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

**Xi Ji**
Dalian Medical University
**Xin-Yi Leng**
Chinese University of Hong Kong
**Yi Dong**
Fudan University
**Ya-Hui Ma**
Dalian Medical University
**Wei Xu**
Qingdao University Medical College
**Hao Hu**
Qingdao University Medical College
**Xi-Peng Cao**
Qingdao Municipal Hospital Group
**Xiao-He Hou**
Qingdao University Medical College
**Lan Tan**
Qingdao Municipal Hospital Group
**Qiang Dong**
Fudan University
**Jin-Tai Yu** ( yu-jintai@163.com )
Huashan Hospital Fudan University

**Research article**

**Keywords:** Carotid atherosclerosis, Carotid plaque, Carotid intima-media thickness, Risk factors,Meta-analysis

**Posted Date:** May 13th, 2019

**DOI:** https://doi.org/10.21203/rs.2.9584/v1



**Version of Record:** A version of this preprint was published at Annals of Translational Medicine on November 1st, 2019. See the published version at https://doi.org/10.21037/atm.2019.10.115.

## 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: 1.42-3.46, $I^2$ =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) (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≥420μmol/L in man or uric acid≥360μmol/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≥15μmol/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 1μmol/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 pressence 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 showed 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 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[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 studies[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 compare 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 indentified 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 progession of carotid atherosclerosis[5]. 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, How 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

This study was supported by grants from the Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZHANGJIANG LAB, Tianqiao and Chrissy Chen Institute, and the State Key Laboratory of Neurobiology and Frontiers Center for Brain Science of Ministry of Education, Fudan University.


### 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.

### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.


### Author details

[1] Department of Neurology, Qingdao Municipal Hospital, Dalian Medical University, Dalian, China. [2] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China.[3] Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China.[4] Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China.[5] Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, Qingdao, China.


## References

1. Shintani Y, Kikuya M, Hara A, Ohkubo T, Metoki H: **Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study**. *Journal of hypertension* 2007, **25**:7.
2. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R *et al*: **Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011**. *Cerebrovascular diseases (Basel, Switzerland)* 2012, **34**(4):290-296.
3. Zwakenberg SR, van der Schouw YT, Vermeer C, Pasterkamp G, den Ruijter HM, Beulens JWJ: **Matrix Gla Protein, Plaque Stability, and Cardiovascular Events in Patients with Severe Atherosclerotic Disease**. *Cardiology* 2018, **141**(1):32-36.
4. Inaba Y, Chen JA, Bergmann SR: **Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis**. *Atherosclerosis* 2012, **220**(1):128-133.
5. Park J, Park H: **Effects of 6 months of aerobic and resistance exercise training on carotid artery intima media thickness in overweight and obese older women**. *Geriatrics & gerontology international* 2017.
6. Maiorino MI, Bellastella G, Petrizzo M, Gicchino M, Caputo M, Giugliano D, Esposito K: **Effect of a Mediterranean diet on endothelial progenitor cells and carotid intima-media thickness in type 2 diabetes: Follow-up of a randomized trial**. *European journal of preventive cardiology* 2017, **24**(4):399-408.
7. Wang SK, Fajardo A, Sawchuk AP, Lemmon GW, Dalsing MC, Gupta AK, Murphy MP, Motaganahalli RL: **Outcomes associated with a transcarotid artery revascularization-centered protocol in high-risk carotid revascularizations using the ENROUTE neuroprotection system**. *Journal of vascular surgery* 2018.
8. Kozakova M, Natali A, Dekker J, Beck-Nielsen H, Laakso M, Nilsson P, Balkau B, Ferrannini E: **Insulin sensitivity and carotid intima-media thickness: relationship between insulin sensitivity and cardiovascular risk study**. *Arteriosclerosis, thrombosis, and vascular biology* 2013, **33**(6):1409-1417.
9. Pena AS, Maftei O, Harrington J, Anderson J, Hirte C, Gent R, Couper J: **Lack of evidence for progression of atherosclerosis during puberty in type 1 diabetes**. *Pediatric diabetes* 2016, **17**(3):199-205.
10. Nevidomskyte D, Tang GL, Shin SH, Hatsukami TS, Khor S, Flum DR, Meissner MH, Shalhub S: **Comparison of outcomes in women and men following carotid interventions in the Washington state's Vascular Interventional Surgical Care and Outcomes Assessment Program**. *Journal of vascular surgery* 2018.
11. Wen L, Wang S, Liu L, Chen L, Geng J, Kuang L, Qian G, Su J, Chen K, Zhou Z: **The Long-Term Efficacy and Safety of Carotid Artery Stenting among the Elderly: A Single-Center Study in China**. *Behavioural neurology* 2018, **2018**:4707104.
12. Sgambat K, Clauss S, Moudgil A: **Comparison of BMI, waist circumference, and waist-to-height ratio for identification of subclinical cardiovascular risk in pediatric kidney transplant recipients**. *Pediatric transplantation* 2018:e13300.
13. Liisberg M, Stenger M, Behr-Rasmussen C, Stubbe J, Lindholt JS: **Experimental comparative study of thrombogenicity of two differently luminal heparinized ePTFE vascular prosthetics**. *Annals of medicine and surgery (2012)* 2018, **35**:76-81.
14. Woo SY, Joh JH, Han SA, Park HC: **Prevalence and risk factors for atherosclerotic carotid stenosis and plaque: A population-based screening study**. *Medicine* 2017, **96**(4):e5999.
15. Zhang Z, Fang X, Hua Y, Liu B, Ji X, Tang Z, Wang C, Guan S, Wu X, Liu H *et al*: **Combined Effect of Hyperhomocysteinemia and Hypertension on the Presence of Early Carotid Artery Atherosclerosis**. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 2016, **25**(5):1254-1262.
16. Idei M, Hirayama S, Miyake N, Kon M, Horiuchi Y, Ueno T, Miyake K, Satoh N, Yoshii H, Yamashiro K *et al*: **Mean postprandial triglyceride concentration is an independent risk factor for carotid atherosclerosis in patients with type 2 diabetes**. *Clinica chimica acta; international journal of clinical chemistry* 2014, **430**:134-139.
17. Hong H, Wang H, Liao H: **Prehypertension is associated with increased carotid atherosclerotic plaque in the community population of Southern China.** *BMC cardiovascular disorders* 2013, **13**:8.
18. Beaussier H, Masson I, Collin C, Bozec E, Laloux B, Calvet D, Zidi M, Boutouyrie P, Laurent S: **Carotid plaque, arterial stiffness gradient, and remodeling in hypertension**. *Hypertension (Dallas, Tex : 1979)* 2008, **52**(4):729-736.
19. Empana JP, Zureik M, Gariepy J, Courbon D, Dartigues JF, Ritchie K, Tzourio C, Alperovitch A, Ducimetiere P: **The metabolic syndrome and the carotid artery structure in noninstitutionalized elderly subjects: the three-city study**. *Stroke* 2007, **38**(3):893-899.
20. Czernichow S, Bertrais S, Blacher J, Oppert JM, Galan P, Ducimetiere P, Hercberg S, Safar M, Zureik M: **Metabolic syndrome in relation to structure and function of large arteries: a predominant effect of blood pressure. A report from the SU.VI.MAX. Vascular Study**. *American journal of hypertension* 2005, **18**(9 Pt 1):1154-1160.
21. Su TC, Jeng JS, Chien KL, Sung FC, Hsu HC, Lee YT: **Hypertension status is the major determinant of carotid atherosclerosis: a community-based study in Taiwan**. *Stroke* 2001, **32**(10):2265-2271.

22. O'Flynn AM, Ho E, Dolan E, Curtin RJ, Kearney PM: **The association of night-time systolic blood pressure with ultrasound markers of subclinical cardiac and vascular disease**. *Blood pressure monitoring* 2017, **22**(1):18-26.
23. Li Y, Lu J, Wu X, Yang C: **Serum uric acid concentration and asymptomatic hyperuricemia with subclinical organ damage in general population**. *Angiology* 2014, **65**(7):634-640.
24. Lovett JK, Howard SC, Rothwell PM: **Pulse pressure is independently associated with carotid plaque ulceration**. *Journal of hypertension* 2003, **21**(9):1669-1676.
25. Cheng CA, Chien WC, Hsu CY, Lin HC, Chiu HW: **Risk analysis of carotid stent from a population-based database in Taiwan**. *Medicine* 2016, **95**(35):e4747.
26. Rubinat E, Marsal JR, Vidal T, Cebrian C, Falguera M, Vilanova MB, Betriu A, Fernandez E, Franch J, Mauricio D: **Subclinical Carotid Atherosclerosis in Asymptomatic Subjects With Type 2 Diabetes Mellitus**. *The Journal of cardiovascular nursing* 2016, **31**(2):E1-7.
27. Casalnuovo G, Gerdts E, de Simone G, Izzo R, De Marco M, Giudice R, Trimarco B, De Luca N: **Arterial stiffness is associated with carotid atherosclerosis in hypertensive patients (the Campania Salute Network)**. *American journal of hypertension* 2012, **25**(7):739-745.
28. Johnson HM, Piper ME, Jorenby DE, Fiore MC, Baker TB, Stein JH: **Risk factors for subclinical carotid atherosclerosis among current smokers**. *Preventive cardiology* 2010, **13**(4):166-171.
29. Yuan C, Lai CW, Chan LW, Chow M, Law HK, Ying M: **Cumulative effects of hypertension, dyslipidemia, and chronic kidney disease on carotid atherosclerosis in Chinese patients with type 2 diabetes mellitus**. *Journal of diabetes research* 2014, **2014**:179686.
30. Irie Y, Katakami N, Kaneto H, Takahara M, Sakamoto K, Kosugi K, Shimomura I: **The risk factors associated with ultrasonic tissue characterization of carotid plaque in type 2 diabetic patients**. *Journal of diabetes and its complications* 2014, **28**(4):523-527.
31. Sato Y, Nagao M, Asai A, Nakajima Y, Takaya M, Takeichi N, Takemitsu S, Sudo M, Kano-Wakakuri T, Ishizaki A *et al*: **Association of glycated albumin with the presence of carotid plaque in patients with type 2 diabetes**. *Journal of diabetes investigation* 2013, **4**(6):634-639.
32. Huang Y, Yu X, Millican D, Wu L, Shi P, Lu M, Wu Y: **The measurement of lipids currently and 9 years ago--which is more associated with carotid intima-media thickness?** *Clinical cardiology* 2012, **35**(8):512-517.
33. James IC: **Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)**. *Jama* 2001, **285**(19):12.
34. Leng XY, Chen XY, Chook P, Xiong L, Lin WH, Liu JY, Tomlinson B, Thomas GN, Lam TH, Lam KS *et al*: **Association between metabolic syndrome and carotid atherosclerosis: a community-based study in Hong Kong**. *Metabolic syndrome and related disorders* 2013, **11**(2):109-114.
35. Chen PC, Chien KL, Hsu HC, Su TC, Chang CW, Sung FC, Lee YT: **C-reactive protein and the metabolic syndrome correlate differently with carotid atherosclerosis between men and women in a Taiwanese community**. *Metabolism: clinical and experimental* 2008, **57**(8):1023-1028.
36. Rundek T, White H, Boden-Albala B, Jin Z, Elkind MS, Sacco RL: **The metabolic syndrome and subclinical carotid atherosclerosis: the Northern Manhattan Study**. *Journal of the cardiometabolic syndrome* 2007, **2**(1):24-29.
37. Ishizaka N, Ishizaka Y, Toda E, Nagai R, Yamakado M: **Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals**. *Arteriosclerosis, thrombosis, and vascular biology* 2005, **25**(5):1038-1044.
38. Jung JM, Young Kwon D, Han C, Park MH: **Metabolic syndrome and early carotid atherosclerosis in the elderly**. *Journal of atherosclerosis and thrombosis* 2014, **21**(5):435-444.
39. Neogi T, Ellison RC, Hunt S, Terkeltaub R, Felson DT, Zhang Y: **Serum uric acid is associated with carotid plaques: the National Heart, Lung, and Blood Institute Family Heart Study**. *The Journal of rheumatology* 2009, **36**(2):378-384.
40. Li Q, Zhou Y, Dong K, Wang A, Yang X, Zhang C, Zhu Y, Wu S, Zhao X: **The Association between Serum Uric Acid Levels and the Prevalence of Vulnerable Atherosclerotic Carotid Plaque: A Cross-sectional Study**. *Scientific reports* 2015, **5**:10003.
41. Zhang Z, Bian L, Choi Y: **Serum uric acid: a marker of metabolic syndrome and subclinical atherosclerosis in Korean men**. *Angiology* 2012, **63**(6):420-428.
42. Oikonen M, Wendelin-Saarenhovi M, Lyytikainen LP, Siitonen N, Loo BM, Jula A, Seppala I, Saarikoski L, Lehtimaki T, Hutri-Kahonen N *et al*: **Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study**. *Atherosclerosis* 2012, **223**(2):497-503.
43. Yang X, Zhou Y, Liu C, Gao X, Wang A, Guo Y, Li W, Zhao X, Liang W: **Homocysteine and carotid plaque stability: a cross-sectional study in Chinese adults**. *PloS one* 2014, **9**(4):e94935.
44. Alsulaimani S, Gardener H, Elkind MS, Cheung K, Sacco RL, Rundek T: **Elevated homocysteine and carotid plaque area and densitometry in the Northern Manhattan Study**. *Stroke* 2013, **44**(2):457-461.

45. Kawamoto R, Doi T, Tokunaga H: **Association of plasma homocysteine concentrations with carotid atherosclerosis in elderly Japanese.** *Internal medicine* 2001, **40**(12):1189-1194.
46. Nakhai-Pour HR, Grobbee DE, Bots ML, Muller M, van der Schouw YT: **Circulating homocysteine and large arterial stiffness and thickness in a population-based sample of middle-aged and elderly men**. *Journal of human hypertension* 2007, **21**(12):942-948.
47. Yang D, Iyer S, Gardener H, Della-Morte D, Crisby M, Dong C, Cheung K, Mora-McLaughlin C, Wright CB, Elkind MS *et al*: **Cigarette Smoking and Carotid Plaque Echodensity in the Northern Manhattan Study**. *Cerebrovascular diseases (Basel, Switzerland)* 2015, **40**(3-4):136-143.
48. Liang LR, Wong ND, Shi P, Zhao LC, Wu LX, Xie GQ, Wu YF: **Cross-sectional and longitudinal association of cigarette smoking with carotid atherosclerosis in Chinese adults**. *Preventive medicine* 2009, **49**(1):62-67.
49. Kianoush S, Yakoob MY, Al-Rifai M, DeFilippis AP, Bittencourt MS, Duncan BB, Bensenor IM, Bhatnagar A, Lotufo PA, Blaha MJ: **Associations of Cigarette Smoking With Subclinical Inflammation and Atherosclerosis: ELSA-Brasil (The Brazilian Longitudinal Study of Adult Health)**. *Journal of the American Heart Association* 2017, **6**(6).
50. Thurston RC, Chang Y, Derby CA, Bromberger JT, Harlow SD, Janssen I, Matthews KA: **Abuse and subclinical cardiovascular disease among midlife women: the study of women's health across the nation**. *Stroke* 2014, **45**(8):2246-2251.
51. Wang Y, Wellenius GA, Hickson DA, Gjelsvik A, Eaton CB, Wyatt SB: **Residential Proximity to Traffic-Related Pollution and Atherosclerosis in 4 Vascular Beds Among African-American Adults: Results From the Jackson Heart Study**. *American journal of epidemiology* 2016.
52. Painschab MS, Davila-Roman VG, Gilman RH, Vasquez-Villar AD, Pollard SL, Wise RA, Miranda JJ, Checkley W: **Chronic exposure to biomass fuel is associated with increased carotid artery intima-media thickness and a higher prevalence of atherosclerotic plaque**. *Heart (British Cardiac Society)* 2013, **99**(14):984-991.
53. Thurston RC, El Khoudary SR, Derby CA, Barinas-Mitchell E, Lewis TT, McClure CK, Matthews KA: **Low socioeconomic status over 12 years and subclinical cardiovascular disease: the study of women's health across the nation**. *Stroke* 2014, **45**(4):954-960.
54. Hintsanen M, Kivimaki M, Elovainio M, Pulkki-Raback L, Keskivaara P, Juonala M, Raitakari OT, Keltikangas-Jarvinen L: **Job strain and early atherosclerosis: the Cardiovascular Risk in Young Finns study**. *Psychosomatic medicine* 2005, **67**(5):740-747.
55. Peterson LM, Matthews KA, Derby CA, Bromberger JT, Thurston RC: **The relationship between cumulative unfair treatment and intima media thickness and adventitial diameter: The moderating role of race in the study of women's health across the nation**. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2016, **35**(4):313-321.
56. Haas DC, Davidson KW, Schwartz DJ, Rieckmann N, Roman MJ, Pickering TG, Gerin W, Schwartz JE: **Depressive symptoms are independently predictive of carotid atherosclerosis**. *The American journal of cardiology* 2005, **95**(4):547-550.
57. Rice SC, Zonderman AB, Metter EJ, Najjar SS, Waldstein SR: **Absence of relation between depressive symptoms and carotid intimal medial thickness in the Baltimore Longitudinal Study of Aging**. *Psychosomatic medicine* 2009, **71**(1):70-76.
58. Tiemeier H, van Dijck W, Hofman A, Witteman JC, Stijnen T, Breteler MM: **Relationship between atherosclerosis and late-life depression: the Rotterdam Study**. *Archives of general psychiatry* 2004, **61**(4):369-376.
59. Sands MR, Lauderdale DS, Liu K, Knutson KL, Matthews KA, Eaton CB, Linkletter CD, Loucks EB: **Short sleep duration is associated with carotid intima-media thickness among men in the Coronary Artery Risk Development in Young Adults (CARDIA) Study**. *Stroke* 2012, **43**(11):2858-2864.
60. Kozakova M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Balkau B: **Effect of sedentary behaviour and vigorous physical activity on segment-specific carotid wall thickness and its progression in a healthy population**. *European heart journal* 2010, **31**(12):1511-1519.
61. Lee YH, Shin MH, Kweon SS, Choi SW, Kim HY, Ryu SY, Kim BH, Rhee JA, Choi JS: **Alcohol consumption and carotid artery structure in Korean adults aged 50 years and older**. *BMC public health* 2009, **9**:358.
62. Debette S, Courbon D, Leone N, Gariepy J, Tzourio C, Dartigues JF, Barberger-Gateau P, Ritchie K, Alperovitch A, Amouyel P *et al*: **Tea consumption is inversely associated with carotid plaques in women**. *Arteriosclerosis, thrombosis, and vascular biology* 2008, **28**(2):353-359.
63. Goldberg S, Gardener H, Tiozzo E, Ying Kuen C, Elkind MS, Sacco RL, Rundek T: **Egg consumption and carotid atherosclerosis in the Northern Manhattan study**. *Atherosclerosis* 2014, **235**(2):273-280.
64. Buscemi S, Nicolucci A, Mattina A, Rosafio G, Massenti FM, Lucisano G, Galvano F, Amodio E, Pellegrini F, Barile AM *et al*: **Association of dietary patterns with insulin resistance and clinically silent carotid atherosclerosis in apparently healthy people**. *European journal of clinical nutrition* 2013, **67**(12):1284-1290.
65. Kesse-Guyot E, Vergnaud AC, Fezeu L, Zureik M, Blacher J, Peneau S, Hercberg S, Galan P, Czernichow S: **Associations between dietary patterns and arterial stiffness, carotid artery intima-media thickness and atherosclerosis**. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 2010, **17**(6):718-724.

66. Zureik M, Galan P, Bertrais S, Mennen L, Czernichow S, Blacher J, Ducimetiere P, Hercberg S: **Effects of long-term daily low-dose supplementation with antioxidant vitamins and minerals on structure and function of large arteries**. *Arteriosclerosis, thrombosis, and vascular biology* 2004, **24**(8):1485-1491.
67. Thoenes M, Oguchi A, Nagamia S, Vaccari CS, Hammoud R, Umpierrez GE, Khan BV: **The effects of extended-release niacin on carotid intimal media thickness, endothelial function and inflammatory markers in patients with the metabolic syndrome**. *International journal of clinical practice* 2007, **61**(11):1942-1948.
68. Bondonno CP, Blekkenhorst LC, Prince RL, Ivey KL, Lewis JR, Devine A, Woodman RJ, Lundberg JO, Croft KD, Thompson PL *et al*: **Association of Vegetable Nitrate Intake With Carotid Atherosclerosis and Ischemic Cerebrovascular Disease in Older Women**. *Stroke* 2017, **48**(7):1724-1729.
69. Blekkenhorst LC, Bondonno CP, Lewis JR, Woodman RJ, Devine A, Bondonno NP, Lim WH, Zhu K, Beilin LJ, Thompson PL *et al*: **Cruciferous and Total Vegetable Intakes Are Inversely Associated With Subclinical Atherosclerosis in Older Adult Women**. *Journal of the American Heart Association* 2018, **7**(8).
70. Johnsen SH, Jacobsen BK, Braekkan SK, Hansen JB, Mathiesen EB: **Fish consumption, fish oil supplements and risk of atherosclerosis in the Tromso study**. *Nutrition journal* 2018, **17**(1):56.
71. Ramadan R, Dhawan SS, Binongo JN, Alkhoder A, Jones DP, Oshinski JN, Quyyumi AA: **Effect of Angiotensin II Type I Receptor Blockade with Valsartan on Carotid Artery Atherosclerosis: A Double Blind Randomized Clinical Trial Comparing Valsartan and Placebo (EFFERVESCENT)**. *American heart journal* 2016, **174**:68-79.
72. Wikstrand J, Berglund G, Hedblad B, Hulthe J: **Antiatherosclerotic effects of beta-blockers**. *The American journal of cardiology* 2003, **91**(12A):25H-29H.
73. Hosomi N, Mizushige K, Ohyama H, Takahashi T, Kitadai M, Hatanaka Y, Matsuo H, Kohno M, Koziol JA: **Angiotensin-converting enzyme inhibition with enalapril slows progressive intima-media thickening of the common carotid artery in patients with non-insulin-dependent diabetes mellitus**. *Stroke* 2001, **32**(7):1539-1545.
74. Meuwese MC, de Groot E, Duivenvoorden R, Trip MD, Ose L, Maritz FJ, Basart DC, Kastelein JJ, Habib R, Davidson MH *et al*: **ACAT inhibition and progression of carotid atherosclerosis in patients with familial hypercholesterolemia: the CAPTIVATE randomized trial**. *Jama* 2009, **301**(11):1131-1139.
75. Yamagami H, Sakaguchi M, Furukado S, Hoshi T, Abe Y, Hougaku H, Hori M, Kitagawa K: **Statin therapy increases carotid plaque echogenicity in hypercholesterolemic patients**. *Ultrasound in medicine & biology* 2008, **34**(9):1353-1359.
76. Bots ML, Palmer MK, Dogan S, Plantinga Y, Raichlen JS, Evans GW, O'Leary DH, Grobbee DE, Crouse JR, 3rd: **Intensive lipid lowering may reduce progression of carotid atherosclerosis within 12 months of treatment: the METEOR study**. *Journal of internal medicine* 2009, **265**(6):698-707.
77. Patel YR, Kirkman MS, Considine RV, Hannon TS, Mather KJ: **Effect of acarbose to delay progression of carotid intima-media thickness in early diabetes**. *Diabetes/metabolism research and reviews* 2013, **29**(7):582-591.
78. Christoph M, Herold J, Berg-Holldack A, Rauwolf T, Ziemssen T, Schmeisser A, Weinert S, Ebner B, Ibrahim K, Strasser RH *et al*: **Effects of the Peroxisome Proliferator-Activated Receptor-gamma Agonist Pioglitazone on Peripheral Vessel Function and Clinical Parameters in Nondiabetic Patients: A Double-Center, Randomized Controlled Pilot Trial**. *Cardiology* 2015, **131**(3):165-171.
79. Hanefeld M, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T: **Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance**. *Stroke* 2004, **35**(5):1073-1078.
80. Mita T, Watada H, Shimizu T, Tamura Y, Sato F, Watanabe T, Choi JB, Hirose T, Tanaka Y, Kawamori R: **Nateglinide reduces carotid intima-media thickening in type 2 diabetic patients under good glycemic control**. *Arteriosclerosis, thrombosis, and vascular biology* 2007, **27**(11):2456-2462.
81. Gunnarsson SI, Peppard PE, Korcarz CE, Barnet JH, Aeschlimann SE, Hagen EW, Young T, Hla KM, Stein JH: **Obstructive sleep apnea is associated with future subclinical carotid artery disease: thirteen-year follow-up from the Wisconsin sleep cohort**. *Arteriosclerosis, thrombosis, and vascular biology* 2014, **34**(10):2338-2342.
82. Fox N, Ayas N, Park JE, Fleetham J, Frank Ryan C, Lear SA, Mulgrew A, Chan S, Hill J, John Mancini GB *et al*: **Carotid intima media thickness in patients with obstructive sleep apnea: comparison with a community-based cohort**. *Lung* 2014, **192**(2):297-303.
83. Chien KL, Tu YK, Hsu HC, Su TC, Lin HJ, Chen MF, Lee YT: **Differential effects of the changes of LDL cholesterol and systolic blood pressure on the risk of carotid artery atherosclerosis**. *BMC cardiovascular disorders* 2012, **12**:66.
84. Gardener H, Della Morte D, Elkind MS, Sacco RL, Rundek T: **Lipids and carotid plaque in the Northern Manhattan Study (NOMAS)**. *BMC cardiovascular disorders* 2009, **9**:55.
85. Herder M, Arntzen KA, Johnsen SH, Eggen AE, Mathiesen EB: **Long-term use of lipid-lowering drugs slows progression of carotid atherosclerosis: the Tromso study 1994 to 2008**. *Arteriosclerosis, thrombosis, and vascular biology* 2013, **33**(4):858-862.

86. Yamasaki Y, Katakami N, Furukado S, Kitagawa K, Nagatsuka K, Kashiwagi A, Daida H, Kawamori R, Kaku K: **Long-term effects of pioglitazone on carotid atherosclerosis in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity**. *Journal of atherosclerosis and thrombosis* 2010, **17**(11):1132-1140.
87. Bae JS, Shin DH, Park PS, Choi BY, Kim MK, Shin MH, Lee YH, Chun BY, Kim SK: **The impact of serum uric acid level on arterial stiffness and carotid atherosclerosis: the Korean Multi-Rural Communities Cohort study**. *Atherosclerosis* 2013, **231**(1):145-151.
88. Ljunggren M, Lindberg E, Franklin KA, Ohagen P, Larsson M, Theorell-Haglow J, Naessen T: **Obstructive sleep apnea during rapid eye movement sleep is associated with early signs of atherosclerosis in women**. *Sleep* 2018, **41**(7).
89. Kim J, Pack A, Maislin G, Lee SK, Kim SH, Shin C: **Prospective observation on the association of snoring with subclinical changes in carotid atherosclerosis over four years**. *Sleep medicine* 2014, **15**(7):769-775.
90. Kostopoulos K, Alhanatis E, Pampoukas K, Georgiopoulos G, Zourla A, Panoutsopoulos A, Kallianos A, Velentza L, Zarogoulidis P, Trakada G: **CPAP therapy induces favorable short-term changes in epicardial fat thickness and vascular and metabolic markers in apparently healthy subjects with obstructive sleep apnea-hypopnea syndrome (OSAHS)**. *Sleep & breathing = Schlaf & Atmung* 2016, **20**(2):483-493.
91. Paterniti S, Zureik M, Ducimetiere P, Touboul PJ, Feve JM, Alperovitch A: **Sustained anxiety and 4-year progression of carotid atherosclerosis**. *Arteriosclerosis, thrombosis, and vascular biology* 2001, **21**(1):136-141.
92. Elovainio M, Keltikangas-Jarvinen L, Kivimaki M, Pulkki L, Puttonen S, Heponiemi T, Juonala M, Viikari JS, Raitakari OT: **Depressive symptoms and carotid artery intima-media thickness in young adults: the Cardiovascular Risk in Young Finns Study**. *Psychosomatic medicine* 2005, **67**(4):561-567.
93. Ranjit N, Diez-Roux AV, Chambless L, Jacobs DR, Jr., Nieto FJ, Szklo M: **Socioeconomic differences in progression of carotid intima-media thickness in the Atherosclerosis Risk in Communities study**. *Arteriosclerosis, thrombosis, and vascular biology* 2006, **26**(2):411-416.
94. Garshick M, Wu F, Demmer R, Parvez F, Ahmed A, Eunus M, Hasan R, Nahar J, Shaheen I, Sarwar G *et al*: **The association between socioeconomic status and subclinical atherosclerosis in a rural Bangladesh population**. *Preventive medicine* 2017, **102**:6-11.
95. Ji R, Pan Y, Yan H, Zhang R, Liu G, Wang P, Wang Y, Li H, Zhao X, Wang Y: **Current smoking is associated with extracranial carotid atherosclerotic stenosis but not with intracranial large artery disease**. *BMC neurology* 2017, **17**(1).
96. West HW, Juonala M, Gall SL, Kahonen M, Laitinen T, Taittonen L, Viikari JS, Raitakari OT, Magnussen 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.
97. Kauhanen J, Kaplan GA, Goldberg DE, Salonen R, Salonen JT: **Pattern of alcohol drinking and progression of atherosclerosis**. *Arteriosclerosis, thrombosis, and vascular biology* 1999, **19**(12):3001-3006.
98. Suzuki S, Arima H, Miyazaki S, Fujiyoshi A, Kadota A, Takashima N, Hisamatsu T, Kadowaki S, Zaid M, Torii S *et al*: **Self-reported Sleep Duration and Subclinical Atherosclerosis in a General Population of Japanese Men**. *Journal of atherosclerosis and thrombosis* 2018, **25**(2):186-198.

## Tables

Table 1 General Characteristics of Studies Included in the Meta-analysis

| Risk Factors | Study | Recruitment Period | N(total) | Country | Ethnicity | Age | Sex(female%) | Outcome | Result (OR and 95%CI) |
|---|---|---|---|---|---|---|---|---|---|
| Hypertension | Woo,2017 | 2008-2012 | 3030 | Korea | Korean | 70 (50-100) | 56.30% | plaque* | OR 1.72 (1.21-2.45) |
| | Zhang,2016 | 1992 | 1257 | China | Chinese | 69.16 ± 8.10 | 56.20% | plaque* | OR 1.75 (1.18-2.60) |
| | Idei,2014 | 2007-2009 | 64 | Japan | Japanese | NA | 47.80% | plaque* | OR 3.26 (1.15-9.62) |
| | Hong,2013 | 2008 | 942 | China | Chinese | 46-75 | 67.20% | plaque* | OR 1.88 (1.15-3.07) |
| | Beaussier,2008 | NA | 92 | France | NA | 50-80 | 23.91% | plaque* | OR 6.90 (1.40-34.9) |
| | Empana,2007 | 1999-2001 | 5585 | France | French | 73.5 ± 4.9 | 38.00% | plaque* | OR 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* | OR 1.55 (1.12-2.15) |
| | Su,2001 | 1990 | 533 | Taiwan | Chinese | >35 | 57.20% | plaque* | OR 3.70 (1.80-7.90) |
| | Zhang,2016 | 1992 | 1257 | China | Chinese | 69.16 ± 8.10 | 56.20% | CIMT† | OR 1.58 (1.08-2.33) |
| | Hong,2013 | 2008 | 942 | China | Chinese | 46-75 | 67.20% | CIMT† | OR 2.33 (1.40-3.87) |
| | Su,2001 | 1990 | 533 | Taiwan | Chinese | >35 | 57.20% | CIMT† | OR 5.00 (3.00-8.40) |
| Diabetes mellitus | O'Flynn,2017 | 2010 | 50 | Ireland | NA | 59 ± 6 | 51.00% | plaque* | OR 0.93 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | (0.05-16.23) |
| | Woo,2017 | 2008-2012 | 3030 | Korea | Korean | 70 (50-100) | 56.30% | plaque* | OR 1.17 (0.81-1.69) |
| | Rubinat,2016 | NA | 374 | Spain | NA | 56.1 ± 10.8 | 59.90% | plaque* | OR 1.00 (0.60-1.65) |
| | Casalnuovo,2012 | 2011 | 6209 | Italy | NA | 54 ± 11 | 42.90% | plaque* | OR 1.51 (1.18-1.93) |
| | Empana,2007 | 1999-2001 | 5585 | France | French | 73.5 ± 4.9 | 38.00% | plaque* | OR 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* | OR 1.42 (0.81-2.48) |
| | Su,2001 | 1990 | 533 | Taiwan | Chinese | >35 | 57.20% | plaque* | OR 1.80 (0.70-4.90) |
| Hyperlipidemia | Woo,2017 | 2008-2012 | 3030 | Korea | Korean | 70 (50-100) | 56.30% | plaque* | OR 1.84 (1.30-2.62) |
| | Yuan,2014 | NA | 106 | China | Chinese | 58.1 ± 9.0 | 63.20% | plaque* | OR 2.41 (1.05-5.51) |
| Hypercholesterolemia | O'Flynn,2017 | 2010 | 50 | Ireland | NA | 59 ± 6 | 51.00% | plaque* | OR 0.70 (0.29-1.70) |
| | Rubinat,2016 | NA | 374 | Spain | NA | 56.1 ± 10.8 | 59.90% | plaque* | OR 1.47 (0.91-2.38) |
| | Su,2001 | 1990 | 533 | Taiwan | Chinese | >35 | 57.20% | plaque* | OR 1.10 (0.40-3.00) |
| Hypertriglyceridemia | Empana,2007 | 1999-2001 | 5585 | France | French | 73.5 ± 4.9 | 38.00% | plaque* | OR 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* | OR 1.28 (0.83-1.98) |
| Lower high density lipoprotein | Irie,2014 | 2007-2009 | 179 | Japan | Japanese | 65 ± 7 | 18.00% | plaque* | OR 2.30 (1.03-5.13) |
| | Empana,2007 | 1999-2001 | 5585 | France | French | 73.5 ± 4.9 | 38.00% | plaque* | OR 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* | OR 1.52 (1.01-2.28) |
| | Su,2001 | 1990 | 533 | Taiwan | Chinese | >35 | 57.20% | plaque* | OR 1.00 (0.50-1.90) |
| Higher low density lipoprotein | Sato,2013 | 2005-2012 | 236 | Japan | Japanese | 56 ± 13 | 34.30% | plaque* | OR 1.01 (0.74-1.37) |
| | Johnson,2010 | 2005-2007 | 1504 | America | 84% white, 14% black, 2% American | 45.0 (37.8–53.0) | 58.00% | plaque* | OR 1.11 (1.08-1.13) |
| | Su,2001 | 1990 | 533 | Taiwan | Chinese | >35 | 57.20% | plaque* | OR 0.60 (0.20-1.80) |
| Metabolic syndrome | Leng,2013 | 2007-2008 | 653 | Hong Kong | Chinese | 55.1 ± 10.4 | 52.80% | plaque* | OR 1.50 (0.92-2.46) |
| | Chen,2008 | 1990-1991 | 810 | Taiwan | Taiwanese | 66.1 ± 10.9 | 43.70% | plaque* | OR 1.37 (0.93-2.01) |
| | Empana,2007 | 1999-2001 | 5585 | France | French | 73.5 ± 4.9 | 38.00% | plaque* | OR 1.30 (1.09-1.55) |
| | Rundek,2007 | 2000 | 1895 | Northern | 25% were | 68.0 ± 9.7 | 59.00% | plaque* | OR 1.36 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Manhattan | black, 22% white, 51% Hispanic, and 1% of other ethnicity | | | | (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* | OR 1.07 (0.63-1.83) |
| | Ishizaka,2005 | 1994-2003 | 8144 | Japan | Japanese | 56.6 ± 10.5 | 32.80% | plaque* | OR 1.99 (1.39-2.85) |
| Smoking | O'Flynn,2017 | 2010 | 50 | Ireland | NA | 59 ± 6 | 51.00% | plaque* | OR 9.16 (0.39-217.16) ‡ |
| | Woo,2017 | 2008-2012 | 3030 | Korea | Korean | 70 (50-100) | 56.30% | plaque* | OR 1.46 (0.89-2.40) ‡ |
| | Yang,2015 | NA | 1746 | Northern Manhattan | 18% white, 63% Hispanic, 19% black. | 65.5 ± 8.9 | 60.00% | plaque* | OR 2.13 (1.27-3.57) ‡ |
| | Johnson,2010 | 2005-2007 | 1504 | America | 84% white, 14% black, 2% American | 45.0 (37.8–53.0) | 58.00% | plaque* | OR 1.14 (1.05-1.23) ‡ |
| | Liang,2009 | 1993-1994 | 1132 | China | Chinese | 35-64 | 66.10% | plaque* | OR 1.50 (1.00-2.10) ‡ |
| | Su,2001 | 1990 | 533 | Taiwan | Chinese | >35 | 57.20% | plaque* | OR 2.40 (1.00-5.60) ‡ |
| | Woo,2017 | 2008-2012 | 3030 | Korea | Korean | 70 (50-100) | 56.30% | plaque* | OR 1.08 (0.63-1.85) § |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 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

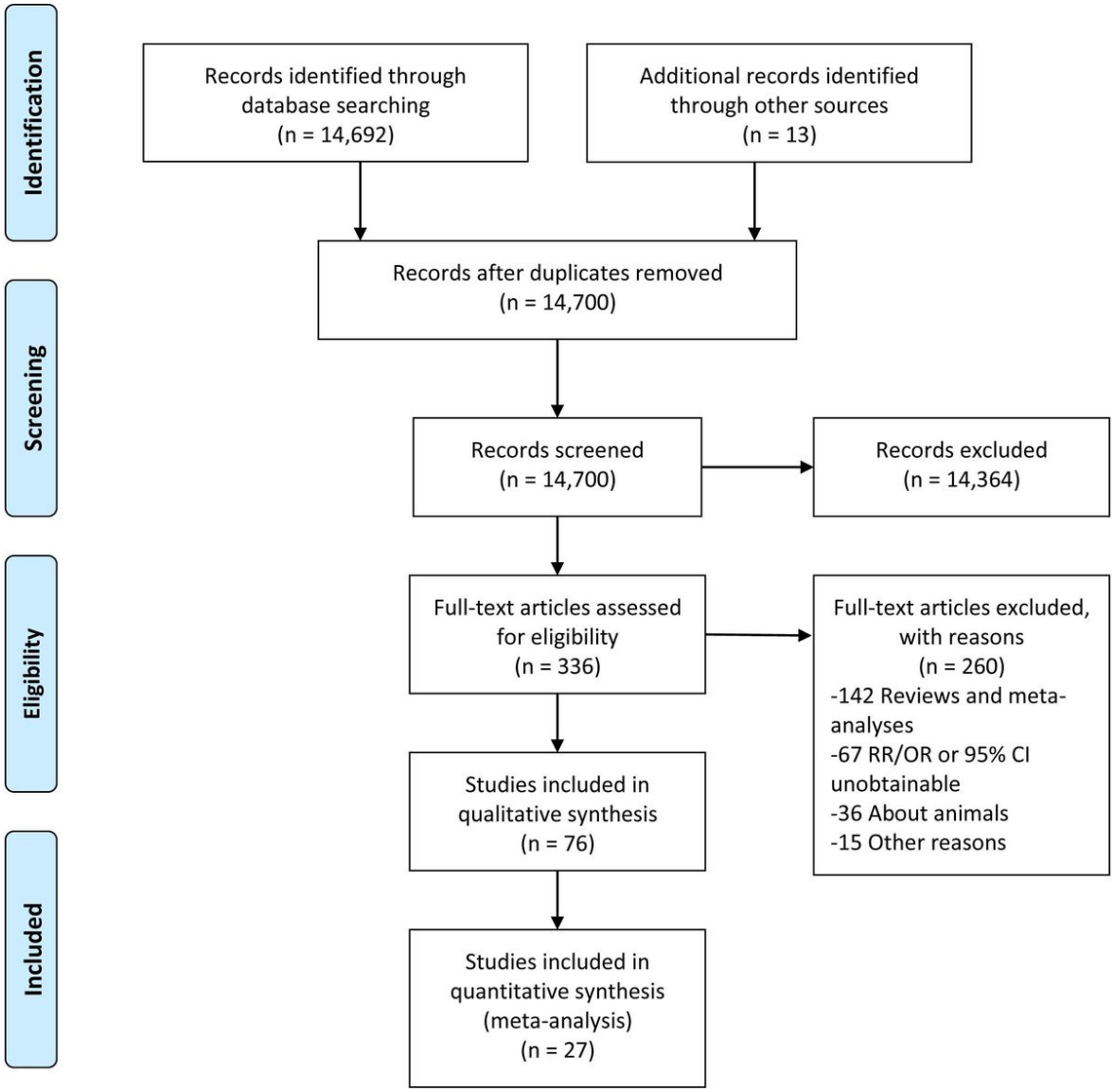


**Figure 1**

Flow chart of identified studies

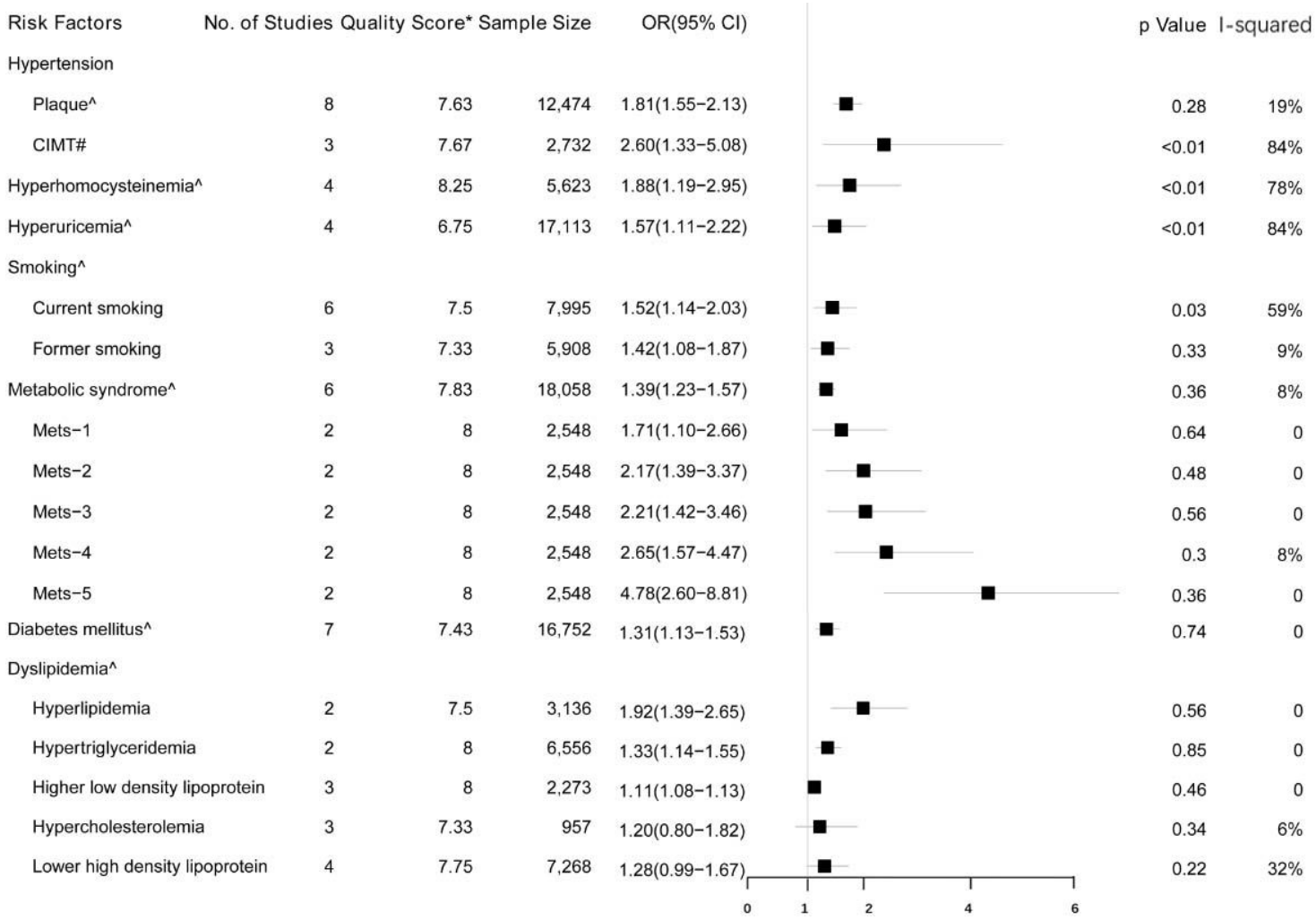


Figure 2

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

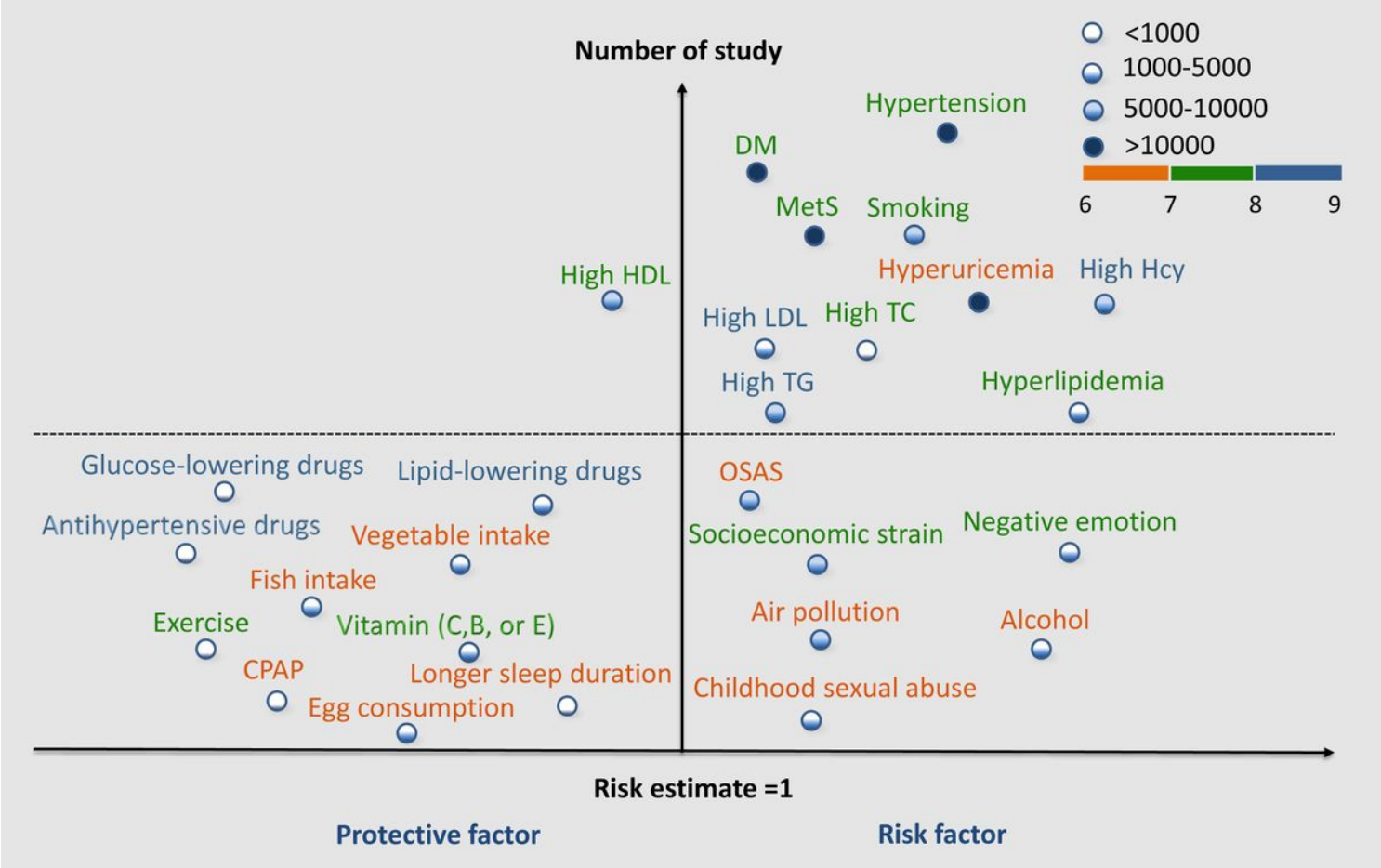


**Figure 3**

Factors showing significant positive and negative association with carotid atherosclerosis Abbreviations: 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 Table 1 General characteristics of studies included in the meta-analysis 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

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.pdf