

## **A Letter of Concern Regarding *Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors* by Almario, Chey, and Spiegel**

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We are writing to share our concerns about a recent paper entitled *Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors* by Almario, Chey, and Spiegel (hereby *the authors*) which will soon be published in the *American Journal of Gastroenterology*<sup>1</sup>. The research, taken at face value, suggests that the risk of COVID-19 is increased for adults taking proton-pump inhibitors (PPIs). However, there are multiple irregularities about the underlying data that give pause. Because the current version of the paper appears to have been peer-reviewed but not yet finalized, we wanted to raise these concerns prior to the paper's final publication.

The data are from a large cross-sectional sample of American adults who responded between May 3rd to June 24th (2020) to an online survey administered by the market research company CINT ([www.cint.com](http://www.cint.com)). Of the 129k people that accessed the survey (out of 264k invited to participate), just over 86k eligible adults completed it. Of these, 53,130 noted prior GI symptoms and so were asked about their use of antisecretory drugs. While the survey was initially designed solely for the purposes of studying GI symptoms, questions about COVID-19 status and related symptoms were added prior to the launch of the survey.

The first thing that stands out about the study is that 6.4% of this sample reported having a positive test for SARS-CoV-2, despite the fact that the number of confirmed cases in the US overall is about 1%. Though the original paper doesn't make note of this seemingly remarkable finding, one of the authors argued in an interview<sup>2</sup> that this was plausible, since the sample was of people reporting GI symptoms, which are sometimes reported by those with COVID-19. However, the authors have seemingly lost sight of the fact that this subsample reporting GI symptoms was still part of the larger sample of 86k that was supposedly representative of all American adults. Thus we might still reasonably expect to see around 1% of cases in that larger sample. Of course this would still only be 860 cases, which is about a quarter of the 3,386 cases reported in the GI subsample alone. So we are left to conclude that cases were substantially over-reported in the study, or that the sample wasn't representative. Neither bodes well for the validity or generalizability of the results. The lack of representativeness is further illustrated by the age distribution of the sample, where 13% of respondents are listed as being  $\geq 60$  years old. However, this same age group makes up 29% of the nationally representative 2017 Medical Expenditure Panel Survey (MEPS)<sup>3</sup>.

Another noteworthy finding was that 78% of patients with COVID-19 were on a PPI ( $n = 2,634$ ), but only 109 of them (3.2%) described having gastroesophageal reflux disease (GERD). Thus, at most, only 4.1% of their COVID-19 patients on a PPI described having GERD, which is completely at odds with similar studies. For example, a recent national study of PPIs and CKD

found that 50% of their PPI patients described having GERD<sup>4</sup>, which is a more logical figure given that GERD is one of the main indications for PPI use.

Further, while we would expect to see some differences in respondent characteristics when comparing 3,386 cases to the overall sample of 53,130, there are a number of differences that seem extreme. For example, the male:female split in the overall sample was 48:51, while in the subset of cases it was 35:65. This means that the crude risk associated with being a female in this sample is 76% greater than that associated with being a male ( $RR = 1.76 = \left( \frac{2192 \text{ female cases} / 27071 \text{ total}}{1168 \text{ male cases} / 25492 \text{ total}} \right)$ ). While the roles of sex and gender in COVID-19 risks are not yet fully clear, data from the CDC up to May 31 suggest very similar levels of risk for males and females<sup>5</sup> (NOTE: the paper's results actually state that males were at higher risk, so perhaps the labels in the table are switched, though this wouldn't change our point). An even more surprising finding was that in the overall sample, 14k (27%) were in the 30-39 year-old age bracket, while this group made up 74% of the cases. Comparing the risk in this group against all other age groups combined would result in a crude RR of 7.8 ( $\frac{2524 \text{ 30-39 y/o cases} / 14400 \text{ total}}{862 \text{ all other cases} / 38730 \text{ total}}$ ), a noteworthy result to say the least, especially since the median age of cases in the US is 49 years, and the incidence rate in the 30-39 year-olds nationally is less than the risk in any older age bracket<sup>5</sup>.

Finally, and perhaps most tellingly, was that the overall demographic profile of the cases was not plausible for a nationally representative sample, particularly with respect to reported ethnicity, education, and household income. Among the 3386 cases, 70% were Latinx ( $n = 2360$ ), 70% had a high school education or less ( $n = 2357$ ), and yet 64% reported a household income of 200k/year ( $n = 2151$ ). Even if we assumed that the 30% of cases with *more* than a high school education ( $n = 1029$ ) all reported being in this highest household income group, it would still mean that 48% ( $(2151 - 1029)/2357$ ) of those with a high school education or less were still in it (and similarly for Latinx respondents). This is despite that fact that 200k/year is greater than the 90th percentile of all household incomes in the US, and that's irrespective of education or ethnicity<sup>6</sup>.

Taken further, the same group would still be 33% of the total COVID-19 cases in the sample ( $1122 / 3386$ ). However, people with this same profile would make up just 0.3% of the United States population, based on 2017 MEPS data<sup>3</sup>. Since this subgroup makes up just 0.3% of both the Hispanic and non-Hispanic population (according to MEPS data), and given that the 16% of the US population identifies as Hispanic, then Hispanics with a high school degree or less and a  $\geq 200k/year$  household income would be just 0.05% of the overall US population ( $0.16 \times 0.003 = 0.0005$ ). By comparison, this subgroup makes up roughly a quarter of the COVID-19 positive cases in the sample ( $\sim 33\%$  of the 70% Latinx respondents, assuming independence, mirroring the MEPS data). Thus to accept this sample as anything close to representative of the larger US experience with COVID-19, would be to accept that nearly a quarter of the positive COVID-19 cases came from 0.05% of the population, meaning that the relative risk in this group compared to the rest of the US population is over 600 ( $\frac{0.25}{0.0005} / \frac{0.75}{0.9995}$ ).

Having highlighted some of the apparent discrepancies in the data, we hope that the authors will take them seriously, as any results derived from them can not be accepted by the wider scientific and medical community. We thus strongly suggest a deeper look into the data to confirm and resolve any problems prior to the final publication of the manuscript, especially in light of the recent issues around the veracity of data in other COVID-19 research<sup>7</sup>.

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### *References*

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