Original Article

Modifiable risk factors for carotid atherosclerosis: a meta-analysis and systematic review

Xi Ji[1,2], Xin-Yi Leng[3], Yi Dong[4], Ya-Hui Ma[1], Wei Xu[5], Xi-Peng Cao[6], Xiao-He Hou[5], Qiang Dong[4], Lan Tan[1,5], Jin-Tai Yu[4]

[1]Department of Neurology, Qingdao Municipal Hospital, Dalian Medical University, Dalian 116044, China; [2]Department of Neurology, Xuchang People's Hospital, Xuchang 461000, China; [3]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China; [4]Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai 200040, China; [5]Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao 266071, China; [6]Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, Qingdao 266071, China

Contributions: (I) Conception and design: J Yu, XY Leng; (II) Administrative support: JT Yu; (III) Provision of study materials or patients: JT Yu, L Tan; (IV) Collection and assembly of data: X Ji, YH Ma, W Xu; (V) Data analysis and interpretation: X Ji, YH Ma, W Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Jin-Tai Yu, MD, PhD, Department of Neurology and Institute of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, 12th Wulumuqi Zhong Road, Shanghai 200040, China. Email: jintai_yu@fudan.edu.cn; Prof. Lan Tan, MD, PhD. Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao 266071, China. Email: dr.tanlan@163.com.

Background: Carotid atherosclerosis is a major cause of stroke, but the conclusion about risk factors for carotid atherosclerosis is still controversial. The aim of our present meta-analysis and systematic review was to explore the modifiable risk factors for carotid atherosclerosis.

Methods: We searched PubMed from January 1962 to October 2018 to include longitudinal and cross-sectional studies. The results were pooled using random effects model. Heterogeneity was measured by I^2 statistic and publication bias was assessed by funnel plots.

Results: A total of 14,700 articles were screened, of which 76 with 27 factors were eligible. Our meta-analysis of cross-sectional studies indicated nine factors (hyperlipidemia, hyperhomocysteinemia, hypertension, hyperuricemia, smoking, metabolic syndrome, hypertriglyceridemia, diabetes, and higher low density lipoprotein) were significantly associated with the presence of carotid plaque, among which four (hyperlipidemia, hyperhomocysteinemia, hypertension, and hyperuricemia) could elevate the risk of atherosclerosis by at least 50%; and one factor (hypertension) was associated with increased carotid intima-media thickness. In the systematic review, another five factors [negative emotion, socioeconomic strain, alcohol, air pollution, and obstructive sleep apnea syndrome (OSAS)] were also related to the presence of atherosclerosis. The cross-sectional associations with most of the above 14 factors were further confirmed by longitudinal studies. Among them, the managements of 4 factors (hypertension, hyperlipidemia, diabetes and OSAS) were indicated to prevent carotid atherosclerosis by cohort studies.

Conclusions: Effective interventions targeting pre-existing disease, negative emotion, lifestyle and diet may reduce the risk of carotid atherosclerosis. Further good-quality prospective studies are needed to confirm these findings.

Keywords: Carotid atherosclerosis; carotid plaque; carotid intima-media thickness; risk factors; meta-analysis

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Introduction

Carotid atherosclerosis is a major cause of ischemic stroke, which remains clinically silent for a long time before an outbreak of acute events. As a global public health problem, stroke is the second leading cause for death worldwide (1), which leads to a huge burden on individuals and society because of the high rate of residual disability (2). Therefore, the prevention of the disease in a subclinical phase is important (3). Among the different stages of carotid atherosclerosis, we selected increased carotid intima media thickness (CIMT) and the presence of carotid plaque because these two were the most commonly used parameters (4).

Recently, it was indicated that healthy lifestyles might contribute to a decline in the prevalence of carotid atherosclerosis in the long term (5,6). In addition, a considerable amount of studies suggested that carotid atherosclerosis could be prevented by medications targeting several comorbidities, such as hypertension, diabetes, and dyslipidemia (7). Nonetheless, the conclusions concerning these potentially modifiable risk factors are still in dispute (8,9). As yet no article has been published on the detail of the risk factors for carotid atherosclerosis. Therefore, we performed a meta-analysis and systematic review to explore the modifiable risk factors for carotid atherosclerosis identified in previous reports, which is expected to throw light on the prevention of carotid atherosclerosis.

Methods

Search strategy

We adhered to the meta-analysis in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (10). We searched PubMed for studies that reported risk factors for carotid atherosclerosis from January 1962 to October 2018. Search terms were "carotid", "risk", and "risk factor" (the detailed retrieval strategy was shown in Supplementary Material). The reference lists of relevant reviews, meta-analyses and systematic reviews were hand-searched for further supplement.

Inclusion and exclusion criteria

Longitudinal and cross-sectional studies were included if they fulfilled the following criteria simultaneously: (I) the study included community-based population, (II) the exposures considered to be risk or protective factors for carotid atherosclerosis were potentially modifiable, (III) the control group were people without carotid atherosclerosis, and (IV) the outcome of carotid atherosclerosis was measured by increased carotid intima-media thickness (CIMT) or carotid plaque burden which included both non-stenotic and stenotic plaques (4). Increased CIMT was defined as CIMT ≥1.0 mm whether in the distal wall of the common carotid artery or in the bulb where there is no plaque and the presence of carotid plaque was defined as CIMT >1.5 mm or focal structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding CIMT value (2). We restricted our search to those published in English. The detailed exclusion criteria were shown in *Figure 1*. If there was any disagreement between authors, the articles would be discussed until an agreement was reached.

Data extraction and quality assessment

General characteristics of studies were extracted, including authors, publication year, baseline characteristics (total sample size, recruitment period, mean age and sex distribution), study design (prospective or cross-sectional), follow-up information (mean or maximum follow-up and the number of lost to follow-up), and outcomes (increased CIMT or the presence of carotid plaque). All data were extracted using an electronic spreadsheet. We preferred multivariate-adjusted OR/RR/HR rather than crude results.

Agency for Healthcare Research and Quality (AHRQ) (11) was used to assess the quality of cross-sectional observational studies *(Table S1)*. Newcastle-Ottawa Scale (NOS) was employed to assess the quality of longitudinal studies *(Table S2)*.

Statistical analyses

Heterogeneity among studies was assessed using the I^2 statistic and values <75%, P>0.05 were considered as possibly low heterogeneity (12). A random effects model was used to quantitatively synthesize data. When the heterogeneity was high, the source would be explored further (13,14). First, sensitivity analyses were performed to examine whether the pooled effect was influenced by omitting any single study. Second, subgroup analyses were conducted according to the characteristics of studies (e.g., different outcomes). Funnel plot and trim-and-fill method were used to evaluate whether the asymmetry of funnel plot was related to publication bias (15). All statistical analyses were performed with R 3.2.0 software.

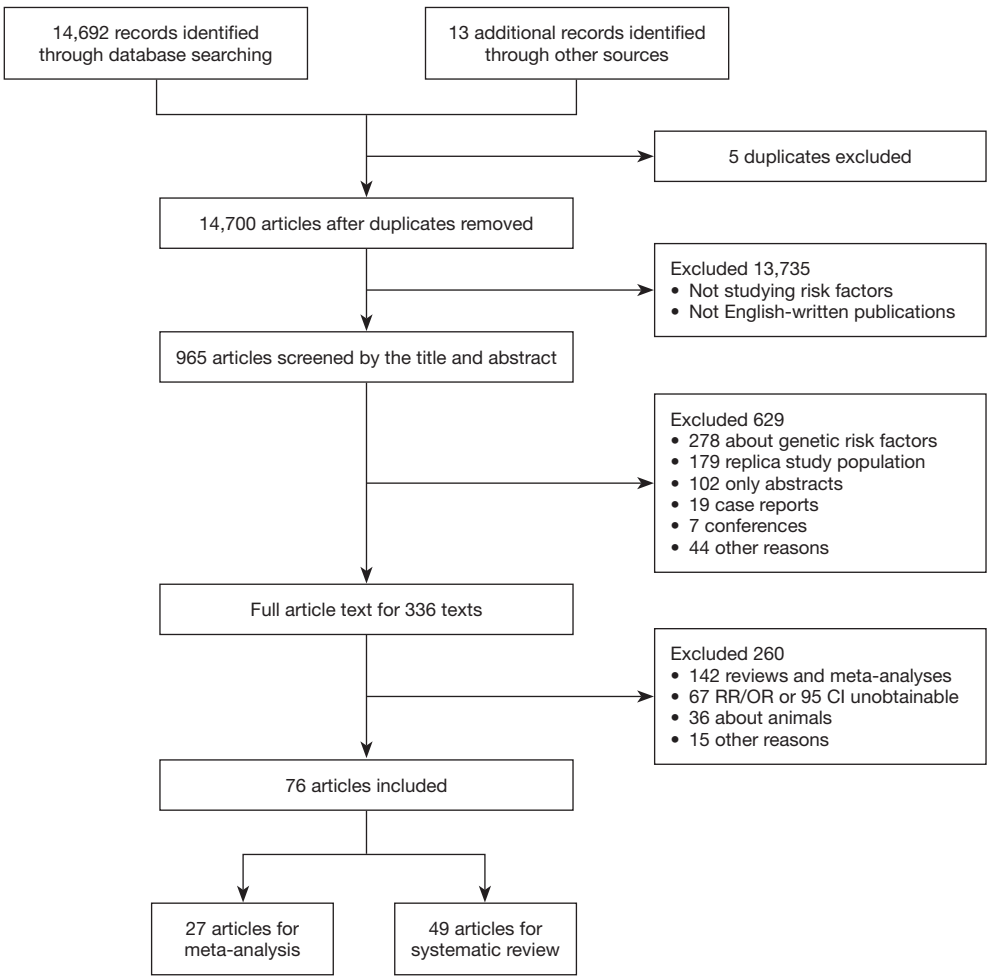

Figure 1 Flow chart of identified studies.

Ethics approval

It was not required, because the study type of our article is meta-analysis and systematic review.

Results

A total of 14,700 articles were identified, of which 76 with 27 factors met the inclusion criteria. Finally, eleven factors had data eligible for the meta-analysis and all relevant studies were cross-sectional *(Figure 2)*. The general characteristics of the articles included in the meta-analysis were presented in *Table 1*. A total of 48,847 subjects were included in the meta-analysis, 92.6% studies were published from 2005 onwards and 72.8% samples were recruited from Asia and North America. The age range of all recruited subjects was from 35 to 100. Where reported, the proportion of females in the samples ranged from 18% to 67.2%. More baseline characteristics of the included population were presented in *Table S3*.

Cigarette smokers and people with metabolic syndrome (including its components of hypertension, dyslipidemia, and diabetes mellitus), hyperuricemia, hyperhomocysteinemia, negative emotion, socioeconomic strain, obstructive sleep apnea syndrome (OSAS), alcohol, air pollution, and childhood sexual abuse are more likely to have carotid atherosclerosis. Furthermore, interventions against risk factors may prevent atherosclerosis.

Modifiable risk factors

Blood pressure

Data from eight studies (16-23) including 12,474 individuals

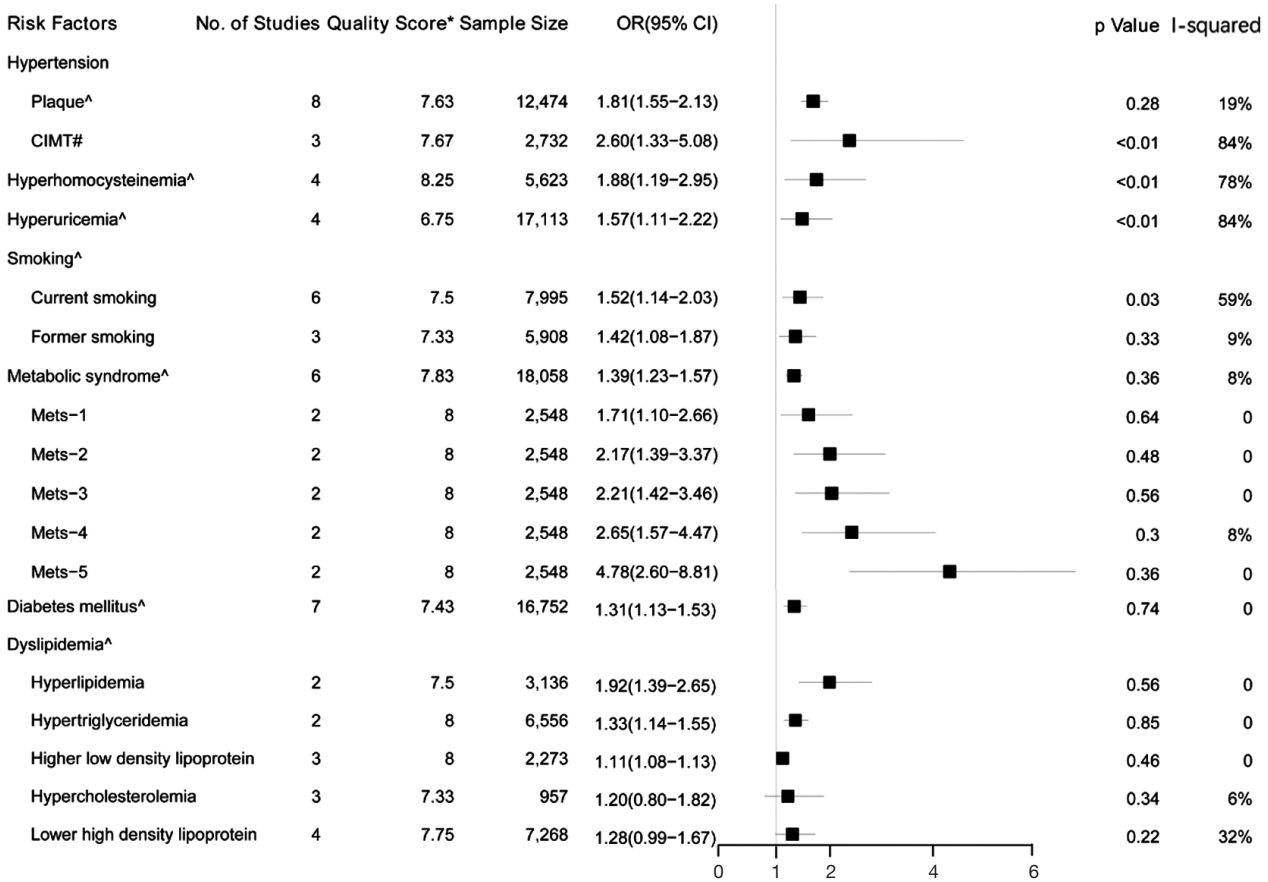

Figure 2 Forest plot shows the risk factors for carotid atherosclerosis in the meta-analysis. OR, odds ratio; 95% CI, 95% confidence interval. Quality Score*, mean quality score of included studies; ^ presence of carotid plaque; # increased carotid intima-media thickness.

were pooled in the meta-analysis (*Figure 2*), which showed that hypertension could increase the risk of carotid plaque by 81% (OR =1.81, 95% CI: 1.55–2.13, I^2=19%, P=0.28) (*Figure S1)*. Three studies (17,19,23) with 2,732 subjects exhibited hypertension has higher risk of increased CIMT (OR =2.60, 95% CI: 1.33–5.08, I^2=84%, P<0.01) (*Figure S2*).

Additionally, it was indicated that the risk of plaque was significantly greater in people with increased systolic blood pressure (SBP) variability (every 10 mmHg increase) and diastolic blood pressure (DBP) variability (1,24,25). Pulse pressure (PP) variability (every 10 mmHg increase) raises the risk of carotid plaque for both community-based subjects and stroke patients (26,27).

Diabetes mellitus

Seven studies (16,21-24,28,29) with 16,752 patients were included in the meta-analysis *(Figure 2)*. The results showed that diabetics might have carotid plaque than non-diabetics (OR =1.31, 95% CI: 1.13–1.53, I^2=0%, P=0.74) (*Figure S3)*.

Dyslipidemia

The meta-analysis of ten studies (16,21-24,28,30-33) including 12,568 patients showed that patients with hyperlipidemia (OR =1.92, 95% CI: 1.39–2.65, I^2=0, P=0.56), hypertriglyceridemia (triglyceride ≥1.7 mmol/L) (OR =1.33, 95% CI: 1.14–1.55, I^2=0%, P=0.85), and higher low density lipoprotein (low density lipoprotein ≥3.4 mmol/L) (OR =1.11, 95% CI: 1.08–1.13, I^2=0%, P=0.46) were more likely to have carotid plaque (*Figures S4*,*S5*,*S6*). Moreover, there was strong likelihood of positive relationship between lower high density lipoprotein (high density lipoprotein ≤1.0 mmol/L) (OR =1.28, 95% CI: 0.99–1.67, I^2=32%, P=0.22) or hypercholesterolemia (total cholesterol ≥5.2 mmol/L) (OR =1.20, 95% CI: 0.80–1.82, I^2=6%, P=0.34) with carotid plaque (*Figures S7*,*S8*). One cohort study (34) indicated that hypercholesterolemia, hypertriglyceridemia, and

Table 1 General characteristics of studies included in the meta-analysis

Risk factors	Study	Recruitment period	N (total)	Country	Ethnicity	Age	Sex (female), %	Outcome	OR (95% CI)
Hypertension	Woo, 2017	2008–2012	3,030	Korea	Korean	70 [50–100]	56.30	Plaque*	1.72 (1.21–2.45)
	Zhang, 2016	1992	1,257	China	Chinese	69.16±8.10	56.20	Plaque*	1.75 (1.18–2.60)
	Idei, 2014	2007–2009	64	Japan	Japanese	NA	47.80	Plaque*	3.26 (1.15–9.62)
	Hong, 2013	2008	942	China	Chinese	46–75	67.20	Plaque*	1.88 (1.15–3.07)
	Beaussier, 2008	NA	92	France	NA	50–80	23.91	Plaque*	6.90 (1.40–34.9)
	Empana, 2007	1999–2001	5,585	France	French	73.5±4.9	38.00	Plaque*	1.72 (1.43–2.06)
	Czernichow, 2005	2001–2002	971	France	French	58.9±4.7 (without MetS), 58.8±4.9 (MetS)	49.84	Plaque*	1.55 (1.12–2.15)
	Su, 2001	1990	533	China	Chinese	>35	57.20	Plaque*	3.70 (1.80–7.90)
	Zhang, 2016	1992	1,257	China	Chinese	69.16±8.10	56.20	Cimt†	1.58 (1.08–2.33)
	Hong, 2013	2008	942	China	Chinese	46–75	67.20	Cimt†	2.33 (1.40–3.87)
	Su, 2001	1990	533	China	Chinese	>35	57.20	Cimt†	5.00 (3.00–8.40)
Diabetes mellitus	O'Flynn, 2017	2010	50	Ireland	NA	59±6	51.00	Plaque*	0.93 (0.05–16.23)
	Woo, 2017	2008–2012	3,030	Korea	Korean	70 [50–100]	56.30	Plaque*	1.17 (0.81–1.69)
	Rubinat, 2016	NA	374	Spain	NA	56.1±10.8	59.90	Plaque*	1.00 (0.60–1.65)
	Casalnuovo, 2012	2011	6,209	Italy	NA	54±11	42.90	Plaque*	1.51 (1.18–1.93)
	Empana, 2007	1999–2001	5,585	France	French	73.5±4.9	38.00	Plaque*	1.21 (0.89–1.64)
	Czernichow, 2005	2001–2002	971	France	French	58.9±4.7 (without MetS), 58.8±4.9 (MetS)	49.84	Plaque*	1.42 (0.81–2.48)
	Su, 2001	1990	533	China	Chinese	>35	57.20	Plaque*	1.80 (0.70–4.90)
Hyperlipidemia	Woo, 2017	2008–2012	3,030	Korea	Korean	70 [50–100]	56.30	Plaque*	1.84 (1.30–2.62)
	Yuan, 2014	NA	106	China	Chinese	58.1±9.0	63.20	Plaque*	2.41 (1.05–5.51)
Hypercholesterolemia	O'Flynn, 2017	2010	50	Ireland	NA	59±6	51.00	Plaque*	0.70 (0.29–1.70)
	Rubinat, 2016	NA	374	Spain	NA	56.1±10.8	59.90	Plaque*	1.47 (0.91–2.38)
	Su, 2001	1990	533	China	Chinese	>35	57.20	Plaque*	1.10 (0.40–3.00)

Table 1 (*continued*)

Table 1 (*continued*)

Risk factors	Study	Recruitment period	N (total)	Country	Ethnicity	Age	Sex (female), %	Outcome	OR (95% CI)
Hypertriglyceridemia	Empana, 2007	1999–2001	5,585	France	French	73.5±4.9	38.00	Plaque*	1.34 (1.14–1.58)
	Czernichow, 2005	2001–2002	971	France	French	58.9±4.7 (without MetS), 58.8±4.9 (MetS)	49.84	Plaque*	1.28 (0.83–1.98)
Lower high density lipoprotein	Irie, 2014	2007–2009	179	Japan	Japanese	65±7	18.00	Plaque*	2.30 (1.03–5.13)
	Empana, 2007	1999–2001	5,585	France	French	73.5±4.9	38.00	Plaque*	1.13 (0.93–1.38)
	Czernichow, 2005	2001–2002	971	France	French	58.9±4.7 (without MetS), 58.8±4.9 (MetS)	49.84	Plaque*	1.52 (1.01–2.28)
	Su, 2001	1990	533	China	Chinese	>35	57.20	Plaque*	1.00 (0.50–1.90)
Higher low density lipoprotein	Sato, 2013	2005–2012	236	Japan	Japanese	56±13	34.30	Plaque*	1.01 (0.74–1.37)
	Johnson, 2010	2005–2007	1,504	America	84% white, 14% black, 2% American	45.0 [37.8–53.0]	58.00	Plaque*	1.11 (1.08–1.13)
	Su, 2001	1990	533	China	Chinese	>35	57.20	Plaque*	0.60 (0.20–1.80)
Metabolic syndrome	Leng, 2013	2007–2008	653	China	Chinese	55.1±10.4	52.80	Plaque*	1.50 (0.92–2.46)
	Chen, 2008	1990–1991	810	China	Chinese	66.1±10.9	43.70	Plaque*	1.37 (0.93–2.01)
	Empana, 2007	1999–2001	5,585	France	French	73.5±4.9	38.00	Plaque*	1.30 (1.09–1.55)
	Rundek, 2007	2000	1,895	Northern Manhattan	25% were black, 22% white, 51% Hispanic, and 1% of other ethnicity	68.0±9.7	59.00	Plaque*	1.36 (1.10–1.67)
	Czernichow, 2005	2001–2002	971	France	French	58.9±4.7 (without MetS), 58.8±4.9 (MetS)	49.84	Plaque*	1.07 (0.63–1.83)
	Ishizaka, 2005	1994–2003	8,144	Japan	Japanese	56.6±10.5	32.80	Plaque*	1.99 (1.39–2.85)

Table 1 (*continued*)

Table 1 (*continued*)

Risk factors	Study	Recruitment period	N (total)	Country	Ethnicity	Age	Sex (female), %	Outcome	OR (95% CI)
Smoking	O'Flynn, 2017	2010	50	Ireland	NA	59±6	51.00	Plaque*	9.16 (0.39–217.16)‡
	Woo, 2017	2008–2012	3,030	Korea	Korean	70 [50–100]	56.30	Plaque*	1.46 (0.89–2.40)‡
	Yang, 2015	NA	1,746	Northern Manhattan	18% white, 63% Hispanic, 19% black.	65.5±8.9	60.00	Plaque*	2.13 (1.27–3.57)‡
	Johnson, 2010	2005–2007	1,504	America	84% white, 14% black, 2% American	45.0 [37.8–53.0]	58.00	Plaque*	1.14 (1.05–1.23)‡
	Liang, 2009	1993–1994	1,132	China	Chinese	35–64	66.10	Plaque*	1.50 (1.00–2.10)‡
	Su, 2001	1990	533	China	Chinese	>35	57.20	Plaque*	2.40 (1.00–5.60)‡
	Woo, 2017	2008–2012	3,030	Korea	Korean	70 [50–100]	56.30	Plaque*	1.08 (0.63–1.85)§
	Yang, 2015	NA	1,746	Northern Manhattan	18% white, 63% Hispanic, 19% black.	65.5±8.9	60.00	Plaque*	1.73 (1.19–2.51)§
	Liang, 2009	1993–1994	1,132	China	Chinese	35–64	66.10	Plaque*	1.30 (0.80–2.10)§
Hyperuricemia	Li, 2015	2010	2,860	China	Chinese	57.7 [40–94]	28.40	Plaque*	1.37 (1.09–1.74)
	Li, 2014	1992	1,243	China	Chinese	69.6±8.1	54.80	Plaque*	0.99 (0.63–1.55)
	Neogi, 2009	2002–2004	4,866	America	Caucasian	52.2	54.00	Plaque*	1.75 (1.21–2.51)
	Ishizaka, 2005	1994–2003	8,144	Japan	Japanese	56.6±10.5	32.80	Plaque*	2.27 (1.90–2.72)
Hyperhomocysteinemia	Zhang, 2016	1992	1,257	China	Chinese	69.16±8.10	56.20	Plaque*	1.56 (1.05–2.33)
	Yang, 2014	2010–2011	2,919	China	Chinese	60.1±12.4	28.60	Plaque*	1.28 (1.09–1.51)
	Alsulaimani, 2013	1993–2001	1,327	Northern Manhattan	19% black, 62% Hispanic, 17% white.	66±9	59.00	Plaque*	1.90 (1.20–3.10)
	Kawamoto, 2001	2000	120	Japan	Japanese	77±9	55.80	Plaque*	8.24 (2.87–23.70)

OR, odds ratio; 95% CI, 95% confidence interval; MetS, Metabolic syndrome. Plaque*, presence of carotid plaque; CIMT†, increased carotid intima-media thickness; ‡, current smoking; §, former smoking.

higher low density lipoprotein were risk factors for CIMT. Nevertheless, one cross-sectional study (33) failed to prove the relationship of total cholesterol (every 1 mmol/L increase) or triglyceride (every 1 mmol/L increase) with carotid plaque.

Metabolic syndrome (MetS)

MetS was defined according to the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) (35). Six studies (21,22,36-39) including 18,058 individuals explored the association between MetS and carotid atherosclerosis, which showed that people with MetS might have more carotid plaque than non- MetS (OR =1.39, 95% CI: 1.23–1.57, I^2=8%, P=0.36) (*Figure S9*). Notably, there was a dose-response relationship between the presence of carotid plaque and an increasing number of components of MetS (OR =1.71, 95% CI: 1.10–2.66, I^2=0%, P=0.64 for MetS-1; OR =2.17, 95% CI: 1.39–3.37, I^2=0%, P=0.48 for MetS-2; OR =2.21, 95% CI: 1.42–3.46, I^2=0%, P=0.56 for MetS-3; OR =2.65, 95% CI: 1.57–4.47, I^2=8%, P=0.30 for MetS-4; OR =4.78, 95% CI: 2.60–8.81, I^2=0%, P=0.36 for MetS-5) (*Figures S10,S11,S12,S13,S14*). Consistently, the association was confirmed by one cohort study (40) showing that individuals with MetS had higher risk of carotid plaque (HR =1.92, 95% CI: 1.06–3.47).

Hyperuricemia

The association between hyperuricemia (uric acid ≥420 μmol/L in man or uric acid ≥360 μmol/L in woman) and carotid plaque was reported in four studies (25,39,41,42) including 17,113 participants. Pooled results indicated that hyperuricemia might increase the presence of plaque (OR =1.57, 95% CI: 1.11–2.22, I^2=84%, P<0.01) (*Figure S15*). Similarly, the increased CIMT was presented in those with higher uric acid level (OR =1.24, 95% CI: 1.04–1.47) (43). Further, people with carotid plaque or stenosis were reported to have higher uric acid level. But another cross-sectional study (44) failed to find the relationship between uric acid and plaque.

Hyperhomocysteinemia

Four studies (17,45-47) with 5,623 individuals were included and a significant positive relationship between hyperhomocysteinemia (homocysteine ≥15 μmol/L) and carotid plaque was found (OR =1.88, 95% CI: 1.19–2.95, I^2=78%, P<0.01) (*Figure S16*). Additionally, one cross-sectional study (48) found CIMT increased 0.06mm as the level of homocysteine elevated per 1 μmol/L.

Smoking

A pooled analysis of six studies (16,23,24,30,49,50) including 7,995 participants indicated that smoking had a significant association with the risk of carotid plaque. Subgroup analyses showed that current smoking (current smokers *vs.* non-smokers, OR =1.52, 95% CI: 1.14–2.03, I^2=59%, P=0.03) conferred greater risk than former smoking (former smokers *vs.* non-smokers, OR =1.42, 95% CI: 1.08–1.87, I^2=9%, P=0.33) for the presence of carotid plaque (*Figures S17,S18*). Similarly, tobacco smoking is associated with increased CIMT, especially current smokers (51).

Sensitivity analyses

In sensitivity analyses (*Table S4*), the results were robust for hypertension, hyperhomocysteinemia, MetS, and hypercholesterolemia. For current smoking, the heterogeneity was reduced after omitting one study (30) without changing the significance of the results. For hyperuricemia, the pooled effect became non-significant (OR=1.50, 95% CI: 0.95–2.38) after omitting one study (41) with different races.

Assessment of publication bias

For studies reporting the association between hypertension, diabetes mellitus, MetS, current smoking and the presence of carotid plaque, there was evidence of publication bias. After using the trim and fill method, the result barely changed for hypertension, diabetes mellitus, and MetS, but not for current smoking (*Figure S19,S20,S21,S22,S23,S24,S25,S26*).

Others

Some modifiable factors could not be included in the meta-analysis due to insufficient data, consisting of sexual abuse in early life (52), air pollution (53,54), socioeconomic strain (55-57), negative emotion (58-60), lifestyles (drinking, physical activity, and sleep duration) (5,61-64), diet (vitamin supplementation, egg consumption, vegetable intake and fish consumption) (65-72), medications (antihypertensive drugs, lipid-lowering drugs, and glucose-lowering drugs) (73-82), and pre-existing disease (OSAS) (apnea-hypopnea index >15 events/h) (83,84) in mid-to-late life (*Figure 3* and *Table S5*).

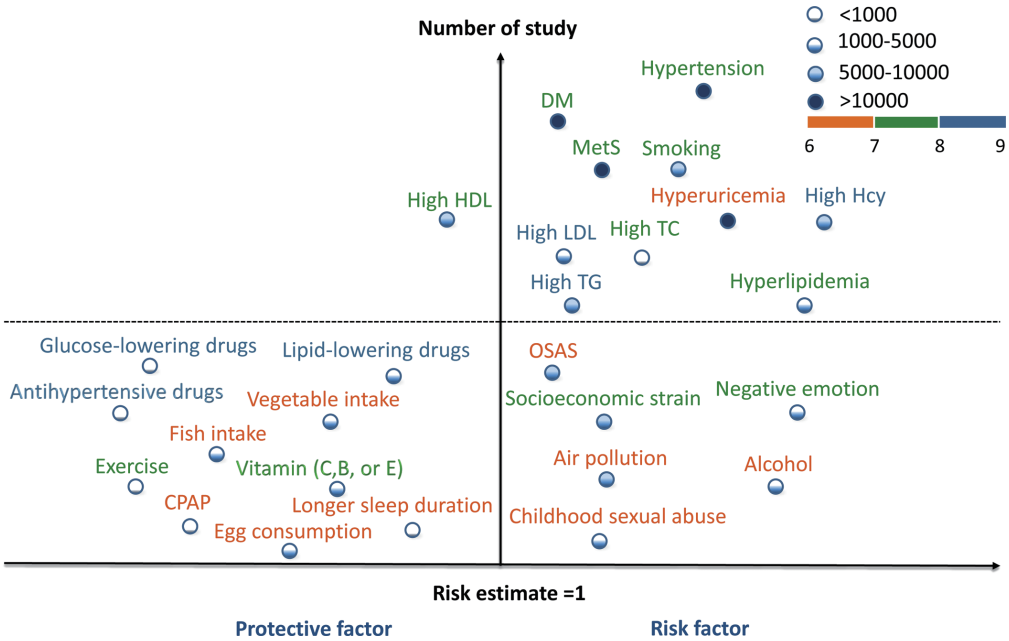

Figure 3 Factors showing significant positive and negative association with carotid atherosclerosis. DM, diabetes mellitus; MetS, metabolic syndrome; Hcy, homocysteine; HDL, how density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol; TG, Triglyceride; OSAS, obstructive sleep apnea syndrome; CPAP, continuous positive airway pressure. Risk factors of meta-analysis are above the dotted line; Risk factors of systematic review are below the dotted line; The dots with four different filled ratios below risk factors represent different total sample size ranges; Different colors represent different quality score ranges.

Discussion

There were 27 studies included in the meta-analysis and 49 studies included in the systematic review. The meta-analysis suggested that dyslipidemia, hyperhomocysteinemia, hypertension, hyperuricemia, smoking, MetS, and diabetes mellitus could increase the risk of carotid plaque. Some low- and medium-quality references were included in the meta-analysis and systematic review; therefore, more high-quality and large-scale prospective studies were needed to obtain more reliable results.

It is known that atherosclerosis affects other vascular beds before it causes significant carotid disease. The prevalence of carotid atherosclerosis and carotid plaque was 27.22% and 20.15% of Chinese people aged 30–79 years in 2010 (85). Among patients with diagnosed coronary artery disease, 56.3% patients had raised CIMT, 74.8% patients had carotid plaques, and 8.4% patients had stenosis in carotid arteries (86). Patients with coronary artery disease more often had multiple plaques (86.7% versus 13.8%, P<0.001) (87). This suggests that coronary artery disease may be an early marker of carotid atherosclerosis.

MetS and its components were associated with both the presence and the progression of carotid atherosclerosis via multiple pathways. The association of hypertension with carotid atherosclerosis might be explained by hemodynamic changes which were related to the severity of CIMT (88). High plasma glucose levels could induce carotid structural changes by promoting endothelial dysfunction and vascular smooth muscle cell proliferation (8). Dyslipidemia might play an important role through the influx of lipids into the sites of vascular lesions. Interestingly, it was showed that higher high-density lipoprotein could reverse the transport of cholesterol and return it to the liver to protect against carotid atherosclerosis (89). The effect of triglyceride on carotid atherosclerosis was controversial because the criteria of hypertriglyceridemia were inconsistent. Recently, a large number of studies have been conducted to investigate whether drugs targeting comorbidities could reduce the incidence of carotid atherosclerosis. Some cohort studies showed that medications including antihypertensive drugs, lipid-lowering drugs and glucose-lowering drugs were protective against CIMT progression. The protective role of these drugs in atherosclerosis relies not only on their therapeutic effects on the pre-existing disease, but also on

their direct protective effects on the arterial wall (75). A number of longitudinal studies showed that long-term use of lipid-lowering drugs for prevention of atherosclerosis might be more effective than short-term use (78,90). Moreover, the results in our analysis were supportive of the roles of glucose-lowering drugs in preventing CIMT progression (81,82,91). However, one cohort study showed no relationship between glucose-lowering drugs and the progression of CIMT, which could be explained either by insufficient follow-up or by the different inclusion criteria for people free from diabetes (80).

In addition, it was indicated that hyperuricemia could increase the occurrence of carotid plaque and accelerate CIMT progression through the production of reactive oxygen species, which could lead to oxidative stress and endothelial dysfunction (92). Besides, OSAS was reported to have a similar impact on carotid atherosclerosis (83), especially in rapid eye movement sleep (93), which may be attributed to nocturnal hypoxemia that could augment local inflammatory responses and exacerbate vessel damage in carotid arteries (94). Therefore, continuous positive airway pressure (CPAP) was considered the treatment for OSAS by ameliorating inflammation to protect against carotid atherosclerosis (95).

Negative emotion including depression, anger, and anxiety was identified as a risk factor for the progression of carotid atherosclerosis by many cohort studies (58,96), which might be accounted for by sympathetic nervous system hyperreactivity, abnormalities in platelet function, hypercortisolemia, endothelial dysfunction, and heart rate variability (97). One cohort study (59) failed to prove that depression symptoms could increase the risk of CIMT, but the inconsistencies could be explained by threshold effect (depression *vs*. depression symptoms). The relationship between anger and CIMT was controversial according to different socioeconomic status (SES). People with low SES would have a greater likelihood of increased CIMT (52,55,98). Business workers are considered to have higher CIMT when compare with factory workers (99). More evidence is required to explore the relationship between social, psychological condition and carotid atherosclerosis. Moreover, psychosocial interventions may play an important role in the prevention of carotid atherosclerosis.

Healthy lifestyles (e.g., no smoking, little drink and exercise) could protect against atherosclerosis through increasing endothelial dilatory factors and blood volume in the carotid artery. The mechanism for the influence of smoking on carotid atherosclerosis might be attributed to chronic inflammation which could damage endothelial cells exposed to circulating thrombogenic factors. These factors might increase macrophage infiltration and plaque thrombogenicity (49). One longitudinal study identified current smoking is related with extracranial carotid atherosclerosis but not with intracranial artery (100). Interestingly, if mothers smoked in pregnancy, children had thicker CIMT, and the impact was stronger if both parents smoked during pregnancy (101). Drinking could increase low density lipoprotein oxidation and oxidative stress to accelerate the progression of atherosclerosis when a man consumes alcohol over 40 g/d, and the CIMT progression had a dose-response relationship with alcohol intake, no matter what he drinks: beer, wine or spirits (102). Moderate exercise could increase antioxidant stress and anti-inflammatory processes, which could protect against the progression of carotid atherosclerosis (5). Shorter sleep duration may have higher CIMT in Western populations rather than Asian populations (103). More evidence is needed to confirm the association between sleep duration and carotid atherosclerosis.

Compared with a low-fat diet, a long-term use of the Mediterranean diet prevented the progression of carotid atherosclerosis in patients who were newly diagnosed with type 2 diabetes. Because Mediterranean diet is rich in vegetables and fish, which have beneficial effects on carotid via inhibition of oxidative stress (71). A number of cohort studies showed that vitamin supplementation (including vitamin C, vitamin B, or vitamin E) could protect from CIMT progression, and it was speculated that the potential mechanism was the improved endothelial vasodilator function, but the effect might depend on dose (68). Vitamin B12 deficiency may increase the risk of carotid atherosclerosis by elevating total homocysteine (104), and vitamin B supplementation may slow the progression of carotid plaque burden by reducing homocysteine (105). Further longitudinal studies should be conducted to clarify the association between diet and carotid atherosclerosis.

Strength and limitations

As far as we know, this is the first meta-analysis and systematic review exploring the modifiable risk factors for carotid atherosclerosis. We tried to search all available studies and synthesise all suitable data.

Our study had a few limitations. First, our meta-analysis was based on cross-sectional studies, which could not reflect causal links between risk factors and carotid atherosclerosis.

Hence, we carried out a systematic review based on the longitudinal studies. Second, as the analysis included observational studies, some unmeasured confounding factors and biases might exist. Therefore, the quality assessment of individual studies was carried out. Third, the number of population was relatively small for some risk factors, which should be clarified with caution. Fourth, there was publication bias when exploring the association between current smoking and the presence of carotid plaque, but the result was robust after sensitivity analyses. Therefore, the conclusion should be drawn with caution.

Conclusions

The current meta-analysis and systematic review indicated that pre-existing disease, negative emotion, lifestyle, and diet could increase the risk of carotid atherosclerosis, suggesting that these factors may serve as prevention targets. More investigation is needed to clarify the association of mood, lifestyle, and medication with carotid atherosclerosis. Further good-quality prospective studies are warranted.

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Footnote

Conflicts of Interest: 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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Supplementary

Retrieval strategy

[PubMed]

((risk) OR risk factor) OR hypertension) OR hypertensive disease) OR blood pressure) OR BP) OR systolic blood pressure) OR SBP) OR diastolic blood pressure) OR DBP) OR diabetes) OR diabetes mellitus) OR DM) OR hyperglycemia) OR hyperlipidemia) OR hyperlipaemia) OR dyslipidemia) OR triglyceride) OR TG) OR high density lipoprotein) OR HDL) OR low density lipoprotein) OR LDL) OR cholesterin) OR cholesterol) OR hypercholesterolemia) OR apolipoprotein) OR Apo) OR BMI) OR body mass index) OR overweight) OR overload) OR obesity) OR high weight circumference) OR fat) OR adiposis) OR corpulence) OR metabolic syndrome) OR Mets) OR metabolic dysfunction) OR metabolic disorder) OR metabolic disturbance) OR smoking) OR smoke) OR smoker) OR tabacco) OR nicotine addiction) OR uric acid) OR UA) OR hyperuricemia) OR hyperuricaemia) OR homocysteine) OR HCY) OR homocystinemia) OR diet) OR food) OR wine) OR alcohol) OR drinking) OR drink) OR drinker) OR vitamin) OR niacin) OR nicotinic acid) OR folic acid) OR folate) OR folacin) OR cobalamin) OR sport) OR exercise) OR movement) OR activity)) AND (carotid)) AND (((((prospective) OR cohort) OR follow) OR longitudinal) OR nested case-control)

Table S1 The quality evaluation of cross-sectional studies by agency for healthcare research and quality (AHRQ)

Study	Define the source of information (survey, record review)	List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Indicate time period used for identifying patients	Indicate whether or not subjects were consecutive if not population-based	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	Explain any patient exclusions from analysis	Describe how confounding was assessed and/or controlled	If applicable, explain how missing data were handled in the analysis	Summarize patient response rates and completeness of data collection	Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	Total score
Blekkenhorst, 2018	☆	☆	☆		☆		☆	☆		☆	☆	8
Bondonno, 2018	☆	☆	☆		☆		☆	☆		☆	☆	8
Johnsen, 2018	☆	☆	☆		☆		☆	☆		☆	☆	8
Kianoush, 2017	☆	☆	☆		☆	☆	☆	☆		☆	☆	9
Woo, 2017	☆		☆	☆	☆			☆		☆	☆	7
O'Flynn, 2017	☆		☆	☆	☆			☆		☆	☆	7
Rubinat, 2016	☆		☆	☆	☆			☆		☆	☆	7
Cheng, 2016	☆	☆	☆		☆		☆	☆		☆		7
Zhang, 2016	☆	☆	☆	☆	☆			☆		☆	☆	8
Li, 2015	☆	☆	☆	☆	☆			☆			☆	7
Yang, 2015	☆	☆		☆		☆		☆		☆	☆	6
Yang, 2014	☆	☆	☆	☆	☆			☆		☆	☆	8
Li, 2014	☆		☆	☆	☆			☆		☆	☆	7
Yuan, 2014	☆	☆	☆	☆	☆			☆		☆	☆	8
Fox, 2014	☆		☆	☆	☆			☆		☆		6
Irie, 2014	☆	☆	☆				☆	☆		☆	☆	7
Idei, 2014	☆		☆	☆	☆			☆		☆	☆	7
Painschab, 2013	☆		☆			☆	☆			☆		5
Sato, 2013	☆	☆	☆	☆	☆			☆		☆	☆	8
Hong, 2013	☆		☆	☆	☆			☆		☆	☆	7
Alsulaimani, .2013	☆	☆	☆	☆	☆			☆		☆	☆	8
Buscemi, 2013	☆		☆				☆	☆		☆		5
Leng, 2013	☆		☆	☆	☆			☆		☆	☆	7
Oikonen, 2012	☆		☆	☆	☆		☆	☆		☆	☆	8
Casalnuovo, 2012	☆		☆	☆	☆			☆		☆	☆	7
Zhang, 2012	☆	☆	☆	☆				☆				5
Sands, 2012	☆	☆	☆					☆		☆		5
Johnson, 2010	☆	☆	☆	☆	☆			☆		☆	☆	8
Kozakova, 2010	☆	☆	☆	☆	☆	☆	☆	☆		☆		9
Gardener, 2009	☆	☆		☆				☆		☆	☆	6
Neogi, 2009			☆	☆	☆			☆		☆	☆	7
Lee, 2009	☆		☆				☆	☆		☆		5
Liang, 2009	☆	☆	☆	☆	☆		☆	☆		☆	☆	9
Chen, 2008	☆	☆	☆	☆	☆		☆	☆		☆	☆	9
Beaussier, 2008	☆	☆	☆	☆	☆	☆		☆		☆		8
Debette, 2008	☆		☆			☆	☆	☆				5
Rundek, 2007	☆	☆	☆	☆	☆		☆	☆		☆	☆	9
Shintani, 2007	☆	☆	☆		☆			☆		☆		6
Empana, 2007	☆		☆	☆	☆	☆	☆	☆		☆	☆	9
Nakhai-pour, 2007	☆		☆					☆	☆	☆		5
Ishizaka, 2005	☆		☆		☆			☆		☆	☆	6
Hintsanen, 2005	☆	☆	☆		☆		☆	☆		☆		7
Baguet, 2005	☆		☆		☆			☆		☆		5
Kawamoto, 2005	☆		☆	☆				☆		☆		5
Czernichow, 2005	☆		☆	☆	☆			☆		☆	☆	7
Lu, 2004	☆	☆	☆		☆	☆	☆	☆		☆		8
Tiemeier, 2004	☆		☆	☆			☆			☆		5
Kawamoto, 2001	☆	☆	☆	☆	☆		☆	☆		☆	☆	9
Su, 2001	☆	☆	☆	☆	☆			☆		☆	☆	8

Table S2 The quality evaluation of cohort studies by the Newcastle Ottawa scale (NOS)

Study	Selection				Comparability		Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	According the most important factor to choose control	According the other important factor to choose control	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Park, 2017	☆	☆	☆		☆	☆	☆		☆	7
Peterson, 2016		☆	☆	☆	☆	☆	☆		☆	7
Wang, 2016			☆		☆		☆		☆	4
Ramadan, 2016		☆	☆		☆		☆	☆		5
Christoph, 2015	☆	☆	☆		☆		☆		☆	6
Goldberg, 2014		☆	☆			☆	☆			4
Thurston, 2014	☆	☆	☆	☆	☆	☆				6
Gunnarsson, 2014	☆	☆	☆	☆	☆	☆	☆			7
Kim, 2014		☆	☆		☆	☆				4
Jung, 2014	☆	☆	☆		☆		☆	☆	☆	7
Patel, 2013	☆	☆	☆				☆	☆		5
Hui, 2012	☆	☆	☆		☆		☆		☆	6
Huang, 2012	☆	☆			☆		☆	☆		5
Kesse-Guyot, 2010		☆	☆	☆		☆	☆			5
Rice, 2009	☆				☆	☆	☆			4
Meuwese, 2009	☆	☆	☆		☆	☆	☆	☆	☆	8
Bots, 2009	☆	☆	☆				☆	☆	☆	6
Yamagami, 2008	☆		☆		☆		☆		☆	5
Lee, 2008		☆	☆		☆	☆				4
Thoenes, 2007		☆	☆		☆	☆	☆		☆	6
Mita, 2007	☆		☆		☆	☆	☆		☆	6
Haas, 2005		☆	☆	☆	☆	☆	☆			6
Hanefeld, 2004	☆	☆	☆		☆	☆	☆	☆	☆	8
Zureik, 2004	☆	☆	☆		☆	☆	☆	☆		7
Lovett, 2003	☆		☆		☆	☆	☆		☆	6
Wikstrand, 2003		☆	☆		☆		☆	☆	☆	6
Hosomi, 2001	☆	☆	☆		☆	☆	☆	☆	☆	8

Table S3 Baseline characteristics of the included population

Study	Sample types	Symptomatic status (TIA/Stroke)	Comorbidities	Drugs
Woo, 2017	Community population	None	Hypertension (50.13%); diabetes (19.87%); hyperlipidemia (25.71%)	None
Zhang, 2016	Community population	None	Hypertension (60.6%); diabetes (17.3%); dyslipidemia (58.6%)	Antihypertensive therapy (49%); hypoglycemic therapy (83%); lipid-lowering therapy (36%)
Idei, 2014	Juntendo Tokyo Koto Geriatric Medical Center	None	Hypertension (63%); diabetes (100%); dyslipidemia (83%)	Antihypertensive therapy (45.3%); hypoglycemic therapy (47.2%); lipid-lowering therapy (4.8%)
Hong, 2013	Community population	None	Hypertension (41.61%); diabetes (9.6%)	Antihypertensive therapy (59.7%); hypoglycemic therapy (7.0%); lipid-lowering therapy (4.4%)
Beaussier, 2008	George Pompidou Hospital, and the neurology department of Sainte-Anne Hospital	None	Hypertension (71.74%)	Antihypertensive therapy (61.96%)
Empana, 2007	Community population	None	Metabolic syndrome (12.1%)	Antihypertensive therapy (48.1%); lipid-lowering therapy (29.7%)
Czernichow, 2005	Hotel- Dieu Hospital	None	Metabolic syndrome (8.7%)	Antihypertensive therapy (19.5%); hypoglycemic therapy (1.1%); lipid-lowering therapy (16.8%)
Su, 2001	Community population	None	Hypertension (49.34%); diabetes (17.64%); dyslipidemia (3 5.08%)	NA
O'Flynn, 2017	Primary care centre	None	Hypertension (29%); diabetes (9%)	Antihypertensive therapy (29%); lipid-lowering therapy (36%)
Rubinat, 2016	Hospital Universitari Arnaude Vilanova	None	Hypertension (50%); diabetes (38.5%); dyslipidemia (30.2%)	NA
Casalnuovo, 2012	Community population	None	Hypertension (100%); diabetes (9.5%); dyslipidemia (51.9%)	Antihypertensive therapy (90.8%); hypoglycemic therapy (24.3%); lipid-lowering therapy (6.7%)
Yuan, 2014	Angel of Diabetics Organisation	Stroke (2.8%)	Hypertension (56.6%); diabetes (100%); dyslipidemia (51.3%)	NA
Irie, 2014	Osaca Police Hospital	None	Hypertension (80%); diabetes (100%); dyslipidemia (60%)	Antihypertensive therapy (63%); hypoglycemic therapy (77%); lipid-lowering therapy (4.4%)
Sato, 2013	Nippon Medical School Hospital	None	Diabetes (100%)	Antihypertensive therapy (32%); hypoglycemic therapy (63%); lipid-lowering therapy (20%)
Johnson, 2010	Community population	None	NA	Antihypertensive therapy (13.6%); lipid-lowering therapy (11.1%)
Leng, 2013	Community population	None	Hypertension (47.8%); diabetes (21.7%); metabolic syndrome (62.1%)	NA
Chen, 2008	Community population	None	Hypertension (38.3%); diabetes (21.7%); dyslipidemia (44.9%)	NA
Rundek, 2007	Community population	None	NA	Hypoglycemic therapy (12%); lipid- lowering therapy (18%)
Ishizaka, 2005	Mitsui Memorial Hospital	None	NA	NA
Yang, 2015	Community population	None	Hypertension (71%); diabetes (19%); dyslipidemia (64%)	NA
Liang, 2009	Fuwai Hospital	None	Hypertension (29.8%); angina (3.4%)	NA
Li, 2015	Community population	None	Hypertension (59.3%); diabetes (16.3%); dyslipidemia (45.0%)	Diuretics therapy (2.7%); lipid- lowering therapy (0.8%)
Li, 2014	Beijing An Zhen Hospital	None	Hyperuricemia (24.9%)	NA
Neogi, 2009	Community population	None	Hypertension (32.8%); diabetes (9.4%); coronary artery disease (12.3%); renal insufficiency (9.4%)	NA
Yang, 2014	Community population	None	Hypertension (59.3%); diabetes (54.2%); dyslipidemia (16. 3%)	NA
Alsulaimani, 2013	Community population	None	Hypertension (71%); diabetes (20%)	NA
Kawamoto, 2001	Community population	Stroke (40%)	NA	NA
Cheng, 2016	Community population	None	Hypertension (48.6%); diabetes (18%)	NA
Lu, 2004	Suburban general population	None	Hypertension (43.41%)	Antihypertensive therapy (17.61%)
Shintani, 2007	Community population	None	Hypertension (100%); diabetes (14.6%); dyslipidemia (42.7%)	Antihypertensive therapy (39%)
Lovett, 2003	European Carotid Surgery Trial	None	Hypertension (100%)	Antihypertensive therapy (39%); lipid-lowering therapy (8.8%)
Huang, 2012	Fuwai Hospital	None	NA	None
Gardener, 2009	Community population	None	Hypertension (73.5%); diabetes (21.2%); dyslipidemia (42.7%)	NA
Jung, 2014	Ansan Hospital	Stroke (1.9%)	Hypertension (45.7%); diabetes (23.0%); depression (0.8%); metabolic syndrome (42.7%); heart disease (14.6%)	Antihypertensive therapy (7.8%); hypoglycemic therapy (4.6%); lipid-lowering therapy (4.6%)
Oikonen, 2012	NA	None	NA	Antihypertensive therapy (6.9%); hypoglycemic therapy (0.6%); lipid-lowering therapy (2.2%)
Zhang, 2012	Samsung Medical Center	None	Hypertension (35.4%); dyslipidemia (55.7%); metabolic syndrome (11.1%); abnormal liver function (28.7%)	Lipid-lowering therapy (1.4%)
Kawamoto, 2005	Community population	Stroke (36.9%)	Hypertension (68.2%); dyslipidemia (54.5%)	Antihypertensive therapy (46.8%); lipid-lowering therapy (4.0%)
Nakhai-Pour, 2007	Community population	None	Hypertension (45%); diabetes (10.6%); cardiovascular disease (14.1%)	NA
Fox, 2014	Community population	None	None	None
Gunnarsson, 2014	Community population	None	NA	Antihypertensive therapy (13%); hypoglycemic therapy (2%); lipid-lowering therapy (4%); continuous positive airway pressure user (1%)
Kim, 2014	Community population	None	Snorers (73.6%)	Antihypertensive therapy (14.9%)
Lee, 2008	Community population	None	Hypertension (27.3%); dyslipidemia (69%)	NA
Baguet, 2005	Grenoble University Hospital	None	Hypertension (40%)	Antihypertensive therapy (65%); hypoglycemic therapy (4%); lipid-lowering therapy (11%)
Haas, 2005	Community population	None	Diabetes (0.9%)	NA
Rice, 2009	Gerontology Research Center	NA	Diabetes (5.4%)	Antihypertensive or lipid-lowering therapy (22.3%); antidepressants (8.8%)
Tiemeier, 2004	Community population	Stroke (3.0%)	Diabetes (9.8%); depressive disorders (3.0%); peripheral arterial disease (16.9%)	Antidepressants (2.6%)
Peterson, 2016	Massachusetts General Hospital	None	NA	Antihypertensive therapy (36.36%); hypoglycemic therapy (1.14%); lipid-lowering therapy (27.84%); anticoagulant therapy (10.7%)
Thurston, 2014	Community population	None	NA	Antihypertensive therapy (43.6%); hypoglycemic therapy (11.6%); lipid-lowering therapy (33.4%); anticoagulant therapy (13%); hormone therapy (37.4%)
Hintsanen, 2005	Social Insurance Institution	None	NA	NA
Wang, 2016	Community population	Stroke (5.8%)	Hypertension (61.6%); diabetes (21.6%); dyslipidemia (54. 7%)	NA
Painschab, 2013	Community population	None	Hypertension (11%); diabetes (1%); cardiovascular disease (8%)	Antihypertensive therapy (5%); hypoglycemic therapy (1%); lipid-lowering therapy (2%); aspirin (2%)
Park, 2017	Community population	None	None	None
Goldberg, 2014	Community population	Stroke (12%)	Hypertension (71%); diabetes (20%)	Lipid-lowering therapy (15%)
Buscemi, 201 3	Community population	None	NA	NA
Sands, 2012	NA	None	Diabetes (6.5%); depression (15.8%)	None
Kesse-Guyot, 2010	Community population	None	NA	Antihypertensive therapy (19.3%); hypoglycemic therapy (1.4%); lipid-lowering therapy (17.8%)
Kozakova, 20 10	Healthy subjects	None	None	None
Lee, 2009	Community population	NA	Hypertension (41.0%); diabetes (15.1%); dyslipidemia (24.3%)	NA
Debette, 2008	Community population	NA	Hypertension (59.5%); diabetes (10.6%); dyslipidemia (36.7%)	NA
Hui, 2012	Community population	NA	Obstructive sleep apnea syndrome (100%)	Continuous positive airway pressure user (56%)
Thoenes, 2007	NA	None	Metabolic syndrome (100%)	Niacin (66.7%)
Zureik, 2004	Community population	None	Hypertension (19.8%); diabetes (3.8%)	Antihypertensive therapy (11.2%); vitamins supplementation (51.5%)
Ramadan, 2016	NA	Stroke (3.0%)	Hypertension (39%); diabetes (7%); myocardial infarction (7%)	Antihypertensive therapy (66.6%); lipid-lowering therapy (50%)
Wikstrand, 2003	NA	None	Hypercholesterolemia (100%)	B-blockerstherapy (50%); lipid- lowering therapy (100%)
Hosomi, 2001	Kagawa Medical University and Takamats u National Hospital	NA	Hypertension (50%); diabetes (100%); myocardial infarction (55.1%)	Antihypertensive therapy (49.0%); hypoglycemic therapy (40.3%); lipid-lowering therapy (25.5%)
Meuwese, 2009	NA	Stroke (2.8%)	Hypertension (29.5%); diabetes (4.9%); dyslipidemia (100%); myocardial infarction (14.5%)	Lipid-lowering therapy (50.3%)
Bots, 2009	Caritas Carney Hospital	NA	Hypertension (19.9%); dyslipidemia (100%)	Lipid-lowering therapy (71.3%)
Yamagami, 2008	Kobe City General Hospital	NA	Hypertension (76.5%); diabetes (12.3%); dyslipidemia (100%); cardiovascular disease (32.1%)	Antihypertensive therapy (28.4%); lipid-lowering therapy (49.4%); aspirin (12.3%); ticlopidine (19.8%)
Christoph, 2015	University hospital	NA	Hypertension (79.7%); diabetes (100%); dyslipidemia (77.8%)	Antihypertensive therapy (94.5%); hypoglycemic therapy (50%); lipid-lowering therapy (100%); antiplatelet therapy (100%)
Patel, 2013	Indiana University and Washington University School of Medicine	NA	Diabetes (100%)	Antihypertensive therapy (37.9%); hypoglycemic therapy (50%); lipid-lowering therapy (9.1%)
Mita, 2007	Juntendo University Hospital, Junseikai hospital, and Chiba Tokushyu kai hospital	NA	Hypertension (32.9%); diabetes (74.5%); dyslipidemia (50%)	Antihypertensive therapy (30%); hypoglycemic therapy (48.6%); lipid-lowering therapy (10%)
Hanefeld, 2004	NA	NA	Diabetes (100%)	Antihypertensive therapy (26.1%); hypoglycemic therapy (48.7%); lipid-lowering therapy (29.6%)
Blekkenhorst, 2018	Community population	None	NA	Antihypertensive therapy (40.2%); lipid-lowering therapy (15.2%); aspirin (14.7%)
Bondonno, 2018	NA	None	None	Antihypertensive therapy (40%); lipid- lowering therapy (15%); aspirin (16%)
Johnsen, 2018	Community population	None	Hypertension (55.9%); diabetes (2.7%)	Antihypertensive therapy (10.3%); lipid-lowering therapy (1.7%)
Kianoush, 2017	Community population	None	Diabetes (18.5%); myocardial infarction (12.8%)	Antihypertensive therapy (25.5%); lipid-lowering therapy (11.4%)

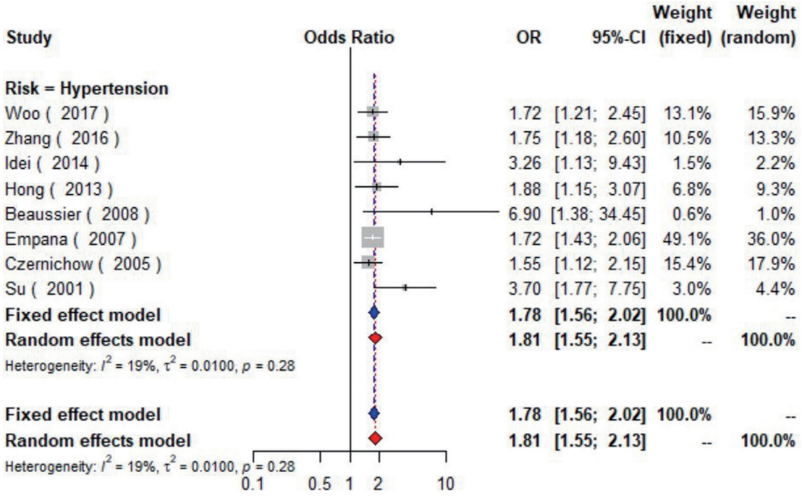

Figure S1 The forest plot shows the relationship between hypertension and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.81 (95% CI: 1.55–2.13, P=0.28) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with hypertension. CI indicates confidence interval; OR, odds ratio.

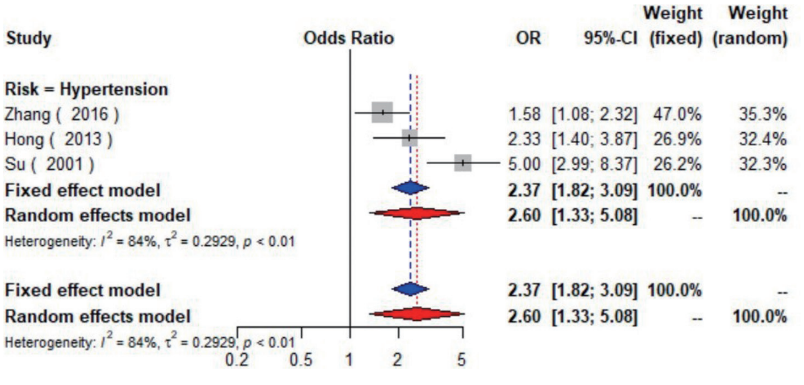

Figure S2 The forest plot shows the relationship between hypertension and the increased carotid intima media thickness. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 2.60 (95% CI: 1.33–5.08, P<0.01) in the random effects model. Values more than 1 denote an increased risk for the increased carotid intima media thickness with hypertension. CI, confidence interval; OR, odds ratio.

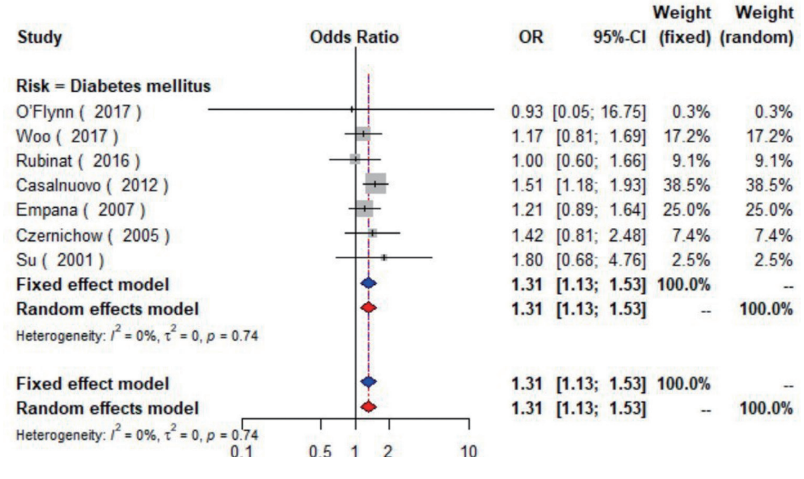

Figure S3 The forest plot shows the relationship between diabetes mellitus and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.31 (95% CI: 1.13–1.53, P=0.74) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with diabetes mellitus. CI, confidence interval; OR, odds ratio.

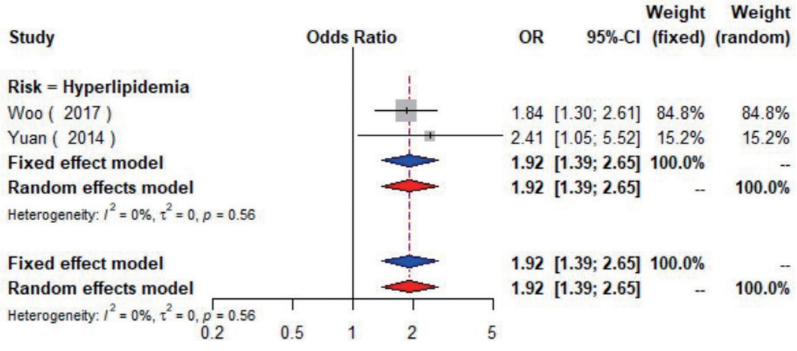

Figure S4 The forest plot shows the relationship between hyperlipidemia and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.92 (95% CI: 1.39–2.65, P=0.56) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with hyperlipidemia. CI, confidence interval; OR, odds ratio.

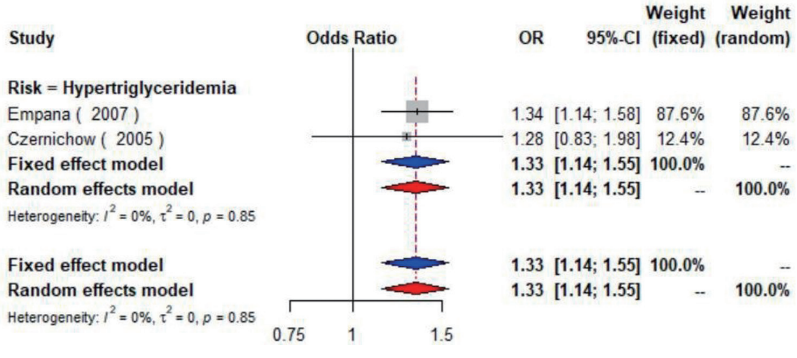

Figure S5 The forest plot shows the relationship between hypertriglyceridemia and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.33 (95% CI: 1.14–1.55, P=0.85) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with hyperlipidemia. CI, confidence interval; OR, odds ratio.

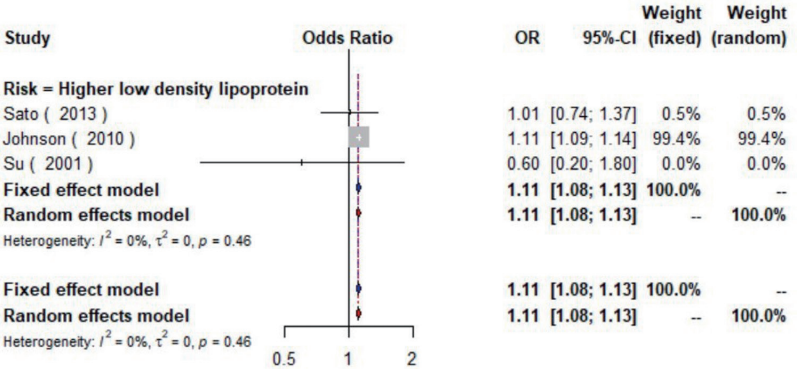

Figure S6 The forest plot shows the relationship between higher low density lipoprotein and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.11 (95% CI: 1.08–1.13, P=0.46) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with higher low-density lipoprotein. CI, confidence interval; OR, odds ratio.

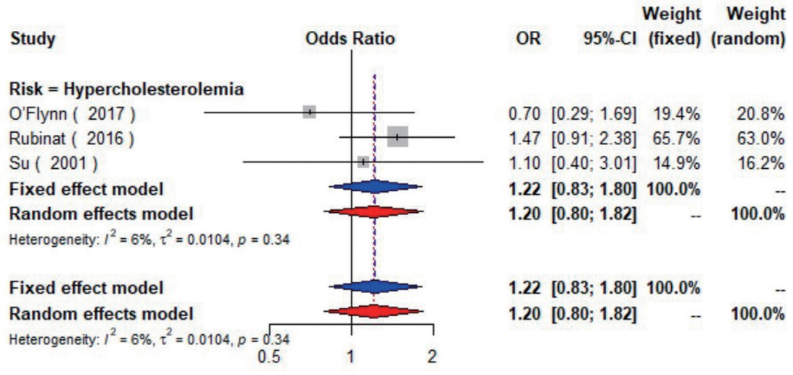

Figure S7 The forest plot shows the relationship between hypercholesterolemia and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.20 (95% CI: 0.80–1.82, P=0.34) in the random effects model. Values across 1 means there are no relationship between hypercholesterolemia and the presence of carotid plaque. CI, confidence interval; OR, odds ratio.

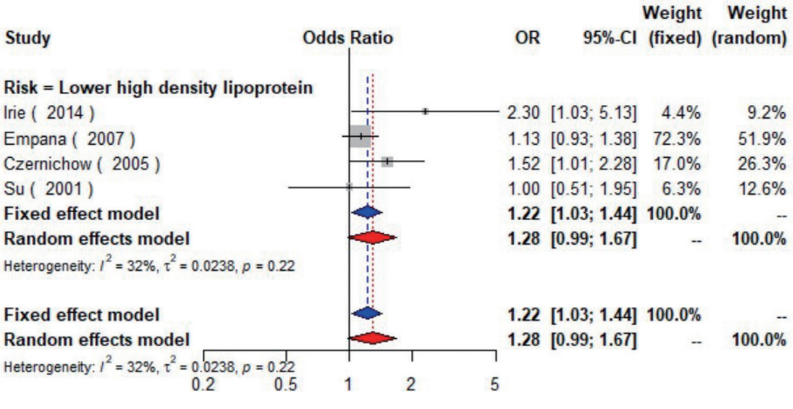

Figure S8 The forest plot shows the relationship between lower high density lipoprotein and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.28 (95% CI: 0.99–1.67, P=0.22) in the random effects model. Values across 1 means there are no relationship between lower high-density lipoprotein and the presence of carotid plaque. CI, confidence interval; OR, odds ratio.

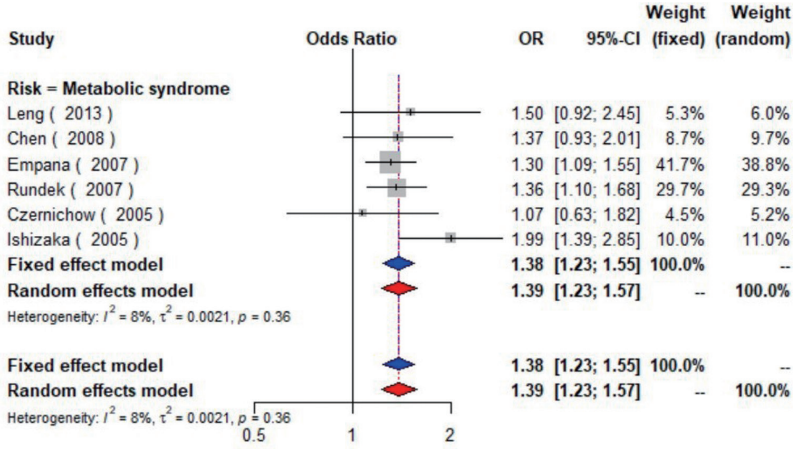

Figure S9 The forest plot shows the relationship between metabolic syndrome and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.39 (95% CI: 1.23–1.57, P=0.36) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with metabolic syndrome. CI, confidence interval; OR, odds ratio.

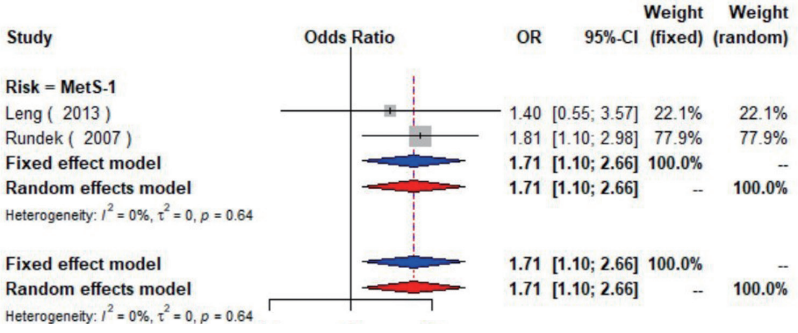

Figure S10 The forest plot shows the relationship between one component of metabolic syndrome and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.71 (95% CI: 1.10–2.66, P=0.64) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with one component of metabolic syndrome. CI, confidence interval; OR, odds ratio; MetS-1, one component of metabolic syndrome.

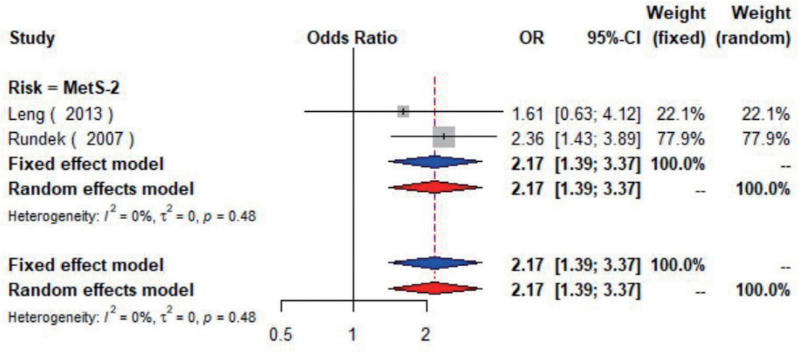

Figure S11 The forest plot shows the relationship between two components of metabolic syndrome and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 2.17 (95% CI: 1.39–3.37, P=0.48) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with two components of metabolic syndrome. CI, confidence interval; OR, odds ratio; MetS-2, two components of metabolic syndrome.

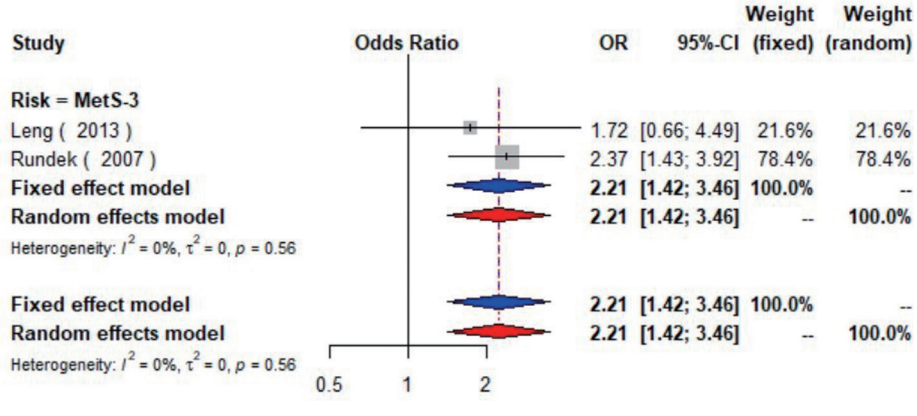

Figure S12 The forest plot shows the relationship between three components of metabolic syndrome and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 2.21 (95% CI: 1.42–3.46, P=0.56) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with three components of metabolic syndrome. CI, confidence interval; OR, odds ratio; MetS-3, three components of metabolic syndrome.

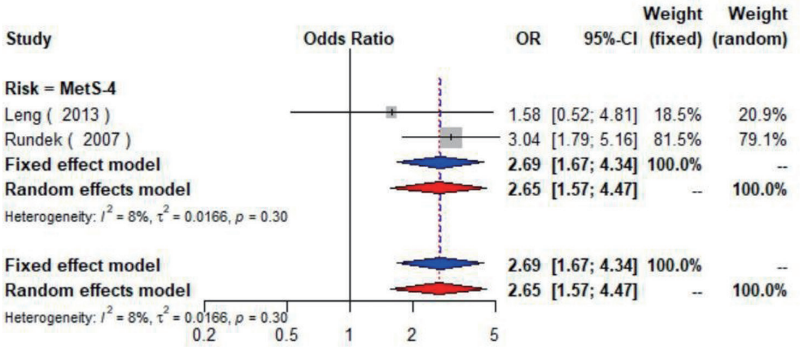

Figure S13 The forest plot shows the relationship between four components of metabolic syndrome and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 2.65 (95% CI: 1.57–4.47, P=0.30) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with four components of metabolic syndrome. CI, confidence interval; OR, odds ratio; MetS-4, four components of metabolic syndrome.

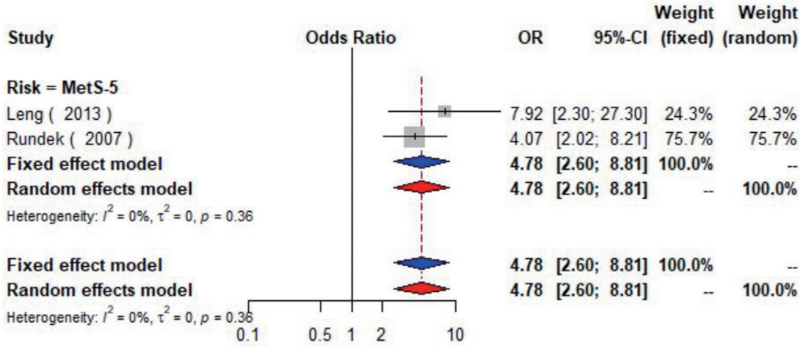

Figure S14 The forest plot shows the relationship between five components of metabolic syndrome and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 4.78 (95% CI: 2.60–8.81, P=0.36) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with five components of metabolic syndrome. CI, confidence interval; OR, odds ratio; MetS-5, five components of metabolic syndrome.

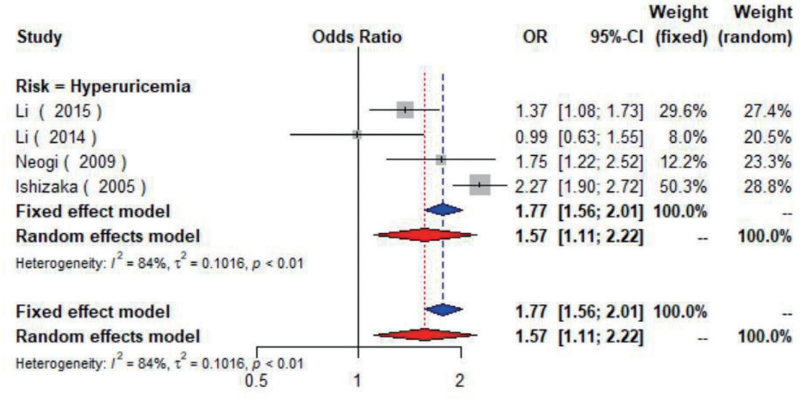

Figure S15 The forest plot shows the relationship between hyperuricemia and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.57 (95% CI: 1.11–2.22, P<0.01) in the random effects model. Values more than 1 denote an increased risk for the presence of carotid plaque with hyperuricemia. CI, confidence interval; OR, odds ratio.

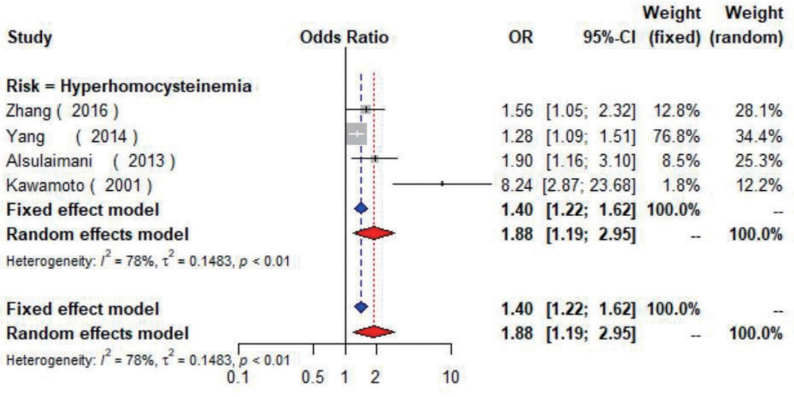

Figure S16 The forest plot shows the relationship between hyperhomocysteinemia and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.88 (95% CI: 1.19–2.95, P<0.01) in the random effects model. Values more than an increased risk for the presence of carotid plaque with hyperhomocysteinemia. CI, confidence interval; OR, odds ratio.

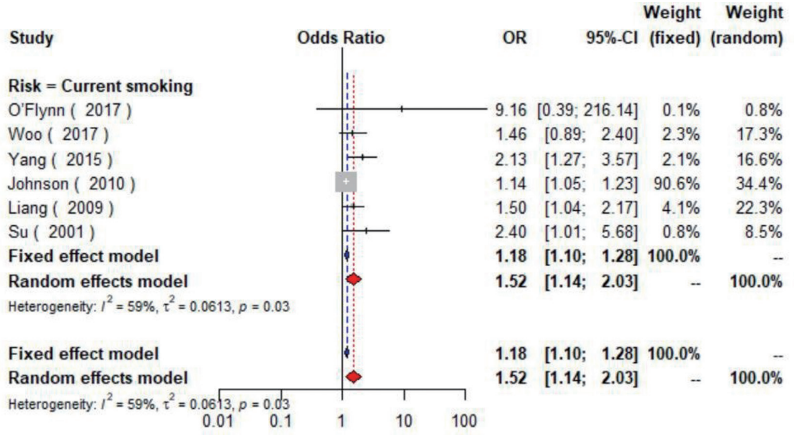

Figure S17 The forest plot shows the relationship between current smoking and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.52 (95% CI: 1.14–2.03, P=0.03) in the random effects model. Values more than an increased risk for the presence of carotid plaque with current smoking. CI, confidence interval; OR, odds ratio.

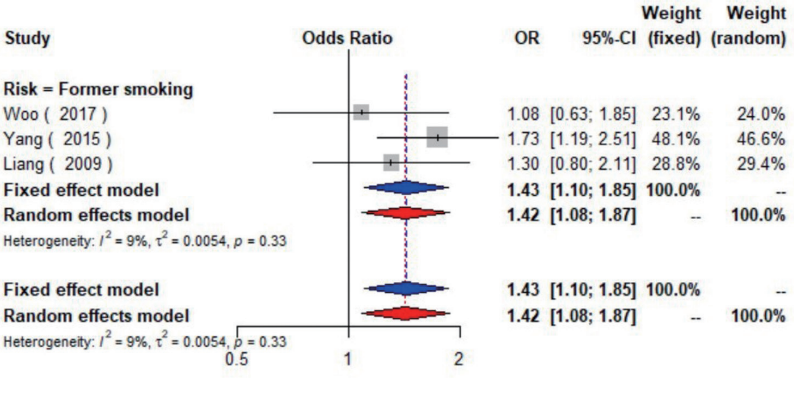

Figure S18 The forest plot shows the relationship between former smoking and the presence of carotid plaque. Each comparison is presented by the name of the first author and the year of publication. The contrast has an OR of 1.42 (95% CI: 1.08–1.87, P=0.33) in the random effects model. Values more than an increased risk for the presence of carotid plaque with former smoking. CI, confidence interval; OR, odds ratio.

Table S4 Sensitivity analysis of the meta-analysis

Risk factor	Study omitted	OR	LCI	LCI	Heterogeneity (I^2)	P value
Hypertension (presence of plaque)	None	1.81	1.55	2.13	19%	0.28
	Woo, 2017	1.87	1.53	2.29	30%	0.20
	Zhang, 2016	1.86	1.53	2.26	31%	0.19
	Idei, 2014	1.79	1.52	2.10	19%	0.29
	Hong, 2013	1.83	1.52	2.22	30%	0.20
	Beaussier, 2008	1.76	1.55	2.00	0%	0.43
	Empana, 2007	1.92	1.52	2.41	29%	0.21
	Czernichow, 2005	1.90	1.57	2.30	24%	0.25
	Su, 2001	1.74	1.53	1.98	0%	0.57
Hypertension (increased CIMT)	None	2.60	1.33	5.08	84%	<0.01
	Zhang, 2016	3.41	1.61	7.21	77%	0.04
	Hong, 2013	2.77	0.90	8.57	92%	<0.01
	Su, 2001	1.85	1.27	2.69	30%	0.23
Diabetes mellitus	None	1.31	1.13	1.53	0%	0.74
	O'Flynn, 2017	1.32	1.13	1.53	0%	0.63
	Woo, 2017	1.34	1.14	1.59	0%	0.69
	Rubinat, 2016	1.35	1.15	1.59	0%	0.81
	Casalnuovo, 2014	1.21	0.99	1.46	0%	0.91
	Empana, 2007	1.35	1.13	1.61	0%	0.68
	Czernichow, 2005	1.31	1.11	1.53	0%	0.63
	Su, 2001	1.30	1.12	1.52	0%	0.68
Hypercholesterolemia	None	1.20	0.80	1.82	6%	0.34
	O'Flynn, 2017	1.39	0.90	2.15	0%	0.61
	Rubinat, 2016	0.85	0.44	1.66	0%	0.51
	Su, 2001	1.12	0.55	2.25	52%	0.15
Higher low-density lipoprotein	None	1.11	1.08	1.13	0%	0.46
	Sato, 2013	1.05	0.75	1.47	17%	0.27
	Johnson, 2010	0.97	0.73	1.31	0%	0.37
	Su, 2001	1.11	1.08	1.13	0%	0.55
Lower high density lipoprotein	None	1.28	0.99	1.67	32%	0.22
	Irie, 2014	1.18	1.00	1.40	0%	0.39
	Empana, 2007	1.47	1.01	2.15	20%	0.29
	Czernichow, 2005	1.27	0.83	1.75	34%	0.22
	Su, 2001	1.37	0.98	1.92	51%	0.13
Metabolic syndrome	None	1.39	1.23	1.57	8%	0.36
	Leng, 2013	1.39	1.20	1.60	25%	0.26
	Chen, 2008	1.40	1.20	1.63	26%	0.25
	Empana, 2007	1.45	1.22	1.75	15%	0.32
	Rundek, 2007	1.42	1.18	1.69	26%	0.25
	Czernichow, 2005	1.41	1.24	1.60	12%	0.34
	Ishizaka, 2005	1.32	1.17	1.49	0%	0.91
Hyperuricemia	None	1.57	1.11	2.22	84%	<0.01
	Li, 2015	1.64	1.04	2.58	83%	<0.01
	Li, 2014	1.77	1.26	2.5	82%	<0.01
	Neogi, 2009	1.5	0.95	2.38	89%	<0.01
	Ishizaka, 2005	1.37	1.05	1.79	46%	0.16
Hyperhomocysteinemia	None	1.88	1.19	2.95	78%	<0.01
	Zhang, 2016	2.24	1.08	4.67	85%	<0.01
	Yang, 2014	2.43	1.22	4.83	76%	0.02
	Alsulaimani, 2013	1.97	1.07	3.61	84%	<0.01
	Kawamoto, 2001	1.42	1.15	1.75	28%	0.25
Current smoking	None	1.52	1.14	2.03	59%	0.09
	O'Flynn, 2017	1.49	1.13	1.98	63%	0.03
	Woo, 2017	1.57	1.10	2.24	66%	0.02
	Yang, 2015	1.37	1.06	1.78	44%	0.13
	Johnson, 2010	1.70	1.33	2.17	0	0.52
	Liang, 2009	1.59	1.08	2.33	63%	0.03
	Su, 2001	1.44	1.09	1.92	59%	0.05
Former smoking	None	1.42	1.08	1.87	9%	0.33
	Woo, 2017	1.55	1.16	2.09	0%	0.36
	Yang, 2015	1.20	0.84	1.71	0%	0.62
	Liang, 2009	1.43	0.90	2.24	50%	0.16

OR, odds ratio; LCI, lower confidence interval; UCI, upper confidence interval.

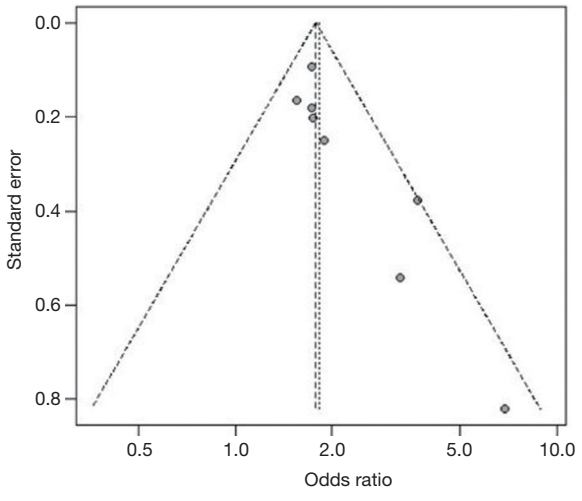

Figure S19 Funnel plot for publication bias in studies on hypertension and the presence of carotid plaque. The asymmetry of the funnel plot suggests that publication bias may exist.

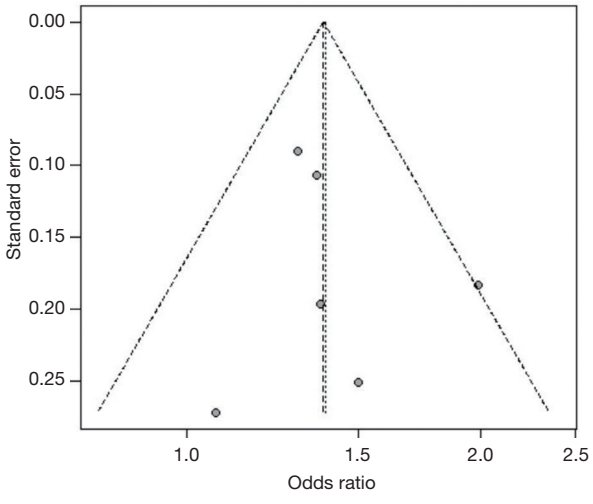

Figure S21 Funnel plot for publication bias in studies on metabolic syndrome and the presence of carotid plaque. The asymmetry of the funnel plot suggests that publication bias may exist.

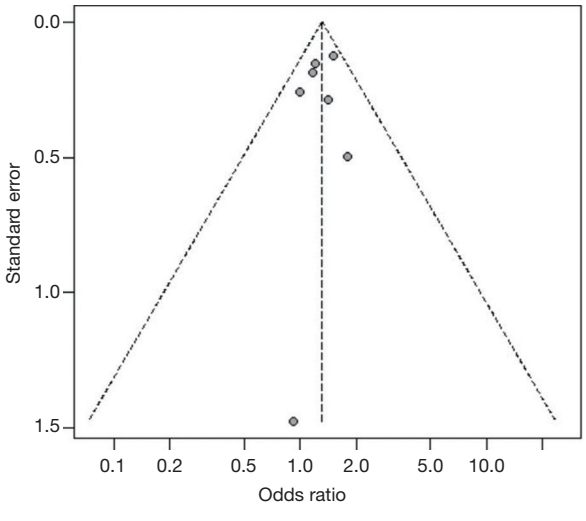

Figure S20 Funnel plot for publication bias in studies on diabetes mellitus and the presence of carotid plaque. The asymmetry of the funnel plot suggests that publication bias may exist.

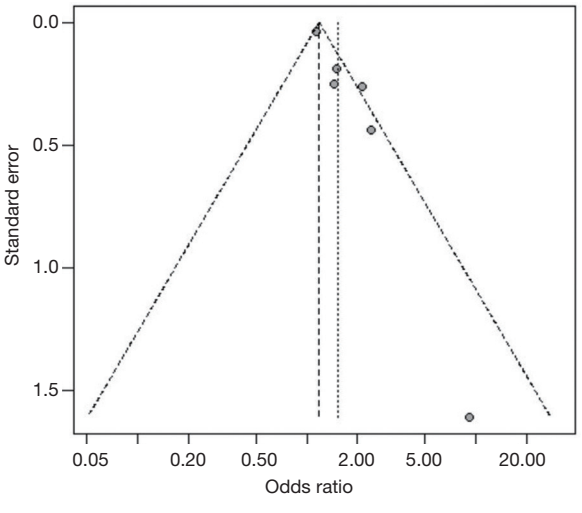

Figure S22 Funnel plot for publication bias in studies on current smoking and the presence of carotid plaque. The asymmetry of the funnel plot suggests that publication bias may exist.

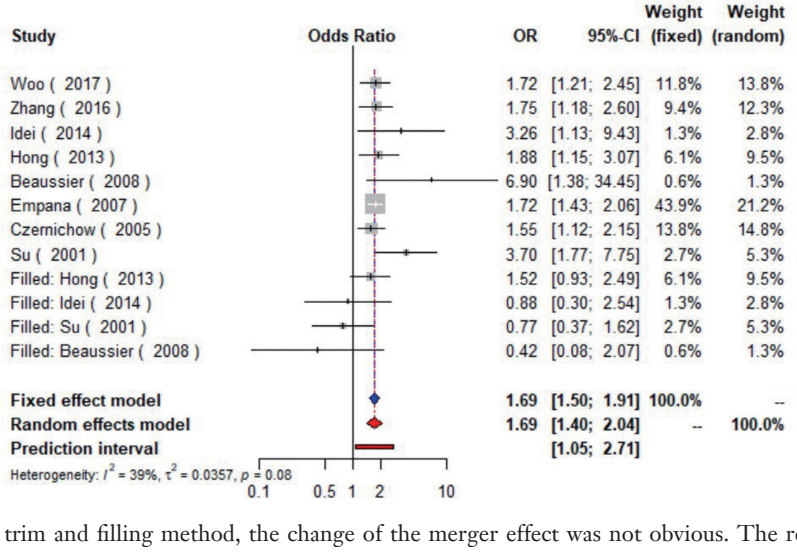

Figure S23 After using the trim and filling method, the change of the merger effect was not obvious. The results were moderate, which means hypertension is a risk factor for the presence of carotid plaque.

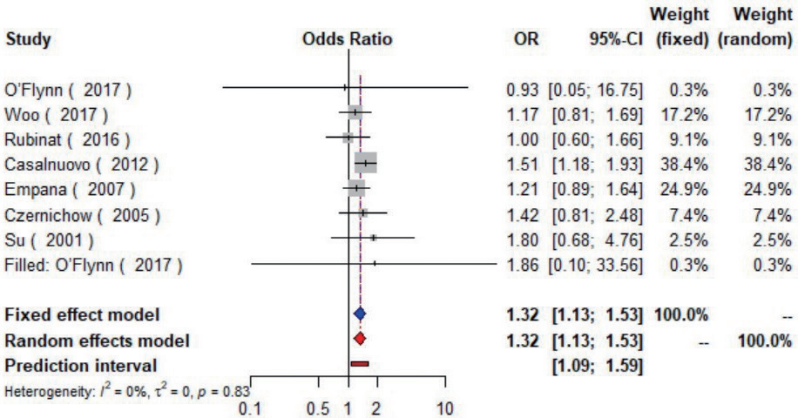

Figure S24 After using the trim and filling method, the change of the merger effect was not obvious. The results were moderate, which means diabetes mellitus is a risk factor for the presence of carotid plaque.

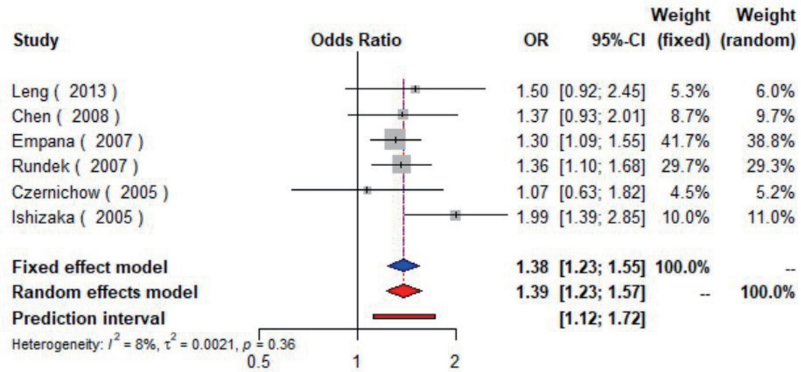

Figure S25 After using the trim and filling method, the change of the merger effect was not obvious. The results were moderate, which means metabolic syndrome is a risk factor for the presence of carotid plaque.

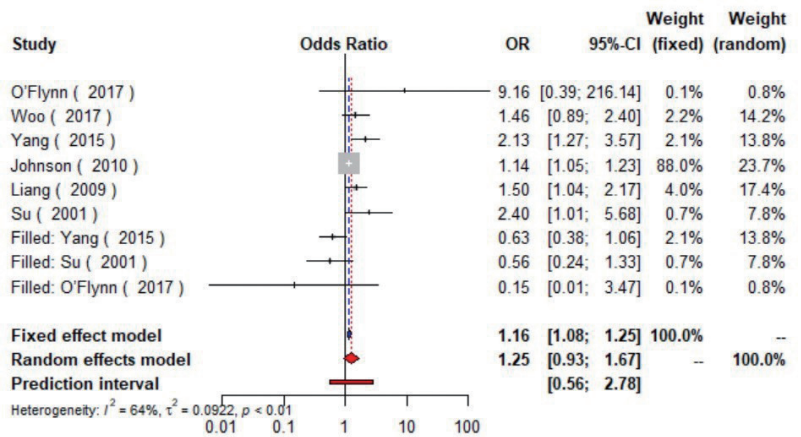

Figure S26 After using the trim and filling method, the merger effect became non-significant. The results were not moderate, which means the caution is needed in drawing conclusion.

Table S5 General characteristics of studies included in the systematic reviews

Risk factors	Study	Study type	Recruitment period	N (total)	Age (range, mean ± SD)	Sex (female), %	Follow-up	Lost to follow-up	Outcome	Result
Hypertension										
Systolic blood pressure variability	O'Flynn, 2017	Cross-sectional	2010	50	59±6 years	51.00	NA	NA	Plaque*	OR 1.90 (1.10–3.20)
Pulse pressure	Cheng, 2016	Cross-sectional	2011–2012	5,403	56.59±9.1 years	63.00	NA	NA	CIMT†	OR 1.11 (1.05–1.08)
Diastolic blood pressure variability	Li, 2014	Cross-sectional	2007	1,222	65.2±8.0 years	54.50	NA	NA	Plaque*	OR 6.07 (1.31–28.10)
Duration of hypertension	Lu, 2004	Cross-sectional	2002	1,198	43–73 years	64.77	NA	NA	Plaque*	OR 2.2(1.1–4.3) (woman), OR 1.0 (0.4–2.4) (man)
Systolic blood pressure variability	Shintani, 2007	Cross-sectional	1998	775	66.2±6.2 years	68.80	NA	NA	Plaque*	OR 1.17(1.04–1.32)
Pulse pressure‡	Lovett, 2003	Cohort study	NA	3,018	62±8 years	27.77	12 months	346	Plaque*	OR 2.07(1.25–3.44)
Hypercholesterolemia										
Total cholesterol (per 1 mmol/L)	Sato, 2013	Cross-sectional	2005–2012	236	56±13 (19–86) years	34.30	NA	NA	Plaque*	OR 0.93 (0.72–1.20)
Hypercholesterolemia	Huang, 2012	Cohort study	1981–1982	1,626	47.8±8.1 years	64.52	9 years	431	CIMT	P<0.001
Total cholesterol (per 1-SD)	Gardener, 2009	Cross-sectional	1993–2001	1,804	68.5±10.1 years	60.20	NA	NA	Plaque*	OR 1.12 (1.01–1.25)
Hypertriglyceridemia										
Triglyceride (per 1 mmol/L)	Sato, 2013	Cross-sectional	2005–2012	236	56±13 (19–86) years	34.30	NA	NA	Plaque*	OR 1.15 (0.85–1.59)
Hypertriglyceridemia	Huang, 2012	Cohort study	1981–1982	1,626	47.8±8.1 years	64.52	9 years	431	CIMT	P<0.001
Triglyceride (per 1-SD)	Gardener, 2009	Cross-sectional	1993–2001	1,804	68.5±10.1 years	60.20	NA	NA	Plaque*	OR 0.99 (0.88–1.10)
Higher low-density lipoprotein	Huang, 2012	Cohort study	1981–1982	1,626	47.8±8.1 years	64.52	9 years	431	CIMT	P<0.001
Low density lipoprotein (per 100 nmol/L)	Johnson, 2010	Cross-sectional	2005–2007	1,504	45.0 (37.8–53.0) years	58.00	NA	NA	Plaque*	OR 1.11 (1.08–1.13)
Low density lipoprotein (per 1-SD)	Gardener, 2009	Cross-sectional	1993–2001	1,804	68.5±10.1 years	60.20	NA	NA	Plaque*	OR 1.14 (1.02–1.27)
Metabolic syndrome	Jung, 2014	Cohort study	2004–2006	370	66 (64–71) years	65.90	25 months	0	Plaque*	HR 1.92 (1.06–3.47)
Hyperuricemia										
Uric acid	Oikonen, 2012	Cross-sectional	1980	1,985	30–45 years	53.50	NA	NA	Plaque*	OR 1.00 (0.99–1.01)
Uric acid (per 1 mg/dl)	Zhang, 2012	Cross-sectional	2008–2010	3,010	50 years	0.00	NA	NA	CIMT†	OR 1.24 (1.04–1.47)
Hyperhomocysteinemia										
Hyperuricemia	Kawamoto, 2005	Cross-sectional	1996–2004	919	>60 years	56.69	NA	NA	CIMT	OR 1.66 (1.16–1.39)
Homocysteine (per unit increase log homocysteine)	Nakhai-Pour, 2007	Cross-sectional	NA	376	60±11 years	0.00	NA	NA	CIMT	P<0.01
Current smoking	Kianoush, 2017	Cross-sectional	2012	14,103	51.7±8.9 years	54.00	NA	NA	CIMT	P<0.001
Obstructive sleep apnea syndrome										
Obstructive sleep apnea syndrome	Fox, 2014	Cross-sectional	2006–2007	51	>40 years	41.18	NA	NA	CIMT	P=0.03
Obstructive sleep apnea syndrome	Gunnarsson, 2014	Cohort study	1989	2,884	47.6±7.7 years	45.00	13 years	2094	Plaque*	OR 1.55 (1.02–2.35)
Habitual snoring	Kim, 2014	Cohort study	2005–2006	3,487	>40 years	48.10	4 years	358	CIMT†	OR 1.11 (0.72–1.70) (man), 1.80 (1.13–2.87) (woman)
Heavy snoring	Lee, 2008	Cohort study	NA	110	45–80 years	46.36	NA	13	Plaque*	OR 10.5 (2.10–51.8)
Mean nocturnal SaO_2 <92% and minimal nocturnal SaO_2 <80%	Baguet, 2005	Cross-sectional	2001–2004	83	48±11 years	10.84	NA	Na	Plaque*	OR 3.10 (1.00–9.40)
Negative emotion										
Depressive symptoms	Haas, 2005	Cohort study	1985–1988	219	30–60 years	9.70	10 years	89	Plaque*	OR 2.31 (1.19–4.50)
Depressive symptoms	Rice, 2009	Cohort study	1980	556	20–93 years	54.50	3.9 years	0	CIMT	P=0.34
Depression	Tiemeier, 2004	Cross-sectional	1997–1999	4,019	>60 years	57.77	NA	NA	CIMT	OR 1.24 (1.02–1.51)
Socioeconomic strain										
Unfair treatment	Peterson, 2016	Cohort study	1996–1997	1056	42–52 years	100.00	12 years	NA	CIMT	P=0.009
Low Socioeconomic status	Thurston, 2014	Cohort study	1996–1997	3,302	59.5±2.7 years	100.00	12 years	1900	Plaque*	OR 1.78 (1.21–2.61)
Job strain	Hintsanen, 2005	Cross-sectional	1980	1,020	32.3 years	53.14	NA	NA	CIMT	P=0.029(man), P>0.05(woman)
Childhood sexual abuse	Thurston, 2014	Cohort study	1996–1997	1,402	59.55±2.7 years	100.00	12 years	0	CIMT	P<0.05
Air pollution										
Traffic-related pollution (living less than 150m (versus more than 300m) from major roadways)	Wang, 2016	Cohort study	2000–2004	5,301	55.5±12.7 years	63.70	5 years	501	CIMT	P=0.12
Chronic exposure to biomass fuel	Painschab, 2013	Cross-sectional	2011	266	>35 years	54.00	NA	NA	Plaque*	OR 2.60 (1.10–6.00)
Lifestyle										
Vegetable intake (each 10 g/d)	Blekkenhorst, 2018	Cross-sectional	1998	968	75.0±2.6 years	100.00	NA	NA	CIMT	P<0.01
Vegetable nitrate intake (each 29 mg/d)	Bondonno, 2018	Cross-sectional	2001	1,226	72±3 years	100.00	NA	NA	CIMT	P=0.04
Fish intake (≥3 times/week)	Johnsen, 2018	Cross-sectional	2001	3,900	45–74 years	49.03	NA	NA	Plaque*	OR 1.32 (1.01–1.73)
Exercise 40-80 min in length 5 days per week	Park, 2017	Cohort study	NA	44	71.1±4.6 years	100.00	24 weeks	3	CIMT	P<0.05
Egg consumption (per additional egg/week)	Goldberg, 2014	Cohort study	NA	1,429	65.8±8.8 years	60.00	11 years	0	Plaque*	OR 0.89(0.80-0.98)
Mediterranean diet *vs.* unhealthy diet	Buscemi, 2013	Cross-sectional	2011	929	10–54 years	65.00	NA	NA	Plaque*	OR 1.34 (0.72–2.52)
Longer sleep duration (1 h/d)	Sands, 2012	Cross-sectional	1985	617	37–52 years	58.00	NA	NA	CIMT	P=0.02 (man), P=0.91 (woman)
Nutrient's density	Kesse-Guyot, 2010	Cohort study	1994–1995	1,026	35–60 years	48.44	7.5 years	126	CIMT	P=0.40
Vigorous activity	Kozakova, 2010	Cross-sectional	2001	614	44±8 years	60.26	NA	NA	CIMT	P<0.05
Consume alcohol >40 g/d	Lee, 2009	Cross-sectional	2007–2008	4,302	>50 years	63.34	NA	NA	Plaque*	OR 1.81 (1.13–2.91)
Drinking tea ≥3 cups/d *vs.* none	Debette, 2008	Cross-sectional	1999–2001	6,597	>65 years	60.93	NA	NA	Plaque*	OR 1.02 (0.31–5.90) (man), 0.47 (0.20–1.11) (woman)
Continuous positive airway pressure	Hui, 2012	Cohort study	2005	50	49.5±1.4 years	18.00	12 months	26	CIMT	P=0.002
Vitamin supplementary										
Niacin (1,000 mg/day)	Thoenes, 2007	Cohort study	2004–2005	55	>18 years	44.44	52 weeks	10	CIMT	P=0.006
Low-dose of antioxidant vitamins	Zureik, 2004	Cohort study	1994	1,302	52.6±4.7 years	49.80	7.2±0.3 years	140	CIMT	P=0.38
Antihypertensive drugs										
Valsartan *vs.* placebo	Ramadan, 2016	Cohort study	2005–2008	120	21–80 years	49.17	2 years	44	Delta CMT	P=0.009
Metoprolol controlled release/extended release *vs.* placebo	Wikstrand, 2003	Cohort study	NA	793	49–70 years	NA	3 years	0	Delta CMT	P<0.05
Lipid-lowering drugs										
Enalapril at 10 mg/d *vs.* control	Hosomi, 2001	Cohort study	1997	98	56.3±8.5 years (control), 56.4±8.7 years (intervention)	37.76	2 years	7	Annual change of CIMT	P=0.011
Pactimibe at 100 mg/d *vs.* placebo	Meuwese, 2009	Cohort study	2004–2005	881	54.7±8.5 years (control), 55.5±8.5 years (intervention)	39.05	24 months	165	CIMT	P=0.04
Rosuvastatin at 40 mg/d *vs.* placebo	Bots, 2009	Cohort study	NA	984	57.0±6.0 years (control), 57.0±6.2 years (intervention)	40.65	24 months	0	Annual change of CIMT	P<0.001
Simvastatin or atorvastatin *vs.* no statin therapy	Yamagami, 2008	Cohort study	2001–2003	81	65.4±6.9 years (control), 63.4±8.3 years (intervention)	42.00	1 year	0	Plaque thickness	P=0.008
Glucose-lowering drugs										
Pioglitazone *vs.* placebo	Christoph, 2015	Cohort study	2007–2010	54	62.2±10.0 years (control), 59.5±10.4 years (intervention)	18.52	9 months	0	CMT	P>0.05
Acarbose *vs.* placebo	Patel, 2013	Cohort study	2004	219	53.6±11.7 years (control), 53.6±11.1 years (intervention)	66.21	5 years	56	Annual change of CIMT	P=0.047
Nateglinide *vs.* no treatment	Mita, 2007	Cohort study	2005	70	51.3±8.3 years (control) 61.8±6.0 years (intervention)	47.00	12 months	0	Annual change of CIMT	P=0.0064
Acarbose *vs.* placebo	Hanefeld, 2004	Cohort study	NA	115	55.6±6.9 years (control), 54.8±7.4 years (intervention)	39.13	3.9±0.6 years	17	Delta CIMT	P=0.027

Plaque*, presence of carotid plaque; CIMT†, increased carotid intima-media thickness; ‡ indicated stroke patients.