small E-value does not mean that no association exists. In our study, we carefully adjusted for multiple potential confounding factors, including age, sex, race/ethnicity, education, family income, smoking, alcohol drinking, physical activity, total energy intake, body mass index, family history of diabetes and heart disease, and prevalence of chronic disease at baseline. After multivariable adjustment, when comparing the highest with the lowest quintiles, the hazard ratio (95% CI) of mortality was 0.73 (0.63-0.85) for healthy low-carbohydrate diet score. The corresponding E-value (CI bound) was 2.08 (1.63), which means, after carefully controlling for multiple confounding factors, a potential unmeasured confounder associated with healthy low-carbohydrate diet score and total mortality with at least a hazard ratio of 2.08 (CI bound,1.63) each could explain away the association, but a weaker confounder would not. Similar results were found for the association between healthy low-fat diet score and total mortality. Considering that we have controlled for most important confounders, an unmeasured confounder with such a strong association with mortality is unlikely to be missed. The potential confounders mentioned in the letter such as mental health, stress, and social interactions typically have moderate associations with mortality. In addition, they are not necessarily confounders, as evidence suggests that stress and social interactions could be determinants of eating behaviors and mental health could be a mediator between diet and other health outcomes.

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The Uncertain Role of Corticosteroids in the Treatment of COVID-19

To the Editor: Infection with coronavirus disease 2019 (COVID-19) causes exuberant lung inflammation leading to respiratory failure, acute respiratory distress syndrome (ARDS), and death. Wu et al present early experience and retrospective analysis highlighting potential mortality reduction of COVID-19–associated ARDS using corticosteroids to reduce inflammation. However, despite a novel cause, the clinical syndrome resembles that of older diseases, and the analysis faces statistical challenges that have been encountered previously.

Prior studies in ARDS reveal variable steroid effects potentially related to different causes and resulting pathophysologies invisible at the bedside. Different studies have found corticosteroid effects ranging from harmful to beneficial. Within 3 cohort studies of influenza A (H1N1) during the 2009 pandemic, as cited, steroid use appeared either ineffective or harmful. Other cohort studies and randomized clinical trials for treatment of ARDS wrestled with artifacts due to indication and survivor bias. The former bias is a familiar issue created when unblinded clinicians treat individuals with more serious illness more aggressively, in this case using steroids to prevent or mitigate ARDS. The latter bias arises in 2 ways, either by missing patients unable to survive long enough to receive steroids or failing to follow up with patients long enough to record late deaths due to secondary infections or other steroid-associated complications.

Wu et al found that steroid therapy had a low hazard ratio for death for patients receiving steroids for ARDS. However, the result is at odds with results suggesting harm caused by steroids used to prevent ARDS and is at odds with another recent report using a potentially overlapping patient cohort that found no steroid association with mortality. Wu et al suggest that because indication bias usually erroneously suggests harm from a therapy, a beneficial hazard ratio for steroid treatment of ARDS should be believed. However, this assumes that other biases are inconsequential, such as survivor bias due to rapid disease progression compounded by health care resource exhaustion. We note that the Kaplan-Meier curves presented in the original article show that substantial numbers of patients were censored, follow-up was substantially shorter than needed to observe steroid adverse reactions, the last observed Kaplan-Meier survival data points of the 2 groups were not statistically different, and, finally, use of steroids was not statistically different between survivors and nonsurvivors of ARDS (Table 3). Thus, we urge caution before using steroids for ARDS due to COVID-19. Meticulous observation as performed by Wu et al should continue; however, a rigorous blinded randomized clinical trial is needed to determine whether corticosteroids are beneficial in ARDS.
clinical trial is needed to discover the benefit or harm of this therapy with confidence.5

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To the Editor We question the conclusion of Wu et al1 about the benefit of corticosteroid use in the treatment of coronavirus disease 2019 (COVID-19). The World Health Organization and the US Centers for Disease Control and Prevention have issued clinical guidance against the use of corticosteroids in the treatment of COVID-19 unless another indication is present, such as a chronic obstructive pulmonary disease exacerbation, or as adjunct treatment of septic shock. This guidance was made on the basis of systematic reviews of observational studies of corticosteroids that demonstrated an association with increased mortality and secondary infections in influenza2 and no benefit with possible harms in severe acute respiratory syndrome.3 A retrospective cohort study of Middle East respiratory syndrome showed that corticosteroids were associated with no difference in mortality and prolonged respiratory viral shedding.4

It is unclear that the proportional hazards analysis in the study modeled methylprednisolone administration as a time-dependent covariate, which is necessary to mitigate what has been termed survivor treatment selection bias.5 Stated simply, patients who died rapidly may have been less likely to receive methylprednisolone, leading to an observed difference in mortality that was incorrectly associated with this intervention. Mortality was 23 of 50 (46%) among those with acute respiratory distress syndrome who received methylprednisolone vs 21 of 34 (62%) among those who did not. Even if there were no bias present and methylprednisolone provided some short-term survival benefit, the end point difference of 16% less mortality in those who received corticosteroids is not significant (95% CI, –40% to 8%; P = .23). From the Kaplan-Meier curves, the ultimate mortality rate was roughly similar in both groups—around 60%.

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In Reply In response to the concerns about survival bias and the findings regarding methylprednisolone in our Original Investigation,1 we treated methylprednisolone use as a time-dependent variable with the Cox model in the same subgroup of 84 patients. The hazard ratio of methylprednisolone use for death was 0.52 (95% CI, 0.27-1.02; P = .06), suggesting a trend toward a lower mortality.

Similarly, Ellsworth et al indicated that there was no difference in mortality between patients with acute respiratory distress syndrome who received methylprednisolone (23 of 50 [46%]) and those who did not (21 of 34 [62%]; 95% CI, –40% to 8%; P = .23). There was a trend toward a better outcome, and the nonsignificant P value might indicate that this subgroup analysis was underpowered. We followed up with patients to hospital discharge or death. We agree that the follow-up might be substantially shorter than needed to observe steroid adverse effects. As we discussed,1 the findings in our cohort study should be interpreted with caution because of potential bias, residual confounding, and the small sample size.

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The role of corticosteroids in treating acute respiratory distress syndrome remains controversial and inconclusive. For patients with coronavirus disease 2019 (COVID-19), there are insufficient data to recommend for or against the use of systemic corticosteroids. Although our findings about methylprednisolone use contribute to the evidence base for the systemic corticosteroids in patients with COVID-19 and acute respiratory distress syndrome, well-designed double-blinded randomized clinical trials are needed.

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Inaccurate Estimates of Negotiated Reimbursement Prices for Insulin

To the Editor In their recently published Research Letter, Meiri and colleagues reported temporal trends in actual out-of-pocket and estimated reimbursement prices for insulin. The results for the out-of-pocket costs were informative, but the authors ignored the substantial contribution of manufacturer rebates in reducing an insurer’s actual financial liability well beyond the reimbursed amount. Rebates are critical to include in pharmacoeconomic analyses. While the lack of rebate data was noted as a limitation, this omission invalidates a primary conclusion of the article, namely “increasing insulin prices paid by insurers.”

In fact, after accounting for rebate payments, the net price Eli Lilly and Company realized on its most widely used insulin has decreased since 2015 and was 12% lower in 2019 than 2006 in the commercial market.

Approximately 50% of the total amount spent on branded prescription drugs is retained by payers, hospitals, distributors, and others in the supply chain. Unlike other categories of health care spending, such as physician office visits and hospitalizations, manufacturer price concessions are not typically applied to an insurer’s network discount directly at the point of sale. Instead, rebates are provided to drug plans months after a prescription is filled and are often used to subsidize plan premiums. This system can create preferences for products that can offer larger rebates from higher list prices, which hurts people in plans with chronic conditions and with high deductibles or coinsurance.

Changing the American drug reimbursement system, which often favors high rebates, can happen if the rules for drug financing are modernized. Eli Lilly and Company supports policies that allow patients to benefit directly from lower out-of-pocket spending at the pharmacy counter. We must work toward an insurance model that treats prescription drug spending the same as all other types of health care—one that applies manufacturer price concessions to the point-of-sale price in real time. This would lead to significant out-of-pocket savings for patients and create the conditions for list prices to decrease.

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In Reply As acknowledged in our Research Letter, our analysis did not account for manufacturer rebates in estimating health insurers’ financial liability for insulin; we lacked these data, which are proprietary and nontransparent. Meadows et al imply that the health insurer represented in our data did not pay increased net insulin prices between 2006 and 2017. We disagree based on research that has accounted for manufacturer rebates; for example, Hernandez and colleagues found that net insulin prices increased by 51% from 2007 to 2018 using national data and adjusting for inflation.

Meadows et al cite internal Eli Lilly and Company data on a single insulin formulation to support their claim that net insulin prices have declined since 2015. These data may have limited generalizability to the population in our report, and to all insulin users. Furthermore, the Lilly report includes data only from 2015 to 2019. Inflation-adjusted net insulin prices increased by more than 80% between 2007 and 2014, so a downward trend for 1 product beginning in 2015 is unlikely to represent overall 2007 through 2018 insulin price trends.

The imputed median insulin price we reported reflects an amount negotiated between the health insurer and the pharmacy benefit manager. This approximates the actual price paid.