



Review article

Metabolic syndrome and stroke: A meta-analysis of prospective cohort studies



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ABSTRACT

Background and aim: The relationships between metabolic syndrome (MetS) and risk of incident stroke are inconsistent. We summarized the evidence by a meta-analysis of prospective cohort studies.

Methods and results: We searched the PubMed, EMBASE, and Google Scholar databases from their inception until June 2016 for prospective cohort studies investigating this research question, relevant information was extracted by two independent investigators, and then aggregated using the fixed-effects models.

Methods and results: We identified 16 studies, including 116,496 participants who were initially free of cardiovascular diseases. Comparing the persons without MetS, those with MetS have a significantly higher risk of incident stroke, and the pooled relative risk (RR) was 1.70 (95% confidence interval (CI): 1.49–1.95). Subgroup analyses suggested that women were more sensitive to this effect (with an RR of 1.83, 95% CI: 1.31–2.56) than men (RR = 1.47 (95% CI: 1.22–1.78)). And those with MetS have a significantly higher risk of ischemic stroke (RR = 2.12, 95% CI: 1.46–3.08) than hemorrhagic stroke (RR = 1.48, 95% CI: 0.98–2.24).

Conclusions: This meta-analysis suggests that metabolic syndrome might be an important risk factor of stroke, particularly among women and those with ischemic stroke.

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1. Introduction

Metabolic syndrome (MetS) represents a group of risk factors that may increase one's risk for heart disease and other health problems, which is characterized by at least three of the following five conditions: central obesity, hypertension, elevated urine glucose, high serum triglycerides, and low high-density lipoprotein (HDL) levels [1]. MetS has been now recognized as one of leading health threats in most countries around the world. Data from the Population-Based National Health and Nutrition Examination Survey (NHANES) showed that more than 47 million individuals in the United States have metabolic syndrome [2], and a previous population-based epidemiological study reported that more than 30% Chinese adults suffered from metabolic syndrome [3].

The term “metabolic syndrome” (MetS) was first described about 20 years ago [4], since then, several MetS definitions have been proposed by different organizations (including the World Health Organization [5], European Group for Study of Insulin Resis-

tance, National Cholesterol Education Program (NCEP) Adult Treatment Panel III [6], American Association of Endocrinologists, International Diabetes Foundation (IDF) [7], and American Heart Association/National Heart, Lung, and Blood Institute) [8]. Among them, The NCEP guidelines have become the most widely used definition because of its ease of use for diagnosing the metabolic syndrome [9]. This definition uses only simple clinical measurements of fasting plasma glucose (PG), waist circumference (WC), triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) levels as well as blood pressure (BP), the NCEP criteria is more practical and found to be a better predictor of cardiocerebrovascular disease risk.

A number of studies have examined the association between MetS and cardiovascular diseases with conflicting findings [10,11]. In 2005, the American Diabetes Association and the European Association for the Study of Diabetes issued a joint statement summarizing the issues surrounding the metabolic syndrome. They underscore the need to quantify the cardiovascular risk associated with the metabolic syndrome [12]. Among them, the association between MetS and stroke incidence has not been well established. We therefore performed a meta-analysis of cohort

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studies with the aim to examine the association between metabolic syndrome and stroke.

2. Methods

2.1. Literature search

We searched PubMed, EMBASE, and Google Scholar databases from their inception through June 2016 by using the following Mesh Terms or key words: cardiovascular risk, cardiovascular disease, stroke, metabolic syndrome, syndrome X, National Cholesterol Education Program Adult Treatment Panel III, 'cohort studies' and 'prospective study'. Furthermore, a manual search of citations from relevant original studies and review articles was performed for additional studies not identified in the database search. The search was restricted to studies conducted in human subjects and the language was restricted to English.

2.2. Study selection

Studies meeting the following criteria were included in the meta-analysis: (1) prospective cohort studies published as original articles; (2) use of the NCEP definition of metabolic syndrome; (3) reported outcomes as count data, or as relative risk (RR) or hazard ratio (HR) with a corresponding measure of variance or sufficient data to calculate them; (4) a minimum follow-up period of one year; and (5) participants with CVD at baseline were excluded.

2.3. Data extraction and quality assessment

The following information was independently extracted from the original studies by two investigators. These data included information about study design sample size, characteristics of the participants, study period and duration of follow-up, characteristics of study population, the setting, and definitions for metabolic syndrome. Quality assessment for cohort studies in this meta-analysis was assessed using the Newcastle Ottawa scale (NOS), which regarded five or more of the NOS criteria as high quality.

2.4. Statistical analyses

The pooled RR with corresponding 95% CI was calculated to represent the overall association between Mets and incident stroke using the "metafor" package in R. The pooled RR was computed using either fixed-effects models ($I^2 < 50.0\%$) or random-effects models in the presence of heterogeneity ($I^2 > 50.0\%$). The amount of possible heterogeneity was tested with the Q-test of homogeneity. A sensitivity analysis was performed to validate the stability of outcomes by sequential removal of each individual study. Publication bias was estimated using a funnel plot and modified Egger's linear regression test. All statistical analyses were performed with R 3.2.3. All tests were two-sided and a p value < 0.05 was considered statistically significant.

3. Results

3.1. Literature search and study characteristics

Our initial searches identified a total of 133 studies, after removal of duplicate and irrelevant articles by title and abstract review, a total of 16 eligible studies met our inclusion criteria and were included in our systematic review [13–28]. A total of 116,496 participants were included in these studies. Study follow-up period ranged from 3.0 to 21.3 years. The prevalence of metabolic syndrome varied from 9.0% to 51.8%. Among the 16

studies, three were performed in the USA, three in Europe, and 10 in Asia. All the included studies showed high quality, with quality scores ranging from six to nine points (Table 1).

3.2. The metabolic syndrome and risk of stroke

The RR of stroke associated with metabolic syndrome in each study and the overall estimate was shown in Fig. 1 according to NCEP definitions. No significant heterogeneity was observed among those studies. Overall, the pooled RR of stroke in studies that adopted the NCEP definition was 1.70 (95% CI, 1.49–1.95).

3.3. Individual components of metabolic syndrome and the risk of stroke

As shown in Table 2, all the five components of the MetS had an increased risk of developing stroke. The point estimates was highest in the group with elevated blood pressure (RR = 1.69, 95% CI: 1.16–2.47). In addition, we evaluated the association between the five components of MetS and stroke risk by dividing into male and female respectively, which showed that woman with elevated glycemia, obesity, elevated triglycerides and man with elevated blood pressure were independent predictors for stroke risk.

3.4. Subgroup and sensitivity analyses

The results of the subgroup analyses by sex, country, study duration and stroke subtype were shown in Table 3. The analyses suggested that women were more sensitive to this effect (with an RR of 1.83, 95% CI: 1.31–2.56) than men (RR = 1.47, 95% CI: 1.22–1.78). And it appeared that MetS was more strongly associated with ischemic stroke (RR = 2.12, 95% CI: 1.46–3.08) than hemorrhagic stroke (RR = 1.48, 95% CI: 0.98–2.24). There was no evidence of statistical differences in terms of study country and durations. The sensitivity analyses in which one study was omitted in each turn did not markedly change the results, indicating robust main meta-analysis results.

3.5. Publication bias evaluation

Neither Begg's test nor Egger's test ($p = 0.6262$) revealed evidence of publication bias, visual inspection of the funnel plots did not find an obvious evidence of publication bias (Fig. 2).

4. Discussion

MetS is a series of metabolic disorders including impaired glucose tolerance, central obesity, dyslipidemia, and hypertension that was first recognized with an international definition in 1998. In the past decade, the role of MetS on the development of stroke has been explored extensively, the results were controversy because of the different definitions they used [29,30]. Therefore, our systematic review and meta-analysis was designed to estimate the stroke risk associated with the metabolic syndrome as defined only by the NCEP definitions, which is most commonly used nowadays, the results showed that Mets was associated with a significantly increase in risk of stroke incidence, and women and ischemic stroke were more sensitive to this effect. Besides, of the five components of the MetS, the point estimates was highest in the group with elevated blood pressure.

Although the major components of these MetS definitions are similar, special components of MetS and their diagnostic threshold are different among different definitions [31], the main focus is central obesity defined by waist circumference and has specific cut-off value for different ethnic populations as a mandatory indi-

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