MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 2687-2694
DOI: 10.12659/MSM.913528

Received: 2018.10.09
Accepted: 2018.12.03
Published: 2019.04.12

Role of Endothelial Nitric Oxide Synthase Polymorphisms in Atrial Fibrillation: A PRISMA-Compliant Meta-Analysis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This work was supported by grants from the National Natural Science Foundation of China (81873486), the Natural Scientific Fund of Jiangsu Province (BK20161226), the Jiangsu Province's Key Provincial Talents Program (ZDRCA2016043), and Jiangsu Province's 333 High-Level Talents Project (BRA2017539)

Background: Research interest in endothelial nitric oxide synthase(eNOS) polymorphisms and atrial fibrillation (AF) has grown in last recent years, but the results of individual studies are inconsistent due to their small sample sizes.

Material/Methods: We searched databases for eligible studies on eNOS and AF, extracted the relevant data, and rigorously screened them according to inclusion and exclusion criteria. Then, we evaluated the study quality according to the Newcastle-Ottawa scale score, and we pooled the odds ratios (ORs) and 95% confidence intervals (CIs) by using a random-effects model or fixed-effects model based on inter-study heterogeneity. In addition, we performed subgroup analysis and sensitivity analysis and assessed publication bias.

Results: According to the inclusion and exclusion criteria, we finally found 8 studies in this search. The recessive (OR=0.81; 95% CI=0.67 to 0.97; p=0.988; I^2=0.0%) model showed that the eNOS 786T/C polymorphism was relevant to AF. We also found that the eNOS 786T/C polymorphism decreases the risk of AF, especially in white people (OR=0.81; 95% CI=0.67 to 0.97; P=0.023 for recessive model) and in the control population (OR=0.79; 95% CI=0.65 to 0.97; P=0.022 for recessive model). We found no obvious publication bias.

Conclusions: The eNOS gene *loci* 786T/C polymorphism is relevant to the risk of AF. Our results suggest that the 786T/C polymorphism significantly decreases AF risks in white people and control populations. Larger studies are required for further evaluation.

MeSH Keywords: Atrial Fibrillation • Meta-Analysis • Nitric Oxide Synthase Type III

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/913528

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Background

Atrial fibrillation (AF) is one of the most sustained tachyarrhythmias in clinical practice, with an increasing prevalence in humans, which is relevant to cardiogenic cerebral infarction, heart failure, and peripheral arterial embolism [1]. AF is an important public health problem and imposes a heavy financial burden on society and patients' families [2]. Risk factors for AF include obesity, pre-hypertension, pericardial fat, excessive endurance exercise, obstructive sleep apnea, significant heart murmur, and new genetic variants [3–7], but the pathogenic mechanisms of AF have not been clearly defined and are complex and variable in different individuals [8]. Recent studies suggest mechanisms that may be relevant to microRNAs, including autonomics, heat shock proteins, and intracellular calcium homeostasis [9–11].

In recent years, the technology of gene sequencing has developed greatly and is likely to offer valuable perspectives into the genetic basis of AF [12]; therefore, genotypic variants are potential modifiers of predisposition to AF. Recently, researchers have revealed a series of new potential mutations associated with the ion channel genes of AF [13]. It has been indicated that loss of calcium channel mutations function increases atrial action potential [14]. Thus, it is important to understand its genetic background for better personalized management of this disorder [15].

There are multiple published reports on eNOS 786T/C and AF, but the results are controversial. There are at least 3 nitric oxide synthase (NOS) isoforms: inducible NOS, constitutive neuronal NOS, and endothelial NOS (eNOS). NOS can synthesize nitric oxide (NO), which is an important endothelium-derived relaxing factor [16]. eNOS is located on the chromosome 7q35-36 and can be triggered by gene variants, leading to reduced NO levels in human cardiomyocytes [17]. It has been hypothesized that decreased NO levels contribute to the development of AF [18]. The eNOS gene polymorphisms are related to variability in NO plasmatic levels. The mutation of 786 T/C point can suppress eNOS gene transcription, influencing the level of NO, and resulting in atrium contraction disorder [19].

A meta-analysis on the eNOS 786T/C polymorphism and AF was published in 2012, which showed that the 786T/C polymorphism is associated with decreased AF risk, especially in white people and in Italians. However, the sample size of the study was small, and additional case-control studies published after 2012 have reported a relationship between eNOS polymorphism and AF susceptibility. Based on the above evidence, we conducted the present meta-analysis of all available studies to evaluate associations between eNOS 786 T/C genetic polymorphisms and the risk of AF.

Material and Methods

The present study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement [20], which is a set of guidelines for performing meta-analyses.

Search strategy

Two investigators (Yi-Qing Zhang and Yu-Feng Jiang) searched the China National Knowledge Infrastructure, WanFang, Embase, Web of Science, and PubMed databases to identify eligible studies published before July 2018. We also searched the reference lists in the identified studies to obtain more potential studies. The key words for searching were: endothelial nitric oxide synthase or eNOS, atrial fibrillation or AF, and polymorphism or mutation, without language restrict.

Selection and exclusion criteria

To obtain the eligible studies in this meta-analysis, we pre-established the inclusion criteria: 1) case-control studies on eNOS 786 T/C gene polymorphism and AF susceptibility; 2) molecular detection methods were used to identify individual genotypes; and 3) human subject. The exclusion criteria were: 1) reviews, meta-analyses, abstracts-only, and unpublished studies; 2) laboratory or animal studies, not relevant to the AF and eNOS 786 T/C genetic polymorphism, or did not find the specific genotypes of TT/TC/CC; 3) studies that provided insufficient data; and 4) duplicate studies.

Data extraction

Significant data in all eligible studies that were screened according to the inclusion and exclusion criteria were extracted by 2 authors (Yi-Qing Zhang and Yu-Feng Jiang). Disagreement were resolved by discussion with a third investigator (Ya-Feng Zhou). We extracted data including: first author, publication year, country where study was performed, ethnicity, source of controls, number of case and control individuals, and frequencies of the allele and genotypes distribution. If we found a study had been published in more than 1 journal, we only included 1 publication. We tried to contact the corresponding author for information for any incomplete data. Study quality was assessed according to the 9-point Newcastle-Ottawa scale (NOS) [21].

Statistical analysis

In this meta-analysis, we conducted Hardy-Weinberg equilibrium (HWE) analysis to assess all the included studies. Heterogeneity was evaluated by the I^2 test under a fixed- or random-effects model. To evaluate the association between

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Table 1. Characteristics of the studies included for meta-analysis.

Author	Year	Country	Ethnicity	Source of controls	NOS score	HWE test
Lixin Xu, et al. [22]	2008	China	Asian	HB	8	0.12
Fatini, et al. [23]	2006	Italy	White	PB	7	<0.001
Bedi, et al. [24]	2006	America	White	HB	7	0.08
Gensini, et al. [25]	2003	Italy	White	PB	8	0.78
Giust, et al. [26]	2007	Italy	White	PB	8	0.18
Anton, et al. [27]	2009	Croatia	White	PB	7	0.01
Shanshan Wang, et al. [28]	2015	China	Asian	HB	8	0.12
Nejia Tousi, et al. [29]	2018	Tunisia	White	HB	8	0.43

Case-control design was used in all the included studies. Year – publication year; NOS – Newcastle-Ottawa scale; HWE – Hardy-Weinberg equilibrium; HB – hospital-based; PB –population-based.

Table 2. The results of Newcastle-Ottawa Scale.

	Selection	Comparability	Exposure
Lixin Xu, et al. [22]	***	**	***
Fatini, et al. [23]	***	**	**
Bedi, et al. [24]	***	**	**
Gensini, et al. [25]	***	**	***
Giust, et al. [26]	***	**	***
Anton, et al. [27]	***	**	**
Shanshan Wang, et al. [28]	***	**	***
Nejia Tousi, et al. [29]	***	**	***

eNOS polymorphism and susceptibility to AF, we integrated 95% confidence intervals (95% CI) and odds ratios (OR) according to the consequence of the heterogeneity. Potential inter-study heterogeneity was represented by I^2 ranging from 0% to 100%. If the calculated I^2 >50% was regarded as heterogeneity among studies, we used a random-effects model (Der Simonian and Laird method) for pooled analysis. Otherwise, a fixed-effects model (Mantel-Haenszel method) was used. We conducted subgroup analyses according to source of control and ethnicity to identify potential heterogeneity. Five genetic models were used in overall analyses: allele, additive, dominant, recessive, and codominant models. We did not process the adjustment on ORs in view of scanty eligible data on the other environmental effects. On the basis of combining ORs with sequential omission of each study, sensitivity analysis was performed to identify latent alternation of the overall meta-data. We performed Egger's test and drew Begg's funnel plots to assess publication bias. Stata version 14.0 (Stata Corporation, USA) was used in all statistical tests.

Results

Study characteristics

Researching databases, we found 102 potential records, from which we excluded 40 records that were duplicate studies, not related to the current study, and review articles. We screened 62 articles left, of which articles 44 were eliminated because they were not relevant to eNOS 786T/C polymorphisms. We read 18 full-text articles for detailed assessment, and because of inadequate data (n=4), inappropriate study design (n=4), and not relevant to AF (n=2), 10 of the full-text articles were excluded. Eventually, there were 8 studies [22–29] – 2 in Asian populations and 6 in white populations – containing 1372 cases and 2575 controls. Sample sizes of all eligible studies ranged from 75 to 1368. Study characteristics are presented in Table 1. Six studies [22,24–26,28,29] conformed to Hardy-Weinberg equilibrium. Moreover, all eligible studies were checked by NOS and scores were more than 6 points, showing the studies

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Table 3. Endothelial nitric oxide synthase (eNOS) 786T/C polymorphisms genotype distribution and allele frequency in cases and controls.

Author	Genotype (N)								Allele frequency (N, %)					
	Cases				Controls				Cases			Controls		
	Total	TT	TC	CC	Total	TT	TC	CC	T	C	MAF	T	C	MAF
Lixin Xu, et al. [22]	147	126	19	2	147	130	15	2	271	23	0.08	275	19	0.06
Fatini, et al. [23]	331	93	172	66	808	441	163	204	358	304	0.46	1045	571	0.35
Bedi, et al. [24]	48	17	23	8	263	114	108	41	57	39	0.41	336	190	0.36
Gensini, et al. [25]	148	49	77	22	210	69	105	36	175	121	0.41	243	177	0.42
Giust, et al. [26]	456	132	239	85	912	283	432	197	503	409	0.45	998	826	0.45
Anton, et al. [27]	40	18	22	0	35	12	23	0	58	22	0.28	47	23	0.33
Shanshan Wang, et al. [28]	100	80	17	3	100	76	20	4	177	23	0.12	172	28	0.14
Nejia Tousi, et al. [29]	102	31	53	18	100	36	48	22	115	89	0.44	120	92	0.43

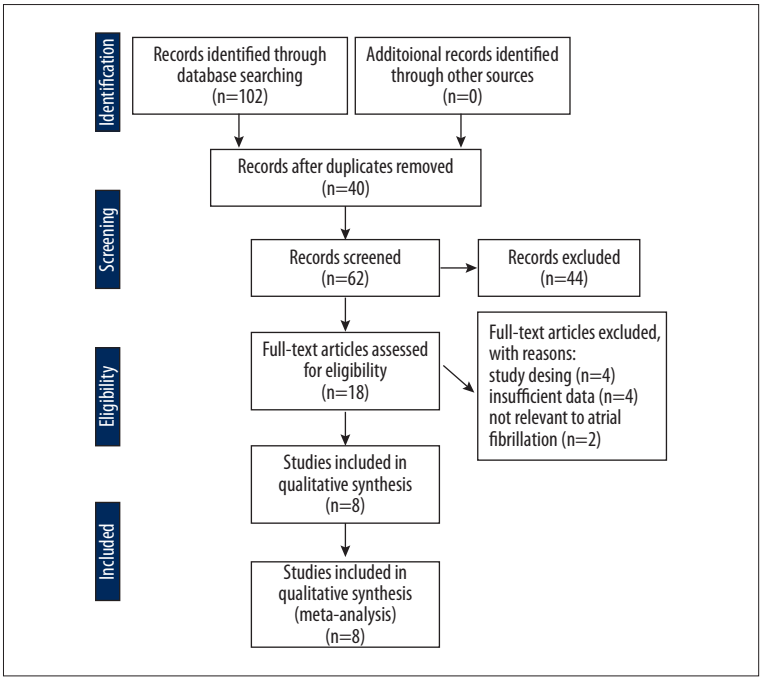

Figure 1. The PRISMA flow diagram of the study selection and exclusion.

were high-quality (Table 2). The distribution of genotype and allele frequency in all the finally included studies are shown in Table 3. Figure 1 shows the complete procedure of study selection and exclusion.

Meta-analysis results

We conducted the data analysis according to I^2, when I^2 >50% with a random-effects model. The pooled analysis showed that

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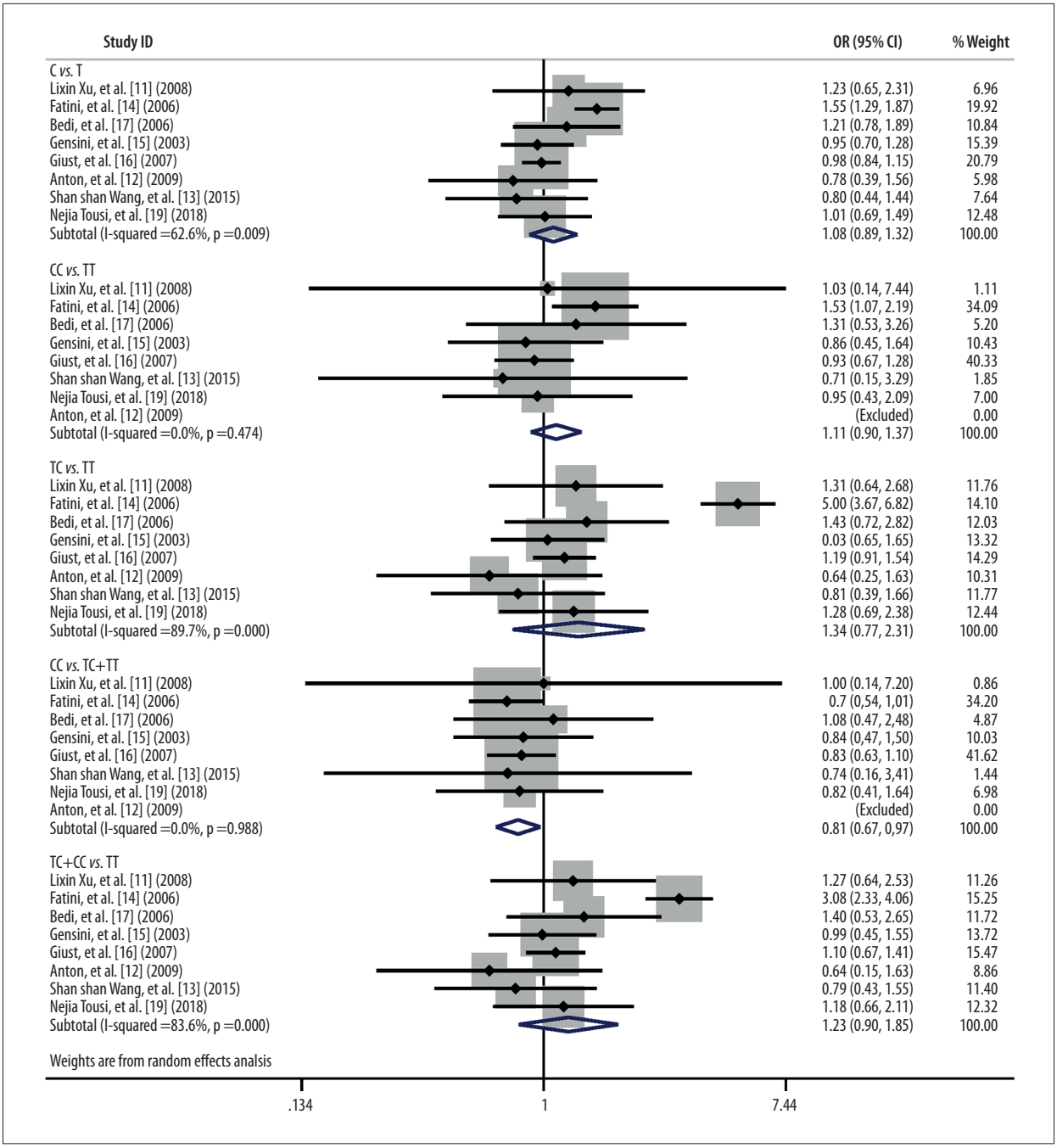

Figure 2. Forest plot from the meta-analysis on the association of the endothelial nitric oxide synthase polymorphism and atrial fibrillation risk in allele model (C *vs.* T); homozygote model (CC *vs.* TT); heterozygote model (TC *vs.* TT); recessive model (CC *vs.* TC+TT) and dominant model (TC+CC *vs.* TT). CI – confidence interval, OR – odds ratio.

there was no obvious relationship between eNOS 786T/C polymorphisms and AF in the 4 genetic models: allele (OR=1.08; 95% CI=0.89 to 1.32; p=0.009; I^2=62.6%), homozygote (OR=1.11; 95% CI=0.90 to 1.37; p=0.474; I^2=0.0%), heterozygote (OR=1.34; 95% CI=0.77 to 2.31; p<0.001; I^2=89.7%), and dominant (OR=1.23; 95% CI=0.81 to 1.85; p<0.001; I^2=83.6%). However, recessive (OR=0.81; 95% CI=0.67 to 0.97; p=0.988; I^2=0.0%) model analysis showed that the eNOS 786T/C polymorphism was relevant to AF, and the forest plot is shown in Figure 2.

Sensitivity analysis

We assessed heterogeneity on the basis of the results of I^2 and Q tests. The assessment of heterogeneity was performed

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Table 4. Subgroup analyses of association between eNOS 786 T/C gene polymorphism and AF.

Subgroup		Number	Odds ratio	95% confidential interval	p Value	I^2 (%)
Recessive model						
Source of Control	HB	4	0.90	(0.55, 1.47)	0.68	0.00
	PB	4	0.79	(0.65, 0.97)	0.02	0.00
Ethnicity	Asian	2	0.83	(0.25, 2.76)	0.76	0.00
	white	6	0.81	(0.67, 0.97)	0.02	0.00

HB – hospital-based; PB – population-based.

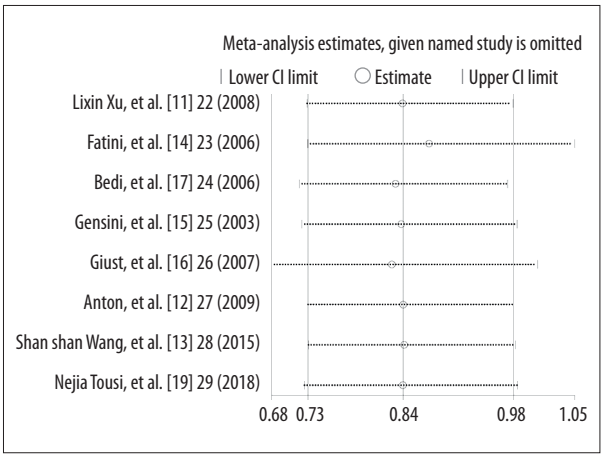

Figure 3. Sensitivity analysis of the relationship between endothelial nitric oxide synthase polymorphism and atrial fibrillation risk. CI – confidence interval, OR – odds ratio.

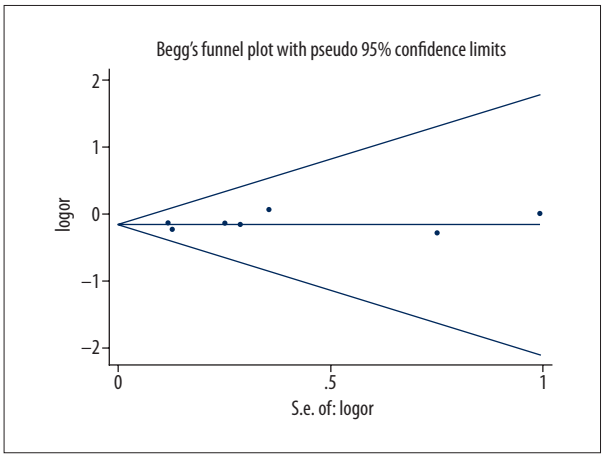

Figure 4. 0Begg's funnel plot with pseudo 95% confidence limits in recessive model.

according to the value for I^2: $I^2 \leq 25\%$, no significant heterogeneity; $25\% < I^2 \leq 50\%$, moderate heterogeneity; $50 < I^2 \leq 75\%$, high heterogeneity; and $75 < I^2 \leq 100\%$, extreme heterogeneity. To find the cause of heterogeneity, we performed subgroup analysis to discover whether the source of control and ethnicity would alter the results (Table 4). We found that the eNOS 786T/C polymorphism decreased the risk of AF, especially in whites (OR=0.81; 95% CI=0.67 to 0.97; P=0.023 for recessive model). After subgrouping by source of control, the results revealed that the control population source had a significant influence (OR=0.79; 95% CI=0.65 to 0.97; P=0.022 for recessive model) on eNOS 786T/C polymorphism and AF, but not for hospital-based controls. Moreover, we performed sensitivity analysis to explore whether exclusion of any individuality study would influence the pooled ORs. As shown in Figure 3, after each individual study was omitted, the results were not altered; therefore, the results showing that eNOS 786T/C polymorphism decreased the risk of AF are reliable (Figure 3).

Publication bias

We performed the Begg's funnel plot assessment to evaluate publication bias, and found there was no apparent asymmetry in the shape of the Begg's funnel plots (Figure 4) with P value=0.54, suggesting that there was no significant publication bias in our study.

Discussion

This meta-analysis of 8 eligible studies showed that there was no obvious relationship between endothelial eNOS polymorphisms and AF, as assessed by 4 genetic models: allele, homozygote, heterozygote, and dominant; however, recessive analysis showed there was some degree of correlation between them. Many single-nucleotide polymorphism gene studies have demonstrated that genetic variations are meaningful risk factors for AF, and this is associated with increasing morbidity and mortality [7]. There have been many case-control studies on the relationship between eNOS polymorphism and risk of AF, but the final results are still controversial. Of the 8 studies included in our meta-analysis, 3 of them [22,23,27] reported

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an association between eNOS polymorphism and risk of AF, whereas the other 5 studies [24–26,28,29] reported no significant association. Therefore, we performed this meta-analysis to pool the all eligible case-control studies for a more reliable result. Compared with a previous meta-analysis, we had more 3 studies, giving a more reliable result, and we conducted the subgroup analysis on source of controls to reduce the bias from the included population.

Subgroup analyses showed that the eNOS 786T/C polymorphism clearly decreased AF risk in whites but not in Asians; the cause of this difference is unclear and requires further research. In addition to eNOS 786T/C, there are many other gene polymorphisms that showed similar results and may be associated with genetic background [30,31].

Sources of control subjects from a hospital-based population are usually classified by type of disease. However, the general population is different in susceptibility [32]. Thus, we conducted subgroup analysis according to the different sources of control subjects, and we got a positive result in population-based but not in hospital-based studies. We thought that the general population would contain less bias than the hospital-based studies. Although the results revealed that eNOS 786T/C polymorphism may be associated with AF in population-based samples, studies with larger sample sizes are needed to confirm this finding.

The functional mechanism of eNOS 786T/C polymorphisms is still unclear. Nakayama et al. reported that the mutation of 786 T/C point suppresses eNOS gene transcription, which influences the level of NO, resulting in the development of atrium disorder [19]. Elvan et al. also demonstrated that decreased NO levels may contribute to the development of AF [18]. In addition, data from basic experiments showed that NO plays an important role as a second messenger. NO can adjust the cardiac L-type calcium channel, which influences myocyte contractility and normal sinus function [33]. Han et al. showed that low NO levels were associated with the presence of eNOS 786T/C polymorphisms genetic variant. Moreover, low NO levels, by affecting the channel of the L-type calcium, leads to further vulnerability to arrhythmia [34]. Therefore, the most important potential mechanism is that eNOS 786T/C polymorphisms decrease the levels of NO, which can influence the cardiac L-type calcium channel and then contribute to the development of AF.

There are some limitations to this meta-analysis: (1) Before initiating searching for eligible studies, we developed a retrieval strategy through computer and manual searching. Thus, there may be some suitable studies that were excluded, such as unpublished studies, which would inevitably cause publication bias. (2) Although 2 of the studies did not conform to the Hardy–Weinberg equilibrium test in the control group, excluding them during the sensitivity analysis did not alter the conclusions made in the meta-analysis. In addition, the disease subspecialty depends on the combination of multiple genes acting together, and it is likely that the presence of other genes will alter the results [35]. (3) The present meta-analysis demonstrated that mutation of eNOS 786 T/C in white populations decreases the risk of AF, possibly related to the included study. Only 2 of the studies [22,28] were conducted in Asian populations, which may be a small sample size and could have influenced the statistical power of the results. Further research in various ethnic groups with more detailed information and larger sample sizes is needed.

Conclusions

This meta-analysis revealed that the eNOS gene *loci* 786T/C polymorphism is relevant to reduce the risk of AF in recessive genetic model. Our results suggest that the eNOS gene *loci* 786T/C significantly decreases AF risks in whites but not in Asians. The subgroup analysis showed that sources of population of control subjects is relevant to AF. To further elucidate the gene-environment and gene-gene interactions between eNOS gene polymorphisms and AF susceptibility, studies with larger sample sizes are needed to explore the link between eNOS 786T/C polymorphisms and AF in different populations around the world.

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