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Relationship between methylenetetrahydrofolate reductase (MTHFR) gene (A1298C) polymorphism with the risk of stroke: A systematic review and meta-analysis

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ABSTRACT

Studies on relationship between methylenetetrahydrofolate reductase gene (MTHFR) gene A1298C polymorphism with the risk of ischemic as well as hemorrhagic stroke have shown discordant results. Present meta-analysis was aimed to clarify the relationship between MTHFR gene A1298C polymorphism with risk of stroke. A comprehensive literature search for all published articles was performed in electronic database including PubMed, EMbase, Cochrane Library, Trip Databases, Worldwide Science, CINAHL, and Google Scholar up to 31st December 2019. Pooled odds ratio (ORs) with 95% confidence interval (CIs) under dominant, recessive, and allelic models was calculated. Sensitivity analysis was also performed to detect the heterogeneity. In our meta-analysis, a total of 20 studies with 19 case control studies involving 2871 ischemic stroke (IS) cases and 3984 controls and 3 studies with 201 hemorrhagic stroke cases and 1349 controls were included. Our findings suggest that there was a significant relationship between MTHFR gene A1298C gene polymorphism with risk of ischemic stroke (dominant model: OR = 1.32, 95% CI = 1.06–1.66, recessive model: OR = 1.45, 95% CI = 1.06–1.99 and allelic model: OR = 1.35, 95% CI = 1.00–1.84, respectively). However, no significant relationship between MTHFR gene A1298C gene polymorphism with the risk of hemorrhagic stroke. Findings of this meta-analysis concludes that MTHFR gene A1298 C polymorphism could be capable of increasing stroke susceptibility in Asian, but not in Caucasian population. Genotyping of MTHFR gene A1298C polymorphism may be used as a predictor for the occurrence of ischemic stroke.

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KEYWORDS
Methylenetetrahydrofolate reductase; gene polymorphism; stroke; ischemic stroke; hemorrhagic stroke; meta-analysis

Introduction

Stroke is one of the most complex diseases with diverse etiologies and second leading cause of death worldwide and most common cause of long term disability [1]. Almost 80% of stroke are ischemic and 15–20% are hemorrhagic in origin [2,3]. Genetic and environmental factors are known to play a crucial role in the pathogenesis of stroke [4]. Currently, numerous candidate genes have been linked to stroke as evident from genome wide association studies, but the contribution of these susceptible genes to stroke still remains unclear.

Homocysteine (Hcy) is a sulphur containing amino acid formed during the metabolism of the essential amino acid methionine (Met) to cysteine (cys) [5,6]. Elevated circulatory levels of Hcy has been recognised as an independent risk factor for cerebral, coronary, and peripheral artherosclerosis [7,8]. Hcy levels can be increased by defective metabolism of Met, resulting either from the deficiencies of certain vitamin cofactors or mutations in genes encoding for Met [9,10]. Methylenetetrahydrofolate reductase (MTHFR) gene located on chromosome 1p36.3 in humans encodes for MTHFR enzyme which plays a crucial role in regulating intracellular Hcy and folate metabolism by catalyzing the transformation of 5,10-methylentetrahydrofolate to 5-methyltetrahydrofolate, which serves as the methyl group donor for converting homocysteine into methionine [11,12].

The two most commonly investigated MTHFR gene polymorphisms include C677 T (rs1801133) and A1298 C (rs1801131). C677 T polymorphism leads to the replacement at codon 222 for alanine to valine, causing increased thermolability and reduced activity of enzyme MTHFR and, subsequently, an elevated plasma level of Hcy. On the other hand, A1298 C polymorphism leads to the replacement of glutamate by an alanine residue in exon 7 and is also reported to hold relatively higher MTHFR activity than C677 T polymorphism [13,14]. Results from published genetic-association studies for A1298 C polymorphism have been contradictory rather than conclusive. Some reported a significant impact of A1298 C polymorphism on stroke risk [15, 16] while some failed to replicate these findings. Current meta-analysis was therefore designed to clarify the relationship between the MTHFR A1298 C gene polymorphism in adult as

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well as pediatric stroke and also based on ethnicity distribution by estimating pooled analysis of the published association studies.

Methods

Literature search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines [15]. Relevant publications (until 31 December 2019) were identified by searching in electronic databases including PubMed, EMbase, Cochrane Library, Trip Databases, Worldwide Science, CINAHL, and Google Scholar. Following key terms were used: 'methylenetetrahydrofolate reductase' OR 'MTHFR' AND 'polymorphism' OR 'variant' OR 'mutation' OR 'genotype' OR 'A1298 C' AND 'stroke' OR 'ischemic stroke' OR 'Cerebral Infarction' OR 'Brain Infarction' OR 'Intracerebral hemorrhage' OR Hemorrhagic Stroke' OR 'Cerebrovascular Disease' OR 'Cerebrovascular Disorder' OR 'Cerebral Ischemia', Child OR Paediatric OR Pediatric OR Adult OR Adolescent. Additionally, the reference list of retrieved studies, review articles and previous meta-analyses, were manually searched for collecting more relevant studies often missed while performing the electronic search.

Eligibility criteria

Studies were included if they met the following criteria: **Inclusion Criteria**: (1) case-control studies investigating the relationship of MTHFR A1298 C gene polymorphism with the risk of stroke; (2) clinically confirmed diagnosis of stroke (ischemic or hemorrhagic) using CT or MRI scan; (3) patients aged <18 years for pediatric and >18 years for adult population; (4) studies with sufficient available data to calculate ORs with corresponding 95% CIs. **Exclusion Criteria** were: (1) not a case–control study; (2) duplicate publications with overlapping subjects from the same study; and (3) no available data reported.

Data Extraction

Two investigators independently extracted the data. Following data were extracted from each study: first author's name, published year, ethnicity, country, number of cases and controls, matching criteria, sample source, duration of inclusion, mean age, genotyping method, and frequency distribution of A1298 C genotype. Hardy-Weinberg Equilibrium (HWE) were calculated for allelic frequency distribution. Ethnicities were categorized as Asian and Caucasian and population were categorized into adult and pediatric groups.

Quality assessment

Newcastle – Ottawa Scale (NOS) [16] was used for assessing the quality of the included studies based on three components: selection, comparability and ascertainment of outcome. Scores were ranged from 01 to 09. Two authors independently assessed the quality of included studies. Discrepancies over quality scores were resolved by discussion among all the authors and subsequent consensus was reached.

Statistical analysis

Odds ratio (ORs) with 95% Confidence Intervals (CIs) were calculated to investigate the relationship between A1298 C gene polymorphism and risk of stroke using fixed (Mantel-Haenszel method) or random effects (Dersimonian and Laird method) models [17,18]. Heterogeneity between study was compared by using Cochran's Q statistic and I^2 metric [19,20]. I^2 metric was used to describe degree of heterogeneity between included studies, where 0–25% indicated no observed heterogeneity and larger values showed increasing heterogeneity, with 25–50% regarded as low, 50–75% as moderate and 75–100% as high. Heterogeneity between studies was adjusted by subgroup analysis, HWE status and meta-regression by quality score of the included studies.

One way sensitivity analyses were performed to assess the stability of results, namely a single study in the meta-analysis was deleted each time to reflect the influence of the individual dataset on the pooled OR. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias [21,22]. Presence of selection bias in control participants was evaluated by calculating HWE and genotypic frequencies of the control subjects were compared by using chi-square test. Stratified analysis based on ethnicity (Asian vs. Caucasian) and population type (Adult vs. Pediatrics) were performed. To ensure reliability and accuracy of the results, two investigators entered data into the software and reached a consensus. All statistical analyses were performed using STATA 13.0 and Review Manager 5.3 softwares. All the P values were two-sided, and a p value <0.05 was considered to be statistically significant.

Results

Literature search

The initial search yielded 53 records from PubMed, Embase, Scopus, Web of Science CENTRAL (Cochrane Central Register of Controlled Trials) and Google scholar databases. Of them, 27 were excluded after the review of title/abstract, leaving 26 potential studies for full-text information review. Finally, 20 studies met the inclusion criteria and were included in this study (Figure 1).

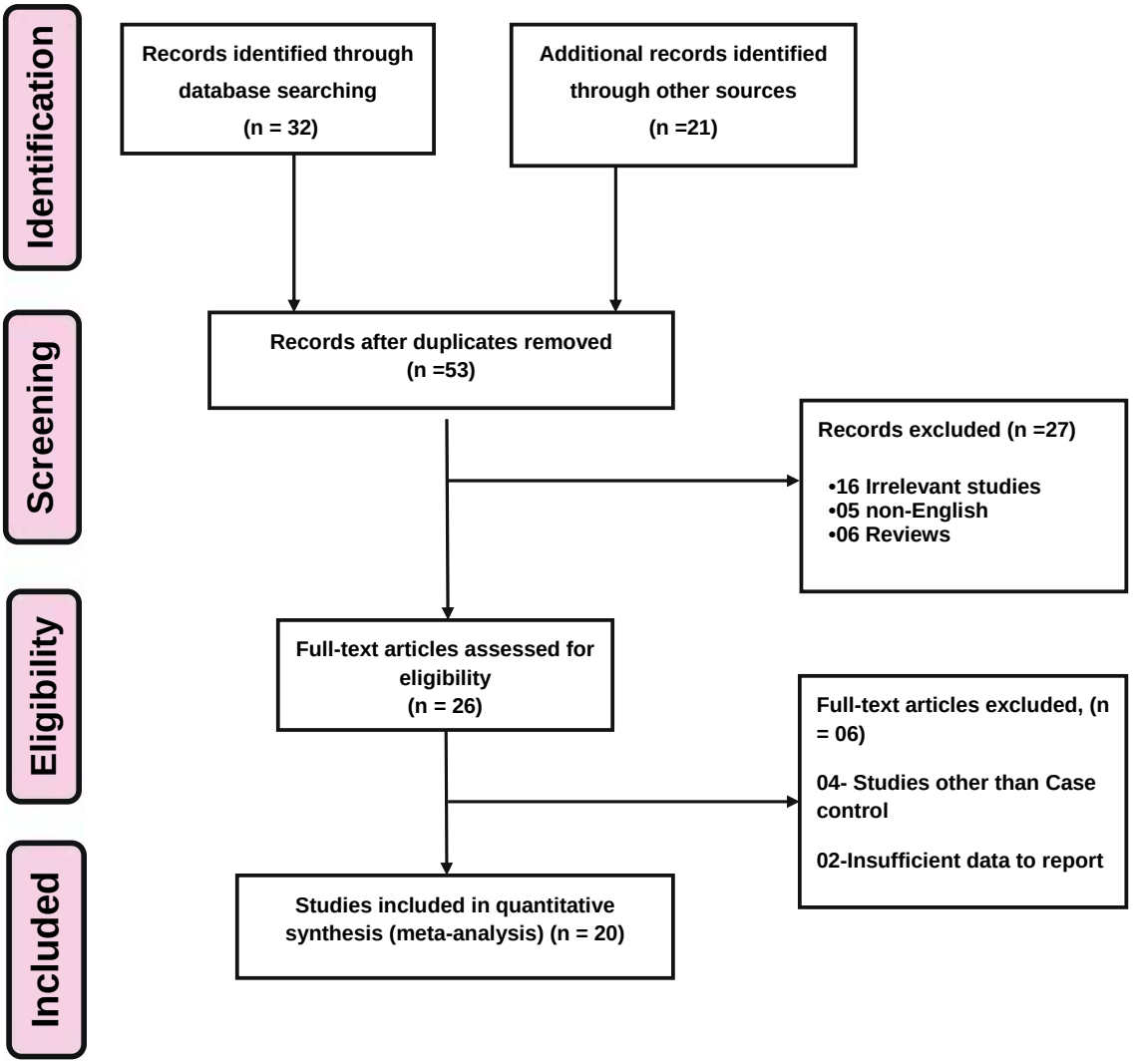

Figure 1. Flow diagram for the selection of studies and specific reasons for exclusion from the present meta-analysis.

Characteristics of eligible studies

The main characteristics of included studies are presented in Table 1. The publication years of the studies included in our analysis ranged from 1998 to 2019. The sample size in each study ranged from 8 to 778. Twenty case-control studies (19 for IS and 3 studies for HS) were included in our meta-analysis. Studies were carried out in two major ethnic populations; 06 studies were in Asian while 14 studies were in Caucasian population. All studies in this meta-analysis had controls in HWE. The quality scores of all included studies were moderately high. Out of 20 studies, 17 studies had hospital based, 03 studies had population-based source of controls. Table 1 gives a summary of the characteristics and methodological quality of all the included studies. In our meta-analysis, a total of 20 studies with 19 case-control studies involving 2700 ischemic stroke (IS) cases and 3661 controls and 3 studies with 201 hemorrhagic stroke (HS) cases and 1349 controls were included.

Relationship between MTHFR A1298 C gene polymorphism and ischemic stroke risk

A significant relationship between MTHFR A1298 C gene polymorphism and risk of IS was observed under dominant model [OR = 1.32, 95% CI = 1.06–1.66]; recessive model [OR = 1.45, 95% CI = 1.06–1.99] and allelic model [OR = 1.35, 95% CI = 1.00–1.84], respectively (Figure 2(a-f)). Upon conducting the subgroup analysis based on ethnicity of study population, significant association was observed based in Asian population under dominant model [OR = 1.77, 95% CI = 1.23–2.55]; recessive model [OR = 1.87, 95% CI = 1.42–2.46]; and allelic model [OR = 1.59, 95% CI = 1.21–2.09]. In Caucasian population, significant association under allelic model [OR = 1.49, 95% CI = 1.41–1.94] was observed but no significant association was observed under dominant [OR = 1.17, 95% CI = 0.91–1.51] as well as recessive model [OR = 1.31, 95% CI = 0.83–2.07], respectively.

Further subgroup analysis based on the population group (Adult vs. Pediatrics), observed overall significant

Table 1. Characteristic of the included studies in the meta-analysis for the relationship between MTHFR gene A1298 C polymorphism with the risk of stroke.

S. no.	Author	Year	Origin	Ethnicity	Population	Study Period	Stroke types	Sample Size Case/ Control	MTHFR SNP Investigated	Genotyping Method	Matching criteria	M/F Case/ Control	Age (Mean ± SD) Case	Age (Mean ± SD) Control	HWE	Source of control	Quality score
1	Seyed Mehdi Hashemi [26]	2019	Iran	Asian	Adults	May 2016- Sept 2017	IS	106/ 157	C677 T A1298 C C2572A C4869 G	PCR-RFLP	Age-Sex	42/64 69/88	36.9 ± 10.3	37.2 ± 10.8	Yes	HB	7
2	Omar Abidi [27]	2018	Morocco	Caucasian	Adults	July 2010 – Oct 2012	HS	113/ 323	C677 T A1298 C	PCR-RFLP	Age-Sex	67/46 135/188	43.3 ± 15.2	54.5 ± 8.8	Yes	HB	7
3	De sire´e Coen Herak[28]	2017	Croatia	Caucasian	Children	Feb1998 -Sept 2010	IS	73/100	C677 T A1298 C	Mutiplex PCR	Age-Sex	20/15 28/10	6.5	6.5	Yes	HB	6
4	Anna Balcerzyk [29]	2015	Poland	Caucasian	Children	NA	IS	88/111	C677 T A1298 C	PCR-RFLP	Age-Sex	129/112 116/83	8.8 ± 5.6	8.8 ± 5.6	Yes	HB	5
5	Q.-Q. Lv[30]	2015	China	Asian	Adults	June 2011 -June 2012	IS	199/ 241	C677 T A1298 C	Taqman Sequencing	Age-Sex	129/112 116/83	68.78 ± 10.63	67.19 ± 9.49	Yes	PB	6
6	Bao-Sheng Zhou[31]	2014	China	Asian	Adults	June 2011- June 2013	IS	543/ 655	C677 T A1298 C C2572A C4869 G	Taqman Sequencing	Age-Sex	346/197 402/253	66 (61–70)	66 (60–70)	Yes	HB	5
7	Fekih-Mrissa [32]	2013	Tunisia	Caucasian	Adults	NA	IS	84/100	C677 T A1298 C	DNA STRIP technology	Age-Sex	55/29 66/34	56.0 ± 12.5	50.5 ± 12.8	Yes	HB	5
8	Hultdin J[33]	2011	Sweden	Caucasian	Adults	1986–1999	IS & HS	321/ 778 60/ 778	C677 T A1298 C	PCR-RFLP	Age-Sex	179/142 43/17 456/322	55.0 ± 8.0 54.8 ± 8.2	55.0 ± 8.1	Yes	HB	6
9	Arsene D[34]	2011	Romania	Caucasian	Adult	NA	IS	67/60	C677 T A1298 C	DNA STRIP technology	Age-Sex	NA	68.73 ± 11.57	71.26 ± 10.94	Yes	HB	4
10	Almawi WY [35]	2009	Bahrain	Caucasian	NA	NA	NA	118/ 120	C677 T A1298 C	PCR-RFLP	Age-Sex	NA	NA	NA	Yes	HB	4
11	Sawula W[36]	2009	Poland	Caucasian	Adults	NA	IS	131/64	C677 T A1298 C	PCR-RFLP	Age-Sex	NA	NA	NA	Yes	HB	4
12	Morita DC[37]	2009	America	Caucasian	Children	Jan 2003- Dec 2006	IS & HS	15/90 8/90	C677 T A1298 C	NA	NA	NA	NA	NA	Yes	HB	4
13	Biswas a[38]	2009	India	Asian	Children	Dec2003 to Mar 2007	IS	58/58	C677 T A1298 C	Allele-specific PCRs & PCR-RFLP	Age-Sex	NA	NA	NA	Yes	HB	4
14	Sirachainan N [39]	2008	Thailand	Asian	Children	NA	IS	51/169	C677 T A1298 C	PCR-RFLP	Age-Sex	28/23 91/78	9.0 ± 5.5	9.3 ± 5.7	Yes	HB	5
15	Dikmen[40]	2006	Turkey	Caucasian	Adults	NA	IS	203/55	C677 T A1298 C	PCR-RFLP	NA	110/93 16/39	63.4 ± 0.87,	56.8 ± 1.18	Yes	HB	5
16	Komitopoulou a[41]	2006	Greece	Caucasian	Neonates	NA	IS	90/103	C677 T A1298 C	Mutiplex PCR	NA	NA	2026 ± 174 4 days	1422 ± 1467 days	Yes	HB	4
17	Sazci a[42]	2006	Turkey	Caucasian	Adults	Mar 2001 – Mar 2003	IS HS	120/ 259	C677 T A1298 C	PCR-RFLP	Age-Sex	67/53 114/155	53.45 ± 9.21	56.70 ± 15.38	Yes	HB	6
18	Linnebank M [43]	2005	Germany	Caucasian	Adults	1999–2001	IS	159/ 159	C677 T A1298 C C2572A	PCR-RFLP	Age-Sex	102/57 79/80	55 ± 16	58.4 ± 16	Yes	HB	5

(*Continued*)

Table 1. (Continued).

S. no.	Author	Year	Origin	Ethnicity	Population	Study Period	Stroke types	Sample Size Case/ Control	MTHFR SNP Investigated	Genotyping Method	Matching criteria	M/F Case/ Control	Age (Mean ± SD) Case	Age (Mean ± SD) Control	HWE	Source of control	Quality score
19	Akar N[44]	2001	Turkey	Caucasian	Children	NA	IS	46/68	C677 T A1298 C	PCR-RFLP	NA	NA	NA	NA	Yes	PB	4
20	Hiroyuki Morita[45]	1998	Japan	Asian	Adults	Sept 1996-May 1997	IS	256/325	A1298 C	PCR-RFLP	Age-Sex	123/133,174/151	70.3 ± 8.6,	67.7 ± 7.5	Yes	PB	7

M = Male; F = Female; IS = Ischemic Stroke; HS = Hemorrhagic Stroke; HWE = Hardy Weinberg Equilibrium; PB = Population Based; HB = Hospital Based, PCR-RFLP = Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; SNP = Single Nucleotide Polymorphism; NA = Not Available.

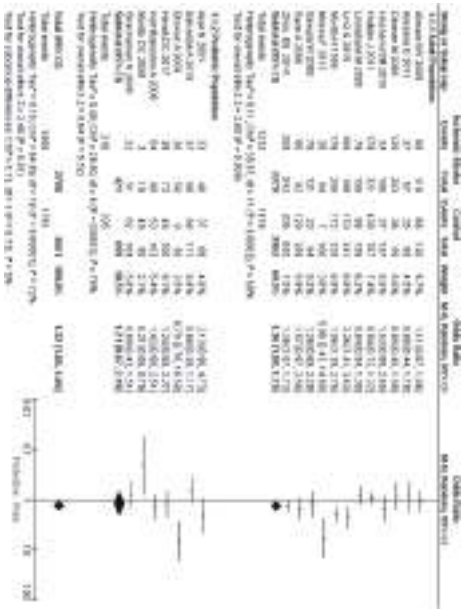

Figure 2. (a-f): Forest plot for the relationship between MTHFR A1298C Gene Polymorphism and the Risk of Ischemic Stroke in adult population v/s paediatric population. 2 (a). Dominant model (CC + AC vs, AA) for Adult vs. Pediatric.

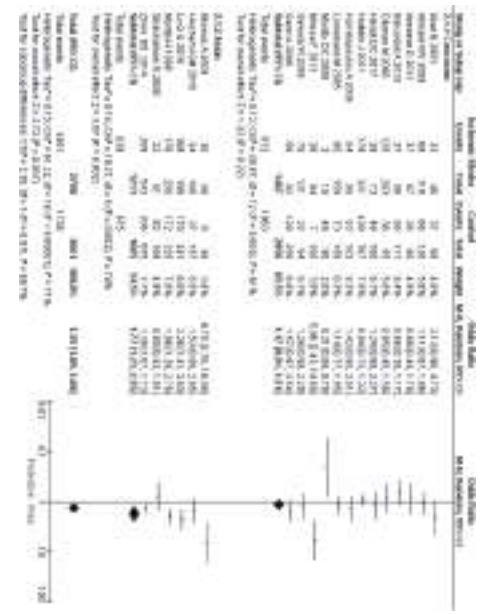

Figure 2. (b): Dominant model (CC + AC vs, AA) for Caucasian vs. Asian Population.

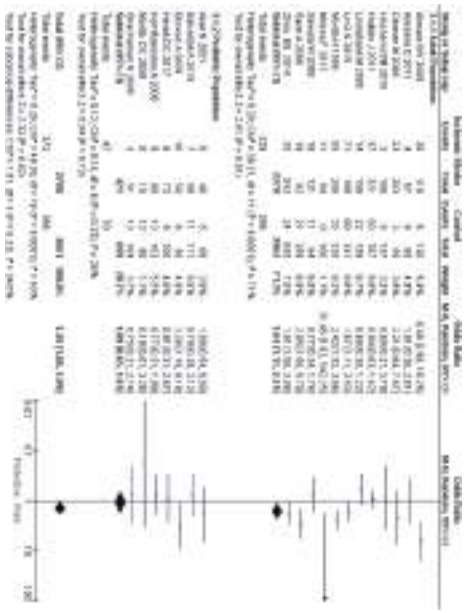

Figure 2. (c): Recessive model (CC vs. AA + GC) for Adult vs. Pediatric.

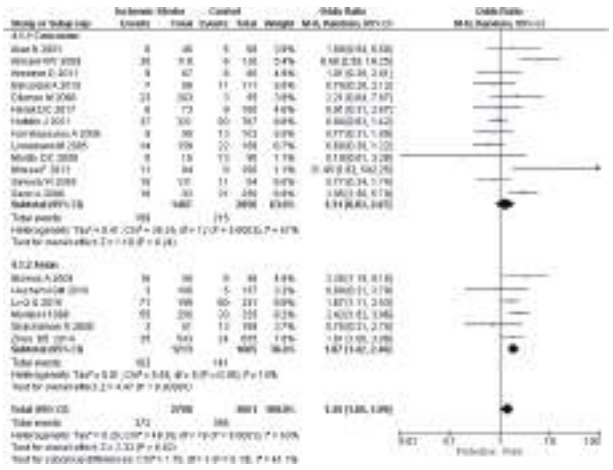

Figure 2. (d): Recessive model (CC vs. AA + GC) for Caucasian vs. Asian Population.

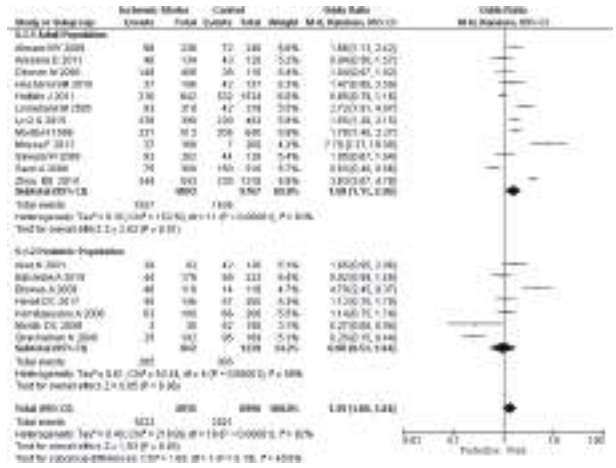

Figure 2. (e): Allelic model (C vs. G Allele) for Adult vs. Pediatric.

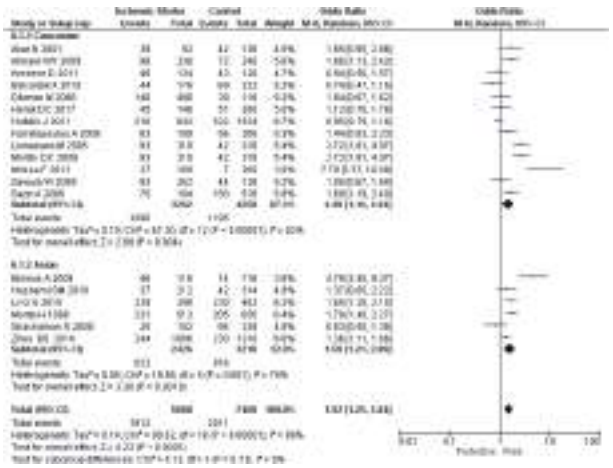

Figure 2. (f): Allelic model (C vs. G Allele) for Caucasian vs. Asian Population.

relationship between MTHFR A1298 C gene polymorphism and risk of IS under dominant model [OR = 1.39, 95% CI = 1.08–1.73]; recessive model [OR = 1.64, 95% CI = 1.11–2.41]; and allelic model [OR = 1.58, 95% CI = 1.11–2.26] for adult population. However, no significant association was found in pediatric population under dominant model [OR = 1.21, 95% CI = 0.67–2.19]; recessive model [OR = 1.09, 95% CI = 0.65–1.83]; and allelic model [OR = 0.98, 95% CI = 0.53–1.84].

Publication bias

Begg's funnel plot and the Egger test were performed to assess the publication bias arising from the literature. No obvious asymmetry was observed in any genetic model according to the visual assessment of the funnel plot (Figure 3(a-b)). In addition, there was no statistical evidence of publication bias among studies using Egger's regression test.

Sensitivity analyses

Furthermore, we performed sensitivity analyses to assess the influence of each individual study on the pooled ORs by sequential omission of individual included studies. However, the corresponding pooled ORs were not significantly altered by removing any individual study except for allelic model (Figure 4). Therefore, the sensitivity analysis confirmed that the results of this meta-analysis were statistically reliable and robust.

Meta regression analysis

Meta regression analysis based on quality score for the relationship between MTHFR A1298 C Gene Polymorphism and the risk of IS did not confirm any deviation of findings ($p = 0.86$) (Figure 5).

Relationship between MTHFR A1298 C gene polymorphism and Hemorrhagic Stroke risk

No significant relationship between MTHFR A1298 C gene polymorphism and risk of HS was observed under dominant model [OR = 0.88, 95% CI = 0.65–1.20]; recessive model [OR = 0.51, 95% CI = 0.14–1.88]; and allelic model [OR = 0.79, 95% CI = 0.61–1.02] respectively (Figure 6(a-c)). No publication bias was observed for the included studies (Figure 7). Due to limited number of studies for HS, a sensitivity analysis and meta-regression analysis could not be performed.

Discussion

In the present meta-analysis, we retrieved 20 studies (19 case-control studies involving 2770 ischemic cases with 3661 controls and 3 studies with 201 hemorrhagic cases with 1349 controls) to evaluate the relationship between MTHFR A1298 C gene polymorphism and the risk of stroke in adults as well as pediatric population. Our findings demonstrate that MTHFR A1298 C gene polymorphism is significanltly associated with

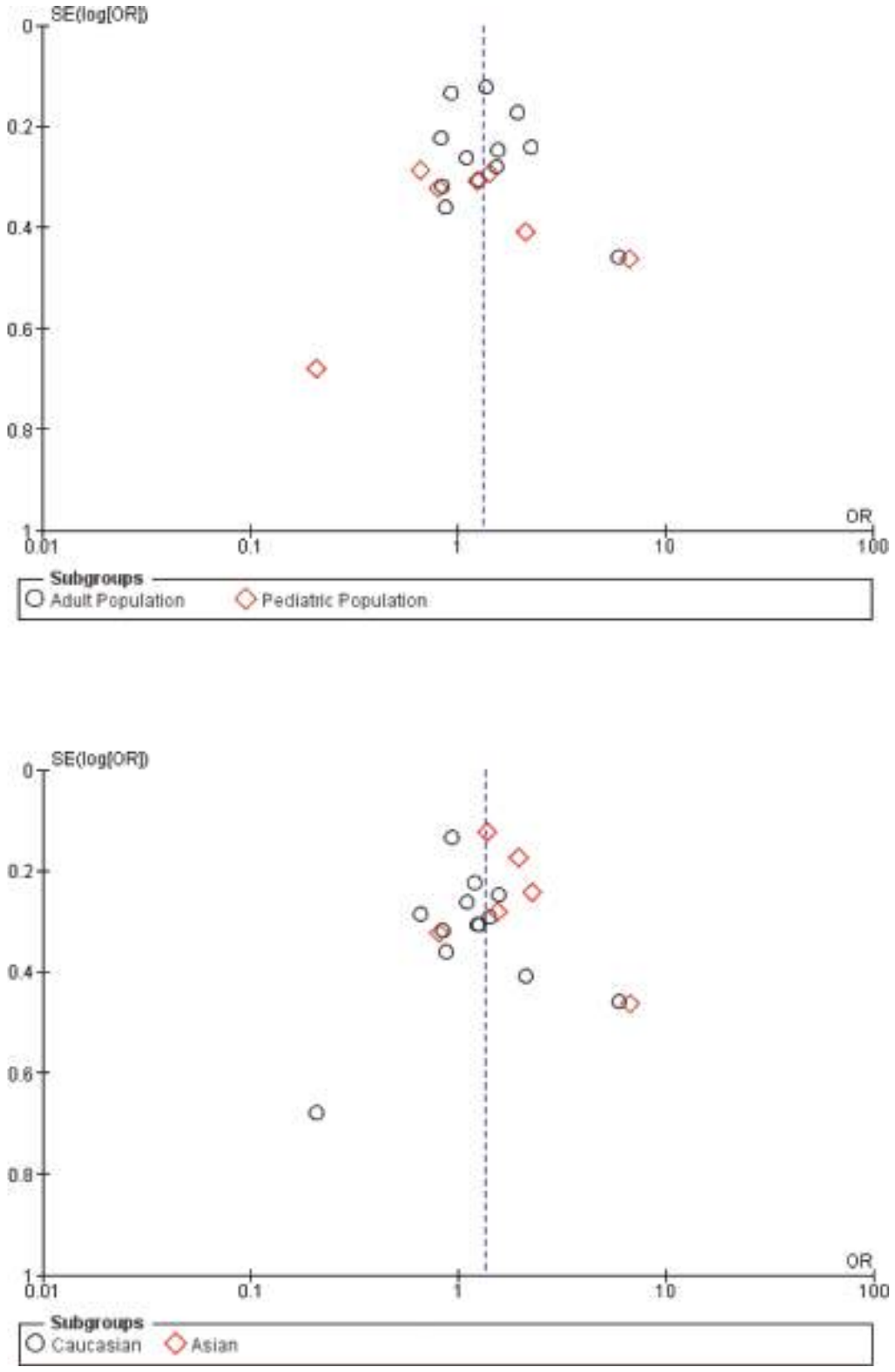

Figure 3. (a-b): Beggs Funnel plot for the relationship between MTHFR Gene (A1298C) Polymorphism with the Risk of Ischemic Stroke in (a) adult populations v/s paediatric populations (b) Caucasian vs. Asian.

the risk of IS especially in Asian ethnicity and in adult population. No significant association was observed for HS. To our knowledge, our meta-analysis is the first meta-analysis which was performed to ascertain the relationship between MTHFR A1298 C gene polymorphism and the risk of overall stroke (ischemic and/or hemorrhagic) in adults well as pediatric population. In this meta-analysis, we also found MTHFR C allele which might be an important risk factor for IS. In Caucasian ethnicity, our results indicated that

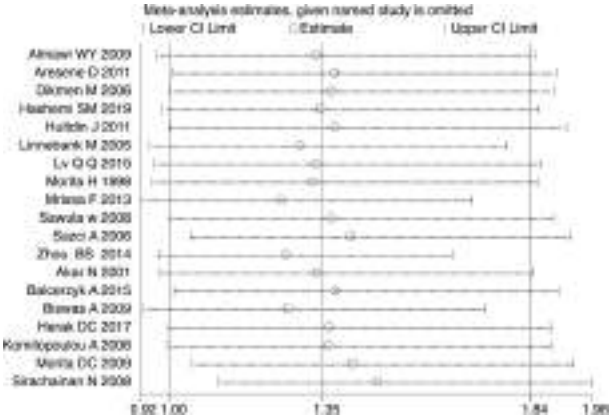

Figure 4. Sensitivity Analysis for Allelic Model (Adult-Pediatric) for the relationship between MTHFR Gene (A1298 C) polymorphism with the risk of ischemic stroke.

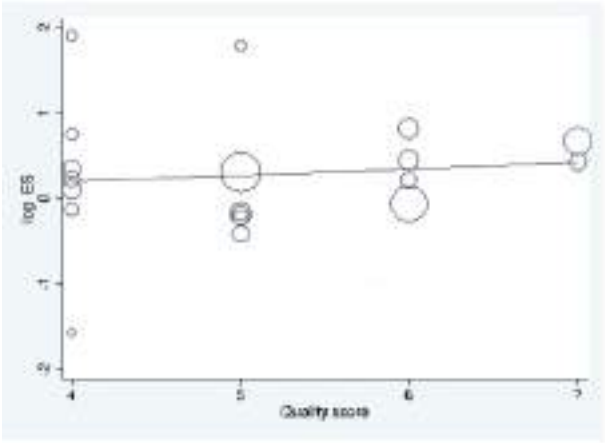

Figure 5. Meta regression plot based on quality score for the relationship between MTHFR A1298C Gene Polymorphism and the Risk of Ischemic Stroke.

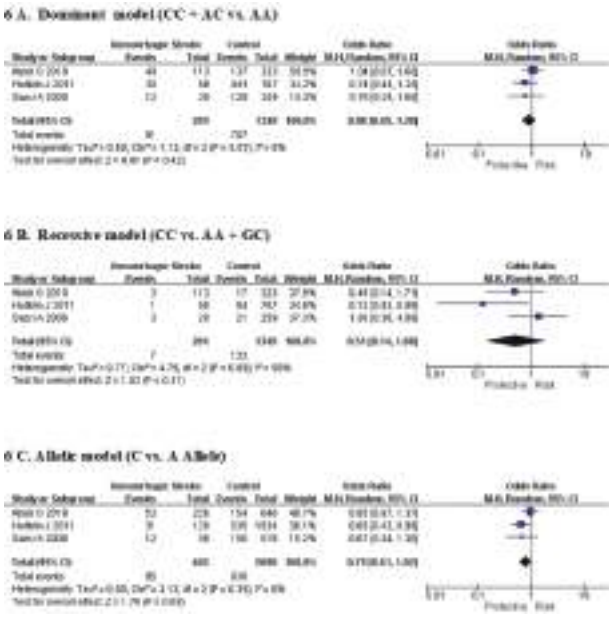

Figure 6. (a–c): Forest plot for the relationship between MTHFR gene (A1298 C) polymorphism with the risk of hemorrhagic stroke. 6(a). Dominant model (CC + AC vs, AA); 6(b). Recessive model (CC vs. AA + GC); 6(c). Allelic model (a vs. C Allele).

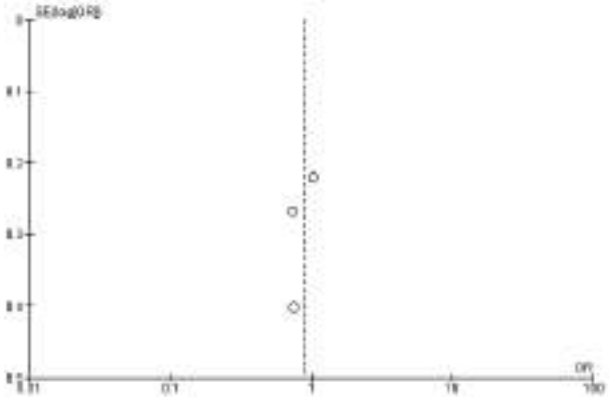

Figure 7. Begg's Funnel plot for the relationship between MTHFR gene (A1298 C) polymorphism with the risk of hemorrhagic stroke.

MTHFR A1298 C gene polymorphism leads to a decreased risk of IS which may be due to the fact that Caucasian and Asian populations are genetically different. The number of included studies was moderate in number.

Previous published meta-analyses of 13 case-control studies published by Lv *et al.* (2013) [23] and Kang *et al.* (2014) [24] and 15 case-control studies published by Zhang *et al.* (2014) [25] also confirmed a significant association of MTHFR A1298 C gene polymorphism in most of the genetic models in Asians but not in the European population. Even though meta-analyses aim to combine the comparable studies, to increase sample size and statistical significance, and identify patterns in various studies, the quality of such analyses might be limited by publication bias, sampling methods, variations in genetic background of the subjects as we included both Caucasian and Asian populations including South Asian and East Asian population, and differences in the used protocols. We aimed to minimize these limitations by using appropriate inclusion and exclusion criteria to reduce selection bias, tested HWE for genotypic distribution to eliminate different genetic backgrounds among the participants. Overall, the results from our study support the notion that MTHFR A1298C C allele or CC genotype may be considered as an important risk factor for IS but not for HS. However, studies embedded with larger sample size are needed to validate our findings in future.

Conclusion

Overall analysis suggests that MTHFR A1298C gene polymorphism might be capable of increasing stroke susceptibility in Asian, but not in the Caucasian population. Genotyping of MTHFR A1298C gene

polymorphism may be used as a predictor for the occurrence of stroke.

Disclosure statement

No potential conflict of interest.

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REVIEW

WILEY

Association of modifiable risk factors with ischaemic stroke subtypes in Asian versus Caucasian populations: A systematic review and meta-analysis

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Abstract

Background: Ischaemic stroke (IS) is associated with various modifiable risk factors but the association of these risk factors based on TOAST classification, which characterises IS into five subtypes: large artery atherosclerosis (LAA), small vessel occlusion (SVO), cardioembolic disease (CE), other determined aetiology (ODE) and undetermined aetiology (UDE), is unknown. We aimed to summarise the published evidence for the association of modifiable risk factors with IS subtypes based on TOAST classification, specifically focussing on the Asian versus Caucasian population.

Method: A comprehensive search for all the published articles was performed in electronic databases including PubMed, EMBASE, Cochrane Library, and Google Scholar from 01st January 1950 to 10th April 2022 based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Odds ratio (OR) with 95% confidence interval (CIs) along with random-effect models was used to calculate summary estimates.

Results: In our meta-analysis, 32 studies with a total of 23,404 IS (14,364 in Asian vs. 9040 in Caucasian population), 7121 LAA (5219 in Asian vs. 1902 in Caucasian), 5532 SVO (3604 in Asian vs. 1928 in Caucasian), 3498 CE (1634 in Asian vs. 1864 in Caucasian), 1131 ODE (546 in Asian vs. 585 in Caucasian) and 4519 UDE (2076 in Asian vs. 2443 in Caucasian) were included. Our findings suggest a significant association between LAA and hypertension (OR = 1.07, 95% CI = 1.02–1.12), smoking (OR = 1.11, 95% CI = 1.04–1.17), dyslipidemia (OR = 1.13, 95% CI = 1.06–1.21), diabetes mellitus (OR = 1.18, 95% CI = 1.11–1.25) and atrial fibrillation (OR = 0.55, 95% CI = 0.40–0.75). Significantly strong association of hypertension, smoking, dyslipidemia, diabetes mellitus and atrial fibrillation was observed with SVO and CE stroke subtypes. Subgroup analysis based on ethnicity revealed a significant association for dyslipidemia, diabetes mellitus and atrial fibrillation in LAA for both Asians and Caucasians.

Statistical Analysis Conducted by Pradeep Kumar, PhD, Department of Neurology, All India Institute of Medical Sciences, New Delhi, India.

Hypertension was significantly associated with SVO and ODE subtypes in both Asians and Caucasians; however, only Asian population showed significant association of hypertension in LAA and CE subtypes. The other risk factors did not show any statistical difference between the ethnic groups for the different stroke subtypes. The majority of the risk factors depicted positive association with LAA and SVO, negative with CE and neutral with ODE and UDE.

Conclusion: Our findings suggest strong association of smoking, dyslipidemia and diabetes mellitus with LAA and SVO subtypes in the Caucasian population. However, only diabetes mellitus showed significant association with both LAA and SVO subtypes in Asian population as well. Thus, a majority of the traditional modifiable risk factors had a positive association in LAA and SVO, while a negative protective association was observed in CE subtype, among both the Asian and the Caucasian subgroups.

KEYWORDS

ischaemic stroke, modifiable risk factors, TOAST classification

1 | INTRODUCTION

Stroke is reported as the most common cause of long-term disability and second most leading cause of death worldwide.[1] Almost 80% of stroke are ischaemic stroke (IS), and 15%–20% are haemorrhagic in origin.[2,3] According to the Trial of Org 10,172 in acute stroke treatment (TOST) classification, IS has been categorised according to the presumed aetiological mechanism into five groups: large artery atherosclerosis (LAA), small vessel occlusion (SVO), cardioembolic disease (CE), other determined aetiology (ODE) and undetermined aetiology (UDE).[4] The TOAST classification has been proven to be valid and reliable even in retrospective study.[5,6]

Several studies have reported the association of modifiable risk factors such as hypertension, diabetes mellitus, dyslipidemia, heart disease, atrial fibrillation, smoking, body mass index (BMI) and alcoholism and have showed variable correlation with different stroke subtypes in different population.[7–11] Currently, there are no definite data for the risk factors for IS subtypes based on TOAST classification. The findings associated with modifiable risk factors in each IS subtype may influence prevention, management and prognosis of the disease. Moreover, population subgroups have not been elucidated based on modifiable risk factors, particularly among the Asian and Caucasian subgroups, for understanding the impact of risk factors on different populations across various geographical niches. Therefore, the present meta-analysis was aimed to clarifying the association of modifiable risk factors with IS subtypes based on TOAST classification by estimating a pooled analysis of the published observational studies.

2 | METHODS

2.1 | Search strategy

This systematic literature review was performed using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[12] A comprehensive search for all the published articles was undergone in electronic databases including PubMed, EMBASE, Cochrane Library and Google Scholar from 01st January 1950 to 10th April 2022. Following key terms were used: 'Risk Factor' OR 'Modifiable Risk Factor' AND 'Ischaemic Stroke' OR 'Subtypes' OR 'TOAST Classification' OR 'Stroke Classification'. Additionally, the reference list of retrieved studies, review articles and previous meta-analyses was manually searched for collecting more relevant studies, which were not found while performing the electronic search.

2.2 | Eligibility criteria

2.2.1 | Inclusion criteria

(1) Observational studies including case–control, nested case–control and cohort design investigating the association of modifiable risk factors with the risk of IS subtypes

based on TOAST classification; (2) imaging confirmed diagnosis of IS using CT or MRI scans; (3) patients aged 16 years or above; (4) data available for risk factors including hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol intake and atrial fibrillation for IS subtypes.

2.2.2 | Exclusion criteria

Duplicates, case reports and case series shall be excluded.

2.3 | Risk of bias in individual studies

The risk of bias was assessed by Newcastle Ottawa Scale (NOS) for quality assessment of all the included studies in the meta-analysis.[13] Publication bias was assessed using the funnel plot analysis. The asymmetry of the funnel plot was determined by using the Begg's and Egger's regression test.[14,15]

2.4 | Data extraction

All relevant studies were analysed separately by two reviewers (PK and PS) based on the inclusion and exclusion criteria listed above. The analysis was made first at the title and abstract level and then at the full-text level. Any disagreement was resolved by discussion with a third reviewer. Following data were extracted from the studies: first author's name, published year, ethnicity (Asian versus Caucasian), country, study design and number of cases as per IS subtypes, history of hypertension, diabetes, dyslipidemia, atrial fibrillation and smoking. Data were extracted independently by two authors (PK and PS) using a standardised extraction table. Two authors independently extracted the data using the same table on a random sample of studies, and the extraction results were cross-checked.

2.5 | Statistical analysis

A random-effect model was used to calculate the pooled odds ratio (OR) with 95% confidence interval (CI). Heterogeneity was calculated with the I^2 statistic. I^2 of less than 50% is considered unimportant while that of more than 50% is viewed as moderate to considerable heterogeneity. Heterogeneity between studies was adjusted by subgroup analysis and meta-regression by the quality score of the included studies. A sensitivity analysis was performed by sequentially omitting a single study in each turn, to validate the pooled observed effect. Subgroup analysis based on Asian and Caucasian populations was also undergone to compare the effect of risk factors. All statistical analyses were made by STATA version 13.1 software. A p-value $< .05$ was considered to be statistically significant.

3 | RESULTS

Figure-1 depicts the schematic representation of the PRISMA flowchart for the selection and inclusion of the studies. PRISMA checklist has been provided as a Table S1. The initial literature search yielded 651 records by searching the records from PubMed, EMBASE, Cochrane Library, Google Scholar and 18 additional articles were identified through other sources. After screening the title and abstract of 617 records (587 irrelevant studies, 13 non-English and 17 reviews were removed), 46 full-text articles were evaluated for their eligibility out of which 32 were finally included in our systematic review and meta-analysis.

3.1 | Characteristics of eligible studies

Of the 32 studies, four were case–control, and 28 were population-based cohort studies. The year of publication of the included studies was in the range of 1997–2021. The baseline characteristics of all the studies included are given in Table 1. The studies were categorised into two ethnicities: 19 in Asian and 13 in Caucasian populations. The sample size ranged from 100 to 4548 which included 23,404 IS cases. Of which, 14,364 patients belonged to the Asian subgroup and 9040 belonged to the Caucasian subgroup. The quality scores based on NOS scale of the included studies ranged from moderate to high (Table 1). In our meta-analysis, 32 studies with a total of 7121 large artery atherosclerosis (LAA), 5532 small vessel occlusion (SVO), 3498 cardioembolism (CE), 1131 stroke of other determined aetiology (ODE) and 4519 stroke of undetermined aetiology (UDE) were included. The Asian population comprised 5219 LAA, 3604 SVO, 1634 CE, 546 ODE and 2076 UDE patients. In contrast, the Caucasian population had 1902 LAA, 1928 SVO, 1864 CE, 585 ODE and 2443 UDE patients (Table 2).

3.1.1 | Association of modifiable risk factors with the risk of large artery atherosclerosis (LAA) subtypes (Asian versus Caucasian subgroups)

In the current meta-analysis, we included 29 studies with 22,860 IS (14,156 Asian vs. 8704 Caucasian population)

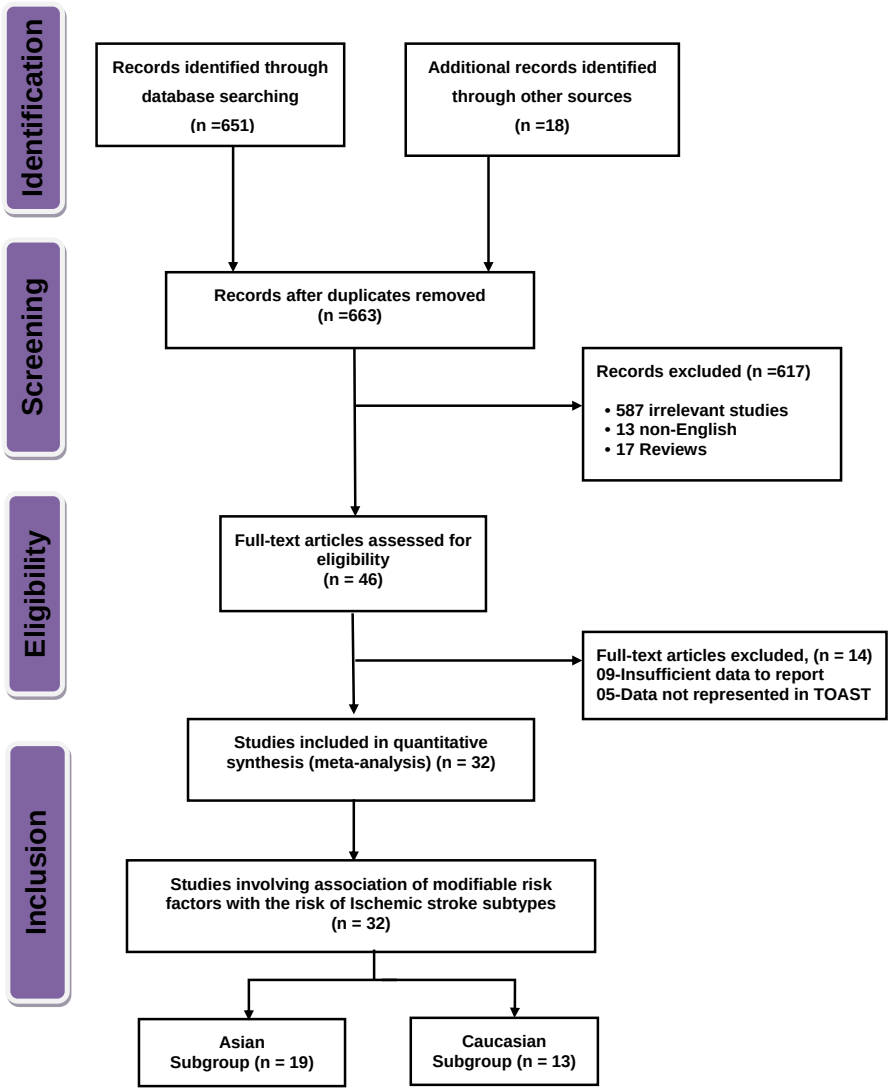

FIGURE 1 Flow diagram for the selection of studies and specific reasons for exclusion from the present meta-analysis

and 6889 LAA (5131 Asian vs. 1758 Caucasian population) cases for determining the association of modifiable risk factors with LAA risk. Our findings suggest a significant association between LAA and hypertension (OR = 1.07, 95% CI = 1.02–1.12), smoking (OR = 1.12, 95% CI = 1.05–1.19), dyslipidemia (OR = 1.14, 95% CI = 1.07–1.21) and diabetes mellitus (OR = 1.18, 95% CI = 1.12–1.25). Protective nature of association was observed for atrial fibrillation with the risk of LAA (OR = 0.55, 95% CI = 0.40–0.75). After conducting subgroup analysis based on ethnicity, a significant association for hypertension (OR = 1.07, 95% CI = 1.01–1.12), dyslipidemia (OR = 1.11, 95% CI = 1.02–1.20) and diabetes mellitus (OR = 1.18, 95% CI = 1.11–1.26) was observed in the Asian population and for smoking (OR = 1.29, 95% CI = 1.16–1.43), dyslipidemia (OR = 1.18, 95% CI = 1.07–1.30) and diabetes mellitus (OR = 1.20, 95% CI = 1.05–1.36) in the Caucasian population. Moreover, protective association was observed in both the Asian (OR = 0.62, 95% CI = 0.52–0.74) and the Caucasian population (OR = 0.10, 95% CI = 0.01–0.77) for atrial fibrillation with LAA (Figure 2A and Figures S1A–S4A). However, no significant association was observed for hypertension in the Caucasian population (OR = 1.07, 95% CI = 0.99–1.16) and smoking in the Asian population (OR = 1.04, 95% CI = 0.97–1.12).

3.1.2 | Association of modifiable risk factors with the risk of small vessel occlusion (SVO) subtypes (Asian versus Caucasian subgroups)

We enrolled 29 studies with 22,860 IS (14,156 Asian vs. 8704 Caucasian population) and 6889 SVO (5131 Asian vs. 1758 Caucasian population) cases in our meta-analysis for identifying the association of modifiable risk factors with SVO risk. Overall, strong association between hypertension (OR = 1.13, 95% CI = 1.05–1.22), smoking (OR = 1.08, 95% CI = 1.01–1.15), dyslipidemia (OR = 1.08, 95% CI = 1.01–1.17) and diabetes mellitus (OR = 1.16, 95% CI = 1.09–1.24) with the risk of SVO was observed.

TABLE 1 Baseline characteristics of studies included in the systematic review and meta-analysis for the association of modifiable risk factors for the risk of ischaemic stroke subtypes based on TOAST classification

S. No	Author Name & Year	Country	Ethnicity	Study design	Total IS	Total LAA	Total SVO	Total CE	Total UDE	Total ODE	NOS quality score
1	Aquil et al, 2011[19]	Pakistan	Asian	CCS	100	31	43	8	18	1	6
2	Harris et al, 2018[20]	Indonesia	Asian	CCS	235	140	65	5	23	2	6
3	Zafar et al, 2018[21]	Pakistan	Asian	CCS	145	19	25	58	38	5	5
4	Renjen et al, 2015[9]	India	Asian	RCS	244	141	18	11	66		5
5	Kim et al, 2006[22]	Korea	Asian	PCS	1167	491	313	177	169	17	5
6	Huang et al, 2019[23]	China	Asian	RCS	961	309	201	277	98	76	7
7	Sumer. M et al, 2002[11]	Turkey	Asian	PCS	236	23	66	88	87	2	7
8	Lee et al, 2001[24]	Korea	Asian	PCS	1000	165	215	183	406	31	6
9	Tan et al, 2018[25]	China	Asian	PCS	530	198	193	41	98		4
10	Yip et al, 1997[26]	China	Asian	PCS	676	113	195	133	196	39	6
11	Kaul S et al, 2018[27]	India	Asian	PCS	2072	779	413	228	566	86	5
12	Rasulova, 2014[28]	Uzbekistan	Asian	PCS	100	42	41	17			7
13	Shubhakaran et al, 2019[29]	India	Asian	CCS	100	44	39	10	3	4	6
14	Deleu et al, 2011[30]	Qatar	Asian	PCS	780	297	271	105	32	55	6
15	Pan et al, 2016[31]	China	Asian	PCS	4548	1915	1071	115		163	9
16	Qawasmeh et al, 2020[32]	Jordan	Asian	RCS	142	31	77	10	15	9	4
17	Shahidullah et al, 2019[33]	Bangladesh	Asian	PCS	877	385	209	74	169	40	4
18	Taj et al, 2010[34]	Pakistan	Asian	RCS	108	46	39	19			6
19	Zafar et al, 2016[35]	Kingdom of Saudi Arabia	Asian	RCS	343	50	110	75	92	16	4
Sub-total			19	PCS – 10 RCS – 5 CCS – 4	14,364	5219	3604	1634	2076	546	
20	Sabre H et al, 2016[36]	USA	Caucasian	PCS	512	72	114	77	226	23	8
21	Malek et al, 2019[10]	Lebanon	Caucasian	PCS	284	43	48	88	76	29	6
22	Jackova J et al, 2019[37]	Czech Republic	Caucasian	PCS	682	189	160	237	49	47	7
23	Ihle- Hansen et al, 2012[5]	Norway	Caucasian	PCS	210	24	66	66	54	0	6
24	Bejot et al, 2008[7]	France	Caucasian	PCS	332	119	89	81	43		5
25	Hajat C et al, 2010[38]	UK	Caucasian	PCS	1169	109	316	325	283	40	9
26	Lavados M et al, 2007[39]	Chile	Caucasian	PCS	239	8	57	50	69	1	7

(Continues)

TABLE 1 (Continued)

S. No	Author Name & Year	Country	Ethnicity	Study design	Total IS	Total LAA	Total SVO	Total CE	Total UDE	Total ODE	NOS quality score
27	Marrone et al, 2013[40]	Brazil	Caucasian	PCS	688	223	127	195	113	30	5
28	Hauer et al, 2017[41]	Netherlands	Caucasian	PCS	3311	817	632	469	1130	214	5
29	Kolominsky-Rabas et al, 2012[42]	Germany	Caucasian	PCS	531	71	120	143	188	9	7
30	Pena et al, 2021[43]	Colombia	Caucasian	RCS	152	10	4	36	51	51	4
31	Redfors et al, 2012[44]	Sweden	Caucasian	RCS	594	73	122	97	161	141	7
32	Roquer et al, 2004[45]	Spain	Caucasian	PCS	336	144	73				4
Sub-total			13	PCS – 11 RCS – 2	9040	1902	1928	1864	2443	585	
Total			Asian – 19 Caucasian – 13	PCS – 21 RCS – 7 CCS – 4	23,404	7121	5532	3498	4519	1131	

Abbreviations: CCS, case control study; CE, cardioembolism; IS, ischaemic stroke; LAA, large-artery atherosclerosis; NOS, newcastle ottawa scale; ODE, stroke of other determined aetiology; PCS, prospective cohort study; RCS, retrospective cohort study; SVO, small vessel occlusion; UDE, stroke of undetermined aetiology; UK, United Kingdom; USA, United States of America.

Moreover, strong protective association with SVO was observed with atrial fibrillation (OR = 0.25, 95% CI = 0.14–0.44). Based on ethnicity, significant association of hypertension (OR = 1.15, 95% CI = 1.02–1.30) and diabetes mellitus (OR = 1.16, 95% CI = 1.05–1.29) was found in Asian Population, whereas hypertension (OR = 1.10, 95% CI = 1.02–1.19), smoking (OR = 1.18, 95% CI = 1.06–1.31), dyslipidemia (OR = 1.11, 95% CI = 1.00–1.23) and diabetes mellitus (OR = 1.16, 95% CI = 1.03–1.30) were found to be more associated with Caucasian population for the risk of SVO subtypes. In addition, there was a significant protective association with SVO in the Asian (OR = 0.39, 95% CI = 0.23–0.64) and the Caucasian (OR = 0.02, 95% CI = 0.01–0.10) population for atrial fibrillation (Figure-2B and Figures S1B–S4B). However, no significant association of smoking (OR = 1.03, 95% CI = 0.95–1.12) and dyslipidemia (OR = 1.06, 95% CI = 0.94–1.19) was observed in the Asian population.

3.1.3 | Association of modifiable risk factors with the risk of cardioembolism (CE) subtypes (Asian versus Caucasian subgroups)

In the present meta-analysis, 28 studies with 22,616 IS (13,912 in Asian vs. 8704 in Caucasian population) and 3498 CE (1587 in Asian vs. 1864 in Caucasian) cases were included for finding the association of modifiable risk factors with CE risk. Our findings suggest a significant protective association of smoking (OR = 0.73, 95% CI = 0.67–0.80), dyslipidemia (OR = 0.88, 95% CI = 0.80–0.95) and diabetes mellitus (OR = 0.84, 95% CI = 0.76–0.93) with CE subtypes of IS in overall analysis as well as in Asian subgroups [(OR = 0.80, 95% CI = 0.71–0.90), (OR = 0.82, 95% CI = 0.68–0.98), and (OR = 0.75, 95% CI = 0.64–0.89), respectively] based on ethnicity. In addition, a significant association was observed for atrial fibrillation with the risk of CE in overall (OR = 4.51, 95% CI = 3.01–6.77) as well as both the Asian (OR = 5.35, 95% CI = 2.98–9.61) and the Caucasian (OR = 3.11, 95% CI = 2.33–4.15) populations based on subgroup analysis. Moreover, a significant protective association was also observed for hypertension in the Asian population (OR = 0.85, 95% CI = 0.75–0.95) and smoking in the Caucasian (OR = 0.67, 95% CI = 0.58–0.76) population with the CE subtype (Figure 2C and Figures S1C–S4C). However, there was no significant association of hypertension in the overall (OR = 0.93, 95% CI = 0.86–1.00) and the Caucasian population (OR = 1.01, 95% CI = 0.93–1.10) with the CE subtype. Additionally, dyslipidemia (OR = 0.90, 95% CI = 0.80–1.00) and diabetes mellitus (OR = 0.94, 95% CI = 0.83–1.06) did not show any significant association in the Caucasian population with the

TABLE 2 Meta-analysis of overall population and subgroup analyses for modifiable risk factors and ischaemic stroke subtypes

	Hypertension		Smoking		Dyslipidemia		Diabetes mellitus		Atrial fibrillation	
Population	**OR (95% CI)**	I^2	**OR (95% CI)**	I^2	**OR (95% CI)**	I^2	**OR (95% CI)**	I^2	**OR (95% CI)**	I^2
Large artery atherosclerosis										
Overall	**1.07 (1.02–1.12)**	0.0%	**1.12 (1.05–1.19)**	9.0%	**1.14 (1.07–1.21)**	0.0%	**1.18 (1.12–1.25)**	0.0%	**0.55 (0.40–0.75)**	43.2%
Asian	**1.07 (1.01–1.12)**	0.0%	1.04 (0.97–1.12)	0.0%	**1.11 (1.02–1.20)**	0.0%	**1.18 (1.11–1.26)**	0.2%	**0.62 (0.52–0.74)**	0.0%
Caucasian	1.07 (0.99–1.16)	0.0%	**1.29 (1.16–1.43)**	0.0%	**1.18 (1.07–1.30)**	0.0%	**1.20 (1.05–1.36)**	7.4%	**0.10 (0.01–0.77)**	75.6%
Small vessel occlusion										
Overall	**1.13 (1.05–1.22)**	50.3%	**1.08 (1.01–1.15)**	0.0%	**1.08 (1.01–1.17)**	6.9%	**1.16 (1.09–1.24)**	8.1%	**0.25 (0.14–0.44)**	70.2%
Asian	**1.15 (1.02–1.30)**	68.0%	1.03 (0.95–1.12)	0.0%	1.06 (0.94–1.19)	23.6%	**1.16 (1.05–1.29)**	34.1%	**0.39 (0.23–0.64)**	63.0%
Caucasian	**1.10 (1.02–1.19)**	0.0%	**1.18 (1.06–1.31)**	0.0%	**1.11 (1.00–1.23)**	0.0%	**1.16 (1.03–1.30)**	0.0%	**0.02 (0.01–0.10)**	0.0%
Cardioembolism										
Overall	0.93 (0.86–1.00)	21.7%	**0.73 (0.67–0. 80)**	0.0%	**0.88 (0.80–0.95)**	0.0%	**0.84 (0.76–0.93)**	16.6%	**4.51 (3.01–6.77)**	91.6%
Asian	**0.85 (0.75–0.95)**	29.5%	**0.80 (0.71–0.90)**	0.0%	**0.82 (0.68–0.98)**	29.8%	**0.75 (0.64–0.89)**	30.8%	**5.35 (2.98–9.61)**	93.3%
Caucasian	1.01 (0.93–1.10)	0.0%	**0.67 (0.58–0.76)**	0.0%	0.90 (0.80–1.00)	0.0%	0.94 (0.83–1.06)	0.0%	**3.11 (2.33–4.15)**	56.3%
Stroke of other determined aetiology										
Overall	**0.71 (0.60–0.84)**	28.3%	0.92 (0.79–1.08)	1.4%	0.88 (0.74–1.03)	1.1%	**0.76 (0.63–0.92)**	9.3%	0.48 (0.22–1.06)	53.6%
Asian	**0.70 (0.58–0.84)**	13.5%	0.85 (0.64–1.13)	33.1%	0.81 (0.64–1.03)	0.0%	0.72 (0.55–0.94)	25.0%	0.81 (0.43–1.53)	35.2%
Caucasian	**0.71 (0.52–0.97)**	44.9%	0.95 (0.75–1.20)	0.0%	0.83 (0.59–1.17)	38.9%	0.79 (0.59–1.05)	0.0%	**0.08 (0.02–0.39)**	0.0%
Stroke of undetermined aetiology										
Overall	0.95 (0.89–1.01)	0.0%	1.03 (0.94–1.12)	0.0%	0.92 (0.84–1.02)	0.0%	0.97 (0.89–1.07)	0.0%	**0.50 (0.33–0.75)**	43.6%
Asian	0.94 (0.87–1.02)	0.0%	1.04 (0.94–1.16)	0.0%	0.92 (0.81–1.04)	0.0%	0.97 (0.88–1.08)	0.0%	0.62 (0.39–1.00)	34.9%
Caucasian	0.96 (0.87–1.07)	0.0%	0.99 (0.86–1.15)	0.0%	0.93 (0.80–1.08)	0.0%	0.93 (0.78–1.11)	22.5%	**0.35 (0.20–0.59)**	9.8%

Note: Bold values of OR represent statistically significant results.

Abbreviations: CI, confidence interval; OR, Odds ratio.

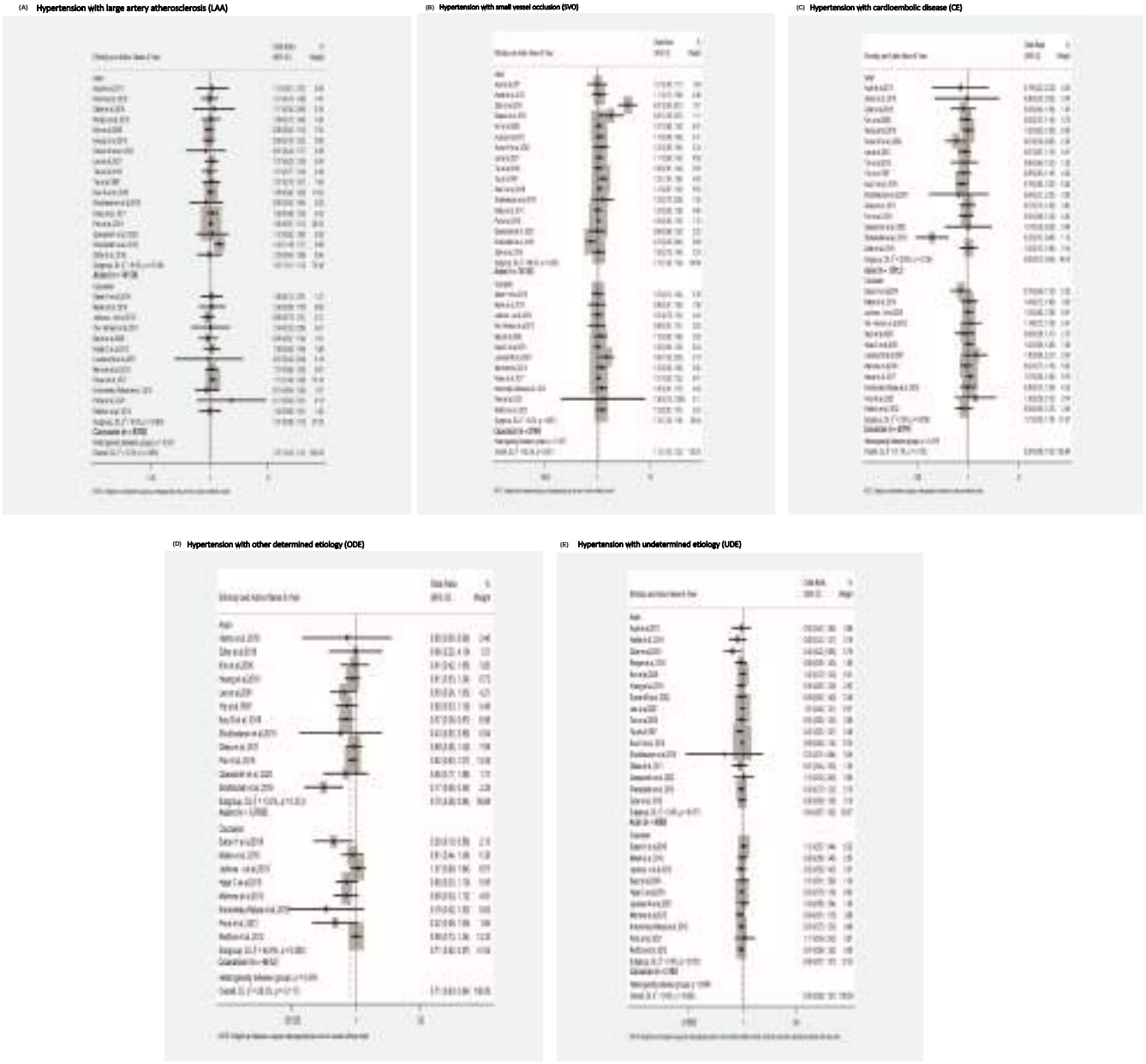

FIGURE 2 (A–E) Forest plot for the association of Hypertension with the risk of ischaemic stroke (IS) subtypes. (A) Hypertension with large artery atherosclerosis (LAA). (B) Hypertension with small vessel occlusion (SVO). (C) Hypertension with cardioembolic disease (CE). (D) Hypertension with other determined aetiology (ODE). (E) Hypertension with undetermined aetiology (UDE)

CE subtype. Detailed summary of association in context to OR is represented in Table-2.

3.1.4 | Association of modifiable risk factors with the risk of other determined aetiology (ODE) subtypes (Asian versus Caucasian subgroups)

In our meta-analysis, a total of 20 studies for the association of modifiable risk factors and risk of ODE subtypes involving 17,315 IS (12,703 in Asian vs. 4612 in Caucasian population) cases and 897 ODE (527 in Asian vs. 370 in Caucasian) cases were included. Our findings suggest a protective nature of association between modifiable risk factors including hypertension (OR = 0.71, 95% CI = 0.60–0.84) and diabetes mellitus (OR = 0.76, 95% CI = 0.63–0.92) with the risk of ODE subtypes. No significant association was found between ODE subtype and smoking (OR = 0.92, 95% CI = 0.79–1.08), dyslipidemia (OR = 0.88, 95% CI = 0.74–1.03) and atrial fibrillation (OR = 0.48, 95% CI = 0.22–1.06). Subgroup analysis based on ethnicity revealed a significant protective association for the risk factors including hypertension (OR = 0.70,

95% CI = 0.58–0.84) and diabetes mellitus (OR = 0.72, 95% CI = 0.55–0.94) with the ODE subtypes in the Asian population and hypertension (OR = 0.71, 95% CI = 0.52–0.97) and atrial fibrillation (OR = 0.08, 95% CI = 0.02–0.39) in the Caucasian population (Figure 2D and Figures S1D–S4D). However, no significant association was observed for smoking [(OR = 0.85, 95% CI = 0.64–1.13) and (OR = 0.95, 95% CI = 0.75–1.20)] and dyslipidemia [(OR = 0.81, 95% CI = 0.64–1.03) and (OR = 0.83, 95% CI = 0.59–1.17)] for both the Asian and the Caucasian population, respectively, with the ODE subtype. In addition, no significant association was observed for diabetes mellitus (OR = 0.79, 95% CI = 0.59–1.05) in the Caucasian population and atrial fibrillation (OR = 0.81, 95% CI = 0.43–1.53) in the Asian population with the ODE subtype.

3.1.5 | Association of modifiable risk factors with the risk of undetermined aetiology (UDE) subtypes (Asian versus Caucasian subgroups)

In our meta-analysis, a total of 26 studies for the association of modifiable risk factors and risk of UDE subtypes involving 14,791 IS (9608 Asian vs. 5183 Caucasian population) cases and 3335 UDE (2076 Asian vs. 1259 Caucasian) cases were included. Our findings suggest a nonsignificant association between modifiable risk factors including hypertension (OR = 0.95, 95% CI = 0.89–1.01), smoking (OR = 1.03, 95% CI = 0.94–1.12), diabetes mellitus (OR = 0.97, 95% CI = 0.89–1.07) and dyslipidemia (OR = 0.92, 95% CI = 0.84–1.02) with the risk of UDE subtypes. A protective association was observed between atrial fibrillation and UDE subtype (OR = 0.50, 95% CI = 0.33–0.75). Subgroup analysis based on ethnicity also revealed a significant protective association of atrial fibrillation (OR = 0.35, 95% CI = 0.20–0.59) with the UDE subtypes in the Caucasian population. However, no association could be observed in the rest of the modifiable risk factors with the risk of UDE in the Asian and Caucasian population subgroups (Figure 2E and Figures S1E–S4E).

3.2 | Publication bias

Funnel plot and the Egger's test were performed to assess the publication bias arising from the literature included in our meta-analysis. No obvious asymmetry was observed for the included studies according to the visual assessment of the funnel plot. In addition, there was no statistical evidence of publication bias among the studies using Egger's regression test (*p*-value: .634 for LAA; .07 for SVO; .086 for CE). However, the analysis revealed significant bias for ODE (*p*-value: .04) and UDE subtypes (*p*-value: .034) studies [Figure S5A–E].

3.3 | Meta-regression analysis

A meta-regression analysis based on quality score of the included studies for the association between modifiable risk factors and the risk of IS subtypes did not confirm any deviation in the overall effect size (*p*-value: .077 for LAA; .481 for SVO; .253 for CE; and .51 for UDE subtype studies). However, there was a significant deviation from the effect size for the ODE subtype (*p*-value: .029) [Figure S6A–D].

3.4 | Sensitivity analyses

Furthermore, we performed sensitivity analyses to assess the influence of each individual study on the pooled ORs by sequential omission of individual included studies. However, the corresponding pooled ORs were not significantly altered by removing any of the studies [Figure S7A–E]. Therefore, the sensitivity analysis confirmed that the results of this meta-analysis were statistically reliable and robust.

4 | DISCUSSION

Our systematic review and meta-analysis summarises the published evidence till date on the association of various modifiable risk factors with the IS subtypes based on TOAST classification, particularly characterising the Asian versus Caucasian subgroup of population. In 32 studies, our meta-analysis observed that hypertension, smoking, dyslipidemia and diabetes mellitus were significantly associated with the risk of LAA and SVO. Moreover, smoking, dyslipidemia and diabetes mellitus depicted protective association with the risk of CE. In addition, atrial fibrillation was associated with the risk of CE, whereas it had a protective effect with LAA, SVO and UDE subtypes of stroke. A protective association was also observed for hypertension and diabetes mellitus with the ODE subtype of IS. Furthermore, we conducted subgroup analysis on the basis of ethnicity (Asian versus Caucasian population) and observed that dyslipidemia was associated with the risk of LAA in Asian population and with the risk of both LAA and SVO in Caucasian population. Diabetes mellitus was associated with the risk of LAA and SVO in both the Asian and the Caucasian populations. Hypertension was associated with the risk of LAA and SVO in Asian population

and with SVO in the Caucasian population. Moreover, smoking was associated with the risk of LAA and SVO in Caucasian population. In addition, atrial fibrillation was associated with the risk of CE in both the Asian and the Caucasian populations. The majority of the modifiable risk factors showed significant association with the LAA and SVO subtypes of ischaemic stroke. Moreover, the CE subtype showed a negative protective association with the risk of IS, while ODE and UDE subtypes were mostly non-significant in their association among the Asian and Caucasian ethnicities. To the best of our knowledge, this is the first systematic review and meta-analysis which has provided the evidence for the association of various modifiable risk factors with the subtypes of IS as well as stratifies the pooled evidence on the basis of ethnicity focussing on Asian versus Caucasian population.

According to The Atherosclerosis Risk in Communities (ARIC) study published in 2006, current smoking, hypertension, diabetes and low HDL cholesterol were found to be associated with both the lacunar, nonlacunar and cardioembolic subtype of IS .[16] A review published in 2004 classified the risk factors associated with subtypes of IS. They observed that diabetes mellitus was associated with the risk of SVO but had a protective effect on ODE subtype of stroke. Smoking and hypercholesterolemia were associated with the risk of LAA while hypercholesterolemia also had a protective association with the UDE stroke subtype. Hypertension was found to be a risk factor for SVO and a protective factor for CE stroke subtype.[17] Another review published in 2009 confirmed the above findings in terms of dyslipidemia (hypercholesterolemia) and concluded that it was less likely to be a crucial risk factor for the pathogenesis of lacunar (SVO) and cardioembolic stroke subtypes. [18]

Although conducted comprehensively, certain limitations were present in our meta-analysis. First, the studies included in our systematic review and meta-analysis varied in terms of ethnicity, age and environmental factors. Second, we did not check for the false discovery rate which might arise from the multiple comparisons made in the meta-analysis. Lastly, significant heterogeneity was present in some of the comparisons made in our meta-analysis, including atrial fibrillation in SVO, CE and ODE representing high heterogeneity. However, we used a random-effect model throughout to account for the between-study heterogeneity and conducted meta-regression analysis to assess the heterogeneity arising from the quality of each included study.

Nonetheless, our systematic review and meta-analysis provides strong evidence from the pooled synthesis of 32 studies on the various modifiable risk factors associated with IS subtypes.

5 | CONCLUSION

Our findings suggest a strong association of smoking, dyslipidemia and diabetes mellitus with LAA and SVO subtypes. Hypertension was found to be associated with the risk of SVO and atrial fibrillation with CE stroke subtypes. Moreover, dyslipidemia and diabetes mellitus were associated with the risk of LAA, and hypertension was associated with the risk of SVO in both Asian and Caucasian subgroups, depicting the role of ethnicity with the risk of IS. Therefore, the traditional modifiable risk factors depicted a significant positive association with large artery atherosclerosis and small vessel occlusion while cardioembolic disease depicted a negative association, showing protective relation in both the Asian and the Caucasian population.

AUTHOR CONTRIBUTIONS

PK and MN were involved in study selection and data extraction for the included study; MN, PS, RS, AK and SM contributed in writing the manuscript to its final version. PK contributed to the concept, designing, statistical analysis and writing the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

All authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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