Social Isolation as Risk Factor of Stroke: Protocol for Systematic Review

Laura Flavorta Billong, Jiantong Shen, Garba Betchem

School of Nursing sciences, Huzhou University, Huzhou, China.

Abstract— Introduction: The purpose of this study protocol is to provide the methodology of the review and to estimate the influence of social isolation on stroke incidence. The negative influence of psycho-social factors on the health of individuals has been discussed in several literatures [7–13] but the mechanism of social isolation on stroke occurrence has been not clearly explained in the previous studies as a very high risk factor to fear. It's that why is very important to plan this systematic review in view to have a good understanding about the relationship existing between isolation and stroke occurs to have a good follow-up of this disease.

Methodology: A complete search of published studies will be conduct until May, 2021 using MEDLINE, Embase, PubMed, Science Direct and Springer. Prospective and retrospective studies to evaluate the influence of social isolation on stroke incidence. After eliminating copies, the eligible articles will be screened by researchers then extraction and evaluation of the quality data will be done independently. Any disputes will be solved by discussion or the arbitration of a third author.

Ethics: Moral consent is not intended for the study, as we will only collect data from published available articles. This paper will be conducted to a peer journal for publication after completion.

I. INTRODUCTION

Stroke also known as a cerebrovascular accident that occurs when the supply of blood to the brain is reduced or blocked completely. This chronic disability has a significant emotional and socio economic repercussion in the world [12,3]. Moreover, it is also one of the main causes of death in China [4]. Consequently stroke constitutes and remains a major public health issue, especially due the significant costs it generates for example in United States, every 30 seconds we have a new stroke, and every 5 minutes we record one death from stroke; the estimated cost of stroke in the United States is $33 billion [5]. Stroke affects the physical, cognitive and social functioning of humans [6]. The primary prevention of this pathology in most cases is to

resumed lifestyle habits such as not smoking, eating a healthy diet, regularly physical activities. Social isolation is an irregularity of social support can be cause by health issues or loss of mobility.

The physical and mental health are linked and the negative health effects of social isolation range from insomnia to reduced immune function. Isolation is linked to very high rates of depression, suicide and anxiety. It is also associated with poor cognitive function. Nevertheless the poor influence of psycho-social factors on the health of individuals has been discussed in several literature [7–13] and social isolation in particular has been demonstrated as a very high risk factor of stroke with a global rate of about 48% of cases and an underappreciated determinant of physical

health[14–19]. Therefore, this factor should be given careful consideration and should be regarded the same way as other risk factors of stroke cited by WHO, 2011 (alcoholism, hypertension, hypercholesterolemia, diabetes, lack physical exercise, smoking).

Problem research: Current studies comprising of more than 600,000 participants established that socially isolated people have a 70% chance of being exposed to risk factors of stroke than people who have high levels of social support [20]. Therefore social isolation contributes to the overall process of stroke in humans [21]. Nonetheless, the underlying mechanisms in this regard are still unknown [22]. Moreover, it is important to note that the harmful effects of social isolation can be modeled in humans and given that many "isolated" people are unidentified until they come to medical attention when a stroke occurs. Therefore, assessing the effects of social isolation on the occurrence of stroke is essential in translating efforts done in targeting social factors in stroke.

Seen from this perspective, the purpose of our study is to evaluate the link between social isolation and the incidence of stroke, which is recognized as one of the most frequent reasons of death in the world. We therefore showed a systematic analysis to answer the main **question**: what is the impact of the absence of social contact on the occurrence of strokes in the world?

The second goal is to identify the relationship between the absence of social interactions and the incidence of stroke and whether it varies by age, socioeconomic status and sex.

Why this review is important

The purpose of this study is to comprehensively examine social isolation as a potential risk factor of stroke. Identifying and understanding social isolation relation to stroke could allow future research to address specific risks and update potential studies to target stroke prevalence. Thus, this review not only takes a dimensional approach to include social isolation as a risk factor of stroke, but also includes age and gender difference.

Objectives

The primary aim of the systematic review is to determine whether people with socially isolated are at greater risk of a subsequent cerebrovascular event (stroke) than those socially active.

1. To examine risk factors linked to social isolation and incidence of stroke

2. To examine whether there is a significant effect of age, sex difference between social deprivation and incidence of stroke.

II. MATERIAL AND STATISTICAL ANALYSIS METHODS

2.1 Search Strategy

We will identify studies published through the articles of MEDLINE, Embase, PubMed, Science Direct and Springer (from the databases' until May, 2021).To capture relevant articles, the multiple search terms will be use, including: "lack of social relationship", "social skills", "social contact deprivation", "living alone", "social isolation" which will be cross with the terms such as "transient ischemic stroke", "cerebrovascular disease", "cardiovascular event", "intracranial hemorrhage", "isolation" "stroke", And we will use the following search strategy: ((((((deprivation[Title/Abstract]) OR isolation[Title/Abstract]) OR exclusion[Title/Abstract])) OR lack of[Title/Abstract]))) AND (((((social support [Title/Abstract]) OR social contact [Title/Abstract]) OR social interaction[Title/Abstract]) OR social intercourse[Title/Abstract]) OR social communication[Title/Abstract] OR social skills[Title/Abstract]))))) AND ((((ischemic stroke[Title/Abstract] OR hemorrhagic stroke[Title/Abstract] OR all strokes[Title/Abstract] OR transient ischemic attack[Title/Abstract]) OR intracranial hemorrhage[Title/Abstract]) cardiovascular event OR cerebrovascular disease[Title/Abstract]))))).In addition to this search approach, reference lists of all important analyses will be explored, and a reference search cited will be conducted using the Institute of Scientific Information's Web of Science. The search strategy will be developed after discussion among reviewers, according to the guidance of the Cochrane handbook. The indexes of all retrieved and relevant publications identified by the above strategies will be searched for further studies. To minimize accidental omissions, we will perform two searches of each database, with searches ending in May 2021. Second, we will look the references of previous reviews and studies that meet the inclusion criteria to find articles.

2.2. Selection criteria

Inclusion criteria: articles that studied the influence of social isolation in situations where people lived alone with a few group activity circle and/or a few physical contacts (structural isolation) or they were not interacting with the others by phone, internet as no call, no message, no email (functional isolation), presenting an incident of stroke as a result and had reported either odds ratios, relative risk or risk ratios with 95% of CIs. Case controlled studies, cohort studies, randomized controlled studies and controlled studies, correspondence with relevant clinical data, will be included for further review.

Exclusion criteria: ineligible studies will not be reported and the motives for exclusion will be documented. Additionally, repeated publications on the same subjects will also be excluded.

2.3. Study Selection and Data Extraction

We will import our search results into Mendley software before selecting. We will screen through two processes. In the primary phase, two investigators will independently browse identified articles' titles or abstracts or both, and full text to identify the potentially eligible ones. In the second phase, a third investigator will resolve any discrepancies till an eventual consensus is reached. This will be done according to the Cochrane book methods for Reviews [23], the extraction sheet will include information such as study design, interventions, method, conclusions, participants, sources of bias and outcomes. The PRISMA flow diagram will be shown in a flowchart (figure 1).

We will construct extraction tables in Microsoft software. Data from included papers will be drawn by two authors. Disputes will be decided by discussion with a third author. The data will be drawn according the categories: study designs, Main population, control/ comparator groups, and the investigated clinical outcomes. The liaison between social isolation and stroke incidence will be also included, measuring as odd ratio (OR) or hazard ratios (HRs).

Participant(s): Patients who have all kind of stroke (men or women) no sex restriction.

Investigation(s): Social isolation is a state when people withdraw and become disconnected from family, friends and community.

Control/Comparator(s): No restrictions will be made on the comparisons and/or control group

Outcome(s): The key outcome of the review is to identify published article describing indicators relevant to incidence of stroke.

Other important outcomes include stroke mortality and social isolation risks factors, as well as all other unintended effects of the stroke. We will prioritize those studies with a longitudinal study design that calculate effect estimates as either HRs or incidence rate ratios, but will also consider those studies that report ORs if it can be determined that subjects had not had a stroke event preceding the starting of study period.

2.4. Bias risk assessment

The bias risk assessment tool revised by the Cochrane Effective Practice and Organization of Care (EPOC) Group[24]. Authors will independently assess the risk of bias in the included studies. Any discrepancies will be fixed through discussion or in consultation with a third reviewer.

We will evaluate individual studies to have 'low', 'unclear' or 'high' risk of bias. Low risk of bias is plausible bias unlikely to alter results, unclear risk of bias is plausible bias that raises some doubt about the results and high risk of bias is plausible bias that seriously weakens confidence in results.

For non-randomized controlled studies, we will judge the risk bias from seven aspects, and distinguish confusion bias, study participants, intervention classification, expected intervention bias and missing data. We summarize the overall deviation as "low", "medium" or "critical". We summarize the risks of bias in two tables to illustrate these findings. Differences will be resolved through discussions between authors or with third-party authors until consensus is reached.

2.5. Data synthesis

The effect of social isolation on the incidence of stroke will be included as relative risk (RR) without tuning of initial variables. If adjustments are made, we will use risk ratios (SSR) taking account the basic differences in the relevant prognostic variables. More specifically, these HRs will represent the pure effect of social isolation on morbidity or mortality. For both measurements, corresponding confidence intervals (CI) will be used to calculate the accuracy of the effect. The final results will appear in a table two by two, we will calculate the RR values separately. As a result, all odds ratios will be converted to RRs according to Yu & Wang approach[25]. All analysis will be conducted using StataSE[26], and the reported summary statistics will be calculated as random effect models based on the idea of heterogeneity between studies. The ICR will represent 95% ranges, which will indicate a significant effect when the values of 1.0 are excluded from the RR or HR values. HR or RR 1.0 values will indicate a social isolation effect on stroke development.

Heterogeneity between studies will be assessed by examining forest plots of study, calculating a chi^2 heterogeneity test, and statistics I^2[23]. The chi^2 test value between studies will be heterogeneous if exists a statistically significance. In addition, higher I^2 values will indicate greater variability between studies which might be expected, due to the random threshold (0% to 100%) [27] Proposed indicators of low-slung, moderate or high I2 values of 20%, 40% and 70% heterogeneity. If possible, we will also perform a subgroup analyses for age, gender and social activity. The results of selected studies will be presented in tabular form, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach will be used to evaluate the quality of evidence[28].

2.6. Subgroup and sensitivity analysis

If there is ample data available, subgroups analyses will be performed. These analyses will assess Age, sex, between the patients, stroke risk factors (obesity or overweight, physical inactivity, dietary factors), quality and risk of bias. We will also conduct a sensitivity analysis to determine the effect of various factors, where applicable, and the degree of the effect. We will stratify analyses per journal status and level of risk of bias to decide if studies with high risk of bias affects the results.
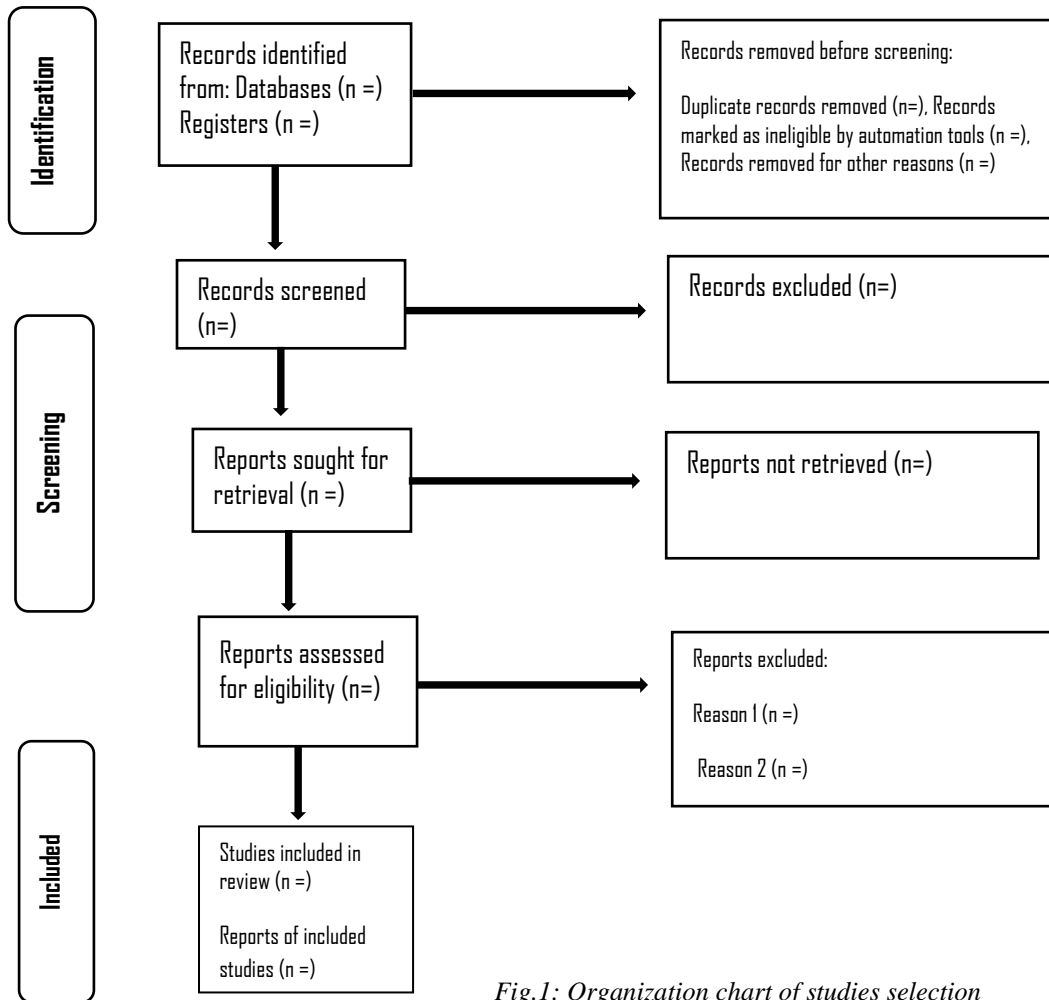

Fig.1: Organization chart of studies selection

Evaluating reporting bias

Given sufficient numbers of papers (more than 10), the funnel plots will be used to measure the probability of outcome reporting bias (publication) and a Begg's test for asymmetric tests. If, however this is not possible we will discuss the able bias sources across studies and bear this limitation in mind when drawing our conclusions.

Patient involvement

No patient is involved in the development of the plans for the project and the implementation of this study. They are not invited to give advice on reading the results. The final results will be disclosed through the author's publications.

III.   DISCUSSION

The findings of this systematic review may influence future health policies for stroke prevention and management. By understanding all the risk factors that can contribute to the incidence of stroke worldwide, psychosocial factors such as social isolation could be re-examined and taken into account as one of the silent factors with serious consequences in order to increase relevance for better follow-up. As noted in the approach, most reviews of stroke risk factors were limited to factors such as: hypertension, obesity, chronic stress, poor diet, alcoholism, smoking, physical inactivity. Although these factors are recognized globally, this study will aim to capture data demonstrating the impact of social isolation in stroke occurrence.

However, there is still ambiguity about the implication of social isolation in the occurrence of strokes, as others have

presented it as one of the methods of post-stroke recovery. In view of this, despite the relevance of the strong evidence that positively associates it with the risk of many non-communicable diseases, it would be difficult to judge the role that social isolation plays on the incidence of stroke. It remains to be seen whether social isolation is really a factor in promoting stroke, but so far the answer is still controversial because there is not enough meta-analysis to discuss the questioning.

The study eligibility criteria included for this systematic review will ensure that global data on social isolation and stroke are captured. Currently, psychosocial factors and stroke prognosis are misunderstood, which may partly explain why interventions at this level are neglected. Clinicians tend to focus on education and communication interventions related to lifestyle (food hygiene, physical activities) public awareness campaigns. Current data on the psycho-social factor associated with stroke in this study may be of future input into evidence-based health policies. Therefore, it is very important to conduct this systematic review to shed light on the impact of social isolation on stroke development. Nevertheless, this systematic review will have some limitations. The medical databases in other languages (e.g., Dutch, Spanish, Korean and Japanese) will not be covered because of language barriers, so a language bias may exist. However, our goal is to summarize the published direct evidence and provide evidence-based suggestions for clinical use in stroke prevention.

AUTHOR CONTRIBUTIONS

IV. INSTITUTIONAL REVIEW BOARD STATEMENT

This study was conducted according to the guidelines of the Declaration of Huzhou University, and approved by the Institutional Review Board of PROSPERO (registration number: **CRD42021254102,** approved on 10 September 2021)

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