SUPPLEMENTAL MATERIAL

"Proton pump inhibitor use is not associated with severe COVID-19 related outcomes: A propensity score weighted analysis of a national veteran cohort." *Shah et al.*

Supplemental Methods

The present study was designed to avoid exposure misclassification and immortal time, lag time, and protopathic biases, which have been present in some PPI studies as described by Suissa and Suissa (*Gut* 2018; **67**;2228-2229). Immortal time bias related to exposure misclassification and latency bias pose potentially major issues for exposure (i.e. PPI)-outcome studies where the outcome is a long-term outcome, such as cancer. However, our study design avoids immortal time bias and our study question is not impacted by latency bias. Regarding immortal time, it is essential that exposure classification is restricted to exposures that occur on or before time 0, when follow-up begins. Both our exposed and unexposed statuses strictly meet these criteria—that is, PPI use after the index date was not considered for exposure classification since this would introduce potential immortal time bias. To be eligible for categorization as a current PPI user, a patient needed at least two outpatient PPI prescription fills prior to the index date. The drug persistence was calculated using the dates of the two most recent PPI prescription fills and the dispensed "days supply" of PPI therapy. The days supply was added to the date of the prescription fill, and if this persistence window included the date of the positive SARS-CoV-2 test, the person was categorized as a "current PPI user" (See Supplemental Figure 1 below). Patients were categorized as "PPI non-users" if they had not filled an outpatient PPI prescription for at least 365 days prior to the SARS-CoV-2 positive test date. Patients with PPI persistence windows that included -1 to -364 days prior to the index date were considered recent former users and excluded.

PPI exposure was not analyzed as a time-varying exposure nor cumulative exposure, since doing so might misclassify active PPI use at the time of testing. Modeling PPI as a time-varying variable would not be appropriate for this present analysis since classifying PPI use after the index date (date of positive SARS-CoV-2 testing) as exposure would introduce bias into the analysis (patients with more comorbidities are more likely to be prescribed PPIs and are also more likely to be admitted to the hospital and have a more severe disease course), including immortal time bias (Suissa and Suissa, *Gut* 2018; **67**;2228-2229). Cumulative exposure is most relevant for long-term outcomes, such as cancer outcomes, and would be less relevant for the present analysis focused on active PPI use and COVID-19 related outcomes out to 60 days of follow-up. Low pH deactivates most pathogens, including coronaviruses. The biological mechanism hypothesized to underlie an association between PPI use and severe COVID-19 related outcomes, if a true association did exist, is that PPI-mediated inhibition of gastric acid secretion would allow for a higher SARS-CoV-2 viral load to reach enterocytes, with subsequent downstream negative clinical consequences. The rigorous definition of PPI exposure in this study ensures a high probability of active PPI use at the time patients tested positive for COVID-19.

Protopathic bias is a valid concern, which is why we required at least 2 PPI fills in the baseline year. To evaluate for protopathic bias among the current PPI users—that is, use of PPIs in response to symptoms that might be the result of COVID-19—we evaluated the number of days between the first and second PPI prescription fills, as well as the days between the date of the most recent PPI prescription fill and the date of SARS-CoV-2 positive testing. Among current PPI users, nearly all (>96%) current users had persistent PPI use with: 2 outpatient PPI

prescriptions filled in the 365 days prior to the index date; at least 14 days between their first and second most recent PPI prescriptions; and at least 14 days between their first most recent PPI fill and their index date.

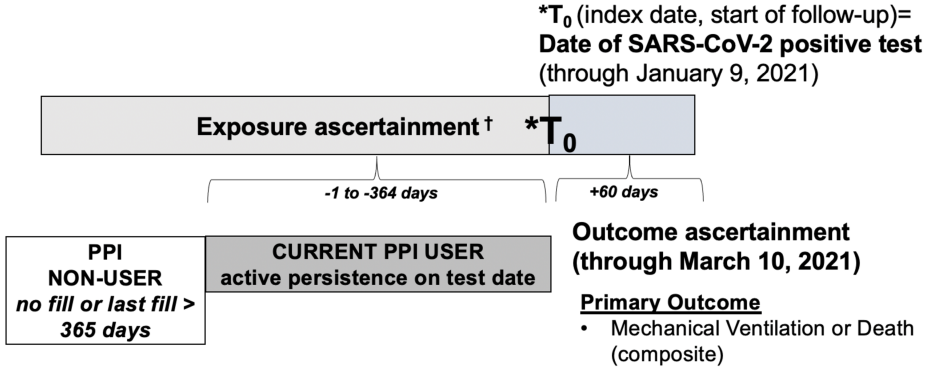
Regarding latency bias, cancer is an excellent example of an outcome where this is a concern. Cancer begins long before it is diagnosed. Therefore, it is important to have a sufficient lag time after the start of exposure to ensure the exposure has sufficient time to influence any cancers being diagnosed. In the case of severe COVID-19 outcomes within 60 days of hospitalization and their association with PPI (the present study), both the outcomes and the exposure are acute.

E-value calculation

The topic of residual confounding is relevant, particularly with studies of PPIs, irrespective of the outcome per se. In their 2017 publication in *Annals of Internal Medicine*, VanderWeele and Ding introduced a new measure, known as the "E-value". (VanderWeele and Ding. *Ann Intern Med* 2017; **167**: 268–74.) The E-value is defined as "the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates." A large E-value is interpreted as considerable unmeasured confounding is needed to explain away an effect estimate and render the treatment-outcome association null (i.e. the findings are robust); whereas a small E-value indicates that only slight unmeasured confounding is sufficient to explain away an effect estimate and render the association null. Importantly, according to VanderWeele and Ding, "if the confidence interval (CI) includes the null of a risk ratio of 1, then the E-value for the CI is simply 1 because no confounding is needed to move the CI to include 1."

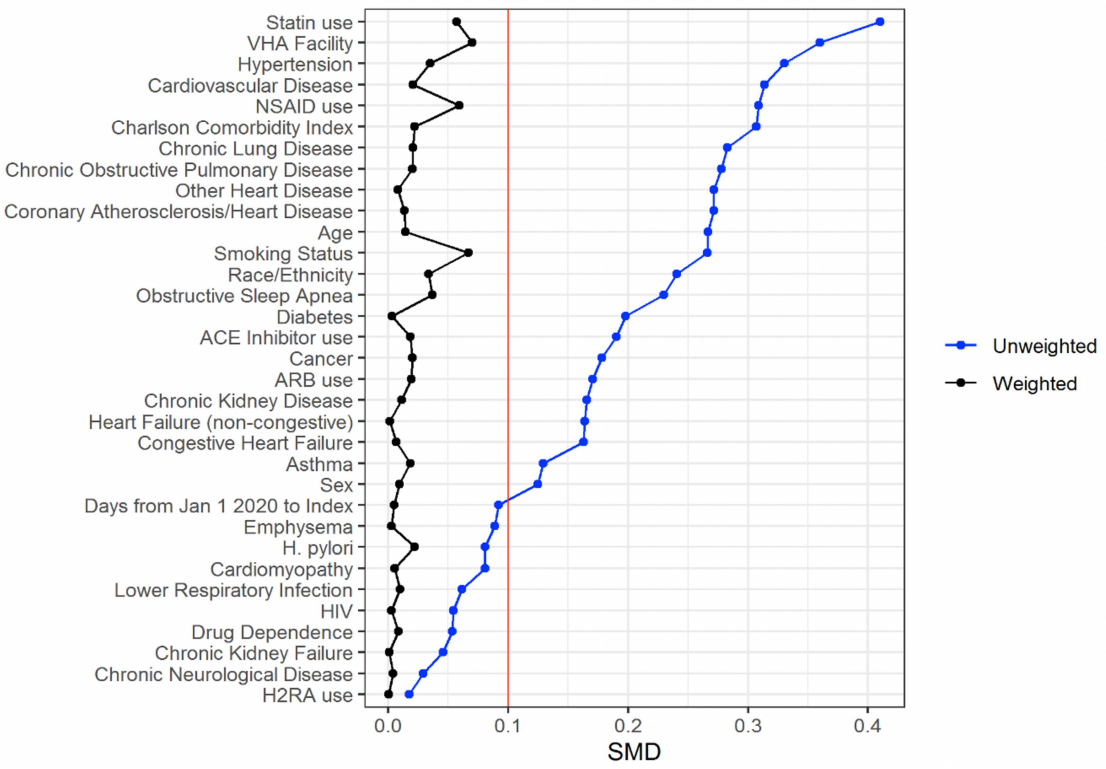
The E-value is typically calculated for the adjusted analysis. Because our adjusted analyses (i.e. the weighted analyses) were all null findings—that is, the CIs all included 1.0 (see Figure 1)—all of the E-values would be 1 by definition. To help interpret the magnitude of confounding needed to render the unadjusted (unweighted) analyses null, we calculated the E-value for each. The E-values for the analyses of the association between PPI use vs. non-use and 60-day primary (mechanical ventilation or death) were 1.51 for the effect estimate and 1.32 for the confidence interval; for the secondary (hospitalization, ICU admission, mechanical ventilation, or death) composite outcomes the E-values were 1.51 for the effect estimate and 1.39 for the confidence interval (source: https://www.evalue-calculator.com/evalue/, derived from VanderWeele and Ding. *Ann Intern Med* 2017; **167**: 268–74.). This is interpreted as: the observed OR of 1.27 for the primary and secondary composite outcomes could be explained away by unmeasured confounding that was associated with both the treatment and the outcome by an OR of 1.5-fold each, but weaker confounding cannot do so. Since these are unweighted analyses, the measured confounders are not accounted for; if these were weighted, i.e. adjusted analyses, then the interpretation would be 1.5-fold above and beyond the measured confounders. That our weighted analyses all demonstrated null associations suggests that we did at least sufficiently address (measured) confounding. Certainly we cannot account for all unmeasured residual confounding, but given the null findings, this should not impact the overall conclusion that active PPI use is not associated with significantly increased likelihood of adverse COVID-19 related outcomes.

Supplemental Figure 1. Study design for the primary analysis. The date of a patient's first positive test for COVID-19 was the index date (T_0) and the start of follow-up. Only patients with a positive SARS-CoV-2 test through January 9, 2021 were included to allow all patients to complete 60 days of follow-up for outcome assessment. The primary exposure was current outpatient PPI use up to and including the index date of testing positive for SARS-CoV-2. Patients were categorized as "PPI non-users" if they had not filled an outpatient PPI prescription for at least 365 days prior to the SARS-CoV-2 positive test date. Patients with PPI persistence windows that included -1 to -364 days prior to the index date were considered recent former users and excluded. The primary outcome was a composite of mechanical ventilation or death within 60 days from the index date, which were also analyzed as separate outcomes (see text).



† *Patients designated as former PPI users (persistence does not cross the index date) and those with only one PPI fill are excluded*

Supplemental Figure 2. Plot of standardized mean differences for covariates between current PPI users and non-users for the unweighted and weighted cohorts. Standardized mean differences (SMDs) were used to compare the means and standard deviations (SD) for continuous variables and proportions for categorical variables between current PPI users and non-users. SMDs are the preferred measure of covariate balance in large cohorts. Smaller SMDs indicate better balance between groups, with a threshold of <0.1 (red vertical line) indicating adequate balance. As depicted in the SMD plot of both the unweighted and propensity score-weighted cohort, full covariate balance was achieved in the weighted cohort.



Supplemental Table 1. Associations between current PPI use vs. PPI non-use and COVID-19-related disease severity outcomes (primary analysis, unweighted and weighted cohorts)

OUTCOMES	**PPI non-users**	**Current PPI users**	**Odds Ratio (95% CI)**
N in WEIGHTED COHORT	**8,696**	**6,262**	
Primary Composite- Composite of death or mechanical ventilation within 60 days from index date *N with outcome (%)*	691 (8.0%)	511 (8.2%)	1.03 (0.91-1.16)
Secondary Composite- Composite of hospitalization, admission to intensive care unit, mechanical ventilation or death within 60 days from index date *N with outcome (%)*	1,990 (22.9%)	1,467 (23.4%)	1.03 (0.95-1.12)
Individual Components- within 60 days from index date, *N with outcome (%)*			
Death	598 (6.9%)	418 (6.7%)	0.97 (0.85-1.10)
Mechanical ventilation	233 (2.7%)	202 (3.2%)	1.21 (0.99-1.48)
ICU admission	631 (7.3%)	507 (8.1%)	1.13 (0.99-1.28)
Hospitalization	1,655 (19.0%)	1,244 (19.9%)	1.05 (0.97-1.15)
N in UNWEIGHTED COHORT	**8,696**	**6,262**	
Primary Composite- Composite of death or mechanical ventilation within 60 days from index date *N with outcome (%)*	649 (7.5%)	582 (9.3%)	1.27 (1.13-1.43)
Secondary Composite- Composite of hospitalization, admission to intensive care unit, mechanical ventilation or death within 60 days from index date *N with outcome (%)*	1,863 (21.4%)	1,613 (25.8%)	1.27 (1.18-1.37)
Individual Components- within 60 days from index date, *N with outcome (%)*			
Death	565 (6.5%)	482 (7.7%)	1.20 (1.06-1.36)
Mechanical ventilation	209 (2.4%)	226 (3.6%)	1.52 (1.26-1.84)
ICU admission	582 (6.7%)	559 (8.9%)	1.37 (1.21-1.54)
Hospitalization	1,543 (17.7%)	1,363 (21.8%)	1.29 (1.19-1.40)

**Note: p-interaction between age and PPI use on each of the composite and separate outcomes was >0.05, indicating no statistically significant interaction*.