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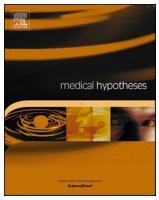
Medical Hypotheses 148 (2021) 110502

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



Letter to Editors

Could diet and exercise reduce risk of COVID-19 syndemic?

ARTICLE INFO

Keywords
Blood glucose
Exercise
SARS-CoV-2
COVID-19
Pandemic
Syndemic

ABSTRACT

We present a hypothesis for increased sugar consumption and a lack of physical exercise as possible determinants of COVID-19 disease severity by impaired glucose metabolism, concurring into a syndemic. National data demonstrate that increased sugar consumption, a high daily caloric intake, and low levels of daily physical activity are independently associated with COVID-19 mortality. Further, genetic factors such as variations in the androgen receptor may compound the effects of an unhealthy lifestyle and increase the risk of severe COVID-19 symptoms in some patients. A diet high in sugar in combination with a low level of physical activity may increase blood glucose levels and impair glucose metabolism. Recent data show that patients admitted to the hospital with high levels of fasting blood glucose are at an increased risk for severe COVID-19 symptoms. Moreover, elevated glucose levels resulted in increased SARS-CoV-2 viral loads *in vitro*. We believe that healthier habits of diet and exercise, by improving glucose homeostasis could modulate the individual risk of severe COVID-19 symptoms.

To the editor

The COVID-19 pandemic has affected over 31 million people and taking over 1 million lives [1]. Individual vulnerability still needs further elucidation. High levels of fasting blood glucose (FBG) upon hospital admission has been associated with an increased risk for more severe COVID-19 symptoms [2]. Elevated glucose levels has been observed to enhance viral replication trigger increased cytokine production by monocytes *in vitro* [3]. Here we hypothesize that reduced consumption of added sugars (refined carbohydrates), as well as increased physical activity per capita, could lead to increased individual resistance to COVID-19 pathogenicity.

A *meta*-analysis of 35 studies revealed that each 1 mmol/L increase in FBG levels augmented the risk of COVID-19 severity by 33% (risk ratio 1.33 [95% CI: 1.26–1.40]). The odds ratio of ICU admission with a FBG of 5.5–6.9 mmol/L was 1.69 and increased to 19.21 when FBG was over 7.0 mmol/L [3]. Furthermore, elevated Hemoglobin A1c levels has been associated with worse COVID-19 prognosis [4]. Hyperglycemia was also associated with requirement for mechanical ventilation, intensive care unit (ICU) admission and mortality [5]. After adjusting for age, diabetes, hypertension and other confounding factors, hyperglycemia was reported to be an independent risk factor of mortality: when >180 mg/dL (hazard ratio 1.50 [95% CI: 1.31–1.73]), when 140–180 mg/dL (hazard ratio 1.48 [95%CI: 1.29–1.70]) [5]. Patients with higher blood glucose levels have more severe symptoms associated with SARS-CoV-2 infection (weighted mean difference 2.21 [95% CI: 1.30–3.13, $P < 0.001$]) [6].

Genetic factors may put some individuals at additional risk of severe COVID-19. It is known that AR regulates transcription of the transmembrane protease, serine 2, which is required for SARS-CoV-2 infectivity [7]. The AR gene contains a polymorphic CAG repeat sequence which varies in length between 12 and 30 repeats [8]. COVID-19 patients with longer CAG repeats were shown to have longer hospitalizations and an increased likelihood of being admitted to the intensive care unit than patients with shorter CAG repeats [7,9]. Longer CAG repeats have been associated with higher body fat mass, plasma insulin, and leptin levels [10]. The concurrent syndemic in which socially disadvantaged groups such as minorities, poorly paid key workers and the elderly lack the resources and knowledge necessary to conduct and maintain a healthy lifestyle [11].

There is a marked difference is COVID-19 mortality globally. In Western and Central Africa, death rates are remarkedly low. For example, the death rates in Niger and Chad are 2.85 per million and 5.84 per million, respectively [1], contrasting to death rates of 677.27 per million for the USA and 662.85 per million for the UK [1,12]. The numbers from Western and Central Africa, are unexpected, because of local challenges in healthcare and PPE, one of the explanations could be a more active lifestyle and healthier diet. Individuals on a typical Western diet consume copious amounts of sugar but do not expend the energy the excess sugar provides. Due to increased sugar consumption and a lack of physical activity, these individuals are prone to obesity and Type 2 Diabetes Mellitus (DM), which are associated with insulin resistance and impaired glucose metabolism [13]. Fig. 1a shows a general trend between national sugar consumption per capita and COVID-19 mortality rates [1,14]. Countries with low rates of sugar consumption per capita, like Niger at 1 Kg and Chad at 2 Kg, have low mortality rates of 2.85 and 5.84 per million, respectively. In contrast, countries with high rates of sugar consumption per capita such as the Russian Federation at 42 Kg and Israel at 56 Kg have high mortality rates of 178.5 and 267.34 per million, respectively. An exception to this trend is Singapore; despite a high rate of sugar consumption per capita at 46 Kg, the country has a remarkedly low mortality rate of 4.79 per million. One possible explanation is that Singapore has instituted strict lockdown policies and excellent testing and contact tracing efforts, which have proven effective in halting the spread of SARS-CoV-2 [15]. Fig. 1b shows trend between daily caloric intake per capita and mortality rates [1,16]. Countries with low national averages for daily caloric intake generally

https://doi.org/10.1016/j.mehy.2021.110502
Received 22 December 2020; Received in revised form 22 December 2020; Accepted 12 January 2021
Available online 24 January 2021
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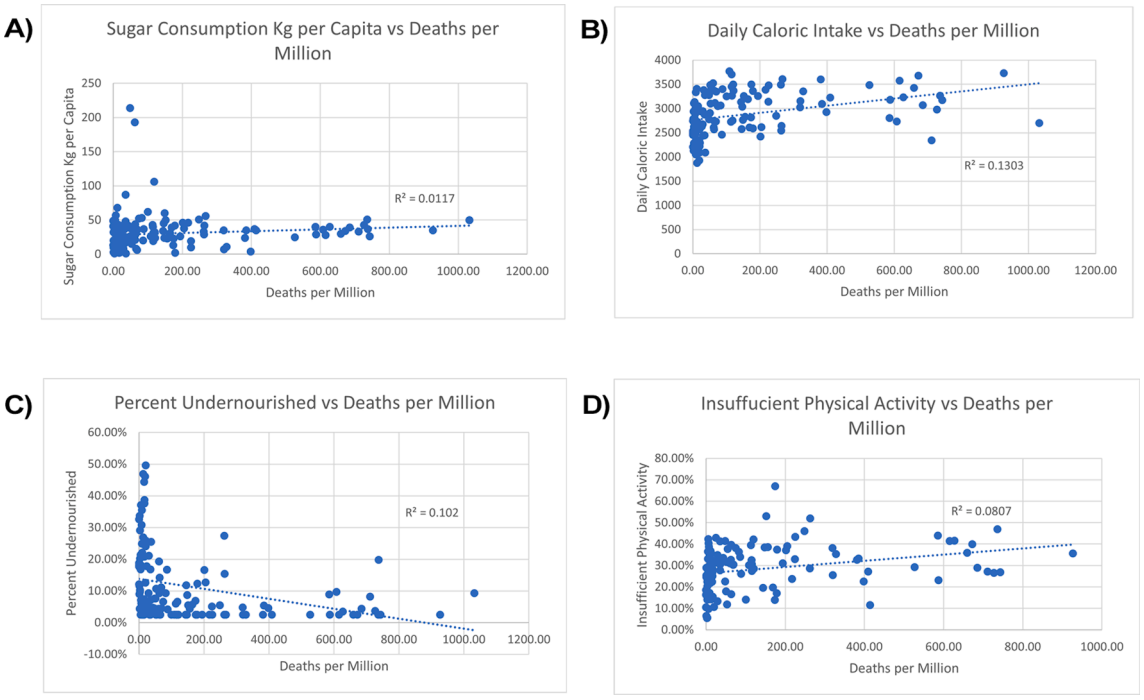

Fig. 1. Comparison of International Data (per country) of Sugar Consumption (kg) per Capita (A), Daily Caloric Intake (B), Percent Undernourished (C) and Insufficient Physical Activity (D) vs COVID-19 Deaths per Million inhabitants. Sources: Deaths per Million (137 Countries): WHO Dashboard 2020; Sugar Consumption (137 Countries): Data for year 2015, Protectivity Insurance compiled from USDA/Washington Post/Six Single Nation Resources; Caloric Intake (131 Countries): Data for year 2013. Our World in Data; Undernourishment (131 Countries): Data for year 2013. Our World in Data; Insufficient Physical Activity (117 Countries): GHO/WHO data for year 2017.

have lower death rates than countries with high averages. For example, the Central African Republic and Uganda have low national averages for daily caloric intake at 1879 and 2130, respectively, and have low mortality rates of 12.85 and 2.16 per million, respectively. In contrast, the United States and Belgium report national averages of 3682 and 3733 calories per day, respectively, and have high mortality rates of 672.22 and 926.43 per million, respectively. Fig. 1c shows that calorie restriction plays a role in reducing COVID-19 severity, as seen in undernourished individuals [1,16]. Using data from the countries just mentioned, the Central African Republic and Uganda each have an undernourished population of 46.9% and 33.7%, respectively. The United States and Belgium each have only 2.5% of their population undernourished. Lastly, Fig. 1d shows a trend between a lack of physical activity and severe COVID-19 symptoms and mortality [1,17]. Countries with low rates of insufficient physical activity, such as the Central African Republic and Uganda, which report 14.3% and 5.5% of their respective populations not meeting the daily requirements for sufficient physical activity, have low death rates as mentioned above. In contrast, countries that have a high percentage of their population that does not meet the daily requirements for sufficient physical activity have high death rates. For example, 40% and 35.7% of the populations in the United States and Belgium, respectively, do not meet the daily requirements for sufficient physical activity. For certain countries, there was a strong correlation between multiple factors analyzed. For example, Belgium has a high per capita death rate of 926.43 per million, a high daily caloric intake rate of 3733 calories, a high percentage of the population that does not get the recommended amount of exercise (35.7%) and a high annual consumption rate of sugar (35 Kg per capita). Other countries, such as China, which has a high caloric intake per capita (3108) yet have a very active public, with only 14.1% of sedentary population. China has a low death rate of 3.23 per million. These observations are in accord with Horton's point that "Syndemics are characterized by biological and social interactions between conditions and states, interactions that increase a person's susceptibility to harm or worsen their health outcomes" [11].

Adopting a healthy lifestyle which includes a balanced diet and exercise may be key to reducing SARS-CoV-2 disease severity. In individuals who are overweight and obese, decreasing the consumption of sugars and increasing physical activity may improve insulin resistance and glucose metabolism [18]. Reduced blood glucose levels may create a suboptimal environment for SARS-CoV-2 replication. The WHO has recently established daily and weekly exercise guidelines published on their website under the title #HealthyAtHome. These guidelines recommend a combination of cardio and strength training regimens for all individuals, categorized by age group [19]. These insights could guide individual efforts and public health policies to decrease the burden of the underlying global syndemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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