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Review Article

Systematic Review and Meta-Analysis of Prevalence in Post-Stroke Neurocognitive Disorders in Hospital-Based Studies

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Keywords
Dementia · Mild cognitive impairment · Infarct · Hemorrhage · Stroke · Diagnosis

Abstract
Background/Aims: Post-stroke neurocognitive disorders (post-stroke NCD) have been reported with a very variable prevalence. ***Methods:*** Based on a systematic literature search, hospital-based studies published between January 1990 and September 2015 were selected when they reported the prevalence of total, mild, and major post-stroke NCD diagnosed by using specified criteria. Factors affecting prevalence were assessed using meta-regression analysis. ***Results:*** Among the 7,440 references evaluated, 16 hospital-based studies were selected, corresponding to a total of 3,087 patients. The overall prevalence of total post-stroke NCD was 53.4% (95% CI: 46.9–59.8): 36.4% for mild post-stroke NCD (95% CI: 29–43.8) and 16.5% (95% CI: 12.1–20.8) for major post-stroke NCD. The overall prevalence was mainly influenced by the threshold score used for categorization (p = 0.0001) and, in the subgroup of studies using a conservative threshold (i.e., ≤7th percentile), by the recurrent stroke rate (p = 0.0005). The prevalence of major post-stroke NCD was mainly influenced by age (p = 0.003). ***Conclusion:*** More than half of stroke survivors experience post-stroke NCD, corresponding to mild post-stroke NCD in two-thirds of cases and major post-stroke NCD in one-third of cases. Harmonization of stroke assessment and cognitive score thresholds is urgently needed to allow more accurate estimation of post-stroke NCD prevalence, especially mild post-stroke NCD.
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Introduction

The prevalence of post-stroke neurocognitive disorders (post-stroke NCD) has been documented in a large number of studies, mostly focusing on major post-stroke NCD (i.e., post-stroke dementia). A systematic review and a meta-analysis [1, 2] have shown that the prevalence of major post-stroke NCD ranges from 7 to 67.3%, depending on the study setting (hospital- or population-based studies), stroke type (ischemic or hemorrhagic), the prevalence of pre-stroke dementia and recurrent stroke, and the post-stroke interval [2]. In contrast, the prevalence of mild post-stroke NCD and total post-stroke NCD (i.e., mild + major post-stroke NCD) has been less extensively studied and has not been systematically reviewed. However, the presence of post-stroke NCD, regardless of its severity, constitutes an independent risk factor for dependence and institutionalization [3, 4], highlighting the need to determine the prevalence of post-stroke NCD regardless of its severity. Factors associated with the prevalence of NCD also need to be identified. We hypothesized that stroke characteristics and the diagnostic criteria of cognitive impairment both influence the prevalence of post-stroke cognitive impairment. We deliberately focused on hospital-based cohorts because they correspond to populations entering a management circuit designed to reduce disability. In addition, diagnosis on mild NCD requires a comprehensive neuropsychological assessment, which does not form a part of usual standard of care for stroke patients.

The objective of this study was to assess the prevalence of total, mild, and major post-stroke NCD by a meta-analysis based on a systematic review of hospital-based studies and to determine factors affecting this prevalence.

Methods

Eligibility Criteria

A systematic review was conducted according to the Meta-Analysis of Observational Studies in Epidemiology criteria [5].Studies published between January 1990 and September 2015 were eligible when they (1) included ≥50 consecutive patients (2) initially hospitalized for ischemic or hemorrhagic stroke, (3) assessed ≥1 month post-stroke (4) using a neuropsychological battery, (5) reported the prevalence of total, mild, and major post-stroke NCD determined (6) according to specified criteria of mild and major NCD. Studies including patients with transient ischemic attack were eligible when they also included cerebral infarct or hemorrhage and when the prevalence of each condition was reported. Studies in which evaluation was limited to screening tests were not eligible. When data from the same cohort were reported in several papers, the study reporting the largest sample fitting our eligibility criteria was selected. Corresponding authors were contacted when necessary.

Procedure

The literature search was conducted using MEDLINE, Web of Science, and Embase to retrieve papers that met the eligibility criteria. Searches were based on combinations of the following terms in the title or abstract: "*cognit*, neuropsychol*, dement*, MCI*" with "*stroke, cerebral infarct, cerebral hemorrhag*, cerebral ischem**". The reference lists of selected papers as well as subsequent citations of these papers were also examined. All titles and abstracts were reviewed by two investigators (M.B. and O.G.) and the full texts of eligible papers were examined.

Data Extraction

The following data were extracted from published papers, protocols, appendices, and post hoc analyses and, when necessary, from direct contact with the authors: author, year, country, name of cohort, mean age, sex ratio (percentage of men), proportion of patients with low education level in the study (defined as primary education or <9 years of education or illiteracy), stroke subtypes (transient ischemic attack, infarct, hemorrhage) and their frequencies, the inclusion of patients with recurrent stroke and the recurrent stroke rate, the assessment of pre-stroke cognitive impairment (previously diagnosed dementia or systematic

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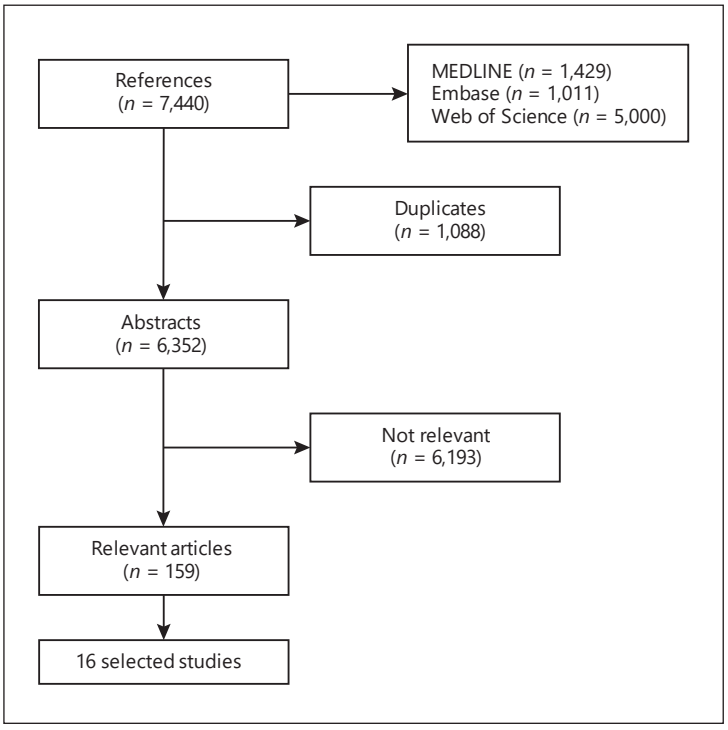

Fig. 1. Literature searches and results.

assessment of pre-stroke cognitive status) and its frequency, the mean interval between stroke and the cognitive assessment, diagnostic criteria of mild and major NCD, the threshold (defined as ≤7th percentile, i.e., 1.5 SD, or not) used to categorize cognitive scores as normal versus impaired, the method used to define cutoff scores (published scores or scores defined on a control population and its size), the use of methods to control for false-positive rate (adjustment of the number of impaired scores, computation of domain scores or global score), number of patients effectively evaluated using the neuropsychological battery, and number of patients classified in the mild and major post-stroke NCD subgroups.

Statistical Analysis

Prevalence of NCD and its variance were computed for each study. Due to heterogeneity between studies, meta-analysis was performed with a random effect model using restricted maximum likelihood (REML) estimates [6]. Variance within and between studies was therefore used to compute the variance of the final pooled prevalence. Heterogeneity was assessed by the inconsistency index I^2 and the Q test [7]. Statistical heterogeneity was declared for a p value ≤0.05 with the Q test. Forest plots were used to visualize the prevalence in each study and the combined estimated prevalence with their 95% confidence intervals (95% CI). Publication bias was assessed graphically using funnel plots and tested using Egger's method [8]. Study characteristics influencing the resulting prevalence were evaluated by REML random effect meta-regression [9]. Pooled odds ratios were calculated for patients with a random effects analysis when there was evidence of heterogeneity ($p \leq 0.1$). The effect of each factor on the reduction of variability between studies was calculated. A p value ≤0.05 was considered for statistical significance. All statistical analyses were performed with R software version 3.1.0 and SAS version 7.12.

Results

From the 7,440 references extracted by the literature search (Fig. 1), 159 articles were analyzed and 16 studies were selected, corresponding to a total of 3,087 patients. Ineligible studies on post-stroke NCD included cross-sectional studies resulting in variable post-stroke intervals [10], non-consecutive patients [11–16], studies which failed to report the rates of

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Table 1. Characteristics of the 16 studies selected

Cohorts [Ref.]	Patients, *n*	Mean age, years	Male, %	Exclusion of recurrent stroke	Stroke recurrence, %	Exclusion of pre-stroke dementia	Pre-stroke dementia, %	Stroke type	Infarct, %	Post-stroke interval, months	Criteria of mild NCD	Criteria of major NCD	Threshold ≤7th percentile
New York, USA [51]	251	72	43	No	6.4	No	9.6	IS	100	3	Other	DSM-III-R	Yes
Maastricht, The Netherlands [53]	154	68.4	55	Yes	0.0	Yes	NA	IS, ICH	89.4	6	Petersen	DSM-IV, NINDS AIREN	No
Bergamo, Italy [54]	110	65.1	65	Yes	0.0	Yes	NA	IS	100	3.5	Other	NINDSAIREN	NA
Finland [55]	451	71.2	51	No	22.2	No	12.2	IS	100	3	Other	DSM-IV	No
Lisbon, Portugal [56]	220	59	55	No	NA	Yes	NA	IS, ICH	75.9	3	Other	NINDSAIREN	Yes
Madrid, Spain [57]	209	69.1	53	No	NA	No	12.6	IS	88.4	3	Other	DSM-IV	Yes
Sydney, Australia [58]	160	72.1	61	Yes	0.0	Yes	0	IS, TIA	83.8	4.5	Petersen	VASCOG	No
Hong Kong, China [31]	75	71	52	No	22.7	No	NA	IS	100	3	Other	DSM-IV	NA
Mexico, Mexico [59]	107	56	62	Yes	0.0	Yes	NA	IS, ICH, CVT	84.0	3	CHSA	NINDSAIREN/ DSM4	Yes
Singapore [60]	318	59.8	70	No	19.2	Yes	NA	IS, TIA	78.6	4.5	Petersen	DSM-IV	Yes
South Korea [41]	353	63.9	61	No	18.4	No	0.1	IS	100	3	Other	DSM-IV	No
Norway [61]	184	72	51	Yes	0.0	Yes	NA	IS, ICH, TIA	76.4	12	Petersen	ICD10	NA
Sweden [62]	149	81	35	No	13.4	Yes	NA	IS, ICH	94.5	18	CHSA	DSM-III-R	No
Chile [63]	101	72	58	No	20.0	Yes	26.7	IS, ICH	85.0	12	Other	Other	NA
India [64]	102	59.4	74	Yes	26.5	Yes	NA	IS, ICH	88.2	6	CSHA	NINDS-AIREN	NA
Nigeria [65]	143	60.4	57	No	12.6	Yes	11.2	IS, ICH	79.5	3	VASCOG	DSM-IV	Yes

NCD, neurocognitive disorders, Lac, lacunar stroke, CVT, cerebral venous thrombosis, IS, ischemic stroke, ICH, intracerebral hemorrhage, TIA, transient ischemic attack, NA, not available.

both mild and major post-stroke NCD, and studies that did not use a neuropsychological battery [12–14, 17–44].

Selected studies (Table 1) were characterized by heterogeneity of general characteristics, with age ranging from 56 to 81 years (weighted mean: 67 years), a slight male predominance (weighted frequency: 55.8%; range: 34.9–73.5), low education level in 34.4% (8.8–70.4) (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000492920) with a mean schooling of 6.96 (4.7–10.1) years. Regarding stroke type, 6 studies only included patients with infarct, while the remaining 10 studies included mixed stroke types, in which infarcts represented 89.9% (75.9–100) and stroke due to either cerebral infarct or hemorrhage represented 96% (78.6–100) of the pooled population. Recurrent strokes were excluded in 6 studies and represented 12.95% (0–26.5) of the pooled population. Pre-stroke cognitive impairment was excluded in 11 studies (8 on clinical grounds and 3 based on a formal assessment) and was observed with a weighted mean frequency of 7.54% (0–26.7). Cognitive assessment was performed after a mean post-stroke interval of 5 months (3–18). The mean Mini-Mental State Examination score (computed using mean scores available in 10 studies) was 24.9 (20.4–27.8). The most commonly used diagnostic criteria were DSM-IV criteria (n = 8) for dementia and the cognitive impairment, no-dementia (n = 11) subgroup of the Canadian Study of Health and Aging classification [4] for mild cognitive impairment. Cutoff scores for test interpretation were based on published norms in 8 studies and were computed using control groups in 4 of these studies with a mean sample size of

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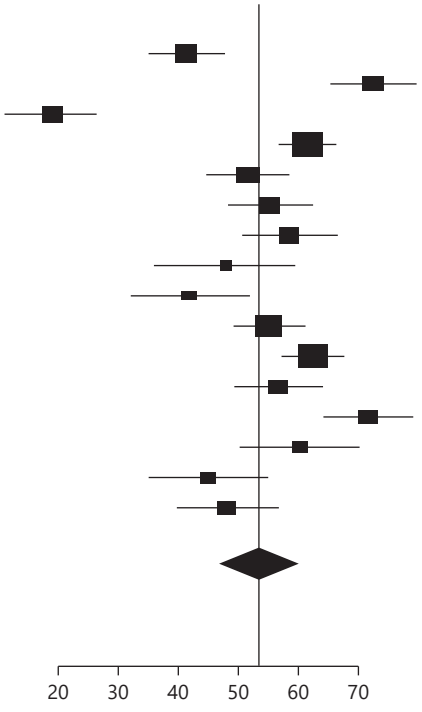
Studies	Total NCD/Total	Prevalence, %	95% CI
New York, USA	104/251	41.4	35.3–47.5
Maastricht CODAS, The Netherlands	112/154	72.7	66.7–79.8
Bergamo, Italy	21/110	19.1	11.7–26.4
Helsinki SAM Cohort, Finland	278/451	61.6	57.2–66.1
Lisbon, Portugal	114/220	51.8	45.2–58.4
Madrid, Spain	116/209	55.5	48.8–62.2
Sydney Stroke Study, Australia	94/160	58.5	51.1–66.4
Hong Kong, China	36/75	48.0	36.7–59.3
Mexico, Mexico	45/107	42.1	32.7–51.4
Singapore	176/318	55.3	49.9–60.8
Seoul MCenter, South Korea	221/353	62.6	57.6–67.7
Asker Bærum hospital, Norway	105/184	57.1	49.9–64.2
Göteborg Stroke Study, Sweden	107/149	71.8	50.9–69.9
Chile	61/101	60.4	35.4–54.8
Lucknow, India	46/102	45.1	40.1–56.4
Nigeria	69/143	48.3	40.1–56.4
Summary		**53.4**	**46.9–59.8**

Q (df = 15) = 192
$p < 0.0001$
$I^2 = 93\%$



Studies	Mild NCD/Total	Prevalence, %	95% CI
New York, USA	38/251	15.14	10.7–19.6
Maastricht CODAS, The Netherlands	99/154	64.29	56.7–71.9
Bergamo, Italy	6/110	5.45	1.2–9.7
Helsinki SAM Cohort, Finland	195/451	43.24	38.7–47.8
Lisbon, Portugal	101/220	45.91	39.3–52.5
Madrid, Spain	41/209	19.62	14.2–25.0
Sydney Stroke Study, Australia	58/160	36.25	28.8–43.7
Hong Kong, China	26/75	34.67	23.9–45.4
Mexico, Mexico	32/107	29.91	21.2–38.6
Singapore	167/318	52.52	47.0–58.0
Seoul MCenter, South Korea	176/353	49.86	44.6–55.1
Asker Bærum Hospital, Norway	69/184	37.50	30.5–44.5
Göteborg Stroke Study, Sweden	66/149	44.30	36.3V52.3
Chile	39/101	38.61	29.1–48.1
Lucknow, India	27/102	26.47	17.9–35.0
Nigeria	57/143	39.86	31.8–47.9
Summary		**36.4**	**29–43.8**

Q (df = 15) = 453
$p < 0.0001$
$I^2 = 95\%$

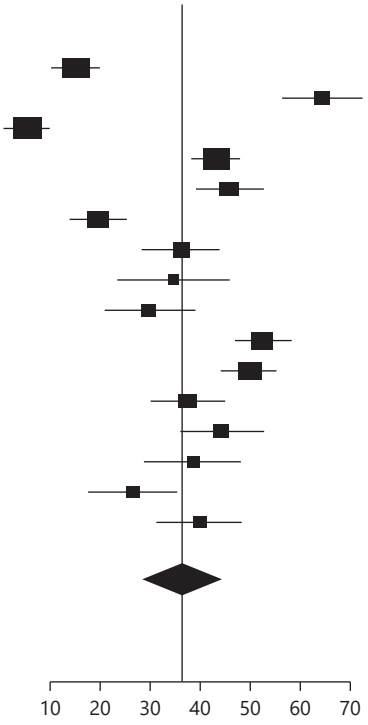


Fig. 2. Prevalence of total (top), mild (middle), and major (bottom) post-stroke neurocognitive disorders (NCD).

(Figure continued on next page.)

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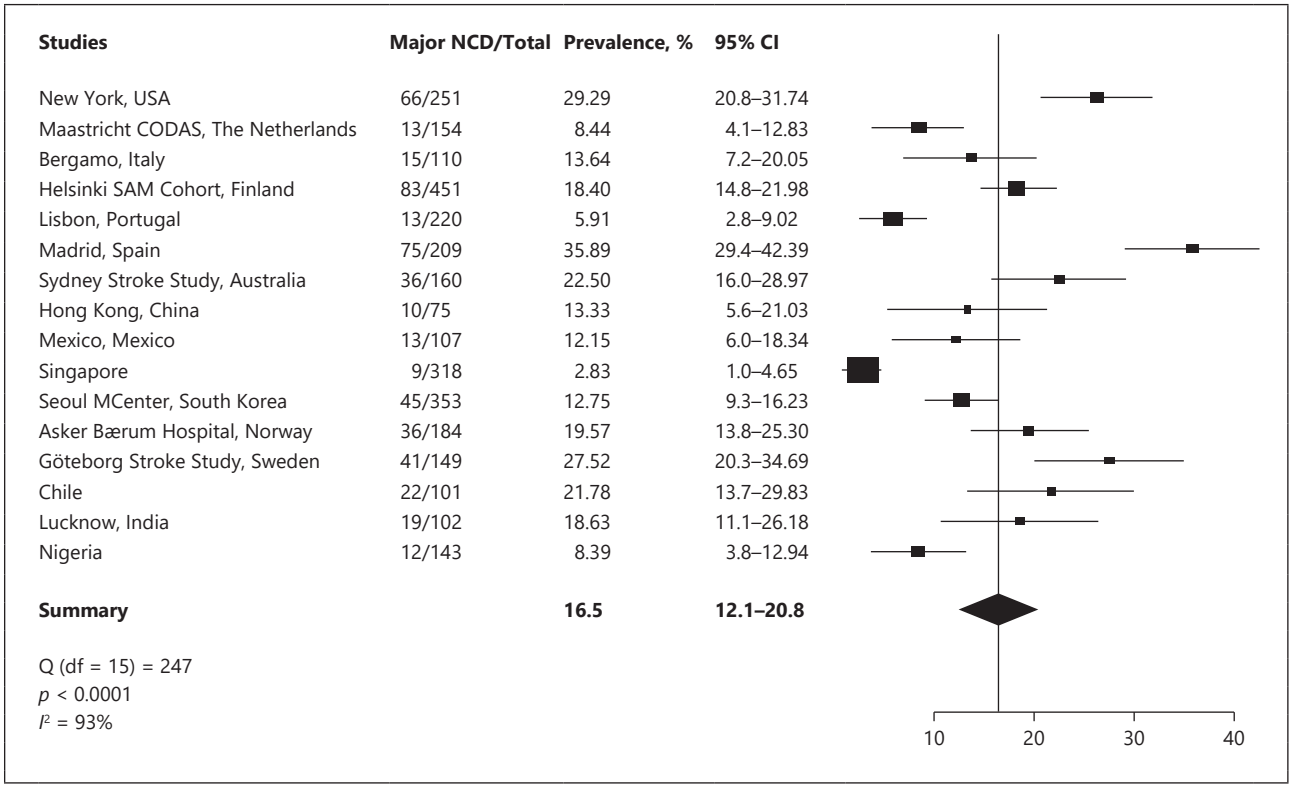

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Table 2. Factors influencing the frequency of post-stroke neurocognitive disorders (NCD)

	Age	Prevalence of pre-stroke dementia	Parenchymal lesions	Stroke recurrence	Low education level	Post-stroke interval	Threshold score ≤7th percentile
Total NCD							
Coefficient	0.84±0.47	0.21±0.51	−0.21±0.41	0.25±0.39	0.05±0.17	1.4±0.7	−15.9.0±3.7
p	0.0748	0.4	0.6	0.5	0.8	0.053	0.0001*
Reduction of variability	−13.4%	+23.1%	+5.5%	+21.8%	−37.8%	−16%	−82.7%
Mild NCD							
Coefficient	0.01±0.57	−0.17±0.60	−0.32±0.45	0.32±0.42	−0.06±0.25	0.61±0.86	−12.0±7.50
p	0.98	0.77	0.48	0.44	0.82	0.47	0.108
Reduction of variability	+7.1%	+72.4%	+3.5%	+44.2%	+11.2%	+3.5%	−28.9%
Major NCD							
Coefficient	1.06±0.36	0.54±0.33	0.27±0.37	0.18±0.29	0.20±0.17	0.36±0.70	−2.00±7.19
p	0.003*	0.11	0.4	0.5	0.25	0.6	0.78
Reduction of variability	−38.6%	−48.7%	+4.7%	−34.6%	−18.1%	+5.5%	+5.5%

186.8 (42–539). The threshold was available in 11 studies and was ≤7th percentile in 6 studies.

The pooled prevalence (Fig. 2) was 53.4% (95% CI: 46.9–59.8) for total post-stroke NCD, 36.4% (95% CI: 29–43.8) for mild post-stroke NCD, and 16.5% (95% CI: 12.1–20.8) for major post-stroke NCD (Fig. 2). Substantial heterogeneity (I^2 ≥93%, all) was observed across studies in the 3 analyses. A publication bias resulting in a low prevalence of major post-stroke NCD in studies based on small sizes cannot be excluded (online suppl. Fig. S2).

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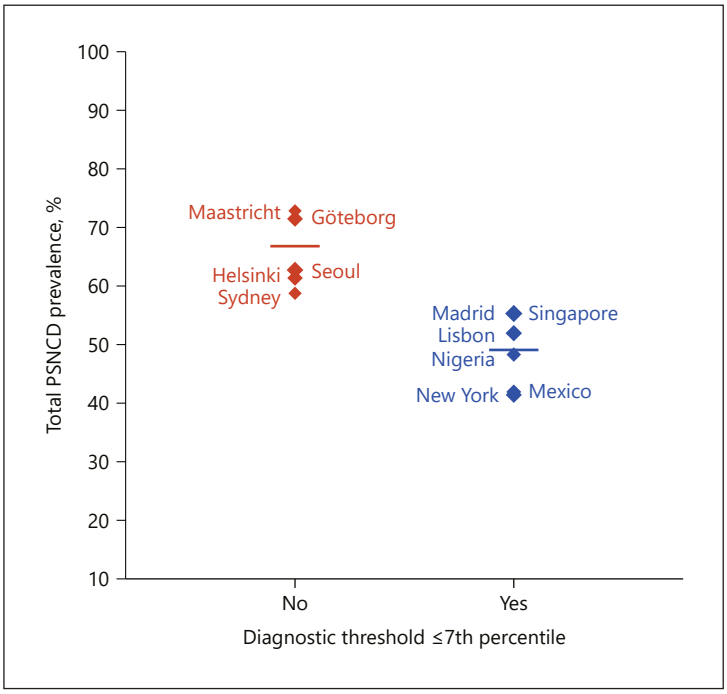

Fig. 3. Overall prevalence of post-stroke neurocognitive disorders (PSNCD) according to threshold.

Meta-regression analysis was performed in the subgroup of 11 studies providing factors submitted to meta-regression (online suppl. Table 1), representing a total of 2,515 patients. Meta-regression analysis was significant for total post-stroke NCD (Table 2) due to the threshold used for score categorization (p = 0.0001) with a strong tendency (p = 0.053) for increasing prevalence with longer post-stroke interval. The use of a threshold >7th percentile (Fig. 3) was associated with a 14.1% increase of the estimated prevalence (64.1 vs. 49.9% for threshold ≤7th percentile). In view of the strong effect of the threshold on the resulting prevalence of total post-stroke NCD and the marked heterogeneity of studies using a threshold >7th percentile, meta-regression was conducted on a subgroup of 4 studies using a threshold ≤7th percentile and showed that the variability across studies was explained by the recurrent stroke rate (estimated coefficient: 0.76 ± 0.22; p = 0.0005; reduction of variability: 100%), but not by the prevalence of pre-stroke dementia (estimated coefficient: 0.03 ± 0.66; p = 0.9689) (Fig. 4). No factor was significantly associated with mild post-stroke NCD. Meta-regression analysis of major post-stroke NCD (Table 2) showed a significant effect of age (p = 0.003) with a higher prevalence in studies including older patients, corresponding to a prevalence increment of approximately 1.1% per year (online suppl. Fig. S3).

Discussion

The main result of this study is that 53.4% (95% CI: 46.9–59.8) of patients surviving a stroke experience post-stroke NCD, corresponding to mild post-stroke NCD in 36.4% (95% CI: 29–43.8) and major NCD in 16.5% (95% CI: 12.1–20.8) of cases. To our knowledge, this is the first study to estimate the pooled prevalence of total and mild post-stroke NCD. Although most previous studies and pooled analyses have focused on major post-stroke NCD, the overall prevalence of post-stroke NCD is the outcome of interest, as the presence of post-stroke NCD, regardless of its severity, has been shown to be associated with mortality, depen-

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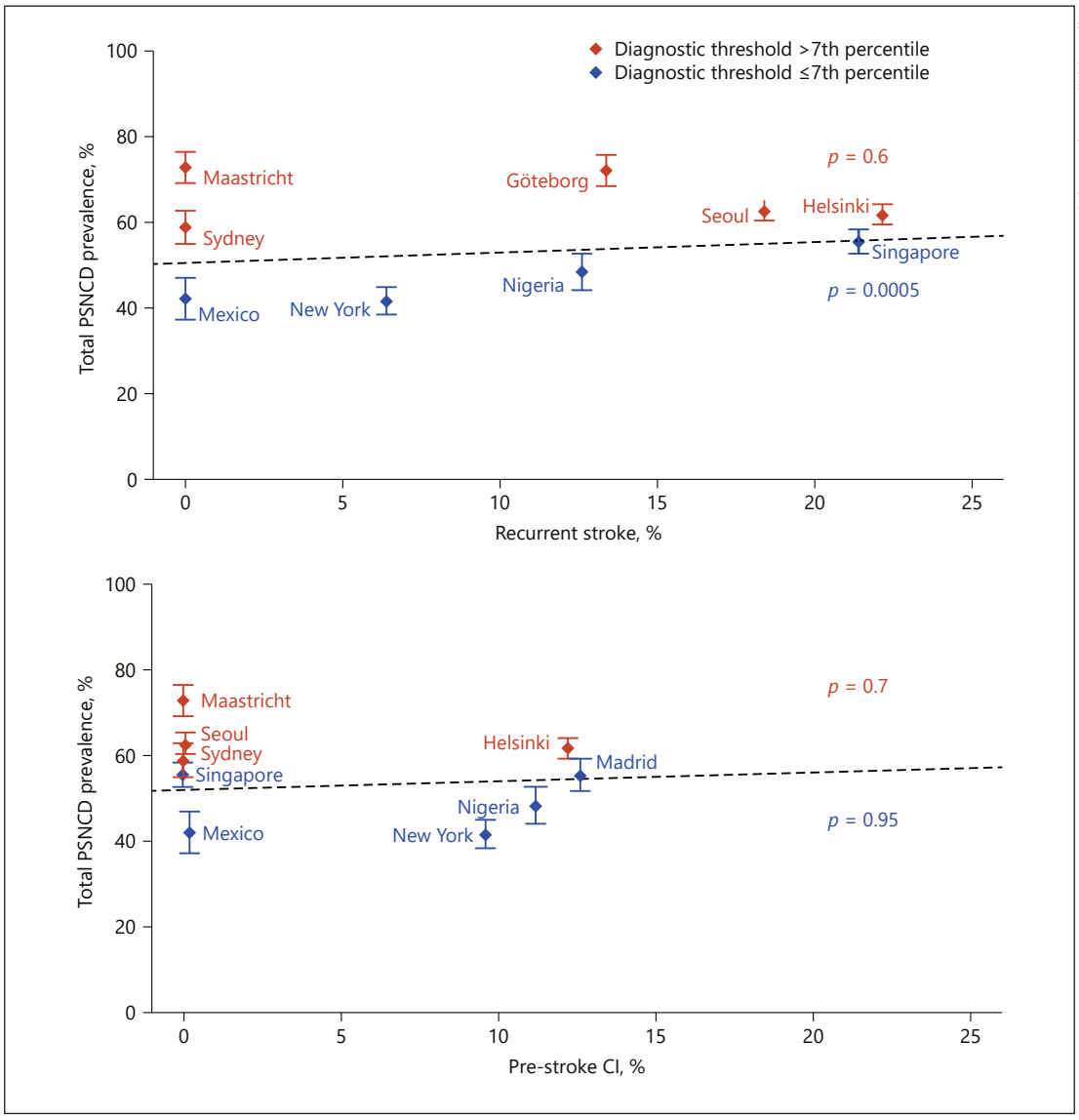

Fig. 4. Effect of the recurrent stroke rate (top) and pre-stroke dementia (bottom) on the overall prevalence of post-stroke neurocognitive disorders (PSNCD) according to threshold. CI, cognitive impairment.

dency, and institutionalization [3, 4]. The present study also showed that about two-thirds of patients with NCD experienced mild post-stroke NCD and that failure to take these cases into account would seriously underestimate the impact of NCD. Finally, mild NCD could constitute a more appropriate target for future trials, justifying a more thorough analysis of this entity. The present pooled estimation of major post-stroke NCD was similar to that reported in a previous meta-analysis focusing on hospital-based cohorts with the exclusion of pre-stroke dementia (20.3%) [2], which can be partly explained by the predominance of studies excluding patients with pre-stroke dementia in our pooled analysis.

Another major result of this study was the marked heterogeneity across studies of the estimated prevalence of mild, major, and total NCD. This heterogeneity cannot be attributed to differences in the classification of cognitive impairment into mild or major subtypes, i.e., diagnostic criteria of dementia, as it was also observed for the overall prevalence of NCD. A

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large proportion of the variability of the prevalence of total post-stroke NCD across studies can be attributed to methodological differences, especially the threshold (≤7th percentile or not) used to determine cognitive impairment and, to a lesser extent, the interval between stroke and neuropsychological assessment. The use of a less conservative threshold (i.e., >7th percentile) was associated with a 14% increment of the estimated prevalence of total NCD. To our knowledge, this major effect has never been previously reported and is consistent with previous studies demonstrating the role of four methodological factors influencing the resulting prevalence of cognitive impairment: control for demographic factors (particularly age and education), procedures controlling for the false-positive rate (adjustment of the number of unpaired scores, computation of domain scores or global score), the size of the control group used to determine the cutoff score, and the threshold used to categorize cognitive score as normal versus impaired [45–47]. Eight studies used norms based on a control group: only 6 of these studies indicated the sample size of this group, which was greater than 500 in only 1 study, indicating that at least 5, and possibly 7, of the 8 studies were at risk of inaccurate determination of the cutoff and consequently inaccurate estimation of the prevalence of post-stroke NCD [45–58]. The effect of post-stroke interval supports the previous observation of an increased incidence of dementia according to post-stroke interval [2]. Heterogeneity was also related to casemix, which was significant only for age and prevalence of major NCD, supporting the previously reported older age of patients with post-stroke dementia [2]. The recurrent stroke rate also influenced the prevalence of total post-stroke NCD in the subgroup of studies using a threshold ≤7th percentile, which is consistent with previous reports of a higher prevalence of post-stroke dementia in patients with recurrent stroke [2]. Inversely, low education level and the prevalence of pre-stroke dementia were not statistically significant despite their association with variability >20%, in contrast with the effect of these factors in major post-stroke NCD [2], which is probably due to multiple sources of heterogeneity, as illustrated by the wide variation of coefficient estimates.

Our study presents several limitations. Heterogeneity was very marked, mainly due to methodological and casemix differences. Several studies also failed to provide details concerning factors influencing the prevalence of NCD, resulting in a smaller population included in meta-regression analyses, which may have biased our results. Nevertheless, this study provides pooled estimates based on the inclusion of studies performed in various countries all over the world. We deliberately focused on hospital-based cohorts and did not include population-based series, as hospital-based cohorts correspond to populations of stroke patients entering a management circuit designed to reduce disability. In addition, diagnosis on mild NCD requires a comprehensive neuropsychological assessment which is hardly performed in stroke patients that are not initially managed in hospital. Finally, our study did not examine the mechanisms of NCD, especially the possible contribution of associated Alzheimer's disease. Although some studies classified the causes of major post-stroke NCD, this classification remains very variable from one study to another and therefore tends to be unreliable.

The major finding of the present study is that half of stroke survivors experience some degree of post-stroke NCD several months post-stroke: two-thirds of them experience mild NCD and one-third experience major NCD. The prevalence of post-stroke NCD increases with age, recurrent stroke rate and, to a lesser degree, with post-stroke interval. This result has major implications for the organization of post-stroke care. The role of the cognitive impairment threshold and, more generally, the heterogeneity of post-stroke NCD across studies also have major implications for future studies, indicating the need for standardization of the assessment of post-stroke cognitive status in line with the Harmonization Standards groups [49]. The present study suggests four major sources of improvement. The first is the need to identify easily in routine practice patients at risk of cognitive impairment

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requiring comprehensive assessment. The second concerns the adoption of a standardized cognitive assessment according to the proposed neuropsychological battery assessing 5 cognitive domains (language, visuo-constructive abilities, memory, action speed, and executive functions), in addition to depression and behavioral changes [49]. The third source of improvement concerns the standardized analysis of a combination of cognitive scores, as proposed in a recent validation study [45]. Finally, common criteria for mild and major post-stroke NCD must be adopted, as recently proposed by the VASCOG group [50]. Within the VASCOG criteria, harmonization of the threshold used to determine cognitive impairment will be an important point considering its major influence on the diagnosis of cognitive deficit. The recent finding that the 5th percentile threshold applied to a global cognitive score provides the highest sensitivity and specificity among various deficit criteria [51] may contribute to this objective.

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Disclosure Statement

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Author Contributions

Mélanie Barbay and Olivier Godefroy performed the literature search, figure production, study design, data collection, data analysis, data interpretation, and writing. Momar Diouf carried out the figure production, data analysis, data interpretation, and writing. Martine Roussel conducted the study design. Other members of the GRECOGVASC study group took part in data collection.

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