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Nocturia in CPAP-Treated Obstructive Sleep Apnea Patients: a Systematic Review and Meta-Analysis

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Abstract

Several studies propose that nocturia, which is common among obstructive sleep apnea (OSA) patients, might be benefited from continuous positive airway pressure (CPAP) treatment. However, related literature remains obscure and thus needs further consolidation and clarification. The present study aimed to provide further evidence regarding potent correlation between CPAP and nocturia in OSA patients. Five hundred and thirty publications were selected after a search in PubMed, Cochrane Library, ClinicalTrials.gov, Google Scholar databases, as well as in unpublished literature. Study eligibility criteria were fulfilled by 11 studies. A systematic review and meta-analysis with subgroup analyses and meta-regressions examined 11 means regarding nocturia rates before and after treatment with CPAP in a total of 830 patients. Mean differences (MD) and confidence intervals (CI) were estimated using random effects model. The study was registered to PROSPERO database (ID: 160600). Nocturia rates are diminished after CPAP treatment, when compared with nocturia rates before CPAP treatment: Overall MD = − 1.13, 95% CI: [− 1.48, − 0.78], $P < 0.001$; however, increased heterogeneity ($I^2 = 93\%$, $P = < 0.001$) was observed. No statistically significant publication bias was detected (Eggers' regression $P = 0.095$; Begg and Mazumdar's $P = 1.000$). Meta-regression revealed that the beneficial impact of CPAP treatment regarding nocturia episodes is independently enhanced in patient groups with ≤ 60% severe OSA cases ($P = 0.001$), ≤ 50 years old ($P = 0.001$), and > 27 mg/m^2 BMI ($P = 0.012$). Nocturia is alleviated in CPAP-treated OSA patients; CPAP beneficial effect is independently correlated with younger age, increased BMI, and less severe cases.

Keywords Continuous positive airway pressure · Obstructive sleep apnea · Nocturia · Meta-analysis

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of partial or complete collapse of the upper airway during sleep. The ensuing reduction or cessation of breathing often leads to acute derangements in gas exchange and recurrent arousals from sleep. The prevalence of obstructive sleep apnea associated with accompanying daytime sleepiness is approximately 3 to 7% for adult men and 2 to 5% for adult women in the general population [1].

Nocturia, awaking from sleep to void, negatively affects health and well-being. Nocturia is more prevalent among the elderly. Although nocturia traditionally has been regarded as a predominantly male condition, it is just as prevalent in women as in men. OSA has been recognized as a major non-urologic cause of nocturia [2].

Several studies propose that OSA patients, when treated with continuous positive airway pressure (CPAP), might have a subsidiary beneficial effect by reducing nocturia [3–11]. On the contrary, the only randomized control trial (RCT) published up to date failed to demonstrate similar results [12, 13]. A systematic review and meta-analysis including the latter RCT and four previously published studies [4, 6–8] concluded that CPAP treatment produced a statistically significant reduction in the mean number of nocturia incidents [14].

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The present study aimed to provide further evidence regarding potent correlation between CPAP and nocturia in OSA patients by identifying all relevant studies and summarize their results.

Materials and Methods

Literature Search

A systematic literature review was conducted using PubMed/MEDLINE, EMBASE, Cochrane Library, and ClinicalTrials.gov databases from December 01, 1999, until September 15, 2020, to identify all studies that reported data concerning frequency of nocturia before and after the use of CPAP in patients with obstructive sleep apnea. The Google Scholar and ResearchGate databases were used as an additional pool of published data, dissertations, and other unpublished work; an iterative search was performed until no additional publication could be traced. Personal communication was followed where needed. The relevant protocol was registered in PROSPERO database on April 28, 2020 (ID: 160600); a revision submitted on September 29, 2020, was emerged during the review process.

Study Selection

The review was independently conducted by two authors (VP and NA) using a search strategy that included the PubMed search terms (nocturia) AND (continuous positive airway pressure) or (nocturia) AND (apnea). A third author (DF) was responsible for any discordance. No software was used for study retrieval. Sources of financial support were traced where possible.

Outcome Measures

The present study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to formulate the basis of pre-specified eligibility criteria using the PICO (P—Populations/People/Patient/Problem: OSA patients, I—Intervention(s): CPAP, C—Comparison: frequency of nocturia episodes before and after the use of CPAP, O—Outcome: mean differences) worksheet and search strategy [15]. The AMSTAR checklist was used to confirm the high quality of the present meta-analysis [16].

Eligible studies were all that (1) are at least partly written in English (e.g., report an abstract in English); (2) are either RCTs or non-RCTs (cohorts) with NOS ≥ 6; (3) report frequency of episodes of nocturia, either as recorded in the 7th question (Q7) of the International Prostate Symptom Score questionnaire (IPSS) or referred separately, before and after the use of CPAP, in both male and female patients with obstructive sleep apnea; (4) report a relevant measure of statistical significance; (5) report either a relevant effect estimate (means accompanied by their standard deviations) or enough data to compute it; and (6) are not duplicates. The two lead authors (VP and NA) determined publication eligibility; a third author (DF) was responsible for any discordance.

Data Extraction

A structured data collection was used to extract the following data from each eligible study: title of the study, name of the first author, year of publication, country where the study was conducted, duration of the study (in months), loss of follow-up (LOF) percentage, female ratio in patient sample, age, BMI, apnea-hypopnea index (AHI), percentage of severe OSAs, sample size, episodes of nocturia before and after CPAP, adjustment for confounders, and Newcastle-Ottawa quality assessment scale (NOS) score. The two lead authors (VP and NA) performed data extraction; a third author (DF) was responsible for any discordance.

Quality Assessment of the Studies

For all eligible studies, the following were performed: (1) Cochrane risk of bias tool (RoB 2.0 tool) evaluating selection, performance, detection, attrition, reporting, and other biases was estimated for RCTs; (2) quality assessment for non-RCTs (either before-after (pre-post) studies without a separate control group or cohorts) was approached using the Newcastle-Ottawa scale (NOS) which evaluates selection, comparability, and outcome, mainly focusing on risk of bias; in detail, selection item was given a maximum of 4 stars, comparability item a maximum of 2 stars, and exposure (for case-control studies) or outcome of interest (for cross-sectional studies) a maximum of 3 stars; (3) the USA National Institute of Health (NIH) quality assessment-based tool for before-after (pre-post) studies with no control group available on https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools was additionally used for all studies with an adaptation for the RCT intervention group when appropriate; quality rate was arbitrarily described as good, fair, and poor when a positive record was attributed to all 12, 9–11, and ≤ 8 criteria, respectively [17]. The two lead authors (VP and NA) performed quality assessment; kappa statistics were used for the evaluation of inter-rater agreement for quality assessment tools. A third author (DF) was responsible for any discordance.

Data Synthesis and Statistical Analysis

Data synthesis was performed using RevMan 5.3 software from the Cochrane Collaboration (London, UK). As effect

estimates, mean differences (MD) and confidence intervals (CI) expressed in nocturia episodes per night were extracted from each study and combined together using the random effects, generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study in the pooled analysis inversely to its variance [18]. Random effects model allows generalizing common effect size beyond the (narrowly defined) population included in the analysis [19]. As data between before and during treatment are paired, pooled SD was used as approached by the formula $[SD_{before}^2 + SD_{after}^2 - 2*r*SD_{before}*SD_{after}]^{½}$, where SD_{before}, SD_{after}, and r denote SD before initiation of treatment with CPAP, SD after treatment with CPAP, and correlation coefficient between data consequently. In cases that r was unknown, it was arbitrary given a value of 0.7 if statistical significance; this is consistent with Rosenthal's conservative approach [20]. In cases that only median, range, and sample size was provided, means and SD were estimated as described by Luo et al. [21] and Wan et al. [22], respectively.

Statistical Analysis

Analysis of publication bias was performed through Eggers' regression, Begg and Mazumdar's rank correlation test, funnel plot (Precision vs MD) with trim-and-fill analysis, Rosenthal failsafe-N test for number of unpublished studies with the aid of Comprehensive Meta-Analysis software, version 3.3.070.

Heterogeneity was based on Q test and I^2; Q test P value < 0.10 and/or $I^2 > 50\%$ was indicative of significant heterogeneity and was further analyzed. Analysis of heterogeneity was performed through sensitivity analysis, meta-regressions, and subgroup analysis focusing on study characteristics, biases, and confounders.

Sensitivity analysis was used to explore the impact of excluding or including individual studies. Subgroup analysis was used to seek whether qualitative or quantitative interaction exists. Meta-regression was conducted separately for study characteristics and quality assessment as described by NOS items (selection, comparability, and outcome).

OSAs patients with AHI > 30 were regarded as severe. Years passed since publication, sample size, duration of CPAP treatment, female ratio, mean age, mean BMI, percentage of severe OSAs, and percentage of LOF were treated as arbitrarily defined binary variables in both univariate and multivariate analysis (meta-regression). All parameters analyzed in univariate analysis were also included in meta-regression independently of the level of statistical significance in the former analysis; this was supposed to be the safe and informative process given that the linear regression model used was based on bootstrapping (number of samples, 1000; CI level, 95%; sampling, simple) thus compensating for instability that might result from small sample size. Variables with variance inflation factor (VIF) > 2.5 (or tolerance < 0.4) were discarded to avoid collinearity. Missing cases were listwise excluded for multivariate analysis. All statistical tests were carried out using SPSS 20.0 software (IBM Corp ©).

Results

Study Characteristics

We identified 245 and 284 publications in PubMed and EMBASE databases, respectively. ClinicalTrials.gov and Cochrane Library failed to contribute any additional publications. One more publication of interest was identified through Google Scholar. One unpublished pre-print was provided by the second author through personal communication [Apergis, 2019].

Summing up, all publications taken under consideration for eligibility were 530. Of these, 326 were duplicates, and 190 were excluded from title or abstract. The remaining 14 publications were assessed for eligibility through full-text; three of them were excluded for various reasons, and 11 were found to satisfy all inclusion criteria thus providing 11 means regarding nocturia incidents before and after treatment with CPAP in 830 OSA patients (Fig. 1).

Quality Assessment and Risk of Bias

Cochrane risk of bias (RoB) tool did not reveal any selection, performance, detection, attrition, reporting, or other bias in the

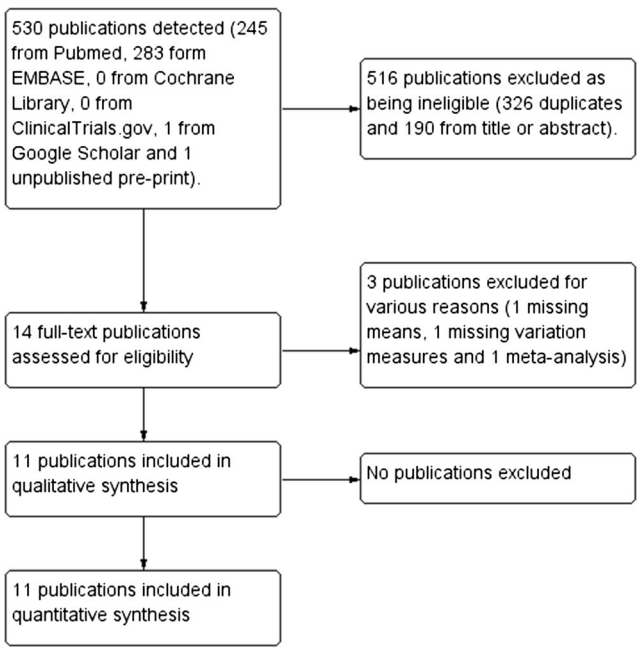

Fig. 1 Flow chart

Table 1 Eligible studies along with study characteristics and quality/risk of bias assessment based on NOS

Study	Design	Region	Duration (months)	LOF	Female ratio	Age	BMI	AHI	Severe OSAs	*N*	Before CPAP	After CPAP	Adjusted confounders	NOS sel†	NOS com‡	NOS exp‖
Apergis, 2019	Non-RCT	Greece	12	6%	0.00	47.7 ± 9.0	37.5 ± 8.2	70.5 ± 24.1	94%	62	2.10 ± 1.26	0.31 ± 0.50	Age, BMI	4	2	3
Fernandez, 2019	Non-RCT	Spain	12	0%	0.33	59.3 ± 8.7	32.4 ± 5.4	42.11	65%	43	1.38 ± 1.20	0.49 ± 0.69	None	4	2	3
Guilleminault, 2004	Non-RCT	USA, Portugal	1	0%	0.00	68.6 ± 3.3	28.0 ± 3.1	36.9 ± 9.5	54%	60	2.30 ± 0.24	0.69 ± 0.24	Age	3	2	3
Irer, 2018	Non-RCT	Turkey	3	30%	0.00	43.5 ± 6.5	32.1 ± 5.1	48.0 ± 21.1	75%	54	2.10 ± 1.30	0.50 ± 0.50	None	3	2	2
Liu, 2001	Non-RCT	China		0%						15	2.90 ± 1.10	1.30 ± 1.10	None	3	2	3
Margel, 2006	Non-RCT	Israel	1–3	0%	0.23	55.6 ± 14.0	32.9 ± 6.1		48%	97	2.50 ± 2.40	0.70 ± 0.60	Age, BMI	4	1	3
McMillan, 2014	RCT	USA	3	14%	0.14	70.9 ± 4.7	33.9 ± 5.7			113	1.90 ± 1.30	1.60 ± 1.40	Age, BMI	NA	NA	NA
Miyauchi, 2015	Non-RCT	Japan	1	19%	0.16	55.9 ± 10.8	26.8 ± 3.6	48.0 ± 25.9	75%	51	1.60 ± 1.30	1.10 ± 0.90	None	4	2	3
Miyazato, 2015	Non-RCT	Japan	3	25%	0.17	56.9 ± 14.1	28.4 ± 4.2	56.8 ± 28.1	83%	40	2.10 ± 1.20	1.20 ± 1.10	BMI	4	2	3
Vrooman, 2020	Non-RCT	The Netherlands	12	26%	0.31	60.3 ± 11.6				274	3.09 ± 1.58	2.00 ± 1.58	None	4	2	3
Yu, 2019	Non-RCT	China	0.1	0%	0.14	58.2 ± 10.2	26.8 ± 9.1	43.0 ± 17.3	67%	21	2.20 ± 1.30	1.74 ± 1.06	Age, BMI	4	2	3

† Selection (number of ☆); ‡ comparability (number of ☆); ‖exposure (number of ☆); *NA* not applicable

single RCT included in the present meta-analysis. All detailed data concerning quality assessment for cohorts based on NOS items, mainly focusing on risk of bias, are provided in Table 1. Furthermore, quality assessment based on USA NIH Quality assessment-based tool for before-after (pre-post) studies with no control group is analytically presented at Table 2. The overall inter-rater agreement for NOS as well as for NIH tool was kappa = 0.89 and 1.00, respectively.

Primary Outcome

In general, nocturia incidents are decreased at a statistically significant extent ($P < 0.001$) when compared before and after CPAP treatment; the relevant overall MD is − 1.13 (95% CI: − 1.48, − 0.78) clearly favoring CPAP treatment ($P < 0.001$); however, increased heterogeneity ($I^2 = 93\%$, $P = <0.001$) was observed (Fig. 2).

Publication Bias

No significant publication bias was suspected as funnel plot was not indicative of lack of symmetry, and trim-and-fill analysis produced no imputed data points (Fig. 3), and Rosenthal failsafe-N test rejected ad hoc rule (failsafe-$N = 2055$). Moreover, Eggers' regression ($P = 0.095$) as well as Begg and Mazumdar's rank correlation test ($P = 1.000$) yielded a non-statistically significant result.

Analysis of Heterogeneity

Sensitivity analysis was used to explore the impact of excluding or including studies. Interestingly, excluding studies one by one failed to compromise heterogeneity as yielded to comparable levels (88–94%).

Subgroup analysis revealed differences in MD thus indicating potent sources of heterogeneity regarding source (gray literature vs publications, $P = 0.005$), type of study (non-RCTs vs RCTs, $P < 0.001$), year of publication (2009 and before vs 2010 and after, $P < 0.001$), origin of study (Europe/USA vs Asia, $P = 0.090$), sample size (> 50 vs ≤ 50 patients, $P = 0.020$), female ratio (no females vs mixed sample, $P < 0.001$), age (≤ 50 years old vs > 50 years old, $P = 0.002$), body mass index (BMI) (> 27 mg/m^2 vs ≤ 27 kg/m^2, $P = 0.005$), severe OSA cases (≤ 60% vs > 60%, $P = 0.003$), and quality assessment for both NOS and NIH tool; on the contrary, no differences were detected regarding duration of observation period, loss of follow-up, and adjustment of effect estimates for potent confounders as age and BMI (Table 3).

Meta-regression analysis yielded to a robust model ($n = 8$, overall $P < 0.001$, adjusted $R^2 = 0.971$, VIF ≤ 1.5 for all included variables) concluding that the beneficial impact of CPAP treatment in nocturia episodes of OSA patients is

Table 2 Quality assessment based tool for before-after (pre-post) studies with no control

Criteria	Apergis	Fernandez	Guilleminault	Irer	Liu	Margel	McMillan†	Miyauchi	Miyazato	Vrooman	Yu
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	No	No	No	No	No	Yes	No	Yes	No	Yes	No
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	NR	NR	NR	NR	NR	Yes	NR	NR	NR	NR
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided *P* values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	No	No	No	No	No	Yes	No	No	No	No
12. If the intervention was conducted at a group level (e.g., a whole hospital and a community), did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No	Yes
Quality rating (good/fair/poor)	Fair	Poor	Fair	Poor	Poor	Fair	Fair	Poor	Poor	Poor	Poor

† RCT; adapted only for the intervention group; *NR* not reported

independently enhanced in groups of OSA patients that had ≤ 60% severe OSA cases ($b = 0.810$, $P = 0.001$), were ≤ 50 years old ($b = 0.800$, $P = 0.001$), and had > 27 mg/m^2 BMI ($b = 0.415$, $P = 0.012$). Detailed data are presented at Table 3.

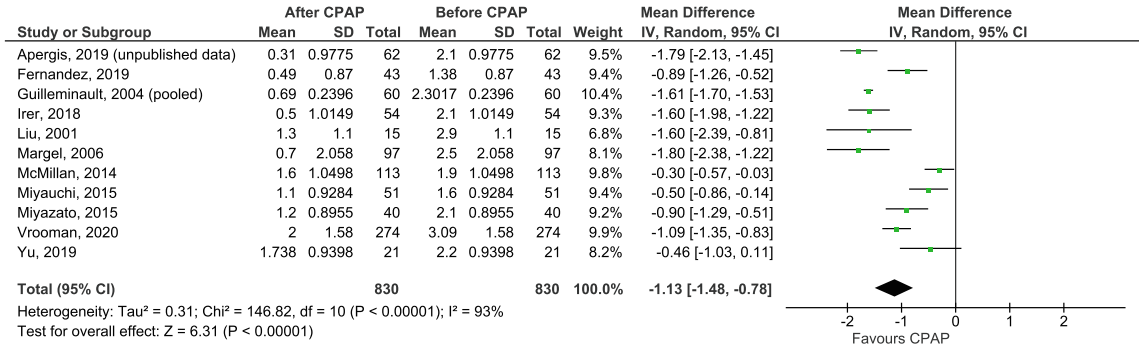

Fig. 2 Meta-analysis

Discussion

As nocturia is frequent among OSA patients and CPAP has been proposed to ameliorate the relevant morbidity, we have conducted a systematic review and meta-analysis including the only RCT published previously on the topic along with ten relevant cohort studies that met all eligibility criteria. We have demonstrated that the use of CPAP decreases nocturia incidents at a mean of − 1.13 episodes of nocturia/night (95% CI: − 1.48, − 0.78) at a statistically significant extent ($P < 0.001$). The augmented heterogeneity observed (I^2 = 93%, $P = <0.001$) has been mainly attributed to non-publication bias factors; meta-regression analysis suggests that the profile of patients who might benefit mostly by the use of CPAP includes those who suffer from moderate OSA, are young, and have increased BMI.

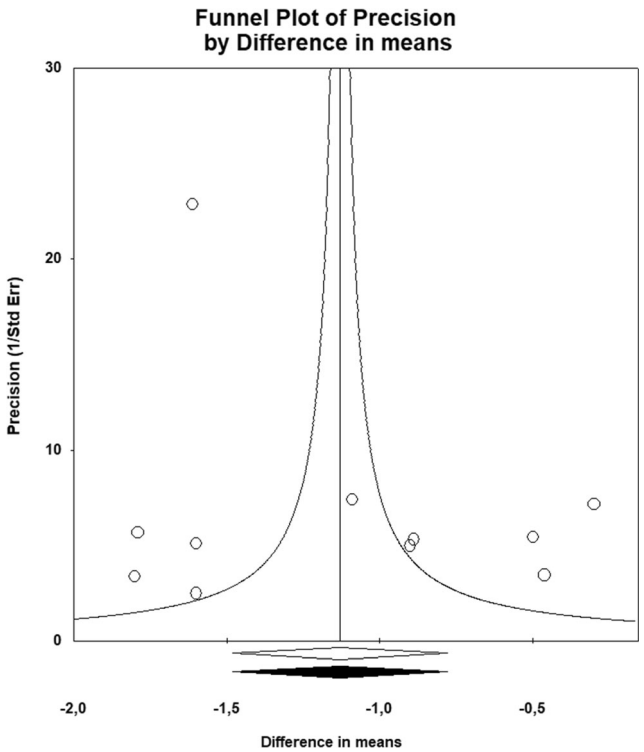

Fig. 3 Funnel plot with trim-and-fill analysis

One can argue that the present meta-analysis is redundant since Wang et al. first published a meta-analysis on the same topic [14]. However, it is our strong belief that a number of issues concerning the latter study could justify an alternative approach on the field. First, the inevitable limited number of studies included ($n = 5$), prevented from broader evaluation of the available literature under less strict inclusion criteria and concrete investigation of the potent causes of substantial heterogeneity, other than publication bias, which might be clinically useful. Second, the use of fixed effects model could be replaced with random effects model, as there is urge to enlighten the increased (and unaccountable) heterogeneity. Third, the computation of MDs has to be performed over paired data, as the opposite approach introduces reporting bias; of note, if we apply random effects model in MDs computed for paired samples with $r = 0.7$ in the meta-analysis of Wang et al., overall MD is computed to be − 1.14 (95% CI: − 1.85, − 0.43), namely, the same as the one reported hereby by ours, with an I^2 of 96% ($P < 0.001$). Fourth, the data of Guilleminault et al. [4] reported in the meta-analysis of Wang et al. disregard all OSA patients who did not exhibit nocturia, thus introducing a strong selection bias. Lastly, the authors failed to search for unpublished material.

Our current approach has the advantage of triple analysis towards potent sources of heterogeneity: sensitivity analysis, subgroup analysis, and meta-regression. Sensitivity analysis illustrated that no single study account for the substantial heterogeneity was observed, as one-by-one exclusion of published studies does not limit heterogeneity more than 5%. This is also true for the introduction of unpublished material, whose exclusion yields to comparable I^2 (94%); therefore, even if data from Apergis were eliminated to avoid an additional publication bias linked to the fact that he is also one of the authors of the present study, no substantial difference

Table 3 Subgroup analysis and meta-regression; subgroups reported by decreasing effect estimate

	Subgroup analysis					Meta-regression			
Parameter	Subgroups	MD	95% CI	I^2	*P* value	Univariate rho	Univariate *P*	Multivariate *b*	Multivariate *P*
Study characteristics									
Source	Gray literature	− 1.79	− 2.13, − 1.45	NA	0.005	0.401	0.222		
	Publications	− 1.06	− 1.44, − 0.68	94%					
Type of study	Non-RCTs	− 1.22	− 1.52, − 0.92	90%	< 0.001	0.501	0.116		
	RCTs	− 0.30	− 0.57, − 0.03	NA					
Year of study	2009 and before	− 1.62	− 1.70, − 1.53	0%	< 0.001	0.615	0.044		
	2010 and after	− 0.95	− 1.33, − 0.57	89%					
Origin of study	Europe / USA	− 1.28	− 1.70, − 0.87	94%	0.09	0.389	0.237		
	Asia	− 0.79	− 1.18, − 0.39	62%					
Sample size	> 50	− 1.39	− 1.74, − 1.03	90%	0.02	0.608	0.047		
	≤ 50	− 0.76	− 1.14, − 0.38	74%					
Duration of study	≤ 6 months	− 1.15	− 1.62, − 0.69	92%	0.72	0.142	0.695		
	> 6 months	− 1.01	− 1.61, − 0.41	93%					
Female ratio	0% (males only)	− 1.62	− 1.70, − 1.54	0%	< 0.001	0.570	0.086		
	> 0%	− 0.83	− 1.16, − 0.50	82%					
Age (mean)	≤ 50 years old	− 1.71	− 1.96, − 1.45	0%	0.002	0.435	0.209	0.800	0.001
	> 50 years old	− 0.94	− 1.36, − 0.53	95%					
BMI (mean)	> 27 kg/m^2	− 1.26	− 1.71, − 0.81	94%	0.005	0.518	0.154	0.415	0.012
	≤ 27 kg/m^2	− 0.49	− 0.79, − 0.18	0%					
Severe OSAs (%)	≤ 60%	− 1.62	− 1.70, − 1.53	0%	0.003	0.630	0.094	0.810	0.001
	> 60%	− 0.92	− 1.38, − 0.47	91%					
Loss of follow-up (%)	> 20%	− 1.25	− 1.94, − 0.57	84%	0.72	0.037	0.913		
	≤ 20%	− 1.10	− 1.52, − 0.69	94%					
Adjustment for confounders									
Age adjustment	Yes	− 1.20	− 1.84, − 0.56	96%	0.59	0.174	0.631		
	No	− 1.00	− 1.33, − 0.67	78%					
BMI adjustment	Yes	− 1.04	− 1.71, − 0.38	93%	0.79	0.035	0.924		
	No	− 1.15	− 1.58, − 0.72	93%					
Quality assessment and risk of bias									
NOS									
Optimal selection	No	− 1.61	−1.69, −1.53	0%	0.004	0.343	0.332		
	Yes	− 1.06	−1.43, −0.69	84%					
Optimal comparability	No	− 1.80	−2.38, −1.22	NA	0.06	0.524	0.120		
	Yes	− 1.17	−1.49, −0.84	90%					
Optimal exposure	No	− 1.60	−1.98, −1.22	NA	0.10	0.116	0.749		
	Yes	− 1.18	−1.51, −0.84	90%					
NIH tool									
	Good	NA	NA	NA	0.33	0.419	0.199		
	Fair	− 1.36	−2.06, −0.66	96%					
	Poor	− 0.98	−1.29, −0.68	74%					

NA Not applicable

regarding heterogeneity would be produced. Furthermore, as far as subgroup analysis is concerned, qualitative interaction, a rare phenomenon that may be used as an argument that the most appropriate result of a meta-analysis is the overall effect across all subgroups, was not observed in our case; however, quantitative interaction exists as the size of the effect varies but not the direction, thus indicating that the intervention, hereby CPAP, is beneficial to

different degrees in different subgroups. In detail, source (publications or gray literature), study design, year of publication, origin of study, sample size, female ratio in patients group, age, BMI, and severity of OSA cases have been accounted as potent heterogeneity sources according to subgroup analysis; however, multivariate analysis (meta-regression) confirmed the former proposal only for age, BMI, and severity of OSA cases.

All already published data derived from cohorts are qualitatively in keeping with our results, as they all report that the use of CPAP limits nocturia episodes to a variable extent. However, the only RCT included [12, 13], based on intention to treat, fails to exhibit a beneficial role of CPAP in OSA patients regarding nocturia; this could be explained by the fact that the trial refers to elderly patients and thus is not at all representative as far as the total age spectrum of the disease.

Interestingly, no publication bias was detected as implied by results derived from funnel plot with trim-and-fill analysis, Eggers' regression, Begg and Mazumdar's rank correlation test, and Rosenthal failsafe-N test; this result could reflect that no clear-cut pre-defined or pre-judged size or even direction of difference was suspected in the scientific community as a whole.

The major limitation of the present study might be the combination of data from different kind of studies, namely, an RCT and ten non-RCT studies (mainly cohorts). However, both univariate analysis and multivariate analysis (meta-regression) did not prove any statistically significant difference regarding overall effect estimates. Thus, this practice might be considered non-misleading. Moreover, the small size of samples analyzed in meta-regression ($n = 8$) might result to obtain spurious results without any clear indication of there being a problem [23].

A serious query could focus on the decision to proceed to the meta-analysis despite the high heterogeneity. However, several reasons might support our approach: (1) there was little evidence of publication bias (as trim-and-fill analysis suggested no imputed studies) or small size studies effect (as Egger's regression was not statistically significant), (2) there was no considerable qualitative interaction, (3) although quantitative interaction existed, the direction did not vary, (4) sensitivity analysis did not reveal any particular study to account for the increased heterogeneity, and (5) the vast proportion of the heterogeneity could be explained by the performed meta-regression, as deduced by the relevant adjusted R^2 (0.971).

In conclusion, the present meta-analysis illustrated that CPAP may well ameliorate nocturia by reducing nocturia rates at a mean of 1.13 episodes per night; the extent of CPAP beneficial intervention is independently correlated with less severe OSA cases, young age, and increased BMI. Future, cumulative evidence are welcome to further enlighten this field.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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