Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Conflicts of interest
The authors disclose no conflicts.

Most current article

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Reply. We thank Dai and coworkers for their interest in our article and for their valuable comments. As we noted in our article, sofosbuvir-velpatasvir-based regimens were not formally reviewed by the Evidence Review Team at the time of guideline publication. However, the Food and Drug Administration has recently indicated that no dose adjustments are required for these regimens in patients with chronic kidney disease including those on dialysis.[1] Since then, as rightly pointed out by Dai and coworkers, US Food and Drug Administration and Taiwan Food and Drug Administration have approved the use of sofosbuvir for patients with glomerular filtration rate <30 mL/min/1.73 m^2, including patients on dialysis. However, this recommendation has not been adopted elsewhere, including European countries. Kidney Disease: Improving Global Outcome (KDIGO) will soon initiate a focused guideline update in which treatment regimens will be revisited so as to incorporate the most recent data. Lastly, we would like to suggest that such terminologies as "moderate, severe, or advanced renal impairment" be avoided and instead more precise terms (such as chronic kidney disease stage G4 or G5) should be used as outlined in our recent KDIGO Nomenclature Consensus Conference report.[2]

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Conflicts of interest
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COVID-19 Mortality: The Culprit May Not Be Proton Pump Inhibitors

Dear Editor:

We read with interest the study by Israelsen et al[1] and congratulate the authors on conducting this nationwide study and meta-analysis. In their study, they found a slightly increased risk of infection and hospital admission in 4473 current proton pump inhibitor users but no association with other severe outcomes. Their updated meta-analysis showed no association with risk of infection or mortality.[1] This study is very interesting and important in the context of the COVID-19 pandemic. However, several confounding factors that might blur the association between proton pump inhibitors and COVID-19 disease severity were not described. Furthermore, we would like to put forth several suggestions for future studies regarding COVID-19 and proton pump inhibitors.

It has been known that COVID-19 mortality is affected by multiple factors, including male sex, age, geographic region, comorbidities, and mechanical ventilation.[2,3] Thus, when discussing COVID-19-related mortality, the results need to be interpreted in relation to a specific population.

First, Gao et al[4] reported that patients with a body mass index (BMI) greater than 23 kg/m^2 had a linear increase in the risk of severe COVID-19 leading to death. However, BMI was not discussed in the study.[1] Thus, the effect of the BMI of the patients on the study's outcomes is unknown.

Second, a recent study published in *Science* showed that socioeconomic status affected COVID-19-related mortality in Santiago, Chile.[5] Therefore, socioeconomic status should be considered in future studies regarding COVID-19 mortality.

Third, the diet of the patients with COVID-19 in the study of Israelsen et al[1] was unknown. As reported by Perez-Araluce et al,[6] adherence to the Mediterranean diet was associated with a lower risk of COVID-19. It could be explained by the benefits of such high-quality diet to the immune system.[6] Therefore, the effect of a patient's diet on survival cannot be ignored.

Fourth, as reported by Burchill et al,[7] COVID-19 pandemic has direct and indirect impact on the gut microbiota. Such factors as repeated lockdowns, frequent hand hygiene, changes in alcohol intake and smoking habit, travel limitation, reduction in social interaction, a shift toward working from home, poor sleep, and low mood could all affect the gut microbiome.[7] It has been reported that gut microbiome is involved in the magnitude of COVID-19 severity possibly via modulating host immune responses.[8] In addition, usual use of masks, types of masks, how and how often masks are worn, social distancing, working in crowded/enclosed spaces, and other factors may also affect COVID-19 outcomes. Taking all these factors into account is more relevant and more reliable for the study.

In summary, we believed that Israelsen et al[1] have shown that current proton pump inhibitor use does not have a significant clinical impact on risk of SARS-CoV-2 infection or related severe outcomes, and previous conflicting results rather arise from between-study differences. However, as the authors mentioned, although a wide range of relevant comorbidity and medication was used to adjust their analyses, there may inherently remain residual confounding by imperfectly measured, unmeasured, or unknown factors. In fact, considering all

the potential confounders, such as BMI, socioeconomic status, diet, travel, hand-washing, smoking, alcohol use, mask use, and other unknown factors, seems impossible in the real world in the context of COVID-19. These studies have shown that although valuable knowledge about COVID-19 has been amassed, more information is needed to address the pandemic. To reduce confounding effects of potential risk factors on COVID-19 mortality and proton pump inhibitor use, we encourage health professionals, including nutritionists, social economists, pharmacists, epidemiologists, and those in other departments, to participate in the study of COVID-19.

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Conflicts of interest
The authors disclose no conflicts.

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Reply. We thank the authors Duan et al[1] for the interest in our study and their comments. The concerns raised primarily arise from the generalizability of results and the risk of bias from unmeasured confounders. We fully agree that our results should be interpreted with respect to the study population. As we have noted in our article, the heterogenous study populations from the studies included in the meta-analysis may partly explain their conflicting results.

First, we acknowledge that obesity is a well-established risk factor for poor outcomes including death in patients with COVID-19. Unfortunately, we do not have clinical data on height and weight from the applied registries. Possible confounding by obesity could be present because of an observed higher body mass index (BMI) among individuals with gastroesophageal reflux disease,[2] a common indication for prescription of proton pump inhibitors (PPI). To explore the direction, magnitude, and uncertainty caused by obesity on our estimate of 30-day mortality we have conducted a quantitative bias analysis.[3]

In our analysis we first assign reasonable values to the bias parameters including (1) the association between the confounder (obesity) and the outcome (mortality in COVID-19 patients), (2) the prevalence of the confounder in the exposed group (current PPI use), and (3) the prevalence of the confounder in the unexposed group (never PPI use). As the first bias parameter we used the pooled odds ratio of mortality from multivariate analysis in a meta-analysis on obesity (BMI $\geq$30) as a risk factor for severe COVID-19 outcomes: pooled odds ratio of 1.49 (95% confidence interval, 1.20–1.85).[4] The proportions of individuals with obesity in the exposed and unexposed group were assumed based on data from another Danish cohort study on hospitalized patients with COVID-19, reporting a proportion of 8% of individuals with BMI $>$35.[5] To align with the meta-analysis[4] that used a BMI of 30 as cutoff, we set the prevalence proportions higher than the 8% reported with cutoff of 35 (ie, to median 0.20 with a range from 0.10 to 0.30 among PPI users and median 0.10 with a range from 0.05 to 0.15 among PPI nonusers, both with trapezoidal distributions).

Using these bias parameters, and assuming a true null-association between PPI use and adverse outcome, we performed 10,000 probabilistic bias analysis simulations. We found a median relative risk of 0.84 (95% simulation interval, 0.67–1.04). The simulation interval incorporates the uncertainty in the bias parameters and the random error from the original study estimate, adjusted relative risk of 0.88 (95% confidence interval 0.72–1.08). The quantitative bias analysis suggests that the estimate is biased slightly away from the null, thus supporting our conclusion of a null association from the original study.

Second, it would be interesting to obtain data on socioeconomic status and test whether the findings by Mena et al[6] could be replicated in our cohort. However, we would assume that the impact of socioeconomic status on mortality would be less pronounced because Denmark is a less segregated society where all residents have tax-funded universal access to health care.

Third, based on the findings in the survey study by Perez-Araluce et al[7] it is not possible to infer what effect a Mediterranean diet would have on COVID-19 outcomes because this was not examined. The authors observed a protective effect concerning risk of acquiring SARS-CoV-2 infection in a cohort of well-educated Spanish residents and only when restricting the analyses to non–health professionals. The generalizability of these results to our or other study populations is probably limited, being based on self-reported test results with unknown test type and by using a design inherently prone to selection bias. Therefore, we welcome more studies before considering diet a plausible confounder.