jraas

Journal of the Renin-Angiotensin-Aldosterone System
April-June 2020: 1–7

DOI: 10.1177/1470320320934716
journals.sagepub.com/home/jra
SAGE

Association of angiotensin-converting enzyme gene insertion/deletion polymorphism and obstructive sleep apnoea in a Chinese population: A meta-analysis

Jian Xu[1*], Jiming Chen[2*], Yilu Li[2*], Dandan Zhang[1*] and Xiaoli Li[1]

Abstract

Introduction: Many studies have investigated the association between angiotensin-converting enzyme (*ACE*) gene insertion/deletion (I/D) polymorphism and susceptibility to obstructive sleep apnoea (OSA). However, few have confirmed the relationship between ACE and OSA in the Chinese population. We performed a meta-analysis of studies relating the *ACE* I/D polymorphism to the risk of OSA in a Chinese population.

Methods: We evaluated eligible published studies from several databases for this meta-analysis. Subgroup analyses were performed for hypertension. Pooled odds ratios and 95% confidence intervals were calculated using a fixed- or random-effects model.

Results: Ten studies were identified to analyse the association between *ACE* I/D polymorphism and OSA risk. No marked associations were found in any genetic model ($p>0.05$). Subgroup analysis showed an association with hypertension (D vs. I, DD vs. II, ID vs. DD+II, DD+ID vs. II, ID vs. II; $p<0.05$), which was confirmed by sensitivity analyses. No obvious publication bias was found using Egger's test ($p>0.05$).

Conclusions: The *ACE* I/D polymorphism was not associated with an increased risk of OSA in a Chinese population. However, within the hypertensive subgroup, we detected a significant association between the *ACE* polymorphism and OSA. More case-control investigations are required.

Keywords

Angiotensin-converting enzyme (ACE), obstructive sleep apnoea (OSA), insertion/deletion (I/D) gene, polymorphism, meta-analysis

Date received: 26 December 2019; accepted: 8 May 2020

Introduction

Obstructive sleep apnoea (OSA) has an estimated prevalence of 2% in women and 4% in men.[1] OSA is characterised by repetitive bouts of upper-airway collapse during sleep, resulting in intermittent periods of hypoxia and hypercapnia, fragmented sleep and heightened sympathetic nervous system activity.[2] Patients with OSA have an increased incidence of various diseases, including insulin resistance, hypertension, stroke, acute myocardial infarct, arrhythmia and cerebrovascular ischaemic complications.[3–6]

Previous studies have indicated that OSA is a complex disorder affected by a combination of genetic, environmental and developmental factors that interact to determine the overall phenotype.[7] Despite extensive research in this field, the aetiology of most OSA remains unclear, and genetic

[1]Department of Respiratory and Critical Care Medicine, ShenZhen Hospital of Southern Medical University, PR China
[2]Department of Respiratory and Critical Care Medicine, Huazhong University of Science and Technology Union Shenzhen Hospital, PR China

*These authors contributed equally to this work.

Corresponding author:
Xiaoli Li, Department of Respiratory and Critical Care Medicine, ShenZhen Hospital of Southern Medical University, Xinhu Road 1333, Baoan District, Shenzhen City, 518101, PR China.
Email: lixiaolinfy@163.com

polymorphisms have been proposed as susceptibility factors in patients with OSA.[8–11]

During the past decade, the role of the renin–angiotensin system (RAS) in the development of OSA has generated interest. Angiotensin-converting enzyme (ACE) – the key enzyme in the RAS – is released from the cell membrane.[12] ACE is a zinc metallopeptidase that converts angiotensin I to angiotensin II.[13]

The angiotensin-converting enzyme (*ACE*) gene consists of either an insertion (I) allele or a deletion (D) allele, forming three possible genotypes: II, ID and DD.[14,15] The *ACE* gene locus is the major locus that determines serum and tissue concentrations of ACE.[16,17] Several studies have shown that the *ACE* I/D polymorphism is a possible risk factor for myocardial infarction,[18] overweight/obesity,[19] hypertrophic cardiomyopathies[20] and hypertension.[21]

The hypothesis that *ACE* I/D polymorphisms may play important roles in the risk of OSA in Chinese has also been debated. Many studies have investigated the potential relationship between *ACE* I/D gene polymorphisms and OSA, but the results have been inconsistent. Some meta-analyses have reported a correlation between *ACE* I/D gene polymorphisms and OSA, although the results were negative or the subjects were not Chinese.[22–25]

The *ACE* I/D polymorphism has been associated with other disorders in the Chinese population.[26,27] Therefore, this association should be investigated in Chinese patients and more comparisons should be performed.

To evaluate the association between the *ACE* I/D polymorphism and the risk of OSA in the Chinese population further, we conducted a meta-analysis by combining genotype data from all eligible studies published to date.

Methods

Publication search

We searched relevant studies from PubMed, Embase, Cochrane Library, the Chinese National Knowledge Infrastructure (CNKI) database, the Wan Fang database and the Weipu database. The search strategy to identify all possible studies involved the use of the following keywords in the abstract: 'OSAHS', 'OSAS', 'OSA', 'obstructive sleep apnoea syndrome', 'obstructive sleep apnoea hypopnoea syndrome', 'obstructive sleep apnoea', 'angiotensin converting enzyme' and 'ACE'. The reference lists of retrieved reviews and articles were searched by hand. If more than one article was published using the same case series, only the study with largest sample size was included. The literature search was updated on 30 July 2019.

Inclusion criteria

The included studies had to meet the following criteria: (a) evaluated *ACE* mutation status and relationship to OSA in Chinese children or adults; (b) were full-text articles; (c) were case-control studies; (d) had sufficient published data to estimate an odds ratio (OR) and 95% confidence interval (CI); (e) included at least two comparison groups (OSA group vs. control group); (f) mentioned hypertension in the OSA group; and (g) were observational studies published in Chinese or English.

Data extraction and quality evaluation

Two authors independently reviewed the titles, abstracts and full text to assess the articles for compliance with the inclusion criteria. Disagreement was followed by discussion until consensus was reached. Information was carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria listed above. The following information was extracted from each study: (a) name of the first author; (b) year of publication; (c) sample size of cases and controls; (d) genotype distributions of cases and controls; (e) presence or absence of hypertension; and (f) results of Hardy–Weinberg equilibrium (HWE) test in controls. The quality of the included literature was evaluated using the Newcastle–Ottawa Scale (NOS). According to the NOS evaluation criteria, each included study scored $\geqslant$6 stars, indicating that it was of high quality.

Statistical methods

We assessed HWE in the controls for each study using a goodness-of-fit test (chi-square or Fisher's exact test), and a p-value of <0.05 was considered to indicate significant disequilibrium. ORs with 95% CI were used to assess the strength of association between the *ACE* I/D gene polymorphism and OSA risk. The pooled ORs were performed for the following comparisons: D versus I, DD versus II, ID versus II; DD+ID versus II; DD versus ID+II and ID versus DD+II. Assumption of heterogeneity was checked by the chi-square-based Q-test. A p-value of >0.1 for the Q-test indicates a lack of heterogeneity among studies. So, the pooled OR estimate of each study was calculated by the fixed-effects model (the Mantel–Haenszel method).[18] Otherwise, the random-effects model (DerSimonian and Laird method) was used.[19]

Subgroup analyses were performed for hypertension. The diagnostic standard used for hypertension was according to 2010 Chinese guidelines for the prevention and treatment of hypertension: in the absence of antihypertensive drugs, blood pressure was measured three times on different days. Patients with hypertension were those with a systolic blood pressure $\geqslant$140 mmHg or a diastolic blood pressure $\geqslant$90 mmHg, or patients who were previously diagnosed with hypertension and were currently using antihypertensive drugs and whose blood pressure was $<$140/90 mmHg.

An estimate of potential publication bias was carried out by assessing funnel plots, in which the standard error

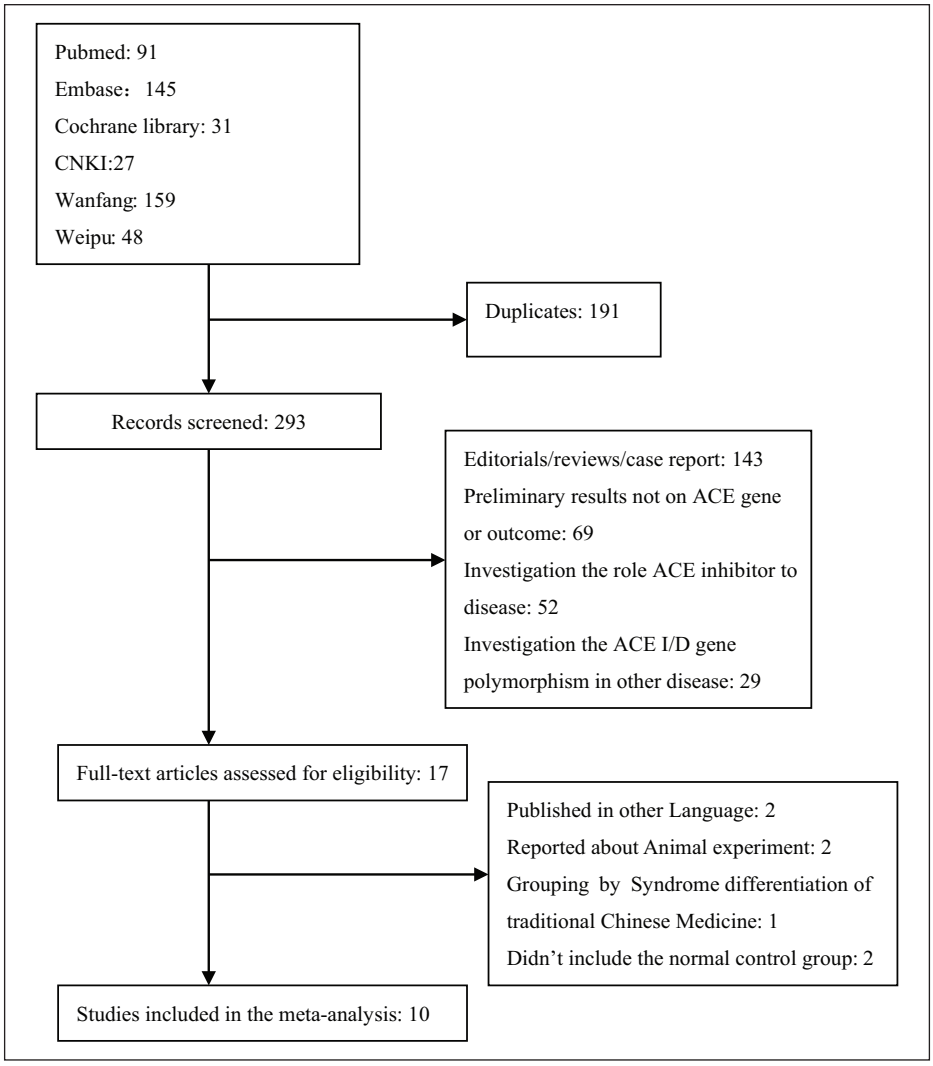

Figure 1. Flow chart of study selection.

of log (OR) of each study was plotted against its log (OR). An asymmetric plot indicates possible publication bias. Funnel plot asymmetry was assessed with Egger's linear regression test on the natural logarithm scale of the OR. The significance of the intercept was determined by the *t*-test suggested by Egger ($p<0.05$ was considered indicative of statistically significant publication bias).[28] If publication bias existed, the Duval and Tweedie non-parametric 'trim and fill' method was used to adjust for it. All statistical tests were performed using Stata v15.0 (StataCorp, College Station, TX).

Results

Study characteristics

A total of 501 articles were retrieved from PubMed (n=91), Embase (n=145), the Cochrane Library (n=31), CNKI (n=27), the Wanfang database (n=159) and the Weipu database (n=48). Of these, 191 articles published in Chinese or English were excluded because they were duplicates. In addition, 293 articles were excluded for the following reasons: they were review articles, editorials or case reports; the preliminary result was not about the *ACE* I/D gene polymorphism or outcome; they investigated the relationship of ACE inhibitor to diseases; or polymorphisms or the *ACE* I/D polymorphism did not concern OSA or include Chinese in the study population.

Seventeen investigations were reported on the association of the *ACE* I/D gene polymorphism with OSA susceptibility. However, two were published in a language other than Chinese or English, two reported animal experiments, one reported grouping in syndrome differentiation of Traditional Chinese Medicine and two did not include a control group.

Finally, 10 studies were identified to analyse the association between the *ACE* I/D gene polymorphism and OSA susceptibility in our review (Figure 1).[29–38] One of the

Table 1. Main characteristics of all studies included in the meta-analysis.

First author (year)	Language	Case					Control					Sample size	With hypertension	HWE	NOS
		DD	ID	II	D	I	DD	ID	II	D	I				
Xiao (1998)	Chinese	0	28	22	28	72	8	26	16	42	58	50/50	30	Yes	6
Zhang (2000)	English	11	20	30	42	80	18	31	19	67	69	61/68	61	Yes	8
Ping (2001)	Chinese	8	30	42	46	114	15	30	15	60	60	80/60	41	Yes	7
Li S (2004)	Chinese	13	71	8	97	87	16	34	0	66	34	92/50	0	No	6
Li (2004)	Chinese	21	12	27	54	66	19	3	8	41	19	60/30	30	No	7
Zhang (2004)	Chinese	36	46	39	118	124	19	40	41	78	122	121/100	0	Yes	7
Gu (2006)	Chinese	60	42	22	162	86	30	38	56	98	140	124/124	0	No	8
Tong (2011)	Chinese	32	13	6	77	25	11	36	13	58	62	51/60	51	Yes	6
Huang (2016)	Chinese	25	55	77	105	209	27	40	25	94	90	92/157	85	Yes	7
Huang (2017)	Chinese	12	46	54	70	154	16	30	14	62	58	112/60	60	Yes	6

D: deletion; I: insertion; HWE: Hardy–Weinberg equilibrium; NOS: Newcastle–Ottawa Scale for quality assessment of study.

investigations was performed in children. Study characteristics are summarised in Table 1. Genotype distributions in the control groups of the included studies were in agreement with HWE, except for three studies (Table 1). The quality of the studies was assessed using the NOS quality assessment scale; quality scores ranged from 6 to 8 (mean 6.8; Table 1).

Meta-analysis results

In the meta-analysis of 10 studies, we found obvious between-study heterogeneity in the six comparison models. Thus, the random-effects model was used to calculate pooled ORs with corresponding 95% CIs. The overall result showed that there was no statistically significant association between the *ACE* gene polymorphism and OSA: D versus I, OR=0.770, 95% CI 0.461–1.287, p=0.319; DD versus II, OR=0.538, 95% CI 0.204–1.419, p=0.211; DD versus DI+II, OR=0.720, 95% CI 0.342–1.516, p=0.388; ID versus DD+II, OR=0.804, 95% CI 0.585–1.106, p=0.181; DD+ID versus II, OR=0.664, 95% CI 0.351–1.257, p=0.209; ID versus II, OR=0.695, 95% CI 0.420–1.149, p=0.156 (Table 2).

Subgroup analysis

In the subgroup analysis of patients with and without hypertension, significant associations were found in patients with hypertension: D versus I, OR=0.517, 95% CI 0.277–0.966, p=0.039; DD versus II, OR=0.299, 95% CI 0.104–0.864, p=0.026; DD versus (DI+II), OR=0.441, 95% CI 0.143–1.362, p=0.155; ID versus DD+II, OR=0.602, 95% CI 0.449–0.808, p=0.001; DD+ID versus II, OR=0.407, 95% CI 0.253–0.654, p=0.000 (Table 2).

Sensitivity analysis

Sensitivity analysis was carried out to identify potentially influential studies by sequential omission of each individual study. We found statistically similar results after sequentially excluding each study, suggesting high stability of the meta-analysis results.

Publication bias

To investigate publication bias, Egger's linear regression was performed for the association between *ACE* I/D polymorphisms and OSA. We did not detect publication bias of the meta-analysis for the association between the *ACE* I/D gene polymorphism and OSA risk ($p>0.05$). There was no obvious asymmetry in the shape of the funnel plots.

Discussion

OSA is a complex disease caused by multiple genetic and other factors.[39] Recently, epidemiological studies have evaluated the association between the *ACE* I/D polymorphism and OSA risk, but the results remain inconclusive. Barcelo et al.[40] reported that *ACE* I/D polymorphisms were not associated with increased susceptibility to OSA, whereas Chmielewska[41] suggested that the *ACE* I/D polymorphism was associated with OSA. Therefore, we performed this meta-analysis to investigate whether an association exists between potential polymorphisms of the *ACE* I/D gene and OSA risk.

The present meta-analysis comprised 10 studies, including 843 cases and 759 controls. Only one study was in children, and our study covered a wide range of the Chinese population. The strength of our meta-analysis is based on the high number of published studies, which allowed us to achieve sufficient statistical power to detect a modest effect estimate. The results indicated that the *ACE* I/D polymorphism was not associated with elevated OSA risk in the overall study population. This finding was consistent with those from previous meta-analyses, which indicated no association among the Chinese population.[22,24,42] Considering the association of OSA and hypertension, we conducted a subgroup analysis in patients based on the

Table 2. Meta-analysis of the association between the ACE I/D polymorphism and OSA.

Genetic contrasts	Design	No. of studies	Test of association			Test of heterogeneity	
			OR (95% CI)	*Z*	*p*	I^2 (%)	*p*
D vs. I	All	10	0.770 (0.461–1.287)	1.00	0.319	91.6	0.000
	All in HT	14	0.611 (0.397–0.939)	2.24	0.025	88.4	0.000
	OSA with HT	7	0.517 (0.277–0.966)	2.07	0.039	88.0	0.000
	OSA WO HT	7	0.720 (0.399–1.299)	1.09	0.275	88.2	0.000
DD vs. II	All	10	0.538 (0.204–1.419)	1.25	0.211	89.3	0.000
	All in HT	14	0.364 (0.160–0.827)	2.41	0.016	85.1	0.000
	OSA with HT	7	0.299 (0.104–0.864)	2.23	0.026	80.8	0.000
	OSA WO HT	7	0.444 (0.130–1.515)	1.30	0.195	86.5	0.000
DD vs. (DI+II)	All	10	0.720 (0.342–1.516)	0.86	0.388	88.0	0.000
	All in HT	14	0.518 (0.270–0.994)	1.98	0.048	83.6	0.000
	OSA with HT	7	0.441 (0.143–1.362)	1.42	0.155	86.8	0.000
	OSA WO HT	7	0.593 (0.264–1.330)	1.27	0.205	81.0	0.000
ID vs. (DD+II)	All	10	0.804 (0.585–1.106)	1.34	0.181	53.5	0.022
	All in HT	14	0.787 (0.642–0.963)	2.32	0.020	40.5	0.058
	OSA with HT	7	0.602 (0.449–0.808)	3.38	0.001	36.1	0.153
	OSA WO HT	7	1.007 (0.759–1.334)	0.05	0.964	9.10	0.359
DD+ID vs. II	All	10	0.664 (0.351–1.257)	1.26	0.209	85.6	0.000
	All in HT	14	0.524 (0.313–0.877)	2.46	0.014	79.9	0.000
	OSA with HT	7	0.407 (0.253–0.654)	3.71	0.00	55.0	0.038
	OSA WO HT	7	0.657 (0.275–1.568)	0.95	0.344	84.5	0.000
ID vs. II	All	10	0.695 (0.420–1.149)	1.42	0.156	70.9	0.000
	All in HT	14	0.603 (0.401–0.906)	2.43	0.015	59.9	0.002
	OSA with HT	7	0.448 (0.319–0.631)	4.61	0.505	0.00	0.755
	OSA WO HT	7	0.778 (0.373–1.626)	0.67	0.75	72.8	0.001

ACE: angiotensin-converting enzyme; OSA: obstructive sleep apnoea; OR: odds ratio; CI: confidence interval; HT: hypertension.

presence or absence of hypertension. The significant association between this polymorphism and OSA risk in some genotypes in hypertensive patients was consistent with a previous report, but that study included Caucasians and Asians.[24] Lin reported that the *ACE* I/D polymorphism may be a risk factor for OSA with hypertension in Asians, but only four studies were included.[25] Our results also differ from research by Lee et al., which reported no association between this polymorphism and OSA with hypertension.[22] To our knowledge, the previous research differed from our current research because our study targeted only the Chinese population, and subgroup analysis was performed in patients with hypertension.

Heterogeneity is an important issue when performing meta-analyses. Between-study heterogeneity existed in overall comparisons. In the hypertension subgroup analysis, we found that heterogeneity was decreased in the subgroup, suggesting that certain effects of genetic variants are specific to hypertension.

In addition, we obtained statistically similar results in the sensitivity analysis, which sequentially excluded individual studies. Further, we assessed publication bias by using Egger's test in the present study. These analyses indicated the stability and reliability of the meta-analysis results in our study.

Some limitations of this meta-analysis should be acknowledged. First, the heterogeneity and small sample size may have distorted the meta-analysis, although some of the heterogeneity was resolved in the hypertension subgroup analysis. Second, our results were based on unadjusted effect estimates and confidence intervals, and confounding factors were not controlled. Third, the subgroup results should be interpreted with caution because of the limited statistical power. We could not examine the association of *ACE* I/D polymorphism and OSA activity or clinical features due to the limited amount of data. Despite these limitations, our meta-analysis had some advantages. First, a substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, the results of the subgroup and sensitivity analyses were not materially altered and did not result in different conclusions, indicating that our results were robust. Third, Egger's test did not detect any publication bias, indicating that our results were unbiased.

In conclusion, this meta-analysis of 10 studies strongly suggested that the *ACE* I/D polymorphism is not associated with increased risk of OSA in a Chinese population. Subgroup analysis revealed a significant correlation in the hypertension subpopulation. Accordingly, our findings

indicate that the *ACE* I/D polymorphism plays a role in the pathogenesis of OSA with hypertension in a Chinese population. However, *ACE* I/D gene polymorphisms are not the only cause of OSA, and further studies are essential to elucidate the potential relationship between other genes and OSA.

Acknowledgements

The author is grateful to Dr Danhua He for her contributions to and encouragement in preparing this article. We thank Louise Adam, ELS(D), from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac) for editing the English text of a draft of this manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Jian Xu https://orcid.org/0000-0002-5014-2950

Xiaoli Li https://orcid.org/0000-0002-2157-0649

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