GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Meta-analysis demonstrates lack of association between the ACE gene I/D polymorphism and obstructive sleep apnea-hypopnea syndrome occurrence and severity

Y. Feng[1]*, J. Ri[2]*, H.Y. Wan[1], G.C. Shi[1], Q.Y. Li[1] and L. Fan[1]

[1]Department of Pulmonary Medicine, Rui Jin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[2]Department of Ultrasonography, Rui Jin Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

*These authors contributed equally to this study.
Corresponding author: H.Y. Wan
E-mail: hywan_fy@yahoo.com.cn

Genet. Mol. Res. 12 (1): 74-84 (2013)
Received May 30, 2012
Accepted August 21, 2012
Published January 22, 2013
DOI http://dx.doi.org/10.4238/2013.January.22.6

ABSTRACT. Published data on a possible association between the angiotensin-converting enzyme (ACE) gene I/D polymorphism and obstructive sleep apnea-hypopnea syndrome (OSAHS) occurrence and its severity risk are inconclusive. We performed a meta-analysis of case-control studies published in English or Chinese. Thirteen studies, totaling 1361 cases and 1373 controls, were investigated for association of the ACE I/D polymorphism with OSAHS. We also made a study of ACE I/D with OSAHS severity risk, including 879 mild/moderate OSAHS patients and 357 severe OSAHS patients. A random-effects model was used, irrespective of between-study heterogeneity. Study quality was assessed in duplicate. Overall, the ACE I/D polymorphism was not significantly associated with an increase in OSAHS risk [odds ratio (OR) = 1.21; 95% confidence interval (95%CI) = 0.88-1.65; P = 0.24]. In subgroup analysis by ethnicity, comparison of alleles I with D demonstrated a 58% (nonsignificantly) increased risk for OSAHS

in Chinese (OR = 1.58; 95%CI = 0.92-2.70; P = 0.09). We also found that there was no significant association between ACE I/D and OSAHS severity risk. No publication biases were observed. This meta-analysis suggests that there is no significantly increased risk for OSAHS occurrence or severity associated with the ACE I/D polymorphism.

Key words: Meta-analysis; OSAHS; ACE I/D polymorphism; Severity

INTRODUCTION

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is the coexistence of excessive daytime sleepiness and obstructive sleep-disordered breathing. It is more prevalent than asthma and diabetes mellitus in adults (Ahmadi et al., 2009). OSAHS is associated with several cardiovascular diseases including arterial hypertension, acute myocardial infarction, and stroke, and increases cardiovascular mortality and morbidity (Yaggi et al., 2005). The whole genome study published by Palmer et al. (2004) suggested that multiple genetic factors are associated with the development of OSAS; the angiotensin-converting enzyme (ACE) gene is one such factor that has been extensively studied. ACE converts angiotensin I to angiotensin II; alterations in ACE production have been implicated in the pathogenesis of various diseases. The human ACE gene is located on chromosome 17q23, where an insertion/deletion polymorphism (I/D, dbSNP rs4646994) in intron 16 has been identified. This polymorphism is based on the presence (insertion, I) or absence (deletion, D) of a 287-bp nonsense DNA fragment. The ACE I/D polymorphism accounts for 47% of the total variance of serum ACE levels; the DD genotype yields higher ACE activity than the II genotype (Seckin et al., 2006). Several case-control studies have investigated the association between ACE polymorphisms and OSAHS, although these studies had low statistical power and their results were often not reproducible. We performed a meta-analysis of all available case-control studies reported in either English or Chinese to investigate the association between ACE polymorphism and the occurrence of OSAHS systematically.

MATERIAL AND METHODS

Publication search

The electronic databases Medline (Ovid), PubMed, CNKI, Wanfang, and Weipu were used to search for electronic publications that were published as of November 2011. Key words included “OSAS or OSAHS or obstructive sleep apnea hypopnea syndrome” and “angiotensin-converting enzyme or ACE” combined with “gene/variants/polymorphism/alleles”. If there were multiple publications from the same study group, the most complete and recent results were used. Search results were limited to articles published in English or Chinese and studies performed in humans. We did not restrict our selections based on the countries in which the studies were performed. To avoid selection bias, no study was rejected because of poor-quality scores.

Inclusion/exclusion criteria

Case-control studies were included in this meta-analysis, regardless of sample size, if they made an effort to explore the association between ACE polymorphisms and hyperten-

sion among unrelated subjects, if genotyping was performed using validated methods, and if they provided sufficient information on genotype or allele frequencies to allow estimation of relative risk and its corresponding confidence interval (CI). Apnea was defined as complete cessation of airflow lasting ≥10 s. Hypopnea was defined as 70% or more reduction in respiratory airflow lasting ≥10 s and accompanied by a ≥4% decrease in oxygen saturation. An apnea-hypopnea index (AHI; average number of episodes of apnea and hypopnea per hour of sleep) was used to determine the degree of OSAS. OSAHS was defined as AHI >5; 5-15 was considered mild; 15-30, moderate, and >30, severe OSAS.

Data extraction

Two reviewers (Y.F. and J.R.) independently assessed all potentially relevant studies and reached a consensus on all items. In case of disagreement, a third author provided an assessment. The following data were collected from each study: first author, year of publication, ethnicity, study design, diagnostic criteria, baseline characteristics of the study population, total number of cases and controls, and genotype distributions in cases and controls. Information on Hardy-Weinberg equilibrium (HWE) was also tracked or calculated if unavailable. After data extraction, discrepancies were adjudicated by discussion and a consensus was reached.

Statistical methods

The meta-analysis was calculated using the Review Manager software (version 5.0.19). HWE was assessed by the Pearson chi-square test or the Fisher exact test (SAS version 9.1.3, Institute Inc., Cary, NC, USA) for studies without a track record. No assumptions were required for genetic models of inherence for the polymorphism under study.

Generally, the I^2 is used to identify between-study heterogeneity with a statistical significance of 0.1. We applied the random-effects model for all comparisons because this accommodates the possibility that the underlying effect differs across studies. For practical use, the random-effects model is more conservative and has a wider CI than the fixed-effects model.

In addition, sensitivity analysis or subgroup analysis was performed to look at more narrowly drawn subsets by removing an individual study each time or studies with similar features such as deviation from HWE to assess their separate influence.

Finally, we assessed publication bias using the fail-safe number (N_{fs}) with the significance set at 0.05 for each meta-comparison. Specifically, if the calculated N_{fs} value was smaller than the number of observed studies, then the meta-analysis results might be subject to publication bias. We calculated the $N_{fs0.05}$ according to the formula $N_{fs0.05} = (\sum Z / 1.64)2 - k$, where *k* is the number of included articles.

RESULTS

Search results

Based on our search strategy, the primary screening produced 21 potentially relevant articles, of which 15 met the inclusion criteria as an attempt to evaluate the association between the ACE I/D polymorphism and occurrence of OSAHS (Xiao et al., 1999; Zhang et al., 2000; Barcelo et al., 2001; Ping et al., 2001; Li et al., 2004a,b; Lin et al., 2004; Zhang et al.,

2004; Gu et al., 2006; Li et al., 2006; Bostrom et al., 2007; Benjamin et al., 2008; Koyama et al., 2009; Ogus et al., 2010; Yakut et al., 2010). A total of 1361 OSAHS patients and 1373 controls were analyzed. Of these 15 articles, 9 (Xiao et al., 1999; Zhang et al., 2000; Barcelo et al., 2001; Lin et al., 2004; Bostrom et al., 2007; Benjamin et al., 2008; Koyama et al., 2009; Ogus et al., 2010; Yakut et al., 2010) were published in English and 6 in Chinese (Ping et al., 2001; Li et al., 2004a,b; Zhang et al., 2004; Gu et al., 2006; Li et al., 2006). The detailed selection process is presented in Figure 1.

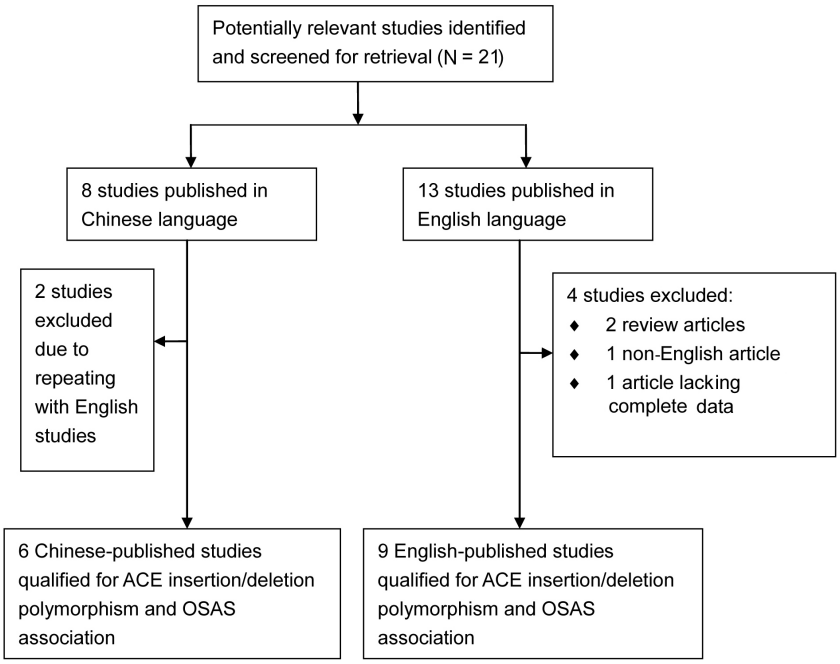

Figure 1. Flow diagram of search strategy and study selection. ACE = angiotensin-converting enzyme; OSAS = obstructive sleep apnea-hypopnea syndrome.

Study characteristics

The baseline characteristics of qualified studies are presented in Table 1. Distribution of the ACE genotype by OSAHS severity is shown in Table 2. Of these 15 articles, 13 studies followed a hospital-based study design and 2 followed a population-based study design. Five studies were included in the analysis of the ACE I/D polymorphism and OSAHS severity (Zhang et al., 2000; Lin et al., 2004; Bostrom et al., 2007; Koyama et al., 2009; Ogus et al., 2010). There were 13 case-control studies including a study of the association between the ACE I/D polymorphism and OSAHS risk, 8 of Chinese, 3 of Caucasians, and 2 of Arabs. Among the 15 articles, the studies by Benjamin et al. (2008) and Barcelo et al. (2001) used different OSAHS diagnostic criteria; Zhang et al. (2000) used different OSAHS severity criteria, and Gu et al. (2006) addressed the relationship between the ACE I/D polymorphism and the occurrence of pediatric OSAHS. In the meta-analysis, we also studied the association between ACE I/D and OSAHS severity.

Table 1. Characteristics and distribution of angiotensin-converting enzyme genotype of the 15 case-control studies included in the meta-analysis.

Study	Ethnicity	Study design	Controls	Cases	Characteristics	Diagnosis
			II/ID/DD	II/ID/DD		
Xiao et al. (1998)	Chinese	HB	16/26/8	22/28/0	Cases (M:F, 45:5) and controls (M:F, 45:5)	AHI >5
Zhang et al. (2000)	Chinese	HB	34/51/28	30/20/11		AHI >5
Barcelo et al. (2001)	Spanish	HB	9/13/10	7/24/13	Male younger than 65 years Cases (age: 50 ± 1 years; M:F, 63:0; BMI, 32.8 ± 0.6) and Controls (age: 49 ± 1 years; M:F, 32:0; BMI, 25.6 ± 0.6)	AHI >20
Ping et al. (2001)	Chinese	HB	15/30/15	42/30/8	Cases (age: 35-72 years, average 60 years; M:F, 65:15) and Controls (age: 34-70 years, average 62; M:F, 38:22)	AHI >5
Zhang et al. (2004)	Chinese	HB	41/40/19	39/46/36	Cases (age: 43.2 ± 2.3 years; M:F, 121:0; BMI, 28.8 ± 1.4) and Controls (age: 40.1 ± 2.1 years; M:F, 100:0; BMI, 26.2 ± 2.0)	AHI >5
Li et al. (2004)	Chinese	HB	8/3/19	27/12/21	OSAS with Hypertension (age: 44.6 ± 8.7 years; M:F, 28:2; BMI, 29.7 ± 4.1) Normotension (age: 41.2 ± 7.9 years; M:F, 28:2; BMI, 28.9 ± 3.7) and Controls (age: 45.2 years; M:F, 26:4; BMI, 26.9)	AHI >5
Li et al. (2004)	Chinese	HB	0/34/16	8/71/13	Cases (age: 45.37 ± 11.53 years; M:F, 77:18; BMI, 28.97 ± 3.78) and Controls (age: 45 ± 13.78 years; M:F, 39:11; BMI, 25.01 ± 4.63)	AHI >5
Lin et al. (2004)	American	PB	128/318/180	92/250/132	96.7% white (1.4% African American, 0.6% Asian, 0.4% Native American, 0.4% Latin, and 0.6% others), age: 35 to 70 years	AHI >5
Gu et al. (2006)	Chinese	HB	56/38/30	22/42/60	Cases (age: 5.6 ± 2.2 years; M:F, 96:28) and Controls (age: 4.9 ± 2.6 years; M:F, 98:26)	AHI >5
Li et al. (2006)	Chinese	HB	7/4/9	39/4/22	Cases (age: 45 ± 11 years; M:F, 57:8) and Controls (age: 45 ± 13 years; M:F, 18:2; BMI, 23.22 ± 2.48)	AHI >5
Bostrom et al. (2007)	Swedish	PB	NA	Mild to moderate: 47/121/68 Severe: 17/52/33	Age: 40 years or over to less than 65 years	AHI >5
Benjamin et al. (2008)	UK	HB	10/27/15	6/9/11	OSAS (age: 47.5 ± 11.2 years; M:F, 21:5; BMI, 38.4 ± 8.0), Healthy controls (age: 40.1 ± 12.0 years; M:F, 14:12) and Sleepy controls (age: 47.8 ± 7.3 years; M:F, 16:10; BMI, 32.3 ± 5.2)	OSAS: 4% oxygen DR ≥10/h DR ≤9/h
Koyama et al. (2009)	Brazilian	HB	NA	Mild to moderate: 33/66/48 Severe: 17/71/31	All male OSAS patients (age: 48 ± 13 years; BMI, 29 ± 5)	AHI >5
Yakut et al. (2010)	Turks	HB	7/19/11	10/27/27	Cases (age: 50.37 ± 11.2 years; M:F, 53:11; BMI, 30.64 ± 4.3) and Controls (age: 49.97 ± 10.4 years; M:F, 26:11; BMI, 28.51 ± 4.6)	AHI >5
Ogus et al. (2010)	Turks	HB	12/30/37	19/52/26	Cases (age: 51.27 ± 9.97 years; M:F, 88:9; BMI, 30.58 ± 5.79) and Controls (age: 60.1 ± 10.0 years; M:F, 36:43)	AHI >5

HB = hospital-based study; PB = population-based study; NA = not available; M = male; F = female; BMI = body mass index; OSAS = obstructive sleep apnea-hypopnea syndrome; AHI = apnea-hypopnea index; DR = 4% oxygen deep rate.

Table 2. Distribution of angiotensin-converting enzyme genotype among different severity of patients with obstructive sleep apnea hypopnea syndrome (OSAHS).

Study	Mild/moderate	Severe	Diagnosis
	II/ID/DD	II/ID/DD	
Ogus et al. (2010)	13/34/19	6/18/7	Mild to moderate: 5 < AHI < 30 Severe OSA: AHI >30
Lin et al. (2004)	73/219/111	19/31/21	Mild to moderate: 5 < AHI < 30 Severe OSA: AHI >30
Koyama et al. (2009)	33/66/48	17/71/31	Mild to moderate: 5 < AHI < 30 Severe OSA: AHI >30
Bostrom et al. (2007)	47/121/68	17/52/33	Mild to moderate: 5 < AHI < 30 Severe OSA: AHI >30
Zhang et al. (2000)	10/11/6	20/9/5	AHI >5 Mild OSA: 5 < AHI < 20 Moderate OSA: 20 < AHI < 50 Severe OSA: AHI >50

Main results

As shown in Table 3, we analyzed the I allele (relative to the D allele) and OSAHS risk for all 13 studies; the I^2 was 85% and $P < 0.0001$, suggesting strong heterogeneity. Thus, we chose the random-effects model to analyze the data. Overall, comparison of alleles I and D generated a 22% increased, albeit nonsignificant, risk for OSAHS (95%CI = 0.79-1.89; P = 0.37). Sensitivity analyses were performed by excluding studies with cases and/or controls not in HWE (Li et al., 2004a,b; Gu et al., 2006). The results showed that the association between ACE I/D and OSAHS was not significantly altered. There were also no material changes after excluding studies that used different diagnostic criteria in HWE (Barcelo et al., 2001; Benjamin et al., 2008).

We performed codominant (II *vs* DD and ID *vs* DD), dominant (II+ID *vs* DD), and recessive model (II *vs* ID+DD) analyses. Compared with the DD genotype, II and ID genotypes both conferred a nonsignificant increased risk. Under the dominant model, I allele carriers still had an increased OSAHS risk. Exclusion of studies with different diagnostic criteria did not change the association.

Subgroup analyses

In the subgroup analysis by ethnicity, allele comparison revealed nonsignificant increased risks among Chinese (OR = 1.41; 95%CI = 0.81-2.45; P = 0.22), Caucasians (OR = 0.97; 95%CI = 0.83-1.14; P = 0.75), and Arabs (OR = 1.12; 95%CI = 0.49-2.55; P = 0.78). After excluding studies deviating from HWE, the overall associations detected under all genetic models were not significantly altered. However, the I allele carried a significant 58% increased risk after excluding studies not in HWE in Chinese. Similar trends persisted for both II and DD genotype associations, as well as the dominant and recessive associations. A summary of other genetic comparisons are listed in Table 3.

ACE I/D polymorphism and OSAHS severity analyses

As shown in Table 4, we analyzed the I allele (relative to the D allele) and OSAHS severity risk for 5 studies. Overall, comparison of I and D alleles generated a 3% reduced,

Table 3. Summary of different comparative results.

Genetic model	Overall or subgroup (ethnicity)	Study number (N)	Participant (N)	OR (95%CI)	Z	P	I^2 (%)	P_{het}
I *vs* D	All	13	5452	1.21 (0.88-1.65)	1.17	0.24	85	<0.0001
	All in HWE	10	4502	1.23 (0.93-1.63)	1.45	0.15	74	<0.0001
	All in HWE excluding different criteria	8	4194	1.34 (0.97-1.85)	1.77	0.08	79	<0.0001
	Chinese	8	2390	1.41 (0.81-2.45)	1.22	0.22	90	<0.0001
	Chinese in HWE	5	1440	1.58 (0.92-2.70)	1.67	0.09	82	0.0002
	Caucasians	3	2508	0.97 (0.83-1.14)	0.32	0.75	0	0.73
	Arabs	2	554	1.12 (0.49-2.55)	0.28	0.78	80	0.02
II *vs* DD	All	13	1483	1.35 (0.75-2.42)	1.01	0.31	80	<0.0001
	All in HWE	10	1203	1.37 (0.82-2.28)	1.21	0.23	67	0.001
	All in HWE excluding different criteria	8	1122	1.59 (0.88-2.88)	1.53	0.13	73	0.0006
	Chinese	8	721	2.03 (0.71-5.82)	1.32	0.19	87	<0.0001
	Chinese in HWE	5	441	2.31 (0.80-6.70)	1.54	0.12	80	0.0006
	Caucasians	3	613	0.94 (0.68-1.30)	0.38	0.7	0	0.75
	Arabs	2	149	1.22 (0.33-4.57)	0.29	0.77	69	0.07
ID *vs* DD	All	13	2025	1.12 (0.77-1.62)	0.59	0.56	61	0.002
	All in HWE	10	1666	1.04 (0.71-1.55)	0.22	0.83	53	0.02
	All in HWE excluding different criteria	8	1544	1.10 (0.71-1.71)	0.42	0.67	58	0.02
	Chinese	8	794	1.22 (0.66-2.24)	0.64	0.52	66	0.005
	Chinese in HWE	5	435	1.04 (0.49-2.19)	0.09	0.93	54	0.07
	Caucasians	3	1002	0.99 (0.64-1.54)	0.05	0.96	23	0.27
	Arabs	2	229	1.24 (0.30-5.11)	0.29	0.77	84	0.01
II+ID *vs* DD	All	13	2731	1.25 (0.81-1.91)	1.01	0.31	77	<0.0001
	All in HWE	10	2251	1.20 (0.81-1.78)	0.90	0.37	63	0.004
	All in HWE excluding different criteria	8	2097	1.32 (0.84-2.09)	1.20	0.23	68	0.003
	Chinese	8	1200	1.56 (0.74-3.29)	1.17	0.24	83	<0.0001
	Chinese in HWE	5	720	1.61 (0.71-3.64)	1.14	0.25	71	0.008
	Caucasians	3	1254	1.01 (0.79-1.29)	0.05	0.96	0	0.47
	Arabs	2	277	1.22 (0.30-4.91)	0.28	0.78	85	0.009
II *vs* ID+DD	All	13	2731	1.22 (0.79-1.89)	0.90	0.37	77	<0.0001
	All in HWE	10	2251	1.31 (0.90-1.91)	1.41	0.16	62	0.004
	All in HWE excluding different criteria	8	2097	1.43 (0.94-2.16)	1.69	0.09	67	0.003
	Chinese	8	1200	1.55 (0.73-3.25)	1.15	0.25	85	<0.0001
	Chinese in HWE	5	720	1.81 (0.96-3.41)	1.83	0.07	74	0.005
	Caucasians	3	1254	0.91 (0.69-1.21)	0.62	0.53	0	0.54
	Arabs	2	277	1.12 (0.59-2.12)	0.35	0.72	0	0.43

HWE = Hardy-Weinberg equilibrium; OR = odds ratio; 95%CI = 95% confidence interval.

albeit nonsignificant, risk for OSAHS severity (95%CI = 0.80-1.16; P = 0.72). Meanwhile, there was no evidence of between-study heterogeneity (I^2 = 2%, P = 0.40). The I allele had a 1% increased risk excluding the different OSAHS severity criteria in the studies by Zhang et al. (2000). Similar trends persisted for both II and DD genotype associations, as well as the dominant and recessive associations.

Table 4. Summary of different comparative results of the relationship between the angiotensin-converting enzyme (ACE) gene polymorphism and obstructive sleep apnea-hypopnea syndrome severity.

Genetic model	Overall or subgroup	Study number (N)	Participant (N)	OR (95%CI)	Z	P	I^2 (%)	P_{het}
I *vs* D	All	5	2472	0.97 (0.80-1.16)	0.36	0.72	2	0.40
	All but different criteria	4	2350	1.01 (0.83-1.21)	0.06	0.95	0	0.71
II *vs* DD	All	5	604	0.97 (0.67-1.41)	0.16	0.87	0	0.49
	All excluding different criteria	4	338	0.92 (0.31-2.74)	0.15	0.88	67	0.03
ID *vs* DD	All	5	981	0.94 (0.67-1.30)	0.39	0.69	12	0.33
	All excluding different criteria	4	950	0.93 (0.63-1.37)	0.38	0.70	34	0.21
II+ID *vs* DD	All	5	1236	0.94 (0.71-1.25)	0.42	0.68	0	0.60
	All excluding different criteria	4	1175	0.96 (0.72-1.29)	0.26	0.79	0	0.52
II *vs* ID+DD	All	5	1236	0.93 (0.57-1.54)	0.27	0.79	55	0.06
	All excluding different criteria	4	1175	1.07 (0.65-1.75)	0.26	0.79	51	0.11

OR = odds ratio; 95%CI = 95% confidence interval.

Publication bias

The funnel plot and the Egger test were performed to assess the possibility of publication bias. In the analysis of the ACE I/D polymorphism and OSAHS risk, the resultant symmetrical funnel shape was consistent with the absence of publication bias in the funnel plot for contrasts of I versus D (P-Egger test = 0.721) (Figure 2A). Besides the suggestive symmetry of the funnel plot (Figure 2B), the Egger test indicated no publication bias in the ACE I/D polymorphism and OSAHS severity analysis (P = 0.086).

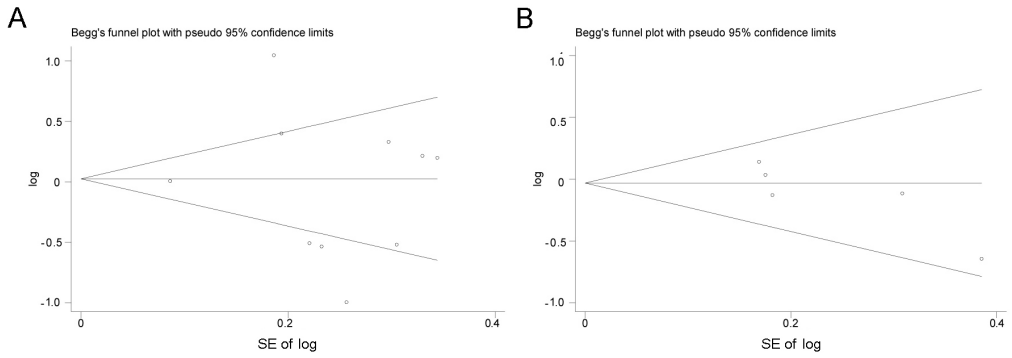

Figure 2. Begg's funnel plot of the Egger test for publication bias of the angiotensin-converting enzyme (ACE) insertion (I)/deletion (D) polymorphism and obstructive sleep apnea-hypopnea syndrome (OSAHS) risk or the severity of OSAHS risk. The horizontal line in the funnel plot indicates the fixed-effects summary estimates and the sloping lines indicate the expected 95%CI for a given standard error. The size of circles in each plot is positively proportional to the sample size of each study. **A.** Contrast of I *vs* D allele in the analysis of the ACE I/D polymorphism and OSAHS risk in Hardy-Weinberg equilibrium (HWE). **B.** Contrast of I *vs* D allele in the ACE I/D polymorphism and OSAHS severity analysis in HWE. SE = standard error of log.

DISCUSSION

Several studies have investigated the association between ACE activity and OSAHS (Rohatgi, 1982; Kanazawa et al., 2000; Barcelo et al., 2001) but the results are inconsistent. A correlation between homozygous gene deletion (DD genotype) and high ACE activity has been reported in many studies (Ozen et al., 1997; Seckin et al., 2006). To date, the association between the ACE I/D polymorphism and OSAHS has been unclear; a recent meta-analysis of genetic association studies of OSAHS (Varvarigou et al., 2011) included 6 studies, with 342 cases and 318 controls. Our meta-analysis included 1361 patients with OSAHS and 1373 controls from 13 English and Chinese studies, and investigated the association between the ACE I/D polymorphism and OSAHS overall and in ethnic subgroups. We also studied ACE I/D and OSAHS severity in 879 mild/moderate and 357 severe OSAHS cases. Although some statistical biases could not be eliminated, our results suggested that the ACE I/D polymorphism is not associated with increased OSAHS risk. We also found that the I allele showed an increased but nonsignificant trend, in HWE in Chinese. To our knowledge, this study represents the first meta-analysis of the ACE I/D polymorphism and OSAHS in a Chinese population.

We also performed a subgroup analysis by ethnicity. Barley et al. (1994) studied the ACE gene polymorphism in different populations and found that the I allele frequency was higher in Samoan Polynesians and Yanomami Indians than in Europeans or black Nigerians, and concluded that the polymorphism is associated with ethnic origin. Our results showed that the I allele carried a significant 58% increased OSAHS risk excluding studies not in HWE in Chinese. Similar trends were found under other models. Considering the wider confidence intervals and small sample sizes of population-based studies, more studies are required to quantify this effect size reliably.

We also studied the relationship between the ACE I/D polymorphism and OSAHS severity. Ogus et al. (2010) found that ACE activity was significantly lower in severe than in mild OSAS. However, genotype differences do not exist between mild/moderate OSAHS and severe OSAHS in Ogus et al. (2010) and 4 other studies in our meta-analysis.

This study has several limitations. First, only published studies in English or Chinese were included; it is possible that some relevant published or unpublished studies with null results were missed, which might bias the results. Second, due to the relatively small number of eligible studies, we were unable to perform further subgroup analyses, such as by age or gender, because of limited data. Third, some studies had small sample sizes, which may affect the statistical power of the publication bias. Finally, considering the complex genetic network within or between ACE and other operators in the renin-angiotensin system, the potential role of the I/D polymorphism might be diluted or masked by other gene-gene or gene-environment interactions. Therefore, the jury must remain out before the eventual truth prevails. We minimized the likelihood of bias by creating a detailed protocol before initiating our study, performing a meticulous search for publications, and using explicit methods for publication selection, data extraction, and analysis.

This meta-analysis demonstrated an absence of association between the ACE I/D polymorphism and OSAHS risk. We also identified a nonsignificant increasing trend of the I allele in HWE in Chinese. Further studies should investigate adjacent markers to confirm whether the association is causal or due to linkage disequilibrium. Moreover, studies on the biological mechanism and function of the ACE I/D polymorphism in OSAHS are also warranted.

ACKNOWLEDGMENTS

Research supported by a grant from the National Natural Science Foundation of China (#81071925) and the National Natural Science Foundation of China (#81201837).

REFERENCES

Ahmadi N, Shapiro GK, Chung SA and Shapiro CM (2009). Clinical diagnosis of sleep apnea based on single night of polysomnography vs. two nights of polysomnography. *Sleep Breath.* 13: 221-226.

Barcelo A, Elorza MA, Barbe F, Santos C, et al. (2001). Angiotensin converting enzyme in patients with sleep apnoea syndrome: plasma activity and gene polymorphisms. *Eur. Respir. J.* 17: 728-732.

Barley J, Blackwood A, Carter ND, Crews DE, et al. (1994). Angiotensin converting enzyme insertion/deletion polymorphism: association with ethnic origin. *J. Hypertens.* 12: 955-957.

Benjamin JA, Moller M, Ebden P, Bartle I, et al. (2008). Serum angiotensin converting enzyme and the obstructive sleep apnea hypopnea syndrome. *J. Clin. Sleep Med.* 4: 325-331.

Bostrom KB, Hedner J, Melander O, Grote L, et al. (2007). Interaction between the angiotensin-converting enzyme gene insertion/deletion polymorphism and obstructive sleep apnoea as a mechanism for hypertension. *J. Hypertens.* 25: 779-783.

Gu XQ, Liu DB and Wan GP (2006). Polymorphism of angiotensin converting enzyme genes in children with obstructive sleep apnea-syndrome. *Zhonghua Er. Ke. Za Zhi.* 44: 874-875.

Kanazawa H, Okamoto T, Hirata K and Yoshikawa J (2000). Deletion polymorphisms in the angiotensin converting enzyme gene are associated with pulmonary hypertension evoked by exercise challenge in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 162: 1235-1238.

Koyama RG, Drager LF, Lorenzi-Filho G, Cintra FD, et al. (2009). Reciprocal interactions of obstructive sleep apnea and hypertension associated with ACE I/D polymorphism in males. *Sleep Med.* 10: 1107-1111.

Li S, Cao J and Chen BY (2004a). Investigation of the angiotensin-converting enzyme gene polymorphism in obstructive sleep apnea hypopnea syndrome. *Zhongguo Hu Xi Yu Wei Zhong Jian Hu Za Zhi* 3: 350-353.

Li Y, Zhang W, Wang T, Lu H, et al. (2004b). Study on the polymorphism of angiotensin converting enzyme genes and serum angiotensin II level in patients with obstructive sleep apnea hypopnea syndrome accompanied hypertension. *Lin. Chuang. Er. Bi Yan. Hou Ke. Za Zhi* 18: 456-459.

Li WQ, Li WQ, Li CQ, Liao WS, et al. (2006). Investigation of the angiotensin-converting enzyme gene polymorphism in obstructive sleep apnea hypopnea syndrome patients with XU YU ZHENG. *Zhongguo Zhong Yi Yao Ke Ji* 13: 75-79.

Lin L, Finn L, Zhang J, Young T, et al. (2004). Angiotensin-converting enzyme, sleep-disordered breathing, and hypertension. *Am. J. Respir. Crit. Care Med.* 170: 1349-1353.

Ogus C, Ket S, Bilgen T, Keser I, et al. (2010). Insertion/deletion polymorphism and serum activity of the angiotensin-converting enzyme in Turkish patients with obstructive sleep apnea syndrome. *Biochem. Genet.* 48: 516-523.

Ozen S, Alikasifoglu M, Tuncbilek E, Bakkaloglu A, et al. (1997). Polymorphisms in angiotensin converting enzyme gene and reflux nephropathy: a genetic predisposition to scar formation? *Nephrol. Dial. Transplant.* 12: 2031-2033.

Palmer LJ, Buxbaum SG, Larkin EK, Patel SR, et al. (2004). Whole genome scan for obstructive sleep apnea and obesity in African-American families. *Am. J. Respir. Crit. Care Med.* 169: 1314-1321.

Ping F, Zhao JC, Zhang XQ, Gao FQ, et al. (2001). Association of the polymorphism of angiotensin converting enzyme with OSAS and OSAS accompanied by hypertension. *Chin. Gen. Pract.* 4: 24-26.

Rohatgi PK (1982). Serum angiotensin converting enzyme in pulmonary disease. *Lung* 160: 287-301.

Seckin D, Ilhan N, Ilhan N and Ozbay Y (2006). The relationship between ACE insertion/deletion polymorphism and coronary artery disease with or without myocardial infarction. *Clin. Biochem.* 39: 50-54.

Varvarigou V, Dahabreh IJ, Malhotra A and Kales SN (2011). A review of genetic association studies of obstructive sleep apnea: field synopsis and meta-analysis. *Sleep* 34: 1461-1468.

Xiao Y, Huang X, Qiu C, Zhu X, et al. (1999). Angiotensin I-converting enzyme gene polymorphism in Chinese patients with obstructive sleep apnea syndrome. *Chin. Med. J.* 112: 701-704.

Yaggi HK, Concato J, Kernan WN, Lichtman JH, et al. (2005). Obstructive sleep apnea as a risk factor for stroke and death. *N. Engl. J. Med.* 353: 2034-2041.

Yakut T, Karkucak M, Ursavas A, Gulten T, et al. (2010). Lack of association of ACE gene I/D polymorphism with obstructive sleep apnea syndrome in Turkish patients. *Genet Mol Res.* 9: 734-738.

Zhang J, Zhao B, Gesongluobu, Sun Y, et al. (2000). Angiotensin-converting enzyme gene insertion/deletion (I/D)

polymorphism in hypertensive patients with different degrees of obstructive sleep apnea. *Hypertens. Res.* 23: 407-411.

Zhang LQ, Yao WZ, He QY, Wang YZ, et al. (2004). Association of polymorphisms in the angiotensin system genes with obstructive sleep apnea-hypopnea syndrome. *Zhonghua Jie. He. He. Hu Xi Za Zhi* 27: 507-510.