Research Article

A geographical approach to the development of hypotheses relating to Covid-19 death rates

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ABSTRACT

Covid-19 deaths per million vary greatly between continents, with countries in South America having higher death rates even than Europe and North America, while Asia, Africa and Oceania have death rates which are only a fifth of those in South America. By analysing national level data on body weight, diet and latitude, we hypothesise and demonstrate that difference in the percentage of people with overweight (BMI > 25) may be the major factor that explains these differences in Covid-19 death rates. Meanwhile, within the group of countries where adult overweight is prevalent (i.e., where more than 50% of the population has BMI > 25), we hypothesise and demonstrate that latitude plays a role, with relatively lower death rates occurring in countries at lower latitudes. We further suggest that these relationships may be explained by two possible medical hypotheses relating to solar radiation: (1) In overweight people there is less penetration to important organs of near-infrared radiation (NIR) which stimulates production of subcellular melatonin, a strong anti-oxidizing factor and (2) In overweight people, fatty tissue holds much of the body´s 25(OH)D_3 leaving less circulating in the blood stream. Several pathways have been proposed by other researchers to explain the link between Vitamin D deficiency and severity of Covid-19, but the possible link of Covid-19 outcome with NIR has not been explored. Latitude, of course, determines the amount of incoming NIR and as well as UV-B, which is the main stimulant for the body´s production of Vitamin D. It may well be that these two physiological processes operate simultaneously.

Key words: Covid-19 deaths/million, near infrared NIR, vitamin D, overweight, obesity, latitude

1. INTRODUCTION

Academics in the medical profession tend to hold a poor view of observational studies which attempt to link medical outcomes to geographical conditions, with good reason; they have been

trained to trust science only when it is carried out to a very high degree of certainty, for example by using multiple double blind controlled experiments with unbiased sample data from hospitalized individuals. Ecological fallacy and confounding variables can easily compromise studies which rely on data which are aggregated or averaged over spatial units such as counties, states or countries. Nevertheless, a geographical approach to the analysis of data on Covid-19 outcomes can produce important insights and support the development and testing of new medical hypotheses. The purpose of this paper is to use data on the variation in Covid-19 death rates across 179 countries up to the end of 2021 to explore hypotheses that could explain these variations, in the statistical sense. A number of key potential explanatory factors are considered, including percentage of the population that is overweight (BMI > 25), percentage that is obese (BMI > 30), mean intake of sugar in various forms, percentage vaccinated, and latitude. We then use the results of this analysis to assess which of a number of recent medical hypotheses relating to solar radiation and Covid-19 death rates might be considered worthy of further testing. These include not only theories concerning ultraviolet radiation (UV-B) and Vitamin D, but also the possible influence of near-infrared radiation (NIR), and in addition the role of UV-A and temperature.

This approach is motivated in the first instance by the fact that inter-continental differences in rates of Covid-19 deaths per million are very striking (Figure 1). South America is the worst affected (cumulative deaths due to Covid-19: +/- 2750 per million), followed by North America (which includes all of Central America, Mexico and the Caribbean) and Europe (including Russia), which pegged almost equal by the end of 2021 at about 2000 per million (1). Asia (including the Middle East, with 600 per million) and Africa (500 per million) have Covid-19 death rates which are only one fifth of those in South America, while in Oceania rates are even lower (400 per million).

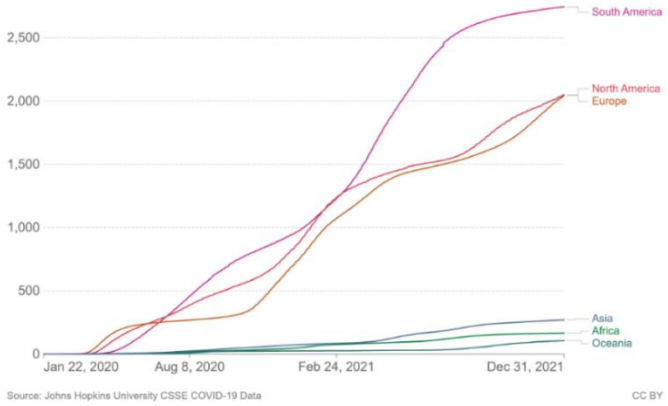

Fig. 1. Cumulative Covid-19 deaths per million up to December 31, 2021. Data from Johns Hopkins Corona Virus Resource Center, compiled by Our World in Data (1).

Two common assumptions are immediately called into doubt by these figures. Firstly, it would appear that the lower death rates in African and Asian countries cannot largely be explained by their comparatively youthful population, because the demographic pyramid of South America is very similar to that of Asia (24% and 23% of the populations are aged 0-14 respectively, and in both cases 63% of the population is aged 15-59), while Africa is more youthful (40% below the age of 14, 54% aged 15-59) (2). Secondly, it seems unlikely that the differences can be explained by poorer standards of reporting in developing countries, since although better reporting might possibly be expected in the upper income countries, it is doubtful that South American countries

would be so much more assiduous in this than African and Asian countries. Furthermore, although there is much clinical evidence in the literature of an association between Vitamin D deficiency, as measured by serum 25(OH)D_3, and severe outcomes in Covid-19 patients (3-11), this does not appear in the first instance to explain the observed inter-continental differences, in the sense that ultra-violet light (UV-B), the main stimulant of Vitamin D production in the body, is similar at any given latitude, so all tropical parts of the world are in principle similar in this respect. And finally, while very stringent public health measures including strict border closures, tightly controlled lockdowns and track and trace measures may perhaps explain the low numbers in Oceania, the same in no way applies to Africa and Asia (with the exception of China). Vaccination rates by the end of 2021 were also much lower in Africa (14% with first or first and second vaccines) than in South America (76%) and Asia (67%), while they were 68% in North America and 65% in Europe (1). At the global scale, it might therefore appear that genetic or lifestyle differences are more likely to explain the intercontinental patterns observed. Before settling for such a broad-brush conclusion however, the data must first be subjected to more careful analysis.

2. MATERIALS AND METHODS

2.1. Methods.

Data on cumulative Covid-19 deaths per million up to 31 December 2021 and on percentage of the population that had received first and second vaccinations by 30 November (since most vaccines take around a month to become fully effective), were taken from Our World in Data (1) which compiles data gathered by the Johns Hopkins Covid-19 Resource Center. These data cover the first wave of infection and the Alpha and the Delta variants that followed but pre-date most of the effects of the Omicron variant. Data on percentage of the population with body mass index greater than 25 (overweight, BMI > 25) and greater than 30 (obese, BMI > 30) are from the World Obesity Foundation (12), and are derived from a World Health Organization database (13). Data on total sugar intake per capita and on consumption of sweetened drinks is also from the WOF report and are derived from the FAO database FAOSTAT (14). The set of countries included in the analysis is constrained by the fact BMI data is not available for all countries or territories; many small island states are not represented, nor Palestine, South Sudan, North Korea, etc. The total maximum sample size for the current study was thus 180 countries, but for statistical data processing reasons the outlier, Peru, which has an extremely high apparent death rate, was removed. It is understood that the data for Peru may reflect a non-standard way of recording Covid-19 deaths (i.e., based on excess deaths rather than recorded Covid-19 deaths). Average latitude of each country was obtained from Google´s Dataset Publishing Language (https://developers.google.com/public-data/docs/canonical/countries_csv). Limitations of all these data are considered at the end of this section.

For correlations between two variables, we used Pearson´s correlation test, with linear regression to ´explain´ one variable by a group of others, after eliminating those which were internally correlated. The Elbow method was used to create clusters of countries on the basis of overweight and Covid-19 deaths. The Elbow method uses the unsupervised K-means Algorithm to create clusters; it groups data according their similarity, selecting the optimal (most efficiently defined) clusters such that the total intra-cluster variation or total within-cluster sum of squares is minimized (15, 16). Comparisons between clusters were made using ANOVA tests. Statistical significance throughout was assumed for any value $p \leq 0.05$.

Literature on possible physiological routes by which Vitamin D (which is derived mainly from UV-B radiation) could influence Covid-19 outcomes is abundant and both peer reviewed and pre-print articles were reviewed to obtain lines of argument that have been presented in favour of this. Also surveyed was literature on two much less well-examined relationships between solar radiation and Covid-19 death rates; the role of UV-A in generating nitric oxide on the surface of the skin, creating a sterilising effect, and the role of infrared (IR) radiation in enhancing immunity. The credibility of each of these arguments is then assessed in the light of the findings given in the first part of the study.

2.2. Data limitations.

We have used the best available data for this exercise but are aware that they have many limitations. Firstly, the standards and procedures for reporting Covid-19 deaths are not the same in all countries. We have relied on the material provided by the Johns Hopkins Covid-19 Resource Center because this is the best available global repository for data on Covid-19. We were only able to include in our study the countries for which BMI data were also available (180 countries). As noted above, we eliminated Peru from the sample because it is thought to use excess deaths rather than reported Covid-19 deaths when reporting internationally. Data on vaccination rates are likely to be somewhat more reliable than death rates in the sense that vaccinations are easier to record than deaths, given that some Covid-19 deaths may be attributed to other causes. However, while data on deaths as reported by Our World in Data probably includes all Covid-19 deaths registered, whether of nationals or non-nationals within a country, it is not clear whether the data on BMI include resident foreigners, who can make up a large part of the total population e.g., in some Gulf states. If they are not included, then %BMI in these countries will have been considerably overestimated in these specific places. In any case, the reliability of these BMI estimates is difficult to ascertain, but this is the only comprehensive data set available on BMI at national level across the globe.

Latitude is perhaps the variable most difficult to quantify in an adequate manner. Some countries span a broad range of latitudes (e.g., Chile, Argentina, Australia), and for these cases the average latitude is not very meaningful. For the case of Canada for example, the vast majority of the population lives within 50 km of the border with the USA but the average latitude is far to the north. To attempt to adjust for these kinds of cases was beyond the scope of this study.

Given the messy nature of the data, we do not put much reliance on the quantitative values produced by our statistical analysis (R^2 values etc). Rather, the aim is to identify which variables demonstrate some relationship with the dependent variable, which is cumulative Covid-19 deaths by 31 December 2021.

3. RESULTS

3.1. The relation of Covid-19 deaths to overweight.

From the beginning of the pandemic, it has been clear that at the clinical level overweight and obesity correlate highly with poor Covid-19 outcomes. Not surprisingly, this pattern also appears in aggregate at the international level. In March 2021, the World Obesity Foundation published data (12) correlating Covid-19 deaths up to the end of 2020 with percentage of the adult population that is overweight (BMI > 25) at national level across 164 countries.This resulted in a simple

correlation coefficient of 0.55, explaining about 30% of the variance. Moreover, they found a tipping point, with Covid-19 deaths per million being low in all countries where less than 50% of the population have a BMI > 25, but then shooting up when more than 50% have BMI > 25 (1, p. 15). Using log BMI > 25 data to correct for this non-linearity, the correlation was 0.70 (explaining about 50% of the variance). Interestingly, the correlation coefficient between death rates and obesity (BMI > 30) were somewhat lower, a finding which is not explained. Given that the proportion of population with BMI > 25 includes also those with BMI > 30, the effect of weight would seem to be non-linear, with decreasing effect of weight on death rates beyond a certain BMI level. We note that other researchers have identified BMI > 23 as being a turning point in this respect at the individual level (17), but as no data on this is available for global analysis, in what follows we focus on the percentage of population with BMI > 25.

For the present study, the calculations made by the WOF were repeated using the same sources of data but updating the Covid-19 death data to the end of 2021, and including a number of countries which had had no deaths in 2020 and appear to have been excluded from the WOF study for that reason. Our results are generally in line with those of the WOF (Table 1), including the fact that %BMI > 25 is better correlated with death rates than %BMI > 30.

Table 1. Simple correlations between national level Covid-19 death rates and percentage of population with overweight (BMI > 25) and obesity (BMI > 30).

	WOF (2021) Correlation coefficient Covid-19 deaths up to end 2020		This study Correlation coefficient Covid-19 deaths up to end 2021	
Variable	Pearson´s r	N	Pearson´s r	N
% of population with BMI > 25	0.547 ($p < 0.001$)	164	0.50 ($p < 0.001$)	179
Log % population with BMI > 25	0.703 ($p < 0.001$)	164	0.51 ($p < 0.001$)	179
% of population with BMI > 30	0.45($p < 0.001$)	164	0.16 ($p < 0.001$)	179
Log % population with BMI > 30	N/A	N/A	0.43 ($p < 0.001$)	179

Correlation between Covid-19 death rates and percentage of population that is overweight cannot be taken to prove cause, since each death is individual and there is no way of knowing whether those who die are also those who are overweight. Moreover, overweight and obesity at the individual level correlate highly with diabetes, insulin resistance and hypertension, all of which are also Covid-19 comorbidity factors. This means that overweight could be just a marker for other factors and not a cause as such. Nevertheless, the relationship is compelling in that it explains, in a statistical sense, a significant if relatively small part of the variance in national Covid-19 death rates, a difference which has not yet been satisfactorily explained by other factors.

Closer examination shows that data on percentage of the population overweight follows a two-humped curve (Figure 2), indicating that with respect to this variable there are essentially two quite different populations; one set of countries with a mean of about 28% BMI > 25, and another with a mean of about 60% BMI > 25; the apparent association of high Covid-19 death rates with the

´breakpoint´ of 50% BMI > 25, as noted by the World Obesity Foundation (12) is simply the reflection of this double humped distribution.

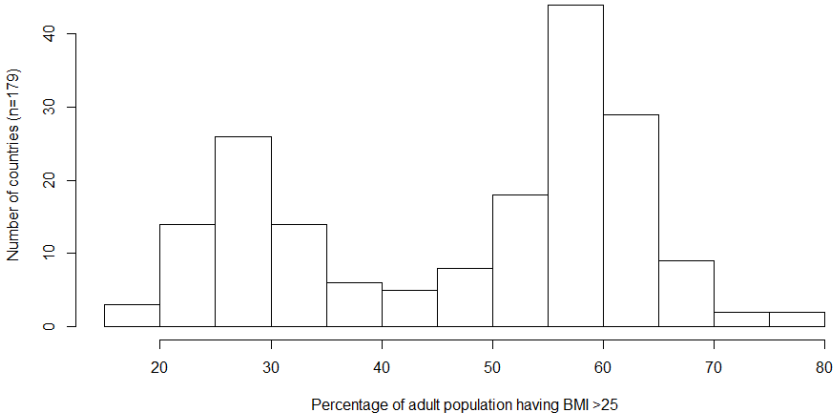

Fig. 2. Distribution of countries (n= 179) according to the percentage of their adult population having BMI > 25. Source: (12).

We therefore used Elbow cluster analysis (15, 16) on the Covid-19 death rate and %BMI > 25 data and found that the statistically most efficient solution was four clusters (country groups), as shown in Figure 3, also shown as a map in Supplementary Materials Figure SM1.

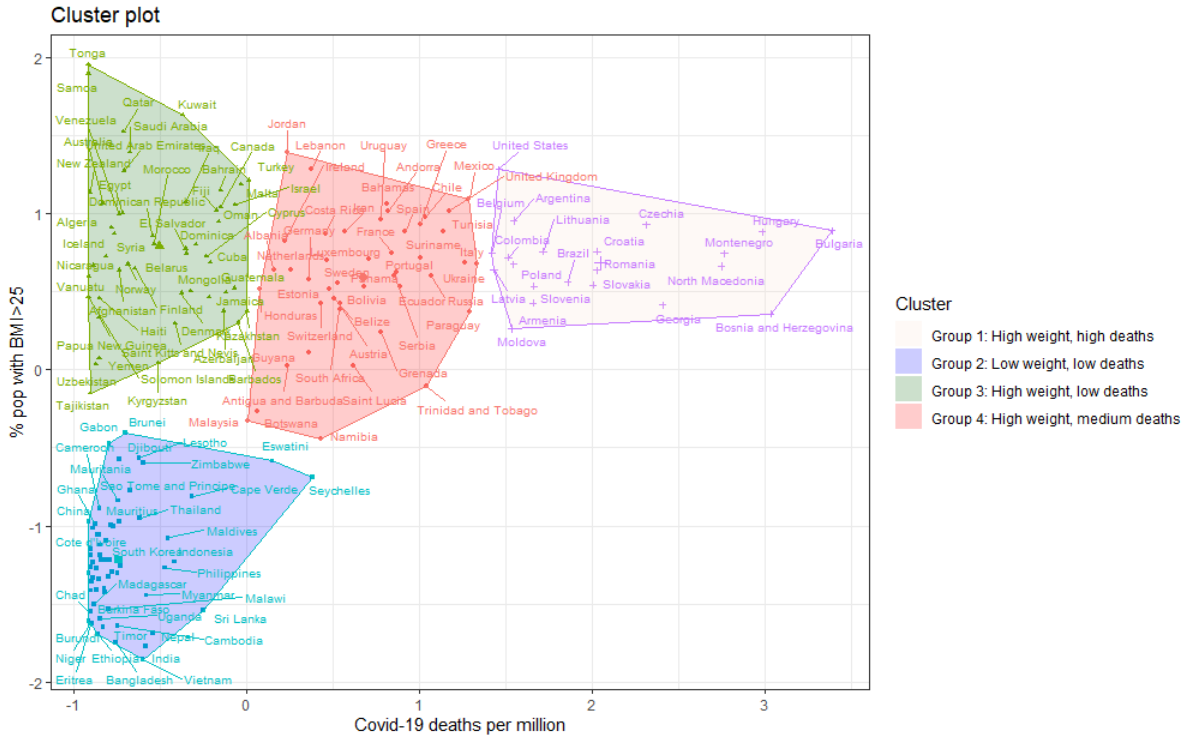

Fig. 3. Results of Elbow analysis showing four clusters of countries (not all countries are labelled; see Supplementary Materials Table SM1 for complete list).

Note: scales on the axes refer to standard deviations from the mean of the entire sample.

Here we clearly see one cluster of countries exclusively in Africa and Asia with both low incidence of overweight and low Covid-19 death rates (**low/low**, cluster 2 in the Figure 3). The remainder of the countries have high proportions of their populations with overweight, but their Covid-19 outcomes vary greatly (Table 2). Cluster 1, with high BMI and high death rates (**high/high**), consists almost entirely of eastern European states, plus Brazil and the USA. The middle cluster (cluster 4, **high/medium**) includes most of the European countries, with a scattering of countries from other continents, including Mexico. Cluster 3 includes countries with percentage overweight similar to that of clusters 1 and 4, but with much lower death rates (**high/low**). This includes as expected most of the countries in Oceania, that have exercised strong Covid-19 transmission controls, but also many countries in the Middle East and some Caribbean nations, where such controls were not strongly in place. This diversity of outcomes makes it clear that while overweight may be a major factor, other systematic variables must be at work here.

Table 2: Key characteristics of the four clusters of countries. BMI in cluster 2 is significantly lower than that of the other three clusters, at p<0.001. Differences in BMI between the other clusters are not statistically significant.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
	High weight, high deaths	Low weight, low deaths	High weight, low deaths	High weight, medium deaths
% BMI > 25	58.46	28.38	60.15	56.96
Deaths/million	3093	183	428	1656

The clear questions that Figure 2 and Table 2 raise about overweight as the explanation for Covid-19 death rates are:

(1). If % overweight is roughly similar across clusters 1, 3 and 4, what other variable(s) can explain the differences in death rates across these three?

(2). What factor(s) might explain why death rates in cluster 3 are similar to those in cluster 2, despite the fact that % overweight in this cluster is the highest of all clusters?

We first turn to diet as a possible candidate for this.

3.2. Relationship of diet to overweight and Covid-19 deaths.

The WOF also analysed data on nutrition, since clearly diet, together with (lack of) exercise, is likely the main determinant of overweight. They used data from WHO which give average intake of various foodstuffs, based on national totals consumed per year. The two diet variables that demonstrated the highest correlations with Covid-19 deaths were mean sugar energy intake (kcal/cap/year), with $r = 0.53$, $p < 0.001$, and sugar sweetened beverages (litres/cap/year), with $r = 0.6$, $p < 0.001$. Our updated analysis gave correlation coefficients for these same relationships at 0.42, $p < 0.001$ and 0.47, $p < 0.001$, respectively.

We therefore analysed sugar intake for the four clusters identified in Figure 2, see Table 3. Here it is quite clear that in cluster 2, the large set of African and Asian countries with low BMI levels, much less sugar in all forms is consumed per capita than in the three clusters which have high proportions of their populations with BMI > 25. A direct causal relationship might reasonably be assumed here. The differences in overall sugar energy intake (kcal/cap/year) between clusters

1, 3 and 4 are not statistically different, but differences in consumption of sweetened beverages between these three clusters are significant at $p < 0.05$, and this follows the pattern of deaths more closely than overweight itself.

Table 3. Characteristics of sugar intake and BMI in the different clusters.

Variable	Cluster 1 High weight/ high deaths	Cluster 2 Low weight/ low deaths	Cluster 3 high weight/ low deaths	Cluster 4 high weight/ medium deaths
n	21	65	49	44
% BMI>25	58.46	28.38	60.15	56.96
Deaths/million	3093	183	428	1656
Sugar energy kcal/cap/day	364.3	158.33	321.64	355.39
Sweetened drinks, l/cap/year	89.64	20.66	66.41	83.89

3.3. The impact of latitude.

As noted in the introduction, latitude does not at first sight appear to offer an explanation for global variations in Covid-19 deaths since the three tropical continents display very different outcomes. However, while latitude does not correlate with death rates in any of the clusters taken individually, it does correlate with death rates taken across all the countries where overweight is high, that is, clusters 1, 3 and 4 taken together ($r = 0.29$, $p < 0.001$), providing a possible statistical explanation for the lower death rates in clusters 3 and 4 compared to cluster 1. An ANOVA indicates that the difference in latitude between clusters 1, 3 and 4 is significant at $p < 0.01$, with countries in Cluster 3 being at lower latitudes (i.e., closer to the equator) than those in cluster 4, while cluster 1 incorporates countries at higher latitudes. ANOVA also shows a significant difference in latitude between cluster 2 and cluster 3 ($p < 0.001$) (cluster 2 contains countries at the lowest latitudes).

3.3. Impact of vaccines and other public health measures.

One obvious factor that might influence Covid-19 death rates is vaccinations, which were well rolled out in many countries before the end of 2021. Table 4 provides the evidence, based on the percentage of people in each country who had received their first and second vaccines by 30 November 2020. This shows that although in the countries most affected by Covid-19 deaths, i.e., those in cluster 1, the vaccination rate is negatively related the death rates, which is as would be expected, the same is not true across all countries with high percentage overweight (clusters 1, 3 and 4 combined. Moreover, the reverse is true among the countries with low percentage overweight and low death rates (cluster 2), where vaccination appears to be positively, rather than negatively, related to death rates. This cluster includes the poorest countries in the world where vaccine rates have been extremely low, which are by and large also those at the lowest latitudes. In other words, it would appear that the latitude effect is stronger than lack of vaccine. It has been suggested that the population of these countries may have increased immunity built up from life-long exposure to viral and other diseases, but a strong alternative case may be made that lack of

interest in vaccines stems from the fact that Covid death rates are so low; given low death rates, the disease may not loom large in the priorities of the public, particularly compared to daily killers such as malaria (18).

Table 4: Pearson correlation coefficients for Covid-19 deaths and vaccinations.

	Cluster 1 High weight/ high deaths	Cluster 2 Low weight/ low deaths	Cluster 3 High weight/ low deaths	Cluster 4 High weight/ medium deaths	Combined clusters 1, 3 and 4
% with 1 dose of vaccine	-0.51 $P < 0.01$	0.44 $p < 0.001$	0.25 ns	0.09 ns	0.05 ns
% with 2 doses of vaccine	-0.45 $P < 0.05$	0.44 $P < 0.001$	0.28 $p < 0.05$	0.07 ns	0.07 ns

Undoubtedly other public health measures, particularly the lockdowns that were very strictly implemented in a number of countries in cluster 3 (Australia, New Zealand, Samoa, Tonga etc) will have played a major part in the low death rates of these particular countries. However, this cannot explain the low death rates for the great majority of countries within the cluster, and since this variable cannot easily be quantified, it has not been included in the formal analysis.

3.4. Combining the variables and clusters.

Having identified sweetened drinks, latitude and vaccinations as being the variables with the most individual explanatory power out of the set of variables we considered, we carried out linear regressions combining these to try to explain, in the statistical sense, the differences in deaths within a group which combines clusters 1, 3 and 4 (´data-group 2´, Supplementary Materials Table SM2**).** This gives a low but significant R^2 (0.13, p=0.002) with sweetened drinks and latitude as significantly contributing variables, but not vaccination.

Considering variables that might explain similarities between clusters 2 and 3, which both have relatively low death rates despite cluster 3 having a much great overweight population, here models using sweetened drinks do not result in significant results, despite the large differences in consumption of these between clusters 2 and 3, nor does latitude. However, within this expanded group, a model based on BMI shows that this factor gives an R^2 of 0.25, $p < 0.001$, with %BMI > 25 and %vaccinated both showing as significant variables, Supplementary materials Table SM3, although as noted above, with a possible explanation, vaccination rates correlate positively with death rates; low vaccination rates are found in countries with low death rates. There is no significant explanation connected to latitude, despite the fact, as noted above, that an ANOVA test shows significant difference in latitude between cluster 2 and cluster 3.

4. DISCUSSION

Our data clearly show that countries in which low proportions of the population suffer overweight have vastly lower death rates from Covid-19 than countries with high proportions of overweight people. Overweight may however not be the direct cause, but simply a marker for conditions which are systematically associated with overweight, such as diabetes, hypertension

and metabolic syndrome more generally; all of these conditions are known from clinical studies to be highly correlated with severity, and death rates, of Covid-19 in patients individually. We note also that the effect of overweight on Covid-19 death rates is non-linear; we find a marked double hump in the distribution of countries with regard to %BMI > 25 and clearly related to this, a marked probability of higher Covid-19 deaths in countries in which more than 50% of the population is overweight.

The percentage of population suffering obesity (BMI > 30) does not correlate as strongly as overweight with Covid-19 death rates, here also a non-linear relationship seems to apply, with the threshold level of BMI for serious Covid-19 outcomes well below that considered ´obese´. In this regard, it is worth noting that hospitals tend to report obesity, rather than overweight, in Covid-19 patient data. It is possible therefore that this effect has been under-reported at the patient level. However, we also found that the effect of overweight, at least in countries in which this is prevalent, is modified by two factors: the amount of sweetened drink consumed per capita and the latitude.

4.1. Medical evidence concerning sweetened drinks.

Baak and Astrup (19) in a meta-study found considerable narrative evidence that sugar (made up of both fructose and glucose) when consumed in liquid form, as in sweetened drinks, is more conducive to weight gain than sugar in solid form. Since then, there have been several studies which corroborate this, but more importantly also relate it to development of many of the conditions which we know to be associated with severity and death rates of Covid-19. Olsen *et al*. (20) found that while consumption of liquid sugars contributed more to BMI and waist circumference in children than solid sugar, this effect was based on decreased insulin sensitivity. Wang *et al*. (21) found that liquid sugar intake was particularly related to impaired glucose homeostasis and insulin resistance while Sundborn *et al*. (22) found that liquid sugar intake was strongly related to metabolic syndrome**.** Thus, the effect of high levels of sweetened drinks may not only be weight gain *per se*, but also independently to increased vulnerability to the processes which cause death in Covid-19.

4.2. Medical evidence concerning factors that vary with latitude.

Our data show that most, but not all, countries in the tropics have much lower Covid-19 death rates than countries in the mid and higher latitudes; but that in particular, countries in South America do *not* follow this rule. Our data suggest that this is because the primary variable affecting risk of severe Covid-19 outcomes in overweight, which is particularly high in South America, on a par with that found in North America and Europe. Once countries with a low proportion of overweight people are removed from the equation, i.e., if we look just at countries where more than 50% of the population is overweight, then latitude comes into play. However, the mechanism by which latitude impacts Covid-19 death rates is not self-evident. We therefore consider four sets of hypotheses regarding the role of latitude.

4.2.1. Temperature.

In general temperature is higher at lower latitudes than at higher ones, but we have not been able to find any theory on mechanisms by which temperature might modify the severity of and

death rates due to Covid-19, for example, a recent study in Nature found that peaks over time in Covid cases in Europe could be related to latitude, but not to either temperature or humidity (23). Early in the pandemic, there were some suggestions that the virus could be inactivated by sun energy while in aerosols (24), although there has been little follow up on this theory. Further, while this might be relevant to transmission rates, it is difficult to see how it could affect severity in persons already infected.

4.2.2. Ultraviolet-B radiation (UV-B) and production of Vitamin D in the body.

Vitamin D production in the body is strongly stimulated by UV-B radiation on the skin, and this effect is much greater in the tropics not only as a result of the higher sun angle but also because it occurs all year round and almost every day, moreover people in general have more skin exposed. However, as we have seen, latitude is only a statistically explicative variable for Covid-19 deaths among the high weight countries, the majority of which are non-tropical. This would imply that even the relatively small variations in UV-B radiation across the mid-latitudes and higher latitudes make a difference, as sun angle is reduced and radiation weakens, particularly during winter months.

There is considerable literature on the link between low Vitamin D levels (as measured by serum $25(OH)D_3$) and fatty liver disease and other metabolic syndrome conditions (25-28). Arjmand and Jafarian (29) further hypothesize that Non-Alcoholic Fatty Liver Disease leads to decreased efficiency of $25(OH)D_3$ production by the liver/kidneys. There is also a link with overweight, since fatty tissue, particularly adipose tissue, absorbs and stores Vitamin D in its non-active form, meaning that other things being equal, there is less circulating in the blood stream. There have been a number of meta-studies which make strong claims for the causal link between Vitamin D deficiency and Covid-19 (30-32) but this has not yet been accepted by the medical establishment, on the basis that the evidence is only circumstantial. Nevertheless, the following suggestions have been made for mechanisms by which $25(OH)D_3$ might play a role in reducing severe Covid-19 effects:

(i) induction of antimicrobial peptides hCAP-18/LL-37 and human β-defensin 2 (33), which also have antiviral properties (34, 35)

(ii) dampening of inflammatory immunopathology during infection (6, 36, 37), with inverse relationship between Vit D concentrations and the exacerbated oxidative stress associated with the RAAS activation (38)

(iii) Vit D is involved in the production of melatonin (38), which is an anti-oxidant (see also hypothesis 4.2.4 below)

4.2.3. Ultraviolet-A radiation (UV-A) and production of nitric oxide by the skin.

This theory suggests that UV-A radiation on exposed skin, particularly on the face, induces immediate release of cutaneous photo-labile nitric oxide (NO) which inhibits replication of SARs-CoV2 on the skin surface (39). NO also impacts the cardiovascular system and metabolic syndrome, both COVID-19 risk factors. This effect is thought to be independent of and additional to any UV-B effects via production of Vitamin D. A strong correlation between Covid-19 deaths and UV-A has been shown at local level (counties/municipalities) in the USA, UK and Italy after eliminating the effects of UV-B/Vit D and possible confounding social variables (39), with Covid-

19 deaths being proportionately higher in the northern parts of these countries where because of shorter days and lower sun angles, less UV-A is received.

4.2.4. Near infra-red radiation (NIR) and production of melatonin in numerous parts of the body.

NIR has been hypothesised to have an immediate (within seconds) stimulating effect on the production of mitochondrial melatonin at subcellular level (40), particularly in blood vessels, brain, skin and retina but also in almost all of the body´s organs. Unlike UV-B, which essentially affects only the surface of the skin, NIR penetrates at least 8cm into the body. It is widely understood that oxidative stress is at the core of severe Covid-19, requiring antioxidants, such as Vitamin C and NAC to neutralize ROS (41, 42). Zimmerman and Reiter´s (40) hypothesis is that melatonin at intra-cell level is formed in response to, and to counteract, the accumulation of free radicals, i.e., it reduces oxidative stress. In particular it is involved in reducing renin–angiotensin–aldosterone system (RAAS) activation and in decreasing ROS generation. They claim that the (daytime) NIR effect dwarfs the much smaller amounts of melatonin that are produced in response to lack of light at night, in the pineal gland; and that the two melatonin systems operate in parallel, the function of the pineal melatonin circulating in the blood stream being in part to top up supplies in critical areas of the body during sleep (40), while the mitochondrial melatonin remains in or close to the cells where it is produced. Zimmerman and Reiter in fact developed their theory before the Covid-19 pandemic began, in relation to other auto-immune diseases, but since the severest effects of Covid-19 fall into the auto immune category (cytokine storm etc), it may be applied to Covid-19.

According to Zimmerman and Reiter (40), NIR penetrates the skin only up to about 8cm, with children receiving relatively far more photons per body cell than adults owing in part to their smaller size (ratio of surface area to body weight). In addition, they claim that the ability of the body to absorb NIR decreases with age and it is well known that the elderly are much more susceptible to severe Covid effect than the young. Importantly, although they do not discuss body weight directly, it might be hypothesized that in people who are overweight, with thicker layers of subcutaneous fat, less NIR will penetrate to the organs which need it to anti-oxidize. This might even explain why it does not make much difference whether an individual is overweight or obese in terms of the severity of effects of Covid-19 effects felt (the threshold level identified earlier in this paper). Moreover, NIR radiation, like UV-A and UV-B, depends on sun angle and length of day, and would therefore also be less effective at higher latitudes, but Zimmerman and Reiter also point out that NIR is received not only from sunlight (and thus, like UV-A and UV-B, more by people with an outdoor life style) but also from incandescent light bulbs and open fires. In societies where these have been replaced by CFL (strip lighting), LED and central heating, it is to be expected that most individuals will have less exposure.

4.2.5. Comparison of hypotheses.

In table 5, the different observations that this study has thrown up are tested against the competing theories described above.

Table 5: Competing theories concerning death rates associated with Covid-19 and solar radiation.

Observations to be explained	**Competing hypotheses**			
	Temperature	UV-B Vitamin D	UV-A Nitric oxide	NIR melatonin
Overweight is overall a strong correlate of Covid-19 deaths	No obvious connection	In overweight individuals, vitamin D tends to be stored in adipose tissue; proportionately less available in blood stream, at any given level of sun exposure	No obvious connection	In overweight adults, subcutaneous fat layers may impede NIR penetration, limiting production of mitochondrial melatonin
BMI > 25 is a better indicator of Covid-19 deaths than BMI>30	No obvious connection	The contrary would be expected, since more fat implies proportionately more inactive Vitamin D	No obvious connection	Once a threshold depth is reached (8 cm) it makes little difference if the individual has more subcutaneous fat, NIR will not penetrate anyway
Lower death rates in cluster 3 compared to equally overweight clusters 4 and 1	No obvious connection	Latitude explains part of variance: more exposure to UV-B	Latitude explains part of variance: more exposure to UV-A	Latitude explains part of variance: more exposure to NIR. Also possible that in countries in clusters 3 and 2, people are more exposed to natural lighting (fewer indoor jobs with CFL /LED lighting)
Sweetened drinks correlate more strongly than overweight itself with death rates. This could be explained by the fact that sugar in beverages contributes more to the development of metabolic syndrome than solid sugar, and could partially explain the lower death rate in cluster 3.	No obvious connection	Vitamin D deficiency is known to be associated with metabolic syndrome, but causality has not yet been proven.	No obvious connection	No obvious connection

5. CONCLUSIONS

Of the four hypotheses we have reviewed here, the last fits best with the observations we have made regarding the role of overweight and latitude in Covid-19 death rates (Table 5). This theory, which places NIR and the development of subcellular melatonin at the centre, is interesting but it is a totally new and untested theory; we suggest merely that it is deserving of serious scientific attention and further research in the context of Covid-19. At the same time, we would stress the fact that many studies have shown that Vitamin D is strongly related to outcomes in Covid-19, as well as to obesity and other Covid-19 morbidity factors. It is plausible that these factors might

even exacerbate Vitamin D deficiency and thus increase the body´s vulnerability to this new disease. Given the complexity of human physiology it would not be surprising if there were multiple mechanisms by which the body becomes more vulnerable to the effects of invasion by viruses like SARS-Cov-2, and that both effects could be operating simultaneously.

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AUTHORSHIP

The concept for the paper was developed by MS and RS. JL was responsible for all the statistical analysis. MS wrote the first draft which was than reviewed and improved by RS and JL. All authors approved the final version.

CONFLICT OF 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.

REFERENCES

1. Our World in Data (2022) https://ourworldindata.org.
2. UN Dept. of Economic and Social Affairs, Population Division (2019). World Population Prospects. https://population.un.org/wpp/#:~:text=The%202019%20Revision%20of%20World,of%20the%20United%20Nations%20Secretariat.
3. Daneshkhah A, Eshein A, Subramanian H, Roy HK, Backman V (2020) The role of vitamin D in suppressing cytokine storm in COVID-19 Patients and Associated Mortality. *medRxiv*. preprint doi: https://doi.org/10.1101/2020.04.08.20058578.
4. Davies G, Garami AR, Byers JC (2020) COVID-19 and vitamin D information. *medRxiv*. https://docs.google.com/document/d/1jffdZOSuIA64L_Eur8qyCQ12T7NXrHSKPxtMe134C0Y/edit.
5. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* **12** (4): 988-1007.
6. Greiller CL, Martineau AR (2015) Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients* **7** (6): 4240-4270.
7. Ilie PC, Stefanescu S, Smith L (2020) The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging. Clin. Exp. Res.* **32** (7): 1195-1198.
8. Laird E, Rhodes J, Kenny RA (2020) Vitamin D and inflammation: potential implications for severity of COVID-19. *Irish Med. J.* **113** (5): 81-88.

9. Pugach IZ, Pugach S (2020) Strong correlation between prevalence of severe vitamin d deficiency and population mortality rate from COVID-19 in Europe. *Wiener Klinische Wochenschrift* **133**: 403-405.
10. Radjukovic A, Hippchen T, Tiwari-Heckler S, Dreher S, Boxberger M, Merle, U (2020) Vitamin D deficiency and outcome of COVID-19 patients. *Nutrients* **12**: 2757.
11. Rodríguez TA, Montelongo MEA, Martinez-Cuazitl A, Puente NAV, Reyes P (2020) Deficiency of Vitamin D is a risk factor of mortality in patients with COVID-19. *Revista de Sanidad Militar* **74**: 1-2.
12. WOF (World Obesity Federation) (2021) COVID-19 and Obesity: The 2021 Atlas. www.worldobesity.org.
13. WHO Global Health Observatory (2020) https://apps.who.int/gho/data/view.main.CTRY2430A.
14. Food and Agriculture Organization, FAOSTAT Food Balance Sheets 2014-2017. http://www.fao.org/faostat/en/#data/FBS.
15. Saji, B. (nd) In-depth intuition of K-means clustering algorithm in machine learning. Analytics Vidhya, https://www.analyticsvidhya.com/blog/2021/01/in-depth-intuition-of-k-means-clustering-algorithm-in-machine-learning/ Consulted 2/2/2022.
16. UC Business Analytics (nd) K-means cluster analysis. https://uc-r.github.io/kmeans_clustering Consulted 2/2/2022.
17. Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O'Rahilly S, Aveyard P, Jebb SA (2021) Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. *Lancet Diabetes Endocrinol.* **9** (6): 350-359.
18. New York Times Apple Podcast (April 7 2022) The Covid mystery in Africa. https://podcasts.apple.com/us/podcast/the-daily6/id1200361736?i=1000556512333.
19. Baak, van MA, Astrup A (2009) Consumption of sugars and body weight. *Obes. Rev.* **10**: 9-23.
20. Olsen NJ, Andersen LB, Wedderkopp N, Kristensen PL, Heitmann BL (2012) Intake of liquid and solid sucrose in relation to changes in body fatness over 6 years among 8-to 10-year-old children: the European Youth Heart Study. *Obes. Facts* **5** (4): 506-512.
21. Wang J, Light K, Henderson M, O'Loughlin J, Mathieu ME, Paradis G, Gray-Donald K (2014) Consumption of added sugars from liquid but not solid sources predicts impaired glucose homeostasis and insulin resistance among youth at risk of obesity. *J. Nutrition* **144** (1): 81-86.
22. Sundborn G, Thornley S, Merriman TR, Lang B, King C, Lanaspa MA, Johnson RJ (2019) Are liquid sugars different from solid sugar in their ability to cause metabolic syndrome? *Obesity* **27** (6): 879-887.
23. Walrand S. (2021) Autumn COVID-19 surge dates in Europe correlated to latitudes, not to temperature-humidity, pointing to vitamin D as contributing factor. *Sci. Rep.* **11** (1): 1-9.
24. Schuit M, Gardner S, Wood S, Bower K, Williams G, Freeburger D, Dabisch P (2020) The influence of simulated sunlight on the inactivation of influenza virus in aerosols. *J. Infect. Dis.* **221** (3): 372-378.
25. Kwok RM, Torres DM, Harrison SA (2013) Vitamin D and non-alcoholic fatty liver disease (NAFLD): is it more than just an association? *Hepatology* **58** (3): 1166-1174.
26. Cordeiro A, Pereira S, Saboya CJ, Ramalho A (2017) Relationship between non-alcoholic fatty liver disease and vitamin D nutritional status in extreme obesity. *Can. J. Gastroenterol. Hepatol*. **9456897**: 1-8.

27. Borges-Canha M, Neves JS, Mendonça F, Silva MM, Costa C, Cabral PM, Guerreiro V, Lourenço R, Meira P, Salazar D, Ferreira MJ (2021) The impact of vitamin D in non-alcoholic fatty liver disease: a cross-sectional study in patients with morbid obesity. *Diabetes Metab. Syndr. Obes.* **14**: 487-495.
28. Eliades M, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, Koteish AA, Clark JM, Guallar E, Hernaez R (2013) Meta-analysis: vitamin D and non-alcoholic fatty liver disease. *Aliment. Pharmacol. Ther.* ***38*** (3): 246-254.
29. Arjmand AT, Jafarian S (2018) Time for a U-turn on understanding the major cause of universal human hypovitaminosis D. *Ann. Clin. Lab. Res.* **6** (2): 1-4.
30. Benskin LL (2020) A basic review of the preliminary evidence that COVID-19 risk and severity is increased in vitamin D deficiency. *Front. Public Health* ***8***: 513, 1-25.
31. Crafa A, Cannarella R, Condorelli RA, Mongioì LM, Barbagallo F, Aversa A, La Vignera S, Calogero AE (2021) Influence of 25-hydroxy-cholecalciferol levels on SARS-CoV-2 infection and COVID-19 severity: A systematic review and meta-analysis. *EClinicalMedicine* **37**: 100967.
32. Borsche L, Glauner B Mendel JV (2021) COVID-19 mortality risk correlates inversely with vitamin D3 status, and a mortality rate close to zero could theoretically be achieved at 50 ng/ml 25 (OH) D3: Results of a systematic review and meta-analysis. *Nutrients* **13** (10): 3596.
33. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, Tavera-Mendoza L, Lin R, Hanrahan JW, Mader S, White JH (2004) Cutting edge: 1, 25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. *J. Immunol.* **173** (5): 2909-2912.
34. Kota S, Sabbah A, Harnack R, Xiang Y, Meng X, Bose S (2008) Role of human β-defensin-2 during tumor necrosis factor-α/NF-κB-mediated innate antiviral response against human respiratory syncytial virus. *J. Biol. Chem.* **283** (33): 22417-22429.
35. Currie SM, Findlay EG, McHugh BJ, Mackellar A, Man T, Macmillan D, Wang H, Fitch PM, Schwarze J, Davidson DJ (2013) The human cathelicidin LL-37 has antiviral activity against respiratory syncytial virus. *PloS One* **8** (8): e73659.
36. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA (2017) Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev. Med. Virol.* **27** (1): 1909.
37. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ, van der Hoeven H (2020) Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. *Elife* **9**: e57555.
38. Heras de las N, Martín Giménez VM, Ferder L, Manucha W, Lahera V (2020) Implications of oxidative stress and potential role of mitochondrial dysfunction in COVID-19: therapeutic effects of vitamin D. *Antioxidants* **9** (9): 897.
39. Cherrie M, Clemens T, Colandrea C, Feng Z, Webb DJ, Weller RB, Dibben C (2021) Ultraviolet A radiation and COVID-19 deaths in the USA with replication studies in England and Italy. *Br. J. Dermatol.* **185** (2): 363-370.
40. Zimmerman S, Reiter RJ (2019) Melatonin and the optics of the human body. *Melatonin Res.* **2** (1): 138-160.
41. Schönrich G, Raftery MJ, Samstag Y (2020) Devilishly radical NETwork in COVID-19: Oxidative stress, neutrophil extracellular traps (NETs), and T cell suppression. *Adv. Biol. Regul.* **77**: 100741.

42. Laforge M, Elbim C, Frère C, Hémadi M, Massaad C, Nuss P, Benoliel JJ, Becker C (2020) Tissue damage from neutrophil-induced oxidative stress in COVID-19. *Nat. Rev. Immunol.* **20** (9): 515-516.

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