



# Metabolically healthy obesity and risk of stroke: a meta-analysis of prospective cohort studies

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**Background:** Metabolic healthy obesity (MHO) is a unique subgroup of overweight and obese individuals with normal metabolic characteristics. Its association with the risk of stroke remains unclear. We aimed to examine the risk of stroke in MHO individuals and the further associations between stroke and metabolic abnormalities under different bodyweight conditions.

**Methods:** We systematically searched PubMed, Embase and Cochrane Library from December 1946 to January 2019, and only included prospective cohort studies. Random effects models were used to evaluate the pooled risk ratios (RR) and 95% confidence intervals (95% CI) of incident stroke.

**Results:** A total of eight studies comprising 4,256,888 participants were included in the meta-analysis. MHO individuals had an increased risk of stroke compared with metabolically healthy normal weight (MH-NW) individuals (RR =1.17, 95% CI: 1.11–1.23). However, the stroke risk of metabolically healthy overweight individuals was the same (RR =1.02, 95% CI: 0.84–1.23). All groups with unhealthy metabolism had a similarly elevated risk: normal weight (RR =1.83, 95% CI: 1.57–2.14), overweight (RR =1.93, 95% CI: 1.44–2.58), and obesity (RR =2.00, 95% CI: 1.40–2.87).

**Conclusions:** The meta-analysis confirms a positive association between MHO phenotype and the risk of stroke. Individuals with metabolic abnormalities under different bodyweight conditions are at elevated risk.

**Keywords:** Metabolism; obesity; stroke; meta-analysis, prospective cohort

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## Introduction

Stroke accounts for approximately 10% of global mortality (1), and ranks as the second most common cause of death (2). Obesity and metabolic syndrome (Mets), which often co-exist, are associated with an increased risk of stroke (3,4). However, quite a few studies reported that obesity might confer a beneficial effect on individuals with stroke

(5-7). The complexity of the association between body mass index (BMI) and stroke may be presumably attributed to the heterogeneity of obese phenotypes: unhealthy or healthy metabolic status. A significant proportion of subjects with obesity do not develop Mets. On the contrary, Mets can be present in normal weight individuals (8). Therefore, it has been increasingly essential to distinguish

between obese individuals at a high risk of obesity-related metabolic diseases and metabolically “healthy” obese individuals. Correspondingly, the population can be divided into 6 subtypes according to BMI and metabolic status: metabolically healthy normal weight (MH-NW), metabolically healthy overweight (MH-OW), metabolically healthy obese (MHO), metabolically unhealthy normal weight (MU-NW), metabolically unhealthy overweight (MU-OW), and metabolically unhealthy obese (MUO) (8).

Obese individuals without metabolic complications, such as elevated blood pressure, elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C) and diabetes, are known as MHO individuals. Despite the excessive weight, MHO displays a beneficial hormonal profile, a favorable metabolic profile characterized by higher insulin sensitivity, a favorable immune profile, and reduced inflammation (8,9). Some studies have confirmed that MHO has a protective effect and does not increase the risk of cardiovascular diseases (CVDs) and mortality, especially when compared with at-risk obesity (10,11). Several other studies have shown that compared with MH-NW individuals, the MHO group has higher incidences of CVD, cancer, and mortality (12-14). However, whether MHO is associated with an excess risk of stroke remains a subject of debate due to lack of evidence. Previous studies on the effects of the BMI-metabolic status phenotypes on stroke morbidity have produced conflicting results (15,16).

It remains unclear whether MHO is associated with an excess risk of stroke. Thus, we conducted this meta-analysis which only included prospective cohorts to explore the associations of stroke risk with the BMI-metabolic status phenotypes, especially the MHO subtype. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-4387>).

## Methods

### *Search strategy and selection criteria*

We complied with the recommendations made by the Meta-Analysis of Observational Studies in Epidemiology Group, the 2009 guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17,18). PubMed, Embase and Cochrane Library were thoroughly searched from December 1946 to January 2019. The following scientific search strategy was used: (“stroke” OR “cerebrovascular” OR “cerebral” OR “transient ischemic

attack” OR “TIA” OR “hemorrhage” OR “hemorrhagic”) AND (“Metabolic\*” OR “metabolism”) AND (“obese” OR “obesity” OR “overweight” OR “BMI” OR “body mass index” OR “waist circumference”). We also manually searched the biographies of eligible studies and related meta-analyses to find possible missing studies.

We included studies that simultaneously met the following criteria: (I) they were conducted in adults; (II) they were prospective cohort studies; (III) participants were stroke-free at baseline; (IV) according to BMI, they categorized participants into three groups, normal weight (BMI <25 kg/m<sup>2</sup>), overweight (BMI ≥25 and <30 kg/m<sup>2</sup>), and obesity (BMI ≥30 kg/m<sup>2</sup>), or into two groups, normal weight (BMI <25 kg/m<sup>2</sup>) and abnormal weight (BMI ≥25 kg/m<sup>2</sup>). A threshold of 24 kg/m<sup>2</sup> was set for Asians; (V) they further classified participants according to healthy or unhealthy metabolic status; (VI) they defined MHO as individuals with less than two common metabolic complications of obesity, such as elevated blood pressure, high triglycerides, decreased HDL-C and diabetes. Studies which met one of the following criteria were excluded: (I) the article was not published in English; (II) the normal weight was defined as BMI <30 kg/m<sup>2</sup>; (III) stroke was not treated as a single outcome. We only included the updated study for overlapping studies. In addition, studies were excluded if their risk ratios (RRs) and 95% confidence intervals (95% CIs) were not accessible even after contacting the authors.

### *Data extraction and quality assessment*

The following detailed information was extracted carefully from each study, including authors’ name, publication dates, follow-up periods, countries, cohort sources, ages at baseline, gender ratios, sample sizes, case numbers, BMI categories, definitions of metabolic status, BMI-metabolic status phenotypes, adjusted confounders, outcome events, effect sizes, and 95% CIs. For studies without reported risk estimates, raw data, if available, were used to calculate effect sizes. Details of all included studies are shown in *Table 1*.

Quality assessments of all potentially eligible studies were conducted using the Newcastle-Ottawa Scale (NOS) (*Table S1*) (19), which contains 8 items categorized into 3 domains: selection, comparability, and exposure. No studies were excluded due to their low quality scores. Data extraction and quality evaluation were conducted by two independent authors, and any disagreement was resolved by consensus with a third author.

Table 1 Characteristics of included studies

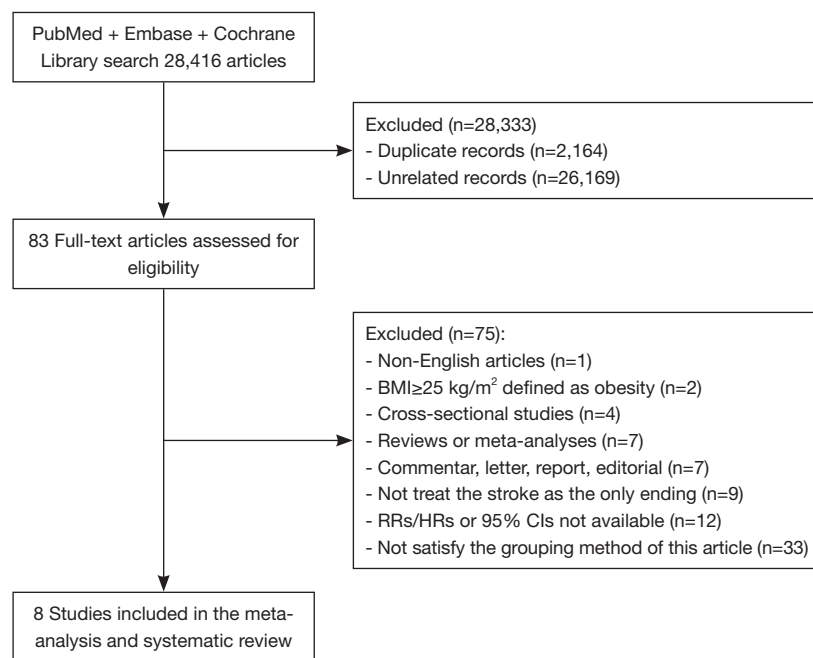
Author, country; Cohort	Follow-up years; sample size/incident case; sex, %male; age (years)	Categories of BMI (kg/m <sup>2</sup> )	Definition of metabolic status	Covariates	Type of stroke	Divide participants into 4 or 6 groups	RRs/HRs (95% CIs)	Quality score
Song, 2007, USA: Women's Health Study	8.8; 25,626/256; 0; 54.6	Normal: <25, overweight: 25–29.9, obese: ≥30	A metabolically healthy state was considered if ≤2 of the metabolic factors (ATPIII criterion): (I) BP ≥135/85 mmHg; (II) triglycerides ≥150 mg/dL; (III) HDL cholesterol <50 mg/dL; (IV) fasting glucose ≥110 mg/dL	Age, randomized treatment assignment in the Women's Health Study, smoking, exercise, alcohol intake, total calorie intake, postmenopausal hormone use, multivitamin use, parental history of myocardial infarction before 60 year	Stroke	MH-NW	1 (ref)	9
						MH-OW	0.83 (0.58–1.18)	
						MHO	1.13 (0.70–1.82)	
						MU-NW	1.24 (0.64–2.39)	
						MU-OW	1.74 (1.05–2.87)	
MUO	1.49 (0.86–2.58)							
Hinnouho, 2015, UK: Whitehall II study	17.4; 7,122/118; 69.7; 49.3	Normal: <25, overweight: 25–29.9, obese: ≥30	A metabolically healthy state was considered if none or one of the metabolic factors (ATPIII criterion): (I) SBP ≥130 mmHg or DBP ≥85 mmHg or under medical treatment; (II) triglycerides (≥1.7 mmol/L) or under medical treatment; (III) HDL cholesterol 1.04 mmol/L in men and 1.29 mmol/L in women; (IV) fasting glucose (≥5.6 mmol/L) or under medical treatment	Sex, socioeconomic status, marital status, ethnicity, physical activity, smoking, alcohol, fruits, vegetables consumption, CVD medication, procedures	One of subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and not specified stroke and transient cerebral ischemic attacks	MH-NW	1 (ref)	8
						MH-OW	0.59 (0.32–1.09)	
						MHO	1.59 (0.68–3.70)	
						MU-NW	1.82 (1.03–3.22)	
						MU-OW	2.05 (1.29–3.26)	
MUO	2.15 (1.12–4.14)							
Andersen, 2015, Denmark: Danish Medical Birth Register	5.6; 261,489/NA; 0; 30.5	Normal: <25, abnormal weight: ≥25	A metabolically healthy state was considered if none of the metabolic factors: (I) hypertension: a registered diagnosis of hypertension in the National Patient Register (ICD-10 = D110-D115) plus at least one claimed prescription for an antihypertensive agent within 90 days, or claims of at least two separate types of antihypertensive agents within 90 days; (II) dyslipidemia: claim of a prescription for a lipid-lowering drug; (III) diabetes: either (i) two separate prescription claims of glucose-lowering agents within 6 months (classifying individuals as having diabetes from the date of the second prescription claim), or (ii) a new entry in the National Patient Register with a diagnosis of diabetes	Age, calendar year, smoking	Ischemic stroke	MH-NW	1 (ref)	8
						MHO	0.99 (0.77–1.26)	
						MU-NW	1.88 (1.24–2.85)	
						MUO	1.87 (1.30–2.71)	
Guo, 2016, USA: ARIC	18.7; 14,685/1,044; 45.6; 54.3	Normal: <25, overweight: 25–29.9, obese: ≥30	A metabolically healthy state was considered if ≤2 of the metabolic factors (ATPIII criterion): (I) SBP ≥130 mmHg or DBP ≥85 mmHg; (II) untreated total cholesterol ≥240 mg/dL and HDL <40 mg/dl in men and <50 mg/dL in women; (III) untreated fasting ≥100 mg/dL or HbA1c ≥5.7%	Age, sex, race, income, education, tobacco smoking, alcohol drinking	Stroke	MH-NW	1 (ref)	8
						MH-OW	1.31 (0.38–4.49)	
						MHO	0.85 (0.36–2.04)	
						MU-NW	2.45 (0.71–8.44)	
						MU-OW	3.92 (1.19–12.94)	
MUO	3.87 (1.17–12.77)							

Table 1 (continued)

Table 1 (continued)

Author, country; Cohort	Follow-up years; sample size/incident case; sex, %male; age (years)	Categories of BMI (kg/m <sup>2</sup> )	Definition of metabolic status	Covariates	Type of stroke	Divide participants into 4 or 6 groups	RRs/HRs (95% CIs)	Quality score
Rishi, 2017, UK: THIN	5.4; 3,495,777/54,705; 45.5; 43.7	Normal: <25, overweight: 25–29.9, obese: ≥30	A metabolically healthy state was considered if none of the metabolic factors: (I) hypertension; (II) hyperlipidemia; (III) diabetes	Age, sex, self-reported smoking status, social deprivation	One of transient ischemic attack, ischemic stroke, hemorrhagic stroke	MH-NW MH-OW MHO MU-NW MU-OW MUO	1 (ref) 1.03 (0.98–1.07) 1.16 (1.10–1.23) 1.54 (1.50–1.58) 1.51 (1.47–1.55) 1.56 (1.52–1.60)	8
Lee, 2018, Korea: NHIS-NSC	7.4; 354,083/4,884; 52.7; 45.8	Normal: <25, abnormal weight: ≥25 (stage I: 25–29.9, stage II: ≥30)	A metabolically healthy state was considered if none of the metabolic factors (ATPIII criterion): (I) SBP ≥130 mmHg or DBP ≥85 mmHg or under medical treatment; (II) total cholesterol (≥240 mg/dL) or under medical treatment; (III) fasting glucose ≥110 mg/dL or under medical treatment	Age, sex, income, area, smoking, drinking, exercise, history of ischemic heart disease, peripheral artery disease, congestive heart failure, transient ischemic	Ischemic stroke	MH-NW MHO MU-NW MUO	1 (ref) 0.99 (0.81–1.20) 1.72 (1.55–1.90) 2.06 (1.85–2.28)	8
Nathalie, 2018, USA: NHS	24; 90,257/3,080; 0; 46.3	Normal: <25, overweight: 25–29.9, obese: ≥30	A metabolically healthy state was considered if none of the metabolic factors: (I) hypertension; (II) hyperlipidemia; (III) diabetes	Age, race, highest educational degree, alcohol consumption, smoking status, postmenopausal status, post-menopausal hormone use, physical examinations for screening purposes, aspirin use, family history of myocardial infarction and diabetes, and physical activity	Stroke	MH-NW MH-OW MHO MU-NW MU-OW MUO	1 (ref) 1.29 (1.05–1.58) 1.37 (1.04–1.81) 2.22 (1.92–2.57) 2.27 (1.97–2.63) 2.58 (2.22–3.00)	8
Li, 2019, China: CHRLS	3.6; 7,849/NA; NA; 58.8	Normal: <24, abnormal weight: ≥24	A metabolically healthy state was considered if none or one of the metabolic factors: (I) SBP ≥130 mmHg or DBP ≥85 mmHg or physician-diagnosed or under medical treatment; (II) triglycerides ≥150 mg/dL or under medical treatment; (III) HDL <40 mg/dL in men and <50 mg/dL in women; (IV) fasting glucose ≥100 mg/dL or doctor's diagnosed diabetes or under medical treatment, orHbA1c ≥6.0%	Age, sex, region, marital status, education level, smoking status, frequency of alcohol consumption in the past year, physical activity	Stroke	MH-NW MHO MU-NW MUO	1 (ref) 1.32 (0.97–1.80) 2.12 (1.87–2.41) 2.20 (1.87–2.60)	7

BMI, body mass index; RR, relative risk; HR, hazard ratio; CI, confidence interval; USA, United States of America; ATPIII, Adult Treatment Panel III; UK, United Kingdom; HDL, high-density lipoprotein; MH-NW, Metabolically Healthy Normal Weight; MH-OW, Metabolically Healthy Overweight; MHO, Metabolically Healthy Obese; MU-NW, Metabolically Unhealthy Obese; MU-OW, Metabolically Unhealthy Overweight; MUO, Metabolically Unhealthy Obese; CVD, cardiovascular disease; BP: blood pressure; ARIC, Atherosclerosis Risk in Communities Study; THIN, The Health Improvement Network; NHIS-NSC, National Health Insurance Service-National Sample Cohort; NHS, Nurses' Health Study; CHRLS, China Health and Retirement Longitudinal Study.



**Figure 1** Flowchart of study selection. CVD, cardiovascular disease; BMI, body mass index.

### Statistical analysis

Overall RRs were calculated to assess the risk for MH-OW, MHO, MU-NW, MU-OW, and MUO phenotypes using MH-NW participants as the reference group. Due to the significant heterogeneity in subject characteristics across studies, effect sizes and 95% CIs were calculated using a random effects model (20). We used Cochrane Q test to assess heterogeneity among studies (20,21). Furthermore, we performed sensitivity analyses after excluding one study at a time to assess the reliability and sensitivity of the results. Subgroup analyses according to follow-up duration were conducted to detect the possible sources of heterogeneity (21). Finally, publication bias was adopted to check up if the pooled values were impacted by part of the studies' positive results using Egger's test. When statistically significant bias was found, the trim and fill method was used to adjust it. All statistical tests used a significance level of  $P < 0.05$ . Statistical analyses were performed using R 3.6.1.

### Results

Figure 1 shows the flowchart of the study selection. We identified 28,416 studies through electronic searches. Eighty-three studies that may be eligible for inclusion were identified after reviewing titles and abstracts. Eight

prospective cohort studies met the inclusion criteria after reviewing the full text (15,16,22-27).

### Characteristics of included studies

Table 1 summarizes the characteristics of studies. Among the included studies, five used Adult Treatment Panel III (ATP III) criteria including elevated blood pressure, higher triglycerides, reduced HDL-C and diabetes, and the other three used medical histories of these diseases to define the metabolic status. The sample size of the studies varied greatly, ranging from 7,122 participants to 3,495,777 participants. The included studies had an average follow-up time of 11.4 years, and the population had a mean age of 47.9 years. The quality scores of these studies according to the NOS are summarized in Table S1. All studies included in this meta-analysis got at least seven stars, indicating that the quality is acceptable.

### Effects of BMI categories on metabolically healthy population

In an overall analysis of eight studies involving 4,256,888 participants (15,16,22-27), metabolically healthy individuals with  $\text{BMI} \geq 25 \text{ kg/m}^2$  had a higher risk of stroke compared

with MH-NW individuals (RR =1.09, 95% CI: 0.99–1.19) (Figure 2A) with non-significant heterogeneity ( $I^2=36\%$ ,  $P=0.14$ ).

### Overweight

In a pooled analysis of five studies involving 3,633,467 participants (16,22–25), no significant association was found between MH-OW and stroke (RR =1.02, 95% CI: 0.84–1.23) (Figure 2B) with moderate heterogeneity across studies measured by a random-effects model ( $I^2=57\%$ ,  $P=0.05$ ). Sensitivity analyses were conducted to explore the sources of heterogeneity; the pooled effect did not vary substantially after excluding any single study (Figure S1). We pooled studies with over 10 years of follow-up to explore the sources of heterogeneity and explore whether the length of follow-up will have an impact on the outcome. The results showed that the stroke risk in MH-OW patients was similar to that in MH-NW patients, both for long-term follow-up (RR =0.99, 95% CI: 0.56–1.77,  $I^2=65\%$ ,  $P=0.06$ ) and short-term follow-up (RR =1.00, 95% CI: 0.86–1.16,  $I^2=28\%$ ,  $P=0.24$ ) (Figure S2), suggesting follow-up duration was not a source of heterogeneity.

### Obesity

In a pooled analysis of five studies involving 3,633,467 participants (16,22–25), a significant association between MHO and a higher risk of stroke was found with non-significant heterogeneity (RR =1.17, 95% CI: 1.11–1.23,  $I^2=0\%$ ,  $P=0.67$ ) (Figure 2C). We performed subgroup analyses according to follow-up duration (more than 10 years or less than 10 years). Compared with the MH-NW phenotype, the pooled RRs of MHO phenotype were extremely higher irrespective of follow-up duration, with their RRs of 1.33 (95% CI: 1.04–1.72,  $I^2=0\%$ ,  $P=0.54$ ) for analysis of studies with over 10 years of follow-up (Figure S3A) and 1.16 (95% CI: 1.10–1.23, and  $I^2=0\%$ ,  $P=0.91$ ) for analysis of studies with less than 10 years of follow-up (Figure S3B) respectively. The results of the funnel plot and Egger test showed that publication biases weren't found in MHO subgroups ( $P=0.632$ ) (Figure S4). The credibility of result was moderate using GRADEpro GDT (Figure S5).

### Effects of BMI categories on metabolically unhealthy individuals

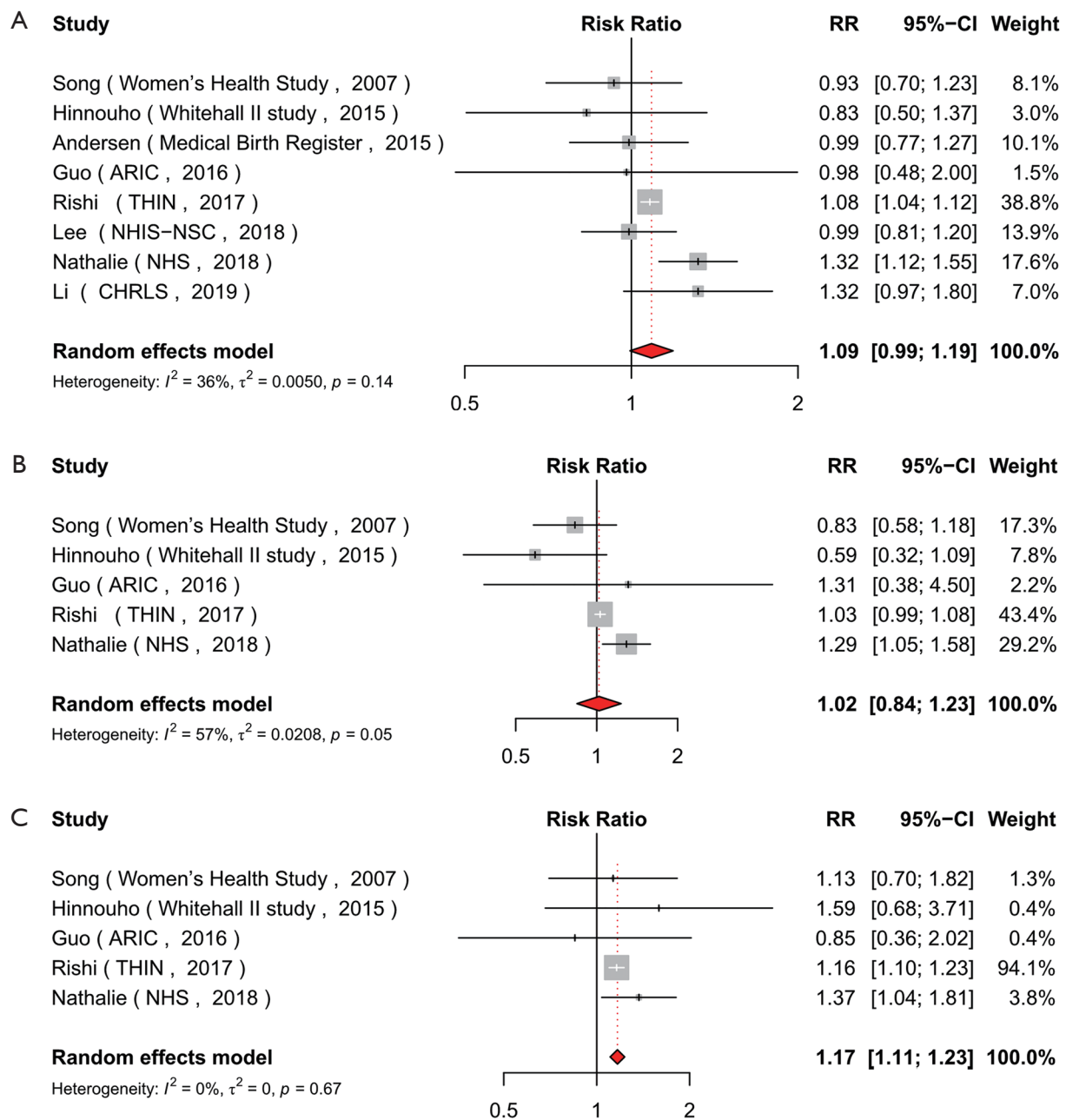
As expected, all groups with metabolically unhealthy status

had a similarly increased risk of stroke. In a pooled analysis of eight studies (15,16,22–27), the MU-NW group had an increased risk of stroke compared to the MH-NW group (RR =1.83, 95% CI: 1.57–2.14) (Figure 3A) with obvious heterogeneity across studies ( $I^2=86\%$ ,  $P<0.01$ ). In a pooled analysis of 5 studies, a significant association was found between MU-OW phenotype and a higher risk of stroke (RR =1.93, 95% CI: 1.44–2.58,  $I^2=88\%$ ,  $P<0.01$ ) (Figure 3B), and a similar result was found for MUO phenotype (RR =2.00, 95% CI: 1.40–2.87) (Figure 3C) with obvious heterogeneity across studies ( $I^2=91\%$ ,  $P<0.01$ ). Subsequently, sensitivity analyses were conducted to explore the sources of heterogeneity. Finally, the study of THIN (16) fully explained the heterogeneity (Figure S1). After carefully comparing this study with other studies, we found that this study only used the medical history provided by the participants rather than rigorous laboratory tests to determine whether participants had metabolic complications of obesity, such as elevated blood pressure, high triglycerides, decreased HDL-C and diabetes. After excluding this study, the heterogeneities in MU-NW, MU-OW and MUO phenotypes were reduced to 52%, 0%, and 30%, respectively. The pooled effects did not vary substantially after excluding this single study (MU-NW: RR =1.95, 95% CI: 1.71–2.22; MU-OW: RR =2.23, 95% CI: 1.95–2.54; MUO: RR =2.30, 95% CI: 1.73–3.06) (Table S2).

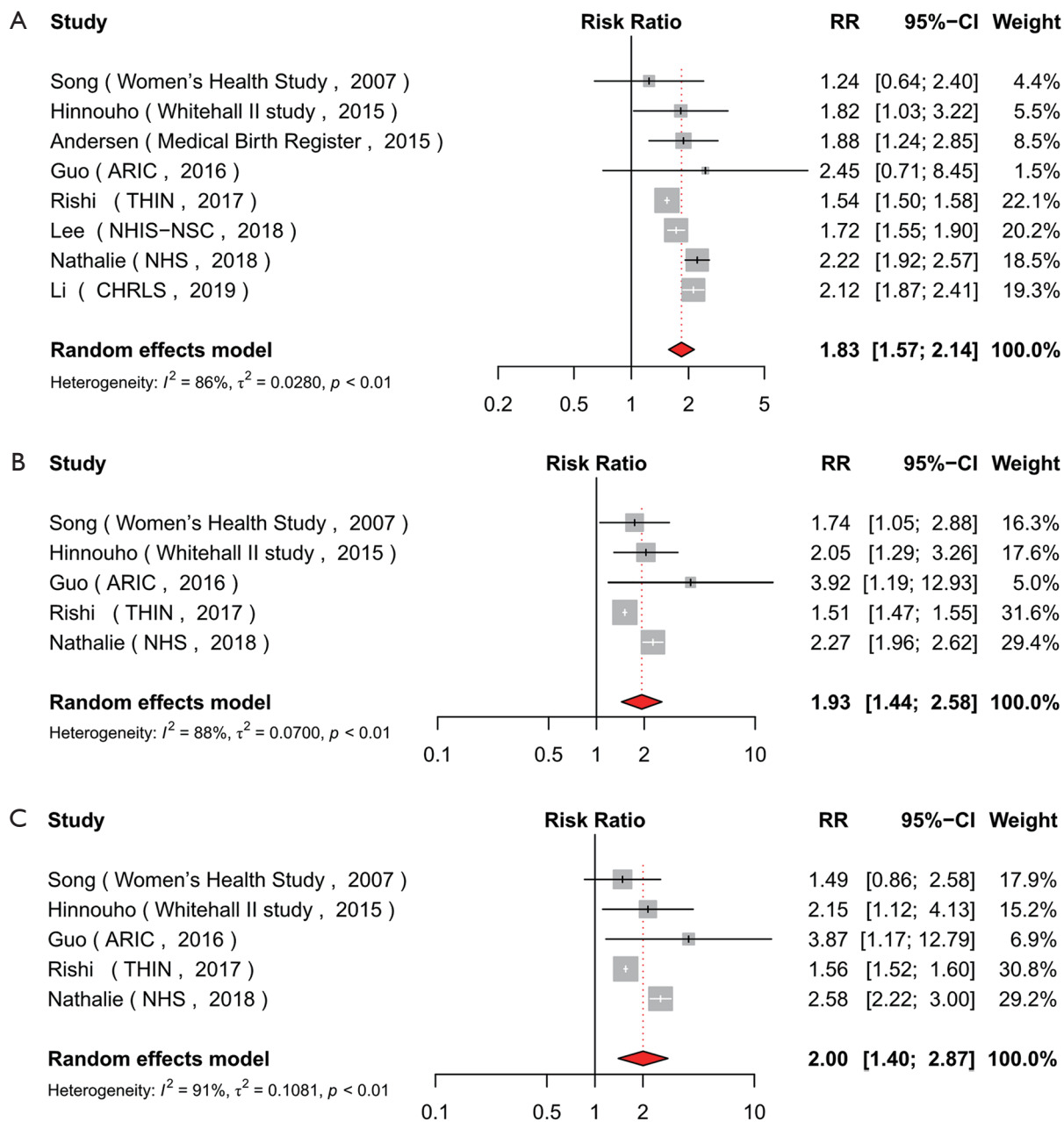
### Discussion

This meta-analysis of prospective studies summarized the inconsistent results from previous studies investigating the associations between BMI-metabolic status phenotypes and stroke risk. There are two critical findings. First, compared with MH-NW individuals, MHO individuals were at an increased risk of stroke. Second, all three unhealthy metabolic status phenotypes showed increased risks, which are not affected by the weight status.

Results suggested that MHO participants were at a higher risk of stroke. And further analyses suggested that regardless of follow-up duration, the MHO phenotype did associate with a higher risk of stroke. MH-OW participants were not at an increased risk of stroke compared with MH-NW individuals, although statistical significance was almost reached. However, the results have to be interpreted with caution, as moderate heterogeneity was observed in these analyses. As expected, the three unhealthy metabolic status phenotypes showed higher risks, which are not affected by



**Figure 2** Meta-analyses of metabolically healthy body mass index categories for the risk of stroke compared with MH-NW individuals. (A) Metabolically healthy and BMI  $\geq 25$  kg/m<sup>2</sup>; (B) metabolically healthy overweight; (C) metabolically healthy obese. ARIC, Atherosclerosis Risk in Communities Study; THIN, The Health Improvement Network; NHIS-NSC, National Health Insurance Service-National Sample Cohort; NHS, Nurses' Health Study; CHRLS, China Health and Retirement Longitudinal Study; MH-NW, metabolically healthy normal weight.



**Figure 3** Meta-analyses of metabolically unhealthy body mass index categories for the risk of stroke compared with MH-NW individuals. (A) Metabolically unhealthy normal weight; (B) metabolically unhealthy overweight; (C) metabolically unhealthy obese. ARIC, Atherosclerosis Risk in Communities Study; THIN, The Health Improvement Network; NHIS-NSC, National Health Insurance Service-National Sample Cohort; NHS, Nurses' Health Study; CHRLS, China Health and Retirement Longitudinal Study; MH-NW, metabolically healthy normal weight.



the weight status.

Obesity has been considered as an indicator of poor health. However, a concept of “obesity paradox” has recently emerged, which is used to describe the unexpected improvement in prognosis and reduction in mortality found in several diseases among patients with higher body weight (28-30). A meta-analysis showed that MHO population had a higher risk of cardiovascular events (stroke was considered as one of the outcomes) over the long term, which indicated that the duration of follow-up is a critical element in evaluating low-risk populations for future events (31). Partially consistent with previous studies, our analyses found, even not considering the effects of follow-up, the risk of stroke in MHO individuals was still higher than that of MH-NW individuals, suggesting that there is no “healthy” pattern of obesity. Some previous reports only assessed MHO individuals over short term (32,33) or compared these individuals with controls without cardiovascular risk (32), which may lead to the “obesity paradox”. Our study once again refuted the view that high BMI may be harmless.

In addition, special attention should be paid to MU-HW individuals. Although the risk of stroke in the MHO group was increased, it was still lower than that of MU-NW participants, suggesting intermediate risk. Indeed, the MU-HW group had a similar risk compared with MU-OW and MUO groups. A possible explanation is that even without excess weight, this group may represent the most severe subtype in the phenotypic profile of individuals genetically predisposed to cardiovascular disease, so they have unfavorable metabolic characteristics. The study reported that compared with the MH-NW group, MU-HW group had the highest weighted differences in LDL cholesterol and glucose levels (even higher than their overweight and obese peers with unhealthy metabolism) (31).

Previous meta-analyses evaluating the association between BMI and the risk of stroke have not considered the presence of metabolic factors (5,34,35). The advantage of this study is that the large sample size can well reflect BMI and metabolic status, which allows us to determine reliable risk estimates related to the six BMI-metabolism categories.

### **Limitations**

It is worth noting that this study has some limitations. First, most of studies used BMI to define obesity. Although waist circumference might more accurately depict an individual’s visceral obesity (36), waist circumference values were not

available from the database. What’s more, weight gain is an essential risk factor, often accompanied by the progression of abnormal metabolic status. However, there were no studies reporting data on BMI changes during follow-up time. It is possible that BMI changes, rather than weight status at the time of data collection, impact stroke risk more profoundly (16). Besides, the study has shown that non-Hispanic black population had a higher rate of MHO, suggesting that ethnic background may be an important factor in determining MHO (37). However, due to the lack of information from original studies, we did not carry out detailed studies of different races.

### **Future directions**

In the future, detailed studies should be conducted for individuals of different ethnic backgrounds. The dynamic changes of participants’ BMI, waist circumference and other indicators should be regularly followed up in more in-depth research.

### **Conclusions**

In conclusion, this meta-analysis of prospective studies showed that obese individuals with metabolic phenotypes considered to be ‘healthy’ still had a higher risk of stroke compared with MH-NW individuals. Existing prospective evidence does not indicate that healthy obesity is a harmless condition. Weight reduction and improvements in health are needed and they are beneficial to reducing the risk of stroke for MHO individuals.

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### **Footnote**

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-4387>.

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-4387>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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