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Association of cognitive reserve with stroke outcome: a protocol for a systematic review

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ABSTRACT

Introduction The concept of cognitive reserve (CR) was introduced to account for individual differences in the clinical manifestation of neurodegenerative diseases. Though several mechanisms and risk factors are shared between neurodegeneration and stroke, the effect of CR on poststroke functional outcome has been poorly addressed. This systematic review aims to synthesise the available research evidence on the association of CR with stroke outcome, in order to implement the understanding of interindividual variability in stroke outcome and to improve its prediction.

Methods and analysis Cochrane Library, Embase, PubMed, Web of Science and reference lists of relevant literature will be searched for publications on CR proxies (eg, education, years of education, occupational attainment, premorbid intelligence) and stroke outcome, published between 1 January 1980 and 10 March 2022. Two reviewers will independently perform the study selection, data extraction and quality assessment. Disagreements between reviewers will be resolved by a third independent reviewer. The Quality In Prognosis Studies tool will be used to assess the quality of each included study. The primary outcome will be functional outcome after stroke assessed with modified Rankin Scale, activities of daily living (eg, Barthel Index), National Institute of Health Stroke Scale, dichotomised as favourable versus not favourable as well as reported as continuous or ordinal variables. Qualitative and quantitative findings will be summarised and, if possible, data will be synthesised using appropriate meta-analytical methods. The quality of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation framework.

Ethics and dissemination No ethical approval is required as it is a protocol for a systematic review and the data used will be extracted from published studies. The findings from this systematic review will be disseminated in a peer-reviewed scientific journal and presented at conferences. The data will be made freely available.

PROSPERO registration number CRD42021256175.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review addresses a gap in the current understanding of the interindividual variability in stroke outcome by assessment of the impact of cognitive reserve (CR).
⇒ This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.
⇒ The search strategy supervised by a medical librarian with extensive experience was adapted according to Medical Subject Headings terms fitting each database, including PubMed, Embase, Cochrane Library and Web of Science.
⇒ Different designs and participant characteristics, as well as different assessment of CR proxies—including application of different cut-offs—are possible and may lead to high heterogeneity.
⇒ Exclusion of non-English publications may cause language bias.

INTRODUCTION

It is well known that stroke is a leading cause of death and disability. Namely in 2019 stroke was worldwide the second leading cause of disability-adjusted life-years in individuals aged 50 and older.[1] Over the last decades, these numbers have significantly increased especially for older patients (≥75 years old) as well as for younger stroke survivors, stressing the relevance of the problem.[2] Although a number of studies on stroke outcome reported a common pattern of recovery, involving the largest recovery in the first weeks poststroke further reaching a plateau, a deterioration in the physical ability may occur.[3] Despite several prognostic models have been proposed to predict clinical and functional outcomes after stroke,[4–7] due to the lack of long-term studies and the heterogeneity of the condition, the understanding and prediction of stroke outcome requires further research.

The concept of cognitive reserve (CR) has been established to explain differences in individual susceptibility to brain pathology in presentation of different clinical deficits.[8] CR moderates the impact of pathology on performance and is suggested to shape the brains' ability to compensate for injury by facilitating neural compensation.[9] Namely, CR is associated with more effective compensation, and

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this represents a protective factor against the expression of the illness.[9] Specifically, CR is a dynamic and active model of reserve that can be boosted through lifetime exposures.[10] CR is defined as cognitive capacities acquired via lifetime intellectual activities, occupational-educational history and other environmental factors, which shape the brain's network efficiency, processing capacity and flexibility.[9] However, CR represents a theoretical latent construct encompassing several variables and can usually be operationalised only partially using a single proxy or multiple static proxies and questionnaires.[11 12] The following sociobehavioural CR proxies have been suggested: years or level of education, occupational attainment, cognitive-stimulating activities, leisure, social activities, bilingualism, crystallised or verbal intelligence.[9 11]

There is increasing evidence that individuals with higher CR demonstrate better cognition than individuals with lower CR despite of comparable level of pathology.[9] The concept of CR is well established in research of neurodegenerative diseases such as Alzheimer disease.[13] However, it was suggested that the CR concept might represent a valuable framework to explain interindividual variability in stroke outcome.[14] Recent studies adapted the concept of CR to stroke research and demonstrated the impact of CR on poststroke cognitive impairment and recovery.[15–18] Thus, CR might be useful in prediction of poststroke cognitive impairment and explain its interindividual variability. However, most studies focused primarily on effects of CR on poststroke cognition, whereas original articles addressing impact of CR on functional (non-cognitive) stroke outcome are scarce. To our best knowledge, the impact of CR on functional (non-cognitive) outcome following stroke has not been addressed with a systematic review or meta-analysis until now despite of increasing evidence.

Aims and objectives

This systematic review aims to synthesise the available research evidence on the association of CR with stroke outcome, in order to implement the understanding of interindividual variability in stroke outcome and improve its prediction.

Specific review objectives include:

Objective 1: to establish whether a higher level of CR is associated with better stroke outcome.

Objective 2: to explore whether different CR proxies have a distinct impact on stroke outcome.

Objective 3: to investigate whether the effect of CR on stroke outcome varies depending on the period following the stroke onset (eg, acute vs chronic stroke phase).

Objectives 2 and 3 will be explored through subgroup analyses only if sufficient data are available.

METHODS AND ANALYSIS

This protocol was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines,[19] as shown in the PRISMA-P checklist (online supplemental file 1). The systematic review is registered with PROSPERO (CRD42021256175). Important protocol amendments will be documented and published together with the results of the systematic review. The start of (preliminary) literature search is March 2021; planned end date for this review is August 2022.

Eligibility criteria
Types of studies

We will include original prospective and retrospective observational studies and controlled trials, published as peer-reviewed original research articles in English, with online (or under request) full-text availability. We will exclude reviews and meta-analyses, but their reference lists will be searched to identify primary studies. We will also exclude case reports and meeting abstracts.

Types of participants

We will include studies on human adult participants (≥18 years old) with first-ever ischaemic stroke. In case of mixed population—for example, including patients with previous or haemorrhagic stroke or transient ischaemic attack (TIA), only studies with a proportion of >80% of patients who had a first-ever stroke or studies *adjusted* for previous stroke or type of stroke in the prediction model will be included. This will be done taking into account the different impact of TIA and haemorrhagic or recurrent stroke onto stroke outcome. For example, haemorrhagic stroke is a very heterogeneous condition including intracerebral haemorrhage or subarachnoid haemorrhage often requiring neurosurgical interventions significantly influencing outcome. In contrast, TIA usually does not lead to brain damage and consequently to any neurological impairment after >24 hours. The threshold of 80% is chosen to allow the inclusion of studies with mixed population on the one hand, but to seek the homogeneity of studied population to avoid the 'composition bias' and consequently the type II error on the other hand.

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Index factor of interest is CR at the time stroke occurred. The scope of the review warrants an examination of a global CR impact, therefore different CR proxies and standardised multi-indicator questionnaires will be included. We will consider all well-established CR proxies proposed by Stern[8 20] and adapted to the stroke population,[14] which are expected to shape cognitive networks: for example, years of education, level of education, prestroke intelligence, leisure activity, occupational attainment and literacy,[9 12 21 22] even if these variables are not referred to CR proxies in the studies explicitly. Furthermore, standardised and validated[23] CR questionnaires to acquire CR index will be also included (eg, Cognitive Reserve Index Questionnaire,[24] Cognitive Reserve Questionnaire,[25] Cognitive Reserve Scale,[26] Lifetime of Experience Questionnaire).[27] We will not include physical activity as a CR

proxy in the current review for the following reasons. First, physical activity does not represent the activity that *directly* shapes cognitive networks, though its positive impact on cognition is undoubtful. Due to the complexity of the topic,[28] we see 'physical activity' across lifespan prestroke and poststroke as a separate issue in the research of stroke outcome. Correspondingly, the impact of prestroke or poststroke physical activity on stroke outcome was investigated and synthesised recently by systematic reviews and meta-analyses.[29]

Since various CR proxies will be included, we will consider both continuous and dichotomised data types. The different CR proxies should refer to the prestroke period (eg, lifelong education) or at stroke onset (eg, working situation).

Comparators
Given the broad perspective for exposure of interest, several comparisons will be relevant. The comparison among different levels of CR (low vs high) on its impact on stroke outcome will be investigated.

Type of outcome measures and prioritisation
The primary outcome of interest will be stroke outcome measured using validated and standardised clinical scores including National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), Barthel Index (BI) and other activity of daily living (ADL) scales. Due to possible variation in definitions (eg, favourable or poor) and poststroke time interval, we will extract definitions of outcomes as reported in individual studies. We will extract outcome measures in all data forms (eg, dichotomous, continuous, ordinal) as reported in the included studies. Studies will be included if reporting stroke outcome from event (acute hospitalisation) up to 5 years after stroke onset (chronic phase). We will extract the exact time of assessment as reported in the included studies. If a study includes different assessment times, we will extract data on the visits up to 5 years' follow-up. In studies, reporting data for several time points (eg, 3, 6 and 12 months), we will consider the earliest time point to ensure the completeness of statistical follow-up data.

As studies report functional outcomes at various time points poststroke, we have decided a priori to subdivide the follow-up period into (1) short-term stroke outcome (stroke event to 3 months (90 days) poststroke) and (2) long-term stroke outcome (91 days until 5 years poststroke).

Information sources
Electronic searches
An extensive literature search will be undertaken from 1 January 1980 to 10 March 2022 to identify relevant publications in the following electronic databases: Cochrane Library, Embase, PubMed and Web of Science. The search strategy combines key terms including appropriate exploded Medical Subject Headings terms and Boolean operators properly adapted for each database (see table 1

Table 1 Proposed search terms which have been combined (AND)

Theme	Search terms
Stroke	Stroke OR (cerebrovascular AND (event OR disease OR accident) OR 'brain ischemia' OR poststroke OR 'post-stroke')
Cognitive reserve	'Cognitive reserve' OR Intelligence OR leisure* OR occupation* OR vocation OR 'social class*' OR 'social status' OR 'socioeconomic status' OR 'years of education' OR education OR literacy
Functional outcome	NIHSS OR mRS OR 'modified Rankin Scale' OR 'Barthel Index' OR BI OR 'activit* of daily living' OR ADL OR 'stroke outcome' OR 'functional outcome' OR 'functional status'

and online supplemental file 2 for a detailed search strategy).

Searching other relevant sources
In order to ensure an exhaustive literature search, reference lists of included studies and relevant reviews or meta-analyses will be manually inspected.

Study records
Data management
We will import the identified publications of all information sources into Zotero software (https://www.zotero.org/) and Microsoft Excel. One review author will screen the references and remove duplicates using Zotero software. Prior to the formal screening process, a calibration exercise will be undertaken by the authors to pilot and refine the screening questions and classifications.
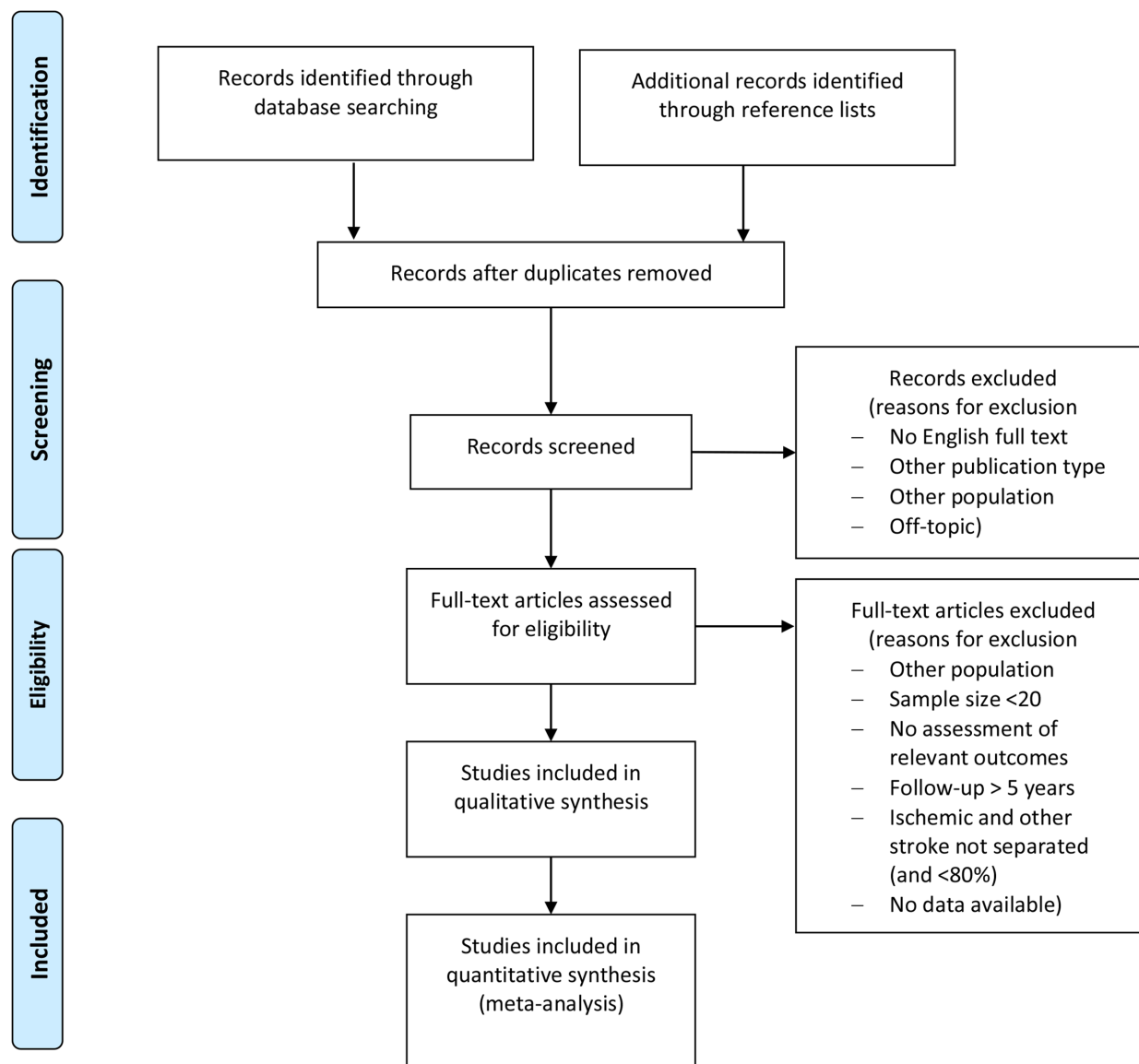
Study selection process
To ensure consistency across review authors, we will conduct calibration exercises before starting the selection process. Amendments will be made if necessary. One review author will independently screen the titles and abstracts yielded by the search against the inclusion and exclusion criteria. Two review authors will screen the potentially eligible full-text reports. A PRISMA flow diagram will be provided to illustrate the selection process. The study selection procedure is shown in figure 1.

Reasons for inclusion and exclusion will be recorded (with citations when possible). Any discrepancies between two authors will be discussed and resolved with consensus or by consulting a third reviewer for arbitration.

Data extraction process
Two review authors will independently extract data according to a prespecified standardised data extraction form and detailed instruction. After piloting, we will extract the data using two independent Microsoft Excel spreadsheets. Any discrepancy between the two authors will be resolved with consensus, if necessary involving a third reviewer. To analyse the data from the included studies, we will combine the two spreadsheets into one

Figure 1 Study selection procedure.

and export the data into statistical software for Review Manager.

We will contact study authors if additional information is required (eg, missing values, reporting only 'not significant' without p values, or OR with respective CIs) or to resolve any uncertainties (eg, bias).

Under consideration of the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies,[30] we will extract data concerning reference, study methods, sample characterisation and statistical results on outcomes of interest. Specifically, we will extract the following data:

1. General study information: author, publication year, title, journal.
2. Participants: population, patient number, stroke type (with number of patients and per cent of the total sample), stroke history (with number of patients and per cent of the total sample with first-ever and recurrent stroke separately), stroke assessment/diagnosis, imaging confirmation, pathology measurement (stroke severity, lesion location, lesion load, lesion volume, etc), comparison group, age, sex, comorbidities/vascular risk factors, time of assessment of functional outcome.
3. Study methods: design, single/multicentre, setting, region/country, overall length of follow-up, methods used to prevent and control biases and confounding. For randomised trials: details of random sequence generation, allocation sequence concealment and masking.
4. Index: CR proxies and time of their assessment and time to which they relate (prestroke or at the time stroke occurred). For CR questionnaires, detailed information on construct, domains, language and assessment details will be recorded.
5. Outcomes: validated and standardised functional clinical score or scale (eg, NIHSS, mRS, BI, ADL). For each variable, we will note the time points of assessment and

the clinical cut-off in case of dichotomisation (eg, favourable vs poor) as reported in the publication.

6. Results: statistic data, statistic methods used if computed effect estimates are extracted from reports, including any covariates used for adjustments, sample size (per group of interest), number of patients excluded and dropouts (per group of interest), adjusted (if none, only unadjusted) measures of associations (risk ratio (RR), OR, HR, mean differences), subgroup or sensitivity analyses performed in the study.

7. Contact details of corresponding authors (email) in case of uncertainties or missing data.

Dealing with missing data

In case of missing data, we will attempt to contact the study authors. If missing data cannot be obtained, the study will not be considered in the qualitative and quantitative analyses.

Quality and risk of bias assessment

We will assess the risk of bias both at the level of each study and at the level of review outcome. To assess the risk of bias of each study, we will collect and analyse information using an adapted version of the Quality In Prognosis Studies (QUIPS) tool.[31] QUIPS is a tool for assessing the risk of bias in studies of prognostic factors. Due to the novelty of the CR construct and since different CR proxies will be analysed as prognostic factors, QUIPS represents an optimal tool allowing an evaluation of risk of bias and specific consideration of the suitability of each used CR proxy. The tool covers six bias domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, as well as statistical analysis and reporting. For each domain, we will describe the procedures undertaken in each study including verbatim quotes. Judgements on the risk of bias of studies will be rated as 'low', 'moderate' or 'high'. These judgements will be made independently by two authors. Disagreements will be resolved by discussion; in case of disparities a third author will be consulted for arbitration.

We will produce graphic representations of potential bias within and across studies, based on the level of risk of bias. We will consider each item in the risk of bias assessment independently as well as assign an overall score. The results of the quality check according to the QUIPS tool will be submitted as supplement materials.

Assessment of reporting bias

We will examine potential publication bias using funnel plots by visual assessment of asymmetry if more than 10 studies will be included in the meta-analysis.

Data synthesis and analysis

We will summarise the characteristics of the included studies in a table.

Data synthesis

We will conduct a descriptive synthesis of all the included studies, including adjusted and, if none, unadjusted estimates. In case of a sufficient number of studies, we will conduct a meta-analysis by application of random-effects model. The pooled OR with corresponding 95% CI will be the primary measure of association. For dichotomous outcomes, we will consider OR along with their 95% CIs by using random-effects model. If these estimates are not readily available, crude effect estimates will be calculated from 2×2 tables. Data presented through other effect measures (eg, RR and β coefficients) will be converted into ORs when possible. We will analyse continuous outcomes using mean differences (with 95% CI) or standardised mean differences (95% CI) if different measurement scales are used. Meta-analysis results will be visualised in forest plot.

Assessment of heterogeneity

We will assess the statistical heterogeneity using the χ^2 test (significance level: p<0.1 denoting heterogeneous results) and the I^2 statistic. An I^2 value of 0%–40% indicates not important heterogeneity; 30%–60% moderate heterogeneity; 50%–90% substantial heterogeneity; and 70%–90% considerable heterogeneity suggesting a variability in effect estimates due to between-study heterogeneity rather than to chance.[32]

Investigation of heterogeneity and subgroup analysis

In case of heterogeneity, we will identify hypotheses for heterogeneity, including study design and characteristics, and explain it by subgroup analysis or sensitivity analysis. Namely, the following subgroup analyses will be performed to explore the heterogeneity:

1. The different CR proxies on their predictive weight on stroke outcome.
2. The CR impact over different time poststroke: acute-subacute stroke phase (0–3 months poststroke) versus chronic phase (>3 months poststroke).

We will present the results of subgroup analyses in forest plots. If applicable, we will further perform a meta-regression analysis to investigate possible sources of heterogeneity.

Sensitivity analysis

We will conduct sensitivity analyses to explore sources of heterogeneity based on quality components and risk of bias (see QUIPS criteria). In case the risk of bias will preclude the quality, reliability and generalisability of the results, the study will not be included in the meta-analysis in agreement between the review authors.

Confidence in cumulative evidence

Certainty and strength of evidence will be evaluated according to the Grading of Recommendations Assessment, Development and Evaluation[33] criteria overall for all CR proxies and separately for different CR proxies in case of sufficient data. In case of sufficient data, certainty of evidence will be also assessed separately for different

outcome measures. Certainty will be rated according to the criteria risk of bias across studies, imprecision, inconsistency, indirectness, publication bias and magnitude of effect. The certainty will be rated as 'very low', 'low', 'moderate' or 'high'.

Patient and public involvement

This review will be based on previously published and online available data identified in the above-mentioned databases. There will be no direct patient and public involvement in setting the research question, design, outcome or implementation and dissemination of the research.

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