NEW RESEARCH

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Serum Inflammatory Markers in Obstructive Sleep Apnea: A Meta-Analysis

Rashid Nadeem, M.D., F.A.A.S.M[1,2]; Janos Molnar, M.D.[2]; Essam M. Madbouly, M.D.[1]; Mahwish Nida, M.D.[3]; Saurabh Aggarwal, M.D.[1]; Hassan Sajid, M.D.[4]; Jawed Naseem, M.D.[5]; Rohit Loomba, M.D.[6]

[1]Captain James A. Lovell Federal Health Care Centre, North Chicago, IL; [2]Rosalind Franklin University of Medicine and Science/ Chicago Medical School, North Chicago, IL; [3]State University of New York, Downstate Medical Center, Brooklyn, NY; [4]McMaster University, Hamilton, Ontario, Canada; [5]University of Karachi, Karachi, Pakistan; [6]Children's Hospital of Wisconsin/Medical College of Wisconsin Affiliated Hospitals, Wauwatosa, WI

SCIENTIFIC INVESTIGATIONS

Study Objectives: Obstructive sleep apnea (OSA) has been linked to and is associated with increased cardiovascular and cerebrovascular morbidity. Ongoing inflammatory responses play an important role in this association. Multiple small size studies addressing the profile of the inflammatory markers in OSA are available therefore we performed a meta-analysis.

Methods: Systematic review of medical literature was conducted using PubMed, Cochrane, and EMBASE databases from 1968 to 2011 by utilizing the key words obstructive sleep apnea, C-Reactive protein, tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM) and Selectins. Inclusion criteria were: full text English articles; studies with adult population; reported values for at least one of the markers of interest; with at least two separate groups (subjects with OSA and control group); OSA was defined as AHI of ≥ 5/h.

Results: Five hundred and twelve studies were reviewed for inclusion with 51 studies pooled for analysis (30 studies for CRP, 19 studies for TNF-α, 8 studies for ICAM, 18 studies for IL-6, six studies for VCAM and 5 studies for Selectins). The levels of inflammatory markers were higher in patients with OSA compared to control group. Standardized pooled Mean differences were calculated to be 1.77 for CRP, 1.03 for TNF-α, 2.16 for IL-6, 4.22 for IL-8, 2.93 for ICAM, 1.45 for Selectins and 2.08 for VCAM.

Conclusions: In this meta-analysis, the levels of systemic inflammatory markers were found to be higher in OSA patients compared to control subjects.

Keywords: Obstructive sleep apnea, inflammatory markers, CRP, TNF-α, ICAM, IL-6, IL-8, VCAM, Selectins

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Obstructive sleep apnea (OSA) is a common disorder affecting about 4% of middle-aged males and 2% of middle-aged women in the developed world[1] and is a significant source of morbidity and mortality.[2] OSA is characterized by recurrent episodes of upper airway collapses during sleep. These recurrent episodes of upper airway collapse usually are accompanied by oxyhemoglobin desaturation and terminated by brief arousals which result in marked sleep fragmentation and chronic excessive daytime sleepiness (EDS).[1,2] As a result, there is an increased expression of systemic inflammatory markers, a sustained activation of the sympathetic nervous system,[3] and derangement in endothelial function.[4] Many of these physiologic and biochemical abnormalities are implicated in the pathogenesis of cardiovascular and cerebrovascular diseases as ongoing inflammatory responses play important roles in atherosclerosis.[5,6]

Obstructive sleep apnea (OSA) has been increasingly linked to cardiovascular and cerebrovascular disease,[7,8] and many studies have shown that OSA is associated with increased cardiovascular and cerebrovascular morbidity.[9-13]

Literatures suggest that an inflammatory etiology, in addition to mechanical factors, may contribute to the pathogenesis of obstructive sleep apnea. Surgical biopsies of the uvula in patients with OSA have demonstrated histological abnormalities, including subepithelial edema and excessive inflammatory cell infiltration[14,15]; and overexpression of interleukin 8 (IL-8) in human bronchial epithelial cells has been seen in response to a vibratory stimulus generated by snoring.[16] Pro-inflammatory cytokines are also up-regulated in patients with OSA.[17-19] In particular, significant elevations in serum levels of tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6) have been seen in patients with obstructive sleep apnea.[20-24,26,29] Many studies have reported that patients with OSA develop systemic inflammation, with increased levels of

BRIEF SUMMARY

Current Knowledge/Study Rationale: Elevated Inflammatory markers are found to be associated with increased atherosclerosis. Multiple small studies provide profile of inflammatory markers in patients with obstructive sleep apnea (OSA).

Study Impact: Levels of systemic inflammatory markers are found to be higher in patients with Obstructive sleep apnea compared to control subjects. This finding suggests that increase inflammatory markers may be the mechanism of increased atherosclerosis in patients with OSA.

mediators of the systemic inflammatory response, including intercellular adhesion molecules (ICAM), coagulation factors (factor VIII, tissue factor), and C-reactive protein (CRP),[26-28] while some studies did not show elevation of CRP in patients with OSA.[30,31]

CRP, an important serum marker of inflammation, is synthesized from the liver and is largely under the regulation of the pro-inflammatory cytokine IL-6.[32] Unlike other cytokines, CRP levels are quite stable in the same individual across 24 hours[33] and may reflect the level of inflammatory response. Epidemiological studies have shown that an elevated CRP level in the high-normal (0.2 to 1.5 mg/dL) range in apparently healthy men and women is a strong predictor of cardiovascular risk.[34,35] In patients with stable angina pectoris, acute coronary artery disease, and a history of myocardial infarction, higher CRP is also associated with future cardiovascular events.[36,37] CRP may play a direct role in initiation and progression of atherosclerosis.[38] Its pro-inflammatory and proatherogenic properties have been found in endothelial cells,[39] vascular smooth muscle cells[40] and monocyte-macrophages and CRP levels are also associated with oxidative stress.[41]

IL-6 is a circulating cytokine known to be secreted from a number of different cells, including activated macrophages and lymphocytes.[44] Inflammation is the main stimulus for IL-6 production, but other stimuli also exist, such as cigarette smoke[44] and adiposity.[45] In normal humans, the hypoxemia of high altitude results in increases in CRP[42,48] and IL-6.[49]

OSA results in repetitive and severe nocturnal hypoxemia and sleep disturbances.[46] The resultant sleep fragmentation and deprivation also induce an increase in cytokines[49] that may underlie inflammatory responses which lead to cardiovascular morbidity.[42]

TNF-α is a pro-inflammatory cytokine which has a significant role in host defense and mediates the pathogenesis of a number of disease processes as atherosclerosis, septic shock, and autoimmune disease.[50] TNF-α has two transmembrane-bound receptors as well as soluble forms that are released by proteolysis of the cell-bound receptor under the control of other inflammatory cytokines (e.g., IL-6, IL-2, IFN-γ), T cell activation, and by TNF-α itself.[50,51]

METHODS

Studies and Endpoint Definitions

Initially, inflammatory markers were selected for study based on review of literature. The following markers were selected: CRP, TNF-α, IL-6, IL-8, ICAM, VCAM, and selectins. Inclusion criteria defined for subsequent study selection were as follows: (1) the study must have been in English, (2) studies with adult population, (3) full text manuscripts had to be available, (4) the study must have reported values for at least one of the markers of interest, (5) the study must have included at least two separate groups with one being a group consisting of individuals with obstructive sleep apnea and the other consisting of individuals without obstructive sleep apnea, (6) OSA was defined as AHI of ≥ 5/h, (7) the study must have reported values in mean and standard deviation or median with range, (8) patient number for all groups must have been reported.

Data Source and Study Selection

Studies for review were found searching the PubMed, Cochrane, and EMBASE databases from January 1, 1968, to December 31, 2011. Unpublished data from scientific meetings were not searched, since most abstract do not provide detail data needed for meta-analysis. Searches were conducted using the previously mentioned inflammatory markers keywords and obstructive sleep apnea. Each inflammatory marker was also searched in its abbreviated forms to ensure that relevant sources were not left out. Additionally, each marker and its abbreviated forms were searched in combination with obstructive sleep apnea. Multiple authors individually searched for and scored manuscripts for inclusion. If manuscripts scored differently by two authors, then it was reviewed by third author to finalize inclusion.

Data Extraction and Statistical Analysis

Studies identified for inclusion then underwent data extraction. Data was extracted at a study level by a single author and then reviewed by a second author to ensure no errors were made. Levels of inflammatory markers were extracted from studies as mean with standard deviation. For studies with data reported in median and range, mean and standard deviation were calculated utilizing methods outlined by Hozo et al.[52]

For studies in which OSA patients were compared with more than one group of control patients (e.g., obese and lean control), each set of data in the study were included in the meta-analysis as a separate data set. For example, Bhushan et al.[53] compared CRP level in obese OSA patients to two control groups, obese control and lean control. Also, Liu et al.,[54] in their work to study the additive effects of obstructive sleep apnea syndrome and hypertension on inflammatory reaction compared the levels of IL-6 and ICAM in hypertensive OSA patients to hypertensive patients, and OSA patients to normal control group. Since there was great heterogeneity in difference of means, we used standardized mean differences, which correct this as it measures how many standard deviation these means values are apart.

Study selection, data extraction and statistical analysis were all done in accordance to previously published methodology for meta-analyses. All statistical analysis was done using Comprehensive Meta Analysis Version 2.

Standardized differences in mean were calculated using a random effects model for all outcomes due to the high level of heterogeneity present. Heterogeneity was assessed by calculating the Cochrane Q statistic. An I^2 statistics was also calculated to help quantify the amount of heterogeneity. An I^2 of 25% to 49% was considered to represent a low level of heterogeneity, 50% to 74% a moderate level, and 75% to 100% a high level.

As mentioned before, for studies with data reported in median and range, mean and standard deviation were calculated utilizing methods outlined by Hozo et al.[52] Measurement units of inflammatory markers we used in the meta-analysis were mg/dL for CRP; pg/mL for IL-6, IL-8, and TNF- α; and ng/mL for ICAM, VCAM, and selectins. If any value of these markers was not reported in the same standard measurement unit that we used, value was converted to the same measurement unit. Also log values were converted to simple numbers as well using standard methods.

RESULTS

The literature was ranked according to the hierarchy of evidence of Sackett et al.[5] A total of 512 studies were reviewed for inclusion. Fifty-one studies met inclusion criteria and were pooled for meta-analysis including 5,736 total subjects (controls [N = 2,784] and OSA subjects [N = 2,952]). A total of 30 studies with 49 datasets including 4,283 subjects were pooled for CRP, while 19 studies with 1,316 subjects pooled for TNF-α, 8 studies with 495 subjects for ICAM, 18 studies with 1,335 subjects for IL-6, 3 studies with 82 subjects for IL-8, 6 studies with 269 subjects for VCAM, and 5 studies with 211 subjects for selectins were pooled and analyzed.

C-Reactive Protein

For CRP, 2 analyses were performed; first with all studies reporting data as sleep apnea patients as one group. Standardized mean difference ranged from -0.50 to 8.58. The pooled mean difference was calculated to be 1.77 (LL 1.28 to UL 2.26, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 31, $p < 0.0001$, $I^2 = 96.4$) (**Figure 1**).[56-68] The second analysis was performed with studies reporting OSA patients in groups (mild, moderate, or severe): standardized mean difference ranged from -0.18 to 8.59. The pooled mean difference was calculated to be 1.07 (LL 0.60 to UL 1.54, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 16, $p < 0.0001$, $I^2 = 88.2$) (**Figure 2**).[69]

TNF-α

For TNF-α, 2 analyses were performed; first with all studies reporting data as sleep apnea patients as one group. Standardized mean difference ranged from -1.18 to 11.4. The pooled mean difference was calculated to be 1.03 (LL 0.67 to UL 1.39, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 18, $p < 0.0001$, $I^2 = 87$) (**Figure 3**). The second analysis with done with studies reporting OSA patients in groups: mild, moderate, or severe. Standardized mean difference ranged from -0.20 to 44.8. The pooled mean difference was calculated to be 6.16 (LL 4.50 to UL 7.81, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 9, $p < 0.0001$, $I^2 = 98.6$) (**Figure 4**).

Interleukin 6

For IL-6, 2 analyses were performed; first with all studies reporting data as sleep apnea patients as one group. Standardized mean difference ranged from -37.55 to 3,700. The pooled mean difference was calculated to be 2.16 (LL 1.62 to UL 2.69,

Figure 1—CRP, one group standardized mean difference, OSA versus controls

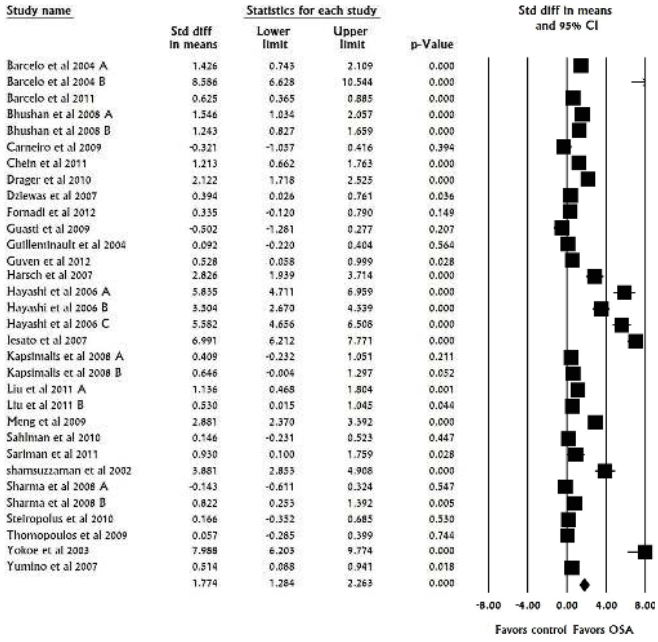


Figure 2—CRP, subgroups (mild, moderate, and severe) standardized mean difference, OSA versus controls

Study name	Subgroup within study	Statistics for each study: Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cofta et al 2009	Mild	-0.074	0.378	0.143	-0.815	0.667	-0.195	0.846
Cofta et al 2009	Moderate	0.515	0.391	0.153	-0.253	1.282	1.315	0.189
Cofta et al 2009	Severe	0.422	0.389	0.152	-0.341	1.185	1.084	0.278
Kanbay et al 2010	Mild	0.534	0.329	0.108	-0.110	1.178	1.626	0.104
Kanbay et al 2010	Moderate	0.758	0.283	0.080	0.204	1.313	2.681	0.007
Kanbay et al 2010	Severe	0.848	0.244	0.059	0.370	1.325	3.481	0.000
Peled et al 2007	Mild	-0.186	0.472	0.223	-1.112	0.740	-0.393	0.694
Peled et al 2007	Moderate	0.016	0.385	0.148	-0.739	0.770	0.040	0.968
Peled et al 2007	Severe	0.518	0.364	0.132	-0.195	1.230	1.424	0.155
Zhao et al 2011	Mild	0.066	0.245	0.060	-0.414	0.546	0.270	0.787
Zhao et al 2011	Moderate	0.436	0.254	0.065	-0.063	0.934	1.714	0.087
Zhao et al 2011	Severe	0.824	0.276	0.076	0.283	1.365	2.987	0.003
Ryan et al 2006	mild+moderate	1.415	0.278	0.077	0.870	1.960	5.090	0.000
Ryan et al 2006 A	Severe	1.764	0.302	0.091	1.173	2.356	5.845	0.000
Ryan et al 2006 B	Severe	3.790	0.518	0.268	2.775	4.804	7.321	0.000
Yokoe et al 2003	Mild	2.727	0.535	0.286	1.679	3.776	5.099	0.000
Yokoe et al 2003	mod severe	8.596	1.150	1.322	6.342	10.849	7.476	0.000
		1.075	0.242	0.058	0.601	1.548	4.449	0.000

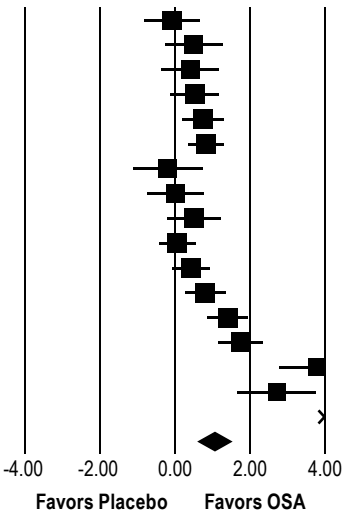


Figure 3—TNF-α, one group standardized mean difference, OSA versus controls

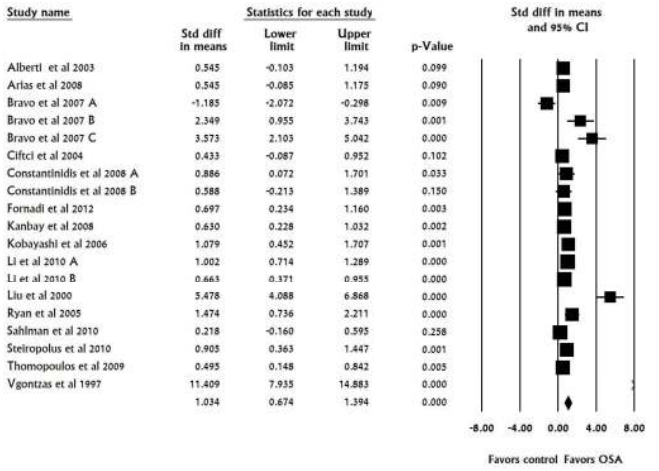


Figure 5—IL-6, one group standardized mean difference, OSA versus controls

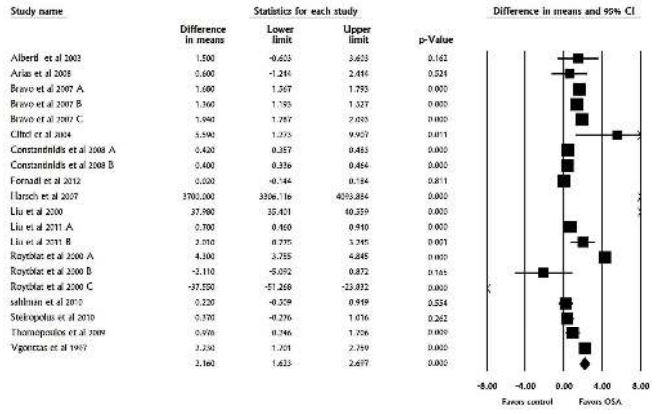
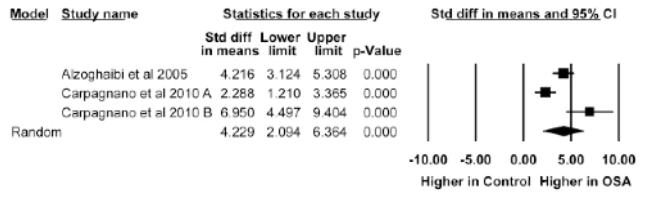


Figure 7—IL-8, standardized mean difference, OSA versus controls



$p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 12, $p < 0.0001$, $I^2 = 96$) (**Figure 5**). The second analysis with performed with studies reporting OSA patients in groups: mild, moderate, or severe. Standardized mean difference ranged from 0.14 to 11.58. The pooled mean difference was calculated to be 2.80 (LL 1.70 to UL 3.89, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 19, $p < 0.0001$, $I^2 = 96$) (**Figure 6**).

Interleukin 8

For IL-8, standardized mean difference ranged from 2.21 to 6.95. The pooled mean difference was calculated to be 4.22 (LL 2.09 to UL 6.36, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 2, $p < 0.0001$, $I^2 = 85$) (**Figure 7**).

Figure 4—TNF-α, OSA subgroups (mild, moderate, and severe) standardized mean difference, OSA versus controls

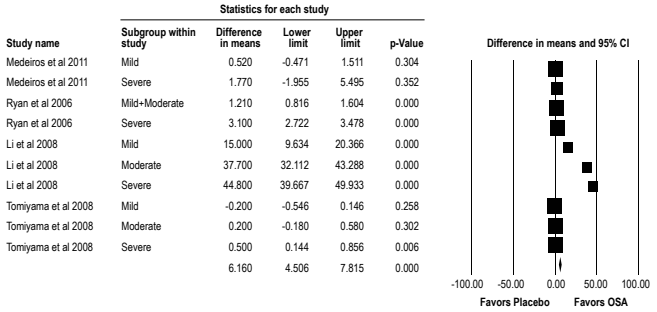
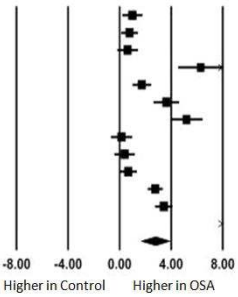


Figure 6—IL-6, subgroups (mild, moderate, and severe) standardized mean difference, OSA versus controls

Study Name	Subgroup	Std Dif	LL	UL	P
Medeiros 2011	Mild	0.994	0.236	1.753	0.01
Medeiros 2011	Severe	0.771	0.148	1.394	0.015
Yokoe 2003	Mild	0.623	-0.15	1.396	0.114
Yokoe 2003	Severe	6.288	4.57	8.005	0.00
Li 2008	Mild	1.723	1.031	2.415	0.00
Li 2008	Moderate	3.618	2.658	4.577	0.00
Li 2008	Severe	5.193	3.985	6.402	0.00
Tomiyama 2008	Mild	0.146	-0.655	0.947	0.721
Tomiyama 2008	Moderate	0.388	-0.378	1.154	0.321
Tomiyama 2008	Severe	0.669	0.026	1.312	0.041
Ye 2010	Mild	2.766	2.202	3.33	0.00
Ye 2010	Moderate	3.429	2.78	4.077	0.00
Ye 2010	Severe	11.581	9.904	13.259	0.00
Random Effect		2.801	1.706	3.897	0.00



Intercellular Adhesion Molecule

For ICAM, standardized mean difference ranged from 1.02 to 12.37. The pooled mean difference was calculated to be 2.93 (LL 1.92 to UL 3.95, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 11, $p < 0.0001$, $I^2 = 94.7$) (**Figure 8**).

Selectins

For selectins, standardized mean difference ranged from -0.07 to 4.44. The pooled mean difference was calculated to be 1.45 (LL 0.67 to UL 2.22, $p < 0.0001$). There was heterogeneity in this endpoint (df (Q) 6, $p < 0.0001$, $I^2 = 87$) (**Figure 9**).

VCAM

For VCAM, standardized mean difference ranged from -1.69 to 3.66. The pooled mean difference was calculated to be 2.08 (LL 0.55 to UL 3.62, $p < 0.008$). There was heterogeneity in this endpoint (df (Q) 6, $p < 0.0001$, $I^2 = 95.4$) (**Figure 10**).

Meta-Regression to Evaluate the Effect of Age, BMI, and AHI on Markers

All of 10 analyses described above were re-analyzed by meta-regression for age, BMI, and AHI. We performed total 30 meta-regression analyses to evaluate the effect of age, BMI, and AHI on levels of CRP, TNF-α, IL-6, IL-8, ICAM, selectins, and VCAM. Each parameter was found be significantly

Figure 8—ICAM standardized mean difference, OSA versus controls

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study						
Bravo et al 2007 A	5.177	0.511	0.261	4.175	6.179	10.125	0.000
Bravo et al 2007 B	4.508	0.581	0.337	3.369	5.646	7.761	0.000
Bravo et al 2007 C	4.638	0.557	0.310	3.547	5.729	8.333	0.000
Carpagnano et al 2010 A	2.132	0.535	0.287	1.083	3.182	3.983	0.000
Carpagnano et al 2010 B	12.373	2.116	4.478	8.226	16.520	5.847	0.000
El Solh et al 2002	1.483	0.412	0.170	0.675	2.291	3.598	0.000
Harsch et al 2007	0.406	0.324	0.105	-0.229	1.040	1.253	0.210
Liu et al 2011 A	3.377	0.493	0.243	2.412	4.343	6.857	0.000
Liu et al 2011 B	2.266	0.316	0.100	1.646	2.887	7.161	0.000
Ogha et al 1999	3.718	0.917	0.841	1.921	5.516	4.054	0.000
Ursavas et al 2007	1.026	0.250	0.062	0.537	1.515	4.112	0.000
Zamarron-Sanz et al 2006	0.313	0.222	0.049	-0.122	0.749	1.411	0.158
	2.938	0.518	0.268	1.922	3.953	5.672	0.000

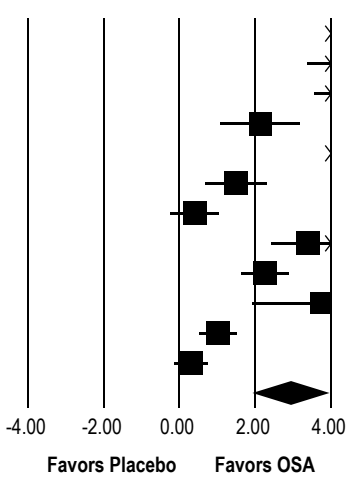
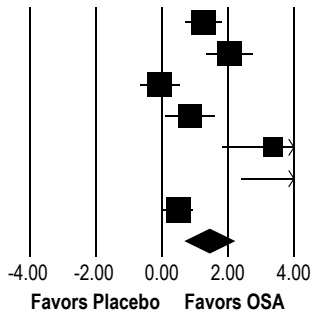


Figure 9—Selectins, standardized mean difference, OSA versus controls

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study						
Bravo et al 2007 A	1.259	0.285	0.081	0.700	1.817	4.414	0.000
Bravo et al 2007 B	2.037	0.359	0.129	1.334	2.741	5.674	0.000
Bravo et al 2007 C	-0.071	0.309	0.096	-0.676	0.535	-0.228	0.819
El Solh et al 2002	0.847	0.381	0.145	0.100	1.594	2.222	0.026
Htoo et al 2006	3.354	0.778	0.605	1.829	4.879	4.310	0.000
Ogha et al 1999	4.446	1.034	1.070	2.419	6.474	4.299	0.000
Zamarron-Sanz et al 2006	0.491	0.224	0.050	0.052	0.931	2.192	0.028
	1.450	0.395	0.156	0.676	2.223	3.672	0.000



effecting inflammatory markers level in OSA subjects ($p < 0.05$; **Figure 11** for effect of age on CRP levels; **Figure 12** for BMI effect on CRP levels; **Figure 13** for AHI effect on CRP levels). Effect of age (B 0.0142, SE 0.006, $p < 0.0234$), BMI (B -0.041, SE 0.013, $p < 0.001$), and AHI (B 0.0128, SE 0.0039, $p < 0.0009$) was modest (**Table 1**).

DISCUSSION

The present meta-analysis (MA) showed that there is an increase in levels of inflammatory markers in subjects with OSA including CRP, TNF α, IL-6, IL-8, ICAM, VCAM, and selectins. This effect is positively influenced by severity of OSA—the higher the AHI, the higher the levels.

C-Reactive Protein

This meta-analysis shows that patients with OSA had a statistically significant higher level of CRP when compared to control individuals. There are conflicting results for the association between obstructive sleep apnea and elevated CRP levels. Most studies evaluating sleep disordered breathing patients have found higher levels of inflammatory markers, including CRP, in patients with OSA, compared with age- and body mass index (BMI)-matched controls.[26,27,53,57] Our meta-regression plots also showed the modest but significant effect of age, BMI, and AHI on all inflammatory markers including CRP.

Yokoe et al.,[26] Shamsuzzaman et al.,[27] Bhushan et al.,[53] Drager et al,[71] and Guven et al.[72] have found OSAS to be a potential driver of elevated CRP levels independent of BMI. A number of others studies have not found this relation; instead, they found obesity, rather than sleep apnea or nocturnal hypoxemia, to be the key predictor of elevated CRP among OSA patients.[30,49,73,74] Barcelo et al.[30] found that CRP levels were significantly higher in obese OSA patients when compared to non-obese OSA patients and normal control.

In a cross-sectional study by Sharma et al.[73] to determine whether obesity or OSA is responsible for increased serum levels of CRP in patients with sleep disordered breathing, they found that CRP levels were higher in obese non apneic patients when compared to apneic patients. They have concluded that obesity and not OSA was associated with elevated serum levels of high sensitivity CRP (hs-CRP), and there was no independent

Figure 10—VCAM, standardized mean difference, OSA versus controls

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study						
El Solh et al 2002	1.119	0.393	0.154	0.349	1.889	2.850	0.004
Harsch et al 2007	-1.693	0.373	0.139	-2.425	-0.961	-4.535	0.000
Htoo et al 2006	2.982	0.729	0.532	1.553	4.412	4.089	0.000
Liu et al 2011 A	2.993	0.460	0.212	2.091	3.895	6.501	0.000
Liu et al 2011 B	2.462	0.326	0.106	1.824	3.100	7.558	0.000
Ogha et al 1999	3.338	0.859	0.738	1.654	5.021	3.885	0.000
Ursavas et al 2007	3.661	0.383	0.147	2.910	4.412	9.553	0.000
	2.088	0.783	0.614	0.553	3.623	2.666	0.008

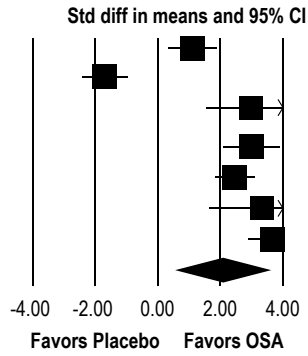
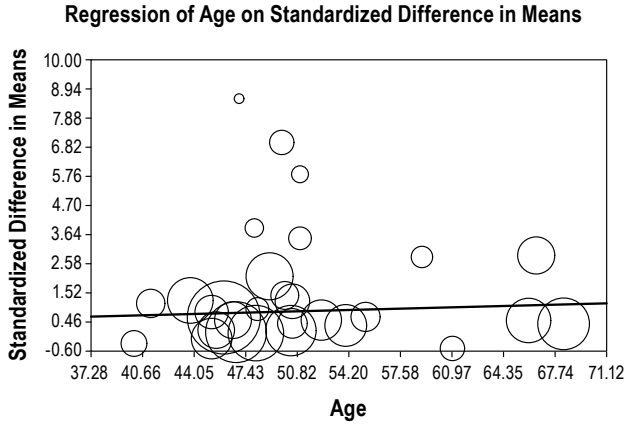
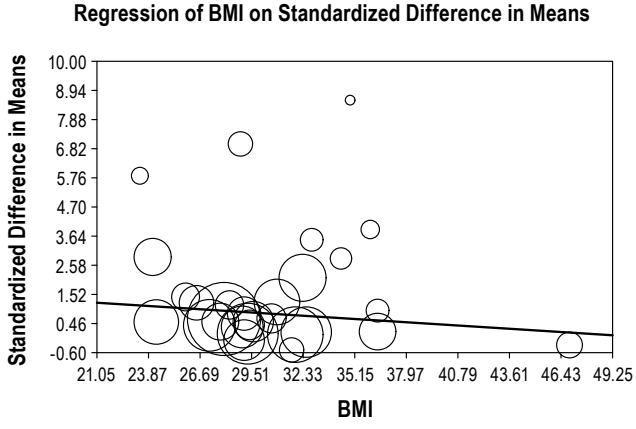


Figure 11—CRP, one group standardized mean difference, meta-regression age



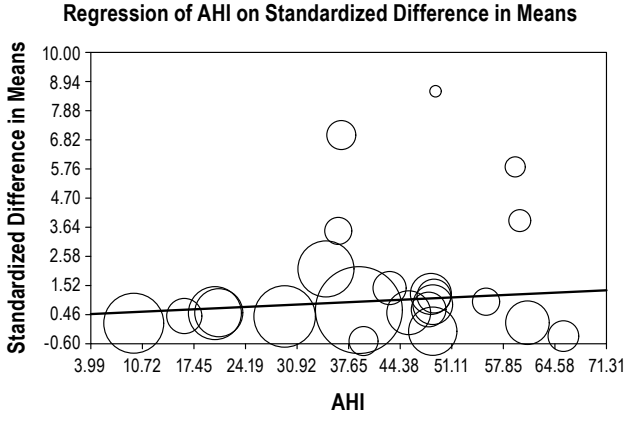
Size of circles is proportional to the weight of the studies.

Figure 12—CRP, one group standardized mean difference, meta-regression BMI



Size of circles is proportional to the weight of the studies (excluding one outlier study with BMI 46.43 did not change the significance level).

Figure 13—CRP, one group standardized mean difference, meta-regression AHI



Size of circles is proportional to the weight of the studies.

correlation found between severity of OSA and hs-CRP.[73] This meta-regression analysis showed modest but significant effect of BMI on inflammatory markers. In contrast, Guilleminault et al.[49] found that mean serum level of CRP was normal in obstructive sleep apnea syndrome (OSAS), upper airway resistance syndrome (UARS), and normal controls. Also, they found that CRP levels were significantly correlated with body mass index and esophageal pressures, and only body mass index was significantly associated with high CRP values.[49]

To determine the cardiovascular risk markers in obstructive sleep apnea syndrome and correlation with obesity, Ryan et al.[74] investigated the levels of CRP in carefully selected patients with OSAS and matched normal controls. They found that levels of CRP were similar in non-OSAS patients, patients with mild/moderate OSAS, and severe OSAS, but were significantly higher in obese severe OSAS patients. They have concluded that CRP levels are not associated with OSAS severity in men, but CRP is independently associated with obesity.[81]

Fornadi et al.,[75] in a cross-sectional study of 100 randomly selected kidney transplant patients (25 with OSA and 75 without OSA) found no significant difference in the levels of CRP between patients with OSA and those without OSA, and there was no significant correlation between AHI and CRP.[75]

Table 1—Meta-regression for age, BMI, and AHI for all inflammatory markers

	Age			BMI			AHI		
	slope	intercept	p	slope	intercept	p	slope	intercept	p
CRP	0.01	0.12	0.02	-0.04	2.09	0.001	0.01	0.43	0.001
TNF	-0.04	3.08	0.01	-0.005	0.88	0.83	0.01	0.07	0.001
IL-6	0.004	0.62	0.82	-0.0009	0.83	0.97	0.02	0.17	0.001
IL-8	0.73	-32.3	0.001	-0.28	14.49	0.001	0.02	2.35	0.45
ICAM	-0.08	6.26	0.001	-0.09	4.63	0.01	0.03	0.55	0.26
VCAM	-0.17	10.99	0.001	-0.23	8.98	0.001	0.03	1.00	0.04
Selectins	-0.03	2.82	0.29	0.04	-0.49	0.53	0.02	-0.05	0.16

Muraki et al.[76] investigated whether nocturnal intermittent hypoxia, as surrogate marker for obstructive sleep apnea, was associated with CRP levels among a community-dwelling Japanese population. In their cross-sectional study involving 3,888 subjects (2,466 females and 1,422 males); they found that nocturnal hypoxia to be an independent predictor of raised serum CRP levels. Also, Yao et al.[77] documented that sleep disordered breathing (SDB) was associated with increased levels of CRP, especially in non-overweight men. However, a major limitation of these trials was the use of home nocturnal oximetry and oxygen desaturation index (ODI) as the sole diagnostic modality for OSAS.[77]

In contrast, Taheri et al.[78] found no significant association between CRP levels and measures of sleep duration (polysomnographic and self-reported). No independent relationship between CRP levels and indices of SDB was observed in 907 adults enrolled in the Wisconsin sleep cohort who underwent inpatient polysomnography, and they concluded that lack of an independent association between CRP levels and SDB suggests that the reported relationship between these two variables may be primarily driven by their association with obesity.[78]

Interleukin 6

Our meta-analysis shows that patients with OSA had higher levels of IL-6 than control individuals. As mentioned before, IL-6 is responsible for CRP production by the liver. Also, it is abundantly produced by visceral adipose tissue in obese individuals. As with CRP, many case control and cross-sectional studies found IL-6 is higher in patients with OSAS, and a significant correlation between IL-6 and AHI was present,[22,26,54,79,80] while other studies found that the production of IL-6 is positively correlated to BMI.[23,80]

On the other hand, some other studies controverted these findings. Mehra et al.[81] found that the participants with moderate to severe sleep related breathing disorder (SRBD) had significantly higher morning and evening IL-6 levels than those without sleep apnea; however, these differences were not statistically significant after adjustment for subject characteristics. They concluded that SRBD was not significantly associated with morning IL-6 levels.

Intracellular Adhesion Molecules

Circulating adhesion molecules have been linked to endothelial dysfunction that is involved in vascular complications associated with obstructive sleep apnea, as these molecules facilitate the interaction between lekcocytes and the vascular endothelium. The role of adhesion molecules and its relation to OSAS patients has been evaluated in a number of studies. In the current meta-analysis, ICAM was found to be higher in OSA patients than the control group. In many studies, ICAM-1 (intercellular adhesion molecule 1) was found to be higher in patients with OSAS[60,82,83] and its level correlated with OSAS severity, particularly with nocturnal hypoxemia.[82,83]

Tumor Necrosis Factor-α

In our meta-analysis, TNF- α was higher in patients with OSA than control individuals. Meta-regression also showed the same modest trend of significant influence of age, BMI, and AHI. Many studies have found that patients with OSAS have higher level of TNF-α,[20,22,23,79,85-87] and the level of TNF-α was correlated to OSA severity and nocturnal hypoxemia.[22,23,80,85] On the other hand, Fornadi et al. did not find any significant difference in TNF-α level in 100 randomly selected kidney transplant patients, and there was no significant correlation with AHI.[75]

IL-8, Selectins, and VCAM

Although fewer data were available on these markers, analysis still showed significantly higher levels in subjects with OSA. Meta-regression also showed the same modest trend of significant influence of age, BMI, and AHI on these marker levels.

Several limitations of this meta-analysis should be emphasized. Firstly, available literature is largely low-level evidence. Secondly, many of the relevant studies regarding the association between OSAS and level of inflammatory markers were cross-sectional in nature, so the temporal relationships between these two factors were unclear. Thirdly, there was some variation in the way in which inflammatory markers were sampled and analyzed. In most of the studies, detection of the plasma level of inflammatory markers was done using a commercially available enzyme linked immunosorbent assay (ELISA). Particle-enhanced immunonephelometry, latex particle-enhanced immunoturbidimetric assay, and chemiluminescent assay were other techniques used for detection of CRP. Despite of these variations in the methods of detection of inflammatory markers, we believed it was reasonable to pool the data retrieved from these studies, as most of the studies reported that the coefficient of variation for intra- and inter-assay to be 1.5% to 9.0% and 3.0% to 10%, respectively, for most of inflammatory markers. There was also heterogeneity in the sample populations across

Table 2—Tests of heterogeneity and publication bias

	Results		Test of Heterogeneity				Publication Bias		
	Z-value	p-value	Q-value	df (Q)	I^2	Tau^2	Funnel plot	Egger's test p	Result
CRP w Subgroups	4.4	0.000	135.1	16	88.2	0.832	Suspect	0.024	Yes
CRP One group	7.1	0.000	862.0	31	96.4	1.857	Yes	0.000	Yes
TNF-α w Subgroups	3.6	0.000	147.3	9	93.9	2.190	No	0.057	No
THF-α One group	5.6	0.000	139.0	18	87.0	0.484	Yes	0.03	Yes
ICAM One group	5.7	0.000	205.6	11	94.7	2.825	Possible	0.001	Yes
IL-6 Subgroups	5.0	0.000	300.5	12	96.0	3.821	Yes	0.021	Yes
IL-6 One group	6.2	0.000	489.6	19	96.1	3.143	Yes	0	Yes
IL-8	3.9	0.000	14.1	2	85.8	2.920	No	0.455	No
Selectins One group	3.7	0.000	46.5	6	87.1	0.859	Yes	0.05	Yes
VCAM One group	2.7	0.008	130.8	6	95.4	4.016	No	0.603	No

the studies. Funnel plots suggest heterogeneity and publication bias for CRP, TNF-α, IL-6, and ICAM, but not for IL-8 or VCAM (**Table 2**). Even within the OSAS group, some subjects were selected on the basis of body weight or body mass index, gender, comorbidities, or severity of OSAS, and, as such, may not represent the general population with OSAS. We could not perform meta-regression for other confounding factors—sleepiness, presence of hypertension, or measures of visceral adipose tissue—since we did not have data on these variables. These factors have been found to be associated with elevated inflammatory markers.[88]

Another weakness of our meta-analysis is that all papers written in languages other than English were excluded, and we relied entirely on published studies, which raise the possibility of publication bias. However, despite all these variations, it was reassuring that in nearly all studies (regardless of sample size and composition of the study and control groups), those with OSAS, on average, had higher levels of systemic inflammatory markers than healthy controls. This suggests that selection and sampling biases were unlikely to be responsible for the observed associations.

In summary, there appears to be some evidence indicating higher levels of markers of systemic inflammation in patients with OSAS; these levels may be correlated to the level of severity of disease in these patients. These findings may explain, at least in part, the mechanism for atherosclerosis leading to cardiovascular disorder in patients with OSA and the common occurrence of systemic complications among these patients. Future studies are needed to further explore the role of these markers as disease associated markers for progression or monitoring of prognosis of disease or to evaluate the correlation between the level of these markers and severity of OSAS and to determine whether levels of systemic inflammatory markers can be modified by therapeutic interventions in these patients.

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Address correspondence to: Rashid Nadeem, James A. Lovell Federal Health Care Centre, 3001 Green Bay Road, North Chicago, IL, 60064; Tel: (224) 610-8275; Fax: (847) 610-8278; E-mail: rashid.nadeem@va.gov

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