Is Cognitive Reserve Associated with the Prevention of Cognitive Decline After Stroke? A Systematic Review and Meta-Analysis

Short Title: Cognitive Reserve & Post-stroke Cognitive Decline

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Abstract

Objective: To conduct a systematic review and meta-analyses of the effect of socio-behavioral cognitive reserve (CR) proxies on cognitive decline after stroke. *Method:* Three journal search and indexing databases (PubMed, Scopus and Web of Sciences) were crossed to examine the scientific evidence systematically. In addition, meta-analytic techniques, using mixed-effect methods, were carried out to estimate the impact (pooled effect size) of CR proxies on either dementia incidence or cognitive decline after stroke. *Results:* Twenty-two studies were included in the systematic revision, whereas nineteen of them were eligible for the meta-analysis. The findings showed that high education is associated with a decreased rate of post-stroke dementia. Moreover, other CR proxies (e.g., occupation, bilingualism or social interaction) demonstrate a protective effect against non-dementia cognitive decline after stroke, although some inconsistencies were found in the literature. Regarding the meta-analysis, occupational attainment (OR = 3.71, CI_{95} = 2.54, 5.41) and education (OR = 1.91, CI_{95} = 1.68, 2.17) showed a protective effect against post-stroke cognitive impairment diagnosis in comparison with a mixed category of different CR proxies. Second, a main cognitive change effect was found (OR = 3.46, CI_{95} = 1.08, 11.04), pointing to greater cognitive change in those with low vs. high CR, mainly regarding the attentional domain. *Conclusions:* Our findings emphasize that CR may prevent cognitive decline after stroke, but this effect can be modulated by different factors such the CR proxy and individual characteristics such as age or type of lesion. The methodological divergences of the studies (i.e., follow-up intervals, cognitive outcomes) need unification to diminish external sources of variability for predicting rates of cognitive decline after stroke.

Keywords: Cerebrovascular Diseases, Cognitive Disorders; Dementia; Reserve; Education.

1. Introduction

Stroke is defined as an acute episode of focal dysfunction of the brain, retina, or spinal cord lasting longer than 24 h, or of any duration if imaging (CT or MRI) or autopsy show focal infarction or hemorrhage relevant to the symptoms (Sacco et al., 2013). This type of vascular insult is the second leading cause of death and a major cause of long-term disability worldwide (Katan & Luft, 2018). Its prevalence is expected to increase due to the aging of the population (Béjot et al., 2016). Thus, three quarters of strokes occur in people over 65 years old (Yousufuddin & Young, 2019), and its incidence rate doubles each decade after the age of 45 (Roger et al., 2011). It is known that stroke (i.e., acute brain infarcts) and transient ischemic attacks (TIA), as a minor form of stroke (less than 24 h duration and with no imaging evidence of infarction), are cerebrovascular diseases (CVD) which produce a wide diversity of clinical signs and symptoms. Remarkably, stroke patients show an increased probability (range: 35-47%) probability of developing mild cognitive impairment or dementia (range:7-23%) along the first year after the event (Béjot et al., 2016). Both conditions (stroke and dementia) share largely modifiable risk and protective factors, estimating that 90% of strokes and 35% of dementias are preventable (Hachinski et al., 2019). In this sense, the concept of vascular cognitive impairment (VCI), defined as any cognitive condition caused or associated with vascular factors, emphasizes the need to identify treatable and preventable factors that may reduce cognitive decline after the emergence of any CVD (Azarpazhooh & Hachinski, 2019).

It is known that age and lesions (severity and location) are non-modifiable factors that play an important role in stroke prognosis, but these factors only account for a partial explanation of the inter-individual variability in cognitive impairment after stroke (Umarova, 2017). In fact, some authors claim that cognitive reserve (CR), understood as a form of "brain resilience", may help to explain this variability in cognitive performance after stroke damage

(Arenaza-Urquijo & Vemuri, 2018; Gil-Pagés et al., 2019). The CR concept was originally defined by Stern (2002) as the brain's ability to optimize and maximize cognitive/functional performance through the differential recruitment of brain networks (i.e, compensatory mechanisms) or the use of alternative cognitive strategies to cope with brain insults. Basically, as a theoretical construct, CR cannot be directly measured and three methods are followed to the estimation: socio-behavioral proxies or indicators (e.g., education, occupation and leisure activities, among others), residual approach (comparison between current brain status vs. the expected for age) and functional brain activity using neuroimaging techniques (Stern et al., 2020). Briefly, CR theory suggests that participation in cognitively stimulating activities throughout life, which is estimated through the mentioned CR proxies, increases the brain's ability to cope with brain damage (Stern, 2002, 2012). This theory has been widely applied in the field of cognitive aging and dementia, but recent contributions indicate its relevance to predict cognitive trajectories in multiple sclerosis (Ifantopoulou et al., 2019), essential tremor (Benito-León et al., 2016), schizophrenia (Herrero et al., 2020) or stroke (Umarova et al., 2019) individuals.

Considering that CR is an emerging concept in stroke recovery (Rosenich et al., 2020), the research in the field is limited and heterogeneous in terms of scientific quality. Exploring the role of CR in stroke and TIA may be of relevance in the field of health promotion and secondary prevention of cognitive impairment; as well as in the establishment of more accurate prognoses on the functionality and recovery after suffering a stroke (Rosenich et al., 2020). For instance, CR proxies (i.e., education) can be useful to adapt the rehabilitation treatment according to the characteristics of the individual and, therefore, should be considered in the choice of the most appropriate and effective rehabilitation program for each patient (Padua et al., 2019).

To our knowledge, this is the first research compiling the scientific evidence on the role

of CR in cognitive progression after stroke. Essentially, this study will address the following scientific question: to what extent do CR indicators (education, occupation or leisure) contribute to slower cognitive decline after stroke? Particularly, this research is aimed to investigate: (a) how CR proxies (i.e., education) may influence incidence and prevalence rates of dementia after stroke; (b) whether CR influences cognitive progression following stroke or TIA. Thus, it is expected that higher CR will be associated with lower prevalence/incidence rates of dementia. Likewise, individuals with high CR will show a slower progression of cognitive decline after stroke versus those with low CR level.

2. Methods

2.1. Study design

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The protocol of this review has been registered in the PROSPERO network (registration number: CRD42020202022).

2.2. Eligibility criteria

Eligible publications met the following inclusion criteria: (a) studies based on stroke or TIA populations; (b) research articles addressing the influence of CR on dementia/mild cognitive impairment risks, individuals' cognitive trajectories, or its benefits for the prevention of cognitive impairment after stroke; (c) CR was assessed through sociocultural proxies (education, occupation, etc.) or standardized questionnaires; and (d) Papers/manuscripts were written in English. Conversely, papers that (1) considered neurological pathologies other than stroke or TIA, (2) investigated cognitive impairment prior to stroke; or (3) were not empirical (i.e., review papers, books or chapters, research protocol) or exclusively based on a case report were excluded. All articles that met the eligibility criteria were included in the qualitative synthesis, while articles reporting data that could be

appropriately pooled were selected for the meta-analysis.

2.3. Search strategy

The literature search was performed using three indexing databases: Pubmed, Scopus and Web of Science. The search was performed covering all publications until December 31, 2021. In addition, reference lists of retrieved publications and secondary literature (review articles, etc.) were examined to identify possible articles of interest, as recommended by Greenhalgh and Peacock (Greenhalgh & Peacock, 2005). The following keywords and booleans operators were combined following this search strategy: "stroke OR transient ischemic attack" AND "cognitive reserve". The reference software package Zotero was used to manage citations.

2.4. Study Selection

One author (P.A.) assessed the titles and abstracts of all articles for duplicity and eligibility according to the inclusion and exclusion criteria. An additional independent reviewer (B.F) verified this and questionable records were discussed with a third independent rater (I.C).

2.5. Data collection and extraction

For the systematic review, one reviewer (P.A.) extracted data from all included full-text manuscripts according to a predefined and standardized data extraction form. The data collected from each article included information on the general description of the study, participants, methodological characteristics, and results. This process was verified by another reviewer (I.C.) and disagreements between the two reviewers were resolved by consensus.

2.6. Data synthesis and risk of bias (quality) assessment

Beyond the general description, data of the revision will be presented within the following sections: type of study (clinical vs. population or cohort based), level of evidence (i.e., quality of the research), sample size, CR estimators (i.e., education, occupation,

bilingualism…), potential moderators of CR findings (e.g., sociodemographic variables), outcomes, and main results of the study.

The quality of the studies was graded using the Oxford Centre for Evidence-Based Medicine (Howick et al., 2011) by two independent assessors (P.A. and I.C.). Five levels were considered: 1) Randomized clinical trials, systematic-review or meta-analyses of these studies; 2) Prospective cohort study; 3) Retrospective cohort study, case-control study, or systematic review of these studies; 4) Case series, cross-sectional study; 5) Single case study, expert opinion.

2.7. Meta-Analysis: Outcomes and Data Analysis

We used three types of outcomes according to following definitions: (1) Cognitive impairment diagnosis: diagnostic decision made by expert clinicians based on diagnostic standardized criteria (e.g., dementia or major neurocognitive disorder, Mild Cognitive Impairment (MCI) or minor neurocognitive disorder, cognitive impairment no dementia or analogous categories); (2) Cognitive change: mean change scores on cognitive measures assessed at different times; and (3) Cognitive performance: mean scores on cognitive measures at a given point in time. Outcomes were classified independently by 2 reviewers (P.A. and A. T-L). All disagreements were resolved by discussion to reach consensus.

Regarding the data analysis, effect size estimates were transformed into a common metric to make the results comparable. The odds ratio (*OR*) was used as an effect size for pooling effects. Then, mixed-effects modeling was used to calculate the overall effect size of CR on the three outcomes independently (Trikalinos & Olkin, 2012). Publication bias was studied by means of Egger's regression asymmetry test. Heterogeneity among the individual effect sizes was quantified by means of the Cochran's *Q* statistic and the Higgins and Thompson I^2 statistic (Higgins et al., 2003; Higgins & Thompson, 2002).

To study the effect of moderating factors on overall effect size of the outcomes, mixed-

effect meta-regression was used, following a comparison model rationale (i.e., compare the fit of models with increasing number of covariates: participant's age, time from stroke to follow-up assessment, diagnosis category-dementia or MCI- and CR proxy; see the Supplementary file for further details). All the analyses were conducted using the software R, version 3.6.2, with packages meta, metafor and mvmeta. According to the outcome of interest, the results of the meta-analysis are described in the supplementary file (see Supplemental Materials).

3. Results

In this study, 22 records were selected for the systematic review, whereas 19 fulfilled the criteria for the quantitative analysis. Figure 1 illustrates the literature search and the process of selection.

[INSERT FIGURE 1]

3.1. Systematic Review

A summary of the main characteristics of the studies and their level of evidence are shown in Table 1s (See Supplemental Materials).

3.1.1. Cognitive reserve and risk of dementia after stroke.

Longitudinal population-based study evidence indicates that the risk of dementia, after stroke or TIA, varies considerably depending on the characteristics of the sample. Pendlebury et al. (2019) found that the factors that most significantly predicted dementia 5-years after stroke were age, severity of injury, previous stroke, dysphasia, previous cognitive impairment, low education, leukoaraiosis and diabetes. It should be noted that stroke patients with severe lesions were older and lower educated than those with less severe infarcts. In addition, Mirza et al., (2016) observed that stroke increased the risk of dementia at 10-years follow-up in those with a low-intermediate educational level in comparison with high educational level (higher vocational or university). In this population-based study, it was also found that patients (stroke or TIA) with high education presented better neuropsychological performance

(i.e., memory, executive functions, motor skill and coordination) both before and after stroke versus those with lower education. Finally, the cognitive scores of the highly educated subjects declined less in memory (i.e., delayed recall tasks) and executive functions (i.e., interference tasks) after stroke compared to their less educated counterparts.

Consistently, other longitudinal cohort-based studies have found similar results. Ojala-Oksala et al., (2012) claimed that, regardless of the white matter lesions that may have caused the stroke (mild/moderate severity), higher educational levels are associated with less impairment on memory, language (aphasia), visuospatial and constructional deficits and dementia rates at 12-years follow-up. Rasquin et al., (2004) observed that between 6 and 12 months after stroke (vs. one month after) low educational level was related to dementia in combination with other variables such as age, territorial infarction and previous brain damage.

Cross-sectional studies have also supported an inverse association between higher level of education and dementia rates. For instance, Jacquin et al., (2014) followed up 220 non-dementia stroke patients (moderate severity) at first episode. After 3 months of follow-up, 47.3% of the subjects were cognitively impaired (MMSE or MoCA test), and 7.7% were demented (DSM-IV criteria). Age, low education and other clinical factors (e.g., acute confusion, silent infarcts, and functional disability at discharge) were associated with poorer cognitive status at 3 months. Besides, De Ronchi et al., (2007) found that the combined effect of stroke with age and lower education remarkably increased the risk of cognitive impairment and dementia in subjects aged 61-74 years (vs. subjects over 75 years old). Finally, Skoog et al., (2017) compared two different birth cohorts of 85-year-old participants with stroke (assessed between 1985-1987 and 2008-2010, respectively). This study found a lower prevalence of dementia in the second cohort. To reach more than 6 years of education (basic/mandatory educational level) was negatively associated with dementia (regardless of sex or cohort to which they belonged), but the interaction between education and stroke on

dementia prevalence did not reached significance.

3.1.2. Cognitive reserve socio-behavioral factors and cognitive functioning after stroke

3.1.2.1.Education

Longitudinal studies have shown that education is implicated in individuals' cognitive trajectories after stroke. Thus, higher education may facilitate a more rapid recovery of cognitive function during the first 3 months after first acute stroke (Shin et al., 2020). Sachdev et al., (2014) also found a protective role of education on cognitive change at 1 year after stroke or TIA, even after controlling for different sociodemographic and clinical covariates (i.e., cerebrovascular risk factors or brain atrophy). However, Lazar et al., (2008) did not find a correlation between the educational level and language performance after the first stroke episode or its recovery at 90-day follow-up. Likewise, Gil-Pagés et al., (2019) did not find evidence of a relationship between education (years) and the rates of cognitive change (i.e., attention, memory and executive functions) in subjects within the chronic stage of stroke.

Cross-sectional studies have also shown that education can modify the effect of stroke on cognitive impairment. Akinyemi et al., (2014), after adjusting for various covariates, reported that only age, low education (< 6 years), daily fish consumption (prior to stroke), and medial temporal lobe atrophy were independently associated with cognitive dysfunction at 3 months after stroke. Umarova et al., (2021) claimed that both age and education could moderate the relationship between lesion size and the cognitive outcome in the chronic phase of stroke. Specifically, they found that cognitive decline, secondary to larger lesion size, may be compensated by high educational level and younger age. In contrast, even a small lesions size has a large impact on cognition in those individuals with lower education and older age. Abdullah et al., (2021) also found a significant correlation between CR and cognitive dysfunction at chronic stage of stroke. In addition, education was better predictor of cognitive

impairment than age or sex in this study. In patients within the acute stage of stroke, more years of education have been associated with a better cognitive performance in different domains (i.e., alertness, working memory, executive functions, and global cognition) (Umarova et al., 2019). Likewise, better linguistic performance has also been observed in high educated patients (> 12 years of education) who had a stroke in the last 24 hours (Gonzalez-Fernandez et al., 2011).

3.1.2.2.Intelligence (IQ)

Some authors suggest that scores in the National Adult Reading Test (NART), which measures crystallized verbal intelligence, may be related to post-stroke cognitive performance. Thus, Makin et al., (2018) found that education and NART were better predictors of Addenbrooke's Cognitive Examination-Revised (ACE-R) scores than vascular risk factors, or stroke severity, in chronic stroke patients. However, Sachdev et al., (2014) found that only education and the subject group (stroke/TIA vs. controls) were significant predictors of cognitive change at 1 year after stroke, but not the NART.

3.1.2.3.Bilingualism

Bilingualism is a CR proxy which has been associated with a better performance in executive control (Alladi et al., 2016). These authors found a better global cognitive recovery in bilingual (vs monolingual) chronic stroke participants, after controlling for age, education, and vascular risk factors. Thus, when excluding aphasics, bilinguals obtained higher scores on ACE-R (total scores) and some specific domains (attention, fluency, and visuospatial domains), but not on memory and language. Moreover, in this study bilingualism did not influence aphasia rates. In contrast, Ardila et al. (2021) found a negative relationship between bilingualism and aphasia severity, which was particularly evident in those with a larger lesion volume, male sex, and subcortical stroke (versus their monolingual counterparts).

3.1.2.4.Occupation and Cognitive Stimulating Activities

Several studies have analyzed the effect of occupation and engagement in cognitive stimulating activities on cognitive performance after stroke. Gil-Pagés et al., (2019) divided the indicators of CR into two groups: objective/static CR proxies (i.e., education and occupation) and subjective/dynamic proxies based on self-reported answers (i.e., activities of daily living, hobbies and social life). Static indicators were not associated with neuropsychological scores within the chronic stage of stroke, while the dynamic ones were positively correlated with self-perceived metacognitive, attentional and functional skills. Consistently, Ihle et al., (2019) found that performance on Trail Making Tests (TMT) was better in stroke patient with high participation in cognitively stimulating activities (e.g., reading, going to a museum, travel…). History of stroke, sex and other CR proxies (education or occupation) did not predict changes in TMT scores. In contrast, Shin et al. [31] found that lower levels of occupation were associated with poorer cognitive performance and increased risk of cognitive impairment both immediately after stroke and 30 months later. In this study, higher occupation and education also improved cognitive recovery within 3 months after stroke.

Social integration is also a promoting factor of recovery after stroke. Stroke patients who reported greater interpersonal relationships and emotional support obtained better scores on cognitive tests (attention, language, memory and executive functions) 6 months after stroke (Glymour et al., 2011). Noteworthy, this study showed that social relationships did not influence cognitive trajectories at follow-up, whereas emotional support was associated with cognitive improvements.

Finally, it has been suggested that musical ability may impact cognitive performance after stroke. Faroqi-Shah et al., (2019) found a negative correlation between musical ability and language deficit severity in people with aphasia secondary to stroke. These findings were

controlled for other CR proxies (education, occupation, and leisure activities) which did not modify the former relationship between musical ability and aphasia severity.

3.2. Meta-analysis

In terms of cognitive impairment diagnosis, a total of 10 studies were used comprising 29 individual effect sizes. An overall OR = 1.10 (CI95 = 0.68, 1.76, Z = 0.38, p > .70) was derived from pooling the studies. The overall OR was not significantly different from 1, stating a lack of effect of CR on cognitive impairment diagnosis (outcome 1) after a stroke. Heterogeneity between individual effect size estimates was high for this outcome, Q (28) = 538.85, p < .01, I^2 = 94.80%, a fact that supports the study of moderators. The full meta-regression model (i.e., including all the covariates: participant's age, time of follow-up assessment, diagnosis category-dementia or MCI- and CR proxy) showed a better fit to data than the remaining meta-regression models (unconstrained model AIC = 211.02; model with clinical covariates AIC = 212.27; full model AIC = 78.47). The full model showed a significant effect of covariates, QM (5) = 144.48 (p < .01), which revealed a significant explanatory loading of the CR proxy covariate on diagnosis outcome. More concretely, studies focused on occupation showed higher risk of lower-reserve group showing a cognitive impairment diagnosis in comparison with other (non-specific) CR proxy, OR = 3.71 (CI95 = 2.54, 5.41, Z = 3.27, p < .01). Similarly, studies on education (in comparison to studies on other CR proxies) showed that lower education groups were associated with higher risk to show cognitive impairment diagnosis, OR = 1.91 (CI95 = 1.68, 2.17, Z = 9.81, p < .01). Egger's regression test revealed asymmetry in the funnel plot, b = -2.18, CI95 = -4.04, -0.33, Z = 2.66, p < .01. This points to the influence of publication bias and results should be taken cautiously.

In terms of cognitive change outcome, five studies were included into analysis comprising 17 individual effect sizes. The overall effect size from pooling the individual

estimates was significant, OR = 3.46 (CI95 = (1.08, 11.04), Z = 2.10, p < .05). This result points to higher cognitive change in lower-reserve participants in comparison to those from higher-reserve groups. Heterogeneity between individual effect size estimates was high, with Q (16) = 450.50 (p < .01, I^2 = 96.45%). Regarding meta-regression model with the covariates, the full meta-regression model fitted better to data than the other meta-regression models (unconstrained model AIC = 192.07; model with outcome type covariate AIC = 176.53; full model AIC = 167.05). The meaningful covariates contribution to explain individual effect size variability was endorsed by QM (7) = 56.62 (p < .01), and the cognitive domain was a significant covariate to explain cognitive change outcome. Thus, a significantly higher estimate was found for attention change, OR = 0.14 (CI95 = 0.04, 0.43, Z = -3.42, p < .01), in comparison to language change effect sizes. Finally, the results from the Egger's regression test endorsed the absence of asymmetry in the funnel plot regarding the cognitive change outcome, b = 1.08, CI95 = (-7.98, 10.15), Z = -0.54, p > .05. This supports the lack of influence of publication bias in the results afore presented.

Regarding cognitive performance outcome, we meta-analyzed data on general cognition effect sizes first. Six studies provided general cognition data. The overall effect size calculated was not significant, OR = 3.25 (CI95 = 0.26, 40.26, Z = 0.92, p = .37). The heterogeneity between individual effect size estimates was high for this outcome, Q (5) = 1383.42 (p < .01, I^2 = 99.60%). Using a more fined-grained analysis, considering domains of cognitive performance, data from six studies were used comprising 32 individual effect sizes. The overall effect size shows a trend to significance, OR = 18.61 (CI95 = 0.82, 421.83, Z = 1.84, p = .07). In specific, the lower-reserve group shows poorer cognitive performance after a stroke. The heterogeneity test also was significant, Q (31) = 6112.60, p < .01, I^2 = 99.49%, pointing to the potential influence of the covariates. In this respect, the full meta-regression model fitted better to data than the remaining meta-regression models (unconstrained model

AIC = 1204.33; model with clinical covariate AIC = 1150.94; full model AIC = 1145.84). The effect of covariates in this model was endorsed by QM (7) = (61.05, $p < .01$). In particular, the cognitive domain showed a significant effect on the cognitive performance effect size. Thus, considering the language domain as a reference category, effect size estimates on executive performance showed a significantly different effect, OR = 0.50 (CI95 = 0.28, 0.87, Z = -2.43, $p < .05$); as well as those for memory effect sizes, OR = 1.09 (CI95 = 1.06, 1.13, Z = 5.09, $p < .01$), and perceptual motor effect sizes, OR = 0.65 (CI95 = 0.53, 0.89, Z = 3.84, $p < .01$). These findings mean that executive function and perceptual motor domains showed significantly lower differences in performance between low versus high CR groups in comparison with the language domain. Conversely, studies assessing memory performance showed significantly higher difference between low versus high CR groups (higher scores in the higher-reserve groups) in comparison to language domain studies. Finally, the results from the Egger's regression test endorsed the absence of asymmetry in the funnel plot regarding the cognitive performance outcome, b = 24.58, CI95 = (-66.64,115.81), Z =- 0.54, $p > .05$. This supports the lack of influence of publication bias in the results afore presented.

4. Discussion

The aim of this systematic review was to analyze the effect of socio-behavioral proxies on cognitive prognosis after stroke. According to our first hypotheses, it was expected that stroke subjects with higher CR would suffer lower prevalence and incidence rates of dementia. This research identified five longitudinal studies (level 2 of evidence) and two prevalence studies (level 3 of evidence). Consistently, follow-up studies indicate that low education is a contributing factor to the risk of developing dementia after stroke (See Table 1s). Moreover, cross-sectional evidence confirmed an inverse relationship (education and dementia) in stroke (Jacquin et al., 2014). However, Skoog et al., (2017) did not confirm this

association in stroke individuals. The meta-analysis also provided evidence supporting a beneficial effect of the CR factors on the risk of developing MCI/dementia after stroke. In particular, education and occupation complexity showed significant effects on the prognosis (outcome 1) in comparison with the mixed category 'other CR proxies'. Regarding the potential publication bias on this outcome, findings should be taken cautiously.

Regarding the second hypothesis, it was proposed that high CR subjects who had suffered a stroke would have a more attenuated cognitive decline compared to those with low CR. This assumption was confirmed by several studies investigating the effect of education (in years) on post-stroke cognitive functioning (Sachdev et al., 2014; Shin et al., 2020); as well as other CR proxies: emotional support (Glymour et al., 2011), cognitive stimulating activities (Ihle et al., 2019) or premorbid intellectual ability (Makin et al., 2018). However, some inconsistencies are found in this field. For instance, neither Lazar et al., (2008) nor Gil-Pagés et al., (2019) found an association between education and post-stroke cognitive performance. Regarding cognitive change after the stroke, the meta-analysis supported a main effect of CR (i.e., the higher CR the lower change/decline in cognitive functions). In this sense, the cognitive change of groups with lower levels of CR was sharper in attention in comparison with other cognitive domains such as language.

Finally, several studies analyzing the relation between CR and post-stroke cognitive performance claimed a positive association. That is, the higher the CR levels assessed through education (Abdullah et al., 2021; Akinyemi et al., 2014; Gonzalez-Fernandez et al., 2011; Umarova et al., 2019, 2021), bilingualism (Ardila et al., 2021) or musical ability (Faroqi-Shah et al., 2019), the better the cognitive function after stroke. The meta-analysis showed that CR effects were not significant on general cognition performance, whereas discrepancies between the CR groups (low vs. high) are wider on memory tasks and language performance (versus executive function and perceptual motor domains).

This systematic review points to a protective effect of CR on post-stroke cognitive decline, but a critical analysis is required to depict the main limitations in the field. To start with, longitudinal population-based evidence for dementia incidence after stroke is very scarce. Besides, several longitudinal studies were based on short term follow-up periods (≤ 6 months), when clinical recovery after the acute episode is not complete (Carey & Seitz, 2007). Hence, the relationship between CR and cognitive decline after stroke may be influenced by the duration of the follow-up interval (Rasquin et al., 2004). In addition, education, measured by different manners (i.e., years of schooling, educational attainment), is almost the unique CR proxy analyzed for this relationship (outcome 1). Current evidence indicates that literacy (vs. education) is associated with dementia even after controlling the recurrence of stroke (Contador et al., 2022), suggesting that CR proxies differ in terms of vulnerability to the effect of brain damage. Otherwise, research on cognitive changes (outcome 2) includes more variability in terms of CR proxies (premorbid IQ, occupation, cognitive stimulation abilities), but most of the studies (four out seven) were classified as level 3/4 of the Oxford Evidence due to methodological limitations. It deserves to be mentioned that age and severity of stroke may act as moderators of the relationship between stroke/education and dementia risk (De Ronchi et al., 2007; Pendlebury et al., 2019), but the selection of covariates (i.e., cardiovascular risk factors) is not consistent across the studies. Finally, measurement of cognition is often restricted to screening instruments (e.g., MMSE, MoCA) or unique cognitive domains (language, executive functions), giving excessive reliance on their ability to detect cognitive changes. In brief, studies' limitations and their heterogeneity make it difficult to integrate the scientific findings and invite caution.

Currently, it is known that brain vascular changes may be crucial in the etiology of neurodegeneration, but the precise mechanistic links are not established. Several regulatory mechanisms and cellular signaling (Ca2+ increases, oxidative stress, neuroinflammation,

endothelial dysfunction, hypoperfusion, brain-barrier disruption, cortical hyperexcitability, and neurotransmitter imbalance) are associated with vascular cognitive impairment (Hachinski et al., 2019; Vinciguerra et al., 2020). Moreover, the weighted and interactive relationships between the vascular lesion (i.e., subtype, location, severity), cognitive prognosis at different intervals or cognitive outcomes, and individual's neuroplasticity capacity (homeostatic changes or compensatory mechanisms) are not completely understood. From the CR perspective, genetics and lifestyle factors are likely associated with more efficient neural systems (Serra et al., 2017), activating compensatory process (i.e., brain resilience mechanism) after the emergence of brain pathology (Bigler & Stern, 2015), including cerebrovascular lesions (Arenaza-Urquijo & Vemuri, 2020). Otherwise, a complementary 'resistance mechanism', due to a genetic predisposition (e.g., APOE genotype), healthy habits (physical activity, healthy diet), or possible interactions between them and CR factors, has been proposed to explain inter-individual differences in the accumulation of neurodegenerative processes related to AD -amyloid /tau deposition- (Arenaza-Urquijo & Vemuri, 2018; Contador et al., 2022). Accordingly, this mechanism would help to prevent neurovascular changes (atherosclerosis) and brain dysregulations (neovascularisation, and inflammation) associated with the occurrence of vascular events (Saba et al., 2019).

The study of CR in stroke patients is relatively novel in comparison with studies developed in dementia or aging fields. Thus, further investigations are required to understand the remaining gaps. Previous research shows that education effect on cognition may be limited at certain levels of neuropathology (Gil-Pagés et al., 2019; Zieren et al., 2013). Thus, longitudinal evidence, including neuroimaging to accurately measure the burden and/or severity of neurological lesions, is required to explore the cognitive trajectories and recovery after stroke. In fact, psychosocial mechanisms underlying the association between CR and

post-stroke cognitive performance are also still unknown. In this context, CR should be understood as a multi-modal and dynamic concept susceptible of modifications throughout life and after brain injury. Moreover, the role of CR on cognitive decline after stroke should be characterized using different CR proxies and outcomes (e.g., cognitive domains) in order to elucidate their specific effects. Predictive models should also take covariates into account to characterize the importance of these moderators on cognitive/functional and behavioral outcomes. Finally, the effect of CR on functional performance after stroke and its influence on cognitive rehabilitation is almost unknown. In this line, further studies addressing this effect may be useful to adapt the rehabilitation treatment to the characteristics of the patients. The application of standardized comprehensive protocols agreed between researchers (i.e., clinical and health factors, cognitive/functional performance and neuroimaging) will be essential to better describe the relationship between CR and trajectories of cognitive change after stroke, as well as for their respective application in the clinical setting.

5. Conclusions

This systematic review highlights the importance of CR on cognitive trajectories after stroke. Nevertheless, individual characteristics (e.g., age, type of lesion, potential interactions between proxies) may contribute to modulate the inter-individual variability cognitive decline after stroke. Moreover, the heterogeneity of methodological approaches between studies (follow-up intervals, cognitive outcomes) have led to some discrepancies in the current findings. In the future, more investigation is required to understand the neurobiological and psychosocial mechanisms underlying CR, its specific contribution to cognitive prognosis and possible interactions with other healthy habits (e.g., diet, physical exercise). The promotion of CR mechanism and maintenance of brain health, through pharmacological or psychosocial intervention, will be essential to slow down the progression of cognitive impairment in vascular cases at risk of dementia/AD.

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7. Disclosure

None.

8. References

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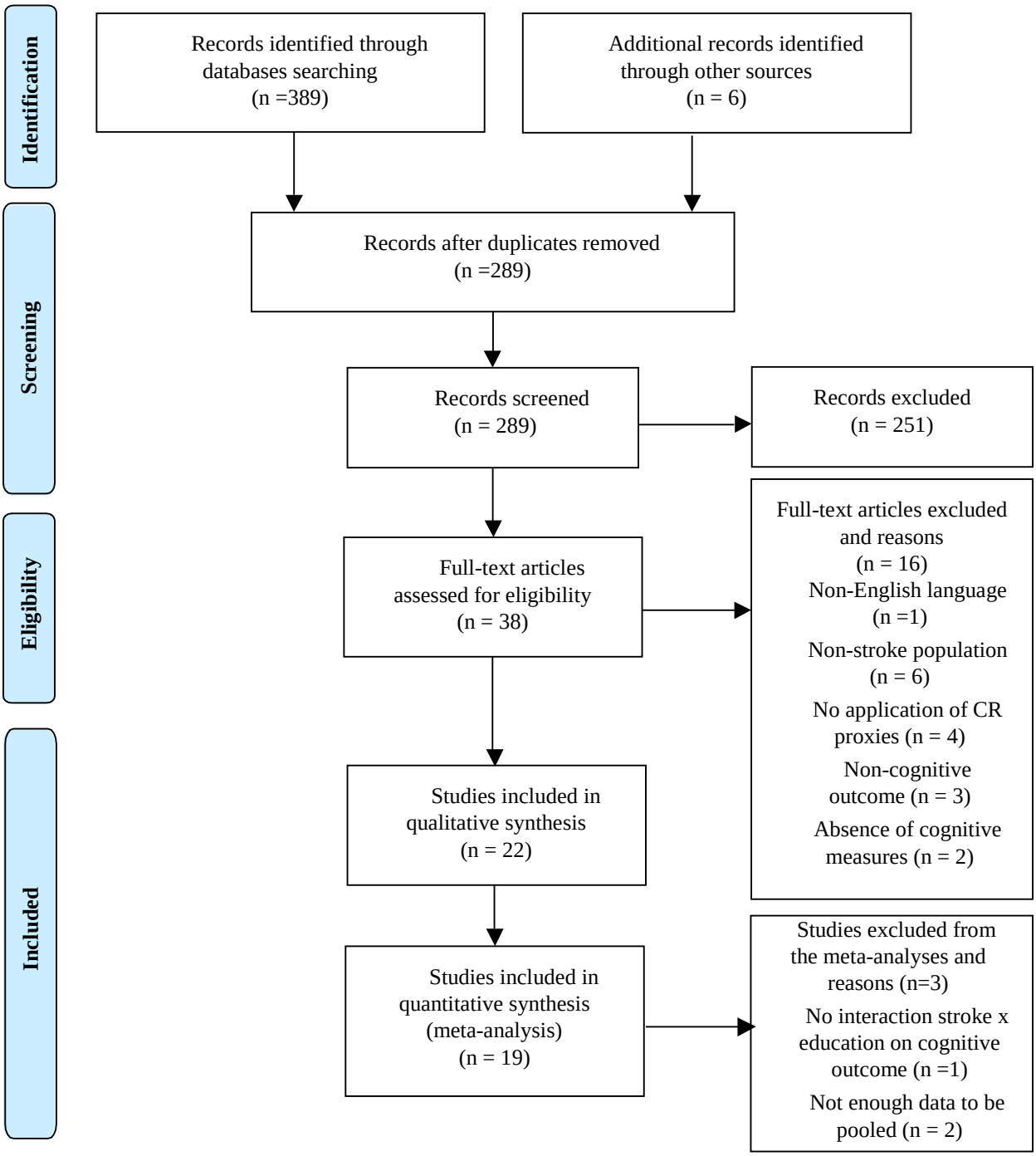
Figure

Figure 1. PRISMA Flow Diagram* for the selection of articles.



*_From:_ Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). _P_referred _R_eporting _I_tems for _S_ystematic _R_eviews and _M_eta- _A_nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Highlights

- Education shows a protective role against dementia after stroke.
- The effect of CR on post-stroke cognition is modulated by sociodemographic and clinical factors.
- Research designs influence the knowledge of prognostic factors associated with cognitive decline after stroke.
- Future research should overcome the methodological divergences between the studies and gaps identified in this field.

Supplementary Information from the Meta-Analysis

a) An *OR* > 1 was indicative of higher risk of cognitive impairment diagnosis (i.e., MCI or dementia) in the group with lower cognitive reserve (outcome 1); b) *OR* > 1 indicated higher cognitive change in the lower-reserve groups (outcome 2); c) *OR* > 1 pointed to poorer scores of the low CR group (vs. high) regarding the cognitive performance (outcome 3). The number of effect size estimates per study was used as a multi-level factor. The restricted maximum-likelihood estimator was used (under the inverse variance method) to estimate model parameters.

I^2 < 25% accounts for low heterogeneity between individual study effect sizes; moderate heterogeneity is endorsed by I^2 between 50%-75%, and high heterogeneity with I^2 > 75%.

Meta-regression model without covariates (i.e., unconstrained model), model including different covariates (covariates: participant's mean age, follow-up interval from stroke, type of diagnosis [dementia vs MCI diagnosis]/cognitive domain, depending on the outcome); and finally, the full model including the previously mentioned covariates and the CR proxy covariate; in meta-regression analysis for cognitive change and cognitive performance outcomes only two reserve types were included (non-specified CR vs. education), due to lack of studies for the occupation CR.

The Akaike information criterion (AIC) was used for selection of meta-regression model. In this regard, a better fit to data was endorsed by lower AIC values.

Supplemental Tables

Table 1s. Main characteristics and level of evidence of the studies by outcomes

Outcome subtype	Author and year	Type of study and level of evidence	Sample	CR proxy	Outcomes / Cognitive Domains	Covariates	Main results
1. CR and risk of dementia after stroke (ordered alphabetically)	De Ronchi et al. (2007)	Cross-sectional (population-based) *Level 3	N= 12.743 n= 7.930 (816 participants with stroke)	Years of Education (Low: 0-3 years)	**Global cognition:** MMSE; GDS	▪ Sociodemographic ▪ Clinical history ▪ Occupation ▪ Cardiovascular RF	Subjects with a history of stroke were at higher risk of suffering dementia and cognitive impairment. The association between stroke and dementia was greater in highly educated subjects aged between 61-74 years versus 75+ years.
	Jacquin et al. (2014)	Longitudinal (cohort-based; 3-months follow-up) *Level 2	280 stroke patients (ischemic or hemorrhagic)	3 levels of Education (Low: primary)	**Global cognition**: MoCA and MMSE **Memory, executive functions, praxis, visuospatial function and language:** Mattis Dementia Rating Scale, Rey Complex Figure, phonological and semantic fluency task, DMS48, and oral naming.	▪ Sociodemographic (age, sex, marital status, associative work) ▪ Cardiovascular RF ▪ Stroke severity ▪ Disability at discharge	The prevalence of dementia after stroke was 7.7% and the frequency of cognitive impairment, 47.3%. The latter was associated with age, low educational level, diabetes mellitus, acute confusion, silent infarcts and functional disability.
	Mirza et al. (2016)	Longitudinal (population-based; 10-years follow-up) *Level 2	N=12.561 n= 1.463 stroke or TIA patients	3 levels of Education (Low: primary, unfinished secondary and lower vocational)	**Global cognition**: MMSE **Executive Functions**: Stroop; Letter-digit substitution task; verbal fluency. **Memory**: 15-word verbal learning test **Fine motor skills and coordination**: Purdue pegboard test	▪ Cardiovascular RF	Stroke or TIA increased the risk of dementia in people with a low and intermediate level of education, versus those with a high level of education. Those with a high level of education scored better on cognitive tests before and after stroke or TIA; moreover, memory and

						executive function showed less decline in individuals with high education.
	Ojala-Oksala et al. (2012)	Longitudinal (cohort-based; 12-years follow-up) *Level 2	486 patients with ischemic stroke	Years of Education (Low: 0-6 years)	**Global cognition and neuropsychological battery** (executive function; memory; language; visuospatial/ visuoconstructive functioning)	▪ Sociodemographic (age, sex, marital status) ▪ Stroke characteristics (severity and location) ▪ White matter lesions	Higher education is associated with fewer cognitive deficits, dementia and favorable long-term survival.
	Pendlebury et al. (2019)	Longitudinal (population-based; 5-years follow-up) *Level 2	N= 92.728 n= 2.305 stroke or TIA patients	Years of Education (Low: <12 years)	**Global cognition:** MMSE and MoCA	▪ Sociodemographic (age, sex) ▪ Stroke characteristics (severity, location, recurrence) ▪ Premorbid Functionality ▪ Leukoaraiosis ▪ Dysphasia ▪ Cardiovascular RF	The risk of dementia 5 years after stroke was associated with age, recurrence and event severity, previous stroke, dysphasia, baseline cognition, low education, premorbid dependence, leukoaraiosis, and diabetes.
	Rasquin et al. (2004)	Longitudinal (cohort-based; 12-months follow-up) *Level 2	176 participants with first-time stroke	Level of Education (Low: primary education and vocational education)	**Global cognition:** MMSE	▪ Sociodemographic (age, sex) ▪ Stroke characteristics (type and severity) ▪ Cardiovascular RF	Six months after stroke, age, low educational level, territorial infarction, and pre-stroke brain damage were associated with dementia. At 12 months, the same variables plus silent infarcts were associated with dementia.

	Skoog et al. (2017)	Cross-sectional Comparing two cohorts (population-based) *Level 3	571 participants born between 1923-1924 and 783 participants born between 1901-1902	Years of Education (Low: <6 years)	**Global cognition**: MMSE	▪ Sociodemographic (age, sex, marital status) ▪ Birth cohort ▪ Stroke history	High educational level is associated with a lower prevalence of dementia; however, this effect is not significant after stroke.
2. CR and cognitive change after stroke (ordered alphabetically)	Gil-Pagés et al. (2019)	Longitudinal (24 months follow-up) case series with retrospective measures *Level 4	34 stroke patients (ischemic or hemorrhagic)	Static: Years of education (Low: <8 years) and occupation complexity Dynamic: cognitive stimulating activities	**Attention**: TMT-A; WAIS-III (Digit Span) **Memory**: RAVLT **Executive Functions**: PMR test; WAIS-III (Digit Span backward, Letter Number Sequencing)	▪ Age ▪ Stroke characteristics (age at stroke onset, type, years since stroke)	Static CR proxies were not associated with cognitive change after stroke. In contrast, dynamic ones were correlated with self-assessment of attention, metacognition, and functional ability.
	Glymour et al. (2008)	Longitudinal (cohort-based; 6-months follow-up) *Level 2	272 stroke participants (ischemic or hemorrhagic)	Emotional support and social ties	**Global cognition**: MMSE **Attention**: Digit Span forward **Language**: Repetition and Comprehension (BDA) **Memory**: Immediate and Delayed Recall of a 10-word list **Executive Functions**: Animal Naming test and TMT A and B	▪ Sociodemographic (age at stroke onset, sex, ethnicity, education) ▪ Stroke characteristics (severity and type) ▪ Previous diseases ▪ Diabetes ▪ Socioeconomic status	Emotional support can promote resilience or cognitive recovery after stroke, while social networks protect against cognitive decline after stroke.
	Ihle et al. (2020)	Longitudinal (cohort-based; 6-years	897 older adults	CRIq	**Executive Function**: TMT A and B	▪ Sociodemographic (age, sex) ▪ Stroke history	Participants with a history of stroke and little participation in cognitively stimulating activities significantly

		follow-up) *Level 3					showed a greater decline on the TMT scores after 6 years versus those with greater participation, where the difference was not significant. No other significant interactions were found between stroke history and other CR proxies (education or occupation).
	Lazar et al. (2008)	Longitudinal (90-days follow-up) *Level 3	22 with first-time stroke and aphasia	Level of Education (Low: less than a high school degree)	**Language (comprehension, repetition, naming):** BDA, WAB	▪ Sociodemographic (age, sex) ▪ Stroke characteristics (size and location) ▪ Language therapy	Education was not correlated with severity of initial language impairment or performance at 90 days.
	Makin et al. (2018)	Longitudinal (12-months follow-up) *Level 3	157 patients with ischemic stroke (lacunar or cortical)	Premorbid intellectual ability (NART-R)	**Global cognition**: ACE-R	▪ Sociodemographic (age, sex) ▪ Stroke characteristics (severity, type, previous history) ▪ Cardiovascular RF	Low levels of premorbid IQ and education are associated with greater cognitive decline after stroke.
	Sachdev et al. (2004)	Longitudinal (cohort-based; 1-year follow-up) *Level 2	128 stroke or TIA patients and 78 healthy controls	Premorbid intellectual ability (years of education and NART-R)	**Memory**: WMS-R **Executive Function**: Digit Span backwards, Similarities, Picture Completion, Arithmetic (WAIS-R); TMT A and B; Symbol-Digit Test; phonemic and semantic verbal fluency **Attention**: Digit Span forwards (WAIS-R) **Language**: Boston Naming	▪ Sociodemographic (age, sex) ▪ Cardiovascular RF ▪ ADLs	Low education and the presence of stroke or TIA were predictors of cognitive change at 1 year.

					Test **Visuoconstruction**: Block Design (WAIS-R) and copying simple figures		
	Shin et al. (2019)	Longitudinal (multicenter; 30-months follow-up) *Level 2	3109 stroke patients (ischemic or hemorrhagic)	Level of Education (Low: no formal education) and occupation	**Global cognition**: MMSE (Korean version)	▪ Sociodemographic (age, sex) ▪ Stroke characteristics (type and severity)	Low CR (composite index: education and occupation) is associated with a higher risk of cognitive impairment. The higher the CR, the faster the cognitive recovery after stroke.
3. CR and cognitive performance after stroke (ordered alphabetically)	Abdullah et al. (2021)	Cross-sectional *Level 4	80 stroke patients (ischemic or hemorrhagic)	CRIq	**Global cognition:** MoCA	▪ Sociodemographic (age, sex) ▪ Depression and anxiety ▪ ADLs ▪ Quality of Life	CR was significantly associated with cognitive function in stroke participants. In the regression analyses, education was a better predictor of post-stroke cognitive impairment than age or sex.
	Akinyemi et al. (2014)	Cross-sectional *Level 3	143 stroke participants and 74 healthy controls	Level of Education (Low: <6 years)	**Global cognition:** CSID; MMSE **Neuropsychological battery:** V-NB (attention, executive function/activation and mental speed; memory; language; visuoconstructive functioning)	▪ Sociodemographic (age, sex) ▪ Clinical factors (Cardiovascular RF, depressive symptoms, Pre-stroke CI) ▪ Stroke characteristics (type, etiology, location, disability)	Advanced age, low education, pre-stroke cognitive decline, and medial temporal lobe atrophy were independently associated with cognitive dysfunction.
	Alladi et al. (2015)	Cross-sectional (cohort-based)	608 patients with ischemic stroke (353	Bilingualism	**Global cognition:** ACE-R	▪ Sociodemographic (age, sex, literacy, occupation) ▪ Cardiovascular RF	Bilingualism leads to better cognitive performance after stroke.

		*Level 3	bilinguals)			▪ Stroke characteristics and previous history	
	Ardila et al. (2021)	Cross-sectional *Level 3	208 participants with post-stroke aphasia	Bilingualism	**Language:** WAB (Bengali version)	▪ Sociodemographic (age, sex) ▪ Level of education ▪ Stroke characteristics (lesion volume, type, and location)	Bilinguals show less severe aphasia than their monolinguals counterparts in the following conditions: more severe lesion, male gender, and subcortical stroke groups. Aphasia severity and education were not significantly correlated.
	Faroqi-Shah et al. (2019)	Cross-sectional *Level 3	23 with aphasia secondary to stroke and 20 healthy controls	Musical ability	**Language**: WAB-R; DSS (syntactic abilities)	▪ Sociodemographic (age, sex, education) ▪ Aphasia type ▪ Stroke characteristics (type, time after stroke onset) ▪ CRIq	Previous musical ability correlated negatively with aphasia severity. The language impairment did not correlate with CRIq scores.
	González-Fernández et al. (2011)	Cross-sectional (cohort-based) *Level 3	173 stroke patients and 62 TIA (controls)	Years of Education (Low: <12 years)	**Language**: Battery of language tests (oral and written naming of objects; tactile naming; reading words and pseudowords; dictation writing; auditory and written word-drawing verification task; repetition of words and pseudowords)	▪ Sociodemographic (age, sex, ethnicity and socioeconomic status) ▪ Stroke volume	Patients with a high level of education (12 years or more) made fewer errors in comprehension (oral and written), naming, reading and oral spelling versus those lower educated.
	Umarova et al. (2019)	Cross-sectional (cohort-	36 patients with ischemic	Years of Education (Low: <13	**Global cognition**: MoCA **Tonic alertness**: reaction time to various tasks	▪ Sociodemographic (age, sex)	More years of education were associated with less impairment in independent

		based) *Level 3	stroke	years)	**Working memory**: Digit Span **Executive functions**: Vocabulary tasks **Spatial neglect**: Bell's test; Ota task; Symbol Cancellation and reading tests **Crystallized intelligence**: IQ **Motor deficits:** Fugl–Meyer test for the upper limb	▪ Cardiovascular RF ▪ Stroke volume	(alertness) and dependent (working memory, executive functions and global cognition) domains of education.
	Umarova et al. (2021)	Cross-sectional *Level 4	153 ischemic stroke patients (chronic stage).	Years of education (Low: <12 years)	**General cognition:** MoCA	▪ Sociodemographic (age) ▪ Stroke characteristics (severity, lesion size)	Younger and high educated individuals performed better in the cognitive outcome. Larger lesion size was compensated by high educational level and younger age. These factors influence cognitive performance even when the lesion size is small.

Abbreviations: ACE-R, Addenbrooke's Cognitive Examination-Revised; ADLs, Activities of Daily Living; BAT, Bilingual Aphasia Test; BDA, Boston Diagnostic Aphasia; CLQT, Cognitive Linguistic Quick Test; CR, Cognitive Reserve; CSID, Community Screening Instrument for Dementia; DMS, Delayed Matching-to-Sample; DSS, Developmental Sentence Score; GDS, Global Deterioration Scale; GNT, Graded Naming Test; IQ, Intelligence Quotient; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NART-R, National Adult Reading Test-Revised; PMR, verbal fluency test using "P" and "M" letters; RF, Risk Factors; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Test; V-NB, Vascular Neuropsychological Battery; WAB, Western Aphasia Battery; WAIS-R, Wechsler Adult Intelligence Scale Revised; WMS-R, Wechsler Memory Scale– Revised.