Original Article

Measures of Abdominal Adiposity and Risk of Stroke: A Dose-Response Meta-analysis of Prospective Studies*

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Abstract

Objective Waist circumference, waist-to-hip ratio and waist-to-height ratio, which are the indicators or measures of abdominal adiposity, have long been hypothesized to increase the risk of stroke; yet evidence accumulated till date is not conclusive. Here, we conducted a dose-response meta-analysis to summarize evidences of the association between these measures of abdominal adiposity and the risk of stroke.

Methods PubMed and Web of Science databases were searched from inception to May 2015. Two investigators independently conducted the study selection and data extraction. Dose-response relationships were assessed by the generalized least squares trend estimation, while the summary effect estimates were evaluated by the use of fixed- or random-effect models. Subgroup and sensitivity analyses were performed to assess the potential sources of heterogeneity and the robustness of the pooled estimation. Publication bias of the literature was evaluated using Begg's and Egger's test.

Results Altogether 15 prospective cohort studies were identified in this study. The summary of relative risks (95% confidence intervals) of stroke for the highest versus the lowest categories was 1.28 (1.18-1.40) for waist circumference, 1.32 (1.21-1.44) for waist-to-hip ratio, and 1.49 (1.24-1.78) for waist-to-height ratio. For a 10-cm increase in waist circumference, the relative risk of stroke increased by 10%; for a 0.1-unit increase in waist-to-hip ratio, the relative risk increased by 16%; and for a 0.05-unit increase in waist-to-height ratio, the relative risk increased by 13%. There was evidence of a nonlinear association between waist-to-hip ratio and stroke risk, $P_{nonlinearity}$=0.028.

Conclusion Findings from our meta-analysis indicated that waist circumference, waist-to-hip ratio, and waist-to-height ratio were positively associated with the risk of stroke, particularly ischemic stroke.

Key words: Abdominal adiposity; Waist circumference; Waist-to-hip ratio; Waist-to-height ratio; Stroke; Cohort studies; Meta-analysis

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INTRODUCTION

Stroke is the second most common cause of death worldwide and the leading cause of long-term neurological disability in adults, with more than half the survivors depending on others for everyday activities[1-2]. Obesity is a major public health concern worldwide and is associated with increased risk of atherosclerotic vascular disease, including myocardial infarction and stroke[3-4].

Abdominal obesity is more closely related to metabolic dysfunctions connected with cardiovascular disease (CVD), than general obesity[4]. Moreover, visceral adipose tissue secretes higher amounts of inflammatory cytokines and is associated with a greater atherosclerotic risk profile than subcutaneous fat, when present in excess[5-7]. Waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are proxy measures of visceral adipose tissue[8]. A previous pooling analysis of 15 prospective studies showed that WC and WHR were strongly associated with the risk of cardiovascular disease incidence[9]. Waist-to-height ratio is less commonly used than WC and WHR, while the cut-off point for CVD is subject to less ethnic variation[10], and several studies have shown that WHtR correlates better to cardiovascular risk factors than BMI[11]. During the past decades, a number of prospective studies have evaluated the association between the measures of abdominal obesity and the risk of stroke[12-29]. However, these results were inconsistent mainly owing to differences in sample size, sex, study population, study quality, or residual confounding among these studies. Some reports have demonstrated a significant correlation of measures of abdominal adiposity with stroke, while others have not. Furthermore, the exact shapes of the dose-response curves for WC, WHR, or WHtR and stroke risk have not been clearly defined.

Thus, we conducted a dose-response meta-analysis to clarify and quantitatively assess the relationship of WC, WHR, and WHtR with stroke risk.

METHODS

Data Sources and Search Strategy

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, 2009[30]. Any prospective study that examined the relationship between measures of abdominal adiposity and stroke was eligible for inclusion in our study. We searched PubMed and Web of Science databases for articles published until May 2015, and used the keywords 'WC', 'WHR', 'WHtR', 'waist', 'waist circumference', 'waist-to-hip ratio', 'waist-to-height ratio', or 'abdominal obesity'; 'stroke', 'cerebral infarction', 'brain infarction', 'cerebrovascular disease', 'cerebral hemorrhage', 'intracranial hemorrhage', or 'cerebrovascular disorder'; and 'nested case-control', 'follow-up study', 'prospective study', or 'cohort study'. We also conducted manual searches of the reference lists of all the retrieved papers and recent reviews to identify additional eligible studies.

Study Selection

The eligible studies met the following inclusion criteria: 1) the study had a prospective design (prospective cohort or prospective nested case-control study); 2) the study investigated the association between measures of abdominal adiposity (WC, WHR, or WHtR) and the risk of nonfatal and/or fatal stroke; 3) the authors reported effect estimates [risk ratio (RR), hazard ratio (HR), or odds ratio (OR)], and 95% confidence intervals (CIs) for at least 3 quantitative categories of abdominal adiposity indices. We excluded all case-control studies because various confounding factors could bias the results. If multiple articles were published from the same cohort, we selected the article for which the primary focus was the association between measures of abdominal adiposity and stroke risk[20,28]. Study selection was conducted independently by two authors (CKZ and XYZ) by using a standardized approach. Any disagreements were resolved by discussion.

Data Collection and Quality Assessment

Data extraction and quality assessment were independently performed by two investigators (CKZ and XYZ), and independently checked for accuracy by a third investigator (YHZ). The following data elements were extracted from each study: first author's or study group's name, publication year, country, study design, sample size, assessment of exposure, number of events, age at baseline, percentage of male, follow-up duration, and covariates in the fully adjusted model. In addition, we extracted the number of cases, person-years or number of non-cases, effects of the different exposure categories, and the 95% CIs. For the studies that reported several multivariable-adjusted

RRs, we selected the effect estimate that was maximally adjusted for potential confounders. The Newcastle-Ottawa Scale (NOS) was used to evaluate methodological quality[31]. The NOS is a comprehensive tool that has been partially validated for evaluating the quality of observational studies in meta-analyses, and a higher score represents better methodological quality[32] (Supplement Table 1, www.besjournal.com for details).

Statistical Analysis

We examined the relationship between anthropometric markers of abdominal adiposity and the risk of stroke on the basis of the adjusted RR and its 95% CI published in each study. We first used fixed- or random-effect models to calculate the summary of RRs and 95% CIs for the highest compared with the lowest category of abdominal adiposity indices[33-34]. For the studies that reported stratified risk estimates by sex or age, or reported results for ischemic stroke subtypes only, we combined these estimates using fixed-effect models and then included the pooled estimates for the meta-analysis[35-36]. Next, we used the method described by Greenland and Longnecker[37] and Orsini et al.[38] for dose-response analysis, and computed study-specific slopes (linear trends), 95% CIs from the natural logs of the RRs, and CIs across categories of anthropometric measures. The method requires that the distributions of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person years in studies that did not report these, but reported the total number of cases or person years, if the results were analyzed by quantiles (and could be approximated)[39]. For every study, the median or mean level of anthropometric measures per category was assigned to each corresponding RR estimate. When the median or mean level per category was not provided, we assigned the midpoint of the upper and lower boundaries in each category as average level. If the highest or lowest category was open ended, we assumed the width of the interval to be the same as in the closest category.

Finally, we examined a potential non-linear relationship between measures of abdominal adiposity and risk of stroke by modeling WC, WHR, and WHtR using restricted cubic splines with three knots at fixed percentiles: 10%, 50%, and 90%, of the distribution[40]. The *P*-value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero.

Heterogeneity test was performed by the use of Q and I^2 statistics[41]. For the Q statistic, a *P*-value<0.1 was considered statistically significant heterogeneity. Subgroup and meta-regression analyses by geographic area, sex, assessment of exposure, duration of follow-up, and the number of cases were conducted to investigate potential sources of heterogeneity. We also performed a sensitivity analysis by removing each individual study from the meta-analysis. Because all the studies included were well-conducted (NOS score ≥7), we did not perform sensitivity analyses according to study quality. Several methods were used to check for potential publication bias. Visual inspection of funnel plots for stroke was conducted; Egger's linear regression tests[42] and Begg's rank correlation tests[43] were also used to statistically and quantitatively assess publication bias. All reported *P* values were 2-sided, and *P*<0.05 was considered statistically significant for all included studies. Statistical analyses were performed using STATA software (version 12.0; STATA Corporation, College Station, TX, USA).

RESULTS

Studies and Patient Characteristics

Of the 679 articles identified from database searches, 15 prospective studies from 16 publications met the inclusion criteria. The results of the study selection process are shown in Figure 1. A manual search of the reference lists of these studies

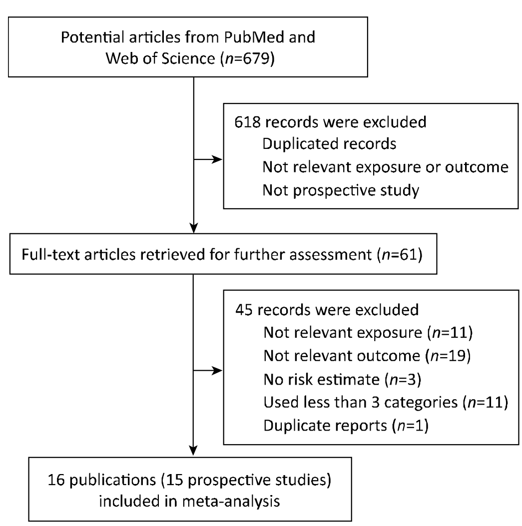

Figure 1. Flow-chart of study selection.

did not yield any new eligible studies. Characteristics of the selected studies are presented in Table 1 and Supplement Table 2, www.besjournal.com for details. All of the included reports were prospective cohort studies that were published between 1996 and 2015. Amongst them, 4 studies were conducted in Asia[12,15-16,22], 4 in the United States[19-20,26-27], 6 in Europe[13-14,17,23-25], and 1 was multinational[18]. The follow-up period for participants was 4-19.5 years, and about 1034-94744 individuals were included in each study. Study quality was assessed by using the NOS. Altogether, four studies had a score of 9[13,15,18,23], six studies had a score of 8[12,17,19-20,25,27], and five studies had a score of 7[14,16,22,24,26]. A total of 12 cohorts consisting of 405,411 participants (11,775 individuals experienced stroke) were included in the analysis for WC and stroke risk; 10 cohorts consisting of 407,074 participants (10,625 experienced stroke) were included in the analysis for WHR and stroke risk; and 7 cohorts with 272,269 participants (6163 experienced stroke) were included in the analysis for WHtR and stroke risk.

Main Analysis

The adjusted RRs for each study and all studies combined, for the highest versus lowest categories of WC, WHR, and WHtR in relation to stroke risk are shown in Figure 2. Overall, the pooled analysis showed that individuals in the highest category of WC, WHR, and WHtR had a significantly increased risk of stroke compared with those in the lowest category. RR was 1.28 (95% CI, 1.18 to 1.40; I^2=15.6%, P=0.291) for WC (n=12), 1.32 (95% CI, 1.21 to 1.44; I^2=0.0%, P=0.761) for WHR (n=10), and 1.49 (95% CI, 1.24 to 1.78; I^2=52.6%, P=0.049) for WHtR (n=7).

The associations between measures of abdominal adiposity and risk of stroke subtypes are presented in Table 2. All RRs were estimated on the basis of the comparison of the highest with the lowest categories of WC, WHR, and WHtR. There was a significant positive association between WC, WHR, and WHtR and ischemic stroke; the summary of RRs (95% CIs) were 1.41 (1.21-1.56), 1.35 (1.21-1.50), and 1.55 (1.37-1.76), respectively. However, no significant relationship was observed between abdominal adiposity indices and hemorrhagic stroke.

Subgroup, Meta-regression, and Sensitivity Analyses

Table 3 shows the results of subgroup analyses stratified by geographic area, sex, assessment of exposure, duration of follow-up, and the number of cases. The associations of stroke risk with high abdominal adiposity indices were positive compared to low abdominal adiposity indices in all strata, and were statistically significant in most of the subgroups. In meta-regression analyses, only geographic location was found to modify the association between WHtR and stroke with a statistically significant positive association among Asian and European studies, but not among those of the United States, $P_{\text{heterogeneity}}$=0.037. Sensitivity analyses investigating the influence of a single study on the overall risk estimate by omitting one study in each turn indicated that the overall risk estimates were not substantially modified by any single study, with a range from 1.24 (95% CI: 1.03-1.51) to 1.31 (95% CI: 1.10-1.57) for WC, from 1.31 (95% CI: 1.09-1.56) to 1.33 (95% CI: 1.11-1.60) for WHR, and from 1.37 (95% CI: 1.07-1.76) to 1.52 (95% CI: 1.20-1.94) for WHtR.

Dose-response Analysis

As shown in Figure 3, for a 10 cm increase in WC, the relative risk of stroke increased by 10% (RR=1.10, 95% CI: 1.07-1.14; I^2=31.7%, P=0.138); for a 0.1 unit increase in WHR, the relative risk of stroke increased by 16% (RR=1.16, 95% CI: 1.06-1.27; I^2=75.2%, P=0.000); and for a 0.05 unit increase in WHtR, the relative risk of stroke increased by 13% (RR=1.13, 95% CI: 1.07-1.19; I^2=55.8%, P=0.035). There was evidence of a nonlinear association between WHR and stroke risk, $P_{\text{nonlinearity}}$=0.028, with a slight flattening of the curve at higher WHR levels; for a WHR of 0.64, the RRs of stroke were 1.2, 1.5, 1.6, and 1.7, and for a WHR of 0.74, 0.94, 1.14, and 1.54, respectively. However, there was no evidence of a nonlinear association between WC and WHtR with stroke risk: $P_{\text{nonlinearity}}$=0.06 for WC, and $P_{\text{nonlinearity}}$=0.93 for WHtR (Figure 4 and Supplement Tables 3-5, www.besjournal.com for details).

Publication Bias

A review of funnel plots could not eliminate the potential for publication bias for stroke (Supplement Figure 1, www.besjournal.com for details). The Begg's and Egger's test results disclosed no evidence of publication bias for stroke (Begg: P=0.945 for WC; P=0.721 for WHR, and P=0.548 for WHtR; Egger: P=0.852 for WC; P=0.524 for WHR, and P=0.234 for WHtR).

Table 1. Characteristics of Prospective Cohort Studies of Abdominal Adiposity Measures and Stroke Included in this Meta-analysis

Study	Country	Study Design	Sample Size	Assessment of Exposure	No of Events	Age at Baseline	Percentage of Males(%)	Follow-up (year)	Study Quality
Xu et al.[12]	China	Cohort	1034	Measured, WHtR	47 IS	≥20	100	9.2	8
Abete et al. [13]	Spain	Cohort	41020	Measured, WC, WHR	674 total strokes; 531 IS; 731 HS; 42 SAH	29-69	37.8	13.8	9
Tikk et al. [14]	Germany	Cohort	23927	Measured, WC	551 total strokes	35-64	46.2	12.7	7
Tatsumi et al. [15]	Japan	Cohort	5488	Measured, WHtR	244 total strokes	20-83	47.4	13	9
Furukawa et al. [21]	Japan	Cohort	5474	Measured, WC	207 total strokes	30-79	46.8	11.7	9
Wang et al. [16]	China	Cohort	94744	Measured, WC, WHR, WHtR	1547 total strokes; 1141 IS; 406 HS	18-98	79.41	4	7
Wannamethee et al. [17]	Britain	Cohort	3411	Measured, WC	192 total strokes	60-79	100	9	8
Bodenant et al. [18]	Multinational	Cohort	54717	Measured, WC, WHR, WHtR	1130 total strokes	52.2 M; 47.8 W	57	11	9
Kizer et al. [19]	USA	Cohort	3754	Measured, WC, WHR, WHtR	622 total strokes; 490 IS	65-100	38.4	14	8
Yatsuya et al. [20]	USA	Cohort	13549	Measured, WC, WHR	598 IS	Mean: 53.9	43.8	16.9	8
Zhang et al. [22]	China	Cohort	67083	Measured, WC, WHR, WHtR	2403 total strokes; 1737 IS; 205 HS	Mean: 51.3	0	7.3	7
Hu et al. [23]	Finland	Cohort	49996	Measured, WC, WHR	3228 total strokes; 2554 IS; 674 HS	25-74	47.9	19.5	9
Lu et al. [24]	Sweden	Cohort	45449	Self-reported, WC, WHR, WHtR	170 total strokes; 111 IS; 47 HS	Blew 60 years	0	11	7
Dey et al. [25]	Sweden	Cohort	2287	Measured, WC	453 total strokes	70-year-olds	45.7	15	8
Walker et al. [26]	USA	Cohort	28643	Self-reported, WHR	118 total strokes; 80 IS; 25 HS	40-75	100	5	7
Sturgeon et al. [27]	USA	Cohort	The ARIC: 15782	Measured, WHR	61 HS	Mean: 54	44.8	13.5	8
			The CHS: 5888	Measured, WHR	74 HS	Mean: 73	42.4	8	8

Note. WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; IS, ischemic stroke; HS, hemorrhagic stroke; SAH, subarachnoid hemorrhagic.

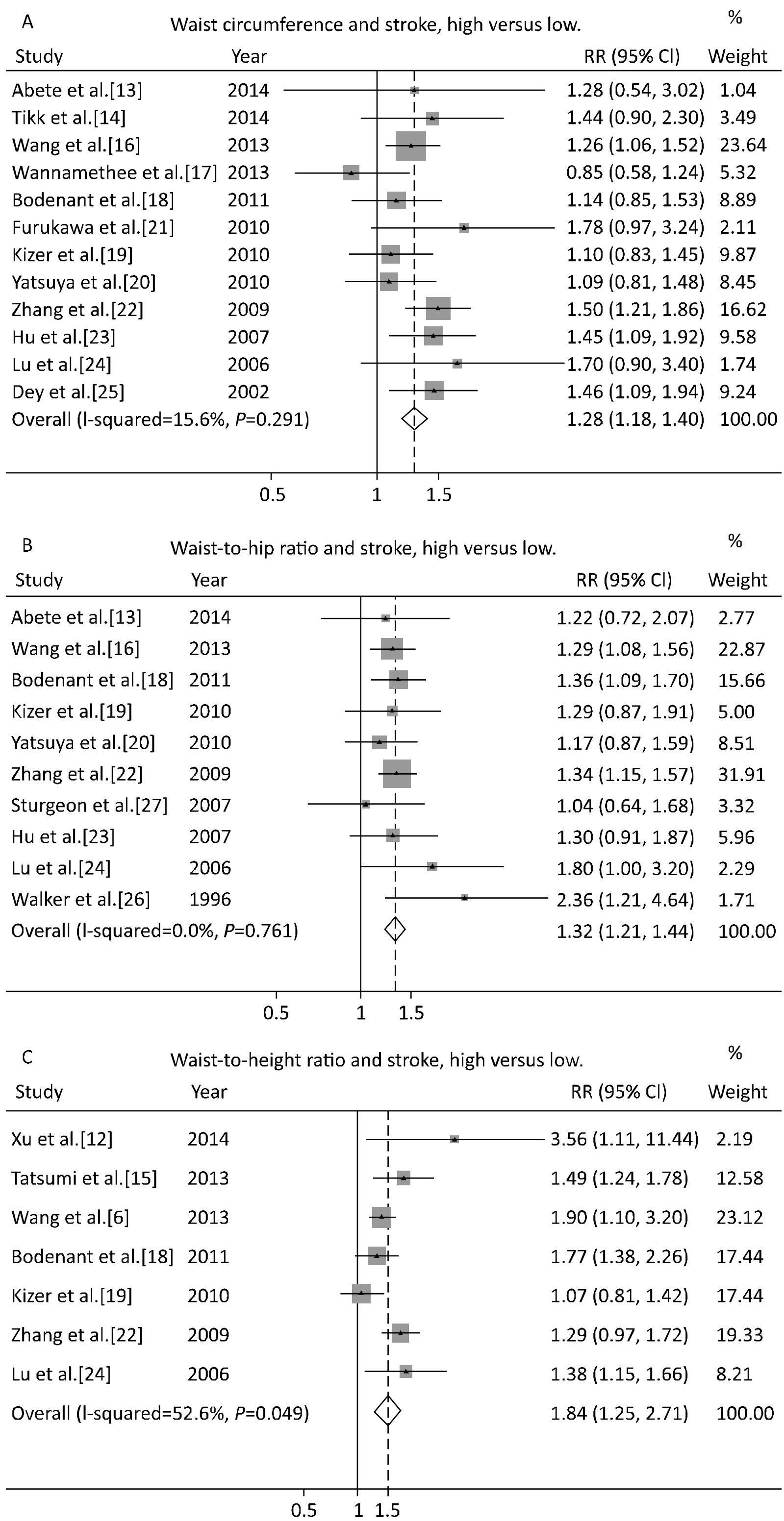

Figure 2. Waist circumference (A), waist-to-hip ratio (B), and waist-to-height (C) and stroke. Summary estimates were calculated using fixed- or random-effects models.

Table 2. Measures of Abdominal Adiposity and Risk of Stroke Subtypes

Abdominal Adiposity Measures	*N*	RR (95% CI)	I^2	$P_{heterogeneity}$
Waist circumference				
Ischemic stroke	7	1.41 (1.27-1.56)	53.6	0.044
Hemorrhagic stroke	4	1.19 (0.94-1.52)	73.1	0.011
Waist-to-hip ratio				
Ischemic stroke	7	1.35 (1.21-1.50)	1.2	0.415
Hemorrhagic stroke	5	1.18 (0.95-1.47)	35.2	0.187
Waist-to-height ratio				
Ischemic stroke	8	1.55 (1.37-1.76)	39.9	0.112
Hemorrhagic stroke	3	1.30 (0.99-1.73)	82.5	0.003

DISCUSSION

This meta-analysis of 15 prospective cohort studies provided a quantitative estimate of the association between measures of abdominal adiposity and stroke risk. In a comparison of the highest with the lowest category of abdominal adiposity indices, the risk of stroke increased significantly, by 28% for WC, by 32% for WHR, and by 49% for WHtR. With respect to stroke subtypes, the association was significantly positive for ischemic stroke, but not for hemorrhagic stroke. In addition, the dose-response analysis also showed consistent associations between measures of abdominal adiposity and increased risk of stroke. To our knowledge, for the first time in a meta-analysis on this correlation, we found a potential nonlinear association between WHR and stroke risk; there was a steep increase in relative risk with increasing WHR from low levels, followed by a slight flattening of the curve with higher WHR.

BMI is the most common anthropometric marker for assessing obesity; however, it cannot distinguish between muscle-related obesity and that due to fat accumulation. Further, BMI does not allow the assessment of fat distribution[29], therefore, it may incorrectly estimate the association of stroke risk with adiposity for individuals with heavy muscle mass. Abdominal obesity measures such as WC, WHR, and WHtR were shown to be a more accurate measure of body fat distribution[18,44], and appear to be more strongly associated with metabolic risk factors, CVD, and death[45-48]. A previous meta-analysis of 15 prospective studies demonstrated that WHR and WC were significantly associated with the risk of CVD incidence events[9]. Specifically, a 1 cm increase in WC was associated with a 2% increase, and a 0.01 increase in WHR was associated with a 5% increase in risk of CVD, after adjusting for age and cohort characteristics. Similarly, in this study, we found that for a 10 cm increase of WC, the relative stroke risk increased by 10%; for a 0.1 unit increase of WHR, the relative stroke risk increased by 16%; and for a 0.05 unit increase in WHtR, the relative stroke risk increased by 13%.

The meta-analysis by the Emerging Risk Factors Collaboration (ERFC) documented that abdominal adiposity measures assessed singly or in combination with BMI, did not significantly improve the prediction of CVD risk when additional information was available on blood pressure, history of diabetes, and cholesterol measures[3]. Moreover, abdominal obesity has been found to be associated with traditional cardiovascular risk factors, such hypertension, diabetes, and hyperlipidemia[49-52]. These may partially explain the observed association between abdominal adiposity measures and stroke. Nevertheless, abdominal obesity per se is a risk factor for stroke because the association between the indicators of abdominal obesity and the risk of stroke remained statistically significant after adjusting for cardiovascular risk factors. The stroke risk associated with abdominal adiposity is mainly attributed to visceral adipose tissue, for it secretes high amounts of inflammatory cytokines. Although visceral adipose tissue stores can be measured by computerized axial tomography and magnetic resonance imaging, these techniques are not feasible for everyone. Early and accurate identification of the population at high risk of stroke is important to predict and prevent stroke development. WC, WHR, and WHtR are inexpensive screening tools and have high reproducibility to identify the individuals with excessive visceral adipose tissue. Therefore, it is important that these simple abdominal adiposity measures be incorporated into stroke risk assessment.

Table 3. Subgroup Analyses of WC, WHR and WHtR, and Stroke Risk, High versus Low Analysis

Group	Waist Circumstance (WC)					Waist-to-hip Ratio (WHR)					Waist-to-height Ratio (WHtR)				
	N	RR (95% CI)	I^2 (%)	P_a	P_b	*N*	RR (95% CI)	I^2 (%)	P_a	P_b	*N*	RR (95% CI)	I^2 (%)	P_a	P_b
All studies	12	1.28 (1.16-1.41)	15.6	0.291		10	1.32 (1.21-1.44)	0.0	0.761		7	1.49 (1.24-1.78)	52.6	0.049	
Geographic area					0.184					0.866					0.037
Asia	3	1.37 (1.20-1.57)	10.5	0.327		2	1.32 (1.17-1.49)	0.0	0.757		4	1.56 (1.36-1.79)	43.8	0.148	
United States	2	1.10 (0.89-1.34)	0.0	0.965		4	1.26 (1.02-1.54)	28.6	0.241		1	1.07 (0.81-1.42)	-	-	
Europe	6	1.33 (1.13-1.56)	25.8	0.241		3	1.37 (1.05-1.78)	0.0	0.573		1	1.90 (1.11-3.24)	-	-	
Sex					0.808					0.215					0.469
Male	8	1.30 (1.13-1.49)	36.2	0.140		5	1.47 (1.25-1.74)	7.9	0.361		4	1.38 (1.12-1.71)	49.4	0.115	
Female	9	1.33 (1.17-1.52)	37.6	0.119		6	1.29 (1.15-1.46)	15.1	0.317		5	1.53 (1.29-1.80)	51.5	0.083	
Assessment of exposure					0.402					0.052					0.305
Measured	11	1.28 (1.17-1.39)	18.9	0.263		8	1.30 (1.18-1.42)	0.0	0.977		6	1.43 (1.28-1.60)	56.9	0.041	
Self-reported	1	1.70 (0.88-3.30)	-	-		2	2.02 (1.30-3.14)	0.0	0.550		1	1.90 (1.11-3.24)	-	-	
Duration (years)					0.956					0.387					0.262
<12	6	1.29 (1.15-1.44)	44.6	0.108		5	1.36 (1.23-1.50)	0.0	0.430		5	1.50 (1.32-1.70)	38.0	0.168	
≥12	6	1.28 (1.12-1.47)	0.0	0.547		4	1.24 (1.03-1.49)	0.0	0.959		2	1.29 (1.03-1.62)	79.8	0.026	
Number of cases					0.510					0.582					0.782
<500	5	1.22 (1.04-1.44)	49.7	0.093		4	1.41 (1.10-1.81)	35.6	0.199		4	1.41 (1.15-1.73)	67.2	0.027	
≥500	7	1.31 (1.18-1.45)	0.0	0.590		6	1.31 (1.19-1.44)	0.0	0.975		3	1.46 (1.28-1.66)	41.5	0.181	

Note. P_a for heterogeneity within each subgroup. P_b for heterogeneity between subgroups with meta-regression analysis.

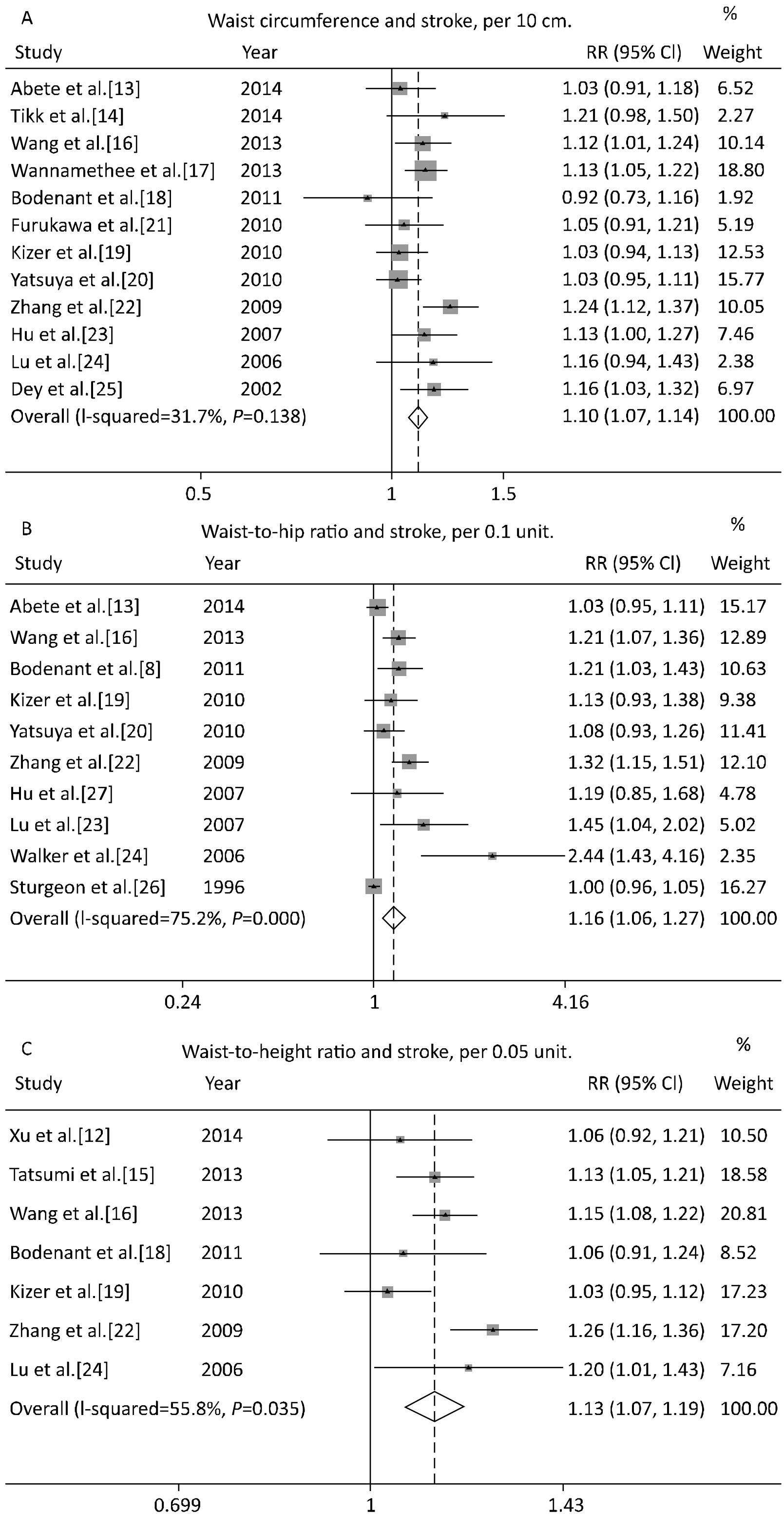

Figure 3. Waist circumference (A), waist-to-hip ratio (B), and waist-to-height (C) and stroke. Summary estimates were calculated using fixed- or random-effects models.

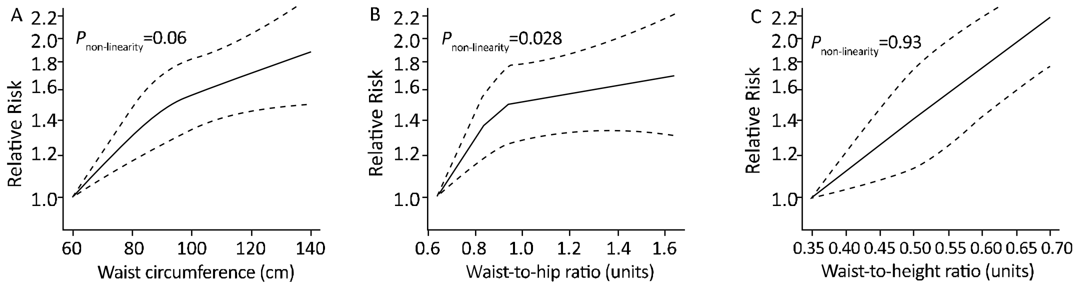

Figure 4. Dose-response relationship between waist circumference (A), waist-to-hip ratio (B), and waist-to-height (C) and stroke risk.

Our meta-analysis has some limitations that may affect the interpretation of results. Unmeasured and residual confounders are always a concern in observational studies. Although there was no evidence of small study effects with the statistical tests in our analysis, it was still possible that a number of studies with null results remained unpublished, and this could lead to exaggerated risk estimates. Further, there was substantial heterogeneity in the main analysis of WHtR and stroke. We did not find subgroup heterogeneity when stratified by sex, or any other study characteristics examined, except for geographic location, which significantly modified the association between WHtR and stroke. Positive association was found in the Asian and European studies, but was not significant in the United States. However, it is not clear whether this is a chance finding because there was only 1 American (USA) study in this subgroup analysis, or if it is due to genetic or other factors. Measurement errors in the assessment of waist, hip, and height may have influenced the results. In the current meta-analysis, the associations persisted in studies where waist, hip, and height had been measured correctly. Self-reported anthropometric measures seemed to overestimate the effects between WC and stroke, although they were not statistically significant. However, there was no significant heterogeneity between studies that used measured and self-reported anthropometric measures. The number of hemorrhagic strokes included in this meta-analysis was relatively small, and thus, might limit our ability to detect a modest association between the abdominal obesity indicators and hemorrhagic stroke.

Our meta-analysis had several strengths that likely increased the reliability and validity of the findings. First, only prospective cohort studies were included, which should eliminate selection and recall bias. Second, the large sample size and high quality of the studies provided statistical power to detect important association. Third, we conducted several subgroup analyses and observed that the positive association persisted in most of the subgroup analyses, and the findings were also robust in sensitivity analyses where each study was excluded one at a time. In addition, the dose-response analysis included a wide range of abdominal adiposity indices, which allowed an accurate assessment of the dose-response relationship between abdominal adiposity and stroke risk.

In conclusion, the findings of our meta-analysis indicated that waist circumference, waist-to-hip ratio, and waist-to-height ratio were positively associated with risk of stroke, in particular, ischemic stroke. There was a nonlinear positive association between waist-to-hip ratio and stroke risk.

AUTHORS CONTRIBUTIONS

ZHONG Chong Ke designed the study, collected and analyzed the data, wrote the manuscript; ZHONG Xiao Yan collected and analyzed the data; XU Tan collected the data; ZHANG Yong Hong designed the study.

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