The Journal of Infectious Diseases

MAJOR ARTICLE

Clinical, Immunological, and Virological SARS-CoV-2 Phenotypes in Obese and Nonobese Military Health System Beneficiaries

Nusrat J. Epsi,[1,2] Stephanie A. Richard,[1,2] Eric D. Laing,[3] Anthony C. Fries,[4] Eugene Millar,[1,2] Mark P. Simons,[1] Caroline English,[1,2] Christopher J. Colombo,[5,6] Rhonda E. Colombo,[1,2,5] David A. Lindholm,[7] Anuradha Ganesan,[1,2,8] Ryan C. Maves,[9] Nikhil Huprikar,[8] Derek Larson,[10] Katrin Mende,[1,2,7] Sharon W. Chi,[1,2,11] Cristian Madar,[11] Tahaniyat Lalani,[1,2,12] Christopher C. Broder,[3] David Tribble,[1] Brian K. Agan,[1,2] Timothy H. Burgess,[1] and Simon D. Pollett,[1,2]; for the EPICC COVID-19 Cohort Study Group

[1]Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, [2]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc, Bethesda, Maryland, USA, [3]Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, [4]US Air Force School of Aerospace Medicine, Dayton, Ohio, USA, [5]Madigan Army Medical Center, Joint Base Lewis McChord, Tacoma, Washington, USA, [6]Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, [7]Brooke Army Medical Center, Fort Sam Houston, Texas, USA, [8]Walter Reed National Military Medical Center, Bethesda, Maryland, USA, [9]Naval Medical Center San Diego, San Diego, California, USA, [10]Fort Belvoir Community Hospital, Fort Belvoir, Virginia, USA, [11]Tripler Army Medical Center, Honolulu, Hawaii, USA, and [12]Naval Medical Center Portsmouth, Portsmouth, Virginia, USA

(See the Editorial Commentary by Lewis et al, on pages 1449–51.)

Background. The mechanisms underlying the association between obesity and coronavirus disease 2019 (COVID-19) severity remain unclear. After verifying that obesity was a correlate of severe COVID-19 in US Military Health System (MHS) beneficiaries, we compared immunological and virological phenotypes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in both obese and nonobese participants.

Methods. COVID-19–infected MHS beneficiaries were enrolled, and anthropometric, clinical, and demographic data were collected. We compared the SARS-CoV-2 peak IgG humoral response and reverse-transcription polymerase chain reaction viral load in obese and nonobese patients, stratified by hospitalization, utilizing logistic regression models.

Results. Data from 511 COVID-19 patients were analyzed, among whom 24% were obese and 14% severely obese. Obesity was independently associated with hospitalization (adjusted odds ratio [aOR], 1.91; 95% confidence interval [CI], 1.15–3.18) and need for oxygen therapy (aOR, 3.39; 95% CI, 1.61–7.11). In outpatients, severely obese had a $\log_{10}$ (1.89) higher nucleocapsid (N1) genome equivalents (GE)/reaction and $\log_{10}$ (2.62) higher N2 GE/reaction than nonobese ($P = 0.03$ and $P < .001$, respectively). We noted a correlation between body mass index and peak anti-spike protein IgG in inpatients and outpatients (coefficient = 5.48, $P < .001$).

Conclusions. Obesity is a strong correlate of COVID-19 severity in MHS beneficiaries. These findings offer new pathophysiological insights into the relationship between obesity and COVID-19 severity.

Keywords. COVID-19 severity; obesity; viral load; antibody response.

Worldwide, nearly 114 million people have been infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and more than 2.5 million people have died from coronavirus disease 2019 (COVID-19) [1]. Manifestations of COVID-19 vary widely, from asymptomatic infection to critical illness. Increased disease severity has been associated with age, race, and medical comorbidities such as diabetes, hypertension, asthma, chronic kidney disease, cancer, and neurological disease [2–9].

Many studies have reported that obesity is one of the strongest risk factors for severe COVID-19 and mortality. Early in the pandemic, investigators in Wuhan, China reported that each 1-unit increase in body mass index (BMI; kg/m^2) was associated with a 12% increase in the risk of severe COVID-19, and obesity was associated with a 3-fold increase in risk of severe COVID-19 compared with nonobesity [10]. A French study reported that, among 124 patients admitted to an intensive care unit for COVID-19, 69% were obese or severely obese [11]. Obesity is associated with complex interactions between genetic, behavioral, metabolic, hormonal, and environmental influences. Obesity is known to be a risk factor for conditions associated with severe COVID-19 (eg, diabetes [12, 13], cardiovascular disease [14, 15], cancer [16–18], and other causes of mortality [19]). Determining the independent effect of obesity on COVID-19 severity requires consideration of these

Received 3 May 2021; editorial decision 13 July 2021; accepted 30 July 2021; published online July 31, 2021.

Correspondence: Simon Pollett, MBBS, 6720A Rockledge Drive, Suite 250, Bethesda, MD 20817 (spollett@idcrp.org).

The Journal of Infectious Diseases® 2021;224:1462–72

https://doi.org/10.1093/infdis/jiab396

comorbidities, which may act as confounders or mediators of this relationship [11, 20–22].

The mechanisms of this association between obesity and severe COVID-19 remain unclear and are likely multifactorial. Obesity-related impairments in cardiovascular, respiratory, metabolic, and thrombotic pathways may decrease a given patient's physiologic reserve and ability to recover from COVID-19 [23]. Obese individuals may have amplified or dysregulated immune responses that lead to greater viral replication, which may potentiate inflammatory immune responses [24–26]. In addition, obesity has been associated with a higher level of angiotensin-converting enzyme 2 (ACE2) receptor expression [27, 28], the membrane-bound host cell protein that mediates SARS-CoV-2 attachment and entry. Some posit that this difference in ACE2 receptor expression may potentially lead to higher SARS-CoV-2 viral loads among obese individuals [25, 26].

It remains unclear whether the association between obesity and COVID-19 severity is due to an individual's putative increased viremia, an aberrant immune response, related comorbidities, or other, yet to be identified, risk factors. Therefore, we leveraged a prospective cohort of 511 Military Health System (MHS) beneficiaries with documented anthropometry and extensively characterized SARS-CoV-2 infection. Clinical and demographic data were collected through prospective methods, and for some participants anthropometry data were collected through routinely collected MHS electronic medical report (EMR). We evaluated whether obesity was independently associated with COVID-19 severity after adjusting for a wide range of covariates, particularly obesity-related comorbidities. Additionally, we compared the SARS-CoV-2 humoral responses in those with and without obesity, adjusted for clinical severity. Finally, we compared sampling-time–adjusted peak SARS-CoV-2 viral load by BMI strata. Collectively, this study clarifies the prognostic associations of obesity and SARS-CoV-2 infection outcomes in MHS beneficiaries, a population characterized by a high prevalence of obesity, and offers new insights into the possible mechanisms underlying the association of obesity and severe COVID-19 [29–31].

METHODS

Population and Setting

The Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study is a longitudinal cohort study conducted in 7 military treatment facilities (Brooke Army Medical Center, Fort Belvoir Community Hospital, Madigan Army Medical Center, Naval Medical Center Portsmouth, Naval Medical Center San Diego, Tripler Army Medical Center, and Walter Reed National Military Medical Center) [32]. Briefly, the EPICC study enrolled participants who were eligible for health care within the MHS and who met 1 of the following criteria: (1) confirmed SARS-CoV-2 infection; (2) COVID-like illness; or (3) high risk of developing COVID-19 due to a recent exposure. Demographic and clinical data were collected at enrollment and periodically during follow-up. Upper respiratory tract swabs were collected on a weekly basis (including day 0 and day 3) for inpatients during hospitalization (and day 14 if discharged), and on days 0 and 14 postenrollment for outpatients. Sera were collected at the same time points plus at 28 days and 6 months for inpatients, and 7 days, 28 days, and 6 months postenrollment for outpatients. Additional clinical records pertaining to hospitalization were reviewed in the MHS EMR. We excluded from the analysis those participants with negative SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) tests (n = 101) and those for whom we did not have height and weight data. In addition, children (aged < 18 years) were excluded from the analysis due to the small number (n = 19) enrolled in the study and the qualitatively different categorization of obesity in pediatric populations (Supplementary Figure 1).

Diagnosis of SARS-CoV-2 Infection and Case Definition

SARS-CoV-2 infection was diagnosed by (1) SARS-CoV-2 RT-PCR of clinical specimens (results from swabs taken at the time of initial diagnosis, retrieved from the MHS electronic medical record and with a range of diagnostic platforms used); (2) SARS-CoV-2 RT-PCR on research specimens (nasopharyngeal, oropharyngeal, nasal, and rectal swabs) collected within 17 days after symptom onset [33–35]; and (3) serological testing, which detects resolving or prior SARS-CoV-2 infection by measuring the humoral immune response to the virus by targeting spike glycoprotein (S) in research serum samples collected within 35 days after symptom onset.

The SARS-CoV-2 RT-PCR assay used in this research is described in detail elsewhere [36]. Briefly, we utilized the SARS-CoV-2 (2019-nCoV) Centers for Disease Control and Prevention (CDC) quantitative PCR (qPCR) Probe Assay research use only kits (catalogue No. 10006770) manufactured by Integrated DNA Technologies, Inc. and consistent with the most recent revision of the emergency use authorization issued to the CDC on 1 December 2020. The assay targets 2 regions of the nucleocapsid (N) gene with an additional primer/probe set to detect the RNase P gene (RP) in specimens. A cycle threshold value of less than 40 for both N gene targets was considered positive for SARS-CoV-2 infection.

Serological testing was performed by a SARS-CoV-2 spike protein-based multiplex microsphere immunoassay, described in detail elsewhere [32]. For the detection of SARS-CoV-2 spike reactive immunoglobulin G (IgG) from serum samples collected 10–60 days after the onset of symptoms, this immunoassay has a sensitivity of 99% and specificity of 100%. Briefly, prefusion stabilized spike protein ectodomain trimers were coupled to magnetic microspheres (Bio-Rad). Samples for serology and spike-coupled microspheres were added to 96-well plates. Serum samples were diluted 1:400, added to 96-well plates, and

tested in technical duplicates. Antibodies in serum samples were detected with biotinylated, cross-absorbed anti-human secondary antibodies. Antigen-antibody complexes were then incubated with streptavidin-phycoerythrin and quantified with a Bio-Plex 200 HTF multiplexing system (Bio-Rad). IgG levels are reported as median fluorescence intensity (MFI).

Measurement of Demographic, Clinical, and Anthropometric Subject Characteristics

The primary outcome of interest in this analysis was SARS-CoV-2 infection-related hospitalization. Hospitalization status was obtained from the case report forms (CRF) (completed at the site using the participant's medical record) and directly using the MHS EMR. Because hospitalization may be a limited proxy of COVID-19 severity (eg, hospital admissions may be for nonmedical reasons and thresholds for admission may vary by provider and setting), we also used an alternative severity outcome based on whether subjects required treatment with supplemental oxygen. Anthropometric measures were obtained either through collection of height and weight during a prior medical visit or from the participant via survey. BMI was calculated using weight and height values, and individuals were classified as normal/underweight (<24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–34.9 kg/m^2), and severely obese (≥35 kg/m^2). In addition, the CRF assessed whether the subject had a diagnosis of obesity along with a range of comorbidities, many of which were possible confounders or mediators of the relationship between obesity and severe COVID-19 (Table 1). To measure the burden of comorbidities in a subject, we calculated the Charlson comorbidity index (CCI) [37], which is a standardized method of categorizing comorbidities of patients; for this study, we used the updated version age-adjusted CCI [38]. Age, sex, race, and ethnicity were reported by the participant.

Table 1. Distribution of Demographic Data by Weight Strata in 511 SARS-CoV-2 Infections in Military Health System Beneficiaries[a]

Characteristic	Normal (n = 140)	Overweight (n = 178)	Obese (n = 121)	Severely Obese (n = 72)	Total (n = 511)	*P* Value[a]
Sex male	82 (58.6)	122 (68.5)	82 (67.8)	42 (58.3)	328 (64.2)	.16
Age group						<.01
18–44	106 (75.7)	120 (67.4)	66 (54.5)	25 (34.7)	317 (62.0)	
45–64	24 (17.1)	39 (21.9)	38 (31.4)	32 (44.4)	133 (26.0)	
65+	10 (7.1)	19 (10.7)	17 (14.0)	15 (20.8)	61 (11.9)	
Race						<.01
Black	15 (10.7)	27 (15.2)	33 (27.3)	19 (26.8)	94 (18.4)	
Hispanic	39 (27.9)	53 (29.8)	39 (32.2)	30 (42.3)	161 (31.6)	
Others	17 (12.1)	23 (12.9)	9 (7.4)	3 (4.2)	52 (10.2)	
White	69 (49.3)	75 (42.1)	40 (33.1)	19 (26.8)	203 (39.8)	
Military status						<.01
Active military	89 (63.6)	111 (62.4)	49 (40.5)	14 (19.4)	263 (51.5)	
Dependent	37 (26.4)	25 (14.0)	33 (27.3)	27 (37.5)	122 (23.9)	
Retired military	14 (10.0)	42 (23.6)	39 (32.2)	31 (43.1)	126 (24.7)	
DOD						.09
Air force	16 (11.4)	27 (15.2)	21 (17.4)	21 (29.2)	85 (16.6)	
Army	49 (35.0)	70 (39.3)	45 (37.2)	26 (36.1)	190 (37.2)	
Coast guard	3 (2.1)	1 (0.6)	1 (0.8)	0 (0.0)	5 (1.0)	
Marines	12 (8.6)	21 (11.8)	11 (9.1)	1 (1.4)	45 (8.8)	
Navy	56 (40.0)	56 (31.5)	42 (34.7)	23 (31.9)	177 (34.6)	
Other	4 (2.9)	3 (1.7)	1 (0.8)	1 (1.4)	9 (1.8)	
Site						<.01
BAMC	18 (12.9)	45 (25.3)	34 (28.1)	32 (44.4)	129 (25.2)	
FBCH	6 (4.3)	9 (5.1)	1 (0.8)	5 (6.9)	21 (4.1)	
MAMC	26 (18.6)	19 (10.7)	10 (8.3)	1 (1.4)	56 (11.0)	
NMCP	3 (2.1)	1 (0.6)	1 (0.8)	0 (0.0)	5 (1.0)	
NMCSD	35 (25.0)	47 (26.4)	29 (24.0)	14 (19.4)	125 (24.5)	
TAMC	16 (11.4)	14 (7.9)	8 (6.6)	4 (5.6)	42 (8.2)	
WRNMMC	36 (25.7)	43 (24.2)	38 (31.4)	16 (22.2)	133 (26.0)	

Data are No. (%).

Abbreviations: BAMC, Brooke Army Medical Center; FBCH, Fort Belvoir Community Hospital; MAMC, Madigan Army Medical Center; NMCP, Naval Medical Center Portsmouth; NMCSD, Naval Medical Center San Diego; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TAMC, Tripler Army Medical Center; WRNMMC, Walter Reed National Military Medical Center

[a]Obesity category defined by body mass index; individuals were classified as normal/underweight (<24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30–34.9 kg/m^2), and severely obese (≥35 kg/m^2).

[b]n × k Fisher exact test.

Quantitation of SARS-CoV-2 Viral Load and IgG Response

The viral load (genome equivalents [GE]/reaction) of each specimen was calculated for each N gene target (N1 and N2) by constructing plate specific standard curves from 3 dilutions of a known SARS-CoV-2 gene copy number standard (10 000, 1000, 100, and 10 copies/μL) on each RT-PCR assay run. The viral load calculations were log transformed for normalization such that a rise in $\log_{10}$ quantity GE/reaction equated to a rise in viral load (Supplementary Figure 2). We defined peak viral load as the highest $\log_{10}$ GE/reaction measured for the subject (from any time point or any specimen type). We used the SARS-CoV-2 spike protein-based multiplex microsphere immunoassay IgG MFI read-out as a quantitative measurement of anti-S IgG antibody against the SARS-CoV-2 spike protein [32].

Statistical Analysis

Descriptive statistics were calculated for the demographic characteristics, comorbidities, and illness severity by BMI category with *P* values computed using Fisher exact test. Univariate logistic regression was performed to evaluate whether COVID-19 severity was significantly associated with other independent variables, and then multivariable regression was performed, adjusting for other putative risk factors for COVID-19 including sex, age group, race, smoking history, and comorbidities (diabetes, hypertension, chronic kidney disease, asthma, chronic pulmonary disease, chronic neurological disorder, peripheral vascular disease, venous thromboembolism, ischemic heart disease, and cancer). Model fit was estimated by the Akaike information criterion and Bayesian information criterion, with the best fitting model used to present the adjusted odds ratio of obesity diagnosis and BMI strata on an outcome of hospitalization. This model was then fit to an alternative outcome of COVID-19 severity, as defined by requirement of supplemental oxygenation. We further carried out sensitivity analyses to minimize the risk of model misspecification by presenting comparative models to ensure that an estimate of the independent association of obesity and severe COVID-19 were robust.

Univariate and multivariate linear regression models were fit to evaluate whether peak viral load and/or peak anti-S IgG antibody response was associated with obesity and BMI strata (Supplementary Figure 3). These analyses aimed to determine whether obesity was associated with a difference in virological and humoral immune response phenotypes. These regression analyses were further stratified by disease severity (inpatient vs outpatient). All statistical analyses were conducted using R version 4.0.2 [39].

Ethics

This study was approved by the Uniformed Services University Human Research Protection Office under protocol IDCRP-085; all participants provided informed consent.

RESULTS

Obesity, Obesity-Associated Comorbidities, and Severe COVID-19 Outcomes Are Prevalent in Those With SARS-CoV-2 Infection in the US Military Health System

Among 619 COVID-19–positive participants who were enrolled in EPICC from 20 March 2020 through 15 September 2020, 511 (69%) were included in this analysis, as they were classified as COVID-19 cases and had anthropometric data available (Supplementary Figure 1). Over half of our study sample was male (64.2%), 18–44 years of age (62%), active-duty military (51.5%), and 48.6% were dependents and retired military; 72.6% were overweight, obese, and/or severely obese (Table 1). Overall, 25% of our participants were inpatients, incrementally from 14% to 52% in normal/underweight to severely obese participants, respectively (Supplementary Table 1). When considered as a continuous variable, average BMI values were higher in inpatients when compared with outpatients, and BMI was higher in those who received supplemental oxygen when compared with those who did not (Figure 1). Thirty-five percent of the participants had at least 1 other comorbidity (range 25%–68% in normal/underweight to severely obese participants, respectively). The most common additional comorbidity in the sample was hypertension (20.1%), followed by diabetes (12%), both of which were more common in increasing categories of obesity (Supplementary Table 1).

Obesity Is Independently Associated With Severe COVID-19 in US Military Health System Beneficiaries

We evaluated both reported and measured obesity in separate models. Logistic regression demonstrated that obesity was associated with an approximately 3-fold (odds ratio [OR] = 2.63; 95% confidence interval [CI], 1.72–4.02) increased odds of hospitalization, and remained significant after controlling for sex, age group, race, and a number of comorbidities (Table 2). Ordinal measured BMI categories were associated with increasing probability of hospitalization, although the ORs were statistically significant in the severely obese (OR = 3.1; 95% CI, 1.39–6.89) category only after multivariate adjustment. Similar results were observed when the need for supplemental oxygen was the outcome of interest (Supplementary Table 4).

Viral Load and Anti-S IgG Responses Correlate With Weight Strata

In upper respiratory tract specimens, we observed peaks in SARS-CoV-2 viral load at the time of or shortly after the onset of symptoms in the early stages of infection and decreasing in the convalescent stage (Figure 2). Conversely, we observed rising serum IgG soon after the onset of symptoms and plateauing thereafter, with persistence out to 3 months after symptom onset (Figure 3).

When pooling inpatient and outpatient participants, we observed no association between viral load and BMI category (Table 3). However, when we stratified by COVID-19

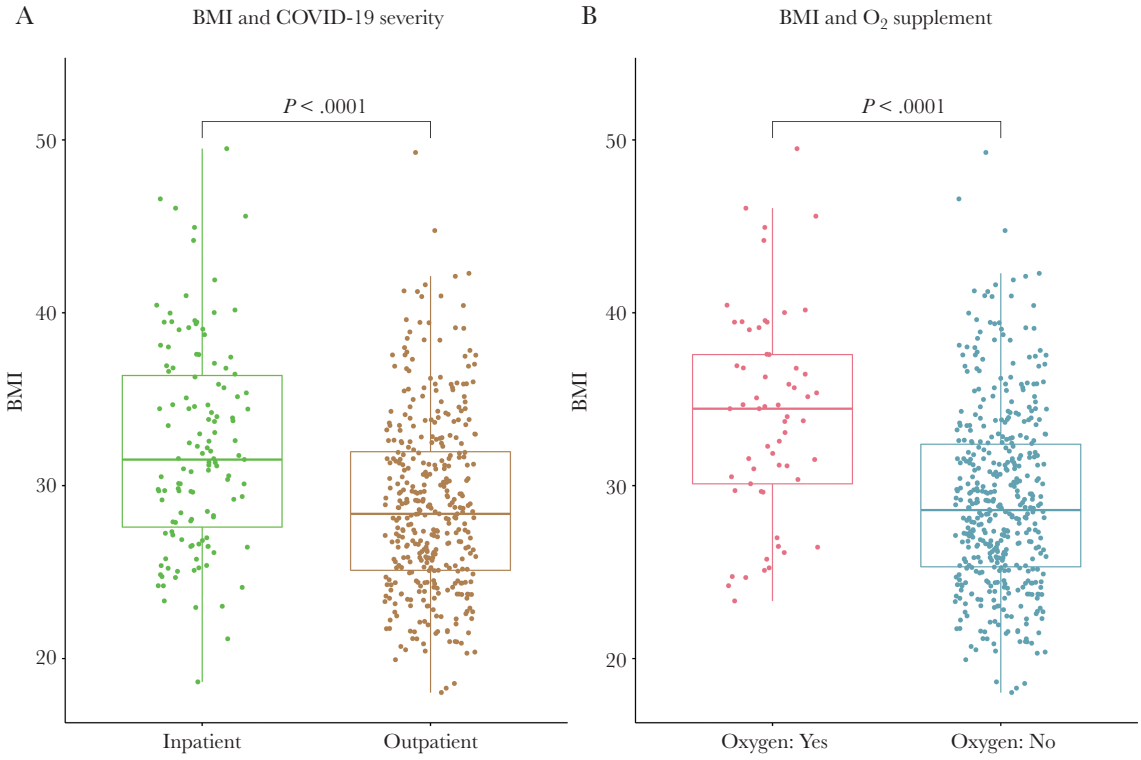

Figure 1. Body mass index (BMI) distribution by severity, stratified into inpatient and outpatient (*A*), and medical oxygen requirements, stratified into oxygen supplement yes and oxygen supplement no, respectively (*B*). Statistically significant differences by nonparametric *t* tests are noted. Each dot represents a subject. Boxplots denote median, first quartile (25th percentile), and third quartile (75th percentile); statistical significance was determined by Wilcoxon rank sum test.

severity (inpatient versus outpatients), outpatients in the severely obese group had a $\log_{10}$ 1.89 higher N1 GE/reaction and a $\log_{10}$ 2.62 N2 GE/reaction increase in peak viral load compared to those with normal weight, adjusting for sampling time (Supplementary Table 3). We also observed that obese or severely obese participants had a higher IgG antibody response compared to normal-weight participants, with an increasing coefficient by weight strata (Table 4). When stratified on inpatients and outpatients, there was an increased IgG response in severely obese subjects compared to

Table 2. Crude and Adjusted Association of Covariates With Hospitalization in 511 SARS-CoV-2 Infections in Military Health System Beneficiaries

Covariates[a]	Unadjusted OR (95% CI)	*P* Value	aOR[b] (95% CI)	*P* Value	aOR[c] (95% CI)	*P* Value
Sex male	1.16 (.76–1.76)	.5	1.33 (.79–2.23)	.28	1.39 (.82–2.35)	.22
Age group 45–64	7 (4.19–11.72)	<.001	5.95 (3.46–10.25)	<.001	5.49 (3.17–9.52)	<.001
Age group 65+	27.93 (14.06–55.49)	<.001	22.53 (10.66–47.6)	<.001	22.19 (10.5–46.88)	<.001
Race Black	1.64 (.93–2.89)	.09	1.38 (.69–2.74)	.36	1.36 (.68–2.73)	.39
Race Hispanic	1.68 (1.03–2.73)	.04	1.73 (.96–3.14)	.07	1.68 (.92–3.06)	.09
Race Others	1.5 (.74–3.03)	.26	2.21 (.94–5.16)	.07	2.27 (.98–5.29)	.06
Obesity	2.63 (1.72–4.02)	<.001	1.91 (1.15–3.18)	.01		
BMI class overweight	1.85 (1.01–3.36)	.04			1.39 (.68–2.81)	.37
BMI class obese	2.59 (1.39–4.83)	<.001			1.71 (.82–3.57)	.15
BMI class severely obese	6.02 (3.09–11.76)	<.001			3.1 (1.39–6.89)	.01
Ischemic heart disease	7.05 (2.81–17.71)	<.001	0.92 (.29–2.88)	.89	0.84 (.27–2.66)	.77
Chronic pulmonary disease	8.69 (3.54–21.33)	<.001	3.16 (1.09–9.2)	.03	3.36 (1.14–9.91)	.03
Chronic neurological disease	4.5 (1.68–12.09)	<.001	3.06 (.88–10.63)	.08	2.93 (.85–10.06)	.09

Obesity was defined by the medical diagnosis. BMI class was computed by participants height and weight.

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Only includes covariates included in multivariable models; referent: severity (inpatient vs. outpatient).

[b]Adjusted for obesity, sex, age groups, race, ischemic heart disease, chronic pulmonary disease, chronic neurological disease

[c]Adjusted for BMI category, sex, age groups, race, ischemic heart disease, chronic pulmonary disease, chronic neurological disease

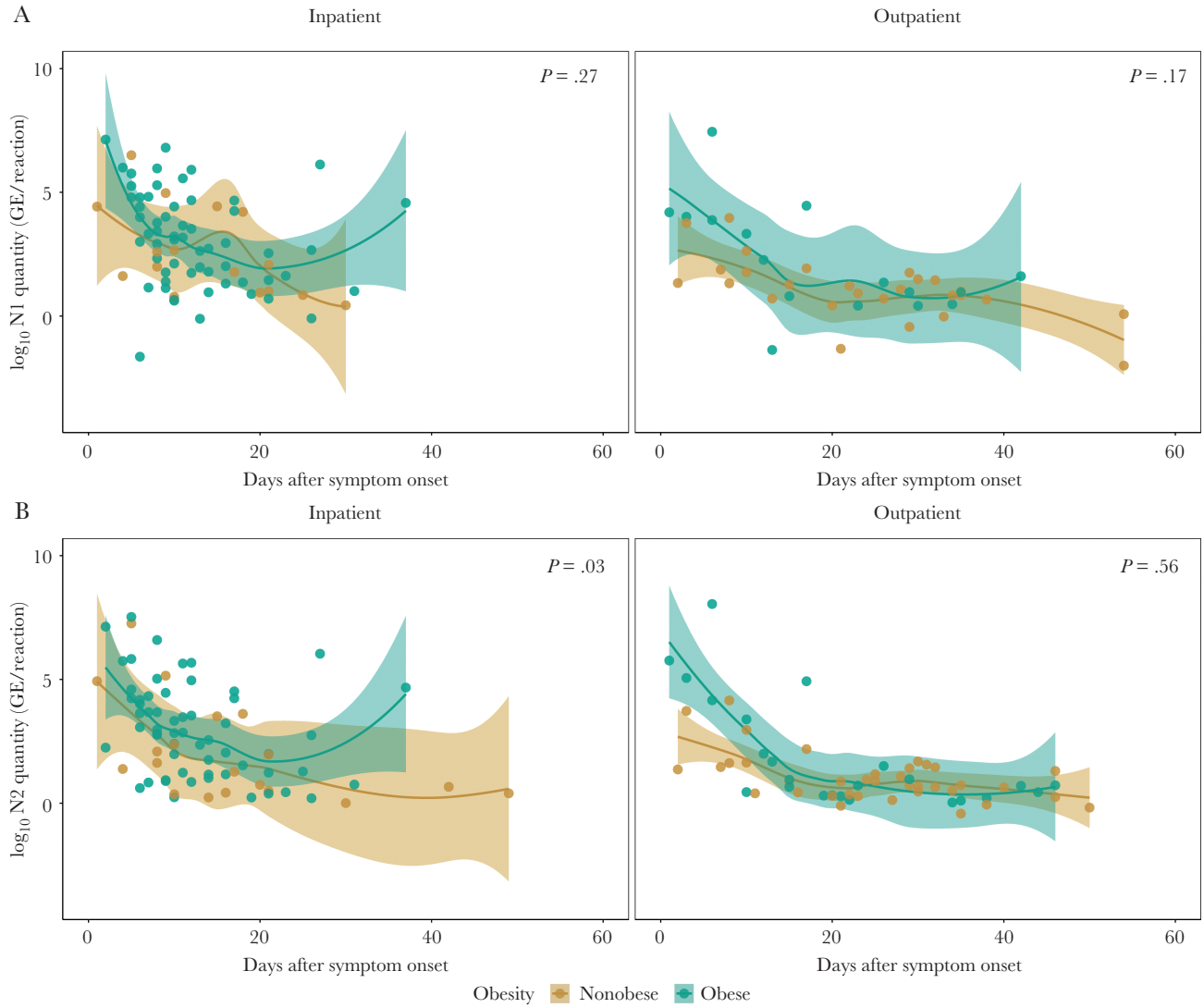

Figure 2. Viral load as measured by qPCR N1 GE/reaction (*A*) and N2 GE/reaction (*B*), $\log_{10}$ transformed and plotted by symptom day and stratified by obesity status. Each dot represents a subject. Local polynomial regression curves were fit to nonobese and obese groups; 95% confidence intervals are shaded for nonobese and obese groups; statistical significance was determined by Wilcoxon rank sum test. Abbreviations: Ct, cycle threshold; GE, genome equivalent; N, nucleocapsid; qPCR, quantitative polymerase chain reaction.

normal-weight participants that was statistically significant (Table 4).

DISCUSSION

The findings of our study corroborate those of previous studies; categories of higher BMI are associated with increased odds for severe COVID-19 [20–24]. Implicating obesity as a risk factor for severe COVID-19 can be challenging, given the multitude of obesity-associated comorbidities that may confound or mediate this association. To account for these, we conducted several sensitivity analyses to examine a range of obesity-associated comorbidities and to reduce the risk of model misspecification (Supplementary Table 2). Our analysis of BMI strata revealed a "dose-response" association between increasing BMI categories and odds of severe COVID-19, thereby strengthening causal inference. These findings are of concern to MHS beneficiaries given the known prevalence of obesity in US military beneficiaries, including active-duty service members who comprised a substantive proportion of our study population [29–31]. Indeed, among the study participants included in this analysis, we noted that over three-quarters of SARS-CoV-2 infections were in overweight MHS beneficiaries, and over one-third of subjects were obese or severely obese (Table 1). These findings also have relevance in other populations where obesity is prevalent.

To elucidate potential underlying mechanisms to which the association between obesity and severe COVID-19 might be attributed, we examined both virological and immunological

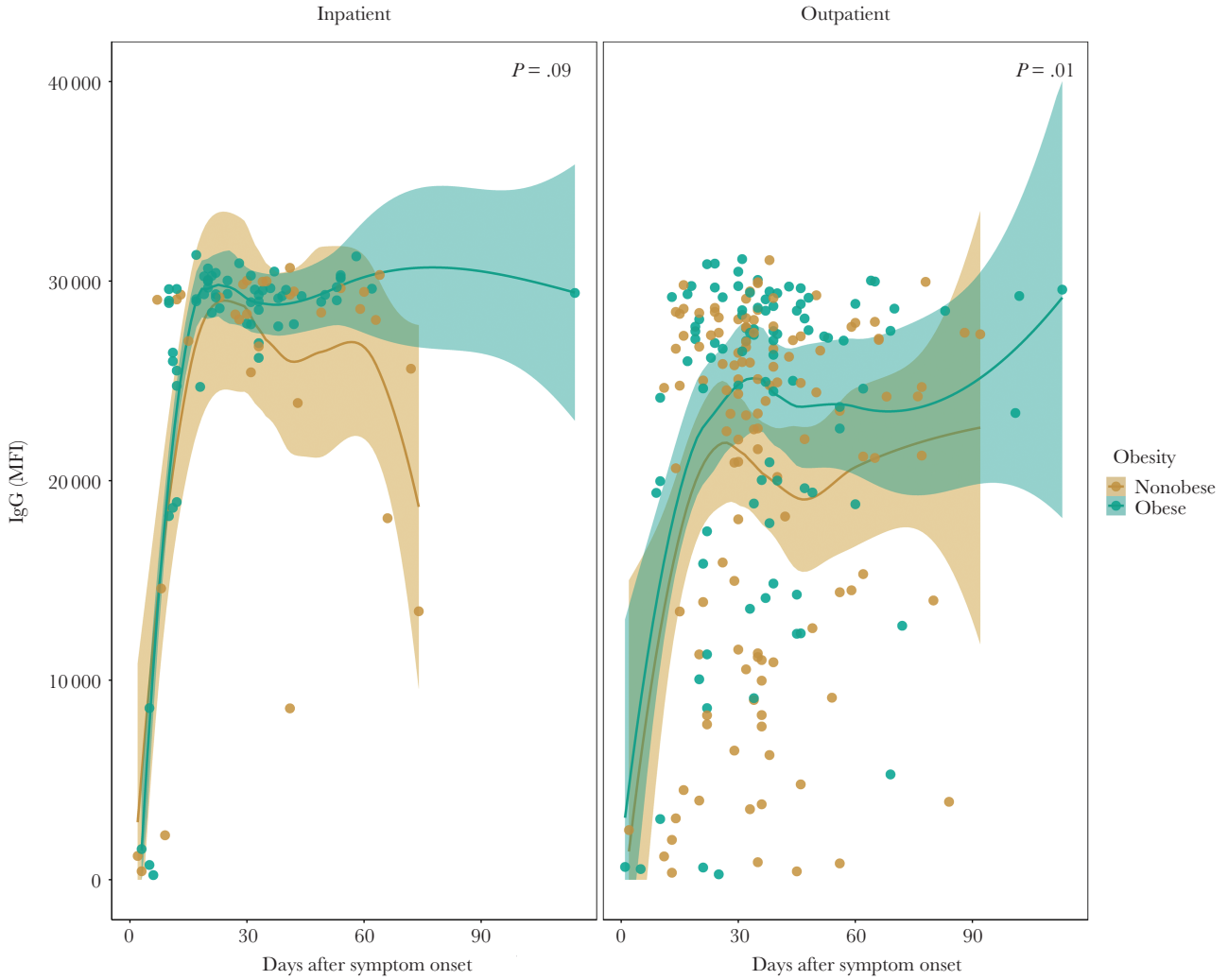

Figure 3. Anti-spike IgG MFI plotted by sampling day and stratified by obesity status. Each dot represents a subject. Local polynomial regression curves were fit to nonobese and obese groups; 95% confidence intervals are shaded for nonobese and obese groups; statistical significance was determined by Wilcoxon rank sum test. Abbreviations: IgG, immunoglobulin G; MFI, median fluorescence intensity.

Table 3. Association of Obesity Category With Peak Viral Load, Adjusted for Sampling Day

Covariates	β Coefficient (95% CI)	*P* Value	Adjusted β Coefficient (95% CI)[a]	*P* Value	Adjusted β Coefficient (95% CI)[b]	*P* Value
log_{10} N1 GE/reaction, inpatients and outpatients (n = 114)						
Obesity	1.2 (.48 to 1.92)	<.001	0.72 (.04 to 1.41)	.04		
BMI class overweight	1.13 (.09 to 2.16)	.03			0.72 (−.23 to 1.67)	.14
BMI class obese	0.96 (−.03 to 1.95)	.06			0.55 (−.37 to 1.47)	.24
BMI class severely obese	1.61 (.58 to 2.65)	<.001			0.83 (−.17 to 1.83)	.1
Symptom day	−0.07 (−.1 to −.05)	<.001	−0.06 (−.09 to −.04)	<.001	−0.07 (−.09 to −.04)	<.001
log_{10} N2 GE/reaction, inpatients and outpatients (n = 114)						
Obesity	1.25 (.51 to 1.98)	<.001	0.81 (.11 to 1.51)	.02		
BMI class overweight	1.21 (.15 to 2.27)	.03			0.94 (−.02 to 1.9)	.06
BMI class obese	1.08 (.07 to 2.1)	.04			0.79 (−.14 to 1.72)	.1
BMI class severely obese	1.67 (.61 to 2.72)	<.001			0.96 (−.05 to 1.97)	.06
Symptom day	−0.07 (−.1 to −.05)	<.001	−0.07 (−.09 to −.04)	<.001	−0.07 (−.09 to −.04)	<.001

Obesity was defined by the medical diagnosis. BMI class was computed by participants height and weight.

Abbreviations: BMI, body mass index; CI, confidence interval; GE, genome equivalent; N, nucleocapsid.

[a]Model contains obesity and sampling day.

[b]Model contains BMI classification and sampling day.

Table 4. Association of Weight Strata With Peak Anti-Spike IgG MFI, Adjusted for Sampling Day and Stratified by Hospitalization Status

Covariates	Coefficient (95% CI)	*P* Value	Adjusted Coefficient[a] (95% CI)	*P* Value	Adjusted Coefficient[b] (95% CI)	*P* Value
Inpatients and outpatients (n = 314)						
Obesity	4.09 (2.35 to 5.83)	<.001	4.06 (2.33 to 5.79)	<0.001		
BMI class overweight	1.69 (−.54 to 3.92)	.14			1.56 (−.65 to 3.78)	.17
BMI class obese	3.18 (.68 to 5.67)	.01			3.21 (.73 to 5.7)	.01
BMI class severely obese	5.53 (2.64 to 8.41)	<.001			5.48 (2.61 to 8.34)	<.001
Symptom day	−0.02 (−.04 to 0)	.03	−0.02 (−.04 to 0)	0.03	−0.02 (−.04 to 0)	.03
Inpatients (n = 79)						
Obesity	3.42 (1.19 to 5.65)	<.001	3.43 (1.24 to 5.61)	<.001		
BMI class overweight	2.15 (−1.13 to 5.44)	.19			1.95 (−1.25 to 5.15)	.23
BMI class obese	3.31 (−.22 to 6.85)	.07			4.17 (.65 to 7.7)	.02
BMI class severely obese	3.97 (.54 to 7.4)	.02			3.53 (.17 to 6.89)	.04
Symptom day	−0.03 (−.07 to 0)	.04	−0.03 (−.07 to 0)	.03	−0.04 (−.07 to 0)	.03
Outpatients (n = 235)						
Obesity	3.12 (.99 to 5.24)	<.001	3.13 (1 to 5.25)	<.001		
BMI class overweight	0.98 (−1.62 to 3.58)	.46			0.92 (−1.68 to 3.52)	.49
BMI class obese	2.46 (−.49 to 5.41)	.1			2.42 (−.52 to 5.37)	.11
BMI class severely obese	3.91 (0 to 7.82)	.05			4.09 (.18 to 8)	.04
Symptom day	−.01 (−.03 to .01)	.27	−0.01 (−.03 to .01)	.25	−0.01 (−.03 to .01)	.22

Obesity was defined by the medical diagnosis. BMI class was computed by participants height and weight.

Abbreviations: BMI, body mass index; CI, confidence interval.

[a]Model contains obesity and sampling day.

[b]Model contains BMI classification and sampling day.

characteristics of SARS-CoV-2 infection in the study population. In outpatients, we noted that obesity (BMI ≥ 30) was associated with a substantively higher viral load. Interestingly, this was not seen in inpatients. It is unknown whether this reflects antiviral drug use in inpatients or sampling of inpatient illness relatively later in their course of illness when viral loads may be expected to fall more precipitously. To date, there has been only limited other data that have reported a positive correlation between obesity and SARS-CoV-2 viral load. Maltezou et al described a higher viral load in obese versus nonobese patients but did not adjust for sampling time or disease severity and only used a dichotomous categorization of obesity [40]. The association between BMI and viral load has also been demonstrated for influenza [41, 42].

In inpatients, we noted an increase in anti-S IgG MFI by BMI strata (BMI ≥ 30, coefficient = 4.17, $P = 0.02$; BMI ≥ 35 coefficient = 3.53, $P = 0.04$). As higher levels of anti-S IgG have been described during hospitalization in patients with more severe disease [43, 44], this may reflect increasing severity in obese inpatients. However, a similar magnitude of effect was seen in severely obese outpatients (coefficient = 4.09, $P = 0.04$; Table 4). Further analyses leveraging this study population will examine whether nonneutralizing antibody, T-cell, and innate immune responses are quantitatively or qualitatively different in obese versus nonobese subjects, within and between strata of clinical severity.

Our study had several strengths. EPICC employs a comprehensive collection of demographic, epidemiologic, clinical, and laboratory data across the time course of infection. This enabled adjustment for important confounders and mediators. The prospective, longitudinal designed allowed ascertainment of peak viral load and anti-S IgG magnitude across illness time, as well as careful ascertainment of COVID-19 case status. Our sample was also relatively heterogeneous for age, sex, and race, as it draws from the population of MHS beneficiaries comprised of active-duty service members, retirees, and their dependents.

There were several limitations of our study. The paucity of early illness sampling was a limitation across this study, with the first study specimen being collected, on average, 34 (interquartile range, 20–54) days after symptom onset. While sampling time was adjusted in regression models this delay likely resulted in many subjects with resolving or resolved viral load. Another possible limitation was use of BMI as one set of criteria for obesity. We determined that our alternative methods of measuring obesity—BMI and a diagnosis of obesity as indicated in the EMR and/or CRF—were highly correlated. In total, 511 participants had both BMI and obesity reported on the EMR and CRF form respectively, among whom 404 (79%) were found to be obese using both data sources (Cohen $\kappa = 0.58$; $P < .001$). Nevertheless, elevated BMI in young muscular active-duty soldiers may be a result of increased muscle mass, and not an overweight status per se [45]. Future studies in this population could use waist circumference, neck circumference, and/or body fat percentage, which is an indicator of abdominal obesity and would resolve the possible misclassification [46]. However, it is important to note that such a misclassification of obesity would be expected to underestimate the magnitude of the association between obesity and severe COVID-19.

Although the current study examined humoral IgG responses in obesity and severe COVID-19, further virological and immunological exploration are necessary for a comprehensive understanding. Obesity is associated with chronic low-grade systemic inflammation, including higher levels of interleukin 6 (IL-6) [47, 48]. Investigation of inflammatory cytokine biomarkers (eg, IL-6, tumor necrosis factor-α [TNF-α], C-reactive protein [CRP]), adipokines, innate immunity such as natural killer cells, memory T cells, macrophages, and inflammasome signaling would allow us to understand complex pathophysiology of obesity and severe COVID-19 [47, 49]. Further studies are also needed to explore the role of obesity-associated insulin resistance and microbiome derangement in COVID-19 outcomes.

Other putative mechanisms that may explain the association between obesity and disease severity that were observed in this study could include excess soft tissue in the upper respiratory tract that results in obstruction of the airway [22], or decreased diaphragm contractility and poor pulmonary mechanics that result in hypoxia or contribute to type II respiratory failure, which may complicate the outcomes of some severe COVID-19 cases [23]. Such physiological pathways are more challenging to measure but could drive future studies in this [47] and other populations at risk of COVID-19.

In conclusion, we recapitulate the epidemiological association between obesity and severe COVID-19 seen in other studies, including using alternative definitions of severity. We further show an increase in SARS-CoV-2 viral load in outpatient COVID-19 with obesity, and a more robust anti-IgG response in obese SARS-CoV-2 infections, even when stratified to outpatients. These findings prompt further study into the mechanisms of severe COVID-19 in those with obesity, including examination of other facets of host response to SARS-CoV-2 such as innate and T-cell immunity.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank Camille Estupigan for her editorial assistance in the preparation of this manuscript. We thank the members of the EPICC COVID-19 Cohort Study Group for their many contributions in conducting the study and ensuring effective protocol operations. The following members were all closely involved with the design, implementation, and oversight of the study. Brooke Army Medical Center, Fort Sam Houston, TX: J. Cowden, D. Lindholm, A. Markelz, K. Mende, T. Merritt, R. Walter, and CPT T. Wellington. Carl R. Darnall Army Medical Center, Fort Hood, TX: MAJ S. Bazan. Fort Belvoir Community Hospital, Fort Belvoir, VA: L. Brandon, N. Dimascio-Johnson, MAJ E. Ewers, LCDR K. Gallagher, LCDR D. Larson, and MAJ M. Odom. Henry M. Jackson Foundation, Inc, Bethesda, MD: P. Blair, and D. Clark. Madigan Army Medical Center, Joint Base Lewis McChord, WA: S. Chambers, LTC C. Colombo, R. Colombo, CPT C. Conlon, CPT K. Everson, LTC P. Faestel, COL T. Ferguson, MAJ L. Gordon, LTC S. Grogan, CPT S. Lis, COL C. Mount, LTC D. Musfeldt, MAJ R. Sainato, C. Schofield, COL C. Skinner, M. Stein, MAJ M. Switzer, MAJ M. Timlin, and MAJ S. Wood. Naval Medical Center Portsmouth, Portsmouth, VA: G. Atwood, R. Carpenter, LCDR C. Eickhoff, CAPT K. Kronmann, T. Lalani, LCDR T. Lee, and CDR T. Warkentien. Naval Medical Center San Diego, San Diego, CA: CAPT J. Arnold, CDR C. Berjohn, S. Cammarata, LCDR S. Husain, N. Kirkland, LCDR A. Lane, CAPT R. Maves, J. Parrish, and G. Utz. Tripler Army Medical Center, Honolulu, HI: S. Chi, MAJ E. Filan, K. Fong, CPT T. Horseman, MAJ M. Jones, COL A. Kanis, LTC A. Kayatani, MAJ W. Londeree, LTC C. Madar, MAJ J. Masel, MAJ M. McMahon, G. Murphy, COL V. Ngauy, MAJ E. Schoenman, C. Uyehara, and LTC R. Villacorta Lyew. Uniformed Services University of the Health Sciences, Bethesda, MD: B. Agan, C. Broder, CAPT T. Burgess, C. Byrne, COL K. Chung, C. Coles, C. English, COL P. Hickey, E. Laing, LTC J. Livezey, A. Malloy, COL T. Oliver, E. Parmelee, S. Pollett, S. Richard, J. Rozman, J. Rusiecki, M. Sanchez, A. Scher, CDR M. Simons, A. Snow, and D. Tribble. United States Air Force School of Medicine, Dayton, OH: A. Fries. Walter Reed National Military Medical Center, Bethesda, MD: A. Ganesan, D. Gunasekera, MAJ N. Huprikar, and M. Oyeneyin. William Beaumont Army Medical Center, El Paso, TX: CPT M. Banda, CPT B. Davis, MAJ T. Hunter, CPT O. Ikpekpe-Magege, CPT S. Kemp, R. Mody, R. Resendez, and COL M. Wiggins.

Disclaimer. Some of the authors are service members or employees of the US Government. This work was prepared as part of their official duties. Title 17 USC. §105 provides that "Copyright protection under this title is not available for any work of the United States Government." Title 17 USC §101 defines a US Government work as a work prepared by a military service member or employee of the US Government as part of that person's official duties.

The contents of this publication are the sole responsibility of the author(s) and do not necessarily reflect the views, opinions, or policies of Uniformed Services University of the Health Sciences; the Department of Defense; the Departments of the Army, Navy, or Air Force; Brooke Army Medical Center; Walter Reed National Military Medical Center; Naval Medical Center San Diego; Madigan Army Medical Center; United States Air Force School of Aerospace Medicine; Naval Medical Center Portsmouth; Tripler Army Medical Center; Fort Belvoir Community Hospital; or the Henry M. Jackson Foundation for the Advancement of Military

Medicine. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government. The investigators have adhered to the policies for protection of human subjects as prescribed in 45 CFR 46.

Financial support. This work was supported by the Defense Health Program; and the National Institute of Allergy and Infectious Diseases (NIAID) (grant number HU00011920111). The protocol was executed by the Infectious Disease Clinical Research Program, a Department of Defense program executed by the Uniformed Services University of the Health Sciences through a cooperative agreement by the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. This project has been funded in part by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health under an interagency agreement (grant number Y1-AI-5072).

Potential conflicts of interest. S. D. P., T. H. B, D.R.T., and M. P.S. report that the Uniformed Services University Infectious Diseases Clinical Research Program (USU IDCRP), a US Department of Defense institution, and the Henry M. Jackson Foundation (HJF) were funded under a Cooperative Research and Development Agreement to conduct an unrelated phase 3 COVID-19 monoclonal antibody immunoprophylaxis trial sponsored by AstraZeneca. The HJF, in support of the USU IDCRP, was funded by the Department of Defense Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense to augment the conduct of an unrelated phase 3 vaccine trial sponsored by AstraZeneca. Both of these trials were part of the US Government COVID-19 response. Neither is related to the work presented here.

All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis **2020**; 20:533–4.
2. Chen R, Liang W, Jiang M, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest **2020**; 158:97–105.
3. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature **2020**; 584:430–6.
4. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect **2020**; 81:e16–25.
5. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis **2020**; 94:91–5.
6. Docherty AB, Harrison EM, Green CA, et al; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ **2020**; 369:m1985.
7. Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: deleterious impact on infected patients. J Infect Public Health **2020**; 13:1833–9.
8. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J **2020**; 55: 2000547.
9. de Lusignan S, Dorward J, Correa A, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis **2020**; 20:1034–42.
10. Gao F, Zheng KI, Wang XB, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care **2020**; 43:e72–4.
11. Simonnet A, Chetboun M, Poissy J, et al; LICORN and the Lille COVID-19 and Obesity Study Group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring) **2020**; 28:1195–9.
12. Jiang Y, Chen Y, Mao Y; CCDPC Obesity Working Group. The contribution of excess weight to prevalent diabetes in Canadian adults. Public Health **2008**; 122:271–6.
13. Power C, Pinto Pereira SM, Law C, Ki M. Obesity and risk factors for cardiovascular disease and type 2 diabetes: investigating the role of physical activity and sedentary behaviour in mid-life in the 1958 British cohort. Atherosclerosis **2014**; 233:363–9.
14. van der Leeuw J, van der Graaf Y, Nathoe HM, de Borst GJ, Kappelle LJ, Visseren FL; SMART Study Group. The separate and combined effects of adiposity and cardiometabolic dysfunction on the risk of recurrent cardiovascular events and mortality in patients with manifest vascular disease. Heart **2014**; 100:1421–9.
15. McCrindle BW. Cardiovascular consequences of childhood obesity. Can J Cardiol **2015**; 31:124–30.
16. Oberman B, Khaku A, Camacho F, Goldenberg D. Relationship between obesity, diabetes and the risk of thyroid cancer. Am J Otolaryngol **2015**; 36:535–41.
17. Benedetto C, Salvagno F, Canuto EM, Gennarelli G. Obesity and female malignancies. Best Pract Res Clin Obstet Gynaecol **2015**; 29:528–40.
18. Agalliu I, Williams S, Adler B, et al. The impact of obesity on prostate cancer recurrence observed after exclusion of diabetics. Cancer Causes Control **2015**; 26:821–30.
19. Pi-Sunyer X. The medical risks of obesity. Postgrad Med **2009**; 121:21–33.

20. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. Clin Infect Dis **2020**; 71:896–7.
21. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ **2020**; 369:m1966.
22. Hamer M, Gale CR, Kivimäki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: a community-based cohort study of adults in the United Kingdom. Proc Natl Acad Sci U S A **2020**; 117:21011–3.
23. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation **2020**; 142:4–6.
24. Di Renzo L, Gualtieri P, Pivari F, et al. COVID-19: Is there a role for immunonutrition in obese patient? J Transl Med **2020**; 18:415.
25. Kruglikov IL, Shah M, Scherer PE. Obesity and diabetes as comorbidities for COVID-19: underlying mechanisms and the role of viral-bacterial interactions. Elife **2020**; 9: e61330.
26. Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and outcomes in COVID-19: when an epidemic and pandemic collide. Mayo Clin Proc **2020**; 95:1445–53.
27. Al-Benna S. Association of high level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients. Obes Med **2020**; 19:100283.
28. Kruglikov IL, Scherer PE. The role of adipocytes and adipocyte-like cells in the severity of COVID-19 infections. Obesity (Silver Spring) **2020**; 28:1187–90.
29. Eilerman PA, Herzog CM, Luce BK, et al. A comparison of obesity prevalence: military health system and United States populations, 2009–2012. Mil Med **2014**; 179:462–70.
30. Tanofsky-Kraff M, Sbrocco T, Theim KR, et al. Obesity and the US military family. Obesity (Silver Spring) **2013**; 21:2205–20.
31. Kress AM, Hartzel MC, Peterson MR. Burden of disease associated with overweight and obesity among U.S. military retirees and their dependents, aged 38–64, 2003. Prev Med **2005**; 41:63–9.
32. Laing ED, Sterling SL, Richard SA, et al. Antigen-based multiplex strategies to discriminate SARS-CoV-2 natural and vaccine induced immunity from seasonal human coronavirus humoral responses. Preprint. medRxiv. 2021;2021.02.10.21251518. Published February 12 2021. doi: 10.1101/2021.02.10.21251518
33. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ **2020**; 369:m1443.
34. Yang Y, Yang M, Yuan J, et al. Laboratory Diagnosis and monitoring the viral shedding of SARS-CoV-2 infection. Innovation (N Y) **2020**; 1:100061.
35. Xiao AT, Tong YX, Gao C, Zhu L, Zhang YJ, Zhang S. Dynamic profile of RT-PCR findings from 301 COVID-19 patients in Wuhan, China: A descriptive study. J Clin Virol **2020**; 127:104346.
36. Centers for Disease Control and Prevention (CDC), Division of Viral Diseases, CDC 2019-novel coronavirus (2019-nCoV) real-time RT-PCR diagnostic panel. Vol. CDC-006-00019, revision: 06 Available at: https://www.fda.gov/media/134922/download.
37. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
38. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol **1994**; 47:1245–51.
39. R Core Team. R: A language environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, **2020**.
40. Maltezou HC, Raftopoulos V, Vorou R, et al. Association between upper respiratory tract viral load, comorbidities, disease severity, and outcome of patients with SARS-CoV-2 infection. J Infect Dis **2021**; 223:1132–8.
41. Meschi S, Selleri M, Lalle E, et al. Duration of viral shedding in hospitalized patients infected with pandemic H1N1. BMC Infect Dis **2011**; 11:140.
42. Yan J, Grantham M, Pantelic J, et al; EMIT Consortium. Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. Proc Natl Acad Sci U S A **2018**; 115:1081–6.
43. Li K, Huang B, Wu M, et al. Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19. Nat Commun **2020**; 11:6044.
44. Bošnjak B, Stein SC, Willenzon S, et al. Low serum neutralizing anti-SARS-CoV-2 S antibody levels in mildly affected COVID-19 convalescent patients revealed by two different detection methods. Cell Mol Immunol **2021**; 18:936–44.
45. Grier T, Canham-Chervak M, Sharp M, Jones BH. Does body mass index misclassify physically active young men. Prev Med Rep **2015**; 2:483–7.
46. Ljungvall Å, Gerdtham UG, Lindblad U. Misreporting and misclassification: implications for socioeconomic disparities in body-mass index and obesity. Eur J Health Econ **2015**; 16:5–20.
47. Kuperberg SJ, Navetta-Modrov B. The role of obesity in the immunopathogenesis of COVID-19 respiratory disease and critical illness. Am J Respir Cell Mol Biol **2021**; 65:13–21.
48. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci **2017**; 13: 851–63.
49. Korakas E, Ikonomidis I, Kousathana F, et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. Am J Physiol Endocrinol Metab **2020**; 319:E105–9.