Neurology Asia 2024; 29(3) : 553 – 558

Risk of stroke in Alzheimer's disease: A meta-analysis

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Abstract

Background: Stroke occurs when a blood vessel of the brain narrowed or completely blocked. Stroke and Alzheimer's disease (AD) are the commonest diseases in elderly. Some studies confirm the association between AD and the increased risk of stroke. *Methods:* In present meta-analysis we conducted a systematic analysis on risk of stroke in AD patients. A thorough literature search was conducted using different databases, including Google Scholar and MEDLINE. The present metanalysis includes all the studies published from 2010 to 2023. We found more than 57,260 matching results and five were relevant to our area of interest and met all the selection criteria. *Results:* All the selected studies confirm the association of stroke with AD. The AD patients were al higher risk of stroke (ischemic and haemorrhagic) than the normal individuals.
Conclusion: Present meta-analysis confirms the significant association of AD with stroke. There were only five studies available. To validate the results further evidences are required.

Keywords: Alzheimer's disease, stroke, age, DALY, ischemic stroke, hemorrhagic stroke

INTRODUCTION

Stroke is one of the leading causes of loss of disability adjusted life years (DALY) and one of the commonest causes of mortality all over the world.[1] It is a very debilitating disease, causing physical as well as mental illness in the patients.[2] It is currently one of the most common causes of health impairment worldwide.[3] According to the Global Stroke Factsheet 2022, the risk of developing stroke has increased by 50% over the last 17 years, and 1 out of 4 people have suffered from stroke in their lifetime.[4] Stroke and Alzheimer's disease (AD) often co-exist, but the cerebrovascular changes associated with AD start many years before the occurrence of stroke.[5] The risk of stroke can be related to many factors, such as gender, age, CVD, smoking, other lifestyle factors, or the medical history of chronic disorders. One of the most common age-related neurodegenerative disorders is AD, but there are only few studies which confirm the high risk of stroke in AD patients.[6] Both ischemic and hemorrhagic strokes can be associated with AD. The most common stroke is ischemic (approximately 85%), which causes more debility and mortality than hemorrhagic (approximately 15%).[7] The aim of the present study was to study the direct relationship between the risks of both ischemic as well as hemorrhagic strokes in AD patients and compare the data with the risk of stroke in the non-AD population. We performed a meta-analysis of available human studies reporting the risk of stroke in AD patients and performed a meta-analysis.

METHODS

Data sources and search

A systematic search of original articles (on human studies only) was conducted by the investigators (J. Liu and X, Wang) from search engines Google Scholar and MEDLINE published between 2010 and 2023. The keywords used were "stroke and Alzheimer's", "risk of stroke and Alzheimer" and "ischemic stroke and Alzheimer". Out of 57,262 articles, most of the studies were not relevant with the area of interest, or were performed on other animals like mice and rats, etc. After a thorough screening, we selected 6 articles for further analysis, but one of those had some missing information about the patients, and included the dementia caused by other neurological disorders such as Parkinson's disease, so we removed that article. In our final analysis, we used five studies from different countries published between 2010 and 2023.

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Date of Submission: 22 August 2023; Date of Acceptance: 29 April 2024
https://doi.org/10.54029/2024jkp

Study selection

The screening of the articles was conducted through review of the title and the abstracts of the articles with relevant topics. The inclusion/ selection criteria include: i. The research was only on human with AD; ii. All the selected articles were in English.

Data extraction

After the primary screening (Data search) and the secondary screening (mentioned in study selection area) secondary screening procedure, based on the predefined inclusion and exclusion criteria, the full-text formats of the selected studies were collated and subjected to a data extraction process. Data extraction followed extrapolative approach, with the selected full-text studies being examined for metanalysis (patients with AD and its association with the stroke) individually by two reviewers who were expert of the topic selected, a process designed to generate redundancy while reducing individual error. After carefully reviewing the data, duplicate information was removed from the list, and the final data set was for analysis.

Data analysis

Data from different and reliable sources was used for the meta-analysis. The meta-analysis was conducted using the Comprehensive Meta-Analysis (CMA) software (version 6). Present metanalysis includes a total of five studies, which comprises 82,190 individuals (42,944 control and 39,246 AD patients. We divided our study into two parts. One included the strokes / 1000-year (Strokes/1000 person-years) AD patients (5 studies were selected for analysis in this part). The other part included three studies (two studies were removed in this case as the data of the control group was not present and the studies were carried out only on AD patients).

RESULTS

The search strategy provided a total of 57,264 studies (56,200 from Google and 1062 from MEDLINE). Most of the studies were excluded from the primary screening itself as most of them were not relevant to the topic, and some of the articles were not freely available. Further, after removing the duplicates and unrelated articles, only six studies with 95% CI values for OS that were directly related to the topic were included in the final meta-analysis. One of the six selected studies had the data of the patients along with other neurological disorder such as Parkinson's disease. We excluded the data of the patients with other neurological disorders. Only the data of the AD's patients was selected for our studies. The data was subsequently extracted from the selected studies as per the defined data extraction procedure to perform the meta-analysis. The entire process of selection was carefully monitored by the other researchers to remove any bias or irrelevance from the study. The selection strategy is represented as a flowchart in Figure 1.

Study characteristics

The five studies were included in the present meta-analysis. The selected studies were conducted in five different countries across the world, as mentioned in Table 1. The studies were from the USA, Taiwan, Finland, Sweden, and the Netherlands, one from each country (n = 1). All of these studies were large-scale retrospective studies except one (Netherlands), representing a total cohort of 152,908 participants; out of them, 109,964 were AD patients. Further analysis of these data confirms that most of the studies had a higher percentage of the female population (53.848 percent of the total cohort). The mean age of the total cohort was 76.488 years, which suggested that the risk of stroke was high in individuals above age 70 and above.

Meta-analysis

As per description in the methodology section, the meta-analysis of high-risk was performed in two subgroups. The subgroups were based on the potential risk of stroke in Alzheimer's patients (n = 109,964) and the risk of stroke in normal individuals (n = 42,944). The pooled results from both studies were represented as a table as well as a forest plot.

Meta-analysis subgroup with Alzheimer's disease patients and risk of stroke

In the present group, we studied the association of AD with the risk or incidence of stroke. The analysis of this subgroup is based on five studies. The random-effects model was employed for the analysis. A total of five cohorts of studies were pooled in this subgroup to determine the incidence or risk of stroke in AD patients (Figure 2). All the studies showed a direct correlation between AD and the incidence or risk of stroke. ($p<0.05$) The pooled effect estimate was found to be statistically

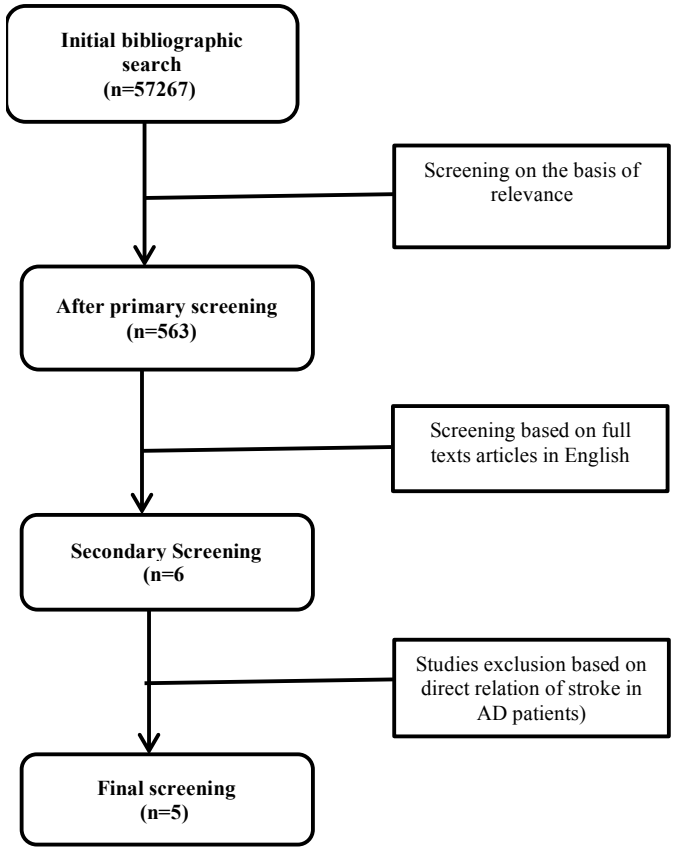

Figure 1. Search strategy

significant, with an event rate of 0.010 (95% CI in Figure 3).

Meta-analysis subgroup with non-Alzheimer's disease individuals and risk of stroke

Two studies in this group were removed as the normal control was missing in them so the present analysis is based on three studies. The incidence of stroke was 0.0.010 (95% CI 0.001-0.005) among AD patients than non-AD individuals, (0.002) (Figure 3).

Table 1: Study characteristics of included studies for meta-analysis

Study Name	Year	Country	Cohort Size	Control	AD patients	Type of Study	% female	Strokes/ 1000 person-years	Strokes/ 1000 person-years	Mean Age
Chi *et al.*[7]	2013	Taiwan	e	4900	980	Population-based	59.06	23.2	37.8	72.12
Cook *et al.*[8]	2015	USA	19,902	9,951	9951	National registry	59.9	12.0	15.9	79
Tolppanen *et al.*[9]	2013	Finland	56,186	28093	28093	national register	67.7	59	57	80.12
Taipale *et al.*[10]	2017	Sweden	70 718	NA	70718	national register	40.58	34	197	80
Benedictus *et al.*[11]	2015	Nether-land	222	NA	222	Clinic Based Study	4	0	42	71.2

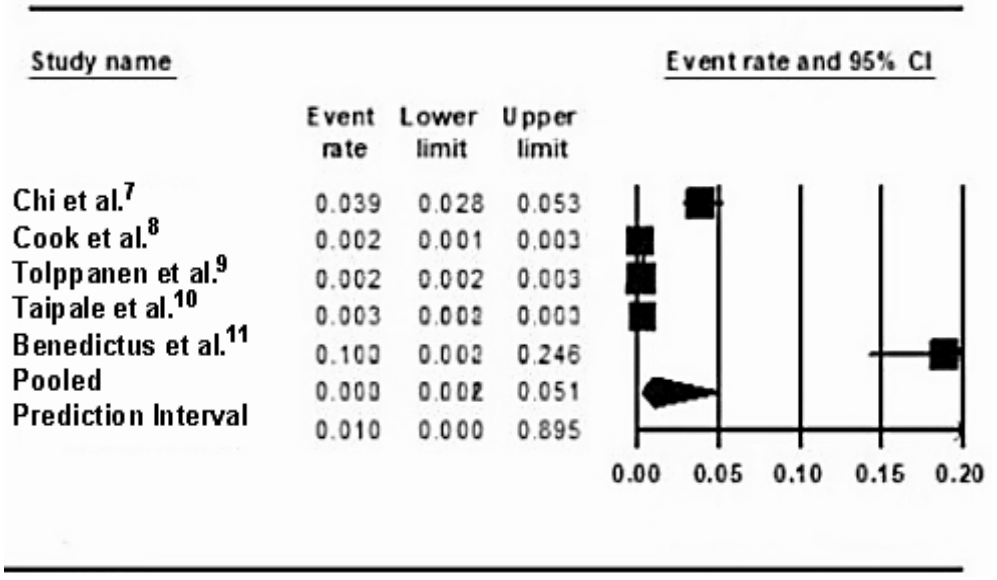

Figure 2. Meta-analysis subgroup Alzheimer's patients and risk of stroke

Assessment of risk of bias

Observational studies' risk of bias was evaluated using a modified version of the Newcastle-Ottawa Scale, which rates the degree of bias as low, high, or uncertain using the same criteria as the Cochrane Risk of Bias tool and evaluates research quality based on selection, comparability, and outcome.[12,13]

DISCUSSION

AD is one of the major causes of dementia. The hallmarks of AD are extracellular accumulation of amyloid-β peptide (Aβ) is one of the significant hallmarks of the AD.[14] Stroke is another major cause of dementia especially ischemic stroke, which is responsible for more than 85% of incidences.[15] Both AD and stroke exert a great burden on public health globally. Recent researchers indicate the link between AD and ischemic stroke. Several evidences suggested that they share some pathophysiological similarities. One of the important shared mechanisms is the change in protein kinase C enzyme (PKC) activity. PKC isoforms are known to have a

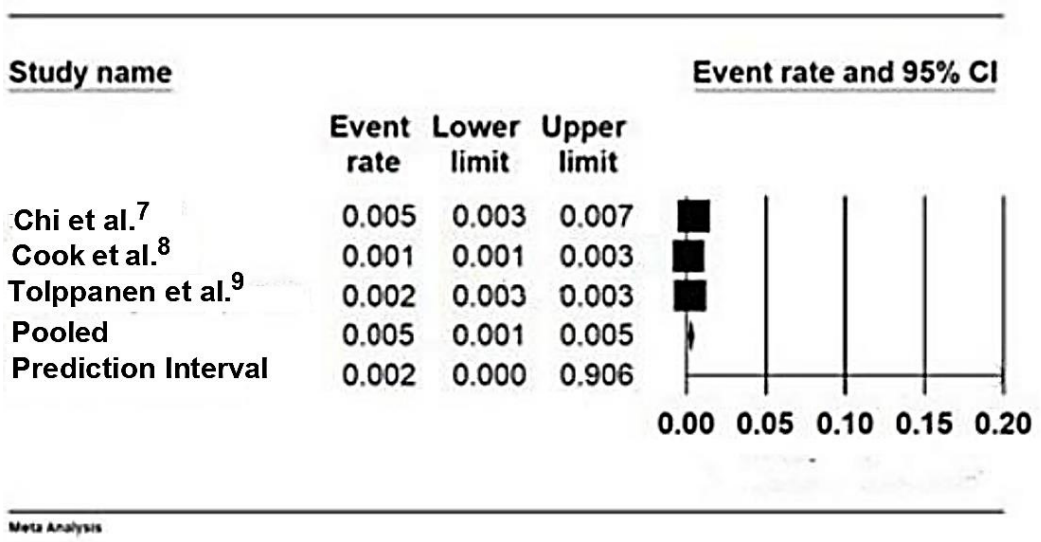

Figure 3. Meta-analysis subgroup with non-Alzheimer's disease individuals and risk of stroke

vital role in blood-brain barrier maintenance, repairing injuries, and, most importantly, in memory.[16] Disease conditions enhance PKC functional modifications, and mutated PKC can be responsible for neurodegenerative disorders.[17] Although in some conditions the PKC isoforms are functional, their translocation within the cells gets disrupted, which can increase the chance of stroke and the accumulation of amyloid-β in the brain. Although the association between AD and stroke is not yet clear, but the role of PKC in both cases could be the link between these two diseases.[18]

In the present study, we performed meta-analyses to confirm the association between stroke and AD. In this meta-analysis, we compiled the data from five pieces of research conducted in 5 different countries across the world. The study comprises 82,190 individuals (42,944 non-AD and 109,964 AD) from the USA, Netherlands, Taiwan, Finland, and Sweden. In all the studies, the relative risk was higher in AD patients than in normal individuals. We did not study the ischemic and haemorrhagic strokes separately, as we had a limited number of studies, and few of them mentioned the risk of ischemic and haemorrhagic strokes separately. In two studies (Taipale *et al*.[10] and Benedictus *et al*.[11]), the study was performed only on AD, and did not have the normal control, so we excluded these two while analysing the risk of stroke in normal individuals.

In conclusion, AD and stroke are certainly associated with each other; the risk of stroke in AD patients is higher than the normal individuals. However, more extensive cohort studies are required on larger populations to prove the association of AD in ischemic or haemorrhagic strokes.

ACKNOWLEDGEMENT

We would like to acknowledge the First Affiliated Hospital of Xi'an Medical University for its financial and technical support.

Financial support: Xi'an Science and Technology Plan Project (No.20YXYJ0007(2)).

Conflicts of interest: None

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