

Changes of circulating biomarkers of inflammation and glycolipid metabolism by CPAP in OSA patients: a meta-analysis of time-dependent profiles

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Abstract

Background: Continuous positive airway pressure (CPAP) is the first-line therapy for moderate-to-severe obstructive sleep apnea (OSA). Specifying timing of CPAP benefits on OSA-related biomarkers will help to assess the effectiveness of CPAP and to optimize the treatment strategies.

Purpose: To explore the time-dependent changes of circulating biomarkers to CPAP treatment in patients with OSA, including inflammatory biomarkers [C-reactive protein (CRP) and tumor necrosis factor- α (TNF- α)] and glycolipid metabolic biomarkers [fasting blood glucose (FBG), fasting insulin (FINS), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), and triglyceride (TG)].

Methods: Searches of PubMed and Embase database were completed. Two independent reviewers extracted data from 68 included studies. A meta-analysis was conducted using a random-effect (or fixed-effect) model and standardized mean difference (SMD) model. The timing profiles of circulating biomarkers changes of inflammation and glycolipid metabolism were analyzed based on different CPAP duration, that is, short-term (<3 months), mid-term (3–6 months), and long-term (≥ 6 months).

Results: Those first improved by short-term treatment include CRP [SMD: 0.73, 95% confidence interval (CI): 0.15–1.31; $p=0.014$], TNF- α [SMD: 0.48 (95% CI: 0.10–0.86; $p=0.014$)], FBG [SMD: 0.32 (95% CI: 0.07–0.57; $p=0.011$)], and LDL [SMD: 0.40 (95% CI: 0.18–0.62; $p=0.000$)]. Those first improved by the mid-term or long-term treatment include HDL [SMD: -0.20 (95% CI: -0.36 to -0.03; $p=0.018$)] and TC [SMD: 0.20 (95% CI: 0.05–0.34; $p=0.007$)]. There were insignificant changes for TG and FINS after short or long CPAP.

Conclusion: Our results imply that changes of circulating biomarkers for patients with OSA under CPAP treatment have a time-dependent profile.

Keywords: circulating biomarkers, continuous positive airway pressure, obstructive sleep apnea, phase-specific effectiveness

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Introduction

Obstructive sleep apnea (OSA), characterized by repetitive overnight hypoxic episodes and subsequent sleep fragmentation due to a complete or partial collapse of the upper airway, has become a

global health burden. It is estimated that 936 million adults worldwide aged 30–69 years suffer from OSA, among whom 425 million suffer from moderate-to-severe OSA.¹ Observational studies have linked OSA with an increased risk of insulin

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resistance, dyslipidemia, and cardiovascular diseases, and an enhanced mortality from COVID-19,²⁻⁵ which could be ascribed to oxidative stress and systemic inflammation.^{6,7} Targeting OSA may reduce the systemic inflammation, and improve the clinical outcomes. Continuous positive airway pressure (CPAP) has been the first-line therapy for moderate-to-severe OSA. It offers continuous positive pressure to prevent the occurrence of airway collapse and hypoxia and sleep fragmentation so as to ablate apneas in sleep and increase oxygen saturation and sleep quality. During the past two decades, circulating inflammatory and metabolic biomarkers including C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), fasting blood glucose (FBG), fasting insulin (FINS), and lipid profiles, which are important predictors for OSA-related cardiometabolic risk, have been widely explored for the evaluation of the role of CPAP treatment,⁸⁻¹⁵ but the results have not always coincided. It might be explained by different CPAP treatment duration. Therefore, we proposed that the choice of biomarkers for the evaluation should be based on the time-response characteristics of them.¹⁶

Several studies have demonstrated that benefits of CPAP on biomarkers have time-related profiles. For example, Mermigkis *et al.*¹⁷ reported a gradual decrease in CRP after 3 months of CPAP treatment, and a sharp drop after 6 months and reached a plateau after this time point. Simon *et al.*¹⁸ found that 2-month CPAP therapy resulted in a significant decrease of both total cholesterol (TC) and low-density lipoprotein (LDL) levels compared with baseline values, and the effect was maintained after 6 months and 5 years of treatment, but no significant change in serum triglycerides (TG) or high-density lipoprotein (HDL) after 2 months, 6 months, and 5 years of CPAP treatment. Till now, current evidence is not conclusive about the time-dependent profiles of the various biomarkers in response to CPAP treatment. This present meta-analysis will provide some evidence for this issue.

Methods

Literature search process

PRISMA guidelines were followed to perform literature search.¹⁹ PICOS format was followed; P: glycolipid metabolic and inflammatory biomarkers (CRP; TNF- α ; FBG; FINS; LDL; HDL;

TC; and TG), I: CPAP treatment, C: levels of biomarkers before and after treatment, O: improvement in biomarker levels. A comprehensive literature search was performed using the PubMed and Embase databases by using the following words: [(obstructive sleep apnea or sleep disorder breathing or obstructive sleep apnea hypopnea syndromes) and (continuous positive airway pressure or continuous positive pressure ventilation) and (markers or C-reactive protein or tumor necrosis factor- α or fasting blood glucose or insulin or low-density lipoprotein or high-density lipoprotein or cholesterol or triglyceride)].

Study selection

The inclusion and exclusion criteria were as follows: (1) studies written in English; (2) studies published between January 2000 and October, 2020; (3) studies performed on adults (>18 years old); (4) full-text manuscripts and quantitative data from before and after prospective CPAP intervention available; (5) studies evaluating the effects of CPAP withdrawal on sleep and physiology were excluded; (6) OSA was strictly defined as an apnea-hypopnea index (AHI) ≥ 5 events/h measured by polysomnography (PSG) or portable devices; (7) all the biomarker samples were derived from fasting blood in the morning; (8) studies using bilevel positive airway pressure and other positive airway pressure treatment were also included; (9) studies with identical data sets or the same study subjects were excluded; and (10) data from patients with poor adherence when reported by the manuscript were excluded. During the process of study selection, we found that there was limited available evidence from randomized controlled trials to analyze the time-dependent profile of the eight biomarkers. And to guarantee a homogeneity of research methods, we included before-and-after self-controlled studies in the meta-analysis. In addition, case reports, conference abstracts, and comments were not reviewed. Two investigators reviewed the titles, abstracts, and the full texts of the selected studies (Figure 1).

Quality assessment and data extraction

Study quality was assessed using the methodological index for nonrandomized studies (MINORS) which includes 12 items with the first 8 being specifically for noncomparative studies.²⁰ The items are scored 0 (not reported), 1 (reported

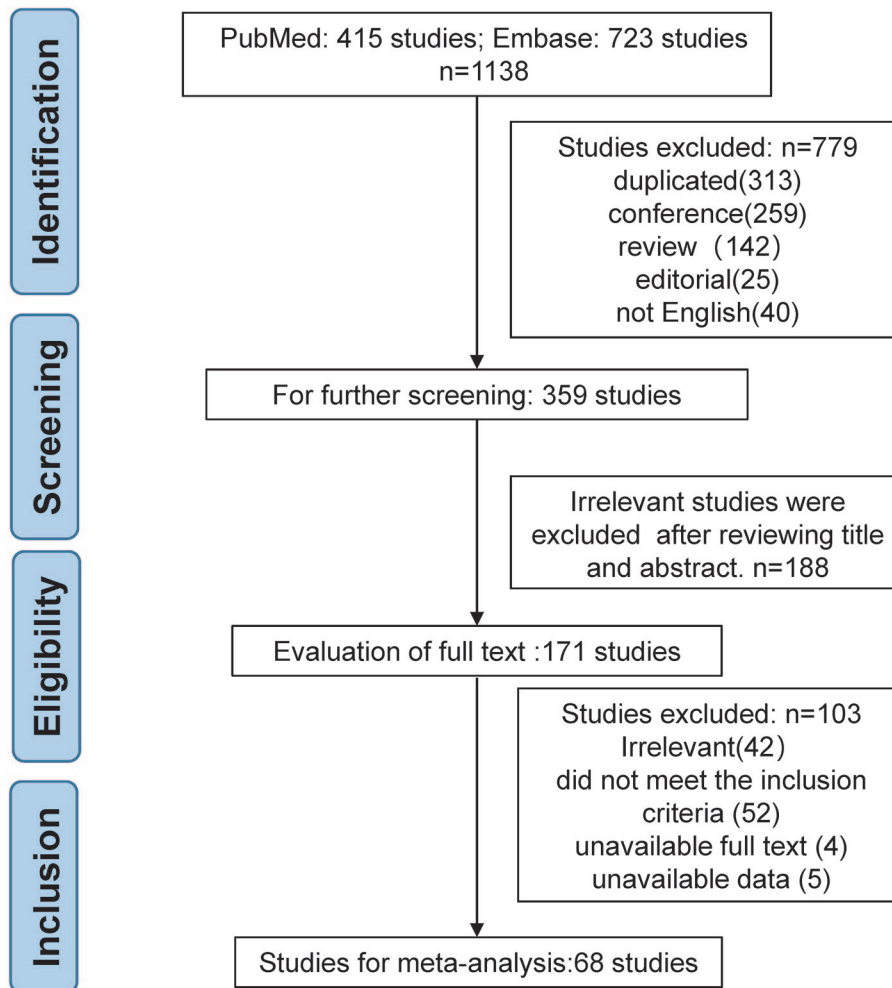


Figure 1. Literature search process.

but inadequate) or 2 (reported and adequate). The global ideal score is 16 for noncomparative studies. A score of ≤ 8 was considered poor quality, 9–14 moderate quality, and ≥ 15 good quality for noncomparative studies.²¹ The assessment of study quality was carried out by two independent investigators, and conflicting assessments were resolved by consensus with a third investigator.

The baseline characteristics of the included patients and quality score of each study were documented (Supplementary Table 1). We calculated estimated mean and standard deviation (SD) for each biomarker showed in median and interquartile ranges or ranges with the method reported in the publications,^{22,23} and to reduce error, data which were skewed significantly away from normality cannot be transformed into mean and SDs according to method by Shi *et al.*²⁴ If

data were reported in mean and standard error (SE), then SD would be calculated by multiplying SE by square root of the number of patients.

Statistical analysis

Meta-analysis was completed using Stata statistical software (Version 14.0; Stata Corporation, College Station, TX, USA), which was combined using a random-effect (or fixed-effect) model and standardized mean difference (SMD) meta-analysis model. The heterogeneity of SMD across studies was evaluated by I^2 and Q statistics. Statistical heterogeneity was defined as an I^2 statistic value $\geq 50\%$ or p value for heterogeneity (p^h) < 0.10 . The Galbraith plot was used to detect the possible studies causing heterogeneity. Egger's test was used to examine publication bias. Meta-regression was used to evaluate

effect of some confounding factors on CPAP effectiveness on biomarkers. Studies were divided into three subgroups based on the duration of CPAP treatment: short term (<3 months), mid-term (≥ 3 and <6 months), and long term (≥ 6 months).

Results

A total of 1138 studies were reviewed for inclusion, of which 68 studies were pooled for analysis of different circulating biomarkers, including 34 studies (1385 patients) for CRP, 15 studies (454 patients) for TNF- α , 33 studies (896 patients) for FBG, 22 studies (471 patients) for FINS, 21 studies (670 patients) for LDL, 26 studies (864 patients) for HDL, 28 studies (918 patients) for TC, and 30 studies (1021 patients) for TG.

Inflammatory biomarkers

1. CRP: The overall pooled SMD and its 95% confidence interval (CI) for CRP was calculated to be 0.50 (95% CI: 0.34–0.67, $Z=6.08$, $p=0.000$; $I^2 = 72.4\%$, $p^h = 0.000$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were 0.73 (95% CI: 0.15–1.31; $p=0.014$), 0.50 (95% CI: 0.28–0.73; $p=0.000$), and 0.40 (95% CI: 0.14–0.67; $p=0.003$), respectively (Figure 2). Galbraith plot suggested that five studies^{17,25–28} may have been the sources of heterogeneity.
2. TNF- α : The overall pooled SMD for TNF- α was 0.49 (95% CI: 0.22–0.76, $Z=3.61$, $p=0.000$; $I^2 = 72.3\%$, $p^h = 0.000$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were 0.48 (95% CI: 0.10–0.86; $p=0.014$), 0.45 (95% CI: –0.15 to 1.05; $p=0.140$), and 0.60 (95% CI: 0.26–0.94; $p=0.001$), respectively (Figure 3). Three studies^{25,29,30} were found to be potential sources of heterogeneity suggested in the Galbraith plot.

Fasting glucose and insulin

1. FBG: The overall pooled SMD for FBG was 0.22 (95% CI: 0.10–0.33, $Z=3.57$, $p=0.000$; $I^2 = 34.7\%$, $p^h = 0.028$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were 0.32

(95% CI: 0.07–0.57; $p=0.011$), 0.30 (95% CI: 0.14–0.46; $p=0.000$), and –0.03 (95% CI: –0.19 to 0.14; $p=0.736$), respectively (Figure 4). Two studies in the short-term³¹ and mid-term subgroup,³²(the IGT group) were found to be potential sources of heterogeneity in the Galbraith plot.

2. FINS: The overall pooled SMD for FINS was 0.05 (95% CI: –0.07 to 0.18, $Z=0.83$, $p=0.409$; $I^2 = 0\%$, $p^h = 0.888$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were 0.16 (95% CI: –0.05 to 0.37; $p=0.129$), 0.10 (95% CI: –0.13 to 0.34, $p=0.392$), and –0.11 (95% CI: –0.33 to 0.11, $p=0.327$), respectively (Figure 5).

Lipids profiles

1. LDL: The overall pooled SMD for LDL was 0.27 (95% CI: 0.16–0.38), $Z=4.93$, $p=0.000$; $I^2 = 0\%$, $p^h = 0.878$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were 0.40 (95% CI: 0.18–0.62; $p=0.000$), 0.19 (95% CI: 0.00–0.39; $p=0.050$), and 0.25 (95% CI: 0.09–0.41; $p=0.002$), respectively (Figure 6).
2. HDL: The overall pooled SMD for HDL was –0.16 (95% CI: –0.25 to –0.06), $Z=3.28$, $p=0.001$; $I^2 = 0\%$, $p^h = 0.878$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were –0.11 (95% CI: –0.36 to 0.14; $p=0.390$), –0.20 (95% CI: –0.36 to –0.03; $p=0.018$), and –0.15 (95% CI: –0.28 to –0.02; $p=0.028$), respectively (Figure 7). One heterogeneous study³³ in the mid-term subgroup was identified by the Galbraith plot.
3. TC: The overall pooled SMD for TC was 0.18 (95% CI: 0.09–0.28, $Z=3.89$, $p=0.000$; $I^2 = 1.6\%$, $p^h = 0.441$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were 0.23 (95% CI: –0.09 to 0.55; $p=0.158$), 0.14 (95% CI: –0.01 to 0.30; $p=0.069$), and 0.20 (95% CI: 0.05–0.34; $p=0.007$), respectively (Figure 8). The Galbraith plot suggested that two studies^{31,34} in the short-term subgroup could have caused heterogeneity.
4. TG: The overall pooled SMD for TG was 0.12 (95% CI: 0.03–0.21, $Z=2.74$,

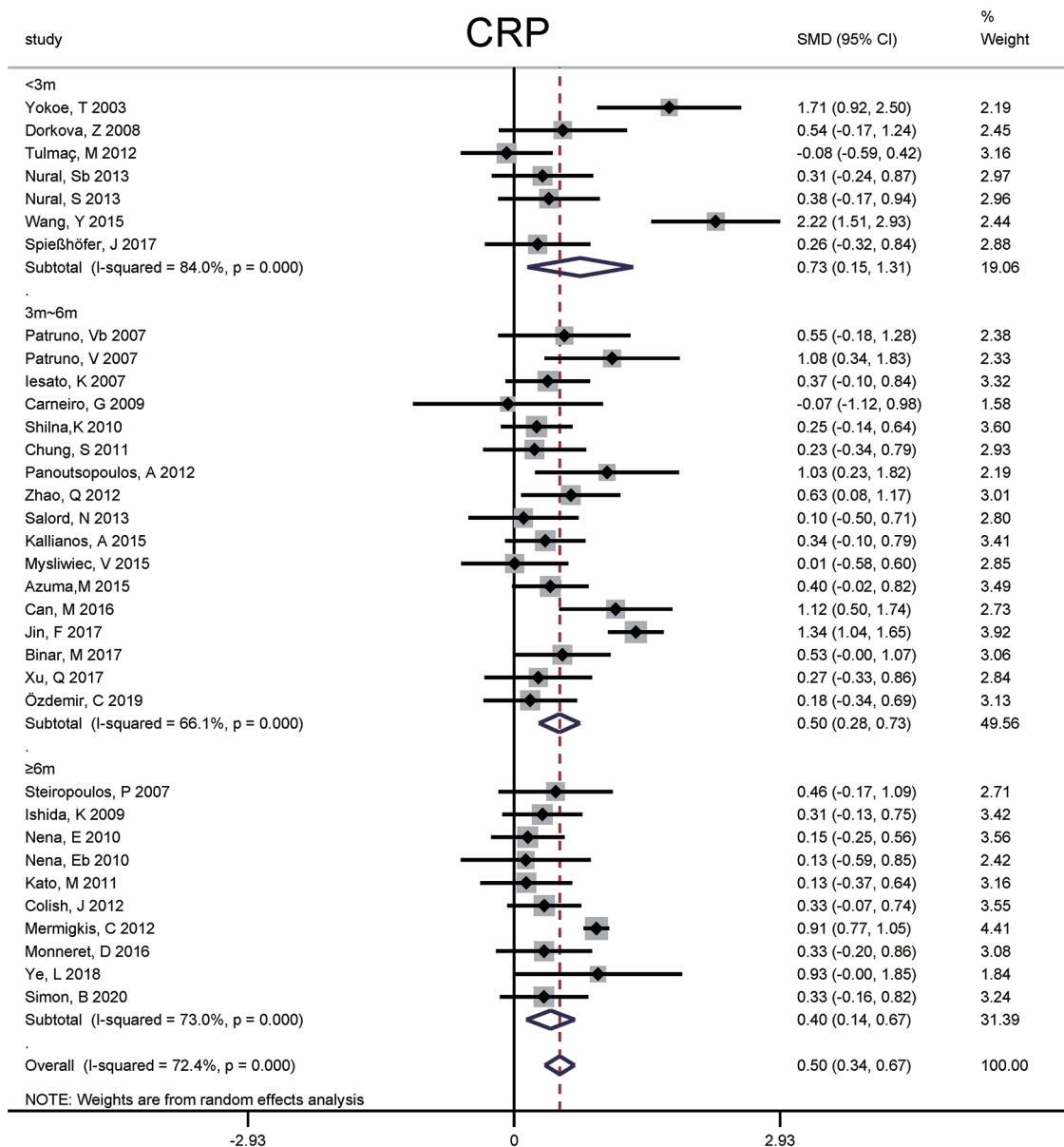


Figure 2. Forest plot for CRP.

$p = 0.006$; $I^2 = 0\%$, $p^h = 1.000$). Subgroup analysis showed that SMDs for the short-term, mid-term, and long-term subgroups were 0.17 (95% CI: -0.02 to 0.37 , $p = 0.084$), 0.11 (95% CI: -0.05 to 0.26 ; $p = 0.179$), and 0.11 (95% CI: -0.01 to 0.24 ; $p = 0.081$), respectively (Figure 9).

In summary, modest reductions in CRP, TNF- α , FBG, and LDL resulting from CPAP occurred in the early phase of treatment while marginal decreases in HDL and TC were only observed

after mid and long duration of CPAP treatment. Besides, no significant changes were found in FINS and TG at any time point (Figure 10).

Heterogeneity, quality score, and publication bias

The influence of heterogeneity on our results should be taken into consideration. Most of the heterogeneous studies^{17,25,26,28,29,31–34} had positive results. Two of the included studies were with low quality,^{35,36} and the rest were with moderate

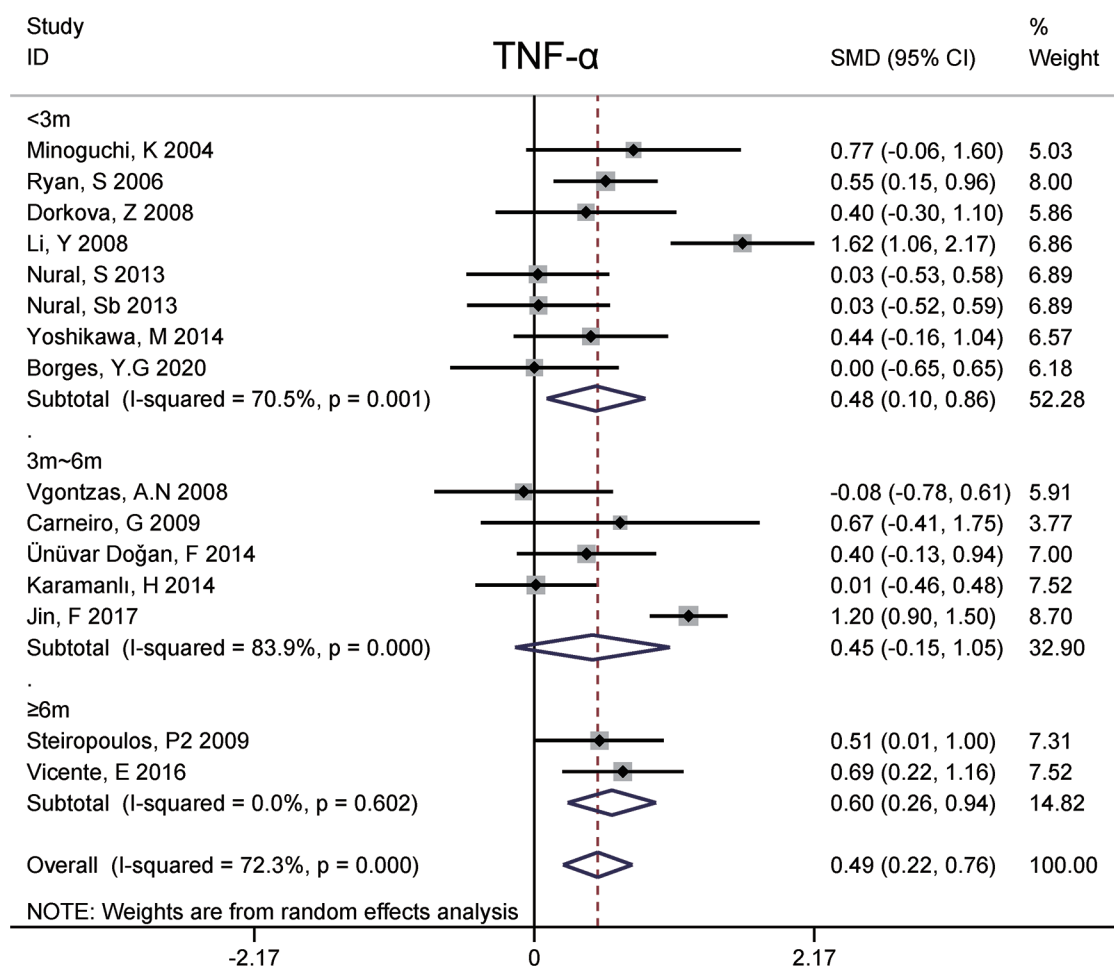


Figure 3. Forest plot for TNF- α .

quality (Supplementary Table 1). The Egger's test showed that there existed significant publication bias for CRP (short-term subgroup, $P_{\text{bias}} = 0.019$; long-term subgroup, $P_{\text{bias}} = 0.047$) and FBG (mid-term subgroup, $P_{\text{bias}} = 0.014$). After removing the heterogeneous and low-quality studies, the bias was still there only for FBG. Nevertheless, the effect of heterogeneity on the time-dependent profile of changes in those biomarkers is tiny if the heterogeneous and low-quality studies were removed.

Meta-regression

Meta-regression was performed to evaluate the effect of age, body mass index (BMI), AHI, and baseline biomarkers levels on the CPAP effectiveness on each biomarker. AHI, BMI, and age do not affect the changes of all biomarkers before and after CPAP treatment. Only baseline level of

FBG ($p=0.000$) and TNF- α ($p=0.003$) was found to have significant effect on improvement of these two biomarkers after treatment.

Discussion

OSA is a long-lasting condition with early repeated oxidative stress injury and pro-inflammatory releases, and several late cardiovascular diseases and other complications. The direct consequence of chronic intermittent hypoxia (CIH) is an oxidative imbalance, with reactive oxygen species production and the inflammatory cascade's activation with pro-inflammatory cytokines releases.³⁷ These products then, interacting with other factors such as sympathetic activation, cause subclinical target organ damage, including cardiac function and metabolic health.³⁸ Compared with the early effect of CPAP on improving respiratory events and daytime

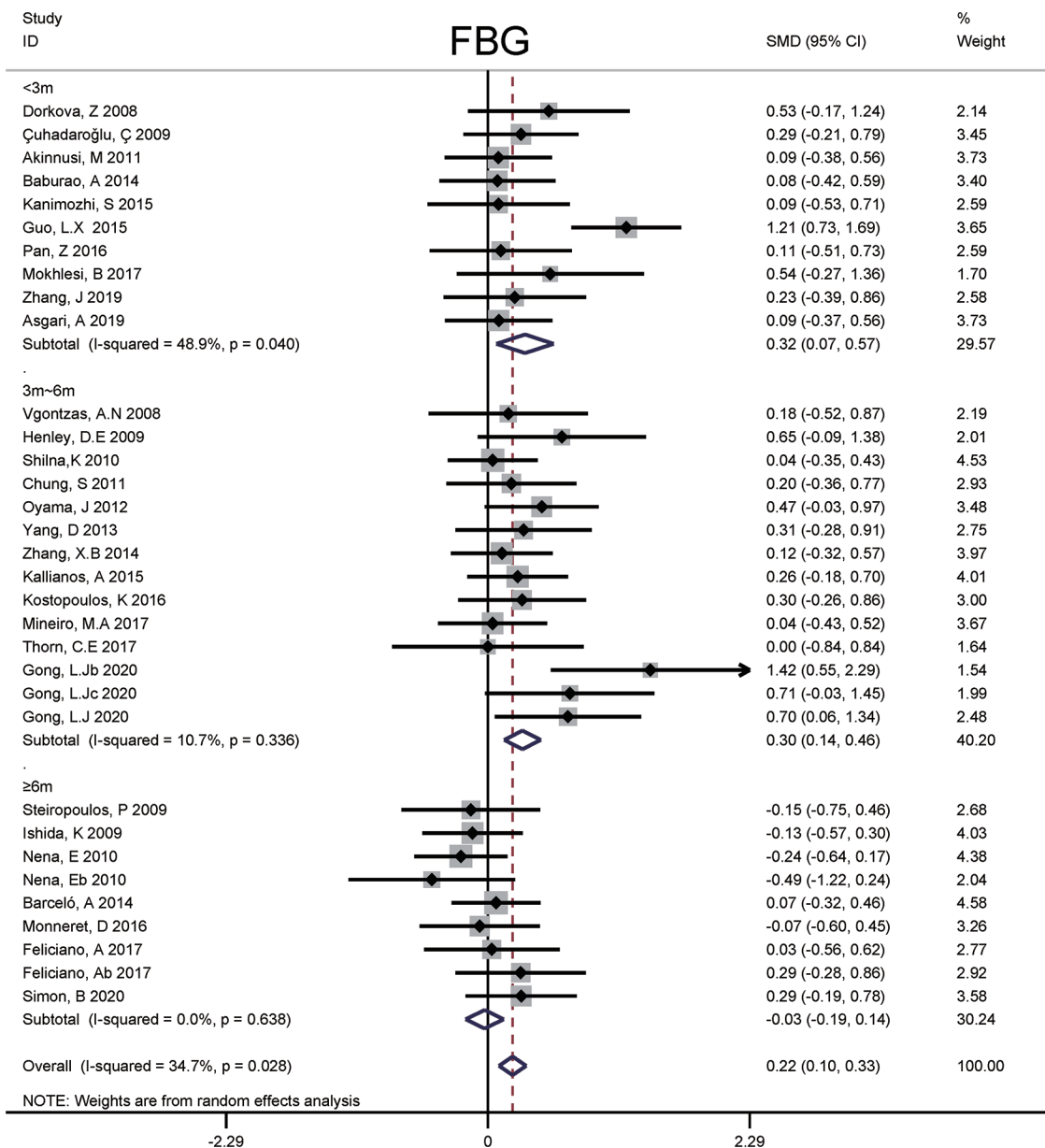


Figure 4. Forest plot for FBG.

sleepiness, improvement of different biomarkers by OSA treatment may show a time-dependent profile.¹⁶ However, how long it takes for CPAP to improve inflammatory and glycolipid metabolic biomarkers remains controversial. In this work, we tried to figure out the duration-different changes in the common inflammatory and glycolipid metabolic biomarkers before and after CPAP treatment. Our results indicated that the timing of CPAP benefits differs among different circulating biomarkers.

CRP and TNF- α were shown to have an early response to short-term CPAP. Increasing evidence suggests OSA should be viewed as low-grade chronic inflammatory disease.⁶ The inflammatory cytokines growth was a direct consequence of intermittent hypoxia by activating nuclear factor- κB (NF- κB), the master transcriptional regulator of inflammatory responses.³⁸ The results proved that a significant change of those biomarkers after short-term CPAP can be predicted. Besides, meta-regression suggested that, with

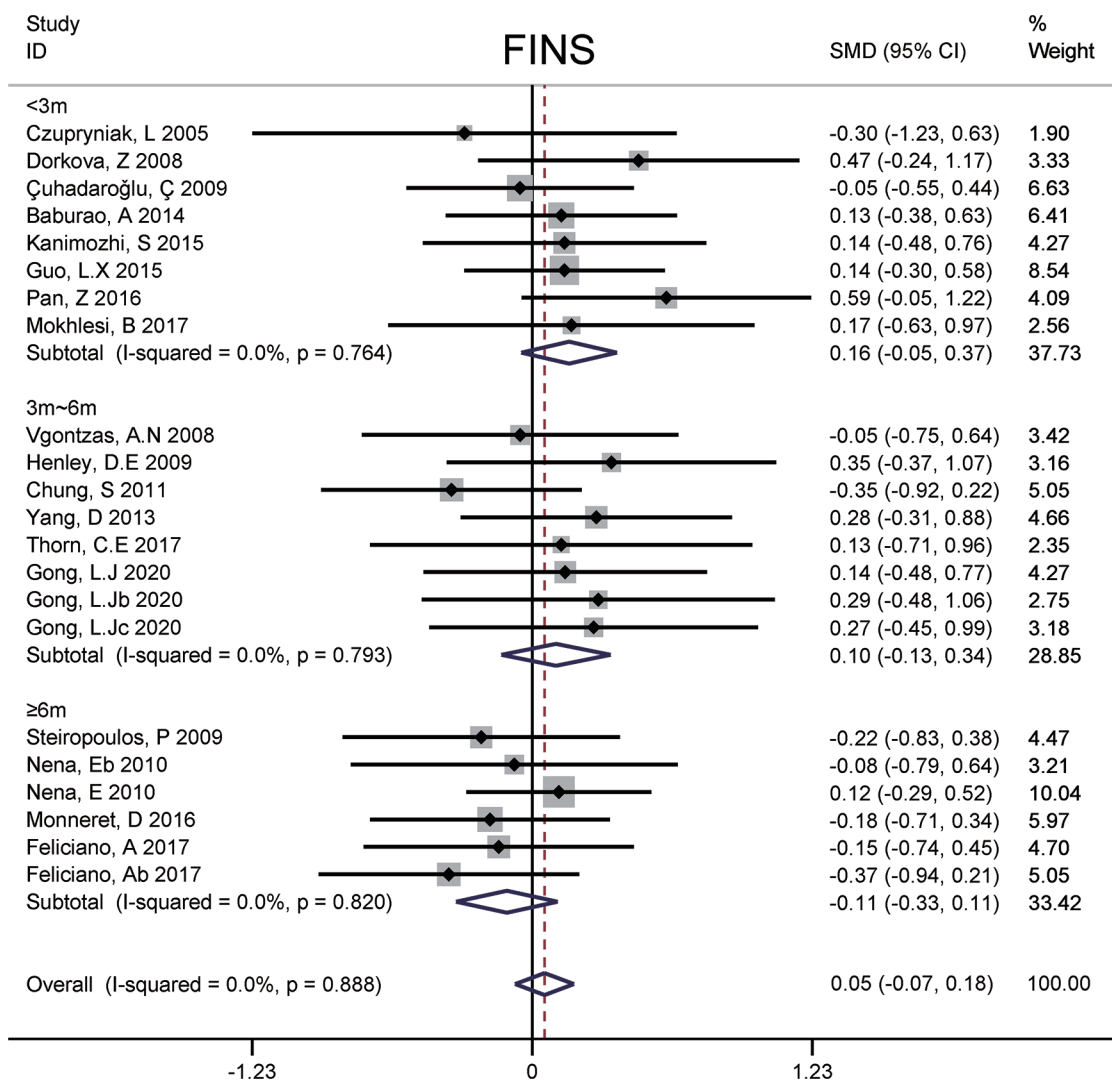


Figure 5. Forest plot for FINS.

baseline serum level ranging from 0.13 to 124.5 pg/ml, TNF- α in higher levels showed more reduction. Several studies demonstrated that patients with moderate-to-severe OSA showed higher level of TNF- α than those with mild OSA, obese control subjects, and healthy controls.^{39,40} Changes in AHI, the percentage of time with oxygen saturation (SpO₂) < 90%, and mean SpO₂ after treatment with CPAP were correlated with changes in serum levels of TNF- α .^{39,41} We did not identify a correlation between baseline AHI and the reduction of TNF- α in meta-regression. Therefore, it is presumable that a change of AHI or SpO₂, but not the baseline AHI, is associated with the reduction of TNF- α after CPAP treatment. However,

we were unable to conduct a meta-regression to evaluate correlation between the change of AHI and SpO₂ and the reduction of the eight biomarkers due to the missing value of post-CPAP polysomnographic parameters in many studies we analyzed.

Short-term CPAP usage significantly decreases serum levels of FBG while FINS remain unchanged after different duration of CPAP. CIH leads to several glucose metabolism alterations, including higher fasting glucose and insulin levels, insulin resistance, glucose intolerance, and β -cell dysfunction. Moreover, intermittent hypoxia-induced sympathetic excitation also

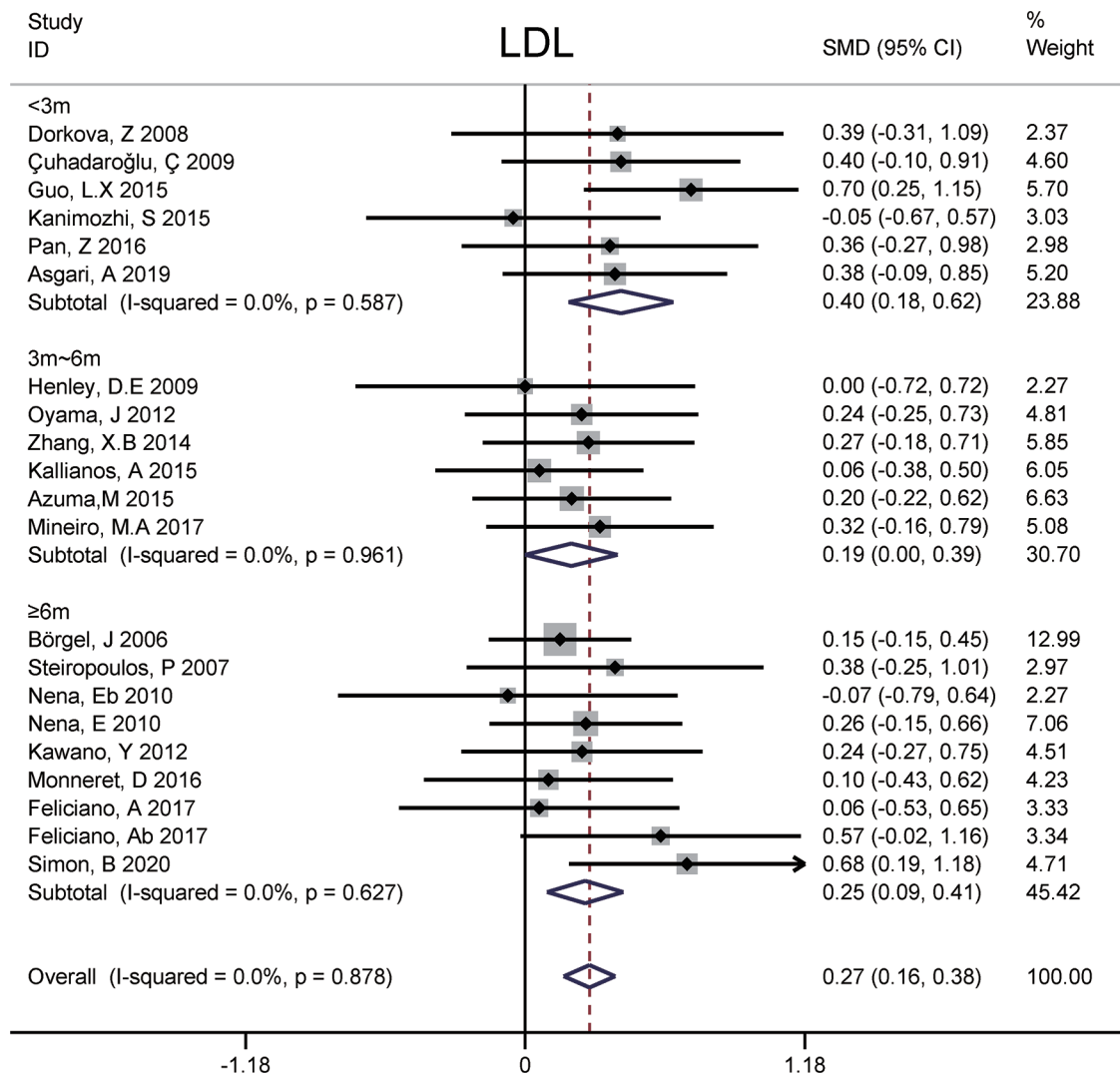


Figure 6. Forest plot for LDL.

probably decreases insulin sensitivity, reduces insulin-mediated glucose uptake, and stimulates hepatic gluconeogenesis.³⁸ SMDs of FBG in the short-term and mid-term subgroup were quite different from that of the long-term subgroup. We noticed that the studies^{31,32,42,43} in the short- and mid-term treatment subgroups displayed abnormal baseline FBG and showed more reduction in FBG. In the long-term subgroup, FBG was not found to be significantly changed after ≥ 6 months of treatment, which might be related to the normal baseline FBG level. The meta-regression analysis also confirmed that baseline FBG played a pivotal role in the effect of CPAP on FBG, which coincides with a previous review that speculated the beneficial effect of

CPAP was of larger magnitude in patients with poor glycemic control at baseline.² Despite no significant changes of FINS, there is clinical evidence^{11,12,14} supporting the effect of CPAP for insulin sensitivity improvement which is also an early response (less than 8 weeks of treatment).¹¹

We found that CPAP treatment improves serum levels of cholesterol in OSA patients, which is consistent with a previous meta-analysis.¹³ Serum levels of LDL could be decreased within short-term treatment, and mid-term or long-term CPAP increased serum levels of HDL and decreased serum levels of TC. CIH increases lipid delivery from the adipose tissue to the liver, up-regulates lipoprotein secretion, and delays

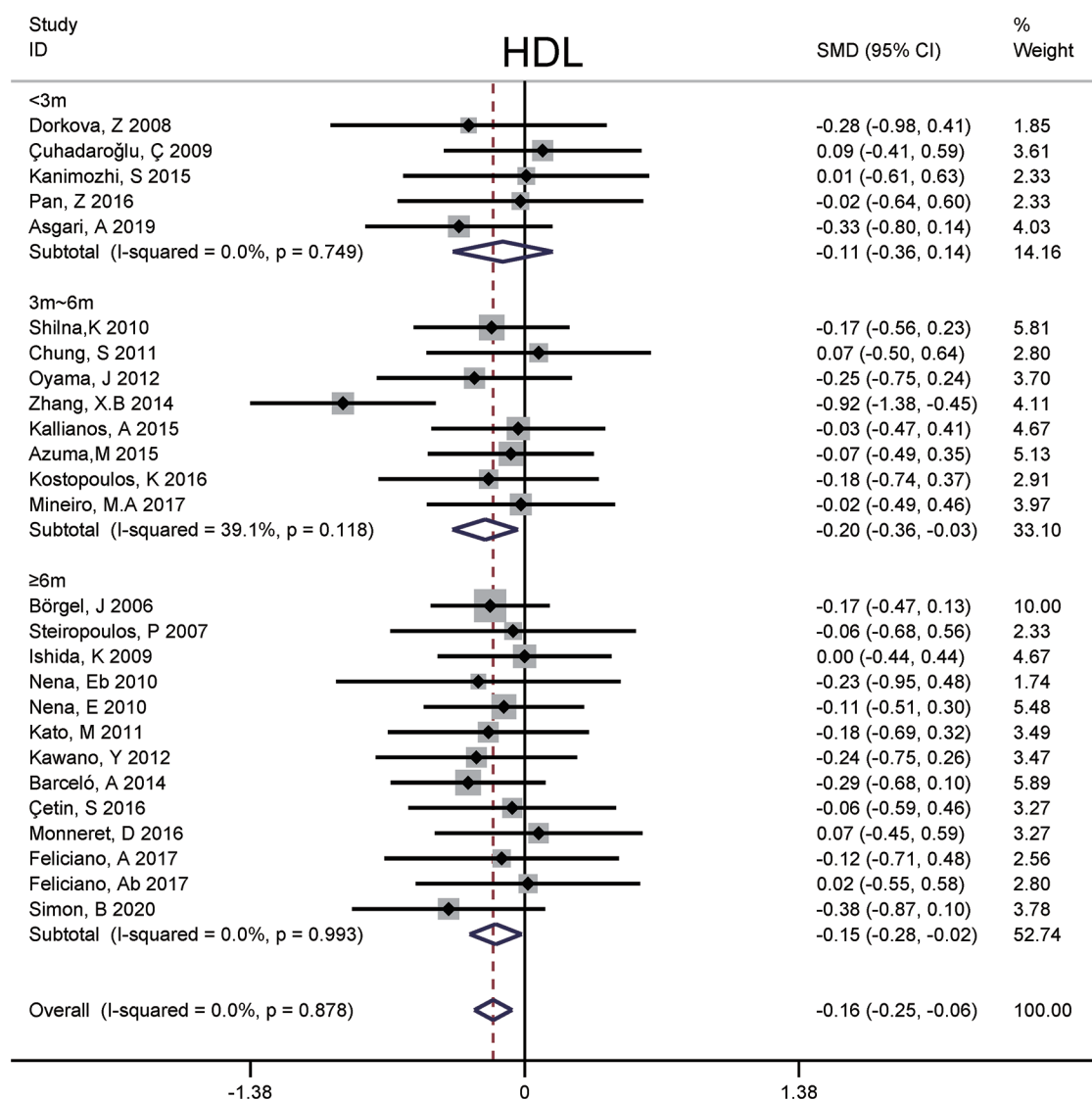


Figure 7. Forest plot for HDL.

lipoprotein clearance.⁴⁴ CPAP effectively corrects CIH and alleviates CIH-induced hypercholesterolemia. Unlike cholesterol, TG level seems to be less affected by CPAP than cholesterol. A previous study⁴⁵ showed that reductions in serum TG levels were greater in the group with combined-intervention of CPAP and weight loss than in the group receiving CPAP only, but were not different between the combined-intervention group and the weight-loss group. Changes in LDL and HDL levels were not different among the three groups (CPAP, weight loss, or both for OSA). It is possible that serum TG levels could be easily affected by confounding factors including weight changes and diet. This reminds clinicians that

interventions including weight loss and diet control should be recommended for OSA patients with hypertriglyceridemia even in participants with normal LDL-C levels.⁴⁶

The results tell us the evaluation of CPAP effectiveness should be a dynamic multi-parameter periodic process. It is a must for clinicians to understand the response time of some important OSA-related parameters to treatment. Time-specific biomarker candidates according to the results could be selected as TNF- α , CRP, FBG, and LDL for short-term effect; HDL and TC for mid- or long-term effects of CPAP treatment. When CPAP does not work at the expected time,

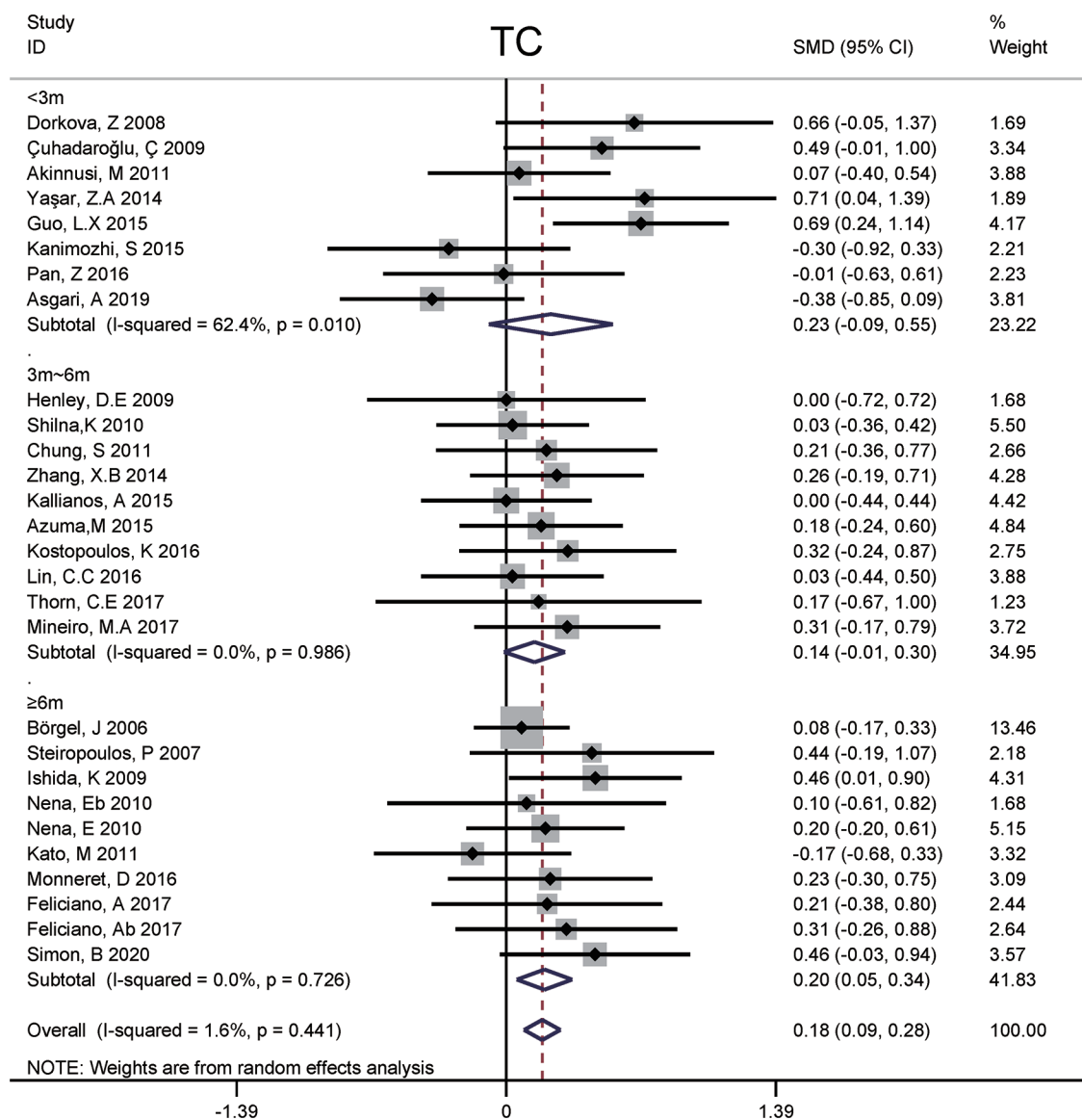


Figure 8. Forest plot for TC.

combination therapy should be considered such as a healthy diet, exercise, or anti-diabetic medications or lipid-lowering drugs.

There were some limitations in this study. We included before-and-after self-controlled studies, most of which were with small sample sizes and moderate quality. Only published studies were enrolled in the analysis, which could raise the possibility of publication bias. Heterogeneity was high in some cases. Besides, we were unable to perform meta-regression for other confounding factors, including sleepiness, nadir oxygen

saturation, or oxygen desaturation index, average use of CPAP every night due to the unavailable variables in many studies. In the future, high-quality research and more randomized controlled trials are necessary to give further insight into the time-dependent benefits of CPAP in OSA patients.

Conclusion

The time-dependent profile of circulating biomarkers under CPAP treatment provides evidence for selecting phase-specific indicators for

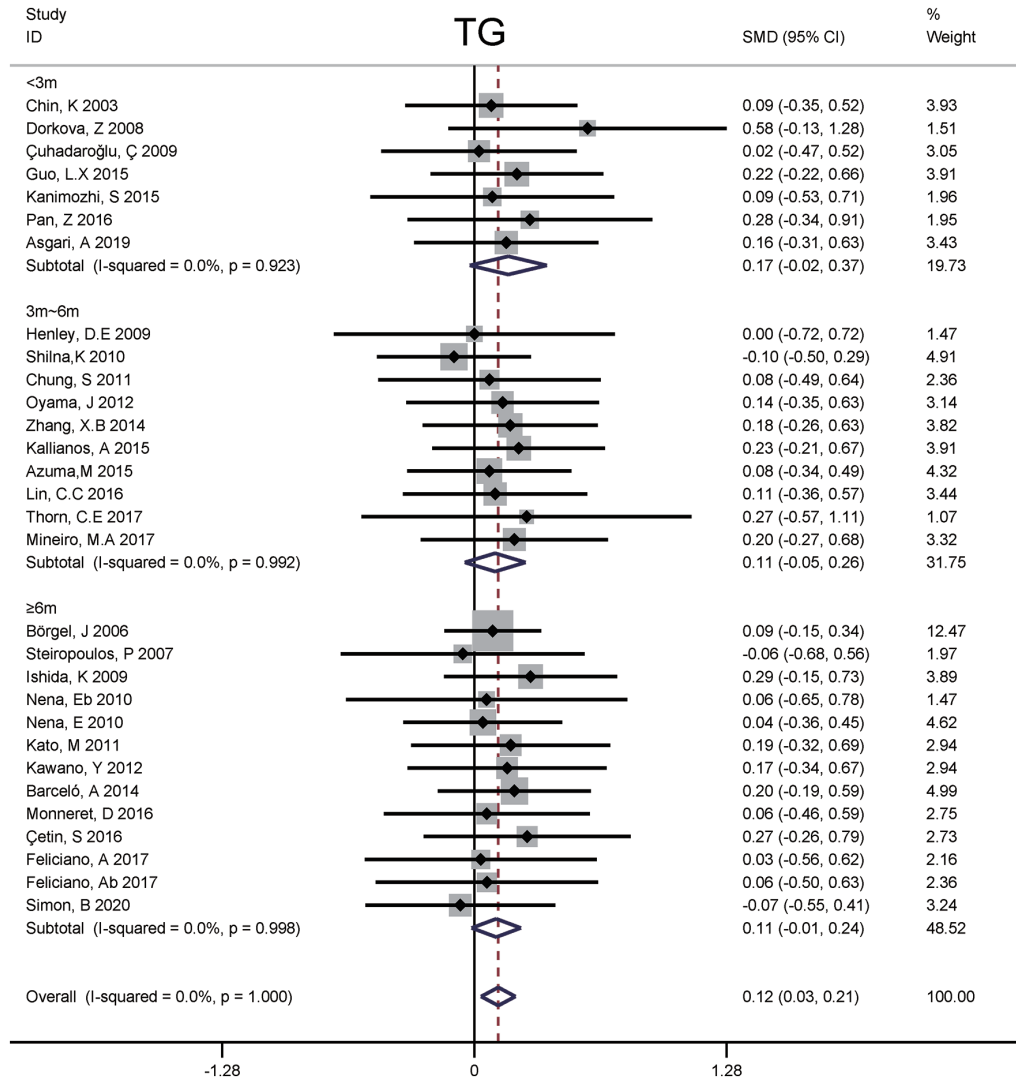


Figure 9. Forest plot for TG.

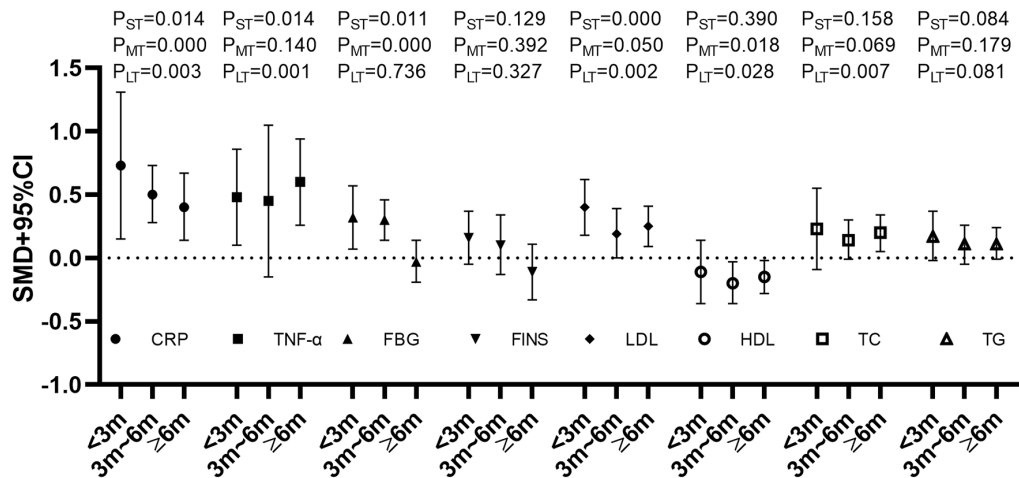


Figure 10. (Continued)

Figure 10. The time-dependent profile of the changes of CRP, TNF- α , FBG, FINS, LDL, HDL, TC, and TG after CPAP treatment in OSA patients. The vertical segments indicate the SMD (standardized mean difference) and its 95% CI (confidence interval). P_{ST} , P_{MT} , and P_{LT} represent the p value of SMD for short-term [ST, <3 m (months)] mid-term (MT, 3–6 m), and long-term (LT, \geq 6 m) subgroups, respectively; p value < 0.05, post-CPAP treatment *versus* pre-CPAP treatment. Reductions in CRP, TNF- α , FBG, and LDL resulting from short-term CPAP treatment, decreases in HDL and TC by mid- and long-term CPAP, and no significant change in FINS and TG at any time point.

the assessment of CPAP effectiveness, and taking comprehensive strategies besides CPAP for OSA treatment. When it comes to designing an interventional study of OSA, such as evaluation of effects of CPAP or mandibular appliance on OSA-related outcomes, a time-dependent manner should never be ignored.

Author contributions

Yi Wang: Conceptualization; Formal analysis; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Ying Ni Lin: Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Li Yue Zhang: Conceptualization; Investigation; Methodology; Writing – review & editing.

Chuan Xiang Li: Investigation; Methodology; Writing – review & editing.

Shi Qi Li: Investigation; Methodology; Writing – review & editing.

Hong Peng Li: Methodology; Writing – review & editing.

Liu Zhang: Formal analysis; Writing – review & editing.

Ning Li: Methodology; Writing – review & editing.

Ya Ru Yan: Methodology; Writing – review & editing.

Qingyun Li: Conceptualization; Methodology; Resources; Writing – original draft; Writing – review & editing.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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