Circulating Malondialdehyde Concentrations in Obstructive Sleep Apnea (OSA): A Systematic Review and Meta-Analysis with Meta-Regression

Maria Carmina Pau 1, Elisabetta Zinellu 2, Sara S. Fois 1, Barbara Piras 1, Gianfranco Pintus 3,4,*, Ciriaco Carru 3,4, Arduino A. Mangoni 3,4,*, Alessandro G. Fois 1,2, Angelo Zinellu 3,4 and Pietro Pirina 1,2,*

1 Department of Medical, Surgical and Experimental Sciences, University of Sassari, 07100 Sassari, Italy; mcpau@uniss.it (M.C.P.); sfois40@studenti.uniss.it (S.S.F.); barbara.piras@aousassari.it (B.P.); agfois@uniss.it (A.G.F.)
2 Clinical and Interventional Pneumology, University Hospital Sassari (AOU), 07100 Sassari, Italy; elisabetta.zinellu@aousassari.it
3 Department of Biomedical Sciences, University of Sassari, 07100 Sassari, Italy; gpintus@uniss.it (G.P.); carru@uniss.it (C.C.); azinellu@uniss.it (A.Z.)
4 Department of Medical Laboratory Sciences, Sharjah Institute for Medical Research, College of Health Sciences, University of Sharjah, 22727 Sharjah, United Arab Emirates
5 College of Medicine and Public Health, Flinders University, Bedford Park, SA 5042, Australia; arduino.mangoni@flinders.edu.au
6 Department of Clinical Pharmacology, Flinders Medical Centre, Bedford Park, SA 5042, Australia
* Correspondence: pirina@uniss.it; Tel.: +39-079-228165

Abstract: Oxidative stress induced by nocturnal intermittent hypoxia plays a significant pathophysiological role in obstructive sleep apnea (OSA). Malondialdehyde (MDA), one of the most commonly investigated markers of lipid peroxidation, might assist with the monitoring of oxidative balance in OSA. We conducted a systematic review and meta-analysis to evaluate the differences in circulating MDA concentrations between patients with OSA and non-OSA controls. A systematic search was conducted in the electronic databases Pubmed, Web of Science, Scopus and Google Scholar from inception to December 2020 by using the following terms: “malondialdehyde” or “MDA”; and “Obstructive Sleep Apnea Syndrome”, “OSAS” or “OSA”. We identified 26 studies in 1223 OSA patients and 716 controls. The pooled MDA concentrations were significantly higher in patients with OSA (standardized mean difference (SMD) 1.43 μmol/L, 95% confidence interval (CI) 1.03 to 1.83 μmol/L, p < 0.001). There was extreme heterogeneity between the studies (I² = 92.3%, p < 0.001).

In meta-regression analysis, the SMD was significantly associated with age, the assay type used and publication year. In our meta-analysis, MDA concentrations were significantly higher in OSA patients than in controls. This finding suggests that MDA, which is a marker of lipid peroxidation, is involved in the pathogenesis of OSA and provides insights for future studies investigating its potential clinical use.

Keywords: obstructive sleep apnea; lipid peroxidation; malondialdehyde; oxidative stress

1. Introduction

The obstructive sleep apnea syndrome (OSA) is a common breathing-related sleep disorder that affects over 900 million people worldwide and results in impaired quality of life and increased risk of motor vehicle accidents and cardiovascular diseases [1,2]. OSA is characterized by intermittent and repeated episodes of collapse of the upper airway during sleep, resulting in partial (hypopnea) or complete (apnea) airflow obstruction with consequent hypoxia and reoxygenation [3]. The fluctuations in oxygen saturation resemble the phenomenon of ischemia-reperfusion injury, which causes mitochondrial dysfunction and stimulates the production of reactive oxygen species (ROS) [4–6]. The excessive
ROS generation results in oxidation and consequent structural and functional damage of proteins, DNA and lipids [7]. In OSA patients, oxidative stress appears to be a major contributor to the adverse outcomes associated with this syndrome, particularly cardiovascular morbidity, vascular damage and endothelial dysfunction [8,9]. Lipid peroxidation, which is a direct consequence of oxidative stress, causes further oxidative damage in membranes, lipoproteins and other molecules that contain lipids. The varieties of secondary products, e.g., lipid hydroperoxides and various aldehydes, are generated during this process [10]. Malondialdehyde (MDA), one of the major aldehyde species, is produced by the peroxidative decomposition of unsaturated fatty acids [10]. This molecule represents one of the most studied indicators of lipid peroxidation degree and is measured as a biomarker of oxidative stress in different diseases, including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and several cancers [11–14]. Several studies have assessed MDA concentrations in OSA patients and controls, with conflicting results [15–17]. Therefore, the biological and clinical role of MDA in OSA is not well established. We sought to address this issue by performing a systematic review and meta-analysis to evaluate the presence and the effect size of the differences in the blood concentrations of MDA between patients with OSA and controls. A meta-regression was also conducted to investigate possible associations between effect size and specific patient, study design and analytical characteristics.

2. Methods

2.1. Search Strategy, Eligibility Criteria and Study Selection

A systematic search of the literature in the electronic databases such as Pubmed, Web of Science, Scopus and Google Scholar, from inception to December 2020, was performed using the following keywords and their combinations: “malondialdehyde” or “MDA”; and “Obstructive Sleep Apnea Syndrome”, “OSAS” or “OSA”. Two investigators independently performed the literature search by screening the abstracts. If they were found to be relevant, then the full articles were reviewed. The Eligibility criteria included the following: (i) analysis of MDA concentrations in plasma or serum; (ii) comparison of subjects with or without OSA (case-control design); (iii) adult patients; (iv) ≥10 patients with OSA; (v) studies reporting apnea-hypopnea index (AHI) values; (vi) English language; and (vii) full-text available. The references of individual articles were also reviewed to identify additional studies. Any discrepancy between the reviewers was resolved by a third investigator. The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) [18].

2.2. Statistical Analysis

In order to assess the differences in MDA concentrations between OSA and non-OSA subjects, standardized mean differences (SMD) were measured to set up forest plots of continuous data. The test was considered statistically significant when the P value was <0.05 and 95% confidence intervals (CIs) were reported. If necessary, the mean and standard deviation were extrapolated from the median and interquartile range, as previously reported by Wan et al. [19], from the median and range, as described by Hozo et al. [20], or from individual graphs using the Graph Data Extractor software. Heterogeneity of SMD across studies was examined using the Q statistic (the significance level was set at p < 0.10). The inconsistency between studies was quantitatively measured by I² statistic (I² < 25%—no heterogeneity; I² between 25% and 50—moderate heterogeneity; I² between 50% and 75%—large heterogeneity; I² > 75%—extreme heterogeneity) [21,22]. Statistical heterogeneity was defined as an I² statistic value ≥50% [22]. A random-effects model was used if the heterogeneity was high. Additionally, a sensitivity analysis was performed to test the influence of each study on the overall risk estimate by excluding one study at a time [23]. The presence of publication bias was evaluated by the analysis of the relation between study size and magnitude of effect using the Begg’s adjusted rank correlation test and the Egger’s regression asymmetry test at the p < 0.05 level of significance [24,25].
The presence of publication bias was further tested and eventually corrected using the Duval and Tweedie “trim and fill” procedure [26]. Confidence intervals at 95% (CIs) were reported for each effect size and the overall effect and \( p < 0.05 \) indicated statistical significance. Statistical analyses were performed using Stata 14 (STATA Corp., College Station, TX, USA). The study followed the principles defined in the PRISMA statement for reporting systematic reviews and meta-analyses [27].

3. Results

A flow chart describing the screening process is presented in Figure 1. The systematic search initially identified 1607 studies. After the first screening, 1567 were excluded because they were either duplicates or irrelevant. After a full-text revision of the remaining 40 articles, 14 were further excluded because of missing information or non-compliance with the inclusion criteria. Thus, 26 studies in 1233 OSA patients (mean age 49 years, 82% males) and 716 controls (mean age 48 years, 76% males) published between 2005 and 2018 were included in the meta-analysis (Table 1) [17,28–52]. The study by Wang L. et al. 2010 [34] divided OSA patients into two groups according to age (elderly and non-elderly patients). Therefore, this study was analyzed by considering the two groups separately in the following manner: (a) elderly and (b) non-elderly.

In all studies, OSA was diagnosed by polysomnography. Patients were recruited from a sleep center in 20 out of 26 studies. In the remaining six studies, patients were recruited from other clinical cohorts in two of the studies whereas no information regarding the recruitment source was provided in four of the studies.

**Figure 1.** Flow chart of study selection.
Table 1. Participant characteristics of the studies included in the meta-analysis.

| First Author Year. Country | Control | OSA | Comorbidities | Control | OSA | Comorbidities |
|----------------------------|---------|-----|---------------|---------|-----|---------------|
| n  | Age Mean ± SD Range | Gender (M/F) | BMI Mean | AHI% | ODI% | SaO2 Mean (%)/SaO2 <90% (Min) | n  | Age Mean ± SD Range | Gender (M/F) | BMI Mean | AHI% | ODI% | SaO2 Mean (%)/SaO2 <90% (Min) | Comorbidities |
|---------------------------|---------|-----|-------------|-------|------|-----------------------------|-----|---------|-------------|-------|------|------|-----------------------------|---------------|
| Svatikova A et al. 2005. USA | 35 | 47 | -2 | 35/0 | 26 | NR | NR | - | 1.1 | 47 | -2 | 41/0 | 29.5 | 47 | NR | - | 13.2 | No comorbidities |
| Alzoghaibi MA et al. 2005. Saudi Arabia | 17 | 31 | ±1.5 | - | NR | 23.4 | NR | NR | NR | 25 | 50 | ±2.2 | - | NR | 36.3 | 62 | 62.3 | 93 | / | NR |
| Dikmenoglu L et al. 2006. Turkey | 11 | 46 | - | 8/3 | 26.6 | NR | NR | NR | DIAB 36.4% | HTN 45.4% | 11 | 50 | - | 8/3 | 31.1 | 55 | NR | NR | NR |
| Itzhaki S et al. 2007. Israel | 10 | 50 | ±4.4 | - | 8/2 | 28 | 7 | 0.9 | NR | HTN / DIAB / DLP 37.5% | 16 | 54 | ±8.3 | - | 11/5 | 28 | 30 | 15 | NR | HTN / DIAB / DLP 40% |
| Lavie L et al. 2007. Israel | 20 | 42 | ±10 | - | 16/4 | 26 | 6 | NR | - | 0.5 | No comorbidities | 20 | 42 | 11.1 | - | 16/4 | 26 | 29 | NR | - | 3.1 | No comorbidities |
| Cofta S et al. 2008. Poland | 21 | 52 | ±7 | - | 11/10 | 33.4 | NR | NR | NR | NR | 61 | 53 | ±6 | - | 43/18 | 32.5 | 23 | NR | NR | NR |
| Singh TD et al. 2010. India | 10 | 31 | ±1.2 | - | 10/0 | 32.9 | 2 | NR | NR | No comorbidities | 20 | 44 | ±2.4 | - | 20/0 | 24.5 | 61 | NR | NR | HTN 15% | DIAB 10% |
| Wang L et al. (a) 2010. China | 29 | 69 | ±4.2 | - | 27/2 | 26.8 | 3 | NR | NR | HTN 13.8% | 32 | 66 | ±7.2 | - | 30/2 | 23.3 | 39 | NR | NR | HTN 15.6% |
| Wang L et al. (b) 2010. China | 23 | 45 | ±12.3 | - | 20/3 | 25 | 3 | NR | NR | HTN 13% | 51 | 43 | ±8.3 | - | 46/5 | 28.3 | 45 | NR | NR | HTN 13.7% |
Table 1. Cont.

| First Author Year, Country | n | Age Mean ± SD Range | Gender (M/F) | BMI Mean | AHI% | ODI% | SaO2 Mean (%)/SaO2 <90% (Min) | Comorbidities | Control | n | Age Mean ± SD Range | Gender (M/F) | BMI Mean | AHI% | ODI% | SaO2 Mean (%)/SaO2 <90% (Min) | Comorbidities | OSA |
|-----------------------------|---|---------------------|--------------|----------|------|------|-------------------------------|---------------|---------|---|---------------------|--------------|----------|------|------|-------------------------------|---------------|-----|
| Ye L et al. 2010. China     | 52| 45 ± 0 -            | 37/15        | 26       | 2    | 3.5 | NR                           | No comorbidities | 127 | 45 ± 11 -            | 102/25       | 26.3    | 36   | 38.7 | NR                           | No comorbidities |     |
| Jurado-Gamez B et al. 2011. Spain | 23| 48 - 44-51          | 15/8         | 30       | 3    | 7   | 94 /-                         | DIAB 8%        | 46  | 45 - 40-47           | 34/12        | 31      | 46   | 49   | 93 /-                         | DIAB 4%        |     |
| Vatansever E et al. 2011. Turkey | 24| 47 ± 8              | 24/0         | 28.4     | 2    | NR  | NR                           | No comorbidities | 26  | 49 ± 9 -              | 26/0         | 28.7    | 38   | NR  | NR                           | No comorbidities |     |
| Lee SD et al. 2010. South Korea | 20| 44 ± 5.7 -          | 20/0         | 26.2     | 3    | 1.9 | 95.7 /0.04                   | HTN 4%         | 53  | 47 ± 8.1 -            | 53/0         | 26.6    | 32   | 26   | 94.4 /9.2                    | No comorbidities |     |
| Yagihara F et al. 2012. Brazil | 27| 66 ± 0.7            | 27/0         | 25.1     | 5    | NR  | 94 /1.2                      | DLP 40.7       | 30  | 66 ± 0.7              | 30/0         | 27.9    | 38   | NR  | 91 /76.7                     | DLP 40%       |     |
| Wysocka E et al. 2013. Poland | 44| 53 - 46-61          | 44/0         | 31.3     | 3    | NR  | NR                           | DIAB 50%       | 44  | 55 - 49-62            | 44/0         | 30      | 26   | NR  | NR                           | DIAB 50%       |     |
| Ashram YA et al. 2013. Egypt | 14| 73 ± 0.7            | 10/4         | NR       | NR   | NR  | NR                           | CVD 39.5% DIAB 42% HTN, 84.2% | 38  | 75 - 33-87            | 22/16        | NR      | 81   | 35   | 87 /23                       | No comorbidities |     |
| Chen PC et al. 2013. Taiwan | 20| 42 ± 11             | 15/5         | 26       | 3.3  | 1   | 94 /-                         | No comorbidities | 44  | 42 ± 12 -             | 33/11        | 26.7    | 15   | 10   | 94 /-                         | No comorbidities |     |
| First Author Year. Country | Control | OSA |
|----------------------------|---------|-----|
| Ntalapascha Met al. 2013. Greece | 13 50 ± 13 | 18 49 ± 10 |
| Okur HK et al. 2013. Turkey | 14 49 ± 8.6 | 44 44 ± 13 |
| Yardim-Akadym S et al. 2013. Turkey | 25 43 ± 8.2 | 117 50 ± 10.7 |
| Youssef HAA et al. 2014. Egypt | 18 45 ± 12.7 | 33 52 ± 11.5 |
| El-Kholy MG et al. 2015. Egypt | 20 49 ± 14.6 | 20 51 ± 8.2 |
| Araujo LdaS et al. 2015. Brazil | 20 33 ± 2 | 33 40 ± 1.5 |
| Lu CH et al. 2015 Taiwan | 31 40 ± 7.7 | 62 42 ± 10 |
| Tichanon P et al. 2016. Thailand | 13 53 ± 12.3 | 13 53 ± 12.4 |
## Table 1. Cont.

| First Author       | Year | Country | Control n | Age Mean ± SD Range | Gender (M/F) | BMI Mean | AHI% | ODI% | SaO2 Mean (%)/tSaO2 < 90% (Min) | Comorbidities | OSA n | Age Mean ± SD Range | Gender (M/F) | BMI Mean | AHI% | ODI% | SaO2 Mean (%)/tSaO2 < 90% (Min) | Comorbidities |
|--------------------|------|---------|-----------|--------------------|--------------|----------|------|------|--------------------------------|---------------|--------|--------------------|--------------|----------|------|------|--------------------------------|---------------|
| Yildirim T et al.  | 2017 | Turkey  | 129       | 51 ± 8.1          | 78/51        | NR       | NR   | NR   | NR                             | No Comorbidities | 81     | 49 ± 8.4            | 58/23        | NR       | 34   | NR   | NR                             | No Comorbidities |
| Li J et al.        | 2018 | China   | 33        | 42 ± 10.1         | 29/4         | 25.8     | 4    | 3.6  | 91.8/4                          | HTN 9%         | 117    | 45 ± 10             | 105/12       | 25       | 25   | 28   | 94/11                          | HTN 13%        |

BMI: body mass index (kg/m²); AHI: apnea-hypopnea index (events/h); ODI: oxygen desaturation index (events/h); SaO2: oxygen saturation; tSaO2 < 90% cumulative time during which the saturation of oxyhemoglobin was below 90%; CVD: cardiovascular diseases; HTN: hypertension; DIAB: diabetes; DLP: dyslipidemia; NR: not reported.
MDA concentrations in the included studies and the forest plot for MDA levels in OSA patients and controls are reported, respectively, in Table 2, Supplementary Figure (Figure S1) and Figure 2. In all studies, OSA patients had higher MDA concentrations compared to the controls (mean difference range, 0.01 to 3.98), although the difference was not statistically significant in five of the studies [28,38,40,43,49]. Our analysis revealed a substantial heterogeneity between studies ($I^2 = 92.3\%$, $p < 0.001$). Thus, random-effects models were used. Overall, pooled results showed significantly higher MDA levels in patients with OSA (SMD 1.43, 95% CI 1.03 to 1.83, $p < 0.001$). The corresponding pooled SMD values were not altered when each study was consecutively removed as shown by sensitivity analysis (effect size range, between 1.31 and 1.49, Figure 3). The funnel plot (Figure 4) indicated a possible distortive effect of five studies on the right side of the graph [37,39,41,44,51]. Their exclusion attenuated both the effect size (SMD 0.98, 95% CI 0.73 to 1.22, $p < 0.001$) and the heterogeneity ($I^2 = 76\%$, $p < 0.001$). Analysis of the remaining studies showed a trend toward publication bias, as indicated by the Begg’s ($p = 0.04$) and Egger’s ($p = 0.16$) test. Accordingly, the trim-and-fill method revealed six potential missing studies to be added to the left side of the funnel plot to obtain symmetry (Figure 5). The resulting SMD remained significant despite the further attenuation (SMD 0.73, 95% CI 0.46 to 0.99, $p < 0.001$).

| Study Name          | Year | SMD (95% CI) | OSA, N mean (SD) | CTRL, N mean (SD) | % Weight |
|---------------------|------|--------------|------------------|-------------------|----------|
| Svatkova A et al.   | 2005 | 0.60 (0.14, 1.06) | 41, 6.3 (5)       | 35, 6.5           | 3.90     |
| Atzoghiabi MA et al.| 2005 | 0.01 (-0.61, 0.62) | 25, 4.64 (2.9)   | 17, 4.82 (2.2)    | 3.74     |
| Dikmenoglu L et al. | 2006 | 1.06 (0.16, 1.95) | 11, 68.7 (30.5)  | 10, 45.5 (11)     | 3.40     |
| Ithaki S et al.     | 2007 | 0.95 (0.11, 1.78) | 16, 18.8 (6.2)   | 10, 13.6 (4)      | 3.48     |
| Lavie L et al.      | 2007 | 1.28 (0.59, 1.96) | 20, 19.1 (7.6)   | 21, 11.5 (3.6)    | 3.67     |
| Cofta S et al.      | 2008 | 1.15 (0.62, 1.67) | 61, 13.7 (8.5)   | 21, 5.7 (5.7)     | 3.84     |
| Singh TD et al.     | 2010 | 1.77 (0.88, 2.66) | 20, 12.7 (4.8)   | 29, 10.7 (4.7)    | 3.82     |
| Wang L et al. (a)   | 2010 | 0.01 (0.08, 0.17) | 32, 6.18 (1.23)  | 24, 11.2 (4.7)    | 3.85     |
| Wang L et al. (b)   | 2010 | 0.07 (0.25, 1.27) | 51, 5.18 (1.51)  | 24, 11.2 (4.7)    | 3.85     |
| Ye L et al.         | 2010 | 0.05 (0.17, 1.39) | 127, 6.4 (2)     | 52, 4.5 (2.9)     | 3.99     |
| Jurado-Gamez B et al.| 2011 | 1.03 (0.50, 1.56) | 46, 2.73 (1.3)   | 23, 1.63 (2.3)    | 3.83     |
| Vatanasever E et al.| 2011 | 2.69 (2.09, 3.69) | 26, 1.08 (0.6)   | 31, 9.7 (8.5)     | 3.85     |
| Lee SD et al.       | 2012 | 0.33 (-0.19, 0.84) | 53, 2.21 (4.7)   | 20, 2.05 (5.2)    | 3.85     |
| Yagihara F et al.   | 2012 | 3.46 (2.63, 4.29) | 30, 3.5 (4.8)    | 27, 1.6 (8)       | 3.49     |
| Wysocka E et al.    | 2013 | 0.13 (-0.29, 0.55) | 44, 6.2 (1.4)    | 44, 6.2 (1.6)     | 3.93     |
| Ashram YA et al.    | 2013 | 3.13 (2.26, 4.00) | 38, 5.0 (17)     | 14, 4.2 (4)       | 3.44     |
| Chen PC et al.      | 2013 | 1.12 (0.65, 1.79) | 44, 5.5 (1.5)    | 20, 3.8 (1.9)     | 3.79     |
| Ntalapacha M et al. | 2013 | 0.53 (-0.20, 1.25) | 16, 6.82 (32)    | 13, 6.45 (10.2)   | 3.62     |
| Okur HK et al.      | 2013 | 3.62 (2.72, 4.52) | 44, 15.7 (3.6)   | 14, 4.1 (1.2)     | 3.40     |
| Yurdum-Akaydın S et al.| 2013 | 0.88 (0.44, 1.33) | 117, 3.17 (1.98) | 25, 2.24 (21)     | 3.91     |
| Youssif HAA et al.  | 2014 | 1.74 (1.07, 2.41) | 33, 4.44 (54)    | 18, 6.86 (17)     | 3.66     |
| El-Holy MG et al.   | 2015 | 1.55 (0.84, 2.27) | 20, 21.8 (7.8)   | 20, 12.4 (3.5)    | 3.64     |
| Araujo LdaS et al.  | 2015 | 0.88 (0.30, 1.46) | 33, 4.05 (21)    | 20, 3.88 (16)     | 3.78     |
| Lu CH et al.        | 2015 | 0.12 (-0.31, 0.55) | 62, 14.8 (6.3)   | 31, 14.1 (4.1)    | 3.92     |
| Tichanop P et al.   | 2016 | 2.26 (1.26, 3.27) | 13, 14.6 (7.8)   | 13, 2.1 (3)       | 3.27     |
| Yildirim T et al.   | 2017 | 3.98 (3.50, 4.45) | 81, 12 (9)       | 129, 7.1 (14)     | 3.89     |
| Li J et al.         | 2018 | 1.95 (1.50, 2.40) | 117, 6.5 (1)     | 33, 4.62 (82)     | 3.91     |
| Overall (I-squared = 92.3%, $p = 0.000$) | | 1.43 (1.03, 1.83) | 1223 | 718 | 100.00 |

**Figure 2.** Forest plot of studies investigating MDA concentrations in OSA patients and controls.
**Table 2.** MDA concentrations in the studies included in the meta-analysis.

| First Author Year. Country | NOS (stars) | Matrix Type | Assay Type | MDA Mean (µmol/l) ± SD |
|-----------------------------|-------------|-------------|------------|------------------------|
|                            |             |             |            | Control                | OSA         |
| Svatikova A et al. 2005. USA | 7           | P           | Sp         | 6.0 ± 0.5              | 6.3 ± 0.5   |
| Alzoghbai MA et al. 2005. Saudi Arabia | 6           | S           | Sp         | 4.6 ± 2.2              | 4.6 ± 2.9   |
| Dikmenoglu L et al. 2006. Turkey | 8           | P           | HPLC       | 45.5 ± 11 $^g$        | 69.7 ± 30.7 $^g$ |
| Itzhaki S et al. 2007. Israel | 9           | P           | Sp         | 13.6 ± 4.0             | 18.8 ± 6.2  |
| Lavie L. et al. 2007. Israel | 8           | P           | Sp         | 11.5 ± 3.6             | 19.1 ± 7.6  |
| Cofta S et al. 2008. Poland | 8           | P           | Sp         | 5.0 ± 3.7              | 13.7 ± 8.5  |
| Singh TD et al. 2010. India | 6           | P           | Sp         | 4.7 ± 1.3              | 12.7 ± 5.4  |
| Wang L et al. (a) 2010. China | 6           | S           | Sp         | 5.0 ± 0.7              | 6.2 ± 1.2   |
| Wang L et al. (b) 2010. China | 6           | S           | Sp         | 4.1 ± 1.1              | 5.2 ± 1.5   |
| Ye L et al. 2010. China | 8           | S           | Sp         | 4.5±1.2                | 6.4±2.0     |
| Jurado-Gamez B et al. 2011. Spain | 7           | P           | Sp         | 1.6±0.2                | 2.7±1.3     |
| Vatansever E et al. 2011. Turkey | 7           | S           | HPLC       | 0.9 ± 0.05             | 1.1 ± 0.06  |
| Lee SD et al. 2010. South Korea | 7           | S           | Sp         | 2.1 ± 0.5              | 2.2 ± 0.5   |
| Yagihara F et al. 2012. Japan | 9           | P           | Sp         | 1.6 ± 0.6              | 3.5 ± 0.5   |
| Wysocka E et al. 2013. Poland | 7           | P           | Sp         | 6.2±1.6                | 6.4±1.4     |
| Ashram YA et al. 2013. Egypt | 6           | S           | Sp         | 4.2 ± 0.4              | 50 ± 17     |
| Chen PC et al. 2013. Taiwan | 7           | P           | Sp         | 3.8 ± 1.1              | 5.5 ± 1.5   |
| Ntalapasa M et al. 2013. Greece | 7           | P           | Sp         | 6.5 ± 1.0              | 6.8 ± 0.3   |
| Okur HK et al. 2013. Turkey | 6           | S           | Sp         | 4.1 ± 1.2              | 15.7 ± 3.6  |
| Yardim-Akadyrm S et al. 2013. Turkey | 7           | P           | HPLC       | 2.2 ± 0.9              | 3.2 ± 1.1   |
| Youssef HAA et al. 2014. Egypt | 7           | P           | Sp         | 0.66 ± 0.17            | 1.44 ± 0.54 |
| El-Kholy MG et al. 2015. Egypt | 7           | P           | Sp         | 12.4 ± 3.5             | 21.8 ± 7.8  |
| Araujo LdaS et al. 2015. Brazil | 7           | S           | Sp         | 3.88 ± 0.16 $^§$      | 4.05 ± 0.21 $^§$ |
Table 2. Cont.

| First Author Year. Country | NOS (stars) | Matrix Type | Assay Type | MDA Mean (µmol/l) ± SD |
|---------------------------|-------------|-------------|------------|------------------------|
|                           |             |             |            | Control                | OSA        |
| Lu CH et al. 2015 Taiwan  | 8           | S           | Sp         | 14.1 ± 4.1             | 14.8 ± 6.3 |
| Tichanon P et al. 2016. Thailand | 8       | P           | Sp         | 2.1 ± 0.3              | 14.6 ± 7.8 |
| Yildirim T et al. 2017 Turkey | 6         | S           | ELISA      | 7.1 ± 1.4              | 12 ± 0.9   |
| Li J et al. 2018. China    | 7           | S           | Sp         | 4.6 ± 0.8              | 6.5 ± 1.0  |

NOS: Newcastle-Ottawa quality assessment scale for case-control studies; P: plasma; S: serum; Sp: spectrophotometric; ELISA: enzyme-linked immunosorbent assay; HPLC: high performance liquid chromatography; NR: not reported; \(^\text{§}\) nmol/L; \(^\text{¶}\) ng/mL.

Figure 3. Sensitivity analysis of the association between MDA and OSA. The influence of individual studies on the overall standardized mean difference (SMD) is shown. The middle vertical axis indicates the overall SMD and the two vertical axes indicate the 95% confidence intervals (CIs). The hollow circles represent the pooled SMD when the remaining study is omitted from the meta-analysis. The two ends of each broken line represent the 95% CIs.
Figure 4. Funnel plot of studies investigating MDA concentrations in OSA. The enclosed circles represent the five studies with a likely distortion effect on the funnel plot symmetry.

Figure 5. Funnel plot of studies investigating MDA concentrations in OSA after trimming and filling. Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively.
In order to explore possible sources of heterogeneity, we investigated, by meta-regression analysis, the effects of different study characteristics including between-group difference in age, gender, body mass index (BMI), publication year, continent where the study was conducted (Europe, Africa, Asia and America), biological sample (plasma or serum), assay type used (spectrophotometric, high-performance liquid chromatography (HPLC) or enzyme-linked immunosorbent (ELISA)), low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (TC), triglyceride (TG) and glucose concentrations and measures of OSA severity (apnea-hypopnea index, AHI). Extreme heterogeneity was observed both in studies reporting serum ($I^2 = 95.7\%, p < 0.001$) and plasma ($I^2 = 80.6\%, p < 0.001$) concentrations, although the between-study variance was relatively lower in the latter (Figure 6). In meta-regression analysis, non-significant differences ($t = 0.78$, $p = 0.44$) in SMD values were observed between plasma (SMD 1.26, 95% CI 0.89 to 1.62, $p < 0.001$) and serum (SMD 1.63, 95% CI 0.89 to 2.37, $p < 0.001$) concentrations. Similarly, non-significant differences ($t = 0.09$, $p = 0.93$) in pooled SMD values were observed across Asian (SMD 1.47, 95% CI 0.92 to 2.01, $p < 0.001$), American (SMD 1.61, 95% CI 0.13 to 3.09, $p < 0.001$), European (SMD 0.70, 95% CI 0.18 to 1.22, $p = 0.001$) and African studies (SMD 2.11, 95% CI 1.21 to 3.00, $p < 0.001$) (Figure 7). However, a relatively lower heterogeneity was observed in African ($I^2 = 76.8\%, p = 0.014$) and European studies ($I^2 = 73.5\%, p = 0.010$). Gender ($t = -0.10$, $p = 0.92$), BMI ($t = -0.41$, $p = 0.69$), TC ($t = -0.01$, $p = 0.99$), LDL ($t = -0.09$, $p = 0.93$), HDL ($t = 0.84$, $p = 0.42$), TG ($t = -0.71$, $p = 0.49$) and glucose ($t = 0.75$, $p = 0.47$) were not associated with the SMD. Conversely, age ($t = -2.06$, $p = 0.049$), assay type ($t = 2.31$, $p = 0.03$) and publication year ($t = 2.08$, $p = 0.048$) were significantly associated with the SMD.

**Figure 6.** Forest plot of studies examining MDA concentrations in OSA and in controls according to the type of biological sample (plasma or serum).
In order to evaluate the relationship between effect size and disease severity we performed a meta-analysis in a sub-group of nine studies reporting MDA concentrations in groups with different disease severity [32,35,37,38,42,45,47,49,52]. The forest plot for MDA concentrations in mild and severe OSA patients is reported in Figure 8. In two studies, patients with mild disease displayed significantly higher MDA values when compared to those with severe form (mean difference range, −0.04 to −0.55) [39,49]. By contrast, in the remaining seven studies, the MDA value was found to be higher in patients with severe disease (mean difference range 0.63 to 1.65), with a significant difference in four studies [35,37,42,52]. The pooled results showed that MDA concentrations were significantly higher in patients with severe disease (SMD 0.59; 95% CI 0.05 to 1.12, \( p = 0.03; \) \( I^2 = 86.7\%, p < 0.001 \)) when compared with mild disease.
4. Discussion

Several studies have reported an increase in oxidative stress in OSA patients, both in terms of enhanced ROS production and as increased lipid peroxidation products [53–56]. Intermittent cycles of hypoxia and reoxygenation, which are the hallmarks of OSA, are likely to be involved in the intracellular generation of ROS that overwhelms the antioxidant defense system [53]. The consequent oxidation of various macromolecules provides further demonstration of the increased oxidative stress in OSA. Among them, lipids are mostly subject to oxidation [8]. Additionally, several authors have reported that continuous positive airway pressure therapy (nCPAP) not only reduces intermittent hypoxia but also attenuates lipid peroxidation in OSA patients [14,57]. A recent systematic review reported the presence of high concentrations of biomarkers of oxidative stress in OSA and a correlation between these biomarkers and the severity of the disease [58]. MDA is the most abundant aldehyde generated during the lipid peroxidation process and represents one of the most investigated markers of oxidative stress status in different lung diseases [12,59]. Thus, MDA may be useful for characterizing and monitoring the oxidative balance in OSA over time.

Our meta-analysis showed that pooled MDA concentrations were significantly higher in OSA patients compared to non-OSA controls. The observed SMD value, 1.43, suggests an effect size that is both biologically and clinically significant [60]. There was a large between-study heterogeneity, but, nevertheless, the sensitivity analysis showed that the overall SMD did not change significantly when each study was removed in turn. After excluding five studies that impaired the funnel plot symmetry the effect size was reduced but the SMD value remained significant and the magnitude of the heterogeneity decreased. In addition, the Begg’s test, but not the Egger’s test, revealed the presence of publication bias. Accord-

---

**Figure 8.** Forest plot of studies examining MDA concentrations in mild and severe OSA patients.

| Study          | Year | SEVERE | MILD | %   |
|----------------|------|--------|------|-----|
|                |      | SMD (95% CI) | N, mean (SD) | N, mean (SD) | Weight |
| Coffa S et al. | 2008 | 0.23 (-0.39, 0.84) | 19, 14.7 (4.8) | 22, 13.4 (6.4) | 11.14 |
| Ye L et al.    | 2010 | 1.58 (1.10, 2.06) | 45, 8.1 (2.9) | 43, 4.6 (1.1) | 11.82 |
| Vatanseven E et al. | 2011 | 1.04 (0.18, 1.90) | 17, 1.11 (0.07) | 9, 1.03 (0.09) | 9.78 |
| Lee SD et al.  | 2012 | -0.04 (-0.59, 0.50) | 22, 2.2 (0.48) | 31, 2.22 (0.74) | 11.50 |
| Chen PC et al. | 2013 | 0.78 (0.17, 1.40) | 21, 6.1 (1.9) | 23, 4.9 (1.1) | 11.14 |
| Yardim-Akady et al. | 2013 | 0.26 (-0.23, 0.75) | 39, 3.3 (1.1) | 28, 3 (1.2) | 11.78 |
| El-Kholy MG et al | 2015 | 0.32 (-0.57, 1.20) | 10, 23.1 (10.4) | 10, 20.5 (5.2) | 9.64 |
| Lu CH et al.   | 2015 | -0.55 (-1.08, -0.02) | 40, 14.5 (5.5) | 22, 17.5 (5.3) | 11.58 |
| Li J et al.    | 2018 | 1.65 (1.13, 2.17) | 36, 7.3 (1.1) | 41, 5.3 (1.3) | 11.63 |
| Overall (I-squared = 86.7%, p = 0.000) | | 0.59 (0.05, 1.12) | 249 | 229 | 100.00 |

**NOTE:** Weights are from random effects analysis.
ingly, the trim and fill analysis showed that six studies were potentially missing. Their addition to the left side of the funnel plot decreased the effect size without affecting the statistical significance. We conducted a subgroup analysis to further investigate the effect of different patient and study characteristics on the pooled SMD. Extreme heterogeneity was observed both in plasma and serum studies, whereas African and European studies were characterized by a relatively lower heterogeneity. Difference in age between controls and OSA; publication year; and assay type used were significantly related to the pooled SMD. In particular, the different assay type (spectrophotometric, ELISA or HPLC) may significantly account for between-study variance, with more specific assays as HPLC reporting larger between-group differences when compared with less specific spectrophotometric assays involving the use of thiobarbituric acid that is affected by interference with other chemical compounds in addition to MDA [61,62]. Several unreported factors might account for the observed heterogeneity including pre-analytical factors, e.g., time and conditions of sample storage; and specific methodologies and laboratory equipment for samples processing. Furthermore, control selection in case-control studies might have also affected the between-group difference. Whilst controls usually consisted of healthy subjects in some studies, their definition was not specified in others and they were simply described as “patients without OSA”. Additionally, the studies with unreported clinical parameters, e.g., smoking status, use of specific medications and presence of comorbidities that are known to affect oxidative/antioxidative balance and hence circulating MDA concentrations, might have accounted for the reported heterogeneity and publication bias. Unfortunately, the low number of articles reporting these data prevents further meta-regression analyses.

In the evaluation of the relationship between effect size and disease severity, the pooled SMD showed that MDA concentrations were significantly higher in patients with severe OSA compared to those with mild OSA. Although the number of studies that analyzed OSA patients according to the AHI is limited, our findings suggest the presence of a relation between severity of disease and oxidative stress.

The analysis of the effect of OSA treatment on circulating MDA concentrations, particularly in relation with different degrees of severity, represents an important issue. However, the lack of randomized controlled studies reporting this feature represents another limitation of our study. Nevertheless, our meta-analysis provides robust background information for the adequate design and conduct of further studies addressing this issue, particularly the usefulness of this marker for monitoring OSA and the effects of therapies. A recent meta-analysis has already demonstrated an increase of MDA in patients with OSA compared to the controls [63]. Even though the data obtained in terms of pooled SMD is similar in the two meta-analyses, our systematic search retrieved 26 studies involving a higher number of subjects compared to 14 studies analyzed by Fadaei R. et al. 2021 [63]. Additionally, the largest number of included articles permitted more factors relative to the investigation which might be related to the pooled SMD; these factors include publication year, geographic area, lipid profile and type of biological sample. Finally, our study also analyzed the concentrations of MDA in relation to disease severity. Therefore, our study provides a more complete and detailed picture with respect to MDA levels in OSA patients.

5. Conclusions

In conclusion, in our meta-analysis the significantly higher MDA concentrations observed in OSA patients, when compared to non-OSA subjects, supports the presence of lipid peroxidation in OSA. The significant heterogeneity observed warrants the use of standardized methods and adequate definitions of non-OSA subjects in future studies investigating the possible use of MDA as a clinical biomarker of OSA and to monitor the effects of interventions.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/antiox10071053/s1, Figure S1: Bar chart showing MDA concentrations means in OSA patients and controls in the studies included in the meta-analysis. The assay type used is indicated above the bars. Sp: spectrophotometric. ELISA: enzyme-linked immunosorbent assay; HPLC: High
Performance Liquid Chromatography. * Statistical significance in presence of \( p < 0.05; \# \text{nmol/L}; \& \text{ng/mL}. \\

**Author Contributions:** Conceptualization, M.C.P., P.P. and A.Z.; methodology, M.C.P., A.Z. and E.Z.; formal analysis, A.A.M., A.Z. and G.P.; data curation and investigation, M.C.P., B.P. and S.S.F.; writing—original draft preparation, M.C.P. and E.Z.; writing—review, and editing, M.C.P., A.A.M., A.G.F. and P.P.; visualization, A.Z. and A.G.F.; supervision, P.P. and C.C.; funding acquisition, P.P. and C.C. All authors have read and agreed to the published version of the manuscript.

**Funding:** The research was supported by grants from the Sardinian Fondo di Sviluppo e Coesione (FSC) 2014–2020 and Patto per lo Sviluppo della Regione Sardegna, L.R.7-2017 (RASSR2005).

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

**References**

1. Benjafield, A.V.; Ayas, N.T.; Eastwood, P.R.; Heinzer, R.; Ip, M.S.M.; Morrell, M.J.; Nunez, C.M.; Patel, S.R.; Penzel, T.; Pépin, J.L.D.; et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: A literature-based analysis. *Lancet Respir. Med.* 2019, *7*, 687–698. [CrossRef]

2. Garvey, J.F.; Pengo, M.F.; Drakatos, P.; Kent, B.D. Epidemiological aspects of obstructive sleep apnea. *J. Thorac. Dis.* 2015, *7*, 920–929. [CrossRef] [PubMed]

3. Azagra-Calero, E.; Espinar-Escalona, E.; Barrera-Mora, J.M.; Llamas-Carreras, J.M.; Solano-Reina, E. Obstructive sleep apnea syndrome (OSA). Review of the literature. *Med. Oral. Patol. Oral. Cir. Bucal.* 2012, *17*, e925–e929. [CrossRef]

4. Suzuki, Y.J.; Jain, V.; Park, A.-M.; Day, R.M. Oxidative stress and oxidant signaling in obstructive sleep apnea and associated cardiovascular diseases. *Free Radic. Biol. Med.* 2006, *40*, 1683–1692. [CrossRef] [PubMed]

5. Lavie, L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia-Revisited-The bad ugly and good: Implications to the heart and brain. *Sleep Med. Rev.* 2015, *20*, 27–45. [CrossRef]

6. Peng, Y.-J.; Yuan, G.; Overholt, J.L.; Kumar, G.K.; Prabhakar, N.R. Systemic and cellular responses to intermittent hypoxia: Evidence for oxidative stress and mitochondrial dysfunction. *Adv. Exp. Med. Biol.* 2003, *536*, 559–564. [CrossRef]

7. Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.D.; Mazur, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.* 2007, *39*, 44–84. [CrossRef] [PubMed]

8. Lavie, L.; Lavie, P. Molecular mechanisms of cardiovascular disease in OSAHS: The oxidative stress link. *Eur. Respir. J.* 2009, *33*, 1467–1484. [CrossRef] [PubMed]

9. Mannarino, M.R.; di Filippo, F.; Pirro, M. Obstructive sleep apnea syndrome. *Eur. J. Intern. Med.* 2012, *23*, 586–593. [CrossRef]

10. Niki, E. Lipid peroxidation: Physiological levels and dual biological effects. *Free. Radic. Biol. Med.* 2009, *47*, 469–484. [CrossRef]

11. Fois, A.G.; Paliogiannis, P.; Sotgia, S.; Mangoni, A.A.; Zinellu, E.; Pirina, P.; Carru, C.; Zinellu, A. Evaluation of oxidative stress bi-markers in idiopathic pulmonary fibrosis and therapeutic applications: A systematic review. *Respir. Res.* 2018, *19*, 51. [CrossRef]

12. Paliogiannis, P.; Fois, A.G.; Sotgia, S.; Mangoni, A.A.; Zinellu, E.; Pirina, P.; Carru, C.; Zinellu, A. Circulating malondialdehyde concentration in patients with stable COPD: A systematic review and meta-analysis. *Biomark. Med.* 2018, *12*, 771–781. [CrossRef]

13. Jelic, M.; Mandic, A.; Maricic, S.; Srdjenovic, B. Oxidative stress and its role in cancer. *J. Cancer Res. Ther.* 2021, *17*, 22–28. [CrossRef]

14. Niki, E. Lipid peroxidation products as oxidative stress biomarkers. *BioFactors* 2008, *34*, 171–180. [CrossRef]

15. Barcelo, A.; Miralles, C.; Barbe, F.; Vila, M.; Pons, S.; Agusti, A.G.N. Abnormal lipid peroxidation in patients with sleep ap-noea. *Eur. Resp. J.* 2000, *16*, 644–647. [CrossRef]

16. Hopps, E.; Canino, B.; Calandrino, V.; Montana, M.; Presti, R.L.; Caimi, G. Lipid peroxidation and protein oxidation are related to the severity of OSAS. *Eur. Rev. Med Pharmacol. Sci.* 2014, *18*, 3773–3778.

17. Svatikova, A.; Wolk, R.; Lerman, L.O.; Juncos, L.A.; Greene, E.L.; McConnell, J.P.; Somers, V.K. Oxidative stress in obstructive sleep apnoea. *Eur. Heart J.* 2005, *26*, 2435–2439. [CrossRef]

18. Wells, G.; Shea, B.; O’Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non Randomised Studies in Meta-Analyses. 2013. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 29 June 2021).

19. 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*, 1–13. [CrossRef] [PubMed]

20. 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] [PubMed]

21. Bowden, J.; Tierney, J.F.; Copas, A.J.; Burdett, S. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. *BMC Med. Res. Methodol.* 2011, *11*, 41. [CrossRef] [PubMed]

22. Higgins, J.P.T.; Thompson, S.G. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 2002, *21*, 1539–1558. [CrossRef]

23. Tobias, A. Assessing the influence of a single study in the meta-analysis estimate. *Stata Tech. Bull.* 1999, *47*, 15–17.
24. Begg, C.B.; Mazumdar, M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* **1994**, *50*, 1088. [CrossRef]

25. Sterne, J.A.; Egger, M. Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *J. Clin. Epidemiol.* **2001**, *54*, 1046–1055. [CrossRef]

26. Duval, S.; Tweedie, R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biomet 2000*, *56*, 455–463. [CrossRef] [PubMed]

27. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gotzsche, P.C.; Ioannidis, J.P.; Clarke, M.; Devereaux, P.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *J. Clin. Epidemiol.* **2009**, *62*. [CrossRef] [PubMed]

28. Alzoghalbi, M.A.; Bahammam, A.S.O. Lipid peroxides, superoxide dismutase and circulating IL-8 and GCP-2 in patients with severe obstructive sleep apnea: A pilot study. *Sleep Breath.* **2005**, *9*, 119–126. [CrossRef] [PubMed]

29. Dikmenoglu, N.; Çiftçi, B.; Ileri, E.; Güven, S.F.; Seringeç, N.; Aksoy, Y.; Ercil, D. Erythrocyte deformability, plasma viscosities and oxidative status in patients with severe obstructive sleep apnea. *Sleep Med.* **2006**, *7*, 255–261. [CrossRef]

30. Itzhaki, S.; Dorchin, H.; Clark, G.; Lavie, L.; Lavie, P.; Pillar, G. The effects of 1-year treatment with a herbst mandibular ad-ancement splint on obstructive sleep apnea, oxidative stress, and endothelial function. *Chest* **2007**, *13*, 740–749. [CrossRef]

31. Lavie, L.; Vishnevsky, A.; Lavie, P. Oxidative stress and systemic inflammation in patients with sleep apnea: Role of obesity. *Sleep Biol. Rhyms.* **2007**, *5*, 100–110. [CrossRef]

32. Cofta, S.; Wysocka, E.; Piorunek, T.; Ryzymkowska, M.; Batura-Gabryel, H.; Torlinski, L. Oxidative stress markers in the blood of persons with different stages of obstructive sleep apnea syndrome. *J. Physiol. Pharmacol.* **2008**, *59* (Suppl. 6), 183–190. [PubMed]

33. Singh, T.D.; Patial, K.; Vijayan, V.K.; Ravi, K. Oxidative stress and obstructive sleep apnoea syndrome. *Indian J. Chest Dis. Allied Sci.* **2009**, *51*, 217–224. [PubMed]

34. Wang, L.; Li, J.; Xie, Y.; Zhang, X.-G. Association between serum homocysteine and oxidative stress in elderly patients with obstructive sleep apnea/hypopnea syndrome. *Biomed. Environ. Sci.* **2010**, *23*, 42–47. [CrossRef]

35. Ye, L.; Ma, G.-H.; Chen, L.; Li, M.; Liu, J.-L.; Yang, K.; Li, Q.-Y.; Li, N.; Wan, H.-Y. Quantification of circulating cell-free DNA in the serum of patients with obstructive sleep apnea–hypopnea syndrome. *Lung* **2010**, *188*, 469–474. [CrossRef]

36. Jurado-Gamez, B.; Fernandez-Marin, M.C.; Gomez-Chaparro, J.L.; Munoz-Cabrera, L.; Lopez-Barea, J.; Perez-Jimenez, F.; Lopez-Miranda, J. Relationship of oxidative stress and endothelial dysfunction in sleep apnoea. *Eur. Respir. J.* **2010**, *37*, 873–879. [CrossRef]

37. Vanatsever, E.; Surmen-Gur, E.; Urasvas, A.; Karadag, M. Obstructive sleep apnea causes oxidative damage to plasma lipids and proteins and decreases adiponectin secretion. *Sleep Breath.* **2011**, *15*, 275–282. [CrossRef] [PubMed]

38. Lee, S.D.; Ju, G.; Choi, J.-A.; Kim, J.-W.; Yoon, I.-Y. The association of oxidative stress with central obesity in obstructive sleep apnea. *Sleep Breath.* **2011**, *16*, 511–517. [CrossRef]

39. Yagihara, F.; Lucchesi, L.M.; D’Almeida, V.; de Mello, M.T.; Tufik, S.; Bittencourt, L.R.A. Oxidative stress and quality of life in elderly patients with obstructive sleep apnea syndrome: Are there differences after six months of continuous positive airway pressure treatment? *Clinics* **2012**, *67*, 556–571. [CrossRef]

40. Wysocka, E.; Cofta, S.; Piorunek, T.; Dziegielewksa-Gesia, S.; Bryl, W.; Torlinski, L. Blood antioxidant status, dysglycemia and obstructive sleep apnea. *Adv. Exp. Med. Biol.* **2016**, *785*, 121–129. [CrossRef]

41. Ashram, Y.A.; Wahab, N.H.A.; Diab, I.H. Non-dipping pattern of nocturnal blood pressure in patients with obstructive sleep apnea. *Sleep Breath.* **2011**, *15*, 367–371. [CrossRef] [PubMed]

42. Chen, P.-C.; Guo, C.-H.; Tseng, C.-J.; Wang, K.-C.; Liu, P.-J. Blood trace minerals concentrations and oxidative stress in patients with obstructive sleep apnea. *J. Nutr. Health Aging* **2013**, *17*, 639–644. [CrossRef] [PubMed]

43. Ntalapascha, M.; Makris, D.; Kyparos, A.; Tsilioni, I.; Kostikas, K.; Gourgoulianis, K.; Kouretas, D.; Zakynthinos, E. Oxida-tive stress in patients with obstructive sleep apnea syndrome. *Sleep Breath.* **2013**, *17*, 549–555. [CrossRef]

44. Okur, H.K.; Pelin, Z.; Yuksel, M.; Yosunkaya, S. Lipid peroxidation and paraoxonase activity in nocturnal cyclic and sustained intermittent hypoxia. *Sleep Breath.* **2013**, *17*, 365–371. [CrossRef] [PubMed]

45. Yardim-Akaydin, S.; Caliskan-Can, E.; Gokalp, F.; Firat, H.; Ardic, S.; Simsek, B. Lipid peroxidation and DNA damage in apnea patients with or without metabolic syndrome. *Sleep Biol. Rhythm.* **2013**, *11*, 116–124. [CrossRef]

46. Abu Youssef, H.A.; Elshazly, M.I.; Rashed, L.A.; Sabry, I.M.; Ibrahim, E.K. Thiobarbituric acid reactive substance (TBARS) a marker of oxidative stress in sleep apnea. *Egypt. J. Chest Dis. Tuberc.* **2014**, *63*, 119–124. [CrossRef]

47. El-Kholy, M.G.; El-Shafey, B.I.; Hanterra, M.S.; Ganna, S.A.; El-Sorogy, H.A.; Faisl, A.E.-R.F. Effect of continuous positive airway pressure on oxidative stress accompanied by obstructive sleep apnea. *Egypypt J. Bronc* **2015**, *9*, 192–197. [CrossRef]

48. Araújo, L.D.S.; Fernandes, J.F.R.; Klein, M.R.S.T.; Sanjuliani, A.F. 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*, 1351–1357. [CrossRef] [PubMed]

49. Lu, C.-H.; Lin, H.-C.; Huang, C.-C.; Lin, W.-C.; Chen, H.-L.; Chang, H.-W.; Friedman, M.; Chen, C.T.; Tsai, N.-W.; Wang, H.-C.; et al. Increased circulating endothelial progenitor cells and anti-oxidant capacity in obstructive sleep apnea after surgical treatment. *Clin. Chim. Acta* **2015**, *448*, 1–7. [CrossRef]

50. Tichanon, P.; Wilaivan, K.; Sopida, S.; Orapin, P.; Watchara, B.; Banjamas, I. Effect of continuous positive airway pressure on airway inflammation and oxidative stress in patients with obstructive sleep apnea. *Can. Respir. J.* **2016**, *2016*, 1–7. [CrossRef]
51. Yildirim, T.; Alp, R. The role of oxidative stress in the relation between fibromyalgia and obstructive sleep apnea syndrome. *Eur. Rev. Med. Pharm. Sci.* **2017**, *21*, 20–29.

52. Li, J.; Yu, L.Q.; Jiang, M.; Wang, L.; Fang, Q. Homocysteine level in patients with obstructive sleep apnea/hypopnea syndrome and the impact of continuous positive airway pressure treatment. *Adv. Clin. Exp. Med.* **2018**, *27*, 1549–1554. [CrossRef]

53. Avezov, K.; Aizenbud, D.; Lavie, L. Intermittent hypoxia induced formation of “endothelial cell-colony forming units” (EC-CFUS) is affected by ROS and oxidative stress. *Front. Neurol.* **2018**, *9*. [CrossRef] [PubMed]

54. Christou, K.; Kostikas, K.; Pastaka, C.; Tanou, K.; Antoniadou, I.; Gourgoulianis, K.I. Nasal continuous positive airway pressure treatment reduces systemic oxidative stress in patients with severe obstructive sleep apnea syndrome. *Sleep Med.* **2009**, *10*, 87–94. [CrossRef] [PubMed]

55. Dyugovskaya, L.; Lavie, P.; Lavie, L. Increased Adhesion Molecules Expression and Production of Reactive Oxygen Species in Leukocytes of Sleep Apnea Patients. *Am. J. Respir. Crit. Care Med.* **2002**, *165*, 934–939. [CrossRef]

56. Lavie, L. Oxidative stress—A unifying paradigm in obstructive sleep apnea and comorbidities. *Prog. Cardiovasc. Dis.* **2009**, *51*, 303–312. [CrossRef] [PubMed]

57. Minoguchi, K.; Yokoe, T.; Tanaka, A.; Ohta, S.; Hirano, T.; Yoshino, G.; O’Donnell, C.P.; Adachi, M. Association between lipid peroxidation and inflammation in obstructive sleep apnoea. *Eur. Respir. J.* **2006**, *28*, 378–385. [CrossRef] [PubMed]

58. Fiedorczuk, P.; Stróżyński, A.; Olszewska, E. Is the oxidative stress in obstructive sleep apnea associated with cardiovascular complications? Systematic review. *J. Clin. Med.* **2020**, *7*, 3734. [CrossRef] [PubMed]

59. Wood, L.; Gibson, P.; Garg, M. Biomarkers of lipid peroxidation, airway inflammation and asthma. *Eur. Respir. J.* **2003**, *21*, 177–186. [CrossRef]

60. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd ed.; Lawrence Erlbaum Associates: Mahwah, NJ, USA, 1998.

61. Ito, F.; Sono, Y.; Ito, T. Measurement and clinical significance of lipid peroxidation as a biomarker of oxidative stress: Oxidative stress in diabetes, atherosclerosis, and chronic inflammation. *Antioxidants* **2019**, *8*, 72. [CrossRef]

62. Tug, T.; Karatas, F.; Terzi, S.M.; Ozdemir, N. Comparison of serum malondialdehyde levels determined by two different methods in patients with COPD: HPLC or TBARS methods. *Lab. Med.* **2005**, *36*, 41–44. [CrossRef]

63. Fadaei, R.; Safari-Faramani, R.; Hosseini, H.; Koushki, M.; Ahmadi, R.; Rostampour, M.; Khazaie, H. Increased the circulating levels of malondialdehyde in patients with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep Breath.* **2021**, 1–8. [CrossRef]