Association between overweight/obesity and risk of chronic rhinosinusitis: a prisma-compliant meta-analysis

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Abstract

Background

Previously increasing studies revealed that overweight/obesity patients were significantly higher in groups of patients with common otorhinolaryngological inflammatory diseases. Although there still may have some controversies remaining in the effect of overweight/obesity on CRS. Therefore, this study aimed to perform a meta-analysis to explore whether overweight/obesity is a significant risk factor for CRS.

Methods

In this meta-analysis, we comprehensively and systematically searched for relevant published literatures concerning the correlation between overweight/obesity and risk of CRS through applying a predefined search terms as follows: ("overweight" OR "obesity") AND ("chronic rhinosinusitis" OR "nasal polyps" OR "CRS" OR "CRSsNP" OR "CRSwNP") in the following databases: PubMed, Web of science, Embase, Cochrane Library, and Google Scholar from inception to July 31, 2022. To explore the association between overweight/obesity and risk of developing CRS, multivariate odds ratio (OR) or relative risk (RR) and 95% confidence intervals (CI) were analyzed by using STATA software version16.0. This meta-analysis was registered with PROSPERO, CRD42022353658.

Results

Of 376 studies initially identified, only 7 studies concerning on the association between overweight/obesity and risk of CRS were eligible for the inclusion criteria eventually. The meta-analysis indicated that overweight was closely related to elevated risk of CRS (OR/RR = 1.04, 95%CI 0.90–1.18, P < 0.001). Meanwhile, the meta-analysis suggested that obesity was significantly related to elevated risk of CRS (OR/RR = 1.01, 95%CI 0.99–1.03, P < 0.001). Sensitivity analyses showed that there are no changes in the direction of effect when any one study was omitted from all meta-analyses. In addition, there was no significant risk of publication bias in this meta-analysis by performing Bgg's test, Egger's test, and funnel plot.

Conclusion

We found that overweight/obesity contributed to increasing the risk of developing CRS. Certainty, the result should be interpreted cautiously. Certainty, to obtain a more convincible result, more rigorous and high-quality clinical research will be warranted to be performed to evaluate the relationship between overweight/obesity and CRS in future.

Introduction

With the fast development of economic and social over the past few decades, the incidence of overweight/obesity presented an alarmingly rapid increasing in countries in recent years, owing to the lifestyles of the residents changed dramatically all over the world, including intaking excessive energies, increasing sedentary activities, and so on [1, 2]. Based on Chinese criteria, the latest national prevalence estimated for 2015 to 2019 was 6.8% for overweight and 3.6% for obesity in children younger than 6 years, 11.1% for overweight and 7.9% for obesity in children and adolescents aged 6–17 year, and 34.3% for overweight and 16.4% for obesity in adults (≥ 18 year) [3]. Luhar S, et al. forecasted that the prevalence of overweight and obesity will reach 30.5% (27.4%-34.4%) and 9.5% (5.4%-13.3%) among men, and 27.4% (24.5%-30.6%) and 13.9% (10.1%-16.9%) among women by 2040 in India, respectively [4]. Hemmingsson E, et al. reported that the prevalence of overweight, obesity and severe obesity were 55.1%, 16.6% and 4.2% in 447,925 Swedish adults, respectively [5]. While, Szczysra J, et al. reported that the prevalence of overweight was 7.49% (7.91% of girls and 7.07% of boys), and the prevalence of obesity was 4.24% (4.47% of girls and 3.99% of boys) in Poland [6]. Phan HD, et al. conducted a national cross-sectional study on 2788 children aged from 11–14 years old and shown that the prevalence of overweight and obesity in Vietnamese children was 17.4% and 8.6% by WHO Z-score criteria, and 17.1% and 5.4% by IOTF reference [7]. Hua J, et al. reported that the overall prevalence rate between 2013 and 2018 significantly increased from 20.81–26.97% for overweight and from 4.09–7.13% for obesity in Hunan province of China [8]. Musa TH, et al. carried out a cross-sectional study on 255,581 students aged 7–22 years in 82 school and 10 universities in Jiangsu province, China. They pointed out the overall prevalence of overweight and obesity was 12.4% and 5.7%, also pointed out the incidence of overweight and obesity was 14.5% and 10.3% at age of 7–11 years, 11.2% and 6.8% at age
of 12–14 years, 11.7% and 3.1% at age of 15–17 years, 11.4% and 2.3% at age of 18–22 years [9]. A community-based cross-sectional study shown that the prevalence of general obesity was 7.1% among rural residents in Yunnan province of China [10]. The proportion of overweight and obese was 30% and 5% in Bhaktapur, Nepal in 2015–2017 [11]. The prevalence of overweight, I* obesity (25<BMI≤29.99kg/m²), II* obesity (30<BMI≤34.99kg/m²), and III* obesity (35<BMI≤59.99kg/m²) was 27.3%, 32.3%, 2.7%, and 0.2%, respectively, among 496,469 Korean [12]. Cecchini M forecasted that 20.5 million individuals will be severely obese in 2025 in the US [13].

Overweight/obesity is one of growing and leading public health problems worldwide that causes tremendous medical burdens on the healthcare system [14]. The global deaths attributable to high BMI had increased from 1.2 million in 1990 to 2.4 million in 2017 for females, from 1.0 million in 1990 to 2.3 million in 2017 for males [15]. In Egypt, the annual deaths due to obesity was up to 115 thousand (nearly 19.8% of total deaths in 2020). The annual economic burden imposed by obesity was approximately 62 billion Egyptian pounds [16]. In Sweden, approximately 4% of all deaths in 2016 were attributed to obesity, and the cost of obesity in 2016 was €2.7 billion [17]. In Italy, the total cost attributable to obesity was €13.34 billion in 2020 [18]. In South Africa, the total cost of overweight and obesity was estimated to be ZAR33,194 million in 2020. Annual per person cost of overweight and obesity was ZAR2,769 [19]. In Ghana, the average total costs for normal weight, overweight and obesity per person was $35, $78, and $132, respectively. The total direct healthcare costs burden for overweight and obesity was $121 million [20]. While in the US, the aggregate medical cost due to obesity among adults was up to $260.6 billion [21]. The percent of US national medical expenditures on treating obesity-related illness in adults increased from 6.13% in 2001 to 7.91% in 2015 [22]. Ward ZJ et al. pointed out the annual medical cost for obesity was $1,861 per adult, accounting for $172.74 billion annual expenditures. the annual medical cost for severe obesity was $3,097 per adult [23]. Hamilton D et al. conducted a systematic review and pointed out the mean total lifetime cost of a child or adolescent with obesity was €149,206 for a boy and €148,196 for a girl [24].

Overweight/obesity not only heavily affects the physical as well as mental health, resulting in developing of chronic inflammatory diseases and posing an enormous impact on quality of life, but also leads to a long-term chronic subclinical systematic inflammation constantly existing which contributed to induce the onset of lower airway inflammation disorders [25]. Chronic rhinosinusitis (CRS) is a heterogeneous disorder, which caused by a combination of multiples factors (e.g., inflammatory, environmental, host factors, etc) [26]. Accumulative studies suggested that overweight/obesity was a risk factor that increasing the incidence of CRS, exacerbating symptom of CRS, or decreasing the improvement of quality-of-life (QOL) in refractory CRS patients after endoscopic sinus surgery (ESS) in recent decades [27–30]. Meanwhile, as first-line therapeutic drugs of CRS, long-term and systematically using glucocorticoids also will contribute to weight gain and exacerbate overweight/obesity by increasing appetite. No relevant meta-analysis on the association between overweight/obesity and CRS had been synthesized previously. Considering the constantly rising prevalence as well as the heavy burdens of overweight/obesity and CRS, it is significant that we conducted this study to review the published literatures concerning the relationship between overweight/obesity and CRS to verify whether overweight/obesity is a risk factor for CRS.

Methods
Registration
This meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration No. CRD42022353658) and conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) reporting guideline [31].

Search strategy and selection criteria
We searched for relevant articles published before July 31, 2022, with search terms as follows: ("overweight" OR "obesity") AND ("chronic rhinosinusitis" OR “nasal polyps” OR "CRS" OR "CRSsNP" OR "CRSsNP") from the following databases: PubMed, Web of Science, Embase, Cochrane Library and Google Scholar.

Studies that met the following criteria were included: (a) studies that provided sufficient information regarding odd ratio (OR) or relative risk (RR) and 95% confidence intervals (CI) associated with overweight/obesity and risks of CRS; and (b) studies whose OR or RR and 95%CI could be calculated from the data in the studies; and (c) studies whose participants were clearly diagnosed with overweight/obesity/CRS. Exclusion criteria were shown as follows: (a) university dissertations, conventional reviews, meta-analysis, commentaries, conference summaries, editorials, letters, opinion pieces, the protocols of systematic review/clinical trial, case report/ a series of case report, and the like will be excluded. (b) Certainty, the language of literatures which is non-English will be excluded. (c)
Literatures that cannot be obtained the full text will be excluded. All the abstracts and full texts were reviewed independently by four investigators (B ZHU, H LIU, K PANG, and P LI). Any discrepancies were resolved by discussion or consultation with an investigator (L TIAN).

### Data extraction

Two investigators (L ZHANG and R ZHANG) independently used a predefined Micorsoft Excel form to extract data from finally included studies. The extracted information included author first name, publication year, the type of study design, study location, diagnosis criteria of overweight/obesity, diagnosis criteria of CRS, relevant results (RR/OR/95%CI), and so on.

### 2.4 Quality appraisal

Risk of bias for included studies was assessed using the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist of 22 items for cross-sectional, cohort and case-control studies [32, 33]. The studies were classified into the following three categories: A, more than 80% of STROBE criteria fulfilled; B, 50%-80% of STROBE criteria fulfilled; C, less than 50% of STROBE criteria fulfilled. Quality assessment was performed by two independent investigators (J LIAO and H SHEN). Any discrepancies were resolved by discussion with a third investigator (L TIAN).

### Data analysis

We used STATA 16.0 software to analyze the data extracted from finally included studies and compute the results. We assessed heterogeneities between studies by using Q test and inconsistency index ($I^2$). When the heterogeneity was high ($P$ value for Q test $\leq 0.05$ and $I^2 > 50$%), random-effects models were applied; when the heterogeneity was low ($P$ value for Q test $> 0.05$ and $I^2 < 50$%), fixed-effects models were adopted to calculate the results. The stabilization of study was evaluated by performing sensitivity analysis. Publication bias was evaluated by performing Begg's test, Egger's test, and funnel plot.

### Results

#### Study selection and characteristics

After excluding duplications and irrelevant literatures, 7 studies were included in this meta-analysis eventually. Flowchart of the selection process and finally inclusion results are presented in Fig. 1. Characteristics of finally included studies are shown in Table 1.

The present study finally included 1 case-control study (Hirsch AG, et al.,2015; including 1,246 obesity patients and 3,853 CRS patients), 1 prospective cohort study (Clarhed UKE, et al.,2022; including 2,001 overweight patients, 799 obesity patients, and 5,769 CRS patients), and 5 cross-sectional studies (Sidell D, et al.,2013, including 1,539 overweight patients, 2,776 obese patients, and 1.7 million CRS patients; Nam JS, et al.,2021, including 7,657 overweight patients, 10,295 obese patients, and 32,384 CRS patients; Chung SD, et al.,2014, including 208 obesity patients and 5,734 CRS patients; Bhattacharyya N, et al.,2013, including 2,016 CRS patients; Ahn JC, et al.,2016, including 28,912 CRS patients) exploring the association between overweight/obesity and risk of CRS.

#### Results of meta-analysis

The meta-analysis indicated that overweight was closely related to elevated risk of CRS (OR/RR = 1.04, 95%CI 0.90–1.18, $P < 0.001$) (Fig. 2). Also, the meta-analysis suggested that obesity was significantly related to elevated risk of CRS (OR/RR = 1.01, 95%CI 0.99–1.03, $P < 0.001$) (Fig. 5).

Sensitivity analysis showed no changes in the direction of effect when any one study was omitted from all meta-analyses (Fig. 3). In addition, Begg's test, Egg's test, and funnel plot showed no significant risks of publication bias (Begg's test: $Z = 0.75$, $P = 0.452$; Egger's test: $t = -0.49$, $P = 0.647$; Fig. 4).

Sensitivity analysis showed no changes in the direction of effect when any one study was omitted from all meta-analyses (Fig. 6). In addition, Begg's test, Egg's test, and funnel plot showed no significant risks of publication bias (Begg's test: $Z = 0.87$, $P = 0.386$; Egger's test: $t = 1.29$, $P = 0.243$; Fig. 7).

#### Quality of studies

All included studies were classified into category A. Most of items were reported in seven included studies. Certainty, some items were not reported. Five studies [34–38] did not report the source of funding, and only two studies [37, 39] did not discuss the limitations of
Discussion

This meta-analysis is the first to explore the effect of overweight/obesity on risk of developing CRS based on seven included studies involving 1,700,000 individuals publishing from 2013 to 2022. We found that patients with overweight/obesity were closely associated with increasing the risk of developing CRS. Meanwhile, increasing studies revealed that overweight/obesity was correlated with multiple otolaryngological diseases as well as some allergic conditions like rhinitis, allergic rhinoconjunctivitis (ARC), asthma, allergic rhinitis (AR), chronic rhinosinusitis (CRS), otitis media with effusion (OME), sensorineural hearing loss (SSNHL), chronic laryngitis, obstructive sleep apnea-hypopnea syndrome (OSAHS), laryngopharyngeal reflux diseases, etc [34–54]. Sugiura S et al. found that the main risk factor for MRI abnormalities which were suspected as sinusitis in a Japanese community-dwelling middle aged and elderly population is obesity [55]. Also, several studies indicated that elevated body mass index (BMI) (≥30Kg/m²) was associated with increasing postoperative adverse events of CRS after ESS (e.g., perioperative bleeding, cerebrospinal fluid (CFS) leakage, etc) [30, 41, 56]. It was strongly recommended that more attention needs to pay on CRS patients with BMI greater than 30Kg/m² during performing ESS.

Although, the underlying mechanisms of the correlation between overweight/obesity and CRS are yet to be fully elucidated. It's well known that overweight/obesity leads to a constantly persisting low-grade chronic systematic inflammation owing to elevating number and volume of adipose cells. While abundant adipose cells contributed to high level of proinflammatory cytokines releasing, especially interleukin 6 (IL-6), tumor necrosis factor (TNF-α), IL-1β, IL-8, C-reactive protein (CRP), etc. Meanwhile, adiponectin levels are inversely related to overweight/obesity. Accumulative adipose tissue leads to decreasing the level of adiponectin, which downregulates the activity of regulatory T-lymphocytes (Tregs) and upregulates the secretion of cytokines such as IL-10, TNF-α, Nuclear factor -κB (NF-κB) [57, 58]. Impaired Treg function and excessive secretion of cytokines play a crucial role in the onset and deterioration of CRS [59–61]. Leptin, expressed predominantly in adipose tissue, has effects on the innate and adaptive immune responses. Evidence indicated that leptin could activate eosinophils to markedly induce the release of inflammatory cytokines, such as IL-β, TNF-α, etc. Also, the elevating of leptin levels also may aggravate the severity of ECRS, promote and enhance systemic type 2-biased inflammatory response as well as the development of eosinophilic inflammation in nasal polyps [51, 62, 63]. While Kanagalingam S et al. pointed out that obesity did not affect the severity of sinonasal diseases in asthma patients, which is paradoxical with our results [64].

Although we included the published literatures on the association between overweight/obesity and risk of CRS as much as possible to increase the credibility of this meta-analysis results and decrease the risk of bias, this systematic review still has several limitations that require consideration. First, the exclusion of unpublished and non-English literatures may result in a potential bias. Second, the diagnosis criteria of overweight/obesity were not reach an agreement, which may affect the accuracy of results of this meta-analysis. Third, the sample of included studies is relatively small. only 5 cross-sectional studies, 1 case-control study and 1 prospective cohort study were included in this study. Considering the differences among study designations, the results of this meta-analysis will be affected. Meanwhile, the exact mechanism underlying of between overweight/obesity and CRS developing requires further exploration. Therefore, it is recommended that more and more studies with large samples involving vivo and in vitro will be still warranted to conduct to verify the correlation between overweight/obesity and increasing risk of developing of CRS in future.

Conclusions

We confirmed that overweight/obesity contributed to significantly increase the risk of developing CRS through this meta-analysis. These findings have important practical significance, which can provide references for clinical management and treatment on CRS patients. However, more cautions are required when interpreting the result of this meta-analysis.

Abbreviations

chronic rhinosinusitis=CRS; eosinophilic chronic rhinosinusitis=ECRS; endoscopic sinus surgery=ESS; allergic rhinitis=AR; allergic rhinoconjunctivitis=ARC; otitis media with effusion=OME; sensorineural hearing loss=SSNHL; obstructive sleep apnea-hypopnea syndrome=OSAHS; body mass index=BMI; interleukin=IL; tumor necrosis factor=TNF; C-reactive protein=CRP; Nuclear factor -κB=NF-κB; regulatory T-lymphocytes=Tregs; odd ratio=OR; relative risk=RR; confidence intervals=CI

Declarations
Authors’ contributions

Four reviewers (L ZHANG, R ZHANG, Y XIE, and L TIAN) contributed to the conception and designation of this study. Y XIE and L TIAN were responsible for administrative support. B ZHU, H LIU, K PANG, and P LI were responsible for literature screening. J LIAO and H SHEN were responsible for quality assessment. L ZHANG and R ZHANG were responsible for data extraction, analysis, and manuscript writing. All authors approved the authorship and final manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files. Also, the data that support the findings of this study are available on request from the corresponding author.

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Ethics approval and consent to participate

The present study was a meta-analysis. No ethical statement is provided.

Consent for publication

Not applicable.

Competing interests

The authors have no potential conflicts of interest relevant to disclose.

Acknowledgement

Not applicable.

References


**Table 1**

Table 1 characteristics of all eligible studies

Abbreviations: EPOS: European Position Paper on Rhinosinusitis and Nasal Polyps; ICD-9: International Statistical Classification of Diseases, 9th Revision; NR: not reported

**Figures**
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**Figure 1**

Flow of information through the different phase of a meta-analysis
Figure 2

Forest plots of the association between overweight and risk of CRS
Figure 3

Sensitivity analysis regarding the association between overweight and risk of CRS
Sensitivity analysis showed no changes in the direction of effect when any one study was omitted from all meta-analyses (Figure 3). In addition, Begg's test, Egger's test, and funnel plot showed no significant risks of publication bias (Begg's test: $Z=0.75$, $P=0.452$; Egger's test: $t=-0.49$, $P=0.647$; Figure 4).

Figure 4

Funnel plots regarding the association between overweight and risk of CRS

Sensitivity analysis showed no changes in the direction of effect when any one study was omitted from all meta-analyses (Figure 3). In addition, Begg's test, Egger's test, and funnel plot showed no significant risks of publication bias (Begg's test: $Z=0.75$, $P=0.452$; Egger's test: $t=-0.49$, $P=0.647$; Figure 4).
Figure 5

Forest plots of the association between obesity and risk of CRS
Sensitivity analysis showed no changes in the direction of effect when any one study was omitted from all meta-analyses (Figure 6). In addition, Begg's test, Egger's test, and funnel plot showed no significant risks of publication bias (Begg’s test: Z=0.87, P=0.386; Egger’s test: t=1.29, P=0.243; Figure 7).