Association between Gamma-Glutamyltransferase Level and Risk of Stroke: A Systematic Review and Meta-analysis of Prospective Studies

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Background: Stroke is often regulated by a number of modifiable and nonmodifiable risk factors. Recently, studies suggested high gamma-glutamyltransferase (GGT) level may be associated with stroke, but drew inconsistent conclusions. So, we conducted a meta-analysis to evaluate the relationship between GGT level and risk of stroke. *Methods:* We systematically searched PubMed, Embase, and Cochrane Library (updated to January 2015) for prospective cohort studies. Then, relative risk (RR) with 95% confidence interval (CI) was used to assess the association. Regression analyses, subgroup analyses, and sensitivity analyses were also performed. The Begg test, Egger test, and the trim-and-fill method were used to assess potential publication bias. *Results:* A total of 5707 cases and 926,497 participants in 10 prospective studies were included. Overall, high GGT level has a positive association with increased risk of stroke (RR = 1.28; 95% CI, 1.16-1.43). In the subgroup analyses, a positive association was consistently observed in each subgroup except in the women subgroup (RR = 1.45; 95% CI, .9-2.34) and a large number of stroke events subgroups (≥500) (RR = 1.25; 95% CI, .85-1.84). Heterogeneity was significantly reduced in the subgroup analysis by population characteristics. In the publication bias test, the resulting adjusted RR remained significant (RR = 1.10; 95% CI, 1.00-1.21) after using the trim-and-fill method. *Conclusions:* Our meta-analysis provides evidence that a high level of GGT is significantly associated with increased risk of stroke independently of alcohol intake. Gender and ethnicity variations may exist in the relationship between high GGT level and risk of stroke. **Key Words:** Gamma-glutamyltransferase—stroke—prospective cohort studies—meta-analysis.

Introduction

Stroke is a cerebrovascular disease that has a serious impact on human health, and has high morbidity and mortality rates. Over the past 4 decades, the rate of stroke incidence has decreased 42% in high-income countries and increased over 100% in low- to middle-income countries globally.[1] Even so, 6.8 million people suffer from stroke and approximately 795,000 people experience new or recurrent stroke in the United States each year.[2] In China, stroke has become a leading cause of death and approximately 1.7 million people died from stroke in 2010.[3]

The risk of stroke is often regulated by a number of modifiable and nonmodifiable risk factors.[4] Recently, several prospective studies have provided insights into the potential importance of high gamma-glutamyltransferase

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Received July 20, 2015; revision received August 7, 2015; accepted August 13, 2015.

The authors declare that they have no conflict of interest.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.08.015

(GGT) level as a risk factor of the stroke, but have drawn inconsistent conclusions.[5-16] GGT is a common biomarker of hepatocyte. The test of GGT has become an important routine for liver function[17] and alcohol abuse.[18] Although a previous meta-analysis[19] has quantified the association of liver enzymes with cardiovascular disease (CVD) and stroke, it did not further investigate the relationship between GGT level and risk of stroke.

Therefore, we conducted a meta-analysis to evaluate the correlation between GGT level and risk of stroke. If GGT level became an independent risk factor for stroke, it should be on high alert in clinical evaluation and primary prevention.

Method

Literature Search

We performed a systematic search of PubMed, Embase, and Cochrane Library (up to January 2015). The following key words were used in our search strategies: "gamma-glutamyltransferase," "gamma-GT," "γ-GT," "GGT," "stroke," "cerebrovascular accident," "intracranial artery disease," "brain ischemic," "cerebrovascular disease," "cerebrovascular disorders," "cerebral infarct," "ischemic stroke," "intracranial hemorrhage," "intracranial artery disease," "longitudinal studies," "cohort studies," "prospective studies," and "follow-up studies." We restricted the search to human studies. There were no language restrictions. In addition, we searched for possible eligible studies in the references within the retrieved articles, as well as review articles and abstracts from recent conferences.

Study Selection

Studies were included if they satisfied the following criteria: (1) The study patients had a community-based or population-based prospective cohort design; (2) the exposure had a high GGT level; and (3) reported quantitative estimates of relative risk (RR) and 95% confidence interval (CI) for risk of stroke along with elevated baseline level of GGT. Studies were excluded if (1) the study design did not include a cohort; (2) the study participants have a history of stroke or liver damage; and (3) the study did not provide all the data information that we needed.

Data Extraction and Quality Assessment

Two authors (X.W.Z. and M.L.) extracted information independently and the disagreements were resolved via discussion and consensus. The following data were extracted from each included article: first author's last name, year of publication, country where the study was performed, size of the cohort, gender proportion, age, follow-up time, stroke ascertainment, cutoff values or quartile of GGT level, adjusted RR, adjusted covariates, and study quality. When the same or similar patient cohort was included in several publications, only the most recent or complete report was selected for analysis. Study quality was assessed based on the 9-star Newcastle–Ottawa Scale (NOS)[20] using predefined criteria, namely, selection (population representativeness), comparability (adjustment for confounders), and ascertainment of outcome. The NOS assigns a maximum of 4 points for selection, 2 points for comparability (2 points were awarded for studies that reported estimates for the highest degree of adjustment defined above +++ and one point for ++), and 3 points for outcome. Nine points on the NOS reflect the highest study quality.

Statistical Analysis

RR and 95% CI were chosen as the effect estimate to assess the association between GGT level and risk of stroke. Hazard ratios were assumed to approximate the same measure of RR. Data analysis used multivariate-adjusted outcome data (expressed as RRs and 95% CIs). Because different studies presented results on different scales, we converted these values in every study by using their natural logarithms and their corresponding 95% CIs. Heterogeneity among studies was examined by using chi-square-based Q test and I^2 test. When significant heterogeneity (P value $< .10$ and $I^2 > 50\%$) was detected, the pooled RR and 95% CI would be estimated in a random effects model. Otherwise, a fixed effects model was chosen.

To evaluate the influence of alcohol intake on the overall results, metaregression analysis and stratified analysis were performed. To explore the possible sources of heterogeneity, we systematically performed subgroup analyses by ethnicity, gender, time of duration, study quality, number of stroke event, degree of adjustment, and sample state. To test the robustness of the association, we performed sensitivity analysis to investigate the influence of a single study on the overall risk estimate, and carried out by sequentially omitting 1 study at each turn with the metainf algorithm.

Finally, we used the Begg test,[21] the Egger test[22] and visual inspection of a funnel plot to assess the potential publication bias. If any possible bias was found, the Duval and Tweedie nonparametric trim-and-fill method[23] was performed to further assess the potential publication bias. For all tests, A P-value less than .05 was considered statistically significant. All statistical analyses were conducted with Stata 12.0 (StataCorp, College Station, TX).

Result

Study Characteristics

We retrieved 624 articles from PubMed, Embase, Science Citation Index (Web of Science), and Cochrane Library. Of these articles, 616 were excluded for one of the following reasons: (1) did not provide the GGT level as an outcome of interest; (2) was a duplicate article; (3) was not a human study; (4) was not a prospective cohort study;