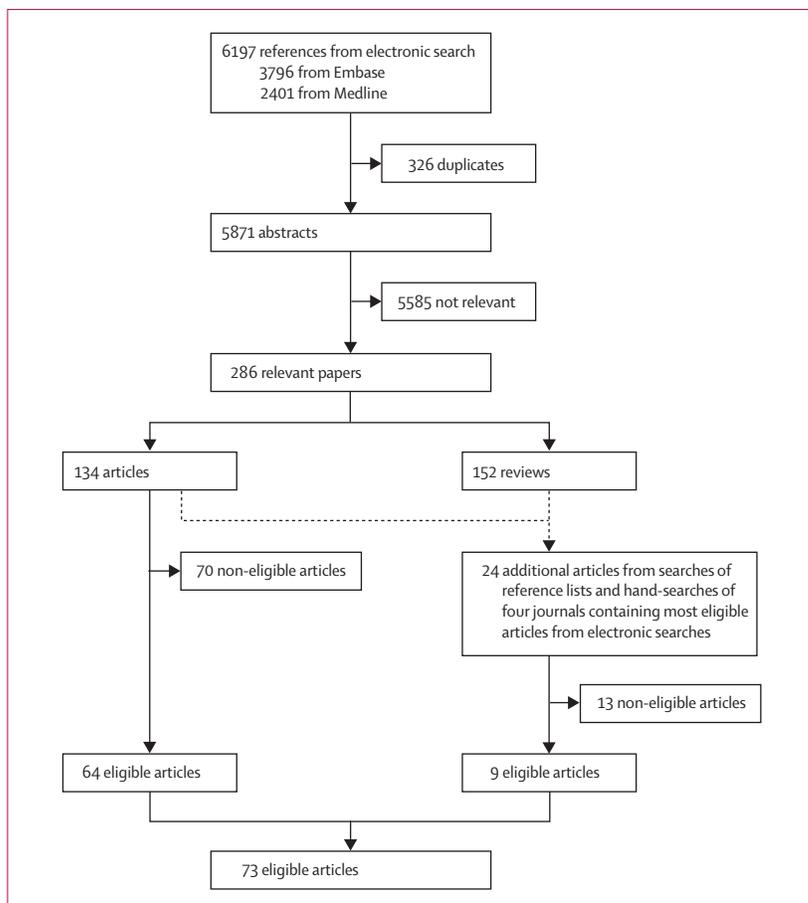


Figure 1: Literature searches and results

	Date of cohort collection	Study type	Mean age (years)	Female	Stroke type	First ever stroke	Exclusion criteria	Pre-stroke dementia excluded	Pre-stroke dementia quantified	Follow-up	Post-stroke dementia diagnosis
Columbia Presbyterian Medical Centre, NY, USA <sup>6,7,34-42</sup>	1988-90 1994-97	X, L	70	53%	IS	N	Dysphasia, unable to speak English or Spanish, low GCS, age <60 years	N (Y in L study)	N	3 months, annually up to 4 years	DSM III-R
Chicago, USA <sup>43</sup>	1987-90	X	72	49%	Multiple IS	N	Aphasia, Parkinson's disease, possible prior Alzheimer's disease	N*	N	2-3 months	DSM III
Tel Aviv, Israel <sup>44-46</sup>	1988-90	L	73	40%	IS	Y	Aphasia	Y	N	6 monthly to 5 years	DSM-III-R
Farsoe and Aalborg Hospitals, Denmark <sup>47</sup>	1991-92†	L	72	49%	IS, H	N	Other neurological or psychiatric disorder, age <60 or >80 years	Y	N	1, 6, 12 months	Mattis dementia rating scale
Bergamo, Italy <sup>48</sup>	1993-94	X	65	35%	IS	Y	Age <40 or ≥80 years, other neurological disorder, unusual cause of stroke, comorbidity, depression, sensory impairment	Y	N	3 months	NINDS-AIREN
Helsinki SAM Study, Finland <sup>8,49-52</sup>	1993-95	X	71	49%	IS	N	Age <55 or >85 years, unable to speak Finnish, non-resident in Helsinki, reduced conscious level, poor hearing, aphasia	N	Y (FU only)	3 months	DSM III and others
Florence, Italy <sup>53</sup>	1993-94	X	71	48%	IS, H‡	N	None given	Y	Y (FU only)	1 year	ICD-10-based interview to informant
Gothenburg, Sweden <sup>32</sup>	1993-94	X	80	65%	IS, H	N	Resident in nursing home, other cerebral lesion, coma, age <70 years	N	N	Mean 20 months	DSM III-R
Madrid, Spain <sup>54-58</sup>	1994-95	X, L	69	47%	IS, H	N	Primary brain lesion, aphasia, comorbidity	N	Y (IQCODE)	3, 6, 24 months	DSM III-R, DSM IV
Lille Stroke/Dementia Study, France <sup>2,59-66</sup>	1995-96	L	72	46%	IS, H	N	Non-white, no informant, age <40 years, not fluent in French, not from Lille, history of severe head trauma	N	Y (IQCODE)	6 months, annually to 3 years	ICD-10, DSM III-R
Rome, Italy <sup>67</sup>	1995-97	L	71	30%	IS, H	N	Severe aphasia or neglect, <5 years' education, SAH, age <40 years, concomitant neurological disorder, severe comorbidity	Y	N	Annually, to mean 45.3 months	ICD-10
Lisbon, Portugal <sup>1</sup>	1995-97	X	59	45%	IS, H	N	Previous dependency, dysphasia	Y	N	3 months	DSM IV
Taiwan <sup>30</sup>	1995-99	X	64	34%	IS	N	Other brain lesion, severe medical comorbidity	Y	N	3 months	ICD-10
Sydney Stroke Study, Australia <sup>31,68,69</sup>	1997-2000	X	72.2	39%	IS‡	N	Other neurological disorder, severe aphasia, too unwell to participate	Y	Y (IQCODE)	3-6 months	By consensus
Chongqing Stroke Study, China <sup>70,71</sup>	1999-2000	X	68	47%	IS	N	Concomitant neurological disorder, age <55 years, severe medical comorbidity or sensory impairment, reduced GCS, severe aphasia	N	Y (FU only) (IQCODE)	3 months	DSM IV
Cracow, Poland <sup>72-75</sup>	2000-01	X	66	55%	IS, H	N	Age ≤40 years, no reliable informant, other brain lesion	N	Y (IQCODE)	3 months	DSM IV and/or IQCODE
Hong Kong, China <sup>76,77</sup>	..	X	71	55%	IS, H	N	Non-Chinese ethnic group, non-Cantonese speaking, age <50 years	N	Y (FU only) (IQCODE)	3 months	DSM IV
Rotterdam-Rijnmond, Netherlands <sup>78,79</sup>	1993-96	X	70	40%	IS, H‡	N	Aphasia, sensory impairment, not fluent in Dutch, reduced consciousness	N	N	3-9 months	DSM III-R
Rotterdam-Rijnmond, Netherlands <sup>80</sup>	2000-02	X	70	38%	IS, H‡	N	Aphasia, sensory impairment, not fluent in Dutch, reduced consciousness	N	Y (FU only)	3-9 months	DSM IV
Maastricht CODAS, Netherlands <sup>33,81</sup>	2000-01†	L	68	45%	IS	Y	Age ≤40 years, severe aphasia, other neurological or psychiatric disorder, not fluent in Dutch, MMSE <15 at 1 month	Y	N¶	1, 6, 12, 24 months	DSM IV
SAFE II dementia substudy, France and Italy <sup>39</sup>	..	NA	79	59%	IS, H‡	N	NA	..	Y (IQCODE)	..	..

X=cross-sectional. L=longitudinal. N=no. Y=yes. IS=ischemic stroke. H=haemorrhagic stroke. GCS=Glasgow coma scale. DSM=diagnostic and statistical manual of mental disorders. FU=follow-up. IQCODE=informant questionnaire on cognitive decline in the elderly. ICD-10=international classification of disease-10. NINDS AIREN=National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences. SAM=Stroke, Ageing and Memory study. CODAS=Cognitive Disorders After Stroke. SAFE=Stroke in Atrial Fibrillation Ensemble II. NA=not applicable. MMSE=mini-mental state examination. ..=data not available. \*Patients with possible prior Alzheimer's disease were excluded, but those with prior cognitive impairment associated with cerebral infarction were not. †Patients were recruited from hospital and the outpatient clinic. ‡Includes subarachnoid haemorrhage (SAH). †Includes transient ischaemic attack. ¶Patients with MMSE <15 were excluded.

**Table 1: Hospital-based studies of pre-stroke and post-stroke dementia**

four population-based studies of post-stroke MMSE included first-ever stroke only,<sup>91-97</sup> whereas the one hospital-based study included first-ever or recurrent

stroke (table 3).<sup>90</sup> There were also differences in the stroke subtype studied: nine of 21 hospital-based studies and one of six population-based studies of

	Date of cohort collection	Study type	Mean age (years)	Female	Stroke type	First-ever stroke	Exclusion criteria	Pre-stroke dementia excluded	Pre-stroke dementia quantified	Follow-up	Post-stroke dementia diagnosis
Rochester, Minnesota, USA <sup>82</sup>	1960–84	L, RPS	..	50%	IS	Y	Previous stroke or dementia	Y	Y	Up to 25 years	Review of medical records
Framingham, USA <sup>83,84</sup>	1982–2001	L, V	79	61%	IS, H	Y	Previous stroke or dementia	Y	Y	10 years	DSM III, MMSE DSM IV
Rotterdam Scan Study, Netherlands <sup>85</sup>	1990–2005	L, V	69*	60%*	IS, H	Y	Age <55 years, previous stroke or dementia	Y	N	Mean 7.3 person-years	DSM III-R
Canadian Study of Health and Aging <sup>86</sup>	1991–97	L, V	72†	59%*	IS, H	Y	Age <65 years, previous stroke or dementia	Y	N	5 years	DSM III-R
Melbourne, Australia (NEMESIS) <sup>87–89</sup>	1998–99	X, L, PPS	69	41%	IS, H	Y	Aphasia, unable to speak English, inadequate vision or hearing	N	N	3 months; 1, 2 years	DSM-IV

L=longitudinal. X=cross-sectional. V=volunteer cohort. RPS=retrospective patient study. PPS=prospective patient study. H=haemorrhagic stroke. IS=ischaemic stroke. Y=yes. N=no. DSM=diagnostic and statistical manual of mental disorders. MMSE=mini-mental state examination. NEMESIS=North East Melbourne Stroke Incidence Study. ..=data not available. \*Mean of total volunteer sample. †Median of total volunteer sample.

**Table 2: Population-based studies of pre-stroke and post-stroke dementia**

	Date of cohort collection	Study setting and type	Mean age (years)	Female	Stroke type	First-ever stroke	Exclusion criteria	Pre-stroke dementia excluded	Pre-stroke dementia quantified	Follow-up	% MMSE <24
Nottingham, UK <sup>90</sup>	8 months, dates not given	HB, X	69	49%	IS, H	N	Aphasia, reduced conscious level, poor spoken English	N	N	6 months	22/189 (12%; 27% estimate with MMSE <24)*
Oxford (OCSF), UK <sup>91</sup>	1990	P, X, L	71	55%	IS, H	Y	None given	N	N	1, 6, 12 months	26/122 (21%) at 6 months, 24/115 (21%) at 1 year
South London Stroke registry, UK <sup>92,93</sup>	1995–99	P, X, L	69	47%	IS, H	Y	Aphasia	N	N	3 months, 1, 2, 3 years	248/645 (38%) at 3 months
Orebro, Sweden <sup>94–97</sup>	1999–2000	P, X	74	50%	IS, H	Y	Aphasia	N	Y	1 year	67/232 (29%) at 1 year

MMSE=mini-mental state examination. HB=hospital-based. P=population-based. L=longitudinal. X=cross-sectional. IS=ischaemic stroke. H=haemorrhagic stroke. Y=yes. N=no. OCSF=Oxford Community Stroke Project. \*MMSE <21 was primary outcome.

**Table 3: Studies of post-stroke MMSE**

post-stroke dementia included only ischaemic stroke (tables 1 and 2).

Most of the patients were screened for depression: 17 of 20 hospital-based studies and five of five population-based studies of post-stroke dementia, and two of four post-stroke MMSE studies. All cross-sectional studies of post-stroke dementia that had a short follow-up (3–6 months) used validated depression questionnaires (Hamilton depression scale,<sup>1,30,48,70,71,72–75</sup> Beck depression scale,<sup>3,49–52</sup> Center for Epidemiologic Studies depression scale,<sup>43</sup> global depression scale,<sup>31,68,69</sup> geriatric mental status),<sup>78,79</sup> or psychiatric interview.<sup>76,77</sup>

Few details were given on the ethnic origins of patients. The Lille stroke dementia study<sup>2,59–66</sup> included only white patients, and the Hong Kong study included only Chinese patients.<sup>76,77</sup> Of the remaining studies, only two hospital-based studies of post-stroke dementia<sup>6,7,34–43</sup> and one population-based study of post-stroke MMSE<sup>92,93</sup> described the patients' ethnic origin. If we assume that the patients in the cohorts based in China or Taiwan<sup>30,70,71</sup> were of Chinese ethnic origin and most of the patients whose ethnic origin was not described were white, there were 20% Chinese, 6% black, and 3% Hispanic patients in hospital-based studies but only white patients in

population-based studies of post-stroke dementia, and less than 1% non-white patients in studies of post-stroke MMSE.

Data on the prevalence of pre-stroke dementia were available for eight hospital-based studies of any (first-ever or recurrent) stroke<sup>50,53,55,56,59–61,64,66,70,72,73,77,80</sup> and three population-based cohorts of first-ever stroke (tables 1, 2, and 3).<sup>82,83,94–97</sup> Five of eight hospital-based studies ascertained rates of pre-stroke dementia at an interview with an informant through the informant questionnaire on cognitive decline in the elderly (IQCODE) questionnaire.<sup>50,55,56,59–61,64,66,70,77</sup> The population-based studies used a variety of methods, including interviews with the IQCODE,<sup>94–97</sup> retrospective review of medical records,<sup>82</sup> or, in the case of volunteer cohorts, premorbid assessment of cognition.<sup>83</sup> Three hospital-based studies<sup>55,56,59–61,64–66</sup> assessed all patients with stroke on admission to hospital and five assessed only those patients who survived to follow-up, some months after stroke (table 1).<sup>50,53,70,77,80</sup> All population-based studies assessed pre-stroke dementia before or shortly after stroke.

Overall, the estimates of the prevalence of pre-stroke dementia were highly heterogeneous (p=0.001), but

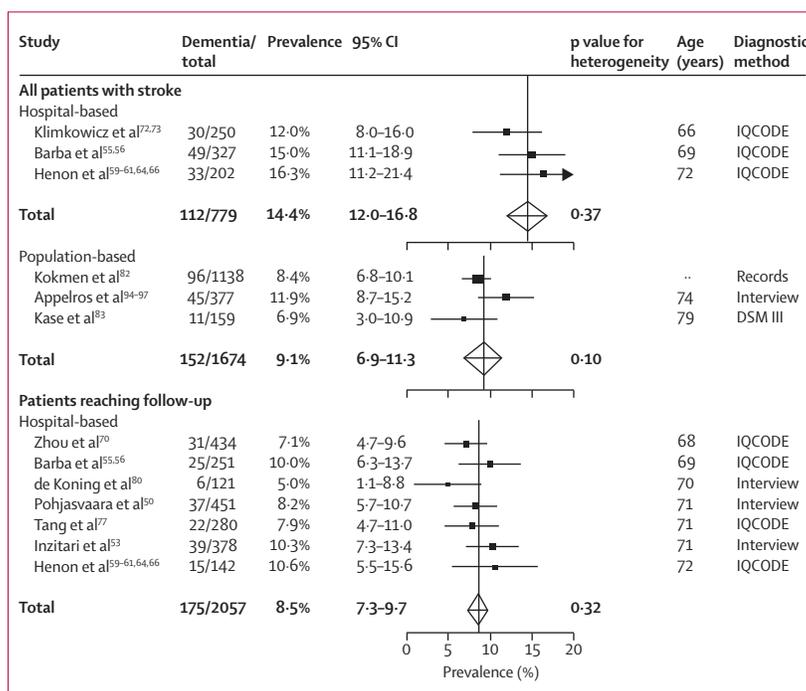
stratification by time to assessment in the hospital-based studies accounted for 56% of the variance, and stratification by study setting for those patients assessed at the time of stroke accounted for 64% of the variance between studies. The pooled prevalence of pre-stroke dementia recorded at the time of admission for all patients with stroke was 14.4% (95% CI 12.0–16.8%;  $p$  for heterogeneity=0.37) in hospital-based studies and 9.1% (6.9–11.3%;  $p$  for heterogeneity=0.10) in population-based studies (figure 2). Pre-stroke dementia rates in hospital-based studies were lower (8.5%, 7.3–9.7%;  $p$  for heterogeneity=0.32) when calculated in only those patients who reached follow-up, between 3 and 12 months after stroke (figure 2).

There was substantial variation in the rates of post-stroke dementia measured by standard criteria (eg, DSM-III or ICD-10) in eligible studies that reported rates in the first year after stroke (overall heterogeneity  $p < 0.0001$ ). However, heterogeneity was substantially reduced when studies were stratified by study setting, by the inclusion or exclusion of patients with pre-stroke dementia, and by whether only the first-ever, any (first-ever or recurrent), or only recurrent strokes were included (figure 3). These factors explained 93% of the overall heterogeneity in the prevalence of post-stroke dementia among all studies. Addition of the method of dementia diagnosis to the model accounted for only a further 2% of the variance between studies.

Rates of post-stroke dementia were highest in the hospital-based studies of recurrent stroke in which pre-stroke dementia was included (41.3%, 95% CI 29.6–53.1) and lowest in the population-based studies of first-ever stroke in which pre-stroke dementia was excluded (7.4%, 4.8–10.0). Rates of dementia were at least twice as high after recurrent stroke (exact rate is likely to depend on the total number of recurrences) than they were after first-ever stroke, and were higher in hospital-based studies than in population-based studies, even if the cohorts were similar in other respects.

The one hospital-based study that used the MMSE alone<sup>90</sup> reported scores of less than 24 in about 27% of patients (table 3) at 6 months after stroke (not excluding pre-stroke dementia). Although the four population-based studies<sup>83,84,91–93,97</sup> that reported post-stroke MMSE score included patients with similar characteristics and all except one<sup>83,84</sup> did not exclude patients with pre-stroke dementia, the reported rates of MMSE scores less than 24 ranged from 21%<sup>91</sup> to 38%<sup>92,93</sup> within 1 year after stroke (tables 2 and 3), with a pooled prevalence rate for those studies that did not exclude pre-stroke dementia of 34.2% (95% CI 25.6–42.7) with significant heterogeneity ( $p$  for heterogeneity  $< 0.0001$ ).

Figure 4 shows the pooled cumulative incidence of post-stroke dementia (excluding pre-stroke dementia). In hospital-based studies of first-ever or recurrent stroke, incidence of dementia increased linearly at a rate of 3.0% per year (95% CI 1.3–4.7%) above the initial post-stroke



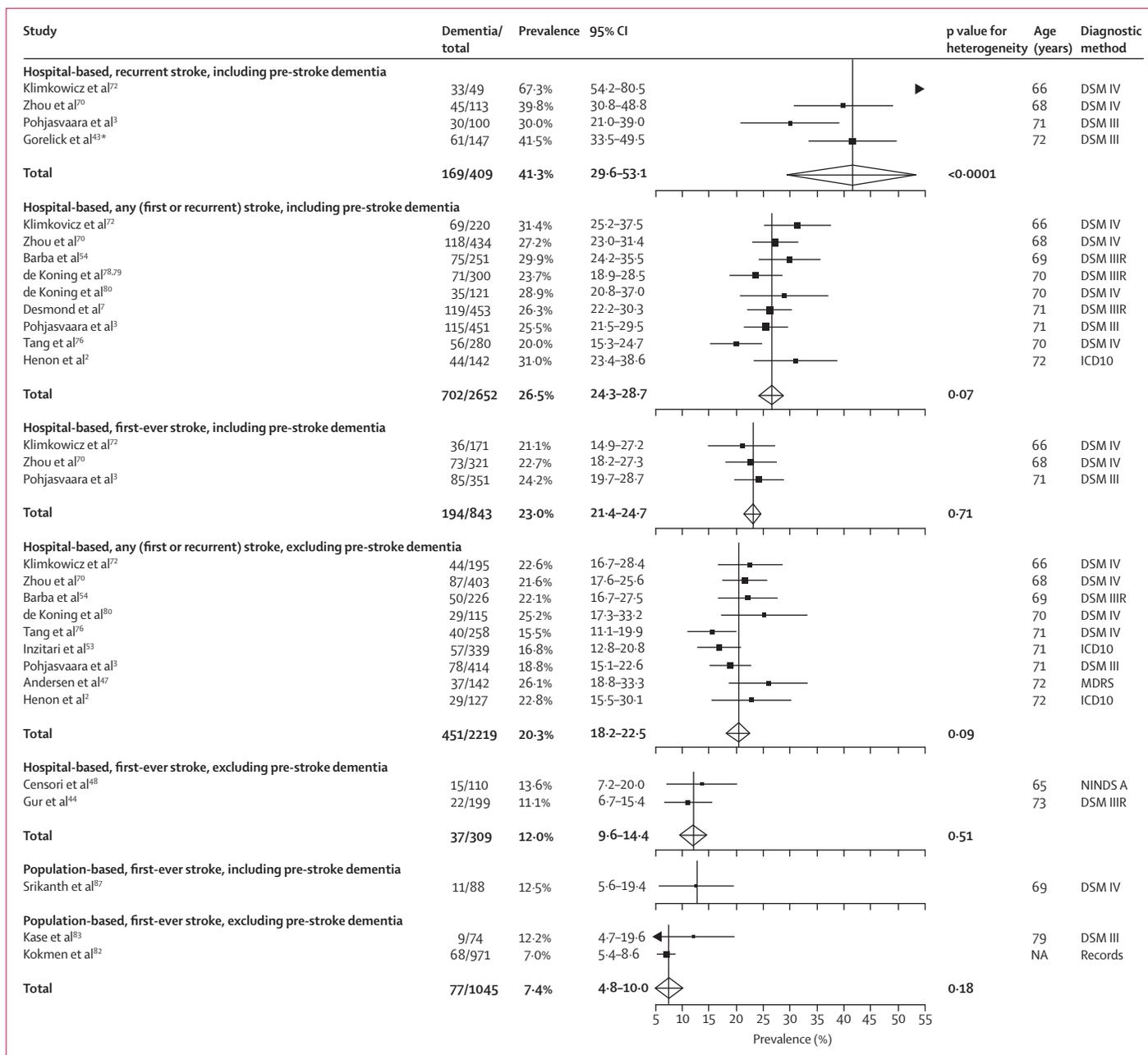
**Figure 2: Prevalence of pre-stroke dementia**

Pooled prevalence of pre-stroke dementia stratified by study setting (hospital-based vs population-based) and time of assessment (at the time of the stroke or at follow-up some months after the stroke) are shown, together with the mean age of the patients in each study and the method of dementia diagnosis. Bars indicate 95% CI. IQCODE=informant questionnaire on cognitive decline in the elderly. Records=retrospective review of medical records. Interview=interview of informant without IQCODE questionnaire. DSM=diagnostic and statistical manual of mental disorders. ..=not known.

incidence (which was about 20% at 3–6 months). The yearly incidence rate (1.7%, 1.4–2.0%) and the initial post-stroke incidence were lower in population-based studies of first-ever stroke, and the yearly incidence was lower still when patients with recurrent stroke were excluded.<sup>82,89</sup> If the rate of recurrent stroke rate is assumed to be 5% per year, and the dementia rate is assumed to be about 30–40% after recurrent stroke, a yearly incidence of 1.5–2.0% in hospital-based studies would be expected. The incidence rate in longitudinal studies of post-stroke dementia is thus only slightly greater than would be expected on the basis of recurrent stroke alone.

Results of studies that compare the incidence of new dementia in patients with stroke versus controls reported up to a 9-fold increased risk in patients with stroke in the first year after stroke,<sup>36,42,82</sup> and the excess incidence, although lower, continued in the following years, with hazard ratios of around four<sup>32,36,42</sup> in hospital-based studies and around two in population-based studies<sup>82,83–86</sup> after the first year post-stroke.

Data on clinical associations of pre-stroke dementia were available from six hospital-based studies<sup>29,50,55,59,73,77</sup> and one population-based study.<sup>94–96</sup> Pooled analysis showed that patients with pre-stroke dementia were significantly older (weighted mean difference=9.1, 8.4–9.8 years;  $p < 0.0001$ ) than those without pre-stroke



**Figure 3: Prevalence of post-stroke dementia**  
 Pooled prevalence (%) of post-stroke dementia up to 1 year after stroke stratified by study setting (hospital-based vs population-based), by inclusion or exclusion of pre-stroke dementia, and by first-ever versus any (first-ever or recurrent) versus recurrent stroke. Mean age of the patients in each study is shown on the right, together with method of dementia diagnosis. Bars indicate 95% CI. DSM=diagnostic and statistical manual of mental disorders. MDRS=Mattis dementia rating scale. NINDS A=NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences. Records=retrospective review of medical records. \*The study from Gorelick and colleagues<sup>48</sup> excluded patients with "possible prior Alzheimer disease" but not with prior cognitive impairment associated with stroke, so actual prevalence rate for this study might have been slightly higher than shown. NA=not available.

dementia (webappendix). Rates of pre-stroke dementia were also significantly higher in women (OR 2.3;  $p < 0.0001$ ), patients with little education (OR 2.1;  $p < 0.0001$ ), medial temporal lobe atrophy (OR 7.7;  $p < 0.0001$ ), a family history of dementia (OR 4.5;  $p < 0.001$ ), previous stroke (OR 2.2;  $p < 0.0001$ ) or transient ischaemic attack (OR 1.8;  $p = 0.02$ ),

leukoaraiosis (OR 2.8;  $p = 0.002$ ), multiple infarcts (OR 1.7;  $p = 0.01$ ), diabetes (OR 1.5;  $p = 0.02$ ), atrial fibrillation (OR 1.9;  $p = 0.001$ ), hypertension (OR 1.4;  $p = 0.04$ ), or overall cerebral atrophy (table 4, webappendix).

The predictors of post-stroke dementia are shown in table 5, with additional data in the webappendix.

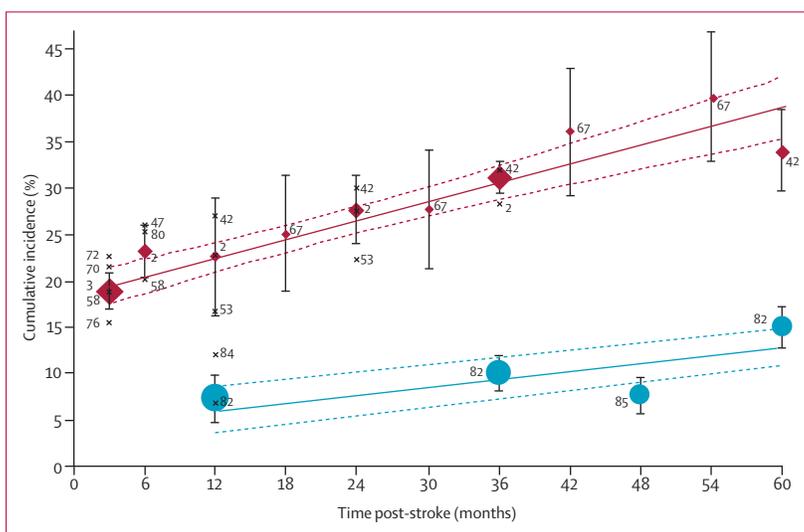
Significant predictors of post-stroke dementia included the demographic factors—older age (weighted mean difference=5.1 years, 95% CI 4.6–5.7;  $p<0.0001$ ), low educational attainment (OR 2.5;  $p<0.0001$ ), previous cognitive decline, and premorbid disability—and vascular risk factors such as diabetes (OR 1.4;  $p<0.0001$ ) and atrial fibrillation (2.0;  $p<0.0001$ ), but not hypertension, ischaemic heart disease, cholesterol, previous transient ischaemic attack, or previous smoking. However, most predictors were related to the stroke itself (haemorrhagic stroke [OR 1.4;  $p=0.02$ ], left hemisphere stroke [1.4;  $p=0.002$ ], dysphasia [3.6;  $p<0.0001$ ], stroke severity, and infarct volume) and the number of strokes separated in space and time (previous stroke [OR 1.9;  $p<0.0001$ ], multiple infarcts [2.5;  $p<0.0001$ ], and recurrent stroke [2.3;  $p<0.0001$ ]) and to the complications of stroke (incontinence [6.2;  $p<0.0001$ ], early seizures [5.4;  $p<0.0001$ ], acute confusion [2.8;  $p=0.001$ ], hypoxic ischaemic episodes [2.4;  $p=0.002$ ], and hypotension<sup>58</sup> (7.4;  $p=0.01$ )). Being white, compared with being black or of Hispanic ethnic origin, was protective (OR 0.6;  $p=0.0004$ ). Predictors of post-stroke dementia were similar in cross-sectional and longitudinal studies, and recurrent stroke was a powerful additional predictor in longitudinal studies: the ORs ranged from 1.3<sup>84</sup> to 13.3<sup>89</sup> and were greater with multiple recurrent events (table 5, webappendix).<sup>82</sup> Only two studies<sup>57,74</sup> looked at the genetic factors associated with post-stroke dementia. An apolipoprotein E genotype and angiotensin converting enzyme polymorphisms were not predictive<sup>57</sup> but there was a reported association with the alpha 1-antichymotrypsin polymorphism.<sup>74</sup>

Ten of 23 studies did not exclude patients with pre-stroke dementia from their analyses of risk factors for post-stroke dementia.<sup>32,43,49,54,70,76,78,80,87,89,92,93</sup> Four of these studies<sup>49,54,70,76</sup> stated that their analyses did not change when only patients with new post-stroke dementia were included. Restricting our pooled results to those studies that excluded patients with pre-stroke dementia gave similar results to those obtained when all studies were included, except that haemorrhagic stroke (OR 0.8;  $p=0.45$ ) and silent infarcts (OR 1.1;  $p=0.8$ ) were no longer significant and the heterogeneity was reduced (webappendix).

Multivariate analyses were done in 19 studies<sup>2,7,30,31,43,46–49,53,54,67,70,75,76,81,82,89,92</sup> to identify the independent predictors of post-stroke dementia (webappendix). The most commonly reported independent predictors were: older age (16 of 19 studies), low educational attainment (7 of 19 studies), previous stroke (6 of 19 studies), diabetes (5 of 19 studies), atrial fibrillation (5 of 19 studies), previous cognitive impairment (5 of 19 studies), aphasia (5 of 19 studies), and stroke severity (5 of 19 studies).

### Discussion

We have shown that more than 90% of the heterogeneity among the reported rates of post-stroke dementia can be explained by study setting (hospital based vs population



**Figure 4:** Pooled cumulative incidence of post-stroke dementia excluding pre-stroke dementia in hospital-based cohorts

Pooled cumulative incidence of post-stroke dementia excluding pre-stroke dementia in hospital-based cohorts of any stroke (first-ever or recurrent, red diamonds and upper lines) and population-based cohorts of first-ever stroke (blue circles and lower lines). Solid line indicates linear regression, broken lines indicate 95% CI. Symbol size is proportional to the inverse of the variance for each time point, error bars indicate 95% CI at each point. Individual studies are denoted by crosses with corresponding article reference numbers. Population data are shown only to month 60 but regression lines are calculated to 25 years post-stroke.

	Number of studies	Patients with factor/total		OR (95% CI)	p value*	I <sup>2</sup>	p value†
		With dementia	No dementia				
<b>Demographic factors</b>							
Female sex	7	172/249	809/1684	2.3 (1.7–3.1)	<0.0001	0	0.53
Low education	5	134/182	613/1135	2.1 (1.5–3.1)	<0.0001	0	0.73
FH	1	10/33	15/169	4.5 (1.8–11.1)	0.001	0	NA
<b>Vascular risk factors</b>							
Diabetes	6	60/204	321/1402	1.5 (1.1–2.1)	0.02	63	0.02
Atrial fibrillation	5	43/165	177/1237	1.9 (1.3–2.8)	0.001	0	0.40
IHD	3	26/104	105/711	1.8 (1.1–2.9)	0.03	0	0.91
Previous TIA	4	23/132	104/1068	1.8 (1.1–3.0)	0.02	49	0.10
Hypertension	6	142/204	862/1402	1.4 (1.0–2.0)	0.04	0	0.92
Smoking	6	37/204	464/1402	0.5 (0.3–0.7)	0.05	48	0.08
<b>Stroke factors</b>							
Previous stroke	6	75/204	288/1402	2.2 (1.6–3.0)	<0.0001	32	0.20
Multiple strokes	3	51/121	187/609	1.7 (1.1–2.5)	0.01	0	0.76
Silent strokes	2	21/72	98/334	1.0 (0.4–2.4)	0.99	57	0.13
<b>Brain imaging factors</b>							
Leukoaraiosis	3	54/100	187/672	2.8 (1.4–5.6)	0.002	53	0.12
MTLA	3	60/77	183/594	7.7 (4.3–13.8)	<0.0001	0	0.71

OR=odds ratio. FH=family history of dementia. IHD=ischaemic heart disease. TIA=transient ischaemic attack. MTLA=medial temporal lobe atrophy. NA=not applicable. \*Significance of pooled OR result. †p value for heterogeneity.

**Table 4:** Pooled odds ratios for factors associated with pre-stroke dementia

based), the inclusion or exclusion of patients with pre-stroke dementia, and whether first ever, any (first ever or recurrent), or recurrent strokes were included. The prevalence of post-stroke dementia in the first year

	Number of studies	Patients with factor/total		OR (95% CI)	p value*	I <sup>2</sup>	p value†
		With dementia	No dementia				
<b>Demographic factors</b>							
Female sex	24	669/1350	1885/4357	1.3 (1.1-1.6)	0.006	49	0.004
White	3	207/428	422/817	0.6 (0.4-0.8)	0.0004	1	0.36
Low education	11	381/685	823/2102	2.5 (1.8-3.4)	<0.0001	56	0.01
<b>Vascular risk factors</b>							
Diabetes	19	325/1183	823/3626	1.4 (1.2-1.7)	<0.0001	10	0.33
Atrial fibrillation	13	201/1018	306/2629	2.0 (1.4-2.8)	<0.0001	55	0.009
IHD	14	196/1034	487/2705	1.0 (0.8-1.3)	0.97	46	0.03
Previous TIA	11	140/929	355/2482	1.0 (0.8-1.3)	0.84	27	0.17
Hypertension	19	767/1184	2290/3616	1.1 (0.9-1.3)	0.22	0	0.89
Smoking	16	438/1111	1173/3052	1.0 (0.8-1.2)	0.36	54	0.006
Moderate alcohol	9	333/816	867/2006	0.8 (0.6-1.0)	0.1	45	0.07
<b>Stroke factors</b>							
Haemorrhagic	9	88/626	202/626	1.4 (1.1-1.9)	0.02	2	0.2
Dysphasia	7	160/658	173/1565	3.6 (2.1-6.1)	<0.0001	71	0.002
Left hemisphere	17	506/1079	1385/3520	1.4 (1.1-1.7)	0.002	48	0.02
Brainstem	9	129/825	449/2217	0.7 (0.4-1.2)	0.16	75	<0.0001
Lacunar	10	217/778	722/2117	0.8 (0.7-1.0)	0.09	0	0.56
Previous stroke	10	184/681	345/2085	1.9 (1.5-2.3)	<0.0001	0	0.99
Multiple strokes	9	189/727	458/2003	2.5 (1.9-3.1)	<0.0001	16	0.3
Recurrent stroke	4	45/190	93/757	2.3 (1.5-3.5)	<0.0001	14	0.2
Silent strokes	5	64/161	162/614	1.8 (0.9-3.5)	0.08	63	0.03
<b>Stroke complications</b>							
HI episodes	2	11/36	16/133	2.4 (1.4-4.2)	0.002	0	0.41
Incontinence	7	271/630	203/1661	6.4 (4.5-9.2)	<0.0001	52	0.05
Acute confusion	2	20/57	45/282	2.8 (1.5-5.3)	0.001	0	0.36
Early seizures	1	17/36	19/133	5.4 (2.4-12.1)	<0.0001	NA	NA
Abnormal EEG	1	45/71	43/109	2.7 (1.4-4.9)	0.002	NA	NA
<b>Brain imaging factors</b>							
Leukoaraiosis	7	132/276	274/1024	2.5 (1.9-3.4)	<0.0001	37	0.14
Atrophy	5	156/240	360/758	2.6 (1.1-6.3)	0.03	80	0.0004
MTLA	2	66/141	93/340	2.7 (1.8-4.2)	<0.0001	0	0.96

Previous stroke is history of a stroke before the stroke that occurred at time of study entry. Recurrent stroke is a stroke occurring on follow-up in longitudinal studies. OR=odds ratio. IHD=ischaemic heart disease. TIA=transient ischaemic attack. HI episodes=hypoxic ischaemic episodes. MTLA=medial temporal lobe atrophy. NA=not applicable.  
\*Significance of pooled OR result. †=p value for heterogeneity.

Table 5: Pooled odds ratios for factors associated with post-stroke dementia

after stroke ranged from around 7% in population-based studies in which pre-stroke dementia was excluded to around 40% in studies of hospital-based patients with recurrent stroke in which pre-stroke dementia was not excluded. Rates were about three times as high overall after recurrent stroke compared with first-ever stroke and seemed to rise after each event.

The pooled cumulative incidence of post-stroke dementia showed a steep rise initially—as seen in most<sup>2,36,42,46,54,58,67,82,83,84</sup> but not all<sup>87</sup> individual studies—followed by a much slower linear increase. We were not able to look at the effect of recurrent stroke in the pooled longitudinal data, but the available data suggest a rise in incidence after each recurrent stroke,<sup>2,42,82,89</sup> which is in

keeping with the stepwise progression of cognitive impairment that is classically associated with vascular dementia. The cumulative incidence of dementia seen in the chronic phase after stroke does not seem to be much greater than would be expected on the basis of recurrent stroke alone and would probably, therefore, be much lower without recurrent stroke.<sup>82,89</sup>

The rate of post-stroke MMSE scores less than 24, which is usually taken to be indicative of dementia, was much higher than the rate of dementia measured by standard criteria (nearly three times the rate in population-based studies in which pre-stroke dementia was not excluded) within 1 year after stroke, which is consistent with the findings of authors who have made direct comparisons.<sup>40,83,98</sup> The MMSE has a high false-positive rate for identifying dementia in general admissions to hospital<sup>99</sup> and is likely to be particularly problematic in patients with stroke who have severe cognitive deficits, including aphasia and neglect. Some MMSE-based studies that we included in our review excluded patients who were aphasic<sup>90,92-97</sup> but others did not,<sup>83,91</sup> and we know of no study that has described how the MMSE was scored in patients who were unable to write or who had visual impairment or neglect.

For post-stroke dementia, much of the heterogeneity in reported prevalence rates of pre-stroke dementia was explained by differences in methods. Again, heterogeneity was greatly reduced when the studies were stratified by study setting and the timing of assessment. The pooled rate of pre-stroke dementia was about 14% in studies of all patients in the acute hospital setting but only about 9% in population-based studies, despite the fact that assessment of pre-stroke dementia was retrospective in all hospital-based studies and might, therefore, have been underestimated. The higher rate of pre-stroke dementia reported in hospital-based studies might be explained by the inclusion of patients with previous stroke, whereas the population-based studies were restricted to first-ever stroke. Also, pre-stroke dementia is associated with strokes that are more severe<sup>94</sup> and a reduction in the ability to cope at home (and hence a greater likelihood of being admitted to hospital). In the hospital-based studies, the reported prevalence of pre-stroke dementia was higher on admission compared with prevalence at follow-up several months later, probably because pre-stroke dementia is associated with low rates of post-stroke survival.<sup>56,61,95,96</sup>

Our findings on the rates of pre-stroke and post-stroke dementia will be useful for properly informing patients and carers, planning clinical services, designing clinical trials, and ascertaining the overall burden of stroke; they also provide some potential insights into the probable causes and pathophysiology of pre-stroke and post-stroke dementia. First, the risk of dementia was closely related to the occurrence of stroke and to the number of strokes, rather than to background vascular risk factors. Although the prevalence of premorbid vascular risk factors was

high, the rate of pre-stroke dementia was only 9% in population-based studies of first-ever symptomatic stroke (albeit about twice the prevalence in the age-specific general population). Second, the prevalence of new-onset dementia shortly after stroke (ie, excluding pre-stroke dementia) was about 10% after first-ever stroke and about 30% after recurrent stroke. In other words, the occurrence of a stroke had a substantial and immediate effect on the absolute rate of dementia that was over and above the risk from previous life-time exposure to vascular risk factors. Although exposure to vascular risk factors might possibly increase susceptibility to the effects of stroke on cognitive function, the occurrence of stroke itself seems to be the trigger for rapid cognitive decline. Third, as is seen in figure 4, the rate of development of dementia in the years after stroke is slow (1.7–3.0% per year) and is probably only a little higher than might be expected on the basis of the effects of recurrent stroke alone.

The importance of stroke itself in the causes of post-stroke dementia was also highlighted by the results of our review of risk factors. Previous symptomatic stroke, previous asymptomatic stroke seen on imaging, recurrent stroke, several stroke lesions, aphasia, severity of stroke, haemorrhagic stroke, volume of the infarct, and location of stroke (increased with left hemisphere, decreased with brainstem) were all significantly associated with post-stroke dementia. The complications of stroke were also predictive, although the extent to which these are related to stroke severity rather than being independent factors is unclear. Several other significant predictors of post-stroke dementia were not related directly to the stroke itself, including increasing age, female sex, low education, race (increased in black people, people with Hispanic ethnic origin, and people from southeast Asia, and lower in white people and people from China), diabetes, atrial fibrillation, leukoaraiosis, and global and medial temporal lobe atrophy; most of these predictors are also associated with Alzheimer's dementia.<sup>100</sup>

In all likelihood, not all of the significant factors identified in our pooled analysis are independent predictors of post-stroke dementia. For example, female sex will be confounded by age and was not generally a significant independent predictor of post-stroke dementia in those studies in which multivariate adjustment was done for age and other risk factors (webappendix). The non-stroke-related risk factors that remained significantly predictive of post-stroke dementia in multivariate analyses were age, low educational attainment, diabetes, atrial fibrillation, and leukoaraiosis. However, although these risk factors are statistically independent, they could still be confounded by stroke-related factors: atrial fibrillation and diabetes are associated with symptomatic stroke, asymptomatic stroke seen on imaging, recurrent stroke, several stroke lesions, and severity of stroke; and leukoaraiosis is associated with stroke severity and stroke recurrence.<sup>62</sup>

In summary, most of the predictors of post-stroke dementia are either directly related to stroke or are potentially related to recurrent stroke or the presence of several lesions. The observation that acute stroke complications are associated with post-stroke dementia, although not proven to be causal, highlights the potential importance of avoiding secondary insults after stroke; such secondary insults are a factor in poor outcome after head injury. Improved cognitive outcome might, thus, be one mechanism by which death and dependency is reduced on acute stroke units compared with general ward care, through reductions in hypoxia, hypotension, and other physiological disturbances. Perhaps unsurprisingly, the factors associated with pre-stroke dementia were broadly similar to those associated with post-stroke dementia; all but one study on the predictors of pre-stroke dementia included recurrent and first-ever stroke. However, medial temporal lobe atrophy, female sex, and a family history of dementia were much stronger predictors of pre-stroke dementia than they were of post-stroke dementia, suggesting a more important role for primary degenerative pathology in pre-stroke dementia. Individual risk factors for pre-stroke and post-stroke dementia are discussed in more detail in the webappendix.

Our study had several potential shortcomings. First, there are only a few population-based studies of pre-stroke and post-stroke dementia, and the population data are dominated by the large Kokmen study,<sup>82</sup> a retrospective study in which dementia was diagnosed by review of medical records and might therefore have been under-diagnosed. Second, differences in methods in longitudinal studies of the incidence of dementia meant that we had to correct the data from individual studies for factors such as the inclusion of pre-stroke dementia or the exclusion of all patients who had dementia at 3 or 6 months after stroke (webappendix). However, this is unlikely to have introduced any major errors because all the studies showed good agreement in cumulative incidence of post-stroke dementia (figure 4). Third, the calculation of pooled odds ratios for a given risk factor did not include data from all studies in our review because all possible risk factors were not looked at in every study and data were not always given in a form that allowed pooled analysis. Furthermore, some bias might have been introduced by the fact that some studies might not have given data on factors they did not find to be predictive. Fourth, although depression can exacerbate cognitive impairment, we do not think that this was a main confounder in our analyses, owing to the high rate of depression screening across individual studies, the fact that rates of dementia were similar after stratification by study characteristics, and that the cross-sectional data were in agreement with the longitudinal data. Finally, our study does not provide information on the specific mechanisms of post-stroke dementia and, in

particular, on the relative contributions of and interactions between degenerative and vascular processes. Although some authors tried to classify the subtype of post-stroke dementia (ie, Alzheimer vs vascular), such classification is problematic and the data available do not provide reliable information.

In conclusion, much of the heterogeneity in the rates of pre-stroke and post-stroke dementia can be explained by differences in study methodology and case mix. About one in ten patients have dementia before their first stroke, one in ten develop new dementia after first-ever stroke, and more than one in three have dementia after a recurrent stroke. The importance of the stroke itself in the causes of post-stroke dementia was confirmed by the strong associations between post-stroke dementia and factors that are indicative of a greater stroke lesion burden and the complications of stroke, whereas the predictors of pre-stroke dementia were more similar to those for Alzheimer's dementia. Optimum acute stroke care and secondary prevention of stroke are likely to be effective for reducing the burden of post-stroke dementia. Further studies are needed to identify independent predictive factors, to develop a risk factor score for use in clinical practice and trials, and to ascertain the relative contributions of and interactions between degenerative and vascular processes in the causes of post-stroke dementia.

#### Contributors

STP did the literature searches, reviewed all titles and abstracts, selected eligible articles, extracted data from these articles, planned and did analyses, and co-wrote the manuscript. PMR reviewed the articles for eligibility, assisted with data extraction, planned the analyses, and co-wrote the manuscript.

#### Conflicts of interest

We have no conflicts of interest.

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