

## Review Article

# Serum non-high-density lipoprotein cholesterol and risk of stroke in the general population: a meta-analysis

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**Abstract:** Non-high-density lipoprotein cholesterol (non-HDL-C) level may link to the development of stroke. This meta-analysis was designed to assess the association of baseline non-HDL-C level with stroke risk in the general population. PubMed and Embase (up to April 2017) were searched for prospective studies reporting risk estimates of stroke for at least 3 categories of baseline non-HDL-C level in the general population. Pooled adjusted hazard ratio (HR) with 95% confidence interval (CI) were calculated for the highest versus the lowest category of non-HDL-C level. Seven prospective studies enrolling 208,790 participants were identified. Compared with the lowest non-HDL-C categories, the pooled HR of total strokes was 1.28 (95% CI 1.13-1.46) in a fixed-effect model. The pooled HR for ischemic and hemorrhagic stroke was 1.33 (95% CI 1.05-1.67) and 1.14 (95% CI 0.86-1.50), respectively. Subgroup analysis indicated that the risk of total strokes was stronger in men (HR 1.54; 95% CI 1.12-2.11) but not in women (RR 1.18; 95% CI 0.86-1.63). Elevated serum non-HDL-C level appeared to be independently associated with increased risk of ischemic stroke but not hemorrhagic stroke in the general population. However, gender-specific risk of stroke should be further evaluated by more prospective studies.

**Keywords:** Non-high-density lipoprotein cholesterol, stroke, meta-analysis

## Introduction

Stroke is caused by a blocked blood vessel or bleeding in the brain. According to its etiology, stroke can be generally classified into ischemic and hemorrhagic categories. Of all strokes, approximately 87% are ischemic stroke [1]. In 2010, global prevalence of stroke was 33 million, with 16.9 million people having a first stroke [2]. The age-standardized prevalence of stroke was 1114.8/100,000 people in China [3]. Stroke remained the second most frequent cause of death, accounting for 6.3 million deaths worldwide in 2015 [4]. Therefore, identification of potential risk factors of stroke is important for the development of screening and early interventions.

Non-high-density lipoprotein cholesterol (non-HDL-C) is composed of very low density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein cholesterol (LDL-C), and lipoprotein particles [5]. Increased non-

HDL-C level is considered as an independent predictor of for coronary heart disease (CHD). The US National Cholesterol Education Program Adult Treatment Panel guideline III has introduced the non-HDL-C as a secondary target for the prevention of CHD [6]. With respect to stroke, the Emerging Risk Factors Collaboration suggested that per 43 mg/dL higher baseline values of non-HDL-C level increased by 12% risk of ischemic stroke [7]. Previous epidemiologic studies [8-15] on the associations of non-HDL-C with the risk of stroke or its subtypes in the general population were less clear. Therefore, the predictive value of non-HDL-C level for stroke risk has not yet been established.

Given these conflict findings in the published studies, we undertook this meta-analysis of prospective studies to evaluate the association of baseline level of non-HDL-C with risk of stroke in the general population. Specific associations of non-HDL-C with stroke subtypes

(ischemic and hemorrhagic) were also evaluated.

### Materials and methods

#### Search strategy

This meta-analysis was performed according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology [16]. Two reviewers independently searched the Pubmed and Embase up to May 2017 using a combination of the following key words: (non-high-density lipoprotein cholesterol OR non-HDL-C) and (stroke OR cerebrovascular disease OR ischemic stroke OR hemorrhagic stroke OR intracerebral hemorrhage) and (longitudinal OR prospective OR follow-up). We restricted the search to human studies publishing in English. Reference lists of relevant articles were also checked to identify additional potential articles.

#### Study selection

To be eligible, studies should be satisfied the following inclusion criteria: 1) prospective observational study in the general population; 2) exposure of interest was baseline non-HDL-C level; 3) outcome of interests were stroke, including ischemic or hemorrhagic; and 4) providing multivariate-adjusted hazard ratio (HR) with 95% confidence interval (CI) of stroke for at least 3 categories (highest versus lowest) of baseline non-HDL-C level. Studies were excluded if: 1) participants were not from the general population; 2) only provided risk estimate by continuous non-HDL-C level; and 3) duplicated publications.

#### Data extraction and quality assessment

Data extraction from each included study were performed by two independent reviewers. We abstracted data on first author's name, year of publication, geographical region, study design, sample sizes, age of participant at baseline, percentage of men, comparison of non-HDL-C cut-off value, duration of follow-up, number of stroke events, type of stroke, multivariate-adjusted HR with 95% CI, and maximum adjusted covariates. The Newcastle Ottawa Scale (NOS) was adopted to assess the methodological quality of the included studies [17]. This scale awarded a maximum of 9 stars for each study. Studies achieving  $\geq 7$  stars were consid-

ered higher quality. Any disagreement in data extraction and quality assessment was resolved via discussion.

#### Data analyses

The pooled HR with 95% CI was used as the summary risk estimate and calculated for the highest versus the lowest serum non-HDL-C level. Between-study heterogeneity of effect sizes was explored using the Cochran's Q test and inconsistency across study results quantified by  $I^2$  statistics. Statistically significant heterogeneity was defined as  $I^2 \geq 50\%$  or  $p < 0.10$  for Cochran's Q test. We pooled these risk estimates using a fixed-effect model in case of lack significant heterogeneity; otherwise, a random effect model was adopted. The possibility of publication bias was assessed by the Egger's test [18] and the Begg's test [19]. All statistical analyses were conducted with the Revman software from the Cochrane Collaboration (version 5.1, Oxford, UK) and STATA 12.0 (Stata, College Station, TX, USA).

### Results

#### Search results and study characteristics

The detailed study selection process is summarized in **Figure 1**. After applied our predefined inclusion criteria, 7 studies [8, 10-15] were finally included in this meta-analysis. **Table 1** shows the main characteristics of the included studies. A total of 208,790 participants with 2,692 stroke, 2,308 ischemic stroke, and 746 hemorrhagic stroke events were identified. Of these studies, three [11, 13, 15] were conducted in Japan, three [10, 12, 14] were conducted in China, one [8] was conducted in the USA. These studies were published from 2007 to 2015. The number of participants ranged from 2,542 to 95,916. The follow-up duration ranged from 4.0 to 24 years. Overall NOS of the selected studies ranged from 6 to 8 stars.

#### Association of non-HDL-C level with stroke risk

Four studies [11-14] reported data on the risk of total strokes. As shown in **Figure 2**, meta-analysis showed that the pooled HR of total strokes comparing the highest to the lowest serum non-HDL-C level was 1.28 (95% CI 1.13-1.46) in a fixed-effect model. There was no significant heterogeneity ( $I^2=37.0\%$ ;  $P=0.19$ ) across 4 included studies. There was no evidence

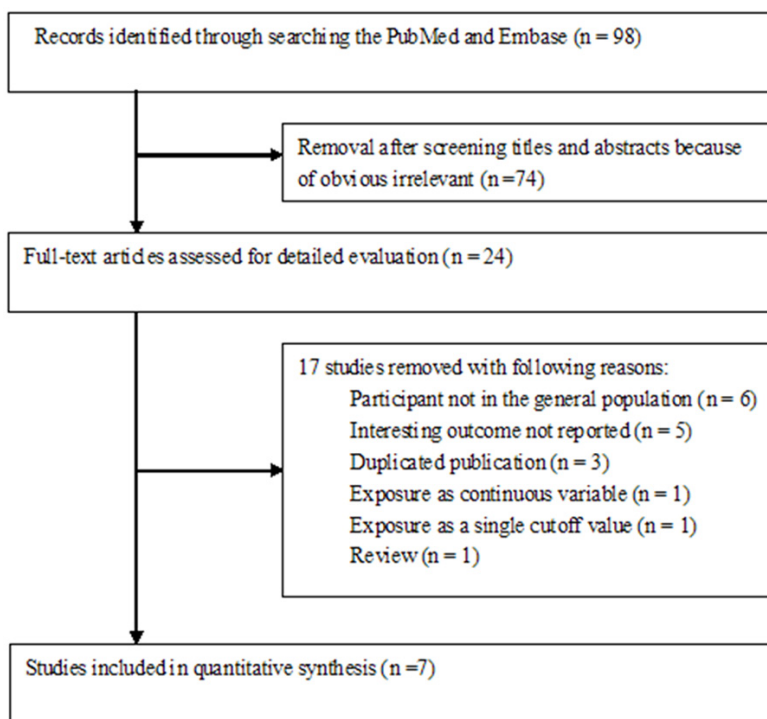


Figure 1. Flow diagram of the study selection process.

of publication bias according to the Begg's test ( $P=0.734$ ) and Egger's test ( $P=0.601$ ). Stratified analysis by gender showed that the significant associations of higher serum non-HDL-C level with total stroke risk were only found in men (HR 1.54; 95% CI 1.12-2.11) but not in women (HR 1.18; 95% CI 0.86-1.63) (Figure 3).

*Association between non-HDL-C level and risk of stroke subtype*

Studies regarding the effect of elevated non-HDL-C level on ischemic and hemorrhagic stroke risk were reported in six [8, 10-13, 15] and four [10-13] studies, respectively. As shown in Figure 4A, the pooled HR of ischemic stroke for the highest versus lowest serum non-HDL-C level was 1.33 (95% CI 1.05-1.67;  $I^2=57.0\%$ ;  $P=0.04$ ) in a random effect model, with no evidence of publication bias based on the Begg's test ( $P=0.260$ ; Figure 5A) and Egger's test ( $P=0.419$ ; Figure 5B). When we removed one study [15] that reported risk estimate for the tertile 3 versus 1, the pooled HR of ischemic stroke was 1.41 (95% CI 1.13-1.75). Figure 4B showed that the pooled HR of hemorrhagic stroke for the highest versus lowest serum non-HDL-C level was 1.14 (95% CI 0.86-1.50) in a fixed-effect model.

**Discussion**

This meta-analysis summarized the available literature and analyzed 7 prospective cohort studies. We found that elevated serum non-HDL-C level appeared to be associated with increased risk of total strokes in the general population. Individuals with the highest serum non-HDL-C had a 28% increased risk of total strokes. Subgroup analysis showed that the risk of total strokes was stronger in men but non-significant in women. Further analysis for stroke subtypes revealed that stroke subtype analysis revealed that increased serum non-HDL-C level was independently associated with higher ischemic stroke risk but exhibit no clear effect on hemorrhagic

stroke. Overall, the included studies had a good methodological quality.

Subgroup analyses revealed that the association of the serum non-HDL-C level with the risk of total strokes seemed particularly pronounced in men. In comparison, increased serum non-HDL-C level in women appeared to be of no significant effect on total strokes. Estrogen might weaken the association of non-HDL-C level with stroke [20, 21]. With respect to stroke subtypes, the association between non-HDL-C level and ischemic stroke risk was stronger. However, the effect of serum non-HDL-C level on hemorrhagic stroke was not significant. This finding suggested that the association between non-HDL-C level and total strokes differs within the stroke subtypes. Our meta-analysis highlights determination of serum level of non-HDL-C level may improve ischemic stroke risk prediction, especially in the male gender.

Lipids play a significant role in stroke etiology. An earlier participant-level meta-analysis [7] has evaluated the prognostic role of serum level of non-HDL-C on future stroke risk by a continuous variable analysis. This meta-analysis summarized that the adjusted HR associated with each 43 mg/dL higher baseline non-

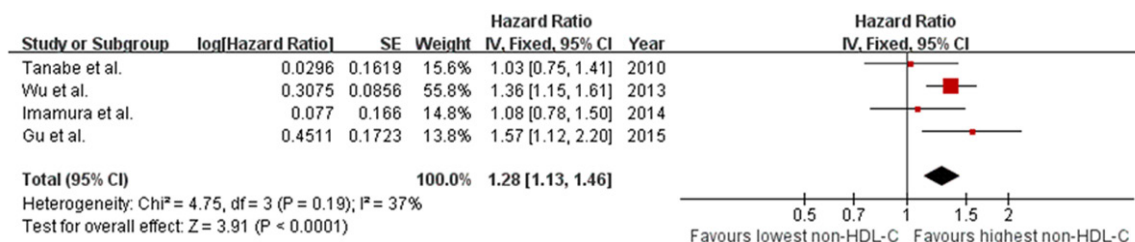
## Non-HDL-C and stroke

**Table 1.** Baseline characteristics of the included studies

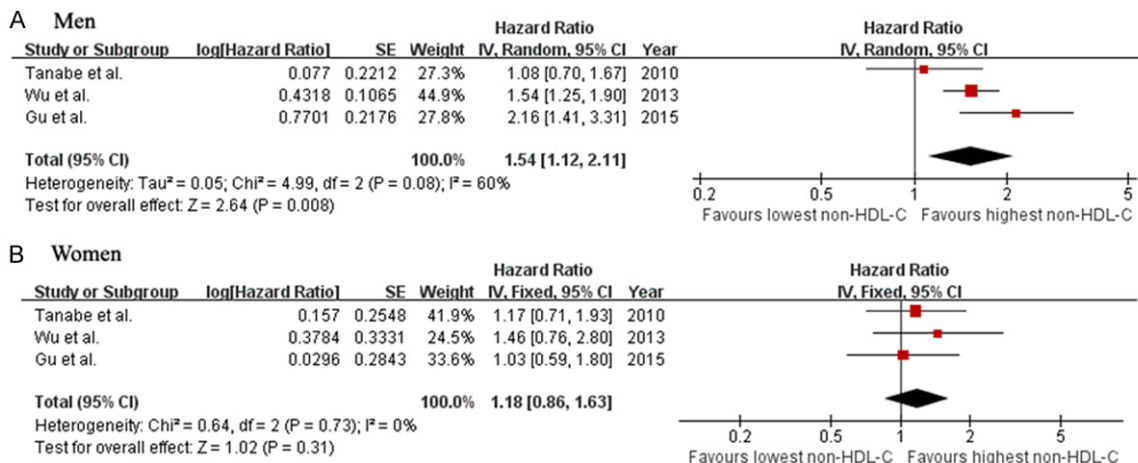
Author/Year	Region	Design	Subjects' number	Gender (% M)	Age (years)	Non-HDL-C cutoff value (mg/dL)	Follow-up (years)	Event number(N) HR (95% CI)	Maximum adjusted covariates	Total NOS
Kurth et al. 2007 [8]	USA	Prospective cohort study	27,937	0	≥45	Quintile 5 vs. 1; ≥190 vs. ≤123	11	IS (282); 2.26 (1.42-3.62)	Age, BMI, alcohol, exercise, smoking, SBP, history of DM, family history of MI, lowering-cholesterol agents, postmenopausal hormone use, migraine status, randomized treatment, and antihypertensive agents	8
Ren et al. 2010 [10]	China	Prospective cohort study	29,937	53.3	35-64	Quartile 4 vs. 1; ≥190 vs. <130	12	IS (152); 1.38 (0.97-1.94); HS (159); 1.28 (0.71-2.31)	Age, sex, smoking, DM, BMI, and SBP	6
Tanabe et al. 2010 [11]	Japan	Prospective cohort study	22,430	39.9	57.8±11.1	Quartile 4 vs. 1; ≥167 vs. ≤117	7.6	TS (339); 1.03 (0.75-1.41); 1.08 (0.70-1.68) M 1.17 (0.71-1.93) F IS (223); 1.15 (0.79-1.69); HS (65); 0.77 (0.37-1.60)	Age, sex, BMI, HDL-C, blood pressure, DM, and current smoking status	7
Wu et al. 2013 [12]	China	Prospective cohort study	95,916	79.6	18-98	Quintile 5 vs. 1; >179.8 vs. ≤87.0	4.0	TS (1,614); 1.36 (1.15-1.62); 1.54 (1.25-1.91) M 1.46 (0.76-2.81) F IS (1,156); 1.53 (1.24-1.88); HS (416); 1.18 (0.78-1.55)	Age, sex, BMI, hypertension, DM, TG, HDL, smoking, drinking, and physical activity .	8
Imamura et al. 2014 [13]	Japan	Prospective community-based cohort	2,542	42.7	57.8±11.5	Quartile 4 vs. 1; ≥174 vs. ≤121	24	TS (352); 1.08 (0.78-1.50); IS (246); 1.05 (0.71-1.54); HS (106); 1.21 (0.66-2.21)	Age, sex, DM, BMI, SBP, electrocardiogram abnormalities, current drinking, current smoking, and regular exercise.	7
Gu et al. 2015 [14]	China	Prospective cohort study	19,268	47.0	48.4±9.1	Quartile 4 vs. 1; ≥190 vs. <130	7.9	TS (387); 1.57 (1.12-2.20); 2.16 (1.41-3.31) M 1.03 (0.59-1.79) F	Age, geographic region, urbanization, smoking, alcohol intake, education, physical activity, BMI, and hypertension	7
Takechi et al. 2015 [15]	Japan	Prospective cohort study	10,760	39.7	55.1±11.2	Tertile 3 vs. 1; >149 vs. <119 for M and >158 vs. <127 for F	10.7	IS (249); 0.76 (0.41-1.41)#	Age, BMI, SBP, TC, blood sugar, percentages of current smoking and alcohol consumption, use of antihypertensive, antidiabetic, and antidiabetic drugs	8

Abbreviations: M, male; F, female; BMI, body mass index; HR, hazard ratio; CI, confidence interval; TS, total strokes; IS, ischemic stroke; HS, hemorrhagic stroke; SBP, systolic blood pressure; DM, diabetes mellitus; CAD, coronary artery disease; MI, myocardial infarction; TG, triglyceride; HDL, high-density lipoprotein; NOS, Newcastle-Ottawa Scale.

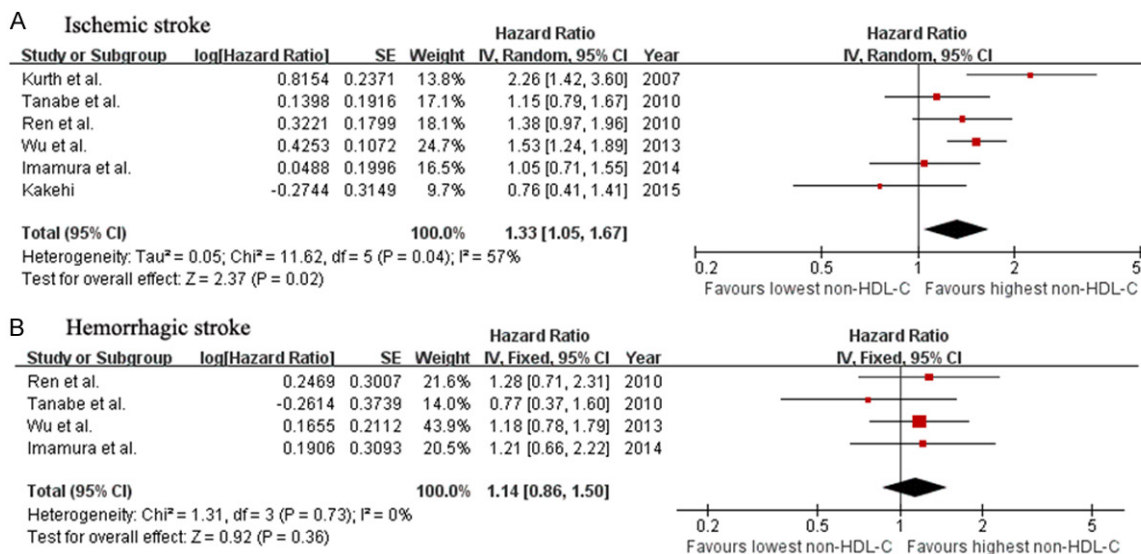
## Non-HDL-C and stroke



**Figure 2.** Forest plots showing pooled HR with 95% CI of stroke for the highest versus lowest category of non-high-density lipoprotein cholesterol in a fixed-effect model.



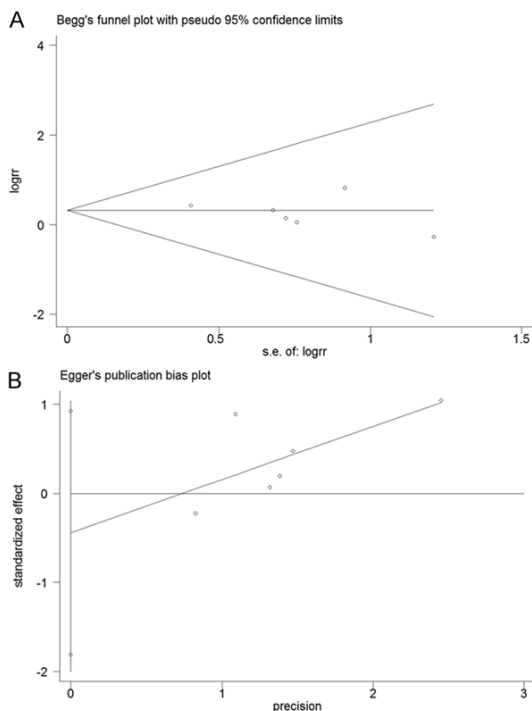
**Figure 3.** Forest plots showing pooled HR with 95% CI of stroke by men (A) and women (B) for the highest versus lowest category of non-high-density lipoprotein cholesterol in a fixed-effect model.



**Figure 4.** Forest plots showing pooled HR with 95% CI of ischemic stroke (A) and hemorrhagic stroke (B) for the highest versus lowest category of non-high-density lipoprotein cholesterol in a fixed-effect model.

HDL-C level for ischemic stroke was 1.12 (95% CI, 1.04-1.20) and 0.98 (95% CI, 0.82-1.17) for hemorrhagic stroke, respectively. A more recent

meta-analysis [22] summarized that total cholesterol and LDL-C level was inversely associated with risk of hemorrhagic stroke. However,



**Figure 5.** Begg's test (A) and Egger's test (B) for publication bias.

this meta-analysis did not focus on non-HDL-C level. Our meta-analysis further confirmed the association of elevated serum non-HDL-C level with stroke risk in the general population. Thus, assessment of serum level of non-HDL-C has potential to identify individuals at risk of ischemic stroke in public health. A large proportion of dyslipidemia patients receiving lipid-lowering agents were not achieved the target non-HDL-C goal [23, 24], indicating they remain at a substantial residual risk for stroke.

Several possible mechanisms may be involved in the association of non-HDL-C level with ischemic stroke risk. Ischemic stroke is commonly classified into three subtypes: lacunar infarction, atherothrombotic brain infarction, and cardioembolic infarction [25]. Non-HDL-C represents several atherogenic lipoproteins, including VLDL, LDL, and lipoprotein (a), and each of them is related to atherosclerosis. The superiority of non-HDL-C is due to it measures all apolipoprotein-B-containing lipoproteins which more closely correlates with the atherogenic particles. Moreover, serum level of non-HDL-C is unlikely affected by non-fasting state [6].

In interpreting these results, several limitations should be acknowledged. First, non-HDL-C level

was only measured once at baseline survey and thus misclassification of the participants in each category could not be excluded. Second, individual studies failed to consistently adjust confounding factors; lack of adjustment for residual and unmeasured confounding may have led to overestimation of an effect. Third, the cutoff value of serum non-HDL-C level varied across the selected studies, therefore, an optimal cutoff value of elevated non-HDL-C level could not achieve in this meta-analysis. Fourth, the presence of heterogeneity in pooling risk estimates could be attributable to differences in gender, country of origin, and stroke subtypes. Finally, sensitivity analysis showed the association of non-HDL-C level with ischemic stroke risk may be unreliable. However, statistically significant positive association with ischemic stroke was detected by excluding Jichi Medical School cohort study [15]. The cutoff value of highest and lowest non-HDL-C groups used in this study was lower relative to that of other studies. Too low non-HDL-C levels may be associated with an increased risk of ischemic stroke. Future well-designed studies on the association with non-HDL-C and risk of stroke subtypes are warranted to confirm our results.

**Conclusions**

Individuals with elevated serum non-HDL-C level appeared to be independently associated with increased risk of ischemic stroke but not hemorrhagic stroke in the general population. However, gender-specific risk of stroke in relation to serum non-HDL-C level should be further evaluated by more future prospective cohort studies.

**Disclosure of conflict of interest**

None.

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