Apolipoprotein E \(\varepsilon2/\varepsilon3/\varepsilon4\) 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 \(\varepsilon2/\varepsilon3/\varepsilon4\) 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 \(\varepsilon2/\varepsilon3/\varepsilon4\) 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 \(\varepsilon4\) allele and OSA risk. The presence of \(\varepsilon4\) was associated with significantly increased total cholesterol and decreased high-density lipoprotein cholesterol, compared with \(\varepsilon4\) allele negative individuals. There was a low probability of publication bias but significant heterogeneity.  

Conclusions: There was no association between APOE \(\varepsilon2/\varepsilon3/\varepsilon4\) and OSA susceptibility. The presence of APOE \(\varepsilon4\) 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 (ε2/ε3/ε4; 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 analyses6–8 in order to re-evaluate the association between OSA risk and APOE ε2/ε3/ε4 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 ε2/ε3/ε4 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 ε2/ε3/ε4 or the counts of ε4 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. 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 ($\hat{I}^2$) statistic, with statistically significant heterogeneity indicated by $\hat{I}^2 > 50\%$. 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%). 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).

Data regarding APOE gene ε2/ε3/ε4 alleles were provided in 11 study populations. 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 ($\hat{I}^2 = 66.2\%$; $P = 0.001$).

Data regarding BMI and lipid parameters were provided by four studies. 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 ($\geq 15$ vs $>5–<15$) and sample size ($\geq 500$ 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).

Meta-regression analysis found that hypertension was significantly correlated with OSA risk in both patients ($r = -0.64$;
potentially relevant articles identified and screened for retrieval (n=55): 44 articles in English and 11 articles in Chinese

36 articles excluded:
- 14 articles: animal or cell relevant
- 10 articles: epidemiologic survey
- 9 articles: without genotype data
- 3 articles: meta-analyses

Potentially relevant articles identified after the first selection (n=19)

5 further articles excluded:
- 3 articles: incomplete data
- 2 articles: duplicated

14 qualified articles:
- 12 articles in English
- 2 articles in Chinese

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) ε2/ε3/ε4 alleles.

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 ε2/ε3/ε4 positivity. The presence of the ε4 allele was significantly correlated with increased total cholesterol and decreased HDLC, however.

Discussion

In accordance with the findings of others,6–8 there was no significant association between OSA risk and APOE ε2/ε3/ε4 positivity. The presence of the ε4 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 apoliprotein gene (APOE) ε2/ε3/ε4 alleles.

| Author, year | Country | Design | Source | AHIl cut off | Method | Cases | Controls | Cases | Controls | Cases | Controls | Male sex, % |
|--------------|---------|--------|--------|--------------|--------|-------|----------|-------|----------|-------|----------|------------|
| 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/m² | Smoking, % | Education, years | AHI | Hypertension, % | Diabetes mellitus, % | OR; 95% CI | Adjusted |
|-----------|------------|------------------|-----|----------------|----------------------|------------|----------|
| 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 | 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 | 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 | 0.0 | NA | NA | NA | 0.0 | 7.12; 3.41, 14.89 | No |
| 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 | 1.03; 0.69, 1.53 | No |
| 29.6 | 30.3 | 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 | 35.0 | 28.7 | NA | NA | 0.64; 0.42, 0.98 | Yes |
| 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 | 33.0 | 33.0 | NA | NA | 2.00; 1.20, 3.50 | Yes |
| 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 | 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;
metabolism, and its function is determined by the presence of three common alleles (ε2, ε3, ε4). 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 that individuals with different APOE ε2/ε3/ε4 genotypes show statistically significant differences in their circulating total cholesterol and HDLC levels. The absence of an association between ε2/ε3/ε4 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 ε2/ε3/ε4 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 ε2/ε3/ε4 alleles and OSA susceptibility across ethnic groups. For example, the presence of the ε4 allele conferred a reduced risk for OSA in one study from the USA but an increased risk in another, and seemed to be neutral in a UK population. This lack of significance may be due to heterogeneity of effect associated with the

Figure 2. Forest plot of a meta-analysis of the association between obstructive sleep apnoea (OSA) risk and the apolipoprotein gene (APOE) ε4 allele. The colour version of this figure is available at: http://imr.sagepub.com.
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) ε4 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.
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

| Parameter | Studies, n | ε4+ | ε4− | WMD | 95% CI | Statistical significance | Heterogeneity |
|-----------|------------|-----|-----|-----|-------|-------------------------|--------------|
| 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 (\(P ≥ 0.05\); random effects model); TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol.

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

| Parameter | Studies, n | Patients | Controls | OR | 95% CI | Heterogeneity |
|-----------|------------|----------|----------|----|--------|--------------|
| 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.
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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References

1. Eckert DJ, Jordan AS, Merchia P, et al. Central sleep apnea: pathophysiology and treatment. Chest 2007; 131: 595–607.
2. Eckert DJ and Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008; 5: 144–153.
3. Redline S, Tishler PV, Tosteson TD, et al. The familial aggregation of obstructive sleep apnea. Am J Respir Crit Care Med 1995; 151(3 pt 1): 682–687.
4. Redline S and Tishler PV. The genetics of sleep apnea. Sleep Med Rev 2000; 4: 583–602.
5. Buxbaum SG, Elston RC, Tishler PV, et al. Genetics of the apnea hypopnea index in Caucasians and African Americans: I. Segregation analysis. Genet Epidemiol 2002; 22: 243–253.
6. Thakre TP, Mamtani MR and Kulkarni H. Lack of association of the APOE epsilon 4 allele with the risk of obstructive sleep apnea: meta-analysis and meta-regression. Sleep 2009; 32: 1507–1511.
7. Varvarigou V, Dahabreh IJ, Malhotra A, et al. A review of genetic association studies of obstructive sleep apnea: field synopsis and meta-analysis. Sleep 2011; 34: 1461–1468.
8. Xu H, Qian Y, Guan J, et al. No association between the ApoE ε2 and ε4 alleles and the risk of obstructive sleep apnea: a systematic review and meta-analysis. Biomed Rep 2015; 3: 313–318.
9. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560.
10. Uyrum E, Balbay O, Annakkaya AN, et al. The relationship between obstructive sleep apnea syndrome and apolipoprotein E genetic variants. Respiration 2015; 89: 195–200.
11. Tisko R, Sopkova Z, Habalova V, et al. Effects of apolipoprotein E genotype on serum lipids in obstructive sleep apnoea. Eur Respir J 2014; 43: 1097–1105.
12. Osorio RS, Ayappa I, Mantua J, et al. Interaction between sleep-disordered breathing and apolipoprotein E genotype on cerebrospinal fluid biomarkers for Alzheimer’s disease in cognitively normal elderly individuals. Neurobiol Aging 2014; 35: 1318–1324.
13. Nikodemova M, Finn L, Mignot E, et al. Association of sleep disordered breathing and cognitive deficit in APOE ε4 carriers. Sleep 2013; 36: 873–880.
14. Cosentino FI, Bosco P, Drago V, et al. The APOE epsilon4 allele increases the risk of impaired spatial working memory in
obstructive sleep apnea. Sleep Med 2008; 9: 831–839.

15. Sheng Y and Yu Q. Relationship between apolipoprotein E gene polymorphism and obstructive sleep apnea hypopnea syndrome. Int J Respir 2008; 28: 659–662.

16. Zheng H and Chang Z-w. Association of obstructive sleep apnea-hypopnea syndrome with gene polymorphism of apolipoprotein E. Clinical Focus 2007; 22: 1752–1756.

17. Gozal D, Capdevila OS, Kheirandish-Gozal L, et al. APOE epsilon 4 allele, cognitive dysfunction, and obstructive sleep apnea in children. Neurology 2007; 69: 243–249.

18. Craig D, Hart DJ and Passmore AP. Genetically increased risk of sleep disruption in Alzheimer’s disease. Sleep 2006; 29: 1003–1007.

19. Larkin EK, Patel SR, Redline S, et al. Apolipoprotein E and obstructive sleep apnea: evaluating whether a candidate gene explains a linkage peak. Genet Epidemiol 2006; 30: 101–110.

20. Gottlieb DJ, DeStefano AL, Foley DJ, et al. APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the sleep heart health study. Neurology 2004; 63: 664–668.

21. Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. JAMA 2001; 285: 2888–2890.

22. Foley DJ, Masaki K, White L, et al. Relationship between apolipoprotein E epsilon4 and sleep-disordered breathing at different ages. JAMA 2001; 286: 1447–1448.

23. Saarelainen S, Lehtimaki T, Kallonen E, et al. No relation between apolipoprotein E alleles and obstructive sleep apnea. Clin Genet 1998; 53: 147–148.

24. Kheirandish L, Row BW, Li RC, et al. Apolipoprotein E-deficient mice exhibit increased vulnerability to intermittent hypoxia-induced spatial learning deficits. Sleep 2005; 28: 1412–1417.

25. Huang Y and Mahley RW. Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer’s diseases. Neurobiol Dis 2014; 72 Pt A: 3–12.

26. Svobodova H, Kucera F, Stulc T, et al. Apolipoprotein E gene polymorphism in the Mongolian population. Folia Biol (Praha) 2007; 53: 138–142.

27. Schulz R, Murzabekova G, Egemenazarov B, et al. Arterial hypertension in a murine model of sleep apnea: role of NADPH oxidase 2. J Hypertens 2014; 32: 300–305.

28. Khan A, Patel NK, O’Hearn DJ, et al. Resistant hypertension and obstructive sleep apnea. Int J Hypertens 2013; 2013: 193010.