Mini Review

Annals of Neurosciences

Ann Neurosci 2016;23:113–121
DOI: 10.1159/000443568

Received: August 8, 2015
Accepted: April 25, 2016
Published online: July 7, 2016

Association between Apolipoprotein ε4 Gene Polymorphism and Risk of Ischemic Stroke: A Meta-Analysis

Amit Kumar Pradeep Kumar Manya Prasad Shubham Misra
Awadh Kishor Pandit Kamalesh Chakravarty

Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Key Words
Apolipoprotein-E · Association study · Ischemic stroke · Cerebral infarction · Meta-analysis · Gene polymorphism

Abstract
Background: Previous studies examining the association of apolipoprotein E (APOE) gene polymorphism with the risk of ischemic stroke (IS) have yielded conflicting results. Therefore, we performed a meta-analysis to investigate the association between APOE ε4 gene polymorphism and risk of IS.
Summary: A literature search for genetic association studies published before May 30, 2015, was conducted in the PubMed, EMBASE and Google Scholar databases. The following search terms were used: (apolipoprotein E) or (APOE) and (ε4) and (polymorphism) or (polymorphisms) and ('ischemic stroke' or 'IS') and ('cerebral infarction' or 'CI') and ('genetic polymorphism' or 'single nucleotide polymorphisms' or 'SNP'). ORs and 95% CIs were used to calculate the strength of association. Begg's funnel plot was used to assess the potential for publication bias. In our meta-analysis, 26 case–control studies involving 6,397 IS cases and 19,053 controls were included. Overall significant association between carrier of ε4 allele and risk of IS was observed (OR 1.43, 95% CI 1.10–1.85, p = 0.007). In the subgroup analysis based on ethnicity, a significant association between Apo ε4 carrier and risk of IS was observed in Asian studies (OR 1.53, 95% CI 1.04–2.25, p = 0.031) whereas borderline significant association between APO ε4 carrier and risk of IS was observed in Caucasian studies (OR 1.36, 95% CI 0.95–1.93, p = 0.093). ***Key Messages:*** Our meta-analysis suggests that APOE ε4 allele is associated with higher risk of IS in Asian population as compared to Caucasian population.

Introduction

Stroke is the second major leading cause of death and adult disability after ischemic heart disease [1]. Stroke has accounted for nearly 5.7 million deaths globally and 87% of these deaths take place in low and middle income nations [2]. In the last 4 decades, incidence of stroke in South Asian countries has been amplified by more than 100% while this is decreased by 42% in the developed European countries [3, 4]. This increase in the incidence of stroke in developing countries could have been influenced by environmental and genetic factors. Ischemic stroke (IS) is a multifactorial, polygenic disease and comprises of 80–85% of overall stroke [5]. Epidemiological

KARGER

E-Mail karger@karger.com
www.karger.com/aon

0972–7531/16/0232–0113$39.50/0

Dr. Amit Kumar, Scientist-C
Department of Neurology
All India Institute of Medical Sciences
Room No. 702, Neurosciences Centre, Ansari Nagar, New Delhi 110029 (India)
E-Mail amit.aiimsndelhi@gmail.com, amits52003@gmail.com

and animal studies have robustly recommended genetic influence in the pathogenesis of IS.

Apolipoprotein E (*APOE*) gene is one of the commonly studied genes in vascular and neurodegenerative diseases, which is located on chromosome 19q13.2 [6]. Its protein products are composed of glycoprotein with 3 common isoforms E2, E3 and E4 encoded by the respective alleles ε2, ε3 and ε4 giving rise to 6 genotypes. Apo-E protein plays an important role in lipid metabolism and transport and is also significantly expressed in the brain. There is substantial evidence of association between Apo ε4 allele and elevated low density lipoprotein cholesterol levels and thereby there is an increase in the risk of cardiovascular disease [7–10]. It has been shown that elevated level of ApoE in plasma is an important risk factor for stroke. Several studies have shown inconsistent results for the association between *APOE* gene polymorphism and risk of IS [11]. Factors responsible for inconsistent results include different study designs and inadequate characterization of phenotypes, variation in sample size and lack of proper case–control matching. Thus, we conducted a meta-analysis to investigate the association between *APOE* gene polymorphism and risk of IS.

Methods

Identification of Relevant Studies

A literature search for genetic association studies published before May 30, 2015, was conducted in the PubMed, EMBASE and Google Scholar databases. The following search terms were used: (apolipoprotein E) or (APOE) and (ε4) and (polymorphism) or (polymorphisms) and ('ischemic stroke' or 'IS') and ('cerebral infarction' or 'CI') and ('genetic polymorphism' or 'single nucleotide polymorphisms' or 'SNP'). We included studies that were conducted on human subjects and the studies were searched without any limitations on language. We thoroughly reviewed all the references to find out the relevant published studies in the literature.

Inclusion and Exclusion Criteria

The inclusion criteria for the studies were as following: (1) case–control studies exploring the association between the APOE ε4 gene polymorphism and risk of IS, (2) diagnosis of IS according to World Health Organization and (3) studies with enough reported genotypic and allelic data. The exclusion criteria were: (1) study design other than case–control study, (2) publications with overlapping cases and controls from the similar study and (3) no genotypic data available. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [12].

Data Extraction

Two authors (A.K. and P.K.) separately reviewed each full-text article for eligibility and extracted the data. Any disagreements were resolved by discussion among all the authors.

Table 1. Scale for quality assessment

Criteria	Score
Representativeness of cases	
Selected from any population disease registry or multiple center sites	2
Selected from any cardiology/neurology	1
Not described	0
Source of controls	
Population or neighbour based	3
Hospital based	2
Healthy volunteers with total description	1
Healthy volunteers without total description	0.5
Matching of controls	
Age and sex match	2
Smoking, hypertensive, diabetics	1
Not matched	0
Ascertainment of IS	
Adequate confirmation	2
Diagnosis of IS by patient medical record	1
Not described	0
Ascertainment of controls	
Stroke frees status by using appropriate QVSS or CT/MRI	1
Not described	0
Genotyping	
Genotyping done under blinded conditions	1
Unblinded or not mentioned	0
Genotyping method	
DNA sequencing/multiplex polymerase chain reaction	2
Polymerase chain reaction-restriction fragment length polymorphism	1
Others	0
HWE	
Allelic frequency in accordance HWE	2
Not HWE but followed statistics to adjust confounding	1
Not checked	0
Association assessment	
Appropriate statistics and examining confounders and effect modifiers	1
Inappropriate statistics used inappropriate statistics used	0
Total score	16

Quality Assessment

We also checked the methodological quality of each study using a methodological quality assessment scale [13] for the genetic association studies and it was modified by us to increase the relevance of our study. This scale took into account both traditional epidemiological considerations and genetic issues. The scores ranged from 0 (worst) to 16 (best). Details of the scale items are presented in table 1. Two authors (A.K. and P.K.) independently

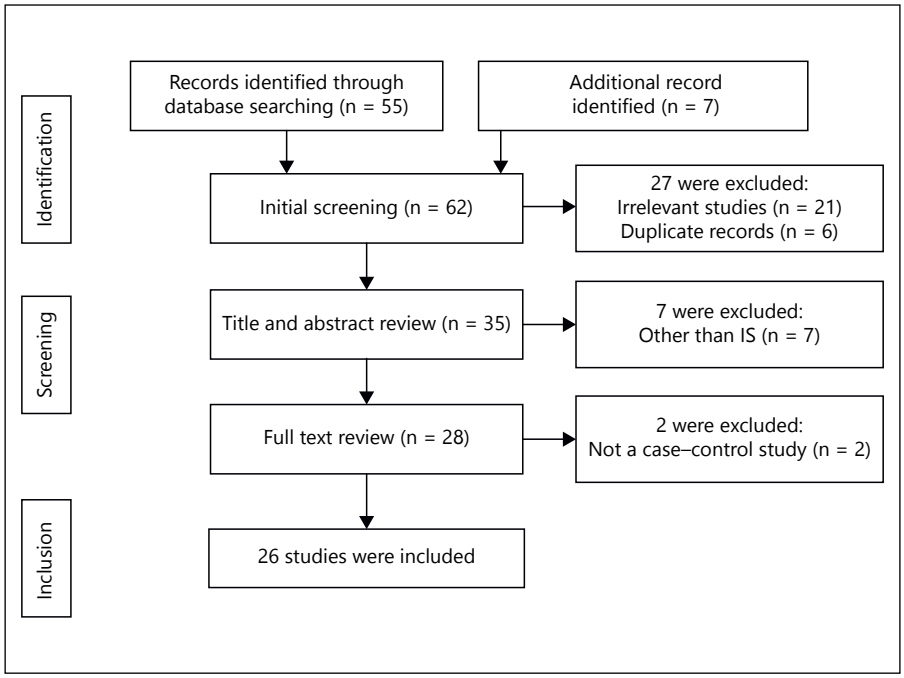

Fig. 1. Flow diagram of the selection of studies and specific reasons for exclusion from the present meta-analysis.

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

Hardy–Weinberg equilibrium (HWE) using the chi-square test was used to check the distribution of genotypes. Pooled OR and 95% CI were used to test the magnitude of association between the APOE ε4 gene polymorphism and risk of IS. Heterogeneity between studies was checked by using I^2 metric [14]. I^2 >50% was considered as presence of significant heterogeneity. Fixed effects model was used when I^2 <50%, or else random effects model was used. Along with an overall comparison, stratified analysis on the basis of ethnicity and age was used to explore whether differences in association are present between different ethnicities and different age groups. Begg's funnel plot was used to assess the potential for publication bias. All the statistical analysis was performed using STATA version 13.1 software.

Results

A total of 62 published articles were identified using the pre-specified search strategy. Figure 1 represents a flow chart of included and excluded studies along with their causes for exclusion. Out of 62 retrieved articles, 21 studies were excluded because they were irrelevant to our interests, 6 studies were excluded as they were in duplicate records, 7 studies were excluded due to conducted in other than IS and 2 studies were excluded as they were not of case–control study design. Keeping the inclusion criteria in mind, 26 case–control studies were included in our meta-analysis. Based on ethnicity, studies were carried out in 2 major ethnic populations; 11 studies were conducted in Asian while 15 studies were conducted in Caucasian population. We found the studies published in the literature from year 1993 to 2013. The genotype distribution in controls of 12 studies included in the present meta-analysis was in accordance with HWE. The methodological qualities of most of the studies were found to be moderately high. Out of 26 studies, the source of controls was hospital based in 13 studies, population based in 10 studies and 3 studies did not report their source of controls. A summary of the characteristics and methodological quality of the included studies in the present meta-analysis are mentioned in table 2.

A total of 26 case–control studies involving 6,397 cases and 19,053 controls were included in our meta-analysis. Overall, a significant association between carrier of ε4 allele and risk of IS was observed (OR 1.43, 95% CI 1.10–1.85, p = 0.007). In the subgroup analysis based on ethnicity, significant association between Apo ε4 carrier and risk of IS was observed in 11 Asian studies involving 2,327 IS cases and 2,546 controls (OR 1.53, 95% CI 1.04–2.25, p = 0.031) but borderline significant association was observed in 15 Caucasian studies involving 4,070 IS cases and 15,507 controls (OR 1.36, 95% CI 0.95–1.93, p = 0.093). A significant heterogeneity was observed (I^2 =

Ann Neurosci 2016;23:113–121
DOI: 10.1159/000443568

Table 2. Characteristic of studies included in the meta-analysis of the association of APOE ε4 gene polymorphism with the risk of ischemic stroke

No.	First author, year	Origin	Ethnicity	Sample size, n (case/control)	PCR method	Matching criteria	M/F (case/control)	Age (case/control)	HWE	Source of control	Quality score
1	Saidi [17], 2007	Tunisia	Caucasian	228/323	PCR-RFLP	Age-sex	114/114 117/146	61.5±12.1/ 60.9±12.8	Yes	PB	12
2	Gao [18], 2006	Chinese	Asian	100/100	PCR-DHPLC	Age-sex	71/29 71/29	60.08±10.77/ 60.9±10.64	No	HB	11
3	Giassakis [19], 2007	Greece	Caucasian	100/96	Nested PCR-RFLP	Age-sex	70/30 66/30	60.7±9.8/ 61.3±9.8	No	PB	9
4	Nakata [20], 1997	Japan	Asian	55/61	PCR-RFLP	Age-sex	25/30 30/31	66±14/ 67±8	Yes	PB	12
5	Abboud [21], 2008	Beligum	Caucasian	237/326	PCR	NA	NA	NA	Yes	PB	12
6	Kang [22], 2006	Korea	Asian	194/168	PCR-sequencing	Age	116/78 94/74	62±9.5/ 62.3±6.3	No	HB	11
7	Tamam [23], 2009	Turkey	Asian	65/30	PCR	Age-sex	44/21 10/20	65.5±14.3/ 61.9±14.7	No	NA	6.5
8	Catto [24], 2000	UK	Caucasian	513/289	PCR-RFLP	Age-sex	297/295 150/139	73 (64–80)/ 72.5 (58–79)	Yes	HB	12
9	Karttunen [25], 2002	Finland	Caucasian	46/104	PCR-RFLP	Age-sex	27/19 59/45	46 (15–60)/ 46 (17–62)	No	PB	10
10	Jin [26], 2004	China	Asian	226/201	PCR-RFLP	Age-sex	129/97 109/92	48.5±3.4/ 47.1±2.4	Yes	PB	11
11	Pezzini [27], 2005	Italy	Caucasian	163/158	Multiplex-PCR	Age-sex	84/79 85/73	35±7.5/ 34±6.1	No	HB	11
12	Luthra [28], 2002	India	Asian	63/57	PCR-RFLP	NA	NA	56.4±13.1/ 39.4±8	No	HB	8
13	Wang [29], 2009	China	Asian	396/396	PCR-RFLP	Age-sex	209/187 201/195	57.3±8/ 57.2±8.09	Yes	HB	12
14	Couderc [30], 1993	France	Caucasian	69/68	PCR-RFLP	Age-sex	36/33 33/35	72.3±11.6/ 72.1±11.5	No	NA	7.5
15	MacLeod [31], 2001	UK	Caucasian	266/225	PCR-RFLP	NA	150/116 94/105	65.7±12.2/ 77±1	Yes	PB	9
16	Kokubo [32], 2000	Japan	Asian	201/1,126	PCR-RFLP	NA	187/135 334/792	67.9±11/ 64.3 vs. 10.5	No	PB	8
17	Souza [33], 2003	Brazil	Caucasian	107/100	PCR-RFLP	Age-sex	NA	68.8±9.17/ 69.4±8.29	No	NA	6

Table 2. (continued)

No.	First author, year	Origin	Ethnicity	Sample size, n (case/control)	PCR method	Matching criteria	M/F (case/control)	Age (case/control)	HWE	Source of control	Quality score
18	Morrison [34], 2002	US	Caucasian	218/964	PCR-RFLP	Age-sex	113/105 415/549	56.6±0.4/ 53.9±0.1	Yes	PB	13
19	Pezzini [35], 2004	Italy	Caucasian	124/147	PCR-RFLP	Age-sex	68/56 80/67	34.7±7.3/ 34.8±6.1	No	HB	9
20	Kessler [36], 1997	Germany	Caucasian	227/225	PCR-RFLP	Age-sex	108/119 108/117	62.3±14.2/ 62.6±14	No	HB	9
21	Mcllroy [37], 2002	Ireland	Caucasian	64/71	PCR-RFLP	Smoking-hypertension	37/27 14/57	73.8±8.1/ 74.3±7.6	No	HB	9
22	Chowdhury [38], 2001	Bangladesh	Asian	147/190	PCR-RFLP	NA	117/30 129/61	57.9±11.1/ 60.3±9.6	No	HB	7
23	Atadzhanov [39], 2013	Zambia	Caucasian	23/116	TaqMan assay – direct sequencing	Age-sex	NA	NA	Yes	HB	13
24	Baum [40], 2006	Hong Kong	Asian	246/336	PCR-RFLP	Age	134/112 152/184	70.7±12/ 71.0±5.9	Yes	HB	12
25	Frikke-Schmidt [41], 2001	Denmark	Caucasian	738/8,938	PCR-RFLP	Age-sex	457/281 4,022/4,916	63.2±0.4/ 57.2±0.2	Yes	PB	11
26	Um [42], 2003	Korea	Asian	196/379	PCR-RFLP	NA	NA	NA	Yes	HB	8

PB = Population based; HB = hospital based; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; NA = not applicable.

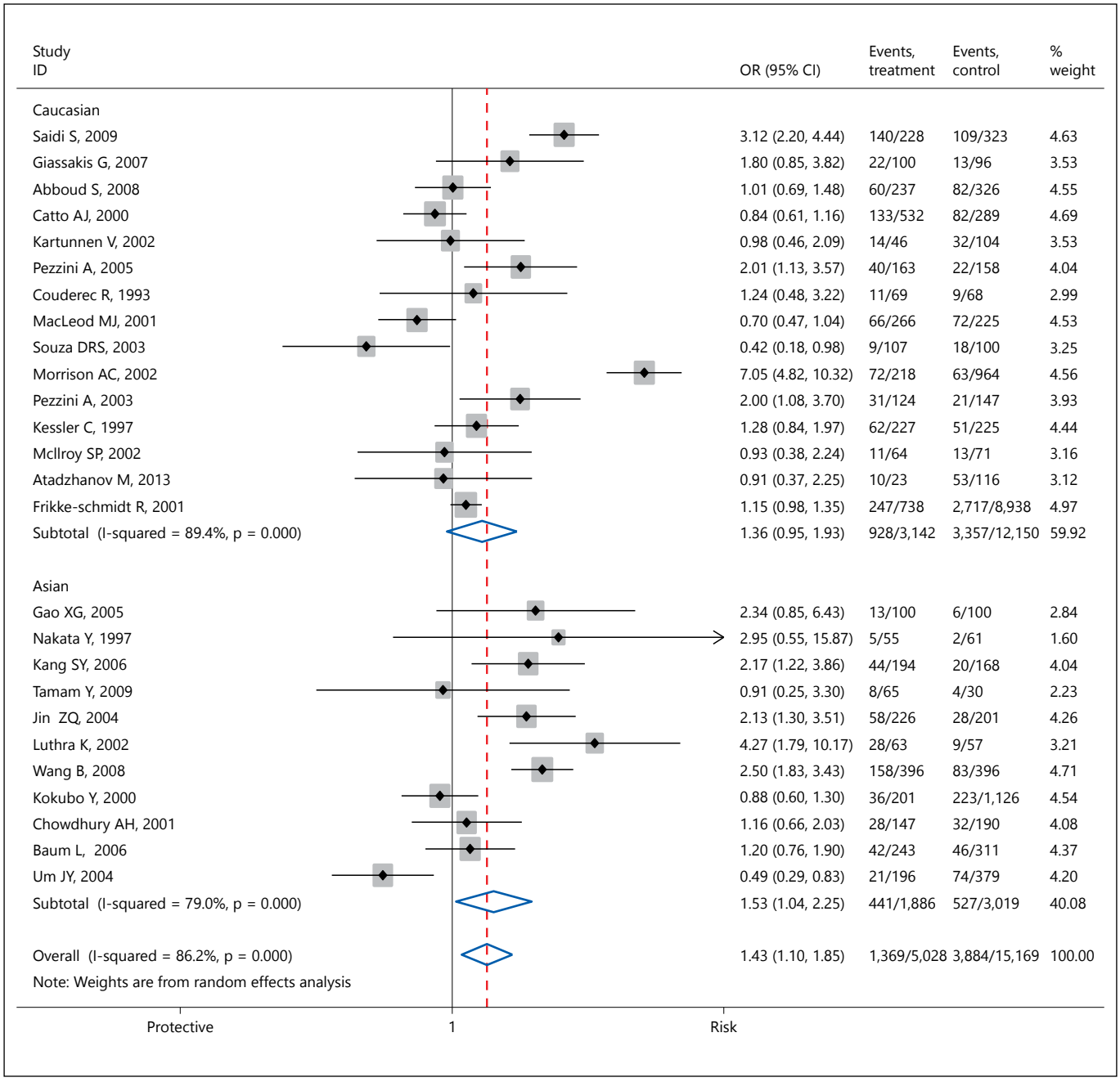

Fig. 2. Forest plot for the association between APOE ε4 gene polymorphism and IS risk.

86.2%; $p_{Het} < 0.0001$; fig. 2). The shape of the Begg's funnel plot suggests the presence of significant publication bias (fig. 3).

We analyzed the data using meta-regression analysis to explore whether age plays a significant role in the association between Apo-E polymorphism and risk of IS and found that increasing age is associated with decrease in effect size of association of APOE polymorphism with the risk of IS (p = 0.05; fig. 4). Further stratified analysis based on age category grouped as ≤60 and >60 years was done, and we found patients with IS having age ≤60 years (OR 2.54, 95% CI 2.13–3.02) and age >60 years (OR 1.19, 95% CI 1.08–1.32) had a significant association of APO-E ε4 genotype with the risk of IS (fig. 5).

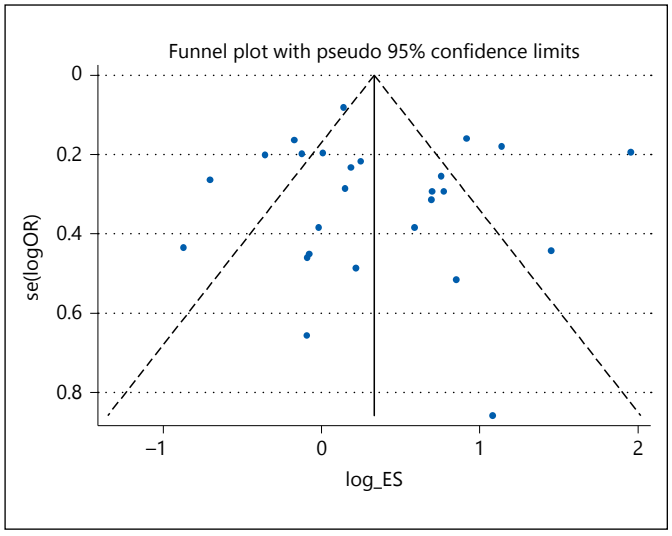

Fig. 3. Begg's funnel plot for investigating publication bias for the included studies.

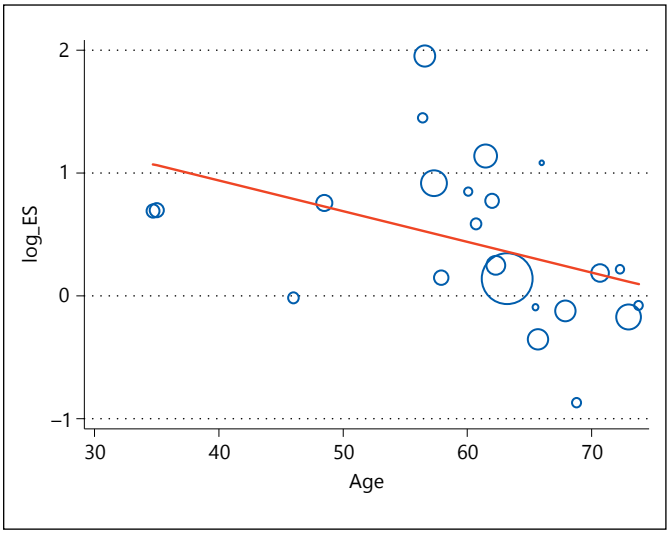

Fig. 4. Meta-regression plot for age-stratified analysis. Increasing age suggests a decrease in log odds of association of APOE polymorphism with IS (p value = 0.05).

Discussion

There is evidence about the involvement of genetic factors for development of IS. In the present meta-analysis, we investigated the association between Apo-ε4 gene polymorphism and risk of IS. Our study results suggest that there is a higher risk of IS in subjects who are carriers of ε4 allele of *APOE* gene. Our findings are consistent with the previously published meta-analysis [15] involving 4,096 IS cases and 16,117 controls suggesting Apo-E polymorphism contributes to the risk of stroke (OR 1.11, 95% CI 1.01–1.22). A recently published meta-analysis suggested that APO-ε4 allele is associated with increased risk for cerebral infarction in Chinese population [16].

We also conducted a subgroup analysis based on ethnicity and observed that the Apo-ε4 carrier allele is more prone to have the risk of IS in Asian population as compared to the Caucasian population. In the current study, we observed that 14 studies were deviated from HWE and a potential publication bias with significant heterogeneity was found.

We conducted a meta-regression analysis using mean age of cases of individual study as continuous variables and found out that increasing age is associated with decrease in effect size of association of APOE polymorphism with the risk of IS (p = 0.05; fig. 4). Furthermore, we stratified the data on the basis of the age category as ≤60 and >60 years and observed that patients with IS having age ≤60 years had significant association of APOE ε4 genotype with the risk of IS with an OR 2.54 and 95% CI 2.13–3.02 while patient with IS having age >60 years had a significant association with an OR 1.19 and 95% CI 1.08–1.32 (fig. 5).

There were a few limitations in our study. (1) Some studies included in the meta-analysis had small sample size and may have provided inconsistent results due to low statistical power. (2) Stroke risk varies as per specific subtypes of stroke; however, most of the studies included in the meta-analysis have not presented the data as per subtype of stroke; therefore, meta-analysis based on association between APOE polymorphism and subtype of stroke has not been done. (3) The use of different methodologies for genotyping method, selection of controls and matching criteria may have led to heterogeneity. (4) Heterogeneity may also be due to the variations in ethnicity, age and environmental factors. (5) Survival bias may be present in included case–control studies as these studies may not be designed to recruit the critically ill patient at the acute onset.

In spite of the limitations listed above, our findings demonstrate that Apo-ε4 allele is associated with increased risk of IS. Our meta-analysis suggests that IS patients have higher frequency of ε4 allele in Asian population than in Caucasian population. To explore a definitive conclusion, further well designed and large sample size epidemiological studies are needed to be performed in the near future.

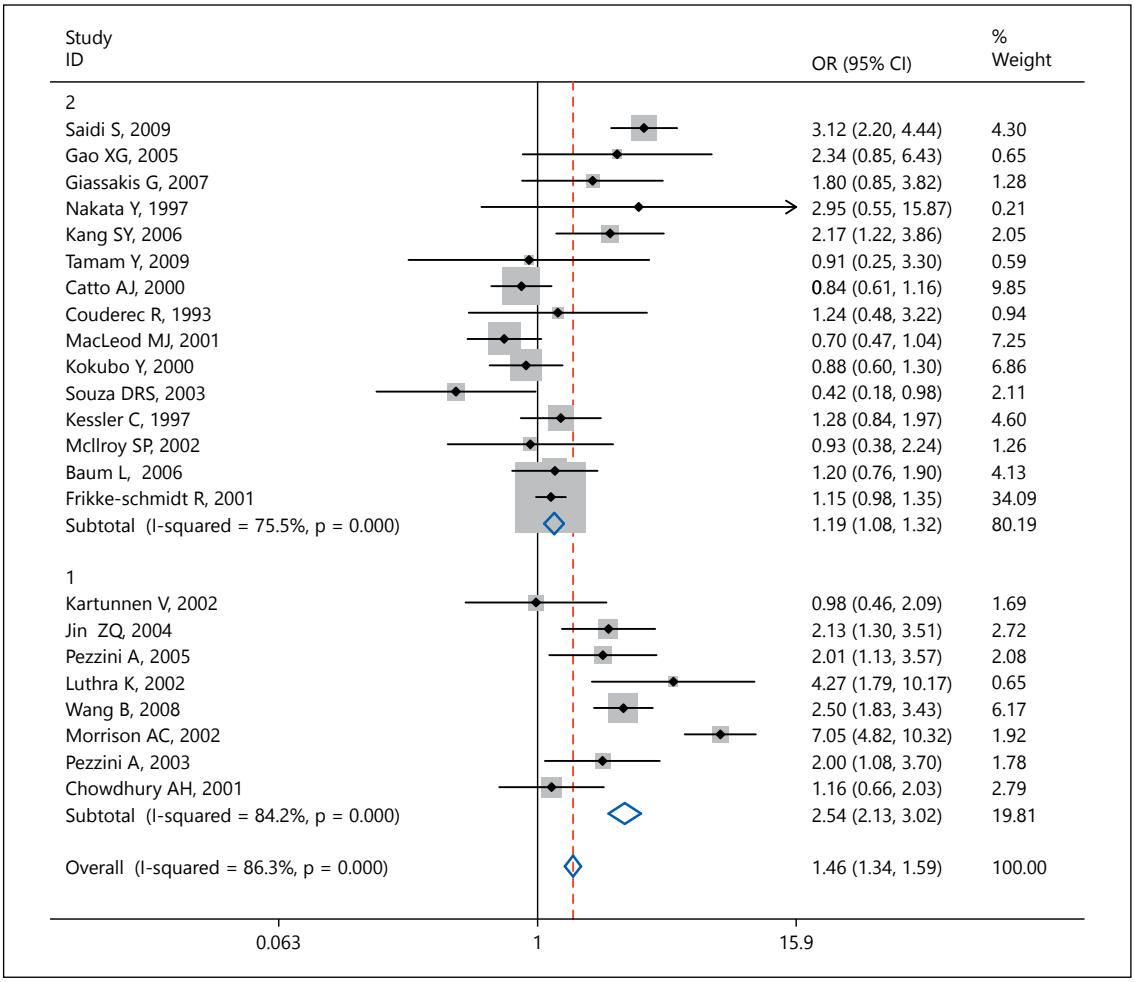

Fig. 5. Forrest plot of stratified analysis by age for association between APOE ε4 gene polymorphism and IS risk. Stratified analysis based on mean age of the cases in individual study ≤60 and >60 years suggests that age ≤60 years had double OR (OR 2.54) as compared to those who had mean age >60 years (OR 1.19).

Authorship Contribution

A.K. and P.K.: concept, data search, extraction; M.P.: writing of manuscript; S.M.: data entry and drafting of manuscript; A.K.P.: manuscript writing; K.C.: writing and drafting of manuscript.

Disclosure Statement

There is no potential conflict of interest. This study received no funding or sponsorship of any form.

References

1 Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V: Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355–369.
2 Reddy KS, Yusuf S: Emerging epidemic of cardiovascular disease in developing countries. Circulation 1998;97:596–601.
3 Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K: The burden and costs of chronic diseases in low-income and middle-income countries. Lancet 2007;370:1929–1938.
4 Strong K, Mathers C, Bonita R: Preventing stroke: saving lives around the world. Lancet Neurol 2007;6:182–187.
5 Della-Morte D, Guadagni F, Palmirotta R, Testa G, Caso V, Paciaroni M, et al: Genetics of ischemic stroke, stroke-related risk factors, stroke precursors and treatments. Pharmacogenomics 2012;13:595–613.
6 Ribalta J, Vallvé JC, Girona J, Masana L: Apolipoprotein and apolipoprotein receptor genes, blood lipids and disease. Curr Opin Clin Nutr Metab Care 2003;6:177–187.
7 Mahley RW: Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 1988;240:622–630.
8 Laskowitz DT, Horsburgh K, Roses AD: Apolipoprotein E and the CNS response to injury. J Cereb Blood Flow Metab 1998;18:465–471.

9 Anthopoulos PG, Hamodrakas SJ, Bagos PG: Apolipoprotein E polymorphisms and type 2 diabetes: a meta-analysis of 30 studies including 5423 cases and 8197 controls. Mol Genet Metab 2010;100:283–291.
10 Al-Khedhairy AA: Apolipoprotein E polymorphism in Saudis. Mol Biol Rep 2004;31:257–260.
11 Mahley RW, Rall SC Jr: Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet 2000;1:507–537.
12 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
13 Attia J, Thakkinstian A, D'Este C: Meta-analyses of molecular association studies: methodologic lessons for genetic epidemiology. J Clin Epidemiol 2003;56:297–303.
14 Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.
15 Gu L, Su L, Chen Q, Liang B, Qin Y, Xie J, et al: Association between the apolipoprotein E gene polymorphism and ischemic stroke in Chinese populations: new data and meta-analysis. Exp Ther Med 2013;5:853–859.
16 Wang Q, Wang WJ, Wu L, Liu L, Han LZ: Meta-analysis of APOE ε2/ε3/ε4 polymorphism and cerebral infarction. J Neural Transm (Vienna) 2013;120:1479–1489.
17 Saidi S, Slamia LB, Ammou SB, Mahjoub T, Almawi WY: Association of apolipoprotein E gene polymorphism with ischemic stroke involving large-vessel disease and its relation to serum lipid levels. J Stroke Cerebrovasc Dis 2007;16:160–166.
18 Gao X, Yang H, ZhiPing T: Association studies of genetic polymorphism, environmental factors and their interaction in ischemic stroke. Neurosci Lett 2006;398:172–177.
19 Giassakis G, Veletza S, Papanas N, Heliopoulos I, Piperidou H: Apolipoprotein E and first-ever ischaemic stroke in Greek hospitalized patients. J Int Med Res 2007;35:127–133.
20 Nakata Y, Katsuya T, Rakugi H, Takami S, Sato N, Kamide K, et al: Polymorphism of angiotensin converting enzyme, angiotensinogen, and apolipoprotein E genes in a Japanese population with cerebrovascular disease. Am J Hypertens 1997;10(12 pt 1):1391–1395.
21 Abboud S, Viiri LE, Lütjohann D, Goebeler S, Luoto T, Friedrichs S, et al: Associations of apolipoprotein E gene with ischemic stroke and intracranial atherosclerosis. Eur J Hum Genet 2008;16:955–960.
22 Kang SY, Lee WI: Apolipoprotein e polymorphism in ischemic stroke patients with different pathogenetic origins. Korean J Lab Med 2006;26:210–216.
23 Tamam Y, Tasdemir N, Toprak R, Tamam B, Iltumur K: Apolipoprotein E genotype in patients with cerebrovascular diseases and its effect on the disease outcome. Int J Neurosci 2009;119:919–935.
24 Catto AJ, McCormack LJ, Mansfield MW, Carter AM, Bamford JM, Robinson P, et al: Apolipoprotein E polymorphism in cerebrovascular disease. Acta Neurol Scand 2000;101:399–404.
25 Karttunen V, Alfthan G, Hiltunen L, Rasi V, Kervinen K, Kesäniemi YA, et al: Risk factors for cryptogenic ischaemic stroke. Eur J Neurol 2002;9:625–632.
26 Jin ZQ, Fan YS, Ding J, Chen M, Fan W, Zhang GJ, et al: Association of apolipoprotein E 4 polymorphism with cerebral infarction in Chinese Han population. Acta Pharmacol Sin 2004;25:352–356.
27 Pezzini A, Grassi M, Del Zotto E, Archetti S, Spezi R, Vergani V, et al: Cumulative effect of predisposing genotypes and their interaction with modifiable factors on the risk of ischemic stroke in young adults. Stroke 2005;36:533–539.
28 Luthra K, Prasad K, Kumar P, Dwivedi M, Pandey RM, Das N: Apolipoprotein E gene polymorphism in cerebrovascular disease: a case-control study. Clin Genet 2002;62:39–44.
29 Wang B, Zhao H, Zhou L, Dai X, Wang D, Cao J, et al: Association of genetic variation in apolipoprotein E and low density lipoprotein receptor with ischemic stroke in Northern Han Chinese. J Neurol Sci 2009;276:118–122.
30 Couderc R, Mahieux F, Bailleul S, Fenelon G, Mary R, Fermanian J: Prevalence of apolipoprotein E phenotypes in ischemic cerebrovascular disease. A case-control study. Stroke 1993;24:661–664.
31 MacLeod MJ, De Lange RP, Breen G, Meiklejohn D, Lemmon H, Clair DS: Lack of association between apolipoprotein E genoype and ischaemic stroke in a Scottish population. Eur J Clin Invest 2001;31:570–573.
32 Kokubo Y, Chowdhury AH, Date C, Yokoyama T, Sobue H, Tanaka H: Age-dependent association of apolipoprotein E genotypes with stroke subtypes in a Japanese rural population. Stroke 2000;31:1299–1306.
33 Souza DR, Campos BF, Arruda EF, Yamamoto LJ, Trindade DM, Tognola WA: Influence of the polymorphism of apolipoprotein E in cerebral vascular disease. Arq Neuropsiquiatr 2003;61:7–13.
34 Morrison AC, Ballantyne CM, Bray M, Chambless LE, Sharrett AR, Boerwinkle E: LPL polymorphism predicts stroke risk in men. Genet Epidemiol 2002;22:233–242.
35 Pezzini A, Grassi M, Del Zotto E, Bazzoli E, Archetti S, Assanelli D, et al: Synergistic effect of apolipoprotein E polymorphisms and cigarette smoking on risk of ischemic stroke in young adults. Stroke 2004;35:438–442.
36 Kessler C, Spitzer C, Stauske D, Mende S, Stadlmüller J, Walther R, et al: The apolipoprotein E and beta-fibrinogen G/A-455 gene polymorphisms are associated with ischemic stroke involving large-vessel disease. Arterioscler Thromb Vasc Biol 1997;17:2880–2884.
37 McIlroy SP, Dynan KB, Lawson JT, Patterson CC, Passmore AP: Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular dementia, and Alzheimer disease in Northern Ireland. Stroke 2002;33:2351–2356.
38 Chowdhury AH, Yokoyama T, Kokubo Y, Zaman MM, Haque A, Tanaka H: Apolipoprotein E genetic polymorphism and stroke subtypes in a Bangladeshi hospital-based study. J Epidemiol 2001;11:131–138.
39 Atadzhanov M, Mwaba MH, Mukomena PN, Lakhi S, Rayaprolu S, Ross OA, et al: Association of the APOE, MTHFR and ACE genes polymorphisms and stroke in Zambian patients. Neurol Int 2013;5:e20.
40 Baum L, Ng HK, Wong KS, Tomlinson B, Rainer TH, Chen X, et al: Associations of apolipoprotein E exon 4 and lipoprotein lipase S447X polymorphisms with acute ischemic stroke and myocardial infarction. Clin Chem Lab Med 2006;44:274–281.
41 Frikke-Schmidt R, Nordestgaard BG, Thudium D, Moes Grønholdt ML, Tybjaerg-Hansen A: APOE genotype predicts AD and other dementia but not ischemic cerebrovascular disease. Neurology 2001;56:194–200.
42 Um JY, Moon KS, Lee KM, Cho KH, Heo Y, Moon BS, et al: Polymorphism of angiotensin-converting enzyme, angiotensinogen, and apolipoprotein E genes in Korean patients with cerebral infarction. J Mol Neurosci 2003;21:23–28.