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An umbrella review of systematic reviews and meta-analyses of observational investigations of obstructive sleep apnea and health outcomes

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Abstract

Purpose The previous analysis of systematic reviews and meta-analyses have illustrated that obstructive sleep apnea (OSA) is correlated with multiple health outcomes. In the present research, our main aim was to execute an umbrella review to assess the available evidence for the associations between OSA and health outcomes.

Methods Herein, a meta-analysis of previous observational investigations that have reported associations between OSA and health outcomes in all human populations and settings was performed. We used these studies to execute an umbrella review of available meta-analyses and systematic reviews.

Results Sixty-six articles comprising 136 unique outcomes were enrolled in this analysis. Of the 136 unique outcomes, 111 unique outcomes had significant associations ($p < 0.05$). Only 7 outcomes (coronary revascularization after PCI, postoperative respiratory failure, steatosis, alaninetrans aminase (ALT) elevation, metabolic syndrome (MS), psoriasis, and Parkinson's disease) had a high quality of evidence. Twenty-four outcomes had a moderate quality of evidence, and the remaining 80 outcomes had a weak quality of evidence. Sixty-nine outcomes exhibited significant heterogeneity. Twenty-five outcomes exhibited publication bias. Sixty-three (95%) studies showed critically low methodological quality.

Conclusion Among the 66 meta-analyses exploring 136 unique outcomes, only 7 statistically significant outcomes were rated as high quality of evidence. OSA may correlate with an increased risk of coronary revascularization after PCI, postoperative respiratory failure, steatosis, ALT elevation, MS, psoriasis, and Parkinson's disease.

Keywords Obstructive sleep apnea · Health · Umbrella review · Meta-analysis

Introduction

Obstructive sleep apnea (OSA) is a prevalent but treatable chronic sleep disorder that is determined through episodes of sleep apnea and hypopnea during sleep and results in recurrent episodes of hypercapnia and hypoxemia [1–3]. OSA has a prevalence of between 5 and 20% depending on the population surveyed and the definition utilized [4, 5]. The prevalence is also increasing due to an increase in body mass index which is one of its major predisposing factors. Apart from causing uncomfortable symptoms such as headache [6] and attention deficit [7], earlier studies indicated that OSA also contributed to the advancement of several diseases including hypertension [8], cardiovascular disease [9, 10], and diabetes [11]. Recent studies have drawn consistent conclusions [12–14]. Recently, a great number of researches have explored the correlation between OSA and other diseases. Multiple investigations and meta-analyses have illustrated that OSA poses a threat to human health because it increases the risk of various diseases, including cancers [15–17], depression [18], laryngopharyngeal reflux disease [19], metabolic disease [20], Parkinson's disease [21], and chronickidney disease (CKD) [22].

These studies suggest a possible causal relationship between OSA and different health outcomes, indicating that OSA has a bad influence on human health. However, several factors are known to decrease the validity and strength

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of reported evidence including publication bias, protocol design flaws, or inconsistencies of studies. Currently, there have been no systematic reviews that have accurately summarized and critically appraised existing studies. In the current study, an umbrella review was executed to comprehensively evaluate published systematic reviews and meta-analyses of observational researches that reported associations between OSA and health information. This work can provide important guidance in the diagnosis and treatment of OSA.

Materials and methods

The protocol of the research was registered with PROSPERO (registration number: CRD42020220015) before the umbrella review began. A systematic exploration of the literature search was accomplished in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols [23].

Literature search

From initiation until November 23, 2020, literature searches were performed using online databases such as Embase, PubMed, the Cochrane Database of Systematic Reviews, and the Web of Science. Literature searches were independently conducted by two researchers (CZ and LG). The search terms applied were ("obstructive sleep apnea" OR "obstructive sleep apnea–hypopnea" OR "OSA" OR "OSAH") AND (Meta-Analysis[ptyp] OR metaanaly*[tiab] OR meta-analy*[tiab] OR Systematic review [ptyp] OR "systematic review"[tiab]). The references were manually screened to identify eligible articles to be included in the study. The article titles, abstracts, and the complete manuscripts of the identified paper were then further assessed. A discussion was used to resolve potential discrepancies; ST acted as an arbiter to deal with discrepancies that could not be resolved by discussion among the investigators.

Eligibility criteria and exclusion criteria

The eligibility of articles was based on a systematic search by the authors to identify the most pertinent studies. Only systematic reviews or meta-analyses on the basis of the epidemiological studies performed in humans were considered in the analysis. Diagnostic trials and meta-analyses of interventional trials were not performed as part of the current study. Furthermore, the abstracts of the conference on review questions were not included in the final analysis. The final systematic reviews and meta-analyses that were analyzed had to include the data of pooled summary effects(i.e., relative risks (RRs); odds ratios (ORs); hazard ratios (HRs); mean difference (MD); weighted mean difference (WMD); standard mean difference (SMD); and their 95% confidence intervals (CIs)), number of included researches, number of participants and cases, heterogeneity, and publication bias. Whenever more than one meta-analysis was executed using on the basis of the same outcome, the agreement with the main conclusions reported in the study were verified. When the reported conclusions were conflicting, the meta-analysis with the greatest number of investigations was considered.

Data extraction

For investigations to be eligible for inclusion in the meta-analysis, two researchers (WC and YL) independently extracted data from the articles. This included the first author, the number of included investigations, the year of publication, the study design, the whole numbers of cases, and participants. The reported relative summary risk evaluates (ORs, RRs, HRs, SMD, WMD, or MD) and the corresponding 95% CIs were extracted, for each eligible systematic review and meta-analysis. The values of p for the total pooled effects, Cochran Q measurement, Egger's measurement, and I^2 were extracted. Discrepancies in the analyses were resolved by discussion among the investigators.

Assessment of methodological quality

Two investigators (WC and YL) independently assessed the quality of the methods reported in the studies. This was performed using a 16-criteria checklist included in AMSTAR 2 [24]. AMSTAR 2 is a fundamental revision of the original instrument of AMSTAR which was devised to evaluate systematic reviews that included randomized controlled experiments. The AMSTAR 2 score is categorized as high in studies that have no or one noncritical weakness, moderate in surveys with more than one noncritical weakness, low when the study has only one serious flaw without or with noncritical weaknesses, and seriously low when a study has more than one serious flaw without or with nonserious weaknesses. Discrepancies between the AMSTARS 2 scores for the articles were resolved by discussion between the investigators.

Assessment of the evidence quality

Two investigators (WC and YL) independently evaluated the quality of the evidence conforming to the parameters that have previously been applied in various fields [25–28]. Discrepancies were resolved by discussion. First, p value

for the estimate < 0.001 [29, 30] and more than 1000 cases of the disease, which indicated fewer false-positive results. Second, I^2 < 50% and p value for Cochran Q test > 0.10, which indicated consistency of results. Third, p value for Egger's test > 0.10, which exhibited no evidence of small-study impacts. When all of the above criteria were satisfied, the strength of the epidemiologic evidence was rated as high. When 1 of the criterion was not satisfied and the p value for the estimate was < 0.001, the strength of the epidemiologic evidence was rated as moderate. Then, the rest was defined as weak ($p < 0.05$). The value of p for the evaluation can be assessed from the 95% confidence interval of the pooled impact estimate utilizing an established method [31] if it was not directly reported in the article.

Data analysis

From each of the published studies, the outcome data of the available meta-analyses was extracted along with the estimated summary effect at the corresponding 95% CI. The total impacts of the pooled meta-analysis were considered significant when the p-value was < 0.05. Heterogeneity was appraised by the I^2 test and Q test, publication bias was estimated by utilizing Egger's test, and both were considered significant at $p < 0.1$. Studies that did not have the heterogeneity or publication bias results were reanalyzed if raw data were available.

Results

Characteristics of the meta-analyses

The outcomes of the systematic investigation and the selection of eligible investigations are summarized in Fig. 1. Overall, 1972 articles were searched from which 66 meta-analyses of observational investigations were identified that had 136 unique outcomes [21, 22, 32–95]. The 66 eligible non-overlapping meta-analyses had publication dates ranging from 2009 to 2020 and are summarized in Table 1. The median number of primary investigations per evidence synthesis was 7 (range 2–64). Furthermore, 1 meta-analysis [54] lacked the data of both participants and cases, and 2 meta-analyses [52, 95] lacked the data of cases. Among the meta-analyses identified in this study, the median number of cases was 900 (88–3,117,496) and the median number of participants was 2962 (170–56,746,100). An extensive

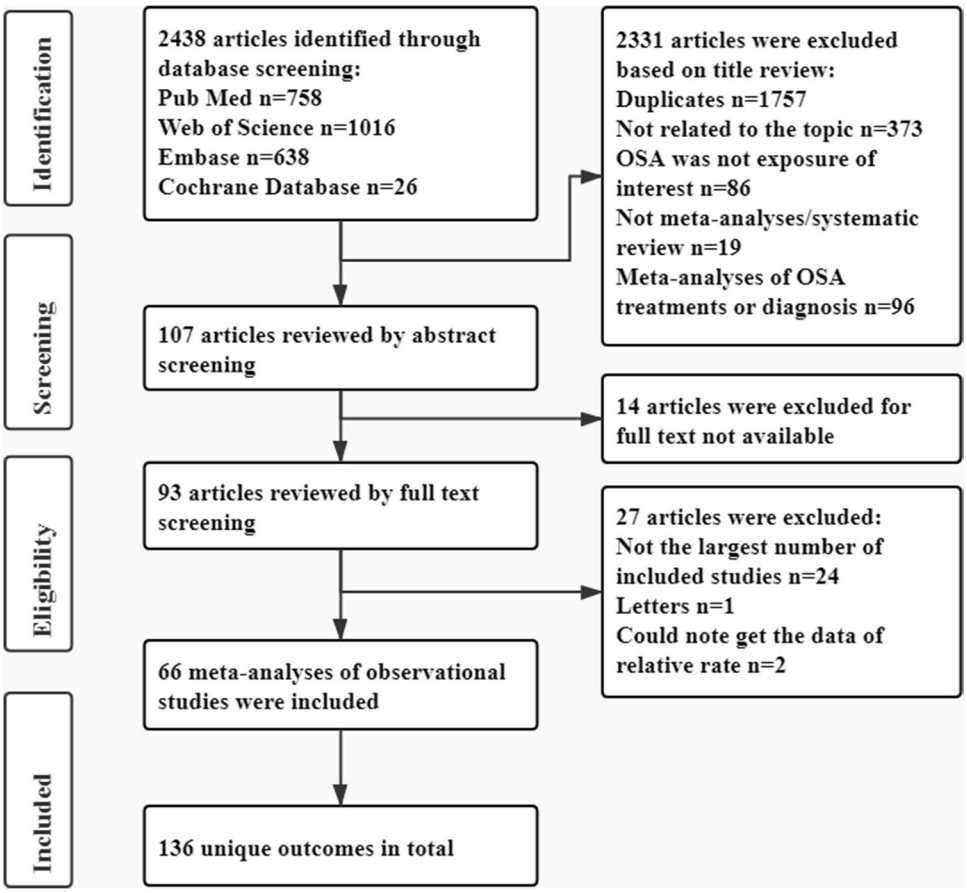

Fig. 1 Flowchart of the selection procedure

Table 1 Associations between OSA and multiple heath outcomes

Outcomes	Publication	Number of studies	Number of participants	Number of cases	Type of metric	Relative risk (95% CI)	*P* value*	*P* value #	I^2 (%)	*P* value※	Whether exist publication bias
Cardiovascular disorders											
Aortic dissection	Xiushi Zhou (2018)	1 cohort study, 2 case–control studies	55,911	16,019	OR	1.60 (1.01–2.53)	0.04	0.44	0	0.58	No
Cardiovascular disease(CVD)	Xia Wang (2013)	11 cohort studies	25,594	2628	RR	1.79 (1.47–2.18)	< 0.001	0.131	31.5	0.028	Yes
Stroke	Min Li (2014)	10 cohort studies	18,609	678	RR	2.10 (1.50–2.93)	< 0.001	0.04	47.5	0.288[&]	No
Ischemic heart disease(IHD)	Wuxiang Xie (2014)	6 cohort studies	1083	625	RR	1.83 (1.15–2.93)	0.011	0.111	44.2	0.006	Yes
Coronary heart disease(CHD)	Chengjuan Xie (2017)	6 cohort studies	18,022	15,562	RR	1.63 (1.18–2.26)	0.003	0.061[&]	52.7[&]	0.145[&]	No
Major adverse cardiac events (MACEs)	Chengjuan Xie (2017)	9 cohort studies	18,022	15,562	RR	2.04 (1.56–2.66)	< 0.001	0.021	55.7	0.132	No
Atrial fibrillation	Irini Youssef (2018)	4 cross-sectional studies, 5 cohort studies	19,837	12,255	OR	2.12 (1.84–2.43)	< 0.001	0.004	64.42	0.097[&]	Yes
Resistant hypertension	Haifeng Hou (2018)	6 case -control studies	1465	925	OR	2.84 (1.70–3.98)	< 0.001	0.816	0	0.187[&]	No
Essential hypertension	Haifeng Hou (2018)	2 case–control studies, 5 cohort studies	7102	4513	OR	1.80 (1.54–2.06)	< 0.001	0.221	26	0.0526[&]	Yes
Atrial fibrillation recurrence after catheter ablation	Chee Yuan Ng (2011)	6 observational studies	3995	958	RR	1.25 (1.08–1.45)	0.003	0.008	49	0.879[&]	No
major adverse cardiovascular event (MACE) after PCI	Xiao Wang (2018)	9 observational studies	2755	1581	RR	1.96 (1.36–2.81)	< 0.001	0.02	54	0.002	Yes
Stroke after PCI	Xiao Wang (2018)	6 observational studies	2110	1254	RR	1.55 (0.90–2.67)	0.11	0.62	0	0.149[&]	No
Myocardial infarction (MI) after PCI	Hua Qu (2018)	6 observational studies	2342	1112	OR	1.59 (1.14–2.23)	0.007	0.32	15	0.655[&]	No
Coronary revascularization after PCI	Hua Qu (2018)	7 observational studies	2415	1163	OR	1.57 (1.23–2.01)	< 0.001	0.7	0	0.483[&]	No
Re-admission for heart failure after PCI	Hua Qu (2018)	4 observational studies	1774	793	OR	1.71 (0.99–2.96)	0.06	0.86	0	0.254[&]	No
Left ventricular hypertrophy (LVH)	Cesare Cuspidi (2020)	9 observational studies	3244	1802	OR	1.70 (1.44–2.00)	< 0.001	< 0.001	60	0.0876[&]	Yes
Left ventricular diastolic diameter (LVEDD)	LeiYu (2019)	13 observational studies	882	563	WMD	1.24 (0.68, 1.80)	< 0.001	0.658	0	0.431	No
Left ventricular systolic diameter (LVESD)	LeiYu (2019)	11 observational studies	630	396	WMD	1.14 (0.47, 1.81)	0.001	0.696	0	0.722	No
Left ventricular mass(LVM)	LeiYu (2019)	6 observational studies	432	304	WMD	35.34 (20.67, 50.00)	< 0.001	< 0.001	79.1	0.914	No
Leftventricular ejection fraction (LVEF)	LeiYu (2019)	15 observational studies	1104	710	WMD	− 3.01 (− 1.90, − 0.79)	0.001	< 0.001	64.7	0.048	Yes
Left atrial diameter (LAD)	LeiYu (2019)	7 observational studies	468	311	WMD	2.13 (1.48, 2.77)	< 0.001	0.408	2.2	0.072	Yes
Left atrial diameter volume index (LAVI)	LeiYu (2019)	3 observational studies	228	159	WMD	3.96 (3.32, 4.61)	< 0.001	0.445	0	0.735	No
Right ventricular internal diameter (RVID)	Abdirashit Maripov (2017)	16 observational studies	1498	902	WMD	2.49 (1.62, 3.37)	< 0.001	< 0.001	96.8	0.001	Yes

Table 1 (continued)

Outcomes	Publication	Number of studies	Number of participants	Number of cases	Type of metric	Relative risk (95% CI)	*P* value*	*P* value #	I^2 (%)	*P* value*	Whether exist publication bias
Right ventricular free wall thickness (RVWT)	Abdirashit Maripov (2017)	9 observational studies	976	579	WMD	0.82 (0.51, 1.13)	< 0.001	< 0.001	95.6	0.671	No
Right ventricular myocardial performance index(RV MPI)	Abdirashit Maripov (2017)	14 observational studies	1298	864	WMD	0.08 (0.06, 0.10)	< 0.001	< 0.001	84.1	0.15	No
Tricuspid annular systolic velocity (RV S′)	Abdirashit Maripov (2017)	14 observational studies	1030	639	WMD	− 0.95 (− 0.32, − 1.59)	0.003	< 0.001	88.4	0.347	No
Tricuspid annular plane systolic excursion (TAPSE)	Abdirashit Maripov (2017)	11 observational studies	1033	655	WMD	− 1.76 (− 0.78, − 2.73)	< 0.001	< 0.001	89.3	0.462	No
Right ventricular fractional area change (RA FAC)	Abdirashit Maripov (2017)	6 observational studies	661	422	WMD	− 3.16 (− 0.73, − 5.60)	0.011	< 0.001	80.2	0.006	Yes
Epicardial adipose tissue (EAT) thickness	Guang Song (2020)	9 observational studies	1178	898	WMD	0.95 (0.73, 1.16)	< 0.001	< 0.001	64.7	0.549	No
Coronary flow reserve (CFR)	Rui-Heng Zhang (2020)	1 case–control study, 4 cross-sectional studies	1336	829	WMD	' − 0.78 (− 0.32, − 1.25)	< 0.001	< 0.001	84.4	0.49	No
Systolic blood pressure (SBP)	De-Lei Kong (2016)	2 cross-sectional studies, 3 cohort studies, 1 case–control studies	1046	534	SMD	0.56 (0.40, 0.71)	< 0.001	0.132	41.03	NA	NA
Cerebral and cerebrovascular disease											
Cerebral white matter changes	Bo-Lin Ho (2018)	10 observational studies	1582	818	OR	2.06 (1.52–2.80)	< 0.001	0.025	48.5	0.338	No
Cerebrovascular (CV) disease	Zesheng Wu (2018)	15 cohort studies	3,120,368	3,117,496	HR	1.94 (1.31–2.89)	0.001	< 0.001	90.3	> 0.05	No
White matter hyperintensities (WMH)	Yuhong Huang (2019)	11 cross-sectional studies, 2 case–control studies	4412	2065	OR	2.23 (1.53–3.25)	< 0.001	< 0.001	80.3	< 0.01	Yes
Silent brain infarction (SBI)	Yuhong Huang (2019)	9 cross-sectional studies, 2 case–control studies, 1 cohort study	3353	1893	OR	1.54 (1.06–2.23)	0.023	0.018	52	0.605	No
Cerebral microbleeds (CMBs)	Yuhong Huang (2019)	3 cross-sectional studies	342	271	OR	2.17 (0.61–7.73)	0.234	< 0.01	60.2	NA	Unclear
Perivascular spaces (PVS)	Yuhong Huang (2019)	2 cross-sectional studies	267	152	OR	1.56 (0.28–8.57)	0.623	< 0.01	69.5	NA	NA
Asymptomatic lacunar infarction (ALI)	Anthipa-Chokesuwattanaskul (2019)	6 cross-sectional studies, 1 cohort study	1756	713	OR	1.78 (1.06–3.01)	0.03	0.128[&]	41	0.43	No
Mortality											
All-cause mortality	Lei Pan (2016)	12 cohort studies	34,382	18,139	HR	1.26 (1.09–1.43)	0.001	< 0.001	70.4	0.003	Yes

Table 1 (continued)

Outcomes	Publication	Number of studies	Number of participants	Number of cases	Type of metric	Relative risk (95% CI)	*P* value*	*P* value #	I^2 (%)	*P* value##	Whether exist publication bias
Cardiovascular mortality	Xiahui Ge (2013)	4 cohort studies	5228	239	RR	2.21 (1.61–3.04)	< 0.001	0.418	0	0.448	No
All-cause death after PCI	Xiao Wang (2018)	4 cohort studies	1919	1154	RR	1.70 (1.05–2.77)	0.03	0.71	0	0.176&	No
Cardiac death after PCI	Hua Qu (2018)	7 cohort studies	2465	1187	OR	2.05 (1.15–3.65)	0.01	0.96	0	0.828&	No
Cancer mortality	Xiaobin Zhang (2017)	3 cohort studies	7346	179	HR	1.38 (0.79–2.41)	0.257	0.004	66.1	0.205	No
Postoperative complications											
Postoperative respiratory failure	Faizi Hai BA (2013)	12 cohort studies	5611	2390	OR	2.42 (1.53–3.84)	< 0.001	0.39	5	0.28	No
Postoperative cardiac events	Faizi Hai BA (2013)	11 cohort studies	3781	2109	OR	1.63 (1.16–2.29)	0.005	0.7	0	0.187&	No
Postoperative desaturation	R. Kaw (2012)	11 cohort studies	3645	1764	OR	2.27 (1.20–4.26)	0.01	< 0.001	68	0.04&	Yes
Postoperative ICU transfer	R. Kaw (2012)	9 cohort studies	5743	2062	OR	2.81 (1.46–5.43)	0.002	0.02	57	0.033&	Yes
Postoperative composite endpoints of postoperative cardiac or cerebrovascular complications	Ka Ting Ng (2020)	12 observational studies	2,003,694	126,027	OR	1.44 (1.17–1.78)	< 0.001	NA	89	NA	Unclear
Postoperative myocardial infarction	Ka Ting Ng (2020)	8 observational studies	714,650	NA	OR	1.37 (1.19–1.59)	< 0.001	NA	36	NA	Unclear
Postoperative congestive cardiac failure	Ka Ting Ng (2020)	3 observational studies	2104	NA	OR	3.16 (1.02–9.81)	0.05	NA	0	NA	Unclear
Postoperative atrial fibrillation	Ka Ting Ng (2020)	6 observational studies	1,463,449	NA	OR	1.50 (1.30–1.73)	< 0.001	NA	87	NA	Unclear
Postoperative cerebrovascular accident	Ka Ting Ng (2020)	5 observational studies	1,641,495	NA	OR	1.09 (0.75–1.60)	0.65	NA	61	NA	Unclear
Postoperative composite endpoints of pulmonary complications	Ka Ting Ng (2020)	8 observational studies	1,983,748	NA	OR	2.52 (1.92–3.31)	< 0.001	NA	96	NA	Unclear
Postoperative pneumonia	Ka Ting Ng (2020)	10 observational studies	2,675,205	NA	OR	1.66 (1.17–2.35)	0.004	NA	96	NA	Unclear
Postoperative reintubation	Ka Ting Ng (2020)	9 observational studies	2,061,268	NA	OR	2.29 (0.90–5.82)	0.08	NA	99	NA	Unclear
Postoperative in-hospital mortality	Ka Ting Ng (2020)	6 observational studies	2,497,794	NA	OR	0.86 (0.42–1.76)	0.68	NA	94	NA	Unclear
Postoperative 30-day mortality	Ka Ting Ng (2020)	6 observational studies	616,754	NA	OR	1.27 (1.03–1.57)	0.02	NA	0	NA	Unclear
Postoperative acute kidney injury	Ka Ting Ng (2020)	5 observational studies	1,724,932	NA	OR	2.41 (1.93–3.02)	< 0.001	NA	92	NA	Unclear
Postoperative delirium	Ka Ting Ng (2020)	6 observational studies	2346	NA	OR	2.45 (1.50–4.01)	< 0.001	NA	2	NA	Unclear
Postoperative venoembolism	Ka Ting Ng (2020)	10 observational studies	2,100,013	NA	OR	1.63 (1.17–2.27)	0.004	NA	94	NA	Unclear
Postoperative surgical site infection	Ka Ting Ng (2020)	5 observational studies	2962	NA	OR	1.30 (0.93–1.83)	0.13	NA	0	NA	Unclear

Table 1 (continued)

Outcomes	Publication	Number of studies	Number of participants	Number of cases	Type of metric	Relative risk (95% CI)	*P* value*	*P* value #	I^2 (%)	*P* value※	Whether exist publication bias
Postoperative bleeding	Ka Ting Ng (2020)	3 observational studies	18,712	NA	OR	1.10 (0.40–3.01)	0.85	NA	63	NA	Unclear
Postoperative length of hospital stay	Ka Ting Ng (2020)	15 observational studies	1,569,278	NA	MD	0.09 (0.00–0.17)	0.04	NA	96	NA	Unclear
Pregnancy-related disorders											
Gestational diabetes mellitus (GDM)	Xinge Zhang (2020	6 cohort studies	2,522,547	139,559	RR	1.60 (1.21–2.12)	0.004	0.003	69.2	0.4829	No
C-section	Lina Liu (2019)	6 observational studies	NA	NA	OR	1.42 (1.12–1.79)	< 0.001	< 0.001	86.5	NA	Unclear
Pregnancy-related prolonged hospital stay	Lina Liu (2019)	3 observational studies	NA	NA	OR	1.94 (0.88–4.28)	0.1	< 0.001	98.6	NA	Unclear
Pregnancy-related wound complication	Lina Liu (2019)	3 observational studies	NA	NA	OR	1.87 (1.56–2.24)	< 0.001	0.883	0	NA	Unclear
Pregnancy-related pulmonary edema	Lina Liu (2019)	3 observational studies	NA	NA	OR	6.35 (4.25–9.50)	< 0.001	0.294	18.2	NA	Unclear
Small for gestational age	Lina Liu (2019)	4 observational studies	NA	NA	OR	1.26 (0.80–2.01)	0.321	0.01	73.8	NA	Unclear
Stillbirth	Lina Liu (2019)	3 observational studies	NA	NA	OR	1.12 (0.85–1.49)	0.413	0.572	0	NA	Unclear
Poor fetal growth	Lina Liu (2019)	4 observational studies	NA	NA	OR	1.15 (0.98–1.34)	0.091	0.266	24.3	NA	Unclear
Gestational hypertension	Liwen Li (2018)	4 cross-sectional studies, 7 cohort studies	56,731,077	19,047	OR	1.80 (1.28–2.52)	0.001	0.72	0	0.649[&]	No
Preeclampsia	Liwen Li (2018)	2 cross-sectional studies, 7 cohort studies	56,097,993	19,776	OR	2.63 (1.87–3.70)	< 0.001	< 0.01	78	0.797[&]	No
Preterm birth	Liwen Li (2018)	2 cross-sectional studies, 3 cohort studies	56,746,100	18,337	OR	1.75 (1.21–2.55)	0.003	< 0.01	90	0.931[&]	No
Birth weight	Liwen Li (2018)	4 cohort studies	4311	1387	WMD	−47.46 (−242.09, 147.16)	0.281	< 0.01	93	NA	No[$]
Neonatal intensive care unit (NICU) admission	Ting Xu (2014)	4 cohort studies	757	177	RR	2.65 (1.86–3.76)	< 0.001	0.235	29.6	0.063[&]	Yes
Ophthalmic disorders											
Diabetic retinopathy (DR)	Zhenliu Zhu (2017)	6 case -control studies	1092	608	OR	2.01 (1.49–2.72)	< 0.001	0.062	52.4	0.112[&]	No
Keratoconus	Marco Pellegrini (2020)	4 case–control studies, 1 cohort study	33,844	16,922	OR	1.84 (1.16–2.91)	0.009	0.003	74.6	0.07	Yes
Glaucoma	Xinhua Wu (2015)	12 observational studies	36,909	11,765	OR	1.65 (1.44–1.88)	< 0.001	0.06	43	0.335	No
Floppy eyelid syndrome (FES)	Leh-Kiong Huon (2016)	7 cross-sectional studies	902	337	OR	4.70 (2.98–7.41)	< 0.001	0.129[&]	39.3[&]	0.379[&]	No
Nonarteritic anterior ischemic optic neuropathy (NAION)	Yong Wu (2015)	4 cohort studies, 1 case–control study	5916	164	OR	6.18 (2.00–19.11)	0.002	0.002	77	0.35	No
Central serous chorioretinopathy (CSCR)	Chris Y.Wu (2018)	6 case–control studies	7238	1479	OR	1.56 (1.16–2.10)	0.003	0.237	26.3	0.281	No

Table 1 (continued)

Outcomes	Publication	Number of studies	Number of participants	Number of cases	Type of metric	Relative risk (95% CI)	*P* value*	*P* value #	I^2 (%)	*P* value※	Whether exist publication bias
retinal nerve fiber layer (RNFL) thickness	Cheng-Lin Sun (2016)	8 case–control studies	1237	763	WMD	−2.92 (−4.61, −1.24)	0.001	0.017	59.1	0.929	No
Choroidal thickness	Chris Y.Wu (2018)	9 case–control studies	778	514	WMD	25.52 (−78.79, −27.76)	0.824	0.001	98.6	0.137	No
Digestive disorders											
Gastroesophageal reflux disease	Zeng-Hong Wu (2019)	1 case–control study, 6 cross-sectional studies	2699	1452	OR	1.75 (1.18–2.59)	0.006	0.04	54	0.052	Yes
Steatosis	Shanshan Jin (2018)	3 cohort studies, 1 cross-sectional study	1635	1375	OR	3.19 (2.34–4.34)	<0.001	0.677	0	0.89	No
Lobular inflammation	Shanshan Jin (2018)	3 cohort studies	350	205	OR	2.85 (1.8–-4.49)	<0.001	0.994	0	0.469	No
Ballooning degeneration	Shanshan Jin (2018)	3 cohort studies	350	205	OR	2.29 (1.36–3.84)	0.002	0.774	0	0.888	No
NAFLD activity score(NAS)	Shanshan Jin (2018)	3 cohort studies	350	205	OR	1.63 (0.68–3.86)	0.271	0.259	25.9	0.839	No
NAFLD defined by liver histology	G. Musso (2013)	8 cross-sectional studies	994	537	OR	2.01 (1.36–2.97)	<0.001	0.4	4	0.303[&]	No
NAFLD defined by radiology	G. Musso (2013)	6 cross-sectional studies	561	269	OR	2.99 (1.79–4.99)	<0.001	0.33	13	0.433[&]	No
NAFLD defined by AST elevation	G. Musso (2013)	11 cross-sectional studies	746	368	OR	2.36 (1.46–3.82)	<0.001	0.99	0	0.65[&]	No
NAFLD defined by ALT elevation	G. Musso (2013)	14 cross-sectional studies	1833	938	OR	2.60 (1.88–3.61)	<0.001	0.74	0	0.179[&]	No
Nonalcoholic steatohepatitis(NASH)	G. Musso (2013)	10 cross-sectional studies	1114	589	OR	2.37 (1.59–3.51)	<0.001	0.81	0	0.404[&]	No
Fibrosis	G. Musso (2013)	10 cross-sectional studies	1114	589	OR	2.16 (1.45–3.20)	<0.001	0.67	0	0.778[&]	No
Alanine transaminase (ALT)	Shanshan Jin (2018)	7 cohort studies, 1 cross-sectional study	2059	1684	SMD	0.21 (0.11, 0.31)	<0.001	0.672	0	0.468	No
Aspartate transaminase (AST)	Shanshan Jin (2018)	7 cohort studies, 1 cross-sectional study	2059	1684	SMD	0.07 (−0.03, 0.17)	0.152	0.918	0	<0.05	Yes
Endocrine and metabolic system disorders											
Type 2 diabetes (T2DM)	Ranran Qie (2020)	16 cohort studies	338,912	19,355	RR	1.40 (1.32–1.48)	<0.001	0.045	40.8	0.221[&]	No
Metabolic syndrome (MS)	Shaoyong Xu (2015)	15 cross-sectional studies	4161	2457	OR	2.87 (2.41–3.42)	<0.001	0.23	20	0.232	No
Fasting blood glucose (FBG)	De-Lei Kong (2016)	3 cross-sectional studies, 5 cohort studies, 2 case–control studies	2053	1296	SMD	0.35 (0.18, 0.53)	<0.001	0.008	59.69	NA	No[$]
Total cholesterol (TC)	Rashid Nadeem (2014)	63 observational studies	18,111	NA	SMD	0.267 (0.146, 0.389)	0.001	NA	NA	NA	No[$]

Table 1 (continued)

Outcomes	Publication	Number of studies	Number of participants	Number of cases	Type of metric	Relative risk (95% CI)	*P* value*	*P* value #	I^2 (%)	*P* value##	Whether exist publication bias
Low-density lipoprotein (LDL)	Rashid Nadeem (2014)	50 observational studies	13,894	NA	SMD	0.296 (0.156, 0.436)	0.001	NA	NA	NA	No$
High-density lipoprotein (HDL)	Rashid Nadeem (2014)	64 observational studies	18,116	NA	SMD	−0.433 (−0.604, −0.262)	<0.001	NA	NA	NA	No$
Triglyceride (TG)	Rashid Nadeem (2014)	62 observational studies	17,831	NA	SMD	0.603 (0.431, 0.775)	<0.001	NA	NA	NA	No$
Adiponectin	Mi Lu (2019)	20 case–control studies	1356	878	SMD	′−0.71 (−0.92, −0.49)	<0.001	<0.01	73	0.09	Yes
Oxidized low-density lipoprotein (Ox-LDL)	Reza Fadaei (2020)	8 case -control studies	623	391	SMD	0.95 (0.24, 1.67)	0.009	<0.001	94.1	<0.161	No
Fibrinogen	Fang Lu (2019)	25 observational studies	3792	1480	WMD	0.38 (0.29, 0.47)	<0.001	<0.001	80.3	0.208	No
Homocysteine	Kun Li (2017)	10 observational studies	773	457	MD	2.40 (0.60, 4.20)	0.009	<0.001	96	0.947	No
Advanced glycation end products (AGEs)	Xingyu Wu (2018)	5 cross-sectional studies	670	323	SMD	0.98 (0.69, 1.27)	<0.001	0.08	51	NA	No$
Plasma renin activity(PRA)	Ze-Ning Jin (2016)	5 case–control studies	300	180	MD	0.17 (−0.22, 0.55)	0.4	<0.001	82	NA	Unclear
Plasma renin concentration(PRC)	Ze-Ning Jin (2016)	5 case–control studies	170	101	MD	0.95 (−0.58, 2.48)	0.23	0.001	78	NA	Unclear
Angiotensin II(AngII)	Ze-Ning Jin (2016)	7 case–control studies	384	207	MD	3.39 (2.00, 4.79)	<0.001	<0.001	95	0.167	No
Aldosterone	Ze-Ning Jin (2016)	9 case–control studies	474	265	MD	0.95 (−0.16, 2.07)	0.09	<0.001	78	0.622	No
Serum vitamin D	Xiaoyan Li (2020)	6 case–control studies, 21 cross-sectional studies, 2 cohort studies	6298	4209	SMD	′−0.84(−1.14, −0.54)	<0.001	<0.001	95	NA	No$
Urological disorders											
Diabetic kidney disease (DKD)	Wen Bun Leong (2016)	7 cross-sectional studies	1877	1159	OR	1.59 (1.16–2.18)	0.004	0.224&	26.8	0.684&	No
Microalbuminuria	Tongtong Liu (2020)	4 cross-sectional studies	667	415	RR	2.32 (1.48–3.62)	<0.001	0.578	0	0.55	No
Chronic kidney disease (CKD)	Der-Wei Hwu (2017)	2 cohort studies, 16 cross-sectional studies	7090	3720	OR	1.77 (1.37–2.29)	<0.001	<0.001&	87.2&	0.011&	Yes
Serum uric acid level	Tingting Shi (2019)	14 observational studies	5219	2656	WMD	50.25 (36.16,64.33)	<0.001	<0.001	91.2	0.001	Yes
Serum cystatin C	Tongtong Liu (2020)	7 cross-sectional studies	1412	274	SMD	0.53 (0.42,0.64)	<0.001	0.16	33.7	0.111	No
Estimated glomerular filtration rate (eGFR)	Tongtong Liu (2020)	13 cross-sectional studies	3344	657	SMD	−0.19 (−0.27, −0.12)	0.001	0.057	33.1	0.516	No
Albumin/creatinine ratio(ACR)	Tongtong Liu (2020)	3 cross-sectional studies	740	88	WMD	0.71 (0.58, 0.84)	<0.001	0.003	69.2	0.574	No

Table 1 (continued)

Outcomes	Publication	Number of studies	Number of participants	Number of cases	Type of metric	Relative risk (95% CI)	*P* value*	*P* value #	I^2 (%)	*P* value※	Whether exist publication bias
Other outcomes											
Diabetic neuropathy	Xiandong Gu (2018)	11 case -control studies	1842	840	OR	1.84 (1.18–2.87)	0.007	< 0.01	68.6	0.13	No
Psoriasis	Tzong-Yun Ger (2020)	3 cohort studies	5,544,674	42,656	RR	2.52 (1.89–3.36)	< 0.001	0.95	0	0.545	No
Nocturia	Jiatong Zhou (2019)	3 cohort studies, 8 case–control studies, 2 cross-sectional studies	9924	406	RR	1.41 (1.26–1.59)	< 0.001	0.001	63.3	0.076	Yes
Allergic rhinitis	Yuan Cao (2018)	1 cross-sectional study, 2 case–control studies, 1 cohort study	1283	371	OR	1.73 (0.94–3.20)	0.078	0.023	64.8	0.977	No
Parkinson's disease	A-Ping Sun (2020)	4 cohort studies, 1 case–control study	83,449	26,070	HR	1.59 (1.36–1.85)	< 0.001	0.17	40	0.186	No
Erectile dysfunction	Luhao Liu (2015)	1 cohort study, 3 case–control studies, 1 cross-sectional study	834	532	RR	1.82 (1.12–2.97)	0.016	0.002	76.5	0.077	Yes
Female sexual dysfunction	Luhao Liu (2015)	2 case–control studies, 2 cohort studies	438	149	RR	2.0 (1.29–3.08)	0.002	0.194	36.4	0.327	No
Sexual dysfunction	Luhao Liu (2015)	3 cohort studies, 5 case–control studies, 1 cross-sectional study	1272	681	RR	1.87 (1.35–2.58)	< 0.001	0.001	70.1	0.692	No
Osteoporosis	Sikarin Upala (2016)	2 cohort studies, 2 cross-sectional studies	113,922	3141	OR	1.13 (0.60–2.14)	0.703	< 0.001	89.1	0.608[&]	No
Gout	Tingting Shi (2019)	3 cohort studies	154,455	30,109	HR	1.25 (0.91–1.70)	0.162	< 0.001	91	0.876	No
Cancer incidence	Ghanshyam Palamaner Subash Shantha (2015)	5 cohort studies	112,226	904	RR	1.40 (1.01–1.95)	0.04	0.04	60	0.069	Yes
Depression	Cass Edwards (2020)	5 cohort studies	45,056	10,983	RR	2.18 (1.47–2.88)	< 0.001	0.005	72.8	0.667[&]	No
Crash risk	Stephen Tregear (2009)	10 observational studies	10,846	2214	RR	2.43 (1.21–4.89)	0.013	< 0.001	89	0.838[&]	No
Work accidents	Sergio Garbarino (2016)	7 cross-sectional studies	8819	2738	OR	2.18 (1.53–3.10)	< 0.001	0.02	61	0.61	No
Carotid intima-media thickness (CIMT)	Min Zhou (2016)	10 case–control studies, 8 case-sectional studies	1896	1247	SMD	0.88 (0.65, 1.12)	< 0.001	< 0.001	81	0.94	No

*p value of significance level

#p value of Q test

※p value for Egger's test

$The publication bias was assessed using funnel plot

&The result was reanalyzed

range of data were reported such as cardiovascular disorders ($n=31$), cerebral and cerebrovascular disease ($n=7$), mortality ($n=5$), postoperative complications ($n=20$), pregnancy-related disorders ($n=13$), ophthalmic disorders ($n=8$), digestive disorders ($n=13$), endocrine and metabolic system disorders($n=17$), urological disorders ($n=7$), and other data ($n=15$) (Fig. 2).

Summary effect size

A brief explanation of the effects of the included meta-analysis is given in Table 1. Overall, 111 (82%) of the 136 data reported significant summary outcomes ($p<0.05$). These associations relate to the outcomes of the following different systems: 29 meta-analyses in cardiovascular disorders, 5 in cerebral and cerebrovascular disease, 4 in mortality, 14 in postoperative complications, 8 in pregnancy-related disorders, 7 in ophthalmic disorders, 11 in digestive disorders, 14 in endocrine and metabolic system, 7 in urological disorders, and 12 in other outcomes. Therefore, it can be concluded that OSA can enhance the risk of disease and have adverse effects on human health.

Heterogeneity and publication bias

For heterogeneity, 5 results in 5 articles were reanalyzed owing to that they did not exhibit the outcomes of heterogeneity [22, 36, 46, 59, 64]. Among the 136 outcomes including the reanalyzed articles, 47 outcomes showed no heterogeneity between researches ($p\geq0.1$ of Q test), whereas 69 indicated significant heterogeneity ($p<0.1$ of Q test). However, there were still 20 results in 2 articles that could not be reanalyzed due to the lack of raw data [52, 95], so we could not evaluate their heterogeneity. For publication bias, 76 outcomes demonstrated no statistical evidence on publication bias ($p\geq0.1$ of Egger's test), whereas 25 outcomes presented publication bias ($p<0.1$ of Egger's test). There were still 35 results in 9 articles that could not be reanalyzed due to the lack of raw data [45, 52, 54, 55, 87, 92–95], so we could not evaluate their publication bias.

AMSTAR 2 and summary of evidence

The results for the evaluation of the methodological qualities of the 66 included articles are shown in Table 2. Only 3 (5%) studies were determined to be low; the remaining 63 (95%) studies were determined to be critically low (Fig. 3). Based on the AMSTAR 2 criteria, none of the investigations were graded as moderate or high quality.

The outcomes of the evidence measurement are shown in Table 3. When a study did not present the result of heterogeneity and publication bias, the corresponding criteria were considered to be not satisfied. Among the 111 statistically significant outcomes, 7 (6%) showed high epidemiologic evidence, 24 (22%) showed moderate epidemiologic evidence, and the remaining 80 (72%) were rated as weak (Fig. 4).

Discussion

In the current umbrella review, we identified 66 meta-analyses of observational studies and evaluated the current evidence supporting an association between OSA and various health outcomes. Also, we provide an extensive overview of the available evidence and critically evaluate the methodological quality of the meta-analyses and the quality of evidence for all the reported associations. OSA increased the risk of 111 health outcomes, including

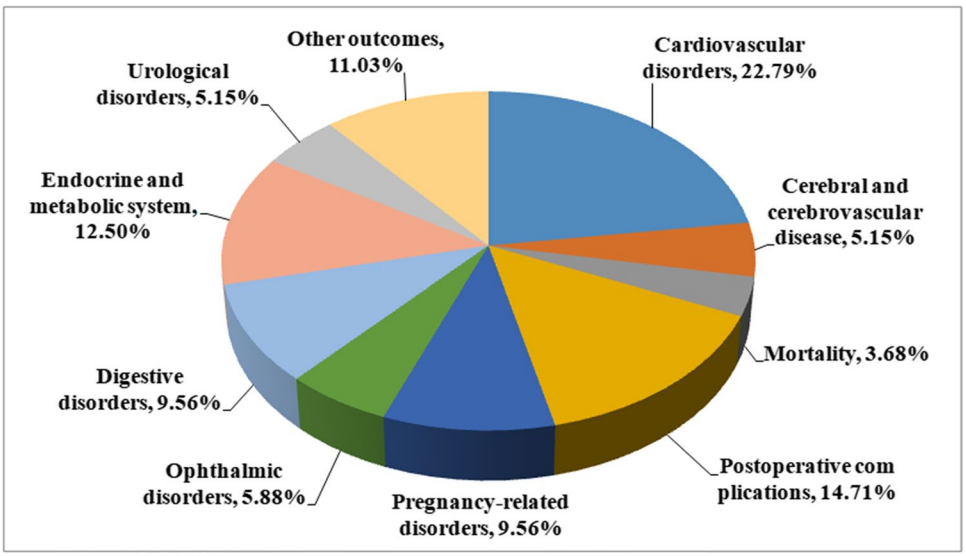

Fig. 2 Map of achievements related to OSA

Table 2 Assessments of AMSTAR 2 scores

Reference	AMSTAR 2 checklist																Overall assessment quality
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12	No. 13	No. 14	No. 15	No. 16	
Xiushi Zhou (2018)	Yes	No	Yes	Partial yes	No	No	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Xia Wang (2013)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Min Li (2014)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	No	No	No	No	No	Critically low
Wuxiang Xie (2014)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Chengjuan Xie (2017)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Irini Youssef (2018)	Yes	No	No	Partial yes	No	No	Partial yes	No	No	No	Yes	No	No	No	No	No	Critically low
Haifeng Hou (2018)	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Chee Yuan Ng (2011)	Yes	No	Yes	Partial yes	Yes	Yes	Yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Xiao Wang (2018)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Hua Qu (2018)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Cesare Cuspidi (2020)	Yes	No	No	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	No	Yes	No	Yes	Critically low
Bo-Lin Ho (2018)	Yes	No	No	Partial yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Zesheng Wu (2018)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Yuhong Huang (2019)	Yes	No	No	Partial yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Anthipa Chokesuwattanaskul (2019)	Yes	No	Yes	Partial yes	No	No	Partial yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Lei Pan (2016)	Yes	No	Yes	Partial yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Xiahui Ge (2013)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Xiaobin Zhang (2017)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Faizi Hai BA (2013)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
R. Kaw (2012)	Yes	No	Yes	Partial yes	Yes	Yes	Yes	Partial yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Ka Ting Ng (2020)	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Xinge Zhang (2020)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Lina Liu (2019)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Liwen Li (2018)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Critically low
Ting Xu (2014)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Critically low
Marco Pellegrini (2020)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Xinhua Wu (2015)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Leh-Kiong Huon (2016)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	No	No	No	Yes	Critically low
Yong Wu (2015)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Chris Y.Wu (2018)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Ranran Qie (2020)	Yes	No	Yes	Partial yes	No	No	Partial yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Xiandong Gu (2018)	Yes	No	Yes	Partial yes	No	No	Partial yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Wen Bun Leong (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zhenliu Zhu (2017)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Zeng-Hong Wu (2019)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low

Table 2 (continued)

Reference	AMSTAR 2 checklist																Overall assessment quality
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	No. 12	No. 13	No. 14	No. 15	No. 16	
Shanshan Jin (2018)	Yes	No	No	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
G. Musso (2013)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Tzong-Yun Ger (2020)	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	No	No	Yes	Critically low
Jiatong Zhou (2019)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Yuan Cao (2018)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	No	No	No	No	Yes	Critically low
A-Ping Sun (2020)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Luhao Liu (2015)	Yes	No	Yes	Partial yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No	Yes	Yes	Critically low
Sikarin Upala (2016)	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Tingting Shi (2019)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	No	No	Yes	Yes	Critically low
Tongtong Liu (2020)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	No	No	No	Yes	Yes	Critically low
Der-Wei Hwu (2017)	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Partial yes	No	No	Yes	No	No	No	No	Yes	Critically low
Ghanshyam Palamaner Subash Shantha (2015)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Shaoyong Xu (2015)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Cass Edwards (2020)	Yes	No	Yes	Partial yes	Yes	Yes	Yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Stephen Tregear (2009)	Yes	No	No	Yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Sergio Garbarino (2016)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Cheng-Lin Sun (2016)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Min Zhou (2016)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Guang Song (2020)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
LeiYu (2019)	Yes	No	No	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Abdirashit Maripov (2017)	Yes	No	No	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Rui-Heng Zhang (2020)	Yes	No	No	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
De-Lei Kong (2016)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Rashid Nadeem (2014)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Mi Lu (2019)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Reza Fadaei (2020)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Fang Lu (2019)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Kun Li (2017)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Xingyu Wu (2018)	Yes	No	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Ze-Ning Jin (2016)	Yes	No	No	Partial yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Critically low
Xiaoyan Li (2020)	Yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low

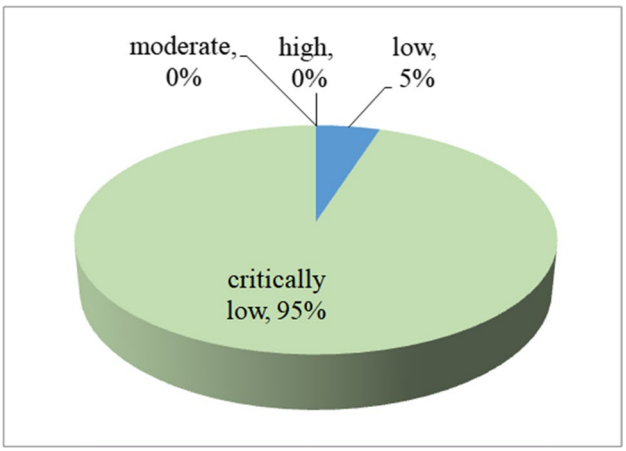

Fig. 3 Map of results of AMSTAR 2

cardiovascular disorders, cerebral and cerebrovascular disease, mortality, postoperative complications, pregnancy-related disorders, ophthalmic disorders, digestive disorders, endocrine and metabolic system disorders, urological disorders, and other outcomes. The evidence quality was graded as high only for coronary revascularization after PCI, postoperative respiratory failure, steatosis, ALT elevation, MS, psoriasis, and Parkinson's disease. The evidence quality was either moderate or low for the other associations. Furthermore, this umbrella review showed there were no considerable associations between OSA and 25 health outcomes.

Among the 111 outcomes, 54 outcomes had serious heterogeneity between studies. These possible confounding parameters (e.g., sex, body mass index, age, method of assessing OSA, OSA severity, smoking, alcohol drinking, the region of study, and follow-up period) may be the cause of heterogeneity. Substantial heterogeneity led to unreliable results. Of the 111 health outcomes, 23 outcomes possessed a remarkable publication bias, demonstrating that some negative achievements were not presented. Several reasons were leading to publication bias. First, when people start a study, they tend to assume that a positive result may ensure their work complies with the hypothesis during publication. Second, positive results have a higher probability of being published compared to negative results. Third, the study population is only a small fraction of the actual population with the disease. According to AMSTAR 2 criteria, 95% of the studies included in this umbrella analysis had "critically low" methodological quality. The critical flaws considered the absence of a registered protocol, the absence of the risk of bias in the considered investigations, and the absence of consideration of the risk of bias in the included investigations when interpreting or discussing the achieved outcomes of each study. Moreover, none of the meta-analyses in this study explained details of the funding source that had supported the work. The majority of the evaluated meta-analyses had considerable heterogeneity and small-study impacts; these were the main reasons for the evidence rating downgrade.

An umbrella review is a more beneficial method compared to a normal systematic review or meta-analysis due to it representing an overall illustration of achievements for phenomena or special questions [96]. To our knowledge, we are the first to use this method to present a comprehensive critical literature appraisal on published associations between OSA and diverse health information. Also, our two authors systematically searched four scientific databases using a strong search strategy with clearly defined eligibility criteria and data extraction parameters. The quality of included systematic reviews was also evaluated through AMSTAR 2. This is a benchmark methodological quality measurement that is utilized to assessing the quality of the methods utilized for meta-analyses. Furthermore, we graded the epidemiologic evidence conforming to established, prespecified criteria. Its criteria included an assessment of heterogeneity, publication bias, and precision of the estimate, which is more objective than the GRADE system criteria.

There are some limitations in our umbrella review. First, in this analysis, we explained associations evaluated through the meta-analyses of observational investigations. In doing so, we may have missed other health outcomes that have not yet been investigated by meta-analyses. Second, this umbrella analysis included systematic reviews and meta-analyses that were only published in English. The potential missing information in other languages could influence the assessment outcomes. Third, the majority of the meta-analyses had heterogeneity; observational researches are susceptible to uncertainty and confounding bias.

Conclusions

The associations between OSA and an extensive range of health information have been broadly reported in many meta-analyses. Based on our umbrella review, 66 meta-analyses explored 136 unique outcomes, only 7 outcomes showed a high level of epidemiologic evidence with statistical significance. OSA could be associated with the enhanced risk of coronary revascularization after PCI, postoperative respiratory failure, steatosis,

Table 3 Detail of results for evidence quality assessing

Outcomes	Reference	Precision of the estimate		Consistency of results	No evidence of small-study effects	Grade
		> 1000 disease cases	$P < 0.001$	($I^2 < 50\%$ and Cochran Q test $P > 0.10$)	($P > 0.10$)	
Cardiovascular disorders						
Aortic dissection	Xiushi Zhou (2018)	Yes	No	Yes	Yes	Weak
Cardiovascular disease (^{CVD})	Xia Wang (2013)	Yes	Yes	Yes	No	Moderate
Stroke	Min Li (2014)	No	Yes	No	Yes	Weak
Ischemic heart disease (IHD)	Wuxiang Xie (2014)	No	No	Yes	No	Weak
Coronary heart disease (CHD)	Chengjuan Xie (2017)	Yes	No	No	Yes	Weak
Major adverse cardiac events (MACEs)	Chengjuan Xie (2017)	Yes	Yes	No	Yes	Moderate
Atrial fibrillation	Irini Youssef (2018)	Yes	Yes	No	No	Weak
Resistant hypertension	Haifeng Hou (2018)	No	Yes	Yes	Yes	Moderate
Essential hypertension	Haifeng Hou (2018)	Yes	Yes	Yes	No	Moderate
Atrial fibrillation recurrence after catheter ablation	Chee Yuan Ng (2011)	No	No	No	Yes	Weak
Major adverse cardiovascular event (MACE) after PCI	Xiao Wang (2018)	Yes	Yes	No	No	Weak
Myocardial infarction(MI) after PCI	Hua Qu (2018)	Yes	No	Yes	Yes	Weak
Coronary revascularization after PCI	Hua Qu (2018)	Yes	Yes	Yes	Yes	High
Left ventricular hypertrophy (LVH)	Cesare Cuspidi (2020)	Yes	Yes	No	No	Weak
Left ventricular diastolic diameter (LVEDD)	LeiYu (2019)	No	Yes	Yes	Yes	Moderate
Left ventricular systolic diameter (LVESD)	LeiYu (2019)	No	No	Yes	Yes	Weak
Left ventricular mass (LVM)	LeiYu (2019)	No	Yes	No	Yes	Weak
Left ventricular ejection fraction (LVEF)	LeiYu (2019)	No	No	No	No	Weak
Left atrial diameter (LAD)	LeiYu (2019)	No	Yes	Yes	No	Weak
Left atrial diameter volume index (LAVI)	LeiYu (2019)	No	Yes	Yes	Yes	Moderate
Right ventricular internal diameter (RVID)	Abdirashit Maripov (2017)	No	Yes	No	No	Weak
Right ventricular free wall thickness (RVWT)	Abdirashit Maripov (2017)	No	Yes	No	Yes	Weak
Right ventricular myocardial performance index (RV MPI)	Abdirashit Maripov (2017)	No	Yes	No	Yes	Weak
Tricuspid annular systolic velocity (RV S′)	Abdirashit Maripov (2017)	No	No	No	Yes	Weak
Tricuspid annular plane systolic excursion (TAPSE)	Abdirashit Maripov (2017)	No	Yes	No	Yes	Weak
Right ventricular fractional area change (RA FAC)	Abdirashit Maripov (2017)	No	No	No	No	Weak
Epicardial adipose tissue (EAT) thickness	Guang Song (2020)	No	Yes	No	Yes	Weak
Coronary flow reserve (CFR)	Rui-Heng Zhang (2020)	No	Yes	No	Yes	Weak
Systolic blood pressure (SBP)	De-Lei Kong (2016)	No	Yes	Yes	NA	Weak
Cerebral and cerebrovascular disease						
Cerebral white matter changes	Bo-Lin Ho (2018)	No	Yes	No	Yes	Weak
Cerebrovascular (CV) disease	Zesheng Wu (2018)	Yes	No	No	No	Weak
White matter hyperintensities (WMH)	Yuhong Huang (2019)	Yes	Yes	No	No	Weak
Silent brain infarction (SBI)	Yuhong Huang (2019)	Yes	No	No	Yes	Weak

Table 3 (continued)

Outcomes	Reference	Precision of the estimate		Consistency of results	No evidence of small-study effects	Grade
		> 1000 disease cases	$P < 0.001$	($I^2 < 50\%$ and Cochran Q test $P > 0.10$)	($P > 0.10$)	
Asymptomatic lacunar infarction (ALI)	Anthipa Chokesuwattanaskul (2019)	No	No	Yes	Yes	Weak
Mortality						
All-cause mortality	Lei Pan (2016)	Yes	No	No	No	Weak
Cardiovascular mortality	Xiahui Ge (2013)	No	Yes	Yes	Yes	Moderate
All-cause death after PCI	Xiao Wang (2018)	Yes	No	Yes	Yes	Weak
Cardiac death after PCI	Hua Qu (2018)	Yes	No	Yes	Yes	Weak
Postoperative complications						
Postoperative respiratory failure	Faizi Hai BA (2013)	Yes	Yes	Yes	Yes	High
Postoperative cardiac events	Faizi Hai BA (2013)	Yes	No	Yes	Yes	Weak
Postoperative desaturation	R. Kaw (2012)	Yes	No	No	No	Weak
Postoperative ICU transfer	R. Kaw (2012)	Yes	No	No	No	Weak
Postoperative composite endpoints of postoperative cardiac or cerebrovascular complications	Ka Ting Ng (2020)	Yes	Yes	No	NA	Weak
Postoperative myocardial infarction	Ka Ting Ng (2020)	NA	Yes	Yes	NA	Weak
Postoperative atrial fibrillation	Ka Ting Ng (2020)	NA	Yes	No	NA	Weak
Postoperative composite endpoints of pulmonary complications	Ka Ting Ng (2020)	NA	Yes	No	NA	Weak
Postoperative pneumonia	Ka Ting Ng (2020)	NA	No	No	NA	Weak
Postoperative 30-day mortality	Ka Ting Ng (2020)	NA	No	Yes	NA	Weak
Postoperative acute kidney injury	Ka Ting Ng (2020)	NA	Yes	No	NA	Weak
Postoperative delirium	Ka Ting Ng (2020)	NA	Yes	Yes	NA	Weak
Postoperative venoembolism	Ka Ting Ng (2020)	NA	No	No	NA	Weak
Postoperative length of hospital stay (days)	Ka Ting Ng (2020)	NA	No	No	NA	Weak
Pregnancy-related disorders						
Gestational diabetes mellitus (GDM)	Xinge Zhang (2020)	Yes	No	No	Yes	Weak
C-section	Lina Liu (2019)	NA	Yes	No	NA	Weak
Pregnancy-related wound complication	Lina Liu (2019)	NA	Yes	Yes	NA	Weak
Pregnancy-related pulmonary edema	Lina Liu (2019)	NA	Yes	Yes	NA	Weak
Gestational hypertension	Liwen Li (2018)	Yes	No	Yes	Yes	Weak
Preeclampsia	Liwen Li (2018)	Yes	Yes	No	Yes	Moderate
Preterm birth	Liwen Li (2018)	Yes	No	No	Yes	Weak
Neonatal intensive care unit (NICU) admission	Ting Xu (2014)	No	Yes	No	No	Weak

Table 3 (continued)

Outcomes	Reference	Precision of the estimate		Consistency of results	No evidence of small-study effects	Grade
		> 1000 disease cases	$P < 0.001$	($I^2 < 50\%$ and Cochran Q test $P > 0.10$)	($P > 0.10$)	
Ophthalmic disorders						
Diabetic retinopathy (DR)	Zhenliu Zhu (2017)	No	Yes	No	Yes	Weak
Keratoconus	Marco Pellegrini (2020)	Yes	No	Yes	No	Weak
Glaucoma	Xinhua Wu (2015)	Yes	Yes	No	Yes	Moderate
Floppy eyelid syndrome (FES)	Leh-Kiong Huon (2016)	No	Yes	Yes	Yes	Moderate
Nonarteritic anterior ischemic optic neuropathy (NAION)	Yong Wu (2015)	No	No	No	Yes	Weak
Central serous chorioretinopathy (CSCR)	Chris Y.Wu (2018)	Yes	No	Yes	Yes	Weak
Retinal nerve fiber layer (RNFL) thickness	Cheng-Lin Sun (2016)	No	No	No	Yes	Weak
Digestive disorders						
Gastroesophageal reflux disease	Zeng-Hong Wu (2019)	Yes	No	No	No	Weak
Steatosis	Shanshan Jin (2018)	Yes	Yes	Yes	Yes	High
Lobular inflammation	Shanshan Jin (2018)	No	Yes	Yes	Yes	Moderate
Ballooning degeneration	Shanshan Jin (2018)	No	No	Yes	Yes	Weak
NAFLD defined by liver histology	G. Musso (2013)	No	Yes	Yes	Yes	Moderate
NAFLD defined by radiology	G. Musso (2013)	No	Yes	Yes	Yes	Moderate
NAFLD defined by AST elevation	G. Musso (2013)	No	Yes	Yes	Yes	Moderate
NAFLD defined by ALT elevation	G. Musso (2013)	No	Yes	Yes	Yes	Moderate
Nonalcoholic steatohepatitis (NASH)	G. Musso (2013)	No	Yes	Yes	Yes	Moderate
Fibrosis	G. Musso (2013)	No	Yes	Yes	Yes	Moderate
Alanine transaminase (ALT)	Shanshan Jin (2018)	Yes	Yes	Yes	Yes	High
Endocrine and metabolic system disorders						
Type 2 diabetes (T2DM)	Ranran Qie (2020)	Yes	Yes	No	Yes	Moderate
Metabolic syndrome (MS)	Shaoyong Xu (2015)	Yes	Yes	Yes	Yes	High
Fasting blood glucose (FBG)	De-Lei Kong (2016)	Yes	Yes	No	NA	Meak
Total cholesterol (TC)	Rashid Nadeem (2014)	NA	No	NA	NA	Weak
Low-density lipoprotein (LDL)	Rashid Nadeem (2014)	NA	No	NA	NA	Weak
High-density lipoprotein (HDL)	Rashid Nadeem (2014)	NA	Yes	NA	NA	Weak
Triglyceride (TG)	Rashid Nadeem (2014)	NA	Yes	NA	NA	Weak
Adiponectin	Mi Lu (2019)	No	Yes	No	No	Weak
Oxidized low-density lipoprotein (Ox-LDL)	Reza Fadaei (2020)	No	No	No	Yes	Weak
Fibrinogen	Fang Lu (2019)	Yes	Yes	No	Yes	Moderate
Homocysteine	Kun Li (2017)	No	No	No	Yes	Weak
Advanced glycation end products (AGEs)	Xingyu Wu (2018)	No	Yes	No	NA	Weak

Table 3 (continued)

Outcomes	Reference	Precision of the estimate		Consistency of results	No evidence of small-study effects	Grade
		> 1000 disease cases	$P < 0.001$	($I^2 < 50\%$ and Cochran Q test $P > 0.10$)	($P > 0.10$)	
Angiotensin II (AngII)	Ze-Ning Jin (2016)	No	Yes	No	Yes	Weak
Serum vitamin D	Xiaoyan Li (2020)	Yes	Yes	No	NA	Weak
Urological disorders						
Diabetic kidney disease (DKD)	Wen Bun Leong (2016)	Yes	No	Yes	Yes	Weak
Microalbuminuria	Tongtong Liu (2020)	No	Yes	Yes	Yes	Moderate
Chronic kidney disease (CKD)	Der-Wei Hwu (2017)	Yes	Yes	No	No	Weak
Serum uric acid level	Tingting Shi (2019)	Yes	Yes	No	No	Weak
Serum cystatin C	Tongtong Liu (2020)	No	Yes	Yes	Yes	Moderate
Estimated glomerular filtration rate (eGFR)	Tongtong Liu (2020)	No	No	No	Yes	Weak
Albumin/creatinine ratio (ACR)	Tongtong Liu (2020)	No	Yes	No	Yes	Weak
Other outcomes						
Diabetic neuropathy	Xiandong Gu (2018)	No	No	No	Yes	Weak
Psoriasis	Tzong-Yun Ger (2020)	Yes	Yes	Yes	Yes	High
Nocturia	Jiatong Zhou (2019)	No	Yes	No	No	Weak
Parkinson's disease	A-Ping Sun (2020)	Yes	Yes	Yes	Yes	High
Erectile dysfunction	Luhao Liu (2015)	No	No	No	No	Weak
Female sexual dysfunction	Luhao Liu (2015)	No	No	Yes	Yes	Weak
Sexual dysfunction	Luhao Liu (2015)	No	Yes	No	Yes	Weak
Cancer incidence	Ghanshyam Palamaner Subash Shantha (2015)	No	No	No	No	Weak
Depression	Cass Edwards (2020)	Yes	Yes	No	Yes	Moderate
Crash risk	Stephen Tregear (2009)	Yes	No	No	Yes	Weak
Work accidents	Sergio Garbarino (2016)	Yes	Yes	No	Yes	Moderate
Carotid intima-media thickness (CIMT)	Min Zhou (2016)	Yes	Yes	No	Yes	Moderate

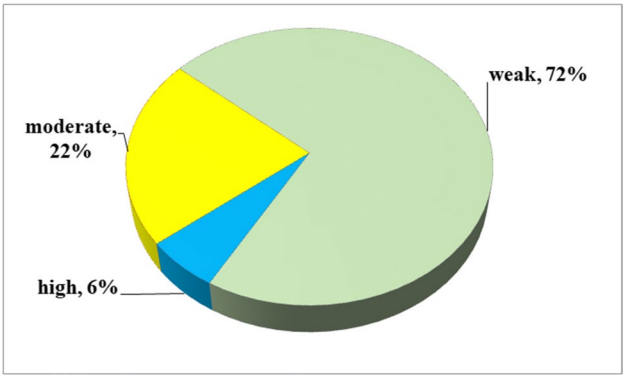

Fig. 4 Map of results of evidence assessment

ALT elevation, MS, psoriasis, and Parkinson's disease. Overall, OSA is harmful to human health but will need further exploration on this topic with high-quality prospective studies.

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Data availability The data used to support the findings of this study are included within the article. The primary data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval All analyses were based on published studies and no ethical approval was required.

Conflict of interest The authors declare no competing interests.

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