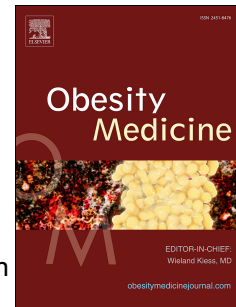


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Highlights

- This was the first study to examine the magnitude of association of overweight and obesity in different population groups.
- Obesity is significantly associated with increased risk of apnoea-hypopnea index (AHI).
- Overweight and obesity are important risk factors for OSA in both adults and children.

Original Article.

Association of overweight and obesity with obstructive sleep apnoea: a systematic review and meta-analysis

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Abstract

Background: Research evidence suggests a close relationship between overweight and obesity with obstructive sleep apnoea (OSA); however, the extent of this relationship among different population groups is relatively unknown. The aim of this paper was to conduct a systematic review and meta-analysis to determine the magnitude of association of overweight and obesity with OSA in different population groups.

Methods: We searched five electronic databases (Medline, Embase, Cochrane Library, CBM and CNKI) from inception to December 2017 for comparative epidemiological studies assessing the relation between overweight and obesity with OSA. Studies were included if they reported OSA by polysomnography and overweight/obesity by body mass index. Two authors independently screened titles and abstracts, selected studies and extracted data. Study quality was assessed using the Newcastle-Ottawa Scale. Random effects meta-analysis was used to estimate pooled effect sizes with 95% confidence intervals (CI). Heterogeneity was examined using Cochrane's Q statistic and I^2 test and explored using subgroup analyses for adults and children, adjusting for potential confounders. Publication bias was assessed using a funnel plot.

Results: Twelve case-control studies encompassing a total of 3214 participants (Obese group $n=773$, Non-Obese group $n=315$; OSA group $n=1742$, Non-OSA group $n=384$) were analyzed. Results showed that increased body mass index was associated with higher risk of OSA in the adult group. The Obese group was associated with increased risk of apnoea-hypopnoea index (AHI) compared to the Non-Obese group and the differences were statistically significant in both children (Mean Difference= 12.29; 95 % CI 8.46–16.11; $P < 0.00001$) and adults (Mean Difference= 12.11; 95 % CI 4.35–19.85; $P = 0.002$).

Conclusions: These findings suggest that overweight and obesity are important risk factors for OSA in both adults and children. Future studies are required to determine the effects of weight loss interventions in the development of obesity-related OSA.

Keywords: Obesity; Overweight; Body mass index; Apnoea-hypopnoea index, Obstructive sleep apnoea (OSA); Meta-analysis.

Introduction

Obstructive sleep apnoea (OSA) is the most common serious sleep disorder globally with prevalence between 9% to 38% in the general population [1]. OSA is characterized by repeated episodes of upper airway obstruction during sleep, resulting in repetitive hypoxemia and intermittent pauses in breathing causing oxygen desaturation, arousal from sleep and excessive daytime sleepiness [2, 3]. People with OSA are often unaware of their condition. Long-term suffering from OSA can lead to hypertension, cardiovascular disease, stroke, diabetes, abnormal glucose metabolism, and sudden-death during sleep [4, 5].

There are well identified risk factors for OSA; prevalence of OSA increases in elderly populations, male populations and in those who are overweight or obese [1]. Links between increased weight and OSA have been well established in both children and adults. In children, obesity and morbid obesity increase the severity of OSA [6, 7] with prevalence of OSA in obese children and adolescents ranging from 46 – 60% [8, 9]. In obese adults, prevalence of OSA is nearly double [10, 11] or higher [12] compared to those who are normal weight. Underlying mechanisms of OSA in overweight people include airway narrowing caused by increased neck circumference and airway obstruction caused from relaxed tongue soft tissue and throat muscles during sleep [13, 14].

As obesity rates have increased to pandemic levels [15], conjointly OSA will also burden both people who are overweight or obese and in turn, the healthcare system. Although several studies have been conducted examining the prevalence and risk factors of OSA, the association between overweight and obesity in different population groups such as children with OSA has not been well-established. Additionally, over time there has been changes and advances in respiratory measurement techniques and classification which makes comparison between study outcomes difficult [16, 17]. We therefore performed a systematic review and meta-analysis to clarify and quantify the association between overweight and obesity with OSA in different population groups.

Methods

This systematic review was conducted and reported in accordance with the Cochrane Collaboration reporting items for systematic reviews and meta-analysis guidelines [18, 19].

Data sources and search strategy: Relevant literature was searched from five electronic databases (PubMed, Embase, Cochrane Library, CBM- China Biological Medicine Database, and CNKI- Chinese National Knowledge Infrastructure Database) using Medical Subject Heading and keywords. The following search terms were used: “obstructive sleep apnoea” OR “apnea” OR “OSA” OR “obstructive sleep apnoea

syndrome” OR “OSAS” AND “obesity OR overweight”. The search was limited to humans with no language restriction. The electronic database was searched from the earliest possible date until December 22, 2017. To supplement the electronic searches, we also examined the reference lists of included studies, literature reviews, and scanned the content of selected relevant grey literature.

Study selection: Two authors (ZD and XX) independently screened all titles and abstracts. To be eligible for inclusion, studies had to report data on participants with confirmed diagnosis of OSA and overweight/obesity. OSA was defined as apnoea-hypopnoea index (AHI) ≥ 5 events/hour and classified as normal= AHI <5 events/hour; mild= AHI 5 to <15 ; moderate= AHI 15 to <30 ; and severe= AHI >30 [20]. Obesity and overweight were measured using body mass index (BMI) in adults (underweight= BMI <18.5 ; normal weight= BMI 18.5 to <25 ; overweight= BMI $25 \geq$ to <30 and obese= BMI ≥ 30) and BMI z-scores in children [21]. Included study designs were case control, cohort, or cross-sectional studies. Study participants were classified into the following groups: Obese group (BMI ≥ 25 kg/m² in adult or a BMI z-score >1.96 in children) [22], Non-Obese group, OSA group (AHI ≥ 5) and Non-OSA group.

Studies were excluded based on the following criteria: (A) did not report the association of overweight or obesity with OSA; (B) included case reports, case series, qualitative studies, or reviews; (C) reported incomplete data; (D) did not provide detailed data on AHI or BMI.

Data extraction: Studies were selected for full-text review by two reviewers (ZD, XX) independently, using a pre-structured standardized form. The following data were extracted: first author, year of publication, country, study design, sample size, participant sex, the number of participants in case and control groups, age, BMI and AHI. Any disagreements between the reviewers were resolved through discussion or in consultation with a third reviewer (CW). The reviewers contacted the corresponding author of studies for any missing information or data.

Quality assessment: All studies were ranked for quality assessment by two reviewers (ZD, XX) independently, using a modified version of the Newcastle-Ottawa Scale (NOS) quality assessment tool [23]. These assessment scores were based on the term of selection, comparability, outcome assessment or exposure of the NOS system. Total scores ranged from 0 (low quality) to 9 (high quality). A score of ≤ 5 points was considered as low quality, while 6 points or more was considered high quality. Any disagreement was resolved by discussion and consensus.

Statistical Analysis: Dichotomous data are presented as relative risk (RR), continuous data as mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (CI). If the study only described median, range and sample size, data were converted into mean and standard deviation. Standard

deviations of two or more groups were combined using an online tool (http://conm.atozmath.com/CONM/Ch2_CombinedSD.aspx.)

Heterogeneity across the included studies were examined by the Cochran's Q (P value) statistic and the I^2 test. An $I^2 \geq 50\%$ or a $P < 0.1$ and $I^2 \geq 25\%$, was interpreted as presence of statistical heterogeneity. Sensitivity analyses were performed to estimate the stability of included studies by removing the likely heterogenic study and repeating the meta-analysis. We performed random effects model meta-analysis and considered study sample size and between-study variation (i.e., heterogeneity) when weighting study effects. Where there was no heterogeneity ($P > 0.1$ and $I^2 < 50\%$), fixed-effects model meta-analysis was conducted. A P value < 0.05 was considered as statistically significant. A funnel plot was used to assess the publication bias. Data analyses were performed using RevMan 5.3 software from the Cochrane Collaboration.

Results

Study selection and description: A total of 771 studies were identified: 107 from PubMed, 295 from EMBASE, 18 from CENTRAL, and 351 from Chinese Databases (CBM-Chinese Biological Medicine Database and CNKI- China National Knowledge Infrastructure) (Figure 1). After title and abstract screening, 705 studies were excluded and 66 potentially studies were selected for full-text review. A further 52 studies were excluded after full-text evaluation due to study design (i.e., case series, non-related studies, review studies). A total of 14 studies reporting OSA, overweight or obesity were identified for final review. Two studies had incomplete outcome data and were subsequently excluded from the review. Finally, 12 case-control studies (N=3214; Obese group n=773, Non-Obese group n=315; OSA group n=1742, Non-OSA group n=384) were included in this meta-analysis. As we did not identify any cohort or cross-sectional studies, we included only the relevant case-control studies. Figure 1 outlines the search and study selection process.

Characteristics and quality assessment of the included studies: Tables 1 and 2 present the key characteristics of the included trials (published from 2003 to 2016). All included studies were case-control studies with varied sample sizes (773:315 in Obese group versus Non-Obese group; 1742:384 in OSA group versus Non-OSA group). Six studies were published in the English language and six in Chinese. Seven studies included participants from China [24-30], two from the United States [31, 32] and three studies included participants from Japan [33], Spain [12], and Turkey [34]. All participants in the included studies reported no comorbidity at enrollment. All studies reported strict measurement standards for BMI and AHI, but information on missing data, interview details, ascertainment to exposure and non-response rates were not available. The 12 studies included a total of 14 sets of data (6 in Obese vs Non-Obese and 8 in OSA vs non-OSA). All 12 studies included in this review were considered high quality by NOS. Table 3 presents the methodological quality and NOS scores of included studies.

Publication bias: Publication bias was evaluated using RevMan 5.3 software. In OSA group versus Non-OSA group, no significant publication bias was shown for BMI (**Figure 2A**). Similarly, there was no significant publication bias for AHI in Obesity group versus Non-Obesity group (**Figure 2B**).

Meta-analysis:

BMI in OSA group versus Non-OSA group

Children group: There was a single study with 76 OSA cases in children. The fixed-effects model showed no statistically significant difference in BMI (MD= 0.05; 95 % CI -0.33–0.43; P= 0.80)

Adult group: Seven studies including a total of 2050 participants (1688 cases and 362 controls) with OSA versus Non-OSA were included for analysis. Heterogeneity was high using fixed-effects model (Chi-square =309.93, P <0.00001; I^2 = 98 %). A sensitivity analysis was performed to estimate the stability of the included studies by excluding the likely heterogenic study. As the results did not change, the random-effects model was used, which showed BMI was significantly associated with OSA (MD= 4.67; 95 % CI 2.37– 6.98; P <0.0001) (**Figure 3A**).

AHI in Obese group versus Non-Obese group

Children group: Two studies with Obese children (N=172) were analyzed. The fixed-effects model showed no heterogeneity (Chi-square = 1.19, P =0.27; I^2 = 16 %). Obesity was significantly associated with increased risk of AHI (MD= 12.29; 95 % CI 8.46–16.11; P <0.00001) (**Figure 3B**).

Adult group: Four studies with a total of 916 cases with Obese versus Non- Obese were analyzed. We found high heterogeneity using fixed-effects model (Chi-square =208.00, P < 0.00001; I^2 = 99%). A sensitivity analysis was performed using the random-effects model. Results showed that obesity was significantly associated with OSA (MD = 12.11; 95 % CI 4.35–19.85; P =0.002) (**Figure 3C**).

Discussion

Overall, results from our meta-analysis showed that overweight and obesity are closely associated with OSA, and that obesity is an important risk factor for OSA. The association between obesity and OSA were separate into two sets of observations, one with high prevalence of OSA among obese, and the other with high proportion of obese participants with OSA. There were no differences in BMI between the OSA and Non-OSA groups in children, but BMI was significantly associated with increased risk of OSA in adults. The Obese group was associated with increased risk of AHI compared to the Non-obese group; differences were statistically significant in both children and adults.

OSA has been reported to be three times higher in obese groups compared to normal

weight groups [35-37]. The mechanism of OSA caused by obesity may be due to accumulation of fat in the airways causing narrowing of the airways, diastolic dysfunction, and fat accumulation in the diaphragm ultimately obstructing breathing. Fat accumulated in obese persons makes the neck relative short, thick, with a small-caliber and soft upper airway, which leads the upper airway easy to close and leading to the occurrence of OSA. In addition, adaptability of the chest walls may decrease due to increasing weight acting on the thorax and abdomen, thereby increasing the mechanical loading of the respiratory system, which leads to reduced functional residual capacity, especially when supine, and finally increasing the risk of OSA [2, 38]. On the other hand, increased BMI may cause the frequency of AHI to gradually increase, which extends the average time for OSA. The occurrence of OSA has also been associated with diseases of the nose and throat [39].

A number of studies have reported that OSA is associated with diabetes and metabolic disease, cerebrovascular and cardiovascular disease, cancer and other related diseases [40-43]. A possible mechanism may be recurring airway obstruction resulting in intermittent hypoxia, fluctuations of intrathoracic pressure and sleep fragmentation, which in turn lead to sympathetic activation, oxidative stress, inflammation, and endothelial dysfunction leading to these chronic conditions [40, 43]. There is also a reported association between OSA and dental arch size in children [33, 44]. Previous studies have reported that obesity, higher age, male sex and genetic factors are common risk factors of OSA [45-47]. The relationship between OSA and obesity is mainly manifested in two ways, one is that OSA patients are more obese, and another is the high prevalence of obesity in patients with OSA.

The high prevalence of obesity in people with OSA suggests that intervention programs for obesity control may have a role in OSA prevention and management. The management of obese patients with OSA includes diet and lifestyle changes, continuous positive airway pressure (CPAP), oral appliance and surgical interventions among others [48, 49]. Previous studies have reported that weight loss has a beneficial effect to reduce the AHI and improve the symptoms of apnea in obese patients with OSA [50]. A recent study reported that treatment with CPAP did not prevent cardiovascular events in patients with moderate to severe OSA and established CVD [51].

Evidence has demonstrated that intensive weight-loss interventions help reduce AHI scores and improve OSA [49]. Several studies have reported that bariatric surgery might be a suitable treatment option for OSA [20, 43, 52-55]. Sarkhosh et al reviewed a total of 69 studies with 13,900 patients, and indicated that all surgical procedures [Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, or biliopancreatic diversion (BPD)] achieved profound effects on OSA with more than two-third of patients reporting improvement in OSA symptoms after surgery [20]. In a longitudinal study of 844 participants with an average 35 years' follow-up, Bazzano and colleagues showed that being overweight in childhood is associated with a high risk

of OSA in middle age [56]. Therefore, a weight loss program targeting young obese people is essential to prevent future obesity and subsequent OSA.

The major limitation of this study is the large heterogeneity of the studies leading to weak quality of evidence. We performed random-effect model analyses which provides the most conservative estimate and a sensitivity analysis using a fixed-effect model for addressing the heterogeneity. All studies included in this systematic review were case-control studies with only four studies including more than 200 cases. Subgroup analysis on gender, age, ethnicity and region were not performed due to limited data. We only searched studies reported in selected databases including two Chinese databases and may fail to include studies published in other languages or regional databases. The strength of this study is the meta-analysis from a large number of participants including adults and children.

In conclusion, this meta-analysis shows that overweight and obesity are associated with OSA in both adults and children. Strategies for prevention and management of obesity through public health programs may have a role in reducing obesity-related OSA.

CRedit author statement

Zhiyong Dong: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing **Xiling Xu:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft **Cunchuan Wang:** Conceptualization, Methodology, Writing - Original Draft, Supervision, Project administration **Susie Cartledge:** Writing - Original Draft, Writing - Review & Editing
Visualization **Ralph Maddison:** Writing - Review & Editing, Supervision **Sheikh Mohammed Shariful Islam:** Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Supervision

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Disclosure: The authors have no conflicts of interest to declare.

Abbreviations: OSA, Obstructive Sleep Apnea; CBM, China Biological Medicine Database; CNKI, Chinese National Knowledge Infrastructure Database; NOS, Newcastle-Ottawa Scale, OB, obese; BMI, body mass index; AHI, apnea-hypopnea index; OR, odds ratio; RR, relative risk; OSAS, obstructive sleep apnea syndrome; MD, mean difference; SMD, standardized mean difference; 95% CI, 95% confidence interval; CPAP, continuous positive airway pressure; BPD, biliopancreatic diversion.

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Figure legends

Table 1. The characteristics of the included studies of OSA versus Non-OSA.

Table 2. The characteristics of the included studies of OB versus Non-OB.

Table 3. The methodological quality of the included studies evaluated by Newcastle-Ottawa Quality Assessment Scale (NOS Scale).

Figure 1. Flow diagram of the search process and study selection.

Figure 2. A: Funnel plot in OSA group versus Non-OSA group; B: Funnel plot in OB group versus Non-OB group.

Figure 3. A: Meta-analysis of BMI Value of OSA group versus Non-OSA group in adult group; B: Meta-analysis of AHI value of OB group versus Non-OB group in Children group; C: Meta-analysis of AHI value of OB group versus Non-OB group in adult group.

What is already known about this subject?

- Obstructive Sleep Apnoea (OSA) is the most common type of potentially serious sleep disorder.
- The prevalence of OSA in obese patients is nearly twice than that of normal-weight adults.
- Evidence suggests a close relationship of overweight and obesity with OSA

What does this study add?

- Obesity is associated with increased risk of apnea-hypopnea index (AHI).
- Overweight and obesity are important risk factors for OSA in both adults and children.
- Preventing and managing obesity may have a role in reducing obesity-related OSA.

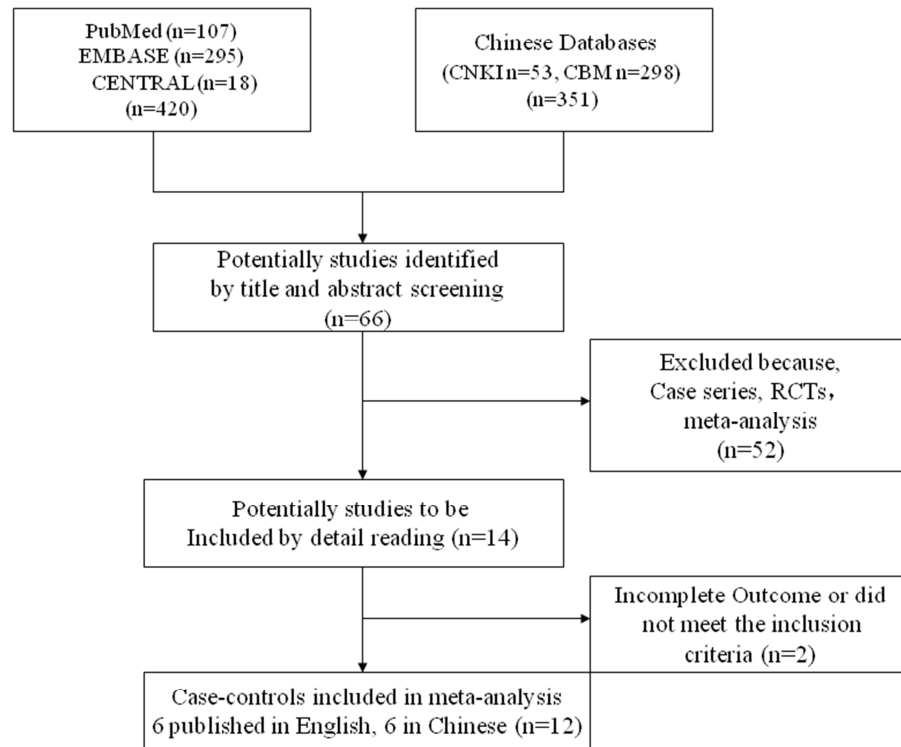
Figure 1. Flow diagram of the search process and study selection

Figure 2. A: Funnel plot in OSA group versus Non-OSA group; B: Funnel plot in OB group versus Non-OB group.

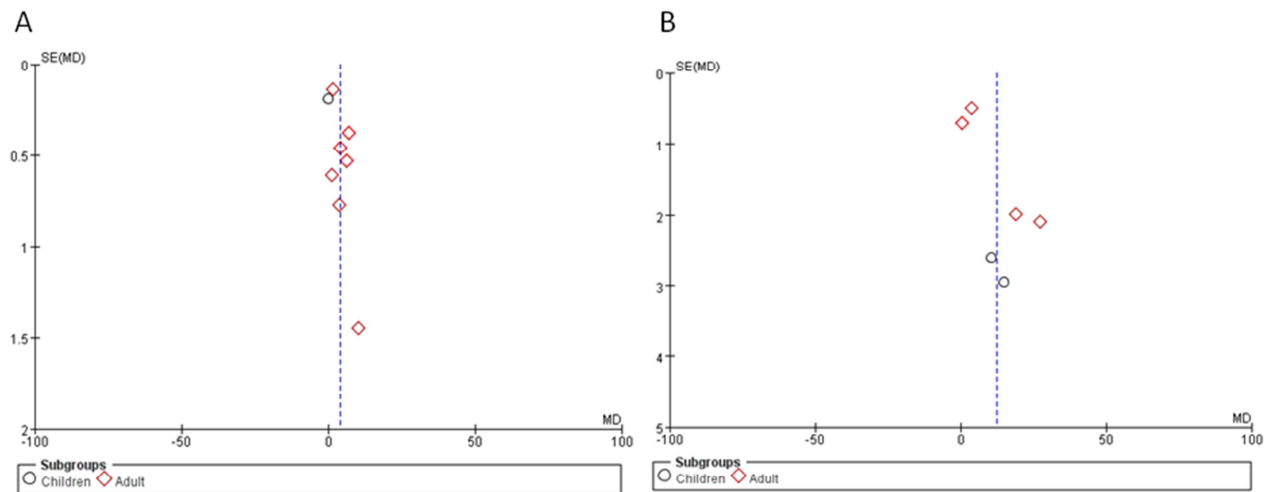
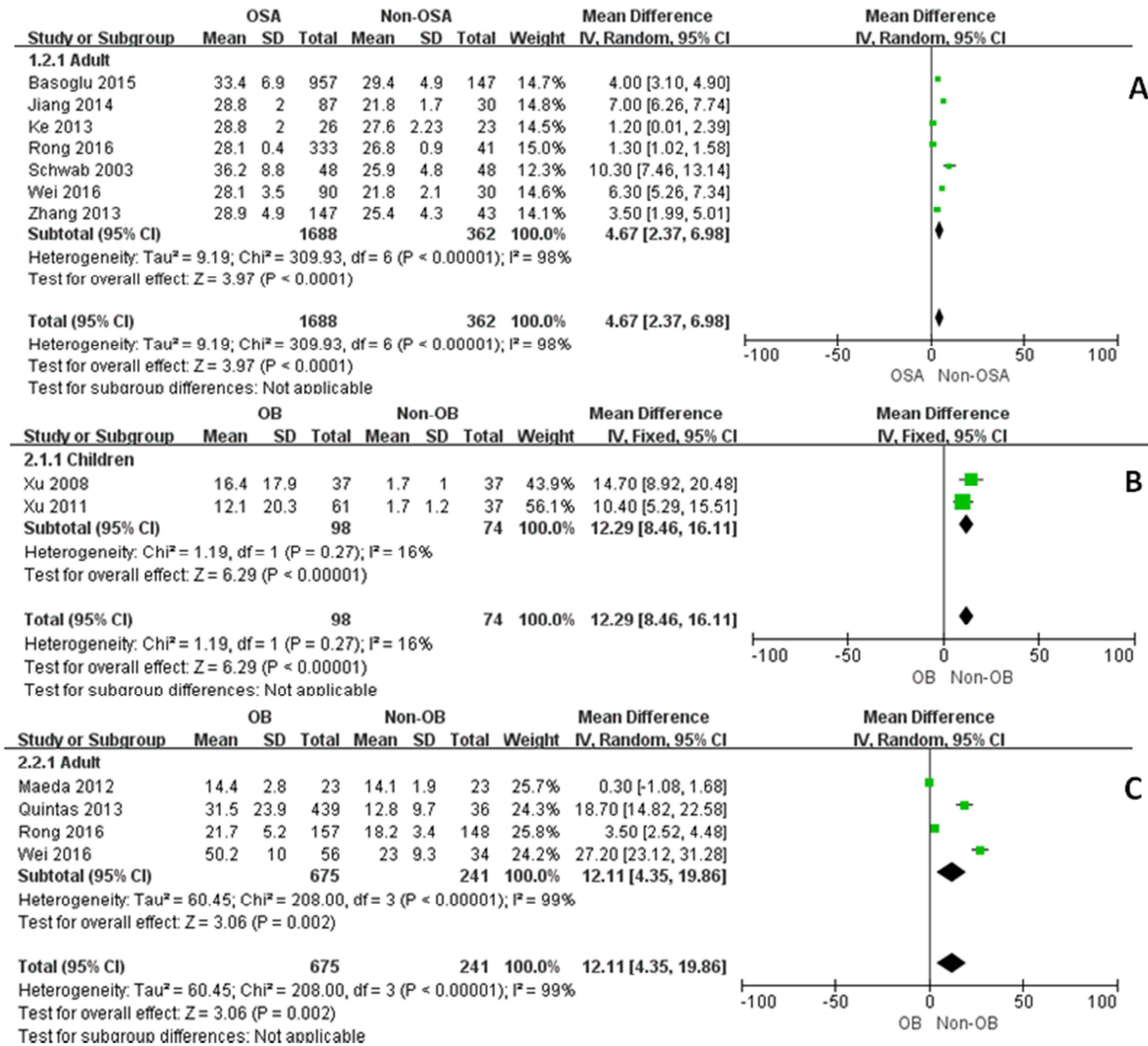


Figure 3. A: Meta-analysis of BMI Value of OSA group versus Non-OSA group in adult group; **B:** Meta-analysis of AHI value of OB group versus Non-OB group in Children group; **C:** Meta-analysis of AHI value of OB group versus Non-OB group in adult group.



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Table 1 Characteristics of included studies of OSA versus Non-OSA

Author, Year	Country	Design	Sample Size	Male: Female		Age		Diagnosis of OSA and OB	BMI kg/m ²	
				OSA	Non-OSA	OSA	Non-OSA		OSA	Non-OSA
Rong 2016a	China	Case-control	365	231:102	16:25	54.5±5.2	52.7±7.8	AHI BMI	28.1±0.4	26.8±0.9
Wei 2016a	China	Case-control	120	90 (NS)	30 (NS)	46±4.2	38±4.0	AHI BMI	28.1±3.5	21.84±2.06
Basoglu 2015	Turkey	Case-control	1104	957(94:53)	147(680:277)	52.2±11.1	46.4±13.2	AHI BMI	33.4±6.9	29.4±4.9
Bhushan 2014	USA	Case-control	76	54 (33: 21)	22 (12: 10)	8.4±2.7	8.0±2.1	AHI BMI z score	2.75±0.7	2.7±0.8
Jiang 2014	China	Case-control	117	87(46:41)	30(17:13)	47.01±8.12	45.93±7.85	AHI BMI	28.75±2.02	21.76±1.68
Ke 2013	China	Case-control	49	14: 12	12: 11	51.3±12.5	49.55±11.61	AHI BMI	28.81±1.97	27.64±2.23
Zhang 2013	China	Case-control	190	108:39	30:13	49.4±8.85	52.3±7.11	AHI BMI	28.8±4.9	25.4±4.27
Schwab 2003	USA	Case-control	96	21:27	21:27	45.3±9.7	41.3±10.5	AHI BMI	36.2±8.8	25.9±4.8

Body mass index (BMI); underweight: BMI < 18.5, normal weight: 18.5 ≤ BMI < 25, overweight: 25 ≤ BMI < 30, obese: BMI ≥ 30

Apnea-hypopnea index; AHI of <5 events/h was considered within normal limits, and numbers of 5 to <15, 15 to <30, and >30 represent mild, moderate, and severe OSA.

Table 2 Characteristics of included studies of Obese versus Non- Obese

Author, Year	Country	Design	Sample Size	Male: Female		Age		OSA/OB		AHI	
				OB	Non-OB	OB	Non-OB			OB	Non-OB
Rong 2016b	Beijing	Case-control	305	157(112:45)	148(101:47)	53.3±6.8	55.4±3.5	AHI		21.7±5.2	18.2±3.4
Wei 2016b	Beijing	Case-control	80	56(NS)	34(NS)	NS	NS	BMI			
Quintas 2013	Spain	Case-control	475	439(337:102)	36(16:20)	57.4±13.2	53.64±16.36	AHI		31.5±23.9	12.08±9.67
Maeda 2012	Japan	Case-control	46	23(23:0)	23(23:0)	36.5(30.0, 44.0)	39.0(32.5, 41.5)	BMI			
Xu 2011	Beijing	Case-control	98	61(43:18)	37(25:12)	10.6±2.4	9.5±2.5	AHI		12.1±20.3	1.7±1.2
Xu 2008	Beijing	Case-control	74	37(26:11)	37(25:12)	10.3±2.1	9.6±2.4	BMI			
								AHI		16.4±17.9	1.7±1.0

Body mass index (BMI); underweight: BMI < 18.5, normal weight: 18.5 ≤ BMI < 25, overweight: 25 ≤ BMI < 30, obese: BMI ≥ 30

Apnea-hypopnea index; AHI of <5 events/h was considered within normal limits, and numbers of 5 to <15, 15 to <30, and >30 represent mild, moderate, and severe

OSA. Obese group, OB: BMI ≥ 25 kg/m², or a BMI z-score of > 1.96 was considered to be obese.

Table 3 Methodological quality of included studies evaluated by Newcastle-Ottawa Quality Assessment Scale (NOS Scale)

Authors year	Selection		Comparability		Outcome Assessment			Score 9 Point	
	Adequate definition (1 point)	Representativeness (1 point)	Controls Selection (1 point)	Controls definition (1 point)	Comparability of cases and controls on the basis of the design or analysis (2 point)	Exposure ascertain (1 point)	Same method of cases and controls (1 point)		Non-response rate (1 point)
Rong 2016a	1	1	1	1	2	0	1	0	7
Wei 2016a	1	1	1	1	1	0	1	0	6
Basoglu 2015	1	1	1	1	2	0	1	0	7
Bhushan 2014	1	1	1	1	2	0	1	0	7
Jiang 2014	1	1	1	1	2	0	1	0	7
Ke 2013	1	1	1	1	2	0	1	0	7
Zhang 2013	1	1	1	1	1	0	1	0	6
Rong 2016b	1	1	1	1	2	0	1	0	7
Wei 2016b	1	1	1	1	2	0	1	0	7
Quintas 2013	1	1	1	1	2	0	1	0	7
Maeda 2012	1	1	1	1	2	0	1	0	7
Xu 2011	1	1	1	1	1	0	1	0	6
Xu 2008	1	1	1	1	2	0	1	0	7
Schwab 2003	1	1	1	1	2	0	1	0	7

a: Included OSA versus Non-OSA group; b: Included OB versus Non-OB group.

Clear = 1 point; Unclear 0 point. Newcastle-Ottawa Scale (NOS): total score = 9 point; ≥ 6 consider as high quality; ≤ 5 consider as low quality

Conflict of interest: The authors have no conflicts of interest to declare.

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CRediT author statement

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