Obstructive Sleep Apnea Is Associated with Elevated High Sensitivity C-Reactive Protein Levels Independent of Obesity: Korean Genome and Epidemiology Study

Jinkwan Kim¹, Seok Jun Lee², Kyung-Mee Choi³, Seung Ku Lee³, Dae Wui Yoon³, Seung Gwan Lee⁵, Chol Shin³,⁴,*

¹ Department of Biomedical Laboratory Science, College of Health Science, Jungwon University, Chung-Buk, Republic of Korea, ² Department of Biomedical Laboratory Science, College of Health Science, Cheong-Ju University, Chung-Buk, Republic of Korea, ³ Institute of Human Genomic Study, Korea University Ansan Hospital, Korea University, Ansan, Republic of Korea, ⁴ Department of Pulmonary Sleep and Critical Care Medicine Disorder Center, College of Medicine, Korea University, Ansan, Republic of Korea, ⁵ Department of Health and Integrative Science, College of Health Science, Korea University, Seoul, Republic of Korea

* chol-shin@korea.ac.kr

Abstract

Obstructive sleep apnea syndrome (OSA) has been recognized as a common health problem, and increasing obesity rates have led to further remarkable increases in the prevalence of OSA, along with more prominent cardiovascular morbidities. Though previous studies have reported an independent relationship between elevated high sensitivity C-reactive protein (hsCRP) levels and OSA, the issue remains controversial owing to inadequate consideration of obesity and various confounding factors. So far, few population based studies of association between OSA and hsCRP levels have been published. Therefore, the purpose of the present study was to investigate whether OSA is associated with increased hsCRP levels independent of obesity in a large population-based study. A total of 1,835 subjects (968 men and 867 women) were selected from a larger cohort of the ongoing Korean Genome and Epidemiology Study (KoGES). Overnight polysomnography was performed on each participant. All participants underwent anthropometric measurements and biochemical analyses, including analysis of lipid profiles and hsCRP levels. Based on anthropometric data, body mass index (BMI) and waist hip ratio (WHR) were calculated and fat mass (FM) were measured by means of multi-frequency bioelectrical impedance analysis (BIA). Mild OSA and moderate to severe OSA were defined by an AHI >5 and ≥15, respectively. The population was sub-divided into 3 groups based on the tertile cut-points for the distribution of hsCRP levels. The percentage of participants in the highest tertile of hsCRP increased dose-dependently according to the severity of OSA. After adjustment for potential confounders and obesity-related variables (BMI, WHR, and body fat) in a multiple logistic model, participants with moderate to severe OSA had 1.73-, 2.01-, and 1.61-fold greater risks of being in the highest tertile of hsCRP levels than participants with non-OSA, respectively. Interaction between obesity (BMI ≥25kg/m²) and the presence of
moderate-to-severe OSA was significant on the middle tertile levels of hsCRP (OR = 2.4), but not on the highest tertile, compared to the lowest tertile. OSA is independently associated with elevated hsCRP levels and may reflect an increased risk for cardiovascular morbidity. However, we found that OSA and obesity interactively contribute to individuals with general levels of hsCRP (<1.01 mg/dl). The short-term and long-term effects of elevated hsCRP levels on cardiovascular risk in the context of OSA remain to be defined in future studies.

Introduction
Obstructive Sleep Apnea (OSA) is caused by repetitive obstruction of the upper airway during sleep, which results in an increase in resistance in the upper airway, leading to snoring and repetitive occurrences of intermittent hypoxia and hypercapnia in the body; thus, cyclical frequent arousals cause sleep fragmentation. Increasing evidence from several lines of investigation strongly supports the concept that OSA is pathophysiologically linked to cardiovascular diseases (CVD) such as hypertension, ischemic heart disease, and cerebrovascular disease [1, 2]. Increased generation of reactive oxygen species and systemic inflammatory responses related to hypoxia-reoxygenation events and to sleep fragmentation are mechanistically involved in the acceleration and propagation of atherogenesis [3, 4]. However, the mechanisms underlying the association between OSA and CVD are currently not fully understood. Furthermore, given that the prevalence of obesity, which is known to be a strong risk factor for OSA, is rapidly rising in Asian countries, the substantial attention to OSA-related comorbidities is expected to continue increasing.

C-reactive protein (CRP), which is known to be an important biomarker of CVD, is an acute-phase protein that is generated in the liver by IL-6. CRP is more specifically found in the lesions of atherosclerosis and is thought to participate actively in atheromatous lesion formation through the induction and enhanced expression of adhesion molecules [5]. Increased levels of CRP have been found in both adults [6–8] and children with OSA [9–12], and CRP levels are substantially reduced after treatment [8, 11, 13]. However, not all studies in adults [14, 15] or in children [16, 17] have confirmed the putative association between CRP levels and OSA severity, owing to small sample sizes and inadequate consideration of confounding factors such as obesity. Moreover, a few population-based studies reported an association between OSA and CRP [18]. Therefore, we sought to investigate whether OSA is associated with elevated hsCRP levels independent of obesity in a large population-based study, and to evaluate the significance of hsCRP as a biomarker that can be used to help predict and reduce the risk of CVD in the context of OSA.

Subjects and Methods
Subjects
Participants in the present study were part of a larger study, the Korean Genome and Epidemiology Study (KoGES), which is an ongoing, population-based cohort study that started in 2001 under the original title “The Korean Health and Genome Study.” Detailed information on the study design and aims of the KoGES has been reported previously [19–21]. In brief, the original study was designed to establish a representative adult cohort in the city of Ansan, Korea, and to identify the epidemiologic characteristics, frequencies and determinants of chronic diseases among Koreans. From June 2001 to January 2003, a longitudinal cohort was formed, consisting
of 5,015 participants (2,521 men and 2,494 women, 40–69 years of age) who participated in a comprehensive health examination and on-site interviews at Korea University Ansan Hospital. Follow-up assessments were conducted biennially with scheduled site visits. At each visit, participants signed an informed consent form and this study was approved by the Human Subjects Review Committee at Korea University Ansan Hospital. Polysomnography (PSG) was included in the study protocol in September 2009 in about half of the KoGES participants. Although PSG will eventually be administered to the entire study population, subjects for the present study include only those with PSG data from the fourth biennial examination from March 2007 to February 2009. After excluding participants who had missing data and those with extreme outliers of biochemical data, a total of 1835 individuals (968 men and 867 women) were recruited into the current study. Participants were also excluded if they had any known systemic inflammatory disease or genetic abnormality using a questionnaire for a general health examination or had a high hsCRP level (hsCRP level >10mg/dl) or, had received any treatment for OSA. All participants underwent anthropometric measurements, a general health examination, an assessment of sleep habits, and polysomnography (PSG).

### Overnight polysomnography (PSG)

An overnight sleep study was performed at each participant’s home with a portable device (Embletta® X-100; Embla Systems, San Carlos, CA, USA), as previously described [22]. In brief, two trained sleep technologists visited participants’ homes in the evening, applied sensors, and instructed participants on how to turn the sensors on and off. Participants also were required to record the times they turned the lights on and off and report those times the following morning. The recording channels were as follows: one electroencephalography (C4-A1), one electrooculography (right upper outer canthus-left lower outer canthus), one chin electromyography, one modified lead II electrocardiography, one airflow from nasal airflow pressure transducer, two respiratory effort from chest and abdominal respiratory inductance plethysmography, one pulse oximeter, and one position sensor. For qualified data, sleep status and respiratory events were scored according to standard guidelines. Obstructive apnea was defined as a clear decrease (>90%) from baseline in the amplitude of the nasal pressure with ongoing chest and abdominal movement, and hypopneas were identified if there was ≥30% reduction in the nasal pressure from baseline, associated with at least 4% oxygen desaturation on pulse oximetry. The duration threshold for these respiratory events was 10 sec. Mild OSA and moderate-to-severe OSA were defined by an AHI >5 and ≥15, respectively. Arousals were defined according to the American Academy of Sleep Medicine Scoring Manual [23, 24].

### Anthropometrics, biochemical data, and assessment of body composition

All subjects were surveyed for their age, sex, marital status, smoking, drinking, and other habits. Blood pressure, height, weight, waist circumference and hip circumference were measured according to standard protocols, as previously reported [22]. Body mass index (BMI) was calculated as the weight divided by the square of height. Obesity was defined with BMI ≥25kg/m², according to the Asian-specific BMI cut-off from the World Health Organization Report [25]. For biochemical tests, when participants visited for their follow-up examinations, blood was collected after the subjects had fasted for at least 8 hours. Biochemical data including glucose, HDL, LDL, triglyceride, and hsCRP levels were measured (ADVIA 1650 and 1680, Siemens, Tarrytown, NY, USA). Body composition was measured by means of multi-frequency bioelectrical impedance analysis (BIA) with 8-point tactile electrodes (InBody 720; Biospace, Seoul, Korea) [26, 27]. This analyzer uses an alternating current of 250 mA at variable
frequencies of 1, 5, 50, 250, 500, and 1,000 kHz. Fat-free mass and fat mass were obtained from a multi-frequency BIA.

**Statistical analysis**

Data are expressed as mean±SD. Significant association of hsCRP with continuous and categorical variables were identified by ANOVA and Chi-square test, respectively. Bonferroni correction was applied for multiple comparisons. The population was grouped based on tertile cut-points of hsCRP levels (>1.01 mg/dl for the highest tertile and <0.42 mg/dl for the lowest tertile). Then, univariate and stepwise multivariate linear regression analyses were done for hsCRP with explained by OSA, obesity, and other variables. Using a logistic regression, odds ratio and 95% confidence interval were estimated for the highest tertile of hsCRP levels compared to the lowest tertile. Statistical significance was identified at the 0.05 level. All the statistical analyses were done using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA).

**Results**

**Study population**

The demographic, polysomnographic, and biochemical characteristics of the 3 groups, divided by the severity of the AHI, are presented in Table 1. Regarding the presence or absence of OSA, 611 participants had mild OSA, 251 had moderate-to-severe OSA, and 973 were non-OSA. The mean ages of participants in the 3 groups were 58, 57 and 53 years, respectively. Polysomnographic data, including the AHI and the SaO2 nadir, showed significant group differences (p<0.01). Metabolic profiles, including those for glucose, triglyceride and HDL cholesterol levels, differed significantly among the 3 groups (p<0.01); however, total cholesterol did not vary significantly. HsCRP levels increased dose-dependently according to the severity of OSA (Moderate-to-Severe OSA vs. Mild OSA vs. Non-OSA among non-obese participants, 1.47 ±1.60 mg/dL vs. 1.20±1.34 mg/dL vs. 0.97±1.22 mg/dL, p<0.01).

**Percentage of participants in the highest tertile of hsCRP levels according to the severity of OSA, based on the presence of obesity**

Fig 1 shows the percentage of participants in the highest tertile of hsCRP levels according to the severity of OSA by the presence or absence of obesity. Because obesity was expected to contribute to increased hsCRP levels as a major confounding factor, we compared the percentage in the highest tertile among the 3 groups of both obese and non-obese participants. Even after controlling for obesity (BMI ≥25 kg/m²), we found that the portion of participants in the highest tertile of hsCRP levels differed significantly according to the severity of OSA (Fig 1A, Moderate-to-Severe OSA vs. Mild OSA vs. Non-OSA among obese participants, 50.0% vs. 42.5% vs. 38.5%, p<0.001; Fig 1B, Moderate-to-Severe OSA vs. Mild OSA vs. Non-OSA among non-obese participants, 35.1% vs. 35.2% vs. 22.7%, p<0.001). Besides, significant differences in hsCRP levels among the 3 groups were exhibited in both the obese and non-obese groups (Moderate-to-Severe OSA vs. Mild OSA vs. Non-OSA among obese participants, 1.69±1.73 mg/dL vs. 1.29±1.35 mg/dL vs. 1.20±1.29 mg/dL, p<0.01; Moderate-to-Severe OSA vs. Mild OSA vs. Non-OSA among non-obese participants, 1.12±1.31 mg/dL vs. 1.11±1.32 mg/dL vs. 0.87±1.17 mg/dL, p<0.01).

**Association between the severity of OSA and hsCRP in participants**

To examine independent predictors of hsCRP levels in participants, we performed regression analyses (Table 2). In univariate analysis, hsCRP level was positively associated with AHI
In multiple regression analysis, hsCRP level was positively associated with AHI (β±SE; 0.055 ±0.02, p<0.01; Table 2) and negatively associated with the SaO2 nadir (β±SE; -1.33±0.41, p<0.01) after adjustment for potential confounding factors including age, sex, smoking status, alcohol use, DM medication, HTN medication, and BMI. In order to further estimate the odds ratio having a given hsCRP level based on the presence and severity of OSA, we performed logistic regression analysis. Table 3 presents the univariate and multivariate odds ratios of being in the highest versus the lowest tertile of hsCRP levels, according to the severity of OSA. In the univariate model, the odds ratios of being in the highest tertile of hsCRP (>1.01 mg/mL) versus the lowest tertile (<0.42 mg/mL) were 2.27 (95% CI, 1.76–2.93, p<0.01) and 2.91 (95% CI, 2.04–4.16, p<0.05) for subjects with mild OSA (5<AHI≤15) and moderate-to-severe OSA (AHI>15), respectively, with reference to non-OSA subjects. After adjustment for age, sex, smoking status, alcohol use, DM medication, HTN medication, and each of the obesity-related variables (BMI, WHR, and FM/body weight), participants with

Table 1. General Characteristics of Study Participants.

|                      | Moderate-to-severe OSA (AHI>15) | Mild OSA (5<AHI≤15) | Non-OSA (AHI<5) | P value1) |
|----------------------|---------------------------------|---------------------|-----------------|-----------|
| N (%)                | 251 (13.7)                      | 611 (33.3)          | 973 (53.0)      | -         |
| Age (years)          | 58.0±7.7                        | 57.2±7.2            | 53.8±6.6&       | <0.01     |
| Male, n (%)          | 167 (66.5)                      | 348 (57.0)          | 453 (46.6)      | <0.001    |
| BMI (kg/m2)          | 25.9±3.2†                       | 25.1±2.6†           | 23.9±2.6       | <0.01     |
| WHR (waist/hip)      | 0.89±0.06†                      | 0.87±0.06†          | 0.84±0.06      | <0.01     |
| FM/Body Weight (kg/kg)| 0.27±0.006§                    | 0.27±0.006‡         | 0.26±0.006     | <0.01     |
| FFM/Body Weight (kg/kg)| 0.72±0.006§                    | 0.73±0.006‡         | 0.74±0.006     | <0.01     |
| ESS                  | 5.89±4.14                       | 5.75±4.57           | 5.85±4.36      | 0.868     |
| Current Smoker, n (%)| 130 (51.8)                      | 253 (41.4)          | 350 (36.0)     | <0.01     |
| Current Drinker, n (%)| 166 (66.1)                      | 356 (58.3)          | 504 (51.8)     | <0.01     |
| Medication for HTN, n (%)| 71 (34.6)                      | 159 (30.3)          | 39 (20.6)      | <0.01     |
| Medication for DM, n (%)| 30 (14.6)                       | 67 (12.8)           | 16 (8.5)       | <0.01     |
| Systolic BP (mmHg)   | 117.1±14.3†                     | 113.3±13.4‡         | 109.6±13.8     | <0.01     |
| Diastolic BP (mmHg)  | 77.7±9.8‡                       | 75.5±9.2‡           | 73.3±9.4       | <0.01     |
| AHI (events/hour)    | 24.7±10.8†                      | 8.8±2.7‡            | 1.9±1.4        | <0.01     |
| (Median, IQR)        | (21.3, 17.3–28.6)               | (8.6, 6.4–10.9)     | (1.7, 0.7–3.2) |           |
| SaO2 Nadir (%)       | 81.4±5.3†                       | 85.4±3.8            | 90.2±2.9       | <0.01     |
| (Median, IQR)        | (82.0, 79.0–85.0)                | (86.0, 83.0–88.0)   | (91.0, 89.0–92.0) |           |
| Fasting Glucose (mg/dL) | 107.9±40.4†                 | 101.5±32.0‡        | 96.7±28.5      | <0.01     |
| Total Cholesterol (mg/dL) | 197.4±36.5                  | 201.7±34.1         | 199.7±34.7     | 0.221     |
| HDL cholesterol (mg/dL) | 42.8±9.2                   | 44.1±10.6‡         | 45.6±10.9&     | <0.01     |
| Triglyceride (mg/dL)  | 161.1±93.2†                    | 147.7±95.0§        | 126.8±76.9&    | <0.01     |
| HsCRP (mg/dL)        | 1.47±1.60†                     | 1.20±1.34‡         | 0.97±1.22&     | <0.01     |
| (Log-transformed)    | (-0.03±0.43)                   | (-0.10±0.39)       | (-0.22±0.42)   |           |

All data are expressed as mean±SD. Statistical significance was estimated after logarithmic transformation if the data were not normally distributed. BMI, body mass index; WHR, waist hip ratio; FM, fat mass; FFM, free fat mass; ESS, Epworth sleepiness scale; HTN, hypertension; DM, diabetes; BP, blood pressure; AHI, apnea hypopnea index; IQR, interquartile range; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein.

1) The combinatorial association is significant for P-value<0.05.

†P<0.01, Mild OSA vs. Moderate to severe OSA
‡P<0.01, Mild OSA vs. Non-OSA
§P<0.05, Mild OSA vs. Moderate to severe OSA
& P<0.01, Moderate to severe OSA vs. Non-OSA

doi:10.1371/journal.pone.0163017.t001

(n = 1835, β±SE; 0.126±0.02, p<0.01). In multiple regression analysis, hsCRP level was positively associated with AHI (β±SE; 0.055 ±0.02, p<0.01; Table 2) and negatively associated with the SaO2 nadir (β±SE; -1.33±0.41, p<0.01) after adjustment for potential confounding factors including age, sex, smoking status, alcohol use, DM medication, HTN medication, and BMI. In order to further estimate the odds ratio having a given hsCRP level based on the presence and severity of OSA, we performed logistic regression analysis. Table 3 presents the univariate and multivariate odds ratios of being in the highest versus the lowest tertile of hsCRP levels, according to the severity of OSA. In the univariate model, the odds ratios of being in the highest tertile of hsCRP (>1.01 mg/mL) versus the lowest tertile (<0.42 mg/mL) were 2.27 (95% CI, 1.76–2.93, p<0.01) and 2.91 (95% CI, 2.04–4.16, p<0.05) for subjects with mild OSA (5<AHI≤15) and moderate-to-severe OSA (AHI>15), respectively, with reference to non-OSA subjects. After adjustment for age, sex, smoking status, alcohol use, DM medication, HTN medication, and each of the obesity-related variables (BMI, WHR, and FM/body weight), participants with
A

![Bar chart showing the highest tertile of Hs-CRP in obese individuals with different OSA severities.](chart1)

- **Non-OSA (n=309)**
- **Mild OSA (n=318)**
- **Moderate to Severe OSA (n=154)**

Comparison: **p < 0.001**

B

![Bar chart showing the highest tertile of Hs-CRP in non-obese individuals with different OSA severities.](chart2)

- **Non-OSA (n=664)**
- **Mild OSA (n=293)**
- **Moderate to Severe OSA (n=97)**

Comparison: **p < 0.001**
moderate-to-severe OSA had 1.73- (BMI adjusted), 2.01- (WHR adjusted), and 1.61- (FM/body weight adjusted) fold greater risks (95% CI, 1.14–2.62, p < 0.05) than non-OSA subjects of being in the highest tertile of hsCRP compared with the lowest tertile. Interestingly, participants with moderate-to-severe OSA had the highest odds ratio for being in the highest tertile of hsCRP levels compared with non-OSA participants after adjustment for confounding factors and WHR, which is major predictor of OSA.

Interaction between OSA and obesity on hsCRP level

After the tertile stratification of hsCRP, log-transformed hsCRP mean was compared among the two OSA groups and non-OSA group using ANOVA with Bonferroni post-hoc analysis. There was a significant difference between moderate-to-severe OSA and mild OSA (mean ± standard error, 0.086 ±0.033), but only for the group of highest hsCRP tertile with obesity (BMI ≥25 kg/m²). Lower tertile groups were not significantly different depending on OSA, regardless of obesity. Further to identify interaction between obesity and OSA on hsCRP, odds ratios of the highest and middle tertiles hsCRP were estimated, compared to the lowest tertile, respectively, using a logistic regression model explained by age, sex, smoking, drinking, hypertension and diabetes medications, obesity, OSA, and interaction of obesity and OSA. As the result, a significant interaction between obesity and the presence of OSA was observed for the middle tertile group of hsCRP only (adjusted odds ratio [OR], 2.4; 95% CI, 1.1–5.4, p = 0.030). In the highest tertile group of hsCRP, the interaction was not significant, but obesity (OR, 1.9; 95% CI, 1.3–3.6, p = 0.001) and mild OSA (OR, 1.9; 95% CI, 1.3–2.8, p = 0.003), diabetes medication (OR, 1.8; 95% CI, 1.2–2.8, p = 0.003) and age (OR, 1.02; 95% CI, 1.01–1.04; p = 0.013) were all significant. Additionally, without the tertile classification of hsCRP, the interaction between obesity related variables BMI, WHR, and OSA on hsCRP was examined using a generalized linear model, in which no such a significant interaction was identified.

Discussion

In this large population-based study, we found that hsCRP levels increased dose-dependently according to the severity of OSA, even in non-obese participants. Furthermore, the percentage

| Table 2. Multivariate linear regression analyses between AHI or SaO2 nadir and hsCRP levels after adjustment for confounding factors. |
|---------------------------------------------------------------|
| Independent Variables | HsCRP levels† | Crude | Model 1* | Model 2** | Model 3*** |
|------------------------|----------------|-------|----------|-----------|-----------|
|                        | Beta | SE   | P-value | Beta    | SE   | P-value | Beta | SE | P-value |
| AHI†                   | 0.126 | 0.018 | <0.01   | 0.055   | 0.02 | <0.01   | 0.078 | 0.019 | <0.001 |
| SaO2 nadir†            | -2.892 | 0.386 | <0.01   | -1.33   | 0.41 | <0.01   | -1.885 | 0.402 | <0.001 |

Abbreviation: AHI, apnea hypopnea index; SE, standard error
† Data were log-transformed
*Adjusted for confounding factors including age, sex, smoking status, alcohol use, DM medication, HTN medication, and BMI.
**Adjusted for confounding factors including age, sex, smoking status, alcohol use, DM medication, HTN medication, and WHR.
***Adjusted for confounding factors including age, sex, smoking status, alcohol use, DM medication, HTN medication, and FM/body weight.

doi:10.1371/journal.pone.0163017.t002
of participants in the highest tertile of hsCRP levels increased dose-dependently according to the severity of OSA, independent of obesity. In multiple regression analysis, hsCRP levels were positively associated with the AHI and negatively associated with the SaO2 nadir, even after adjustment for potential confounding factors and each of the three obesity-related variables (BMI, WHR, and FM). Moreover, in an attempt to further estimate the odds ratio of having a given hsCRP level based on the presence of OSA, we also performed logistic regression analysis. Even after adjustment for various confounding factors and each of the obesity-related variables, participants with moderate-to-severe OSA had 1.78- (BMI adjusted), 2.01- (WHR adjusted), and 1.61-fold (Fat mass/body weight) greater risks of being in the highest tertile of hsCRP levels than non-OSA participants (Table 3), supporting the hypothesis that OSA is associated with elevated levels of hsCRP. However, we also found a significant interaction between obesity and the presence of OSA in the middle tertile group of hsCRP only. Thus, we suggest that other additional confirmatory studies should address the issue of whether obesity level estimated by the different indexes influences how OSA affects hsCRP level in a large population based study more detail.

HsCRP, a ubiquitous protein that can be generated in multiple cell types, is a robust biomarker of underlying systemic inflammation and is regulated by the proinflammatory cytokines, particularly IL-6 and TNF-α [3]. Although the exact mechanisms linking OSA to the inflammatory cascade are not clear, and remain to be fully elucidated, the intermittent hypoxia and reoxygenation that characterize OSA contribute to the cumulative burden of oxidative stress and the generation of reactive oxygen species (ROS), and trigger inflammatory cytokines [4, 28]. In the last two decades, the CRP level has been extensively assessed as an independent marker of future cardiovascular events and metabolic dysfunction [29–32], in addition to endothelial function and integrity. Recent studies revealed that low grade inflammation is reflected by increased levels of hsCRP in patients with type 2 diabetes and small increased CRP level predict the likelihood of developing cardiovascular events both in diabetic and nondiabetic populations [33–35]. Not surprisingly, previous studies have reported a strong association between OSA and hsCRP levels that is independent of other well-established risk factors. After the association between OSA and hsCRP levels was reported initially by Shamsuzzaman and
colleagues [36], many other investigators confirmed that OSA is associated with elevated hsCRP levels, and that such increases in hsCRP levels are reversed by effective treatment of the underlying sleep-disordered breathing [37–51]. Yokoe and colleagues [37] reported that both the level of CRP and the spontaneous production of IL-6 by monocytes were elevated in patients with OSA. Guven and colleagues [52] also found that OSA was associated with elevated CRP levels independent of obesity. Moreover, Lui et al. revealed that elevated CRP levels were associated with OSA independent of visceral obesity in healthy middle-aged men [45]. However, in most of these studies, a case-control study design was used, and a small number of patients suspected of having OSA were studied in clinical settings. More substantial data from a community-based study demonstrated that nocturnal intermittent hypoxia was associated with elevated CRP levels among middle-aged Japanese subjects [48].

However, even though incremental data from both clinical and epidemiological studies have demonstrated a positive association between elevated CRP and OSA, the issue is still controversial. A number of other studies did not find this relation, as these studies did not adequately consider analytical confounders, such as central obesity, smoking status, or hypertension. In a cross-sectional study to determine whether obesity or OSA is responsible for increased levels of CRP in patients with sleep disordered breathing (SDB), Sharma et al. found that obesity, and not obstructive sleep apnea, was associated with elevated serum levels of hsCRP [53]. Guilleminault et al. reported that CRP levels were significantly correlated with BMI and esophageal pressure, and only BMI was significantly associated with high CRP values [15]. Moreover, Taheri et al. found no independent relationship between CRP levels and indices of SDB in 907 adults enrolled in the Wisconsin Sleep Cohort who had undergone inpatient PSG, suggesting that the relationship between these two variables may be driven primarily by their association with obesity [54]. Recently, the Icelandic Sleep Apnea Cohort study interestingly revealed that OSA severity was an independent predictor of IL-6 and CRP levels, but interacted with obesity such that this association was found only in obese patients [55]. In the present study, because obesity was expected to contribute to increased hsCRP levels, we repeated our analysis to examine the percentage of subjects in the highest hsCRP tertile among the 3 groups by severity of OSA after adjusting for obesity. In the analysis stratified by obesity, the percentage of subjects in the highest hsCRP tertile increased according to the severity of OSA in both the obese and non-obese groups. Moreover, in an attempt to examine whether OSA is responsible for increases in hsCRP levels independent of obesity, we separately tested three obesity-related variables (BMI, WHR, and FM/body weight) in regression models. These variables are commonly useful indices of obesity and central obesity in public health and population-based studies. Even though there was a significant interaction between obesity and the presence of OSA in the middle tertile group of hsCRP only, but this was not significant in the highest tertile group of hsCRP (>1.01 mg/dl). This finding indicates that obesity is not fully affect in a wide ranged hsCRP level in OSA. Recently, obesity has become one of the social problems in Korea, and the major cause of the increasing obesity is known to be the change of lifestyle and nutrition. Several studies demonstrated that Asians show markedly different etiology in the onset of obesity-related morbidities [56] and they may have a different susceptibility to OSA [57] and a different pro-inflammatory profile to Caucasians and African Americans [58]. Obviously, since obesity and OSA commonly coexist, more specific assessment of these factors in the context of OSA will have to investigate in future studies.

Compared with previous studies, many of which had methodological limitations, the current study has several strengths. The strengths are the large sample size and community-based study design in the general population among subjects with relatively low BMIs. Most of the previous studies were performed under the constraints of clinical practice and failed to adequately exclude confounding factors while addressing the issue. A precise estimation of the
actual role of obesity is essential if the analysis of hsCRP levels is to be devoid of known confounders. In the present study, we included study participants who were well within the normal range of BMIs in the Asian population (Mean±SD, 24.6±2.85). Thus, our results could be representative of the general population. Another advantage of the present study was the evaluation of OSA with a portable PSG at home, which provided a more realistic assessment of OSA severity than can be achieved in clinical-based studies by allowing the maintenance of regular daily habits of sleep, physical activity, and diet in the general population.

While the present study included a large general population sample and extensive adjustment for obesity with various variables, several limitations should be addressed. First, we did not consider the influence of genetic variance and environmental factors, which play an important role in regulating hsCRP levels. Previous studies have shown that genetic variation in the IL-6/CRP pathway is associated with increased risk for OSA, suggesting that it may account for the higher CRP levels in the context of OSA [59, 60]. It will definitely be important to explore the impact of specific CRP gene polymorphisms on these associations. Second, we did not elucidate the possibility of reverse causality—for instance, whether any treatments for OSA, such as CPAP treatment or surgical treatments, could reduce hsCRP levels. Even though significant reduction in hsCRP levels after CPAP treatment has been reported previously, this issue remains controversial [61]. Therefore, well-designed, randomized controlled trials are needed to address this issue in future research. Third, our results from separately controlling for each of obesity-related factors such as BMI, WHR, and FM in regression model may not sufficient to exclude the influence of obesity on the association between OSA and elevated CRP levels. A previous study from the Asian patients demonstrated an independent associations of AHI and CRP levels, adjusting for BMI and visceral fat measured by MRI [45]. However, MRI measurement of visceral fat mass is an expensive and laborious technique, so we did not use this technique to estimate visceral obesity in the present study population. It definitely will be important to use highly advanced techniques for evaluating obesity to further explore the role of fat distribution in the elevation of hsCRP levels in OSA. Fourth, another potential limitation is that the blood sample for assessment of hsCRP level was not immediately drawn the morning after PSG study. Our data showed that the mean of time difference between dates for performing PSG and blood collection from the participants was 55.3 days. Thus, this difference may be influence of estimating association between hsCRP level and OSA. Finally, we could not consider the effect of alterations of glucose metabolism or insulin resistance, which may also play an important role in elevation of hsCRP level in OSA. Since several studies revealed that significant associations between severity of OSA, insulin resistance, and BMI was found [62, 63]. Moreover, we would like to emphasize that the present study was cross-sectional; thus, the findings of significant associations are insufficient to infer causality. Therefore, well-designed, prospective cohort studies are needed to address whether alterations of glucose and insulin level as well as obesity are interactively associated with elevated hsCRP level in the context of OSA in the future.

In summary, elevated hsCRP levels are independently associated with OSA and may reflect increased risk for cardiovascular morbidity. However, we found that OSA and obesity interactively contribute to elevation of hsCRP levels (middle ranged). Obviously, more specific assessment of interaction between obesity and OSA on elevation of hsCRP level will have to investigate and the short-term and long-term effects of elevated hsCRP levels on cardiovascular risk in the context of OSA remain to be defined in future studies.

**Acknowledgments**

We thank all the participants and research staff of the Institute of Human Genomic Study at Ansan Hospital of the Korea University.
Author Contributions

Conceptualization: JK DY.
Data curation: SKL.
Formal analysis: JK KC.
Funding acquisition: CS.
Investigation: SGL DY SJL.
Methodology: JK SKL.
Project administration: SGL.
Resources: JK CS.
Software: JK CS.
Supervision: CS KC.
Validation: CS.
Visualization: JK.
Writing – original draft: JK DY.
Writing – review & editing: JK SKL CS.

References

1. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. Journal of the American College of Cardiology. 2013; 62(7):569–76. doi: 10.1016/j.jacc.2013.05.045 PMID: 23770180; PubMed Central PMCID: PMC4461232.

2. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. Journal of thoracic disease. 2015; 7(8):1311–22. doi: 10.3978/j.issn.2072-1439.2015.06.11 PMID: 26380759; PubMed Central PMCID: PMC4561280.

3. Kim J, Hakim F, Kheirandish-Gozal L, Gozal D. Inflammatory pathways in children with insufficient or disordered sleep. Respiratory physiology & neurobiology. 2011; 178(3):465–74. doi: 10.1016/j.resp.2011.04.024 PMID: 21569868; PubMed Central PMCID: PMC3168951.

4. Lavie L, Lavie P. Molecular mechanisms of cardiovascular disease in OSAHS: the oxidative stress link. The European respiratory journal. 2009; 33(6):1467–84. doi: 10.1183/09031936.00086008 PMID: 19483049.

5. Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemotactant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation. 2001; 103(21):2531–4. doi: 10.1161/01.cir.103.21.2531 PMID: 11382718.

6. Can M, Acikgoz S, Mungan G, Bayraktaroglu T, Kocak E, Guven B, et al. Serum cardiovascular risk factors in obstructive sleep apnea. Chest. 2006; 129(2):233–7. doi: 10.1378/chest.129.2.233 PMID: 16478836.

7. Chung S, Yoon IY, Shin YK, Lee CH, Kim JW, Lee T, et al. Endothelial dysfunction and C-reactive protein in relation with the severity of obstructive sleep apnea syndrome. Sleep. 2007; 30(8):997–1001. Epub 2007/08/19. PMID: 17702269; PubMed Central PMCID: PMC1978380.

8. Kageyama N, Nomura M, Nakaya Y, Watanabe T, Ito S. Relationship between adhesion molecules with hs-CRP and changes therein after ARB (Valsartan) administration in patients with obstructive sleep apnea syndrome. The journal of medical investigation: JMI. 2006; 53(1–2):134–9. doi: 10.2152/jmi.53.134 PMID: 16538006.

9. Tauman R, Ivanenko A, O'Brien LM, Gozal D. Plasma C-reactive protein levels among children with sleep-disordered breathing. Pediatrics. 2004; 113(6):e564–9. doi: 10.1542/peds.113.6.e564 PMID: 15173538.
Kheirandish-Gozal L, Capdevila OS, Tauman R, Gozal D. Plasma C-reactive protein in nonobese children with obstructive sleep apnea and the effects of treatment. Pediatric pulmonology. 2008; 43(1):34–40. doi: 10.1002/ppul.20732 PMID: 18041751.

Tauman R, O’Brien LM, Gozal D. Hypoxemia and obesity modulate plasma C-reactive protein and interleukin-6 levels in sleep-disordered breathing. Sleep Breath. 2007; 11(2):77–84. Epub 2006/12/16. doi: 10.1007/s11325-006-0085-7 PMID: 17171553.

Kheirandish-Gozal L, Capdevila OS, Tauman R, Gozal D. Plasma C-reactive protein in nonobese children with obstructive sleep apnea before and after adenotonsillectomy. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2006; 2(3):301–4. PMID: 17410279; PubMed Central PMCID: PMC1947566.

Barcelo A, Barbe F, Llopart E, Mayoralas LR, Ladaria A, Bosch M, et al. Effects of obesity on C-reactive protein level and metabolic disturbances in male patients with obstructive sleep apnea. The American journal of medicine. 2004; 117(2):118–21. doi: 10.1016/j.amjmed.2004.01.025 PMID: 15234648.

Guilleminault C, Krisoglu C, Ohayon MM. C-reactive protein and sleep-disordered breathing. Sleep. 2004; 27(8):1507–11. PMID: 15683141.

Kaditis AG, Alexopoulos EI, Kalampouka E, Kostadima E, Germenis A, Zintzaras E, et al. Morning levels of C-reactive protein in children with obstructive sleep-disordered breathing. American journal of respiratory and critical care medicine. 2005; 171(3):282–6. doi: 10.1164/rccm.200407-9280OC PMID: 15557130.

Tam CS, Wong M, McBain R, Bailey S, Waters KA. Inflammatory measures in children with obstructive sleep apnoea. Journal of paediatrics and child health. 2006; 42(5):277–82. doi: 10.1111/j.1440-1754.2006.00854.x PMID: 16712558.

Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, et al. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2013; 9(10):1003–12. doi: 10.5664/jcsm.3070 PMID: 24127144; PubMed Central PMCID: PMC3778171.

Kim J, In K, Kim J, You S, Kang K, Shim J, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. American journal of respiratory and critical care medicine. 2004; 170(10):1108–13. doi: 10.1164/rccm.200407-519OC PMID: 15347562.

Shin C, Abbott RD, Lee H, Kim J, Kimm K. Prevalence and correlates of orthostatic hypotension in middle-aged Korean men and women: the Korean Health and Genome Study. Journal of human hypertension. 2004; 18(10):717–23. doi: 10.1038/sj.jhh.1001732 PMID: 15116144.

Shin C, Kim J, Kim J, Lee S, Shim J, In K, et al. Association of habitual snoring with glucose and insulin metabolism in nonobese Korean adult men. American journal of respiratory and critical care medicine. 2005; 171(3):287–91. doi: 10.1164/rccm.200407-906OC PMID: 15542791.

Kim NH, Cho NY, Yun CH, Lee SK, Yoon DW, Cho HJ, et al. Association of obstructive sleep apnea and glucose metabolism in subjects with or without obesity. Diabetes care. 2013; 36(12):3909–15. doi: 10.2337/dc13-0375 PMID: 24101695; PubMed Central PMCID: PMC3836097.

Schulz H. Phasic or transient? Comment on the terminology of the AASM manual for the scoring of sleep and associated events. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2007; 3(7):752. PMID: 18198811; PubMed Central PMCID: PMC2556904.

EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep. 1992; 15(2):173–84. PMID: 11032543.

World Health Organization; International Association for the Study of Obesity; International Obesity Task Force. The Asia Pacific Perspective: Redefining Obesity and Its Treatment. Melbourne, Health Communications Australia. 2000.

Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. Journal of applied physiology. 1986; 60(4):1327–32. PMID: 3700310.

Ryo M, Maeda K, Onda T, Katashima M, Okumiya A, Nishida M, et al. A new simple method for the measurement of visceral fat accumulation by bioelectrical impedance. Diabetes care. 2005; 28(2):451–3. doi: 10.2337/diacare.28.2.451 PMID: 15677816.

Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. American journal of respiratory and critical care medicine. 2005; 172(12):1590–5. doi: 10.1164/rccm.200504-637OC PMID: 16192452; PubMed Central PMCID: PMC2718458.
29. Koenig W, Sund M, Frohlich M, Fischer HG, Lowel H, Doring A, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999; 99(2):237–42. Epub 1999/01/20. doi: 10.1161/01.cir.99.2.237 PMID: 9892589.

30. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet. 1997; 349(9050):462–6. Epub 1997/02/15. S0140673696075915 [pii]. PMID: 9040575.

31. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. The New England journal of medicine. 2000; 342(12):836–43. doi: 10.1056/NEJM200003233421202 PMID: 10733371.

32. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. The New England journal of medicine. 2002; 347(20):1557–65. doi: 10.1056/NEJMoa021999 PMID: 12432042.

33. Hemingway H, Phillipson P, Chen R, Fitzpatrick NK, Damant J, Shipley M, et al. Evaluating the quality of research into a single prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive protein in stable coronary artery disease. PLoS Med. 2010; 7(6):e1000286. Epub 2010/06/10. doi: 10.1371/journal.pmed.1000286 PMID: 20532236; PubMed Central PMCID: PMC2879408.

34. Ho LP, Tang XY, Ling WH, Chen WQ, Chen YM. Early C-reactive protein in the prediction of long-term outcomes after acute coronary syndromes: a meta-analysis of longitudinal studies. Heart. 2010; 96(5):339–46. Epub 2010/03/04. 96/5/339 [pii] doi: 10.1136/hrt.2009.174912 PMID: 20197361.

35. Mugabo Y, Li L, Renier G. The connection between C-reactive protein (CRP) and diabetic vasculopathy. Focus on preclinical findings. Curr Diabetes Rev. 2010; 6(1):27–34. Epub 2009/12/26. BSP/CDR/1159/00000526 27.99976 .18 PMID: 16549947.

36. Kapsimalis F, Varouchakis G, Manousaki S, Daskas S, Nikita D, Kryger M, et al. Association of sleep apnoea-hypopnoea index with obstructive sleep apnoea severity and obesity with insulin resistance, C-reactive protein, and leptin levels in male patients with obstructive sleep apnea. Sleep. 2007; 30(1):29–34. Epub 2007/02/22. PMID: 17310862; PubMed Central PMCID: PMC1978354.

37. Roche F, Gaspoz JM, Picot V, Picard-Kossovsky M, Maudoux D, Garcia A, et al. Association between C-reactive protein and unrecognised sleep-disordered breathing in the elderly. The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology. 2009; 33(4):797–803. Epub 2009/02/14. doi: 10.1183/09031936.00023208 PMID: 19213794.
Lui MM, Lam JC, Mak HK, Xu A, Ooi C, Lam DC, et al. C-reactive protein is associated with obstructive sleep apnea independent of visceral obesity. Chest. 2009; 135(4):950–6. doi: 10.1378/chest.08-1798 PMID: 19225064.

Ishida K, Kato M, Kato Y, Yanagihara K, Kinugasa Y, Kotani K, et al. Appropriate use of nasal continuous positive airway pressure decreases elevated C-reactive protein in patients with obstructive sleep apnea. Chest. 2009; 136(1):125–9. Epub 2009/03/04. doi: 10.1378/chest.08-1431 PMID: 19255295; PubMed Central PMCID: PMC2821285.

Mills PJ, Natarajan L, Ancoli-Israel S, Dimsdale JE. Diurnal variability of C-reactive protein in obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung. 2009; 13(4):415–20. Epub 2009/06/18. doi: 10.1007/s11325-009-0268-0 PMID: 19533192; PubMed Central PMCID: PMC2764070.

Muraki I, Tanigawa T, Yamagishi K, Sakurai S, Ohira T, Imano H, et al. Nocturnal intermittent hypoxia and C-reactive protein among middle-aged community residents: a cross-sectional survey. Thorax. 2010; 65(6):523–7. doi: 10.1136/thx.2009.128744 PMID: 20522850.

Lee LA, Chen NH, Huang CG, Lin SW, Fang TJ, Li HY. Patients with severe obstructive sleep apnea syndrome and elevated high-sensitivity C-reactive protein need priority treatment. Otolaryngology—head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010; 143(1):72–7. Epub 2010/07/14. doi: 10.1016/j.otohns.2010.04.001 PMID: 20620622.

Schiza SE, Mermigkis C, Panagiotis P, Bouloukaki I, Kallergis E, Tzanakis N, et al. C-reactive protein evolution in obstructive sleep apnoea patients under CPAP therapy. European journal of clinical investigation. 2010; 40(11):968–75. Epub 2010/07/16. doi: 10.1111/j.1365-2362.2010.02348.x PMID: 20629709.

Lee LA, Huang CG, Chen NH, Wang CL, Fang TJ, Li HY. Severity of obstructive sleep apnea syndrome and high-sensitivity C-reactive protein reduced after relocation pharyngoplasty. Otolaryngology—head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011; 144(4):632–8. Epub 2011/04/16. doi: 10.1177/1097184011420372 PMID: 21493247.

Guven SF, Turkkani MH, Ciftci B, Ciftci TU, Erdogan Y. The relationship between high-sensitivity C-reactive protein levels and the severity of obstructive sleep apnea. Sleep & breathing = Schlaf & Atmung. 2012; 16(1):217–21. doi: 10.1007/s11325-011-0492-2 PMID: 21331508.

Sharma SK, Mishra HK, Sharma H, Goel A, Sreenivas V, Gulati V, et al. Obesity, and not obstructive sleep apnea, is responsible for increased serum hs-CRP levels in patients with sleep-disordered breathing in Delhi. Sleep medicine. 2008; 9(2):149–56. doi: 10.1016/j.sleep.2007.02.004 PMID: 17638590.

Taheri S, Austin D, Lin L, Nieto FJ, Young T, Mignot E. Correlates of serum C-reactive protein (CRP)—no association with sleep duration or sleep disordered breathing. Sleep. 2007; 30(8):991–6. doi: 10.15965/sleep.1952 PMID: 17702268; PubMed Central PMCID: PMC1978379.

Amardottir ES, Maislin G, Schwab RJ, Staley B, Benediktsdottir B, Olafsson I, et al. The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort. Sleep. 2012; 35(7):921–32. doi: 10.5665/sleep.1952 PMID: 22754038; PubMed Central PMCID: PMC3369227.

Lee JW, Brancati FL, Yeh HC. Trends in the prevalence of type 2 diabetes in Asians versus whites: results from the United States National Health Interview Survey, 1997–2008. Diabetes care. 2011; 34(2):353–7. doi: 10.2337/dc10-0746 PMID: 21216863; PubMed Central PMCID: PMC3024348.

Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darenderlier MA, et al. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep. 2010; 33(8):1075–80. PMID: 20811589; PubMed Central PMCID: PMC2910536.

Coe CL, Love GD, Karasawa M, Kawakami N, Kitayama S, Markus HR, et al. Population differences in proinflammatory biology: Japanese have healthier profiles than Americans. Brain, behavior, and immunity. 2011; 25(3):494–502. doi: 10.1016/j.bbi.2010.11.013 PMID: 21112385; PubMed Central PMCID: PMC3039107.

Larkin EK, Patel SR, Goodloe RJ, Li Y, Zhu X, Gray-McGuire C, et al. A candidate gene study of obstructive sleep apnea in European Americans and African Americans. American journal of respiratory and critical care medicine. 2010; 182(7):947–53. doi: 10.1164/rcrm.201002-0192OC PMID: 20538960; PubMed Central PMCID: PMC2970685.

Kaddis AG, Gozal D, Khalyfa A, Kheirandish-Gozal L, Capdevila OS, Gourgoulianis K, et al. Variants in C-reactive protein and IL-6 genes and susceptibility to obstructive sleep apnea in children: a candidate-gene association study in European American and Southeast European populations. Sleep medicine. 2014; 15(2):228–35. doi: 10.1016/j.sleep.2013.08.795 PMID: 24380782; PubMed Central PMCID: PMC3940286.
61. Baessler A, Nadeem R, Harvey M, Madbouly E, Younus A, Sajid H, et al. Treatment for sleep apnea by continuous positive airway pressure improves levels of inflammatory markers—a meta-analysis. Journal of inflammation. 2013; 10:13. doi: 10.1186/1476-9255-10-13 PMID: 23518041; PubMed Central PMCID: PMC3637233.

62. Peled N, Kassirer M, Shitrit D, Kogan Y, Shiomi D, Berliner AS, et al. The association of OSA with insulin resistance, inflammation and metabolic syndrome. Respiratory medicine. 2007; 101(8):1696–701. doi: 10.1016/j.rmed.2007.02.025 PMID: 17466499.

63. Araujo Lda S, Fernandes JF, Klein MR, Sanjuliani AF. Obstructive sleep apnea is independently associated with inflammation and insulin resistance, but not with blood pressure, plasma catecholamines, and endothelial function in obese subjects. Nutrition. 2015; 31(11–12):1351–7. doi: 10.1016/j.nut.2015.05.017 PMID: 26429854.