Letter to the Editor in Response to Article Entitled:
"Vitamin D and Inflammation - Potential Implications for Severity of Covid-19"
By E. Laird et al - Ir Med J; Vol 113; No. 5; P81

From: I. Zapata - Department of Biomedical Sciences, Rocky Vista University, Parker, Colorado 80134, USA.

Dear Editor,

We are at a crucial moment when accurate medical research can provide us with an edge to combat the ongoing COVID-19 pandemic. The urgency of applicable results has made evident some of the limitations of the research publication process, which tends to be very slow. For that reason, a large number of research articles manuscripts on the topic have been made available in a very short time on public repositories with only a very small proportion going through the peer-review process in established journals. This recent burden has put enormous pressure in the review process that is unlikely to catch up soon. While understanding the situation but accounting for what is at stake, it is important to maintain a quality level for what goes through review. Because of this, I contact you with deep concerns about the article published in the Irish Medical Journal by Laird et al. in the May issue of 2020[1].

The article presented by Laird et al. presents a compelling story that associates Vitamin D supplementation to COVID-19 severity. This association is demonstrated by combining multi-country data of Vitamin D and COVID -19 death rate. Because on my expertise and previous experience analyzing data, I am deeply concerned with the validity of the claim. To demonstrate my concern, I first recreated the analysis presented with the data they provided and then performed a couple of alternative regression analysis that highlight the coincidental nature of their premise and the lack of evidence for causation. In addition, I question the use of Spearman's correlation to evaluate the association of continuous variables from and interval since it is not justified despite the regression analysis approach presented in the figure. (**Figure 1A**) displays the recreated figure in the manuscript, there were no issues recreating the analysis presented from the data provided. Note how regression (ANOVA) and Spearman's P-values contradict each other, Spearman's being the only significant one. By updating the death rate data (as of May 25, 2020) (**Figure 1B**), the significance of Spearman's test disappears while ANOVA remains consistently non-significant. Alternatively, replacing Vitamin D concentration is the analysis for Gross National Income (GNI) data provides a very similar pattern and ANOVA p-value (**Figure 1C**). The exchange of Vitamin D for GNI data is justified by the close association of national income and vitamin D supplementation which is consistently shown as significant by both Spearman's and ANOVA (**Figure 1D**).

My critique of the article presented by Laird et al. 2020 focuses only in the validity of their claim in terms of known caveats of analyzing multi-country data. Providing an argument without addressing and adjusting for variables that are known have an effect (income, population density, etc.) is not appropriate and should not be encouraged to be published. Please note I only used income in my argument.
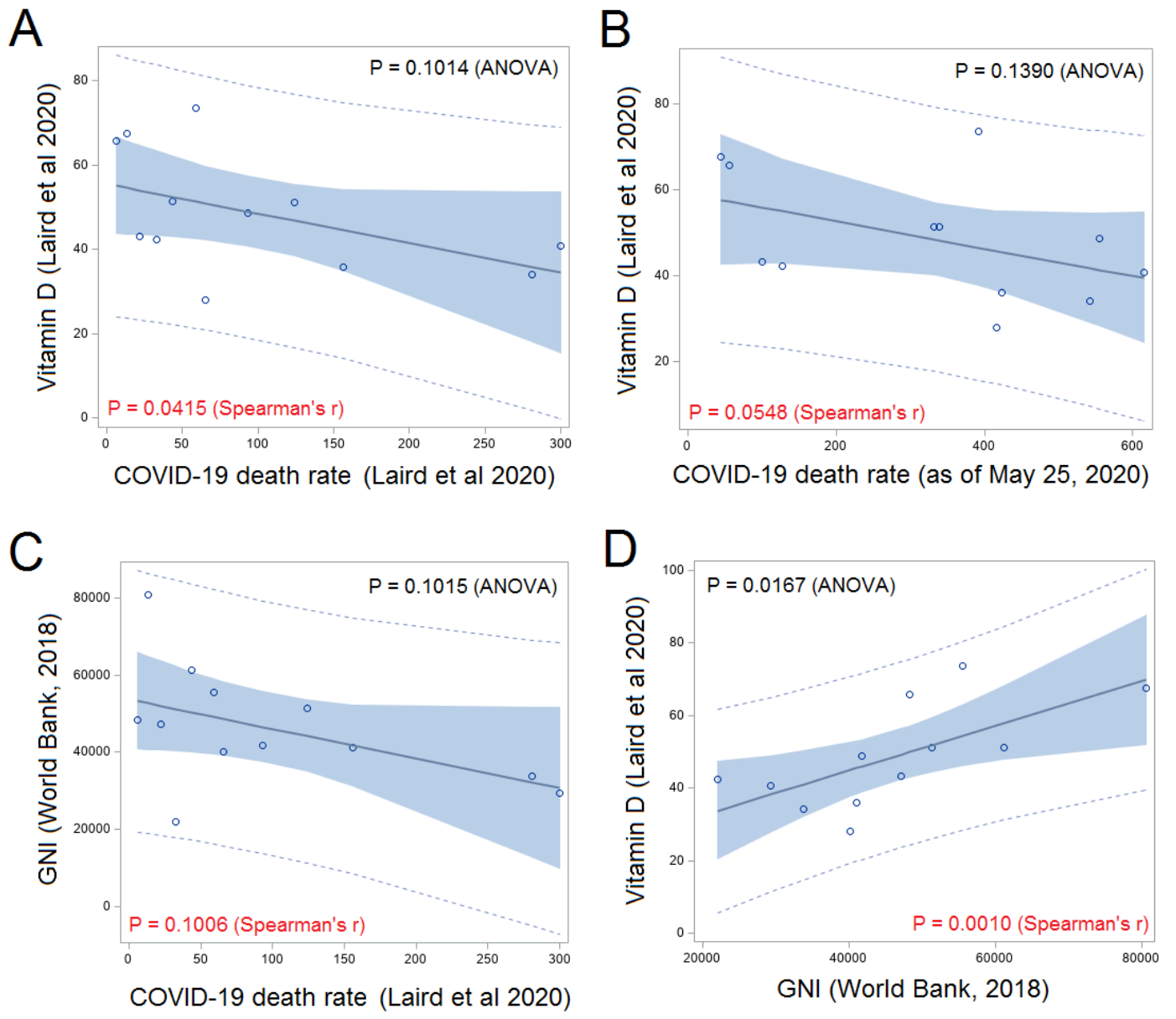
Figure 1. Regression analysis and Spearman's correlations.

A. Vitamin D vs. COVID-19 death rate. Recreation of Laird, et al 2020. Figure 1 using their data.
B. Vitamin D by Laird et al 2020 Vs. COVID-19 death rate as of May 25, 2020.
C. Gross National Income Vs. COVID-19 death rate by Laird et al. 2020.
D. Vitamin D by Laird et al. 2020 Vs. Gross National Income. For all panels. The area in blue presents. 95% confidence limits while dotted line delimits 95% confidence limits. Regression P-value (ANOVA) is presented in each panel, Spearman's correlation P-value is displayed in red in each panel.

In addition, establishing associations with highly volatile variables that are currently evolving (such as COVID death rates) is a very risky endeavor and requires a careful assessments of the predictive limitations of the analysis which are not provided by the authors.

I hope my argument is compelling enough to be considered and I hope the authors of the paper are able to elevate the presented manuscript to satisfactory standards.

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1. Laird, E., Rhodes, J. & Kenny, R. A. Vitamin D and Inflamation: Potential Implications for Severity of COVID-19. *Ir. Med. J.* 113, 81 (2020).