Association between Body Mass Index and Risk of COVID-19: A Nationwide Case-Control Study in South Korea

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Summary

In this large national cohort comprised of 3,788 case patients confirmed with COVID-19 and 15,152 matched controls, higher BMI levels were associated with higher risk of contracting COVID-19 infections, even after adjustment for socio-demographic, comorbidity, laboratory, and medication data.
ABSTRACT

Background. Increased body mass index (BMI) has been associated with higher risk of severe coronavirus disease 2019 (COVID-19) infections. However, whether obesity is a risk factor for contracting COVID-19 has been hardly investigated so far.

Methods. We examined the association between BMI level and the risk of COVID-19 infection in a nationwide case-control study comprised of 3,788 case patients confirmed with COVID-19 between January 24 and April 9, 2020 and 15,152 controls matched by age and sex, who were aged 20 years or more and underwent National Health Insurance Service (NHIS) health examinations between 2015–2017, using data from the Korean NHIS with linkage to the Korea Centers for Disease Control and Prevention data. Our primary exposure of interest was BMI level categorized into four groups; <18.5 (underweight), 18.5-22.9 (normal weight), 23-24.9 (overweight), and ≥25 kg/m² (obese).

Results. Of the entire 18,940 study population, 11,755 (62.1%) were women, and the mean (SD) age of the study participants was 53.7 (13.8) years. In multivariable logistic regression models adjusted for sociodemographic, comorbidity, laboratory and medication data, there was a graded association between higher BMI levels and higher risk of COVID-19 infection; compared to normal weight individuals, the adjusted ORs in the overweight and obese individuals were 1.13 (95% CI, 1.03-1.25) and 1.26 (95% CI, 1.15-1.39), respectively. This association was robust across age and sex subgroups.

Conclusions. Higher BMI levels were associated with higher risk of contracting COVID-19.

Keywords: COVID-19; SARS-COV-2; body mass index; obesity.
INTRODUCTION

The ongoing coronavirus disease 2019 (COVID-19) outbreak has led to an unprecedented worldwide health, economic, and social crisis. In South Korea, the first COVID-19 case was confirmed on January 20, 2020 (1). With proactive containment efforts, comprehensive contact tracing, and extensive testing of symptomatic or suspected individuals for COVID-19, South Korea was able to flatten the curve of new COVID-19 infections by mid-March [1, 2]. However, there are growing concerns of ongoing sporadic community infections spreading via asymptomatic patients or persons of unknown viral transmission route.

Given current limited availability of point-of-care COVID-19 testing, identifying and prioritizing testing in individuals at higher risk of severe COVID-19 has been a key emerging issue. From early reports, elderly patients, especially with comorbidities such as hypertension, diabetes, and cardiovascular disease, had the highest rates of hospitalization [3, 4]. As the prevalence of obesity itself and obesity-related non-communicable diseases increases in older adults, it is possible to speculate that obese patients may be more susceptible to develop a more serious illness. In fact, several recent studies found that obesity was associated with a more severe course of COVID-19, which included higher risk of intensive care unit admission, tracheal intubation for mechanical ventilation, and death among patients hospitalized for COVID-19 [5-9]. Therefore, obese patients, whom comprise around 40% of the US population and around 13% of the world population [10], should be considered as high risk and deserve extra attention and precautions to help improve outcomes in patients requiring hospitalization for severe COVID-19.

Meanwhile, whether obesity is a risk factor for contracting COVID-19 infection is another important issue. It is crucial to identify individuals who are susceptible to COVID-19...
infections in order to contain further COVID-19 transmissions, particularly when testing
capacity is limited, and in the absence of effective vaccines or antiviral drugs. However,
recent studies that have included information regarding body mass index (BMI) of patients
with COVID-19 have largely focused on the severity and outcomes of infection, and to date
there is a paucity of studies that examine the association between BMI and the risk of
COVID-19 infection [11, 12]. To address these gaps in knowledge, we sought to determine
the association between BMI categories and the risk of COVID-19 infection in a nationwide
population-based case-control study.

METHODS

Source Population

We obtained data from the Korean National Health Insurance Service (NHIS)
database, which is linked to national health screening examination information and Korea
Centers for Disease Control and Prevention (KCDC) data. The NHIS covers compulsory
health insurance for all citizens in Korea and provides cost-free annual or biennial health
screening examinations to all insured individuals. Since Korea has a single-payer national
health system, all medical records of covered inpatient and outpatient visits as well as the
results from the national health examinations are centralized in the NHIS database, which
includes diagnostic codes, procedures, prescriptions, medical costs, and personal information
(e.g., age, sex, residential area, income level, and disability) [13, 14]. The KCDC database
provides details on all epidemiological investigations for each individual infected with
COVID-19, which include date of laboratory confirmation, residential area, and exposure
history [15].
In constructing the study population of this nationwide case-control study, we first identified all 10,237 patients confirmed with severe acute respiratory syndrome coronavirus 2 infections by a positive result on polymerase chain reaction test of a nasopharyngeal or oropharyngeal sample between January 24, 2020 and April 9, 2020, in South Korea. We then excluded 481 patients aged 19 years and younger, and 5,945 patients who did not undergo NHIS health examinations between January 1, 2015 and December 31, 2017. We further excluded 23 patients who had missing data for any of the study variables, (see following Methods subsections), and thus a total of 3,788 confirmed cases were included. For each case patient, we randomly matched 4 controls by age (5 year intervals) and sex, who underwent NHIS health examinations during the same period. Individuals who died before April 9, 2020, or had missing information on key study variables were not selected as controls. Therefore, the final study population comprised 18,940 participants, which included 3,788 case patients and 15,152 matched controls (Supplementary Figure 1). The Institutional Review Board of NHIS Ilsan Hospital approved this study and waived the requirement for informed consent as only deidentified data was used.

Data Collection and Measurements

Baseline data on sociodemographic information such as age, sex, income level, and residential area was collected in the year prior to the index date. We defined the index date as the end of the study period (i.e., April 9, 2020), for both case patients and matched controls. Comorbidities (e.g., diabetes, ischemic heart disease, congestive heart failure, cerebrovascular disease, hemiplegia, dementia, peripheral vascular disease, liver disease, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, chronic kidney disease, and malignancy) were assessed using the International Statistical Classification of Disease and Related Health Problems, Tenth Revision coding algorithms (Supplementary...
Table 1), which were ascertained by the presence of at least two or more diagnostic codes up to five years prior to the index date. The Charlson comorbidity index (CCI) score was also calculated as a proxy of disease burden and illness severity [16]. Use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, or dipeptidyl peptidase-4 (DPP-4) inhibitors were defined as the prescription for these medications identified up to five years before the index date.

All anthropometry and laboratory results were collected at every health examination visit between 2015 and 2017, in which results were averaged over the three years. BMI was calculated as weight in kilograms divided by height in meters-squared. Blood pressure was measured using standardized methods while the participant was sitting on a chair after a five-minute rest. Serum lipid, glucose, and creatinine levels were measured from specimens collected while fasting. Estimated glomerular filtration rate (eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation for creatinine [17].

**Statistical Analysis**

Our primary exposure of interest was BMI, which was presented as the average of all measurements in each health examination visit between 2015 and 2017. In the study population, the mean (standard deviation, SD) and median (inter-quartile range, IQR) number of BMI measurements that contributed to each BMI value per individual were 1.7 (0.7) and 2.0 (1.0-2.0), respectively, which were equal between case patients and matched controls. Given a possible non-linear relationship with COVID-19 infection risk, BMI was treated as a categorical variable and divided into four categories: <18.5 (underweight), 18.5-22.9 (normal weight), 23-24.9 (overweight), and ≥25 kg/m² (obese). Obesity was defined as ≥25 kg/m² based on a WHO cut-off point for Asian populations [18]. The normal weight BMI category (18.5-22.9 kg/m²) was chosen as the reference because it included the largest number of
participants and allowed for the most precise comparison with lower and higher BMI categories.

To examine the association between BMI categories and the risk of COVID-19 infection, we used multivariable logistic regression models with four incremental levels of adjustment as follows: (1) Model 1: unadjusted; (2) Model 2: adjusted for age, sex, residential area, income level, smoking status, and CCI score; (3) Model 3: adjusted for all covariates in model 2 plus systolic blood pressure, low-density lipoprotein cholesterol level, triglyceride level, high-density lipoprotein cholesterol level, fasting glucose level, and eGFR; (4) Model 4: adjusted for all covariates in model 3 plus use of ACE inhibitors and/or angiotensin-receptor blockers, and use of DPP-4 inhibitors. To test the robustness of our findings, we further performed subgroup analyses by age (20-39, 40-49, and ≥60 years) and sex (male and female). The risk of developing COVID-19 was expressed as odds ratios (ORs) and 95% confidence intervals (CIs).

For sensitivity analyses, we additionally assessed the optimal cut-off point of BMI value for predicting COVID-19 diagnosis, based on the area under the receiver operating characteristic curve (AUROC). To compare predictive performance of BMI, we also calculated the net reclassification improvement (NRI) and integrated discrimination index (IDI) between adjusting models with and without BMI.

Data from descriptive analyses were summarized using means (SD), medians (IQR), or numbers (proportions) as appropriate, and were compared using independent-sample t-tests or chi-square tests, respectively. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). $P < 0.05$ was used as the threshold for statistical significance for any tests.
RESULTS

Clinical Characteristics of Study Population

Clinical characteristics of the 3,788 case patients with COVID-19 and 15,152 matched controls who met the eligibility criteria for the study are shown in Table 1. The mean (SD) age of the study participants was 53.7 (13.8) years, among whom 62.1% were women, 87.0% were urban residents, and 13.7% had at least one or more comorbidities based on the CCI components. The mean (SD) and median (IQR) BMI values in case patients and matched controls were 24.0 (3.4) kg/m$^2$ and 23.8 (21.6-26.0) kg/m$^2$, and 23.8 (3.4) kg/m$^2$ and 23.5 (21.5-25.7) kg/m$^2$, respectively. Overall, case patients were more likely to reside in rural areas, have lower income levels, higher prevalence of comorbidities, and be prescribed with DPP-4 inhibitors. In contrast, matched controls were more likely to be current smokers, have higher systolic blood pressure, lipid levels, and eGFR.

Association between BMI and risk of COVID-19

In logistic regression models that were adjusted for socio-demographic, comorbidity, laboratory and medication data, there was a graded association between higher BMI levels and higher risk of COVID-19 infection (Figure 1). Specifically, compared to normal weight individuals, we observed a 13% and 25% higher risk of COVID-19 in overweight and obese individuals; adjusted ORs in model (3) were 1.13 (95% CI, 1.03-1.25) and 1.25 (95% CI, 1.14-1.38), respectively (model 3 in Table 2). It should be noted that these associations remained largely unchanged despite additional adjustments for medications known to potentially influence ACE2 expression including ACE inhibitors or angiotensin-receptor blockers, and DPP-4 inhibitors (model 4 in Table 2). In contrast, underweight individuals tended to trend toward increased risk of contracting COVID-19 infections, but this was not statistically significant.
**Subgroup analyses**

We then examined the association between BMI category and risk of COVID-19 across clinically relevant subgroups. In subgroup analyses, a stepwise increase in risk of COVID-19 infection associated with incrementally higher BMI was largely consistent across all age categories and sex (Figure 2). Of note, the magnitude of adjusted ORs in obese individuals was much stronger in gradually younger age categories, which were 1.53 (95% CI, 1.18-1.99), 1.26 (95% CI, 1.10-1.44), and 1.19 (95% CI, 1.02-1.39) in the 20-39, 40-59, and ≥60 years age categories, respectively (Table 3).

**Sensitivity analyses**

Next, we determined the optimal cut-off points for predicting COVID-19 diagnosis based on the AUROC and found that optimal threshold levels of BMI were different across the whole population and various subgroups; these were lowest (21.8 kg/m² of BMI) in patients aged 40-59 years (AUROC 0.525; 95% CI, 0.510-0.539) and women (AUROC 0.525; 95% CI, 0.512-0.538), while the highest (25.9 kg/m² of BMI) in elderly patients aged 60 years and older (AUROC 0.518; 95% CI, 0.500-0.536) and men (AUROC 0.520; 95% CI, 0.503-0.537) (Supplementary Table 2). When we compared the predictive ability of BMI for risk of COVID-19 by calculating NRI and IDI values, positive NRI or IDI values indicated that models incorporating BMI were statistically superior to corresponding models without BMI (Supplementary Table 3).
DISCUSSION

In this nationwide population-based case-control study, we found a graded association between higher BMI levels and higher risk of COVID-19 infections. In particular, obese individuals showed the highest susceptibility to COVID-19, even after adjusting for potential confounding factors including socio-demographic, comorbidity, laboratory, and medication data. This association was robust across age and sex subgroups. These findings suggest that BMI could be an important consideration in estimating an individual’s risk of acquiring COVID-19, and in devising strategies that could contain further spread of COVID-19 at a population level.

While obesity is a well-recognized risk factor for various cardio-metabolic diseases, its role in infection must not be ignored [19]. During the 2009 H1N1 influenza A virus pandemic, obesity emerged as a novel major predisposing factor in transmission and severe course of viral disease [20-22]. Obesity not only prolonged the duration of influenza virus shedding, but was also linked to higher risks of hospitalization and mortality [23-25]. Furthermore, impaired immune responses to vaccination in obese individuals have also been reported in several types of viral infections such as influenza, hepatitis B, and tetanus [26-28].

By analogy to other viral infections, obesity may play an important role in COVID-19 transmission, but this hypothesis has hardly been investigated so far. In the present study using a national cohort of 18,940 case patients and matched controls, we found a significant
The relationship between incrementally higher BMI and the risk of COVID-19 infection, in which obese individuals with a BMI of more than 25 kg/m² was associated with a 26% higher risk of contracting COVID-19 than normal weight individuals. More importantly, these associations were consistent even after adjusting for socio-demographics, co-morbidities, cardio-metabolic components, and medications, which suggest that obesity may be an independent risk factor in acquiring COVID-19 infections. To our knowledge, although several observational studies have reported a higher risk for severe COVID-19 associated with obesity, this is the first case-control study to confirm the relationship between obesity and the risk of COVID-19 acquisition. From the preventive perspective, our study findings are particularly informative in that obesity is not only a risk factor for severe course of COVID-19 disease, but also for acquiring the virus itself. Thus, not only should BMI be a major consideration in informing treatment strategies, but also in preventive strategies for COVID-19. Of note, the Infectious Disease Society of America had recently developed recommendations for diagnostic testing prioritization, with priorities given to critically ill patients, health care workers, immunocompromised, and elderly patients [29]. Based on our findings, future recommendations could include individuals with higher BMI levels. Moreover, although the results of prediction testing in this study may be insufficient to provide concrete guidance for diagnostic testing prioritization and preventive strategies, this study could serve as a starting point for future investigations that could potentially look into the causal relationship between BMI and risk of contracting COVID-19 infections.

Due to a paucity of data at this time, the underlying mechanisms responsible for the association between obesity and COVID-19 infection are unclear, but several plausible explanations could be contemplated. First, COVID-19 is known to have a high affinity for human ACE2, which acts as the putative receptor of entry of COVID-19 into host cells [30]. Notably, ACE2 expression levels are actually higher in adipose tissue than in other organs.
including the lungs, heart, and the kidneys. Obese individuals with more adipose tissue therefore have more ACE2-expressing cells and a larger amount of ACE2, and thus greater vulnerability to COVID-19 [31, 32]. Second, by analogy of other viral agents such as human adenovirus Ad-36, influenza A virus, human immunodeficiency virus, and cytomegalovirus [32, 33], adipose tissue can also act as a reservoir and host entry point for COVID-19.

Finally, metabolic inflammation associated with obesity potentially impairs immune responses to viral infections. For example, obesity appears to confer an inadequate immune response to viral infections such as H1N1 influenza or hepatitis B, and a greater vulnerability to overwhelming sepsis following viral illness [26, 34, 35]. All of these possible mechanisms suggest that studies into the pathogenesis of COVID-19 should not merely consider the microbiologic aspects, but also the metabolic aspects of the viral disease.

The strengths of this study include its availability of detailed patient-level information on socio-demographics, comorbidities, anthropometry, and laboratory data from a large national cohort; utilization of age, sex matched population cohort; and vigorous adjustment for potential confounders of obesity and related infection risk. However, several limitations of our study bear mention. First, potential selection bias cannot be excluded given our restriction of analyses to participants who underwent NHIS health examination between 2015 and 2017, capturing only a third of total confirmed COVID-19 cases between January 24 and April 9, 2020, in South Korea. This proportion of complete health check-ups was particularly lower compared to that of the entire population, which was approximately 77% during the same period. Second, rather than changes in BMI over time, the averaged BMI was assessed in this study. However, the likelihood of BMI substantially changing during the five years of follow up in our study was deemed unlikely. Third, our findings may not be generalizable to populations outside of South Korea, given the social factors, environmental exposures, national healthcare policies, and chronic disease burden including obesity that may be distinct
from other countries. For instance, the small sample size of case patients with a BMI of over 30kg/m², which is a frequently defined obesity threshold in western countries, makes it difficult to further categorize our BMI groups to include higher levels.

In conclusion, higher BMI was associated with higher risk of COVID-19 infections. As the COVID-19 pandemic evolves, continued investigation into the interplay between metabolic health, especially obesity, and the risk of COVID-19 is warranted in order to inform control strategies for COVID-19. While awaiting further evidence supporting causal relationship between obesity and the risk of COVID-19 infections, individuals with a higher BMI could be potentially classified as high risk and thus, prioritized in COVID-19 testing.
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References

1. Korea Ministry of Health and Welfare, Center for Disease Control and Prevention. The updates on COVID-19 in Korea: for press release. 2020. Available at: https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030. Accessed 2 July 2020.

2. Song JY, Yun JG, Noh JY, Cheong HJ, Kim WJ. Covid-19 in South Korea - Challenges of Subclinical Manifestations. N Engl J Med 2020; 382:1858-9.

3. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care 2020; 24:108.

4. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69:458-64.

5. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020; 382:2012-22.

6. Petrelli 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.

7. 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; 28:1195-9.

8. Caussy C, Pattou F, Wallet F, et al. Prevalence of Obesity Among Adult Inpatients With COVID-19 in France. Lancet Diabetes Endocrinol 2020; 8:562-4.

9. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic Characteristics and Prognosis of Inpatients With COVID-19 and Diabetes: The CORONADO Study. Diabetologia 2020; 63:1500-15.

10. World Health Organization. Global Health Observatory (GHO) data: overweight and obesity. Available at: www.who.int/gho/ncd/risk_factors/overweight_obesity/obesity_adults/en. Accessed 2 July 2020.

11. Sattar N, Ho FK, Gill JM, et al. BMI and future risk for COVID-19 infection and death across sex, age, and ethnicity: Preliminary findings from UK biobank. Diabetes Metab Syndr 2020; 14:1149-51.

12. 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; S1473-3099(20)30371-6. doi:10.1016/S1473-3099(20)30371-6.
13. Kwon S. Thirty years of national health insurance in South Korea: lessons for achieving universal health care coverage. Health Policy Plan 2009; 24:63-71.

14. Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the korean national health insurance system. Diabetes Metab J 2014; 38:395-403.

15. Park S, Choi GJ, Ko H. Information Technology-Based Tracing Strategy in Response to COVID-19 in South Korea-Privacy Controversies. JAMA 2020;10.1001/jama.2020.6602. doi:10.1001/jama.2020.6602.

16. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43:1130-9.

17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150:604-12.

18. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363:157-63.

19. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006; 6:438-46.

20. Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ 2013; 347:f5061.

21. Louie JK, Acosta M, Samuel MC, et al. A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis 2011; 52:301-12.

22. Sun Y, Wang Q, Yang G, Lin C, Zhang Y, Yang P. Weight and prognosis for influenza A(H1N1)pdm09 infection during the pandemic period between 2009 and 2011: a systematic review of observational studies with meta-analysis. Infect Dis (Lond) 2016; 48:813-22.

23. Maier HE, Lopez R, Sanchez N, et al. Obesity Increases the Duration of Influenza A Virus Shedding in Adults. J Infect Dis 2018; 218:1378-82.

24. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 2009; 361:1935-44.

25. Louie JK, Acosta M, Winter K, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 2009; 302:1896-902.

26. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes (Lond) 2012; 36:1072-7.

27. Weber DJ, Rutala WA, Samsa GP, Santimaw JE, Lemon SM. Obesity as a predictor of poor antibody response to hepatitis B plasma vaccine. JAMA 1985; 254:3187-9.

28. Eliakim A, Schwindt C, Zaldivar F, Casali P, Cooper DM. Reduced tetanus antibody titers in overweight children. Autoimmunity 2006; 39:137-41.
29. Infectious Diseases Society of America. COVID-19 Prioritization of Diagnostic Testing. Available at: https://www.idsociety.org/globalassets/idsa/public-health/covid-19-prioritization-of-dx-testing.pdf. Accessed 10 August 2020.

30. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579:270-3.

31. Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol 2020; 16:341-2.

32. Kassir R. Risk of COVID-19 for patients with obesity. Obes Rev 2020; 21:e13034.

33. Bourgeois C, Gorwood J, Barrail-Tran A, et al. Specific Biological Features of Adipose Tissue, and Their Impact on HIV Persistence. Front Microbiol 2019; 10:2837.

34. Kim YH, Kim JK, Kim DJ, et al. Diet-induced obesity dramatically reduces the efficacy of a 2009 pandemic H1N1 vaccine in a mouse model. J Infect Dis 2012; 205:244-51.

35. O'Shea D, Corrigan M, Dunne MR, et al. Changes in human dendritic cell number and function in severe obesity may contribute to increased susceptibility to viral infection. Int J Obes (Lond). 2013; 37:1510-3.
Table 1. Clinical Characteristics of Case patients and Matched Controls

| Characteristics                     | Overall (n=18,940) | Case Participants (n=3,788) | Matched Controls (n=15,152) | p    |
|-------------------------------------|--------------------|-----------------------------|-----------------------------|------|
| Age, mean (SD), years               | 53.7 (13.8)        | 53.7 (13.8)                 | 53.7 (13.8)                 | 1.000|
| Age intervals, number (%)           |                    |                             |                             | 1.000|
| 20-29 years                         | 1,160 (6.1)        | 232 (6.1)                   | 928 (6.1)                   |      |
| 30-39 years                         | 1,820 (9.6)        | 364 (9.6)                   | 1,456 (9.6)                 |      |
| 40-49 years                         | 3,750 (19.8)       | 750 (19.8)                  | 3,000 (19.8)                |      |
| 50-59 years                         | 5,685 (30.0)       | 1,137 (30.0)                | 4,548 (30.0)                |      |
| 60-69 years                         | 4,195 (22.2)       | 839 (22.2)                  | 3,356 (22.2)                |      |
| ≥70 years                           | 2,330 (12.3)       | 466 (12.3)                  | 1,864 (12.3)                |      |
| Sex, number (%)                     |                    |                             |                             |      |
| Men                                 | 7,185 (37.9)       | 1,437 (37.9)                | 5,748 (37.9)                | 1.000|
| Women                               | 11,755 (62.1)      | 2,351 (62.1)                | 9,404 (62.1)                |      |
| Residential area, number (%)        |                    |                             |                             | <0.001|
| Large city                          | 13,909 (73.4)      | 2,791 (73.7)                | 11,118 (73.4)               |      |
| Small city                          | 4,081 (21.6)       | 733 (19.4)                  | 3,348 (22.1)                |      |
| Rural area                          | 950 (5.0)          | 264 (7.0)                   | 686 (4.5)                   |      |
| Income quantiles, number (%)        |                    |                             |                             | <0.001|
| First quantile (lowest)             | 4,202 (22.2)       | 1,057 (27.9)                | 3,145 (20.8)                |      |
| Second quantile                     | 2,790 (14.7)       | 562 (14.8)                  | 2,228 (14.7)                |      |
| Third quantile                      | 3,268 (17.3)       | 584 (15.4)                  | 2,684 (17.7)                |      |
| Fourth quantile                     | 4,053 (21.4)       | 716 (18.9)                  | 3,337 (22.0)                |      |
| Fifth quantile (highest)            | 4,627 (24.4)       | 869 (23.0)                  | 3,758 (24.8)                |      |
| Comorbidities, number (%)           |                    |                             |                             |      |
| Diabetes                            | 1,010 (5.3)        | 268 (7.1)                   | 742 (4.9)                   | <0.001|
| Ischemic heart disease              | 336 (1.8)          | 73 (1.9)                    | 263 (1.7)                   | 0.425|
| Heart failure                       | 124 (0.7)          | 24 (0.6)                    | 100 (0.7)                   | 0.857|
| Cerebrovascular disease             | 490 (2.6)          | 135 (3.6)                   | 355 (2.3)                   | <0.001|
| Hemiplegia                          | 101 (0.5)          | 36 (1.0)                    | 65 (0.4)                    | <0.001|
| Dementia                            | 136 (0.7)          | 66 (1.7)                    | 70 (0.5)                    | <0.001|
| Peripheral vascular disease         | 83 (0.4)           | 17 (0.4)                    | 66 (0.4)                    | 0.912|
| Liver disease                       | 234 (1.2)          | 87 (2.3)                    | 147 (1.0)                   | <0.001|
| Chronic pulmonary disease           | 411 (2.2)          | 101 (2.7)                   | 310 (2.0)                   | 0.019|
| Connective tissue disease           | 97 (0.5)           | 25 (0.7)                    | 72 (0.5)                    | 0.154|
| Peptic ulcer disease                | 554 (2.9)          | 107 (2.8)                   | 447 (3.0)                   | 0.682|
| Chronic kidney disease              | 45 (0.2)           | 7 (0.2)                     | 38 (0.3)                    | 0.456|
| Malignancy                          | 555 (2.9)          | 121 (3.2)                   | 434 (2.9)                   | 0.281|
| CCI scores, number (%)              |                    |                             |                             | <0.001|
| 0                                   | 16,351 (86.3)      | 3,159 (83.4)                | 13,192 (87.1)               |      |
| 1                                   | 1,334 (7.0)        | 301 (7.9)                   | 1,033 (6.8)                 |      |
| 2                                   | 697 (3.7)          | 167 (4.4)                   | 530 (3.5)                   |      |
| ≥3                                  | 558 (3.0)          | 161 (4.3)                   | 397 (2.6)                   |      |
| Smoking status, number (%)          |                    |                             |                             | <0.001|
| Never                               | 13,728 (72.5)      | 2,931 (77.4)                | 10,797 (71.3)               |      |
| Former                              | 2,566 (13.5)       | 733 (14.7)                  | 2,007 (13.2)                |      |
| Current                             | 2,646 (14.0)       | 264 (7.9)                   | 2,348 (15.5)                |      |
Prescribed medications, number (%)

| Prescribed Medication            | Number (Percentage) | Number (Percentage) | Number (Percentage) | p-value |
|----------------------------------|---------------------|---------------------|---------------------|---------|
| ACE inhibitor or ARB             | 4,169 (22.0)        | 834 (22.0)          | 3,335 (22.0)        | 0.993   |
| DPP-4 inhibitor                  | 929 (4.9)           | 252 (6.7)           | 677 (4.5)           | 0.044   |
| BMI, mean (SD), kg/m²            | 23.8 (3.4)          | 24.0 (3.4)          | 23.8 (3.4)          | <0.001  |
| SBP, mean (SD), mmHg             | 121.6 (13.9)        | 121.0 (14.2)        | 121.8 (13.9)        | 0.005   |
| LDL-C, mean (SD), mg/dL          | 114.7 (34.3)        | 114.6 (31.6)        | 114.7 (35.0)        | 0.087   |
| HDL-C, mean (SD), mg/dL          | 57.5 (16.5)         | 56.7 (14.2)         | 57.7 (17.0)         | <0.001  |
| Triglyceride, mean (SD), mg/dL   | 123.0 (86.2)        | 120.4 (78.9)        | 123.7 (87.9)        | 0.026   |
| Fasting glucose, mean (SD), mg/dL| 99.1 (22.7)         | 99.8 (22.3)         | 99.0 (22.8)         | 0.039   |
| eGFR, mean (SD), mL/min/1.73m²   | 91.0 (18.1)         | 90.4 (17.8)         | 91.1 (18.2)         | 0.022   |

Data are presented as means (standard deviation) or numbers (percentages). Abbreviations: SD, standard deviation; CCI, Charlson comorbidity index; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; DPP-4, dipeptidyl peptidase-4; BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.
Table 2. Associations between BMI categories and risk of COVID-19 infection.

| BMI (kg/m²) | Study Participants, No (%) | Odds Ratio (95% CI)          |
|-------------|-----------------------------|-----------------------------|
|             | Case Patients | Controls  | Model 1 | Model 2 | Model 3 | Model 4 |
| <18.5       | 132 (3.5)     | 512 (3.4) | 1.13 (0.92-1.38) | 1.11 (0.9-1.35) | 1.10 (0.9-1.35) | 1.10 (0.9-1.35) |
| 18.5 to <23 | 1,414 (37.3) | 6,173 (40.7) | 1.00 | 1.00 | 1.00 | 1.00 |
| 23 to <25   | 933 (24.6)   | 3,704 (24.5) | 1.10 (1.00-1.21) | 1.12 (1.02-1.23) | 1.13 (1.03-1.25) | 1.13 (1.03-1.25) |
| ≥25         | 1,309 (34.6) | 4,763 (31.4) | 1.20 (1.10-1.31) | 1.21 (1.11-1.32) | 1.25 (1.14-1.38) | 1.26 (1.15-1.39) |

Adjustments in (1) Model 1: unadjusted; (2) Model 2: age, sex, residential area, income level, smoking status, and Charlson comorbidity index score; (3) Model 3: all covariates in model (2) plus systolic blood pressure, low-density lipoprotein cholesterol level, triglyceride level, high-density lipoprotein cholesterol level, fasting glucose level, and estimated glomerular filtration rate; and (4) Model 4: all covariates in model (3) plus use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and use of dipeptidyl peptidase-4 inhibitors. Abbreviations: BMI, body mass index; CI, confidence interval.
Table 3. Associations between BMI and risk of COVID-19 infection across subgroups stratified by age and sex.

| BMI (kg/m²) | Study Participants, No (%) | Odds Ratio (95% CI) | Model 1 | Model 2 | Model 3 | Model 4 |
|-------------|-----------------------------|---------------------|---------|---------|---------|---------|
|             | Case Patients (n=3,788)     | Controls (n=15,152) |         |         |         |         |
| Age, 20-39 years |                             |                     |         |         |         |         |
| <18.5       | 49 (8.2)                    | 204 (8.5)           | 1.03 (0.74-1.45) | 1.01 (0.71-1.42) | 0.97 (0.68-1.37) | 0.97 (0.69-1.37) |
| 18.5 to <23 | 268 (45.0)                  | 1,153 (48.4)        | 1.00    | 1.00    | 1.00    | 1.00    |
| 23 to <25   | 104 (14.4)                  | 419 (17.6)          | 1.07 (0.83-1.38) | 1.13 (0.87-1.48) | 1.20 (0.91-1.57) | 1.19 (0.91-1.56) |
| ≥25         | 175 (29.4)                  | 608 (25.5)          | 1.24 (1.00-1.53) | 1.33 (1.05-1.67) | 1.53 (1.17-1.98) | 1.53 (1.18-1.99) |
| Age, 40-59 years |                             |                     |         |         |         |         |
| <18.5       | 54 (2.9)                    | 221 (2.9)           | 1.08 (0.79-1.47) | 1.10 (0.80-1.50) | 1.08 (0.79-1.48) | 1.08 (0.79-1.48) |
| 18.5 to <23 | 735 (38.9)                  | 3,238 (42.9)        | 1.00    | 1.00    | 1.00    | 1.00    |
| 23 to <25   | 467 (24.8)                  | 1,765 (23.4)        | 1.17 (1.02-1.33) | 1.16 (1.01-1.32) | 1.18 (1.06-1.35) | 1.18 (1.03-1.35) |
| ≥25         | 631 (33.4)                  | 2,324 (30.8)        | 1.20 (1.06-1.35) | 1.18 (1.04-1.34) | 1.25 (1.09-1.43) | 1.26 (1.10-1.44) |
| Age, ≥60 years |                             |                     |         |         |         |         |
| <18.5       | 29 (2.2)                    | 87 (1.7)            | 1.45 (0.94-2.23) | 1.43 (0.92-2.23) | 1.47 (0.94-2.29) | 1.47 (0.95-2.30) |
| 18.5 to <23 | 411 (31.5)                  | 1,782 (34.1)        | 1.00    | 1.00    | 1.00    | 1.00    |
| 23 to <25   | 362 (27.8)                  | 1,520 (29.1)        | 1.03 (0.88-1.21) | 1.04 (0.89-1.22) | 1.04 (0.88-1.22) | 1.04 (0.88-1.22) |
| ≥25         | 503 (38.5)                  | 1,831 (35.1)        | 1.19 (1.03-1.38) | 1.17 (1.01-1.36) | 1.18 (1.02-1.38) | 1.19 (1.02-1.39) |
| Men         |                             |                     |         |         |         |         |
| <18.5       | 23 (1.6)                    | 97 (1.7)            | 1.03 (0.65-1.64) | 0.98 (0.60-1.59) | 0.98 (0.60-1.60) | 0.98 (0.60-1.60) |
| 18.5 to <23 | 408 (28.4)                  | 1,770 (30.8)        | 1.00    | 1.00    | 1.00    | 1.00    |
| 23 to <25   | 371 (25.8)                  | 1,569 (27.3)        | 1.03 (0.88-1.20) | 1.04 (0.89-1.22) | 1.05 (0.89-1.24) | 1.06 (0.90-1.24) |
| ≥25         | 635 (44.2)                  | 2,312 (40.2)        | 1.19 (1.04-1.37) | 1.21 (1.05-1.39) | 1.24 (1.07-1.45) | 1.26 (1.08-1.47) |
| Women       |                             |                     |         |         |         |         |
| <18.5       | 109 (4.6)                   | 415 (4.4)           | 1.15 (0.92-1.44) | 1.14 (0.91-1.43) | 1.13 (0.90-1.42) | 1.13 (0.90-1.42) |
| BMI Category | N   (%)   | Cases (SD) | OR Unadjusted (95% CI) | OR Model 2 (95% CI) | OR Model 3 (95% CI) | OR Model 4 (95% CI) |
|--------------|----------|------------|------------------------|---------------------|---------------------|---------------------|
| 18.5 to <23  | 1,006 (42.8) | 4,403 (46.8) | 1.00                   | 1.00                | 1.00                | 1.00                |
| 23 to <25    | 562 (23.9)  | 2,135 (22.7) | 1.15 (1.03-1.29)       | 1.16 (1.03-1.30)    | 1.17 (1.04-1.32)    | 1.17 (1.04-1.32)    |
| ≥25          | 674 (28.7)  | 2,451 (26.1) | 1.21 (1.08-1.34)       | 1.19 (1.07-1.33)    | 1.24 (1.10-1.40)    | 1.24 (1.10-1.40)    |

Adjustments in (1) Model 1: unadjusted; (2) Model 2: age, sex, residential area, income level, smoking status, and Charlson comorbidity index score; (3) Model 3: all covariates in model (2) plus systolic blood pressure, low-density lipoprotein cholesterol level, triglyceride level, high-density lipoprotein cholesterol level, fasting glucose level, and estimated glomerular filtration rate; and (4) Model 4: all covariates in model (3) plus use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and use of dipeptidyl peptidase-4 inhibitors. Abbreviations: BMI, body mass index; CI, confidence interval.
Figure Legends

Figure 1. Associations between BMI and risk of COVID-19 infection. Adjustments in (1) Model 1: unadjusted; (2) Model 2: age, sex, residential area, income level, smoking status, and Charlson comorbidity index score; (3) Model 3: all covariates in model (2) plus systolic blood pressure, low-density lipoprotein cholesterol level, triglyceride level, high-density lipoprotein cholesterol level, fasting glucose level, and estimated glomerular filtration rate; and (4) Model 4: all covariates in model (3) plus use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and use of dipeptidyl peptidase-4 inhibitors. Abbreviations: BMI, body mass index; CI, confidence interval.

Figure 2. Associations between BMI and risk of COVID-19 infection across subgroups stratified by age (A) and sex (B). All models were adjusted for age, sex, residential area, income level, smoking status, Charlson comorbidity index score, systolic blood pressure, low-density lipoprotein cholesterol level, triglyceride level, high-density lipoprotein cholesterol level, fasting glucose level, estimated glomerular filtration rate, use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and use of dipeptidyl peptidase-4 inhibitors. Abbreviations: BMI, body mass index; CI, confidence interval.
| Body Mass Index (kg/m²) | Model 1 | Model 2 | Model 3 | Model 4 |
|------------------------|---------|---------|---------|---------|
| < 18.5                 | 0.8     | 1.0     | 1.2     | 1.4     |
| 18.5 to < 23           | 1.0     | 1.2     | 1.4     | 1.6     |
| 23 to < 25             | 1.2     | 1.4     | 1.6     | 1.8     |
| ≥ 25                   | 1.4     | 1.6     | 1.8     | 2.0     |

Odds Ratio

Model 1

Model 2

Model 3

Model 4

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Body Mass Index (kg/m²)

|         | Men (N=7,185) | Women (N=11,755) |
|---------|---------------|-------------------|
| < 18.5 |               |                   |
| 18.5 to <23 |           |                   |
| 23 to <25 |           |                   |
| ≥ 25    |           |                   |

Odds Ratio

- Men (N=7,185)
- Women (N=11,755)

Ages:
- Age 20-39 years (N=2,980)
- Age 40-59 years (N=9,435)
- Age ≥60 years (N=6,525)