Clinical, immunological and virological SARS-CoV-2 phenotypes in obese and non-obese military health system beneficiaries

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Key Points: In a population of Military Health System beneficiaries, obesity was strongly correlated with COVID-19 severity, viral load, and antibody response, suggesting the relationship between obesity and COVID-19 severity may be mediated by increased viral load in those with a higher body mass index.

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Summary: Obesity is correlated with COVID-19 severity, SARS-CoV-2 viral load, and anti-spike IgG antibody responses. These findings offer new pathophysiological insights into the relationship between obesity and COVID-19 severity.
ABSTRACT:

BACKGROUND: The mechanisms underlying the association between obesity and COVID-19 severity remain unclear. After verifying that obesity was a correlate of severe COVID-19 in U.S. Military Health System (MHS) beneficiaries, we compared immunological and virological phenotypes of SARS-CoV-2 infection in both obese and non-obese 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 RT-PCR viral load in obese and non-obese patients, stratified by hospitalization, utilizing logistic regression models.

RESULTS: 511 COVID-19 patients were analyzed, among whom 24% were obese and 14% severely-obese. Obesity was independently associated with hospitalization (aOR = 1.91, 95% 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 log10 (1.89) higher N1 genome equivalents (GE)/reaction and log10 (2.62) higher N2 GE/reaction than non-obese (p = 0.03 and p < 0.001, respectively). We noted a correlation between BMI and peak anti-spike protein IgG in inpatients and outpatients (coefficient = 5.48, p < 0.001).

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.

Key words: COVID-19 severity, obesity, viral load, antibody response
INTRODUCTION

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/m²) was associated with a 12% increase in the risk of severe COVID-19, and obesity was associated with a three-fold increase in risk of severe COVID-19, compared with non-obesity [10]. A French study reported that, among 124 patients admitted to the 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 (e.g. 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 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 multi-factorial. Obesity-related impairments in cardiovascular, respiratory, metabolic, and thrombotic pathways may decrease a given patient’s physiologic reserve and ability to recover from SARS-CoV-2 [23]. Obese individuals may have amplified or dysregulated immune responses that lead to greater viral replication that 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 proteins that mediate SARS-CoV-2
attachment and entry. Some posit that this difference in ACE2 receptor expression may potentially leading 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 seven 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 healthcare within the MHS and who met one of the following criteria: a) confirmed SARS-CoV-2 infection; b) COVID-like illness; or c) 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 post-enrollment for outpatients. Sera were collected at the same timepoints plus at 28 days and 6 months for inpatients, and 7 days, 28 days and 6 months post enrollment for outpatients. In addition, children (age < 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 (Supplemental Figure 1).

Diagnosis of SARS-CoV-2 infection and case definition

SARS-CoV-2 infection was diagnosed by (i) 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), (ii) SARS-CoV-2 RT-PCR on research specimens (nasopharyngeal, oropharyngeal, nasal, and rectal swabs) collected within 17 days post-symptom onset [33-35] and (iii) serological testing, which detects resolving or prior SARS-CoV-2 infection by measuring the humoral immune response to the virus by targeting spike glycoprotein (spike) in research serum samples collected within 35 days post-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) CDC qPCR Probe Assay research use only kits (Cat. #
10006770) manufactured by Integrated DNA Technologies, Inc. (Coralville, IA) and consistent with
the most recent revision of the Emergency Use Authorization (EUA) issued to the CDC on December
1, 2020. The assay targets two regions of the nucleocapsid (N) gene with an additional primer/probe
set to detect the RNase P gene (RP) in specimens. A cycle threshold (Ct) 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 [37]. For the detection of SARS-CoV-2
spike reactive 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 timers were coupled to magnetic microspheres (Bio-Rad, Hercules, CA). 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 (for example, hospital admissions may
be for non-medical 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 case report form 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 (See Table 1). To measure the burden of comorbidities in a subject, we calculated the Charlson Comorbidity Index (CCI) [38], which is a standardized method of categorizing comorbidities of patients; for this study, we used the updated version age-adjusted CCI [39]. Age, sex, race, and ethnicity were reported by the participant.

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 three dilutions of a known SARS-CoV-2 gene copy number standard (10000, 1000, 100, 10 copies/µL) on each RT-PCR assay run. The viral load calculations were log transformed for normalization such that a rise in log10 quantity GE/reaction equated to a rise in viral load (Supplemental Figure 2). We defined peak viral load as the highest log10 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’s 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 gender, 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 (AIC) and Bayesian information criterion (BIC), 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 (Supplemental 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 versus outpatient). All statistical analyses were conducted using R version 4.0.2 [40].
**Ethics**

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

**RESULTS**

*Obesity, obesity-associated co-morbidities, and severe COVID-19 outcomes are prevalent in those with SARS-CoV-2 infection in the United States Military Health System*

Among 619 COVID-19 positive participants who were enrolled in EPICC from March 20, 2020 through September 15, 2020, 511 (69%) were included in this analysis, as they were classified as COVID-19 cases and had anthropometric data available (Supplemental 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 (Table S1). 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 one 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 (Table S1).
Obesity is independently associated with severe COVID-19 in United States Military Health System beneficiaries

We evaluated both reported and measured obesity in separate models. Logistic regression demonstrated that obesity was associated with an approximately threefold (OR = 2.63 [95% 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 odds ratios 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 (Table S4).

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 three months post 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 severity (inpatient versus outpatients), outpatients in the severely obese group had a log10 1.89 higher N1 GE/reaction and a log10 2.62 N2 GE/reaction increase in peak viral load compared to those with normal weight, adjusting for sampling time (Table S3). 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 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 (Table S2). 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 United States 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 virologic and immunologic 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 which have reported a positive correlation between obesity and SARS-CoV-2 viral load. Maltezou et al., described a higher viral load in obese versus non-obese patients but did not adjust for sampling time or disease severity and only used a dichotomous categorization of obesity [41]. The association between BMI and viral load has also been demonstrated for influenza [42, 43].

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 [44, 45], 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 non-neutralizing antibody, T-cell, and innate immune responses are quantitatively or qualitatively different in obese versus non-obese 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, gender, 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 (IQR: 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. 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’s kappa = 0.58; p < 0.001). Nevertheless, elevated BMI in young muscular active duty soldiers may be a result of increased muscle mass, and not an overweight status per se [46]. 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 [47]. 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 virologic and immunologic exploration are necessary for a comprehensive understanding. Obesity is associated with chronic low-grade systemic inflammation, including higher levels of IL-6 [48, 49]. Investigation of inflammatory cytokine biomarkers (e.g. IL-6, TNF-α, 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 [48, 50]. 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 [48] 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 other examination of other facets of host response to SARS-CoV-2 such as innate and T cell immunity.
CONFLICT OF INTEREST

Potential conflicts of interest. S. D. P., T. H. B, and M.P.S. report that the Uniformed Services University (USU) Infectious Diseases Clinical Research Program (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 III 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 III 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.

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REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. The Lancet Infectious diseases 2020; 20(5): 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(1): 97-105.
3. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020; 584(7821): 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. The Journal of infection 2020; 81(2): e16-e25.
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. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2020; 94: 91-5.
6. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ (Clinical research ed) 2020; 369: m1985.
7. Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: Deteriorating impact on infected patients. Journal of Infection and Public Health 2020; 13(12): 1833-9.
8. Guan W-j, Liang W-h, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. 2020; 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. 2020.
10. Gao F, Zheng KI, Wang X-B, et al. Obesity Is a Risk Factor for Greater COVID-19 Severity. Diabetes Care 2020; 43(7): e72-e4.
11. Simonnet A, Chetboun M, Poissy J, et al. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring) 2020; 28(7): 1195-9.
12. Jiang Y, Chen Y, Mao Y. The contribution of excess weight to prevalent diabetes in Canadian adults. Public health 2008; 122(3): 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(2): 363-9.
14. van der Leeuw J, van der Graaf Y, Nathoe HM, de Borst GJ, Kappelle LJ, Visseren FL. 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 (British Cardiac Society) 2014; 100(18): 1421-9.
15. McCrindle BW. Cardiovascular consequences of childhood obesity. The Canadian journal of cardiology 2015; 31(2): 124-30.
16. Oberman B, Khaku A, Camacho F, Goldenberg D. Relationship between obesity, diabetes and the risk of thyroid cancer. American journal of otolaryngology 2015; 36(4): 535-41.
17. Benedetto C, Salvagno F, Canuto EM, Gennarelli G. Obesity and female malignancies. Best practice & research Clinical obstetrics & gynaecology 2015; 29(4): 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 : CCC 2015; 26(6): 821-30.
19. Pi-Sunyer X. The medical risks of obesity. Postgraduate medicine 2009; 121(6): 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. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2020; 71(15): 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 (Clinical research ed) 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. 2020; 117(35): 21011-3.
23. Sattar N, McInnes IB, McMurray JJJC. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. 2020; 142(1): 4-6.
24. Di Renzo L, Gualtieri P, Pivari F, et al. COVID-19: Is there a role for immunonutrition in obese patient? Journal of Translational Medicine 2020; 18(1): 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.
26. Sanchis-Gomar F, Lavie CJ, Menah MR, Henry BM, Lippi G. Obesity and Outcomes in COVID-19: When an Epidemic and Pandemic Collide. Mayo Clinic proceedings 2020; 95(7): 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. Obesity medicine 2020; 19: 100283.
28. Kruglikov IL, Scherer PE. The Role of Adipocytes and Adipocyte-Like Cells in the Severity of COVID-19 Infections. 2020; 28(7): 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. 2014; 179(5): 462-70.
30. Tanofsky-Kraff M, Sbrocco T, Theim KR, et al. Obesity and the US military family. Obesity (Silver Spring, Md) 2013; 21(11): 2205-20.
31. Kress AM, Hartzel MC, Peterson MRJPm. Burden of disease associated with overweight and obesity among US military retirees and their dependents, aged 38–64, 2003. 2005; 41(1): 63-9.
32. Laing ED, Sterling SL, Richard SA, et al. A betacoronavirus multiplex microsphere immunoassay detects early SARS-CoV-2 seroconversion and controls for pre-existing seasonal human coronavirus antibody cross-reactivity. 2020: 2020.10.14.20207050.
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. 2020: 369: m1443.
34. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. 2020: 2020.02.11.20021493.
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. Journal of Clinical Virology 2020; 127: 104346.
36. Prevention UCfDCa. CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. Vol. CDC-006-00019, Revision: 06.
37. 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. 2021: 2021.02.10.21251518.
38. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases 1987; 40(5): 373-83.
39. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of clinical epidemiology 1994; 47(11): 1245-51.
40. Team TRDC. R: A language environment for statistical computing. R Foundation for Statistical Computing. 2020.
41. 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. The Journal of Infectious Diseases 2021.
42. Meschi S, Selleri M, Lalle E, et al. Duration of viral shedding in hospitalized patients infected with pandemic H1N1. BMC Infectious Diseases 2011; 11(1): 140.
43. Yan J, Grantham M, Pantelic J, et al. Infectious virus in exhaled breath of symptomatic seasonal influenza cases from a college community. 2018; 115(5): 1081-6.
44. 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. Nature Communications 2020; 11(1): 6044.
45. 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. Cellular & Molecular Immunology 2020.
46. Grier T, Canham-Chervak M, Sharp M, Jones BH. Does body mass index misclassify physically active young men. Preventive Medicine Reports 2015; 2: 483-7.
47. Ljungvall Å, Gerdtham UG, Lindblad U. Misreporting and misclassification: implications for socioeconomic disparities in body-mass index and obesity. The European journal of health economics : HEPAC : health economics in prevention and care 2015; 16(1): 5-20.
48. Kuperberg SJ, Navetta-Modrov B. The Role of Obesity in the Immunopathogenesis of COVID-19 Respiratory Disease and Critical Illness. American journal of respiratory cell and molecular biology 2021.
49. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Archives of medical science : AMS 2017; 13(4): 851-63.
50. Korakas E, Ikonomidis I, Kousathana F, et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. American journal of physiology Endocrinology and metabolism 2020; 319(1): E105-e9.
### Table 1. Distribution of demographic data by weight strata in 511 SARS-CoV-2 infections in military health system beneficiaries

| Weight Strata | Normal (N = 140) | Overweight (N = 178) | Obese (N = 121) | Severely Obese (N = 72) | Total (N = 511) | p value<sup>a</sup> |
|---------------|------------------|----------------------|------------------|------------------------|-----------------|-------------------|
| **Gender: Male** |                  |                      |                  |                        |                 | 0.16              |
| Male          | 82 (58.6%)       | 122 (68.5%)         | 82 (67.8%)       | 42 (58.3%)             | 328 (64.2%)     |                   |
| **Age Group** |                  |                      |                  |                        |                 | < 0.01            |
| 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**      |                  |                      |                  |                        |                 | < 0.01            |
| Black         | 15 (10.7%)       | 27 (15.2%)          | 33 (27.3%)       | 19 (26.8%)             | 94 (18.4%)      |                   |
| Category     | BAMC | FBCH | MAMC | Overall |
|--------------|------|------|------|---------|
| Hispanic     | 39 (27.9%) | 53 (29.8%) | 39 (32.2%) | 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 |      |      |      | < 0.01 |
| 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          |      |      |      | 0.09    |
| 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         |      |      |      | < 0.01 |
| 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%) |
| Institution | Normal/Underweight | Overweight | Obese | Severely Obese |
|------------|-------------------|------------|-------|----------------|
| NMCP       | 3 (2.1%)          | 1 (0.6%)   | 1 (0.8%) | 0 (0.0%) |
| NMCSD      | 35 (25.0%)        | 47 (26.4%) | 29 (24.0%) | 14 (19.4%) |
| TAMC       | 16 (11.4%)        | 14 (7.9%)  | 8 (6.6%) | 4 (5.6%) |
| WRNMMC     | 36 (25.7%)        | 43 (24.2%) | 38 (31.4%) | 16 (22.2%) |

*Obesity category defined by body mass index (BMI); individuals were classified as normal/underweight (<24.9 kg/m²), overweight (25-29.9 kg/m²), obese (30-34.9 kg/m²), and severely obese (≥35 kg/m²)

*n x k Fisher’s exact test
Table 2. Crude and adjusted association of covariates with hospitalization in 511 SARS-CoV-2 infections in military health system beneficiaries

| Covariates         | Unadjusted odds ratio (95% CI) | p-value | aORb (95% CI) | p-value | aORc (95% CI) | p-value |
|--------------------|-------------------------------|---------|---------------|---------|---------------|---------|
| Gender: Male       | 1.16 (0.76 - 1.76)            | 0.5     | 1.33 (0.79 - 2.23) | 0.28    | 1.39 (0.82 - 2.35) | 0.22    |
| Age Group: 45-64   | 7 (4.19 - 11.72)              | <0.001  | 5.95 (3.46 - 10.25) | <0.001  | 5.49 (3.17 - 9.52) | <0.001  |
| Age Group: 65+     | 27.93 (14.06 - 55.49)         | <0.001  | 22.53 (10.66 - 47.6) | <0.001  | 22.19 (10.5 - 46.88) | <0.001  |
| Race: Black        | 1.64 (0.93 - 2.89)            | 0.09    | 1.38 (0.69 - 2.74) | 0.36    | 1.36 (0.68 - 2.73) | 0.39    |
| Race: Hispanic     | 1.68 (1.03 - 2.73)            | 0.04    | 1.73 (0.96 - 3.14) | 0.07    | 1.68 (0.92 - 3.06) | 0.09    |
| Race: Others       | 1.5 (0.74 - 3.03)             | 0.26    | 2.21 (0.94 - 5.16) | 0.07    | 2.27 (0.98 - 5.29) | 0.06    |
| Obesity            | 2.63 (1.72 - 4.02)            | <0.001  | 1.91 (1.15 - 3.18) | 0.01    |               |         |
| BMI class: Overweight | 1.85 (1.01 - 3.36)        | 0.04    | 1.39 (0.68 - 2.81) | 0.37    |               |         |
| BMI class: Obese   | 2.59 (1.39 - 4.83)            | <0.001  | 1.71 (0.82 - 3.57) | 0.15    |               |         |
| BMI class: Severely Obese | 6.02 (3.09 - 11.76)   | <0.001  | 3.1 (1.39 - 6.89) | 0.01    |               |         |
| Ischemic heart disease | 7.05 (2.81 - 17.71)    | <0.001  | 0.92 (0.29 - 2.88) | 0.89    | 0.84 (0.27 - 2.66) | 0.77    |
| Condition                        | RR (95% CI)          | p-value | RR (95% CI)          | p-value | RR (95% CI)          | p-value |
|---------------------------------|----------------------|---------|----------------------|---------|----------------------|---------|
| Chronic pulmonary disease       | 8.69 (3.54 - 21.33)  | <0.001  | 3.16 (1.09 - 9.2)    | 0.03    | 3.36 (1.14 - 9.91)   | 0.03    |
| Chronic neurological disease    | 4.5 (1.68 - 12.09)   | <0.001  | 3.06 (0.88 - 10.63)  | 0.08    | 2.93 (0.85 - 10.06)  | 0.09    |

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

*b Adjusted for Obesity

c Adjusted for BMI category

Obesity defined by the medical diagnosis

BMI class computed by participants height and weight
Table 3. Association of obesity category with peak viral load, adjusted for sampling day

Inpatients and outpatients (N = 114)

| Covariates                  | β coefficient (95% CI) | P value | Adjusted β coefficient (95% CI) | P value | Adjusted β coefficient (95% CI) | P value |
|-----------------------------|------------------------|---------|---------------------------------|---------|---------------------------------|---------|
| Obesity                     | 1.2 (0.48, 1.92)       | <0.001  | 0.72 (0.04, 1.41)               | 0.04    |                                 |         |
| BMI class: Overweight       | 1.13 (0.09, 2.16)      | 0.03    | 0.72 (-0.23, 1.67)              | 0.14    |                                 |         |
| BMI class: Obese            | 0.96 (-0.03, 1.95)     | 0.06    | 0.55 (-0.37, 1.47)              | 0.24    |                                 |         |
| BMI class: Severely obese   | 1.61 (0.58, 2.65)      | <0.001  | 0.83 (-0.17, 1.83)              | 0.1     |                                 |         |
| Symptom day                 | -0.07 (-0.1, -0.05)    | <0.001  | -0.06 (-0.09, -0.04)            | <0.001  | -0.07 (-0.09, -0.04)            | <0.001  |

Inpatients and outpatients (N = 114)

| Covariates                  | Coefficient (95% CI) | P value | Adjusted β coefficient (95% CI) | P value | Adjusted β coefficient (95% CI) | P value |
|-----------------------------|----------------------|---------|---------------------------------|---------|---------------------------------|---------|
| Obesity                     | 1.25 (0.51, 1.98)    | <0.001  | 0.81 (0.11, 1.51)               | 0.02    |                                 |         |
| BMI class: Overweight       | 1.21 (0.15, 2.27)    | 0.03    | 0.94 (-0.02, 1.9)               | 0.06    |                                 |         |
| BMI class: Obese            | 1.08 (0.07, 2.1)     | 0.04    | 0.79 (-0.14, 1.72)              | 0.1     |                                 |         |
| BMI class: Severely obese | 1.67 (0.61, 2.72) | <0.001 | 0.96 (-0.05, 1.97) | 0.06 |
|--------------------------|------------------|--------|-------------------|------|
| Symptom day              | -0.07 (-0.1, -0.05) | <0.001 | -0.07 (-0.09, -0.04) | <0.001 | -0.07 (-0.09, -0.04) | <0.001 |

*a Model contains obesity and sampling day

*b Model contains BMI classification and sampling day

Obesity defined by the medical diagnosis

BMI class computed by participants height and weight
Table 4. Association of weight strata with peak anti-spike IgG MFI, adjusted for sampling day and stratified by hospitalization status

|                        | Coefficient (95% CI) | P value | Adjusted coefficient<sup>a</sup> (95% CI) | P value | Adjusted coefficient<sup>b</sup> (95% CI) | P value |
|------------------------|----------------------|---------|------------------------------------------|---------|------------------------------------------|---------|
| **Obesity**            |                      |         |                                          |         |                                          |         |
|                        | 4.09 (2.35, 5.83)    | <0.001  | 4.06 (2.33, 5.79)                        | <0.001  |                                          |         |
| **BMI class: Overweight** | 1.69 (-0.54, 3.92)  | 0.14    |                                          |         | 1.56 (-0.65, 3.78)                      | 0.17    |
| **BMI class: Obese**   | 3.18 (0.68, 5.67)    | 0.01    |                                          |         | 3.21 (0.73, 5.7)                        | 0.01    |
| **BMI class: Severely obese** | 5.53 (2.64, 8.41)  | <0.001  |                                          |         | 5.48 (2.61, 8.34)                      | <0.001  |
| **Symptom day**        | -0.02 (-0.04, 0)     | 0.03    | -0.02 (-0.04, 0)                        | 0.03    | -0.02 (-0.04, 0)                        | 0.03    |

**Inpatients (n = 79)**

|                        | Coefficient (95% CI) | P value | Adjusted coefficient<sup>a</sup> (95% CI) | P value | Adjusted coefficient<sup>b</sup> (95% CI) | P value |
|------------------------|----------------------|---------|------------------------------------------|---------|------------------------------------------|---------|
| **Obesity**            |                      |         |                                          |         |                                          |         |
|                        | 3.42 (1.19, 5.65)    | <0.001  | 3.43 (1.24, 5.61)                        | <0.001  |                                          |         |
| **BMI class: Overweight** | 2.15 (-1.13, 5.44)  | 0.19    |                                          |         | 1.95 (-1.25, 5.15)                      | 0.23    |
| **BMI class: Obese**   | 3.31 (-0.22, 6.85)   | 0.07    |                                          |         | 4.17 (0.65, 7.7)                        | 0.02    |
| **BMI class: Severely obese** | 3.97 (0.54, 7.4)   | 0.02    |                                          |         | 3.53 (0.17, 6.89)                      | 0.04    |
| **Symptom day**        | -0.03 (-0.07, 0)     | 0.04    | -0.03 (-0.07, 0)                        | 0.03    | -0.04 (-0.07, 0)                        | 0.03    |
### Outpatients (n = 235)

|                         | Coefficient (95% CI) | P value | Adjusted coefficient<sup>a</sup> (95% CI) | P value | Adjusted coefficient<sup>b</sup> (95% CI) | P value |
|-------------------------|----------------------|---------|------------------------------------------|---------|------------------------------------------|---------|
| Obesity                 | 3.12 (0.99, 5.24)    | <0.001  | 3.13 (1, 5.25)                           | <0.001  |                                          |         |
| BMI class: Overweight   | 0.98 (-1.62, 3.58)   | 0.46    | 0.92 (-1.68, 3.52)                       | 0.49    |                                          |         |
| BMI class: Obese        | 2.46 (-0.49, 5.41)   | 0.1     | 2.42 (-0.52, 5.37)                       | 0.11    |                                          |         |
| BMI class: Severely obese | 3.91 (0, 7.82)        | 0.05    | 4.09 (0.18, 8)                           | 0.04    |                                          |         |
| Symptom day             | -0.01 (-0.03, 0.01)  | 0.27    | -0.01 (-0.03, 0.01)                      | 0.25    | -0.01 (-0.03, 0.01)                      | 0.22    |

<sup>a</sup>Model contains obesity and sampling day

<sup>b</sup>Model contains BMI classification and sampling day

Obesity defined by the medical diagnosis

BMI class computed by participants height and weight
FIGURE LEGENDS

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

**Figure 2:** Viral load as measured by qPCR N1 GE/reaction (Fig 2A) and N2 GE/reaction (Fig 2B), log10 transformed and plotted by symptom day and stratified by obesity status. Each dot represents as a subject. Local polynomial regression curves were fit to non-obese (*beige*), and obese (*turquoise*) groups; 95% CIs are shaded for non-obese and obese groups, respectively; statistical significance was determined by Wilcoxon rank sum test.

**Figure 3:** Anti-spike IgG MFI plotted by sampling day and stratified by obesity status. Each dot represents as a subject. Local polynomial regression curves were fit to non-obese (*beige*), and obese (*turquoise*) groups; 95% CIs are shaded for non-obese and obese groups, respectively; statistical significance was determined by Wilcoxon rank sum test. MFI, median fluorescence intensity.
Figure 1

A. BMI and COVID-19 severity

B. BMI and O₂ supplement

P < 0.0001
Figure 3

The figure illustrates the IgG (MFI) levels over days post-symptoms onset for inpatient and outpatient groups, categorized by obesity status. The P-values for the comparison are 0.09 for inpatients and 0.01 for outpatients, indicating statistical significance in the obesity effect on IgG levels.

- **Inpatient**:
  - Non-obese: Low IgG levels initially, increasing with time, and reaching a peak around 60 days post-onset.
  - Obese: Higher IgG levels, with a more gradual increase.

- **Outpatient**:
  - Non-obese: Similar to inpatients, with a peak around 60 days.
  - Obese: Higher and more variable IgG levels, with a peak around 40 days.

The data suggests that obesity may influence the IgG response to a viral infection, with obese individuals showing higher IgG levels and a quicker response time compared to non-obese individuals.