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/m², those with BMIs of 40 to 44 kg/m² and greater than 45 kg/m² 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.

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/m²) 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,”
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 diagnostic codes (available at Annals.org), hemoglobin A1c 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 χ² 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 (%)**                           |                             |                         |          |
| Male                                     | 115 (3.7)                   | 3111                    | 0.002    |
| 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                                    | 25 (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/m²                              | 15 (15.5)                   | 97                      |          |
| 18.5–24 kg/m²                            | 53 (4.3)                    | 1240                    |          |
| 25–29 kg/m²                              | 54 (2.4)                    | 2207                    |          |
| 30–34 kg/m²                              | 44 (2.6)                    | 1704                    |          |
| 35–39 kg/m²                              | 14 (1.7)                    | 833                     |          |
| 40–44 kg/m²                              | 14 (3.8)                    | 372                     |          |
| ≥45 kg/m²                                | 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 (%)**                 |                             |                         | <0.001   |
| Myocardial infarction                    | 26 (22.6)                   | 115                     |          |
| Congestive heart failure                 | 44 (19.5)                   | 226                     |          |
| Peripheral vascular disease              | 101 (19.4)                  | 520                     |          |
| Cerebrovascular disease                  | 39 (23.2)                   | 168                     |          |
| Chronic obstructive pulmonary disease    | 41 (4.7)                    | 869                     |          |
| Renal disease                            | 77 (18.2)                   | 424                     |          |
| Metastatic tumor/malignancy              | 18 (11.7)                   | 154                     |          |
| Other immune disease                     | 25 (11.6)                   | 215                     |          |
| Hyperlipidemia                           | 142 (8.8)                   | 1619                    |          |
| Hypertension                             | 150 (8.9)                   | 1693                    |          |
| Asthma                                   | 44 (3.5)                    | 1273                    | 0.27     |
| Organ transplant                         | 6 (35.3)                    | 17                      | <0.001   |
| DM status                                |                             |                         | <0.001   |
| DM with hemoglobin A₁c level missing     | 18 (5.4)                    | 335                     |          |
| DM with hemoglobin A₁c level <7.5%       | 50 (9.3)                    | 535                     |          |
| DM with hemoglobin A₁c level ≥7.5%       | 32 (6.1)                    | 522                     |          |
| No DM                                    | 106 (1.9)                   | 5524                    |          |

Continued on following page
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/m². 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

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

| Risk Ratio (95% CI) |
|---------------------|
| BMI                 |
| <18.5 kg/m²         | 1.81 (0.99–3.30) |
| 18.5–24 kg/m²       | Reference         |
| 25–29 kg/m²         | 0.91 (0.62–1.35)  |
| 30–34 kg/m²         | 1.26 (0.82–1.95)  |
| 35–39 kg/m²         | 1.16 (0.63–2.17)  |
| 40–44 kg/m²         | 2.68 (1.43–5.04)  |
| ≥45 kg/m²           | 4.18 (2.12–8.26)  |

| Age                 |
|---------------------|
| 0–40 y              | Reference         |
| 41–50 y             | 1.88 (0.71–4.95)  |
| 51–60 y             | 3.14 (1.31–7.57)  |
| 61–70 y             | 7.18 (3.08–16.78) |
| 71–80 y             | 16.08 (6.72–38.52) |
| >80 y               | 43.21 (17.80–104.92) |

| Sex                 |
|---------------------|
| Male                | 1.50 (1.12–2.01)  |
| Female              | Reference         |

| Race/ethnicity      |
|---------------------|
| Asian               | 0.92 (0.57–1.49)  |
| Black               | 1.12 (0.73–1.71)  |
| Hispanic            | 0.98 (0.69–1.38)  |
| White               | Reference         |

| Smoking             |
|---------------------|
| Current             | 0.84 (0.30–2.35)  |
| Former              | 1.30 (0.96–1.75)  |
| Never               | Reference         |

| Comorbidities       |
|---------------------|
| Metastatic tumor/cancer | 1.06 (0.64–1.75) |
| Hyperlipidemia       | 1.47 (1.02–2.11) |
| Myocardial infarction | 1.66 (1.04–2.64) |
| Other immune condition | 1.44 (0.92–2.25) |
| Organ transplant     | 6.54 (2.66–16.12) |
| Congestive heart failure | 0.84 (0.56–1.27) |
| Peripheral vascular disease | 1.31 (0.89–1.91) |
| Cerebrovascular disease | 1.37 (0.93–2.03) |
| Chronic pulmonary disease | 0.93 (0.60–1.42) |
| Renal disease        | 1.17 (0.83–1.65)  |
| Hypertension         | 1.38 (0.93–2.06)  |
| Asthma               | 0.81 (0.54–1.21)  |

| DM status           |
|---------------------|
| DM with hemoglobin A₁c level <7.5% | 1.12 (0.79–1.59) |
| DM with hemoglobin A₁c level ≥7.5% | 1.22 (0.81–1.84) |
| No DM               | Reference         |

| Time                |
|---------------------|
| Before week of 22 March | Reference |
| Week of 29 March    | 0.82 (0.55–1.24) |
| Week of 5 April     | 0.71 (0.47–1.08) |
| Week of 12 April    | 0.61 (0.38–0.97) |
| Week of 19 April    | 0.38 (0.23–0.65) |
| Week of 26 April    | 0.32 (0.17–0.58) |

BMI = body mass index; DM = diabetes mellitus.
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/m² (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).

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 Tables 6 and 7, available at Annals.org). In both stratified analyses, increasing

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 A1c level. BMI = body mass index.
calendar time significantly decreased risk for death (Supplement Tables 4 to 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 to 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 dissociate 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.

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