Modifiable Risk Factors for Carotid Atherosclerosis: A Meta-analysis and Systematic Review

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Abstract

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 I² 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.

Background

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 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 File). 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: (1) the study included community-based population, (2) the exposures considered to be risk or protective factors for carotid atherosclerosis were potentially modifiable, (3) the control group were people without carotid atherosclerosis, and (4) 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≥1.0mm and the presence of carotid plaque was defined as CIMT>1.5mm 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)[10] was used to assess the quality of cross-sectional observational studies (Supplementary Table 1). Newcastle-Ottawa Scale (NOS) was employed to assess the quality of longitudinal studies (Supplementary Table 2).

**Statistical analyses**

Heterogeneity among studies was assessed using the $I^2$ statistic and values<30%, $P>0.05$ were considered as possibly low heterogeneity. A random effects model was used to quantitatively synthesize data. When the heterogeneity was high, the source would be explored further[11, 12]. 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[13]. All statistical analyses were performed with R 3.2.0 software.

**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%.

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[14-21] including 12,474 individuals 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, $I^2=19\%$, $P=0.28$) (Supplementary Figure 1). Three studies[15, 17, 21] with 2,732 subjects exhibited hypertension has higher risk of increased CIMT (OR=2.60, 95% CI: 1.33-5.08, $I^2=84\%$, $P<0.01$) (Supplementary Figure 2). Additionally, it was indicated that the risk of plaque was significantly greater in people with increased systolic blood pressure (SBP) variability (every 10mmHg increase) and diastolic blood pressure (DBP) variability[1, 22, 23]. Pulse pressure (PP) variability (every 10mmHg increase) raises the risk of carotid plaque for both community-based subjects and stroke patients[24, 25].

**Diabetes mellitus**

Seven studies[14, 19-22, 26, 27] with 16,752 patients were included in the meta-analysis (Figure 2). The results showed that the risk of carotid plaque in people with diabetes was 1.31 times the risk among those without diabetes (OR=1.31, 95% CI: 1.13-1.53, $I^2=0\%$, $P=0.74$) (Supplementary Figure 3).

**Dyslipidemia**

The meta-analysis of ten studies[14, 19-22, 26, 28-31] including 12,568 patients showed that hyperlipidemia (OR=1.92, 95% CI: 1.39-2.65, $I^2=0\%$, $P=0.56$), hypertriglyceridemia (triglyceride≥1.7mmol/L) (OR=1.33, 95% CI: 1.14-1.55, $I^2=0\%$, $P=0.85$), and higher low density lipoprotein (low density lipoprotein≥3.4mmol/L) (OR=1.11, 95% CI: 1.08-1.13, $I^2=0\%$, $P=0.46$) could significantly increase the risk of carotid plaque (Supplementary Figure 4-6). Moreover, there was strong likelihood of positive relationship between lower high density lipoprotein (high density lipoprotein≤1.0mmol/L) (OR=1.28, 95% CI: 0.99-1.67, $I^2=32\%$, $P=0.22$) or hypercholesterolemia (total cholesterol≥5.2mmol/L) (OR=1.20, 95% CI: 0.80-1.82, $I^2=6\%$, $P=0.34$) with carotid plaque (Supplementary Figure 7-8). One cohort study[32] indicated that hypercholesterolemia, hypertriglyceridemia, and higher low density lipoprotein were risk factors for CIMT. Nevertheless, one cross-sectional study[31] 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)[33]. Six studies[19, 20, 34-37] including 18,058 individuals explored the association between MetS and carotid atherosclerosis, which showed that MetS could elevate the risk of carotid plaque by 39% (OR=1.39, 95% CI: 1.23-1.57, $I^2=8\%$, $P=0.36$) (Supplementary Figure 9). Notably, there was
a dose-response relationship between the elevated risk 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: 1.57-3.47, $I^2=8\%$, $P=0.56$ for MetS-3; OR=2.65, 95% CI: 2.60-8.81, $I^2=0\%$, $P=0.36$ for MetS-5) (Supplementary Figure 10-14). Consistently, the association was confirmed by one cohort study[38] 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 $\geq 420\mu$mol/L in man or uric acid $\geq 360\mu$mol/L in woman) and carotid plaque was reported in four studies[23, 37, 39, 40] including 17,113 participants. Pooled results indicated that hyperuricemia was a risk factor for the presence of plaque (OR=1.57, 95% CI: 1.11-2.22, $I^2=84\%$, $P=0.01$) (Supplementary Figure 15). Similarly, the risk of increased CIMT was elevated in those with higher uric acid level (OR=1.24, 95% CI: 1.04-1.47)[41]. Further, people with carotid plaque or stenosis were reported to have higher uric acid level. But another cross-sectional study [42] failed to find the relationship between uric acid and plaque.

Hyperhomocysteinemia

Four studies[15, 43-45] with 5,623 individuals were included and a significant positive relationship between hyperhomocysteinemia (homocysteine $\geq 15\mu$mol/L) and carotid plaque was found (OR=1.88, 95% CI: 1.19-2.95, $I^2=78\%$, $P<0.01$) (Supplementary Figure 16). Additionally, one cross-sectional study[46] found CIMT increased 0.06mm as the level of homocysteine elevated per 1$\mu$mol/L.

Smoking

A pooled analysis of six studies[14, 21, 22, 28, 47, 48] including 7,995 participants indicated that smoking had a significant association with the risk of carotid plaque. Subgroup analyses showed that current smoking (OR=1.52, 95% CI: 1.14-2.03, $I^2=59\%$, $P=0.03$) conferred greater risk than former smoking (OR=1.42, 95% CI: 1.08-1.87, $I^2=9\%$, $P=0.33$) for the presence of carotid plaque (Supplementary Figure 17-18). Similarly, tobacco smoking is associated with increased CIMT, especially current smokers[49].

Sensitivity analyses

In sensitivity analyses (Supplementary Table 4), the results were robust for hypertension, hyperhomocysteinemia, MetS, and hypercholesterolemia. For current smoking, the heterogeneity was reduced after omitting one study[28] 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[39] 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 (Supplementary Figure 19-26).

Others

Some modifiable factors could not be included in the meta-analysis due to insufficient data, consisting of sexual abuse in early life[50], air pollution[51, 52], socioeconomic strain[53-55], negative emotion[56-58], lifestyles (drinking, physical activity, and sleep duration)[5, 59-62], diet (vitamin supplementation, egg consumption, vegetable intake and fish consumption)[63-70], medications (antihypertensive drugs, lipid-lowering drugs, and glucose-lowering drugs)[71-80], and pre-existing disease (OSAS) (apnea-hypopnea index $>15$ events/h)[81, 82] in mid-to-late life (Figure 3 and Supplementary Table 3).

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.

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[83]. 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 shown that higher high density lipoprotein could reverse the transport of cholesterol and return it to the liver to protect against carotid atherosclerosis[84]. The effect of triglyceride on carotid atherosclerosis was controversial because the criteria of hypertriglyceridermia 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[73]. 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[76, 85]. Moreover, the results in our analysis were supportive of the roles of glucose-lowering drugs in preventing CIMT progression[79, 80, 86]. 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[78].

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[87]. Besides, OSAS was reported to have a similar impact on carotid atherosclerosis[81], especially in rapid eye movement sleep[88], which may be attributed to nocturnal hypoxemia that could augment local inflammatory responses and exacerbate vessel damage in carotid arteries[89]. Therefore, continuous positive airway pressure (CPAP) was considered the treatment for OSAS by ameliorating inflammation to protect against carotid atherosclerosis[90].

Negative emotion including depression, anger, and anxiety was identified as a risk factor for the progression of carotid atherosclerosis by many cohort studies[56, 91], which might be accounted for by sympathetic nervous system hyperreactivity, abnormalities in platelet function, hypercortisolemia, endothelial dysfunction, and heart rate variability[92]. One cohort study[57] 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[50, 53, 93]. Business workers are considered to have higher CIMT when compared with factory workers[94]. 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[47]. One longitudinal study identified current smoking is related with extracranial carotid atherosclerosis but not with intracranial artery[95]. Interestingly, if mothers smoked in pregnancy, children had thicker CIMT, and the impact was stronger if both parents smoked during pregnancy[96]. Drinking could increase low density lipoprotein oxidation and oxidative stress to accelerate the progression of atherosclerosis when a man consumes alcohol over 40g/d, and the CIMT progression had a dose-response relationship with alcohol intake, no matter what he drinks: beer, wine or spirits[97]. Moderate exercise could increase antioxidant stress and anti-inflammatory processes, which could protect against the progression of carotid atherosclerosis[8]. Shorter sleep duration may have higher CIMT in Western populations rather than Asian populations[98]. 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[69]. 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[66]. 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 cohort studies and randomized controlled trials are warranted.

**Abbreviations**

CIMT, Carotid intima media thickness; OR, odds ratio; 95% CI, 95% confidence interval; AHRQ, Agency for Healthcare Research and Quality; NOS, Newcastle-Ottawa Scale; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; PP, Pulse pressure; DM, Diabetes mellitus; MetS, Metabolic syndrome; Hcy, homocysteine; HDL, High density lipoprotein; LDL, Low density lipoprotein; TC, Total cholesterol; TG, Triglyceride; OSAS, Obstructive sleep apnea syndrome; CPAP, Continuous positive airway pressure; SES, Socioeconomic status.

**Declarations**

**Funding**

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**Availability of data and materials**

All data analyzed during this study are included in this article.

**Authors' contributions**

JTY, and XYL conceptualized and designed the study. XJ, XYL, and YHM conducted the study. XJ, WX, YHM, and XHH analyzed and extracted data. XJ, XYL, YD, and JTY wrote the first draft of the manuscript. All authors reviewed the manuscript.

**Ethics approval and consent to participate**

For this type of study formal consent is not required.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no conflict of interest.

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**References**


96. West HW, Juonala M, Gall SL, Kahonen M, Laitinen T, Taittonen L, Viikari JS, Raitakari OT, Magnusen CG: Exposure to parental smoking in childhood is associated with increased risk of carotid atherosclerotic plaque in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation* 2015, **131**(14):1239-1246.


**Tables**
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Study</th>
<th>Recruitment Period</th>
<th>N(total)</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Age</th>
<th>Sex(female%)</th>
<th>Outcome</th>
<th>Result (OR and 95%CI)</th>
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<tbody>
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<td>plaque*</td>
<td>OR 1.72 (1.21-2.45)</td>
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<td>1992</td>
<td>1257</td>
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<td>69.16±8.10</td>
<td>56.20%</td>
<td>plaque*</td>
<td>OR 1.75 (1.18-2.60)</td>
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<td></td>
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<td>942</td>
<td>China</td>
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<td>67.20%</td>
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<td>&gt;35</td>
<td>57.20%</td>
<td>plaque*</td>
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<td></td>
<td>Zhang,2016</td>
<td>1992</td>
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<td>56.20%</td>
<td>CIMT†</td>
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<td>70 (50-100)</td>
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<td>OR 1.17 (0.81-1.69)</td>
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<td>42.90%</td>
<td>OR 1.51 (1.18-1.93)</td>
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<td>Empana, 2007</td>
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<td>5585</td>
<td>France</td>
<td>French</td>
<td>73.5 ± 4.9</td>
<td>38.00%</td>
<td>OR 1.21 (0.89-1.64)</td>
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<td>2001-2002</td>
<td>971</td>
<td>France</td>
<td>French</td>
<td>58.9 ± 4.7(without MetS) 58.8 ± 4.9(MetS)</td>
<td>49.84%</td>
<td>OR 1.42 (0.81-2.48)</td>
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<td>Su, 2001</td>
<td>1990</td>
<td>533</td>
<td>Taiwan</td>
<td>Chinese</td>
<td>&gt;35</td>
<td>57.20%</td>
<td>OR 1.80 (0.70-4.90)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>Woo, 2017</td>
<td>2008-2012</td>
<td>3030</td>
<td>Korea</td>
<td>Korean</td>
<td>70 (50-100)</td>
<td>56.30%</td>
<td>OR 1.84 (1.30-2.62)</td>
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<tr>
<td>Yuan, 2014</td>
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<td>106</td>
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<td>58.1 ± 9.0</td>
<td>63.20%</td>
<td>OR 2.41 (1.05-5.51)</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>O’Flynn, 2017</td>
<td>2010</td>
<td>50</td>
<td>Ireland</td>
<td>NA</td>
<td>59 ± 6</td>
<td>51.00%</td>
<td>OR 0.70 (0.29-1.70)</td>
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<tr>
<td>Rubinat, 2016</td>
<td>NA</td>
<td>374</td>
<td>Spain</td>
<td>NA</td>
<td>56.1 ± 10.8</td>
<td>59.90%</td>
<td>OR 1.47 (0.91-2.38)</td>
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<tr>
<td>Su, 2001</td>
<td>1990</td>
<td>533</td>
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<td>Chinese</td>
<td>&gt;35</td>
<td>57.20%</td>
<td>OR 1.10 (0.40-3.00)</td>
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<tr>
<td>Hypertriglyceridemia</td>
<td>Empana, 2007</td>
<td>1999-2001</td>
<td>5585</td>
<td>France</td>
<td>French</td>
<td>73.5 ± 4.9</td>
<td>38.00%</td>
<td>OR 1.34 (1.14-1.58)</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>n</td>
<td>Country</td>
<td>Ethnicity</td>
<td>Age Mean ± SD</td>
<td>Plaque %</td>
<td>OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
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<tr>
<td>Czernichow,2005</td>
<td>2001-2002</td>
<td>971</td>
<td>France</td>
<td>French</td>
<td>58.9 ± 4.7 (without MetS) 58.8 ± 4.9 (MetS)</td>
<td>49.84%</td>
<td>OR 1.28 (0.83-1.98)</td>
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<tr>
<td>Irie,2014</td>
<td>2007-2009</td>
<td>179</td>
<td>Japan</td>
<td>Japanese</td>
<td>65 ± 7</td>
<td>18.00%</td>
<td>OR 2.30 (1.03-5.13)</td>
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<tr>
<td>Empaná,2007</td>
<td>1999-2001</td>
<td>5585</td>
<td>France</td>
<td>French</td>
<td>73.5 ± 4.9</td>
<td>38.00%</td>
<td>OR 1.13 (0.93-1.38)</td>
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<tr>
<td>Czernichow,2005</td>
<td>2001-2002</td>
<td>971</td>
<td>France</td>
<td>French</td>
<td>58.9 ± 4.7 (without MetS) 58.8 ± 4.9 (MetS)</td>
<td>49.84%</td>
<td>OR 1.52 (1.01-2.28)</td>
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<tr>
<td>Su,2001</td>
<td>1990</td>
<td>533</td>
<td>Taiwan</td>
<td>Chinese</td>
<td>&gt;35</td>
<td>57.20%</td>
<td>OR 1.00 (0.50-1.90)</td>
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</tr>
<tr>
<td>Johnson,2010</td>
<td>2005-2007</td>
<td>1504</td>
<td>America</td>
<td>84% white, 14% black, 2% American</td>
<td>45.0 (37.8-53.0)</td>
<td>58.00%</td>
<td>OR 1.11 (1.08-1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Su,2001</td>
<td>1990</td>
<td>533</td>
<td>Taiwan</td>
<td>Chinese</td>
<td>&gt;35</td>
<td>57.20%</td>
<td>OR 1.01 (0.74-1.37)</td>
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<tr>
<td>Leng,2013</td>
<td>2007-2008</td>
<td>653</td>
<td>Hong Kong</td>
<td>Chinese</td>
<td>55.1 ± 10.4</td>
<td>52.80%</td>
<td>OR 1.50 (0.92-2.46)</td>
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<tr>
<td>Chen,2008</td>
<td>1990-1991</td>
<td>810</td>
<td>Taiwan</td>
<td>Taiwanese</td>
<td>66.1 ± 10.9</td>
<td>43.70%</td>
<td>OR 1.37 (0.93-2.01)</td>
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<tr>
<td>Empaná,2007</td>
<td>1999-2001</td>
<td>5585</td>
<td>France</td>
<td>French</td>
<td>73.5 ± 4.9</td>
<td>38.00%</td>
<td>OR 1.30 (1.09-1.55)</td>
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<td></td>
</tr>
<tr>
<td>Rundek,2007</td>
<td>2000</td>
<td>1895</td>
<td>Northern</td>
<td>25% were</td>
<td>68.0 ± 9.7</td>
<td>59.00%</td>
<td>OR 1.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Country</td>
<td>Ethnicity</td>
<td>Mean Age ± SD</td>
<td>Percentage</td>
<td>Plaque*</td>
<td>OR (95% CI)</td>
<td></td>
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</tr>
<tr>
<td>Czernichow, 2005</td>
<td>2001-2002</td>
<td>971</td>
<td>France</td>
<td>French</td>
<td>58.9 ± 4.7</td>
<td>49.84%</td>
<td>plaque*</td>
<td>1.07 (0.63-1.83)</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>58.8 ± 4.9</td>
<td></td>
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</tr>
<tr>
<td>Ishizaka, 2005</td>
<td>1994-2003</td>
<td>8144</td>
<td>Japan</td>
<td>Japanese</td>
<td>56.6 ± 10.5</td>
<td>32.80%</td>
<td>plaque*</td>
<td>1.99 (1.39-2.85)</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>plaque*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O'Flynn, 2017</td>
<td>2010</td>
<td>50</td>
<td>Ireland</td>
<td>NA</td>
<td>59 ± 6</td>
<td>51.00%</td>
<td>plaque*</td>
<td>9.16 (0.39-217.16) ‡</td>
<td></td>
</tr>
<tr>
<td>Woo, 2017</td>
<td>2008-2012</td>
<td>3030</td>
<td>Korea</td>
<td>Korean</td>
<td>70 (50-100)</td>
<td>56.30%</td>
<td>plaque*</td>
<td>1.46 (0.89-2.40) ‡</td>
<td></td>
</tr>
<tr>
<td>Yang, 2015</td>
<td>NA</td>
<td>1746</td>
<td>Northern Manhattan</td>
<td>18% white, 63% Hispanic, 19% black</td>
<td>65.5 ± 8.9</td>
<td>60.00%</td>
<td>plaque*</td>
<td>2.13 (1.27-3.57) ‡</td>
<td></td>
</tr>
<tr>
<td>Johnson, 2010</td>
<td>2005-2007</td>
<td>1504</td>
<td>America</td>
<td>84% white, 14% black, 2% American</td>
<td>45.0 (37.8-53.0)</td>
<td>58.00%</td>
<td>plaque*</td>
<td>1.14 (1.05-1.23) ‡</td>
<td></td>
</tr>
<tr>
<td>Liang, 2009</td>
<td>1993-1994</td>
<td>1132</td>
<td>China</td>
<td>Chinese</td>
<td>35-64</td>
<td>66.10%</td>
<td>plaque*</td>
<td>1.50 (1.00-2.10) ‡</td>
<td></td>
</tr>
<tr>
<td>Su, 2001</td>
<td>1990</td>
<td>533</td>
<td>Taiwan</td>
<td>Chinese</td>
<td>&gt;35</td>
<td>57.20%</td>
<td>plaque*</td>
<td>2.40 (1.00-5.60) ‡</td>
<td></td>
</tr>
<tr>
<td>Woo, 2017</td>
<td>2008-2012</td>
<td>3030</td>
<td>Korea</td>
<td>Korean</td>
<td>70 (50-100)</td>
<td>56.30%</td>
<td>plaque*</td>
<td>1.08 (0.63-1.85) §</td>
<td></td>
</tr>
</tbody>
</table>
Yang, 2015  
NA  
1746  
Northern Manhattan  
18% white,  
63% Hispanic,  
19% black.  

65.5 ± 8.9  
60.00%  
plaque*  
OR 1.73  
(1.19-2.51) §

Liang, 2009  
1993-1994  
1132  
China  
Chinese  
35-64  
66.10%  
plaque*  
OR 1.30  
(0.80-2.10) §

Hyperuricemia  
Li, 2015  
2010  
2860  
China  
Chinese  
57.7 (40-94)  
28.40%  
plaque*  
OR 1.37  
(1.09-1.74)

Li, 2014  
1992  
1243  
China  
Chinese  
69.6 ± 8.1  
54.80%  
plaque*  
OR 0.99  
(0.63-1.55)

Neogi, 2009  
2002-2004  
4866  
America  
Caucasian  
52.2  
54.00%  
plaque*  
OR 1.75  
(1.21-2.51)

Ishizaka, 2005  
1994-2003  
8144  
Japan  
Japanese  
56.6 ± 10.5  
32.80%  
plaque*  
OR 2.27  
(1.90-2.72)

Hyperhomocysteinemia  
Zhang, 2016  
1992  
1257  
China  
Chinese  
69.16 ± 8.10  
56.20%  
plaque*  
OR 1.56  
(1.05-2.33)

Yang, 2014  
2010-2011  
2919  
China  
Chinese  
60.1 ± 12.4  
28.60%  
plaque*  
OR 1.28  
(1.09-1.51)

Alsulaimani, 2013  
1993-2001  
1327  
Northern Manhattan  
19% black,  
62% Hispanic,  
17% white.  
66 ± 9  
59.00%  
plaque*  
OR 1.90  
(1.20-3.10)

Kawamoto, 2001  
2000  
120  
Japan  
Japanese  
77 ± 9  
55.80%  
plaque*  
OR 8.24  
(2.87-23.70)

Abbreviations: 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

Figures
Figure 1

Flow chart of identified studies
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>No. of Studies</th>
<th>Quality Score*</th>
<th>Sample Size</th>
<th>OR(95% CI)</th>
<th>p Value</th>
<th>I-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque^</td>
<td>8</td>
<td>7.63</td>
<td>12,474</td>
<td>1.81(1.55–2.13)</td>
<td>0.28</td>
<td>19%</td>
</tr>
<tr>
<td>CIMT#</td>
<td>3</td>
<td>7.67</td>
<td>2,732</td>
<td>2.60(1.33–5.08)</td>
<td>&lt;0.01</td>
<td>84%</td>
</tr>
<tr>
<td>Hyperhomocysteinemia^</td>
<td>4</td>
<td>8.25</td>
<td>5,623</td>
<td>1.88(1.19–2.95)</td>
<td>&lt;0.01</td>
<td>78%</td>
</tr>
<tr>
<td>Hyperuricemia^</td>
<td>4</td>
<td>6.75</td>
<td>17,113</td>
<td>1.57(1.11–2.22)</td>
<td>&lt;0.01</td>
<td>84%</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>6</td>
<td>7.5</td>
<td>7,995</td>
<td>1.52(1.14–2.03)</td>
<td>0.03</td>
<td>59%</td>
</tr>
<tr>
<td>Former smoking</td>
<td>3</td>
<td>7.33</td>
<td>5,908</td>
<td>1.42(1.08–1.87)</td>
<td>0.33</td>
<td>9%</td>
</tr>
<tr>
<td>Metabolic syndrome^</td>
<td>6</td>
<td>7.83</td>
<td>18,058</td>
<td>1.39(1.23–1.57)</td>
<td>0.36</td>
<td>8%</td>
</tr>
<tr>
<td>Mets-1</td>
<td>2</td>
<td>8</td>
<td>2,548</td>
<td>1.71(1.10–2.66)</td>
<td>0.64</td>
<td>0</td>
</tr>
<tr>
<td>Mets-2</td>
<td>2</td>
<td>8</td>
<td>2,548</td>
<td>2.17(1.39–3.37)</td>
<td>0.48</td>
<td>0</td>
</tr>
<tr>
<td>Mets-3</td>
<td>2</td>
<td>8</td>
<td>2,548</td>
<td>2.21(1.42–3.46)</td>
<td>0.56</td>
<td>0</td>
</tr>
<tr>
<td>Mets-4</td>
<td>2</td>
<td>8</td>
<td>2,548</td>
<td>2.65(1.57–4.47)</td>
<td>0.3</td>
<td>8%</td>
</tr>
<tr>
<td>Mets-5</td>
<td>2</td>
<td>8</td>
<td>2,548</td>
<td>4.78(2.60–8.81)</td>
<td>0.36</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus^</td>
<td>7</td>
<td>7.43</td>
<td>16,752</td>
<td>1.31(1.13–1.53)</td>
<td>0.74</td>
<td>0</td>
</tr>
<tr>
<td>Dyslipidemia^</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hyperlipidemia</td>
<td>2</td>
<td>7.5</td>
<td>3,136</td>
<td>1.92(1.39–2.65)</td>
<td>0.56</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2</td>
<td>8</td>
<td>6,556</td>
<td>1.33(1.14–1.55)</td>
<td>0.85</td>
<td>0</td>
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<tr>
<td>Higher low density lipoprotein</td>
<td>3</td>
<td>8</td>
<td>2,273</td>
<td>1.11(1.08–1.13)</td>
<td>0.46</td>
<td>0</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3</td>
<td>7.33</td>
<td>957</td>
<td>1.20(0.80–1.82)</td>
<td>0.34</td>
<td>6%</td>
</tr>
<tr>
<td>Lower high density lipoprotein</td>
<td>4</td>
<td>7.75</td>
<td>7,268</td>
<td>1.28(0.99–1.67)</td>
<td>0.22</td>
<td>32%</td>
</tr>
</tbody>
</table>

Figure 2
Forest plot shows the risk factors for carotid atherosclerosis in the meta-analysis. Abbreviations: 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.
Factors showing significant positive and negative association with carotid atherosclerosis: DM, Diabetes mellitus; MetS, Metabolic syndrome; Hcy, homocysteine; HDL, High 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. Table 1: General characteristics of studies included in the meta-analysis.

### Supplementary Files

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