

COVID-19

# The association of obesity-related traits on COVID-19 severity and hospitalization is affected by socio-economic status: a multivariable Mendelian randomization study

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Revised 18 October 2021; Editorial decision 22 May 2022; Accepted 30 May 2022

## Abstract

**Background:** Due to its large impact on human health, socio-economic status (SES) could at least partially influence the established association between obesity and coronavirus disease 2019 (COVID-19) severity. To estimate the independent effect of body size and SES on the clinical manifestations of COVID-19, we conducted a Mendelian randomization (MR) study.

**Methods:** Applying two-sample MR approaches, we evaluated the effects of body mass index (BMI,  $n=322\,154$ ), waist circumference (WC,  $n=234\,069$ ), hip circumference ( $n=213\,019$ ) and waist-hip ratio ( $n=210\,088$ ) with respect to three COVID-19 outcomes: severe respiratory COVID-19 (cases = 8779, controls = 1 000 875), hospitalized COVID-19 (cases = 17 992, controls = 1 810 493) and COVID-19 infection (cases = 87 870, controls = 2 210 804). Applying a multivariable MR (MVMR) approach, we estimated the effect of these anthropometric traits on COVID-19 outcomes accounting for the effect of SES assessed as household income ( $n=286\,301$ ).

**Results:** BMI and WC were associated with severe respiratory COVID-19 [BMI: odds ratio (OR) = 1.51, CI = 1.24–1.84,  $P=3.01e-05$ ; WC: OR = 1.48, 95% CI = 1.15–1.91,  $P=0.0019$ ] and hospitalized COVID-19 (BMI: OR = 1.50, 95% CI = 1.32–1.72,  $P=8.83e-10$ ; WC: OR = 1.41, 95% CI = 1.20–1.67,  $P=3.72e-05$ ). Conversely, income was associated with lower odds of severe respiratory (OR = 0.70, 95% CI = 0.53–0.93,  $P=0.015$ ) and hospitalized COVID-19 (OR = 0.78, 95% CI = 0.66–0.92,  $P=0.003$ ). MVMR analyses showed that the effect of these obesity-related traits on increasing the odds of COVID-19 negative outcomes becomes null when accounting for income. Conversely, the association of income with lower odds of COVID-19 negative outcomes is not affected when including the anthropometric traits in the multivariable model.

**Conclusion:** Our findings indicate that SES contributes to the effect of obesity-related traits on COVID-19 severity and hospitalization.

**Key words:** COVID-19, obesity, socio-economic status, Mendelian randomization

#### Key Messages

- Obesity is one of the main factors associated with severe manifestations of coronavirus disease 2019 (COVID-19).
- Due to its large impact on human health, socio-economic status (SES) could influence the association between obesity and COVID-19 severity.
- Our results indicate that the association between obesity and severe manifestations of COVID-19 is affected by the effect of SES.
- SES association with COVID-19 outcomes is not affected by obesity-related traits.
- Preventive strategies targeting body size to reduce COVID-19 morbidity and mortality could benefit from assessing the SES context.

## Introduction

The coronavirus disease 2019 (COVID-19) resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused a pandemic since early 2020.<sup>1</sup> As of April of 2022, this pandemic has led to ~502 million COVID-19 cases and >6.19 million deaths worldwide.<sup>2</sup> The clinical manifestations of COVID-19 vary from asymptomatic infection to a critical illness, i.e. respiratory failure, septic shock and/or multiple organ dysfunctions.<sup>3,4</sup> Obesity appears to be one of the main factors associated with severe manifestations of COVID-19.<sup>5–8</sup> Leveraging genetic information, few studies conducted causal inference analyses, showing that body mass index (BMI) and other body measure traits have a putative causal effect on severe and critical COVID-19 illness.<sup>9–11</sup> However, to our knowledge, no investigation has been conducted to verify whether the association of body composition with COVID-19 outcomes was affected by socio-economic status (SES). SES has a large impact on many dimensions of health with individuals with poor SES presenting high morbidity and low life expectancy.<sup>12,13</sup> There is consistent evidence of the impact of SES traits on obesity-related anthropometric traits, such as BMI.<sup>14,15</sup> For example, higher levels of material deprivation have been associated with a higher BMI.<sup>16</sup> Also, higher income has been associated with a higher BMI in developing countries, whereas in developed countries, BMI has been found to be correlated inversely with median household income.<sup>17</sup> A causal inference analysis based on genetic information showed that BMI may affect social and SES outcomes, but there is also evidence of horizontal pleiotropy (i.e. shared pathways) between these traits.<sup>14</sup>

There is a growing literature showing consistently that SES is a primary predictor across COVID-19 outcomes, ranging from infection to mortality.<sup>18,19</sup> Due to its clinical implication, it is important to understand whether the relationship between body size and COVID-19 is affected by their associations with SES. Mendelian randomization (MR) studies are a powerful tool to investigate the potential causative role of SES traits across the spectrum of human health.<sup>20–22</sup> Accordingly, we conducted a MR study to assess the effect of traits related to body size and composition on COVID-19 outcomes, accounting for the effect of SES.

## Methods

### Data sources

In our study, we investigated the following anthropometric traits: BMI, waist circumference (WC), hip circumference (HIP) and waist-hip ratio (WHR). To assess the effect of body fat distribution, we also investigated BMI-adjusted anthropometric measures, i.e. BMI-adjusted WC, BMI-adjusted HIP and BMI-adjusted WHR. Genome-wide association studies (GWAS) statistics were derived from the meta-analyses performed by the Genetic Investigation of ANthropometric Traits (GIANT) consortium. This is an international collaboration aimed to identify genetic loci involved in human body size and shape.<sup>23</sup> These GWAS were conducted in up to 322 154 participants of European descent. The cohorts and GWAS procedures for BMI ( $n = 322\,154$ ),<sup>24</sup> WC ( $n = 234\,069$ ), WHR ( $n = 210\,088$ ), HIP ( $n = 213\,019$ ), BMI-adjusted WC ( $n = 234\,069$ ), BMI-adjusted HIP ( $n = 213\,019$ ) and BMI-adjusted WHR

( $n = 2\,100\,880$ )<sup>25</sup> have been previously described. The units of exposure of anthropometric traits were defined as follows: kilograms/metres<sup>2</sup> (kg/m<sup>2</sup>) for BMI, centimetres (cm) for HIP, BMI-adjusted HIP, WC and BMI-adjusted WC. We selected the 2015 versions of the GIANT GWAS meta-analyses because they do not include UK Biobank cohort, which is a contributor to the COVID-19 data described below and could bias causal inference effect estimates.

We evaluated three COVID-19 outcomes: severe respiratory COVID-19, hospitalized COVID-19 and COVID-19 infection. These data were derived from Release 6 of the GWAS meta-analysis conducted by the COVID-19 Host Genetics Initiative (HGI).<sup>26</sup> This is an international genetics collaboration that aims to uncover the genetic determinants of COVID-19 susceptibility, severity and outcomes.<sup>27</sup> For the evaluated COVID-19 outcomes, controls were genetically ancestry-matched individuals without SARS-CoV-2 infection.<sup>26</sup> In our analyses, we used GWAS summary statistics from the comparison between cases and control groups of each exposure. The severe respiratory COVID-19 outcome resulted from the comparison between patients with very severe respiratory failure secondary to COVID-19 ( $n = 8779$ ) vs controls ( $n = 1\,001\,875$ ). The hospitalized COVID-19 data were generated from the comparison of patients with a laboratory-confirmed SARS-CoV-2 infection that were hospitalized due to COVID-19 symptoms ( $n = 17\,992$ ) vs controls ( $n = 1\,810\,493$ ). Finally, the COVID-19 infection analysis was conducted comparing 87 870 individuals reporting SARS-CoV-2 infection with 2 210 804 controls. Information regarding SARS-CoV-2 infection was derived from a laboratory test, electronic health record, clinically confirmed COVID-19 and self-reported COVID-19 (e.g. by questionnaire).<sup>28</sup>

Analysed data were generated from only European-descent individuals to avoid potential population stratification biases in the hospitalized COVID-19 and COVID-19 infection outcomes. However, for the severe respiratory COVID-19 outcome, European specific data were not available. Thus, the analysis for this COVID-19 outcome was conducted using the data generated from a multi-ancestry GWAS meta-analysis. Although the majority of the patients were of European descent (~80% of the effective sample size), we used data from Release 5 of the COVID-19 HGI GWAS meta-analysis including only European-descent individuals (5101 cases vs 1 383 241 controls) to verify the results generated from the Release 6 data. Of note, the analysed data do not include data from 23andMe samples when COVID-19 phenotypes were tested as outcome in the MR analyses.

To investigate the effect of SES, we analysed genetic data related to self-reported household income information

from UK Biobank participants, hereinafter referred as to *income*. Income refers to the combined gross income of all members of a household and was assessed via the touchscreen questionnaire completed by UK Biobank participants.<sup>29</sup> This information was collected using a five-point scale corresponding to the total household income before tax, 1 being <£18 000, 2 being £18 000–£29 999, 3 being £30 000–£51 999, 4 being £52 000–£100 000 and 5 being >£100 000.<sup>30</sup> Genome-wide association statistics were obtained from a previous income GWAS conducted in 286 301 individuals of European descent. The GWAS procedure is described in previously published reports.<sup>30</sup>

## MR

MR is an analytic technique to estimate the effect of an exposure on an outcome of interest.<sup>10</sup> MR uses genetic variants, which are fixed at conception, to support causal inferences about the effects of risk factors, as they are unlikely to be affected by reverse causation, as they temporally precede the outcome, and confounding factors that act after conception.<sup>31</sup> MR is based on three assumptions: (i) the genetic instruments are associated with the outcome of interest; (ii) the genetic instruments are not associated with potential confounders of the risk factor–outcome association; and (iii) the genetic instruments affect the outcome only through their effect on the risk factor.<sup>32,33</sup>

We estimated the putative causal effect of anthropometric traits on COVID-19 phenotypes using a two-sample MR approach. Leveraging information from genome-wide association statistics, we can estimate the putative causal effect of the exposure on the outcome, which represents the sum of all possible paths from the exposure on the outcome.<sup>9,34</sup> This analysis was conducted using the R package TwoSampleMR.<sup>35</sup> For each anthropometric trait, we defined a genetic instrument based on genome-wide significant variants ( $P < 5 \times 10^{-8}$ ) that were linkage disequilibrium (LD)-independent ( $r^2 < 0.001$  within a 10 000-kilobase window) based on the 1000 Genomes Project Phase 3 reference panel for European populations.<sup>36</sup> Also, we excluded those genetic variants that were not present in the COVID-19 outcome GWAS data sets. For each MR test performed, we estimated  $R^2$  that corresponds to the proportion of variance of the exposure explained by the single-nucleotide polymorphism (SNPs) and mean F-statistic to evaluate the strength of the genetic instruments.

Our primary MR analysis was conducted using the inverse-variance weighted (IVW) approach, because it provides the highest statistical power.<sup>37</sup> As a secondary analysis, we also used MR–Egger, weighted median, simple mode and weighted mode.<sup>35</sup> Although the performance is

not comparable to the IVW, these methods can account for certain violations of the MR assumptions due to different pleiotropy scenarios.<sup>38</sup> Accordingly, we evaluated the concordance of the effect direction observed with the IVW approach with those generated using the other MR methods investigated.

Additionally, the presence of horizontal pleiotropy and heterogeneity within the genetic instruments, which are potential confounders in MR analyses, was tested using MR-Egger regression intercept<sup>39</sup> and IVW and MR-Egger heterogeneity tests,<sup>40</sup> respectively. Furthermore, outliers contributing to the heterogeneity (variability in the causal estimates obtained for each SNP) and horizontal pleiotropy (the variant affects the disease indirectly, i.e. outside its effect on the exposure) within the genetic instruments were identified by leave-one-out analyses and the visual assessment of forest and funnel plots. The genetic variants identified as outliers were removed from the analysis and the causal estimates were recalculated to evaluate the potential biases generated by these outliers in the MR results. Similarly to other MR studies,<sup>21,41,42</sup> we avoided inference based simply on *P*-value thresholds. The direction and strength of effect for each MR association, together with the corresponding *P*-value, was considered to better reflect the spectrum of evidence related to these results.<sup>43</sup> For all continuous exposures, i.e. anthropometric traits and income, exposure effects on their respective outcomes were calculated as odds ratio (OR) for the outcome per one standard deviation (SD) increase in each exposure. Whereas for binary exposures, i.e. COVID-19 phenotypes, exposure effects on their respective outcome were calculated as beta estimates that represent one unit increase in the outcome risk per additional copy of the effect allele.

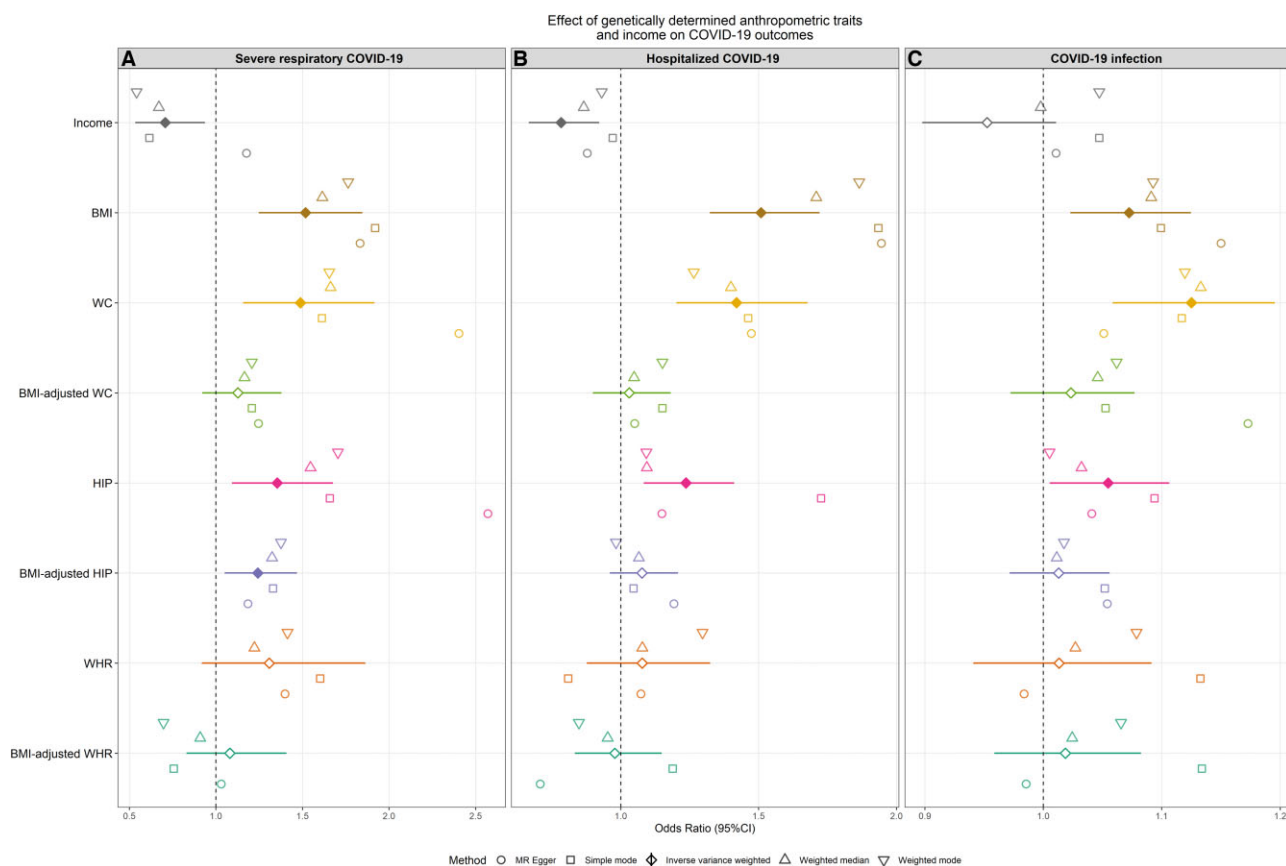
To verify the presence of a bidirectional relationship between the anthropometric traits and COVID-19 outcomes, we defined genetic instruments based on genome-wide significant variants ( $P < 5 \times 10^{-8}$ ) using the same procedure as described above. However, because the number of variants under these criteria was relatively low (six or seven SNPs), we also evaluated an alternative approach based on the inclusion of all LD-independent variants available from the top 10 000 variants released from the COVID HGI meta-analysis including 23andMe data. In this large data set, COVID-19 was investigated in 8779 cases and 1 001 875 controls for the severe respiratory COVID-19 phenotype; 24 274 cases and 2 061 529 controls for the hospitalized COVID-19 phenotype; and 112 612 cases and 2 474 079 controls for the COVID-19 infection phenotype. However, due to 23andMe data-sharing restrictions, genetic association statistics are available only for the top 10 000 variants, i.e. variants with the highest association with each COVID-19 outcome. Accordingly, we extracted the

LD-independent loci among them and used this information to define suggestive genetic instruments for the COVID-19 outcomes investigated. These suggestive genetic instruments including variants not reaching genome-wide significance might lead to the violation of the MR assumptions. Thus, we considered the estimates obtained from the IVW method and the MR-Robust Adjusted Profile Score (MR-RAPS) approach as well.<sup>44</sup> The MR-RAPS approach estimates the causal effect under pervasive horizontal pleiotropy and is robust to occasional outliers and weak genetic instruments.<sup>44</sup> The reliability of the findings was tested using multiple sensitivity analyses described above.

Then, we estimated the putative causal effect of income on anthropometric traits and vice versa using the univariable MR procedure described above. The genetic instruments in both analyses were genome-wide significant variants ( $< 5 \times 10^{-8}$ ) associated with each exposure. Then, we evaluated the direct causal effect of anthropometric traits on income using a multivariable MR (MVMR) analysis. After identifying the putative effects of anthropometric traits, we tested the putative effect of income on COVID-19 outcomes, applying the same analytic pipeline. The genetic instrument defined was then used to verify whether the association of anthropometric traits with COVID-19 outcomes is independent of the SES effect. Specifically, we tested the genetic instruments of anthropometric traits and income with respect to COVID-19 outcomes in a MVMR analysis. This is an extension of the standard MR framework to consider multiple potential risk factors in a single model and calculate the independent association of each risk exposure with the outcome.<sup>33,45,46</sup> The MVMR analysis was conducted using the MendelianRandomization R package.<sup>45</sup> To graphically show the non-overlap of the SNPs for the exposures tested in the MVMR, we used ggVennDiagram R package.<sup>47</sup>

## Results

We observed consistent associations of anthropometric traits on COVID-19 outcomes (Figure 1). The strongest association was observed with respect to BMI and WC: a 1-SD increase in genetically determined BMI ( $\text{kg/m}^2$ ) and WC (cm) was associated with increased odds of severe respiratory COVID-19 (BMI: OR = 1.51, 95% CI = 1.24–1.84,  $P = 3.01 \times 10^{-5}$ ; WC: OR = 1.48, 95% CI = 1.15–1.91,  $P = 0.002$ ) and hospitalized COVID-19 (BMI: OR = 1.50, 95% CI = 1.32–1.72,  $P = 8.83 \times 10^{-10}$ ; WC: OR = 1.41, 95% CI = 1.20–1.67,  $P = 3.72 \times 10^{-5}$ ). Reduced effects were observed for these anthropometric traits with respect to COVID-19 infection (BMI: OR = 1.07, 95% CI = 1.02–1.12,  $P = 0.003$ ; WC:



**Figure 1** Results of the Mendelian randomization (MR) analysis testing the effect of genetically determined anthropometric traits and income on (a) severe respiratory coronavirus disease 2019 (COVID-19), (b) COVID-19 hospitalization and (c) COVID-19 infection. 95% confidence intervals are reported for the inverse variance weighted estimates. Estimates from secondary MR methods are reported for each MR test. Income, household income; BMI, body mass index; WC, waist circumference; HIP, hip circumference; WHR, waist-hip ratio.

OR = 1.12, 95% CI = 1.05–1.19,  $P = 1e-4$ ). Also, a 1-SD increase in genetically determined HIP (cm) showed a positive association with severe respiratory COVID-19 (OR = 1.35, 95% CI = 1.09–1.67,  $P = 0.005$ ), hospitalized COVID-19 (OR = 1.23, 95% CI = 1.08–1.41,  $P = 0.0016$ ) and COVID-19 infection (OR = 1.05, 95% CI = 1.005–1.10,  $P = 0.029$ ). Among the anthropometric traits related to body fat distribution (i.e. WHR and traits adjusted for BMI), a 1-SD increase in genetically determined BMI-adjusted HIP (cm) was associated with severe respiratory COVID-19 (OR = 1.24, 95% CI = 1.05–1.46,  $P = 0.0109$ ), but not with hospitalized COVID-19 (OR = 1.07, 95% CI = 0.96–1.20,  $P = 0.20$ ), and with COVID-19 infection (OR = 1.01, 95% CI = 0.97–1.05,  $P = 0.54$ ). The IVW effect estimate was consistent with those estimated using all other MR methods and no heterogeneity or horizontal pleiotropy was observed within BMI, WC, HIP and BMI-adjusted HIP genetic instruments (Figure 1, Supplementary Table S1 and Supplementary Figures S2–S4, available as Supplementary data at *IJE* online). For the MR tests evaluating the effect of anthropometric traits on COVID-19 outcomes, the F-statistic ranged from 46.20 to 69.49, and  $R^2$

ranged from  $6.08e-07$  to 0.47 (Supplementary Table S1, available as Supplementary data at *IJE* online). The overlap of the LD-independent SNPs associated with the assessed anthropometric traits is shown in Supplementary Figure S1 (available as Supplementary data at *IJE* online). The analysis performed using GWAS data generated from only European-descent individuals from the COVID-19 HGI Release 5 data showed similar effect estimates to those derived from the trans-ancestry GWAS meta-analyses in the COVID-19 HGI data Release 6 (Supplementary Table S2, available as Supplementary data at *IJE* online).

To verify whether the effects of BMI, WC, HIP and BMI-adjusted HIP on COVID-19 outcomes were independent of each other, we entered the genetic instruments in pairwise MVMR models (income and each anthropometric trait) and an all-trait-combined MVMR model (income and all anthropometric traits) testing each COVID-19 outcome. The effects observed in the univariate MR were null after accounting for the effect of other anthropometric traits in the MVMR analysis (Supplementary Table S3, available as Supplementary data at *IJE* online). We also tested the possible reverse association of COVID-19



outcomes on the anthropometric traits (Supplementary Figure S5, available as Supplementary data at *IJE* online). The univariable MR analysis based on genetic instruments considering genome-wide significant variants showed null effects ( $\beta_{\text{Severe respiratory COVID-19} \rightarrow \text{BMI}} = 0.006$ , 95% CI =  $-0.011$ – $0.024$ ;  $\beta_{\text{Severe respiratory COVID-19} \rightarrow \text{WC}} = 0.007$ , 95% CI =  $-0.012$ – $0.027$ ;  $\beta_{\text{Severe respiratory COVID-19} \rightarrow \text{HIP}} = 0.007$ , 95% CI =  $-0.013$ – $0.028$ ;  $\beta_{\text{Severe respiratory COVID-19} \rightarrow \text{BMI-adjusted HIP}} = 0.004$ , 95% CI =  $-0.028$ – $0.018$ ;  $\beta_{\text{Severe respiratory COVID-19} \rightarrow \text{Income}} = 0.006$ , 95% CI =  $-0.004$ – $0.016$ ;  $\beta_{\text{Hospitalized COVID-19} \rightarrow \text{BMI}} = 0.007$ , 95% CI =  $-0.017$ – $0.032$ ;  $\beta_{\text{Hospitalized COVID-19} \rightarrow \text{WC}} = 0.003$ , 95% CI =  $-0.02$ – $0.031$ ;  $\beta_{\text{Hospitalized COVID-19} \rightarrow \text{HIP}} = 0.001$ , 95% CI =  $-0.017$ – $0.040$ ;  $\beta_{\text{Hospitalized COVID-19} \rightarrow \text{Income}} = 0.009$ , 95% CI =  $-0.008$ – $0.026$ ;  $\beta_{\text{COVID-19 Infection} \rightarrow \text{BMI}} = 0.015$ , 95% CI =  $-0.053$ – $0.083$ ;  $\beta_{\text{COVID-19 Infection} \rightarrow \text{WC}} = 0.016$ , 95% CI =  $-0.057$ – $0.090$ ; Supplementary Table S4 and Supplementary Figures S7–S9, available as Supplementary data at *IJE* online). For the MR tests evaluating the effect of COVID-19 on anthropometric traits using genome-wide significant variants, the F-statistic ranged from 90.16 to 125.37, and  $R^2$  ranged from 0.002 to 0.12 (Supplementary Table S3, available as Supplementary data at *IJE* online). The overlap of the LD-independent SNPs associated with the COVID-19 phenotypes using genome-wide significant variants is shown in Supplementary Figure S6 (available as Supplementary data at *IJE* online).

In the MR analysis based on suggestive variants (all LD-independent variants available from the top 10 000 variants released from the COVID HGI meta-analysis including 23andMe data), the leave-one-out tests indicated the presence of major outliers. After their removal, we found no evidence of a possible causal effect of COVID-19 on anthropometric traits for most of the tested associations (Supplementary Figures S11 and S13, available as Supplementary data at *IJE* online) except for an effect of genetically determined hospitalized COVID-19 on HIP ( $\beta = 0.02$ , 95% CI =  $0.01$ – $0.04$ ,  $P = 0.002$ ; Supplementary Figure S12, available as Supplementary data at *IJE* online). However, the effect size is much smaller than that observed in the reverse direction ( $\beta_{\text{Hospitalized COVID-19} \rightarrow \text{HIP}} = 0.02$  vs  $\beta_{\text{HIP} \rightarrow \text{Hospitalized COVID-19}} = 0.21$ ). Additionally, we found evidence of strong heterogeneity within the genetic instruments evaluated that decreased after the removal of several outliers identified in the leave-one-out analysis. Since the leave-one-out analysis did not indicate the presence of additional major outliers, we hypothesized that the heterogeneity observed could be the result of the widespread horizontal pleiotropy among the variants included in the genetic instruments. Thus, we re-estimated the effects using the MR-RAPS approach with using squared error loss method ( $I^2$ ) to account for overdispersion (systematic pleiotropy) within the genetic instrument.<sup>37</sup> The result

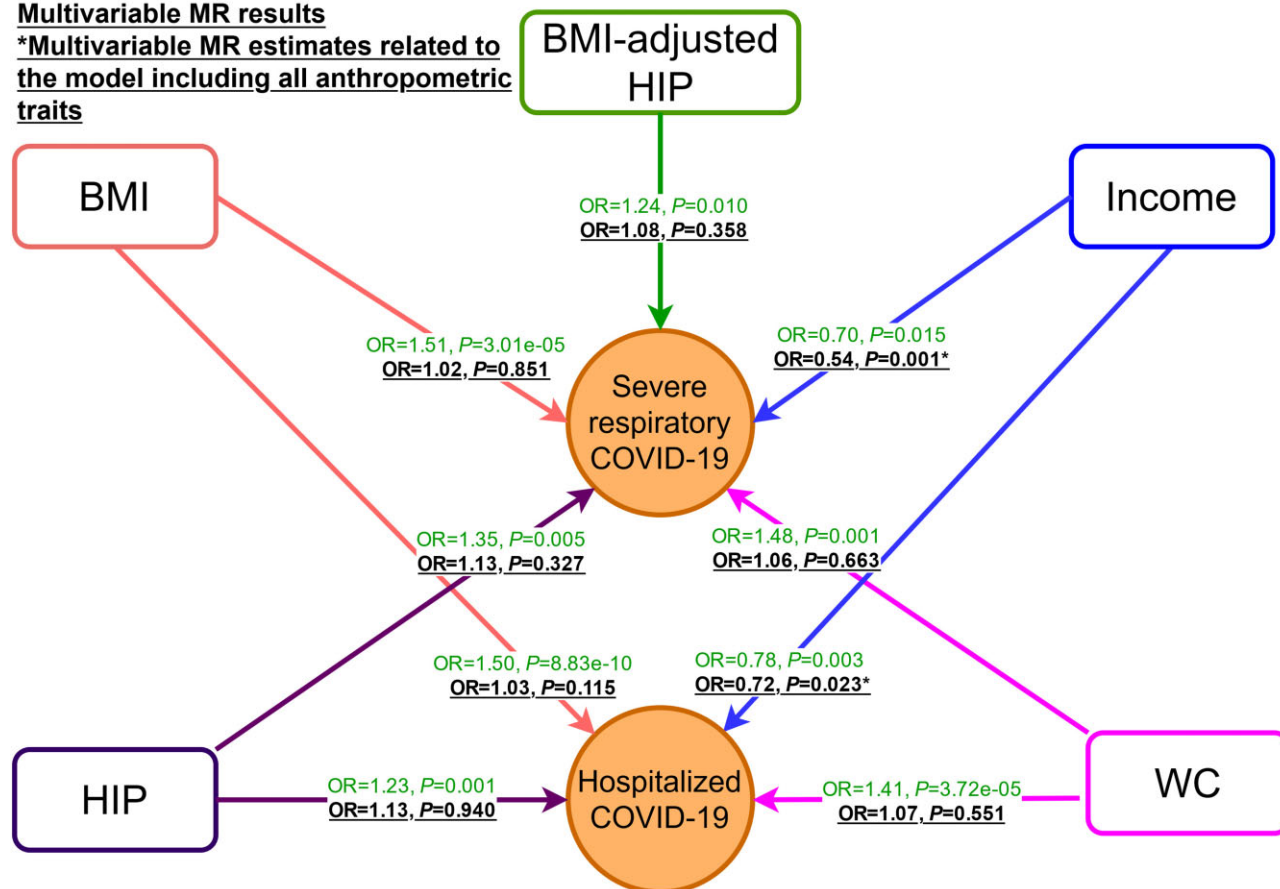
observed was consistent with the IVW estimates ( $\beta = 0.01$ , 95% CI =  $0.004$ – $0.0105$ ,  $P = 0.02$ ) (Supplementary Figure 1 and Supplementary Table S5, available as Supplementary data at *IJE* online). For the MR tests evaluating the effect of COVID-19 on anthropometric traits using suggestive variants, the F-statistic ranged from 11.90 to 20.37, and  $R^2$  ranged from 0.0002 to 0.03 (Supplementary Table S5, available as Supplementary data at *IJE* online). The overlap of the LD-independent SNPs associated with the COVID-19 phenotypes using suggestive variants is shown in Supplementary Figure S10 (available as Supplementary data at *IJE* online).

To test whether the effect of anthropometric traits on COVID-19 is independent of SES, we initially verified the reliability of the income genetic instrument using the univariate MR approach. There was a protective effect of income on severe respiratory COVID-19 (OR = 0.70, 95% CI =  $0.53$ – $0.93$ ,  $P = 0.015$ ) and hospitalized COVID-19 (OR = 0.78, 95% CI =  $0.66$ – $0.92$ ,  $P = 0.003$ ; Supplementary Figure S14, available as Supplementary data at *IJE* online). No causal association of income on COVID-19 infection was found (OR = 0.95, 95% CI =  $0.89$ – $1.01$ ,  $P = 0.108$ ). These estimates were not affected by heterogeneity or horizontal pleiotropy (Supplementary Table S6, available as Supplementary data at *IJE* online). These results were consistent with the estimates observed using the COVID-19 HGI Release 5 data based only on individuals of European descent (Supplementary Table S2, available as Supplementary data at *IJE* online). For the MR tests evaluating the effect of income on COVID-19 outcomes, the F-statistic ranged from 40.88 to 41.83, and  $R^2$  ranged from 0.0008 to 0.045 (Supplementary Table S6, available as Supplementary data at *IJE* online).

Because the UK Biobank cohort was included in both income and COVID-19 GWAS, we verified that this sample overlap did not affect the estimates observed. Using COVID-19 HGI meta-analysis excluding the UK Biobank sample, we observed no statistical difference in the effect size of the associations observed with respect to the analyses obtained using the COVID-19 HGI meta-analyses including the UK Biobank sample (Supplementary Table S7, available as Supplementary data at *IJE* online). Neither the MR analysis with genome-wide significant variants nor that with suggestive variants (top 10 000) indicate an effect of COVID-19 phenotypes on income (Supplementary Table S8 and S9 and Supplementary Figures S16 and S17, available as Supplementary data at *IJE* online). For the MR tests evaluating the effect of COVID-19 on income using genome-wide variants, the F-statistic ranged from 81.95 to 89.38, and  $R^2$  ranged from 0.04 to 0.28 (Supplementary Table S8, available as Supplementary data

## Univariable MR results

## Multivariable MR results

**\*Multivariable MR estimates related to the model including all anthropometric traits**

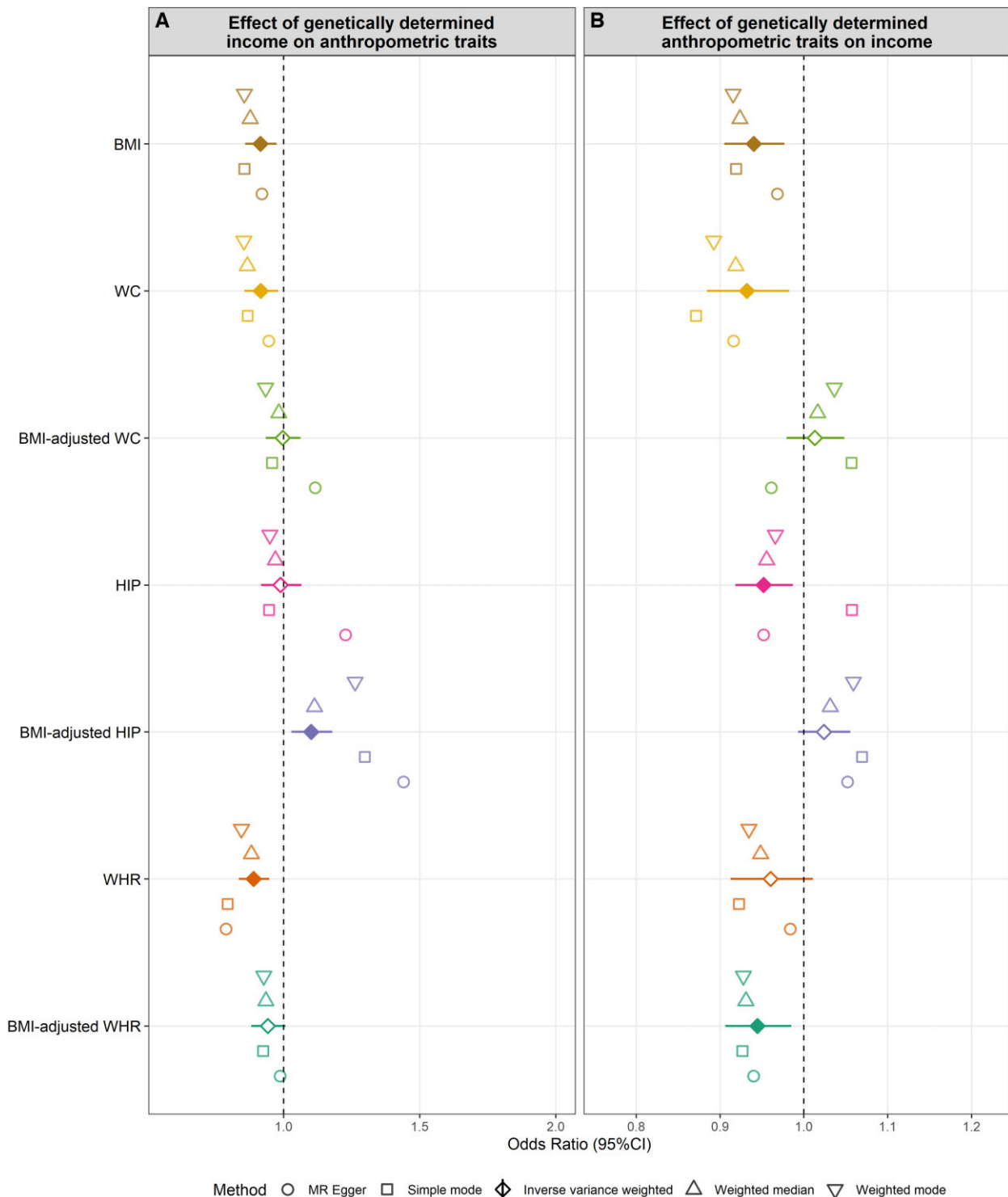
**Figure 2** Multivariable Mendelian randomization (MVMR). Arrows indicate the direction of the effect between the traits. ORs and *P*-values from each association are shown in the middle of the arrows for the univariate MR analysis (regular font) and the MVMR analysis (bold and underlined font). For the anthropometric traits, we report the estimates related to the MVMR model paired with household income (Income; [Supplementary Tables S8 and S9](#), available as [Supplementary data](#) at *IJE* online). For Income, we report the estimate related to the MVMR model including all anthropometric traits with non-null effect in the univariable MR analysis ([Supplementary Table S10](#), available as [Supplementary data](#) at *IJE* online). COVID-19 phenotypes are denoted by circles, whereas anthropometric and socio-economic traits are denoted by rectangles. Income, household income; BMI, body mass index; WC, waist circumference; HIP, hip circumference; OR, odds ratio; *P*, *P*-value.

at *IJE* online), whereas for the MR tests using suggestive variants, the *F*-statistic ranged from 13.78 to 17.29, and  $R^2$  ranged from 0.0001 to 0.001 ([Supplementary Table S9](#), available as [Supplementary data](#) at *IJE* online). The overlap of exposure SNPs using genome-wide and suggestive variants are shown in [Supplementary Figure S15](#) (available as [Supplementary data](#) at *IJE* online).

In the MVMR, the effect of the anthropometric traits on severe respiratory COVID-19 (i.e. BMI and WC) and hospitalized COVID-19 (i.e. BMI, WC and HIP) was null when accounting for the effect of income ([Figure 2](#) and [Supplementary Tables S10 and S11](#), available as [Supplementary data](#) at *IJE* online). Conversely, the effect of income on severe respiratory COVID-19 and hospitalized COVID-19 was not affected when accounting for each anthropometric trait individually and including all anthropometric traits in the same MVMR model ([Supplementary](#)

[Tables S10–S12](#), available as [Supplementary data](#) at *IJE* online). The income genetic instruments did not overlap with those from the anthropometric traits, as shown in [Supplementary Figures S18 and S19](#) (available as [Supplementary data](#) at *IJE* online).

We found an effect of income on anthropometric traits ([Figure 3A](#), [Supplementary Figure S20](#) and [Supplementary Table S13](#), available as [Supplementary data](#) at *IJE* online). A 1-SD increase in income was associated with lower odds of BMI ( $\text{kg/m}^2$ ; OR = 0.91, 95% CI = 0.86–0.97,  $P = 0.006$ ), WC (cm; OR = 0.91, 95% CI = 0.85–0.98,  $P = 0.012$ ) and WHR (OR = 0.89, 95% CI = 0.83–0.94,  $P = 0.0002$ ). Also, we found evidence of a positive effect of income on BMI-adjusted HIP (cm; OR = 1.10, 95% CI = 1.02–1.17,  $P = 0.006$ ). For the MR tests evaluating the effect of income on anthropometric traits, the *F*-statistic ranged from 39.70 to 41.77, and  $R^2$  ranged from 0.002



**Figure 3** Results of the Mendelian randomization (MR) analysis testing the effect of genetically determined income on (a) anthropometric traits and (b) vice versa. 95% confidence intervals are reported for the inverse variance weighted estimates. Estimates from secondary MR methods are reported for each MR test. BMI, body mass index; WC, waist circumference; HIP, hip circumference; WHR, waist-hip ratio.

to 0.30 (Supplementary Table S13, available as Supplementary data at *IJE* online).

We found effects of genetically determined anthropometric traits on income (Figure 3B, Supplementary Table

S14 and Supplementary Figure S22, available as Supplementary data at *IJE* online). We found that 1-SD increases in BMI, WC, HIP and BMI-adjusted WHR were associated with lower odds of income (BMI: OR = 0.94,



95% CI = 0.90–0.97,  $P = 0.0015$ ; WC: OR = 0.93, 95% CI = 0.88–0.98,  $P = 0.0008$ ; HIP: OR = 0.95, 95% CI = 0.91–0.98,  $P = 0.007$ ; BMI-adjusted WHR: OR = 0.94, 95% CI = 0.90–0.98,  $P = 0.007$ ). These estimates were not affected by heterogeneity or horizontal pleiotropy (Supplementary Table S14, available as Supplementary data at *IJE* online). For the MR tests evaluating the effect of anthropometric traits on income, the F-statistic ranged from 48.01 to 66.73, and  $R^2$  ranged from 0.001 to 0.59 (Supplementary Table S14, available as Supplementary data at *IJE* online). The overlap of genetic instruments is shown in Supplementary Figure S21 (available as Supplementary data at *IJE* online). There were no differences between the effect size estimates in the bidirectional relationship between income and the anthropometric traits investigated (Supplementary Table S15, available as Supplementary data at *IJE* online).

Through a MVMR analysis, we demonstrated that the effects of the anthropometric traits on income were not independent from each other (BMI: OR = 1.02, 95% CI = 0.85–1.22,  $P = 0.799$ ; WC: OR = 1.32, 95% CI = 0.73–2.40,  $P = 0.347$ ; HIP: OR = 0.71, 95% CI = 0.46–1.11,  $P = 0.14$ ; BMI-adjusted WHR: OR = 0.82, 95% CI = 0.60–1.13,  $P = 0.229$ ; Supplementary Table S16, available as Supplementary data at *IJE* online).

## Discussion

The association of obesity-related traits with COVID-19 outcomes has been confirmed by multiple studies, also including MR analyses that showed putative causal effects of BMI,<sup>9–11,48,49</sup> WC<sup>9,10</sup> and trunk fat ratio.<sup>9</sup> Some of these previous investigations also have included MVMR analyses that highlighted how the effect of these traits on COVID-19 is independent of several cardiometabolic traits and other known risk factors.<sup>9</sup> However, to our knowledge, no study has evaluated whether the effect of obesity-related traits on COVID-19 outcomes is independent of SES. Because of the unprecedented impact of COVID-19 on individuals and society, it is crucial to identify individuals at risk and relevant modifiable factors to reduce COVID-19 morbidity and mortality. Current findings support that traits related to body size should be among the primary targets to prevent COVID-19 severe symptoms.<sup>50</sup> However, there is a well-established relationship between body size variation and SES that may affect the associations observed.<sup>51</sup>

The results of our univariable MR analysis showed positive associations between genetically determined BMI with COVID-19 outcomes. These findings are consistent with previous reports of a causal impact of BMI on severe respiratory and hospitalized COVID-19.<sup>9–11,48,49</sup>

However, our multivariable analysis indicated that these associations are affected by the effect of SES on COVID-19 outcomes. Specifically, whereas the association of obesity-related traits with COVID-19 severity and hospitalization becomes null when accounting for SES, the effect of income on COVID-19 outcomes becomes stronger when accounting for anthropometric traits. With respect to the latter result, we hypothesize that accounting for the effect of anthropometric traits reduces the phenotypic heterogeneity of COVID-19 outcomes, increasing the accuracy of the estimates of the association of income.

Overall, our findings have major public health implications because whereas previous studies highlighted the importance of considering obesity among the risk factors associated with COVID-19 severe outcomes, our results strongly highlight that this evidence should be put in the context of the effect of SES on both body size and COVID-19. The mechanisms by which income is affecting the association between obesity-related anthropometric traits and COVID-19 might be similar to those proposed for other known health outcomes. In general, low-income populations have reduced access to medical care, with subsequent worse health at baseline and lower opportunity to receive adequate treatment to health complications in comparison with high-income groups.<sup>52,53</sup> Finally, these healthcare inequalities are translated into a higher morbidity and mortality risk in communities with a lower household income.<sup>54</sup>

Nevertheless, we observed a bidirectional relationship between income and the anthropometric traits investigated. This suggests a complex interplay between these traits. In this regard, it has been reported that individuals with a lower SES generally have a higher BMI and an increased risk of obesity.<sup>15</sup> There are multiple social and environmental factors contributing to the association between SES and BMI, i.e. economic difficulties, the affordability of energy-dense foods, low dietary quality, poor health literacy, occupational status and lifestyle behaviours, such as low physical activity and sedentary behaviours.<sup>55–60</sup> There is also evidence that obesity-related traits can affect SES via multiple factors that have been previously grouped into three categories:<sup>61</sup> (i) health effects: high BMI increases the risk of several chronic diseases, which could affect work ability and subsequently income;<sup>61,62</sup> (ii) reduced job performance: body shape affects health capital, presenteeism, self-esteem and employment status, which impact income;<sup>63,64</sup> (iii) discrimination from employers.<sup>65,66</sup> Accordingly, there are likely multiple pathways by which income could affect the association between obesity-related traits and COVID-19 outcomes. Although our MVMR analysis clearly shows that the effect of obesity-related traits on COVID-19 outcomes is not

independent of the income effect, the bidirectional relationship between anthropometric traits and income does not permit us to make a hypothesis regarding the temporal relationship between the exposures investigated.

Furthermore, factors influencing both SES and obesity that also act as modulators of their association in both directions have been identified, such as sex, ethnicity, country's income economy and education.<sup>67,68</sup> For example, in developed countries, obesity is more prevalent in individuals with lower SES, whereas in developing countries there is not a clear trend.<sup>67-69</sup> Despite the relevance of the mentioned environmental and social factors, it is important to consider that obesity is a complex multifactorial disease influenced by both environmental and genetic factors, as well as by the interaction between them.<sup>55</sup>

Similarly to obesity, there is evidence of the effect of genetic factors on SES, particularly on income.<sup>30,70-72</sup> The genetic variants associated with a higher income were functionally linked with GABAergic and serotonergic neurotransmission and linked to cognitive abilities.<sup>30</sup> In our genetically-informed study, we found that income had a negative causal effect on both very severe respiratory confirmed COVID-19 and hospitalized COVID-19. Previously, a longitudinal study reported a negative relationship between income and COVID-19 mortality, which might be considered an extreme COVID-19 phenotype.<sup>52</sup> Interestingly, there was no difference in COVID-19 infection rate among the different income groups.<sup>52</sup> Hence, these previous results and ours suggest that income influences only COVID-19 severe phenotypes. Further exploration of the genetic variants involved in this association might provide information on their biological role in the predisposition to COVID-19 complications. The elucidation of the mechanisms will contribute to the design of strategies and/or treatments that could modulate their effect on COVID-19 outcomes. The mechanisms linking the genetic predisposition to obesity and COVID-19 are likely to be multifactorial and warrant clarification in further research.<sup>72</sup>

Overall, the anthropometric traits evaluated here showed a consistent effect on COVID-19 phenotypes. However, this association is not direct and multiple factors might affect these associations, i.e. health behaviours associated with SES such as physical inactivity, diet and tobacco and alcohol use.<sup>73</sup> Although the results of the reverse MR might suggest an effect of genetically predicted COVID-19 phenotypes on anthropometric traits and SES, the effect size is negligible, suggesting a possible residual effect of horizontal pleiotropy. The identification of factors underlying these causal associations will contribute to the design of adequate risk-stratification instruments for patients with COVID-19. Furthermore, it might contribute

on a higher scale to the design of public policies oriented to the prevention of adverse outcomes in vulnerable groups. Although these public policies will not modify the genetic factors involved in the development of severe COVID-19 symptoms, they might impact modifiable risk factors and reduce social inequalities. For example, strategies that improve the access to adequate medical services might lead to the adverse impact of COVID-19 in low-income communities.<sup>52</sup>

The limitations of the present study should be acknowledged. First, this study was conducted using data generated from participants of European descent. Accordingly, the results obtained may not be generalization to populations with other ancestral origins. Further research is necessary to evaluate the effect of anthropometric and socio-economic traits in populations with diverse ancestral backgrounds. Second, we could not evaluate the presence of sex-specific effects as large-scale data sets informative of sex-specific COVID-19 susceptibility are not available at this time. There are known sex differences in the mechanisms underlying the association of SES with body size and composition.<sup>14,74</sup> Therefore, future sex-stratified studies are required to understand the processes linking these traits with COVID-19 outcomes. Third, although we conducted multiple sensitivity analyses, we cannot discard completely the influence of potential confounders in our results. Therefore, complementary studies are needed to confirm and further explore the findings here reported. Also, in this study, we selected income to measure SES as it has shown a higher association with health when adjusted for other SES variables, i.e. education, social class and occupational complexity.<sup>75</sup> Thus, we considered income as a SES dimension particularly relevant for studying health-related associations such as those evaluated in the present study. Furthermore, the income GWAS identified genetic variants that are associated with partly heritable traits (e.g. intelligence, conscientiousness and health outcomes) that are linked to income but do not act directly on it.<sup>76</sup> Future studies will determine the role of other SES dimensions in the association between anthropometric traits and COVID-19 outcomes.

Furthermore, we acknowledge some limitations in the MVMR approach. First, although MR estimates mostly represent the lifetime effect of the exposure on the outcome, there may be exceptions due to time-varying exposures.<sup>77,78</sup> Specifically, although genetic variants do not vary over an individual's lifetime, variation could arise from different genetic variants having different levels of importance in the development of the exposure at different times.<sup>77,78</sup> Second, whereas an interaction between the two exposures does not affect the direct effects of the exposure included in the MVMR model, an interaction between

exposure can affect MVMR models investigating possible mediation pathways.<sup>79</sup> We observed a bidirectional relationship between income and anthropometric traits. Thus, we cannot discard the presence of an interplay between income and anthropometric traits. Further studies are required to investigate the pathways underlying the association of SES and obesity-related traits with COVID-19 outcomes.

In conclusion, we provide the first evidence that the relationship of obesity-related anthropometric traits with COVID-19 outcomes is not independent of SES. This result has major public health implications because it supports that preventive strategies targeting body size and composition to reduce COVID-19 morbidity and mortality may not be effective if they are not considered in the context of SES.

### Ethics approval

This study was conducted using genome-wide association statistics generated by previous studies. Owing to the use of previously collected, de-identified, aggregated data, this study did not require institutional review board approval.

### Data availability

The data sets used in this study are available on the GIANT consortium website ([http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT\\_consortium](http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium)), the COVID-19 Host Genetics Initiative website (<https://www.covid19hg.org/>) and the UK Biobank website (<https://www.ukbiobank.ac.uk/>). All data discussed in this study are provided in the article and in the [Supplementary material](#).

### Supplementary data

[Supplementary data](#) are available at *IJE* online.

### Author contributions

B.C.M. and R.P. participated in the concept and design of the study, statistical analysis and drafting of the manuscript, and have verified the underlying data. B.C.M., F.R.W., G.A.P., F.D.A., A.D.L., D.K. and R.P. participated in the acquisition, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. F.R.W., D.K. and R.P. obtained the funding for this study. F.R.W., G.A.P., F.D.A., A.D.L., D.K. and R.P. provided the administrative, technical and material support for this study. R.P. supervised the present study. All the authors revised and approved the final version of this manuscript.

### Funding

This work was supported by the National Institutes of Health (R21 DC018098, R33 DA047527, F32 MH122058) and the European

Commission (H2020 Marie Skłodowska-Curie Individual Fellowship 101028810).

### Acknowledgements

We thank study participants and research groups contributing to the GIANT consortium, UK Biobank and the COVID-19 HGI for making their data available.

### Conflict of interest

None declared.

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