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# Casual correlation between overweight, obesity, and severe COVID-19 infection with respiratory failure

## A two-sample Mendelian randomization

Shiqiang Chen, BS[a], Qiang Zhang, BS[a], Xiaobing Zhang, BS[a], Peiyao Xie, BS[a], Hua Guo, BS[a], Fengling Lu, BS[a], Chaoyang Zhou, MPS[b], Fubo Dong, MPS[b,*]

**Abstract**

This study aimed to detect the causal association of overweight and obesity on severe COVID-19 infection with respiratory failure through a two-sample Mendelian randomization (MR) method based on the genome-wide association studies datasets. All genome-wide association studies summary data of exposures and outcome used in this study were obtained from the IEU database derived from Europeans. The study mainly used the inverse variance weighted method to test causal relationship. Simultaneously, MR-PRESSO and MR-EGGER were used to detect the pleiotropy, and sensitivity analysis was performed using leave-one-out analysis. In the inverse variance weighted analyses, we found no causal association between obesity (e.g., OR = 1.15, 95% CIs = 0.96–1.37, $P = .13$ for obesity-ebi-a-GCST90000255), obesity subtypes (e.g., OR = 1.93, 95% CIs = 0.90–4.14, $P = .10$ for obesity and other hyperalimentation) as well as overweight (OR = 0.90, 95% CIs = 0.64–1.27, $P = .54$) and severe COVID-19 infection with respiratory failure. The findings showed no causal association between obesity or overweight and severe COVID-19 infection with respiratory failure. Further validation is needed regarding whether obesity or overweight is a risk factor for it.

**Abbreviations:** GWAS = genome-wide association studies, IVs = instrumental variables, IVW = inverse variance weighted, LD = linkage disequilibrium, LOO = leave-one-out, MR = Mendelian randomization, SNPs = single nucleotide polymorphisms, VitD = vitamin D.

**Keywords:** Mendelian randomization, obesity, overweight, severe COVID-19 infection with respiratory failure

### 1. Introduction

Novel coronavirus infection has been a worldwide pandemic for >4 years.[1,2] Although the pathogenicity of novel coronaviruses is currently weakening and the characteristics of the disease have changed, there is still no sign of disappearing.[3] Since the future variation of the virus cannot be predicted, novel coronavirus infection remains a major global public health problem, which needs continuous attention.[4]

Following the relevant preventive measures, novel coronavirus infection has been largely controlled, and the number of cases has decreased significantly.[5] Most of the infected persons have mild symptoms, but patients with severe symptoms of novel coronavirus infections are still a key concern. One of the major manifestations of severe patients of novel coronavirus infection is severe respiratory failure, which can be directly life-threatening.[6,7] Therefore, identifying the risk factors of severe patients infected with novel coronavirus as soon as possible can effectively reduce the risk of turning into severe patients.

Multiple studies have demonstrated that obesity was independent risk factor of respiratory failure in patients with COVID-19.[8,9] In addition, it was not uncommon for overweight patients to experience respiratory failure in clinical practice. Unfortunately, few studies have proved the causal relationship between overweight, obesity and severe COVID-19 disease patients with respiratory failure. In previous studies, randomized controlled trials were the gold standard for exploring the relationship between risk factors and diseases, but due to the influence of potential confounding factors and reverse causality, they cannot be explained as clear causal relationships.[10] In

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*[a] Department of Emergency and Critical Care Medicine, Yuhuan People's Hospital, Taizhou, China, [b] Department of Critical Care Medicine, Yuhuan People's Hospital, Taizhou, China.*

** Correspondence: Fubo Dong, Department of Critical Care Medicine, Yuhuan People's Hospital, Taizhou 317600, China (e-mail: dongfbyhicu@163.com).*



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recent years, the rapid development of genome-wide association studies (GWAS) has provided an opportunity for the widespread application of Mendelian randomization (MR) research in causal inference.[11,12]

MR is an analytical method that uses genetic variation as latent instrumental variables (IVs) to determine whether the observational association between risk factors and diseases conforms to causal effects.[13] It can address the limitations of traditional epidemiological research methods. The genetic variations used in MR studies are typically single nucleotide polymorphisms (SNPs) with significant differences selected from GWAS, which are reliably associated with the risk factors studied.[14]

In summary, this study aimed to detect the causal association of overweight and obesity on severe COVID-19 infection with respiratory failure through a two-sample MR method based on the GWAS datasets.

## 2. Materials and methods

### 2.1. Data source

All GWAS summary data used in this study were obtained from the IEU database (https://gwas.mrcieu.ac.uk/, accessed on February 2, 2024) derived from Europeans, in which we retrieved all overweight and obesity data as 12 exposures. Of these, overweight and obesity class 1 to 3 were derived from the study published in 2013 by Sonja I Berndt et al of the GIANT consortium including 93,015 cases and 65,840 controls with a total of 2,435,045 SNPs for overweight, 32,858 cases and 65,839 controls totaling 2,380,428 SNPs for obesity class 1, 9889 cases and 62,657 controls with 2,331,456 SNPs for obesity class 2, 2896 cases and 47,468 controls sum up to 2,250,779 SNPs for obesity class 3.[15] We also obtained data on obesity and childhood obesity from a genome-wide association meta-analysis in 2012 that included 5530 cases and 8318 controls with 2,430,514 SNPs for obesity and 2,442,739 SNPs for childhood obesity, respectively.[16] Furthermore, 6 subtypes of obesity, heart failure and body mass index 25plus, drug-induced obesity, extreme obesity with alveolar hypoventilation, obesity, and other hyperalimentation, obesity as well as obesity due to excess calories were also obtained from FinnGen (https://www.finngen.fi/fi).

Severe COVID-19 infection with respiratory failure (analysis I) as an outcome variable was downloaded from the IEU database (https://gwas.mrcieu.ac.uk/, accessed on February 2, 2024) likewise. The study included 1610 cases and 2205 controls after quality control and the exclusion of population outliers, totaling 8,095,360 SNPs published in 2020[17] (Table 1).

### 2.2. Selecting instrumental variables

Firstly, the IVs included in this study were required to meet the following criteria: (i) SNPs significantly associated with obesity and overweight genome-wide were firstly screened, and the screening criterion was $P < 5 \times 10^{-6}$; (ii) SNPs with minimum allele frequency > 0.01 were screened; (iii) SNPs were excluded according to the criteria of $R^2 < 0.001$, window size = 10,000kb when the screened IVs were not present in the summary data of the endpoints, the linkage disequilibrium (LD) effect among SNPs was excluded; (iv) when the screened IVs were not present in the summary data of the outcome, proxy SNPs with high LD ($R^2 > 0.8$) to IVs were searched through the online platforms LD link for replacement[18] (https://ldlink.nci.nih.gov/, February 2, 2024 accessed); (v) *F*-values were calculated for each SNP in the IVs to assess the strength of the IVs and exclude possible weak instrumental variables bias between the IVs and exposure factors, calculated as follows: $F = R^2(N - 2)/(1 - R^2)$ with $R^2$ being the proportion of variation in the exposure explained by the SNPs in the IVs, and the requirement for the *F*-value being > 10.[19,20]

Secondly, we conducted a harmonization process to align the effect alleles of the exposure and outcome SNPs, identify and exclude SNPs with incompatible alleles and palindromic SNP with intermediate frequency.[19]

### 2.3. Mendelian randomization analysis

The inverse variance weighted (IVW) method with high confidence because of calculate the weighted mean to assess the

**Table 1**

**Data sources of overweight, obesity, and severe COVID-19 infection with respiratory failure.**

| Trait | Consortium | GWAS ID | Population | | SNPs | PMID |
|---|---|---|---|---|---|---|
| | | | Case/control | Decent | | |
| *Exposure* | | | | | | |
| Overweight* | GIANT | ieu-a-93 | 93,015/65,840 | European | 2,435,045 | 23563607 |
| Obesity class 1† | GIANT | ieu-a-90 | 32,858/65,839 | European | 2,380,428 | 23563607 |
| Obesity class 2‡ | GIANT | ieu-a-91 | 9889/62,657 | European | 2,331,456 | 23563607 |
| Obesity class 3§ | GIANT | ieu-a-92 | 2896/47,468 | European | 2,250,779 | 23563607 |
| Obesity‖ | NA | ebi-a-GCST001475 | 5530/8318 | European | 2,430,514 | 22484627 |
| Childhood obesity‖ | EGG | ieu-a-1096 | 5530/8318 | European | 2,442,739 | 22484627 |
| Heart failure and BMI 25plus | NA | finn-b-I9_HEARTFAIL_AND_OVERWEIGHT | 23,701/195,091 | European | 16,380,466 | |
| Drug-induced obesity¶ | NA | finn-b-E4_OBESITYDRUG | 115/209,884 | European | 16,380,447 | |
| Extreme obesity with alveolar hypoventilation¶ | NA | finn-b-E4_OBESITYXTRMALV | 454/209,884 | European | 16,380,450 | |
| Obesity and other hyperalimentation¶ | NA | finn-b-E4_OBESITY_HYPER | 8965/209,827 | European | 16,380,466 | |
| Obesity¶ | NA | finn-b-E4_OBESITY | 8908/209,827 | European | 16,380,465 | |
| Obesity due to excess calories¶ | NA | finn-b-E4_OBESITYCAL | 5883/209,884 | European | 16,380,461 | |
| *Outcome* | | | | | | |
| Severe COVID-19 infection with respiratory failure (analysis I) | NA | ebi-a-GCST90000255 | 1610/2205 | European | 8,095,360 | 32558485 |

* Body mass index (BMI) ≥ 25 kg/m$^2$.

† BMI ≥ 30 kg/m$^2$.

‡ BMI ≥ 35 kg/m$^2$.

§ BMI ≥ 40 kg/m$^2$.

‖ ≥95th percentile of BMI achieved before the age of 18 years old, representing 5% to 30% of any given cohort.

¶ A disorder involving an excessive amount of body fat.

GWAS = genome-wide association studies; SNPs = single nucleotide polymorphisms.

causality of the study is the primary method.[21] To assess the robustness and credibility of our MR results, we also performed several sensitivity analyses when necessarily: (1) MR-Egger regression to evaluate the directional pleiotropy of instruments[22]; (2) weighted median-based method[23] when instrumental variables might be invalid; (3) maximum likelihood method[24]; (4) MR-PRESSO test to identify outliers.[25] MR analyses in our study were performed using the "TwoSampleMR" package in R software version 4.3.3. Since there were 12 exposures in this study, the *P*-values of the associations were corrected using the Bonferroni correction method considered statistically significant with a $P_{Bonferroni} < 0.004$ (0.05/12*1).[26]

### 2.4. Sensitivity analysis

To verify the robustness of the above causal associations, we also used Cochran *Q* and funnel plots to test for heterogeneity,[27] as well as MR-Egger regression[28] and MR-PRESSO to test for pleiotropy,[29] with MRPRESSO simultaneously detecting and removing possible outliers. Finally, we also used leave-one-out (LOO) to identify the potential effect of each SNP.[30]

## 3. Results

### 3.1. Included instrumental variables

Our study finally screened 288 IVs strongly related to obesity or overweight, involving a total of 12 exposure variables from the IEU database. The mean value of the *F*-statistic for IVs was calculated to be 32.38, ranging from 20.25 to 306.24. Each $R^2$ and the *F*-statistics indicated no evidence of weak instrumental bias. The proxy SNP would take the place of any SNPs that did not match the information in the summary data. Moreover, SNPs with intermediate or incompatible allele frequencies would be eliminated (Table S1, Supplemental Digital Content,

**Table 2**

**Major Mendelian randomization results of severe COVID-19 infection with respiratory failure and obesity and overweight.**

| Outcome | Exposure | ID. exposure | Methods | N. SNPs | OR (95% CI) | *P* |
|---|---|---|---|---|---|---|
| Severe COVID-19 infection with respiratory failure (analysis I) | Obesity | ebi-a-GCST001475 | IVW | 14 | 1.15 (0.96–1.37) | .13 |
| | Obesity | ebi-a-GCST001475 | MR-Egger | 14 | 1.68 (0.69–4.08) | .28 |
| | Obesity | ebi-a-GCST001475 | Weighted median | 14 | 1.13 (0.89–1.44) | .32 |
| | Obesity | ebi-a-GCST001475 | Weighted mode | 14 | 1.10 (0.77–1.57) | .61 |
| | Obesity | finn-b-E4_OBESITY | IVW | 30 | 1.25 (0.98–1.58) | .07 |
| | Obesity | finn-b-E4_OBESITY | MR-Egger | 30 | 1.60 (0.81–3.15) | .18 |
| | Obesity | finn-b-E4_OBESITY | Weighted median | 30 | 1.14 (0.84–1.57) | .40 |
| | Obesity | finn-b-E4_OBESITY | Weighted mode | 30 | 1.08 (0.56–2.10) | .82 |
| | Obesity and other hyperalimentation | finn-b-E4_OBESITY_HYPER | IVW | 29 | 1.27 (0.99–1.63) | .06 |
| | Obesity and other hyperalimentation | finn-b-E4_OBESITY_HYPER | MR-Egger | 29 | 1.93 (0.90–4.14) | .10 |
| | Obesity and other hyperalimentation | finn-b-E4_OBESITY_HYPER | Weighted median | 29 | 1.30 (0.93–1.81) | .12 |
| | Obesity and other hyperalimentation | finn-b-E4_OBESITY_HYPER | Weighted mode | 29 | 1.77 (0.86–3.65) | .13 |
| | Obesity due to excess calories | finn-b-E4_OBESITYCAL | IVW | 16 | 1.11 (0.89–1.39) | .35 |
| | Obesity due to excess calories | finn-b-E4_OBESITYCAL | MR-Egger | 16 | 1.61 (0.82–3.16) | .19 |
| | Obesity due to excess calories | finn-b-E4_OBESITYCAL | Weighted median | 16 | 0.98 (0.71–1.35) | .90 |
| | Obesity due to excess calories | finn-b-E4_OBESITYCAL | Weighted mode | 16 | 1.01 (0.69–1.46) | .98 |
| | Drug-induced obesity | finn-b-E4_OBESITYDRUG | IVW | 8 | 1.02 (0.97–1.08) | .42 |
| | Drug-induced obesity | finn-b-E4_OBESITYDRUG | MR-Egger | 8 | 1.07 (0.95–1.20) | .33 |
| | Drug-induced obesity | finn-b-E4_OBESITYDRUG | Weighted median | 8 | 1.01 (0.94–1.08) | .74 |
| | Drug-induced obesity | finn-b-E4_OBESITYDRUG | Weighted mode | 8 | 1.01 (0.92–1.11) | .84 |
| | Extreme obesity with alveolar | finn-b-E4_OBESITYXTRMALV | IVW | 12 | 1.01 (0.93–1.09) | .82 |
| | Extreme obesity with alveolar | finn-b-E4_OBESITYXTRMALV | MR-Egger | 12 | 0.98 (0.83–1.16) | .84 |
| | Extreme obesity with alveolar | finn-b-E4_OBESITYXTRMALV | Weighted median | 12 | 0.99 (0.88–1.11) | .83 |
| | Extreme obesity with alveolar | finn-b-E4_OBESITYXTRMALV | Weighted mode | 12 | 0.98 (0.82–1.17) | .86 |
| | Heart failure and BMI 25plus | finn-b-I9_HEARTFAIL_AND_OVERWEIGHT | IVW | 22 | 0.76 (0.54–1.06) | .11 |
| | Heart failure and BMI 25plus | finn-b-I9_HEARTFAIL_AND_OVERWEIGHT | MR-Egger | 22 | 0.77 (0.43–1.37) | .38 |
| | Heart failure and BMI 25plus | finn-b-I9_HEARTFAIL_AND_OVERWEIGHT | Weighted median | 22 | 0.74 (0.47–1.18) | .20 |
| | Heart failure and BMI 25plus | finn-b-I9_HEARTFAIL_AND_OVERWEIGHT | Weighted mode | 22 | 0.75 (0.44–1.26) | .29 |
| | Childhood obesity | ieu-a-1096 | IVW | 14 | 1.15 (0.96–1.37) | .13 |
| | Childhood obesity | ieu-a-1096 | MR-Egger | 14 | 1.68 (0.69–4.08) | .28 |
| | Childhood obesity | ieu-a-1096 | Weighted median | 14 | 1.13 (0.88–1.45) | .33 |
| | Childhood obesity | ieu-a-1096 | Weighted mode | 14 | 1.10 (0.78–1.55) | .60 |
| | Obesity class 1 | ieu-a-90 | IVW | 36 | 1.07 (0.87–1.31) | .52 |
| | Obesity class 1 | ieu-a-90 | MR-Egger | 36 | 0.94 (0.55–1.60) | .82 |
| | Obesity class 1 | ieu-a-90 | Weighted median | 36 | 0.99 (0.74–1.33) | .96 |
| | Obesity class 1 | ieu-a-90 | Weighted mode | 36 | 0.94 (0.65–1.38) | .77 |
| | Obesity class 2 | ieu-a-91 | IVW | 29 | 1.05 (0.90–1.23) | .51 |
| | Obesity class 2 | ieu-a-91 | MR-Egger | 29 | 0.85 (0.55–1.30) | .45 |
| | Obesity class 2 | ieu-a-91 | Weighted median | 29 | 1.08 (0.86–1.35) | .53 |
| | Obesity class 2 | ieu-a-91 | Weighted mode | 29 | 1.02 (0.78–1.35) | .88 |
| | Obesity class 3 | ieu-a-92 | IVW | 10 | 0.95 (0.82–1.10) | .48 |
| | Obesity class 3 | ieu-a-92 | MR-Egger | 10 | 0.80 (0.48–1.32) | .40 |
| | Obesity class 3 | ieu-a-92 | Weighted median | 10 | 0.94 (0.77–1.14) | .51 |
| | Obesity class 3 | ieu-a-92 | Weighted mode | 10 | 0.94 (0.75–1.18) | .60 |
| | Overweight | ieu-a-93 | IVW | 24 | 0.90 (0.64–1.27) | .54 |
| | Overweight | ieu-a-93 | MR-Egger | 24 | 1.06 (0.40–2.77) | .91 |
| | Overweight | ieu-a-93 | Weighted median | 24 | 0.84 (0.49–1.43) | .52 |
| | Overweight | ieu-a-93 | Weighted mode | 24 | 0.76 (0.40–1.45) | .42 |

IVW = inverse variance weighted; SNPs = single nucleotide polymorphisms.

http://links.lww.com/MD/O216, which illustrates details information for each SNP corresponding to exposure and outcome variables).

### 3.2. Casual correlation of overweight and obesity on severe COVID-19 infection with respiratory failure

Table 2 showed the results of obesity and its subtypes or overweight with severe COVID-19 infection with respiratory failure using the 4 MR methods. The IVW method was the main results that we interested. In the IVW analyses, we found no causal association between obesity (e.g., OR = 1.15, 95% CIs = 0.96–1.37, $P$ = .13 for obesity-ebi-a-GCST90000255), obesity subtypes (e.g., OR = 1.93, 95% CIs = 0.90–4.14, $P$ = .10 for obesity and other hyperalimentation) as well as overweight (OR = 0.90, 95% CIs = 0.64–1.27, $P$ = .54) and severe COVID-19 infection with respiratory failure. The MR-Egger, weighted median, and weighted mode also validated this result. In addition, the MR-PRESSO method did not identify any outliers between them. Therefore, there was no causal relationship between exposures and outcome. Figure 1 displayed the scatter plot and forest plot of obesity-ebi-a-GCST90000255 with severe COVID-19 infection with respiratory failure. Other scatter plot and forest plot were shown in Figures S1 to S22, Supplemental Digital Content, http://links.lww.com/MD/O217.

### 3.3. Sensitivity analysis

Several sensitivity analyses, including the heterogeneity test, the pleiotropy test, and the LOO analysis, were performed in this

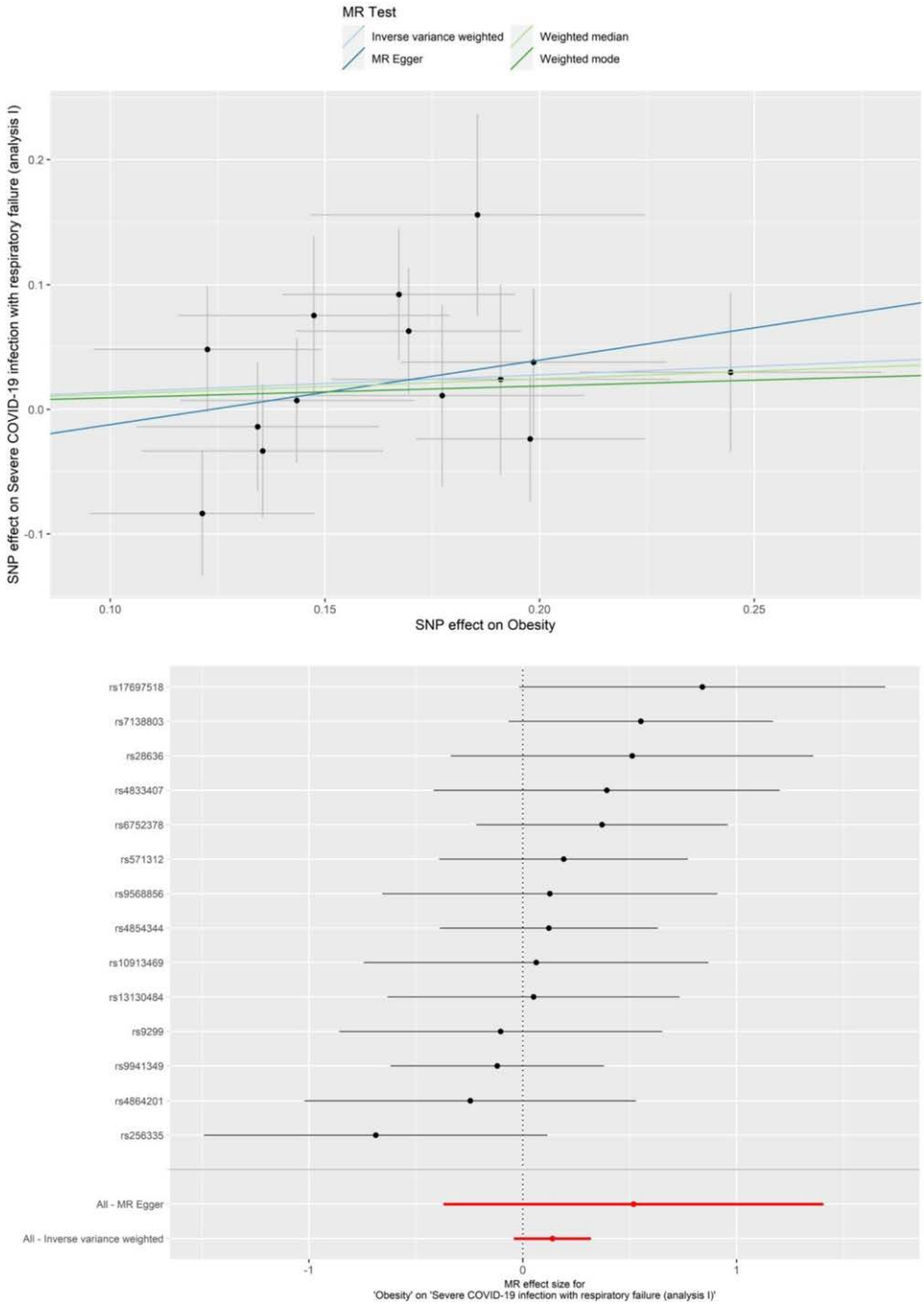


**Figure 1.** MR results of obesity-ebi-a-GCST90000255 and severe COVID-19 infection with respiratory failure (scatter plot and forest plot).

study to confirm the robustness of the MR results. Firstly, the results of funnel plots and Cochran *Q* test showed that there was no heterogeneity in MR analysis (All *P*-values > .05) (Table 3, Fig. 2, and Figs. S23–S33, Supplemental Digital Content, http://links.lww.com/MD/O217). Secondly, the MR-Egger intercept test showed no pleiotropy in the results of the MR analyses (all *P*-values > .05) (Table 3). The results of MR-PRESSO similarly confirmed this result (Table 4). In addition, LOO analysis showed that rs11199714, rs734597, rs2027575, rs1994380, rs79598028, and rs35286147 may potentially affect the IVW result of obesity-finn-b-E4_OBESITY and severe COVID-19 infection with respiratory failure (Fig. S34, Supplemental Digital Content, http://links.lww.com/MD/O217). However, similar SNPs were not found in other LOO analyses (Fig. 3 and Figs. S35–S44, Supplemental Digital Content, http://links.lww.com/MD/O217).

## 4. Discussion

Our study used GWAS data from IEU database to investigate the causal relationship between overweight, obesity, and severe COVID-19 infection with respiratory failure by MR analysis. Moreover, we used various statistical analyses to ensure the accuracy and reliability of the results. The results demonstrated that there was no causal connection between overweight, obesity, and severe COVID-19 infection with respiratory failure.

Previous research on overweight, obesity, and severe COVID-19 infection with respiratory failure were inconsistent with this study. As is well known, obesity causes chronic inflammation and the secretion of various cytokines. In acute infections caused by COVID-19, this relatively high level of cytokines can lead to more severe inflammation.[31] Moreover, obesity-induced elevated blood glucose, blood pressure, and abnormal lipid metabolism are expressed in the form of metabolic syndrome, which weakens the immune system.[31] It can be seen that the inflammation and metabolic adverse effects caused by obesity will have adverse effects on COVID-19. A systematic review highlighted that obesity was a risk factor for more severe disease in past pandemics. People with overweight or obese are particularly vulnerable to severe respiratory failure in a state of chronic low-grade inflammation.[32] Numerous studies have also demonstrated that obesity was an important risk factor for severe COVID-19 disease such as respiratory failure, admission to the intensive care unit, and death.[8,9,33] Remarkably, there was evidence that the severity of COVID-19 was associated with overweight and obesity, that is, the severity of COVID-19 appears to increase with increasing body mass index.[34] A study conducted in Japan to explore the relationship between overweight, obesity, and the risk of COVID-19 severity showed that obesity and overweight were associated with the increased risk of severe COVID-19, respectively. The researchers also found that the relative risk for COVID-19 induced respiratory failure compared to the normal weight category were 1.57 for overweight and 2.45 for obesity.[35] Potential pathophysiological mechanisms that may explain the strong relationship between the severity of COVID-19 and overweight/obesity include chronic pro-inflammatory states, excessive oxidative stress response, and immune impairment.[36–40] Obesity may increase the severity of COVID-19 infection, since the inflammation and immune system of obese patients play a role in viral diseases.[41] Compared with non-obese patients, obese patients have a higher viral load and longer virus shedding time.[42] Patients with obesity affected by the SARS-CoV-2 virus may make disease progression and even experience respiratory failure.[43] In addition, a study involving 56,033 hospitalizations found that obesity was independently associated with poorer patient prognosis in COVID-19 hospitalizations, and was connected with higher in-hospital mortality and higher rates of mechanical ventilation.[44] The deleterious effects of obesity on the immune system increase the severity of infections and reduce the ability of the immune system to produce antibodies.[45]

Although obesity is widely recognized as a predisposing risk factor for adverse outcomes of COVID-19 infection, several

**Table 3**

**Heterogeneity and pleiotropy of severe COVID-19 infection with respiratory failure and obesity and overweight.**

| | | Heterogeneity (IVW) | | Pleiotropy | |
|---|---|---|---|---|---|
| Outcome | Exposure | Q | *P* value | MR-Egger intercept | *P* value |
| Severe COVID-19 infection with respiratory failure (analysis I) | Obesity | 12.59 | .48 | -0.06 | .41 |
| | Obesity | 36.06 | .17 | -0.03 | .45 |
| | Obesity and other hyperalimentation | 37.21 | .11 | -0.05 | .27 |
| | Obesity due to excess calories | 15.76 | .40 | -0.06 | .28 |
| | Drug-induced obesity | 3.62 | .82 | -0.05 | .46 |
| | Extreme obesity with alveolar | 10.40 | .49 | 0.02 | .73 |
| | Heart failure and BMI 25plus | 18.58 | .61 | 0.00 | .98 |
| | Childhood obesity | 12.59 | .48 | -0.06 | .41 |
| | Obesity class 1 | 26.19 | .86 | 0.01 | .61 |
| | Obesity class 2 | 24.17 | .67 | 0.03 | .29 |
| | Obesity class 3 | 6.99 | .64 | 0.04 | .50 |
| | Overweight | 21.60 | .54 | -0.01 | .73 |

BMI = body mass index, IVW = inverse variance weighted.

**Table 4**

**MRPRESSO testing of severe COVID-19 infection with respiratory failure and obesity and overweight.**

| | | Raw | | Outlier corrected | | | | |
|---|---|---|---|---|---|---|---|---|
| Exposure | Outcome | OR (CI%) | *P* | OR (CI%) | *P* | Global *P* | Number of outliers | Distortion P |
| ebi-a-GCST001475 | Severe COVID-19 infection with respiratory failure (analysis I) | 1.12 (0.94–1.33) | .23 | NA | NA | .53 | NA | NA |
| finn-b-E4_OBESITY | | 1.16 (0.96–1.42) | .14 | NA | NA | .23 | NA | NA |
| finn-b-E4_OBESITY_HYPER | | 1.17 (0.96–1.44) | .14 | NA | NA | .18 | NA | NA |
| finn-b-E4_OBESITYCAL | | 1.08 (0.89–1.31) | .44 | NA | NA | .60 | NA | NA |
| finn-b-E4_OBESITYDRUG | | 1.02 (0.99–1.05) | .28 | NA | NA | .88 | NA | NA |
| finn-b-E4_OBESITYXTRMALV | | 1.01 (0.94–1.09) | .82 | NA | NA | .46 | NA | NA |
| finn-b-I9_HEARTFAIL_AND_OVERWEIGHT | | 0.76 (0.56–1.03) | .09 | NA | NA | .71 | NA | NA |
| ieu-a-1096 | | 1.12 (0.94–1.33) | .23 | NA | NA | .49 | NA | NA |
| ieu-a-90 | | 1.07 (0.92–1.26) | .38 | NA | NA | .93 | NA | NA |
| ieu-a-91 | | 1.06 (0.92–1.23) | .41 | NA | NA | .49 | NA | NA |
| ieu-a-92 | | 0.95 (0.83–1.08) | .45 | NA | NA | .69 | NA | NA |
| ieu-a-93 | | 0.99 (0.75–1.29) | .92 | NA | NA | .80 | NA | NA |

studies demonstrated a protective effect. This observation is known as the obesity paradox. Obesity paradox is that obesity does not necessarily shorten the expected survival time of patients, and may even be beneficial in some cases.[46] It was seen in respiratory disease,[47,48] end-stage renal disease,[49] and cardiovascular disease.[50] Obese patients may exhibit higher survival rate and shorter hospital length-of-stay, potentially due to a greater metabolic reserve during the recovery phase

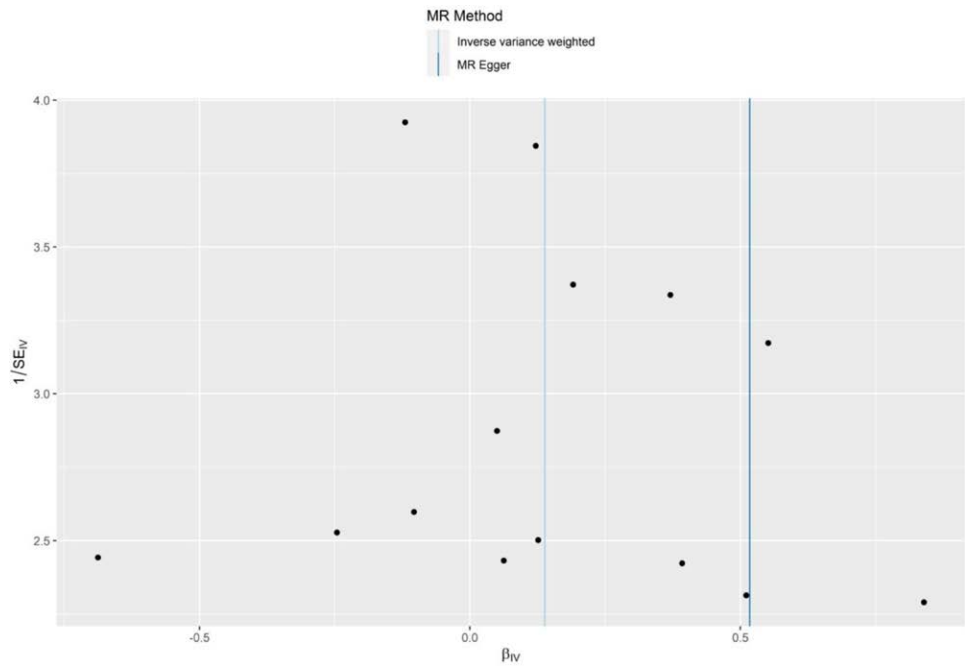


**Figure 2.** Funnel plot of obesity-ebi-a-GCST90000255 and severe COVID-19 infection with respiratory failure.

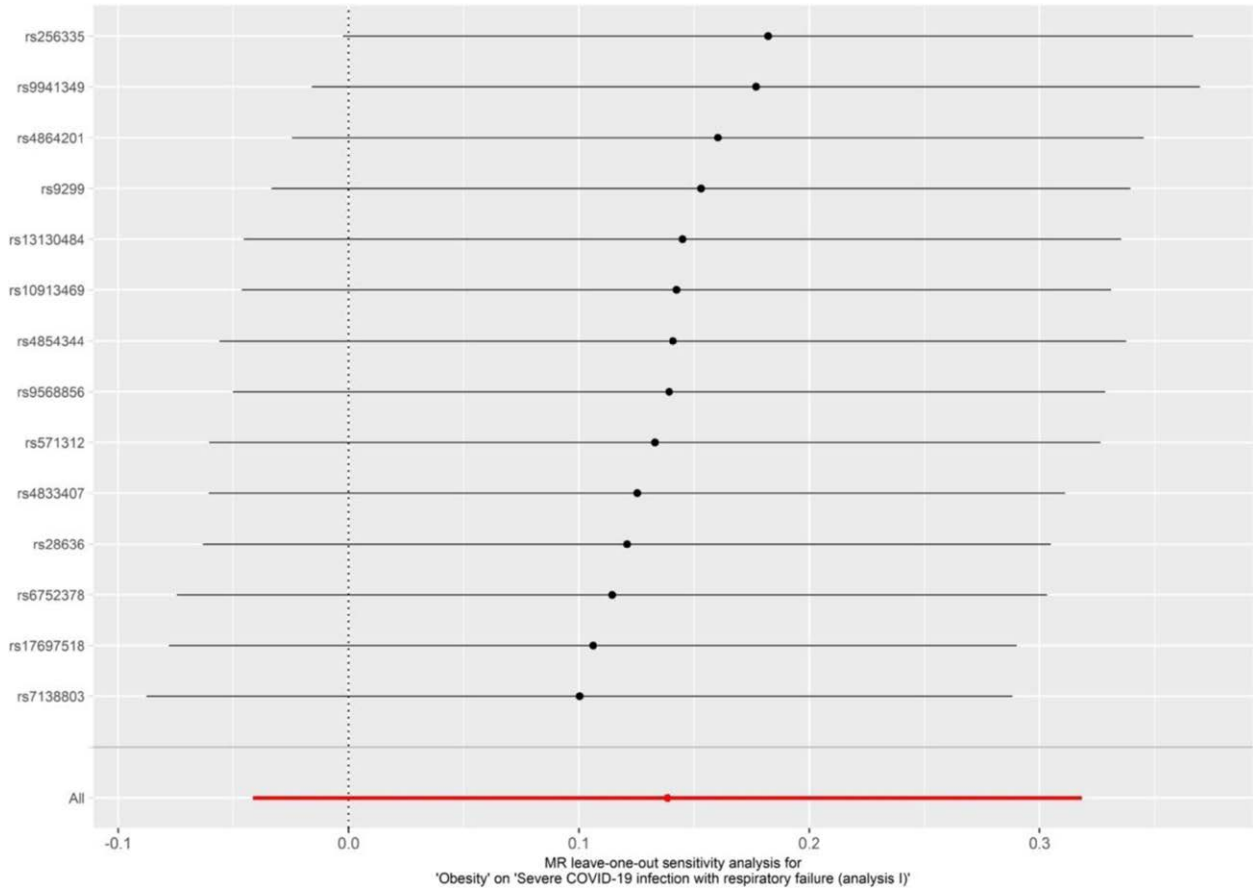


**Figure 3.** Leave-one-out analysis for obesity-ebi-a-GCST90000255 and severe COVID-19 infection with respiratory failure.

of critical illness.[51,52] Lavie et al found that there was an obesity paradox in COVID-19, with obese patients having lower mortality than normal-weight ones. The mortality of overweight patients was 36% lower than in normal-weight group, while the mortality in obese patients was 45% lower than in normal-weight group.[53] Furthermore, Dana et al conducted a retrospective study suggested that COVID-19 patients admitted to the intensive care unit with moderate obesity had a lower risk of death (13.8%) than healthy-weight patients, or those with overweight or severe obesity (17.6%, 21.7%, and 50%, respectively).[54] However, the new emerging evidence demonstrated that obesity was not associated with higher mortality rates in critically ill patients with COVID-19.[55] In addition, a large meta-analysis involving 6268 patients indicated that obesity may have a protective effect in patients with acute respiratory distress syndrome.[56] One proposed pathophysiological mechanism for the reduced mortality in critically ill patients with obesity is preconditioning, a chronic pro-inflammatory state associated with obesity that creates a protective environment, limiting the detrimental effects of a more aggressive second hit.[57] Notably, obesity predisposes to vitamin D (VitD) deficiency,[58,59] and VitD has been shown to play a crucial role in the immune response of the respiratory system.[60] A meta-analysis of randomized controlled trials including 8128 participants found that VitD supplementation may have some beneficial effects on the severity of SARS-CoV-2-induced disease, especially in VitD-deficient patients.[61] Clinical data suggested that VitD reduced respiratory virus replication and had a preventive effect on viral respiratory infections.[60] Therefore, obese patients should pay more attention to supplementing VitD to cope with the risk of SARS-CoV-2 infection.

The strength of this study was the application of MR to infer the causal association between overweight, obesity and severe COVID-19 infection with respiratory failure. As far as we know, the association between overweight, obesity, and severe COVID-19 infection with respiratory failure has not been previously studied using MR. Nevertheless, several limitations of this study were noteworthy. Firstly, MR did not consider the interaction between genes and the environment. Secondly, the population included in this study was of European ethnicity. Therefore, our results cannot represent entire populations. Whether the results of this study represent the entire population still needs to be validated with more diverse populations. In the future studies, our conclusions can be verified by MR analysis of GWAS databases from different sources. Thirdly, although MR analysis can be used as a method to infer causal relationships between exposures and outcomes, there is still a need to confirm our findings with large-scale clinical studies or experiments.

## 5. Conclusions

The findings showed no causal association between obesity or overweight and severe COVID-19 infection with respiratory failure. Further validation is needed regarding whether obesity or overweight is a risk factor for it.

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## Author contributions

**Conceptualization:** Shiqiang Chen, Chaoyang Zhou.
**Formal analysis:** Shiqiang Chen, Qiang Zhang, Xiaobing Zhang, Peiyao Xie, Hua Guo, Fengling Lu.
**Writing – original draft:** Shiqiang Chen, Fubo Dong.
**Writing – review & editing:** Shiqiang Chen, Qiang Zhang, Xiaobing Zhang, Peiyao Xie, Hua Guo, Fengling Lu, Chaoyang Zhou, Fubo Dong.

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