Increased insulin resistance is associated with depressive symptoms due to long COVID

Braz J Psychiatry. 2023 Jul-Aug;45(4):380-381
doi:10.47626/1516-4446-2023-0048

We read Finsterer & Scorza's letter[1] regarding our paper on Long COVID in the *Brazilian Journal of* Psychiatry[2] with great interest.

There is now evidence that Long COVID may exacerbate preexisting type 2 diabetes and cause the onset of insulin resistance (IR).[2] In our paper, IR was estimated using the homeostasis model assessment 2 (HOMA2IR) index, which is an adequate measure of IR as assessed with the glycemic clamp.[2] We found that HOMA2IR scores were associated with increased severity of depression due to Long COVID.

Finsterer & Scorza raise concerns that this association may not be causal, as it has not been previously reported. If this were a criterion, it would never be possible to make any new discoveries. Secondly, they state that the sample size for the study was small, although the study is well powered. We recently confirmed in a study cohort of patients with COVID-19 that 3-6 months after infection, patients with Long COVID have higher HOMA2IR scores than those without Long COVID.[3]

According to the authors, a third argument against causality is the absence of alternative causes. This is yet another peculiar remark, given that the study identified additional "causes," such as inflammatory mediators. Furthermore, in reference 2 the HOMA2IR score contributed to the phenome of Long COVID in addition to the effects of inflammatory mediators of Long COVID (CRP and tryptophan catabolites) and the acute infectious phase (peak body temperature and lowered SpO2).[3]

According to Finsterer & Scorza, the fourth argument is that there would be no information on other Long COVID symptoms that "have contributed to depression." This is incomprehensible because we[2] reported that all symptoms of Long COVID, including depression, anxiety, chronic fatigue, cognitive disorders, and physio-somatic symptoms (including gastrointestinal symptoms), belong to one factor, indicating that all these symptoms are manifestations of the "physio-affective phenome" of Long COVID. In addition, we[3] reported that the HOMA2IR score contributes to the Long COVID physio-affective phenome. Previous papers have frequently shown evidence that IR plays a role in the pathophysiology of major depression.[2-6] The HOMA2IR score is associated with type 2 diabetes mellitus-related depression and anxiety,[4] and in unstable angina, the HOMA2IR score accurately predicts the physio-affective phenome.[5] In severe depression, HOMA2IR contributes to the physio-affective phenome and these effects are partially mediated by neuronal and astroglial projection biomarkers.[6]

The authors then state that 50% of our patients had metabolic syndrome, concluding that IR is not associated with Long COVID but rather with metabolic syndrome. This argument is completely flawed since the aforementioned percentage is only an estimate based on the results of HOMA2IR.[2] We do not believe that measuring C peptide, HbA1C, insulin antibodies, or amylases would alter any of the observed associations between HOMA2IR and the Long COVID phenome. The authors appear to imply that an autopsy would be fascinating, but we are not sure.

We have no interest in how the condition is labelled, whether as Long COVID or any other term. All of these binary diagnoses are man-made constructs, based on symptoms and illness duration that have not been statistically validated as constructs. Instead of using non-validated binary diagnoses, researchers should employ our validated quantitative, physio-affective phenome scores, which are calculated using our precision nomothetic medicine approach.[2-6] Based on prior knowledge in depression and other IR-related conditions, our findings suggest that IR has a causal effect on depression due to Long COVID via amplification of neurotoxic pathways.[2]

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Submitted Apr 15 2023, accepted Apr 15 2023.

Disclosure

The authors report no conflicts of interest.

How to cite this article: Maes M, Almulla AF, Al-Hakeim HK. Increased insulin resistance is associated with depressive symptoms due to long COVID. Braz J Psychiatry. 2023;45:380-381. http://doi.org/10.47626/1516-4446-2023-0048.

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Overdose death rates in Brazil: an ecological analysis by region

Braz J Psychiatry. 2023 Jul-Aug;45(4):381-382
doi:10.47626/1516-4446-2023-3146

Mortality due to drug and alcohol overdose is a significant and understudied public health concern in Brazil.[1] National mortality rates almost doubled between 2000 and 2014.[2] The highest drug-related hospitalization and death rates are in the Midwest and South. This study analyzed drug overdose mortality trends in Brazil from 2000 to 2018 using joinpoint regression models. We also report differences among the five national macroregions (the South, Southeast, Midwest, Northeast, and North) defined by the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística [IBGE]).

We collected data from public-use mortality files (SIM-DATASUS) containing city-level information on deaths between 2000-2018, analyzing unintentional (X40-X44), intentional (X60-64), undetermined (Y10-14), and alcohol-related (X45, X65, and Y15) overdose ICD-10 death codes as underlying causes of death, following other studies on overdose mortality.[3] Total overdose deaths nationwide and in each macroregion per 100,000 inhabitants per year between 2000 and 2018 were calculated.

Potentially significant changes in death trends from overdose over time in the country/regions were identified through joinpoint regression analyses, in which the slopes were converted to annual percentage rates (APRs), i.e., estimated annual change in each identified slope. The joinpoint software[4] yields point estimates for APRs and their statistical significance. Figure 1 was produced using R statistical software 4.1.2. We report overdose rate trends nationwide and according to each macroregion.

The number of yearly overdose deaths in Brazil ranged from about 350 in 2000 to over 1700 in 2018. Overdose death rates in Brazil ranged from 0.20/100,000 in 2000 to 0.82/100,000 persons in 2018. Three different increasing trends in overdose death rates were found: 2000-2009 (APR: +0.02, $p < 0.01$), 2009-2012 (APR: +0.10, $p < 0.01$), and 2012-2018 (APR: +0.02, $p < 0.01$). The most frequently involved substances were, in descending order: alcohol, cocaine, and benzodiazepines.

Overdose death rates in the North were 0.21/100,000 in 2000 and 0.88/100,000 in 2018, with rates significantly increasing between 2010 and 2013 (APR: +0.26, $p < 0.01$) and decreasing between 2016 and 2018 (APR: -0.16, $p = 0.04$). Overdose death rates in the Northeast were 0.26/100,000 in 2000 and 0.55/100,000 in 2018, whereas the rates in the Midwest were 0.24/100,000 in 2000 and 0.99/100,000 in 2018. Those two regions had a significant increasing trend over the study period ($APR_{Northeast}$: +0.02, $p < 0.01$; $APR_{Midwest}$: +0.03, $p < 0.01$). Overdose death rates in the Southeast were 0.16/100,000 in 2000 and 0.85/100,000 in 2018, with the rate increasing significantly between 2000 and 2009 (APR: +0.03, $p < 0.01$). Finally, overdose death rates in the South were 0.20/100,000 in 2000 and 1.15/100,000 in 2018, including upward trends between 2000 and 2010 (APR: +0.03, $p < 0.01$) and 2010-2018 (APR: +0.08, $p < 0.01$) (Figure 1).

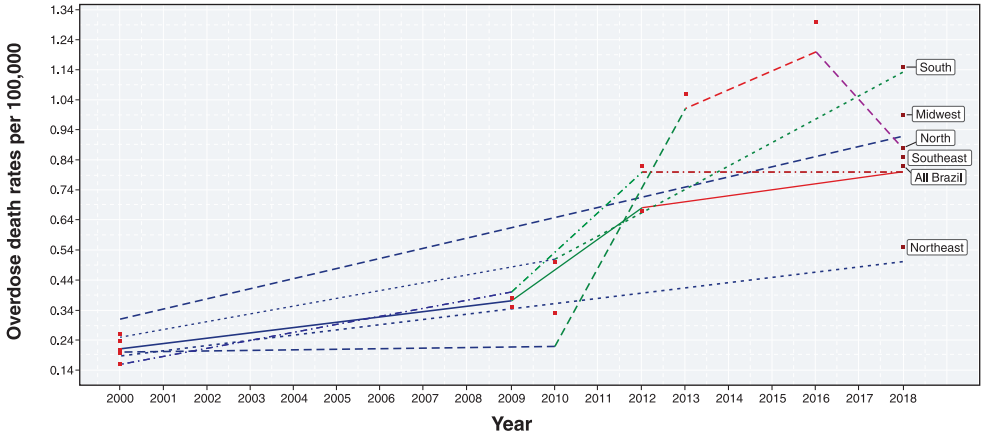

Figure 1 Joinpoint regression analysis of the overdose death rate per 100,000 persons between 2000 and 2018 nationwide and in each macroregion (the North, Northeast, Midwest, Southeast, and South). Different colors indicate trend lines within the same curve.