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EPIDEMIOLOGY • REVIEW

Obstructive sleep apnoea and risks of all-cause mortality: preliminary evidence from prospective cohort studies

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Abstract
Purpose A meta-analysis of prospective cohort studies was conducted to clarify the association between obstructive sleep apnoea (OSA) and future risk of all-cause mortality.
Methods Eligible studies were identified by searching the PubMed and EMBASE databases up to July 2015. Pooled hazard ratios (HRs) and their corresponding 95 % confidence intervals (CIs) were calculated to estimate the association between OSA and risk of all-cause mortality. Sources of heterogeneity were identified by subgroup and meta-regression analyses.
Results Twelve prospective cohort studies involving 34,382 participants were included in this meta-analysis. The pooled HR of all-cause mortality was 1.262 (95 % CI 1.093–1.431) with significant heterogeneity. Subgroup analyses indicated that the pooled HRs of all-cause mortality in patients with mild, moderate and severe OSA were 0.945 (95 % CI 0.810–1.081), 1.178 (95 % CI 0.978–1.378) and 1.601 (95 % CI 1.298–1.902), respectively. OSA severity could be a possible sources of heterogeneity. Existing publication bias produced a minor contribution to effect size.
Conclusion Severe, but not mild to moderate, OSA is significantly associated with increased risk of all-cause mortality.

Keywords Obstructive sleep apnoea · All-cause mortality · Meta-analysis

Introduction

Obstructive sleep apnoea (OSA), the most common sleep disorder in clinical practice, is characterised by upper airway obstruction, which leads to repetitive apnoeas and hypopnoeas during sleep. This condition is associated with sleep fragmentation and intermittent hypoxia. The estimated prevalence of OSA is approximately 4 % in men and 2 % in women [1]. Such prevalence is increasing at an alarming rate [2].

Emerging evidence suggests that OSA is associated with the future risk of mortality. The major of published epidemiologic studies have yielded conflicting results. Recent meta-analyses of all-cause mortality in OSA have concluded that severe OSA significantly increases all-cause mortality [3, 4]. However, two analyses [3, 4] included fewer studies, did not involve patients with mild OSA and exhibited higher prevalence than patients with moderate or severe OSA. The study by Wang et.al [4] only conducted a pooled analysis. Neither studies [3, 4] explored the robustness of pooled results and the influence of several variables on effect size limited by the number of studies. The presence of heterogeneity and publication bias in previous meta-analyses can also influence the reliability of pooled results. Therefore, a meta-analysis of

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cohort study is crucial to verify previous conclusions and to reassess the association between OSA and all-cause mortality. In particular, all-cause mortality in patients' mild OSA and the potential effects of relevant variables on all-cause mortality should be determined.

Methods and materials

Literature search and selection

Eligible studies were identified by systematically searching the PubMed and EMBASE databases up to July 2015. The search was limited to human, but no language restrictions were implemented. The searches combined free-text and subject terms, and the following search terms were used: 'mortality' or 'death', 'apnoea' or 'apnea', and 'cohort' or 'prospective cohort studies'. The reference lists of relevant publications were also manually searched for additional studies.

Two researchers independently identified the eligible studies. Conflicting decisions were resolved through a consensus with a third researcher. Studies were considered eligible if the following criteria were met: (1) the design was prospective cohort study; (2) the studied population was adult; and (3) the outcome of relative risk (hazard ratios (HRs)) with their 95 % confidence intervals (CIs) for all-cause mortality was included, or sufficient data were provided to calculate them.

The fully adjusted HR was used to compute the pooled HR for the associations of OSA with risk of all-cause mortality; otherwise, non-adjusted HR was used. When multiple studies reported outcomes using the same patient group, the study with the largest population was included. Abstracts, case reports, editorials, expert opinions, letters, animal studies and reviews without original data were excluded.

In most studies included in this meta-analysis, the diagnosis of OSA was based on the apnoea–hypopnoea index (AHI). Therefore, the severity of OSA in this study was quantified using AHI; normal (AHI < 5), mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI > 30) respectively [5].

Data extraction

Data extracted from each study included the name of the first author, publication date, country, patient recruitment, sample size (the number of participants and mortality cases), follow-up duration, the diagnosis and severity of OSA, mortality ascertainment, statistical adjustments for confounding factors and participant characteristics (age and body mass index (BMI)).

Statistical analysis

Pooled HR was used to estimate the association between OSA and risk of all-cause mortality across studies. Q and I^2 statistics were used to determine statistical heterogeneity amongst individual studies. $P_{\text{heterogeneity}} < 0.10$ or $I^2 > 60$ % was considered to indicate significant heterogeneity. The random effects model was used when significant heterogeneity was observed; otherwise, the fixed effects model was utilised. In papers that reported HRs from a separate subgroup, the combined HR was computed using the fixed effects model prior to pooling.

Sensitivity analyses using the random effects model were conducted to explore the robustness of pooled results. Planned subgroup analyses using the random effects model were conducted to evaluate the effects of several relevant variables on the effect size and to explore possible sources of heterogeneity. Meta-regressions were also conducted to explore possible sources of heterogeneity.

Publication bias was evaluated visually with funnel plot and statistically with the Begg's and Egger's tests. The trim and fill method was used to identify and correct for funnel plot asymmetry arising from publication bias. Cumulative meta-analyses were conducted to detect the presence of publication bias.

A two-tailed $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were conducted using software Stata 10.0 (StataCorp, College Station, TX, USA).

Results

Literature search and characteristics

Figure 1 shows the selection process for studies included in this meta-analysis. The initial online search on the databases resulted in the identification of 546 potentially related articles. After reviewing the titles and abstracts, 19 articles were selected and further reviewed. Seven articles were excluded for the following reasons: one study duplicated the participants with the study of Marshall 2014 [6], one study did not present original data [3], three studies lacked data for the necessary computations [7–9] and two studies involved participants who were not OSA patients [10, 11]. Twelve cohort studies which involved 34,382 participants finally met the inclusion criteria and were included in this meta-analysis [12–23]. The characteristics of the included studies and the corresponding patient information are summarised in Table 1.

Pooled analysis

The heterogeneity test indicates significant heterogeneity amongst individual studies ($P_{\text{heterogeneity}} = 0.000$,

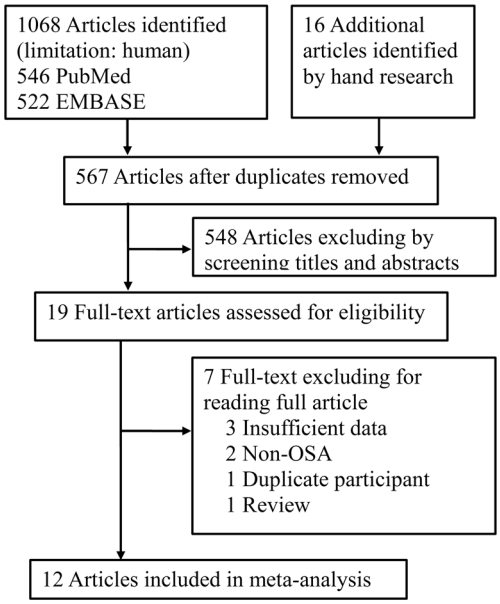

Fig. 1 Flow diagram of study selection

I^2 = 70.4 %). Hence, the random effects model was used for the pooled analysis. The result demonstrated a significant decrease in all-cause mortality (HR, 1.262, 95 % CI 1.093–1.431), whereas the fixed model yielded a non-significant result (HR, 1.024, 95 % CI 0.988 to 1.061) (Fig. 2).

Sensitivity analyses

Sensitivity analyses by omitting one study at a time indicated that the HR ranged from 1.169 (95 % CI 1.021 to 1.318) to 1.379 (95 % CI 1.134 to 1.624) after omitting the studies of Lavie 2005 [14] and Mant 1995 [16]. A borderline result was obtained after excluding two studies that diagnosed OSA on the basis of self-reporting [19, 20] (HR, 1.204, 95 % CI 1.039 to 1.368; $P_{\text{heterogeneity}}$ = 0.002, I^2 = 65.6 %). To decrease the effect of gender, the study of Lavie 2005 [14] which involved male participants only, was excluded, a heterogeneous ($P_{\text{heterogeneity}}$ = 0.009, I^2 = 57.7 %) and non-significant increase in mortality was observed (HR, 1.169, 95 % CI 1.021 to 1.318). Additional sensitivity analysis by restricting the analysis to studies which diagnosing OSA on the basis of AHI revealed a heterogeneous and significant increase in mortality ($P_{\text{heterogeneity}}$ = 0.045, I^2 = 49.5 %; HR, 1.280; 95 % CI 1.059 to 1.5027).

Subgroup analysis

Differences in sample size (≤1000 and >1000), severity of OSA (mild, moderate, severe), patient age (≤60 and >60 years) and BMI (≤30 and >30 kg/m^2) significantly influenced all-cause mortality in patients with OSA, but not significantly in study location (Europe, USA, Asia-Pacific), recruitment-based (community and hospital) and follow-up duration (≤10 and >10 years). Heterogeneity was abolished, when grouped by disease severity. Table 2 presents the detailed results of subgroup analyses.

Specific subgroup analyses were performed by restricting the analysis to studies that directly compared mortality rate with varying OSA severity. Results of OSA severity from four studies [12, 13, 17, 22] indicated that the pooled HR were 0.945 (95 % CI 0.810 to 1.085), 1.180 (95 % CI 0.964 to 1.396) and 1.503 (95 % CI 1.154 to 1.851) for patients with mild, moderate and severe OSA, respectively, without significant heterogeneity ($P_{\text{heterogeneity}}$ = 0.206, I^2 = 24.2 %). Compared with patients with mild and moderate OSA, those with severe OSA exhibited higher mortality.

Meta-regression analysis

Univariate meta-regression analysis showed that the change in all-cause mortality was not statistically associated with publication year (P = 0.149), study location (P = 0.261), patients recruitment (P = 0.146), follow-up duration (P = 0.304), participant number (P = 0.266), as patient age (P = 0.637) and BMI (P = 0.223). Unfortunately, the analysis does not perform in severity of disease based on limited data available.

Publication bias

The funnel plot indicates the potential presence of publication bias. The results of Begg's (P = 0.732) and Egger's test (P = 0.003) further supported the occurrence of publication bias in this meta-analysis. The trim and fill method indicated the need for five additional studies to correct the funnel plot asymmetry (Fig. 3). The corrected HRs after using the fixed and random effects models were 1.015 (95 % CI 0.978 to 1.051) and 1.117 (95 % CI 0.941 to 1.293), indicating a minor contribution of publication bias to the pooled results.

The pooled results showed that the random effects estimate was more beneficial than the fixed effects one, indicating the presence of small-study effects. Accordingly, a cumulative meta-analysis was conducted to identify the presence of small-study effects. The results suggest the contribution of small-study effects (Fig. S1), and this result was strengthened by the outcome of subgroup analysis. Cumulative meta-analysis revealed that the republication year of study exerted no significant influence on publication bias (Fig. S2).

Discussion

This meta-analysis evaluated the association between OSA and future risk of all-cause mortality. Patients with OSA exhibited a significant increase in risk of all-cause mortality. Subgroup analysis suggested the discrepant effect of disease

Table 1 Characteristics of 12 included studies and participant

Study (years)	Country	Recruitment	Number of C/P (deaths)	Follow-up (years)	OSA examination	OSA diagnosis	Patients characteristics		Mortality ascertainment
							Age (years)	BMI (kg/m^2)	
Mant 1995	Australia	Community	148 (33); 15 (4)	4	Portable monitor	RDI ≥ 15	80.5 (50.2)	NR	NR
Yaggi 2005	USA	Sleep medicine	325 (14); 697 (50)	3.4 (M)	Overnight PSG	AH ≥ 5	Control 58.7; OSA 60.9	Control 30.5; OSA 33.8	Family members
Lavie 2005	Israel	Sleep clinics	3227 (NR); 10,626 (NR)	4.6 (2.2) (M)	Full PSG	RDI > 10	OSA 48.4 (12.3)	OSA 28.8 (4.8)	The Ministry of the Interior
Young 2008	USA	Community	1157 (46); 365 (34)	13.8	18-channel PSG	AHI ≥ 5	Control 48 (8); mild 50 (8); moderate 50 (8); severe 50 (9)	Control 27.6; mild 31.5; moderate 33.3; severe 37.2	The US Social Security Death Index and the Wisconsin State Bureau of Health Information and Policy
Punjabi 2009	USA	Community	3429 (477); 2865 (570)	8.2	Portable monitor	AHI ≥ 5	Control 61.3 (11.1); mild 64.8 (10.6); moderate 65.1 (10.5); severe 64.6 (10.7)	Control 27.0 (4.5); mild 29.5 (5.3); moderate 30.7 (5.8); severe 32.1 (6.1)	Follow-up interviews, written annual questionnaires or telephone, surveillance and linkage with the Social Security Administration Death Master File
Gooneratne 2011	Philadelphia	Community	223 (160); 66 (52)	13.8	16-channel PSG	AH ≥ 20	EDS 78.0 (6.3); No-EDS 77.9 (6.4)	EDS 27.0 (4.6); No-EDS 25.8 (4.7)	The social security death index
Johansson 2011	Sweden	Community	148 (20); 183 (27)	1648 days	Portable monitor	AHI ≥ 5	78 (3)	27 (25–30)	The National Board of Health and Welfare, Stockholm
Marshall 2011	Sweden	Community	3019 (237); 934 (117)	C/P 13.2/13.9	NR	Self-reported	Control 47.9 (6.2); OSA 48.1 (6.0)	Control 41.2 (4.7); OSA 41.3 (4.8)	The Swedish Population Register and Address Register
Yeboah 2011	USA	Community	3678 (129); 208 (15)	7.5	Physiological monitoring	Physician-diagnosed	Control 63. 7 (10.2); OSA 61.8 (9.2)	Control 27.8 (5.8); OSA 32.2 (6.2)	NR
Martínez-García 2012	Spain	Sleep clinic cohorts	155 (26); 281 (83)	69 months (M)	Full-PSG	AHI ≥ 15	AHI 15–29: 71.7 (5.2); AHI ≥ 30 71.9 (4.5)	AHI 15–29: 33.6 (4.4); AHI ≥ 30: 34.8 (6)	NR
Lee 2013	Korea	Sleep clinic cohorts	440 (8); 1800 (61)	61.4 months	Full-night PSG	AHI ≥ 5	Control 54.2; mild 56 moderate 56.1; severe 55.5	Control 23.7; mild 24.6; moderate 25.4; severe 26.9	The Statistics Korea
Marshall 2014	Australia	Community	294 (54); 99 (23)	13.4	Portable monitor	RDI ≥ 5	Control 52.6 (7.5); mild 54.3 (7.2); moderate–severe 55.1 (8.2)	Control 26.2 (3.7); mild 27.9 (4.1); moderate–severe 34.3 (7.3)	The National Death Index; listings in the telephone directory; contact with relatives; listing on the electoral role

Values if not otherwise indicated as mean (SD)

AHI apnoea–hypopnoea index, *BMI* body mass index, *C/P* control/patient (OSA), *EDS* excessive daytime sleepiness, *M* median, *NR* not reported; *OSA* obstructive sleep apnoea, *PSG* polysomnography, *RDI* respiratory disturbance index

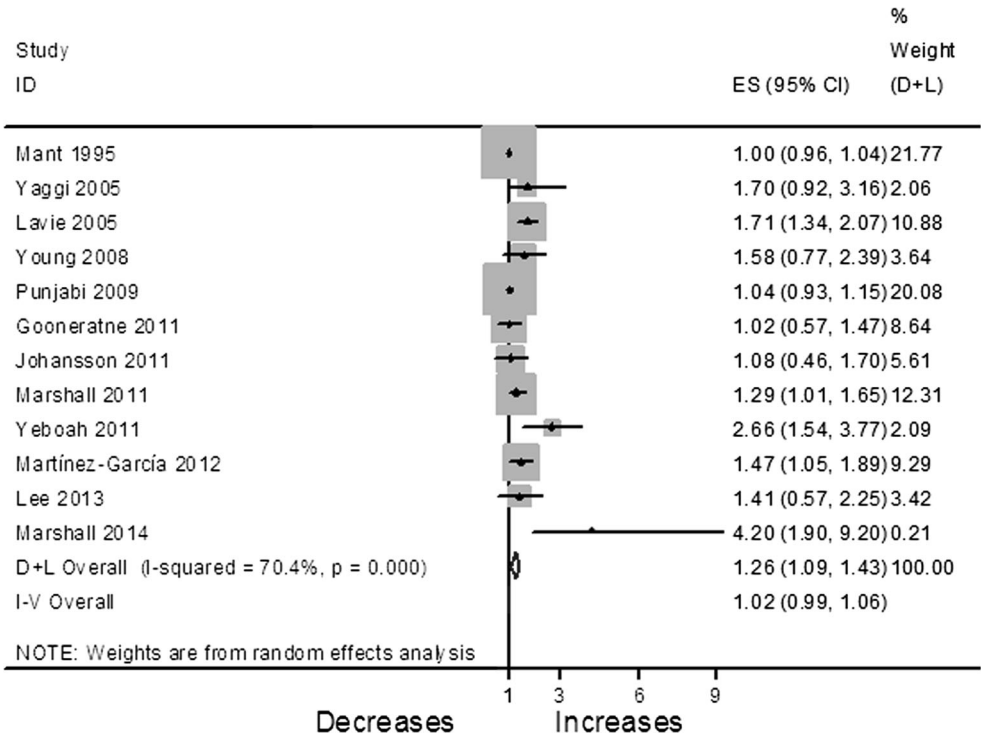

Fig. 2 Meta-analysis of association between OSA and risks of all-cause mortality

severity. Unlike patients with mild to moderate OSA, those with severe OSA exhibited significantly increased mortality.

To the best of our knowledge, this study is the first meta-analysis to evaluate the risk of all-cause mortality in patients with mild, moderate and severe OSA. Different from previous meta-analyses, which included only six studies with moderate or severe OSA [3, 4], the current study included additional six studies with three degrees of OSA severity. Therefore, the current meta-analysis has high statistical power and degree of certainty to detect the association. Inconsistent with the present study, a higher effect size was reported from previous meta-analyses [3, 4], with HRs of 1.67 (95 % CI 1.25 to 2.23) and 1.92 (95 % CI 1.38 to 2.69). When the analysis was restricted to severe OSA, similar HRs were obtained in this analysis. This result may be attributed to the disparity in disease severity.

The precise mechanisms underlying the association between OSA and future risk of all-cause mortality remain unclear. The possibility may be explained by some pathophysiological characteristics associated with OSA. OSA can exert several deleterious effects including sleep fragmentation, swings in negative intrathoracic pressure, fluid redistribution, intermittent hypoxia, alterations in sympathetic activity, increased systemic inflammation, hidden or unaccounted risk factors or other factors related to OSA such as excessive daytime sleepiness, obesity and lung disease [18, 24–27]. All these factors can induce and promote directly or indirectly multi-organ or system function damage, consequently hastening patient death.

Determining whether OSA is an independent risk factor or simply a marker is essential. Current findings seemed to support the role of OSA as an independent factor. First, if OSA is an early marker, then the value of AHI or respiratory disturbance index (RDI) should be higher when patient death is near. The follow-up duration of 4–20 years in studies included in this meta-analysis suggests that OSA is an independent risk factor. Second, although no linear trend analysis was conducted on AHI or RDI change with risk of all-cause mortality because of the limited number of studies, the result indicates a high mortality rate in patients with severe OSA, which is consistent with previous findings [12, 13, 17, 21, 22, 28]. Finally, considerable convincing mechanisms should come from the pathophysiology of OSA. As described above, OSA can induce and promote a multi-organ or system function damage [26] and hasten patient death.

Subgroup analysis suggests that the differences in sample size, severity of OSA, patient age and BMI are significantly associated with the risk of all-cause mortality. At least four studies compared the all-cause mortality in patients with mild, moderate and severe OSA, the studies suggested that severe OSA tended to be associated with increased all-cause mortality compared to mild or moderate OSA [6, 12, 13, 22]. In addition, a similar result was reported by previous meta-analysis [3, 4]. Differences in severity of OSA may be associated with risk of all-cause mortality because severe OSA is prone to develop organ damage, thereby increasing the risk of mortality, compared with mild to moderate OSA. The larger sample sizes have sufficient statistical power to detect the potential association between OSA and mortality compared with smaller sample sizes. Thus, the result

Table 2 The results of subgroup analyses

Study	No. of study	No. of control (death)	No. of patients (death)	Heterogeneity			Pooled HR (95 % CI)		$P_{intergroup}$
				χ^2	P value	I^2 (%)	Fixed models	Random models	
Study location									
Europe	4	6508 (192)	12,026 (673)	4.21	0.240	28.7	1.431 (1.233–1.628)	1.426 (1.186–1.667)	0.000
USA	4	8589 (666)	4135 (679)	10.78	0.013	72.2	1.075 (0.965–1.186)	1.609 (0.917–2.301)	
Asia-Pacific	4	916 (156)	1908 (159)	3.87	0.276	22.5	1.001 (0.962–1.041)	1.043 (0.816–1.269)	
Recruitment-based									
Community	8	11,897 (932)	4789 (991)	16.80	0.019	58.4	1.012 (0.975–1.050)	1.108 (0.962–1.254)	0.311
Hospital	4	4116 (82)	13,278 (520)	0.90	0.829	0.0	1.592 (1.337–1.847)	1.592 (1.337–1.847)	
Follow-up duration (years)									
≤10	8	11,424 (717)	16,603 (1165)	29.70	0.000	76.4	1.019 (0.982–1.057)	1.262 (1.067–1.458)	0.073
>10	4	4589 (297)	1464 (346)	4.25	0.236	29.4	1.248 (1.001–1.495)	1.265 (0.919–1.611)	
Sample size									
≤1000	5	769 (189)	698 (208)	7.78	0.100	48.6	1.005 (0.965–1.045)	1.128 (0.869–1.388)	0.009
>1000	7	15,244 (825)	17,369 (1303)	22.55	0.001	73.4	1.148 (1.048–1.247)	1.474 (1.135–1.812)	
Disease severity									
Mild	4	5102 (546)	2633 (363)	1.07	0.784	0.0	0.945 (0.810–1.081)	0.945 (0.810–1.081)	0.000
Moderate	5	5257 (572)	1540 (256)	1.08	0.897	0.0	1.178 (0.978–1.378)	1.178 (0.978–1.378)	
Severe	5	5257 (573)	1195 (156)	3.75	0.441	0.0	1.601 (1.289–1.912)	1.601 (1.289–1.912)	
Patient age (years)									
≤60	5	8006 (259)	13,698 (681)	5.04	0.283	20.6	1.485 (1.263–1.707)	1.501 (1.221–1.781)	0.000
>60	7	7907 (755)	4369 (830)	15.10	0.019	60.3	1.011 (0.974–1.049)	1.106 (0.956–1.255)	
Patient BMI (kg/m^2)									
≤30	9	12,514 (857)	16,155 (1141)	28.60	0.000	72.0	1.011 (0.979–1.054)	1.213 (1.026–1.401)	0.005
>30	3	3499 (157)	1919 (370)	0.80	0.671	0.0	1.373 (1.125–1.622)	1.373 (1.125–1.622)	

AHI apnoea–hypopnoea index, *BMI* body mass index, *CI* confidence interval, *HR* hazard ratio

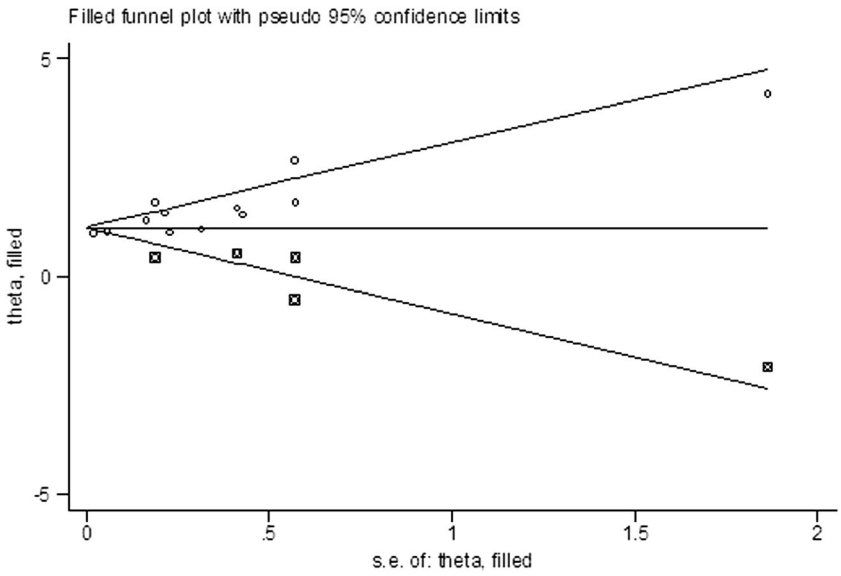

Fig. 3 The filled funnel plot. *Open circles* are for original data, and *squares* are for imputed "filled" values

obtained given a larger sample size and severe OSA subgroups associated with increased risk of all-cause mortality would have a higher degree of certainty. However, the results on the effect of patient age and BMI on mortality must be interpreted with caution. Consistent with the result of this analysis, most studies reported a decrease in mortality risk with increasing age [12, 14, 27, 29, 30]. However, other studies including two large studies have confirmed an association between increased age and increased risk of mortality [31–33]. Obesity has been recognised as an important risk factor for OSA development and progression. Increased BMI may theoretically increase severity of OSA and increase mortality. However, the effects of obesity based on BMI on all-cause mortality remain inconsistent. Three studies examined the effect of BMI on all-cause mortality in patients with OSA have been found [27, 29, 32]; two studies consistent with the result of this analysis indicate a higher mortality in higher BMI [27, 29], but the remaining one suggests otherwise [32]. In addition, no supportive results were found from meta-regression for age and BMI.

Several potential limitations should be noted when interpreting the findings of this meta-analysis. First, significant heterogeneity was present. Subgroup analyses showed that OSA severity and sample size may be possible sources of heterogeneity. However, no supportive results were obtained from meta-regression analyses. Secondly, the potential effect of publication bias was present, although its contribution was minor. Thirdly, the effect size was relatively small despite the large number of participants, and most sensitivity analyses indicated non-robust results. Fourthly, the subgroups were defined post hoc, and the means of subgroup and meta-regression analyses, rather than the individual patients, were used as data points. Finally, AHI or RDI reflecting the respiratory events during sleep including apnoea, hypopnoea and arousals may not accurately reflect the pathophysiological aspects and clinical consequences of OSA [34]. A limited number of studies evaluated the association between OSA-relevant variables, other than AHI and risk of mortality, and found that these variables influence risk of mortality. These variables include symptoms, sleep fragmentation, sympathetic active and hypoxic events [12, 17, 18, 35]. Some studies even recognised that OSA-relevant variables other than AHI were important predictors of all-cause mortality in OSA [35]. Given that OSA is a heterogeneous disorder and the causes are multifactorial [36], the precise effects of these variables on all-cause mortality need further investigation and verification.

Despite the limitations, this meta-analysis supports the hypothesis that OSA is an independent risk factor for all-cause mortality. Further evidence and verification in patients with mild and moderate OSA are needed. Further studies are needed to identify the precise predictors of all-cause mortality and to determine the optimal regimes and patients that would most benefit from OSA intervention.

Authors' contributions Y. Guo conceived and designed the study; L. Pan, X. Xie and Y. Guo selected the studies; D. Liu, D. Ren and Y. Guo extracted the data; X. Xie and Y. Guo performed the statistical analyses; L. Pan, X. Xie, D. Liu and Y. Guo wrote the manuscript. All authors read and revised the manuscript. The final manuscript was approved by all authors.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no competing interests.

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