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Association of obesity and its genetic predisposition with the risk of severe COVID-19: Analysis of population-based cohort data

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Objective: We aimed to examine the associations of obesity-related traits (body mass index [BMI], central obesity) and their genetic predisposition with the risk of developing severe COVID-19 in a population-based data. Research design and methods: We analyzed data from 489,769 adults enrolled in the UK Biobank—a population-based cohort study. The exposures of interest are BMI categories and central obesity (e.g., larger waist circumference). Using genome-wide genotyping data, we also computed polygenic risk scores (PRSs) that represent an individual’s overall genetic risk for each obesity trait. The outcome was severe COVID-19, defined by hospitalization for laboratory-confirmed COVID-19. Results: Of 489,769 individuals, 33% were normal weight (BMI, 18.5–24.9 kg/m²), 43% overweight (25.0–29.9 kg/m²), and 24% obese (≥30.0 kg/m²). The UK Biobank identified 641 patients with severe COVID-19. Compared to adults with normal weight, those with a higher BMI had a dose-response increases in the risk of severe COVID-19, with the following adjusted ORs: for 25.0–29.9 kg/m², 1.40 (95%CI 1.14–1.73; P = 0.002); for 30.0–34.9 kg/m², 1.73 (95%CI 1.36–2.20; P < 0.001); for 35.0–39.9 kg/m², 2.82 (95%CI 2.08–3.83; P < 0.001); and for ≥40.0 kg/m², 3.30 (95%CI 2.17–5.03; P < 0.001). Likewise, central obesity was associated with significantly higher risk of severe COVID-19 (P < 0.001). Furthermore, larger PRS for BMI was associated with higher risk of outcome (adjusted OR per BMI PRS Z-score 1.14, 95%CI 1.05–1.24; P = 0.004).

Conclusions: In this large population-based cohort, individuals with more-severe obesity, central obesity, or genetic predisposition for obesity are at higher risk of developing severe-COVID-19.

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1. Introduction

Coronavirus disease 2019 (COVID-19), the infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global pandemic. Its severity varies widely, ranging from asymptomatic to fatal [1]. The accurate identification of risk factors and mechanisms for severe illness is critical for the development of effective prevention, risk-stratification, and treatment strategies. Emerging evidence has described several risk factors (e.g., older age, cardiovascular disease, chronic lung disease) for COVID-19 severity and mortality [1–3]. Concurrently, the world has been in the midst of obesity epidemic [4]. The Centers for Disease Control and Prevention (CDC) list severe obesity (body mass index [BMI] of ≥40 kg/m²) as a risk factor for severe illness from COVID-19 [5]. This is consistent with evidence that obesity increases susceptibility to severe respiratory infections [6,7] and worsens outcomes of acute respiratory distress syndrome (ARDS) [8]. Additionally, retrospective studies—either single-center [9–17] or single-health system [3,18] have reported associations between obesity and higher severity of illness. Despite the clinical and research significance, no study has examined the relationship of obesity—let alone of its related traits (e.g., central obesity) and their genetic factors—with severe COVID-19.

To address this major knowledge gap, we analyzed the population-based data of 489,769 individuals to investigate the relationship of obesity and its related traits with the risk of developing severe COVID-19. By using the genome-wide genotyping data, we also examined the
relations of genetic predisposition for obesity with the risk of severe COVID-19. A better understanding of the obesity-COVID-19 relationship, and its mechanisms, should inform strategies to address the collision of these two epidemics.

2. Research design and methods

2.1. Design, setting, and participants

The current study is an analysis of data from the UK Biobank, a population-based cohort study. The complete description of the design, settings, participants, and methods of data measurements in the UK Biobank is described elsewhere [19]. In brief, the UK Biobank enrolled approximately 500,000 adults (aged 40–69 years at enrollment) across the UK in 2006–2010, with an overall aim of permitting detailed investigations of nongenetic and genetic determinants of multiple diseases [19]. Using standardized protocols, the study has collected comprehensive phenotypic information (such as demographics, anthropometric measures [e.g., height, weight, waist and hip circumference] and medical history), tested for biochemical assays, performed genome-wide genotyping, and longitudinally measured health outcomes (e.g., hospitalizations) through linkages to national datasets. All participants provided informed consent to the UK Biobank. The institutional review board of Harvard University and Massachusetts General Hospital approved the current study.

2.2. Exposures

The primary exposure was body mass index (BMI). Based on the CDC’s definition [20], we classified the participants into six mutually exclusive groups: underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), class I obesity (30.0–34.9 kg/m²), class II obesity (35.0–39.9 kg/m²), and class III obesity (>40.0 kg/m² [severe obesity]). The secondary exposures were markers of central obesity, defined by waist circumference (≥102 cm in men and ≥88 cm in women) or waist-to-hip ratio (≥0.90 in men and ≥0.85 in women) [21]. With a standardized procedure (https://www.ukbiobank.ac.uk/about-biobank-uk/), trained investigators of the UK Biobank measured the height using Seca 202 height measure, the weight to the nearest 0.1 kg using Tanita BC-418 MA body composition analyser, and circumferences using Wessex non-stretchable sprung tape measure at an assessment visit.

2.3. Outcome measure

In the current study, we analyzed the first set of the UK Biobank data with laboratory-confirmed COVID-19 status, which were released on April 16, 2020. The data contained the SARS-CoV-2 polymerase chain reaction results in hospitalized participants from March 16, 2020 onwards. These hospitalized patients with SARS-CoV-2 infection had “severe COVID-19” [22,23]. The detailed information on released COVID-19 data can be found elsewhere [22].

2.4. Statistical analysis

First, we described the baseline characteristics by BMI status using summary statistics. Second, to visualize the relationship of BMI and two markers of central obesity (i.e., waist circumference and waist-to-hip ratio) with the risk of developing severe COVID-19, we used generalized additive models with penalized cubic regression splines. Third, to investigate the association between BMI categories and the risk of outcome, we constructed unadjusted and adjusted logistic regression models, with the normal weight group being the reference. In the multivariable models, we adjusted for potential confounders (i.e., causes of both exposure and outcome of interest), including age, sex, and race/ethnicity based on clinical plausibility and a priori knowledge [1–3]. The multivariable models did not adjust for obesity-related comorbidities (e.g., cardiovascular disease, diabetes, hypertension) as they were considered intermediate factors in the causal inference of interest [24,25]. Additionally, we repeated the analysis for the two markers of central obesity. To examine the robustness of our inference, we conducted a series of sensitivity analyses. First, to account for the potential effect of socioeconomic status, we constructed multivariable logistic regression models that also adjust for household income. Second, we also repeated the models by adding major obesity-related comorbidities (cardiovascular disease, diabetes, and hypertension) as covariates to examine if adjustment of these intermediate factors attenuates the magnitude of association. Lastly, based on a priori hypotheses, we also stratified the analysis by sex and coexistence of diabetes.

Next, to examine the relationship between the genetic predisposition for obesity traits and the risk of developing severe COVID-19, we computed a polygenic risk score (PRS) for each of three obesity measures—i.e., BMI, BMI-adjusted waist circumference, and BMI-adjusted waist-to-hip ratio, according to prior research [26], using genome-wide genotyping data from the Genetic Investigation of Anthropometric Traits (GIANT) consortium and UK Biobank. PRS is a sum of all risk alleles weighted by the effect size of each variant, thereby representing an individual’s overall genetic risk for obesity (and central obesity). The details of methods used in computation of the PRSs may be found in the Supplemental methods. In brief, we retrieved the genome-wide association study (GWAS) summary statistics of BMI (nmax = 322,154) [27], BMI-adjusted waist circumference (nmax = 231,355) [28], and BMI-adjusted waist-to-hip ratio (nmax = 210,086) [28] from the GIANT consortium data as an independent base dataset. We then applied the LDpred method [29] to compute model coefficients using approximately 1,480,000 single-nucleotide polymorphisms (SNPs), and computed a PRS for each trait in an independent target dataset (n = 459,331) from the UK Biobank. We conducted the genetic analyses restricting to individuals with European ancestry (i.e., white race). Lastly, we investigated the association of derived PRSs with the risk of severe COVID-19 in the UK Biobank by fitting logistic regression models adjusting for age, sex, 30 ancestry principal components (which account for population stratification), and genotyping array. All P values were 2-tailed, with a P < 0.05 considered statistically significant. All analyses were performed using R 4.0.0.

3. Results

3.1. Patient characteristics

The analytic cohort was comprised of 489,769 adults in the UK Biobank. Overall, the median age was 58 (IQR 50–61) years and 55% were female, and 94.5% were white race. Of these, 0.5% were underweight, 33% were normal weight, 43% were overweight, and 24% were obese (17% class I, 5% class II, and 2% class III). The UK Biobank also identified a total of 641 patients with severe COVID-19. The participant characteristics are summarized in Table 1. Compared to the adults with normal weight, those with obesity were more likely to be male, have comorbidities (such as asthma, diabetes, and hypertension), and higher baseline level of C-reactive protein (P < 0.05). BMI was strongly correlated with both waist circumference (ρ = 0.81; P < 0.001) and less strongly correlated with waist-to-hip ratio (ρ = 0.43; P < 0.001).

3.2. Associations of obesity and central obesity with the risk of severe COVID-19

Fig. 1 shows the relationship of BMI and markers of central obesity with the risk of developing severe COVID-19. For example, BMI was positively associated with the risk of severe COVID-19 (unadjusted OR 1.35 per 5 kg/m² increase; 95% CI 1.26–1.43; P < 0.001; Fig. 1A). Likewise, there were positive associations of waist circumference (OR 1.35 for each 10 cm increase; 95% CI 1.28–1.42; P < 0.001; Fig. 1B) and waist-
to-hip ratio (OR 1.59 per 0.1 ratio increase; 95% CI 1.46–1.73; P < 0.001; Fig. 1C) with the risk of outcome.

Compared to adults with normal weight, those with a higher BMI had a dose-response increase in the risk of developing severe COVID-19, with the following ORs: for overweight, 1.55 (95% CI 1.26–1.91; P < 0.001); for class I obesity, 1.92 (95% CI 1.51–2.44; P < 0.001); for class II obesity, 3.06 (95% CI 2.26–4.14; P < 0.001); and for class III obesity, 3.45 (95% CI 2.28–5.21; P < 0.001) (Fig. 2). These association remained significant after adjusting for potential confounders (all P < 0.01). Of note, there was no significant difference in the risk in the overweight group (adjusted OR 2.05; 95%CI 0.76–5.56; P = 0.16).

Likewise, adults with central obesity were at higher risk of severe COVID-19. Indeed, there were significant associations of a larger waist circumference (adjusted OR 1.84; 95% CI 1.57–2.16; P < 0.001) and higher waist-to-hip ratio (adjusted OR 1.79; 95% CI 1.49–2.14; P < 0.001) with the risk of outcome. In the sensitivity analysis adjusting for household income as a measure of socioeconomic status (in addition to age, sex, and race/ethnicity), the inference did not materially change (Table 2). Additionally, as expected, adjusting for major obesity-related comorbidities attenuated the associations of interest (Table 2), suggesting that these covariates served as intermediates in the association of interest.

In the stratified analysis by sex, the BMI-outcome associations were consistent across the strata (Pinteraction = 0.16 indicating no statistically-significant effect modification), except women with class I obesity had a non-significant increase in the risk of severe COVID-19 (adjusted OR, 1.34; 95% CI 0.92–1.93; P = 0.12; Supplemental Table S1). Likewise, there was no clinically-significant between-sex heterogeneity in the associations between the markers of central obesity and the risk of outcome despite their statistical significance. In the stratified analysis by coexistent diabetes, there were consistent results across the strata (Pinteraction = 0.71), while adults with both class III obesity and diabetes appeared to have a larger magnitude of association with a corresponding adjusted OR of 5.43 (95% CI 1.08–27.2; P = 0.04) compared to those without diabetes (adjusted OR of 3.36; 95% CI 2.10–5.39; P < 0.001; Supplemental Table S2). Likewise, adults with both a larger
waist circumference and diabetes appeared to have a larger magnitude of association (adjusted OR 3.02; 95% CI 1.51–6.02; \(P = 0.002\)) compared to those without diabetes (adjusted OR 1.73; 95% CI 1.46–2.04; \(P < 0.001\); \(P_{\text{interaction}} = 0.04\)).

3.3. PRS and the risk of severe COVID-19

To examine the relationship of the individual’s overall genetic risks for obesity and central obesity with the risk of developing severe COVID-19, we examined the associations of the derived PRSs with the outcome risk (Table 3). Individuals with a larger PRS for BMI had a significantly higher risk of outcome in both the unadjusted (OR per PRS Z-score 1.14; 95% CI 1.05–1.24; \(P = 0.003\)) and adjusted (OR 1.14; 95% CI 1.04–1.24; \(P = 0.004\)) models. In addition, the PRSs of BMI-adjusted waist circumference (adjusted OR 1.05; 95% CI 0.96–1.15; \(P = 0.31\)) and BMI-adjusted waist-to-hip ratio (adjusted OR 1.04; 95% CI 0.95–1.14; \(P = 0.40\)) were not significantly associated with the risk, but the direction of effects was consistently positive.

4. Discussion

On the basis of large cohort data, with comprehensive phenotyping and genotyping, we found that adults with more-severe obesity (defined by larger BMI) and those with central obesity (defined either by larger waist circumference or higher waist-to-hip ratio) are at a higher risk for developing severe COVID-19. Further, we also found a significant positive relationship between the individual’s overall genetic risk for BMI—represented by its PRS—and the risk of severe COVID-19, which indicates the role of obesity-related genetics in the pathobiology of illness. Yet, we did not find significant association between PRSs of BMI-adjusted waist circumference or BMI-adjusted waist-to-hip ratio and severe COVID-19 risk, which is possibly due to decreased GWAS power after adjusting BMI. To our knowledge, this is the first analysis of large-scale data that has examined the relationship of BMI, central obesity, and their genetic predisposition with the risk of developing severe COVID-19.

Consistent with these observations, a recent sentinel surveillance of 1482 adults hospitalized with COVID-19 in 14 U.S. states reported that obesity was the second most prevalent underlying condition (48% prevalence), following hypertension [30]. Additionally, retrospective studies—either from single centers [9–16] or health systems [3,18]—have reported associations between obesity and higher morbidity of COVID-19. For example, in a single-center analysis of 389 patients hospitalized for COVID-19 in China, Cai et al. reported patients with obesity (defined by BMI of ≥28 kg/m²) had higher severity of illness [9]. Similarly, in another single-center case-control study of 150 patients hospitalized for
COVID-19 in China, Gao et al. found that patients with obesity (defined by BMI of ≥25 kg/m²) had a longer hospital length-of-stay and higher disease severity [11]. These earlier studies—albeit from different patient populations and settings with varying definitions of obesity and outcomes—collectively indicate that obesity is a risk factor for severe illness from COVID-19. The current study builds on these prior reports, and extends them by demonstrating, in a large cohort, the relations of obesity-related traits (including central obesity) and their genetic predisposition with the risk of developing severe COVID-19.

Fig. 2. Associations of obesity-related traits with risk of developing severe COVID-19 in the UK Biobank. The risk of developing severe COVID-19 was compared between each of the five BMI groups—underweight (<18.5 kg/m²), overweight (25.0–29.9 kg/m²), class I obesity (30.0–34.9 kg/m²), class II obesity (35.0–39.9 kg/m²), and class III obesity (≥40.0 kg/m²)—and the reference (normal weight group [18.5–24.9 kg/m²]). In addition, we also examined the association of markers for central obesity—defined by waist circumference (≥102 cm in men and ≥88 cm in women) and waist-to-hip ratio (0.90 in men and ≥0.85 in women)—with the risk of severe COVID-19. The multivariable logistic regression models adjusted for potential confounders, including patient’s age, sex, and race/ethnicity. Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019.

Table 2
Associations of obesity-related traits with risk of developing severe COVID-19 with adjusting for household income or obesity-related comorbidities in the UK Biobank.

| BMI categories | Number of severe COVID-19, n (%) | Number of participants, n | Odds ratio (95% CI) | P-value |
|----------------|---------------------------------|---------------------------|---------------------|---------|
| Underweight    | 4 (0.2)                         | 2,442                     | 1.97 (0.73 - 5.32)  | 0.18    |
| Normal weight (reference) | 133 (0.1) | 159,591 | Reference |          |
| Overweight     | 269 (0.1)                        | 208,367                   | 1.55 (1.26 - 1.91)  | <0.001  |
| Class I obesity | 137 (0.2) | 85,599 | 1.92 (1.51 - 2.44) | <0.001  |
| Class II obesity | 82 (0.3) | 24,347 | 3.08 (2.26 - 4.14) | <0.001  |
| Class III obesity | 27 (0.3) | 9,423 | 3.45 (2.28 - 5.21) | <0.001  |
| Larger waist circumference | 306 (0.2) | 164,806 | 1.84 (1.57 - 2.15) | <0.001  |
| Higher waist-to-hip ratio | 419 (0.2) | 241,480 | 2.00 (1.70 - 2.36) | <0.001  |

Abbreviations: BMI, body mass index; CI, confidence interval; COVID-19, Coronavirus disease 2019.
Adjusted model 1: the multivariable logistic regression models adjusted for age, sex, and race/ethnicity and household income.
Adjusted model 2: the multivariable logistic regression models adjusted for age, sex, and race/ethnicity, cardiovascular disease, diabetes, and hypertension.
and TH17 pathways, TH1 polarization) [35,36]. Furthermore, research
adiposopathy is characterized by impaired adipogenesis, altered lipid
pulmonary diseases [26,33]. The observed relation between the genetic
pathobiology of complex disease conditions including asthma [34,35].
second, expiratory reserve volume, and functional residual capacity as well as ef-
plexity has hindered efforts to robustly examine the effect of these
(e.g., diet), and behavioral (e.g., physical activity) factors. This com-
plicity has hindered efforts to robustly examine the effect of these
obesity-related factors on various disease conditions, including COVID-19. By contrast, the use of PRS—which captures and summa-
rizes the cumulative effects of many common DNA variants [42]—ef-
rectly captures the obesity-related genetic factors (i.e., well-
defined exposure), and hence potentially enables us to examine its
effects on severe COVID-19 that are independent from the aforemen-
tioned confounders. In addition, conventional research approaches
have evaluated the pathophysiology of obesity with comparison to
lean individuals. Yet, it can be difficult to draw robust inferences
from such research as the observed difference may be attributable ei-
er to a cause or consequence of obesity. In contrast, the use of PRS
for obesity-related traits and careful investigations of individuals at
the extremes of its distribution (even without a clinically-evident
obesity trait) potentially enables us to uncover new causal risk
factors for the development of severe COVID-19 as well as to identify
individuals at risk. For example, research has shown that individuals
free of heart disease with a high PRS for coronary artery disease are
found to have a higher prevalence of coronary risk factors
(e.g., type 2 diabetes, hypertension) [43]. Furthermore, biological
profiling of these individuals at the extremes of obesity-related PRS
distribution may identify molecular pathways that link obesity to se-
vere COVID-19, thereby potentially leading to the development of
novel prevention, prediction, and treatment strategies.

The present study has several potential limitations. First, the UK
Biobank is not a random sample of the entire UK population, while
the study sample consists of socioeconomically- and geographically-
diverse participants [19]. Second, there may have been some misclas-
sification of the exposure and outcome of interest. However, both
were measured using standardized protocols in the UK Biobank
[19,22]. These potential misclassifications were likely independent
of nondifferential measurement errors, thereby biasing our inferences
toward the null [40]. Anthropometric measurements performed at
assessment visits may have not accurately reflected the exposure data at
the COVID-19 inception. Yet, the PRS for BMI—time-invariant genetic
data—was also significantly associated with the risk of developing se-
vere COVID-19. Third, as with any observational study, causal infer-
ence may be confounded by unmeasured factors, such as health
behaviors and access to healthcare. However, the study focused on se-
vere COVID-19 requiring inpatient management, thereby mitigating,
at least partially, this problem. Fourth, information on detailed clinical
parameters and longitudinal outcomes (e.g., post-intensive care syn-
drome) is not yet available in the UK Biobank. Finally, the study sam-
ple consisted mainly of white individuals and we focused on severe
COVID-19. We must cautiously generalize the inferences to other pop-
ulations or patients with mild-to-moderate COVID-19. Nevertheless,
our inferences are directly relevant to hundreds of thousands of pa-
ients hospitalized for COVID-19 [44].

In summary, based on data from a large cohort of 489,769 individ-
uals, we found that adults with more-severe obesity had a signifi-
cantly higher risk of developing severe COVID-19. In addition, these
data also demonstrated that adults with central obesity were at
higher risk of severe COVID-19. Furthermore, we demonstrated a
significant positive relationship between the PRS for BMI—an indi-
vidual’s overall genetic risk for obesity—and the risk of developing
severe COVID-19. These observations should assist clinicians in opti-
mizing risk-stratification among patients with overweight and obe-
sity. Furthermore, our inferences should also facilitate further
investigations into delineating the complex interrelations between
SARS-CoV-2 infection, host genetics and inflammatory response,
and outcomes in patients with obesity.

CRediT authorship contribution statement

Zhaozhong Zhu: conceptualized the study, carried out the main
statistical analysis, drafted the initial manuscript, and approved the
final manuscript as submitted. Kohei Hasegawa: conceptualized and

Table 3
Unadjusted and adjusted associations between obesity polygenic risk scores and risks of severe COVID-19 in the UK Biobank.

| PRS models | Odds ratio | P-value |
|------------|------------|---------|
|            | (95% CI)   |         |
| BMI PRS    |            |         |
| Unadjusted | 1.14 (1.05–1.24) | 0.003 |
| Adjusteda  | 1.14 (1.04–1.24) | 0.004 |
| BMI-adjusted waist circumference PRS | | |
| Unadjusted | 1.05 (0.96–1.14) | 0.31 |
| Adjusteda  | 1.07 (0.98–1.17) | 0.15 |
| BMI-adjusted waist-to-hip ratio PRS | | |
| Unadjusted | 0.99 (0.91–1.08) | 0.84 |
| Adjusteda  | 1.01 (0.92–1.10) | 0.89 |

Abbreviations: BMI, body mass index; CI, confidence interval; PRS, polygenic risk score.

a Odds ratios and 95% CIs (per one Z-score of the corresponding PRS) were estimated by multivariable model adjusting for age, sex, 30 ancestry principal components in the corre-
sponding genome-wide association analysis, and genotyping array.
designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Baoshan Ma: conducted genetics analysis, assisted in data interpretation, critically reviewed and revised the initial manuscript, and approved the final manuscript as submitted. Michimasa Fujisugi: assisted in the study design and data interpretation, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. Carlos A. Camargo, Jr. and Liming Liang: conceptualized the study, supervised the conduct of study and the analysis, critically reviewed and revised the initial manuscript, and approved the final manuscript as submitted.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2020.154345.

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