

Review

Evaluation of Blood Levels of Omentin-1 and Orexin-A in Adults with Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis

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Citation: Mohammadi, I.; Sadeghi, M.; Tajmiri, G.; Brühl, A.B.; Sadeghi Bahmani, L.; Brand, S. Evaluation of Blood Levels of Omentin-1 and Orexin-A in Adults with Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. *Life* **2023**, *13*, 245. <https://doi.org/10.3390/life13010245>

Academic Editor: Larry D. Sanford

Received: 27 November 2022

Revised: 29 December 2022

Accepted: 10 January 2023

Published: 16 January 2023



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Abstract: Background and objective: Obstructive sleep apnea (OSA) can be related to changes in the levels of adipokines and neuropeptides, which in turn may affect the energy balance components of neuronal cells. Herein, a systematic review and meta-analysis checked the changes in serum/plasma levels of omentin-1 (OM-1: an adipokine) and orexin-A (OXA: a neuropeptide) in adults (age > 18 years old) with OSA (aOSA) compared to controls. Materials and methods: Four databases (Cochrane Library, PubMed, Web of Science, and Scopus) were systematically searched until 14 November 2022, without any restrictions. The Joanna Briggs Institute (JBI) critical appraisal checklist adapted for case-control studies was used to assess the quality of the papers. The effect sizes were extracted using the Review Manager 5.3 software for the blood levels of OM-1 and OXA in aOSA compared with controls. Results: Thirteen articles, with six studies for OM-1 levels and eight for OXA levels, were included. The pooled standardized mean differences were -0.85 (95% confidence interval (CI): $-2.19, 0.48$; $p = 0.21$; $I^2 = 98\%$) and -0.20 (95%CI: $-1.16, 0.76$; $p = 0.68$; $I^2 = 96\%$) for OM-1 and OXA levels, respectively. Among the studies reporting OM-1, five were high and one was moderate quality. Among the studies reporting OXA, six were moderate, one was high, and one was low quality. Based on the trial sequential analysis, more participants are needed to confirm the pooled results of the analyses of blood levels of OM-1 and OXA. In addition, the radial plot showed outliers as significant factors for high heterogeneity. Conclusions: The main findings indicated a lack of association between the blood levels of OM-1 and OXA and OSA risk. Therefore, OM-1 and OXA did not appear to be suitable biomarkers for the diagnosis and development of OSA.

Keywords: omentin protein; orexins; serum; plasma; meta-analysis

1. Introduction

Obstructive sleep apnea (OSA) is a status determined by repeated episodes of partial or complete airway obstruction during sleep [1,2], which usually remains undiagnosed and

untreated [3]. A systematic review in 2017 reported that the overall prevalence of any OSA ranged from 9% to 38% in the general adult population, from 13% to 33% and 6% to 19% in females and males, respectively, while the overall prevalence increases in older adults [4]. The global prevalence of moderate to severe OSA is approximately 20% [5]. Clinically, the apnea-hypopnea index (AHI) provides well-established and useful cutoff-values which can be applied to diagnose both the OSA severity and to assess the effects of interventions [6,7]. A diagnosis using polysomnography (PSG: the gold standard test for diagnosing OSA) [8,9] with an AHI ≥ 5 is considered indicative of OSA among adults [8,10,11].

Several factors including environmental and genetic factors, and even internal conditions (hormones, cytokines, and other biomarkers), might lead to the emergence and maintenance of OSA. Smoking [12] and alcohol consumption [13], and alterations in the blood levels of intercellular adhesion molecule-1 [14], monocyte chemoattractant protein-1 [15], adiponectin [16], C-reactive protein [17], cortisol [18], interleukin-6 [19], tumor necrosis factor-alpha [20], astrocytic protein (S100B) [21], neuron-specific enolase [21], and polymorphisms [22–24] were observed among adults with OSA, compared to healthy controls.

Furthermore, OSA is linked to other diseases such as diabetes, hypertension, cardiovascular diseases, congestive heart failure, and stroke [25,26]; therefore, OSA can be seen as a risk factor for other diseases. As such, the evaluation and treatment of OSA should focus on the recognition of patients at risk of OSA [27]. Obesity is the highest risk factor for OSA and it is estimated that 58% of moderate-to-severe OSA development can be attributed to obesity [28]. Continuous positive airway pressure is still the main treatment for patients with OSA because of its effect on the symptoms and on quality of life [29,30].

Obesity—an energy balance disorder—is associated with a positive energy balance, understood as an imbalance between higher energy storage and energy consumption [31,32]. Orexin-A (OXA or hypocretin-1) is a neuropeptide that plays a role in appetite [33], sleep, and arousal arrangement [34]. OXA can play a role in obesity [35]. The adipocytokine omentin-1 (OM-1 or intelectin-1) is expressed in visceral adipose tissue and is related to the inflammatory response [36]. The reduced serum levels of OM-1 are linked with obesity and type 2 diabetes mellitus (T2DM) [37]. OM-1 may be necessary for holding the energy balance in a time of insulin resistance pathogenesis and T2DM [38]. The energy balance components can be affected by OSA and thus allow clinicians to more effectively guide overall therapeutic approaches to optimize weight loss and promote cardiovascular health in individuals with OSA [39].

A number of studies have evaluated the association between blood OM-1 [40,41] and OXA [42,43] levels in adults with OSA (aOSA) compared to controls, but there were different and, above all, contrasting results. In addition, based on our knowledge, there was no previous meta-analysis in the English-language literature. Therefore, we designed a systematic review and meta-analysis evaluating the association between blood OM-1 and OXA levels in aOSA versus controls.

2. Materials and Methods

To design the present meta-analysis, the PRISMA-P items [44] were followed. The PECO question [45,46] was: Are blood OM-1 and OXA levels different in aOSA in comparison with controls? (P: human adults with/without OSA, E: OSA disorder, C: aOSA in comparison with controls; and O: the plasma/serum levels of OM-1 or OXA).

2.1. Search Strategy

The databases of Cochrane Library, PubMed, Web of Science, and Scopus were comprehensively searched by one author (M.S.) until 14 November 2022, without any restrictions. The search terms were: (“obstructive sleep apnea” or “OSA” or “sleep apnea” or “obstructive sleep apnea-hypopnea syndrome” or “OSAHS” or “obstructive sleep apnea syndrome” or “OSAS”) AND (“hypocretin” or “orexin-A” or “OXA” or “omentin-1” or “OM-1” or “intelectin-1”). The citations of any article linked to the subject and the databases of “Google Scholar”, “Elsevier publishers”, and “BMJ publishers” were checked so that no study was

missed. Two authors working independently (M.S. and I.M.) were responsible for removing irrelevant articles and excluding articles with reasons. There was no disagreement.

2.2. Eligibility Criteria

Inclusion criteria: (1) Studies involving both groups of adults (aOSA and controls); (2) Both groups had no treatment during sampling; (3) In both groups, participants were 18 years old or older, with no restrictions on BMI values; (4) Studies reporting plasma/serum hypocretin, orexin-A, omentin-1, or interlectin-1 levels in OSA and controls; (5) PSG was used for diagnosing OSA; (6) OSA in adults was defined as an AHI ≥ 5 events/h; (7) Participants included in the studies did not report other systemic diseases (cardiovascular diseases; diabetes mellitus; infectious diseases; any malignancy; heart, renal, and hepatic failures; lung diseases; and other sleep disorders); (8) Controls had no OSA or systemic diseases (see the previous criterion); (9) Venous blood was taken in a fasting state in the morning to measure OM-1 and OXA levels. Exclusion criteria: (1) Meta-analyses, letters to the editor, book chapters, conference papers, reviews, and commentaries; (2) Studies with a lack of complete data; (3) Studies with no control group.

2.3. Data Collection

The data were extracted for any study by one author (I.M.), including the country and ethnicity of participants, the first author, the publication year, OM-1 and OXA sampling, the sample size of both groups (aOSA and controls), mean BMI, mean age and mean AHI of two groups, quality or quality score, and mean serum/plasma levels of OM-1 and OXA in two groups. Another author (G.T) re-checked the process of extraction; in case of disagreements between the two authors' decisions, a discussion between all three authors resolved the issue.

2.4. Quality Assessment

Two authors (M.S. and S.B.) independently evaluated the quality based on the Joanna Briggs Institute (JBI) critical appraisal checklist adapted for case-control studies including ten questions or ten scores. Low-quality studies had a score of 1–4; moderate-quality studies, 5–7; and high-quality studies: 8–10 [47] (See Supplementary Materials).

2.5. Statistical Analyses

The statistical analyses were performed by one author (M.S.). The standardized mean difference (SMD) and 95% confidence interval (CI) of blood levels of OM-1 and OXA amongst aOSA and controls were extracted using the Review Manager 5.3 (RevMan 5.3; the Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark) software. A significant value was considered when the p -value (2-sided) was less than 0.05. The significant heterogeneity was considered while $P_{\text{heterogeneity}} < 0.1$ ($I^2 > 50\%$) and in the state, the analysis was performed in a random-effect model [48]; otherwise, it was performed in a fixed-effect model [49]. In addition, the radial plot result was reported to confirm or reject the heterogeneity due to outliers among the studies.

The subgroup and mixed-effect meta-regression analyses were based on several variables, and the stability of initial pooled SMDs was assessed by both "one-study-removed" and "cumulative" analyses as sensitivity analyses.

Begg's and Egger's tests were applied to test the potential publication bias [50] and to report the degree of asymmetry [51], respectively; the data for publication bias and sensitivity analyses were extracted using the Comprehensive Meta-Analysis version 2.0 (CMA 2.0; Biostat Inc., Englewood, NJ, USA) software, with a p -value (2-sided) less than 0.10 recommending the existence of the significant publication bias.

To report the potential random error (false-positive and -negative results) in the meta-analysis [52], trial sequential analysis (TSA) was accomplished using TSA software (version 0.9.5.10 beta) (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark) [53]. The futility threshold could show a no-impact

result before attaining the information size. To calculate the required information size (RIS), an α -risk of 5%, β -risk of 20%, and two-sided border type were used to extract the mean difference and variance according to the empirical assumptions created by the TSA software automatically. If the Z-curve reached the RIS line, enough participants were included in the studies, the conclusions were reliable or crossed the boundaries, and the results could be strong. On the other hand, the volume of information was not large enough and more evidence was needed.

Some studies reported the effect sizes based on median and 25th–75th percentiles [54] or median (min-max) [55], and in the state, we changed them to the mean (standard deviation) based on just entering the format into the software.

All authors checked the last version of the article and the disagreement was resolved by a discussion between them.

3. Results

3.1. Study Selection

To search the databases, 716 records were extracted, and after removing duplicates and irrelevant records, 26 full-text articles were assessed using the eligibility criteria. Then, 13 full-text articles were removed for different reasons (Figure 1). Finally, 13 articles including 6 studies reporting blood OM-1 levels and 9 reporting OXA levels entered the meta-analysis.

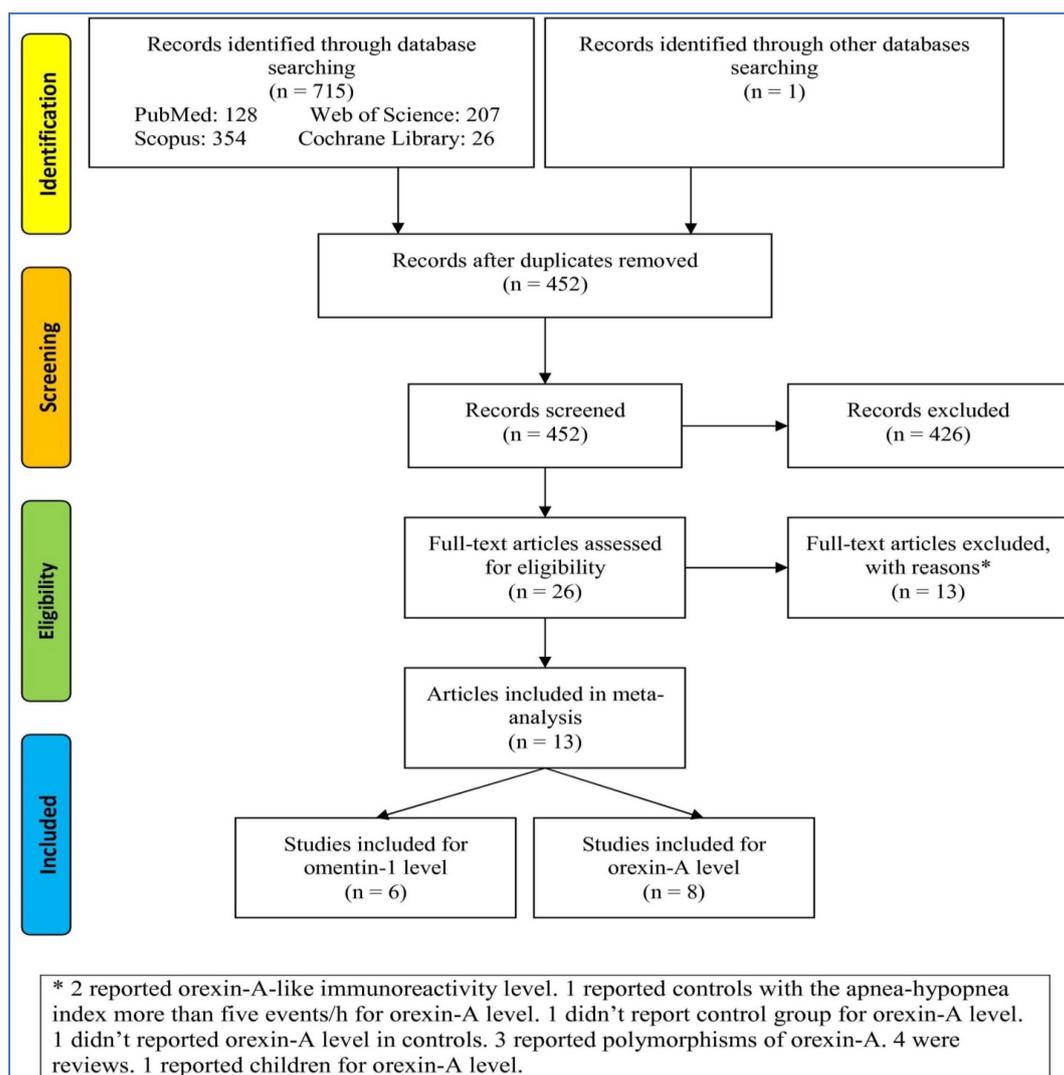


Figure 1. Flowchart of the study selection. * The reasons of exclusion of full-text articles.

3.2. Characteristics of Studies

Table 1 reports the data for the variables of fourteen studies from the thirteen articles [40–43,56–64] included in the meta-analysis. With regard to the studies reporting OM-1 levels, four were reported among Caucasians and two among Asians, and for the studies reporting OXA levels, three were among Caucasians and five among Asians. For OM-1, three studies reported plasma and three reported serum levels; however, for OXA, seven reported plasma levels and one reported the serum level.

Table 1. Characteristics of the studies.

| First Author, Publication Year | Country | Ethnicity | Case | | | Control | | | Sample | Measured Factor | | |
|--------------------------------|---------|-----------|--------|-----------------|-----------------------------|--------------------|--------|-----------------|--------|-----------------|-----------------------------|--------------------|
| | | | Number | Mean Age, Years | Mean BMI, kg/m ² | Mean AHI, events/h | Number | Mean Age, Years | | | Mean BMI, kg/m ² | Mean AHI, events/h |
| Igarashi, 2003 [57] | Japan | Asian | 30 | 45.3 | 28.6 | 31.8 | 20 | 46.5 | 26.4 | 1.9 | Plasma | Orexin-A |
| Busquets, 2004 [42] | Spain | Caucasian | 27 | 52 | 31 | 54 | 13 | 46 | 24 | <5 | Plasma | Orexin-A |
| Liao, 2005 (i) [43] | China | Asian | 30 | 53 | 30.2 | ≥5 | 20 | 48 | 22.1 | 1.7 | Plasma | Orexin-A |
| Liao, 2005 (ii) [43] | China | Asian | 30 | 53 | 30.2 | ≥5 | 30 | 51 | 30.9 | 2.3 | Plasma | Orexin-A |
| Yao, 2006 [61] | China | Asian | 54 | 47 | 34 | 64 | 20 | 45 | 32 | 3.5 | Plasma | Orexin-A |
| Wang, 2013 [41] | China | Asian | 192 | 49.2 | 26.7 | 24 | 144 | 48.7 | 27.1 | 2 | Serum | Omentin-1 |
| Zirlik, 2013 [64] | Germany | Caucasian | 10 | 58.9 | 31.7 | 40.4 | 10 | 53.6 | 26.7 | 2.7 | Plasma | Omentin-1 |
| Kurt, 2014 [40] | Turkey | Caucasian | 46 | 48.1 | 30.4 | ≥5 | 35 | 42.8 | 26.4 | <5 | Serum | Omentin-1 |
| Strueva, 2015 [59] | Russia | Caucasian | 29 | 41 | 39.2 | ≥30 | 10 | 38 | 22.4 | <5 | Plasma | Orexin-A |
| Uygur, 2016 [60] | Turkey | Caucasian | 96 | 51.4 | 30.8 | 27.9 | 31 | 50.6 | 29.6 | 1.9 | Serum | Omentin-1 |
| Zhang, 2018 [62] | China | Asian | 30 | 40.7 | 28.8 | 61.5 | 20 | 36.1 | 27.6 | 1.9 | Plasma | Omentin-1 |
| Bilcer, 2021 [56] | Turkey | Caucasian | 75 | 44.2 | 29.4 | ≥5 | 75 | 34.1 | 25.9 | <5 | Plasma | Omentin-1 |
| Oztürk, 2022 [58] | Turkey | Caucasian | 210 | 46.4 | 32.6 | 31.6 | 62 | 42.2 | 30.3 | 2.8 | Serum | Orexin-A |
| Zhu, 2022 [63] | China | Asian | 78 | 56.6 | 26.9 | 25.8 | 28 | 55.6 | 26.2 | 3.4 | Plasma | Orexin-A |

BMI: Body mass index. AHI: Apnea-hypopnea index. Please note that Liao et al. [43] reported two independent studies.

3.3. Quality Assessment

Table 2 reports the JBI critical appraisal checklist for both blood OM-1 and OXA levels in case–control studies. Among the studies reporting OM-1, five were high and one was moderate quality. Among the studies reporting OXA, six were moderate, one was high, and one was low quality. The questions for the JBI critical appraisal checklist are located in Supplementary Materials.

3.4. Meta-Analysis for OM-1 Levels

Figure 2 shows the random-effect analysis of blood OM-1 levels in aOSA compared to controls. The pooled result showed a lack of association between the blood levels of OM-1 and OSA risk (SMD = −0.85; 95%CI: −2.19, 0.48; $p = 0.21$; $I^2 = 98\%$).

3.5. Meta-Analysis for OXA Levels

Figure 3 illustrates the random-effect analysis of blood OXA levels in aOSA compared to controls. The pooled result showed a lack of association between the blood levels of OXA and OSA risk (SMD = −0.20; 95%CI: −1.16, 0.76; $p = 0.68$; $I^2 = 96\%$).

Table 2. The Joanna Briggs Institute (JBI) critical appraisal checklist for case–control studies.

| First Author, Publication Year | The Joanna Briggs Institute (JBI) Critical Appraisal Checklist | | | | | | | | | | Quality (Total Quality Score) |
|--------------------------------|--|-----|-----|-----|-----|-----|-----|-----|-----|-----|-------------------------------|
| | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | |
| Igarashi, 2003 [57] | No | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Moderate (7) |
| Busquets, 2004 [42] | No | No | Yes | Moderate (7) |
| Liao, 2005 (i) [43] | No | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Moderate (6) |
| Liao, 2005 (ii) [43] | No | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Moderate (6) |
| Yao, 2006 [61] | No | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Moderate (7) |
| Wang, 2013 [41] | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High (9) |
| Zirlik, 2013 [64] | Yes | No | Yes | High (9) |
| Kurt, 2014 [40] | Yes | No | Yes | High (9) |
| Strueva, 2015 [59] | Un | No | No | Yes | Un | Un | Un | Yes | Yes | Yes | Low (4) |
| Uygur, 2016 [60] | No | Yes | High (9) |
| Zhang, 2018 [62] | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High (9) |
| Bıçer, 2021 [56] | Yes | No | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Moderate (7) |
| Oztürk, 2022 [58] | Yes | No | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Moderate (8) |
| Zhu, 2022 [63] | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | High (10) |

Low: score of 1–4, Moderate: score of 5–7, High: score of 8–10. Un: Unclear.

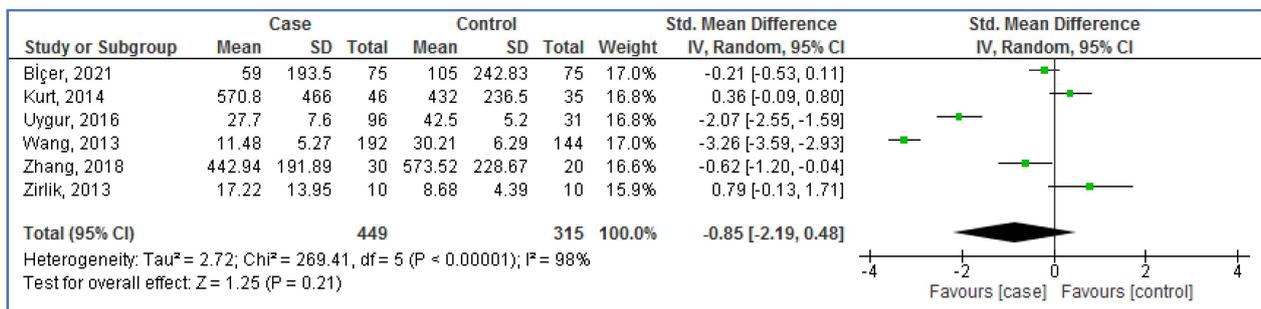


Figure 2. Forest plot analysis of blood omentin-1 levels in adults with obstructive sleep apnea compared to controls. SD: Standard deviation. CI: Confidence interval.

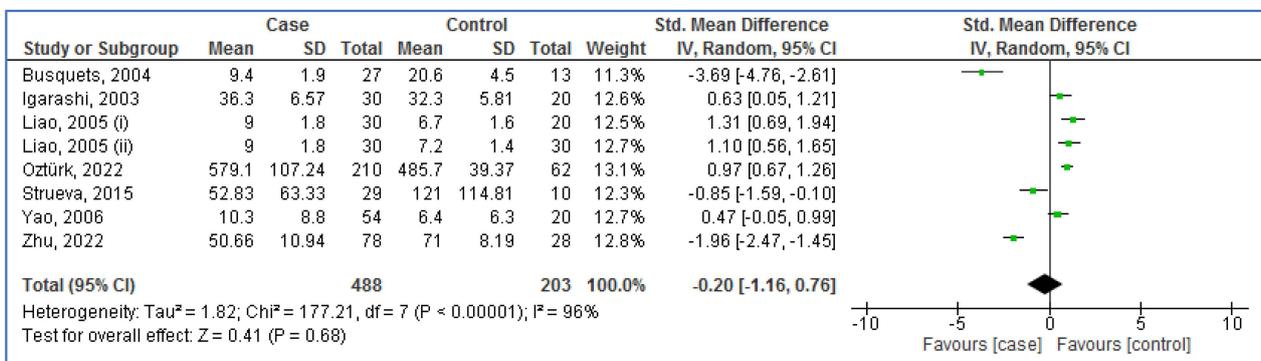


Figure 3. Forest plot analysis of blood orexin-A levels in adults with obstructive sleep apnea compared to controls. SD: Standard deviation. CI: Confidence interval.

3.6. Subgroup Analysis for OM-1 Levels

Table 3 reports the subgroup analysis based on the variables for finding confounding factors in the pooled analysis of the serum/plasma levels of OM-1 in aOSA compared with controls. The results reported that the mean AHI of aOSA and quality were two confounding factors in the pooled SMD.

Table 3. Subgroup analysis of the correlation between blood levels of omentin-1 and several variables.

| Variable | Subgroup (N) | SMD | 95%CI | | p-Value | I ² , % |
|---|---------------|-------|-------|-------|----------|--------------------|
| | | | Min. | Max. | | |
| Ethnicity | | | | | | |
| | Caucasian (4) | −0.29 | −1.42 | 0.84 | 0.62 | 96 |
| | Asian (2) | −1.95 | −4.54 | 0.64 | 0.14 | 98 |
| Sample | | | | | | |
| | Serum (3) | −1.66 | −3.83 | 0.51 | 0.13 | 99 |
| | Plasma (3) | −0.08 | −0.68 | 0.52 | 0.79 | 70 |
| Sample size | | | | | | |
| | ≥100 (3) | −1.82 | −3.85 | 0.21 | 0.08 | 99 |
| | <100 (3) | 0.13 | −0.64 | 0.91 | 0.74 | 79 |
| Mean BMI of aOSA, kg/m ² | | | | | | |
| | ≥30 (3) | −0.33 | −2.17 | 1.51 | 0.73 | 97 |
| | <30 (3) | −1.34 | −3.52 | 0.85 | 0.23 | 99 |
| Mean BMI of controls, kg/m ² | | | | | | |
| | ≥30 (0) | - | - | - | - | - |
| | <30 (6) | −0.84 | −2.19 | 0.52 | 0.23 | 98 |
| Mean age of aOSA, year | | | | | | |
| | ≥45 (4) | −1.07 | −3.01 | 0.88 | 0.28 | 98 |
| | <45 (2) | −0.31 | −0.79 | 0.17 | 0.20 | 54 |
| Mean age of controls, year | | | | | | |
| | ≥45 (3) | −1.57 | −3.36 | 0.23 | 0.09 | 97 |
| | <45 (3) | −0.10 | −0.58 | 0.38 | 0.68 | 72 |
| Mean AHI of aOSA, events/h | | | | | | |
| | ≥40 (2) | 0.04 | −1.34 | 1.42 | 0.96 | 85 |
| | <40 (2) | −2.68 | −3.85 | −1.52 | <0.00001 | 94 |
| Quality | | | | | | |
| | Moderate (5) | −0.98 | −2.59 | 0.62 | 0.23 | 98 |
| | High (1) | −0.12 | −0.44 | 0.20 | 0.46 | - |

SMD: Std. mean difference. CI: Confidence interval. BMI: Body mass index. AHI: Apnea-hypopnea index. Adults with OSA: aOSA.

3.7. Subgroup Analysis for OXA Levels

Table 4 reports the subgroup analysis based on the variables for finding confounding factors in the pooled analysis of the serum/plasma levels of OXA in aOSA compared to

controls. The results reported that the mean BMI in controls, the mean age of aOSA, and the quality were three confounding factors in the pooled SMD.

Table 4. Subgroup analysis of the correlation between blood levels of orexin-A and several variables.

| Variable | Subgroup (N) | SMD | 95%CI | | p-Value | I ² , % |
|---|---------------|-------|-------|-------|----------|--------------------|
| | | | Min. | Max. | | |
| Ethnicity | | | | | | |
| | Caucasian (3) | −1.14 | −3.58 | 1.29 | 0.36 | 98 |
| | Asian (5) | 0.30 | −0.90 | 1.51 | 0.62 | 96 |
| Sample | | | | | | |
| | Serum (1) | 0.97 | 0.67 | 1.26 | <0.00001 | - |
| | Plasma (7) | −0.39 | −1.54 | 0.76 | 0.51 | 96 |
| Sample size | | | | | | |
| | ≥100 (2) | −0.49 | −3.36 | 2.38 | 0.74 | 99 |
| | <100 (4) | −0.10 | −1.15 | 0.95 | 0.85 | 94 |
| Mean BMI of aOSA, kg/m² | | | | | | |
| | ≥30 (6) | −0.02 | −0.98 | 0.94 | 0.97 | 94 |
| | <30 (2) | −0.67 | −3.21 | 1.87 | 0.60 | 98 |
| Mean BMI of controls, kg/m² | | | | | | |
| | ≥30 (3) | 0.89 | 0.66 | 1.12 | <0.00001 | 41 |
| | <30 (5) | −0.88 | 2.45 | 0.69 | 0.27 | 96 |
| Mean age of aOSA, year | | | | | | |
| | ≥45 (7) | −0.11 | −1.16 | 0.93 | 0.83 | 96 |
| | <45 (1) | −0.85 | −1.59 | −0.10 | 0.03 | - |
| Mean age of controls, year | | | | | | |
| | ≥45 (6) | −0.32 | −1.62 | 0.99 | 0.64 | 96 |
| | <45 (2) | 0.10 | −1.68 | 1.87 | 0.92 | 95 |
| Mean AHI of aOSA, events/h | | | | | | |
| | ≥40 (2) | −1.58 | −5.65 | 2.49 | 0.45 | 98 |
| | <40 (2) | −0.12 | −1.93 | 1.70 | 0.90 | 98 |
| Quality | | | | | | |
| | Moderate (6) | 0.25 | −0.59 | 1.08 | 0.56 | 93 |
| | High (1) | −1.96 | −2.74 | −1.45 | <0.00001 | - |
| | Low (1) | −0.85 | −1.59 | −0.10 | 0.03 | - |

SMD: Std. mean difference. CI: Confidence interval. BMI: Body mass index. AHI: Apnea–hypopnea index. Adults with OSA: aOSA.

3.8. Meta-Regression Analysis

As Table 5 shows, among the eight variables checked in the meta-regression analysis for both OM-1 and OXA levels, just sample size was an effective factor for the pooled SMD of blood OM-1 levels ($p = 0.00445$). With an increasing sample size, OM-1 levels were significantly reduced.

Table 5. Meta-regression analysis (mixed-effect model) of the correlation between blood levels of omentin-1 and orexin-A and several variables in the case-control studies in the meta-analysis.

| Variable | Point Estimate | Standard Error | Omentin-1 | | Z-Value | p-Value |
|----------------------|----------------|----------------|-------------|-------------|-----------|----------------|
| | | | Lower Limit | Upper Limit | | |
| Publication year | 0.08398 | 0.24376 | −0.39379 | 0.56175 | 0.34450 | 0.73047 |
| Sample size | −0.01156 | 0.00406 | −0.01952 | −0.00359 | −2.84445 | 0.00445 |
| Mean BMI of aOSA | 0.62114 | 0.33477 | −0.03499 | 1.27727 | 1.85545 | 0.06353 |
| Mean BMI of controls | −0.62930 | 0.57486 | −1.75600 | 0.49740 | −1.09471 | 0.27364 |
| Mean age of aOSA | 0.03104 | 0.12756 | −0.21897 | 0.28106 | 0.24335 | 0.80773 |
| Mean age of controls | −0.04958 | 0.08698 | −0.22006 | 0.12090 | −0.057001 | 0.56867 |
| Mean AHI of aOSA | 0.06554 | 0.04650 | −0.02560 | 0.15668 | 1.40940 | 0.15872 |
| Quality score | −0.42984 | 0.99973 | −2.38927 | 1.52959 | −0.42996 | 0.66722 |
| Orexin-A | | | | | | |
| Variable | Point estimate | Standard error | Lower limit | Upper limit | Z-value | p-value |
| Publication year | −0.02853 | 0.07419 | −0.17393 | 0.11687 | −0.38457 | 0.70056 |
| Sample size | 0.00559 | 0.00772 | −0.00954 | 0.02072 | 0.72432 | 0.46887 |
| Mean BMI of aOSA | 0.01832 | 0.14761 | −0.27099 | 0.30763 | 0.12411 | 0.90123 |
| Mean BMI of controls | 0.17726 | 0.13499 | −0.08731 | 0.44183 | 1.31314 | 0.18914 |
| Mean age of aOSA | −0.07771 | 0.10418 | −0.28190 | 0.12647 | −0.74595 | 0.45570 |
| Mean age of controls | −0.03628 | 0.10193 | −0.23607 | 0.16351 | −0.35589 | 0.72192 |
| Mean AHI of aOSA | −0.32946 | 0.60582 | −151685 | 0.85793 | −0.54382 | 0.58657 |
| Quality score | −0.24502 | 0.31513 | −0.82267 | 0.37262 | −0.77753 | 0.43685 |

BMI: Body mass index. AHI: Apnea-hypopnea index. Bold number means statistically significant ($p < 0.05$). Adults with OSA: aOSA.

3.9. Radial Plot

Figure 4 shows radial plots for OM-1 and OXA levels in aOSA compared to controls. The results confirmed a significant high heterogeneity due to outliers among the studies reporting OM-1 (Cochran's $Q = 46.01$; $p < 0.01$) and OXA (Cochran's $Q = 299.08$; $p < 0.01$) levels.

3.10. Sensitivity Analysis

The sensitivity analyses (one-study-removed and cumulative analyses) showed the stability of the pooled results for both OM-1 and OXA levels in aOSA compared to controls. The plots for the sensitivity analyses are located in the Supplementary Materials.

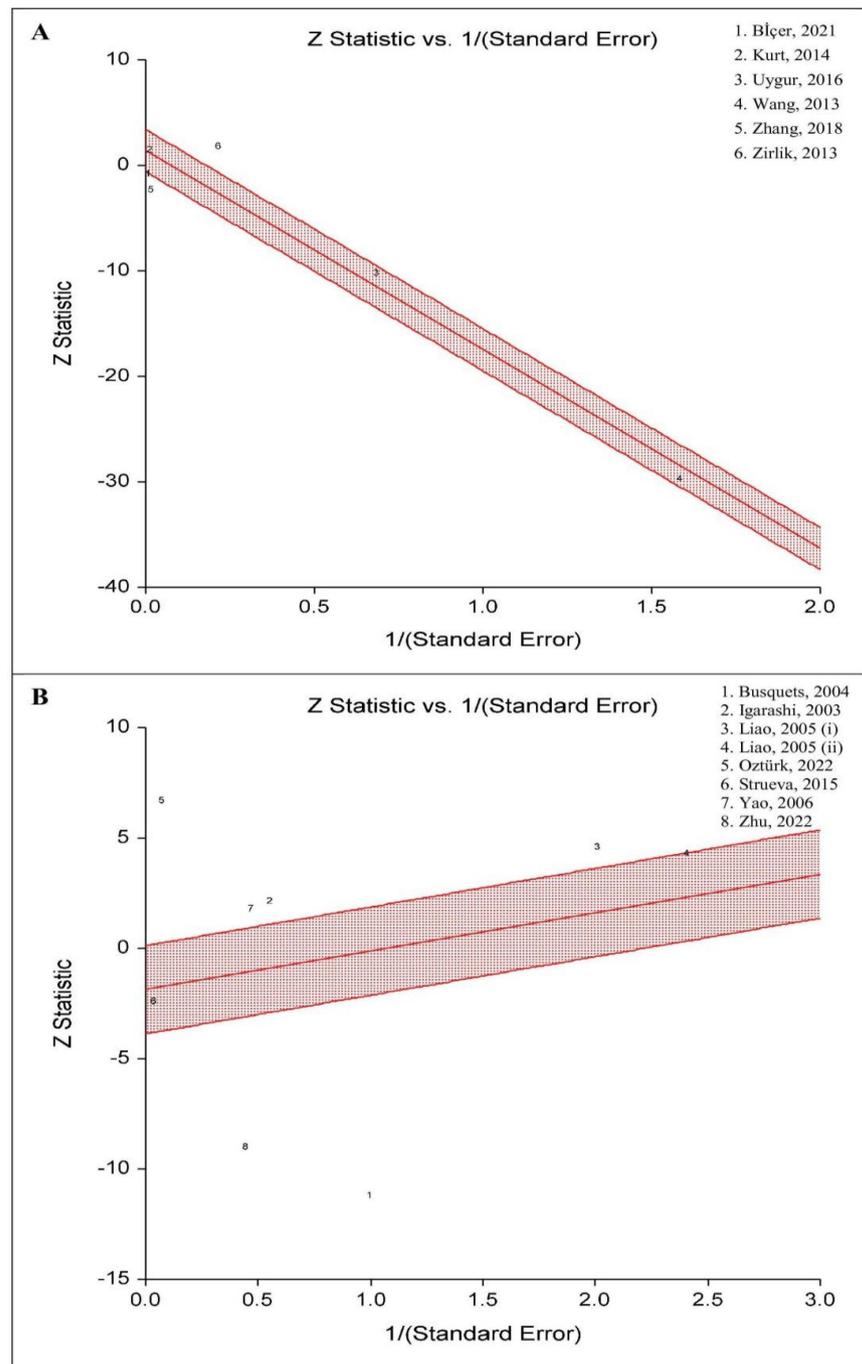


Figure 4. The radial (or Galbraith) plot of the blood levels of (A) omentin-1 and (B) orexin-A in adults with obstructive sleep apnea compared to controls. This plot shows the z-statistic on the Y axis and 1/standard error on the X axis. Studies within and outside the limits are interpreted as homogeneous and may be outliers, respectively.

3.11. Trial Sequential Analysis (TSA)

Figure 5 shows the TSAs of the blood levels of OM-1 and OXA in aOSA compared to controls. The TSA of six studies for blood OM-1 levels shows the line of the cumulative Z-curve crossed the line of the trial sequential monitoring boundary for benefit, but not the line of RIS (heterogeneity (D^2) = 98%). The result was robust, before reaching the information size needed to obtain reliable evidence adjusted for random error risk and suggesting further studies. The TSA of eight studies for blood OXA levels shows the line of

the cumulative Z-curve did not cross any line ($D^2 = 99\%$). Therefore, it indicated an absence of evidence if the information size is not reached and that further studies are needed.

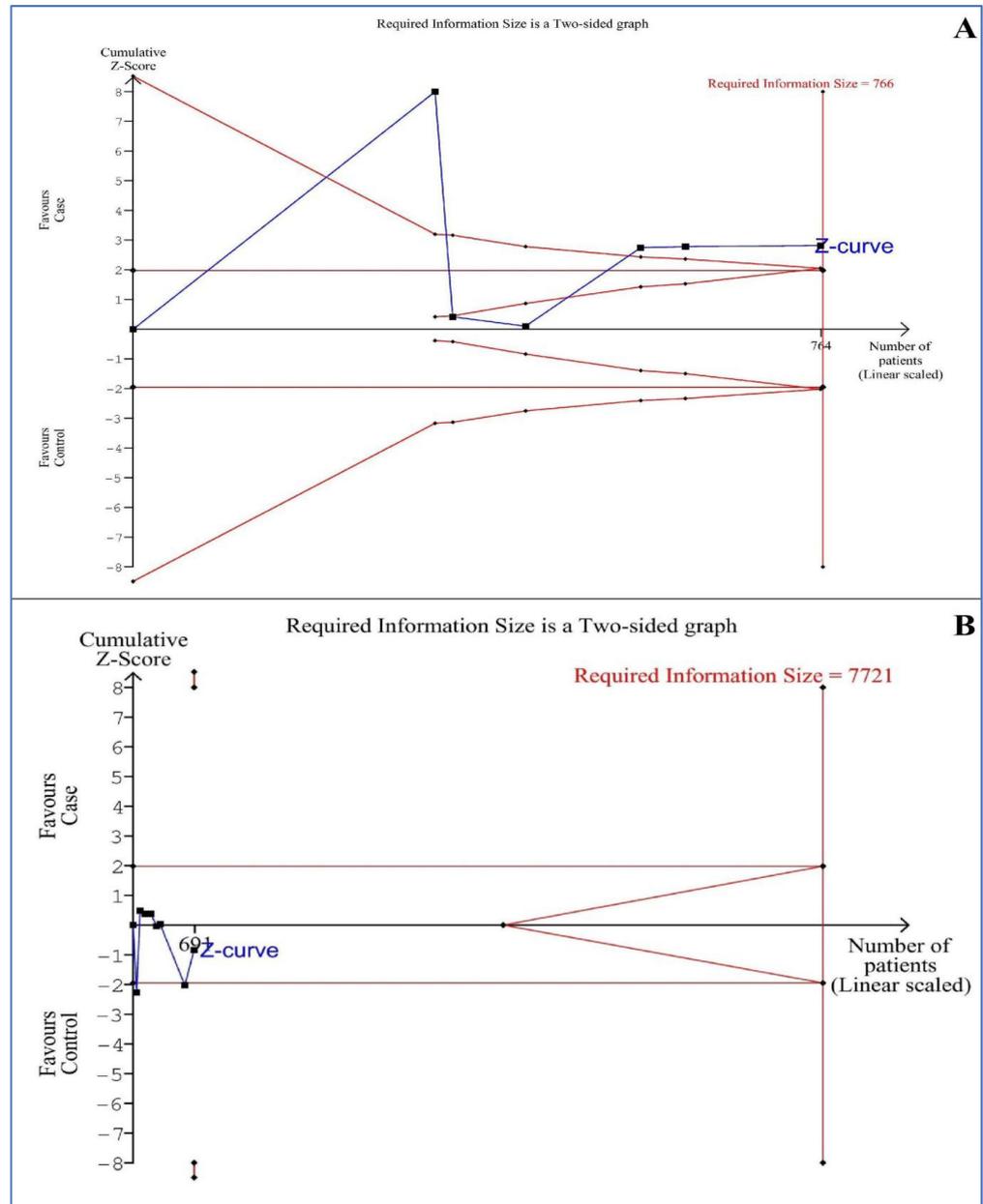


Figure 5. The trial sequential analyses of the blood levels of (A) omentin-1 and (B) orexin-A in adults with obstructive sleep apnea compared to controls. Each black square fill icon shows a study. X-axis and Y-axis show the number of patients and cumulative Z-score, respectively. Horizontal brown lines: conventional boundaries for benefit (up) or harm (down). Sloping full red lines with black square fill icons: trial sequential monitoring boundaries for benefit (up) or harm (down), and futility boundaries. Full blue line with black square fill icons: Z-curve. Vertical red full line: Required information size boundary.

3.12. Publication Bias

Figure 6 shows the funnel plots of serum/plasma OM-1 and OXA levels with the results of the trim-fill method in aOSA compared to controls. The p-values of Egger’s/ Begg’s tests for OM-1 and OXA levels were 0.516/0.851 and 0.161/0.458, respectively. For serum/plasma OM-1 levels and having one imputed study, under the fixed-effects model, the point estimate and pseudo 95% CI for the combined studies was $-1.214 (-1.389,$

−1.039); using the trim-fill method, the imputed point estimate was −1.292 (−1.463, −1.120). In addition, under the random-effects model, the point estimate and 95% CI for the combined studies was −0.837 (−2.197, 0.523); using the trim-fill method, the imputed point estimate was −1.190 (−2.764, 0.085). Therefore, the overall effect sizes on blood OM-1 levels reported in the forest plot appeared valid; with a trivial publication bias effect based the on fixed-effects and random-effects models, because the observed estimates were similar to the adjusted estimates.

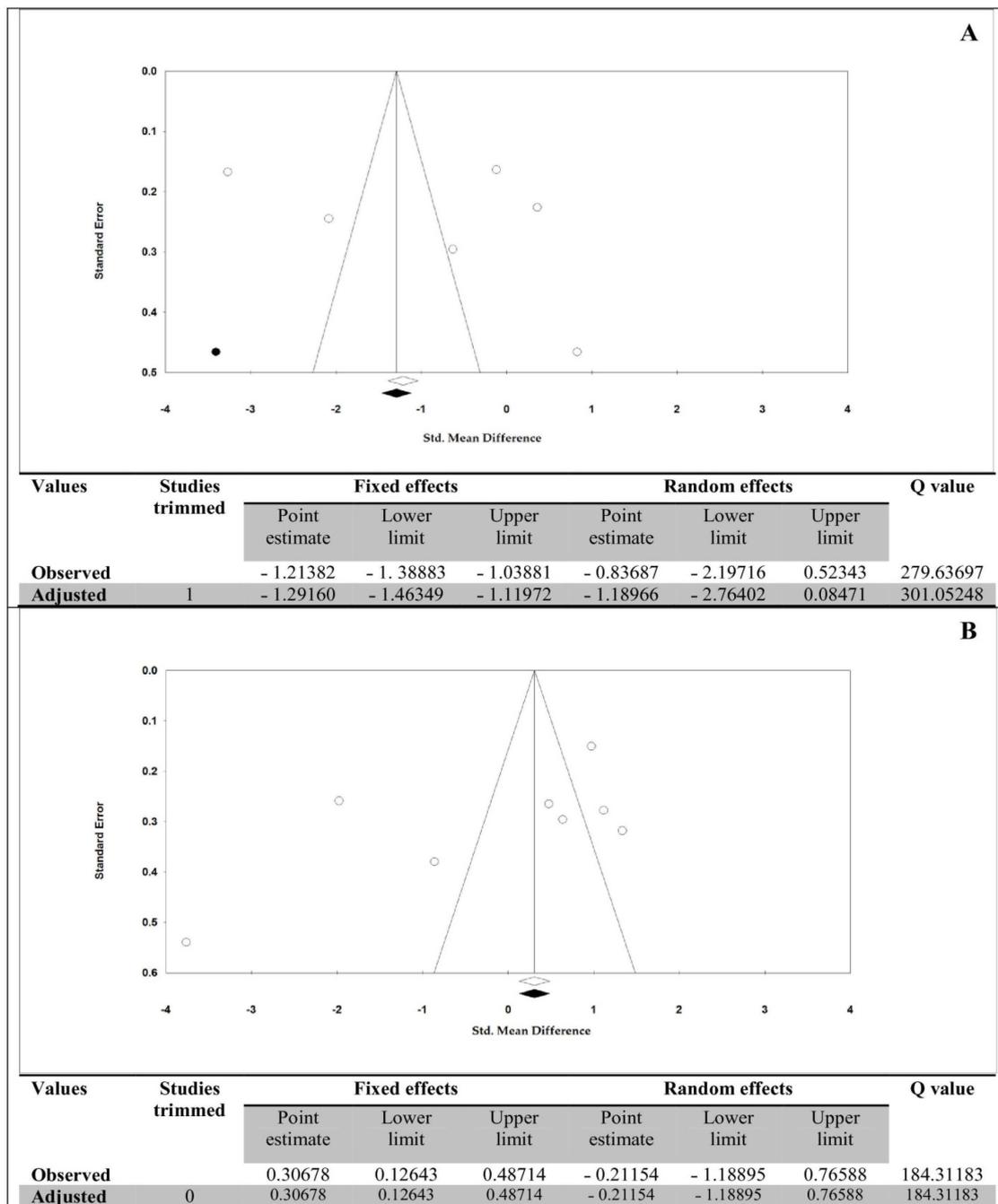


Figure 6. Funnel plots of the blood levels of (A) omentin-1 and (B) orexin-A in adults with obstructive sleep apnea compared to controls with the trim-fill method. Each white circle shows an included study in the meta-analysis and each black circle shows an unpublished study. The white diamond shows overall effect size as calculated in the meta-analysis, and the black diamond shows the corrected effect size.

For serum/plasma OXA levels and without any imputed study, under the fixed-effects model, the point estimate and pseudo 95% CI for the combined studies was 0.307 (0.126, 0.487); using the trim-fill method, the imputed point estimate was 0.307 (0.126, 0.487). In addition, under the random-effects model, the point estimate and 95% CI for the combined studies was -0.211 (-1.189 , 0.766); using the trim-fill method, the imputed point estimate was -0.211 (-1.189 , 0.766). Therefore, the overall effect sizes on blood OXA levels reported in the forest plot appeared valid, with a trivial publication bias effect based on the fixed-effects and random-effects models, because the observed estimates were similar to the adjusted estimates.

4. Discussion

Despite a low number of cases and high heterogeneity, the results of the meta-analysis represented a lack of association between the blood levels of OM-1 and OXA and OSA risk. Sample size, mean AHI of aOSA, and quality were confounding factors for OM-1 levels, whereas, mean BMI in controls, mean age of aOSA, and quality were confounding factors for OXA levels.

OSA must be investigated as a multifactorial disease in which multiple polymorphisms, environmental influences, and developmental factors are closely related to it [65]; OSA is also strongly correlated with obesity [66]. The main mechanisms of OSA are hypoxia and oxidative stress; however, several studies have shown that inflammation also plays an important role in the occurrence and progression of OSA [67–69]. OSA appears to affect parameters involved in the regulation of energy balance, including food consumption, physical activity, energy metabolism, and the hormonal regulation of hunger/satiety [70,71].

There is a relationship between OM-1 level, body composition, and physical activity in elderly women [72]. Aging, physical activity, and body weight are several significant factors affecting OM-1 concentration. However, it is not clear what factors can be used as predictors of the impact of the circulating OM-1 concentration [73,74]. OXA stimulates both nutrition and energy intake, and OXA's increase in energy intake is mainly due to increased spontaneous physical activity, and this effect on energy intake is stronger than the effect on nutrition [75]. OXA has been demonstrated to cause obesity and its related diseases [35].

Three studies [41,60,62] reported that the OM-1 levels were significantly lower in aOSA than those in controls. The decreased levels of OM-1 are related to insulin resistance T2DM, coronary artery disease, and arterial stiffness, or on the other hand, associated inversely with metabolic syndrome [76–81]. In contrast, two studies [40,64], in line with the present meta-analysis, reported there was no association between OM-1 levels and OSA risk. These different results of the studies can be due to the differences in sample size, BMI status, age, and quality of the studies.

Three studies [42,59,63] showed a reduced significant level of OXA in aOSA compared to controls. In contrast, three articles [43,57,58] reported an elevated significant level of OXA in aOSA compared to controls. Low levels of OXA may prevent arousal during sleep or may be the result of sleepiness from repeated arousals caused by a mechanism independent of OXA [42], and also obesity in individuals with OSA may be induced by decreased orexin neuron activity or levels of OXA [82]. Higher levels of OXA were related to high breakfast energy intake [83]. In addition, elevated orexin transmission, reflected as elevated plasma levels of OXA, may impact the arousal response in individuals with OSA [57]. The results of the present meta-analysis are in line with another study [61] which found a lack of association between OXA levels in aOSA versus controls. These different results of the studies can be due to the differences in AHI status and the quality of the studies.

The present results should be counterbalanced by the following limitations: (1) A low number of cases in most studies; (2) A low number of studies in each analysis; (3) A high heterogeneity across or among the studies; (4) Some studies were outliers; (5) A lack of high

quality in most studies. In contrast, there were two strengths: (1) Stability of the pooled results; (2) A lack of publication bias.

5. Conclusions

The main results indicated a lack of association between the blood levels of OM-1 and OXA and OSA risk. Therefore, OM-1 and OXA did not appear to be suitable biomarkers for the diagnosis and development of OSA. Although we used eligibility criteria, our results must be interpreted with precaution, because the levels of the two biomarkers may be impacted by several factors (age, BMI, AHI, sample size, etc.). Finally, the sample sizes in most studies were relatively small, and, therefore, larger and multi-center studies should be analyzed to clarify the relationship between the blood levels of these biomarkers and OSA development.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/life13010245/s1>, Figure S1: One-study-remove analysis of blood omentin-1 levels in adults with OSA compared to control; Figure S2: Cumulative analysis of blood omentin-1 levels in adults with OSA compared to controls; Figure S3: One-study-remove analysis of blood orexin-A levels in adults with OSA compared to controls; Figure S4: Cumulative analysis of blood orexin-A levels in adults with OSA compared to controls; Table S1: The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for case-control studies.

Author Contributions: Conceptualization, I.M.; methodology, M.S.; software, M.S.; validation, M.S. and S.B.; formal analysis, M.S.; investigation, I.M.; resources, G.T.; data curation, M.S.; writing—original draft preparation, S.B.; writing—review and editing, M.S., L.S.B. and A.B.B. visualization, M.S.; supervision, I.M.; project administration, I.M.; funding acquisition, I.M. and S.B. All authors have read and agreed to the published version of the manuscript.

Funding: University and University Hospital of Basel (Basel, Switzerland) funded the Article Processing Charge (APC) of this manuscript.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Pretto, J.J.; Gyulay, S.G.; Hensley, M.J. Trends in anthropometry and severity of sleep-disordered breathing over two decades of diagnostic sleep studies in an Australian adult sleep laboratory. *Med. J. Aust.* **2010**, *193*, 213–216. [[CrossRef](#)] [[PubMed](#)]
2. Park, J.G.; Ramar, K.; Olson, E.J. Updates on definition, consequences, and management of obstructive sleep apnea. *Mayo Clin. Proc.* **2011**, *86*, 549–554, quiz 554–555. [[CrossRef](#)] [[PubMed](#)]
3. Kuczyński, W.; Mokros, Ł.; Stolarz, A.; Białasiewicz, P. The utility of STOP-BANG questionnaire in the sleep-lab setting. *Sci. Rep.* **2019**, *9*, 6676. [[CrossRef](#)] [[PubMed](#)]
4. Senaratna, C.V.; Perret, J.L.; Lodge, C.J.; Lowe, A.J.; Campbell, B.E.; Matheson, M.C.; Hamilton, G.S.; Dharmage, S.C. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med. Rev.* **2017**, *34*, 70–81. [[CrossRef](#)] [[PubMed](#)]
5. Lechat, B.; Naik, G.; Reynolds, A.; Aishah, A.; Scott, H.; Loffler, K.A.; Vakulin, A.; Escourrou, P.; McEvoy, R.D.; Adams, R.J. Multinight prevalence, variability, and diagnostic misclassification of obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* **2022**, *205*, 563–569. [[CrossRef](#)]
6. Cielo, C.M.; Tapia, I.E. Diving deeper: Rethinking AHI as the primary measure of OSA severity. *J. Clin. Sleep Med.* **2019**, *15*, 1075–1076. [[CrossRef](#)]
7. Quan, S.; Gillin, J.C.; Littner, M.; Shepard, J. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. editorials. *Sleep* **1999**, *22*, 662–689. [[CrossRef](#)]
8. Goyal, M.; Johnson, J. Obstructive sleep apnea diagnosis and management. *Mo. Med.* **2017**, *114*, 120.
9. Epstein, L.J.; Kristo, D.; Strollo, P.J., Jr.; Friedman, N.; Malhotra, A.; Patil, S.P.; Ramar, K.; Rogers, R.; Schwab, R.J.; Weaver, E.M.; et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J. Clin. Sleep Med.* **2009**, *5*, 263–276.

10. Franklin, K.A.; Lindberg, E. Obstructive sleep apnea is a common disorder in the population—A review on the epidemiology of sleep apnea. *J. Thorac. Dis.* **2015**, *7*, 1311.
11. Schwartz, M.; Acosta, L.; Hung, Y.-L.; Padilla, M.; Enciso, R. Effects of CPAP and mandibular advancement device treatment in obstructive sleep apnea patients: A systematic review and meta-analysis. *Sleep Breath.* **2018**, *22*, 555–568. [[CrossRef](#)]
12. Bielicki, P.; Trojnar, A.; Sobieraj, P. The impact of smoking status on obstructive sleep apnea (OSA) severity. *Eur. Respir. J.* **2018**, *52*, PA4356.
13. Simou, E.; Britton, J.; Leonardi-Bee, J. Alcohol and the risk of sleep apnoea: A systematic review and meta-analysis. *Sleep Med.* **2018**, *42*, 38–46. [[CrossRef](#)]
14. Imani, M.M.; Sadeghi, M.; Gholamipour, M.A.; Brühl, A.B.; Sadeghi-Bahmani, D.; Brand, S. Evaluation of Blood Intercellular Adhesion Molecule-1 (ICAM-1) Level in Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. *Medicina* **2022**, *58*, 1499. [[CrossRef](#)]
15. Imani, M.M.; Sadeghi, M.; Mohammadi, M.; Brühl, A.B.; Sadeghi-Bahmani, D.; Brand, S. Association of Blood MCP-1 Levels with Risk of Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis. *Medicina* **2022**, *58*, 1266. [[CrossRef](#)]
16. Najafi, A.; Mohammadi, I.; Sadeghi, M.; Brühl, A.B.; Sadeghi-Bahmani, D.; Brand, S. Evaluation of Plasma/Serum Adiponectin (an Anti-Inflammatory Factor) Levels in Adult Patients with Obstructive Sleep Apnea Syndrome: A Systematic Review and Meta-Analysis. *Life* **2022**, *12*, 738. [[CrossRef](#)]
17. Imani, M.M.; Sadeghi, M.; Farokhzadeh, F.; Khazaie, H.; Brand, S.; Dürsteler, K.M.; Brühl, A.; Sadeghi-Bahmani, D. Evaluation of Blood Levels of C-Reactive Protein Marker in Obstructive Sleep Apnea: A Systematic Review, Meta-Analysis and Meta-Regression. *Life* **2021**, *11*, 362. [[CrossRef](#)]
18. Imani, M.M.; Sadeghi, M.; Khazaie, H.; Sanjabi, A.; Brand, S.; Brühl, A.; Sadeghi Bahmani, D. Associations Between Morning Salivary and Blood Cortisol Concentrations in Individuals With Obstructive Sleep Apnea Syndrome: A Meta-Analysis. *Front. Endocrinol.* **2020**, *11*, 568823. [[CrossRef](#)]
19. Imani, M.M.; Sadeghi, M.; Khazaie, H.; Emami, M.; Sadeghi Bahmani, D.; Brand, S. Evaluation of Serum and Plasma Interleukin-6 Levels in Obstructive Sleep Apnea Syndrome: A Meta-Analysis and Meta-Regression. *Front. Immunol.* **2020**, *11*, 1343. [[CrossRef](#)]
20. Imani, M.M.; Sadeghi, M.; Khazaie, H.; Emami, M.; Sadeghi Bahmani, D.; Brand, S. Serum and Plasma Tumor Necrosis Factor Alpha Levels in Individuals with Obstructive Sleep Apnea Syndrome: A Meta-Analysis and Meta-Regression. *Life* **2020**, *10*, 87. [[CrossRef](#)]
21. Rezaei, F.; Abbasi, H.; Sadeghi, M.; Imani, M.M. The effect of obstructive sleep apnea syndrome on serum S100B and NSE levels: A systematic review and meta-analysis of observational studies. *BMC Pulm. Med.* **2020**, *20*, 31. [[CrossRef](#)] [[PubMed](#)]
22. Bhatt, S.P.; Guleria, R. Association of IRS1 (Gly972Arg) and IRS2 (Gly1057Asp) genes polymorphisms with OSA and NAFLD in Asian Indians. *PLoS ONE* **2021**, *16*, e0245408. [[CrossRef](#)] [[PubMed](#)]
23. Kerget, B.; Kerget, F.; Kahraman, Ç.Y.; Aksakal, A.; Araz, Ö. The relationship between NLRP3 rs10159239 and Vaspin rs2236242 gene variants and obstructive sleep apnea. *Uppsala J. Med. Sci.* **2021**, *126*, e7603. [[CrossRef](#)]
24. Behboudi, A.; Thelander, T.; Yazici, D.; Celik, Y.; Yucel-Lindberg, T.; Thunström, E.; Peker, Y. Association of TNF- α (-308G/A) Gene Polymorphism with Circulating TNF- α Levels and Excessive Daytime Sleepiness in Adults with Coronary Artery Disease and Concomitant Obstructive Sleep Apnea. *J. Clin. Med.* **2021**, *10*, 3413. [[CrossRef](#)] [[PubMed](#)]
25. Netzer, N.C.; Stoohs, R.A.; Netzer, C.M.; Clark, K.; Strohl, K.P. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann. Intern. Med.* **1999**, *131*, 485–491. [[CrossRef](#)]
26. Shamsuzzaman, A.S.; Gersh, B.J.; Somers, V.K. Obstructive sleep apnea: Implications for cardiac and vascular disease. *JAMA* **2003**, *290*, 1906–1914. [[CrossRef](#)]
27. Gunta, S.P.; Jakulla, R.S.; Ubaid, A.; Mohamed, K.; Bhat, A.; López-Candales, A.; Norgard, N. Obstructive Sleep Apnea and Cardiovascular Diseases: Sad Realities and Untold Truths regarding Care of Patients in 2022. *Cardiovasc. Ther.* **2022**, *2022*, 6006127. [[CrossRef](#)]
28. Young, T.; Peppard, P.E.; Taheri, S. Excess weight and sleep-disordered breathing. *J. Appl. Physiol.* **2005**, *99*, 1592–1599. [[CrossRef](#)]
29. Patel, S.R.; White, D.P.; Malhotra, A.; Stanchina, M.L.; Ayas, N.T. Continuous positive airway pressure therapy for treating gess in a diverse population with obstructive sleep apnea: Results of a meta-analysis. *Arch. Intern. Med.* **2003**, *163*, 565–571. [[CrossRef](#)]
30. Patil, S.P.; Ayappa, I.A.; Caples, S.M.; Kimoff, R.J.; Patel, S.R.; Harrod, C.G. Treatment of adult obstructive sleep apnea with positive airway pressure: An American Academy of Sleep Medicine clinical practice guideline. *J. Clin. Sleep Med.* **2019**, *15*, 335–343. [[CrossRef](#)]
31. Jaacks, L.M.; Vandevijvere, S.; Pan, A.; McGowan, C.J.; Wallace, C.; Imamura, F.; Mozaffarian, D.; Swinburn, B.; Ezzati, M. The obesity transition: Stages of the global epidemic. *Lancet Diabetes Endocrinol.* **2019**, *7*, 231–240. [[CrossRef](#)]
32. Bi, X.; Loo, Y.T.; Henry, C.J. Does circulating leptin play a role in energy expenditure? *Nutrition* **2019**, *60*, 6–10. [[CrossRef](#)]
33. Sartin, J.; Dyer, C.; Matteri, R.; Buxton, D.; Buonomo, F.; Shores, M.; Baker, J.; Osborne, J.; Braden, T.; Steele, B. Effect of intracerebroventricular orexin-B on food intake in sheep. *J. Anim. Sci.* **2001**, *79*, 1573–1577. [[CrossRef](#)]
34. Taheri, S.; Ward, H.; Ghatei, M.; Bloom, S. Role of orexins in sleep and arousal mechanisms. *Lancet* **2000**, *355*, 847. [[CrossRef](#)]
35. Imperatore, R.; Palomba, L.; Cristino, L. Role of orexin-A in hypertension and obesity. *Curr. Hypertens. Rep.* **2017**, *19*, 34. [[CrossRef](#)]
36. Yin, J.; Hou, P.; Wu, Z.; Nie, Y. Decreased levels of serum omentin-1 in patients with inflammatory bowel disease. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **2015**, *21*, 118.

37. El-Mesallamy, H.; El-Derany, M.; Hamdy, N. Serum omentin-1 and chemerin levels are interrelated in patients with Type 2 diabetes mellitus with or without ischaemic heart disease. *Diabet. Med.* **2011**, *28*, 1194–1200. [CrossRef]
38. Elsaid, N.H.; Sadik, N.A.; Ahmed, N.R.; Fayez, S.E.; Mohammed, N.A.E.-G. Serum omentin-1 levels in type 2 diabetic obese women in relation to glycemic control, insulin resistance and metabolic parameters. *J. Clin. Transl. Endocrinol.* **2018**, *13*, 14–19. [CrossRef]
39. Shechter, A. Obstructive sleep apnea and energy balance regulation: A systematic review. *Sleep Med. Rev.* **2017**, *34*, 59–69. [CrossRef]
40. Kurt, O.K.; Tosun, M.; Alcelik, A.; Yilmaz, B.; Talay, F. Serum omentin levels in patients with obstructive sleep apnea. *Sleep Breath.* **2014**, *18*, 391–395. [CrossRef]
41. Wang, Q.; Feng, X.; Zhou, C.; Li, P.; Kang, J. Decreased levels of serum omentin-1 in patients with obstructive sleep apnoea syndrome. *Ann. Clin. Biochem.* **2013**, *50*, 230–235. [CrossRef] [PubMed]
42. Busquets, X.; Barbé, F.; Barceló, A.; de la Peña, M.; Sigriz, N.; Mayoralas, L.R.; Ladaría, A.; Agustí, A. Decreased plasma levels of orexin-A in sleep apnea. *Respiration* **2004**, *71*, 575–579. [CrossRef] [PubMed]
43. Liao, X.; Yu, Q. The changes and implications of plasma orexin-A levels in patients with obstructive sleep apnea-hypopnea syndrome. *Zhonghua Jie He He Hu Xi Za Zhi/Zhonghua Jiehe He Huxi Zazhi/Chin. J. Tuberc. Respir. Dis.* **2005**, *28*, 368–371.
44. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* **2015**, *4*, 1. [CrossRef] [PubMed]
45. Morgan, R.L.; Thayer, K.A.; Bero, L.; Bruce, N.; Falck-Ytter, Y.; Ghersi, D.; Guyatt, G.; Hooijmans, C.; Langendam, M.; Mandrioli, D. GRADE: Assessing the quality of evidence in environmental and occupational health. *Environ. Int.* **2016**, *92*, 611–616. [CrossRef]
46. Morgan, R.L.; Thayer, K.A.; Santesso, N.; Holloway, A.C.; Blain, R.; Eftim, S.E.; Goldstone, A.E.; Ross, P.; Guyatt, G.; Schünemann, H.J. Evaluation of the risk of bias in non-randomized studies of interventions (ROBINS-I) and the ‘target experiment’ concept in studies of exposures: Rationale and preliminary instrument development. *Environ. Int.* **2018**, *120*, 382–387. [CrossRef]
47. Institute, J. The Joanna Briggs Institute Critical Appraisal Tools for Use in JBI Systematic Reviews Checklist for Analytical Clinical Trial Studies. 2017. Available online: <https://jbi.global/critical-appraisal-tools> (accessed on 27 November 2022).
48. DerSimonian, R.; Laird, N. Meta-analysis in clinical trials revisited. *Contemp. Clin. Trials* **2015**, *45*, 139–145. [CrossRef]
49. Mantel, N.; Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl. Cancer Inst.* **1959**, *22*, 719–748.
50. Begg, C.B.; Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* **1994**, *50*, 1088–1101. [CrossRef]
51. Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. *Bmj* **1997**, *315*, 629–634. [CrossRef]
52. Imberger, G.; Thorlund, K.; Gluud, C.; Wetterslev, J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: An empirical review. *BMJ Open* **2016**, *6*, e011890. [CrossRef]
53. Wetterslev, J.; Jakobsen, J.C.; Gluud, C. Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med. Res. Methodol.* **2017**, *17*, 39. [CrossRef]
54. Wan, X.; Wang, W.; Liu, J.; Tong, T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med. Res. Methodol.* **2014**, *14*, 135. [CrossRef]
55. Hozo, S.P.; Djulbegovic, B.; Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med. Res. Methodol.* **2005**, *5*, 13. [CrossRef]
56. Bıçer, Ü.; Kutlu, R.; Yosunkaya, S.; Kılınç, İ. Evaluation of Plasma Ghrelin, Omentin-1 Levels and Insulin Resistance in Patients With Obstructive Sleep Apnea Syndrome. *Konuralp Med. J.* **2021**, *13*, 114–121. [CrossRef]
57. Igarashi, N.; Tatsumi, K.; Nakamura, A.; Sakao, S.; Takiguchi, Y.; Nishikawa, T.; Kuriyama, T. Plasma orexin-A levels in obstructive sleep apnea-hypopnea syndrome. *Chest* **2003**, *124*, 1381–1385. [CrossRef]
58. Öztürk, Ö.; Cebeci, D.; Şahin, U.; Tülüceoğlu, E.E.; Calapoğlu, N.Ş.; Gonca, T.; Calapoğlu, M. Circulating levels of ghrelin, galanin, and orexin-A orexigenic neuropeptides in obstructive sleep apnea syndrome. *Sleep Breath.* **2022**, *26*, 1209–1218. [CrossRef]
59. Strueva, N.; Poluektov, M.; Melnichenko, G.; Savelyeva, L.; Katsya, G.; Goncharov, N. Decreased plasma orexin-A levels in obese patients with and without obstructive sleep apnea. *Sleep Med.* **2015**, *16*, S86. [CrossRef]
60. Uygur, F.; Tanrıverdi, H.; Can, M.; Erboyl, F.; Altınsoy, B.; Atalay, F.; Ornek, T.; Damar, M.; Kokturk, F.; Tor, M. Association between continuous positive airway pressure and circulating omentin levels in patients with obstructive sleep apnoea. *Sleep Breath.* **2016**, *20*, 939–945. [CrossRef]
61. Yao, X.; Yang, H.; Zhang, G.; Tang, Y. Plasma orexin-A level in patients with obstructive apnea-hypopnea syndrome. *Lin Chuang Er Bi Yan Hou Ke Za Zhi/J. Clin. Otorhinolaryngol.* **2006**, *20*, 547–549.
62. Zhang, D.-m.; Pang, X.-l.; Huang, R.; Gong, F.-y.; Zhong, X.; Xiao, Y. Adiponectin, omentin, ghrelin, and visfatin levels in obese patients with severe obstructive sleep apnea. *BioMed Res. Int.* **2018**, *2018*, 3410135. [CrossRef] [PubMed]
63. Zhu, J.; Zeng, Z.; Xiong, M.; Mo, H.; Jin, M.; Hu, K. Associations between daytime and nighttime plasma orexin A levels and cognitive function in patients with obstructive sleep apnea. *Sleep Biol. Rhythm.* **2022**, *20*, 421–429. [CrossRef]
64. Zirlik, S.; Hildner, K.; Targosz, A.; Neurath, M.; Fuchs, F.; Brzozowski, T.; Konturek, P.C. Melatonin and omentin: Influence factors in the obstructive sleep apnoea syndrome. *J Physiol Pharm.* **2013**, *64*, 353–360.

65. Casale, M.; Pappacena, M.; Rinaldi, V.; Bressi, F.; Baptista, P.; Salvinelli, F. Obstructive sleep apnea syndrome: From phenotype to genetic basis. *Curr. Genom.* **2009**, *10*, 119–126. [[CrossRef](#)] [[PubMed](#)]
66. Glicksman, A.; Hadjiyannakis, S.; Barrowman, N.; Walker, S.; Hoey, L.; Katz, S.L. Body fat distribution ratios and obstructive sleep apnea severity in youth with obesity. *J. Clin. Sleep Med.* **2017**, *13*, 545–550. [[CrossRef](#)]
67. Unnikrishnan, D.; Jun, J.; Polotsky, V. Inflammation in sleep apnea: An update. *Rev. Endocr. Metab. Disord.* **2015**, *16*, 25–34. [[CrossRef](#)]
68. Yilmaz Avci, A.; Avci, S.; Lakadamyali, H.; Can, U. Hypoxia and inflammation indicate significant differences in the severity of obstructive sleep apnea within similar apnea-hypopnea index groups. *Sleep Breath.* **2017**, *21*, 703–711. [[CrossRef](#)]
69. Vicente, E.; Marin, J.M.; Carrizo, S.J.; Osuna, C.S.; González, R.; Marin-Oto, M.; Forner, M.; Vicente, P.; Cubero, P.; Gil, A.V. Upper airway and systemic inflammation in obstructive sleep apnoea. *Eur. Respir. J.* **2016**, *48*, 1108–1117. [[CrossRef](#)]
70. St-Onge, M.-P.; Shechter, A. Sleep disturbances, body fat distribution, food intake and/or energy expenditure: Pathophysiological aspects. *Horm. Mol. Biol. Clin. Investig.* **2014**, *17*, 29–37. [[CrossRef](#)]
71. Shechter, A. Effects of continuous positive airway pressure on energy balance regulation: A systematic review. *Eur. Respir. J.* **2016**, *48*, 1640–1657. [[CrossRef](#)]
72. Li, S.; Xue, J.; Hong, P. Relationships between serum omentin-1 concentration, body composition and physical activity levels in older women. *Medicine* **2021**, *100*, e25020. [[CrossRef](#)]
73. Alissa, E.M.; Maisa'a, M.; Alama, N.A.; Ferns, G.A. Role of omentin-1 and C-reactive protein in obese subjects with subclinical inflammation. *J. Clin. Transl. Endocrinol.* **2016**, *3*, 7–11. [[CrossRef](#)]
74. Wang, D.; Jiang, T.-J.; Liao, L.; Huang, J. Relationships between serum omentin-1 concentration and bone mineral density, and bone biochemical markers in Chinese women. *Clin. Chim. Acta* **2013**, *426*, 64–67. [[CrossRef](#)]
75. Nixon, J.P.; Kotz, C.M.; Novak, C.M.; Billington, C.J.; Teske, J.A. Neuropeptides controlling energy balance: Orexins and neuromedins. *Appet. Control* **2012**, *209*, 77–109.
76. Biscetti, F.; Nardella, E.; Bonadia, N.; Angelini, F.; Pitocco, D.; Santoliquido, A.; Filipponi, M.; Landolfi, R.; Flex, A. Association between plasma omentin-1 levels in type 2 diabetic patients and peripheral artery disease. *Cardiovasc. Diabetol.* **2019**, *18*, 74. [[CrossRef](#)]
77. Knaus, C. Diagnosis and treatment of obstructive sleep apnea syndrome. *Ther. Umschau. Rev. Ther.* **2016**, *73*, 209–212. [[CrossRef](#)]
78. Pan, X.; Kaminga, A.C.; Wen, S.W.; Acheampong, K.; Liu, A. Omentin-1 in diabetes mellitus: A systematic review and meta-analysis. *PLoS ONE* **2019**, *14*, e0226292. [[CrossRef](#)]
79. Svatikova, A.; Wolk, R.; Gami, A.S.; Pohanka, M.; Somers, V.K. Interactions between obstructive sleep apnea and the metabolic syndrome. *Curr. Diabetes Rep.* **2005**, *5*, 53–58. [[CrossRef](#)]
80. Watanabe, K.; Watanabe, R.; Konii, H.; Shirai, R.; Sato, K.; Matsuyama, T.-a.; Ishibashi-Ueda, H.; Koba, S.; Kobayashi, Y.; Hirano, T. Counteractive effects of omentin-1 against atherogenesis. *Cardiovasc. Res.* **2016**, *110*, 118–128. [[CrossRef](#)]
81. Yoo, H.J.; Hwang, S.Y.; Hong, H.C.; Choi, H.Y.; Yang, S.J.; Seo, J.A.; Kim, S.G.; Kim, N.H.; Choi, K.M.; Choi, D.S. Association of circulating omentin-1 level with arterial stiffness and carotid plaque in type 2 diabetes. *Cardiovasc. Diabetol.* **2011**, *10*, 103. [[CrossRef](#)]
82. Wang, W.; Pan, Y.; Li, Q.; Wang, L. Orexin: A potential role in the process of obstructive sleep apnea. *Peptides* **2013**, *42*, 48–54. [[CrossRef](#)] [[PubMed](#)]
83. Rilling, F.L.; Reyes, M.; Blanco, E.; Burrows, R.; Peirano, P.; Algarín, C.; Meroño, T.; Gahagan, S. Association of fasting Orexin-A levels with energy intake at breakfast and subsequent snack in Chilean adolescents. *Psychoneuroendocrinology* **2022**, *140*, 105718. [[CrossRef](#)] [[PubMed](#)]

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