

# Effect of positive airway pressure on glomerular filtration rate in patients with sleep-disordered breathing: a meta-analysis

Li-Da Chen<sup>1</sup> · Li Lin<sup>1</sup> · Yang-Wu Ou<sup>1</sup> · Zhi Wu<sup>1</sup> · Zhi-Ming Cai<sup>1</sup> · Tie-Zhu Wang<sup>1</sup> · Jian-Nan Liu<sup>1</sup>

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## Abstract

**Objective** Sleep-disordered breathing (SDB) has been suggested to be associated with chronic kidney disease (CKD). Positive airway pressure (PAP) is an effective treatment for SDB, but the impact of PAP therapy on glomerular filtration rate (GFR) in patients with SDB remains unclear. The present meta-analysis was performed to determine whether PAP therapy could increase GFR.

**Design** A systematic search of PubMed, Embase, Web of Science, and Cochrane library was performed for literature published up to January 2016. Standardized mean difference (SMD) was calculated to estimate the treatment effects of pre- and post-PAP therapy.

**Results** A total of eight studies with 240 patients were pooled into a meta-analysis. The meta-analysis showed that there was no change of GFR before and after PAP treatment in SDB patients (SMD = 0.010, 95 % confidence interval (CI) = -0.331 to 0.350,  $z = 0.06$ ,  $p = 0.956$ ). Subgroup analyses indicated that GFR was significantly increased after PAP treatment in elder patients ( $\geq 55$  years) (SMD = -0.283, 95 % CI = -0.518 to -0.047,  $z = 2.35$ ,  $p = 0.019$ ) and patients with therapeutic duration  $\geq 3$  months (SMD = -0.276, 95 % CI = -0.522 to -0.031,  $z = 2.20$ ,  $p = 0.027$ ).

**Conclusion** The present meta-analysis suggested that PAP treatment had no impact on GFR in SDB patients. However, longer PAP usage for SDB patients significantly improved

GFR. In elder SDB subjects, PAP was also associated with a statistically significant increase in GFR.

**Keywords** Sleep-disordered breathing · Positive airway pressure · Chronic kidney disease · Glomerular filtration rate · Meta-analysis

## Introduction

Sleep-disordered breathing (SDB) is a common disorder characterized by repetitive apneas and hypopneas during sleep. SDB, including obstructive sleep apnea (OSA), and Cheyne–Stokes respiration (CSR) and central sleep apnea (CSA), is common in patients with chronic kidney disease (CKD) [1]. CKD describes patients with a chronically decreased glomerular filtration rate (GFR) or other evidence of kidney damage. The prevalence of OSA in CKD population has been reported to range from 27 to 54 % [1–3], which is considerably higher than the general population. The prevalence of CKD is up to 18 % in severe OSA patients without hypertension or diabetes [4]. The overlap of both conditions has been receiving increasing attention in the medical literature.

GFR is widely accepted as the best overall measure of kidney function [5]. The urinary or plasma clearance of an ideal filtration marker such as inulin or of alternative exogenous markers such as iothalamate, EDTA, diethylene triamine pentaacetic acid, and iohexol are used to determine GFR. Some equations based on serum creatinine, age, race, and sex are used to obtain an estimation of GFR (eGFR). Positive airway pressure (PAP) is the primary treatment of SDB including OSA, CSR, and CSA. Continuous positive airway pressure (CPAP) is the most common form to treat SDB. Other forms that provide noninvasive positive pressure

✉ Jian-Nan Liu  
ljnzzsy123@163.com

<sup>1</sup> Department of Respiratory Medicine, Zhangzhou Affiliated Hospital of Fujian Medical University, No 59, Shenglixi road, Xiangcheng district, Zhangzhou, Fujian province 363000, People's Republic of China

ventilation include bi-level positive airway pressure (BiPAP), and adaptive servo-ventilation (ASV). Some studies demonstrated the favorable effect of PAP on GFR [6–8], while others did not [9, 10].

The purpose of the present meta-analysis was to quantitatively evaluate the efficacy of PAP ventilation on GFR in patients with SDB.

## Methods

### Search strategy

We looked for relevant articles in the following databases from inception to January 5, 2016: PubMed, Embase, Web of Science, and Cochrane library. The reference lists of selected articles were manually searched. The search terms used were sleep apnea or sleep-disordered breathing and positive airway pressure or adaptive servo ventilation or noninvasive ventilation combined with glomerular filtration rate or GFR. Two researchers independently identified the eligible studies.

### Study selection

Studies were considered eligible if the following criteria were met: (1) The study populations were limited to adults (age > 18) with SDB (OSA, CSA, or CSR); (2) The intervention was an application of PAP (CPAP, BiPAP, or ASV); (3) Mean and SD (or SE) of GFR needed to be reported in before and after PAP therapy. Reviews, abstracts, case reports, editorials, non-human studies, and non-English studies were excluded. Unpublished studies for which we could not obtain data from the authors were also excluded.

### Data extraction

The following information was abstracted and evaluated independently by two investigators: first author, publication year, country of the study, sample size, patient inclusion criteria, participant characteristics, study design, PAP type, mean daily PAP usage time, duration of PAP therapy, GFR measurement, and GFR values before and after PAP treatment.

### Statistical analysis

Statistical analyses were performed by using STATA version 12.0. The pooled estimate of the standardized mean difference (SMD) and 95 % confidence interval (CI) were calculated. The fixed or random effects model was used for non-heterogeneous or heterogeneous data, respectively, as appropriate. Statistical heterogeneity among individual was assessed on the basis of  $Q$  and  $I^2$  statistics. To explore the possible sources of heterogeneity in PAP treatment effects,

sensitive analysis and subgroup analyses were conducted. Publication bias was assessed by Begg's correlation and Egger's regression.

## Results

### Searching results

Our search yielded a total of 68 studies of potential interest after excluding duplicates. Of the 68 studies, 12 studies were obtained after careful review of the titles and abstracts. Of these, four studies were excluded. Two studies did not report data as mean and SD (or SE) [11, 12], while the other two studies in which the diagnostic criteria of SDB was not reported [13, 14]. Finally, eight studies were included in the meta-analysis. The detailed steps of the literature search were presented in Fig. 1.

### Characteristics of the studies

A total of eight studies with 240 patients met the inclusion criteria and were included in this meta-analysis. All studies were observational. Patients with heart failure in three studies received ASV therapy [7, 8, 15], and patients in the remaining five studies received CPAP therapy [6, 9, 10, 16, 17]. The characteristics of the eight included studies and the patients' characteristics were summarized in Tables 1 and 2, respectively.

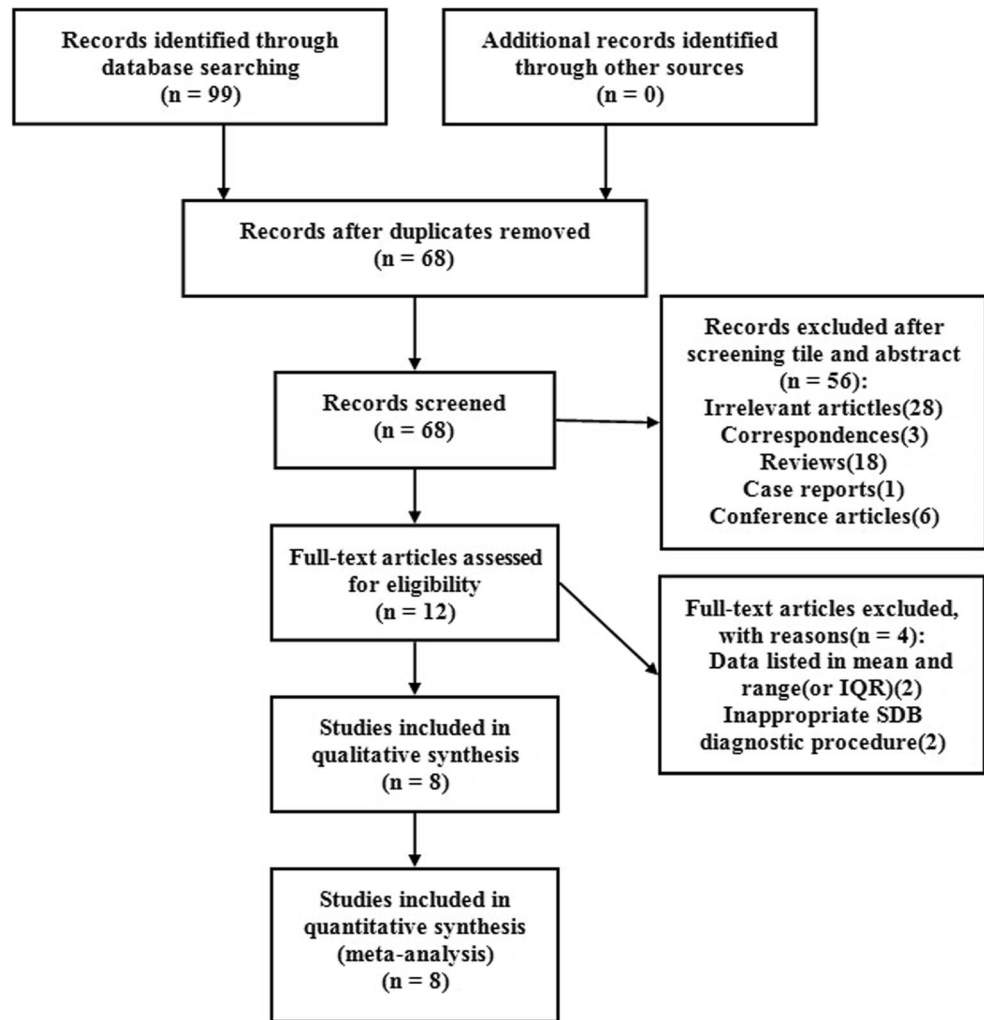
### Impact of PAP on GFR

Significant heterogeneity was detected among these studies (chi-squared = 23.69,  $p = 0.001$ ;  $I^2 = 70.5\%$ ). Consequently, a random-effect model was used for the pooled analysis. Pooling the data with a random-effect model meta-analysis showed that PAP therapy had no impact on GFR in SDB patients (SMD = 0.010, 95 % confidence interval (CI) = -0.331 to 0.350,  $z = 0.06$ ,  $p = 0.956$ ) (Fig. 2). A similar result (SMD = -0.055, 95 % CI = -0.237 to 0.126,  $z = 0.60$ ,  $p = 0.549$ ) was observed from a fixed-effect model.

### Sensitivity and subgroup analyses

In addition, the sensitivity analysis showed that the overall risk estimates were stable (Fig. 3). Since the effectiveness of PAP could be influenced by many factors, subgroup analyses were performed (Table 3). The results showed that GFR was significantly increased after PAP treatment in elder patients ( $\geq 55$  years) (SMD = -0.283, 95 % CI = -0.518 to -0.047,  $z = 2.35$ ,  $p = 0.019$ ) and patients with therapeutic duration  $\geq 3$  months (SMD = -0.276, 95 % CI = -0.522 to -0.031,  $z = 2.20$ ,  $p = 0.027$ ). While the differences in body mass index

**Fig 1** Flow diagram of study selection. *IQR* interquartile range, *SDB* sleep-disordered breathing



(BMI), apnea-hypopnea index (AHI), and sample size hardly influenced effectiveness of PAP. ASV therapy might have a trend in increase of GFR in comparison with pre-ASV treatment (SMD = -0.250, 95 % CI = -0.512 to 0.012,  $z = 1.87$ ,  $p = 0.061$ ).

### Publication bias

There was no statistical significance of publication bias in the present meta-analysis (Begg's test,  $p = 0.174$ ; Egger's test,  $p = 0.108$ ) (Fig. 4). In addition, the trim-and-fill method showed that no study needed to be statistically corrected for funnel plot asymmetry.

### Discussion

The present meta-analysis, comprised of 240 patients, suggested that PAP had no impact on GFR in SDB patients.

However, subgroup analyses indicated that PAP was associated with a statistically significant increase on GFR in elder SDB patients ( $\geq 55$  years) or patients with therapeutic duration  $\geq 3$  months. ASV therapy might have a trend in increase of GFR in SDB patients compared with baseline.

The impact of SDB on the development of CKD has been demonstrated by accumulating evidence [4, 18–20]. A retrospective cohort study including 4674 adult sleep apnea (SA) patients and 23,370 non-SA patients as the comparison group found that patients with SA experienced a 1.94-fold and 2.2-fold increase in the incidence of CKD and ESRD, respectively, after adjustment for sex, age, and comorbid medical conditions [18]. A cross-sectional study that enrolled 40 severe OSA patients without diabetes or hypertension showed that the prevalence of CKD in severe OSA subjects was 18 %. Further stepwise multivariate linear regression analysis revealed that AHI and desaturation index were the only independent predictor of urine albumin-to-creatinine ratio and eGFR [4]. Sakaguchi et al. [20] followed 161 patients with stage

**Table 1** Characteristics of include studies

Study	Year	Nation	Sample size/ male	Inclusion criteria	Ventilation duration/ night (h)	Therapy duration	PAP type	GFR measurement	CKD	Study design
Zhang	1997	China	20/17	AHI $\geq$ 30	NR	1 d	CPAP	Creatinineclearance rate	No	Observational study
Kinebuchi	2004	Japan	21/NR	AHI>5 <sup>a</sup>	7.6 $\pm$ 1.0	7 d	CPAP	Sodium thiosulphate clearance	No	Observational study
Koyama	2011	Japan	27/23	AHI $\geq$ 15 and HF	5.8 $\pm$ 0.8	12 M	ASV	MDRD	Yes	Observational study
Koga	2013	Japan	27/27	AHI $\geq$ 20	$\geq$ 3.5	3 M	CPAP	MDRD	NR	Observational study
Yoshihisa	2013	Japan	50/45	AHI>15 and HF	>4	1d	ASV	Based on Cyst C	NR	Observational study
Owada	2013	Japan	36/32	AHI>15 and HF	5.3 $\pm$ 1.1	6 M	ASV	MDRD	Yes	Observational study
Zhang	2014	China	39/ 29	AHI $\geq$ 30	6.45 $\pm$ 2.39	3 M	CPAP	MDRD	NR	Observational study
Nicholl	2014	Canada	20/15	RDI $\geq$ 15	6.4 $\pm$ 1.3	1 M	CPAP	Based on inulin and PAH	No	Observational study

AHI apnea-hypopnea index, RDI respiratory disturbance index, HF heart failure, NR not reported, d day, M month, CPAP continuous positive airway pressure, ASV adaptive servo-ventilation, MDRD modification of diet in renal disease, PAP positive airway pressure, GFR glomerular filtration rate, CKD chronic kidney disease, PAH para-aminohippuric acid

<sup>a</sup> AHI was >30 events/h, regardless of symptoms, or AHI was 5–30 events/h accompanied by symptoms

3 to 4 CKD for over 1 year and found that the eGFR declined three- to fourfold faster in patients with moderate-to-severe nocturnal hypoxemia than patients with no or mild nocturnal hypoxemia (the mean values were  $-2.14$ ,  $-3.02$ , and  $-8.59$  ml/min/1.73 m<sup>2</sup> per year in the no, mild, and moderate-to-severe nocturnal hypoxemia groups, respectively). After controlling for various baseline confounding factors, nocturnal hypoxemia remained a significant predictor of decline in eGFR. The pathogenesis of CKD in SDB is likely to be a multifactorial process involving several mechanisms: direct effects of hypoxia on the kidney [21, 22], or oxidative stress,

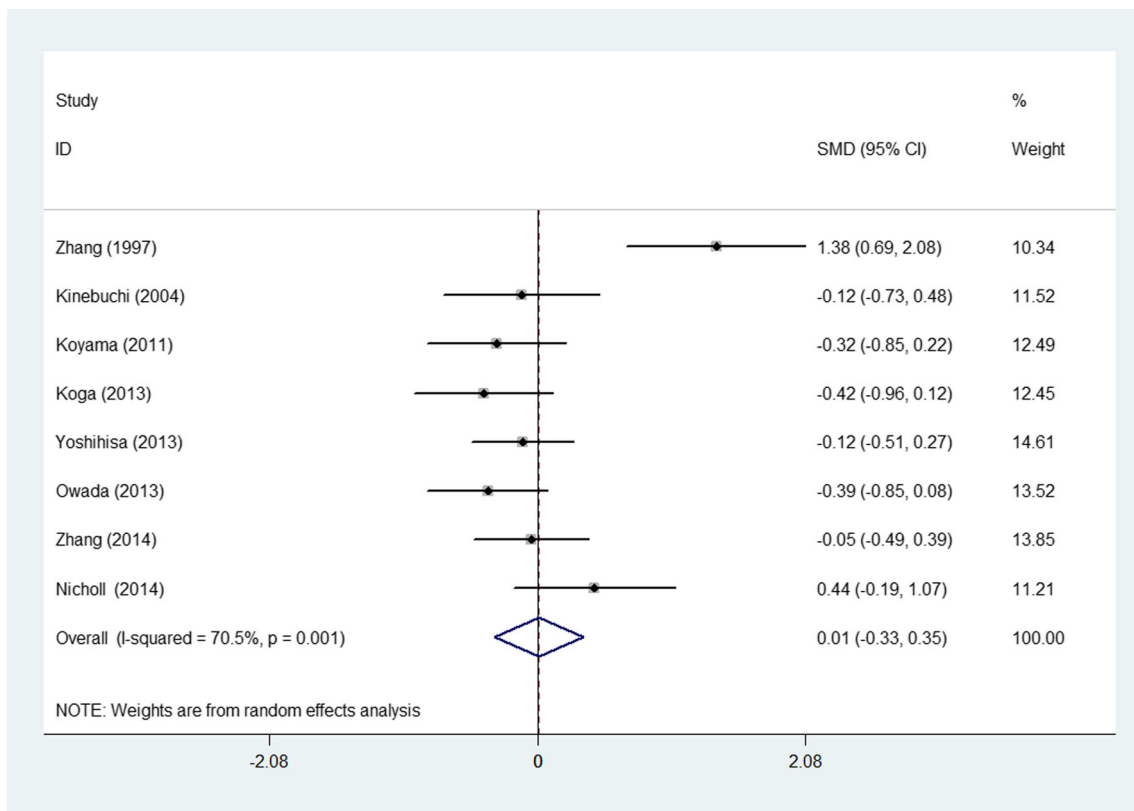
endothelial dysfunction, inflammatory cytokine levels, sympathetic nervous system activity, and systemic blood pressure dysfunction [23, 24], all of which have been proposed to reduce kidney function.

PAP, as first choice for SDB treatment, has been reported to reverse SDB-associated hypoxia, sympathetic activation [25], inflammatory cytokine levels [26], blood pressure [27], and ameliorate glomerular hyperfiltration [16], which contributed to CKD in SDB. Our meta-analysis indicated that PAP treatment appeared to have no impact on GFR in SDB patients. As effectiveness of PAP treatment was influenced by multiple factors, we

**Table 2** Patients' characteristics of the trials included in the meta-analysis

Study	Age	AHI/RDI	Low SO <sub>2</sub>	BMI	Pre-PAP GFR	Post-PAP GFR
Zhang	52 $\pm$ 8	64.3 $\pm$ 18.1	NR	28.1 $\pm$ 3.0	110.1 $\pm$ 9.5 ml/min	98.5 $\pm$ 7.1 ml/min
Kinebuchi	52.8 $\pm$ 13.4(27)	57.8 $\pm$ 22.0	65.0 $\pm$ 17.3	30.4 $\pm$ 6.5(27)	122.2 $\pm$ 39.0 ml/min	127.1 $\pm$ 40.1 ml/min
Koyama	74.8 $\pm$ 7.6	32.2 $\pm$ 17.1	NR	23.4 $\pm$ 3.1	44.2 $\pm$ 12.3 ml/min/1.73 m <sup>2</sup>	48.2 $\pm$ 12.9 ml/min/1.73 m <sup>2</sup>
Koga	55 $\pm$ 10(38)	41.8 $\pm$ 19.8	77.9 $\pm$ 7.7	28.6 $\pm$ 4.5	72.9 $\pm$ 12.0 ml/min/1.73 m <sup>2</sup>	79.3 $\pm$ 17.9 ml/min/1.73 m <sup>2</sup>
Yoshihisa	59.9 $\pm$ 9.9	37.3 $\pm$ 18.2	79.2 $\pm$ 9.7	25.0 $\pm$ 4.5	61.9 $\pm$ 30.8 ml/min/1.73 m <sup>2</sup>	65.7 $\pm$ 33.8 ml/min/1.73 m <sup>2</sup>
Owada	66.6 $\pm$ 10.8	36.7 $\pm$ 15.2	78.4 $\pm$ 9.4	25.0 $\pm$ 3.6	46.6 $\pm$ 13.4 ml/min/1.73 m <sup>2</sup>	53.8 $\pm$ 22.6 ml/min/1.73 m <sup>2</sup>
Zhang	51.18 $\pm$ 12.22	51.57 $\pm$ 16.69	61.00 $\pm$ 13.21	30.1 $\pm$ 4.6	98.69 $\pm$ 31.74 ml/min/1.73 m <sup>2</sup>	100.20 $\pm$ 28.30 ml/min/1.73 m <sup>2</sup>
Nicholl	50 $\pm$ 9	41.7 $\pm$ 18.8	72.3 $\pm$ 5.4	33 $\pm$ 4	124 $\pm$ 36 ml/min	110 $\pm$ 27 ml/min

BMI body mass index, AHI apnea-hypopnea index, RDI respiratory disturbance index, LowSO<sub>2</sub> lowest O<sub>2</sub> saturation, BMI body mass index, PAP positive airway pressure, GFR glomerular filtration rate, NR not reported

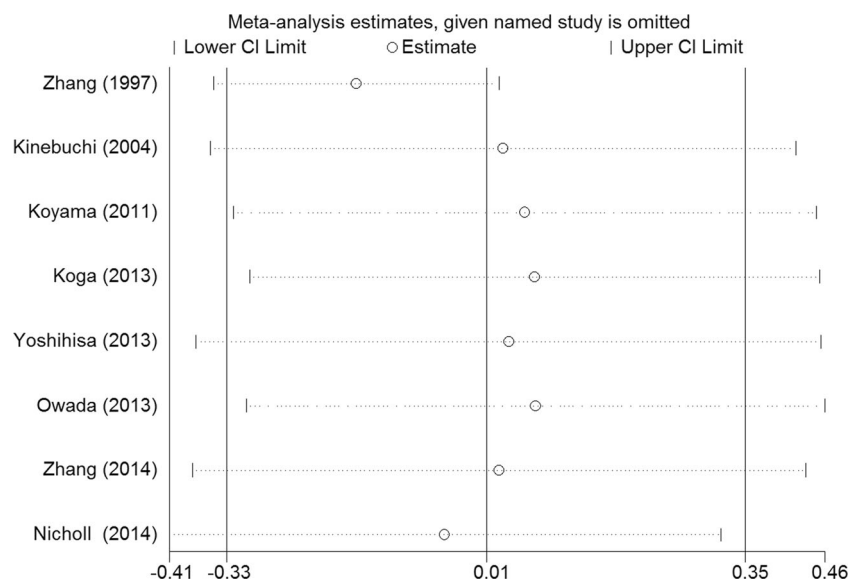


**Fig. 2** Forest plot for the change in GFR before and after PAP treatment. *GFR* glomerular filtration rate, *PAP* positive airway pressure, *CI* confidence interval

performed subgroup analyses in terms of age, baseline BMI, baseline AHI, treatment duration, sample size, and PAP type. The results of subgroup analyses supported that as little as 3 months of PAP was required to have a change on GFR. Besides treatment duration, our results suggested that GFR in elder patients might respond better to PAP therapy.

Our meta-analysis has several strengths. Firstly, this was the first meta-analysis that examined the effect of PAP on GFR in SDB patients. Secondly, pooling of information from all eligible studies yielded more precise and reliable results than that of individual studies. Thirdly, most of the included studies had an effective PAP use of 4 h/night or more, suggesting a good PAP

**Fig 3** Sensitivity analysis of the included studies. *SMD* standardized mean difference, *CI* confidence interval



**Table 3** The results of subgroup analyses

Subgroup	Number of studies/patients	Heterogeneity			SMD			
		$\chi^2$	<i>P</i>	$I^2$ (%)	SMD	95 % CI	<i>Z</i>	<i>P</i>
<b>Age</b>								
<55	4/100	13.81	0.003	78.3	0.382	−0.244 to 1.009	1.20	0.232
≥55	4/140	1.14	0.767	0.0	−0.283	−0.518 to −0.047	2.35	0.019
<b>BMI</b>								
<30	5/160	21.02	0.000	81.0	−0.012	−0.536 to 0.512	0.05	0.964
≥30	3/80	2.00	0.369	0.0	0.051	−0.260 to 0.362	0.32	0.749
<b>AHI</b>								
<50	5/160	5.60	0.231	28.6	−0.188	−0.454 to 0.077	1.39	0.164
≥50	3/80	13.47	0.001	85.1	0.375	−0.486 to 1.237	0.85	0.393
<b>Follow time (months)</b>								
<3	4/111	15.36	0.002	80.5	0.361	−0.280 to 1.002	1.10	0.269
≥3	4/129	1.51	0.680	0.0	−0.276	−0.522 to −0.031	2.20	0.027
<b>Sample size</b>								
<30	5/115	20.67	0.000	80.6	0.168	−0.438 to 0.774	0.54	0.587
≥30	3/125	1.18	0.553	0.0	−0.173	−0.422 to 0.076	1.36	0.172
<b>PAP type</b>								
CPAP	5/127	18.78	0.001	78.7	0.216	−0.338 to 0.771	0.76	0.445
ASV	3/113	0.83	0.659	0.0	−0.250	−0.512 to 0.012	1.87	0.061

*SMD* standardized mean difference, *BMI* body mass index, *AHI* apnea-hypopnea index, *PAP* positive airway pressure, *CPAP* continuous positive airway pressure, *ASV* adaptive servo-ventilation, *CI* confidence interval, *SMD* standardized mean difference

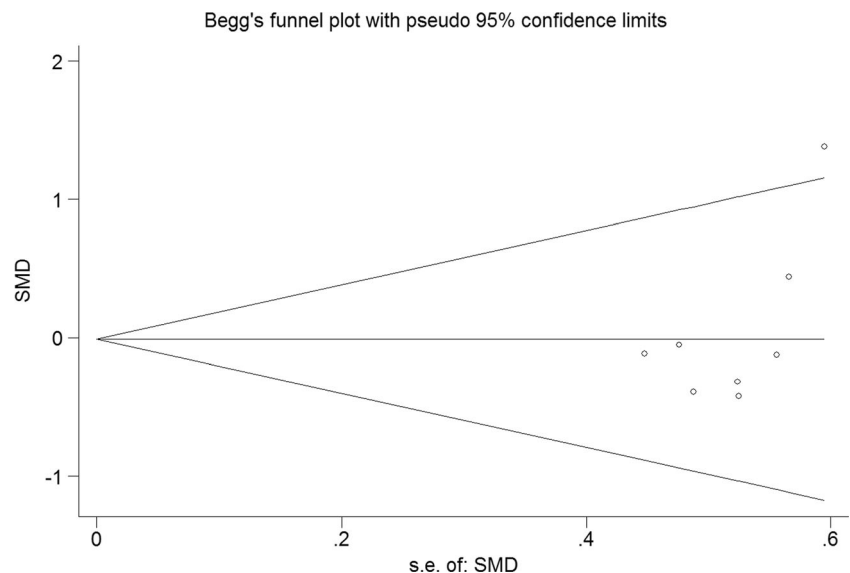
compliance. Lastly, Begg's tests and Egger's tests showed there was no evidence to support publication bias in our study.

Nevertheless, the meta-analysis also has several limitations. Firstly, the sample sizes of the included studies were small. Secondly, all of the included studies were self-control, not RCT. Thirdly, in our meta-analysis, different studies utilized a variety of measurement

techniques for GFR. In addition, the use of only English language papers only may cause some publication biases.

In conclusion, the present meta-analysis suggested that PAP treatment had no impact on GFR in SDB patients. However, longer PAP usage for SDB patients significantly improved GFR. In elder SDB subjects, PAP was also associated with a statistically significant increase in GFR.

**Fig 4** Funnel plots for assessing publication bias of studies included. *SE* standard error, *SMD* standardized mean difference



**Compliance with ethical standards** This article does not contain any studies with human participants performed by any of the authors.

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

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