Editor's Note:

The original pre-print version of this manuscript was posted online on July 7th, 2020, as a brief communication. The brief communication format is designed for correspondences that are limited in size to promote a concise and focused discussion. Since the paper has gained interest among readers, the authors have conducted extensive supplementary analyses and prepared additional discussion points that further describe their results. This has allowed the authors to expand their article beyond the constraints of the brief communication format. None of the original results have changed as a result of these supplemental analyses.

The initial submission underwent three peer reviews from internationally known experts prior to acceptance. Because the study remains in pre-print format and has been expanded with supplemental analyses, we obtained two additional external peer reviews who offered further insights. Given the special attention paid to this particular study, the Journal took the additional step of obtaining the full, locked dataset from the authors, which was provided to two statisticians who separately reproduced the results. As with all submissions to the Journal, all peer reviews were conducted independently from the authors. The current manuscript reflects an unprecedented amount of peer review, not only from content and methods experts, but also from the general readership. The results remain consistent despite conducting additional analyses, as outlined by the authors in their comprehensive, point-by-point cover letter, below. The supplementary materials reflect the peer input and the result is a robust study, with appropriate emphasis on limitations, that addresses an important topic for our readership.

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On behalf of the AJG Editorial Board

Authors' Note:

We have received helpful comments from the general readership and from additional independent peer reviews. We are grateful for this input because it has allowed us to consider the comments and offer supplementary analyses and discussion points. None of our original findings have changed, but the supplementary analyses and expanded discussion illuminate the study and dataset further. We acknowledge the authors of a recent letter that we reviewed and cite as a reference in this expanded pre-print (reference 46). As a result of their input, and that of many others both online and via formal peer reviews, we have conducted supplemental analyses designed to further elucidate the findings. We view the input from the recent letter and other reviewers as an integral part of the scientific process of idea exchange and dialogue that has strengthened our analysis.

We found that after conducting multiple additional sensitivity analyses, the results remain robust in a manner that continues to follow an apparent dose-response biological gradient between

anti-secretory dose and risk of COVID-19. Here, we highlight the additions as a guide to the expanded pre-print:

First, we expanded the discussion on the biological plausibility of gastric acid suppression and potential risk of COVID-19. In the Introduction, we highlight additional lines of inquiry, both past and recent, supporting the potential for a linkage between proton pump inhibitors (PPIs) and COVID-19. We thank the many people who brought this wealth of previous literature to our attention.

Second, we positioned our findings within the framework of the Hill criteria for causation vs. association. In this section, we assess the evidence for biological plausibility, strength of effect, dose-response gradient, consistency of effect, and temporality (including protopathic bias and time lag bias). We also expanded our previous discussion regarding residual confounding. In applying the Hill criteria, we followed guidance from Vaezi and colleagues (reference 1) specific to assessing PPI adverse event associations. We note, for example, that Vaezi *et al.* explain that most purported PPI adverse events have not withstood the test of time, with the notable exception of gastrointestinal (GI) infections (both bacterial and viral), of which COVID-19 is an instance. Thus, the notion of PPIs causing enteric infection is not new; it has been shown in prospective randomized data and in meta-analyses. COVID-19, a proven enteropathic virus, is what is new (references 10-17). We also note that Vaezi and colleagues highlight an adjusted odds ratio (aOR) greater than 3 as being within the "zone of interest" and outside the "zone of potential bias," which is why we further emphasize the aOR of 3.67 for twice daily PPI, and further de-emphasize the smaller aOR for lower-dose PPIs. The discussion may have applicability for clinicians and patients considering the non-U.S. Food and Drug Administration (FDA)-approved yet commonly-used twice daily PPI dose, while providing more reassurance that once daily PPI, including label use of low-dose over-the-counter (OTC) and prescription PPIs, yields a smaller effect of much lower clinical significance. As before, we emphasize that our results only reflect an association, but not causation. Please refer to the Discussion section for more details.

Third, it has been suggested that few individuals in the cohort endorsed symptoms of gastroesophageal reflux disease (GERD), which would be unexpected for a group of people taking PPI therapy (reference 46). However, 75.2% and 48.0% of respondents in our cohort reported experiencing acid reflux/heartburn or regurgitation, respectively. It is the case that only a small percentage endorsed having *received a formal diagnosis* of GERD by a physician. That does not mean, however, that the cohort of PPI users did not experience GERD-related symptoms. This disconnect between the high prevalence of GERD symptoms but low rate of formal physician diagnosis suggests that many individuals in this sample were self-managing their GERD symptoms with PPIs or histamine-2 receptor antagonists (H2RAs) without guidance from a clinician and thus would not have received a formal diagnosis. It is also possible that some respondents did not recognize the medical term "gastroesophageal reflux disease" when they were asked to select among a list of physician-diagnosed conditions, but did endorse symptoms when presented with a list of cardinal GERD symptoms. Some may also have forgotten having received a formal diagnosis of GERD. In any event, the PPI users did have a high prevalence of GERD symptoms, as would be expected.

Fourth, some noted what appeared to be an anomalous result regarding sex (reference 46): in unadjusted analysis there was a higher proportion of women than men among those with COVID-19, but in adjusted analysis men had slightly increased odds for being positive. At first glance, this may appear paradoxical. However, in bivariate analyses we found that women in this sample were more likely to be insured (potentially allowing easier access to COVID-19 testing), more likely to be Latinx (a group disproportionately affected by COVID-19 in both this sample and nationally), and more likely to be from the South (a region with a high and increasing prevalence of COVID-19 during the study period). Thus, there were multiple imbalances operating together to increase risk of COVID-19 among women in this cohort. When multivariable regression analysis was performed while accounting for these covariates, the analysis revealed that being a man was independently associated with slightly increased risk of COVID-19. That is, being a woman was a surrogate for other predictors of COVID-19, but was not, itself, a predictor of COVID-19 in this study. While U.S. data reveals that men appear to have higher rates for COVID-19-related hospitalizations vs. women (reference 63), the pandemic is rapidly evolving and time will determine whether there are also sex disparities with acquiring COVID-19.

Fifth, although this was a study of individuals with GI symptoms—not a study of the general population—we now provide supplementary data to compare the GI study population against the general U.S. population. **Supplementary Table 1** presents those data and shows that the overall cohort resembles the general population across most sociodemographic strata with the notable exception of age ≥60 years (29.8% of U.S. population; 13.3% of cohort). This may reflect a "digital divide" among older vs. younger individuals regarding participating in online surveys. It may also reflect the known epidemiology of common GI syndromes which are more prevalent in younger age groups, such as irritable bowel syndrome and other functional GI disorders. Regardless, we recognize that older individuals are under-represented in this survey of individuals with GI symptoms and highlight that fact in the manuscript.

Sixth, we have further explored the demographics of the COVID-19 subpopulation, in which readers identified apparent anomalies in the descriptive data (reference 46). It was noted that COVID-19 patients in this survey tended to be less educated yet have a higher total household income, with a large Latinx proportion. In exploring the source of these results, we observed marked shifts in the respondent demographics as the study progressed. Among the first half of subjects enrolled into the survey, the subgroup with COVID-19 appeared more consistent with the overall U.S. population across sociodemographic strata. As the survey administration continued, the COVID-19 population of survey takers became younger, more likely to be from the South region of the U.S., more likely to be Latinx, less educated, and more likely to report a total annual household income ≥$200,001.

Therefore, combining all the demographics into a single table makes it difficult to disambiguate between what appear as two different COVID-19 populations comingled in this study. This becomes evident when reporting the demographics across the first vs. second half cohorts of the survey, which we have now added as **Supplementary Table 2**. The table shows that the latter group revealed the unexpected demographic trends, whereas the earlier group appears more

aligned with the expectations of reviewers. We have retained the combined demographic table to remain consistent with the original submission, but now offer the expanded supplementary table to demonstrate the marked shift in COVID-19 demographics between the two periods. We discuss why these shifts may have occurred later in this document.

Given these shifts in the COVID-19 study population over the course of the pandemic, we sought to confirm whether our results could be reproduced across multiple sensitivity analyses. First, we repeated the analyses within the first vs. second COVID-19 cohorts. We found that in both groups, regardless of the sociodemographic makeup of that group, those taking PPIs up to once daily or twice daily remained at significantly increased odds for reporting a positive COVID-19 test in a dose-response manner; no statistically significant associations were seen for H2RA use in either period (**Supplementary Table 3**). To test the robustness of this finding, we repeated the analyses again for every two-week block of the study (four blocks in total) and again found a dose-response effect for each analysis despite smaller sample sizes by subgroup. In short, although the demographics of the COVID-19 population changed throughout the study, the relationship between PPIs and COVID-19 remained stable and significant in an apparent dose-response pattern; this relationship appeared invariant despite demographic shifts.

As the survey progressed, there was an increasing proportion of Latinxs reporting a high school education or less while also reporting a total household income of ≥$200,001. As we did not obtain data on number of individuals in the household, we do not know whether there were other cohabitants contributing to the reported total annual household income (in contrast to personal income, which we did not ask about). Of note, Latinx individuals in the U.S. are considerably more likely to live in multigenerational households than other groups (reference 64). It is also possible that some respondents in the second half of the study were simply dishonest about their income or education.

Because of the change in demographic mix of participants with COVID-19 in the latter part of the study, we conducted another series of sensitivity analyses to further test whether the results could reproduce under different scenarios. First, we excluded Latinx participants altogether and repeated the regression analyses; the results were again consistent with a dose-response effect (**Supplementary Table 3**). Then we progressed a step further by excluding all Latinx subjects with total annual household income ≥$200,001; we observed the same findings. We next excluded all Latinx subjects with total annual household income ≥$200,001 and with a high school education or less—a combination suggested to be unlikely by some readers (reference 46); nonetheless, removing this subgroup did not affect the results. In all, we conducted a total of 17 separate sensitivity analyses and found a statistically significant PPI dose-response in all but one sub-analysis (Midwest U.S. region). Observing the same dose-response association in all these subgroups provides further support of the main results.

While it is unclear why the proportion of younger and Latinx individuals with COVID-19 was so pronounced in the latter part of the study, it is notable that during the study period the median age for U.S. cases decreased and also that Latinxs continue to be disproportionately affected. As of July 12, 2020, California, Florida, and Texas—States that are COVID-19 “hot spots” and have

the highest share of the U.S. Hispanic population—reported the following with respect to the age groups with the highest proportion of cases and overall percentage that are Latinx: California—age group: 18 to 34 years old, Latinx: 55%; Florida—age group: 25 to 34 years old, Latinx: 44%; Texas—age group: 20 to 39 years old, Latinx: 50%.

We inquired with the survey research firm, Cint, to determine whether there had been any changes in their inclusion or exclusion criteria during the course of the study, or whether any other change in their procedure might explain the differences in COVID-19 demographics between the first and second halves of the study. Of note, the Cint research panels have been widely used by investigators across the globe on a range of studies, including GI research supported by the National Institutes of Health and the Rome Foundation (references 29-37). The Cint platform complies with ESOMAR, MRS, ARF, MRIA, AMA, AMSRO and Insight Association standards for quality control and fraud detection of survey respondents. Details regarding the Cint Quality Charter may be found at this website: https://www.cint.com/quality. The authors have no relationship, financial or otherwise, with Cint.

The team at Cint indicated no changes were made in their recruitment process during the study. They enforced standard measures to reduce fraudulent answers and bots, as outlined in their Quality Charter web page. They did note, however, that during the COVID-19 pandemic there has been a surge of engagement with Cint surveys that occurred in tandem with the conduct of this study, possibly because people have been social distancing and staying home, or have lost a job or suffered a pay cut, and therefore joined survey panels for additional income and to pass time at home. Others may have been quarantined *because* they had COVID-19. As the COVID-19 pandemic has expanded sociodemographic disparities, particularly among Latinx and less educated individuals who have experienced progressive pay cuts and job losses at a higher rate than other groups (references 71, 72), it is plausible to observe a disproportionate increase in these demographics in the second half of this survey (see June 9th report from Pew Research Center: "Hispanic women, immigrants, young adults, those with less education hit hardest by COVID-19 job losses": https://www.pewresearch.org/fact-tank/2020/06/09/hispanic-women-immigrants-young-adults-those-with-less-education-hit-hardest-by-covid-19-job-losses/). We do not believe this summarily invalidates the second half respondents, but it does indicate they may be systematically different from the first half respondents, as shown in **Supplementary Table 2**. In any event, we found the same results in both groups as well as in sensitivity analyses that systematically removed the demographic combinations considered unlikely by others (reference 46), as previously discussed.

Seventh, the prevalence of COVID-19 in the overall study population (6.4%) was higher than current national estimates. Some readers found this to be unexpected (reference 46). As previously noted, this was not a study of the general population; it was a study of individuals with GI symptoms completing an online survey and was not designed to arrive at a population estimate for COVID-19. Most survey questions focused on GI symptoms and those with such symptoms may well have been predisposed to completing the full survey (the COVID-19 questions came at the end of the survey). As COVID-19 commonly leads to GI symptoms, this selection may have contributed to the higher than expected positivity rate. There are other

potential explanations for this finding. While we generically positioned our survey at the outset as a “national health survey” and not as a COVID-19- or PPI-focused study, our results may be subject to participation bias as it occurred during a pandemic and, as a result, may have oversampled patients with COVID-19 who considered a “health survey” particularly relevant at a time of illness. It is also possible that those with COVID-19 may have been more likely to complete an online health survey while quarantined at home, or may have heard about it from friends or family who received the survey.

Even with these potential explanations, it is also possible that some respondents were simply dishonest regarding their diagnosis of COVID-19, particularly among those who completed the survey in the second half of the recruitment period when the prevalence rose beyond national estimates. Although it is unclear why an individual would falsify his or her COVID-19 status, it is perhaps less clear how dishonesty would fall along a biological gradient of acid suppression. For example, it is not clear why people using twice daily PPI would be more dishonest about COVID-19 than patients on once daily PPI, or why those on once daily PPI would be more dishonest than those using H2RAs. Perhaps use of PPIs—but not H2RAs—is a surrogate marker for other factors associated with dishonesty, but we are challenged to offer a reasonable explanation.

We again thank the peer reviewers and readers for their assessment of our paper. We hope our responses are helpful and further elucidate the study. As before, we wish to reiterate that this observational study does not offer evidence of causation in the absence of prospective data and should be further investigated in different populations and settings. As gastroenterologists who all routinely prescribe PPIs to our patients and will continue to rely on these important medicines when clinically indicated, our driving motivation is to understand the potential for PPI risk—particularly that of high dose off-label PPIs—as we live through a pandemic with a virus proven to rapidly invade and replicate within the GI tract. We hope others will continue to explore this topic. As with any hypothesis-generating study, the results may ultimately be supported by other work, or not.

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Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors

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ABSTRACT

Background: Proton pump inhibitors (PPIs) increase the risk for enteric infections which is likely related to PPI-induced hypochlorhydria. Although the impact of acid suppression on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown thus far, prior data revealed that pH ≤3 impairs the infectivity of the similar SARS-CoV-1. Thus, we aimed to determine whether use of PPIs increases the odds for acquiring COVID-19 among community-dwelling Americans.

Methods: From May 3 to June 24, 2020, we performed an online survey described to participating adults as a "national health survey." A multivariable logistic regression was performed on reporting a positive COVID-19 test in order to adjust for a wide range of confounding factors and to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Results: Of 53,130 participants, 3,386 (6.4%) reported a positive COVID-19 test. In regression analysis, individuals using PPIs up to once daily (aOR 2.15; 95% CI, 1.90–2.44) or twice daily (aOR 3.67; 95% CI, 2.93–4.60) had significantly increased odds for reporting a positive COVID-19 test when compared to those not taking PPIs. Individuals taking histamine-2 receptor antagonists (H2RAs) were not at elevated risk.

Conclusions: We found evidence of an independent, dose-response relationship between the use of anti-secretory medications and COVID-19 positivity; individuals taking PPIs twice daily have higher odds for reporting a positive test when compared to those using lower-dose PPIs up to once daily, and those taking the less potent H2RAs are not at increased risk. These findings emphasize good clinical practice that PPIs should only be used when indicated at the lowest effective dose, such as the approved once-daily label dosage of over-the-counter and prescription PPIs. Further studies examining the association between PPIs and COVID-19 are needed.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most commonly used medications in the U.S. and have been linked to side effects including bone fracture, chronic kidney disease, and gastrointestinal (GI) infections, among others (1). While a recent randomized controlled trial did not confirm most of these purported complications, it found that once daily PPI use increased the odds for enteric infection by 33% (2). Meta-analyses also reveal that PPIs are associated with increased risk of both enteric infections and small intestinal bacterial overgrowth (3-5), and a 2019 study by Vilcu and colleagues found that continuous use of PPIs is associated with increased risk of viral infection during periods of high endemic prevalence (6). Thus, although most hypothesized complications from PPIs have not withstood the test of time (1), enteric infection is one adverse event supported by both meta-analyses and randomized controlled trial data. This effect is likely related to PPI-induced hypochlorhydria, which impairs the body's proximal defense against ingested bacteria and viruses (1), and may also occur because prolonged use of PPIs reduces microbial diversity in the gut (7), an effect thought to enable colonization of some enteric pathogens (8).

Although the impact of acid suppression on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown thus far, prior data revealed that pH ≤3—the normal pH of a healthy stomach—impairs the infectivity of the similar SARS-CoV-1, whereas less acidic pH in the range achieved with PPI therapy does not inactivate the virus (9). This is relevant because SARS-CoV-2 can enter the body not only through the respiratory system, but also through the GI system (10, 11). The virus employs the angiotensin-converting enzyme-2 (ACE-2) receptor, which

is widely expressed throughout the intestinal tract (12), to rapidly invade and replicate within enterocytes (13). Once SARS-CoV-2 colonizes the GI tract, it can lead to gastritis, enteritis, and colitis (10, 14), and a recent report posted by the U.S. Centers for Disease Control and Prevention (CDC) documented evidence of infectious virus—not just viral RNA—in the stool from a patient with severe COVID-19 infection (15). Similarly, a report published in JAMA also described finding "live" virus in feces (16). Other reports reveal that nearly half of COVID-19 patients have viral RNA in their stool (17), at times when not concurrently found in the respiratory tract (18), and research suggests that monitoring SARS-CoV-2 levels in sewage may provide a lead-time indicator for COVID-19 cases and hospitalizations within a community (19-22); this technique is now being tested by municipalities around the world. Taken together, this body of research, in addition to other studies (23, 24), strongly implicates the GI system as a major portal for SARS-CoV-2 infection.

In addition, since the gut is the largest immune organ in the body and can host colonies of rapidly replicating SARS-CoV-2 (13), there is concern the virus could spread beyond the GI tract, not only by causing digestive symptoms, but also by seeding infection or promoting inflammation in other organ systems, including the respiratory tract via a "gut-lung axis" (11, 25, 26). Previous research with the Middle East Respiratory Syndrome (MERS) coronavirus found that pre-treating mice with pantoprazole, a PPI, showed "exaggerated" evidence of not only enteric infection, but also revealed epithelial degeneration in the small bowel. Notably, the virus was subsequently found to emerge in lung tissue. The authors note that the spread of virus from intestine to lungs indicates "development of sequential respiratory infection" after inoculating the stomach—not the lungs—with a coronavirus that uses the ACE-2 receptor to gain gut entry into the body (26).

Other investigators posit that SARS-CoV-2 disruption of the epithelial layer can lead to release of endotoxins and microbial metabolites that subsequently trigger inflammation and cytokine release in distant organs, such as the lungs (11, 25). Because PPIs may undermine the gastric barrier to SARS-CoV-2 entry and reduce microbial diversity in the gut, coupled with the established link between PPIs and GI infection shown in meta-analyses (3-5) and randomized controlled trial data (2), it is possible that PPIs might also increase the risk for COVID-19, a hypothesis previously posed by other researchers (27, 28). In this study, we further investigated the potential link between PPIs and COVID-19 in a nationwide survey of Americans.

METHODS

To test our *a priori* hypothesis, based on a foundation of biological plausibility, we used data from an online, self-administered survey of Americans collected from May 3 to June 24, 2020. We collaborated with an online survey research firm (Cint; www.cint.com) that sought to recruit a nationwide, representative sample based on U.S. Census data on age, sex and region. The Cint research panels have been widely used by investigators across the globe on a range of studies, including GI research supported by the National Institutes of Health and the Rome Foundation (29-37). The Cint platform complies with ESOMAR, MRS, ARF, MRIA, AMA, AMSRO and Insight Association standards for quality control and fraud detection of survey respondents. Details regarding the Cint Quality Charter may be found at this website: www.cint.com/quality. The authors have no relationship, financial or otherwise, with Cint. Adult panelists received an email inviting them to complete a "national health survey," which was administered solely in English. The Cedars-Sinai Institutional Review Board approved this study (Pro56183).

All participants who were ≥18 years of age were eligible for the study. Respondents were first shown a list of common GI symptoms, and those endorsing a history of abdominal pain or discomfort, acid reflux, heartburn, or regurgitation, were separately asked about any current PPI and/or histamine-2 receptor antagonist (H2RA) use. For those currently taking PPIs and H2RAs, we assessed their frequency and duration of use. We also examined whether respondents were tested for COVID-19; those with a positive test were asked about new symptoms they experienced, if any, at the time of diagnosis, including ageusia, anosmia, GI (abdominal pain, diarrhea, nausea/vomiting), respiratory, or systemic symptoms. Individuals taking a PPI or H2RA

for ≤1 month and who were diagnosed with COVID-19 at least two months prior to survey completion were classified as non-users to help reduce the risk of protopathic bias.

All statistical analyses were performed in Stata 13.1 (StataCorp LP, College Station, TX) and a two-tailed p-value <.05 was considered statistically significant. We performed a multivariable logistic regression on reporting a positive COVID-19 test in order to adjust for a wide range of potentially confounding factors and to calculate adjusted odds ratios (aOR) and 95% confidence intervals (CI). Among respondents who were COVID-19 positive, we also conducted a regression model on the presence of GI symptoms associated with COVID-19 (abdominal pain, diarrhea, nausea/vomiting). Both regression models included PPI and H2RA exposures as well as relevant demographic, socioeconomic, lifestyle, and comorbidity variables.

RESULTS

Overall, 264,058 individuals were invited by Cint to complete the survey, of whom 128,847 (48.8%) accessed the site. Of the 86,602 eligible respondents who completed the survey, 53,130 (61.3%) noted prior abdominal pain or discomfort (n=36,498, 68.7%), acid reflux or heartburn (n=39,969, 75.2%), or regurgitation (n=25,522, 48.0%) and were thus asked about use of anti-secretory medications. The study cohort's demographics are shown in **Table 1** with comparisons to the general U.S. population noted in **Supplementary Table 1**. The cohort resembled the general U.S. population across most sociodemographic strata with the notable exception of age ≥60 years (29.8% of U.S. population; 13.3% of cohort).

We found that 3,386 (6.4%) participants reported a positive COVID-19 test; **Table 1** presents the demographics of those who tested positive. Because this study was conducted between early May and late June 2020, during a time of dynamic epidemiologic changes in the COVID-19 pandemic in America, we divided the cohort into first half vs. second half groups to examine potential differences in the study population over time (**Supplementary Table 2**)**.** The data revealed shifts in the respondent profile as the study progressed; the latter group was meaningfully different from the initial group across many sociodemographic characteristics. For example, in the first half of the survey period, the COVID-19 positivity rate was 2.5% and the overall demographics appeared more consistent with the overall U.S. population. In the second half the self-reported positivity rate rose substantially. Similarly, as the study progressed, the COVID-19 population of survey takers became younger, more likely to be from the South region of the U.S., more likely to be Latinx, less educated, and more likely to report a total annual

household income ≥$200,001. We comment on these demographic results further in the Discussion section.

In multivariable regression analysis across the full sample, PPI use was independently associated with increased odds for reporting a positive COVID-19 test, even after adjusting for a wide range of sociodemographic, lifestyle, and clinical variables (**Table 2**). When compared to individuals not using PPIs, those taking PPIs up to once daily (aOR 2.15; 95% CI, 1.90–2.44) or twice daily (aOR 3.67; 95% CI, 2.93–4.60) had significantly increased odds for reporting a positive COVID-19 test. Regarding H2RAs, which cause less hypochlorhydria than PPIs, use of lower-dose H2RAs was associated with slightly decreased odds for reporting a positive test while no association was seen for higher-dose H2RAs. In addition to PPI usage, we found that men (aOR 1.23; 95% CI, 1.10–1.38), everyday smokers (aOR 5.05; 95% CI, 4.39–5.80), non-Hispanic blacks (aOR 1.80; 95% CI, 1.45–2.24), and Latinxs (aOR 3.54; 95% CI, 3.09–4.04) were significantly more likely to report being positive for COVID-19, consistent with previous data (38-45).

In another regression analysis among the overall cohort that included duration of anti-secretory use, we found the following with respect to PPI exposure: no current PPI use—reference; up to once-daily PPI for ≤6 months—aOR 3.25 (95% CI, 2.81–3.77); up to once-daily PPI use for >6 months—aOR 1.44 (95% CI, 1.22–1.70); twice daily PPI use for ≤6 months—aOR 2.31 (95% CI, 1.42–3.77); twice daily PPI use for >6 months—aOR 3.81 (95% CI, 2.97–4.87).

Given the shifts in the COVID-19 study population observed in **Supplementary Table 2**, we sought to confirm whether our results could be reproduced across multiple sensitivity analyses. First, we repeated the analyses within the first vs. second half cohorts. We found that in both groups, regardless of the sociodemographic makeup of that group, those taking PPIs up

to once daily or twice daily remained at significantly increased odds for reporting a positive COVID-19 test in a dose-response manner; no statistically significant associations were seen for H2RA use in either period (**Supplementary Table 3**). To test the robustness of this finding, we repeated the analyses again for every two-week block of the study (four blocks in total) and again found a dose-response effect for each analysis despite smaller sample sizes by subgroup. In short, although the demographics of the population changed throughout the study, the relationship between PPIs and COVID-19 remained stable and significant in an apparent dose-response pattern; this relationship appeared invariant despite demographic shifts.

Because of comments related to the demographic mix of participants with COVID-19 in the study (46), we conducted another series of sensitivity analyses to further test whether the results could reproduce under different scenarios. First, we excluded Latinx participants and repeated the regression analyses; the results were again consistent with a PPI dose-response effect (**Supplementary Table 3**). Then we progressed a step further by excluding all Latinx subjects with total annual household income ≥$200,001; we observed similar findings. We next excluded all Latinx subjects with total annual household income ≥$200,001 and with a high school education or less—a combination suggested to be unlikely by some readers (46); nonetheless, removing this subgroup did not affect the results. In all, we conducted a total of 17 separate sensitivity analyses and found a statistically significant PPI dose-response in all but one geographical sub-analysis (Midwest U.S. region).

Among those who tested positive for COVID-19 (n=3,386), 3,267 (96.5%) were symptomatic (ageusia, anosmia, GI, respiratory, or systemic symptoms) and 674 (19.9%) reported new onset of abdominal pain, diarrhea, or nausea/vomiting. In regression analysis, we found that

individuals taking lower-dose PPIs (n=266, 10.9%; aOR 0.62 [95% CI, 0.49–0.78]) had lower odds for reporting GI COVID-19 symptoms vs. those not on PPIs (n=297, 39.5%; reference). Conversely, no association was seen with twice daily use (n=111, 56.1%; aOR 1.04 [95% CI, 0.70–1.57]).

DISCUSSION

In a nationwide study of individuals with a history of GI symptoms, we found that use of PPIs is associated with increased odds for reporting a positive COVID-19 test. The highest risk is seen among individuals taking PPIs twice daily—a common off-label practice in both primary and secondary care (47, 48)—as they are nearly four-times more likely to report COVID-19 positivity when compared to those not on PPIs. Since meta-analysis reveals that twice daily PPIs do not offer clinically meaningful benefits over once daily dosing for gastroesophageal reflux disease (GERD) (49), and given that many patients on PPIs have no clear indication for use (50-56), our findings further emphasize that PPIs should only be used when clinically indicated at the lowest effective dose. Data also indicate that 80% of patients on greater than single-dose PPI are able to step-down to daily PPI without recurrence of reflux symptoms (57). Moreover, investigators tested a step-down therapy approach among patients whose GERD symptoms were under control with PPIs and found that 34% were able to switch to H2RAs and 15% remained asymptomatic off PPI therapy 1 year later (58).

Our study has several strengths. To our knowledge, this is the first study examining the relationship between PPIs and COVID-19 among a nationwide sample of Americans. Our finding that PPI use is associated with increased odds for acquiring SARS-CoV-2, which invades and replicates within enterocytes (13), is consistent with prior literature showing that PPIs also increase the risk for other enteric infections (1-6). Most of these studies, though, did not assess the impact of twice-daily dosing; further research examining whether PPI twice daily increases the risk for such infections over once-daily dosing are needed. We also examined the association

between PPIs and GI COVID-19 symptoms and found that PPIs do not increase the odds for reporting such symptoms. As GI symptoms are prevalent in those with COVID-19 (14), further studies assessing the mechanisms behind its differential presentations are needed. Moreover, unlike many studies that use retrospective data to examine potential PPI side effects (1), we prospectively constructed this online survey to test an *a priori* hypothesis. While this approach has inherent limitations, as described below, leveraging an online, self-administered platform allows for efficient recruitment of a national sample; findings from single-site studies with limited sample sizes of patients presenting with COVID-19 may be less generalizable to other settings and populations.

There are also limitations to our study. First, the prevalence of COVID-19 in the overall study population (6.4%) was higher than current national estimates (46). As previously noted, this was not a study of the general population; it was a study of individuals with prior abdominal pain or discomfort, acid reflux, heartburn, or regurgitation and was not designed to arrive at a population estimate for COVID-19. Since most survey questions focused on GI symptoms, those with such symptoms may have been predisposed to completing the survey (the COVID-19 questions came at the end of the survey). As COVID-19 commonly leads to GI symptoms (14), this selection may have contributed to the higher than expected positivity rate. There are other potential explanations for this finding. While we generically positioned our survey at the outset as a “national health survey” and not as a COVID-19- or PPI-focused study, our results may be subject to participation bias as it occurred during a pandemic and, as a result, may have oversampled patients with COVID-19 who considered a “health survey” particularly relevant at a time of illness. It is also possible that those with COVID-19 may have been more likely to complete

an online health survey while quarantined at home, or may have heard about it from friends or family who received the survey.

Even with these potential explanations, it is possible that some respondents were simply dishonest regarding their diagnosis of COVID-19, particularly among those who completed the survey towards the end of the recruitment period when the prevalence rose considerably at a rate outpacing national data. Although it is unclear why an individual would falsify his or her COVID-19 status, it is also less clear how dishonesty would fall along a biological gradient of acid suppression. For example, it is not clear why people using twice daily PPI would be more dishonest about COVID-19 than patients on once daily PPI, or why those on once daily PPI would be more dishonest than those using H2RAs. Perhaps use of PPIs—but not H2RAs—is a surrogate marker for other factors associated with dishonesty, but we are challenged to offer a reasonable explanation. Additionally, self-reported COVID-19 status has been used in other recent surveys regarding pandemic epidemiology (59, 60).

While there are many appropriate indications for PPIs, few individuals in the cohort specifically endorsed having received a formal diagnosis of GERD by a physician. That does not mean, however, that this cohort of PPI users did not experience GERD-related symptoms, as 75.2% and 48.0% of respondents reported experiencing acid reflux/heartburn or regurgitation, respectively. This disconnect between the high prevalence of GERD symptoms but low rate of formal physician diagnosis suggests that many individuals in this sample were self-managing their GERD symptoms with over-the-counter PPIs or H2RAs without guidance from a clinician, consistent with published data (61), and thus would not have received a formal diagnosis. It is also possible that some respondents mistakenly failed to endorse “gastroesophageal reflux

disease”—a medical term—in contrast to “acid reflux” when they were asked to select among a list of physician-diagnosed conditions, but did endorse symptoms when presented with a list of cardinal GERD symptoms. Some may also have forgotten having received a formal diagnosis of GERD. In any event, the PPI users did have a high prevalence of GERD symptoms, as expected.

With respect to sex, we noted in unadjusted analysis that there was a higher proportion of women than men among those with COVID-19. However, in adjusted analysis, men had slightly increased odds for being positive. At first glance, this may appear paradoxical. However, in bivariate analyses we found that women in this sample were more likely to be insured (potentially allowing easier access to COVID-19 testing), more likely to be Latinx (a group disproportionately affected by COVID-19 (45)), and more likely to be from the South (a region with a high and increasing prevalence of COVID-19 during the conduct of this study (62)). Thus, there were multiple imbalances likely operating together to increase risk of COVID-19 among women in this cohort. When multivariable regression analysis was performed while accounting for these multiple imbalances, the analysis revealed that being a man was independently associated with slightly increased risk of COVID-19. That is, being a woman was a surrogate for several predictors of COVID-19, but was not, itself, a predictor of COVID-19. While men appear to have higher rates for COVID-19-related hospitalizations vs. women (63), the pandemic is rapidly evolving and time will determine whether there are also disparities with respect to cases of COVID-19.

As the survey progressed, there was an increasing proportion of Latinxs reporting a high school education or less while also reporting a total household income of ≥$200,001. As we did not obtain data on number of individuals in the household, we do not know whether there were

other cohabitants contributing to the reported total annual household income (in contrast to personal income, which we did not ask about). Of note, Latinx individuals in the U.S. are considerably more likely to live in multigenerational households than other groups (64). It is also possible that more respondents in the second half of the study were simply dishonest about their income or education.

While it is unclear why the proportion of younger and Latinx individuals with COVID-19 was so pronounced in the latter part of the study, it is important to note that during the study period the median age for cases decreased (65) when compared to the start of the pandemic (66) and that Latinxs continue to be disproportionately affected (45). As of July 12, 2020, California, Florida, and Texas—States that are COVID-19 "hot spots" (62) and have the highest share of the U.S. Hispanic population (64)—reported the following with respect to the age groups with the highest proportion of cases and overall percentage that are Latinx (45, 67-69): California—age group: 18 to 34 years old; Latinx: 55% (vs. 39% of state population); Florida—age group: 25 to 34 years old; Latinx: 44% (vs. 25% of state population); Texas—age group: 20 to 39 years old; Latinx: 50% (vs. 39% of state population).

We inquired with the survey research firm, Cint, to determine whether there had been any changes in their inclusion or exclusion criteria during the course of the study, or whether any other change in their procedure might explain the differences in COVID-19 demographics between the first and second halves of the study. Cint indicated no changes were made in their recruitment process during the study. They enforced standard measures to reduce fraudulent answers and bots, as outlined in their Quality Charter (70). They did note, however, that during the COVID-19 pandemic there has been a surge of engagement with Cint surveys in tandem with

the conduct of this study, possibly because people have been social distancing and staying home, or have lost a job or suffered a pay cut, and therefore joined survey panels for additional income and to pass time at home. Others may have been quarantined *because* they had COVID-19. As the COVID-19 pandemic has expanded sociodemographic disparities, particularly among Latinx and less educated individuals who have experienced pay cuts and job losses at a higher rate than other groups (71, 72), it is plausible to observe a disproportionate increase in these demographics in the second half of this survey. We do not believe this summarily invalidates the second half respondents but does indicate they may be systematically different from the first half respondents. In any event, we found the same results in both groups.

These evolving demographics during the survey period notwithstanding, we found consistent evidence that those using PPIs remained at significantly increased odds for being COVID-19-positive in each timeframe while those on H2RAs were not, following a lockstep biological gradient in each period. Thus, although there were potential demographic anomalies in the latter period of the survey, the results of the study remained stable throughout all periods despite dynamic changes in the study population. In the first two weeks of the study, when the demographic distributions of the COVID-19 sample appeared more closely tied to the general population, there was a dose-response effect between use of PPIs and COVID-19. Similarly, in every period thereafter, no matter the demographic shifts that occurred, the same result remained consistent.

As with all observational studies, our study is susceptible to residual confounding. While the aOR of 3.67 seen with twice-daily PPI use is in the “zone of interest” (odds ratio [OR] >3) (1), suggesting that bias alone might not entirely explain that degree of effect size, the aOR of 2.15

noted with up to once daily PPI use falls within the “zone of potential bias” (0.33< OR<3) and may reflect residual confounding from unmeasured variables not included in the model. For instance, individuals with certain comorbidities that increase the risk for severe COVID-19 (e.g., cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease (63)) may also be more likely to take PPIs. However, it is unclear whether these risk factors apply to acquiring COVID-19, which was the subject of this study, in contrast to developing severe COVID-19. Nevertheless, while our regression model included age and smoking status as surrogates for these conditions, their non-inclusion is a potential limitation of the study.

Selection bias may also be an issue as those severely ill and hospitalized with COVID-19 were unlikely to have taken the survey. Our survey was also conducted solely online and thus had a lower than expected proportion of individuals ≥60 years old; while 73% of those 65 years of age and older currently use the internet (73), we may have selected for an elderly population that was more functional and independent.

There is also potential risks for misclassification and recall biases for medications. It is unclear, however, why misreporting of PPI vs. H2RAs would vary by COVID-19 status. That is, it seems unlikely that people with COVID-19 would misreport using a PPI (but not an H2RA), while people without COVID-19 would correctly classify such use. The short recall period also reduces risk of recall bias and it is less of a concern for the medication data as we asked respondents about their current usage. Another potential limitation is that we did not determine how respondents tested positive for COVID-19 (e.g., polymerase chain reaction [PCR] or serology testing) nor did we measure disease severity. We suspect, though, that most participants underwent PCR testing, in contrast to antibody surveillance, as the vast majority of respondents

had symptomatic COVID-19. Finally, there are limitations related to generalizability as the survey was administered only in English and did not assess reading ability; the findings may not be generalizable to non-English speakers or those with limited literacy.

In light of the strengths and limitations of this study, it is useful to place the results within the context of the traditional Hill criteria for establishing causality between a risk factor and an outcome, particularly since Vaezi and colleagues recommend applying these criteria when assessing purported PPI associations (1). In the case of PPIs, it is vital to first pose and defend a biological mechanism linking the PPI to the adverse event; this can help protect against spurious or random associations that may be inadvertently discovered during data analysis in the absence of an *a priori* hypothesis. In the case of PPIs and COVID-19, we believe there is sufficient biological plausibility based on the literature discussed in the Introduction section, although we recognize that biological plausibility does not imply biological certainty.

Next, it is worth considering the strength of association. Vaezi *et al.* emphasize that an OR of 0.1 to 0.33 suggests "reduced risk," an OR of 0.33 to 3 implies "potential bias" from residual confounders or other data anomalies, and an OR of 3 or greater implies "increased risk" and is considered a "zone of interest" (1). In this study, we found an aOR of 3.67 for use of twice daily PPIs, which falls within the "zone of interest." In contrast, up to once daily use of PPIs was associated with an aOR of 2.15, which falls within the upper range of the "zone of potential bias." On this criterion, it would appear that the risk of twice daily PPI should be more closely noted, and that the once daily dose, although conferring a statistically higher odds of COVID-19 than non-use, is of lower interest.

One must also consider whether there is a biological gradient, often manifesting as a dose-response relationship between the PPI and adverse event. Here, we find that twice daily PPI has a higher aOR than up to once daily PPI, and that up to once daily PPI has a higher aOR than use of H2RA, following a stepwise biological gradient of gastric acid suppression.

Another criterion is consistency, meaning reproducibility of the findings among multiple analyses and studies. For the current study, the consistency criterion can be addressed in both general and specific forms. Generally, this study reveals a link between use of PPIs and acquiring an enteric pathogen. Of all the purported adverse events linked to PPIs, Vaezi and colleagues acknowledge that "consistency has been shown among various studies examining this association" based on the strength of meta-analyses and prospective, randomized data discussed earlier (1-6). Moreover, the pooled OR in meta-analysis is 3.33 (4), a value similar to the aOR of 3.67 for twice daily PPI found in this study, supporting consistency with the published literature. Additionally, we found consistent results across subgroup analyses, such as across study time periods and when excluding certain subgroups, further supporting the durability of the findings. The specific form of consistency relates to the link between PPIs and SARS-CoV-2 as an instance of enteric infection risk. Here, there is currently very little published data, as this study represents the first large effort, to our knowledge, evaluating the relationship. We are aware of other efforts underway to evaluate the link between PPI exposure and COVID-19 outcomes, including mortality, and await the results of those analyses. As with any hypothesis-generating observational study, the results may ultimately be supported by other work, or not.

The temporality criterion refers to the timing between PPI exposure and onset of the adverse event. For example, if the event occurred before the exposure, then clearly there would

be no causal link. Protopathic bias is a form of time bias in which a drug is used to manage the adverse event itself. In the case of COVID-19 and PPIs, one might imagine someone with COVID-19 developing GI symptoms and then turning to a PPI for relief. Failing to account for protopathic bias would artificially inflate the effect of PPIs. For that reason, individuals taking a PPI or H2RA for ≤1 month and who were diagnosed with COVID-19 at least two months prior to survey completion were classified as non-users to help reduce the risk of protopathic bias. Another related form of bias is time lag between the expected effect of PPIs and the onset of the adverse effect. For example, it is possible that patients on long-term PPIs have a different gastric acid profile than those on short-term PPIs. For that reason, we compared results among those using PPIs for ≤6 months vs. those using it for >6 months, and found significant results for all analyses, with the highest odds seen for those on long-term twice daily PPI (aOR 3.81). However, despite these efforts to address protopathic bias and time lag, only a prospective study can generate sufficient data to satisfy the temporality criterion.

In short, we found preliminary evidence of an association between use of PPIs and COVID-19, most notably among those using twice daily PPIs. Evidence for association includes biological plausibility, the strength of effect of twice daily PPIs within the “zone of interest” noted by Vaezi and colleagues, evidence of a dose-response biological gradient, consistency with other literature examining the link between PPIs and enteric infections, and partial evidence in support of temporality. However, this study does not offer evidence of causation in the absence of a prospective trial and should be further investigated in different populations and settings. In the meantime, our findings support good clinical practice that PPIs should only be used when indicated at the lowest effective dose, such as the approved once-daily label dosage of over-the-

counter and prescription PPIs. Additional studies should also assess whether there is an association between PPIs and indicators of COVID-19 severity, such as hospitalization, need for intubation, or mortality.

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TABLE 1. Demographics of the study cohort

Variable	Overall cohort (N=53,130)	Tested positive for COVID-19 (n=3,386)
Age:		
18-29 yo	12,064 (22.7)	385 (11.4)
30-39 yo	14,400 (27.1)	2,524 (74.5)
40-49 yo	10,498 (19.8)	320 (9.5)
50-59 yo	9,078 (17.1)	106 (3.1)
≥60 yo	7,090 (13.3)	51 (1.5)
Sex:		
Male	25,492 (48.0)	1,168 (34.5)
Female	27,071 (51.0)	2,192 (64.7)
Prefer not to say	567 (1.1)	26 (0.8)
Race/ethnicity:		
Non-Hispanic white	34,401 (64.8)	624 (18.4)
Non-Hispanic black	4,261 (8.0)	119 (3.5)
Latinx	8,115 (15.3)	2,360 (69.7)
Non-Hispanic Asian	2,388 (4.5)	48 (1.4)
Other/prefer not to say	3,965 (7.5)	235 (6.9)
Education level:		
High school degree or less	15,248 (28.7)	2,357 (69.6)
Some college	13,499 (25.4)	299 (8.8)
College degree	17,470 (32.9)	506 (14.9)
Graduate degree	6,913 (13.0)	224 (6.6)
Marital status:		
Married	24,547 (46.2)	2,752 (81.3)
Not married	28,583 (53.8)	634 (18.7)
Employment status:		
Not employed (unemployed, on disability, on leave of absence from work, retired, or homemaker)	19,906 (37.5)	697 (20.6)
Employed or student	33,224 (62.5)	2,689 (79.4)
Total household annual income:		
≤$50,000	22,489 (42.3)	495 (14.6)
$50,001–$100,000	15,721 (29.6)	309 (9.1)
$100,001–$200,000	8,146 (15.3)	380 (11.2)
≥$200,001	3,950 (7.4)	2,151 (63.5)
Prefer not to say	2,824 (5.3)	51 (1.5)
Body mass index (kg/m^2):		
Normal or underweight (<25)	20,591 (38.8)	2,554 (75.4)
Overweight (25–29.9)	14,879 (28.0)	266 (7.9)

Obese (≥30)	17,554 (33.0)	563 (16.6)
Unknown	106 (0.2)	3 (0.1)
Current smoking status:		
Not at all	36,528 (68.8)	461 (13.6)
Some days	4,649 (8.8)	451 (13.3)
Every day	11,953 (22.5)	2,474 (73.1)
Average alcohol use per week:		
No days	26,468 (49.8)	495 (14.6)
1–3 days	19,386 (36.5)	2,344 (69.2)
4–6 days	4,641 (8.7)	341 (10.1)
Every day	2,635 (5.0)	206 (6.1)
U.S. region:		
Northeast	9,779 (18.4)	321 (9.5)
South	22,175 (41.7)	2,321 (68.5)
Midwest	10,875 (20.5)	205 (6.1)
West	10,301 (19.4)	539 (15.9)
Insurance status:		
Insured	47,010 (88.5)	3,304 (97.6)
Not insured	6,120 (11.5)	82 (2.4)
Has usual source of care:		
Yes	41,089 (77.3)	3,004 (88.7)
No	12,041 (22.7)	382 (11.3)
Rome IV irritable bowel syndrome	7,214 (13.6)	438 (12.9)
Celiac disease[a]	1,430 (2.7)	214 (6.3)
Gastroesophageal reflux disease[a]	6,662 (12.5)	109 (3.2)
Liver cirrhosis[a]	1,227 (2.3)	182 (5.4)
Crohn's disease[a]	1,176 (2.2)	114 (3.4)
Ulcerative colitis[a]	911 (1.7)	40 (1.2)
Diabetes[a]	5,634 (10.6)	243 (7.2)
HIV/AIDS[a]	610 (1.1)	54 (1.6)
PPI exposure:		
No current PPI use	36,583 (68.9)	752 (22.2)
Daily PPI use or less	14,855 (28.0)	2,436 (71.9)
Twice daily PPI use	1,692 (3.2)	198 (5.8)
H2RA exposure:		
No current H2RA use	44,586 (83.9)	2,828 (83.5)
Daily H2RA use or less	7,387 (13.9)	415 (12.3)
Twice daily H2RA use	1,157 (2.2)	143 (4.2)

Note: data are presented as n (%).

H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

a Respondents were asked whether they were ever diagnosed by a healthcare provider with the condition.

TABLE 2. Results from the multivariable logistic regression model on reporting a positive COVID-19 test (N=53,130)

Variable	Positive COVID-19 test (n=3,386)	aOR [95% CI][a]
PPI exposure:		
No current PPI use	752 (2.1)	Reference
Once daily PPI use or less	2,436 (16.4)	2.15 [1.90–2.44][b]
Twice daily PPI use	198 (11.7)	3.67 [2.93–4.60][b]
H2RA exposure:		
No current H2RA use	2,828 (6.3)	Reference
Once daily H2RA use or less	415 (5.6)	0.85 [0.74–0.99][c]
Twice daily H2RA use	143 (12.4)	0.86 [0.66–1.11]

Note: data are presented as n (% of row).

aOR, adjusted odds ratio; CI, confidence interval; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

a The multivariable logistic regression model included PPI use, H2RA use, age, sex, race/ethnicity, education level, marital status, employment status, total household annual income, body mass index, current smoking status, alcohol use per week, U.S. region, insurance status, usual source of care, and presence of Rome IV irritable bowel syndrome, celiac disease, gastroesophageal reflux disease, liver cirrhosis, Crohn's disease, ulcerative colitis, diabetes, and HIV/AIDS.

b $p<.001$

c $p=.032$

SUPPLEMENTARY TABLE 1. Demographics of the study cohort with comparisons to the U.S. population

Variable	Overall cohort (N=53,130)	2018 U.S. Population, % (latest available data)
Age[a]:		
18-29 yo	12,064 (22.7)	18.4%
30-39 yo	14,400 (27.1)	17.8%
40-49 yo	10,498 (19.8)	16.6%
50-59 yo	9,078 (17.1)	17.4%
≥60 yo	7,090 (13.3)	29.8%
Sex[b]:		
Male	25,492 (48.0)	48.6%
Female	27,071 (51.0)	51.4%
Prefer not to say	567 (1.1)	---
Race/ethnicity:		
Non-Hispanic white	34,401 (64.8)	60.3%
Non-Hispanic black	4,261 (8.0)	12.1%
Latinx	8,115 (15.3)	18.4%
Non-Hispanic Asian	2,388 (4.5)	5.6%
Other/prefer not to say	3,965 (7.5)	3.6%
Education level[c]:		
High school degree or less	15,248 (28.7)	38.5%
Some college	13,499 (25.4)	20.3%
College degree	17,470 (32.9)	28.6%
Graduate degree	6,913 (13.0)	12.6%
Marital status[d]:		
Married	24,547 (46.2)	47.8%
Not married	28,583 (53.8)	52.3%
Employment status[e]:		
Not employed (unemployed, on disability, on leave of absence from work, retired, or homemaker)	19,906 (37.5)	40.2%
Employed or student	33,224 (62.5)	59.8%
Total household annual income:		
≤$50,000	22,489 (42.3)	40.9%
$50,001–$100,000	15,721 (29.6)	30.0%
$100,001–$200,000	8,146 (15.3)	21.6%
≥$200,001	3,950 (7.4)	7.6%
Prefer not to say	2,824 (5.3)	---

U.S. region:		
Northeast	9,779 (18.4)	17.2%
South	22,175 (41.7)	38.1%
Midwest	10,875 (20.5)	20.9%
West	10,301 (19.4)	23.8%
Insurance status[f]:		
Insured	47,010 (88.5)	90.0%
Not insured	6,120 (11.5)	10.0%

Note: U.S. population data estimates are from the 2018 U.S. Census American Community Survey (https://data.census.gov/) or Kaiser Family Foundation (https://www.kff.org/state-category/demographics-and-the-economy/population/). Data were accessed on July 14, 2020.

a The U.S. Census American Community Survey reports data for those aged 15–19 and 20–24 years; no separate estimate was made for those aged 18–19 years. Therefore, the U.S. population data estimates for all age groups were recalculated with the denominator being all adults ≥20 years of age.

b The U.S. population data are calculated among those ≥20 years old.

c The U.S. population data are calculated among those ≥25 years old.

d The U.S. population data are calculated among those ≥15 years old.

e For the U.S. population data, we report the employment/population ratio which is the portion of the noninstitutionalized population that is employed among those ≥16 years old.

f The U.S. population data are calculated among those ≥19 years old.

SUPPLEMENTARY TABLE 2. Trends in COVID-19-related demographics over the study period

Overall cohort (N=53,130)	First half of cohort (n=26,852)	Second half of cohort (n=26,278)
Tested positive for COVID-19	659 (2.5)	2,727 (10.4)

Tested positive for COVID-19 (n=3,386)	First half of cohort (n=659)	Second half of cohort (n=2,727)
Age:		
18-29 yo	203 (30.8)	182 (6.7)
30-39 yo	263 (39.9)	2,261 (82.9)
40-49 yo	127 (19.3)	193 (7.1)
50-59 yo	51 (7.7)	55 (2.0)
≥60 yo	15 (2.3)	36 (1.3)
Race/ethnicity:		
Non-Hispanic white	261 (39.6)	363 (13.3)
Non-Hispanic black	57 (8.6)	62 (2.3)
Latinx	214 (32.5)	2,146 (78.7)
Non-Hispanic Asian	23 (3.5)	25 (0.9)
Other/prefer not to say	104 (15.8)	131 (4.8)
U.S. region:		
Northeast	138 (20.9)	183 (6.7)
South	251 (38.1)	2,070 (75.9)
Midwest	89 (13.5)	116 (4.3)
West	181 (27.5)	358 (13.1)
Education level:		
High school degree or less	226 (34.3)	2,131 (78.1)
Some college	102 (15.5)	197 (7.2)
College degree	237 (36.0)	269 (9.9)
Graduate degree	94 (14.3)	130 (4.8)
Total household annual income:		
≤$50,000	227 (34.4)	268 (9.8)
$50,001–$100,000	142 (21.5)	167 (6.1)
$100,001–$200,000	146 (22.2)	234 (8.6)
≥$200,001	118 (17.9)	2,033 (74.6)
Prefer not to say	26 (3.9)	25 (0.9)

Note: data are presented as n (%).

SUPPLEMENTARY TABLE 3. Results from the multivariable logistic regression model on reporting a positive COVID-19 test, stratified by subgroups [a]

Group	No current PPI use	Once daily PPI use or less	Twice daily PPI use		No current H2RA use	Once daily H2RA use or less	Twice daily H2RA use
Overall cohort (N=53,130)	Reference	2.15 [1.90–2.44]	3.67 [2.93–4.60]		Reference	0.85 [0.74–0.99]	0.86 [0.66–1.11]
First half of cohort (n=26,852)	Reference	1.79 [1.48–2.18]	2.68 [1.89–3.80]		Reference	1.03 [0.83–1.28]	1.17 [0.79–1.74]
Second half of cohort (n=26,278)	Reference	1.90 [1.60–2.26]	3.58 [2.66–4.81]		Reference	0.89 [0.73–1.07]	0.89 [0.64–1.25]
1st 2-week block (n=20,648)	Reference	1.62 [1.27–2.07]	2.94 [1.96–4.42]		Reference	1.07 [0.82–1.40]	1.35 [0.85–2.13]
2nd 2-week block (n=12,857)	Reference	2.15 [1.72–2.67]	3.06 [2.02–4.63]		Reference	0.83 [0.64–1.07]	0.83 [0.53–1.29]
3rd 2-week block (n=8,876)	Reference	1.88 [1.43–2.48]	3.76 [2.40–5.88]		Reference	1.26 [0.94–1.70]	0.97 [0.57–1.67]
4th 2-week block (n=10,749)	Reference	1.60 [1.11–2.31]	2.90 [1.44–5.83]		Reference	0.65 [0.42–1.02]	0.64 [0.29–1.42]
Men (n=25,492)	Reference	1.60 [1.36–1.87]	3.39 [2.58–4.45]		Reference	1.06 [0.89–1.26]	0.96 [0.71–1.30]
Women (n=27,071)	Reference	2.61 [2.10–3.24]	2.87 [1.84–4.46]		Reference	0.74 [0.57–0.96]	1.06 [0.65–1.74]
Excluding Latinxs (n=45,015)	Reference	1.59 [1.35–1.86]	2.79 [2.14–3.64]		Reference	1.34 [1.13–1.59]	2.08 [1.56–2.77]
Excluding Latinxs with total annual household income ≥$200,001 (n=50,828)	Reference	1.66 [1.45–1.90]	2.85 [2.26–3.58]		Reference	1.17 [1.01–1.36]	1.86 [1.45–2.41]
Excluding Latinxs with total annual household income ≥$200,001 and high school education or less (n=51,234)	Reference	1.59 [1.39–1.82]	3.01 [2.42–3.76]		Reference	1.14 [0.98–1.31]	1.14 [0.88–1.46]

Excluding Latinxs with total annual household income ≥$200,001 and high school education or less and age 30-39 yo (n=51,284)	Reference	1.56 [1.36–1.77]	2.95 [2.37–3.68]		Reference	1.14 [0.99–1.32]	1.11 [0.86–1.43]
Excluding 30-39 yos (n=38,730)	Reference	1.37 [1.16–1.63]	2.87 [2.17–3.79]		Reference	1.04 [0.86–1.25]	1.27 [0.92–1.75]
Northeast U.S. region (n=9,779)	Reference	2.18 [1.64–2.91]	3.39 [2.00–5.76]		Reference	0.78 [0.56–1.10]	1.04 [0.55–1.98]
South U.S. region (n=22,175)	Reference	2.06 [1.68–2.53]	3.98 [2.78–5.70]		Reference	0.82 [0.65–1.03]	0.68 [0.45–1.01]
Midwest U.S. region (n=10,875)	Reference	1.37 [0.94–1.99]	1.95 [1.05–3.63]		Reference	1.45 [0.97–2.17]	3.02 [1.59–5.74]
West U.S. region (n=10,301)	Reference	1.78 [1.39–2.27]	2.87 [1.86–4.45]		Reference	1.12 [0.86–1.47]	1.57 [0.95–2.58]

Note: data are presented as aOR [95% CI].

aOR, adjusted odds ratio; CI, confidence interval; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

a The multivariable logistic regression models included PPI use, H2RA use, age, sex, race/ethnicity, education level, marital status, employment status, total household annual income, body mass index, current smoking status, alcohol use per week, U.S. region, insurance status, usual source of care, and presence of Rome IV irritable bowel syndrome and physician-diagnosed celiac disease, gastroesophageal reflux disease, liver cirrhosis, Crohn's disease, ulcerative colitis, diabetes, and HIV/AIDS.