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Causality between Obesity and Pneumonia: A Two-Sample Mendelian Randomization Analysis

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Abstract: *Many clinical studies have indicated that there is a close relationship between obesity and pneumonia, but the causal relationship between them has not been reported. Body mass index (BMI), waist-to-hip ratio (WHR) and waist-to-hip ratio adjusted for BMI (WHRadjBMI), which are closely related to obesity. Single nucleotide polymorphisms (SNPs) associated with them were used as instrumental variables for MR analysis. Inverse variance weighted (IVW), weighted median, MR-Egger, simple mode and weighted mode were used to analyze the causal effect. The result of IVW showed a potential causal relationship between BMI and pneumonia (P = 0.006, OR = 1.22, 95 % CI = 1.06-1.40), but no causal relationship between WHR and pneumonia (P = 0.351, OR = 0.93, 95 % CI = 0.79-1.09). The result of MR Egger showed a potential causal relationship between WHR and pneumonia (P = 0.020, OR = 1.87, 95 % CI = 1.11-3.16). The result of IVW showed that WHRadjBMI had no causal effect on pneumonia (P = 0.708, OR = 1.03, 95 % CI = 0.87-1.22). The study showed that obesity increased the risk of pneumonia, which may help to further explore the pathogenesis of pneumonia.*

Keywords: *Pneumonia, Obesity, Causality, Mendelian Randomization*

1. Introduction

Pneumonia is a common acute respiratory infection that affects the bronchus and alveolus pulmonis[1]. A variety of microbiome can cause pneumonia, including bacteria, respiratory viruses, and fungi, and their prevalence varies geographically. According to data from the 2019 Global Burden of Disease study, lower respiratory tract infection (LRTI), including pneumonia and bronchiolitis, affect 489 million people worldwide, with children under the age of 5 and older people over the age of 70 being the most affected by pneumonia. LRTI is responsible for 1.49 million deaths, with the largest number of deaths (1.23 million) among those aged 70 and over[2].

Obesity and its concomitant diseases have become a significant public health problem worldwide. The World Health Organization (WHO) defines obesity as "abnormal or excessive fat accumulation that may impair health," and further clarifies that "the root cause of obesity and overweight is the energy imbalance between calories intaked and consumed"[3]. The main measures of obesity include body mass index (BMI), waist-to-hip ratio (WHR) and waist-to-hip ratio adjusted for BMI (WHRadjBMI). BMI can be measured by calculating weight in kilograms divided by the square of height in meters and is designed to classify adults into three categories: "underweight," "overweight" or "obese." The WHO estimates that more than 1.9 billion people aged 18 and over were overweight, of whom more than 650 million were obese in 2016[3]. Studies have found that all forms of obesity, including abdominal obesity, are associated with a variety of chronic diseases, such as cancer[4], diabetes[5]and cardiovascular disease[6]. Obesity is therefore not only a disease, it also leads to new diseases. The effects of obesity on the immune system are widespread and complex. Previous studies have shown that obesity is associated with an increased risk of pneumonia[7-10]. In addition, adipose tissue is highly metabolically active, and visceral adipose tissue in particular has a harmful adipocyte secretion profile, leading to insulin resistance, chronic low-grade inflammation and procoagulant states[8]. The above indicates that obesity may be related to pulmonary inflammation, but it is still unclear whether obesity is one of the causes of pneumonia.

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2. Research hypotheses

This study further explored the causal relationship between obesity and pneumonia through the two-sample Mendelian randomization (MR) analysis method, in order to provide a theoretical basis for the pathogenesis of pneumonia.

3. Research design

In the study, qualified single nucleotide polymorphism (SNP) was selected as instrumental variable (IV) for genome wide association study (GWAS) MR analysis to explore the causal relationship between obesity and pneumonia. The MR analysis was based on three core assumptions: (1) IV must be significantly associated with exposure; (2) IV was not associated with any potential confounders associated with outcome; (3) IV was not directly associated with outcome, and can only be causally associated with outcome through exposure[11](Figure 1).

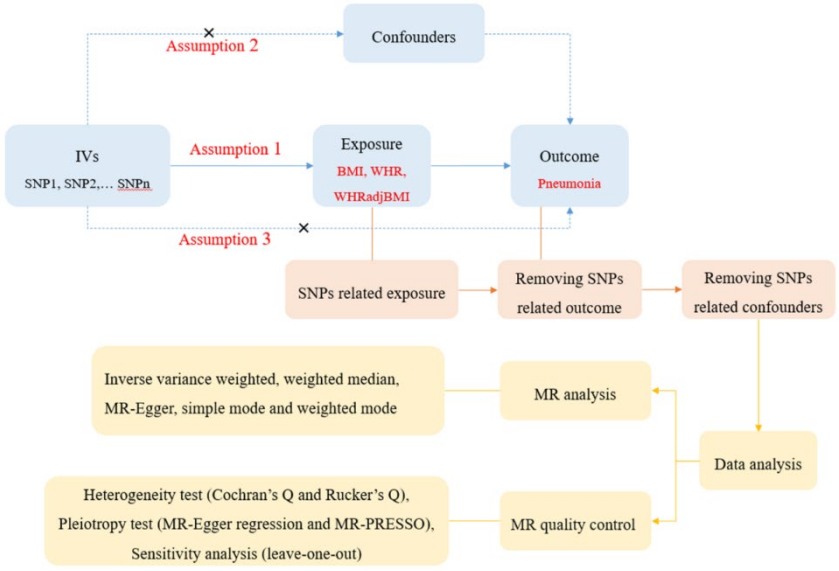

Figure 1: The study design sketch of the three core assumptions of the MR analysis.

The study analyzed the association between genetic susceptibility to obesity (BMI, WHR, WHRadjBMI) and pneumonia. The GWAS summary statistics data of BMI was obtained from a study by the MRC-IEU consortium (GWAS ID: ukb-b-19953), which included 472,174 Europeans with 20,134,421 SNPs. The GWAS summary statistics data of WHR was obtained from a study by the GIANT consortium (GWAS ID: ieu-a-73), which included 212,244 Europeans with 2,560,782 SNPs[12]. And the GWAS summary statistics data of WHRadjBMI was obtained from a European individual study (GWAS ID: ebi-a-GCST90025996), which included 458,349 Europeans with 4,238,887 SNPs[13]. The GWAS summary statistics data for pneumonia was obtained from an East Asian individual study (GWAS ID: ebi-a-GCST90018681), which included 7,423 patients with pneumonia and 171,303 healthy controls with 171,303 SNPs[14]. The GWAS summary statistics data for exposure and outcome can be downloaded from public directory web site of GWAS (https://www.ebi.ac.uk/gwas/downloads/summary-statistics) or IEU GWAS database. In the study, individuals with exposure and outcome came from different regions, with little overlap between the two samples. Furthermore, all data were derived from published studies or published GWAS summary statistics data, and ethical approval and informed consent have been provided in these studies or databases, and separate ethical approval and informed consent were not required for this study.

Appropriate IVs were selected from GWAS summary statistics data based on the three core assumptions of MR analysis through stringent quality control. SNPs with genome-wide significance were extracted from the GWAS summary statistics data of BMI, WHR, and WHRadjBMI ($P < 5\times10\text{-}8$). Then, all SNPS were in a linkage disequilibrium (LD) within the exposure range, clumping the sample data of 1KGP (1000 genomes project) (parameter setting: $R2 = 0.001$, window size=10,000 kb), used to estimate the LD among SNPs. And the SNPs that were missing from the LD reference panel and minor allele frequency (MAF) < 0.01 were removed.

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According to the second core hypothesis of MR analysis, clinical phenotypes corresponding to each IV were retrieved and screened one by one using PhenoScanner database, and SNPs potentially related to outcome and confounding were excluded[15].

Previous studies have reported that confounding factors affecting pneumonia include: children under the age of 5[16], older adults over 65 years of age and those with comorbidities[17-19], immunity-low [18, 20], premature delivery, malnutrition, household air pollution, ambient particulate and unsatisfactory breastfeeding[21], respiratory diseases (such as chronic obstructive pulmonary disease), diabetes, cardiovascular disease and chronic liver disease[18], gender[22], smoking, excessive drinking and underweight[18], dysphagia, decreased consciousness, impaired cough reflex[23].

According to the core assumption of MR analysis, the instrumental variable SNP must be strongly correlated with exposure. The F statistic for a single SNP was calculated to assess the potency of proxy exposure for selected IVs. The F statistic was to measure the strength of the IVs, which relates to the proportion of phenotypic variation explained by genetic variation (R2), sample size (N) and number of IVs (K)[24]. The formula for calculating the F statistic was as follows: $F=\frac{N-K-1}{K}\times\frac{R2}{1-R2}$[25]. F > 10 indicated a small probability of weak IVs[26]. These strictly screened SNPs would be used as the IVs for the subsequent MR analysis.

In the study, a two-sample MR was used to reveal the causal estimation of obesity for pneumonia. Inverse variance weighted (IVW), weighted median, MR-Egger, simple mode and weighted mode under random effects model were used to calculate the causal association between genetic variation in obesity and pneumonia. IVW provided the most accurate estimate [27]and would therefore be used as the primary method for this analysis.

Cochran's Q statistics (IVW) and Rucker's Q statistics (MR Egger) were used to detect the heterogeneity of MR analysis, and $P < 0.05$ was considered as significant heterogeneity[27]. MR Egger regression was used to evaluate the pleiotropy of IV[28]and the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) was used to identify horizontal pleiotropy outliers[29]. Briefly, horizontal pleiotropy was detected by the MR-PRESSO global test. If there was pleiotropy ($P < 0.05$), the MR-PRESSO outlier test can be performed to remove the outlier to correct the pleiotropy. In addition, sensitivity analysis was performed using the leave-one method to identify the undue influence of a single SNP on the MR analysis[30]. The mRnd (https://shiny.cnsgenomics.com/mRnd/) was used evaluate the statistical power of MR analysis[31]. The estimates were expressed as odds ratio (OR) and 95% confidence interval (CI). All analyses were performed in R (version 4.1.3), using the "TwoSampleMR" package (version 0.5.6) to estimate the effect of obesity genetic variants on pneumonia. All tests were bilateral, with $P < 0.05$ indicating significant differences.

4. Empirical analysis

In the study, 571 SNPs that were closely related to BMI ($P < 5\times10\text{-}8$) without LD ($r2 < 0.001$, kb = 10,000) were selected. 68 SNPs associated with confounding were excluded, and the remaining 503 SNPs were used for subsequent analysis. Further, 415 SNPs shared by BMI and pneumonia were identified as IVs (F statistic > 10), of which 48 palindromic SNPs would be removed. The scatter plot depicting the main results was shown in Figure 2A. The result of IVW suggested a potential causal association between BMI and the risk of pneumonia ($P = 0.006$, OR = 1.22, 95 % CI = 1.06-1.40). The direction of the causal effect of MR Egger ($P = 0.488$, OR = 1.21, 95 % CI = 0.71-22.06), weighted median ($P = 0.223$, OR = 1.14, 95 % CI = 0.92-1.40), simple mode ($P = 0.762$, OR = 1.09, 95 % CI = 0.62-1.91) and weighted mode ($P=0.991$, OR=1.00, 95 % CI = 0.64-1.58) were consistent with that of IVW, but there was no statistical difference (Figure 3). The results of Cochran's Q statistic (IVW) and Rucker's Q statistic (MR Egger) showed that there was no heterogeneity in the MR analysis of BMI and pneumonia (IVW: Q = 295.059, P = 0.997; MR Egger: Q = 295.058, P = 0.996) (Table 1). The result of MR Egger regression showed that there was no significant pleiotropy ($P = 0.978$), and the sensitivity analysis showed that the results of MR analysis were robust. MR-PRESSO global test showed no horizontal pleiotropy between BMI and pneumonia ($P = 0.529$), and MR-PRESSO outlier test showed no outlier (Table 1). However, genetic variation could only explain a small fraction of risk factor variation, and significant associations between genetic variation and outcomes may be underestimated in the context of MR, a large enough sample size was therefore needed to ensure statistical efficacy[32]. The result of mRnd showed that MR analysis of BMI had sound statistical power (power = 1.00 > 0.8). And the distribution of causal effects shown in the funnel plot was basically symmetrical, with no significant bias (Figure 4A).

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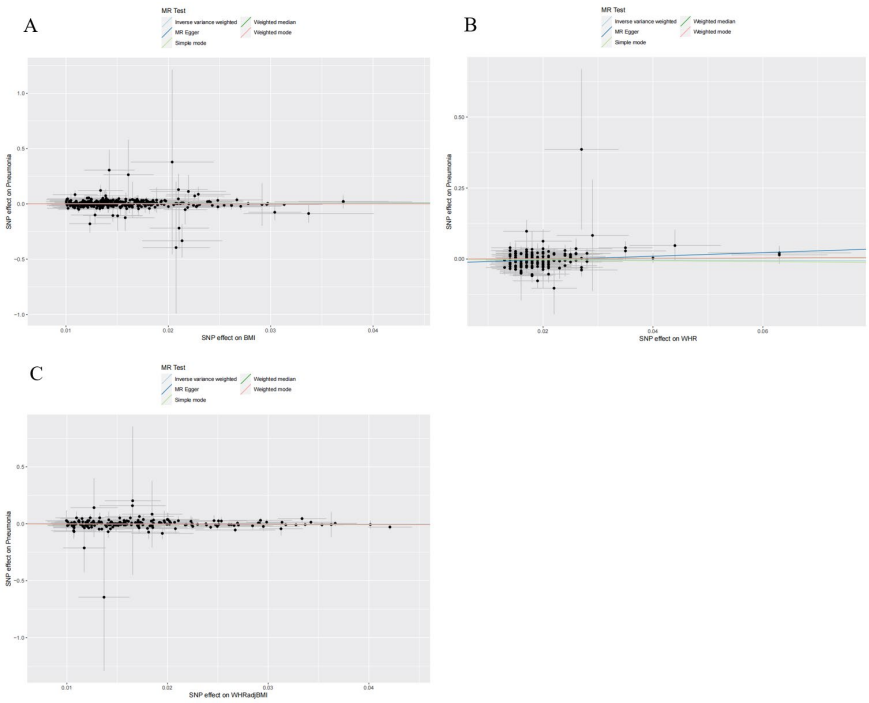

Figure 2: Scatter plot of MR analysis. A: scatter plot of BMI and pneumonia; B: scatter plot of WHR and pneumonia; C: scatter plot of WHRadjBMI.

Method	P value	OR (95% CI)
MR Egger	0.488	1.21 (0.71 to 2.06)
Weighted median	0.223	1.14 (0.92 to 1.40)
Inverse variance weighted	0.006	1.22 (1.06 to 1.40)
Simple mode	0.762	1.09 (0.62 to 1.91)
Weighted mode	0.991	1.00 (0.64 to 1.58)

Figure 3: MR analysis between BMI and pneumonia.

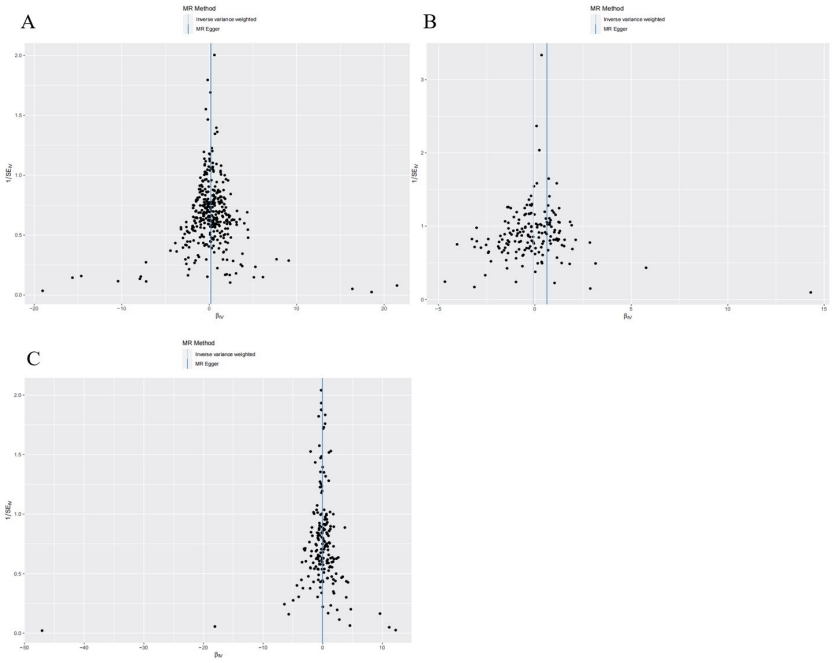

Figure 4: Funnel plot of MR analysis. A: funnel plot of BMI and pneumonia; B: funnel plot of WHR and pneumonia; C: funnel plot of WHRadjBMI.

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For the causal association analysis between WHR and pneumonia, a total of 226 SNPs that were closely related to WHR without LD were selected. 31 SNPs associated with confounding were excluded, leaving 195 SNPs for subsequent analysis. Further, 175 SNPs shared by WHR and pneumonia were identified (F statistic > 10), of which 6 palindrome SNPs were excluded. The 169 SNPs selected were treated as IVs for MR analysis, and the scatter plot describing the main results was shown in Figure 2B. The result of IVW showed that WHR had no causal relationship with pneumonia (P = 0.351, OR = 0.93, 95 % CI = 0.79-1.09). The result of MR Egger showed that WHR had potential causal relationship with pneumonia (P = 0.020, OR = 1.87, 95 % CI = 1.11-3.16). And the causal direction of the simple mode was consistent with that of IVW, but there was still no statistical difference (Figure 5). The results showed no significant heterogeneity (IVW: Q = 178.641, P = 0.273; MR Egger: Q = 170.787, P = 0.404) and pleiotropy (P = 0.078) (Table 1). And sensitivity analysis found no SNPs with strong influence on the results. MR-PRESSO also had no horizontal pleiotropy (P = 0.772) and outlier (Table 1). MR analyses of WHR and pneumonia had sound statistical efficacy (power = 0.84 > 0.8). The distribution of causal effects shown in the funnel plot was basically symmetrical, and no significant bias was observed (Figure 4B).

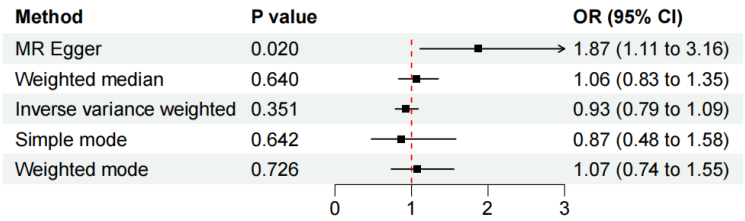

Figure 5: MR analysis between WHR and pneumonia.

For the causal association between WHRadjBMI and pneumonia, a total of 292 SNPs that were closely related to WHRadjBMI without LD were screened. 45 SNPs associated with confounding were excluded, leaving 247 SNPs for subsequent analysis. Further, 203 SNPs (F statistic > 10) shared by WHRadjBMI and pneumonia were identified, of which 8 palindrome SNPs were excluded. The remaining195 SNPs as IVs were used to MR analysis, and the scatter plot describing the main results was shown in Figure 2C. The result of IVW showed no potential causal association between WHRadjBMI and pneumonia (P = 0.708, OR = 1.03, 95%CI = 0.87-1.22). The causal effect direction of MR Egger was consistent with that of IVW, and there was no statistical difference (Figure 6). No significant heterogeneity was found (IVW: Q = 147.027, P = 0.999; MR Egger: Q = 146.814, P = 0.999) and pleiotropy (P = 0.706) (Table 1). Sensitivity analysis also found no SNP that had a strong influence on the results. No horizontal pleiotropy (P = 0.999) and outliers were found (Table 1). MR analyses of WHRadjBMI and pneumonia had sound statistical power (power = 1.00 > 0.8). The distribution of causal effects shown in the funnel plot was basically symmetrical, and no significant bias was observed (Figure 4C).

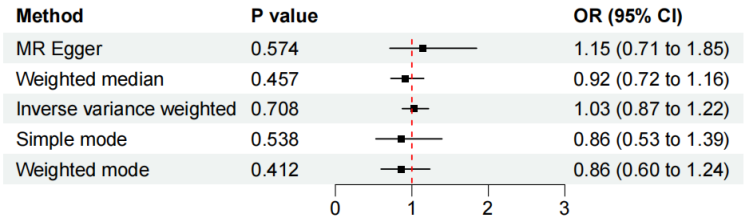

Figure 6: MR analysis between WHRadjBMI and pneumonia.

Table 1 Quality control of MR analysis for obesity and pneumonia

Exposure	Outcome	Heterogeneity		Pleiotropy	MR-PRESSO	
		IVW	MR Egger	MR Egger regression	Global test	Outlier test
BMI	Pneumonia	P=0.997	P=0.996	P=0.978	P=0.529	NA
WHR	Pneumonia	P=0.273	P=0.404	P=0.078	P=0.772	NA
WHRadjBMI	Pneumonia	P=0.999	P=0.999	P=0.706	P=0.999	NA

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5. Conclusion

Overall, our study showed that obesity was positively associated with the risk of pneumonia. This result may provide new insights into the pathogenesis of pneumonia and provide new ideas for preventing the occurrence of pneumonia. However, further research is needed to analyze the relationship between obesity and an increased risk of pneumonia.

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