Systematic Review and Meta-Analysis

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The differences in plasma/serum ghrelin levels between obstructive sleep apnea-hypopnea patients and controls

A protocol for systematic review and meta-analysis

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Abstract

Background: The association between obstructive sleep apnea-hypopnea syndrome (OSAHS) and plasma/serum ghrelin levels remains controversial. We performed a meta-analysis to evaluate the difference in plasma/serum ghrelin levels between OSAHS patients and controls.

Methods: Database of PubMed, SCI, and Elsevier were searched entirely. Two independents identified eligible studies of ghrelin levels in OSAHS patients. ReviewManager (version 5.3) was adopted for data synthesis.

Results: The meta-analysis A pooled the comparison of ghrelin concentrations in OSAHS patients and controls, which included 7 studies and involving 446 participants. The result of the meta-analysis A indicated that plasma/serum ghrelin levels were no significant differences between the OSAHS group and the control group (standard mean difference (SMD) = 0.08, 95% confidence interval (CI) = −0.12 to 0.28, $P = .43$). As a supplementary, meta-analysis B pooled the comparison of plasma/serum ghrelin levels in OSAHS patients before and after continuous positive airway pressure (CPAP) therapy, which included 155 participants from 4 studies, it revealed that plasma/serum ghrelin levels were no significant differences between before and after CPAP therapy (SMD = 0.12, 95% CI = −0.07 to 0.31, $P = .22$).

Conclusion: The meta-analysis A demonstrated that plasma/serum ghrelin levels were no significant differences between the OSAHS group and the control group. The meta-analysis B showed plasma/serum ghrelin levels have no significant changes after CPAP therapy in OSAHS patients.

Abbreviations: AHI = apnea-hypopnea index, BMI = body mass index, CI = confidence interval, CPAP = continuous positive airway pressure, OSAHS = obstructive sleep apnea-hypopnea syndrome.

Keywords: continuous positive airway pressure, CPAP, ghrelin, meta-analysis, obesity, obstructive sleep apnea-hypopnea syndrome, OSAHS

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MS and XN contributed equally to this study.

The authors have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is featured in repetitive upper respiratory tract obstruction during sleep.[1] The clinical manifestation is snoring, sleep fragmentation, and apneic episodes during sleeping.[2] It is a common situation, affecting an estimated 9% of adult females and 24% of males.[3] The prevalence of OSAHS in obese patients has been reported exceeding 30%,[4,5] and 60% to 90% of adults with OSAHS are overweight.[5] Beyond that, insulin resistance[6] and disturbances of the cardiovascular system[7] are frequently observed in patients with OSAHS, which lead to type 2 diabetes and cardiovascular disease. Ghrelin was first discovered and extracted from the stomach of the rat,[8] and it was found to promote fat accumulation, stimulates hunger, and food intake, which is related to obesity,[9] and sleep deprivation,[10] regulate the cardiovascular system[11] and insulin resistance.[12] Whether plasma/serum ghrelin levels in OSAHS patients have significant differences with their counterparts have long been controversial, these controversies may be the result of confounding factors, insufficient sample size, or deviation of in study design in the studies. By pooling the results of all relevant studies, we designed this meta-analysis to try to figure it out that the difference in

plasma/serum ghrelin levels between OSAHS patients and control subjects.

Continuous positive airway pressure (CPAP) is the first-line therapy for OSAHS.[13] It improves the collapse of the upper airway during sleep, relieves intermittent sleep fragmentation.[14] We designed another meta-analysis regard as the differences in plasma/serum ghrelin levels between before and after CPAP therapy, which make sure of the association between OSAHS and ghrelin from another perspective.

2. Methods

2.1. Search strategy

We searched for English papers included in PubMed, Elsevier, and SCI database. Search keywords: sleep apnea, obstructive sleep apnea, sleep-disordered breathing, obstructive sleep-hypopnea, obstructive sleep apnea-hypopnea syndrome, and ghrelin. The references of relative articles searched manually is utilized to supplement the computerized search.

2.2. Exclusion and inclusion criteria of articles

Studies are included when they meet the following criteria,

1. Participants were over 18 years old and monitored by polysomnography (PSG). OSAHS is considered to have an average apnea-hypopnea index (AHI) greater than 5. AHI is defined as the total number of episodes of apnea or hypopnea lasting at least 10 seconds per hour.[15]
2. No statistically significant difference in age and body mass index (BMI) between the OSAHS group and the control group.
3. Morning fasting venous blood was measured for plasma/serum ghrelin concentration.
4. The data in the study are sufficient and provided in the form of mean ± standard deviation.
5. The patients had good adherence to CPAP treatment.

2.3. Statistical methods

Statistical results for dichotomy outcomes were represented by risk ratio (RR) and a 95% CI, and statistical results for continuous outcomes were represented by SMD and a 95% CI. Mantel–Haenszel analysis was adopted to dichotomous variables, and the inverse variance method applied to continuous variables.[16] The difference was statistically significant when $P < .05$.

We assessed statistical heterogeneity based on the *I*-square (I^2) value. It is considered statistically significant when $P < .01$. According to the I^2 value, the statistical heterogeneity was divided into homogeneous ($I^2 < 25\%$), low heterogeneity ($25\% \leq I^2 < 50\%$), moderate heterogeneity ($50\% \leq I^2 < 75\%$), and highly heterogeneity ($I^2 \geq 75\%$).[17] When a study is a homogeneous or low heterogeneity, the data from this study is pooled by using the fixed-effects model. When a study is moderate or highly heterogeneity, the data from this study is pooled by using the random-effects model.[18,19] ReviewManeger (version 5.3) was adopted for data synthesis.

While the meta-analysis B had insufficient data to carry out a representative subgroup analysis, we only performed a subgroup analysis on meta-analysis A. By performing subgroup analysis, we accessed the impact of BMI (<30 and ≥30), AHI (<45 and ≥45). The sensitivity analysis was implemented to assess the stability of the result of the meta-analysis. The funnel plot was computer-generated and to evaluate potential publication bias.[20] We identified and corrected for funnel plot's dissymmetry due to publication bias, through employing the trim and fill method.[21]

2.4. Ethical approval

The study does not have access to raw data and therefore does not require ethical approval.

3. Results

3.1. Search results

Two reviewers performed the preliminary search for relevant articles independently, 55 articles were initially selected in all. Filter titles and abstracts strictly according to inclusion and exclusion criteria, then, we found 17 articles related to our study. After an in-depth full text review, a total of 7 studies were considered eligible and contained in the meta-analysis A, which studies are concerned with the comparison of ghrelin concentrations in OSAHS patients and controls, and 4 studies were screened out in total for meta-analysis B, which studies involved the comparison of ghrelin levels in OSAHS patients before and after treatment. Details of the literature retrieval steps are illustrated in Figure 1.

3.2. Characteristics of included studies

The meta-analysis A included 7 studies[22–28] and involved data from 446 participants. The necessary information for the included studies was presented in Table 1. One of the studies[25] provided 2 sets of data, and the other 6 studies provided 6 sets of data. Depending on the study design, the case-control trial was defined as level 3, and the cross-sectional trial was defined as level 2,[29] and the 7 included studies are all case-control trials. Table 2 lists the data of BMI, age, AHI, and ghrelin level of each study. The meta-analysis B included 4 studies[25,30–32] and involved data from 155 participants. The basic information of each study was listed in Table 3. Two of the studies[25,30] each provided 2 sets of data. Table 4 lists the data of BMI, age, AHI, and ghrelin of each study.

3.3. Pooled analysis

The studies included in meta-analysis A were found low heterogeneous because of the I^2 value was 34%. Therefore, we combined effect size by using the fix effects model. The meta-analysis revealed that plasma/serum ghrelin was no significant difference between the OSAHS group and the control group (SMD = 0.08, 95% CI = 0.08–0.12, $P = .43$) (Fig. 2).

I^2 value was 0% and using the fix effects model to pool analysis. The SMD for meta-analysis B was 0.12(95% CI = −0.07 to 0.31, $P = .22$) (Fig. 3). The result showed that CPAP therapy has no significant impact on plasma/serum ghrelin levels in OSAHS patients.

3.4. Subgroup analysis-BMI

BMI ≥ 30: in studies with a BMI higher than or equal to 30, the total SMD was 0.16 (95% CI = −0.15 to 0.47, P = .31) (Fig. 4).
BMI < 30: in studies with a BMI of less than 30, the total SMD was 0.10 (95% CI = −0.37 to 0.56, $P = .68$) (Fig. 5).

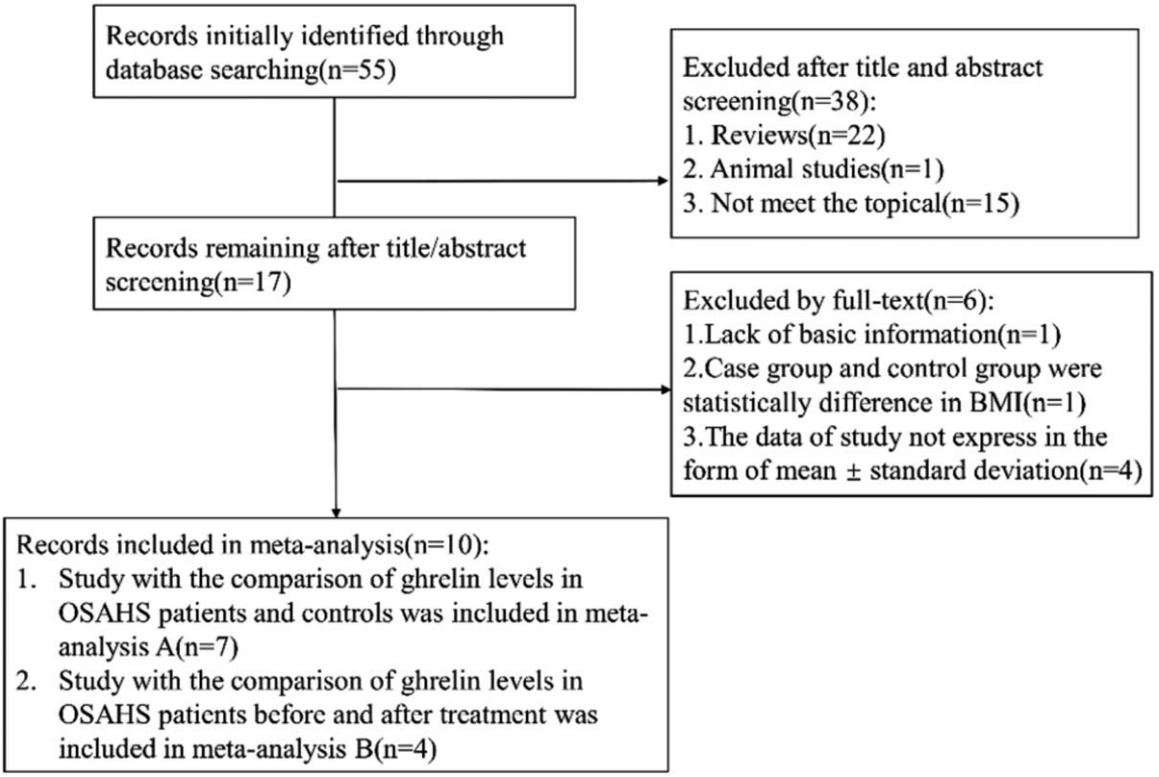

Figure 1. Flow chart of the literature retrieval step.

Table 1

Characteristics of the studies in the meta-analysis A.

Author	Year	Country	Study design	LOE	Sample Size (OG/CG)
De Santis et al[1]	2015	Italy	CCT	3b	26/24
Liu, W et al[2]	2014	China	CCT	3b	95/30
Ulukavak Ciftci et al[3]	2005	Turkey	CCT	3b	30/22
Yang et al[4]	2013	China	CCT	3b	25/25
Zhang. M et al[5]	2018	China	CCT	3b	30/20
Sánchez-de-la-Torre et al[6] A	2012	Spain	CCT	3b	10/24
Sánchez-de-la-Torre et al[6] B	2012	Spain	CCT	3b	21/20
Papaioannou[7]	2011	UK	CCT	3b	33/11

2B = level2, 3B = level3, A = obese group, based on studies among the obese subject, B = no obese group, based on studies among the no obese subject, CCT = case-control trial, CG = control group, LOE = level of evidence, OG = OSAHS group.

Table 2

Data for the studies included in the meta-analysis A.

	mean(SD) Ghrelin, (pg/ml)		mean BMI, kg/m^2		mean Age, Y		mean AHI, events/h	
Study	OG	CG	OG	CG	OG	CG	OG	CG
De Santis[1]	119.8 (12.5)	114.6 (14.9)	33.0	30.8	41.8	43.7	26.15	1.65
Liu[2]	778.28(290.77)	889.30(229.47)	28.45	27.85	47.57	45.35	30.28	3.07
Ulukavak Ciftci[3]	130.8 (2)	130.5 (2.4)	32.12	31.03	NSD	44.24	1.55	
Yang[4]	532.51 (152.54)	453.69 (79.06)	27.5	26.22	53	54	25	3
Zhang[5]	154.83 (24.19)	154.75 (30.68)	28.85	27.55	40.73	36.10	61.48	1.93
Sánchez-de-la-Torre[6] A	699.61 (272.55)	733.3 (198.13)	34.34	32.01	46.61	48.7	48.92	2.87
Sánchez-de-la-Torre[6] B	1,024.69 (533.5)	906.77 (313.5)	25.02	24.71	49.33	42.9	41.45	3.06
Papaioannou[7]	303 (237)	275 (201)	30	28	48	43	30	2

A = obese group, based on studies among the obese subject, AHI = apnea-hypopnea index, B = no obese group, based on studies among the no, BMI = body mass index, CG = control group, NSD = no statistical difference, OG = OSAHS group, SD = standard deviation.

Table 3

Characteristics of the studies included in the meta-analysis B.

Author	Year	Country	No. of Patients	Treatment	Follow-up Duration	Study design	LOE
Tachikawa et al[8] C	2016	Japan	63	CPAP	6 w	SCT	2
Tachikawa et al[8] D	2016	Japan	63	CPAP	3 m	SCT	2
Takahashi et al [9]	2008	Japan	21	CPAP	1 m	SCT	2
Yang et al [10]	2013	China	22	CPAP	3 m	SCT	2
Sánchez-de-la-Torre et al[6] A	2012	Italy	21	CPAP	3 m	SCT	2
Sánchez-de-la-Torre et al [6]] B	2012	Italy	28	CPAP	3 m	SCT	2

A = obese group, based on studies among the obese subject, B = no obese group, based on studies among the no obese subject, C = 6-week group, the treatment lasted for 6 weeks, D = 3-month group, the treatment lasted for 3 month, LOE = level of evidence, SCT = self-control trials.

Table 4

Data for the studies included in the meta-analysis B.

	mean (SD) Ghrelin,(ng/ml)		Mean BMI, kg/m^2	mean Age, Y	mean (SD) AHI, events/h	
Study	Pre-CPAP	Post-CPAP	—	—	Pre-CPAP	Post-CPAP
Tachikawa[8] C	7.1 (5.7)	7.0 (6.3)	27.9	60.6	42.2 (19.9)	5.6 (6.2)
Tachikawa[8] D	7.1 (5.7)	6.7 (6.6)	27.9	60.6	42.2 (19.9)	3.9 (3.7)
Takahashi[9]	12.1 (6.50)	9.64 (4.81)	28.5	53.2	39.4 (15.5)	16.1 (6.72)
Yang[10]	583 (255)	468 (195)	26.7	60	26 (13)	3 (2)
Sánchez-de-la-Torre[6] B	699.61 (272.55)	719.52 (318.9)	34.34	46.61	48.92 (17.52)	—
Sánchez-de-la-Torre[6] A	1,024.69 (533.5)	938.85 (601.15)	25.02	34.34	41.45 (18.3)	—

A = obese group, based on studies among the obese subject, AHI = apnea-hypopnea index, B = no obese group, based on studies among the no obese subject, BMI = body mass index, C = 6-week group, the treatment lasted for 6 weeks, CG = control group, D = 3-month group, the treatment lasted for 3month, OG = OSAHS group, SD = standard deviation.

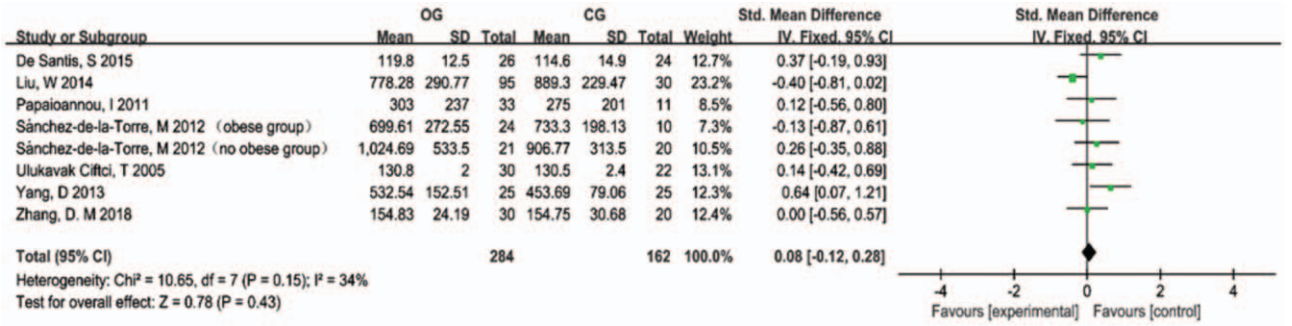

Figure 2. Meta-analysis A, the comparison of ghrelin levels in the OSAHS group and the control group.

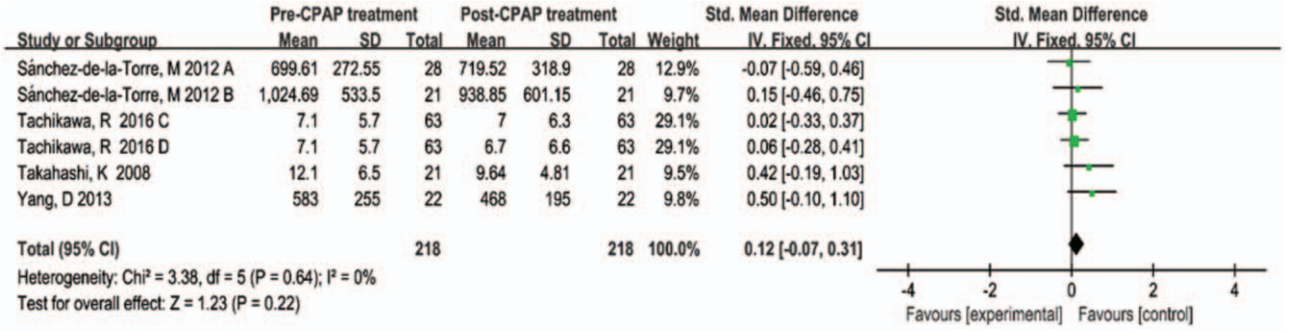

Figure 3. Meta-analysis B, the comparison of ghrelin levels before and after CPAP therapy.

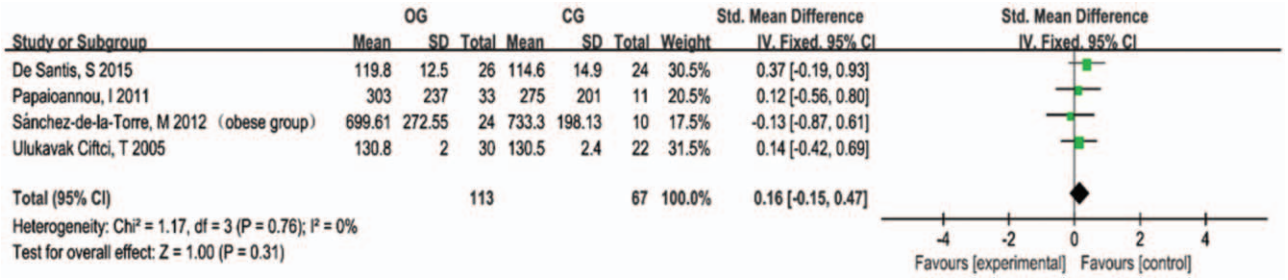

Figure 4. Meta-analysis A, subgroup analysis-BMI ≥ 30.

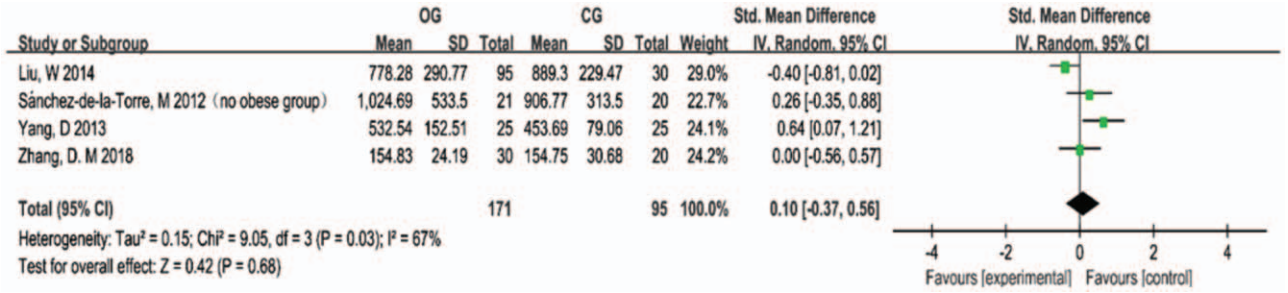

Figure 5. Meta-analysis A, Subgroup analysis-BMI < 30.

3.5. Subgroup analysis-AHI

AHI ≥ 45: in studies with an AHI higher than or equal to 45, the total SMD was -−0.05 (95% CI = −0.49 to 0.57, *P* = .84) (Fig. 6). **AHI < 45:** in studies with an AHI of less than 45, the total SMD was 0.16 (95% CI = 0.16–0.48, P = .33) (Fig. 7).

3.6. Sensitivity analysis

The sensitivity analysis suggested that deleting anyone study from the 2 meta-analyses would not overturn the present result. In meta-analysis A, by using the fixed-effects model, the pooled analysis had shown no significant difference in ghrelin between

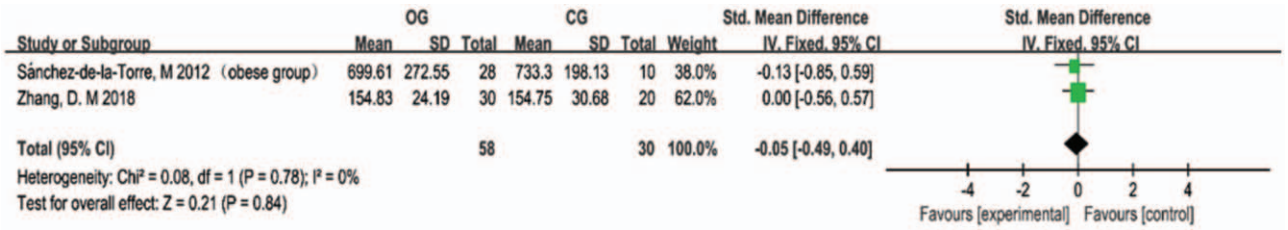

Figure 6. Meta-analysis A, Subgroup analysis-AHI ≥45.

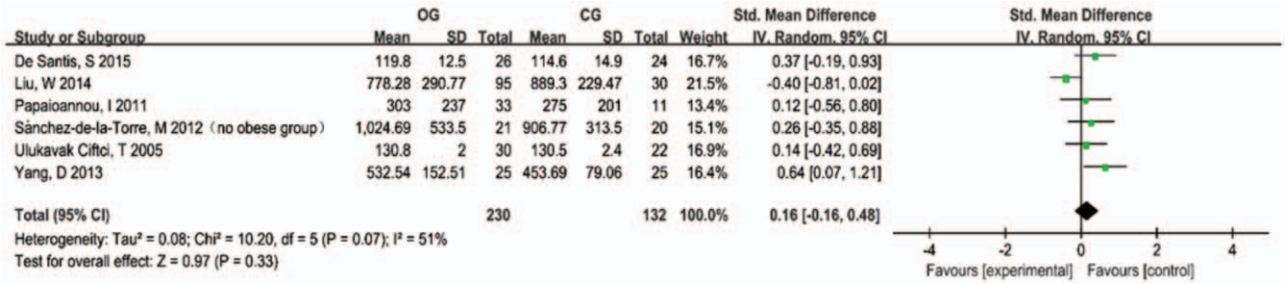

Figure 7. Meta-analysis A, Subgroup analysis-AHI < 45.

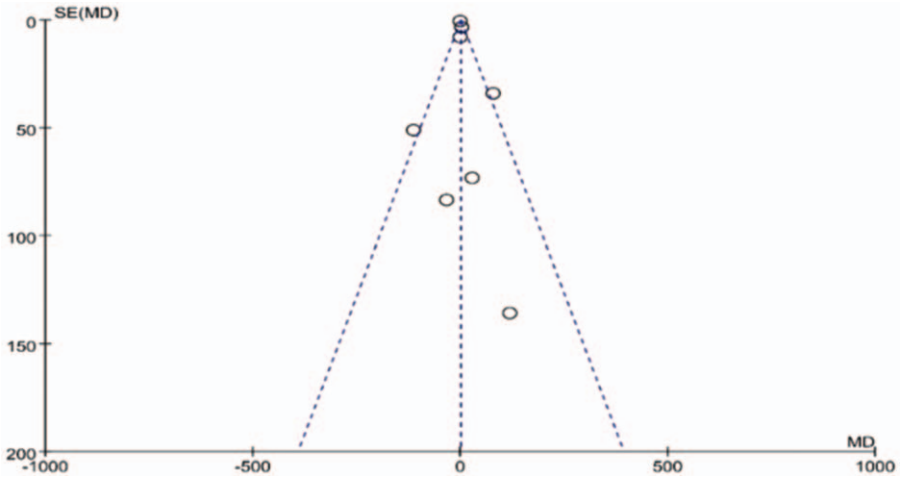

Figure 8. The funnel plot of included studies. MD = mean difference, SE = standard error.

the OSAHS patients and controls (SMD = 0.08, 95%CI = −0.12 to 0.28, $P = .43$). The random-effects model reached a similar consequence (SMD = 2.38; 95%CI = −5.58 to 10.36; $P = .56$). In meta-analysis B, sensitivity analysis shows that no significant change in ghrelin levels after CPAP therapy in fixed-effects model (SMD = 0.08, 95% CI = 0.08–0.12, $P = .43$) and random-effects model (SMD = 0.08, 95% CI = 0.07–0.31, $P = .43$).

3.7. Publication bias

Figure 8 is the funnel plot of meta-analysis A. It is not entirely symmetric, which means there may be slight publication bias. The trim and fill method indicated that no studies required to be statistically corrected to the dissymmetry of the funnel plot. Publication bias should not be used to evaluate the results of meta-analysis B because of the limited number of studies included.

4. Discussion

The meta-analysis A suggested that no correlation was found between ghrelin and OSAHS. Similarly, the meta-analysis B showed that no changes in plasma/serum ghrelin levels after CPAP treatment, which is also considered to support that OSAHS is not related to ghrelin from a therapeutic perspective. De Santis et al,[22] Papaioannou et al,[24] Sánchez-de-la-Torre et al,[25] and Ulukavak Ciftci et al[26] revealed that ghrelin is not associated with OSAHS and no association between ghrelin and apnea-hypopnea index (AHI), which is consistent with our findings. Liu et al[23] found that OSAHS patients had lower ghrelin levels compared with control subjects, but it had no relationship with sleep parameters. However, Harsch et al[33] reported that significantly higher levels of ghrelin in OSAHS patients than in the controls, and decreased significantly during 2 days after initiation of CPAP treatment. They did not investigate the independent effects of OSAHS and obesity on ghrelin levels. As we all know, obesity is one of the essential factors affecting OSAHS[34] and ghrelin.[9]

To further evaluate the impact of BMI and AHI on ghrelin levels, we conducted a subgroup analysis regard as BMI and AHI (we had not performed the analysis of age-related subgroup because the age data of the participants was insufficient). The results of each subgroup showed that ghrelin levels in OSAHS patients have no significantly differences with controls, which suggests that age and BMI are not sources of heterogeneity.

To our knowledge, this is the first meta-analysis regard as the relationship between OSAHS and ghrelin. We included age and BMI matched control groups to exclude possible confounders, and we had studied the effect of age and BMI on ghrelin through subgroup analysis. In addition, our study indicated that OSAHS is not related to ghrelin from therapeutic perspective by analyzing changes in ghrelin before and after CPAP treatment. Those are the advantages of our study.

There are some limitations in our study. First, in meta-analysis A, all the 7 studies we included were case-control trials. In meta-analysis B, only 4 self-control trials were included. The limited number of studies included may lead to bias in the final results, and each included study was subject to experimental bias because of limited population. Secondly, low heterogeneity is an actual problem, but no evidence of heterogeneity was found in any of the comparisons in this study. And then, the publication bias exists in the meta-analysis A according to the funnel plot. Since the limited number of studies were eligible for inclusion in the meta-analysis B, we failed to carry out an evaluation of publication bias. Finally, the small sample size was contained in the subgroup analysis, so the result of the subgroups should be explained with caution. Thus, more studies with larger samples are needed to examine those correlations further.

5. Conclusion

Though there are still various opinions regarding the correlation between OSAHS and ghrelin, this meta-analysis suggested that plasma/serum ghrelin levels in OSAHS patients have no differences with controls, and the plasma/serum ghrelin levels did not change significantly after CPAP treatment.

Author contributions

Meng-Ling Sun: Conceptualization, Data curation, Formal analysis, Writing-Original draft preparation. Xun Niu: Conceptualization, Methodology, Data curation, Formal analysis.

Xi-Yue Xiao: Software, Validation. Xiong Chen: Writing-review &editing, Supervision.
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Data curation: Meng-Ling Sun, Xun Niu.
Formal analysis: Meng-Ling Sun, Xun Niu.
Software: Xi-Yue Xiao.
Supervision: Xiong Chen.
Validation: Xi-Yue Xiao.
Writing – original draft: Meng-Ling Sun.
Writing – review & editing: Xiong Chen.

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