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Risk factors for intracranial atherosclerosis: A systematic review and meta-analysis

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HIGHLIGHTS

- Seven factors suggested by meta-analyses were associated with the risk of Intracranial atherosclerosis (ICAS).
- Four well-established factors elevated risk of ICAS among community subjects and stroke patients.
- The discrepancies of well-established risk factors were observed in diverse ethnic origins.
- Further evidence is needed for less well-established factors revealed in the current review.

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ABSTRACT

Background and aims: Intracranial atherosclerosis (ICAS) is a predictable and preventable condition, but existing evidence concerning its risk factors has not been quantitatively assessed. The aim of this meta-analysis is to identify the non-modifiable and modifiable risk factors for ICAS.

Methods: PubMed and EMBASE were searched (1995–May 15, 2018) for cross-sectional and longitudinal studies exploring risk factors for ICAS. The risk estimates and 95% confidence intervals (CIs) in multivariate analysis were aggregated using random-effect models.

Results: Thirty-four studies comprising 59,736 subjects met the inclusion criteria for the systematic review involving thirty-one risk or protective factors. Seven factors were associated with ICAS, as suggested by the meta-analysis, including advanced age (odds ratio (OR) 1.05, 95% CI 1.03–1.08), metabolic syndrome (OR 2.13, 95% CI 1.35–3.37), diabetes mellitus (OR 1.98, 95% CI 1.69–2.31), hypertension (OR 1.97, 95% CI 1.69–2.31), dyslipidemia (OR 1.29, 95% CI 1.04–1.59), high levels of low-density lipoprotein cholesterol (OR 1.06, 95% CI 1.00–1.12) and high levels of apolipoprotein A1 (OR 0.34, 95% CI 0.15–0.75). The subgroup analysis for study populations indicated advanced age, metabolic syndrome, diabetes mellitus and hypertension as an elevated risk of ICAS among community subjects and stroke patients; according to the subgroup analysis for ethnicity, similar associations remained in Asians, but only metabolic syndrome and diabetes mellitus were correlated with ICAS in Caucasians.

Conclusions: Individuals with advanced age, metabolic syndrome, diabetes mellitus, hypertension and dyslipidemia might have a higher risk of ICAS, whereas high levels of apolipoprotein A1 might protect against ICAS.

1. Introduction

As one of the most common causes of ischemic stroke worldwide [1,2], intracranial atherosclerosis (ICAS) accounts for about 30–50% of ischemic stroke or transient ischemic attacks in Asia, 15–29% in Africa, and 5–10% in Europe or North America [3–5]. Twenty to 40 per 100,000 people worldwide are estimated to be prone to an ICAS related ischemic event [6]. The most common sites are basilar artery, followed

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by the internal carotid arteries, the middle cerebral arteries, the intracranial vertebral arteries, the posterior cerebral arteries, and the anterior cerebral arteries [3]. ICAS is usually referred to as asymptomatic and symptomatic atherosclerotic lesions [7], and the annual incidence of ipsilateral stroke for individuals with symptomatic ICAS is higher compared to the incidence in those with asymptomatic ICAS [2].

The high incidence, disability and mortality of ischemic stroke impose a heavy economic burden on society and families. Prevention and evaluation of ICAS is particularly important for the prevention and treatment of ischemic stroke, and given the high prevalence of ICAS and its poor clinical outcomes, identifying risk factors of ICAS is crucial to specify target populations. Due to the variety of risk profiles and uneven quality of studies, there is still a lack of systematic and reliable evidence of evidence-based medicine. An increasing number of studies on possible risk factors for ICAS, such as age, ethnicity, hypertension, diabetes mellitus, smoking status and dyslipidemia, yielded inconsistent conclusions for diverse study populations and different imaging modalities of intracranial arteries [7–9]. We assume there might be several factors associated only with ICAS or stroke although they could all be affected by similar factors. Thus, we performed this comprehensive systematic review and meta-analysis to summarize the non-modifiable and modifiable risk factors for ICAS identified in previous reports and suggest well-established and less well-established factors.

2. Materials and methods

2.1. Search strategy

We adhered to the meta-analysis of observational studies in epidemiology statement (MOOSE) and the preferred items for systematic reviews and meta-analyses (PRISMA) statement (Supplementary Table 1 for the MOOSE checklist) [10,11]. PubMed and EMBASE databases were searched for studies exploring risk factors for ICAS (1995–May 15, 2018), using terms including "intracranial asclero*", "intracranial arter*", "atherosclero*", "intracranial steno*", "intracranial occlus*", "intracranial large artery occlus*", "intracranial large artery steno*", "risk factor" and "protective factor". The language was limited to English. Additional pertinent studies were added by the search of reference lists for eligible studies, reviews and meta-analyses.

2.2. Selection criteria

Cross-sectional or longitudinal studies were included if they: (1) explored the associations of risk and/or protective factors for ICAS (ICAS was defined as varying degrees of luminal stenotic lesions involving intracranial arteries, which included anterior cerebral artery, middle cerebral artery, posterior cerebral artery, intracranial vertebral artery, basilar artery and intracranial carotid artery in the current meta-analysis); (2) used objective imaging methods to diagnose ICAS, such as transcranial doppler (TCD), computed tomography angiography (CTA), digital subtraction angiography (DSA), or magnetic resonance angiography (MRA); (3) selected individuals without ICAS (non-ICAS) rather than those with extracranial atherosclerosis (ECAS) as controls. We excluded review articles, editorials, commentaries, hypothesis papers, case reports, animal studies and meta-analyses.

2.3. Data extraction and quality assessment

The following study characteristics were extracted independently by two investigators using a standard form: name of the first author, year of publication, country, recruitment period, average age of subjects, proportion of males, sample size, study population (community-dwelling subjects or stroke patients), imaging modalities to diagnose ICAS, covariates in multivariate analysis, multivariable-adjusted estimates and 95% CIs (Supplementary Table 2). For studies without reported risk estimates (odds ratio (OR), relative risk (RR) or hazard ratio (HR)), raw data, if available, were used to calculate effect sizes. For sex-stratified studies, we extracted the two estimates separately. For studies from the same population and with the same recruitment period, the most comprehensive or the latest report was selected to avoid overlapping. The Newcastle Ottawa Scale (NOS) [12] was used to assess the quality of longitudinal studies and the Agency for Healthcare Research and Quality (AHRQ) [13] was used for cross-sectional studies (Supplementary Table 3). High quality studies on these two scales were defined respectively as scores of more than six or seven. All disagreements were resolved via discussion until a consensus was reached.

2.4. Statistical analyses

Quantitative data syntheses were conducted using a random-effects model due to significant heterogeneity in subject characteristics anticipated across studies [14]. Statistical heterogeneity across studies was detected using the Cochran's Q test and I^2 statistics [14]. Furthermore, subgroup analyses according to study populations and ethnicity, as well as meta-regression analyses, were performed to explore the source of heterogeneity. Each variable, including demographic factors (average age of subjects, proportion of males), year of publication, sample characteristics (sample size, study population and ethnicity), was analyzed independently for meta-regression if at least ten studies reported a certain factor for ICAS. Sensitivity analyses by removing a single study at the time were performed to examine the robustness of the pooled results. Publication bias was evaluated through Egger's test and adjusted by the trim and fill method (Supplementary Table 4) [15]. Studies without available data in quantitative synthesis or studies which are the only ones to report a given risk factor were included in the systematic review. All statistical tests used a significance level of $p < 0.05$. R 3.2.0 software was employed for all statistical analyses.

3. Results

3.1. Search results

A total of 45,360 titles and abstracts were initially screened (Fig. 1). After exclusion of duplicates and irrelevant studies, 131 studies were retained for full-text assessment. Of these potentially relevant studies, 34 met the inclusion criteria for the systematic review [4,16–48], among which 24 studies were for the meta-analysis [4,16–34,36,37,39,40].

3.2. Study characteristics

Two longitudinal [45,48] and 32 cross-sectional studies [4,16–44,46,47] with a total of 59,736 subjects met the inclusion criteria for the systematic review. Among them, 13 enrolled subjects from China [18,27,30–34,39,42–45,47], 11 from Korea [16,19,22–25,29,36–38,46], 2 from Japan [21,35], 3 from America [26,41,48], 2 from Spain [4,40], and one each from Pakistan [28], Norway [20] and multi-nation regions [17] (Supplementary Table 2). All studies eligible for meta-analysis were cross-sectional ones with 55,746 subjects. As for study populations, 20 studies recruited community-dwelling populations (without stroke) (44,613 subjects, 7477 with ICAS) [4,16,18,19,21,25–27,30,33,35,37–39,42–47], and 14 studies recruited stroke patients (10,612 subjects, 3655 with ICAS) [17,20,22–24,28,29,31,32,34,36,40,41,48]. As for the degree of stenosis evaluated by CTA or MRA, 14 studies established the definition of ICAS as ≥50% luminal stenosis [4,20,23–25,28,29,32,34,37,38,44,46,48], 6 studies defined potential atherosclerosis as any degree of stenotic lesion [22,26,31,36,40,43], 2 defined ICAS as ≥25% luminal stenosis [21,35] and one defined ICAS as ≥30% luminal stenosis [17]. Among them, 6 studies reported details about exclusion of subjects with non-atherosclerotic causes of intracranial stenosis [20,22,24,28,29,40], such as moyamoya disease or arterial dissection. The other 11 studies diagnosed ICAS according to the TCD criteria

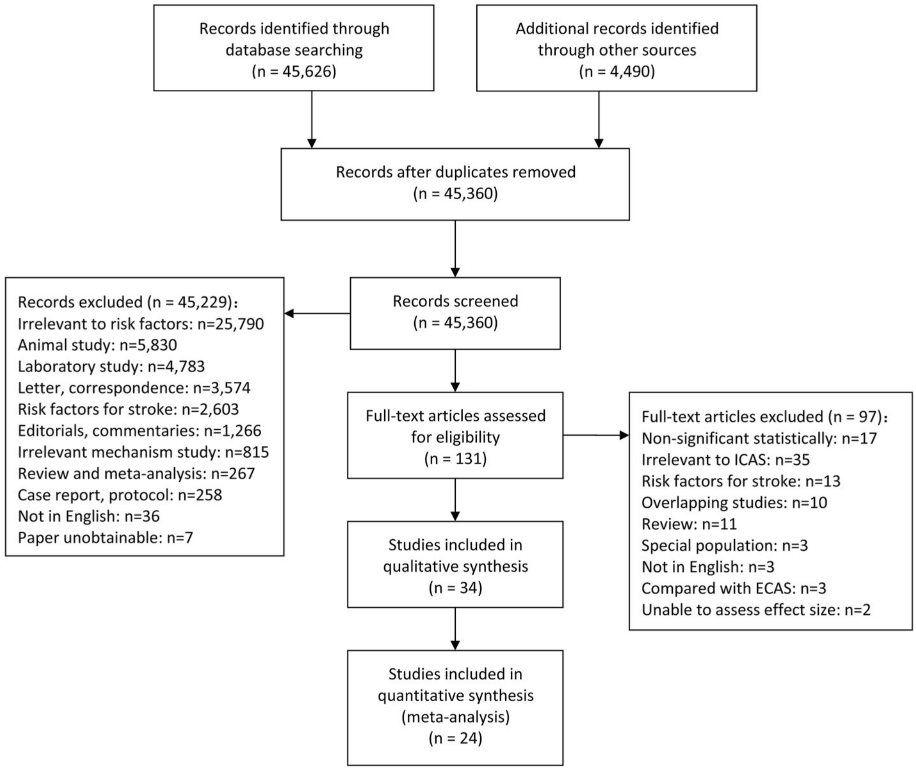

Fig. 1. Flow chart summarizing the literature review process.

[16,18,19,27,30,33,39,41,42,45,47]. The score of quality assessment ranged from 6 to 9 (median = 7) for cross-sectional studies and from 7 to 9 (median = 8) for longitudinal ones (Supplementary Table 3).

3.3. Non-modifiable risk factors for ICAS

3.3.1. Demographic factors

Advanced age (1–10 years greater) was associated with ICAS (OR = 1.05, 95% CI = 1.03–1.08, I^2 = 87%, p < 0.01) after pooling thirteen studies (Fig. 2) [4,16–27]. No significant difference was found for sex (OR = 0.96, 95% CI = 0.77–1.20, I^2 = 44%, p = 0.1) (Fig. 2) [4,16,17,20,22,23,30]. For the subgroup analysis of study populations, similar results were presented for advanced age in community subjects and stroke patients (OR = 1.06, 95% CI = 1.04–1.08, I^2 = 71%, p < 0.01; OR = 1.06, 95% CI = 1.01–1.11, I^2 = 92%, p < 0.01, respectively). Intriguingly, the aggregated estimates for community-dwelling subjects presented a negative association between male sex and ICAS (OR = 0.80, 95% CI = 0.67–0.96, I^2 = 0%, p = 0.91). Further subgroup analyses were conducted to evaluate the discrepancy in ethnicity. Age was associated with ICAS for Asians (nine studies) [16,18,19,21–25,27] but not for Caucasians (two studies) [4,20] and multiethnic populations (two studies) [17,26] (Supplementary Fig. 1). There was a negative association between male sex and ICAS for Asians (four studies) [16,22,23,30] but not for Caucasians (two studies) [4,20] and multiethnic populations (one study) [17](Supplementary Fig. 2).

Regarding ethnicity, the Atherosclerosis Risk in Communities study comprising 1765 subjects reported that non-whites were associated with the presence of ICAS compared with whites (OR = 1.46, 95%CI = 1.07–1.98) (Supplementary Table 5) [26]. A trend of high risk between non-whites and ICAS was found in the Northern Manhattan Stroke Study (OR = 4.4, 95%CI = 0.6–35) [41]. Further, Asian ethnicity independently increased atherosclerotic risk, as shown by a European study with 786 stroke subjects (OR = 2.68, 95%CI = 1.20–5.98) [17].

3.4. Modifiable risk factors for ICAS

3.4.1. Diabetes mellitus

The random-effect model showed that patients with DM had 1.98 times the odds of ICAS than those without (OR = 1.98, 95%CI = 1.69–2.31, I^2 = 40%, p = 0.07) (Fig. 2) [4,16–21,23,26,28–30]. Similar associations were observed in subgroup analyses according to ethnicity (Supplementary Fig. 4) and study populations (OR = 1.95, 95%CI = 1.53–2.50, I^2 = 60%, p = 0.01 for community-dwelling population; OR = 2.12, 95%CI = 1.74–2.58, I^2 = 0%, p = 0.98 for stroke patients).

3.4.2. Hypertension

With low-to-moderate heterogeneity (I^2 = 43%, p = 0.05) among twelve studies comprising 17,133 subjects, hypertension nearly doubled the risk of ICAS (OR = 1.97, 95%CI = 1.69–2.31) (Fig. 2) [4,16–21,23,25,28–30]. Further subgroup analysis provided similar estimates among different populations (OR = 1.94, 95%CI = 1.63–2.31, I^2 = 36%, p = 0.14 for community subjects; OR = 1.99, 95%CI = 1.40–2.82, I^2 = 59%, p = 0.04 for stroke patients). The subgroup analysis for ethnicity indicated that hypertension was associated with ICAS among Asians and multiethnic populations but not in Caucasians (OR = 1.52, 95%CI = 0.85–2.70) (Supplementary Fig. 5).

High systolic blood pressure (SBP) (every 10 mmHg increase) and pulse pressure (PP) (≥45 mmHg) raised the risk of ICAS in the general population [26,42,44]. Furthermore, high early morning SBP and inter-arm diastolic blood pressure (DBP) differences (≥4 mmHg) were revealed as risk factors of ICAS for hypertensive patients (Supplementary Table 5) [43].

3.4.3. Metabolic syndrome

Four studies including 6697 subjects evaluated the association between metabolic syndrome (Mets) and ICAS [4,23,24,27] with well-defined Mets according to the criteria of International Diabetes

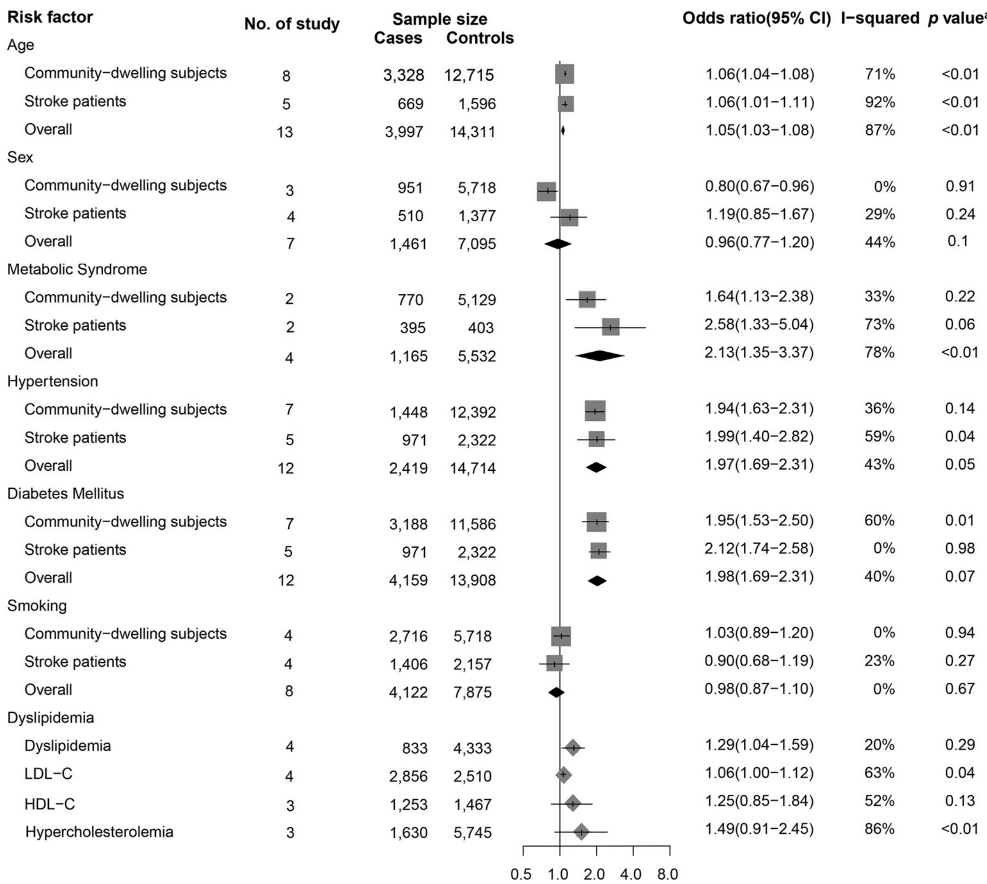

Fig. 2. Forest plot of the associations between factors and intracranial atherosclerosis (ICAS).
Advanced age, metabolic syndrome, diabetes mellitus, hypertension, dyslipidemia and high levels of LDL-C were identified as possible risk factors in the meta-analysis. [a] p values were for heterogeneity (I^2) in the meta-analysis. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Federation [49]. The random-effect model showed that patients with Mets had 2.13 times the odds of ICAS than those without (OR = 2.13, 95%CI = 1.35–3.37, I^2 = 78%, p < 0.01). Similar associations were observed in subgroup analyses for study population and ethnicity (Fig. 2 and Supplement Fig. 6). Notably, a dose–response relationship was noticed, in which ICAS risk increased with the increase in the number of Mets criteria (OR = 2.89, 95% CI = 2.10–3.98 for Mets-3; OR = 3.66, 95% CI = 1.85–7.26 for Mets-4; OR = 4.99, 95% CI = 2.63–9.44 for Mets-5) (Supplementary Fig. 7).

3.4.4. Dyslipidemia

In each included study, dyslipidemia was defined based on the levels of total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or a/no history of lipid-lowering medication. After pooling the results of four studies, we found a higher risk of ICAS among patients with dyslipidemia in the overall analysis (OR = 1.29, 95% CI = 1.04–1.59, I^2 = 20%, p = 0.29) (Fig. 2) [4,16,21,28] and a trend of high ICAS risk was observed in subgroup analyses for study populations and ethnicity (Supplementary Figs. 8 and 9). Higher levels of low-density lipoprotein cholesterol (LDL-C) were associated with the presence of ICAS in the overall analysis (OR = 1.06, 95% CI = 1.00–1.12; I^2 = 63%, p = 0.04) [17,25,26,32] and the subgroup analysis of community-dwelling subjects (Supplementary Fig. 10). Moreover, no significant association with low levels of high-density lipoprotein cholesterol (HDL-C) (OR = 1.25, 95% CI = 0.85–1.84; I^2 = 52%, p = 0.13) [22,32,46] or hypercholesterolemia (OR = 1.49, 95% CI = 0.91–2.45; I^2 = 86%, p < 0.01) [22,32,33] was found (Fig. 2 and Supplementary Fig. 11). No correlation of ICAS with normal levels of HDL-C was found in the Asymptomatic Polyvascular Abnormalities Community study comprising 5351 subjects [47], whereas our meta-analysis found high levels of apolipoprotein A1 (apo A1) was negatively associated with the risk of ICAS (OR = 0.34, 95% CI = 0.15–0.75) (Supplementary Fig. 11) [22,34].

High levels of lipoprotein (a) (Lp(a)) (OR = 2.52, 95% CI = 1.03–6.18) and apolipoprotein B (apo B) (OR = 6.41, 95% CI = 2.82–14.49) were also identified as two potential risk factors for ICAS (Supplementary Table 5) [29,34,40]. Interestingly, the high apo B/apo A1 ratio predicted ICAS risk among stroke patients in Asia (OR = 2.13, 95%CI = 1.05–4.33), and a dose–response relationship was noted between ICAS and the apo B/apo A1 ratio [23]. Furthermore, findings of the cohort study with a two-year follow-up suggested non-HDL-C as an independent risk factor for ICAS (HR = 1.22; 95%CI = 1.06–1.40) [45].

3.4.5. Lifestyles and comorbidity

Eight studies comprising 13,762 patients were included for the association between smoking and ICAS. No significant relationship of smoking (OR = 0.98, 95% CI = 0.87–1.10, I^2 = 0%, p = 0.67) with ICAS was revealed among different study populations (Fig. 2) [4,16,20,22,23,26,30,31]. Similar associations were observed in the subgroup analysis for smoking statuses (OR = 0.98, 95% CI = 0.78–1.22 for former smoker; OR = 0.98, 95% CI = 0.86–1.12 for current smoker) and ethnicity (Supplementary Figs. 12–13).

Furthermore, the meta-analysis of included studies indicated that high body mass index (BMI) (OR = 0.90, 95%CI = 0.76–1.06, I^2 = 44%, p = 0.13) [19,26,39] and coronary artery disease (CAD) (OR = 1.22, 95% CI = 0.48–3.10, I^2 = 73%, p = 0.03) [20,23,26] had no significant association with ICAS (Supplementary Fig. 3 and Table 5), whereas patients with obstructive sleep apnea (OSA) tended to have ICAS lesions (OR = 4.17, 95%CI = 1.40–12.40) [38].

As for socioeconomic and psychosocial factors, high monthly income (OR = 1.59, 95%CI = 1.01–2.51), employment (OR = 2.15, 95%CI = 1.21–3.83) and chronic stress (OR = 3.67, 95%CI = 2.13–6.34) were potential predictors of the presence of ICAS, but education attainment had no obvious association with ICAS (OR = 0.76, 95%CI = 0.49–1.18) (Supplementary Table 5) [28].

3.4.6. Blood biomarkers

Biomarkers were identified as important predictors of cerebral vascular disease in previous studies. The current meta-analysis found high homocysteine had no significant association with ICAS (OR = 1.17, 95% CI = 0.76–1.79, $I^2 = 74\%$, $p = 0.02$) (Supplementary Fig. 3 and Table 5) [30,36,37].High levels of high-sensitivity *C*-reactive protein and erythrocyte sedimentation rate were reported by other researches to increase ICAS risk even after adjustment for potential confounders [17,39]. In particular, increased levels of circulating interleukin-6 (IL-6) were reported to be significantly associated with ICAS in a cross-sectional study in Japan [35]. Besides, high serum calcium concentration corrected for serum albumin concentration was positively associated with ICAS (OR = 3.70, 95% CI = 1.50–9.01) [46].

3.4.7. Sensitivity and meta-regression analyses

Sources of evident heterogeneity among studies were explored in sensitivity analyses for potential factors with the number of studies ≥ 3 (Supplementary Table 6). As for age, the pooled effect did not vary substantially after excluding any single study. However, as for sex, dyslipidemia, levels of LDL-C, hypercholesterolemia, CAD and high homocysteine, the associations between each one of these factors and the presence of ICAS might have been driven by a single study, which needs further investigations. Meta-regressions were undertaken to investigate such variables as demographic factors (average age of subjects, proportion of males), year of publication and sample characteristics (sample size, study population and ethnicity). The year of publication was a significant moderator to explain 64.71% of heterogeneity ($p = 0.041$) in the meta-analysis of the association between hypertension and ICAS. The pooled results for other risk factors assessed by more than nine studies were not influenced by any variable analyzed in meta-regression.

3.4.8. Publication bias

For studies reporting the association between DM and the presence of ICAS, there was evident publication bias suggested by Egger's test ($p = 0.03348$) (Supplementary Table 4). The summary estimates were barely altered (OR = 1.77, 95% CI = 1.51–2.09) after adjusted for publication bias by the trim and fill method (Supplementary Fig. 14). No publication bias was found for other risk factors.

4. Discussion

This systematic review and meta-analysis suggested the role of thirty-one potential factors, categorized as non-modifiable and modifiable risk factors, in specifying high-risk population for ICAS (Fig. 3). Four well-established factors above the dotted line in Fig. 3, including advanced age, metabolic syndrome, diabetes mellitus and hypertension, were underscored from quantitative analyses with large sample sizes (> 3000 subjects), moderate to high quality scores and stable methodological evidence, which would facilitate decision-making in primary and secondary prevention of ICAS. Four less-well-established factors, including sex, dyslipidemia, LDL-C level and apo A1 level, were identified from the quantitative analyses of relevant inconsistent risk estimates, which suggests further large-scale, prospective research would be necessary to clarify the effects of those factors.

4.1. Non-modifiable risk factors

Older individuals were prone to ICAS lesions, which might be explained by the decreasing activity of antioxidant enzymes in intracranial arteries [17]. This positive correlation was found in the subgroup analysis for study populations and the one for Asian ethnicity. As for Caucasians and multiethnic populations, we failed to find similar correlations due to the small number of studies. Large and prospective cross-sectional or longitudinal studies are warranted to confirm our conclusions in the future.

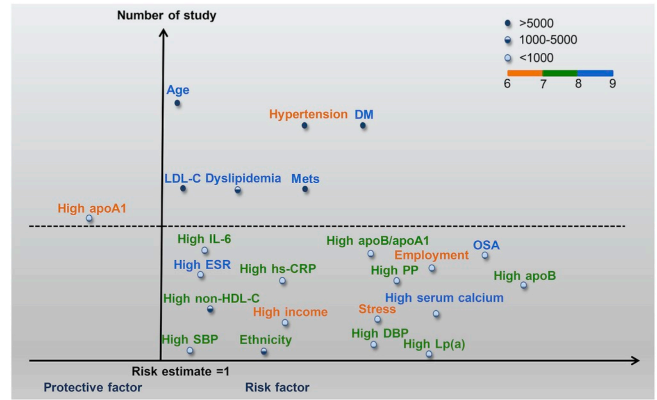

Fig. 3. Potential non-modifiable and modifiable risk or protective factors for intracranial atherosclerosis (ICAS).
Factors above or below the dotted line are assessed by quantitative or qualitative analyses, respectively. Different colors represent different quality assessment scores. The circles below the factors with different filled ratios represent total sample sizes of pooled studies. ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; DBP, diastolic blood pressure; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity *C*-reactive protein; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Mets, metabolic syndrome; OSA, obstructive sleep apnea; PP, pulse pressure; SBP, systolic blood pressure. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

A recent meta-analysis of fifteen studies comprising 2661 patients with ICAS and 1126 patients with ECAS indicated that females were prone to suffer more from ICAS than from ECAS in Asian population [50]. There was no obvious association between sex and ICAS in the current overall meta-analysis. However, our sensitivity analyses indicated male sex might decrease the risk of ICAS after omitting one study (6 scores in quality assessment) in multiethnic populations, which revealed male sex was an independent risk factor with heterogeneity reduced from 44% to 0% [17]. A variation of ethnic origin might account for the discrepancy in this literature, which was supported by the evidence of a similar protective correlation for Asians in the subgroup analysis.

4.2. Modifiable risk factors

The detrimental effects of Mets, DM and hypertension on progression and recurrence of stroke have been confirmed in previous studies. Our meta-analysis suggested a similar association with ICAS. Oxidative stress might accelerate the atherosclerotic process in Mets patients with reduced antioxidants; hemodynamic instability might affect the circulating components in different vascular beds [51]. A meta-analysis including fifteen studies, as mentioned before, also revealed that Mets was more correlated with ICAS than with ECAS in Asian populations. However, further large and comprehensive epidemiology explorations focused on the identification of risk factors more specific to ICAS are needed for designation of preventive strategies different from that of ECAS. Recently, a nested case-control study comprising 1205 subjects showed that patients with DM had nearly 10 times the odds of symptomatic ICAS [48]. Patients with diabetes mellitus had a higher number of atherosclerotic vessels than non-diabetic subjects, and the decrease of fibrinolytic activity related to insulin resistance may be especially relevant to the accelerated formation of atherosclerotic stenosis [40]. For the population with hypertension, factors implicated in the process of ICAS include degraded buffering capacity of arterial wall, aggregated platelet, and elevated activity of sympathetic and renin–angiotensin–aldosterone systems, which confirms the significant risk characteristics of blood pressure indexes [44]. As Mets, DM and hypertension could be managed through routine monitoring, diet modification and medication treatment, defining a role for these factors involved in the modulation of the risk of ICAS would have important practical implications.

4.3. Strengths and implications

In this study, we summarized quantitative and qualitative associations between potential risk or protective factors for the presence of ICAS in community-dwelling subjects and in stroke patients, through a comprehensive review of the existing literature on cross-sectional and longitudinal studies with objective methods to diagnose ICAS. Preventive medicine has been developed into the mainstream of acute and chronic diseases. The prevention of ischemic stroke is not only limited to the regulation of known risk factors, great importance of it has been attached to the prevention of ICAS. The purpose of this study is to achieve super-early prevention of stroke through management of modifiable factors and individual risk stratification by non-modifiable factors of ICAS. Several well-established risk/protective factors were identified as expected. More importantly, the current review reveals quite a few less well-established factors that might be associated with ICAS; further efforts are warranted to verify the associations between these factors and ICAS and the underlying mechanisms for such links, so that the current prevention strategy could be improved or new strategies could be developed to halt or even reverse the process of intracranial atherosclerosis and reduce the risk of subsequent stroke.

4.4. Limitations

Several limitations exist. First, some relevant studies might have been omitted due to the language restriction to English. Although further publication bias was just observed in the meta-analysis for studies exploring the association between DM and the presence of ICAS, the adjusted result by trim and fill method was barely altered. Second, the limitation that most studies were cross-sectional made us hardly to establish a specific causal association between predictors and ICAS lesions. What is more, we failed to identify risk factors for the progression of ICAS for the lack of enough prospective studies. Third, substantial heterogeneity was observed in the meta-analysis due to the differences in population characteristics and diagnostic imaging modalities. Therefore, the random-effects model and subgroup analyses were selected to explore relevant moderators. Fourth, compared to numerous data from Asian populations with extensive and repeated utility of imaging modalities, inconsistent conclusions from insufficient evidence among Caucasians might affect the identification of statistically significant correlations, such as those of advanced age and hypertension with ICAS, which should be interpreted with caution. Large, prospective, and population-based studies stratified by ethnic origins are necessary to confirm these results. Finally, the designation of ICAS as intracranial stenosis in several included studies limits our assessments of potential surrogate factors for non-stenotic lesions with respect to the characterization of ICAS. Therefore, the use of a precise terminology and a specific classification of ICAS in subsequent research and clinical trials will refine the prevention strategies for this disease.

4.5. Conclusion

The present study summarized the non-modifiable and modifiable risk factors for ICAS. Advanced age, metabolic syndrome, diabetes mellitus, hypertension and dyslipidemia were probable risk factors, whereas high levels of apoA1 might render protection against ICAS. The current review also revealed several less well-established factors that might be associated with ICAS, which warrants further research into the associations and the underlying mechanisms for the links. Further relevant research will help establish more effective prevention strategy for intracranial atherosclerosis and subsequent stroke.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributors

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.12.015.

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