Annals of Internal Medicine ORIGINAL RESEARCH

Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization

Sara Y. Tartof, PhD, MPH; Lei Qian, PhD, MS; Vennis Hong, MPH; Rong Wei, MA; Ron F. Nadjafi, MD, MS; Heidi Fischer, PhD, MS; Zhuoxin Li, MS; Sally F. Shaw, DrPH, MPH; Susan L. Caparosa, MA; Claudia L. Nau, PhD, MA; Tanmai Saxena, MD, PhD; Gunter K. Rieg, MD; Bradley K. Ackerson, MD; Adam L. Sharp, MD, MSc; Jacek Skarbinski, MD; Tej K. Naik, MD; and Sameer B. Murali, MD

Background: Obesity, race/ethnicity, and other correlated characteristics have emerged as high-profile risk factors for adverse coronavirus disease 2019 (COVID-19)–associated outcomes, yet studies have not adequately disentangled their effects.

Objective: To determine the adjusted effect of body mass index (BMI), associated comorbidities, time, neighborhood-level sociodemographic factors, and other factors on risk for death due to COVID-19.

Design: Retrospective cohort study.

Setting: Kaiser Permanente Southern California, a large integrated health care organization.

Patients: Kaiser Permanente Southern California members diagnosed with COVID-19 from 13 February to 2 May 2020.

Measurements: Multivariable Poisson regression estimated the adjusted effect of BMI and other factors on risk for death at 21 days; models were also stratified by age and sex.

Results: Among 6916 patients with COVID-19, there was a J-shaped association between BMI and risk for death, even after adjustment for obesity-related comorbidities. Compared with patients with a BMI of 18.5 to 24 kg/m^2, those with BMIs of 40 to 44 kg/m^2 and greater than 45 kg/m^2 had relative risks of 2.68 (95% CI, 1.43 to 5.04) and 4.18 (CI, 2.12 to 8.26), respectively. This risk was most striking among those aged 60 years or younger and men. Increased risk for death associated with Black or Latino race/ethnicity or other sociodemographic characteristics was not detected.

Limitation: Deaths occurring outside a health care setting and not captured in membership files may have been missed.

Conclusion: Obesity plays a profound role in risk for death from COVID-19, particularly in male patients and younger populations. Our capitated system with more equalized health care access may explain the absence of effect of racial/ethnic and socioeconomic disparities on death. Our data highlight the leading role of severe obesity over correlated risk factors, providing a target for early intervention.

Primary Funding Source: Roche–Genentech.

Ann Intern Med. doi:10.7326/M20-3742 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 12 August 2020.

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since first detection of the virus in December 2019 (1), more than 4.4 million cases have spread throughout the world. The disease is primarily transmitted through large respiratory droplets, and disease severity ranges from mild self-limiting flu-like illness to fulminant pneumonia, respiratory failure, and death. Estimated mortality rates vary considerably over time and geography, likely because of evolving testing strategies and other factors (2). Although several risk factors for severe disease, such as increasing age and male sex, are frequently cited in research, other high-risk characteristics predominate by geographic region and may explain differences in COVID-19 morbidity and mortality. For example, Italy has the second most elderly population in the world, and older age groups have featured prominently in its burden of COVID-19–related morbidity and mortality (3). In China, older age and comorbidities, including diabetes, hypertension, and cardiovascular and chronic respiratory diseases, have been the most prominent high-risk characteristics (4–6). In the United States, obesity is emerging as an important risk factor (7–9).

Approximately 42.4% of the U.S. adult population is obese, and 9.2% is severely obese (10). The Centers for Disease Control and Prevention lists severe obesity at any age (body mass index [BMI] ≥40 kg/m^2) as a high-risk condition for COVID-19 (11). Given the high prevalence of obesity, the potential effect of COVID-19 in the U.S. population is tremendous.

Social determinants of health, such as race/ethnicity, income level, and education, have been shown to be risk factors for both obesity and COVID-19 (12, 13). Obesity's association with chronic conditions, such as diabetes, hypertension, cardiac conditions, and cerebrovascular disease, is well described; however, its relationship with critical illness is less clear. Increased risk for proinflammatory and prothrombotic states as well as poor ventilatory lung mechanics correlated with obesity are potentially poor prognostic factors in severe illness, such as H1N1 influenza, and likely play a role in COVID-19 outcomes (14–18). However, several studies have also demonstrated an "obesity paradox,"

See also:

Editorial comment
Related article
Summary for Patients

Web-Only
Supplement

or an inverse relationship between obesity and mortality among critically ill patients, including those with acute respiratory distress syndrome (19–21).

Literature that adjusts for factors associated with obesity and COVID-19 mortality is emerging, yet publications thus far have been small, have not adequately captured BMI, and have not simultaneously considered sufficient risk factors in a single model (4, 6, 22, 23). Furthermore, most publications have focused on patients who are hospitalized or in the intensive care unit (24–28), have neglected risk factors like income level and education, and have not adjusted for changes in testing or clinical practice over time. Therefore, we report our findings on a large cohort of patients in an integrated health care system at the point of diagnosis of COVID-19 to disentangle the effect of BMI, associated comorbidities and medications, time, neighborhood-level income and education, and other factors on the risk for COVID-19, while describing important risk profiles by age and sex.

METHODS

Study Setting

Kaiser Permanente Southern California (KPSC) is an integrated health care organization located throughout 9 counties in Southern California. Its comprehensive electronic health record stores linked information on all aspects of health care for each patient across all care settings (for example, outpatient, inpatient, emergency department, and virtual). Each member is assigned a unique medical record number that allows for linkage of data across all aspects of health care. Clinical care of members outside the KP system is captured in the electronic health record through reimbursement requests in the claims system.

Kaiser Permanente Southern California has a diverse member population, with more than 4.7 million members representing more than 260 ethnicities and 150 languages. As of December 2018, most members were Hispanic or Latino (43%), followed by White (35%), Asian/Pacific Islander (12%), Black or African American (9%), and other race/ethnicity (1%), and 22% of patients were enrolled through Medicare or Medi-Cal and the Children's Health Insurance Program.

Study Design

We conducted a retrospective cohort study including all KPSC members diagnosed with COVID-19 by diagnostic codes (**Supplement Table 1**, available at Annals.org) or positive laboratory test results from 13 February to 2 May 2020, with 6-month continuous membership at KPSC (allowing up to a 31-day gap) before diagnosis. We excluded women who were pregnant at the time of diagnosis (BMI measurements not comparable).

Exposure

The primary exposure of interest was BMI, categorized by National Institutes of Health subcategories of less than 18.5 kg/m^2 (underweight), 18.5 to 24 kg/m^2 (normal), 25 to 29 kg/m^2 (overweight), 30 to 34 kg/m^2 (obese class I), 35 to 39 kg/m^2 (obese class II), and greater than 40 kg/m^2 (obese class III or extreme obesity) (29). The BMI measurement at the index date or the value closest to that date (to 2016) was selected.

Outcomes

The primary outcome was death within the 21 days after the index date. To allow equal opportunity for all patients to develop the outcome, the date the last patient was enrolled (index date) was set to 21 days before the study end date. We present the proportion hospitalized and intubated among those who died versus those who survived.

Covariates

We considered individual-level factors, including race/ethnicity, sex, age, and Medicaid status, and clinical risk factors, including 20 comorbidities (**Supplement Table 2**, available at Annals.org), hemoglobin A_{1c} level, prior medication use (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin II (ATII) type-1 receptor blockers [ARBs]), health care use (outpatient, inpatient, and emergency department) in the 6 months before the index date, tobacco use, alcohol use, and illicit drug use. We also considered the following neighborhood-level factors: population density, median household income, and proportion of household members with more than a high school education (**Table**). We included time as a covariate in our models to adjust for testing practice changes, effects of social distancing, and potential changes in clinical treatments over the study period.

Statistical Analysis

We assessed the association of each covariate with the outcome in bivariate analyses, comparing those who survived and those who died using the χ^2 test or the Fisher exact test for categorical covariates and the Kruskal–Wallis test for continuous variables, as appropriate. Covariates of clinical importance were selected for the adjusted analyses (**Figure 1**). Missing data were handled by multiple imputation with 5 imputed data sets. The adjusted relative risks (that is, incidence rate ratio) for death for different BMI categories and other selected characteristics were estimated using multivariable Poisson regression. Adjusted incidence rates and absolute risk for different BMI categories were estimated using the same model. Confounding by time was adjusted by including a calendar week variable in the model. The trend of BMI on risk for death was also assessed by modeling a cubic smoothing spline of continuous BMI in a separate generalized additive model adjusting for other covariates (30).

We explored interaction terms between age group (≤60 or >60 years) and BMI and between sex (male or female) and BMI, with adjustment for all variables in the final model. We also conducted 2 sets of adjusted stratified analyses for age and sex. All analyses were done using SAS statistical software, version 9.4 (SAS Institute).

Role of the Funding Source

This study was funded by Roche–Genentech but was solely done at KPSC. The funder did not contribute to the design, conduct, or analysis of this study, or to manuscript development, writing, or review.

Table. Characteristics of Study Cohort Considered for Selection in the Final Model (*n* = 6916)

Characteristic	Patients Who Died (*n* = 206)	All Patients (*n* = 6916)	*P* Value*
Sex, *n* (%)			0.002
Male	115 (3.7)	3111	
Female	91 (2.4)	3805	
Race/ethnicity, *n* (%)			<0.001
Hispanic	82 (2.2)	3751	
White	64 (5.3)	1210	
Asian	25 (2.4)	1036	
Black	35 (6)	584	
Other/unknown	0 (0)	335	
Age at index date			<0.001
Mean (SD), *y*	73.7 (14.7)	49.1 (16.6)	
Median (Q1-Q3), *y*	76 (65.0–84.0)	49 (36.0–60.0)	
By age group, *n (%)*			
0–10 y	0 (0)	28	
11–20 y	0 (0)	158	
21–30 y	1 (0.1)	863	
31–40 y	6 (0.5)	1178	
41–50 y	10 (0.7)	1422	
51–60 y	20 (1.3)	1545	
61–70 y	41 (3.9)	1045	
71–80 y	53 (12.4)	427	
>80 y	75 (30)	250	
BMI, *n* (%)			<0.001
<18.5 kg/m^2	15 (15.5)	97	
18.5–24 kg/m^2	53 (4.3)	1240	
25–29 kg/m^2	54 (2.4)	2207	
30–34 kg/m^2	44 (2.6)	1704	
35–39 kg/m^2	14 (1.7)	833	
40–44 kg/m^2	14 (3.8)	372	
≥45 kg/m^2	12 (4.6)	262	
Missing	0 (0)	201	
Days between BMI measurement and index date†			<0.001
Mean (SD)	18.1 (89.8)	123.0 (195.2)	
Median (Q1-Q3)	0 (0.0–2.0)	50 (1.0–157.0)	
Tobacco use, *n* (%)			<0.001
Current	4 (2.1)	191	
Former	88 (6.9)	1278	
Never	106 (2.5)	4271	
Unknown	8 (0.7)	1176	
Comorbidities, *n* (%)			
Myocardial infarction	26 (22.6)	115	<0.001
Congestive heart failure	44 (19.5)	226	<0.001
Peripheral vascular disease	101 (19.4)	520	<0.001
Cerebrovascular disease	39 (23.2)	168	<0.001
Chronic obstructive pulmonary disease	41 (4.7)	869	0.001
Renal disease	77 (18.2)	424	<0.001
Metastatic tumor/malignancy	18 (11.7)	154	<0.001
Other immune disease	25 (11.6)	215	<0.001
Hyperlipidemia	142 (8.8)	1619	<0.001
Hypertension	150 (8.9)	1693	<0.001
Asthma	44 (3.5)	1273	0.27
Organ transplant	6 (35.3)	17	<0.001
DM status			<0.001
DM with hemoglobin A_{1c} level missing	18 (5.4)	335	
DM with hemoglobin A_{1c} level <7.5%	50 (9.3)	535	
DM with hemoglobin A_{1c} level ≥7.5%	32 (6.1)	522	
No DM	106 (1.9)	5524	

Continued on following page

Table–Continued

Characteristic	Patients Who Died (*n* = 206)	All Patients (*n* = 6916)	*P* Value*
Variables not included in the final model			
Population density per square mile, *n* (%)			<0.001
≤Q2 population density	97 (2.8)	3442	
>Q3 population density	109 (3.1)	3468	
Missing	0 (0)	6	
Median household income, *n* (%)			<0.001
<$40 000	49 (3.2)	1513	
$40 000–$79 999	114 (2.9)	3911	
>$80 000	43 (2.9)	1486	
Missing	0 (0)	6	
More than high school education, *n* (%)			<0.001
<50% neighborhood (census block level)	86 (2.7)	3223	
≥50% neighborhood (census block level)	120 (3.3)	3687	
Missing	0 (0)	6	
Outpatient encounters, *n* (%)			<0.001
0	4 (0.7)	574	
1–5	39 (1.5)	2663	
6–10	45 (3)	1490	
11–20	49 (3.6)	1379	
≥21	69 (8.5)	810	
Inpatient encounters, *n* (%)			<0.001
0	151 (2.3)	6529	
1	42 (15.4)	272	
2	6 (9.5)	63	
≥3	7 (13.5)	52	
Emergency encounters, *n* (%)			<0.001
0	123 (2.2)	5643	
1	43 (4.5)	951	
2	20 (10.8)	186	
≥3	20 (14.7)	136	
Medicaid, *n* (%)			<0.001
Yes	35 (6.5)	537	
No	171 (2.7)	6377	
Missing	0 (0)	2	
Alcohol use, *n* (%)			<0.001
Current	56 (2.6)	2177	
Former	8 (4)	199	
Never	127 (4.3)	2921	
Unknown	15 (0.9)	1619	
Illicit drug use, *n* (%)			0.001
Current	6 (3.3)	181	
Former	2 (2.7)	73	
Never	159 (3.6)	4443	
Unknown	39 (1.8)	2219	
Comorbidities, *n* (%)			
Moderate/severe liver disease	0 (0.0)	7	0.64
Rheumatic/inflammatory disease	4 (4.0)	99	0.53
Obstructive sleep apnea	19 (7.2)	264	<0.001
Depression	40 (8.3)	484	<0.001
Hypothyroid	24 (8.4)	287	<0.001
AIDS/HIV	0 (0.0)	11	0.56
Medications in prior 6 months, *n* (%)			
ACEI	25 (5.7)	441	0.001
ARB	22 (7.2)	304	<0.001

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type-1 receptor blocker; BMI = body mass index; DM = diabetes mellitus; Q = quartile.
* The Fisher exact test was used for variables with a count <5, the Kruskal–Wallis test was used for age at index date and days between BMI measurement and index date, and the χ^2 test was used for all other variables.
† Data were available for 6715 patients.

RESULTS

We identified 6916 patients with COVID-19 diagnoses during the study period. Of these, 5652 (82%) were identified by a positive result on polymerase chain reaction testing. Kaiser Permanente Southern California internalized SARS-CoV-2 testing on 19 March 2020, and the volume of positive results increased substantially the week of 22 March. Overall, the majority of patients with COVID-19 were female (55.0%) and Hispanic (54.2%) (**Table**). At the index date, the mean age was 49.1 years, and the mean BMI was 30.6 kg/m^2. The most prevalent comorbidities were hypertension (24%),

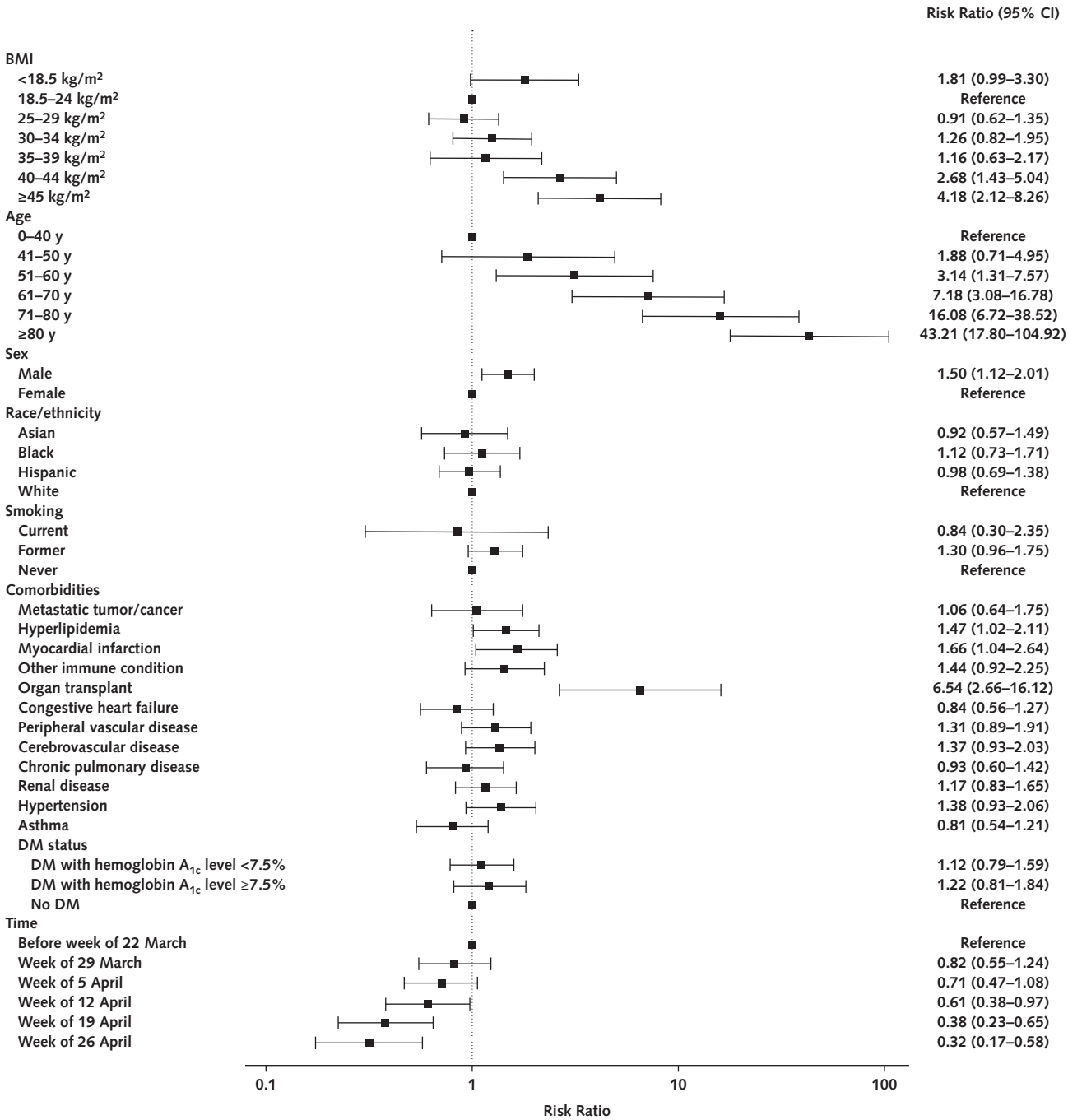
hyperlipidemia (23%), diabetes (20%), and asthma (18%). Approximately 8% of patients were Medicaid beneficiaries (Table).

At the neighborhood level, 78% of patients lived in census tracts with median household incomes less than $80 000 per year; mean income was approximately $62 000 per year. A total of 206 (3%) patients died within 21 days of their COVID-19 diagnosis, with 67% and 43% of patients hospitalized or intubated, respectively, between the index date and date of death. Of those that survived, 15% were hospitalized and 3% were intubated.

Overall Adjusted Analyses

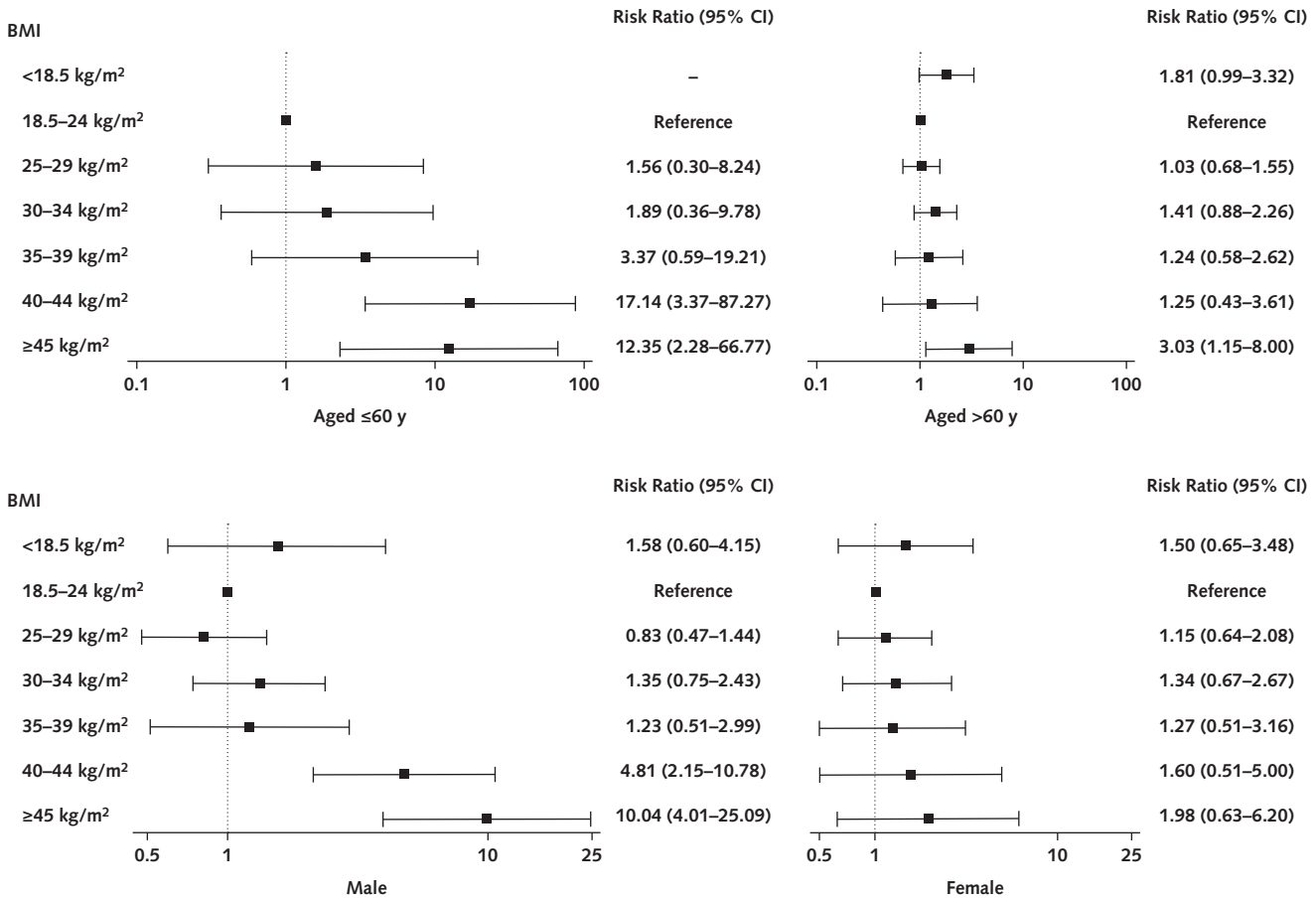
After covariate selection, our final adjusted model included the covariates displayed in Figure 1. We note a J-shaped association between BMI and risk for death. In adjusted analyses, high BMI was strongly associated

Figure 1. Forest plot of final adjusted risk factors for death in overall population (n = 6916).



BMI = body mass index; DM = diabetes mellitus; RR = risk ratio.

Figure 2. Forest plots of adjusted risk factors for death (n = 6916), stratified by age (*top*) and sex (*bottom*).



Models were adjusted for sex, race/ethnicity, age, tobacco use, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease, metastatic tumor or malignancy, other immune disease, hyperlipidemia, hypertension, asthma, organ transplant, and diabetes status and hemoglobin A_{1c} level. BMI = body mass index; RR = risk ratio.

with higher risk for death, with more than 4 times the risk (**Figure 1**) for the highest BMI measures. The adjusted incidence rate of death for the highest BMI measures was 7.08 (95% CI, 3.58 to 14.00) per 100 patients, corresponding to an attributable excess of 5.52 (CI, 0.63 to 10.42) deaths per 100 patients when compared with the incidence rate estimate for BMI of 18.5 to 24 kg/m^2 (**Supplement Table 3**, available at Annals.org). When BMI was modeled as a continuous variable, a nonlinear risk relationship was detected (P = 0.005). We detected a strongly monotonic increased risk for death with increasing age. Male patients had higher risk for death than female patients. The comorbidities with elevated risk in adjusted analyses included prior myocardial infarction, prior organ transplant, and hyperlipidemia. Progression in time was strongly associated with decreased risk for death over the study period (**Figure 1**).

We detected a statistically significant interaction between categorical BMI and age (P = 0.002) but not categorical BMI and sex (P = 0.077), likely because of the small sample size. The interaction between BMI and sex was statistically significant (P = 0.005) when BMI was modeled as a linear variable.

Age- and Sex-Stratified Analyses

In age-stratified adjusted analyses, among those aged 60 years or younger, we found a markedly increased risk for death associated with high BMI compared with the overall model (**Figure 2**, *A*; **Supplement Table 4**, available at Annals.org). For those aged 61 years or older, BMI was associated with death to a much lesser degree, and only for the highest measures. In the older patients, increasing age escalated in importance, with a 127% increased risk for death per decade (**Figure 2**, *A*; **Supplement Table 5**, available at Annals.org).

In sex-stratified analyses, high BMI was associated with substantial risk for death in male patients, with risk estimates above those in the overall model. Female patients had no increased risk for death associated with BMI (**Figure 2**, *B*; **Supplement Table 6** and **Table 7**, available at Annals.org). In both stratified analyses, in-

creasing calendar time significantly decreased risk for death (Supplement Tables 4–7).

DISCUSSION

We found a striking association between BMI and risk for death among patients with a diagnosis of COVID-19 in an integrated health care system; this association was independent of obesity-related comorbidities and other potential confounders. Our data also suggest that risk may not be uniform across different populations, with high BMI more strongly associated with COVID-19 mortality in younger adults and male patients, but not in female patients and older adults. Comorbidities related to immunocompromised status and prior myocardial infarction increased risk; however, other comorbidities often correlated with obesity were less prominently associated with mortality. In contrast to other reports, we did not detect an independent effect of African American or Hispanic race/ethnicity compared with White race/ethnicity, even though our study included a sizable proportion of racial and ethnic minority patients. Our death rate of 2.98% was consistent with that of Los Angeles County (2.94% of those testing positive in the same period [31]).

Our study contributes to our understanding of the effect of obesity on adverse outcomes associated with COVID-19 in several important ways. Although previous studies have primarily focused on risk among the hospitalized population (24–28), we present findings that can inform decisions much earlier in the triage process, including in the ambulatory setting. We included a time variable in our adjusted models, which is a critical feature not addressed in prior literature. Our time variable was highly statistically significant for decreasing mortality risk over time in all analyses (Figure 1; Supplement Tables 4–7), likely because of expansion of the COVID-19 testing approach and evolution of hospital-based patient management.

Our finding that severe obesity, particularly among younger patients, eclipses the mortality risk posed by other obesity-related conditions, such as history of myocardial infarction, diabetes, hypertension, or hyperlipidemia, suggests a significant pathophysiologic link between excess adiposity and severe COVID-19 illness. Obesity is not only an expansion of subcutaneous adipose tissue but is also associated with increased ectopic fat, including visceral, perivascular, and epicardial adipose tissue. Several studies have shown that this fat distribution promotes chronic proinflammatory, prothrombotic, and vasoconstrictive states, which can manifest as insulin resistance, type 2 diabetes, hypertension, atherosclerosis, cardiovascular disease, and immunocompromised state (32–36). Apart from chronic disease, visceral adiposity also promotes increased mortality among critically ill patients with acute respiratory distress syndrome (37).

Although the exact mechanism is unclear, ectopic fat and COVID-19 share a common link in the upregulation of proinflammatory, prothrombotic, and vasoconstrictive peptide hormone, ATII. Reduced levels of anti-inflammatory adipokines, such as adiponectin, in obesity are associated with increased ATII (38–41). Similarly, COVID-19 has been shown to increase ATII due to downregulation of its inhibitory enzyme, ACE2 (42–46). It is possible that COVID-19 is able to accelerate pathologic injuries from existing substrates like ATII among persons with severe obesity.

Anti-ATII therapies, such as ACEIs and ARBs, have been mainstay therapies for hypertension in obese patients, with some effectiveness against insulin resistance (47). With respect to COVID-19, ongoing clinical trials are exploring the effectiveness of anti-ATII therapies, such as recombinant ACE2 and ARBs (48–50).

We did not detect a statistically significant association between African American or Hispanic race/ethnicity or neighborhood-level variables on risk for death. There has been widespread concern about the dramatically disproportionate risk for death among African Americans in this pandemic (12, 51). Although African Americans constitute 18% (weighted distribution) of the U.S. population, they account for 22% of COVID-19 deaths, according to data released by the Centers for Disease Control and Prevention (52). In some geographic regions, the disparities are much greater. Commonly cited speculations are that higher prevalence of comorbid conditions, such as asthma and diabetes; income constraints leading to pressure to return to work, primarily in high-exposure service industries; household density; and decreased access to health care contribute to these findings. Our data did not show an increased risk for death associated with asthma, neighborhood population density, neighborhood income, or African American race or Hispanic ethnicity. In our capitated system, access to care is more equalized, which may influence the absence of socioeconomic disparities in adverse outcomes observed in our data. Additional studies with more comprehensive capture of social determinants of health will be helpful to confirm this observation.

This study has several important strengths. Our large, capitated, diverse, integrated health care system documents all aspects of care and medication use across inpatient as well as outpatient settings. This allowed us to construct a comprehensive cohort with complete capture of prior risk factors that occur across settings (such as ambulatory ACEI and ARB prescriptions) and enhanced capture of our outcome as well as neighborhood-level variables through membership files. This study also has potential limitations. Our covariate data set is more complete among patients with more severe disease courses resulting in hospitalization. Consequently, there is differential missingness for some variables. Further, although we may have missed deaths that occurred outside the hospital, we incorporated data from membership files in addition to hospital files for completeness.

In summary, we found that obesity was strongly associated with risk for death among our study population of patients with COVID-19. Male and younger patients with high BMI seemed to be at particularly high risk. In our prepaid system with more equalized access to care, we did not detect elevated risk associated with

many of the sociodemographic and clinical characteristics seen in prior literature. Although we cannot expect to disassociate the constellations of social and clinical factors that contribute to health disparities and multifactorial chronic conditions in our patients, our data help define the main drivers of adverse outcomes. Principally, we demonstrate the leading role severe obesity has over other highly correlated risk factors, providing a clear target for early intervention. Our findings also reveal the distressing collision of 2 pandemics: COVID-19 and obesity. As COVID-19 continues to spread unabated, we must focus our immediate efforts on containing the crisis at hand. Yet, our findings also underscore the need for future collective efforts to combat the equally devastating, and potentially synergistic, force of the obesity epidemic.

From Kaiser Permanente Southern California, Pasadena, California (S.Y.T., L.Q., V.H., R.W., H.F., Z.L., S.F.S., S.L.C., C.L.N.); Kaiser Permanente Southern California Clinical Informatics, Pasadena, California (R.F.N.); Southern California Permanente Medical Group, Anaheim, California (T.S.); Southern California Permanente Medical Group, Harbor City, California (G.K.R., B.K.A.); Kaiser Permanente Southern California, Pasadena, California, and Southern California Permanente Medical Group, Los Angeles, California (A.L.S.); The Permanente Medical Group, Oakland, California (J.S.); Southern California Permanente Medical Group, Ontario, California (T.K.N.); and Southern California Permanente Medical Group, Fontana, California (S.B.M.).

Financial Support: By Roche–Genentech.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-3742.

Reproducible Research Statement: *Study protocol:* Available from Dr. Tartof (e-mail, sara.y.tartof@kp.org). *Statistical code:* Available from Lei Qian (e-mail, Lei.x.Qian@kp.org). *Data set:* Not available.

Corresponding Author: Sara Y. Tartof, PhD, MPH, Kaiser Permanente Southern California, 100 South Los Robles, 2nd Floor, Pasadena, CA 91101; e-mail, sara.y.tartof@kp.org.

Current author addresses and author contributions are available at Annals.org.

References

1. **Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19.** Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20. [PMID: 32109013] doi:10.1056/NEJMoa2002032
2. **Baud D, Qi X, Nielsen-Saines K, et al.** Real estimates of mortality following COVID-19 infection [Letter]. Lancet Infect Dis. 2020;20:773. [PMID: 32171390] doi:10.1016/S1473-3099(20)30195-X
3. **Boccia S, Ricciardi W, Ioannidis JPA.** What other countries can learn from Italy during the COVID-19 pandemic. JAMA Intern Med. 2020. [PMID: 32259190] doi:10.1001/jamainternmed.2020.1447
4. **Zhou F, Yu T, Du R, et al.** Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62. [PMID: 32171076] doi:10.1016/S0140-6736(20)30566-3
5. **Li X, Xu S, Yu M, et al.** Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146:110-8. [PMID: 32294485] doi:10.1016/j.jaci.2020.04.006
6. **Wu Z, McGoogan JM.** Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020. [PMID: 32091533] doi:10.1001/jama.2020.2648
7. **Petrilli CM, Jones SA, Yang J, et al.** Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966. [PMID: 32444366] doi:10.1136/bmj.m1966
8. **Stefan N, Birkenfeld AL, Schulze MB, et al.** Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol. 2020;16:341-2. [PMID: 32327737] doi:10.1038/s41574-020-0364-6
9. **Kass DA, Duggal P, Cingolani O.** Obesity could shift severe COVID-19 disease to younger ages [Letter]. Lancet. 2020;395:1544-5. [PMID: 32380044] doi:10.1016/S0140-6736(20)31024-2
10. **Hales CM, Carroll MD, Fryar CD, et al.** Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. National Center for Health Statistics, Centers for Disease Control and Prevention; 2020. NCHS Data Brief No. 360
11. **Centers for Disease Control and Prevention.** People who are at increased risk for severe illness. Accessed at www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html on 7 May 2020.
12. **Yancy CW.** COVID-19 and African Americans. JAMA. 2020. [PMID: 32293639] doi:10.1001/jama.2020.6548
13. **Webb Hooper M, Nápoles AM, Pérez-Stable EJ.** COVID-19 and racial/ethnic disparities. JAMA. 2020. [PMID: 32391864] doi:10.1001/jama.2020.8598
14. **Jain S, Chaves SS.** Obesity and influenza [Editorial]. Clin Infect Dis. 2011;53:422-4. [PMID: 21844025] doi:10.1093/cid/cir448
15. **Hanslik T, Boelle PY, Flahault A.** Preliminary estimation of risk factors for admission to intensive care units and for death in patients infected with A(H1N1)2009 influenza virus, France, 2009-2010. PLoS Curr. 2010;2:RRN1150. [PMID: 20228857]
16. **Louie JK, Acosta M, Samuel MC, et al; California Pandemic (H1N1) Working Group.** A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). Clin Infect Dis. 2011;52:301-12. [PMID: 21208911] doi:10.1093/cid/ciq152
17. **Morgan OW, Bramley A, Fowlkes A, et al.** Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. PLoS One. 2010;5:e9694. [PMID: 20300571] doi:10.1371/journal.pone.0009694
18. **Díaz E, Rodríguez A, Martin-Loeches I, et al; H1N1 SEMICYUC Working Group.** Impact of obesity in patients infected with 2009 influenza A(H1N1). Chest. 2011;139:382-386. [PMID: 20688928] doi:10.1378/chest.10-1160
19. **O'Brien JM Jr, Welsh CH, Fish RH, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network.** Excess body weight is not independently associated with outcome in mechanically ventilated patients with acute lung injury. Ann Intern Med. 2004;140:338-45. [PMID: 14996675]
20. **Zhi G, Xin W, Ying W, et al.** "Obesity paradox" in acute respiratory distress syndrome: a systematic review and meta-analysis. PLoS One. 2016;11:e0163677. [PMID: 27684705] doi:10.1371/journal.pone.0163677
21. **Ni YN, Luo J, Yu H, et al.** Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. Crit Care. 2017;21:36. [PMID: 28222804] doi:10.1186/s13054-017-1615-3
22. **Grasselli G, Zangrillo A, Zanella A, et al; COVID-19 Lombardy ICU Network.** Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020. [PMID: 32250385] doi:10.1001/jama.2020.5394

23. **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. [PMID: 32227758] doi:10.1056/NEJMoa2004500
24. **Goyal P, Ringel JB, Rajan M, et al.** Obesity and COVID-19 in New York City. A retrospective cohort study [Letter]. Ann Intern Med. 2020. [PMID: 32628537] doi:10.7326/M20-2730
25. **Rottoli M, Bernante P, Belvedere A, et al.** How important is obesity as a risk factor for respiratory failure, intensive care admission and death in hospitalised COVID-19 patients? Results from a single Italian centre. Eur J Endocrinol. 2020. [PMID: 32674071] doi:10.1530/EJE-20-0541
26. **Palaiodimos L, Kokkinidis DG, Li W, et al.** Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262. [PMID: 32422233] doi:10.1016/j.metabol.2020.154262
27. **Kalligeros M, Shehadeh F, Mylona EK, et al.** Association of obesity with disease severity among patients with coronavirus disease 2019. Obesity (Silver Spring). 2020;28:1200-4. [PMID: 32352637] doi:10.1002/oby.22859
28. **Anderson MR, Geleris J, Anderson DR, et al.** Body mass index and risk for intubation or death in SARS-CoV-2 infection. A retrospective cohort study. Ann Intern Med. 2020. [PMID: 32726151] doi:10.7326/M20-3214
29. **National Heart, Lung, and Blood Institute.** Managing overweight and obesity in adults: systematic evidence review from the Obesity Expert Panel, 2013. Accessed at www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm on 25 March 2020.
30. **Hastie T, Tibshirani R.** Generalized additive models for medical research. Stat Methods Med Res. 1995;4:187-96. [PMID: 8548102]
31. COVID death rate. Accessed at www.google.com/search?q=COVID+death+rate&safe=active&ssui=on on 11 July 2020.
32. **Gustafson B.** Adipose tissue, inflammation and atherosclerosis. J Atheroscler Thromb. 2010;17:332-41. [PMID: 20124732]
33. **Sattar N, McInnes IB, McMurray JJV.** Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation. 2020;142:4-6. [PMID: 32320270] doi:10.1161/CIRCULATIONAHA.120.047659
34. **Longo M, Zatterale F, Naderi J, et al.** Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. Int J Mol Sci. 2019;20. [PMID: 31085992] doi:10.3390/ijms20092358
35. **Britton KA, Fox CS.** Ectopic fat depots and cardiovascular disease. Circulation. 2011;124:e837-41. [PMID: 22156000] doi:10.1161/CIRCULATIONAHA.111.077602
36. **Bastien M, Poirier P, Lemieux I, et al.** Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis. 2014;56:369-81. [PMID: 24438728] doi:10.1016/j.pcad.2013.10.016
37. **Ni YN, Yu H, Xu H, et al.** High visceral adipose tissue to subcutaneous adipose tissue ratio as a predictor of mortality in acute respiratory distress syndrome. Am J Med Sci. 2019;357:213-22. [PMID: 30797502] doi:10.1016/j.amjms.2018.11.015
38. **Sharma AM.** Is there a rationale for angiotensin blockade in the management of obesity hypertension? Hypertension. 2004;44:12-9. [PMID: 15173127]
39. **Fujita K, Maeda N, Sonoda M, et al.** Adiponectin protects against angiotensin II-induced cardiac fibrosis through activation of PPAR-alpha. Arterioscler Thromb Vasc Biol. 2008;28:863-70. [PMID: 18309113] doi:10.1161/ATVBAHA.107.156687
40. **Ran J, Hirano T, Fukui T, et al.** Angiotensin II infusion decreases plasma adiponectin level via its type 1 receptor in rats: an implication for hypertension-related insulin resistance. Metabolism. 2006;55:478-88. [PMID: 16546478]
41. **Zorad S, Dou JT, Benicky J, et al.** Long-term angiotensin II AT1 receptor inhibition produces adipose tissue hypotrophy accompanied by increased expression of adiponectin and PPARγ. Eur J Pharmacol. 2006;552:112-22. [PMID: 17064684]
42. **Cheng H, Wang Y, Wang GQ.** Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol. 2020;92:726-30. [PMID: 32221983] doi:10.1002/jmv.25785
43. **Gheblawi M, Wang K, Viveiros A, et al.** Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res. 2020;126:1456-74. [PMID: 32264791] doi:10.1161/CIRCRESAHA.120.317015
44. **Vaduganathan M, Vardeny O, Michel T, et al.** Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020;382:1653-9. [PMID: 32227760] doi:10.1056/NEJMsr2005760
45. **Glowacka I, Bertram S, Herzog P, et al.** Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. J Virol. 2010;84:1198-205. [PMID: 19864379] doi:10.1128/JVI.01248-09
46. **Wu Z, Hu R, Zhang C, et al.** Elevation of plasma angiotensin II level is a potential pathogenesis for the critically ill COVID-19 patients [Letter]. Crit Care. 2020;24:290. [PMID: 32503680] doi:10.1186/s13054-020-03015-0
47. **Putnam K, Shoemaker R, Yiannikouris F, et al.** The renin-angiotensin system: a target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. Am J Physiol Heart Circ Physiol. 2012;302:H1219-30. [PMID: 22227126] doi:10.1152/ajpheart.00796.2011
48. Recombinant human angiotensin-converting enzyme 2 (rhACE2) as a treatment for patients with COVID-19 (APN01-COVID-19) [clinical trial]. Accessed at https://clinicaltrials.gov/ct2/show/NCT04335136 on 13 July 2020.
49. Losartan for patients with COVID-19 requiring hospitalization [clinical trial]. Accessed at https://clinicaltrials.gov/ct2/show/NCT04312009 on 13 July 2020.
50. Losartan for patients with COVID-19 not requiring hospitalization [clinical trial]. Accessed at https://clinicaltrials.gov/ct2/show/NCT04311177 on 13 July 2020.
51. **Thebault R, Ba Tran A, Williams V.** The coronavirus is infecting and killing black Americans at an alarmingly high rate. The Washington Post. 7 April 2020. Accessed at www.washingtonpost.com/nation/2020/04/07/coronavirus-is-infecting-killing-black-americans-an-alarmingly-high-rate-post-analysis-shows/?arc404=true on 11 April 2020.
52. **National Center for Health Statistics, Centers for Disease Control and Prevention.** Weekly updates by select demographic and geographic characteristics. Accessed at www.cdc.gov/nchs/nvss/vsrr/covid_weekly on 6 May 2020.

Current Author Addresses: Drs. Tartof and Shaw: Kaiser Permanente Southern California, 100 South Los Robles, 2nd Floor, Pasadena, CA 91101.
Drs. Qian and Fischer, Ms. Hong, Ms. Wei, and Mr. Li: Kaiser Permanente Southern California, 100 South Los Robles, 5th Floor, Pasadena, CA 91101.
Dr. Nadjafi: 74 South Pasadena Avenue, Parsons West, 1st Floor, Pasadena, CA 91105.
Ms. Caparosa: Bostonia-El Cajon Call Center, 1620 East Main Street, Room 1102, El Cajon, CA 92021.
Dr. Nau and Dr. Sharp: Kaiser Permanente Southern California, 100 South Los Robles, 4th Floor, Pasadena, CA 91101.
Dr. Saxena: 3460 East La Palma Avenue, Anaheim, CA 92806.
Dr. Rieg: Kaiser Permanente South Bay Medical Center, Southern California Permanente Medical Group, 25825 South Vermont Avenue, Harbor City, CA 90710.
Dr. Ackerson: Kaiser Permanente Southern California South Bay Medical Center, 25965 South Normandie Avenue, Harbor City, CA 90710.
Dr. Skarbinski: 275 West MacArthur Boulevard, Oakland, CA 94611.
Dr. Naik: Pulmonary and Critical Care, 2295 South Vineyard Avenue, Medical Building D, Ontario, CA 91761.
Dr. Murali: Palm Court I, 17296 Slover Avenue, Fontana, CA 92337.

Author Contributions: Conception and design: S.Y. Tartof, L. Qian, R.F. Nadjafi, G.K. Rieg, B.K. Ackerson, J. Skarbinski, S.B. Murali.
Analysis and interpretation of the data: S.Y. Tartof, L. Qian, V. Hong, R. Wei, R.F. Nadjafi, H. Fischer, Z. Li, C.L. Nau, T. Saxena, G.K. Rieg, B.K. Ackerson, A.L. Sharp, J. Skarbinski, S.B. Murali.
Drafting of the article: S.Y. Tartof, T. Saxena, T.K. Naik, S.B. Murali.
Critical revision of the article for important intellectual content: S.Y. Tartof, L. Qian, H. Fischer, T. Saxena, B.K. Ackerson, A.L. Sharp, J. Skarbinski, T.K. Naik, S.B. Murali.
Final approval of the article: S.Y. Tartof, L. Qian, V. Hong, R. Wei, R.F. Nadjafi, H. Fischer, Z. Li, S.F. Shaw, S.L. Caparosa, C.L. Nau, T. Saxena, G.K. Rieg, B.K. Ackerson, A.L. Sharp, J. Skarbinski, T.K. Naik, S.B. Murali.
Statistical expertise: S.Y. Tartof, L. Qian, H. Fischer, T. Saxena.
Obtaining of funding: S.Y. Tartof, J. Skarbinski.
Administrative, technical, or logistic support: S.F. Shaw, S.L. Caparosa.
Collection and assembly of data: V. Hong, R. Wei, R.F. Nadjafi, H. Fischer, Z. Li.