

Title: Sunlight and vitamin D in the prevention of coronavirus disease (COVID-19) infection and mortality in the United States

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Running Title: Vitamin D in the prevention of coronavirus disease

Abstract

The coronavirus disease (COVID-19) is an infectious disease caused by the most recently discovered coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study aims to investigate associations between sunlight and vitamin D, using latitude as an indicator, with COVID-19 cases and related deaths in the United States. General regression and Chi-square test were used to examine the associations between latitude and COVID-19 cases and deaths. The analyses indicated that latitudes were marginally associated with cases ($p = 0.0792$) and deaths ($p = 0.0599$), with an increase of 2491 cases and 189 deaths of the total numbers in the mainland of US for every unit of increase of the latitude. When the states were classified into high latitude ($>N 37^{\circ}$) and low latitude ($<N 37^{\circ}$) groups, both the cases (702 vs 255 cases/100k population) and deaths (43 vs 11 deaths/100k population) were significantly different ($p < 0.001$) between the two categories. The results suggested that sunlight and vitamin D, with latitude as an indicator, might be associated with decreased risks for both COVID-19 cases and deaths. These findings warranted urgent needs of large cohort, clinical and pre-clinical studies to assess the impact of VD on the prevention of COVID-19.

Keywords: Coronavirus, COVID-19, Infection, Latitude, Sunshine, Vitamin D

Introduction

Since a novel coronavirus, which was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported in December, 2019¹, the disease caused by this virus, denominated as COVID-19 by the World Health Organization (WHO) on March 11, 2020, has been rapidly spreading across the world. It has reached a pandemic level², representing the 3rd epidemic of coronavirus infections in the 21st century following severe acute respiratory syndrome (SARS)-CoV (2002)³ and the Middle East respiratory syndrome (MERS)-CoV (2012)⁴. COVID-19 manifests as a severe acute respiratory illness that can be complicated by acute respiratory distress syndrome, multi-organ failures and death^{5,6}.

Vitamin D (VD) is both a nutrient and a hormone that is important for normal bone development and maintenance^{7,8}. VD is naturally present in very few foods, and our best resources are via sunlight exposure or dietary fortification/supplementation. Ultraviolet radiation with a wavelength of 290–320 nanometers penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to previtamin D₃, which eventually becomes the active 1,25(OH)D₃⁹. The current Recommended Dietary Allowance (RDA) is 600 IU/day for age of 19-70 years⁹. In the United States, VD inadequacy and deficiency are common; 1/3 to 40% of the population in the United States is still at the risk of VD inadequacy (*i.e.* 30-49 nmol/L in blood of 25-hydroxyvitamin D₃ (25(OH)D₃)) or deficiency (*i.e.* <30 nmol/L)¹⁰⁻¹³. Particularly, 60% of nursing home residents¹⁴ and 57% of hospitalized patients¹⁵ were found to be VD deficient.

In addition to its skeletal functions, the deficiency of VD has also been associated with increased risks of a wide range of diseases, including cancers, cardiovascular diseases, immune and inflammatory diseases¹⁶. In terms of respiratory illness, observational studies have reported that a high level of serum 25(OH)D₃ resulted from either ultraviolet radiation or dietary sources,

was associated with reduced incidence of viral respiratory infections¹⁷⁻¹⁹. A recent meta-analysis including 10,933 subjects reported that VD supplementation reduced the risk of acute respiratory tract infection by 12%, and the protective effects were particularly stronger in those with low baseline 25(OH)D₃ level (<25 nmol/L)²⁰. The possible role of VD in infections is implied from its impact on the innate and adaptive immune responses²¹⁻²³, as well as the suppression of inflammatory processes^{18,24}.

While substantial evidence supported a critical role of VD in immune function, it is largely unknown whether there exists a possible link between VD deficiencies with the new COVID-19. Using the cases and deaths data in the United States, the primary aim of this study is to assess if there is any association between the latitudes across different states, using as an indirect indicator of VD status, and COVID-19 cases and mortalities. The analysis provided preliminary but important knowledge regarding the role of sunlight and VD in the prevention of COVID-19.

Results

Characteristics of the population

As of May 23, 2020, there are a total of 1,622,114 cases in 4 months after the first case reported on Jan 22, 2020 (CDC, Fig. 1A). As described in the Materials and Methods section, Alaska, Hawaii and other territories has significant different latitudes comparing the states in the mainland of the United States; we therefore excluded Alaska, Hawaii and other territories and only included 48 states plus the District of Columbia (DC). The range of latitudes covers from N28° to N48° (Fig. 1B). A total of 1,609,488 cases and 91,094 COVID-19-related deaths (COVIDTracking) were included in our analysis (Fig. 1C and 1D).

Correlations between geographic latitude and COVID-19 cases and related deaths

Latitude is a statistically significant risk factor for VD deficiency ²⁵. A linear regression was performed to examine the associations between latitude and COVID-19 cases and deaths. With the consideration that the population and COVID-19 testing rates across the states are significant confounding factors of COVID-19 cases and mortalities, we adjusted for these two confounders in our model. The analyses indicated that the geographic latitude were marginally associated with cases ($p = 0.0792$) and deaths ($p = 0.0599$) across the states, with increases of 2491 cases and 189 deaths of the total numbers in the mainland of the United States for every unit of increase of the latitude (Fig. 2A and 2B).

Among the top 5 states with cases more than 90,000, four states (New York, New Jersey, Illinois, and Massachusetts) are with latitudes greater than 37 degree, a cut-off value for VD synthesis from ultraviolet ²⁶; only one state (California) is on the bottom-line of the latitude of N37⁰. Among the top 5 states with fatalities more than 5,000, all of them (New York, New Jersey, Massachusetts, Michigan, Pennsylvania) are with latitudes greater than 37 degree (Fig. 2A and 2B).

COVID-19 cases and related deaths across the N37⁰ degree geographic latitude line

Based on Harvard Women's Health Watch ²⁶, except during the summer months, the skin makes little if any VD from the sun at latitudes above 37° degrees north (Fig. 1B) or below 37 degrees south of the equator. We therefore divided the states into high latitude state group (H_LT) and low latitude state group (L_LT) according their latitudes using the N37⁰ as a cut-off value. Chi-square test were performed to compare COVID-19 cases and related deaths between these two categories of states. The analyses showed that the states with high latitudes (latitude $\geq 37^\circ$), when comparing to the states with low latitudes (latitude $< 37^\circ$) groups, both the COVID-19 cases (702

vs 255 cases/100k population) and related deaths (43 vs 11 deaths/100k population) were significantly higher ($p < 0.001$) (Fig. 3A and 3B).

It is noted that the COVID-19 testing in the states with latitude $\geq 37^\circ$ was even higher than those states with latitude $< 37^\circ$ (4591 vs 3741 individuals/100K population) (Fig.3C). However, the significant higher levels of COVID-19 cases and related deaths per 100K population are not attributed to the high testing rate, as positive rate of testing in the states with latitudes $\geq 37^\circ$ are even higher than those states with latitude $< 37^\circ$ (Fig. 3D). The high positive rate of testing indicates the COVID-19 is more prevalent in the states with latitude $\geq 37^\circ$ than the states with latitude < 37 degrees (Fig. 3D).

Discussion

Using the COVID-19 cases and related deaths data within 4 months starting from the first case reported by CDC on Jan 22, 2020 to May 23, 2020 (The COVIDTracking), we have identified a potential association between the geographic latitudes, as an indicator of sunlight exposure and VD status, with COVID-19 cases and associated mortalities in 48 states plus DC in the mainland of the United States.

When the COVID-19 cases and related deaths across different states were plotted against latitudes after adjusting for population and testing rates, we observed that the geographic latitudes were marginally associated with COVID-19 cases ($p = 0.0792$) and related deaths ($p = 0.0599$). When the states were divided into two categories with the latitude of 37° degrees as a cut-off value²⁶, both the COVID-19 cases and related deaths were significantly higher ($p < 0.001$) in the states with latitudes $\geq 37^\circ$ degrees, when compared to the states with latitudes $< 37^\circ$ degrees. Our findings based on the data in the United State is consistent with the observation from a recent study based on European countries^{27,28} and other countries²⁹, which showed a crude association between mean

levels of VD in various countries with cases and mortalities caused by COVID-19. These findings warranted the necessary of large cohort, clinical and pre-clinical studies to assess the potential protective effect of VD on COVID-19 as it is still widely spreading globally.

Except for the summer months, people who live in areas above 37° degrees north or below 37° degrees south of the equator makes little if any VD from the sun²⁶. In this study, we observed the top states with COVID-19 cases more than 90,000 or related deaths > 5, 000 were those states with the latitudes greater (New York, New Jersey, Massachusetts, Michigan, Pennsylvania) or just close to (California) the N37° latitude line (Figure 2A and 2B). We did observe that some states with high latitudes but have low numbers of COVID-19 cases and related deaths, i.e. Montana, Wyoming, North Dakota, South Dakota (Fig. 1C and 1D). This is largely due the low population density. These 4 states are among the bottom of states with the lowest population density. This observation emphasized the importance of the low population density and maintaining social distance in preventing the spreading of COVID-19.

In terms of the biological mechanisms that guide VD against COVID-19, the experimental research are currently extremely limited. However, there are substantial biological evidence showing that VD is important in regulating immune function^{21-23,30} and inflammatory response^{18,24,31}. Particularly, studies have demonstrated that VD is critical in regulating immune functions and suppressing the inflammatory cytokine response of respiratory epithelial cells to various pathogens including respiratory viruses^{30,32}. For instances, a recent study reported that VD₃ suppressed bleomycin-induced expression of inflammatory cytokines and fibrosis markers *in vitro* and *in vivo*³³. Another study showed that VD decreased rhinovirus replication and release, and increased rhinovirus-induced interferon stimulated genes and cathelicidin, which has direct anti-rhinovirus activity³⁴. The pathology of COVID-19 involves a complex interaction with the immune

system. The regulatory role of VD on immune function implies its potential for the prevention of COVID-19. Mechanistic studies are urgently needed for the clarification.

We acknowledge that this study has limitations: a) There are large variations of the COVID-19 cases and related mortalities across the states, which reduced the precision of the estimate. b) The number of cases/state is affected by the number of tests, which are unequally performed across the states. However, even with unequal test rates between the states above or below the N37° latitude cut-off line (15.3 vs 6.8%, Fig. 3D), the higher test rate/state and higher positive rate/tests (702 cases/100K population, Fig. 3A) for the states with latitude >37° clearly suggested the higher prevalence of COVID-19 in the people living in the areas with high latitude. c) COVID-19 is a highly infectious disease, and population density in large cities are a critical risk factor. We recognized the bias from the New York City, which is included in the group of states with high latitude. d) In this study, latitude was used as an indicator for sunlight and VD. Even though latitude is strongly correlated with VD status ²⁵, it is also influenced by many factors including clothing, sunscreen use, skin pigmentation, dietary supplement as well as age, obesity etc. Therefore, serum 25(OH)VD should be used as biomarkers in epidemiological or clinical studies. Nevertheless, the present study aimed to lay out a hypothesis to be taken forward and to be investigated utilizing robust study designs. It also stimulated interest in this area, and if the mechanism(s) is proved, it will lead to new preventive strategies.

In conclusion, we found potential relationships between latitude, as an indicator of sunlight and VD status, and the number of COVID-19 cases and related mortalities. Although the findings could not be interpreted as strong evidence that VD is effective in preventing COVID-19, as VD deficiency is harmful and is still prevalent in US, our study warranted further studies to assess

possible impacts of VD deficiency on the risk of COVID-19, which should be highly beneficial for fighting the COVID-19 pandemic.

Materials and methods

We searched the incidence and mortality data in the United States from three different resources: the COVIDTracking Project (COVIDTracking, <https://covidtracking.com>), Centers for Disease Control and Prevention (CDC, <https://www.cdc.gov/coronavirus/2019-nCoV>), and The Coronavirus Resource Center in John Hopkins University (JHU, <https://coronavirus.jhu.edu>). We access the data from these resources on May 23, 2020, which covers the cases and deaths in a spectrum of 4 months from the first case identified on January 22, 2020 according to CDC. The population data for each state was the estimated population by July 1, 2019 and was released by the U.S. Census Bureau, Population Division (<https://www.census.gov>).

As Alaska, Hawaii and other territories are away from the mainland of US with significant different latitudes, we eliminated the data from both Alaska and Hawaii and other territories, only include 48 states plus the District of Columbia on the mainland in our data for analysis. Statistical analyses were carried out using linear regression analysis and Pearson Correlation, adjusting with population and confounding factors including COVID-19 testing rate across each state. All data were shown in the Supplementary Information File (Table S1). Statistical analyses were performed using SAS program (Version 9.4, SAS Institute, Cary, NC, USA).

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Author Contributions: Z.L. conceived the concept, collected the data, did the data analysis and wrote the manuscript. Y.L. and Q.L. equally contributed to this study by providing background review of COVID-19. Y.L. also participated the data analysis and provided background of vitamin D synthesis via ultraviolet in skin. Q.L. also participated the discussion of the design and interpretation of the results. N.Z. participated the discussion of the concept, the design, the interpretation of the data and the review of the manuscript.

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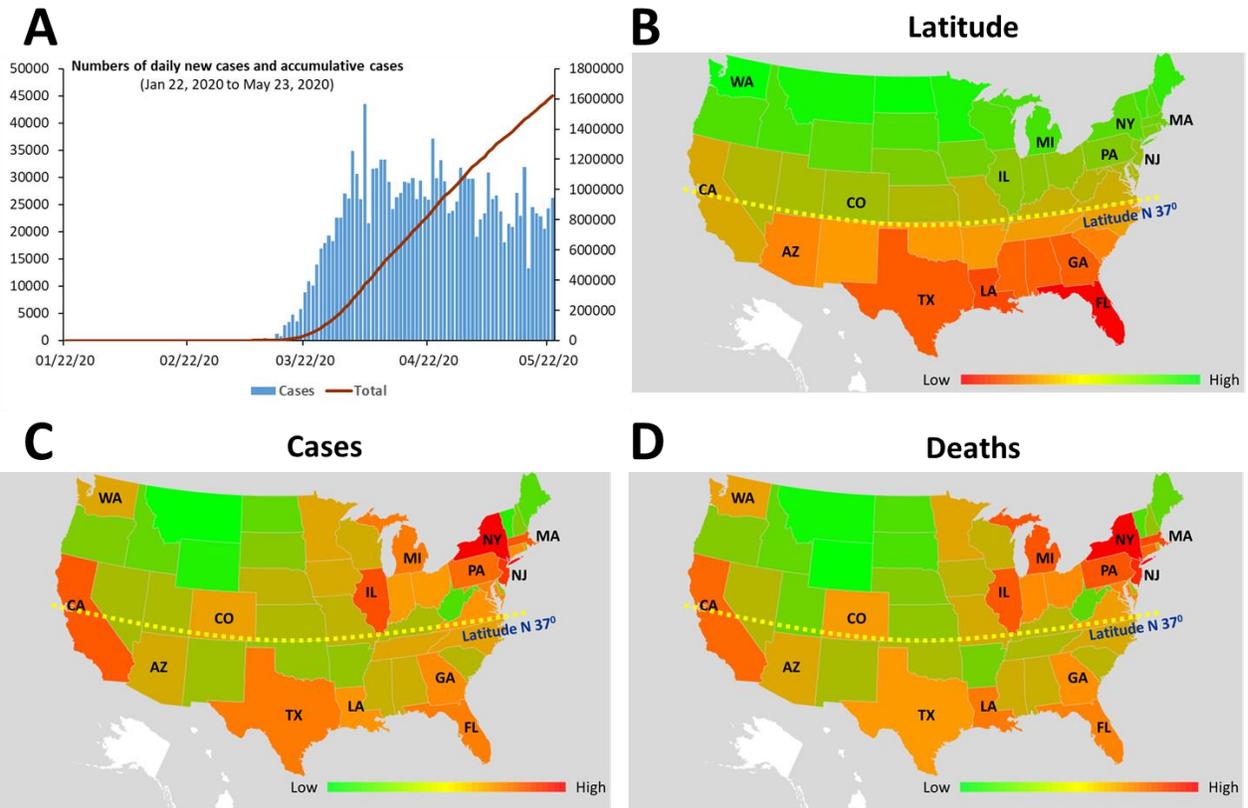


Figure 1. Characteristics of the population. A) By May 23, 2020, there are a total of 1,622,114 cases in 4 months after the first case reported on Jan 22, 2020 (data from CDC); B) Latitudes across states; C) COVID-19 cases across states; D) COVID-19-related deaths across states.

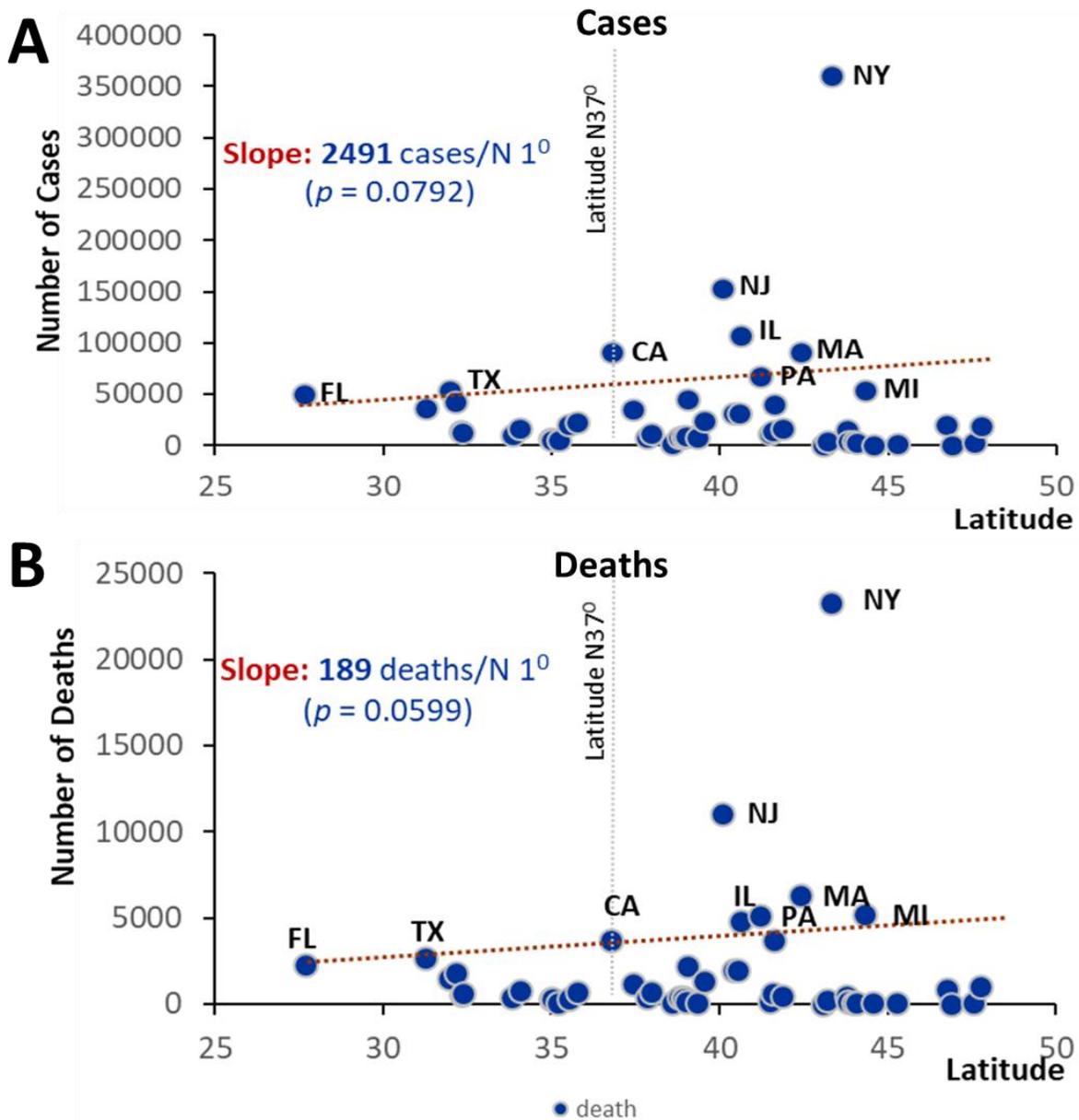


Figure 2. Correlations between geographic latitudes and COVID-19 cases and related deaths. A) Cases. One degree of the latitude to the north represents an increase 2491 cases in the total numbers of cases in the mainland of the United States, B) Deaths. One degree of the latitude to the north represents an increase 189 COVID-19 related deaths in the total numbers of deaths in the mainland of the United States.

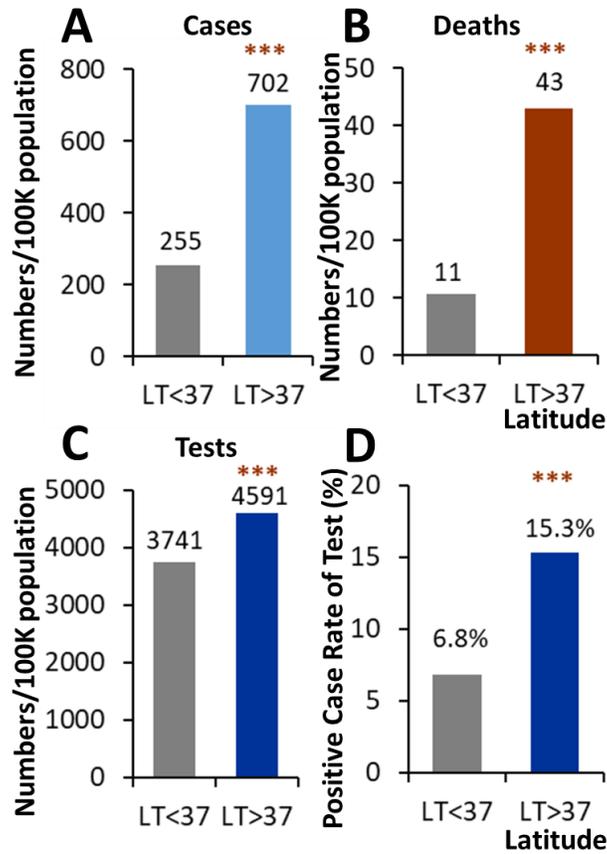


Figure 3. COVID-19 cases and related deaths across the N37° degree geographic latitude line. A) COVID-19 cases (cases/100K population); B) COVID-19 mortalities (deaths/100K population); C) Test rate (numbers/100K population). How many individuals were tested per 100K population; D) Positive case rate (%). The percentage of positive case in the subject tested for COVID-19. LT < 37 and LT > 37: the latitudes less than or greater than 37° degrees.