Meta-Analysis

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Apolipoprotein E ε2/ε3/ε4 variant in association with obstructive sleep apnoea and lipid profile: A meta-analysis

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Abstract

Objective: A meta-analysis of the association between haplotypical variants of the apolipoprotein E (*APOE*) gene (ε2/ε3/ε4) and obstructive sleep apnoea (OSA) risk and changes in lipid profile.

Methods: Electronic databases were searched to retrieve articles that provided data on *APOE* gene ε2/ε3/ε4 variants in patients with OSA and healthy controls. Data were extracted from eligible articles and statistical analyses were performed.

Results: The meta-analysis included 14 articles involving 19 study populations (3198 patients and 6031 controls). There was no significant association between the presence of the ε4 allele and OSA risk. The presence of ε4 was associated with significantly increased total cholesterol and decreased high-density lipoprotein cholesterol, compared with ε4 allele negative individuals. There was a low probability of publication bias but significant heterogeneity.

Conclusions: There was no association between *APOE* ε2/ε3/ε4 and OSA susceptibility. The presence of *APOE* ε4 was associated with changes in lipid profile.

Keywords

Obstructive sleep apnoea, apolipoprotein E, variant, meta-analysis

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Introduction

Obstructive sleep apnoea (OSA) is the most common form of apnoea, and is characterized by snoring, periodic apnoea, hypoxemia during sleep and daytime hypersomnolence.[1] Despite several well-established modifiable risk factors such as obesity, compelling evidence supports a genetic component underlying the pathogenesis of OSA.[2] As documented by family studies, individuals

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who had affected first-degree relatives were more likely to be at risk of OSA compared with those without an affected first-degree relative, and the risk increased in proportion to the number of affected relatives.[3,4] It is estimated that up to 35% of the variability in OSA severity (as measured by apnoea–hypopnea index [AHI]) may be due to genetic determinants.[5] Thus far, 85 genes have been listed as candidate OSA-susceptibility genes (hugenavigator.net/), with the gene encoding apolipoprotein E (*APOE*) ranked in the top three. Over the past decade, several association studies have independently assessed the relationship between OSA risk and a well-characterized haplotypical variant of the *APOE* gene ($\varepsilon2/\varepsilon3/\varepsilon4$; defined by the loci rs429358 and rs7412).[6–8] These studies had poor reproducibility, possibly due to genetic heterogeneity across ethnic groups, methodological divergences and other confounding factors such as the coexistence of hypertension. To fully address this issue, this meta-analysis updates the findings of these analyses[6–8] in order to re-evaluate the association between OSA risk and *APOE* $\varepsilon2/\varepsilon3/\varepsilon4$ alleles. In addition, we analysed changes in lipid profile and explored potential sources of heterogeneity.

Materials and methods

The implementation of this meta-analysis adheres to the protocols outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary PRISMA checklist).

Literature search

The electronic databases PubMed®, Web of Science™, Wanfang (Chinese) and CNKI (Chinese) were searched to retrieve potentially eligible articles that provided data on *APOE* $\varepsilon2/\varepsilon3/\varepsilon4$ in patients with OSA and healthy controls published up to and including 10 May 2015. The key words were 'obstructive sleep apnoea' or 'sleep disorder' or 'breathing' [Title] and 'apolipoprotein E' or 'APOE' or 'APO E' [Abstract], and 'allele' or 'genotype' or 'polymorphism' or 'variant' or 'SNP' [Abstract]. We additionally checked the reference list of each major article to ensure comprehensive coverage.

Eligibility criteria

Inclusion criteria were: (i) OSA as the clinical endpoint; (ii) case–control design; (iii) the genotype or allele counts of *APOE* gene $\varepsilon2/\varepsilon3/\varepsilon4$ or the counts of $\varepsilon4$ allele positive and negative individuals in patients and controls; (iv) effect-size estimates presented as odds ratio (OR) with 95% confidence interval (95% CI). In the case of sample duplication the study with the larger sample size and more complete information was retained. Articles written in languages other than English and/or Chinese were excluded.

The title and abstract of each article were assessed for primary eligibility by two investigators acting independently and in duplicate (Z.L. and X.W.). In the case of uncertainty, the full text was retrieved for further evaluation and disagreements were resolved by consensus.

Data retrieval

The following data were extracted independently and in duplicate by two investigators (Z.L. and X.W.): first author's last name; year of publication; race; study design; source of controls; AHI; diagnostic method for OSA; sample size; genotype/allele counts/ORs and 95% CIs; mean body mass index (BMI); triglyceride; total cholesterol; high- and low-density lipoprotein cholesterol (HDLC and LDLC); age; sex; prevalence of smoking; duration of education; and prevalence of hypertension and diabetes mellitus. Any disagreements were resolved during data retrieval by consensus and review of the full text of the article in question.

Statistical analyses

The DerSimonian and Laird method and a random-effects model were used to pool individual effect-size estimates for the association between *APOE* ε2/ε3/ε4 and OSA susceptibility.[9] Differences in BMI, triglyceride, total cholesterol, HDLC and LDLC between ε4 allele positive and negative carriers were expressed as weighted mean difference (WMD) with 95% CI.

Heterogeneity was judged by the inconsistency index (I^2) statistic, with statistically significant heterogeneity indicated by $I^2 > 50\%$. Sources of heterogeneity were evaluated by stratified analysis of categorical variables (study design, source of controls, AHI cut off, sample size) and by meta-regression analysis of continuous variables (age, sex, BMI, smoking, education, hypertension and diabetes mellitus). The probability of publication bias was visually inspected using Begg's funnel plots and statistically assessed with Egger's test (significance level 10%), using the trim-and-fill method to impute the presence of missing studies to yield an unbiased pooled estimate.

All statistical analyses were completed with Stata® software version 12.0 (StataCorp, College Station, TX, USA) for Windows®. Unless otherwise indicated, P-values < 0.05 were considered statistically significant.

Results

The initial literature search identified 55 potential articles. After exclusions, data were extracted from 14 articles (12 in English and two in Chinese) that fulfilled the predetermined eligibility criteria.[10–23] Figure 1 presents a flow diagram of search strategy and study selection; Table 1 shows the characteristics of all study populations. A total of 19 study populations were available from the 14 included studies, with 3198 patients and 6031 controls. There were no statistically significant between-group differences in age, smoking, hypertension and diabetes mellitus. Patients were significantly more likely to be obese ($P = 0.0009$) and male ($P = 0.0016$) than controls (Table 1).

There was no significant association between *APOE* ε4-positivity and OSA risk in the pooled study population. There was significant heterogeneity ($I^2 = 72.2\%$; $P < 0.0005$; Figure 2) and a low probability of publication bias for this comparison, as illustrated by Begg's funnel plot (Figure 3) and Egger's test. Trim-and-fill analysis suggested that three studies were missing to general a symmetrical filled funnel plot (Figure 3). After adjusting for the three missing studies, the presence of ε4 allele was associated with a nonsignificant 2% reduction in OSA risk (95% CI 0.77, 1.25).

There was no significant association between *APOE* ε4-positivity and OSA risk in adults[10–17,19–23] or when analysis was limited to study populations with adjusted effect-size estimates.[19–22]

Data regarding *APOE* gene ε2/ε3/ε4 alleles were provided in 11 study populations.[10–12,14–16,18,23] When using the ε3 allele as a reference, there was no significant association between either ε2 or ε4 and OSA risk. There was significant heterogeneity for this comparison ($I^2 = 66.2\%$; $P = 0.001$).

Data regarding BMI and lipid parameters were provided by four studies.[15,16,20,21] Total cholesterol was significantly higher ($P = 0.007$) and HDLC was significantly lower ($P = 0.040$) in ε4-positive individuals than ε4-negative individuals (Table 2).

Stratified analyses revealed no effect of study design (prospective vs retrospective), source of controls (population-based vs hospital-based), AHI cut off (≥15 vs >5–<15) and sample size (≥500 vs <500) on heterogeneity (Table 3). The presence of ε4 was significantly associated with OSA risk in studies including only Chinese individuals (OR 5.87; 95% CI 3.13, 11.00).[15,16]

Meta-regression analysis found that hypertension was significantly correlated with OSA risk in both patients ($r = -0.64$;

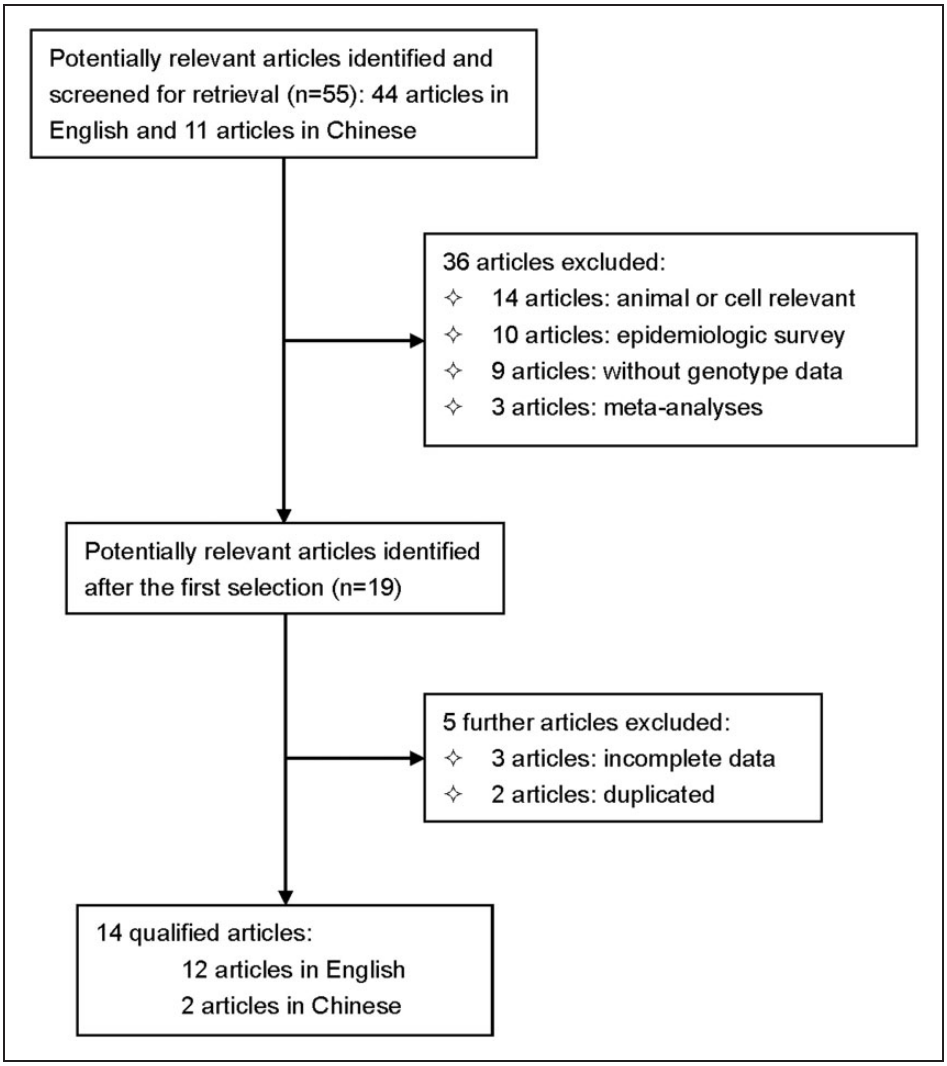

Figure 1. Flow diagram of search strategy and study selection for a meta-analysis evaluating the association between obstructive sleep apnoea (OSA) risk and the apolipoprotein gene (*APOE*) $\varepsilon 2/\varepsilon 3/\varepsilon 4$ alleles.

$P = 0.024$) and controls ($r = -0.68$; $P = 0.01$; Figure 4). There was no significant association between OSA risk and age, sex, BMI, smoking, duration of education, or diabetes mellitus.

Discussion

In accordance with the findings of others,[6–8] the present meta-analysis of 14 articles and 9229 study subjects found no association between OSA risk and *APOE* $\varepsilon 2/\varepsilon 3/\varepsilon 4$ positivity. The presence of the $\varepsilon 4$ allele was significantly correlated with increased total cholesterol and decreased HDLC, however.

There is a growing recognition that pathophysiological mechanisms involving dysregulated lipid metabolism underlie OSA.[11,24] APOE is a lipid transport and signalling protein with a key role in lipid

Table 1. Characteristics of studies included in a meta-analysis evaluating the association between obstructive sleep apnoea risk and the apolipoprotein gene (*APOE*) ε2/ε3/ε4 alleles.

						n		Age, years		Male sex, %	
Author, year	Country	Design	Source	AHI cut off	Method	Cases	Controls	Cases	Controls	Cases	Controls
Uyrum, 2015[10]	Turkey	Pro	Hosp	≥5	PSG	42	31	54	44	59.5	38.8
Tisko (mild), 2014[11]	Slovakia	Retro	Hosp	>5–<15	PSG	126	128	49.5	47.8	70.6	53.1
Tisko (moderate), 2014[11]	Slovakia	Retro	Hosp	> 15–<30	PSG	66	128	51.6	47.8	68.2	53.1
Tisko (severe), 2014[11]	Slovakia	Retro	Hosp	≥30	PSG	199	128	51.2	47.8	83.9	53.1
Osorio (mild), 2014[12]	USA	Pro	Pop	>5–15	PSG	52	25	67.8	65.3	41.2	32.0
Osorio (moderate/ severe), 2014[12]	USA	Pro	Pop	≥15	PSG	19	25	70.1	65.3	42.1	32.0
Nikodemova (mild), 2013[13]	USA	Pro	Pop	>5–<15	PSG	399	1146	56.4	52.1	62.2	54.1
Nikodemova (moderate/ severe), 2013[13]	USA	Pro	Pop	≥15	PSG	298	1146	56.6	52.1	71.5	54.1
Cosentino, 2008[14]	Italy	Retro	Pop	≥15	PSG	123	121	58.6	57.9	66.7	64.5
Sheng, 2008[15]	China	Retro	Pop	≥5	PSG	84	106	48.6	49.8	86.9	86.8
Zheng, 2007[16]	China	Retro	Hosp	≥5	PSG	50	40	39	44.5	100	100
Gozal, 2007[17]	USA	Retro	Pop	>1	PSG	112	146	6.3	6.4	54.1	55.4
Craig, 2006[18]	UK	Retro	Hosp	Other	NPI-D	217	185	78	78	40.0	33.0
Larkin (white), 2006[19]	USA	Pro	Pop	≥15	PSG	218	796	40	38.7	48.2	45.7
Larkin (black), 2006[19]	USA	Pro	Pop	≥15	PSG	197	796	37.1	38.7	42.8	45.7
Gottlieb, 2004[20]	USA	Pro	Pop	≥15	PSG	337	1438	71	71	45.0	45.0
Kadotani, 2001[21]	USA	Pro	Pop	≥15	PSG	66	725	49	49	58.3	58.3
Foley, 2001[22]	USA	Pro	Pop	≥15	PSG	302	416	NA	NA	100	100
Saarelainen, 1998[23]	Finland	Retro	Pop	≥5	PSG	291	728	53.3	53.7	90.7	77.6

(continued)

Table 1. Continued.

BMI, kg/m^2		Smoking, %		Education, years		AHI		Hypertension, %		Diabetes mellitus, %			
Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	OR; 95% CI	Adjusted
35	31.8	NA	NA	NA	NA	31.3	2.2	NA	NA	NA	NA	2.90; 0.56, 15.05	No
29.6	28.4	34.9	34.4	NA	NA	9.4	2.3	33.3	45.3	6.3	3.1	0.71; 0.40, 1.24	No
31.1	28.4	30.3	34.4	NA	NA	20.8	2.3	56.1	45.3	10.6	3.1	0.58; 0.28, 1.19	No
33.9	28.4	45.7	34.4	NA	NA	60.4	2.3	62.3	45.3	17.6	3.1	0.77; 0.47, 1.27	No
25.5	24.2	NA	NA	17.2	16.2	8.3	2.3	29.4	24.0	7.8	8.0	1.18; 0.41, 3.37	No
28.9	24.2	NA	NA	16.3	16.2	30.7	2.3	31.6	24.0	5.3	8.0	1.19; 0.32, 4.37	No
32.5	28.9	12.0	14.5	14.2	14.7	8.7	1.4	34.8	20.5	NA	NA	0.81; 0.62, 1.06	No
36.6	28.9	11.4	14.5	14.0	14.7	29.4	1.4	51.3	20.5	NA	NA	1.14; 0.86, 1.50	No
36.1	30.2	45.5	20.0	8.1	7.4	NA	NA	61.8	57.1	18.7	8.6	1.22; 0.64, 2.31	No
29.58	24.71	NA	NA	NA	NA	NA	NA	NA	0.0	NA	0.0	7.12; 3.41, 14.89	No
NA	NA	NA	NA	NA	NA	NA	NA	0.0	0.0	0.0	0.0	3.50; 1.05, 11.66	No
17	16.9	NA	NA	NA	NA	8.6	0.8	NA	NA	NA	NA	4.47; 1.27, 15.75	No
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.03; 0.69, 1.53	No
29.6	30.3	NA	NA	NA	NA	NA	NA	23.6	28.7	NA	NA	0.85; 0.56, 1.00	Yes
31.1	30.3	NA	NA	NA	NA	NA	NA	35.0	28.7	NA	NA	0.64; 0.42, 0.98	Yes
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.41; 1.06, 1.87	Yes
30	30	16.4	16.4	NA	NA	NA	NA	33.0	33.0	NA	NA	2.00; 1.20, 3.50	Yes
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.77; 0.52, 1.14	Yes
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.00; 0.75, 1.33	No

AHI, apnoea–hypopnea index; BMI, body mass index; OR, odds ratio; 95% CI, 95% confidence interval. Pro, prospective; Retro, retrospective; Hosp, hospital; Pop, population; PSG, polysomnography; NPI-D, neuropsychiatric inventory with caregiver distress; NA, not available;

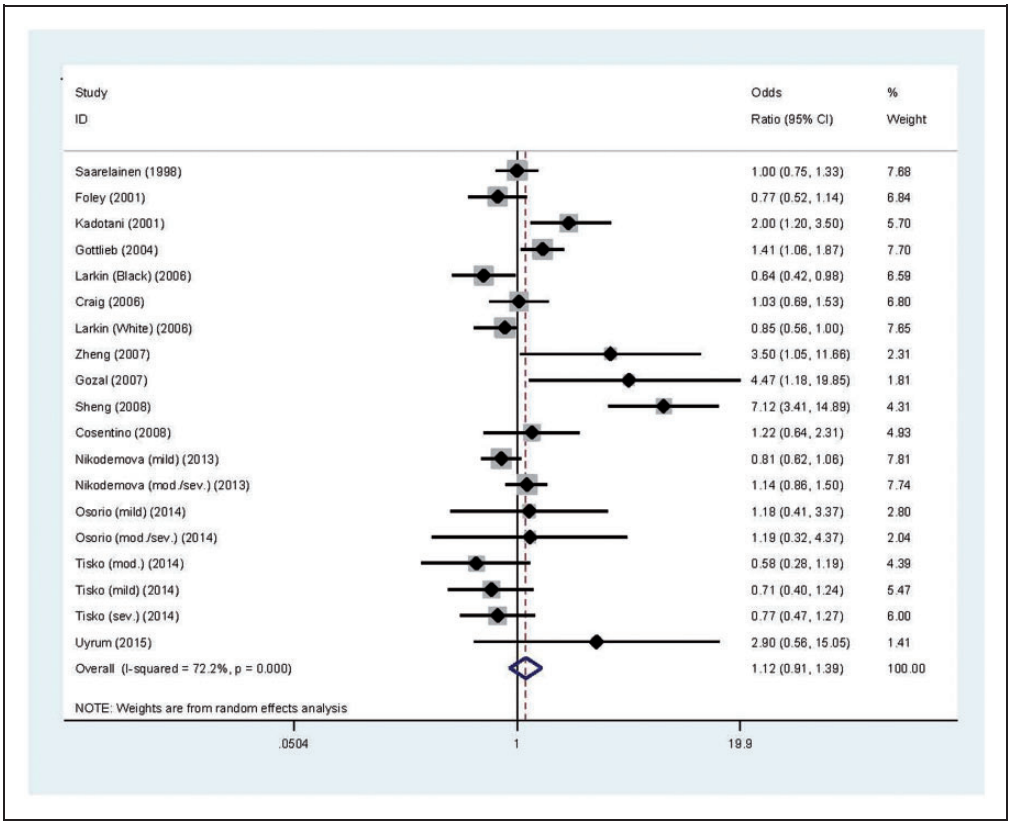

Figure 2. Forest plot of a meta-analysis of the association between obstructive sleep apnoea (OSA) risk and the apolipoprotein gene (*APOE*) $\varepsilon 4$ allele.[10–23] The colour version of this figure is available at: http://imr.sagepub.com.

metabolism,[25] and its function is determined by the presence of three common alleles ($\varepsilon 2$, $\varepsilon 3$, $\varepsilon 4$).[26] Generally, a particular genetic variant could alter disease risk through its effects on either circulating concentrations or physiological function of a particular protein. The present analysis confirms the observation of others[6–8] that individuals with different *APOE* $\varepsilon 2/\varepsilon 3/\varepsilon 4$ genotypes show statistically significant differences in their circulating total cholesterol and HDLC levels. The absence of an association between $\varepsilon 2/\varepsilon 3/\varepsilon 4$ alleles and OSA risk in the present analysis suggest that the principal differences in lipid profile driven by these variants relate to protein concentrations rather than function. The $\varepsilon 2/\varepsilon 3/\varepsilon 4$ alleles appear to play a significant role in cholesterol regulation, although this is not strong enough to predict individual differences in OSA susceptibility.

Genetic epidemiological studies have shown varying and often nonreproducible findings regarding the association between *APOE* $\varepsilon 2/\varepsilon 3/\varepsilon 4$ alleles and OSA susceptibility across ethnic groups. For example, the presence of the $\varepsilon 4$ allele conferred a reduced risk for OSA in one study from the USA[19] but an increased risk in another,[21] and seemed to be neutral in a UK population.[18] This lack of significance may be due to heterogeneity of effect associated with the

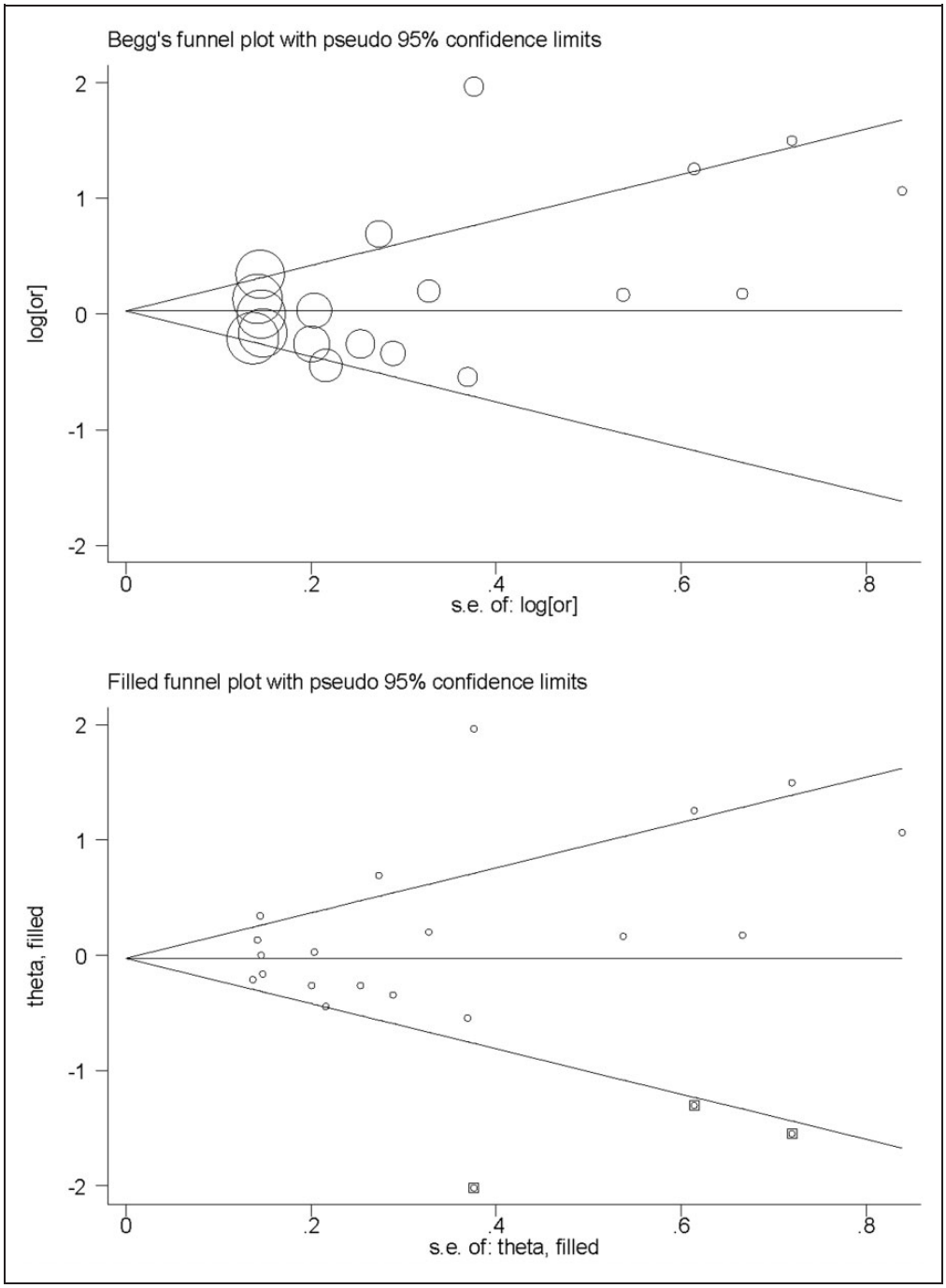

Figure 3. Begg's and Filled funnel plots for a meta-analysis of the association between obstructive sleep apnoea (OSA) risk and the apolipoprotein gene (*APOE*) $\varepsilon 4$ allele.[10–23]

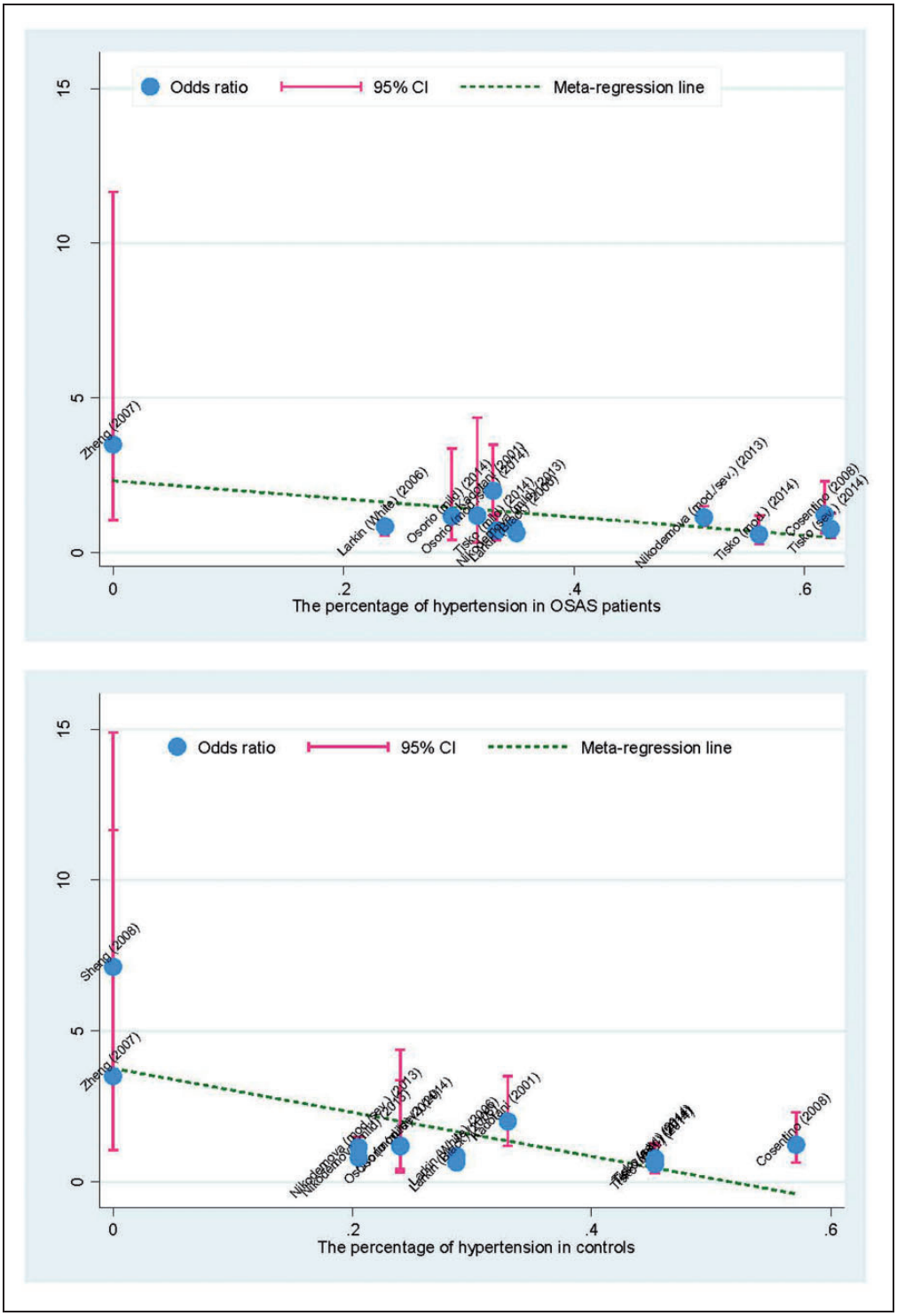

Figure 4. Meta-regression analysis of the association between hypertension and risk of obstructive sleep apnoea (OSA). The colour version of this figure is available at: http://imr.sagepub.com.

Table 2. Body mass index and lipid parameters in apolipoprotein gene (*APOE*) ε4-positive and negative individuals.

Parameter	Studies, *n*	*n*		WMD	95% CI	Statistical significance	Heterogeneity
		ε4+	ε4−				
BMI, kg/m^2	4	713	2017	0.027	−0.817, 0.871	NS	$I^2 = 56.4\%$
TG, mmol/l	4	713	2017	0.203	−0.085, 0.491	NS	$I^2 = 77.4\%$
TC, mmol/l	4	713	2017	0.342	0.095, 0.590	$P = 0.007$	$I^2 = 78.7\%$
HDLC, mmol/l	4	713	2017	−0.052	−0.103, −0.002	$P = 0.040$	$I^2 = 31.5\%$
LDLC, mmol/l	3	274	681	0.197	−0.097, 0.491	NS	$I^2 = 64.4\%$

WMD, weighted mean difference; CI, confidence interval; BMI, body mass index; NS, not statistically significant ($P \geq 0.05$; random effects model); TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol.

Table 3. Stratified analyses of the association between obstructive sleep apnoea (OSA) risk and the apolipoprotein gene (*APOE*) ε4 allele.

Subgroups	Studies, *n*	*n*		OR	95% CI	Heterogeneity
		Patients	Controls			
Study design						
Prospective	10	1930	6544	1.02	0.82, 1.28	$I^2 = 62.9\%$
Retrospective	9	1268	1710	1.33	0.86, 2.05	$I^2 = 80.0\%$
Source of controls						
Population-based	13	2498	7614	1.20	0.93,1.55	$I^2 = 77.7\%$
Hospital-based	6	700	640		0.64, 1.38	$I^2 = 48.7\%$
AHI cut off						
>5–<15	3	577	1299	0.88	0.64, 1.02	$I^2 = 0.0\%$
≥15	10	1825	5719	0.99	0.79, 1.24	$I^2 = 62.1\%$
≥5	4	467	905	2.82	0.84, 9.45	$I^2 = 88.9\%$
Total sample size						
<500	11	1090	1063	1.45	0.91, 2.31	$I^2 = 75.9\%$
≥500	8	2108	7191	1.00	0.81, 1.22	$I^2 = 68.8\%$
Chinese subjects	2	134	146	5.87	3.13, 11.00	$I^2 = 0.0\%$

OR, odds ratio; CI, confidence interval; AHI, apnoea–hypopnea index.

presence of hypertension, as reflected in our meta-regression analysis. It is worth noting that the presence of hypertension might neutralize the contributory role of the ε4 allele in the pathogenesis of OSA, since ε4 was strongly associated with OSA risk after restricting analysis to the two studies of Chinese ancestry with normotensive controls.[15,16] This finding may be too underpowered to be generalizable to a general population and other ethnic groups. On the other hand, OSA is an established risk factor for arterial hypertension,[27] and the severity of hypertension is reported to be in proportion to that of OSA.[28] Analyses stratified by OSA severity were still not significant in this meta-analysis, however. In view of the lack of necessary information, we agree that further

adjustment for the severity of hypertension is critical to quantify reliably the association between *APOE* ε2/ε3/ε4 and OSA susceptibility.

The present analysis has several limitations. First, OSA is a polygenic disease, and it is not possible to unravel its genetic underpinnings by evaluating *APOE* ε2/ε3/ε4 alone. Secondly, all studies included in this meta-analysis were case–control in design. Thirdly, there was a very high level of heterogeneity between studies, but the level of publication bias was low. Finally, the limited sample sizes (especially in some stratified analyses) underline the requirement for large-scale, prospective studies.

In conclusion, this meta-analysis of 14 articles and 9229 study subjects failed to identify any association between *APOE* ε2/ε3/ε4 and OSA susceptibility. The presence of *APOE* ε4 was associated with changes in lipid profile. Importantly, hypertension was identified as a plausible source of heterogeneity between studies, and further studies incorporating information on the severity of hypertension are required to elucidate its role in OSA.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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