Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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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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ABSTRACT

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/m^2), 43% overweight (25.0–29.9 kg/m^2), and 24% obese (≥30.0 kg/m^2). 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/m^2, 1.40 (95%CI 1.14–1.73; $P = 0.002$); for 30.0–34.9 kg/m^2, 1.73 (95%CI 1.36–2.20; $P < 0.001$); for 35.0–39.9 kg/m^2, 2.82 (95%CI 2.08–3.83; $P < 0.001$); and for ≥40.0 kg/m^2, 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.

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/m^2) 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

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COVID-19, coronavirus disease 2019; PRS, polygenic risk score; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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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/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), class I obesity (30.0–34.9 kg/m^2), class II obesity (35.0–39.9 kg/m^2), and class III obesity (≥40.0 kg/m^2 [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 model, 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 ($n_{max} = 322{,}154$) [27], BMI-adjusted waist circumference ($n_{max} = 231{,}355$) [28], and BMI-adjusted waist-to-hip ratio ($n_{max} = 210{,}086$) [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 50–63) 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 ($\rho = 0.81$; $P < 0.001$) and less strongly correlated with waist-to-hip ratio ($\rho = 0.43$; $P < 0.001$).

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/m^2 increase; 95% CI 1.26–1.45; $P < 0.001$; 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-

Table 1
Baseline characteristics in 489,769 UK Biobank participants.

	Underweight (n = 2442; 0.5%)		Normal (n = 159,591; 32.6%)		Overweight (n = 208,367; 42.5%)		Obesity classes I–III (n = 119,369; 24.4%)		P-value
Demographics									
Age (year), median (IQR)	56	(48–62)	56	(49–62)	58	(51–64)	58	(51–63)	<0.001
Female	1975	(80.9)	104,260	(65.3)	98,417	(47.2)	63,154	(52.9)	<0.001
Race/ethnicity									<0.001
White	2262	(92.6)	151,116	(94.7)	196,343	(94.2)	111,488	(93.4)	
Asian or Asian British	55	(2.3)	3066	(1.9)	4353	(2.1)	2050	(1.7)	
Black or Black British	10	(0.4)	1484	(0.9)	3240	(1.6)	3136	(2.6)	
Mixed	24	(1.0)	1023	(0.6)	1126	(0.5)	723	(0.6)	
Chinese	35	(1.4)	957	(0.6)	463	(0.2)	88	(0.1)	
Other groups	36	(1.5)	1294	(0.8)	1878	(0.9)	1214	(1.0)	
Anthropometric measurements									
Waist circumference (cm), mean (SD)	66	(5.7)	79	(8.1)	91	(8.4)	105	(11.0)	<0.001
Hip circumference (cm), mean (SD)	87	(4.3)	96	(4.8)	103	(4.9)	114	(9.2)	<0.001
Waist-to-hip ratio, mean (SD)	0.77	(0.06)	0.82	(0.07)	0.88	(0.08)	0.92	(0.09)	<0.001
Smoking status									<0.001
Never	1453	(59.5)	95,065	(59.6)	112,330	(53.9)	61,426	(51.5)	
Previous	502	(20.6)	46,759	(29.3)	74,410	(35.7)	45,995	(38.5)	
Current	475	(19.5)	17,160	(10.8)	20,563	(9.9)	11,158	(9.4)	
Total annual household income (£)									<0.001
≤18,000	583	(24.4)	26,107	(16.5)	38,218	(18.5)	27,786	(23.6)	
18,000 to 30,999	474	(19.8)	33,307	(21.1)	45,529	(22.1)	26,311	(22.3)	
31,000 to 51,999	484	(20.2)	36,345	(23.0)	47,371	(23.0)	24,899	(21.1)	
52,000 to 100,000	335	(14.0)	30,992	(19.6)	36,881	(17.9)	17,200	(14.6)	
≥100,000	115	(4.8)	9285	(5.9)	9690	(4.7)	3649	(3.1)	
Do not know	134	(5.6)	6447	(4.1)	7974	(3.9)	5842	(5.0)	
Prefer not to answer	267	(11.2)	15,511	(9.8)	20,559	(10.0)	12,112	(10.3)	
Comorbidities									
Asthma	309	(12.7)	18,534	(11.6)	26,421	(12.7)	19,962	(16.7)	<0.001
Diabetes	31	(1.3)	2980	(1.9)	8704	(4.2)	13,444	(11.3)	<0.001
Cardiovascular disease	237	(9.7)	14,659	(9.2)	28,376	(13.6)	22,588	(18.9)	<0.001
Coronary artery disease	36	(1.6)	3371	(2.2)	8982	(4.5)	8132	(7.1)	
Chronic kidney disease	23	(0.9)	910	(0.6)	2008	(1.0)	2255	(1.9)	<0.001
Chronic obstructive pulmonary disease	78	(3.2)	1851	(1.2)	2801	(1.3)	3016	(2.5)	<0.001
Hypertension	273	(11.2)	24,189	(15.2)	55,741	(26.8)	50,893	(42.6)	<0.001
Stroke	18	(0.7)	1449	(0.9)	2852	(1.4)	2469	(2.1)	<0.001
Blood test at assessment visit									
Fasting glucose (mg/dL), mean (SD)	88.2	(17.1)	89.1	(16.6)	91.6	(20.0)	97.4	(30.1)	<0.001
HbA1c (mmol/mol), mean (SD)	34.9	(4.7)	34.7	(4.8)	35.8	(6.1)	38.5	(8.9)	<0.001
HbA1c (%), mean (SD)	5.4	(0.4)	5.3	(0.4)	5.4	(0.6)	5.7	(0.8)	<0.001
Total cholesterol (mg/dL), mean (SD)	215.0	(41.0)	220.4	(41.8)	222.7	(44.5)	216.2	(46.4)	<0.001
HDL-Cholesterol (mg/dL), mean (SD)	70.4	(17.0)	62.6	(15.1)	54.5	(13.5)	49.5	(12.0)	<0.001
LDL-Cholesterol (mg/dL), mean (SD)	125.7	(29.8)	135.0	(31.7)	140.4	(34.0)	137.3	(35.2)	<0.001
Triglycerides (mg/dL), mean (SD)	93.9	(46.9)	119.6	(65.5)	162.1	(91.2)	189.5	(103.6)	<0.001
C-reactive protein (mg/L), mean (SD)	1.4	(4.5)	1.7	(3.7)	2.4	(4.0)	4.1	(5.0)	<0.001
Insulin-like growth factor-1 (nmol/L), mean (SD)	20.0	(5.5)	21.9	(5.6)	21.8	(5.6)	20.2	(5.8)	<0.001
Pulmonary function test at assessment visit									
FEV_1 (L/s), mean (SD)	2.56	(0.66)	2.84	(0.74)	2.91	(0.78)	2.72	(0.75)	<0.001
FVC (L), mean (SD)	3.41	(0.82)	3.76	(0.96)	3.82	(0.99)	3.52	(0.95)	<0.001
FEV1/FVC ratio, mean (SD)	0.75	(0.09)	0.76	(0.06)	0.76	(0.06)	0.77	(0.06)	<0.001
SARS-CoV-2 PCR test during hospitalization, positive	4	(0.2)	133	(0.1)	269	(0.1)	226	(0.2)	<0.001

Data are n (%) of participants unless otherwise indicated. Percentages may not equal 100, because of missingness.

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, OR 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 underweight 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 ($P_{interaction} = 0.16$ 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 ($P_{interaction} = 0.71$), 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

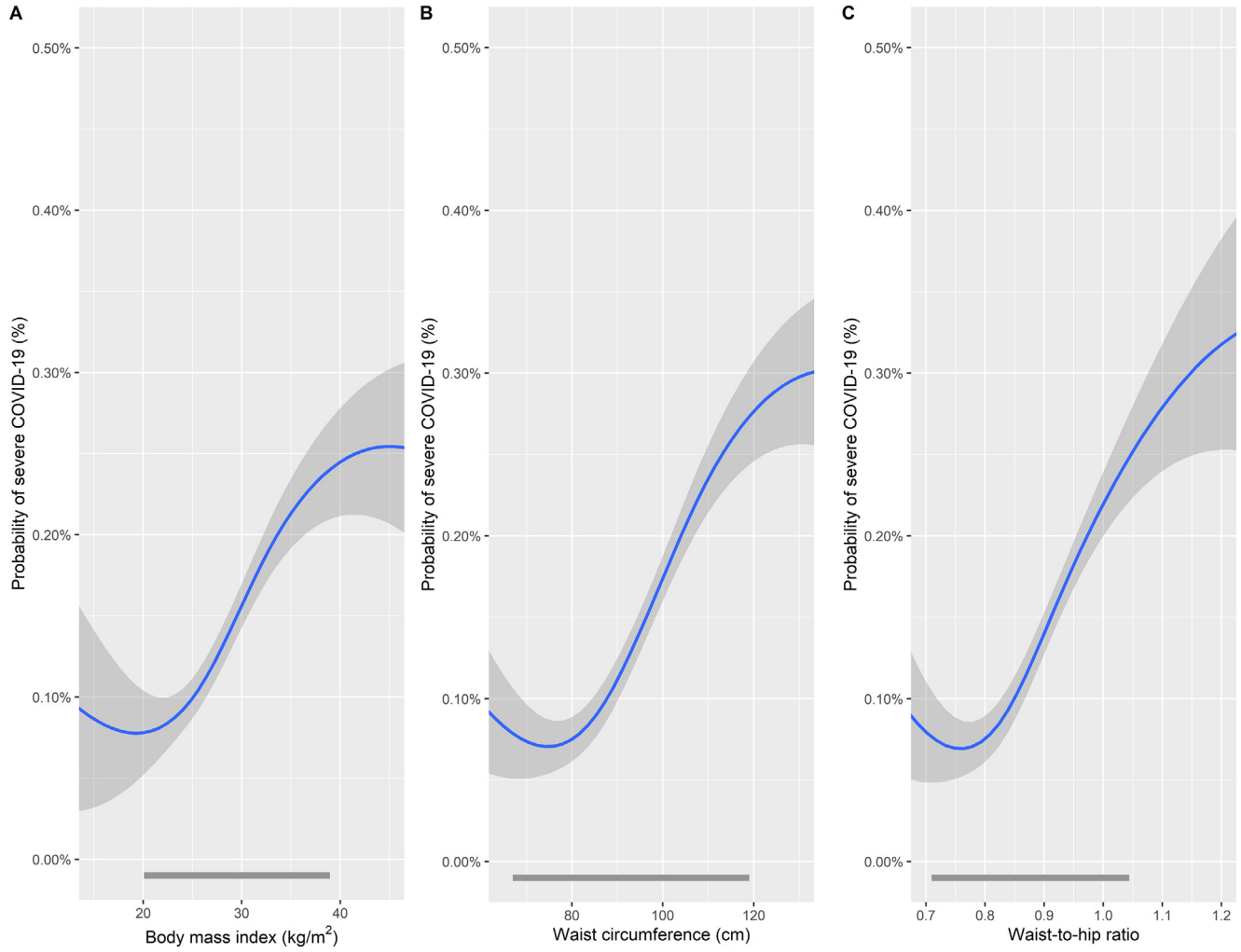

Fig. 1. Relationships of body mass index, waist circumference, and waist-to-hip ratio with risk of developing severe COVID-19 in the UK Biobank. The fitted lines represent smoothed curves—using a generalized additive model with penalized cubic regression splines—with 95% CI for the three obesity-related traits: A) BMI: There was a positive relationship of BMI with the risk of developing severe COVID-19. B) Waist circumference: Likewise, there was a positive relationship of waist circumference with the risk of outcome. C) Waist-to-hip ratio: Similarly, there was a positive relationship of waist-to-hip ratio with the risk of outcome. The grey bars in the bottom represent the range in which 95% of corresponding data are present. Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019.

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; $P < 0.001$; $P_{interaction} = 0.04$).

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/m^2) had higher severity of illness [9]. Similarly, in another single-center case-control study of 150 patients hospitalized for

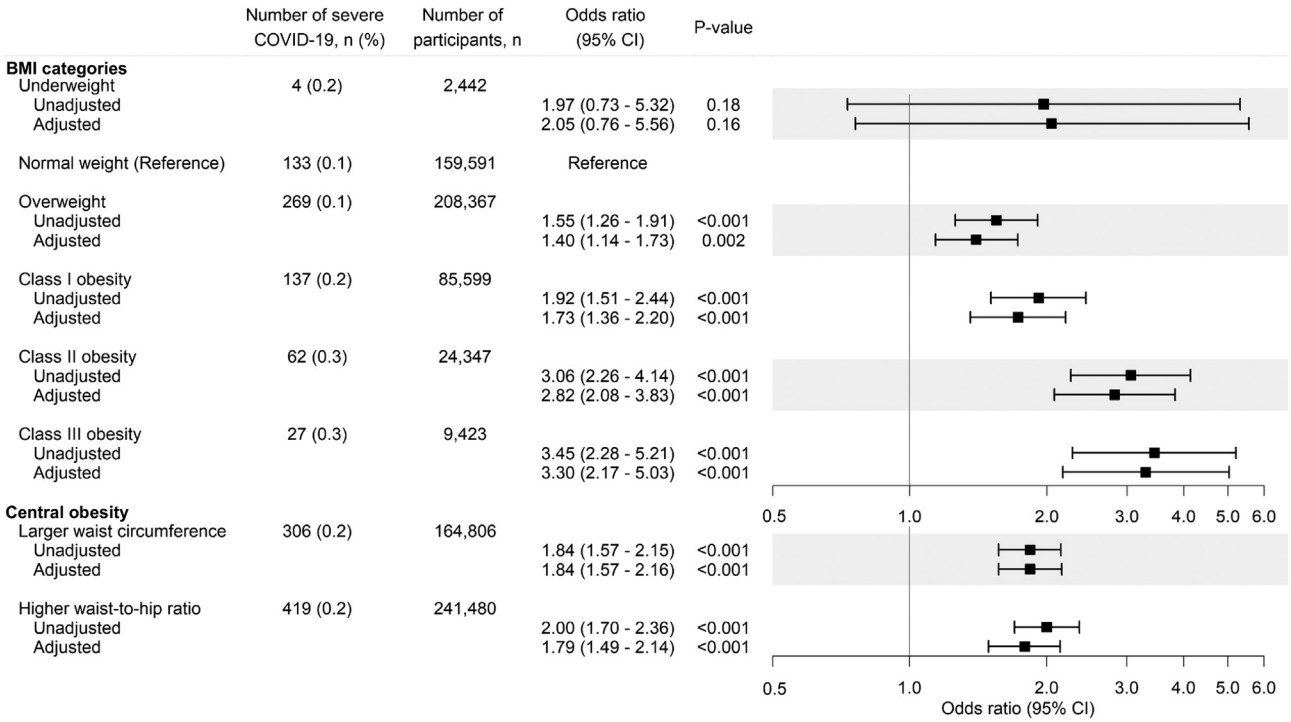

Fig. 2. Associations of obesity-related traits with risk of developing severe COVID-19 in the UK Biobank. The risk of developing severe COVID-19 was compared between each of the five BMI groups—underweight (<18.5 kg/m^2), overweight (25.0–29.9 kg/m^2), class I obesity (30.0–34.9 kg/m^2), class II obesity (35.0–39.9 kg/m^2), and class III obesity (≥40.0 kg/m^2)—and the reference (normal weight group [18.5–24.9 kg/m^2]). 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.

COVID-19 in China, Gao et al. found that patients with obesity (defined by BMI of ≥25 kg/m^2) 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.

The exact mechanisms linking the observed obesity (and its genetic predisposition) to severe COVID-19 are likely multifactorial—which stem from obesity-related changes in pulmonary physiology and the

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.

	Number of severe COVID-19, n (%)	Number of participants, n	Odds ratio (95% CI)	P-value
BMI categories				
Underweight	4 (0.2)	2442		
Adjusted model 1			1.19 (−0.20–2.59)	0.80
Adjusted model 2			2.99 (0.98–5.00)	0.28
Normal weight (reference)	133 (0.1)	159,591	Reference	–
Overweight	269 (0.1)	208,367		
Adjusted model 1			1.40 (1.17–1.62)	0.004
Adjusted model 2			1.13 (0.66–1.60)	0.62
Class I obesity	137 (0.2)	85,599		
Adjusted model 1			1.62 (1.35–1.89)	<0.001
Adjusted model 2			1.08 (0.55–1.61)	0.78
Class II obesity	62 (0.3)	24,347		
Adjusted model 1			2.63 (2.29–2.97)	<0.001
Adjusted model 2			1.88 (1.26–2.51)	0.05
Class III obesity	27 (0.3)	9423		
Adjusted model 1			3.08 (2.62–3.55)	<0.001
Adjusted model 2			1.22 (0.23–2.21)	0.69
Central obesity				
Larger waist circumference	306 (0.2)	164,806		
Adjusted model 1			1.71 (1.51–1.91)	<0.001
Adjusted model 2			1.64 (1.20–2.08)	0.03
Higher waist-to-hip ratio	419 (0.2)	241,480		
Adjusted model 1			1.82 (1.64–1.99)	<0.001
Adjusted model 2			1.25 (0.91–1.59)	0.20

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.

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 (95% CI)	P-value
BMI PRS		
Unadjusted	1.14 (1.05–1.24)	0.003
Adjusted[a]	1.14 (1.04–1.24)	0.004
BMI-adjusted waist circumference PRS		
Unadjusted	1.05 (0.96–1.14)	0.31
Adjusted[a]	1.07 (0.98–1.17)	0.15
BMI-adjusted waist-to-hip ratio PRS		
Unadjusted	0.99 (0.91–1.08)	0.84
Adjusted[a]	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 corresponding genome-wide association analysis, and genotyping array.

genetics to alterations in immune response and inflammatory profiles, endothelial dysfunction, and metabolic dysfunction [31]—and warrant clarification. More specifically, severe obesity reduces lung compliance, expiratory reserve volume, and functional residual capacity as well as effectiveness of respiratory muscle, leading to increased respiratory effort, oxygen consumption, and respiratory energy consumption [32]. Second, recent research has shown the role of genetics (e.g., genes related to cell proliferation and inflammatory response) shared between obesity and pulmonary diseases [26,33]. The observed relation between the genetic preposition to obesity and severe COVID-19 also suggest the role of genetics in the pathogenesis of severe COVID-19. Third, emerging evidence suggests the role of adiposopathy—adipose tissue dysfunction—in the pathobiology of complex disease conditions including asthma [34,35]. Adiposopathy is characterized by impaired adipogenesis, altered lipid metabolism, and adipose/systemic inflammation (e.g., upregulated IL-6 and T_H17 pathways, T_H1 polarization) [35,36]. Furthermore, research of obesity and dyslipidemia has suggested "priming" of the lung for ARDS, reflecting activation of not only systemic immune response but lung-resident cells (e.g., alveolar macrophages, endothelial cells) [37]. Fourth, a recent non-COVID-19 study also demonstrated that patients with a higher BMI had higher expression of *ACE2* (the SARS-CoV-2 receptor [38]) in their bronchial epithelium [39], suggesting an increased susceptibility to SARS-CoV-2 infection in patients with obesity. In addition to these potential mechanisms, the literature has documented that obesity—particularly central obesity—is also causally linked to other comorbidities (e.g., cardiovascular disease, diabetes, hypertension) [24,25]. These underlying conditions increase susceptibility to ARDS-related end-organ failure. Lastly, these possibilities are not mutually exclusive. Notwithstanding the complexity, the identification of obesity and its genetic predisposition as a culprit of COVID-19 morbidity is an important finding. Our observations should encourage future research disentangling the complex web of the pathogen, obesity, airway and systemic inflammation, and COVID-19 pathobiology.

The observed relationship between PRS for BMI and risks of severe COVID-19 has several clinical and research implications. First, the simple use of "obesity" as the exposure of causal inference has several important limitations, particularly a potential violation of consistency assumption (one of the major identifiability assumptions in causal inference [40]). Indeed, in most past research, the obesity exposure was ill-defined and had "multiple-versions" while the study exposure needs to be sufficiently well-defined (e.g., an increase in BMI from 30–34.9 kg/m^2 to 35–39.9 kg/m^2 between ages 50 and 55 years) to make a robust causal inference [41]. The use of PRS strengthens the causal inference, such as the causal effects of obesity on severity of COVID-19. Additionally, obesity is a physical representation of a complex interplay between genetic, environmental (e.g., diet), and behavioral (e.g., physical activity) factors. This complexity 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 summarizes the cumulative effects of many common DNA variants [42]—effectively 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 aforementioned 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 either 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 severe 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 misclassification 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 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 severe COVID-19. Third, as with any observational study, causal inference may be confounded by unmeasured factors, such as health behaviors and access to healthcare. However, the study focused on severe 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 syndrome) is not yet available in the UK Biobank. Finally, the study sample consisted mainly of white individuals and we focused on severe COVID-19. We must cautiously generalize the inferences to other populations or patients with mild-to-moderate COVID-19. Nevertheless, our inferences are directly relevant to hundreds of thousands of patients hospitalized for COVID-19 [44].

In summary, based on data from a large cohort of 489,769 individuals, we found that adults with more-severe obesity had a significantly 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 individual's overall genetic risk for obesity—and the risk of developing severe COVID-19. These observations should assist clinicians in optimizing risk-stratification among patients with overweight and obesity. 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

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 Fujiogi:** 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

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