

Research Article

Apolipoprotein E ε 4 Polymorphism as a Risk Factor for Ischemic Stroke: A Systematic Review and Meta-Analysis

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Introduction. Rising studies indicate that the apolipoprotein E (APOE) gene is related to the susceptibility of ischemic stroke (IS). However, certain consensus is limited by the lack of a large sample size of researches. This meta-analysis was performed to explore the potential association between the APOE gene and IS. *Methods*. To identify relevant case control studies in English publications by October 2020, we searched PubMed, Embase, Web of Science, and the Cochrane Library. Pooled odds ratios (ORs) with fixed-or random-effect models and corresponding 95% confidence intervals (CIs) were calculated to analyze potential associations. *Results*. A total of 55 researches from 32 countries containing 12207 IS cases and 27742 controls were included. The association between APOE gene $\varepsilon 4$ mutation and IS was confirmed ($\varepsilon 4$ vs. $\varepsilon 3$ allele: pooled OR = 1.374, 95% CI, 1.214-1.556; $\varepsilon 2/\varepsilon 4$ vs. $\varepsilon 3/\varepsilon 3$: pooled OR = 1.233, 95% CI, 1.056-1.440; $\varepsilon 3/\varepsilon 4$ vs. $\varepsilon 3/\varepsilon 3$: pooled OR = 1.377, 95% CI, 1.244-1.556; $\varepsilon 2/\varepsilon 4$ vs. $\varepsilon 3/\varepsilon 3$: pooled OR = 1.333, 95% CI, 1.056-1.440; $\varepsilon 3/\varepsilon 4$ vs. $\varepsilon 3/\varepsilon 3$: pooled OR = 1.377, 95% CI, 1.203-1.576). Interestingly, APOE $\varepsilon 4$ mutation showed a dose-response correlation with IS risk ($\varepsilon 4/\varepsilon 4$ vs. $\varepsilon 2/\varepsilon 4$: pooled OR = 1.625; 95% CI, 1.281-2.060; $\varepsilon 4/\varepsilon 4$ vs. $\varepsilon 3/\varepsilon 4$: pooled OR = 1.301; 95% CI, 1.077-1.571). Similar conclusions were drawn in the small artery disease (SAD) subtype, but not in large artery atherosclerosis (LAA) or in cardioaortic embolism (CE), by subgroup analysis. *Conclusions*. These observations reveal that specific APOE $\varepsilon 4$ mutation was related to SAD subtype onset without a cumulative effect.

1. Introduction

Ischemic stroke (IS) is a disturbing problem worldwide, which is attributable to its leading role in disability and mortality worldwide, regardless of age, ethnicity, or gender [1]. Uncovering the etiology of IS is crucial for recognition and prevention of this disorder. Genetic elements and environmental components positively contribute to this multifactorial disease [2, 3]. Genetic inheritance provides a guide to the identification of high-risk individual. It deserves to investigate candidate gene polymorphisms in IS pathophysiological pathways. The apolipoprotein E (APOE) gene locates on chromosome 19q13.2. Two single polymorphisms (rs7412 and rs729358), three common alleles (ϵ_2 , ϵ_3 , and ϵ_4), and six genotypes (ϵ_2/ϵ_2 , ϵ_2/ϵ_3 , ϵ_2/ϵ_4 , ϵ_3/ϵ_3 , ϵ_3/ϵ_4 , and ϵ_4/ϵ_4) generate in populations [4]. The product of the APOE gene is a polymorphic protein named apolipoprotein E, which modulates the translocation of the cholesterol and other lipids among highly diverse cells [5], involved with neuroinflammation [6] and myelin integrity maintenance [7]. A study indicated that the activated CypA–MMP9 pathway in APOE4 carriers facilitated pericyte injury, which caused blood vessel dysfunction [8]. APOE polymorphisms and its risk associations with coronary artery disease [9], hypertension [10], diabetes [11], and carotid arterial atherosclerosis [12] are widely debated. The abovementioned diseases place individuals at a potential serious risk of IS. Individual studies of the association between IS and APOE polymorphisms have been explored extensively. Clinical differences, ethnic diversities, and small sample sizes restricted the present finding to an inconsistent and controversial one. Previous meta-analyses concerning to this issue have been published several years ago [13] or limited to specific ethnicity [14, 15]. Accordingly, researches from 32 countries are qualified to form our meta-analysis to clarify how APOE genotypes are associated with IS. Moreover, we firstly revealed the correlation of the APOE gene and three IS subtypes (large artery atherosclerosis (LAA), small artery disease (SAD), and cardioaortic embolism (CE)).

2. Materials and Methods

We followed the rules of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement to make this meta-analysis [16].

2.1. Data Availability. The data that contribute to the findings in our study are available and the corresponding authors can be contacted for data access.

2.2. Literature Search. Online databases (PubMed, Embase, Web of Science, and the Cochrane Library) were comprehensively searched for studies potentially involved and published in English publications and prior to October 30, 2020. We used a combination of some search terms relevant for IS (stroke, cerebral infarct, brain infarct, ischemic stroke, cerebral ischemia, transient ischemic attack, and cerebrovascular accident) and for the APOE gene (apolipoprotein E, APOE polymorphisms, apolipoprotein E polymorphisms, apolipoprotein E gene, rs429358, rs7412, apolipoprotein E epsilon 4, APOE e4, apolipoprotein E epsilon 2, and APOE e2). The detailed search strategies were showed next.

2.3. Selection Criteria. The selection of the studies was independently completed by two investigators, and any difference was resolved by discussion until an agreement was reached. We carefully selected case control studies that evaluated the relationship of the APOE gene and IS with definite IS diagnoses (using computed tomography, magnetic resonance, or autopsy) regardless of the ethnic background. The detailed inclusion criteria were (1) high-quality studies which explore the relationship between the APOE gene and IS, (2) explicit IS diagnostic criteria, (3) nonstroke individuals as the control group, and (4) original data including independent and sufficient APOE genotype data, to compute ORs and 95% CIs. The newest and largest studies were chosen to avoid duplicate or overlapped data information.

2.4. Data Extraction. Two investigators separately finished full-text reading to extract the needed information from each selected study and resolved the controversial items through serious discussion. The extracted information was (1) research characteristics, including the first author's name, year of publication, and geographical location of the study; (2) participant details, such as the sex ratio, mean age, and the sample size of case and control groups; (3) diagnostic criteria for IS; (4) determination methods of the APOE gene; (5) each genotype frequency; (6) the sample sizes of IS subtypes according to TOAST norms and respective genotype frequency; and (7) HWE in controls. 2.5. Quality Assessment. We performed the quality assessment through the Newcastle-Ottawa Scale (NOS) score considering selection, comparability, and exposure. It ranged from 0 (worst) to 9 (best) and high-quality studies were known as with a NOS score \geq 7.

2.6. Statistical Analysis. We performed Stata 14.0 to complete all data analyses. The chi-square test was used to examine the Hardy-Weinberg equilibrium (HWE) in control groups. An overt deviation from HWE was regarded as P < 0.05. The compositive ORs and 95% CI were calculated. We explored five genetic models to generate the respective pooled ORs: (1) allele comparisons (ɛ2 allele vs. ɛ3 allele; ϵ 4 allele vs. ϵ 3 allele); (2) genotype comparisons (ϵ 2/ ϵ 2 vs. ε3/ε3; ε2/ε3 vs. ε3/ε3; ε2/ε4 vs. ε3/ε3; ε3/ε4 vs. ε3/ε3; ε4/ε4 vs. $\varepsilon 3/\varepsilon 3$; (3) APOE $\varepsilon 4$ carrier comparisons: we defined three ε 4-containing genotypes ($\varepsilon 2/\varepsilon 4 + \varepsilon 3/\varepsilon 4 + \varepsilon 4/\varepsilon 4$) as genotypes carriers and the other APOE $\epsilon 4$ $(\varepsilon 2/\varepsilon 2 + \varepsilon 2/\varepsilon 3 + \varepsilon 3/\varepsilon 3)$ as non-APOE $\varepsilon 4$ carriers; (4) APOE $\varepsilon 2$ carrier comparisons: similar comparisons of $\varepsilon 2$ -containing genotypes $(\varepsilon 2/\varepsilon 2 + \varepsilon 2/\varepsilon 3 + \varepsilon 2/\varepsilon 4)$ vs. non- $\varepsilon 2$ -containing genotypes $(\varepsilon 3/\varepsilon 3 + \varepsilon 3/\varepsilon 4 + \varepsilon 4/\varepsilon 4)$; and (5) comparisons between APOE ε 4 homozygosis and ε 4 heterozygote (ε 4/ ε 4 vs. $\varepsilon 2/\varepsilon 4$; $\varepsilon 4/\varepsilon 4$ vs. $\varepsilon 3/\varepsilon 4$). The I^2 statistic and Cochran's Q test were applied to measure the heterogeneity between studies [17]. We selected the random effect model (DerSimonian-Laird method) when heterogeneity was found between studies $(I^2 > 50.0\%)$ and fixed-effect model (Mantel-Haenszel method) when no heterogeneity existed $(I^2 < 50.0\%)$. Subgroup analysis was conducted to confirm the relationship between the APOE polymorphisms and the risk of different IS subgroups. Sensitivity analysis was performed by successively removing a single study one by one to verify the stability and reliability of our conclusions. Meta-regression analysis was operated to recognize sources of heterogeneity. Funnel plots and quantified Egger's tests were accomplished to test publication bias. Significant publication bias was considered as the *P* value of Egger's test less than 0.10 or obvious asymmetric funnel plot.

2.7. The Result of Trial Sequential Analysis (TSA). Insufficient sample size, continuous updating, and repeating " significance testing" could increase the risk of type I errors. Therefore, traditional meta-analysis that focuses on the specific topic may suffer an increased risk of random error. Trial sequential analysis (TSA) was used to reduce the risk of type I error and obtain important information regarding the required sample size for such trials. Set the time sequence of a single study as the research node, and then, perform an interim analysis between the new study that will be included in meta-analysis and existing data accumulation. The required information size (RIS), trial sequential monitoring boundary, and futility boundary are estimated using the TSA. As the sample size of meta-analysis reaching the RIS or the z-curve crossing the trial sequential monitoring boundary, we can conclude that the results of metaanalysis are quite stable and further studies were not needed. We accomplished TSA following the guidelines of the user manual and previous article [18] by setting a



FIGURE 1: A flow diagram of identification and selection process of the included literatures in this meta-analysis.

significance of 5% for type I error, a relative risk reduction of 20%, and a statistical test power of 80% with TSA software (TSA, version 0.9 beta; Copenhagen Trial Unit, Copenhagen, Denmark).

3. Results

3.1. Characteristics of Eligible Studies. We collect a total of 55 studies from 32 countries containing 12207 IS cases and 27742 controls to make the meta-analysis [19–73]. Figure 1 showed the detailed selection process. The selected studies and their main characteristics were exhibited in Table 1. Fifteen of the studies provided data about different subtypes (grouped by classification of cerebrovascular diseases III or TOAST classification) of IS: large artery atherosclerosis (LAA), small artery disease (SAD), and cardioaortic embolism (CE). We extracted them independently and specific information was showed in supplementary material table 1. There were seven studies (Koopal et al. 2016, Lai et al. 2007, Chowdhury et al. 2001, Kokubo et al. 2000, Ji et al. 1998, Couderc et al. 1993, Saidi et al. 2009) which deviated HWE obviously, and one study (Schneider et al. 2005) did not contain enough data to obtain HWE. Forty-eight studies used PCR-based method and seven researches (Slowik et al. 2003, Karttunen et al. 2002, Hachinski et al. 1996, Couderc et al. 1993, Brewin et al. 2020, Aalto-Setala et al. 1998, Schneider et al. 2005) used other methods to identify APOE genotypes. These studies used computed tomography or magnetic resonance to diagnose IS except that one research which used autopsy (Schneider et al. 2005). The NOS score mean value was 7.509, which suggested that the quality of included studies was reliable (supplementary material Table 2). PRISMA2020 checklist

was provided to present our meta-analysis items (supplementary material Table 3).

3.2. Main Results of the Comparisons in the Abovementioned Five Genetic Models

3.2.1. Allele Comparisons. In comparison with the ε 3 allele, the ε 2 allele did not show association of the risk of IS (pooled OR = 0.983, 95% CI, 0.867-1.115, P = 0.79) (as showed in Table 2), while the ε 4 allele contributed to an obviously increased risk of IS with the pooled OR = 1.374 (95% CI, 1.214-1.556, P < 0.0001) (Figure 2(d)).

3.2.2. Genotype Comparisons. When compared with the $\epsilon 3/\epsilon 3$ genotype, the pooled effects of the APOE genotype in the meta-analysis were as follows: for the $\epsilon 2/\epsilon 2$ genotype, pooled OR = 0.985, 95% CI, 0.653-1.486, P = 0.94, and for the $\epsilon 2/\epsilon 3$ genotype, pooled OR = 0.980, 95% CI, 0.900-1.066, P = 0.63; those two genotypes presented no association with the risk of IS (as showed in Table 2). Genotypes $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$ were related to a higher risk of IS than $\epsilon 3/\epsilon 3$. The respective IS risk ORs were 1.233 (95% CI, 1.056-1.440, P = 0.01) (Figure 2(a)), 1.340 (95% CI, 1.165-1.542, P < 0.0001) (Figure 2(b)), and 1.833 (95% CI, 1.542-2.179, P < 0.0001) (Figure 2(c)). The above results could be found in Table 2. A conclusion was drawn: every genotype which contained APOE $\epsilon 4$ mutation increased the risk of IS.

3.2.3. APOE $\varepsilon 4$ Carrier Comparisons. Compared with the non- $\varepsilon 4$ carriers, we confirmed that the $\varepsilon 4$ carriers were associated with the increased risk of IS; the pooled outcome was pooled OR = 1.377 (95% CI, 1.203-1.576, *P* < 0.0001) (Figure 2(e)).

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TABL

Study ID	Region	Criteria for IS	Genotyping method	Source of control	Group	Sample size	Chai Male/ <i>n</i> (%)	acteristics and Age(years)	1 the $\varepsilon 2/\varepsilon 2$	$\varepsilon 2/\epsilon$	s of ev ε2/ ε4	ery gei 3/ 5	notype 33/ε ε4 ε	4/ £2 34 alle	$\frac{\varepsilon}{\varepsilon}$	3 ele al	e4 I lele	N E	
	, ito	TALAT	d C d	4	Case	938	581 (61.9%)	65.6 ± 10.6	2	63	18 (84 1	56 1	5 85	5 158	87 2	04	0	
Wu el ál., 2020 [19]	CIIIIa	C1/MIN	FOR	Q-L1	Control	1028	622 (60.5%)	63.7 ± 12.4	6	131	13	763]	90	6 16	2 170	53 1	31	0	
Zhan et al 2017 [20]	China	CT/MRI	DCR	H_R	Case	513	294 (57.3%)	62.3 ± 12.2	Э	63	7	347	85	8 76	6 84	1	80		
ביוומט כו מוי, בטוו [בט]	Cullia			G_11	Control	514	288 (56.0%)	61.7 ± 13.5	5	70	8	366	64	1 88	3 86	99	74		
Coen Herak et al.,	Crootio	CTMDI	۵J۵	а 2	Case	73	48 (65.8%)	$4.3 \pm X$	0	10	5	50	11	0 12	12	1		α 2	
2017 [21]	Ol Udua		I CIV	<u>с</u> - 1	Control	100	63 (63.0%)	$6.5 \pm X$	1	11	0	74	13	1 13	3 17	2	15	0	
Dac at al 2016 [22]	Indian	CTME	DCP_PEI D	а 2	Case	620	434 (70.0%)	49.4 ± 17.4	5	46	9	[31]	[20]	2 62	2 10	28 1	50	α 2	
17 as c1 at., 2010 [44]				<u>,</u>	Control	620	428 (69.0%)	49.1 ± 16.9	2	50	4	136]	[13]	2 64	1 10	35 1	41		
Koopal et al., 2016	- F	Ę	u ب	-	Case	278	NA	NA	3	30	8	. 60	69	8 44	4 41	6)3	ז -	
[23]	INETHERIANDS	CI S	PUK	P-D	Control	4220	NA	NA	50	389	96 2	422 1	127 1.	36 58	5 63(60 14	195 ¹	-	
1 بنہ 1 میں 1 15 [127]	China	CT/MRI	DCR	H_R	Case	712	465 (65.3%)	65.2 ± 13.9	4	93	13 4	[194	101	7 11	4 113	82 1	28	L 7	
דמס כו מוי, בטוט [בד]	CIIIIa			d _11	Control	774	418 (54.0%)	51.5 ± 16.9	3	107	8	35 1	13	8 12	1 129	90 1	37	`	
Woi of al 2015 [25]	Molonia	CTMDI	den	a Q	Case	297	33 (11.1%)	52.6 ± 8.8	80	68	23	37	54	7 10	7 39	5 9	, 16	0 2	
WEI EL 41, 2013 [2]	זעדמדמ אסדמ		LCN	ст- 1	Control	297	119 (40.0%)	51.8 ± 8.7	4	12	27	.63	89	2 47	7 42	7 1	20	0	
Van et al 2015 [26]	China	CT/MRI	DCR-REI D	H_R	Case	580	387 (66.7%)	59.8 ± 13.7	11	41	33	351	82 (52 96	6 82	5 2	39	×	
[07] 0107 (in 12 lin 1				1	Control	580	379 (65.3%)	59.4 ± 13.1	61	54	49 🔅	354	33 2	9 22	5 79	5 1	40		
Chatzistefanidis et al.,	Greece	CT/MRI	рСк	H-R	Case	329	225 (68.4%)	59.7 ± 11.6	33	36	ŝ	27	56	4 45	5 54	9	22	~ ~	
2014 [27]				1	Control	361	205 (56.8%)	60.4 ± 13.7	5	24	8	278	47	2 3(§ 62	5	65		

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UIFr-43	Locico C	Criteria	Genotyping	Source of			Chai Mala/12	racteristics an	d the	count	s of ev	rery ge	notype		ç	5	5	1	
study ID	kegion	for IS	method	control	Group	size	Male/n (%)	Age(years)	ε21 ε2	Е2I Е3	ε4	ез/ е3	e 1c3 e4	ε4/ a ε4 al	ez lele a	es Ilele a	ε4 allele	ц	2
A tadzhanov et al					Case	23	NA	54.0 ± 16.0	0	4	3	6	4	0	7	29	10		
2013 [28]	Zambian	CT	PCR	P-B	Control	116	50 (41.4%)	NA	0	25	4	38	37	6	32	138	62	Y	6
Gelfand et al., 2013	America	CT/MRI	DCR-REI D	Я.Н	Case	13	10 (77.0%)	NA	0	1	7	5	ŝ	2	3	14	6	>	α
[29]	111111110			л-11	Control	84	46 (55.0%)	NA	0	8	3	55	16	5	11	134	23	-	0
Balcerzyk et al., 2010	Poland	CT/MRI	PCR	P.R	Case	72	42 (58.3%)	8.8 ± 5.6	1	6	0	52	9	4	E	119	14	7	
[30]			, , ,	4	Control	71	41 (57.8%)	8.2 ± 5.4	0	×	0	51	11	1	∞	121	13	•	
Tamam et al 2000					Case	65	NA	NA	0	~	2	50	5	1	6	112	6		I
[31]	Turkey	CT/MRI	PCR	H-B	Control	30	10 (33.3%)	61.9 ± 14.7	0	1	П	25	5	П	5	53	5	Y	
Tascilar et al., 2009	Turkev	CT/MRI	PCR	р. я	Case	85	51 (60.0%)	61.7 ± 13.6	Э	18	ŝ	45	6	~	27	117	26	>	
[32]	i ann i			-	Control	77	25 (32.5%)	54.7 ± 8.4	3	16	4	40	6	2	50	105	20	-	
Wang et al 2009 [33]	China	CT/MRI	рСк	H.R	Case	396	209 (52.8%)	57.3 ± 8.2	16	98	60	124	87	11 1	, 06	433	169	z	
1007 (201) [20]					Control	396	202 (51.0%)	57.3 ± 8.1	33	116	41	164	39	3 2	23	483	86		、
I ai et al 2007 [34]	China	MRI	DCP	Я.Н	Case	257	164 (63.8%)	63.7 ± 8.2	1	17	10	162	67	0	, 61	408	77	Z	×
דמו עו מוי, ביטט [יד]		INITAT		-11 -	Control	112	54 (48.2%)	71.0 ± 10.6	4	5	5	78	19	1	8	180	26	4	b
Parfenov et al., 2007	Vakutek	CT/MRI	рСк	Р. Я	Case	107	69 (64.5%)	58.4 ± 11.5	1	5	-	63	33	4	8	164	42	>	x
[35]				-	Control	101	61 (59.4%)	57.6 ± 11.6	1	15	3	58	22	2	20	153	29	4	>
Kang and Lee.2006	Korea	MRI	DCR	н. в	Case	194	116 (59.8%)	62.0 ± 9.5	0	24	0	126	44	0	24	320	44	>	x
[36]	1001				Control	168	94 (55.9%)	62.3 ± 6.3	5	18	0	128	19	-	52	293	21		>

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Study ID	Region	Criteria for IS	Genotyping method	Source of control	Group	Sample size	Char Male/ <i>n</i> (%)	acteristics an Age(years)	d the ε2/ ε2	count: ɛ2/ ɛ3	s of ev ε2/ ε4	rery ge ɛ3/ ɛ3	notype ɛ3/ . ɛ4	e4/ e/ e4 alle	$2 \varepsilon^{2}$	3 ε ele all	4 <i>I</i> ele	N I	
Gan et al 2006 [37]	China	CT/MRI	рСв	ЯД	Case	100	71 (71.0%)	61.1 ± 10.8	-	11	0	75	13	0 1	3 17	4 1		∝	1
Uau et at., 2000 [77]	CIIIIIa		ION	n-11	Control	100	71 (71.0%)	61.0 ± 10.6	1	13	0	80	9	0 1	5 17	6		0	
Baum at al 2006 [20]	Chino	UT/MDI	aJa	a a	Case	243	134 (54.5%)	70.7 ± 12.0	7	39	9	155	32	4 5	9 38	1 4	9	0	
Daum et al., 2000 [20]	CIIIIId		ICN	d-1	Control	311	152 (45.2%)	70.0 ± 5.9	7	60	9	203	39	1 7	0 50	5 4		0	
Pezzini et al., 2005	Italy	CT/MRI	ЪСR	H_R	Case	163	84 (51.5%)	35.0 ± 7.5	7	12	1	109	38	1 1	7 26	8 4		α	
[39]	, mut			n-11	Control	158	85 (53.8%)	34.8 ± 6.1	0	16	1	120	21	0 1	7 27	7 2	5	0	
Cerrato et al., 2005	140]	TUMPT	aJa	а С	Case	302	100 (33.1%)	57.0 ± 11.0	6	31	0	230	28	4 4	9 51	9 3	۔ و		
[40]	тнагу		LON	ц-1	Control	228	104 (33.1%)	55.0 ± 16.0	3	25	1	158	37	4 3.	2 37	8		`	
[11] 2000 [2] 2001	, inc.	IdMAD	חכם חכם	ם	Case	226	129 (57.1%)	48.5 ± 3.4	2	14	3	152	52	3 2	1 37	9 0.	1	0	
JIII El al., 2004 [41]	Cullia	C1/MINI	FUR-RFLF	<u>а</u> -7	Control	201	109 (54.2%)	47.1 ± 2.4	5	17	5	156	22	2	3 35	1 2	~ ∞	0	
Duzenli et al 2004					Case	62	NA	NA	0	×		52	-	5 0	11	3			
[42]	Turkey	CT	PCR	P-B	Control	126	61 (48.4%)	58.0 ± 1.9	2	23	2	80	18	1 2	9 20	1 2	2	8	
Slowik et al., 2003	paelod	CT/MRI	Immuno-	н_в	Case	71	49 (69.0%)	59.6 ± 9.5	0	3	0	53	14	1 3	12	3 1	9	-	
[43]	n nimin		blotting	<u>a</u> -11	Control	30	19 (63.4%)	63.1 ± 8.8	0	1	0	21	×	0 1	5	1	~		
Source of al 2003 [AA]	Rraril	ΤĊ	DCP	a d	Case	107	NA	68.8 ± 9.2	0	5	0	93	×	1	19	9 1	0	, ,	
JULLA EL AL., 2003 [71]	דו מבוו	0	LUN	ц-1	Control	100	NA	69.4 ± 8.3	0	8	5	74	16	0 1	0 17	2 1	_ ∞	0	
Karttunen et al., 2002	Finland	CT/MRI	Immuno-	р_R	Case	44	27 (61.4%)	15-60	0	З	П	27	13	0	f 70	0 1	4	x	
[45]			blotting	-	Control	104	59 (56.7%)	15-60	1	4	1	67	28	3 7	, 16	6 3	5		
Morrison et al., 2002	America	MRI	PCR	P-B	Case	400	NA	NA	1	48	19	199	118	15 6	9 56	4 10	57	7	
[46]		;	1	I	Control	1104	NA	NA	5	148	39	596	288	28 15	7 16	28 38	33		1

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TABLE

e3 e4 H N lele allele	25 69 Y 7	•	49 75	49 75 55 30 M 6	49 75 55 30 33 34 N 6	49 75 55 30 33 34 6 102 264 v 6	49 75 55 30 53 34 33 34 102 264 102 264 103 2958	49 75 55 30 6 33 34 6 102 264 7 102 264 7 102 2958 7 18 143 7	49 75 55 30 53 34 33 34 102 264 102 264 470 2958 18 143 18 143 46 88	49 75 55 30 53 34 33 34 102 264 102 264 470 2958 18 143 18 143 18 143 18 188 24 37	49 75 55 30 53 34 133 34 102 264 470 2958 143 Y 166 88 24 37	49 75 55 30 55 30 33 34 102 264 102 264 470 2958 18 143 146 88 24 37 313 236 24 37	$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	49 75 55 30 55 30 33 34 6 33 470 2958 18 143 18 143 146 88 24 37 21 37 913 236 42 24 42 24 43 7 44 33	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	49 75 55 30 55 30 33 34 102 264 102 264 470 2958 470 2958 13 24 24 37 24 37 24 37 24 37 25 11 96 38 97 38 98 98 96 38 97 38 98 11 98 18 90 38 91 7	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	49 75 55 30 55 30 33 34 33 34 102 264 470 2958 470 2958 18 143 143 7 46 88 313 236 42 24 313 236 42 24 50 11 7 7 61 87 86 38 61 87 45 69 45 53 45 53 7 8	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
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ε4 ε4	56 3	63 3		26 2	26 2 29 2	26 2 29 2 207 17	26 2 29 2 207 17 244 241	26 2 29 2 207 17 244 241 244 241 115 10	26 2 29 2 207 17 244 241 115 10 69 6	26 2 29 2 207 17 244 241 115 10 69 6 33 1	26 2 29 2 207 17 244 241 115 10 115 10 69 6 63 1 33 1	26 2 29 2 207 17 244 241 15 10 69 6 69 6 33 1 202 13 19 2	26 2 29 2 207 17 204 241 115 10 115 10 69 6 69 6 33 1 33 1 33 1 8 1	26 2 29 2 207 17 207 17 215 10 115 10 69 6 63 1 202 13 19 2 8 1 23 3	26 2 29 2 207 17 207 17 215 10 115 10 69 6 33 1 33 1 202 13 19 2 8 1 8 1 19 2 14 0	26 2 29 2 207 17 207 17 215 10 115 10 33 1 33 1 33 1 202 13 202 13 202 13 202 13 219 2 19 2 14 0 14 0	26 2 29 2 207 17 207 17 244 241 15 10 69 6 69 6 33 1 202 13 202 13 8 1 19 2 8 1 19 2 8 1 14 0 78 1	26 2 29 2 207 17 207 17 204 241 215 10 115 10 233 1 33 1 202 13 202 13 219 2 29 3 14 0 244 1 78 1 78 1	26 2 29 2 207 17 207 17 207 17 207 17 203 1 33 1 33 1 202 13 202 13 202 13 214 0 19 2 214 0 14 0 14 0 15 7 50 7 43 2	26 2 29 2 207 17 207 17 207 17 207 17 208 6 69 6 33 1 202 13 202 13 202 13 214 0 19 2 24 6 33 1 202 13 214 0 78 1 78 1 250 7 24 3 24 3
3	170 5	133 (113	7 CTT	149	149 2	149 2 149 2 1409 2 2 5050 22	149 2 149 2 2 5050 2 321 1	149 2 149 2 2 5050 2 321 1 170 0	149 2 149 2 2 5050 22 321 1 170 6 138 2	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	149 2 149 2 2 5050 22 321 1 321 1 170 (819 2 55	149 2 149 2 2 5050 22 321 1 170 6 138 5 819 2 63	149 2 149 2 321 1 321 1 170 6 819 2 55 63 63 63	149 2 149 2 321 1 321 1 170 6 819 2 63 63 95 95	149 2 149 2 321 1 321 1 138 5 819 2 55 5 79 5 95 5	149 2 149 2 321 1 321 1 321 1 170 6 819 2 55 2 79 5 59 5 368 368	149 2 149 2 321 1 321 1 321 1 321 1 321 1 321 2 9 3 63 63 59 5 59 5 368 3 132 1	149 2 149 2 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 2 323 3 368 3 368 3 368 1 132 1 149 1	149 2 149 2 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 1 321 2 325 2 368 2 368 2 368 2 132 2 132 2 149 4
	29 7	20 6	3 0		6 1	6 1 77 23	6 1 77 23 1126 232	6 1 77 23 1126 232 61 8	6 1 77 23 1126 232 61 8 37 7	6 1 77 23 1126 232 61 8 37 7 15 2	6 1 77 23 77 23 1126 232 61 8 37 7 15 2 73 8	6 1 77 23 77 232 11126 232 61 8 61 8 37 7 15 2 15 2 13 1	6 1 77 23 77 23 1126 232 61 8 61 8 37 7 15 2 13 1 13 1 16 1	6 1 77 23 77 23 1126 232 61 8 61 8 37 7 15 2 15 2 13 1 13 1 16 1 9 3	6 1 77 23 11126 232 61 8 37 7 15 2 15 2 13 1 13 1 16 1 9 3 9 3 16 1 16 1 16 1 16 1 9 3 9 3 9 3	6 1 77 23 77 23 1126 232 61 8 61 8 37 7 37 7 15 2 15 2 13 1 13 1 16 1 9 3 9 3 10 0	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	6 1 77 23 77 23 1126 232 61 8 61 8 61 8 1126 232 12 2 13 1 16 1 9 3 9 3 9 3 10 0 110 0 231 5 24 6 234 6	6 1 77 23 77 23 1126 232 61 8 61 8 61 8 1126 232 7 7 15 2 13 1 13 1 13 1 13 1
12.2 1 :1.0 0	: 1.0 0		11.1 3	: 9.6 3		: 7.4 5	: 7.4 5 : 0.2 45 1	:7.4 5 :0.2 45 1 ± <i>X</i> 0	:7.4 5 :0.2 45 1 ± X 0 ± X 0	: 7.4 5 : 0.2 45 1 ± X 0 ± X 0 89 12	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
() 65.7 ± 1) 77.0±	() 57.9±1	() 60.3±		() 63.0±	 (3.0 ± (57.2 ± 	$\begin{array}{c} 63.0 \pm \\ 57.2 \pm \\ \end{array}$	$\begin{array}{c} (1) & (5.0 \pm 1) \\ (2) & (57.2 \pm 1) \\ (1) & (73.0 \pm 1) \\ (2) & (72.5 \pm 1) \\ (1) & (72.5 \pm 1) \\ (2) & (1) & (1) \\ (2) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (2) & (2) \\ (3) & (3) & (2) \\ (3) & (3) & (2) \\ (3) & (3) & (2) \\ (3) & (3) & (2) \\ (3) & (3) & (2) \\ (3) & (3) & (3) \\ ($	$\begin{array}{c} (1) & (5.0 \pm \\ (2) & (57.2 \pm \\ (1) & (73.0 \pm \\ (1) & 72.5 \pm \\ (1) & (10-8) \end{array}$	$\begin{array}{c} (1) 63.0 \pm \\ (2) 57.2 \pm \\ (3) 73.0 \pm \\ (3) 72.5 \pm \\ (40-8) 40-8 \\ (4) 64.3 \pm 1 \end{array}$	$\begin{array}{c} (1) 63.0 \pm \\ (2) 57.2 \pm \\ (3) 73.0 \pm \\ (3) 72.5 \pm \\ (40-8 \\ 40-8 \\ (52.6 \pm \\ 62.6 \pm \end{array})$	$\begin{array}{c} (1) 63.0 \pm \\ (2) 57.2 \pm \\ (3) 73.0 \pm \\ (3) 72.5 \pm \\ 40-8 \\ 40-8 \\ 64.3 \pm 1 \\ 62.6 \pm \\ 63.1 \pm \end{array}$	$\begin{array}{c} (0,0) = (0,0) \\ (0,0) =$	$\begin{array}{c} (1) 63.0 \pm \\ (2) 57.2 \pm \\ (3) 73.0 \pm \\ (2) 72.5 \pm \\ 40-8 40-8 40-8 (2) 64.3 \pm 1 (2) 64.3 \pm 1 (2) 62.6 \pm \\ (2) 62.6 \pm 63.1 \pm \\ (7) 70.2 \pm \\ 71.5 \pm \end{array}$	$\begin{array}{c} (0,0) =$	$\begin{array}{c} (1) 63.0 \pm \\ (2) 57.2 \pm \\ (3) 73.0 \pm \\ (3) 72.5 \pm \\ (40-8) 40-8 \\ (40-8) 12 40-8 \\ (40-8) 12 40-8 \\ (53.1 \pm \\ (53.1 \pm \\ 71.5 \pm \\ 71.5 \pm \\ (3) 11.5 \pm \\ (3) 11$	$\begin{array}{c} (1) 63.0 \pm \\ (2) 57.2 \pm \\ (3) 73.0 \pm \\ (3) 72.5 \pm \\ 40-8 \\ 40-8 \\ 40-8 \\ 40-8 \\ 40-8 \\ 12.5 \pm \\ (3) 1 \pm \\ 70.2 \pm \\ 71.5 \pm \\ 71.5 \pm \\ 71.5 \pm \\ 70.2 \pm \\ 1 \end{array}$	$\begin{array}{c} (0,0) = (0,0) \\ (0,0) =$	$\begin{array}{c} (3.0 \pm 1) \\ (3.0 \pm 1) \\$
150	(56.4%)	94 (41.7%)	116 (79.9%)	129	(67.7%)	(67.7%) 282 (61.8%)	(67.7%) 282 (61.8%) 4022 (45.0%)	(67.7%) 282 282 (61.8%) 4022 (4022 (45.0%) (50.3%)	(67.7%) 282 (61.8%) 4022 (45.0%) (50.3%) (50.3%) (52.2%)	(67.7%) 282 (61.8%) 4022 (45.0%) (50.3%) (50.3%) 151 (52.2%) NA	(67.7%) 282 282 (61.8%) 4022 (45.0%) (50.3%) (50.3%) 151 151 151 (52.2%) NA NA 333 (29.7%)	(67.7%) 282 (61.8%) 4022 4022 259 (50.3%) (50.3%) 151 151 (52.2%) NA 333 333 (29.7%) NA	(67.7%) 282 (61.8%) 4022 (45.0%) (45.0%) (50.3%) 151 151 (52.2%) NA NA NA NA	(67.7%) 282 (61.8%) 4022 259 (50.3%) 151 151 (52.2%) NA NA NA NA NA NA	(67.7%) 282 282 (61.8%) 4022 (45.0%) (50.3%) 151 151 151 (52.2%) NA NA NA NA NA	(67.7%) 282 282 (61.8%) 4022 (45.0%) (50.3%) (50.3%) (50.3%) NA NA NA NA NA NA NA NA NA NA NA NA NA	(67.7%) 282 (61.8%) 4022 (45.0%) (50.3%) 151 151 151 151 151 (52.2%) NA NA NA NA NA NA NA NA NA NA NA NA NA	(67.7%) 282 282 (61.8%) 4022 (45.0%) (50.3%) 151 151 151 (52.2%) NA NA NA NA NA NA NA NA NA NA NA NA NA	(67.7%) (61.8%) (61.8%) (61.8%) (61.8%) (4022) (45.0%) (50.3%) (50.3%) (50.3%) (50.3%) (50.3%) (51.0%) NA NA NA NA NA NA NA NA NA (67.7%) (61.8%) (61.	(67.7%) (61.8%) (61.8%) (61.8%) (4022) (45.0%) (405.3%) (4010%) (47.6%) (61) (67.8%) (61) (67.8%)
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	Case	Control	Case		Control	Control Case	Control Case Control	Control Case Control Case	Control Case Control Case Case	Control Case Control Case Control Case Control	Control Case Case Control Control Case Control	Control Case Control Case Control Case Control Case Case Case Case Case Case Case Case	Control Case Control Case Control Case Control Case Control Case Control	Control Case Control Case Control Case Control Case Control Case Control Case Control Case Control Case Case Control Case Control Case Control Control Control Case Control Control Control Control Control Control Control Control Control Control Control Control Case Control Case Control	Control Case Control Case Control Case Control Case Control Case Control Case Control Case Control Control Case Control	Control Case Control Case Control Case Control Case Control Case Control Case Control Case Control Case Case Control Case Control Con Control	Control Case Control Control Control Case Case Case Control Case Control Control Control Control Control Control	Control Case Case Control Case Case Case Control Case Case Case Case Case Case Case Case	Control Case Control Case Control Case Control Case Control Case Case Control Case Control Control Control Control Control	Control Case Control Case Control Case Case Case Control Case Control Case Control Con
	P-B	4	п	д-Ш		a d	P-B	B-q a	P-B P-B	P-B P-B	P-B P-B	P-B	P-B P-B H-B	P-B P-B H-B H-B	P-B P-B H-B P-B	P-B P-B P-B P-B P-B	P-B P-B P-B P-B	P-B P-B P-B P-B P-B	P-B P-B P-B P-B H-B H-B	P-B P-B H-B P-B P-B P-B P-B P-B
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	MacLeod et al., 2001	[47]	Chowdhury et al.,	2001 [48]		Frikke-Schmidt et al.,	Frikke-Schmidt et al., 2001 [49]	Frikke-Schmidt et al., 2001 [49]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kolenbo et al., 2000	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52] Ji et al., 1998 [53]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52] Ji et al., 1998 [53]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52] Ji et al., 1998 [53] Margaglione et al., 1998 [54]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52] Ji et al., 1998 [53] Margaglione et al., 1998 [54] Kessler et al., 1997	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52] ji et al., 1998 [53] Margaglione et al., 1998 [54] Kessler et al., 1997 [55]	Frikke-Schmidt et al., 2001 [49] Catto et al., 2000 [50] Kokubo et al., 2000 [51] Peng et al., 1999 [52] Ji et al., 1998 [53] Margaglione et al., 1998 [54] Margaglione et al., 1997 [55] Hachinski et al., 1996

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TABLE	

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Study ID	Region	Criteria	Genotyping	Source of	C	Sample	Char Male/ <i>n</i>	acteristics an	d the ε2/	count: ε2/	s of ev ε2/	ery ge ɛ3/	notype ɛ3/	ε ε4/ ε	5 5	ŝ	54	N	
)	IOT IS	method	control	Group	size	(%)	Age(years)	ε2	ε3	ε4	ε3	$\varepsilon 4$	ε4 all	ele all	ele al	lele		
Couderc et al., 1993	Ē	Ę	Ë	G 11	Case	69	36 (52.2%)	72.3 ± 11.6	Ц	~	0	50	10	-	9	17	12	г -	
[57]	France	CI	ЧT	п-Б	Control	566	347 (61.3%)	41.3 ± 15.3	8	60	5	377	109	7 8	1 9.	23 1	28	~	
Oion of al 2012 [50]	Chino	CTANDI	aud	п	Case	152	87 (57.2%)	66.8 ± 5.5	0	21	0	95	29	7 2	1 2,	40	43		
Qiall et al., 2012 [30]	CIIIIa		FON	Q-11	Control	40	13 (32.5%)	64.0 ± 12.6	0	5	0	29	9	0	5 6	6	9		
Konialis et al., 2016		μ	aud	п	Case	200	142 (72.0%)	60.0 ± 16.0	0	10	ŝ	145	39	3 1	3	39	48		
[59]	DICCCC	5	LON	<i>п-</i> 11	Control	159	76 (47.5%)	59.0 ± 13.0	п	16	0	126	16	0 1	8	84	16	_	
Earned at al 2000 [60]	Econot	CTMADI	DCD DELD	d H	Case	40	NA	NA	0	3	7	11	11	8	0 3	9	34	2	
rayed et al., 2009 [00]	Egypt		FUR-KFLF	q-Ц	Control	20	NA	NA	0	3	Ч	15	1	0	4	4	2	0	
Stankovic et al., 2004	Coubion	CTME		d d	Case	65	NA	NA	0	6	0	39	18	5	6 1(02	22		
[61]	0C1 D1411		FUN-NFLF	ц-1	Control	330	NA	NA	12	56	7	205	47	3 8	3 5	13 (50	`	
Pedro-Botet et al.,	Croin	Ъ	DCD	аq	Case	100	NA	NA	2	12	0	54	26	6 1	6 1	46	38	7	
1992 [62]	opanı	71	FUN	Г-Л	Control	100	NA	NA	0	13	2	69	13	3 1	5 10	54	21	· _	
Fekih-Mrissa et al.,	Tunicio		DCD	аq	Case	9	NA	NA	0	0	0	0	5	1	0	10	7	7	
2014 [63]	picilin I		ICN	ц-1	Control	42	NA	NA	0	8	0	18	15	1	8 5	6	17		
Brewin et al., 2020	Iondon	CTMDI	Exome	D B	Case	47	NA	NA	0	5	8	14	14	6 1	3 4	2	34	7	
[64]	TIONIOT		sequenc-ing	1-1	Control	236	NA	NA	9	41	11	97	71	10 6	64 30	06 1	02	` _	
Saidi et al 2009 [65]	Tunisia	CT/MRI	РСК	Р.В	Case	228	114 (50.0%)	61.5 ± 12.1	0	14	25	74	87	28 3	9 2	49 1	68	×	
				4	Control	323	177 (54.8%)	60.9 ± 12.8	0	27	28	187	71	10 5	5 4	72 1	19	> -	
	China	MDT	DCD	ад	Case	67	NA	70.7 ± 11.4	4	4	2	41	11	2 1	7 10	00	17	0	
	CIIIIa	TATIAT	ICIV	n- 1	Control	134	NA	NA	2	24	3	89	15	1 3	1 2	17	20		
Giassakis et al., 2007	Treece	CT/MRI	aUd	ц Ц	Case	100	70 (70.0%)	60.7 ± 9.8	NA	NA	NA	AN	NA 1	I AN	2 10	26	22	×	
[67]	mn			n - 1	Control	96	66 (68.8%)	61.3 ± 9.8	NA	NA	NA	AN	NA 1	NA 1	0 10	69	13		

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TABLE	

\$2 \$3 \$4 H N lele allele allele	2 98 10 V 7	7 110 5 1	04 934 340 \mathbf{v} 7	18 1016 170 ¹	17 350 95 _{v 7}	74 861 295 ^Y /	IA NA NA	Y 7 IA NA NA	IA NA NA	IA NA NA	IA NA NA	0
he counts of every genotype ' 22/ 23/ 23/ 24/ 22 23 24 23 24 24 allel	NA NA NA NA NA 2	I NA NA NA NA NA 7	NA NA NA NA NA 104	1 NA NA NA NA NA 118	A NA NA NA NA NA 17	A NA NA NA NA NA 74	$\begin{array}{c} \varepsilon 2 + \varepsilon 2 \\ 3 = 15 \\ 3 = 15 \end{array} 1 110 \begin{array}{c} \varepsilon 3/\varepsilon 4 + \varepsilon 4 \\ \varepsilon 4 = 26 \end{array} \text{ NA}$	$\begin{aligned} \varepsilon 2 + \varepsilon 2 & \varepsilon 3/\varepsilon 4 \\ 3 = 20 & 1 & 164 & + \varepsilon 4/ & \text{NA} \\ \varepsilon 4 = 30 & \end{aligned}$	$\varepsilon 2 = 0; \ \varepsilon 2/\varepsilon 3 + \varepsilon 3/\varepsilon 3 = 45; \ \varepsilon 2/\varepsilon $ 4 + $\varepsilon 3/\varepsilon 4 + \varepsilon 4/\varepsilon 4 = 31$ NA	$\varepsilon 2 = 0; \ \varepsilon 2/\varepsilon 3 + \varepsilon 3/\varepsilon 3 = 104; \ \varepsilon 2/$ $\varepsilon 4 + \varepsilon 3/\varepsilon 4 + \varepsilon 4/\varepsilon 4 = 34$ NA	$(\epsilon^2 + \epsilon^2/\epsilon^3 + \epsilon^3/\epsilon^3 = 110; \epsilon^2/\epsilon^4$ + $\epsilon^3/\epsilon^4 = 42; \epsilon^4/\epsilon^4 = 12$ NA	
n Age(years) $\epsilon 2/\epsilon^{2/k}$	$(66.0 \pm 14.0 \text{ NA})$	%) 67.0±8.0 NA	%) 59.8±17.7 NA	(6) 59.8 ± 16.9 NA	<60 NA	20–55 NA	$61.7 \pm 6.8 \frac{\epsilon 2l}{l\epsilon}$	NA $\frac{\varepsilon 2}{ \varepsilon }$	NA ^{ε2/}	NA ε2/,	$(60.8 \pm 11.9 \ \epsilon^{2/3})$	
Sample Male/ size (%)	55 25 (45.0%	61 30 (49.0%	689 356 (51.79	652 341 (52.39	231 NA	615 NA	152 NA	215 NA	76 NA	138 NA	164 (68.9)	
Group	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	
control	2	а- 1 а	1	g-11		Ч-Ч		P-B	د د	ਹ- <u>7</u>	د د	1
method	aga	ION	a) d	LON	E	IL		PCR	r C	P.CK		2
for IS	CTAADI		IdM	MM	IUV LU	C1/MRI		CT/MRI	Ę	0		
Region	nono ¹	јарап		11uugary	L and and	Finland		Spain	-	America		
Study ID	Nakata et al., 1997	[68]	Szolnoki et al., 2002	[69]	Aalto-Setala et al.,	1998 [70]		Attieda et al., 2008 [71]	Schneider et al., 2005	[72]	[22] 2100 [240 :1	

	Results of association with IS				
Genetic model of APOE gene polymorphisms	Group	No. of included studies	OR	95% CI	<i>P</i> value of ORs
	All	51	0.983	(0.867,1.115)	0.79
	LAA	13	0.962	(0.712,1.299)	0.80
<i>ɛ</i> 2 allele vs. <i>ɛ</i> 3 allele	CE	10	1.517	(0.861,2.674)	0.15
	SAD	12	1.190	(0.997,1.421)	0.05
	All	51	1.374	(1.214,1.556)	< 0.0001
	LAA	13	1.149	(0.898,1.469)	0.27
E4 allele vs. E5 allele	CE	10	1.092	(0.662,1.801)	0.73
	SAD	12	1.318	(1.073,1.618)	0.01
	All	36	0.985	(0.653,1.486)	0.94
-21-2	LAA	11	1.307	(0.750,2.278)	0.35
E2/E2 VS. E3/3	CE	10	4.290	(1.917,9.600)	< 0.0001
	SAD	11	1.803	(1.037,3.134)	0.04
	All	46	0.980	(0.900,1.066)	0.63
-2/-22/2	LAA	13	0.869	(0.705,1.071)	0.19
<i>E2/E3</i> VS. <i>E3/3</i>	CE	10	1.255	(0.849,1.856)	0.26
	SAD	12	1.178	(0.952,1.457)	0.13
	All	42	1.233	(1.056,1.440)	0.01
2/24 ma 22/2	LAA	11	0.978	(0.607,1.576)	0.93
E2/E4 VS. E5/5	CE	10	1.458	(0.534,3.980)	0.46
	SAD	10	0.932	(0.526,1.652)	0.81
	All	47	1.340	(1.165,1.542)	< 0.0001
2/04 ma 02/2	LAA	14	1.154	(0.841,1.584)	0.38
E3/E4 VS. E3/5	CE	10	1.175	(0.627,2.203)	0.62
	SAD	13	1.392	(1.097,1.767)	0.01
	All	46	1.833	(1.542,2.179)	< 0.0001
ad lad wa a 2/2	LAA	13	1.367	(0.836,2.236)	0.21
£4/24 VS. £3/3	CE	10	1.543	(0.591,4.029)	0.38
	SAD	11	1.809	(1.030,3.175)	0.04
	All	50	1.377	(1.203,1.576)	< 0.0001
st ve pop st	LAA	14	1.149	(0.876,1.506)	0.32
24 vs. 11011-24	CE	10	1.091	(0.645,1.845)	0.74
	SAD	13	1.329	(1.064,1.661)	0.01
	All	48	0.956	(0.841,1.086)	0.49
c) ve non c)	LAA	14	0.861	(0.717,1.035)	0.11
εz vs. ποπ-εz	CE	10	1.358	(0.966,1.910)	0.08
	SAD	13	1.117	(0.926,1.347)	0.25
	All	40	1.625	(1.281,2.060)	< 0.0001
s4/s4 vs s2/4	LAA	11	1.551	(0.791,3.043)	0.20
CT/CT V5. C2/T	CE	9	0.771	(0.177,3.352)	0.73
	SAD	4	2.115	(0.919,4.867)	0.08
	All	46	1.301	(1.077,1.571)	0.01
ch/ch ve c3/h	LAA	13	1.353	(0.811,2.258)	0.25
c1/c1 v3. cJ/1	CE	6	1.077	(0.402,2.887)	0.88
	SAD	11	1.332	(0.739,2.400)	0.34

TABLE 2: The main results of the APOE gene associated with IS included in the meta-analysis.

Study ID	OR (95% CI)	% Weight
W11 et al 2020	1 545 (0 751 3 176)	4 27
Zhao et al. 2017	0.923(0.331, 2.572)	2 71
Coen Herak et al 2017	7 376 (0 347 156 894)	0.14
Das et al. 2016	1.517 (0.425, 5.415)	1.39
Koopal et al. 2016	1.261(0.603, 2.641)	4.06
	1.760 (0.723, 4.282)	2.67
Wei et al. 2015	1,014 (0,556, 1,848)	7 50
Chatzistefanidis et al 2014	0.459(0.120, 1.751)	2 50
Atadzhanov et al. 2013	1.810(0.390, 8.401)	0.78
Gelfand et al. 2013	7 333 (0.983, 54 721)	0.16
Tamam et al. 2009	1,000 (0,086, 11,565)	0.45
Brewin et al. 2020	5,039 (1,730, 14,680)	0.84
Yan et al. 2015	0.679(0.426, 1.082)	15 51
Saidi et al. 2009	2,256 (1,235, 4,123)	4.68
Tascilar et al. 2009	0.381(0.092, 1.573)	2.35
Wang et al. 2009	1.935(1.221, 3.068)	9.27
Lai et al. 2007	0.963 (0.318, 2.913)	2.25
Parfenov et al. 2007	0.307 (0.031, 3.034)	1.07
Baum et al. 2006	1.310 (0.414, 4.139)	1.78
Pezzini et al. 2005	1.101(0.068, 17.815)	0.33
Cerrato et al. 2005	0.229 (0.009, 5.663)	0.63
lin et al. 2004	1.539 (0.254, 9.342)	0.69
Duzenli et al. 2004	0.769 (0.068, 8.700)	0.55
Souza et al. 2003	0.159 (0.008, 3.370)	0.97
Karttunen et al. 2002	- 2.481 (0.150, 41.118)	0.20
Morrison et al. 2002	1.459 (0.824, 2.584)	6.46
MacLeod et al. 2001	0.913 (0.300, 2.780)	2.29
Chowdhury et al. 2001	0.439 (0.018, 10.878)	0.46
Frikke-Schmidt et al. 2001	1.224 (0.788, 1.901)	11.78
Catto et al. 2000	0.605 (0.216, 1.698)	3.15
Kokubo et al. 2000	1.484 (0.312, 7.060)	0.81
Peng et al. 1999	1.145 (0.070, 18.748)	0.33
Ji et al. 1998	0.902 (0.196, 4.150)	1.24
Margaglione et al. 1998	0.413 (0.023, 7.324)	0.73
Kessler et al. 1997	0.941 (0.281, 3.154)	1.92
Hachinski et al. 1996	1.213 (0.074, 19.915)	0.31
Couderc et al. 1993	0.680 (0.037, 12.474)	0.45
Konialis et al. 2016	6.086 (0.311, 118.953)	0.19
Fayed et al. 2009	9.545 (1.021, 89.223)	0.23
Stankovic et al. 2004	0.347 (0.019, 6.197)	0.83
Pedro-Botet et al. 1992	0.255 (0.012, 5.423)	0.76
Artieda et al. 2008	1.491 (0.092, 24.088)	0.28
Overall (I-squared = 12.0%, p = 0.254)	1.233 (1.056, 1.440)	100.00
.00637 1	157	
(a)		

FIGURE 2: Continued.

Study ID	OR (95% CI)	% Weight
Wu et al. 2020	1.642 (1.256, 2.145)	3.37
Gelfand et al. 2013	2.063 (0.444, 9.580)	0.69
Coen Herak et al. 2017	1.252 (0.520, 3.018)	1.53
Jin et al. 2004	2.426 (1.405, 4.189)	2.43
Luo et al. 2015	0.968 (0.721, 1.300)	3.29
Pedro-Botet et al. 1992	2.556 (1.201, 5.437)	1.82
Baum et al. 2006	1.075 (0.644, 1.793)	2.54
Yan et al. 2015	2.506 (1.630, 3.853)	2.82
Chatzistefanidis et al. 2014	1.459 (0.953, 2.233)	2.84
Atadzhanov et al. 2013	0.799 (0.270, 2.368)	1.16
Zhao et al. 2017	1.401 (0.981, 2.000)	3.08
Balcerzyk et al. 2010	0.535 (0.184, 1.555)	1.19
Tamam et al. 2009	1.250 (0.226, 6.902)	0.57
Tascilar et al. 2009	0.889 (0.321, 2.459)	1.27
Wang et al. 2009	2.950 (1.893, 4.599)	2.78
Lai et al. 2007	1.698 (0.954, 3.022)	2.33
Peng et al. 1999	2.720 (1.104, 6.703)	1.49
Karttunen et al. 2002	1.152 (0.520, 2.552)	1.72
Duzenli et al. 2004	0.085 (0.011, 0.660)	0.42
Frikke-Schmidt et al. 2001	— 1.139 (0.957, 1.356)	3.63
Pezzini et al. 2005	1.992 (1.101, 3.603)	2.28
Cerrato et al. 2005	0.520 (0.306, 0.884)	2.48
Das et al. 2016	1.074 (0.804, 1.435)	3.31
Kang and Lee. 2006	2.353 (1.302, 4.251)	2.28
Slowik et al. 2003	0.693 (0.254, 1.894)	1.29
Kessler et al. 1997	1.313 (0.820, 2.100)	2.69
Wei et al. 2015	0.722 (0.480, 1.085)	2.90
Chowdhury et al. 2001	1.182 (0.660, 2.118)	2.31
MacLeod et al. 2001	0.695 (0.454, 1.064)	2.84
Fayed et al. 2009	15.000 (1.679, 134.025)	0.37
Catto et al. 2010	0.883 (0.621, 1.255)	3.10
Margaglione et al. 1998	1.919 (1.125, 3.273)	2.47
Kokubo et al. 2000	0.970 (0.644, 1.461)	2.90
Saidi et al. 2009	3.096 (2.048, 4.681)	2.88
Brewin et al. 2020	1.366 (0.613, 3.045)	1.71
Gao et al. 2006	2.311 (0.836, 6.392)	1.27
Souza et al. 2003	0.398 (0.161, 0.980)	1.49
Hachinski et al. 1996	1.617 (0.785, 3.332)	1.90
Couderc et al. 1993	0.692 (0.340, 1.409)	1.93
Qian et al. 2012	1.475 (0.558, 3.902)	1.35
Konialis et al. 2016	2.118 (1.129, 3.973)	2.17
Morrison et al. 2002	1.227 (0.939, 1.604)	3.37
Stankovic et al. 2004	2.013 (1.059, 3.826)	2.13
Koopal et al. 2016	0.927 (0.693, 1.240)	3.30
Fekin-Mirissa et al. 2014	13.129 (0.672, 256.598)	0.21
Partenov et al. 2007		2.12
$\int f(t) dt = \frac{1}{2} \int $		1.95
Overall (1-squared = 68.9% , p = 0.000)	1.340 (1.165, 1.542)	100.00
INO 1 E: Weights are from random effects analysis		
.0039	1 257	
	(b)	

FIGURE 2: Continued.

Study		%
	OR (95% CI)	Weight
Wu et al. 2020	2.789 (1.076, 7.228)	3.07
Zhao et al. 2017	8.438 (1.050, 67.815)	0.53
Coen Herak et al. 2017	0.492 (0.020, 12.314)	0.66
Das et al. 2016	1.012 (0.450, 2.277)	6.38
Atadzhanov et al. 2013	0.213 (0.011, 3.999)	1.71
Luo et al. 2015	0.948 (0.341, 2.632)	4.16
Wei et al. 2015	4.164 (0.851, 20.376)	0.97
Gelfand et al. 2013	11.000 (1.264, 95.692)	0.17
Parfenov et al. 2007	1.841 (0.325, 10.432)	1.09
Koopal et al. 2016	0.890 (0.429, 1.849)	8.77
Tamam et al. 2009	0.500 (0.030, 8.331)	0.71
Yan et al. 2015	2.156 (1.354, 3.433)	14.05
Balcerzyk et al. 2010	3.923 (0.424, 36.305)	0.53
Tascilar et al. 2009	3.111 (0.611, 15.850)	1.05
Wang et al. 2009	4.849 (1.325, 17.754)	1.35
Lai et al. 2007	0.161 (0.006, 3.998)	1.10
Chatzistefanidis et al. 2014	2.449 (0.445, 13.494)	0.98
Kang and Lee. 2006	0.339 (0.014, 8.390)	0.81
Baum et al. 2006	5.239 (0.580, 47.339)	0.47
Pezzini et al. 2005	3.301 (0.133, 81.891)	0.26
Cerrato et al. 2005 -	0.687 (0.169, 2.787)	2.55
Jin et al. 2004	1.539 (0.254, 9.342)	1.07
Duzenli et al. 2004	0.511 (0.020, 12.785)	0.64
Slowik et al. 2003	1.206 (0.047, 30.768)	0.38
Souza et al. 2003	2.390 (0.096, 59.531)	0.30
Karttunen et al. 2002	0.351 (0.018, 7.016)	1.07
Morrison et al. 2002	1.604 (0.840, 3.065)	7.31
MacLeod et al. 2001	0.782 (0.155, 3.939)	1.81
Chowdhury et al. 2001	1.319 (0.183, 9.504)	0.93
Catto et al. 2000	0.883 (0.315, 2.470)	4.17
Kokubo et al. 2000	0.457 (0.059, 3.518)	2.03
Peng et al. 1999	2.291 (0.202, 25.959)	0.50
Ji et al. 1998	8.409 (0.428, 165.235)	0.24
Margaglione et al. 1998	37.424 (4.426, 316.422)	0.15
Frikke-Schmidt et al. 2001	0.871 (0.527, 1.439)	18.95
Saidi et al. 2009	7.076 (3.274, 15.291)	2.72
Hachinski et al. 1996	3.638 (0.366, 36.140)	0.48
Couderc et al. 1993	1.077 (0.130, 8.938)	0.88
Qian et al. 2012	4.634 (0.257, 83.566)	0.39
Konialis et al. 2016	6.086 (0.311, 118.953)	0.29
Fayed et al. 2009	22.913 (1.196, 438.832)	0.18
Stankovic et al. 2004	3.504 (0.567, 21.664)	0.52
Pedro-Botet et al. 1992	2.556 (0.611, 10.689)	1.35
Fekih-Mrissa et al. 2014	→ 37.000 (1.004, 1364.036)	0.04
Brewin et al. 2020	4.157 (1.307, 13.220)	1.21
Kessler et al. 1997	3.951 (0.807, 19.351)	1.00
Overall (I-squared = 38.9%, p = 0.004)	1.833 (1.542, 2.179)	100.00
00073	1 1264	
.000/3	1 1304	
	(c)	

FIGURE 2: Continued.

Study ID	OR (95% CI)	% Weight
Wu et al. 2020	1.730 (1.375, 2.177)	2.80
Zhao et al. 2017	1.501 (1.100, 2.048)	2.59
Coen Herak et al. 2017	1.232 (0.566, 2.683)	1.39
Das et al. 2016	1.071 (0.838, 1.369)	2.76
Koopal et al. 2016 🗕 🚽	0.944 (0.749, 1.190)	2.80
Luo et al. 2015	1.020 (0.791, 1.314)	2.74
Wei et al. 2015	0.818 (0.603, 1.109)	2.61
Yan et al. 2015	1.645 (1.307, 2.071)	2.80
Chatzistetanidis et al. 2014	1.304 (0.902, 1.885)	2.43
Atadzhanov et al. 2013	0.768 (0.352, 1.672)	1.39
	3.745 (1.453, 9.656)	1.10
Balcerzyk et al. 2010	1.095 (0.494, 2.428)	1.36
Tamam et al. 2009	0.852(0.272, 2.666)	0.85
Wang at al. 2009	1.107 (0.015, 2.212) 2.102 (1.640, 2.020)	1.70
	1 307 (0 810 2 107)	2.05
Parfenov et al. 2007	1.307(0.810, 2.107) 1 351(0.802, 2.277)	2.12
Kang and Lee 2006	1.931(0.002, 2.277) 1 918 (1 114 3 303)	1.94
Gao et al. 2006	2.229 (0.829, 5.996)	1.04
Baum et al. 2006	1.297 (0.846, 1.990)	2.26
Pezzini et al. 2005	1.926 (1.117, 3.320)	1.94
Cerrato et al. 2005	0.570 (0.361, 0.899)	2.18
Jin et al. 2004	2.067 (1.291, 3.309)	2.14
Duzenli et al. 2004	0.162 (0.037, 0.700)	0.58
Slowik et al. 2003	0.829 (0.334, 2.059)	1.16
Souza et al. 2003	0.480 (0.216, 1.068)	1.35
Karttunen et al. 2002	0.949 (0.481, 1.872)	1.60
Morrison et al. 2002	1.259 (1.025, 1.546)	2.86
MacLeod et al. 2001	0.755 (0.529, 1.079)	2.47
Chowdhury et al. 2001	1.152 (0.687, 1.933)	2.01
Frikke-Schmidt et al. 2001	1.091 (0.948, 1.255)	2.98
	0.886 (0.663, 1.184)	2.65
Rokubo et al. 2000	0.926(0.642, 1.335)	2.44
First al. 1999	2.305 (1.089, 4.877)	1.45
Ji et al. 1998	2.240(1.237, 4.057) 2.244(1.522, 2.585)	1.81
Kessler et al. 1998	2.344(1.352, 3.383) 1 377 (0 935 2 028)	2.27
Hachinski et al. 1996	1.600 (0.876, 2.923)	1 79
Couderc et al 1993	0.740(0.397, 1.378)	1.75
Oain et al. 2012	2.060 (0.842, 5.043)	1.18
Konialis et al. 2009	2.513 (1.397, 4.522)	1.83
Fayed et al. 2009	16.056 (3.578, 72.038)	0.56
Stankovic et al. 2004	1.844 (1.083, 3.142)	1.97
Pedro-Botet et al. 1992	2.033 (1.141, 3.622)	1.85
Fekih-Mrissa et al. 2014	4.859 (1.367, 17.269)	0.73
Brewin et al. 2020	2.170 (1.323, 3.560)	2.07
Saidi et al. 2009	2.676 (2.021, 3.543)	2.67
Giassakis et al. 2007	1.723 (0.840, 3.534)	1.52
Nakata et al. 1997	2.245 (0.742, 6.795)	0.89
Szolnoki et al. 2002	2.176 (1.773, 2.669)	2.86
Aalto-Setala et al. 1998	0.792 (0.609, 1.030)	2.72
Overall (1-squared = 77.8% , p = 0.000)	1.374 (1.214, 1.556)	100.00
NO1E: weights are from random effects analysis		
0130	72	
.0137 1	12	
(d)		

FIGURE 2: Continued.

Study		%
	OR (95% CI)	Weight
Hachinski et al. 1996	1.584 (0.811, 3.092)	1.81
Gelfand et al. 2013	3.500 (1.057, 11.586)	0.91
Wu et al. 2020	1.823 (1.426, 2.331)	2.93
Atadzhanov et al. 2013	0.914 (0.371, 2.253)	1.33
Zhao et al. 2017	1.463 (1.051, 2.035)	2.72
Balcerzyk et al. 2010	0.793 (0.319, 1.974)	1.31
Coen Herak et al. 2017	1.331 (0.584, 3.033)	1.47
Wang et al. 2009	2.503 (1.828, 3.429)	2.76
Koopal et al. 2016	0.927 (0.713, 1.206)	2.89
Yan et al. 2015	1.856 (1.414, 2.436)	2.87
Wei et al. 2015	0.598(0.424, 0.843)	2.69
Peng et al. 1999	2.588 (1.146, 5.844)	1.49
Chatzistefanidis et al. 2014	1.263 (0.852, 1.8/4)	2.55
Gao et al. 2006	2.341 (0.852, 6.430)	1.15
Taschar et al. 2009	0.944 (0.455, 1.966)	1.00
Correcto et al. 2005	0.912(0.252, 3.303)	0.82
Derfer ov et al. 2007	0.525(0.520, 0.862)	2.20
Parlenov et al. 2007	1.509 (0.835, 2.750)	2.00
Kang and Lee 2006	(0.036, 0.750) 2 171 (1 221 - 3 850)	2.04
Das et al. 2016	2.171(1.221, 3.639) 1 000 (0.831, 1.429)	2.04
Lin et al. 2004	2 324 (1 397 3 865)	2.87
Baum et al. 2004	1.324(1.377, 3.803)	2.22
Soura et al. 2003	0.418(0.178, 0.981)	1.42
Pezzini et al. 2005	$2\ 010\ (1\ 132\ 3\ 571)$	2.05
Slowik et al. 2003	0.737(0.274, 1.982)	1.18
Lai et al. 2007	1.489 (0.886, 2.501)	2.20
Couderc et al. 1993	0 697 (0 355, 1 370)	1.79
Karttunen et al. 2002	1.050 (0.492, 2.243)	1.60
Morrison et al. 2002	1.293 (1.019, 1.641)	2.95
MacLeod et al. 2001	0.701 (0.473, 1.041)	2.54
Stankovic et al. 2004	2.129 (1.169, 3.875)	1.98
Chowdhury et al. 2001	1.162 (0.663, 2.034)	2.08
Ji et al. 1998	2.188 (1.157, 4.136)	1.89
Frikke-Schmidt et al. 2001	1.152 (0.982, 1.351)	3.11
Margaglione et al. 1998	2.093 (1.287, 3.405)	2.29
Catto et al. 2000	0.879 (0.636, 1.214)	2.74
Konialis et al. 2016	2.595 (1.404, 4.795)	1.94
Kokubo et al. 2000	0.883 (0.599, 1.304)	2.56
Pedro-Botet et al. 1992	2.144 (1.107, 4.152)	1.83
Luo et al. 2015	1.024 (0.780, 1.344)	2.87
Fayed et al. 2009	16.714 (3.378, 82.690)	0.58
Kessler et al. 1997	1.282 (0.836, 1.966)	2.45
Qian et al. 2012	1.759 (0.684, 4.525)	1.25
Brewin et al. 2020	2.307 (1.218, 4.368)	1.88
Fekih-Mrissa et al. 2014	20.879 (1.102, 395.483)	0.20
Li et al. 2016	1.739 (0.995, 3.038)	2.09
Saidi et al. 2009	3.123 (2.195, 4.444)	2.66
Artieda et al. 2008	1.282 (0.730, 2.253)	2.07
Schneider et al. 2005	2.107 (1.157, 3.837)	1.98
Overall (I-squared = 74.9%, $p = 0.000$)	1.377 (1.203, 1.576)	100.00
NOTE: Weights are from random effects analysis		
 00253 1	1 395	
.00233 1	575	
(e)		

FIGURE 2: Continued.

Study ID	OR (95% CI)	% Weight
Catto et al. 2000	1.458 (0.348, 6.112)	2.88
Peng et al. 1999	2.000 (0.051, 78.250)	0.37
Wu et al. 2020	1.806 (0.552, 5.908)	3.86
Zhao et al. 2017	9143 (0.905, 92.398)	0.54
Coen Herak et al. 2017	0.067 (0.001, 5.494)	1.39
Das et al. 2016	0.667 (0.149, 2.979)	3.93
Wei et al. 2015	4.109 (0.776, 21.760)	1.45
Koopal et al. 2016	0.706 (0.256, 1.946)	8.15
Wang et al. 2009	2.506 (0.658, 9.540)	2.91
Luo et al. 2015	0.538 (0.141, 2.063)	5.37
Yan et al. 2015	3.175 (1.701, 5.924)	10.27
Atadzhanov et al. 2013	0.113 (0.005, 2.539)	2.94
Chatzistefanidis et al. 2014	5.333 (0.618, 45.991)	0.66
Gelfand et al. 2013	1.500 (0.106, 21.312)	0.83
Tamam et al. 2009	0.500 (0.013, 19.562)	0.74
Tascilar et al. 2009	8.167 (1.027, 64.936)	0.59
Lai et al. 2007	0.175 (0.006, 5.041)	1.63
Parfenov et al. 2007	6.000 (0.354, 101.568)	0.37
Baum et al. 2006	4.000 (0.340, 47.112)	0.66
Pezzini et al. 2005	3000 (0.060, 151,190)	0.28
Cerrato et al. 2005	3.000 (0.095, 95,170)	0.38
Jin et al. 2004	1.000 (0.080, 12.557)	1.11
Duzenli et al. 2004	0.556 (0.013, 24.513)	0.70
Souza et al. 2003		0.09
Karttunen et al. 2002	0.143 (0.003, 5.946)	1.39
Morrison et al. 2002	1,100 (0,478, 2,529)	9.78
Kessler et al. 1997	4.200 (0.586, 30.095)	0.93
MacLeod et al. 2001	0.857 (0.124, 5.944)	2.05
Saidi et al. 2009	3,136 (1,273, 7,723)	5.10
Frikke-Schmidt et al. 2001	0 712 (0 371 1 366)	20.07
Kokubo et al. 2000	0.308 (0.024, 3.968)	2 01
li et al 1998	9 000 (0 340, 238 210)	0.27
Margaglione et al 1998		0.09
Hachinski et al. 1996	3 000 (0.084, 107, 447)	0.09
Couderc et al. 1993		0.31
Eaved et al. 2009	3 400 (0.120, 96, 700)	0.40
Stankovic et al. 2007		0.35
Pedro-Botet et al. 1992	9 286 (0 342 252 450)	0.25
Rewin et al 2020		1 25
Chowdhury et al. 2001		0.33
Overall (Lequared $= 23.8\%$ $p = 0.002$)	5.000((0.0/8, 115.558))	100.00
$V_{1}V_{2} = V_{1} = V_{1} = V_{2} =$	γ 1.023 (1.261, 2.000)	100.00

FIGURE 2: Continued.

Study ID	OR (95% CI)	% Weight
Wu et al. 2020	1 699 (0 639 4 519)	3 56
Zhao et al. 2017	6 024 (0 735 49 387)	0.58
Coen Herak et al 2017	0.024(0.755, 49.567)	0.50
Das et al 2016	0.942 (0.406 2.182)	6.03
Chatzistefanidis et al. 2014	1.679(0.294, 9.574)	1 11
Koopal et al. 2016	0.961 (0.452, 2.041)	7.53
Balcerzyk et al. 2010	7 333 (0 661 81 365)	0.29
	0 979 (0 343 2 796)	3.80
Wei et al. 2015	5 769 (1 156, 28 785)	0.76
Yan et al. 2015	0.860 (0.473, 1.565)	12 42
Atadzhanov et al. 2013	0.263(0.014, 5.027)	1 39
Gelfand et al. 2013	5 333 (0 526 54 032)	0.28
Tamam et al. 2009	0.400 (0.016, 10.017)	0.60
Tascilar et al. 2009	3 500 (0 565, 21 665)	0.72
Wang et al. 2009	1 644 (0 434 6 223)	2.01
Lai et al. 2007	0.096(0.004, 2.459)	1.22
Parfenov et al. 2007	1 333 (0 225 7 915)	1.22
Kang and Lee 2006	0.146(0.006, 3.747)	1.09
Baum et al. 2006	4 875 (0 519 45 821)	0.45
Pezzini et al. 2005	1 675 (0.065 42 941)	0.33
Cerrato et al. 2005	1.321(0.304, 5.749)	1.65
lin et al. 2004	0.635(0.099, 4.066)	1.05
Duzenli et al. 2004	4 111 (0 112 151 560)	0.11
Slowik et al. 2003	1 759 (0.064 48 194)	0.31
Souza et al. 2003	5.824 (0.214, 158,818)	0.17
Karttunen et al. 2002	0.302(0.015, 6.262)	1 10
Morrison et al. 2002	1.308 (0.674, 2.537)	7.92
MacLeod et al. 2001	1,125 (0,218, 5,801)	1.45
Chowdhury et al. 2001	1.115 (0.146, 8.494)	0.95
Ti et al 1998	3 441 (0 166, 71, 151)	0.33
Frikke-Schmidt et al. 2001	0.765 (0.458, 1.276)	19.81
Margaglione et al. 1998	19.500 (2.236, 170.083)	0.24
Catto et al. 2000	1.000 (0.348, 2.873)	3.71
Kokubo et al. 2000	0.471 (0.060, 3.720)	1.85
Peng et al. 1999	0.842 (0.067, 10.663)	0.68
Kessler et al. 1997	3.010 (0.594, 15.263)	1.05
Hachinski et al. 1996	2.250 (0.216, 23.457)	0.56
Couderc et al. 1993	1.557 (0.174, 13.956)	0.59
Oian et al. 2012	3.305 (0.167, 65.463)	0.36
Konialis et al. 2016	2.924 (0.143, 59.820)	0.35
Faved et al. 2009	2.217 (0.080, 61.403)	0.28
Stankovic et al. 2004	1.741 (0.268, 11.293)	0.83
Pedro-Botet et al. 1992	1.000 (0.215, 4.653)	1.75
Fekih-Mrissa et al. 2014	3.000 (0.157, 57.365)	0.24
Brewin et al. 2020	3.043 (0.951, 9.737)	1.49
Saidi et al. 2009	2.285 (1.040, 5.021)	4.77
Overall (I-squared = 0.0%, p = 0.578)	1.301 (1.077, 1.571)	100.00
.00377 1	265	
(g)		

FIGURE 2: (a-g) Forest plots of the relationships between APOE gene polymorphisms in all studies included. (a) Forest plot of $\varepsilon_2/\varepsilon_4$ vs. $\varepsilon_3/\varepsilon_3$ comparison. (b) Forest plot of $\varepsilon_3/\varepsilon_4$ vs. $\varepsilon_3/\varepsilon_3$ comparison. (c) Forest plot of APOE $\varepsilon_4/\varepsilon_4$ vs. the $\varepsilon_3/\varepsilon_3$ genotype. (d) Forest plot of the APOE ε_4 allele vs. ε_3 allele. (e) Forest plot of APOE ε_4 carriers vs. non- ε_4 carriers. (f) Forest plot of APOE $\varepsilon_4/\varepsilon_4$ vs. $\varepsilon_2/\varepsilon_4$. (g) Forest plot of APOE $\varepsilon_4/\varepsilon_4$ vs. $\varepsilon_3/\varepsilon_4$.

3.2.4. APOE ε_2 Carrier Comparisons. In the genetic model of ε_2 carriers vs. non- ε_2 carriers, there was no association with the IS risk (pooled OR = 0.956, 95% CI 0.841-1.086, P = 0.49) (Table 2).

3.2.5. APOE ε 4 Homozygosis versus APOE ε 4 Heterozygote Comparisons. Given the above, the APOE ε 4 mutation

was linked to IS risk. To identify whether there is a dose-response relationship between the ε 4 allele and IS or not, we implemented the comparisons between the ε 4/ ε 4 genotype and ε 4 heterozygotes (ε 2/ ε 4 or ε 3/ ε 4 genotype). Compared with the ε 2/ ε 4 and ε 3/ ε 4 genotypes, the IS risk ORs for ε 4/ ε 4 genotypes were 1.625 (95% CI, 1.281-2.060, *P* < 0.0001) and 1.301 (95% CI, 1.077-1.571,

Study ID	OR (95% CI)	% Weight
LAA		
Zhao et al. 2017	0.252 (0.014, 4.411)	4.89
Das et al. 2016	1.346 (0.299, 6.062)	4.40
Luo et al. 2015	2.081 (0.746, 5.806)	7.21
Chatzistefanidis et al. 2014	0.322 (0.040, 2.603)	6.79
Souza et al. 2003	0.159 (0.008, 3.370)	4.24
Lai et al. 2007	- 1.216 (0.356, 4.150)	7.20
Cerrato et al. 2005	0.597 (0.024, 14.810)	1.65
Tascilar et al. 2009	0.381 (0.092, 1.573)	10.29
Kokubo et al. 2000	3.199 (0.388, 26.352)	0.92
Kessler et al. 1997	2.547 (0.685, 9.471)	3.67
Pedro-Botet et al. 1992	0.567 (0.026, 12.235)	1.96
Subtotal (I-squared = 7.7%, p = 0.370)	0.978 (0.607, 1.576)	53.21
CE		
Zhao et al. 2017	1.003 (0.056, 17.955)	1.43
Das et al. 2016	1.448 (0.076, 27.462)	0.98
Luo et al. 2015	1.760 (0.214, 14.440)	1.62
Cerrato et al. 2005	1.577 (0.063, 39.561)	0.80
Kokubo et al. 2000	5.688 (0.675, 47.892)	0.53
Kessler et al. 1997	0.776 (0.090, 6.670)	3.17
Subtotal (I-squared = 0.0%, p = 0.850)	> 1.458 (0.534, 3.980)	8.53
SAD		
Zhao et al. 2017	0.832 (0.218, 3.175)	7.56
Das et al. 2016	4.360 (0.779, 24.408)	1.26
Luo et al. 2015	0.880 (0.185, 4.187)	5.41
Kokubo et al. 2000	0.810 (0.046, 14.208)	1.77
Lai et al. 2007	0.734 (0.190, 2.832)	7.67
Cerrato et al. 2005	1.006 (0.040, 25.081)	1.15
Chatzistefanidis et al. 2014	0.599 (0.125, 2.864)	7.13
Kessler et al. 1997	0.622 (0.034, 11.488)	2.13
Pedro-Botet et al. 1992	0.897 (0.041, 19.627)	1.37
Wen et al. 2006	1.447 (0.233, 8.995)	2.83
Subtotal (I-squared = 0.0%, p = 0.921)	0.932 (0.526, 1.652)	38.26
Overall (I-squared = 0.0%, p = 0.891)	1.002 (0.709, 1.414)	100.0
00754	133	
.00/34 1	155	

FIGURE 3: Continued.

Study ID	OR (95% CI)	% Weight
LAA		
Zhao et al. 2017	1.413 (0.818, 2.440)	3.91
Das et al. 2016	0.556 (0.369, 0.838)	4.54
Luo et al. 2015	1.136 (0.793, 1.628)	4.77
Cerrato et al. 2005	0.485 (0.230, 1.023)	3.07
Tascilar et al. 2009	0.889(0.321, 2.459)	2.19
Lai et al. 2007	1.226 (0.619, 2.431)	3.31
Kang and Lee. 2006	2.216 (1.145, 4.290)	3.41
Gao et al. 2006	1.533 (0.329, 7.147)	1.22
Chatzistefanidis et al. 2014	1.479 (0.877, 2.494)	4.02
Slowik et al. 2003	0.438 (0.115, 1.663)	1.51
Kokubo et al. 2000	2,154 (1,173, 3,956)	3.63
Souza et al. 2003	0.398(0.161, 0.980)	2.52
Kessler et al. 1997	1.777(0.940, 3.360)	3 51
Pedro-Botet et al 1992	3,096 (1,276, 7,512)	2.57
Subtotal (I-squared = 68.3% p = 0.000)	1.154(0.841, 1.584)	44 16
	1.154 (0.041, 1.504)	11.10
CE		1.00
Zhao et al. 2017	1.089 (0.362, 3.278)	1.98
Das et al. 2016	3.157 (1.823, 5.467)	3.90
Luo et al. 2015	0.997 (0.453, 2.194)	2.90
Cerrato et al. 2005	0.259 (0.059, 1.127)	1.31
Kokubo et al. 2000	1.351 (0.530, 3.448)	2.42
Kessler et al. 1997	0.975 (0.432, 2.199)	2.82
Subtotal (I-squared = 67.4%, p = 0.009)	1.175 (0.627, 2.203)	15.32
SAD		
Zhao et al. 2017	1.178 (0.748, 1.857)	4.33
Das et al. 2016	1.929 (1.144, 3.254)	4.02
Luo et al. 2015	0.872 (0.555, 1.370)	4.35
Chatzistefanidis et al. 2014	1.581 (0.956, 2.613)	4.11
Lai et al. 2007	2.125 (1.144, 3.949)	3.58
Kang and Lee. 2006	2.560 (1.252, 5.233)	3.19
Gao et al. 2006	3.040 (0.765, 12.086)	1.44
Cerrato et al. 2005	0.903 (0.430, 1.898)	3.08
Slowik et al. 2003	0.905 (0.306, 2.682)	2.01
Kokubo et al. 2000	0.687 (0.345, 1.367)	3.29
Kessler et al. 1997	1.540 (0.627, 3.785)	2.53
Pedro-Botet et al. 1992	2.123 (0.695, 6.487)	1.94
Wen et al. 2006	1.592 (0.673, 3.767)	2.65
Subtotal (I-squared = 36.2%, p = 0.093)	1.392 (1.097, 1.767)	40.52
Overall (Lequared $= 59.1\%$ n $= 0.000$)	1 270 (1 0/19 1 539)	100.00
NOTE: Weights are from random effects analysis	1.270 (1.047, 1.338)	100.00
.0594 1	16.8	
(b)		

FIGURE 3: Continued.

Study ID	OR (95% CI)	% Weigh
LAA		
Das et al. 2016	0.748 (0.260, 2.147)	17.48
Zhao et al. 2017	12.918 (1.327, 125.717)	0.78
Luo et al. 2015	1.189 (0.354, 3.988)	9.73
Chatzistefanidis et al. 2014	2.574 (0.358, 18.504)	2.31
Tascilar et al. 2009	3.111 (0.611, 15.850)	4.00
Lai et al. 2007	0.338 (0.014, 8.416)	3.07
Kang and Lee. 2006	0.560 (0.023, 13.917)	2.31
Cerrato et al. 2005	0.449 (0.049, 4.078)	5.85
Slowik et al. 2003	2.633 (0.102, 68.073)	1.07
Souza et al. 2003	2.390 (0.096, 59.531)	1.15
Kokubo et al. 2000	0.934 (0.054, 16.054)	2.11
Kessler et al. 1997	1.910 (0.169, 21.616)	1.70
Pedro-Botet et al. 1992	1.917 (0.302, 12.171)	3.07
Subtotal (I-squared = 0.0%, p = 0.706)	1.367 (0.836, 2.236)	54.63
CE		
Zhao et al. 2017	► 5.682 (0.225, 143.647)	0.35
Das et al. 2016	2.202 (0.473, 10.253)	3.42
Luo et al. 2015	0.818 (0.046, 14.443)	2.34
Cerrato et al. 2005	0.526 (0.028, 9.998)	3.19
Kokubo et al. 2000	1.641 (0.094, 28.649)	1.22
Kessler et al. 1997	2.328 (0.205, 26.462)	1.45
Subtotal (I-squared = 0.0%, p = 0.896)	> 1.543 (0.591, 4.029)	11.98
SAD		
Das et al. 2016	0.727 (0.093, 5.706)	5.02
Zhao et al. 2017	11.091 (1.286, 95.680)	1.28
Luo et al. 2015	0.880 (0.185, 4.187)	7.28
Chatzistefanidis et al. 2014	2.397 (0.334, 17.218)	2.43
Lai et al. 2007	0.306 (0.012, 7.623)	3.22
Kang and Lee. 2006	0.848 (0.034, 21.167)	1.75
Cerrato et al. 2005	0.335 (0.018, 6.335)	4.56
Kokubo et al. 2000	1.068 (0.137, 8.303)	3.59
Kessler et al. 1997	8.278 (1.098, 62.405)	0.88
Pedro-Botet et al. 1992	4.600 (0.845, 25.052)	2.09
Wen et al. 2006	4.341 (0.383, 49.255)	1.29
Subtotal (I-squared = 10.0%, p = 0.349)	1.809 (1.030, 3.175)	33.39
Overall (I-squared = 0.0%, p = 0.802)	1.536 (1.086, 2.171)	100.0
.00696	l 144	

(c)

FIGURE 3: Continued.

Study ID	OR (95% CI)	% Weight
LAA Zhao et al. 2017 Das et al. 2016 Chatzistefanidis et al. 2014 Kang and Lee. 2006 Luo et al. 2015 Tascilar et al. 2009 Lai et al. 2007 Cerrato et al. 2007 Cerrato et al. 2005 Slowik et al. 2003 Souza et al. 2000 Kessler et al. 1997 Pedro-Botet et al. 1992 Subtotal (I-squared = 63.5%, p = 0.001)	$\begin{array}{c} 1.572 \ (0.986, 2.507) \\ 0.657 \ (0.466, 0927) \\ 1.323 \ (0.840, 2.084) \\ 1.855 \ (1.010, 3.409) \\ 1.205 \ (0.887, 1.637) \\ 1.167 \ (0.615, 2.212) \\ 1.091 \ (0.618, 1.925) \\ 0.506 \ (0.262, 0.977) \\ 0.722 \ (0.234, 2.226) \\ 0.480 \ (0.216, 1.068) \\ 1.639 \ (0.971, 2.769) \\ 1.722 \ (1.026, 2.888) \\ 2.037 \ (1.022, 4.060) \\ 1.149 \ (0.898, 1.469) \end{array}$	4.07 4.94 4.16 3.21 5.21 3.05 3.44 2.95 1.43 2.34 3.70 3.74 2.80 45.04
CE Zhao et al. 2017 Das et al. 2016 Luo et al. 2015 Cerrato et al. 2005 Kokubo et al. 2000 Kessler et al. 1997 Subtotal (I-sqiared = 60.8%, p = 0.026)	0.996 (0.349, 2.841) 2.167 (1.399, 3.357) 0.942 (0.464, 1.910) 0.235 (0.056, 0.989) 1.261 (0.562, 2.828) 0.996 (0.509, 1.947) 1.092 (0.662, 1.801)	1.60 4.27 2.72 0.96 2.31 2.89 14.75
SAD Zhao et al. 2017 Lui et al. 2007 Luo et al. 2015 Chatzistefanidis et al. 2014 Kang and Lee. 2006 Das et al. 2016 Cerrato et al. 2005 Slowik et al. 2003 Kokubo et al. 2000 Kessler et al. 1997 Pedro-Botet et al. 1992 Wen et al. 2006 Subtotal (I-squared = 37.7%,p = 0.090)	$\begin{array}{l} 1.385 \ (0.943, 2.035) \\ 1.484 \ (0.886, 2.485) \\ 0.870 \ (0.587, 1.289) \\ 1.375 \ (0.891, 2.122) \\ 2.008 \ (1.045, 3.861) \\ 1.650 \ (1.063, 2.561) \\ 0.729 \ (0.366, 1.451) \\ 0.911 \ (0.336, 2.469) \\ 0.748 \ (0.408, 1.372) \\ 1.722 \ (0.859, 3.450) \\ 2.403 \ (1.090, 5.298) \\ 1.844 \ (0.926, 3.672) \\ 1.318 \ (1.073, 1.618) \end{array}$	4.64 3.75 4.58 4.29 2.98 4.26 2.81 1.72 3.22 2.78 2.37 2.81 40.21
Overall (I-squared = 53.9%, p = 0.000) NOTE: Weights are from random effects analysis	1.220 (1.047, 1.420)	100.00
.0557 1 18 (d)		

FIGURE 3: Continued.

Study ID	OR (95% CI)	% Weight
LAA Zhao at al 2017	1.526 (0.915, 2.546)	3.96
	0.629 (0.432, 0.917)	4.80
Luo et al. 2015	1.240 (0.891, 1.727)	5.08
Chatzistefanidis et al. 2014	1.301 (0.798, 2.122)	4.09
Tascilar et al. 2009	0.944 (0.453, 1.966)	2.82
Lai et al. 2007	1.187 (0.643, 2.191)	3.40
Kang and Lee. 2006	2.126 (1.116, 4.052)	3.24
Gao et al. 2006	1.795 (0.390, 8.270)	0.99
Cerrato et al. 2005	0.482 (0.238, 0.978)	2.95
Slowik et al. 2003	0.550 (0.157, 1.931)	1.36
Souza et al. 2003	0.418 (0.178, 0.981)	2.37
Kokubo et al. 2000	1.657 (0.939, 2.922)	3.64
Kessler	1.895 (1.061, 3.385)	3.57
Pedro-Botet et al. 1992	2.278 (1.036, 5.007)	2.61
Subtotal (I-squared = 63.4%, p = 0.001)	1.149 (0.876, 1.506)	44.88
CE		
Zhao et al. 2017	1.051 (0.353, 3.126)	1.69
Das et al. 2016	2.349 (1.422, 3.879)	1.02
Luo et al. 2015	1.000 (0.477, 2.096)	2.80
Cerrato et al. 2005	0.246 (0.057, 1.062)	1.06
Kokubo et al. 2000	1.181 (0.502, 2.776)	2.36
Kessler et al. 1997	0.894 (0.429, 1.861)	2.83
Subtotal (I-squared = 59.2%, p = 0.031)	1.091 (0.645, 1.845)	14.76
SAD		
Zhao et al. 2017	1.269 (0.838, 1.921)	4.55
Das et al. 2016	1.938 (1.182, 3.179)	4.06
Luo et al. 2015	0.847 (0.556, 1.288)	4.52
Chatzistefanidis et al. 2014	1.324 (0.831, 2.109)	4.24
Lai et al. 2007	1.758 (1.000, 3.091)	3.66
Kang and Lee. 2006	2.232 (1.115, 4.466)	3.00
Gao et al. 2006	2.885 (0.732, 11.375)	1.18
Cerrato et al. 2005	0.749 (0.364, 1.542)	2.88
Slowik et al. 2003	0.887 (0.302, 2.608)	1.72
	0.707 (0.367, 1.364)	3.18
Ressier et al. 1997	1.422 (0.638, 3.167)	2.55
Wan at al. 2006	2.158 (0.840, 5.541)	2.07
we i et al. 2000 Subtotal (L-squared = 37.1% p = 0.087)	1.746 (0.823, 3.704)	2./5
Subiotal (1-squared = $5/.1\%$, p = $0.08/$)	1.329 (1.064, 1.661)	40.37
Overall (L-squared -53.2% p -0.000)	1 224 (1 038 1 444)	100.00
NOTE Weights are from random offects analysis	1.221 (1.030, 1.111)	100.00
NOTE: weights are from random enects analysis	I	
.057 1	17.5	
(e)		

FIGURE 3: Continued.

9.667 (1.279, 1229.867) .556 (0.090, 3.445) .167 (1.027, 64.936) .571 (0.119, 2.751) .000 (0.459, 139.290) .282 (0.000, 8.418)	0.42 11.81 2.49 16.33
9.667 (1.279, 1229.867) 5.56 (0.090, 3.445) 1.67 (1.027, 64.936) 5.571 (0.119, 2.751) 0.00 (0.459, 139.290) 282 (0.000, 8.418)	0.42 11.81 2.49 16.33
.556 (0.090, 3.445) .167 (1.027, 64.936) .571 (0.119, 2.751) .000 (0.459, 139.290) .282 (0.000, 8.418)	11.81 2.49 16.33
.167 (1.027, 64.936) .571 (0.119, 2.751) .000 (0.459, 139.290) .822 (0.000, 8, 418)	2.49 16.33
.571 (0.119, 2.751) .000 (0.459, 139.290) .282 (0.000, 8.418)	16.33
.000 (0.459, 139.290)	
292 (0.000 9.419)	1.21
.282 (0.009, 8.418)	5.48
.000 (0.025, 40.276)	2.21
5.000 (0.182, 1236,183)	0.39
.210 (0.008, 5.769)	6.64
.750 (0.050, 11.311)	4.84
.571 (0.114, 111.707)	1.53
.551 (0.791, 3.043)	53.36
3.333 (1.069, 166.374)	1.39
.167 (0.012, 2.368)	9.94
.000 (0.112, 8.947)	6.30
.000 (0.329, 48.656)	2.25
.407 (0.013, 12.636)	4.43
3.000 (0.448, 377.470)	0.82
.889 (0.069, 51.917)	2.21
.000 (0.170, 146.642)	1.38
.000 (0.150, 59.890)	1.97
.115 (0.919, 4.867)	30.69
.800 (0.072, 45.135)	2.46
.333 (0.012, 9.395)	5.28
.210 (0.008, 5.769)	6.64
.000 (0.122, 73.642)	1.57
.771 (0.177, 3.352)	15.96
.600 (0.980, 2.610)	100.00
-	000 (0.122, 73.642) .771 (0.177, 3.352) .600 (0.980, 2.610)

FIGURE 3: Continued.

Study ID	OR (95% CI)	% Weight
LAA Zhao et al. 2017	9 143 (0 902 92 684)	0.94
	9.143 (0.902, 92.084)	2.12
Dao at al. 2007	1.245(0.442, 4.082)	5.12
Slowik et al. 2002	5,667,(0,180,160,524)	10.13
	1.046 (0.202, 2.627)	0.60
Chetzietofanidie et al. 2014	1.040 (0.302, 3.027) 1.741 (0.232, 13.074)	9.62
Tassilar et al. 2000	1.741(0.232, 13.074)	2.70
Kang and Lee 2006	0.255(0.010, 6.603)	2.00
Correcto et al. 2005	0.255(0.010, 0.005)	3.23
Cerrato et al. 2003	0.925(0.095, 9.226)	5.07
	5.824 (0.214, 158.818)	0.63
Kokubo et al. 2000	0.429 (0.024, 7.518)	4.03
Ressier et al. 1997	1.0/5 (0.092, 12.562)	2.42
	0.619(0.089, 4.316)	5.23
Subtotal (1-squared = 0.0% , p = 0.735)	1.353 (0.811, 2.258)	48.47
CE		0.00
Das et al. 2016	0.698(0.147, 3.302)	8.39
Zhao et al. 2017	4.778 (0.169, 134.855)	0.38
Luo et al. 2015	0.785 (0.042, 14.800)	2.20
Cerrato et al. 2005	1.667 (0.069, 40.478)	1.00
Kokubo et al. 2000	1.154 (0.062, 21.581)	1.57
Kessler et al. 1997	2.389 (0.195, 29.268)	1.30
Subtotal (I-squared = 0.0% , p = 0.905)	1.077 (0.402, 2.887)	14.84
SAD		
Das et al. 2016	0.377 (0.047, 3.032)	7.92
Zhao et al. 2017	9.412 (1.057, 83.840)	1.30
Luo et al. 2015	1.009 (0.203, 5.016)	5.92
Wen et al. 2006	2.727 (0.219, 34.011)	1.51
Chatzistefanidis et al. 2014	1.516 (0.203, 11.335)	3.01
Lai et al. 2007	0.146 (0.006, 3.747)	4.03
Kang and Lee. 2006	0.333 (0.013, 8.697)	2.84
Cerrato et al. 2005	0.362 (0.018, 7.245)	3.82
Kokubo et al. 2000	1.554 (0.185, 13.085)	2.29
Kessler et al. 1997	5.375 (0.658, 43.903)	1.16
Pedro-Botet et al. 1992	2.167 (0.334, 14.057)	2.87
Subtotal (I-squared = 1.0%, p = 0.432)	1.332 (0.739, 2.400)	36.69
Overall (I-squared = 0.0%, p = 0.882)	1.304 (0.911, 1.867)	100.00
	176	
.00569 I	1/6	
(g)		

FIGURE 3: (a-g) Forest plots of the relationships between APOE gene polymorphisms in subgroup analysis. (a) Forest plot of $\epsilon 2/\epsilon 4$ vs. $\epsilon 3/\epsilon 3$ comparison. (b) Forest plot of $\epsilon 3/\epsilon 4$ vs. $\epsilon 3/\epsilon 3$ comparison. (c) Forest plot of APOE $\epsilon 4/\epsilon 4$ vs. the $\epsilon 3/\epsilon 3$ genotype. (d) Forest plot of the APOE $\epsilon 4$ allele vs. $\epsilon 3$ allele. (e) Forest plot of APOE $\epsilon 4$ carriers vs. non- $\epsilon 4$ carriers. (f) Forest plot of APOE $\epsilon 4/\epsilon 4$ vs. $\epsilon 2/\epsilon 4$. (g) Forest plot of APOE $\epsilon 4/\epsilon 4$ vs. $\epsilon 3/\epsilon 4$.

P = 0.01), respectively (Figures 2(f) and 2(g)); this part provided evidence that ε 4 homozygosis might generate a higher risk of IS than ε 4 heterozygotes.

3.3. Main Results of the Relationship between APOE Gene and Three IS Subtypes. We further investigated on the correlation of APOE gene polymorphisms and risks of IS subtypes by making comparisons in five genetic models, with a particular focus on the APOE ε 4 mutation. Subgroup analyses showed that APOE ε 4 mutation significantly increased SAD risk (ε 4 allele vs. ε 3 allele: pooled OR = 1.318, 95% CI, 1.073-1.618, P = 0.01 (Figure 3(d)); ε 3/ ε 4 vs. ε 3/ ε 3: pooled OR = 1.392, 95% CI, 1.097-1.767, P = 0.01(Figure 3(b)); ε 4/ ε 4 vs. ε 3/ ε 3: pooled OR = 1.809, 95%, CI 1.030-3.175, P = 0.04 (Figure 3(c)); and APOE ε 4 carriers vs. non-APOE $\varepsilon 4$ carriers: pooled OR = 1.329, 95% CI, 1.064-1.661, P = 0.01 (Figure 3(e))). But genotype $\varepsilon 2/\varepsilon 4$ did not increase the risk of SAD onset (Figure 3(a)). The result of APOE $\varepsilon 4$ homozygosis versus $\varepsilon 4$ heterozygote comparisons ($\varepsilon 4/\varepsilon 4$ vs. $\varepsilon 2/\varepsilon 4$ and $\varepsilon 4/\varepsilon 4$ vs. $\varepsilon 3/\varepsilon 4$) was a matter of concern: APOE $\varepsilon 4$ mutation could not cause a cumulative effect in generating higher risk of SAD onset, as showed in Figures 3(f) and 3(g).

3.4. Sensitivity Analysis. Sensitivity analysis was performed by removing studies one by one to check the effect of the individual study on overall ORs. No single study influenced on the pooled ORs and 95% CIs in all genetic model comparisons as our data showed (supplementary material table 4).



FIGURE 4: Trial sequential analysis of the association between APOE gene polymorphisms and ischemic stroke.

3.5. Publication Bias. We carried out publication bias analysis by using funnel plots as qualitative description and Egger's regression tests as quantitative outcome. Funnel plots of all genetic model comparisons did not exhibit apparent asymmetry (several funnel plots were showed in supplementary material figure 1 and 2). In addition to subtype analysis of $\varepsilon 2/\varepsilon 2$ vs. $\varepsilon 3/3$, all the Egger's regression test outcomes indicated that there existed no evident publication bias with all *P* values exceeding 0.1 (supplementary material table 5). The above results showed that publication bias of our metaanalysis was not significant.

3.6. Regression Analysis. Meta-regression analysis was then performed to explore sources of heterogeneity as shown in supplementary material table 5, considering the year of publication, region, sample size, genotyping method, HWE, NOS score, and source of control. However, the *P* value of each factor affecting overall heterogeneity was not statistically significant in comparisons of $\varepsilon 3/\varepsilon 4$ vs. $\varepsilon 3/3$, $\varepsilon 4$ vs. non- $\varepsilon 4$, $\varepsilon 2$ vs. non- $\varepsilon 2$, $\varepsilon 4$ allele vs. $\varepsilon 3$ allele, and $\varepsilon 2$ allele vs. $\varepsilon 3$ allele (supplementary material figure 3). Heterogeneity sources were unascertainable.

3.7. The Result of Trial Sequential Analysis (TSA). The RIS was 8901 samples and the sample size of our meta-analysis reached it. Moreover, the cumulative *z*-curve crossed the trial sequential monitoring boundary before reaching the RIS as showed in Figure 4. The result of TSA guaranteed the stability of our meta-analysis results. Our sample size

was proved to be enough for evaluating the relationship between APOE polymorphisms and IS risk.

4. Discussion

Recently, scholars explored more how gene polymorphisms were contributing to the occurrence and prognosis of diseases. And several previous publications had well explored how gene polymorphisms related to diseases onset and potential mechanisms [74, 75]. As a heterogeneous multifactorial disorder, ischemic stroke could be regulated by certain gene synthesis and specific gene products. The genes involved in the pathological process of stroke are also worth of attention. Apolipoprotein E has been proven to affect atherosclerosis, neurodegeneration, and the process of nerve damage repair. That is why we explored the relationship between APOE gene polymorphisms and ischemic stroke risk.

APOE is a 299-amino acid protein encoded by the APOE gene of three common polymorphisms, $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$. The correlation of APOE gene polymorphisms and the risk of cerebral vascular and degenerative diseases have been investigated a lot, especially in Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA) [76]. APOE $\varepsilon 4$ is associated with increased risk for AD whereas APOE $\varepsilon 2$ is associated with decreased risk [77]. Mirza et al. performed a metaanalysis to find that greater WMH volume was associated with worse performance on all cognitive domains in APOE $\varepsilon 4$ carriers only in AD [78]. Charidimou et al. proved that the APOE $\varepsilon 2$ allele might be associated with the pathophysiology and severity of cortical superficial siderosis in CAA [79]. As to IS, there existed quite many researches with inconsistent conclusions. Besides method differences, ethnic difference and unclarified pathophysiological mechanisms are probable reasons of the inconsistency.

In a meta-analysis in 1999, McCarron et al. found that the $\varepsilon 4$ allele and carriers were more frequent among patients with ischemic cerebrovascular disease, compared with control subjects (27% versus 18%; odds ratio, 1.73; 95% CI, 1.34-2.23; *P* < 0.0001) [13]. In another meta-analysis based on Chinese population, the $\varepsilon 4$ allele is associated with an increased risk of developing cerebral infarction, in which the adjusted risk estimate for the ε 4 allele versus ε 3 allele was significant (OR = 2.00, 95% CI 1.59-2.53, P < 0.0001) [14]. Our estimates seemed to be coinciding with the above ones. Compared with the ε 3 allele, the ε 4 allele showed a higher risk of IS. Compared with $\varepsilon_3/\varepsilon_3$, both ε_4 heterozygote $(\varepsilon 2/\varepsilon 4, \varepsilon 3/\varepsilon 4)$ and $\varepsilon 4$ homozygosis $(\varepsilon 4/\varepsilon 4)$ exhibited a significant correlation with an increased risk of IS. Notably, OR in ε4 homozygosis (ε4/ε4 vs. ε3/3: 1.833 (95% CI 1.542-2.179)) was higher than those in $\varepsilon 4$ heterozygotes ($\varepsilon 2/\varepsilon 4$ vs. $\varepsilon 3/3$: 1.233 (95% CI 1.056-1.440) and ɛ3/ɛ4 vs. ɛ3/3: 1.340 (95% CI 1.165-1.542)), which implied that the ε 4 allele might possess a cumulative effect. Then, we performed comparisons between $\varepsilon 4/\varepsilon 4$ and $\varepsilon 2/\varepsilon 4$ or $\varepsilon 3/\varepsilon 4$; there existed significant differences between £4 homozygosis and £4 heterozygote. The OR between £4/£4 and £2/£4 was 1.625 (95% CI 1.281-2.060, P < 0.0001); the OR between $\varepsilon 4/\varepsilon 4$ and $\varepsilon 3/\varepsilon 4$ was 1.301 (95%) CI 1.077-1.571, P = 0.01), giving a hint that $\varepsilon 4$ homozygosis might bring a higher risk of IS than ε 4 heterozygotes.

There are tremendous researches and discussions focusing on the pathogenicity of $\varepsilon 4$. An Indian research reported that VLDL and triglycerides levels were found to be significantly associated with $\varepsilon 2/\varepsilon 4$ and $\varepsilon 3/\varepsilon 4$ genotypes; the $\varepsilon 4$ allele exerted a higher influence than the ε 3 allele in plasma cholesterol levels [22]. As a lipid transport protein, APOE3 and APOE2 preferentially bind to the smaller, more phospholipid-enriched high-density lipoproteins (HDL), while APOE4 preferentially binds to the larger, triglyceride-rich very low-density lipoproteins (VLDL). Miyata and Smith demonstrated an antioxidant activity in the order APOE2 > E3 > E4, and other researchers also reported similar results that APOE4 was associated with increased oxidative stress [25, 80], which might play a role in atherosclerosis and lead to increased risk of ischemic vascular diseases. Besides the above reasons, APOE4 was proved to be neurotoxic by assuming an abnormal conformation (the unique domain interaction between Arg-61 and Glu-255) which was highly susceptible to neuron specific proteolysis and generating neurotoxic fragments that escaped the secretory pathway and entered the cytosol [81]. Totally, from pathophysiological mechanisms to clinical research results, it seems that APOE4 is indeed related to a higher risk of IS, compared with other isoforms, both in ε 4 heterozygote and homozygous. ε 2 allele appears to be unclear and controversial in stroke [13]. In a meta-analysis of Martínez-González et al., compared with $\varepsilon 3/\varepsilon 3$, APOE was associated with intracerebral hemorrhage ε2

(OR = 1.32; 95% CI, 1.01-1.74); meanwhile, APOE *ɛ*2 was more related to lobar hemorrhage than deep hemorrhage [82]. As to the association of IS with APOE based on previous investigation, it is uncertain. Our estimates showed that both $\varepsilon 2/\varepsilon 2$ and $\varepsilon 2/\varepsilon 3$ genotypes exhibited no significant effects on IS risk, compared with $\varepsilon 3/\varepsilon 3$. Also, no differences were found in comparisons of ε_2 allele vs. ε_3 allele and ε_2 vs. non- $\varepsilon 2$ carriers. This result remained consistent with another meta-analysis in 2013 [14]. Interestingly, in subtype analysis, $\varepsilon 2/\varepsilon 2$ displayed significances in the CE group (OR = 4.290; 95% CI, 1.917-9.600; P < 0.0001) and SAD group (OR = 1.803; 95% CI, 1.037-3.134; P = 0.04). The largest meta-analysis of the APOE genotype with IS showed a positive linear association of increasing risk when ordered from $\varepsilon 2/\varepsilon 2$, $\varepsilon 2/\varepsilon 3$, $\varepsilon 2/\varepsilon 4$, $\varepsilon 3/\varepsilon 3$, $\varepsilon 3/\varepsilon 4$, and $\varepsilon 4/\varepsilon 4$ in European ancestry population [83]. The conclusion might explain why APOE4 brings a higher risk of IS but could not clarify that the CE and SAD subgroups in comparison of $\varepsilon 2/$ ε^2 with $\varepsilon^3/\varepsilon^3$ show significances. It is well known that all patients with type III hyperlipidemia (dysbetalipoproteinemia) were APOE ε 2 homozygous, whereas most ε 2/ ε2 subjects (>90%) were normolipidemic or even hypolipidemic, owing to reductions in LDL or HDL or both. Therefore, the APOE $\varepsilon 2$ allele has both increased and decreased risks for atherosclerosis, which induced a comprehensive and undetermined result [84].

As to our subtype analyses, all LAA groups showed no significant difference among comparisons, which raised a question why isoforms of APOE, a lipid transport protein, seemed not to be related with IS caused by large artery atherosclerosis. Besides lipid metabolism and atherosclerosis, there might exist some other pathways underlying the relationships between APOE and risk of IS. Our estimates displayed that APOE isoforms were associated to risk of IS especially in the SAD subgroup. Hypertension was known to be an independent risk factor of SAD. Atherosclerosis, dyslipidemia, and hypertension have a complex interaction, and the causations with APOE need further investigation.

Our meta-analysis has several limitations. First, just as the abovementioned, heterogeneity between studies remains undeterminable. Second, results of our meta-analysis based on case control studies cannot provide a causal relationship, but only an association. Third, age variable and ethnicity can influence APOE frequencies in a population; we cannot obtain sufficient related information to perform further subdivided subgroup analyses. Fourth, other pathogenic factors about IS, a multifactorial disease, such as plasma lipid levels, hypertension, life-style, BMI, and gene-environment interactions, were unachievable. Fifth, the controls in accessible studies were not strictly defined; some were selected from healthy populations and others were from nonstroke people. The expected genotype distribution in controls was not in accordance with HWE in seven studies. Population selection in control groups failed to avoid certain diseases which might have a relation with the APOE gene, such as dyslipidemia, hypertension, other vascular diseases, and diabetes. Sixth, the case groups were not selected by a prospective process and the design of case control studies often caused abnormal gene frequency.

5. Conclusions

In conclusion, our meta-analysis provides rational evidence that APOE ε 4 mutation is a genetic risk factor for IS. Prospective studies of a large sample size, which concerns gene-gene and gene-environment interactions, should be carried out in the future to reach a more comprehensive outcome about the association of APOE gene polymorphisms and IS. What is more, future researches should be designed to elucidate the mechanism by which APOE ε 4 mutation adds the risk of IS.

Data Availability

Data presented within the paper and the supplementary materials contributed to the findings in our study. They are all are available from our corresponding author for reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

The conceptualization was done by S.-Y. Q., K. S., Y.-H.C., and X.C.; the methodology was done by D.-S. T., D.-J. P., and C. Q.; K. S., Y-H.C., H.-H. Y, and X.C. took care of the software; meta-analysis was done by D.-S. T., D.-J. P., C. Q., S.-Y. Q., K. S., and X.C.; writing—original draft preparation—was done by S.-Y. Q., K. S., Y.-H.C., and H.-H. Y.; writing—review and editing—was done by D.-S. T., D.-J. P., and C. Q. All authors have read and agreed to the published version of the manuscript. Su-Ya Qiao and Ke Shang contributed equally to this work.

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Supplementary Materials

Supplementary material Table 1: fifteen of the included studies provide data about different subtypes of IS: LAA, SAD, and CE. Supplementary material Table 2: Newcastle-Ottawa Scale (NOS) score of included studies. Supplementary material Table 3: PRISMA list of our meta-analysis. Supplementary material Table 4: sensitivity analysis of the association between ApoE gene polymorphisms and IS. Supplementary material Table 5: publication bias and heterogeneity of our meta-analysis. Supplementary material Figure 1: funnel plots for studies included in Figures 2A–G. Supplementary material Figure 2: funnel plots for studies included in Figures 3A–G. Supplementary material Figure 3: results of meta-regression. (Supplementary Materials)

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