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Original Article

Efficacy of continuous positive airway pressure (CPAP) preventing type 2 diabetes mellitus in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and insulin resistance: a systematic review and meta-analysis☆

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ABSTRACT

Background: Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a very common, yet undiagnosed, breathing disorder that has many more implications besides disrupted sleep. Its role as an independent risk factor for metabolic abnormalities such as insulin resistance (IR) and impaired glucose tolerance is becoming increasingly recognized. The main treatment for OSAHS is continuous positive airway pressure (CPAP), however the impact of CPAP on IR and glucose metabolism is still debated.
Objectives: Compile all available evidence regarding the effect of CPAP on IR in non-diabetic OSA patients.
Methods: A literature search in Medline, Epistemonikos and the Cochrane Controlled Trial Register were searched through March 2018. We included Randomized Controlled Trials (RCTs) comparing CPAP treatment with sham CPAP, placebo or no treatment in non-diabetic adults with OSAHS. Risk of Bias was evaluated using Cochrane tool and a meta-analysis evaluating the efficacy of CPAP in both HOMA index and fasting glucose was done. Certain of evidence was rated using GRADE approach.
Results: Nine studies consisting of 443 participants were included. CPAP treatment significantly improved HOMA index (Mean difference = −0.39 Ui (CI, −0.69 to −0.08), $p < 0.05$. $I2 = 57\%$ (GRADE = LOW). However, CPAP showed no significant changes in fasting glucose (GRADE = LOW).
Conclusion: This systematic review and meta-analysis shows evidence that metabolic disturbances could be halted and regressed with CPAP treatment in patients with insulin resistance and OSAHS. In conclusion, treatment with CPAP could improve HOMA IR index.

1. Introduction

Obstructive sleep apnea/hypoapnea syndrome (OSAHS) is an underdiagnosed and highly prevalent condition characterized by recurrent episodes of obstruction of the upper airway leading to sleep fragmentation and intermittent hypoxia during sleep [1,2]. Some evidence suggests that OSAHS has an independent association with several metabolic defects such as insulin resistance (IR),

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glucose intolerance and type 2 diabetes mellitus (T2DM) [3–7]. Obesity is often the cause for developing OSAHS and metabolic abnormalities. However, after controlling for obesity and other important confounding factors of IR, recent reports showed that IR was highly correlated in both obese and non-obese patients with OSAHS [5,8]. Nevertheless, the mechanism by which non-obese OSAHS patients leads to IR is not fully understood.

OSAHS is characterized by long-term intermittent hypoxia, which recently has been proposed as a risk factor for OSAHS-associated IR [6]. In this manner, hypoxia and lower nocturnal oxyhemoglobin saturation lead to higher IR indices (homeostasis model of assessment for insulin resistance index, HOMA-IR) and pancreatic beta cell dysfunction in OSAHS patients [9–11].

Several possibilities regarding the relation between hypoxia and IR are conceivable. One is that intermittent hypoxia and arousals result in the activation of the sympathetic nervous system followed by the release of counter-regulatory hormones such as adrenaline and noradrenaline. It might also produce oxidative stress that triggers the production of inflammatory cytokines such as TNF-α and interleukin 6 which are involved in developing insulin resistance [11,12]. Moreover, adipokines such as resistin, adiponectin and leptin secreted by adipose tissue also might play a major role in IR and in the cardiovascular complications associated with obesity and diabetes [13,14]. The adipokines have anti-inflammatory, antiatherogenic and insulin-sensitizing properties. Recent work has shown that the dysregulation of expressions of these adipokines leads to IR and impaired glucose tolerance in non-obese rodent models of OSAHS [14].

However, the mechanisms by which OSAHS leads to IR and impaired glucose tolerance (IGT) are still unknown.

Application of nocturnal nasal continuous positive airway pressure (CPAP) is the gold standard of treatment for patients with OSAHS [15]. The use of a CPAP device in addition to preventing apnea, hypopnea and snoring may improve insulin sensitivity, glucose metabolism, lipids, fat distribution and adipokines, by providing a positive pressure in the upper airways, those effect improves the cardiovascular risk [16,17]. Previous studies on the effect of CPAP treatment on insulin resistance and glucose metabolism in patients with OSA have shown heterogeneous results and the impact is still debated [18]. Therefore, a systematic analysis of randomized studies and a meta-analysis were performed to assess the role of therapeutic CPAP on glucose metabolism biomarkers in non-diabetic patients with OSA.

2. Methods

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19].

2.1. Search strategy and selection criteria

One review author (TR) performed the search strategy. A systematic literature search was performed using the following databases: Medline (PUBMED), the Cochrane Controlled Trial Register, clinicaltrials.gov, Directory of Open Access Journal (DOAJ) and Epistemonikos [20].

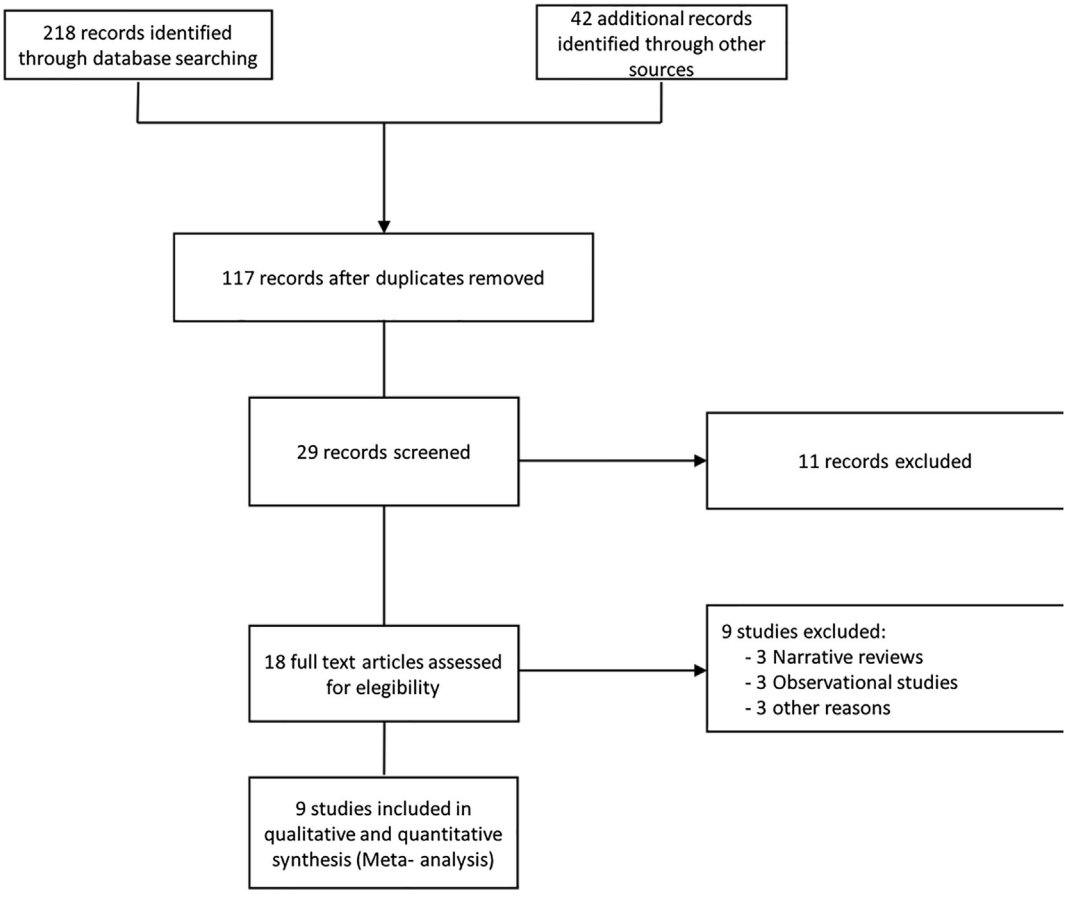

Fig. 1. PRISMA Study flow diagram.

Table 1
Characteristic of included studies.

Author	Study design Duration of CPAP Exposure	nº	Mean age (SD), years	Gender	Mean BMI (SD)	OSAHS definition	AHI (events/h)	Follow up (weeks)	Adherence (hours of use) h/day
Comondore et al., [24]	RCT Crossover 4 weeks 4 weeks wash-out	13 CPAP/no therapy No therapy/CPAP	55.5 (7.07)	M (9) F (4)	31.1	AHI > 15	27.9	12	CPAP 5,53
Coughlin et al., [25]	RCT Crossover 6 weeks No wash-out	34 17 CPAP/sham 17 sham/CPAP	49 (8.3)	M (34)	36.1 (7.6)	AHI > 15 and day time sleepiness (ESS≥10)	39.7 (13.8)	12	CPAP: 3.9 (0–7,4) Sham: 2.6 (0–7,5)
Hoyos et al., [26]	RCT parallel group 12 weeks (+12 weeks CPAP for all patients in open follow-up)	65 34 CPAP 31 Sham	49 (12)	M (65)	31.3 (5.2)	AHI ≥20 and 3% ODI ≥15	39.9 (17.7)	24	CPAP: 3.6 Sham: 2.8 At 24 weeks: 4
Lam et al., [32]	RCT parallel group 1 week (+11 weeks open follow-up for therapeutic CPAP group only)	61 31 CPAP 30 sham	46.3 (10.2)	M (61)	27.5 (3.7)	AHI > 15	39.7 (22.1)	12	CPAP: 6.2 (1.5) Sham: 4.5 (2.0) At 12 weeks: 4.9 (1.4)
Salord et al., [29]	RCT parallel group 12 weeks	80 42 CPAP 38 lifestyle counseling	CPAP: 48.5 (8.6) Counseling: 44.6 (9.4)	M (55) F (25)	CPAP: 45.7 (5) Counseling: 48.3 (6.6)	AHI > 30	CPAP: 68.3 (43–88) Counseling: 52.6 (37–78)	12	CPAP: 5.4 (1.6)
Sivam et al., [30]	RCT Crossover 8 weeks 1 month wash-out	27 CPAP/no therapy No therapy/CPAP	47 (13)	M (26) F (1)	31.3 (3.8)	AHI ≥25 with ODI ≥20	37.2 (24.7)	20	CPAP: 4.6 (2) Sham: 3.4 (2.2)
Pamidi et al., [28]	RCT parallel group 2 weeks	39 26 CPAP 13 Oral placebo	54.3 (6.9)	M (26) F (13)	CPAP: 36.8 (7.8) Placebo: 32.7 (4.3)	AHI ≥ 15	CPAP:6.7 Placebo: 6.9	2	CPAP: 8
Weinstock et al., [31]	RCT Crossover 8 weeks 1 month wash-out	50 25 CPAP/sham 25 sham/CPAP	53.6 (9.9)	M (21) F (29)	39 (8)	AHI > 15	44 (27)	20	CPAP: 4.8 (2) Sham: 3.4 (2.2)
Kritikou et al., [27]	RCT Crossover 8 weeks 1 week wash-out	35 CPAP/sham or sham/CPAP	Male: 54.25 (6.56) Female: 57.64 (5.81)	M (20) F (18)	28.55 (0.57)	♂AHI > 15 ♀ AHI > 10	38.49 (3.66)	17	CPAP: 6.07 (1.21) Sham: 5.26 (1.24)

AHI = apnea hypoapnea index; ODI = oxygen desaturation index; BMI = body mass index; CPAP = continuous positive airway pressure; OSA = Obstructive sleep Apnea syndrome; M = male; F = female; SD = standard deviation.

Results were limited to randomized controlled studies addressing the impact of CPAP on glucose metabolism biomarkers in non-diabetic patients with OSAHS. (See Appendix for a detailed search strategy using MEDLINE Medical Subject Heading (MeSH) criteria).

All relevant published studies were included. The search for the studies was repeated until no additional articles could be identified in March 2018. We did not apply any language restrictions and we also performed a hand search of both major respiratory and sleep medicine society congress meeting such as: European Respiratory Society (ERS; 2014 to date), American Thoracic Society (ATS; 2014 to date) American College of Chest Physicians (CHEST; 2014 to date) and American Society of Sleep Medicine (ASSM; 2014 to date). In addition, we searched the reference list of available related articles.

2.2. Inclusion criteria

An eligible study must meet the following criteria: (1) randomized controlled trials (RCTs) comparing CPAP therapy with either Sham-CPAP, placebo, or a non-treated control group; (2) confirmed insulin resistance according to American diabetes association (ADA) criteria [21]; (3) medically stable insulin resistance age > 18 years old, with newly diagnosed moderate to severe OSAHS as defined by the apnea–hypopnea index (AHI) ≥15; (4) CPAP naive patients; (5) duration of CPAP intervention >2 weeks during the study; and (6) HOMA-IR and fasting glucose as indicators for insulin resistance before and after CPAP.

Exclusion criteria were: (1) non-randomized controlled interventions; (2) patients with central apnea; (3) patients with type 1 or type 2 diabetes or receiving any hypoglycemic medication; (4) patients with any cardiovascular cerebrovascular disease or other chronic diseases; and (5) underage patients.

2.3. Quality assessment of included studies

Two authors (RA and MS) assessed the studies independently using the quality assessment method reported by The Cochrane Collaboration for systematic reviews of interventions [22]. Disagreements between reviewers were resolved by discussion to reach a consensus.

2.4. Data synthesis

Data extraction and synthesis were performed by two independent reviewers (RA and MS), and the data was assessed using an Excel database.

We established changes in HOMA – IR index as primary outcome in a post-CPAP treatment compared to a control group. Secondary outcome was changes in fasting glucose. We also explored difference between duration of treatment.

Qualitative analysis included description of included studies. For outcomes with enough data (more than two studies), we performed a meta-analysis using a randomized-effects model with the Simoniane Lair method following the intention to treat principle. The data were analyzed using the Cochrane Review Manager software (RevMan) version 5.3.

Meta - analysis of both changes in HOMA –IR index and fasting glucose, we used mean differences (MDs) and standard deviations for continuous data; All analyses included 95% CIs with p values < 0.05 indicating significance.

Heterogeneity was evaluated using a visual inspection of a Forest plot and using Q-statistics and chi-square tests with I-2 tests. We considered an I-2 of more than 50% as representing high heterogeneity and publication bias was evaluated using visual inspection of a funnel plot.

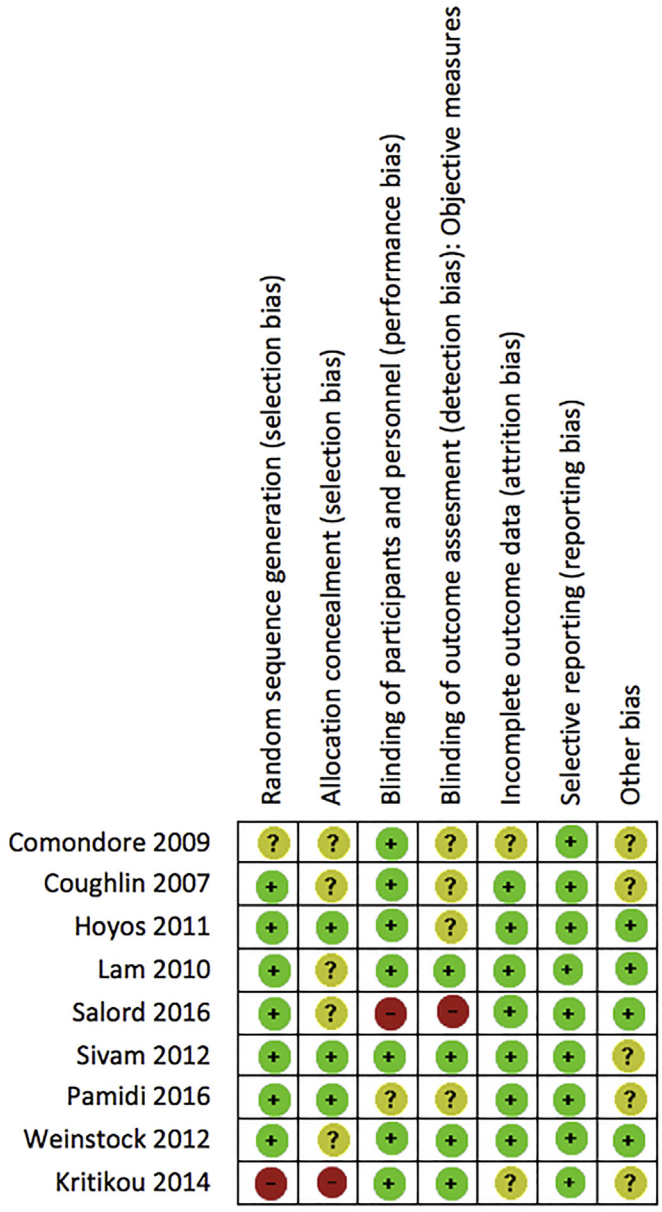

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

For a sensitive analysis, we explore data according to risk of bias (low or high) and efficacy of CPAP treatment in trials with >8 or <8 weeks of therapy using a subgroup analysis.

Finally, summaries of results and evidence grading were performed using the GRADE method. We evaluated the quality of evidence, with downgrading or upgrading performed according the following points: risk of bias, indirectness, imprecision, inconsistency and publication bias. A summary of findings (SoF) table was created using GRADEpro software [23].

3. Results

We identified 260 studies from different databases and society meetings, 18 of which were randomized controlled studies. Furthermore, only nine studies including 443 participants [24–32] were eligible and met the inclusion criteria. Fig. 1 describes the summary of the literature search and PRISMA flow. In addition, a

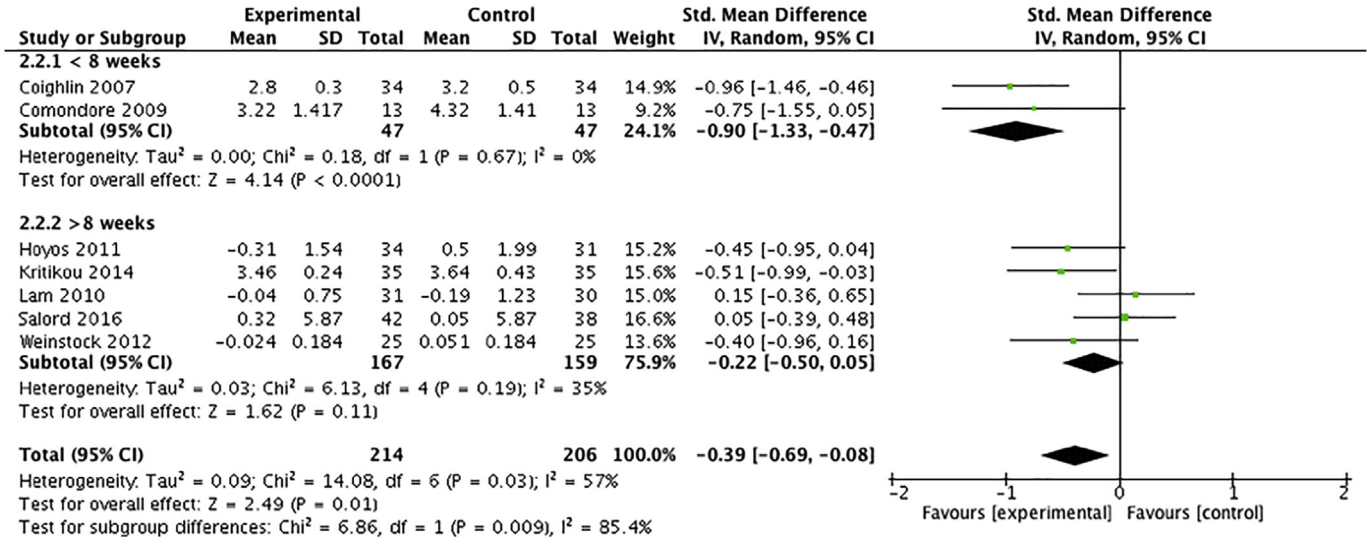

Fig. 3. Forest plot of comparison 1: change on HOMA IR index after CPAP treatment in patients with obstructive sleep apnea hypopnea syndrome OSAHS and impaired glucose tolerance. Subgroup analysis with duration of treatment >8 and <8 weeks.

total of nine studies were excluded from the analysis and one was omitted by retraction [33] (Table 1 supplementary material).

3.1. Qualitative analysis

Mean age range between 46.3 and 55.5 years old, in eight out of nine trials the common gender was male and average body mass index (BMI) range between 27.5 and 39.0 k/mt^2. Criteria of OSAHS was >15 AHI in six out of nine trials, one trial included population with >20 AHI, one >25 AHI and one >30 AHÍ. A summary of characteristics of the studies are shown in Table 1.

3.2. Quality assessment

We reported low risk of bias in three studies. In six studies, we found an unclear risk of bias regarding allocation concealment. A full quality analysis for the involved studies using the Cochrane method is shown in Fig. 2 and funnel plots are showed in Supplementary Figs. S1 and S2.

3.3. Primary outcome

3.3.1. Changes in HOMA IR index

A total of 420 participants included in seven studies were included in our analysis. Pooled meta-analysis showed an improvement in HOMA IR index between intervention and control groups, MD = −0.39 Ui (CI, −0.69 to −0.08), p < 0.05. Heterogeneity was I2 = 57%. (Fig. 3). We rate this evidence as GRADE: MODERATE due to inconsistency and imprecision (Table 2).

Subgroup analysis exploring trial duration showed a significant difference between studies with <8 or >8 weeks of reported therapy. First, studies with <8 weeks included 94 participants and reported a MD = − 0.90 (ci −1.33 to −0.47, p < 0.05) I^2 = 0%. Second, studies with >8 weeks of therapy included 326 participants and reported a MD = − 0.22 (ci, −0.50 to 0.05), I^2 = 35%.

Second analysis according to risk of bias reported low heterogeneity between groups (I2 = 0%). Both subgroups reported significant heterogeneity (I2 = 68% for high risk of bias and I2 = 39% for those with low risk of bias). (Fig. 4).

3.4. Secondary outcome

3.4.1. Changes in fasting glucose

A total of 443 participants included in eight studies were included in our analysis. There were no significant changes in fasting glucose between intervention and control groups. (MD = −0.05; CI −0.16 to 0.05). Heterogeneity assessment using I2 was 0% for this outcome (Fig. 5). We rated this evidence as GRADE: MODERADE due to imprecision and indirectness (Table 2).

4. Discussion

The main finding reported in this systematic review and meta-analysis is the ability of CPAP treatment to improve HOMA index in non-diabetic patients with impaired glucose levels. This finding

Table 2
Summary of finding (SoF) table using GRADE approach.

Outcomes	Anticipated absolute effects[a] (95% CI)		No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with CPAP		
Change in HOMA IR Index (HOMA) assessed with: Units follow up: range 1 weeks−12 weeks	The mean change in HOMA IR Index was **0.39** Ui	The mean change in HOMA IR Index in the intervention group was 0.39 Ui lower (0.69 lower to 0.08 lower)	420 (7 RCTs)	⨁⨁◯◯ [1,2]LOW
Change in fasting glucose (Fasting glucose) assessed with: mg/dL follow up: range 1 weeks−12 weeks	The mean change in fasting glucose was **0.05** mg/dL	The mean change in fasting glucose in the intervention group was 0.05 mg/dL lower (0.16 lower to 0.05 higher)	443 (8 RCTs)	⨁⨁◯◯ [2,3]LOW

HbA1c: Glycated hemoglobin; CI: Confidence interval; RCT: Randomized controlled trial; MD: mean difference; 1: Inconsistency, 2: Imprecision, 3: Indirectness.
[a] quantitative data.

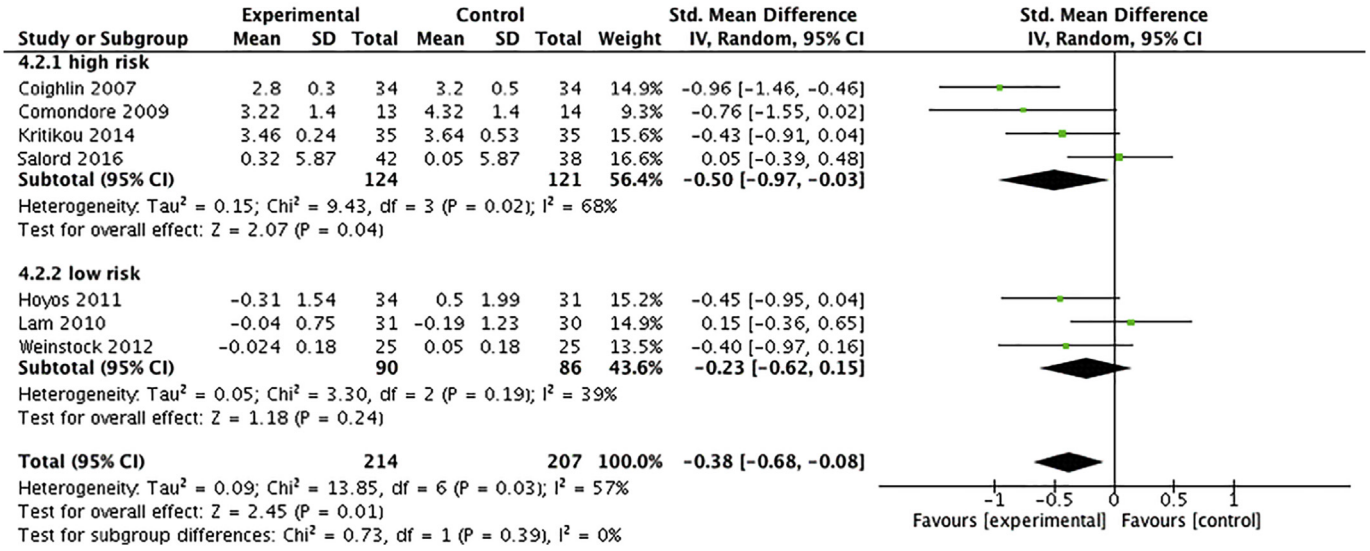

Fig. 4. Forrest plot of comparison 3. Change in HOMA IR index after CPAP treatment in patients with obstructive sleep apnea and impaired glucose tolerance. Subgroup according to Risk of Bias.

is consistent with prior meta-analysis by Chen et al., and Yang et al., that examined the effects of CPAP on HOMA-IR in non-diabetic patients [18,34]. No changes in immediate parameters, such as fasting glucose levels, were found, however, progression of long term parameters of insulin impairment as measured by HOMA index were significantly decreased following CPAP treatment. By lowering the HOMA index, CPAP treatment may delay the progression of pre-diabetes to diabetes mellitus type 2 by potentially limiting the chronic inflammation and oxidative stress that result from intermittent hypoxia [35]. While general prevention of T2DM consists of lifestyle changes, weight loss and control of metabolic parameters such as lipid profiles and blood pressure, our analysis introduces the potential of CPAP intervention as an additional preventative measure in reducing the risk of developing T2DM based on its ability to improve insulin resistance in non-diabetic patients [36].

Our meta-analysis reveals high heterogeneity between studies. Moreover, subgroup analysis according to treatment duration (>8 weeks) was associated with highest heterogeneity. Variance in length of treatment between studies may have impacted our findings for CPAP effectiveness on immediate parameters. Additional studies examining extended length of CPAP treatment is needed to draw better conclusions on immediate measures of CPAP on glucose control. Additionally, subgroup analysis by quality assessment as measured using Cochrane Risk of Bias did not reveal differences between low and high risk of bias. However, heterogeneity in the high risk of bias group was considered high.

This systematic review and meta-analysis was performed according to the PRISMA statement and follows the current recommendation of Cochrane library for systematic reviews of intervention. Certainty of evidence was graded using GRADE approach. This topic was previously reported in other systematic reviews, however, those reviews included both diabetic and non-diabetic populations in addition to weaknesses of the primary studies as reported by the authors of those reviews [18,37].

Furthermore, prior meta-analysis and conclusions were results of both randomized controlled trial and observational studies which is critical for applicability because included data was analyzed from different types of studies which may affect the bias and quality of data in those studies. Our findings are backed by a strong level of evidence (1a) as we only included RCTs in our analysis.

Our review was limited in several aspects. CPAP or sham use ranged an average of 2.6–8 h per day and while many of the follow

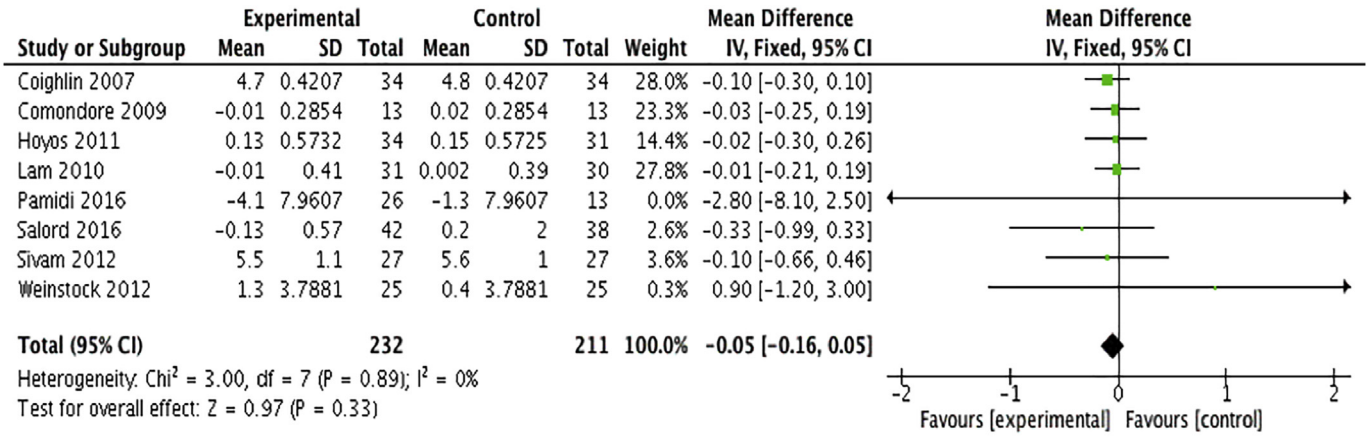

Fig. 5. Forest plot of comparison 2: change on fasting glucose levels (mg/dl) after CPAP treatment in patients with obstructive sleep apnea hypopnea syndrome (OSAHS) and impaired glucose tolerance.

up times were after 12 weeks of treatment, our studies ranged from 2 to 24 weeks at follow up. The variance in treatment and follow up time may have impacted our results on immediate glucose parameters as this type of parameter may be more sensitive to non-standardized treatment or shorter length of treatment. Additionally, we were limited to the patient demographics in the only nine RCTs we analyzed. The studies we included had a larger male than female population overall and this gender inequality should be a cofounder in the analysis. We also found others potential cofounder such as wide variation in BMI and the largest standard deviation of age in one study was 13 years. While more men may be included due to the fact that more men are diagnosed with OSA than women, these differences in gender and age may impact findings of CPAP treatment on immediate and long-term insulin resistance depending on the co-morbidities, medication use and genetic predisposition of patients included in the RCTs.

5. Conclusion

This systematic review and meta-analysis shows evidence that metabolic disturbances could be halted and regressed with CPAP treatment in patients with glucose intolerance and OSAHS. Given the relationship between OSAHS and impaired glucose metabolism, one can extrapolate the likely metabolic benefits from clinical trials of CPAP treatment in this group of patients. Treatment with CPAP improves HOMA IR index and may reduce the risk of developing type 2 diabetes, however, data was limited to inclusion of only nine RCT studies, and potential cofounder as gender inequality and wide variation in BMI are limitations making a strong conclusion untenable. We believe that further research is needed to definitively assess the roll of CPAP in preventing type 2 diabetes.

Contribution

Dr. Reyes: Literature search, data extraction, final approval.

Dr. Labarca, Jorquera: Data extraction, data analysis, critical review, final approval.

Dr. Drake: Data extraction, data analysis, language edition and final approval.

Dr. Abud and Salgueiro: Study selection, quality assessment, data extraction, manuscript preparation and final approval.

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None.

Conflict of interest

All authors declare no conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.12.017.

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