

Lack of association of tumor necrosis factor superfamily member 4 (TNFSF4) gene polymorphisms (rs3850641 and rs17568) with coronary heart disease and stroke: A systematic review and meta-analysis

Jin-Sen Lu[#], Hong Wang[#], Fei-Fei Yuan, Le-Le Wu, Bin Wang*, Dong-Qing Ye*

Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University,

*Anhui Province Key Laboratory of Major Autoimmune Diseases; Anhui- P. R. China

ABSTRACT

Objective: To evaluate the association between the tumor necrosis factor superfamily member 4 (TNFSF4) gene polymorphisms and common cardiovascular and cerebrovascular diseases.

Methods: A literature-based search was conducted through databases including PubMed, EMBASE, Cochrane Library, CNKI, and WanFang data. Crude odds ratios (ORs) and 95% confidence intervals (CI) were calculated to estimate the strength of the association between TNFSF4 polymorphisms (rs3850641 and rs17568) and the risk of coronary heart disease (CHD) and stroke.

Results: Overall, 11 eligible studies were included in this meta-analysis. G allele was showed not to be associated with CHD and stroke, compared with A allele (rs3850641: OR=1.02, 95% CI=0.89–1.17; rs17568: OR=1.09, 95% CI=0.89–1.33). Genotypic analysis demonstrated that there was no significant association between the risk of CHD and stroke and rs3850641 [homozygous comparison (GG vs. AA): OR=1.05, 95% CI=0.74–1.50; heterozygous comparison (GA vs. AA): OR=1.00, 95% CI=0.88–1.13; recessive model (GG vs. GA+AA): OR=1.04, 95% CI=0.76–1.43; dominant model (GG+GA vs. AA): OR=1.01, 95% CI=0.88–1.17]. Similarly, no susceptibility between CHD and stroke and rs17568 polymorphism was uncovered (GG vs. AA: OR=1.04, 95% CI=0.74–1.46; GA vs. AA: OR=1.07, 95% CI=0.62–1.83; GG+GA vs. AA: OR=1.13, 95% CI=0.82–1.56; GG vs. GA+AA: OR=1.01, 95% CI=0.74–1.39).

Conclusion: The present study demonstrated that there is no significant relationship between TNFSF4 gene polymorphism and cerebrovascular and cardiovascular diseases. (*Anatol J Cardiol* 2018; 19: 86-93)

Keywords: tumor necrosis factor superfamily member 4, coronary heart disease, stroke, polymorphism, meta-analysis

Introduction

Coronary heart disease (CHD), one of the most prevalent cardiovascular diseases caused by ischemia and hypoxia of the coronary artery, remains the leading cause of human death throughout the world (1-4). In general, CHD is referred to angina pectoris, myocardial infarction, ischemic cardiomyopathy, and sudden death (5). Past studies revealed that people over the age of 50 had a higher risk of CHD and death (2, 3). Stroke, the third leading cause of death in the USA and the major risk factor of disability and death in Western countries, kills 150,000 people from 700,000 new sufferers per year in the USA (6). Apart from acquired risk factors including excessive alcohol, obesity, and smoking, studies of twins, siblings, and families have provided compelling evi-

dence of heritability for CHD and stroke, but the essential genetic determinants are still unknown. However, one study showed that inflammatory process played a significant role in atherosclerosis, plaque rupture, and thrombosis, which resulted in ischemia, cerebral infarction, myocardial infarction (MI), and stroke (7-10). During the inflammatory process, T cells, the primary mediator of the adaptive immune response, were activated by members of the tumor necrosis factor (TNF) superfamily including CD40/CD40 ligand, LIGHT, TNFRSF4/TNFSF4, and CD137 (11-16). Among those members, TNFSF4 gained more attention for its essential role in the pathogenesis of atherosclerosis due to its regulation to produce OX40 ligand (OX40L), a 34-kDa glycoprotein observed in T cells, B lymphocytes, vascular endothelial cells, macrophages, mast cells, and smooth muscle cells in atherosclerotic lesions (17,

#J.S.L. and H.W. contributed equally to this article.

Address for correspondence: Bin Wang, MD, Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei 230032, Anhui- P. R. China
Phone: +8655165161171 E-mail: wbrst@sina.com

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18). It was reported that increase in OX40L is accompanied with exacerbation of atherosclerosis, whereas decrease in OX40L attenuated the lesions (19). Polymorphisms could directly affect the expression level of certain genetic products; hence, it may be vital to detect the relationships between TNFSF4 polymorphisms and the risk of CHD and stroke from both genetic and epidemiological standpoints. Rs3850641, an SNP located at intron 1 of the OX40L gene, was initially reported because of its association with MI and CAD severity (15). Besides, increasing investigations based on diverse ethnicities had uncovered the relationship between stroke and TNFRSF4 SNPs rs1234313, rs1234314, and rs17568 (20). Although several studies have addressed the association between TNFSF4 polymorphisms and CHD and stroke, no consensus has ever been reached among different investigators. A recently meta-analysis had summarized studies on the association between rs3850641 and CHD, illustrating that no relevance was observed between them. Apart from that, recent investigations have also reported lack of association between rs17568 and MI in south Iran.

For our consideration, cardiovascular and cerebrovascular diseases were tightly linked with each other, owing to similar inflammatory abnormalities in blood vessels. Hence, after a careful research, the present meta-analysis was conducted for assessing the strength of evidence for the influence of rs3850641 and rs17568 on the risk of CHD and stroke via summarizing data from all eligible investigations.

Methods

Literature search

An exhaustive literature search was performed on databases including PubMed, EMBASE, Cochrane Library, CNKI, and Wan-Fang data to identify studies that examined the association of the TNFSF4 polymorphism with CHD and stroke (until July 2017). We also reviewed the reference lists to check additional relevant investigations. The search algorithm was as follows: ("TNFSF4" or "Tumor necrosis factor superfamily number" or "OX40 ligand" or "OX40L") and ("atherosclerosis" or "coronary heart disease" or "CHD" or "coronary artery disease" or "CAD" or "ischemic heart disease" or "IHD" or "myocardial infarction" or "MI" or "CI" or "ACI" or "stroke" or "cerebral infarction") and ("polymorphism" or "genotype" or "variant" or "allele" or "variation" or "mutation"). Besides, the related citations of results in PubMed were searched. In addition, we only selected the study with the largest sample sizes, if there was more than one article using the same case series. The overall process was conducted by two authors independently, and disagreements were solved by discussion.

Selection criteria

The included studies were required to meet the following criteria: (1) the study was used to assess the association between TNFSF4 polymorphisms and the risk of CHD and stroke; (2) the study was a case-control study; (3) the study provided odds ratio (OR) with 95% confidence interval (CI) or other sufficient data to

calculate OR and CI for demonstrating the association between TNFSF4 polymorphisms and the risk of CHD and stroke; (4) when multiple publications reported on the same or overlapping data, the most recent article or the article based on the largest study population was selected. Studies satisfying the following criteria were excluded: conference abstracts and investigations without raw data available for retrieval, republished data, duplicate studies, reviews, animal studies, not a case-control study, and editorials.

Data extraction and quality evaluation

The following information was collected from each enrolled study by two investigators: first authors, publication date, demographic data, country and ethnicity, study design, genotyping assay, information of available allele, and genotype frequency. To check the precision and correctness of the extracted data, raw information was re-inspected by another investigator with inconsistent results settled through group discussion. Quality of each study was evaluated by Newcastle-Ottawa scale (NOS) according to the three leading criteria: selection of the controls and cases, comparability of the cases and controls; and exposure to risk factors. NOS scores ranged from 0 to 9 stars, and studies graded seven stars or greater were considered to be of high quality, whereas those graded five stars or less were considered to be of low quality. Quality appraisal was performed by two investigators independently, and disputes of discordance were resolved by group discussion.

Statistical analysis

The RevMan 5.0 and STATA 12.0 software programs (Stata Corp, College Station, TX, USA) were used to perform this meta-analysis. The OR and 95% CI were calculated to assess the association between TNFSF4 gene polymorphisms and the risk of CHD and stroke. Five different ORs were used to compute allele contrast model (G vs. A), dominant model (GG+GA vs. AA), recessive model (GG vs. GA+AA), heterozygote comparison (GA vs. AA), and homozygote comparison (GG vs. AA) (AA, homozygote for the common allele; GA, heterozygote; GG, homozygote). We adopted chi-square test-based Q statistic test to assess the heterogeneity within the case-control studies. The random model was applied in this study because it is more conservative than the fixed model. We also measured HWE of control groups. The stability of overall results were evaluated by sensibility analysis, in which sensitivity was detected every time following the deletion of one single case-control study from the enrolled pooled data. Finally, Begg's funnel plot and Egger's regression test were conducted to detect the potential publication bias, and $p < 0.05$ was considered statistically significant.

Results

Study inclusion and characteristics

As shown in Figure 1, the literature research identified a total of 26 related publications. After reading the title and ab-

Table 1. Characteristics of eligible studies in this meta-analysis

SNP	Reference	Year	Country	Ethnicity	Genotyping method	Design	Genotype (Case/Control)			HWE	NOS
							GG	GA	AA		
rs3850641	Cheng et al. ²⁰	2011	China	Chinese	PCR-RFLP	HB	19/31	88/215	178/399	yes	8
rs3850641	Chen et al. ²¹	2011	China	Chinese	PCR-RFLP	HB	7/3	51/53	162/179	yes	7
rs3850641	Olofsson et al. (1) ²²	2009	Sweden	Caucasian	Fluorescence-based allelic discrimination method	HB	17/26	163/163	417/408	yes	7
rs3850641	Olofsson et al. (2) ²²	2009	Sweden	Caucasian	Fluorescence-based allelic discrimination method	HB	2/13	70/185	255/581	yes	7
rs3850641	Olofsson et al. (3) ²²	2009	Sweden	Caucasian	Fluorescence-based allelic discrimination method	HB	3/2	67/30	169/106	yes	7
rs3850641	Huang et al. ²³	2015	China	Chinese	TaqMan-PCR	PB	18/18	142/153	350/314	yes	7
rs3850641	Malarstig et al. ²⁴	2008	USA	Caucasian	Fluorescence-based allelic discrimination method	PB	11/67	92/697	241/1622	yes	8
rs3850641	Wang et al. ²⁵	2010	Sweden	Caucasian	PCR	HB	18/20	53/44	170/148	yes	7
rs3850641	Zhao et al. ²⁶	2010	China	Chinese	PCR-RFLP	HB	91/17	190/50	171/71	yes	7
rs3850641	Li et al. ²⁷	2008	China	Chinese	PCR	HB	6/2	64/65	195/280	yes	7
rs3850641	Feng et al. ²⁸	2012	China	Chinese	TaqMan-PCR	HB	11/19	104/117	270/246	yes	8
rs17568	Huang et al. ²⁹	2014	China	Chinese	PCR	HB	46/43	196/150	208/185	yes	7
rs17568	Mehrnoosh et al. ³⁰	2015	Iran	Caucasian	PCR	HB	45/44	2/10	53/46	yes	8
rs17568	Chen et al. ²¹	2011	China	Chinese	PCR-RFLP	HB	19/13	126/101	90/106	yes	7

HWE - Hardy Weinberg equilibrium; HB - hospital based; PCR - polymerase chain reaction; PB - population based; RFLP - restriction fragment length polymorphism; SNP - single nucleotide polymorphism

Table 2. Summary estimates for the OR of TNFSF4 (rs3850641 and rs17568) polymorphism in various genetic model contrasts

Comparison	SNP	No. of studies	Test of association			Model	Test of heterogeneity			Begg's Test		Egger's test	
			OR (CI 95%)	Z	P		Q	P-value	I ² (%)	Z	P	T	P
G vs. A	rs3850641	11	1.02 (0.89-1.17)	0.31	0.75	R	26.75	0.003	63	1.40	0.161	-1.78	0.110
	rs17568	3	1.09 (0.89-1.33)	0.82	0.41	R	3.09	0.213	35	0.00	1.000	0.25	0.844
GG vs. AA	rs3850641	11	1.05 (0.74-1.50)	0.27	0.78	R	20.22	0.03	51	1.09	0.276	0.45	0.664
	rs17568	3	1.04 (0.74-1.46)	0.23	0.81	R	2.13	0.35	6	0.00	1.000	-1.34	0.407
GA vs. AA	rs3850641	11	1.00 (0.88-1.13)	0.08	0.94	R	14.77	0.14	32	1.40	0.161	-3.00	0.015
	rs17568	3	1.07 (0.62-1.83)	0.23	0.82	R	6.97	0.03	71	0.00	1.000	2.65	0.230
GG vs. GA+AA	rs3850641	11	1.04 (0.76-1.43)	0.24	0.81	R	16.74	0.08	40	1.09	0.276	0.53	0.611
	rs17568	3	1.01 (0.74-1.39)	0.09	0.93	R	1.11	0.57	0	1.04	0.296	-1552.01	0.000
GG+GA vs. AA	rs3850641	11	1.01 (0.88-1.17)	0.20	0.84	R	21.20	0.02	53	1.56	0.119	-2.62	0.028
	rs17568	3	1.13 (0.82-1.56)	0.77	0.44	R	4.17	0.12	52	0.00	1.000	0.63	0.641

Statistic methods: Z test was applied to test diversity of OR and chi-square test-based Q statistic test was applied to assess the heterogeneity within the case-control studies. The random model was applied in this study because it is more conservative than the fixed model

stract, we reserved 19 articles concerning the association between TNFSF4 polymorphisms and the risk of CHD and stroke. Eight publications were excluded because there were no data for rs3850641 or rs17568 polymorphisms, were unavailable to raw data, or were about other polymorphisms. Finally, a total

of 11 publications (20-30) were included. For TNFSF4 rs3850641 polymorphism, a total of nine publications with 11 case-control studies comprising 3,865 cases and 6,344 controls were included, whereas three publications with three case-control studies comprising 785 cases and 698 controls were included for rs17568

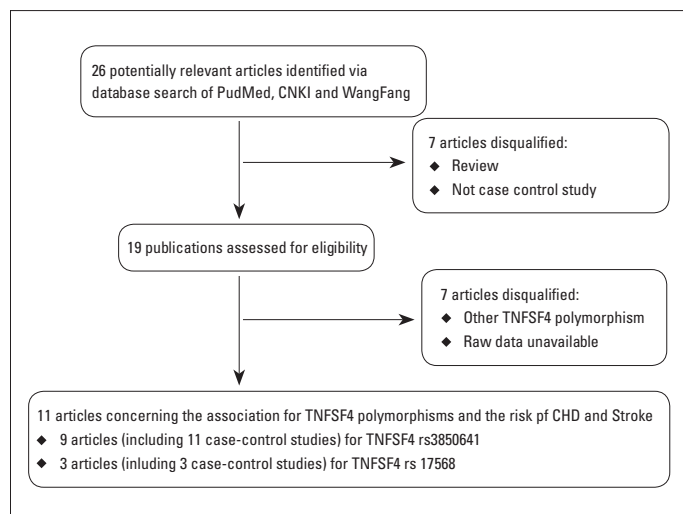


Figure 1. Flow diagram of studies included in this meta-analysis

polymorphism. All enrolled studies were in HWE, with an average NOS score of 7.25, revealing that all articles were of good quality. For rs3850641, there were six Chinese studies and three Caucasian studies. For rs17568, there were three Chinese studies and one Caucasian studies. Among all the studies, only two studies were of population-based and all others were of hospital-based design. Detailed information on allele and genotype distributions for each eligible study is shown in Table 1.

Allelic and genotypic analysis

Our findings for the association between TNFSF4 polymorphism (rs3850641 and rs17568) and the risk of CHD and stroke based on allelic and genotypic analyses are listed in Table 2. The overall fixed effect pooled OR of the G allele versus A allele for the risk of CHD and stroke showed no statistical significance for both rs3850641 and rs17568 (rs3850641: OR=1.02, 95% CI=0.89–1.17, p=0.75; rs17568: OR=1.09, 95% CI=0.89–1.27, p=0.82; Fig. 2). Figures 3–6 present the results of meta-analysis for each genotypic model; these demonstrated that there is no significant association between TNFSF4 polymorphism rs3850641 and the risk of CHD and stroke [Table 2; homozygous comparison (GG vs. AA): OR=1.05, 95% CI=0.74–1.50; heterozygous comparison (GA vs. AA): OR=1.00, 95% CI=0.88–1.13; recessive model (GG vs. GA+AA): OR=1.04, 95% CI=0.76–1.43; dominant model (GG+GA vs. AA): OR=1.01, 95% CI=0.88–1.17]. Similarly, no susceptibility between CHD and stroke and rs17568 polymorphism was uncovered (Table 2, GG vs. AA: OR=1.04, 95% CI=0.74–1.76; GA vs. AA: OR=1.07, 95% CI=0.62–1.83; GG+GA vs. AA: OR=1.13, 95% CI=0.82–1.56; GG vs. GA+AA: OR=1.01, 95% CI=0.74–1.39).

Sensitivity analysis and publication bias

Begg’s funnel plot and Egger’s test were conducted to check publication bias, and no significant publications bias was revealed for rs3850641 (Egger’s test, p=0.110) (Fig. 7). Sensitivity analysis was conducted to assess the effect of a separate study

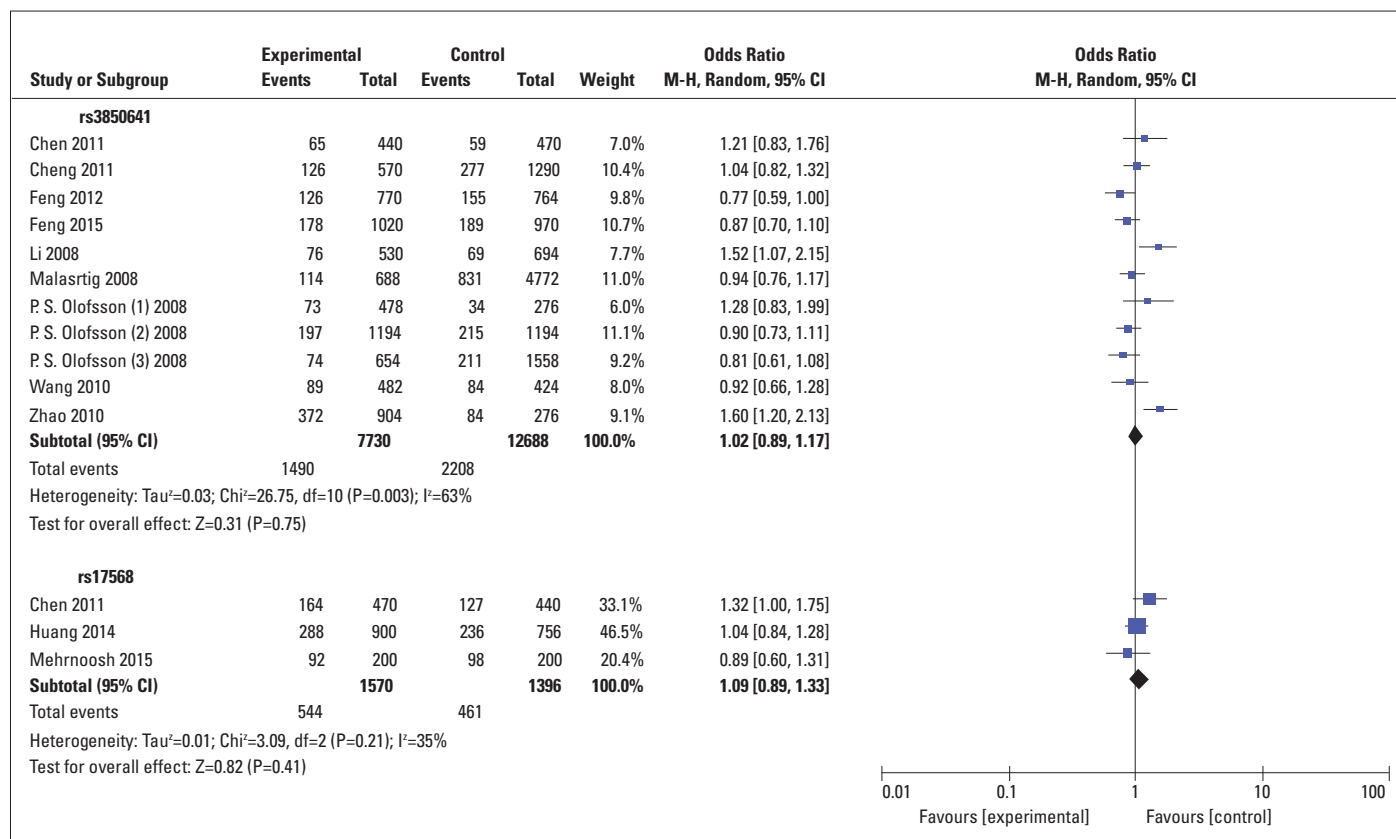


Figure 2. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in allele contrast model

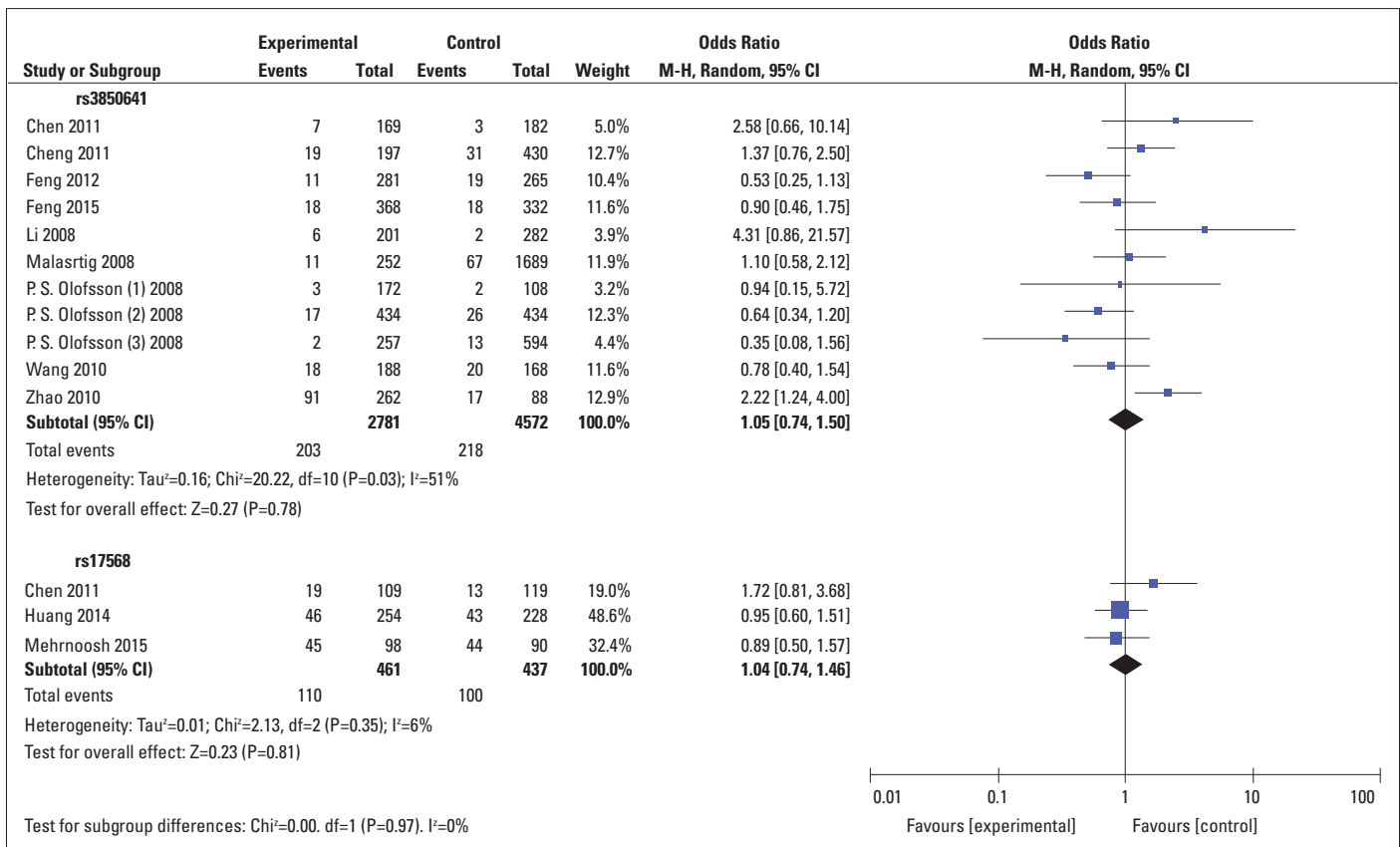


Figure 3. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in homozygous comparison

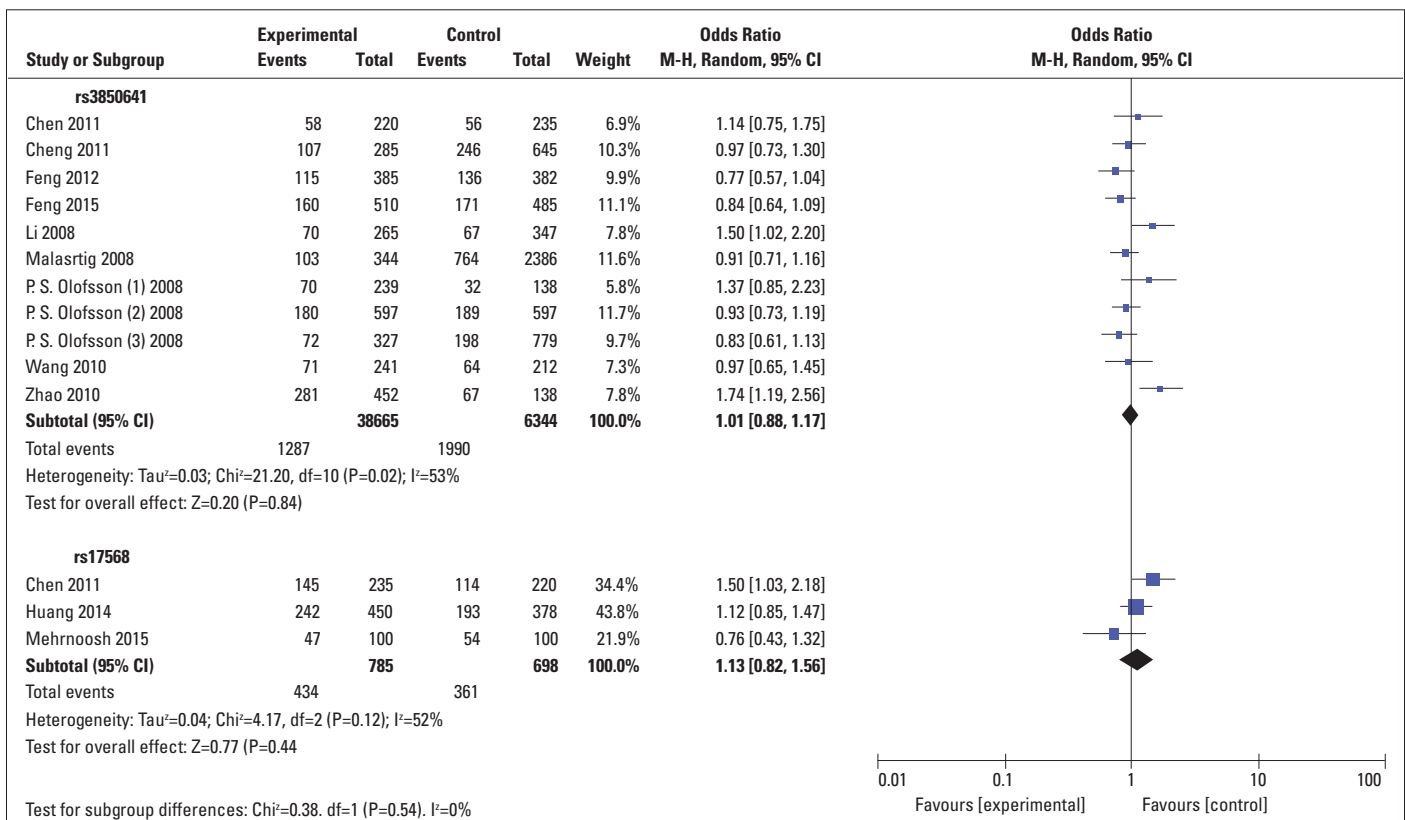


Figure 4. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in dominant model

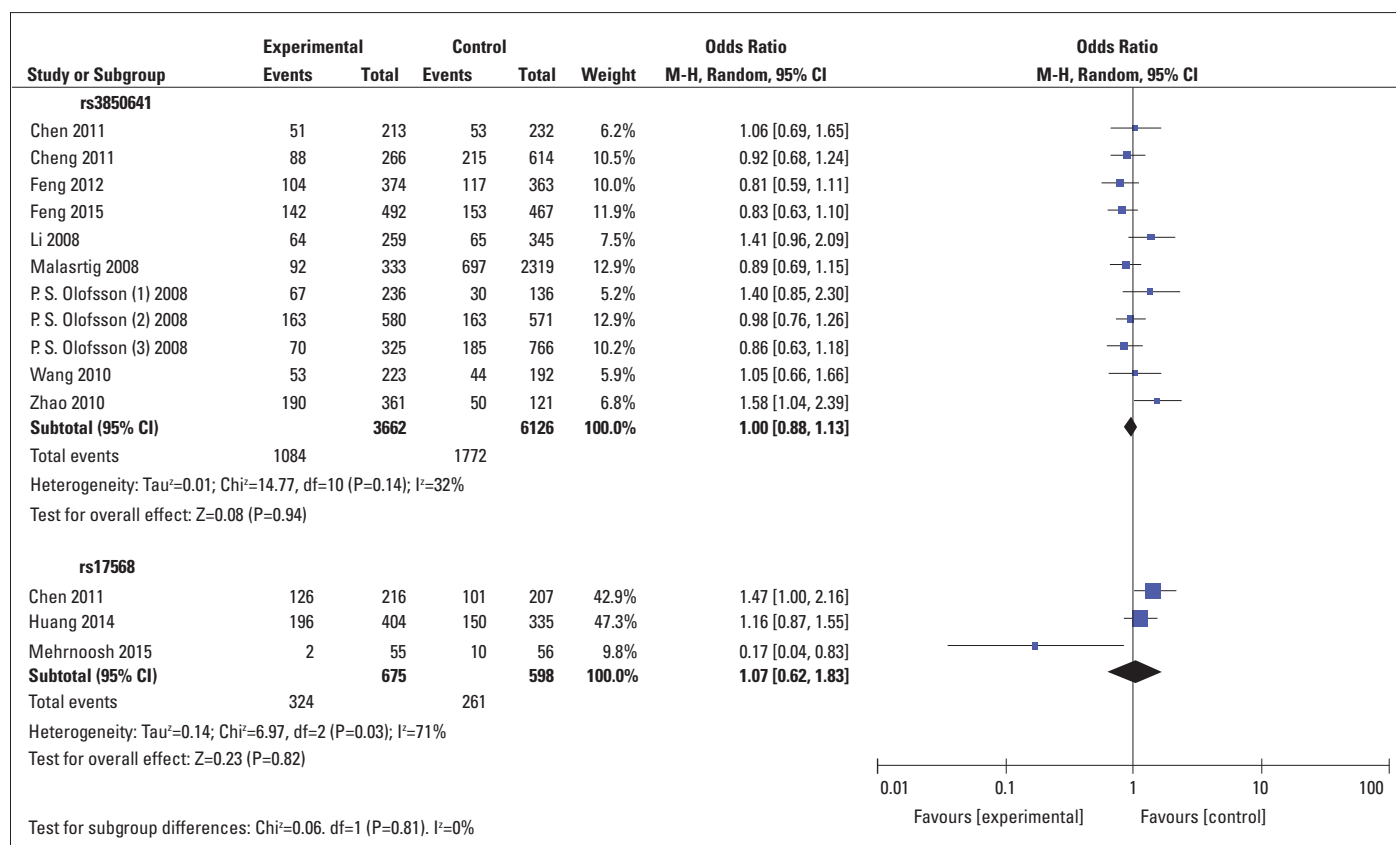


Figure 5. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in heterozygous model

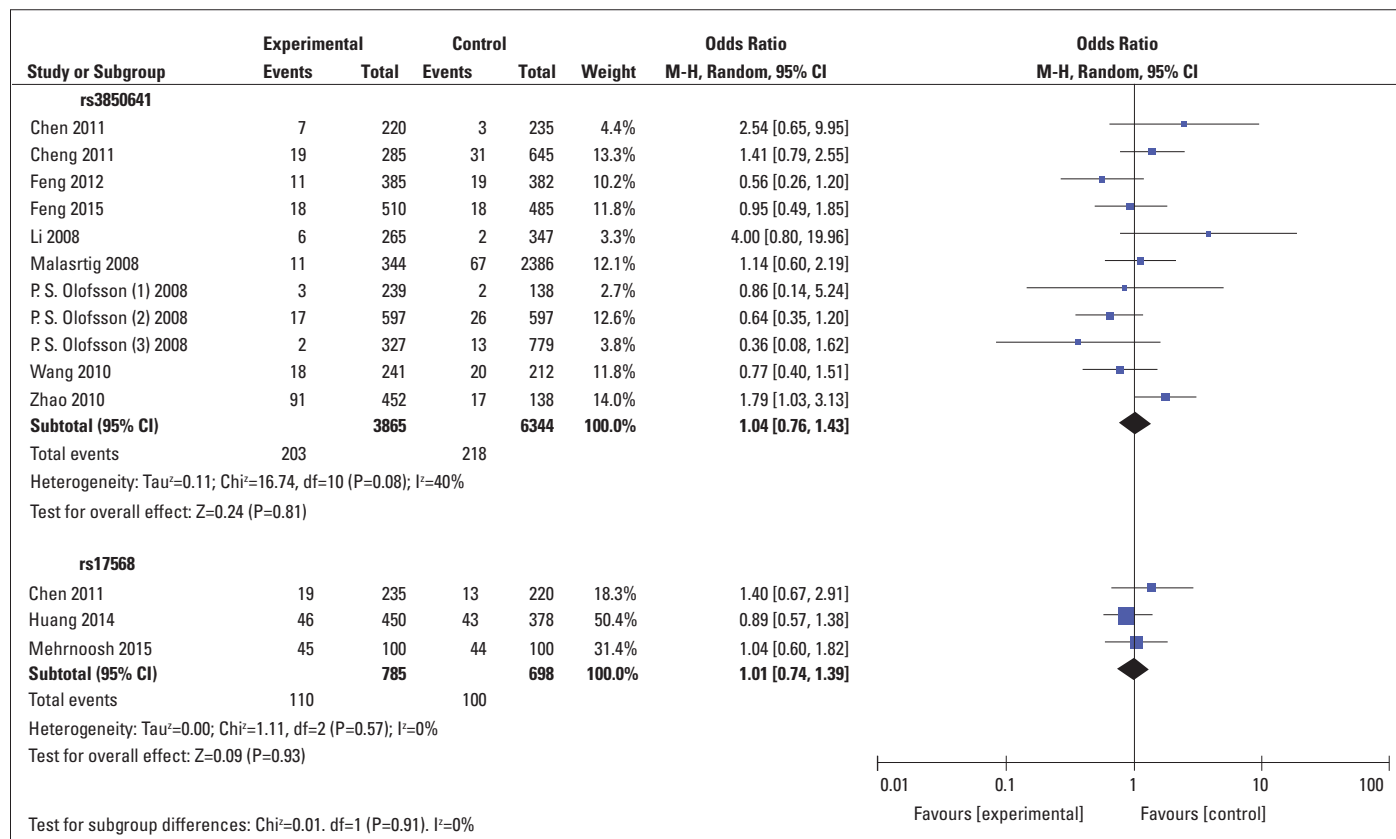


Figure 6. Forest plot of TNFSF4 polymorphism (rs3850641 and rs17568) with CHD and stroke in recessive model

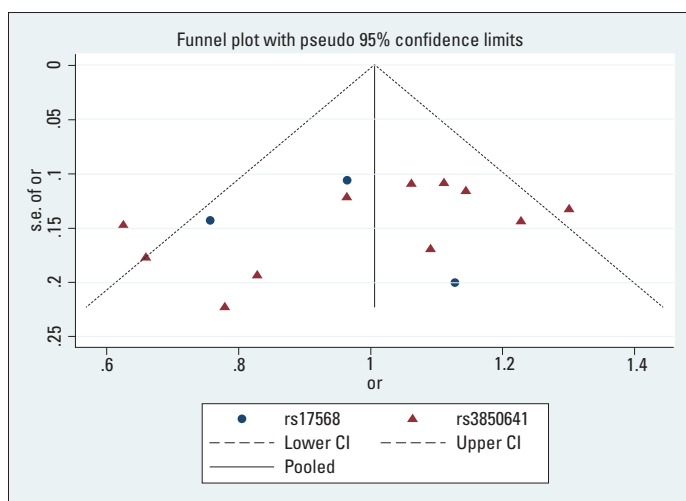


Figure 7. Publication bias in studies of the association between the TNFSF4 polymorphism (rs3850641) and the risk of CHD and stroke assessed by funnel plot for allele contrast model

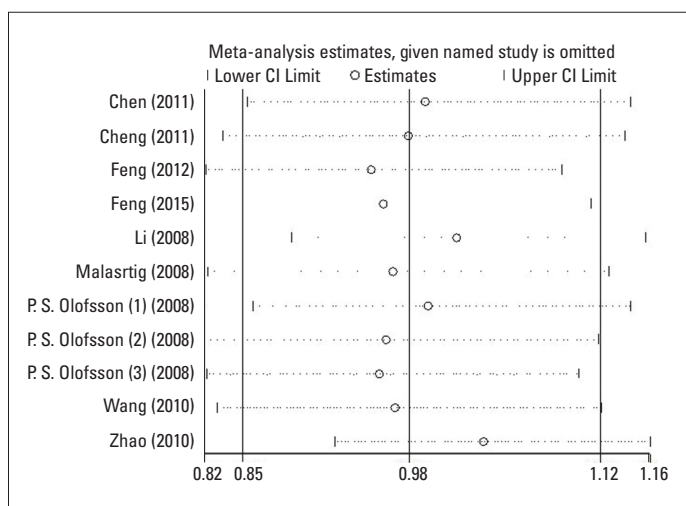


Figure 8. Sensibility analysis in studies of the association between the TNFSF4 polymorphism (rs3850641) and the risk of CHD and stroke for allele contrast model

on the pooled ORs by excluding one single study each time, and a negative result was achieved (Fig. 8).

Discussion

CHD and stroke are the two leading causes of death in the elderly and remained a major health problem among investigators throughout the world. Evidences have revealed that genomic background was closely related to susceptibility of CHD and stroke, explaining why certain population is under severe risk, but still kept out of the two killers. Inflammation of blood vessels leading to atherosclerosis is the most common etiology of both CHD and stroke, and genomic analysis of cytokines revealed many interesting phenomena. Among these findings, TNFSF4 was newly found to be related with the risk of cardiovascular and cerebrovascular diseases (1-7). Several studies have showed the rela-

tionship between TNFSF4 polymorphisms and the risk of CHD and stroke, but contradictory findings were observed (21-30). Among all polymorphisms under investigation, rs3850641 gained more attention than others. A recent meta-analysis demonstrated that there was no correlation between rs3850641 and the risk of CHD (31). Though exhausted retrieval, apart from limited papers of association between rs3850641 and the risk of CHD, we found that there were also some case-control studies that detected the correlation between TNFSF4 polymorphisms and the risk of stroke. Considering the correlation between CHD and stroke, we conducted a meta-analysis to investigate the association between TNFSF4 polymorphisms and the risk of CHD and stroke with 11 eligible case-control studies.

To our best knowledge, the present study is the first meta-analysis demonstrating the association between TNFSF4 polymorphisms (rs3850641 and rs17568) and the risk of CHD and stroke. After the allelic and genotypic analyses were completed, no significant association was found between TNFSF4 polymorphisms (and rs17568) and the risk of CHD and stroke after summarizing data from nine case-control studies comprising 3,865 cases and 6,344 controls for rs3850641 and three case-control studies comprising 785 cases and 698 controls for rs17568. The results of Begg's funnel plot and Egger's regression test revealed that no publication bias was detected.

Study limitations

Although we conducted a comprehensive retrieve and revised the disadvantages of the previous study, there are still several limitations: (1) we could not conduct analysis concerning the influence of gender. (2) Studies collected for rs17568 are limited for analysis and cannot guarantee the validity of results. (3) We could not conduct subgroup analysis of ethnicity, source of control, and genotyping method. (4) All studies included were conducted in the Asian and Caucasian populations; therefore, the conclusions may not be applicable to other populations. Therefore, further studies on other ethnic groups are required.

Conclusion

In conclusion, this study indicates that TNFS (rs3850641 and rs17568) has less effect on CHD and stroke.

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FFY., L.L.W.; Data collection &/or processing – H.W., L.L.W.; Analysis &/or interpretation – J.S.L., H.W.; Literature search – L.L.W., J.S.L.; Writing – J.S.L., H.W.; Critical review – J.S.L., B.W.

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