Ultraviolet A Radiation and COVID19 Deaths in the USA with replication studies in England and Italy

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Running Head: UVA and COVID-19 deaths

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Conflicts of Interest: RW is a director of Sunlab International Ltd (company making sunscreen).

What's already known about this topic?

- Infectious disease often shows seasonality
- Cutaneous production of nitric oxide following UVA exposure reduces blood pressure, a cardiovascular risk factor.
- Comorbid cardiovascular disease worsens COVID-19 outcomes
- Nitric oxide limits SARS CoV and SARS CoV2 replication *in vitro*

What does this study add?

- Higher ambient UVA is associated with lower risk of COVID-19 death in three countries, when vitamin D synthesis would have been limited.
- Sun exposure may reduce death from COVID-19 independently of vitamin D

Abstract

Background

Understanding factors impacting deaths from COVID-19 is of the highest priority. Seasonal variation in environmental meteorological conditions affects the incidence of many infectious diseases and may also affect COVID-19. Ultraviolet A (UVA) radiation induces release of cutaneous photolabile nitric oxide (NO) impacting the cardiovascular system and metabolic syndrome, both COVID-19 risk factors. NO also inhibits the replication of SARS-CoV2.

Objectives

To investigate the relationship between ambient UVA radiation and COVID-19 deaths.

Methods

COVID-19 deaths at the county level, across the USA, were modelled in a Zero Inflated Negative Binomial model with a random effect for States adjusting for confounding by demographic, socioeconomic and long-term environmental variables. Only areas where UVB was too low to be inducing significant cutaneous vitamin D3 synthesis were modelled. We used satellite-derived estimates of UVA, UVB and temperature and relative humidity. Replication models were undertaken using comparable data for England and Italy.

Results

The Mortality Risk Ratio (MRR), in the USA, falls by 29% (40% -15% (95% CI)) per 100 (KJ/m^2) increase in mean daily UVA. We replicate this in independent studies in Italy and England and estimate a pooled decline in MRR of 32% (48%-12%) per 100 KJ/m^2 across the three studies.

Conclusions

Our analysis suggests that higher ambient UVA exposure is associated with lower COVID-19 specific mortality. Further research on the mechanism may indicate novel treatments. Optimised UVA exposure may have population health benefits.

Introduction

Seasonality [1] and variation in temperature [2], humidity [3] and UV radiation [4] are related to the incidence of several infectious diseases. In this paper we explore whether UVA might independently affect COVID-19 outcomes. We have previously described a novel nitric oxide (NO) driven, vitamin D independent, mechanism [5], by which sunlight can lower blood pressure, and at the population level we have shown that UV is associated with lower blood pressure [6] and a reduced incidence of myocardial infarctions [7]. The same UV driven mechanism may also cause seasonal variation in development of diabetes and metabolic syndrome [8].

UV may have a direct effect on the viability of SARS-COV-2 virus in airborne droplets and on fomites [9], thus reducing both infection rates, and the size of inoculum in those becoming infected, with correspondingly reduced disease severity [10, 11] and COVID-19 growth rates [12]. Direct viricidal suppression of SARS-CoV2 appears to be a UVB effect [13] with UVA wavelengths having no effect on SARS-CoV1 [14]. UVA does, however, photo-release NO from stores in the skin whence it is mobilised to the systemic circulation, causing vasodilatation and reduction in blood pressure [5], offering cardiovascular and metabolic benefits from UV exposure [5, 8]. As cardio-metabolic disease and possibly hypertension [15] increase the risk of death from COVID-19, any UV driven improvements in these risk factors would be expected to reduce mortality [16]. NO may also have a specific effect on COVID-19. It inhibits replication of SARS CoV [17] and SARS-CoV2 [18]. In the case of SARS CoV this occurs by S-nitrosation of the spike protein, preventing the post translational

palmitoylation required for fusion with its cognate angiotensin converting enzyme 2 receptor (ACE2R) [19]. The spike protein of SARS CoV is highly homologous to that of SARS CoV2 [20,21] suggesting that NO may similarly limit binding to ACE2R by SARS CoV2 accounting for reduced disease transmission and severity.

Given the apparent greater severity of illness and risk of death from COVID-19 amongst those with cardiometabolic diseases [22, 23], the importance of season for infectious diseases, and a plausible pathway to reduced disease transmission and severity through photo-released NO, we investigate: if ambient UVA exposure is associated with COVID-19 deaths across the USA, independent of other UV pathways, and whether the finding is replicated in studies of England and Italy.

Methods

Study Setting and Participants

We used an ecological regression approach to model COVID-19 deaths in small areas (counties) across the contiguous USA during the early part of the COVID-19 pandemic (January to April 2020). Our main analysis was for USA counties (N=2,474) with replication studies for COVID-19 deaths across English Middle Layer Super Output Areas (MSOAs) (N=6,724) and excess deaths across Italian municipalities (N=6,775). We only included 'small areas' that were experiencing levels of UV too low to be inducing significant cutaneous vitamin D3 synthesis at any time during the study period ('UV vitamin D winter'), to reduce potential confounding through a UVB vitamin D pathway (a monthly mean UV on the 252-330nm spectrum (the Vitamin D active spectrum - UVvitd of under 165 KJ/m2 [24]). This meant that 2,474 counties (out of 3,088) in the USA were within the analysis (Figure 1).

Outcome measure

USA COVID-19 deaths between January 22nd and April 30th, 2020 came from data compiled by the Center for Systems Science and Engineering at Johns Hopkins University. A COVID-19 death was defined as a case if the practitioner suspected that COVID-19 played a role, even if it was not directly attributable to the death. English COVID-19 deaths between March 1st to April 17th, 2020 were drawn from data compiled by the UK Office for National Statistics [25]. Deaths were included if COVID-19 was mentioned on the death certificate, with a delay of usually five days between occurrence and registration. In Italy there is no COVID-19 classified mortality data available for municipalities. Instead, we estimated this from excess deaths drawn from ISTAT

(Italian Institute of Statistics) [26] available for 7,270 of 7,904 municipalities for March 1st to April 30th for 2015-2019 compared to 2020.

Ambient UV data

We derived mean daily UVA for the small-areas in each study – USA (Jan 1st – April 30th); England (Jan 1st – April 17th) and Italy (Jan 1st – April 30th). We start our observation of UVA before the period in which we were recording deaths because of the lag between infection and death. The UVA dataset was produced by JAXA (Japan Aerospace Exploration Agency) using the MODerate resolution Imaging Spectroradiometer (MODIS) instrument on board NASA's Aqua and Terra satellites [27]. Atmospheric absorption due to the ozone and water vapour (cloudiness) were accounted for by using a simplified planetary atmosphere (clear atmosphere positioned above a cloud layer). Downward irradiance values (i.e. combined direct and diffuse radiation on a horizontal plane) for UVA (315nm-400nm) were converted to daily values by using the diurnal cycle of solar zenith angle with instantaneous atmospheric conditions. UVA data were aggregated for USA counties, English MSOAs and Italian municipalities and expressed as mean daily KJ/m^2.

A long term UVvitd dataset (30-year monthly average) developed by the National Center for Atmospheric Research (NCAR) was used [28]. UVvitd data were aggregated and expressed in mean monthly KJ/m2. We used the highest quintile as the cut off for year-round vitamin D synthesis, which corresponds to a monthly mean of over 165 KJ/m^2 [29].

Covariates

A number of demographic, socioeconomic, long term environmental exposures and infection susceptibility variables were used in our models. This was to appropriately adjust for spatial associations, with both UVA and COVID-19 mortality, which might otherwise lead to a spurious relationship between UVA and COVID-19 mortality. We identified these from the existing literature and measured them at the small area level. We assessed for each covariate whether it might be [1] a direct confounder for the UVA-COVID19 relationship, in which case they were added to the NB part of the model and [2] might impact the exposure of individuals to the virus in which case they were added to the ZI part of the model. Covariates might therefore be in both parts of the model.

Older age and ethnicity were associated with higher risk of COVID-19 death, possibly due to higher prevalence of comorbidities, including hypertension, heart disease and respiratory diseases [30]. We used country specific datasets to measure risk factors associated with age and ethnicity.

Poorer citizens are at higher risk of infection due to essential working and death due to pre-existing health conditions [31]. We used country specific datasets of socioeconomic deprivation. For the USA we took the first principal component score from a Principal Component analysis of: percentage in poverty, median house value, median house income, percentage owner occupied and percent of population with less than a high school education. To capture socioeconomic deprivation in England we used percentage of residents under 21 who did not enter higher education and an income deprivation score [32]. For Italy, we used the Italian Deprivation Index.

Long term environment

Higher PM2.5 is linked with a range of respiratory and cardiovascular disease and shown to increase COVID mortality rate in other analyses [33]. Long term PM2.5 (2000-2016) data at a 0.01° by 0.01° resolution were modelled using satellite and monitored PM2.5 station data [34]. We used these data for both the USA and Italy. In England, long term 2014-2018 PM2.5 at a 1km-by-1km resolution was modelled using monitored PM2.5 station data [35]. Variation in temperature is associated with COVID-19 mortality [36]. Long term mean monthly winter temperature (Dec-Feb) at a 4km-by-4km resolution for 2000-2016, was modelled using satellite data [37] for the USA. Long term mean monthly winter temperature (Dec-Feb) at a 1km-by-1km resolution for 1981-2010 was modelled using interpolation of Meteorology Office weather stations for England [38]. Long term median land surface temperature (Dec-Feb) daytime monthly median value at a 1km-by-1km resolution for 2000-2017, was modelled using satellite data for Italy [39].

Viral exposure

The population 'at-risk' needs to be adjusted for exposure to the virus in case factors increasing or decreasing risk of exposure are associated with spatial variance in UVA levels. In densely populated, urban or peri-urban areas, with high use of public transport COVID-19 transmission is faster and the prevalence of cases higher. Probable exposure is therefore estimated through population density, urban/rural status and state percentage of positive COVID-19 tests in the USA. We used population density from the 2018 mid-year

population estimates of ONS, percentage of residents using different forms of transport (bus, train, tube) from the 2011 census and Upper Tier Local Authority (UTLA) number of days since a local authority had 10 confirmed cases in England. We used ISTAT population density from 2019, the municipality area, and total cases in province in Italy up to the 30th of April [26].

Statistical Analysis

We used a zero inflated negative binomial (ZINB) to model counts of death in small geographical areas because the counts of deaths were likely to be spatially variable with the mean counts of deaths across small areas likely to be much smaller than the variance of the counts between the small areas and an excess of zeros (areas with no COVID19 infection).

We included a random effect in the model. This was a random intercept for a higher and administratively important geographical unit in each country. In the USA this was the State, in England the Local Authority and in Italy the Province in order to: [1] capture the systematic way the risk of death from COVID19 might be related to this higher geography (e.g. due to differences in political administration, health services, funding, public health effects or levels of infection) and [2] incorporates spatial clustering in the estimation of standard errors. The linearity of the relationship between UVA and COVID19 deaths was tested using Fractional Polynomial Regression which tests whether fractional powers (nonlinear) improve the fit of the model. The linear model was found to be the best fit for each country. Each of the country models were specified independently by separate team members. All models were fitted using the glmmTMB package for R [40] which fits random effect generalised linear models described in Bolker et. al [41].

We carried out a meta-analysis to estimate the pooled effect across the three studies using a random-effects model. We used a restricted maximum-likelihood estimator with no adjustments.

Software

All analyses were undertaken in R 3.6.1. We predicted the number of deaths per million population at suitable levels of UVA by calculating the marginal means in the 'emmeans' package in R [42]. We used a random effects model as part of the 'metafor' package in R [43] to calculate a cross-county pooled estimate of the MRR.

Data and code

Data and code are presented in the following online repository:
https://github.com/markocherrie/COVID19_UVA

Results

Daily mean UVA (January-April 2020) varied between 450-1,000 KJ/m^2 across the three countries, with lower average levels experienced across England (340 to 460 KJ/m^2) during the period compared to Italy (600 to 900 KJ/m^2) and USA (500 to 1000 KJ/m^2) (Figure 2 a,b,c). For the USA the average County UVA level between Jan-Apr 30th was 696 KJ/m^2 (SD = 83). For England the average MSOA UVA level between Jan-Apr 17th was 412 KJ/m^2 (SD = 18). For Italy the average UVA level between Jan-Apr 30th was 717 KJ/m^2 (SD = 52).

We model the rate of COVID-19 deaths in small areas in a multilevel ZINB model for: the USA, England and Italy (Table 1a). The model estimate is the Mortality Rate Ratio (MMR) per 100 (KJ/m^2) increase in UVA or the ratio of the mortality rate in a small area with a similar area exposed to 100 (KJ/m^2) more UVA. Adjusting for other confounders measured at the small area (County, MSOA and Municipality) and adjusting for infection rates at a higher level of geography (State, UTLA, Province) (Table 1b) our estimates show reductions in MRR of 0.71 in the USA per 100 increase in UVA (KJ/m^2) (Table 1). We found a similar size of effect in our two replication studies: an MRR in Italy of 0.81 and in England 0.49 . For the random effects meta-analysis across the three countries we find a pooled MMR estimate of 0.68 per 100 increase in UVA (KJ/m^2) (table 2).

Using the model (including the random effects) we predict what the rate of mortality (deaths per million population) would be for different experienced levels of UVA (all other coefficients in the model held at their means) in the three countries (Figure 3 a,b,c). This illustrates that the models predict a similar approximate fall by a third to a half in the average risk of death across the levels of UVA experienced across the three countries. This despite the very different levels of death being experienced between the countries at this point in the epidemic. The models also suggest that the size of the risk reduction per 100 (KJ/m^2) UVA is largest for England which has the lowest average level of UVA during the period.

Discussion

Our analysis finds that higher ambient UVA exposure is associated with lower COVID-19 specific mortality. This effect appears independent of differences in socio-economic composition, temperature, humidity and UV within the vitamin D action spectrum. Our models are consistent with a situation where UVA exposure may be an additional UV protective factor against COVID-19, along with other potential UV related pathways through vitamin D production and direct viricidal suppression. This is an observational study and so further research is required.

Given that UVA does not appear to directly act in viricidal suppression of SARS-CoV2 [13, 14], the reduction in the observed risk might be the result of either behavioural change or a biological pathway. Warm and sunny days might increase the chance of time spent outdoors or away from indoor spaces where close contact with others would be higher. Although UVA and air temperature are associated, in our models we also control for temperature. Our findings are consistent between three countries and with varying latitudes. It seems unlikely that time spent outdoors would be sufficiently linearly associated with UVA for the same calendar period, after controlling for temperature, over such a wide range of latitude and UVA to produce the same effect on time spent outdoors (e.g. between Newcastle and Naples in March). In contrast there is increasing evidence that UVA photo-releases NO from skin and that NO has important potential impacts on virus replication [17-19]. NO S-nitrosates the spike protein of SARS-CoV and also the SARS-CoV and SARS-CoV2 protease. This double action blocks the myristolation of the spike protein necessary for it to bind to the ACE2 receptor, and also inhibits viral protease activity, with consequent reduced viral replication and cytopathic effects [17-19]. Maintenance of the health vasculature is dependent on constitutive endothelial NO synthase derived NO. Endothelial damage and excess coagulation may underlie widespread organ involvement [44] in COVID-19 which would be mitigated by photochemical NO production. Although further research is required, we suggest that this NO biological pathway is a plausible explanation for our model results. UVA also correlates inversely with population blood pressure and cardiovascular disease [6, 7] and associates with reduced all-cause mortality, largely through a reduction in cardiovascular deaths [46].

Tolerance to UVA, as shown by the reduced fall in COVID deaths we demonstrated for a given incremental rise in UVA at higher irradiances in the USA and Italy, compared to England, could be explained by increasing melanin in the skin blocking UV penetration. Adaptive pigmentation occurs even at relatively low levels of UVA, with approximately half of the annual variation in forehead pigmentation for Caucasian individuals living in Copenhagen (55.68°N) occurring between January and April [45].

Deaths from COVID-19 are disproportionately high in people of black African or Asian ancestry in Europe and the USA [47, 48]. Social factors probably account for much of this, but we have shown that the vitamin D and temperature independent fall in blood pressure with increased UV is attenuated in black compared to white Americans [6]. White skin colour is an evolutionary adaptation that occurred around 5,000 years before present in Neolithic agriculturalists migrating to low light northern Europe [49]. Darker skin colour would thus be anticipated to reduce any biological benefits from UV, whether blood pressure reduction or infection prevention, particularly at higher latitudes. The remarkably low COVID mortality in equatorial Africa is consistent with this [50].

There are of course weaknesses in our design. We have adjusted our models for all the clinically significant factors that we believe might be spatially or temporally associated with both UVA and COVID-19 mortality risk but if any unmeasured factors exist, they might plausibly explain the relationships identified. UVA and covariates are measured at the small area level not in individuals. We therefore assume the unmeasured individual level model is replicated in the ecological model and this may not be the case. However, it is unclear what relationship between UVA and different geographical areas could exist that would modify its relationship with COVID-19. Ambient UVA is likely to be a poor measure of individual level UVA level exposure (eg exposure could be mainly derived from indoor environments). However in an ecological model the risk associated with personal exposure is averaged across all people in a small area and therefore the 'mismeasurement' of personal UVA exposure is predominantly Berkson error. This type of error will not bias an ecological model, unless the error is associated, at the small area, with ambient UVA level. For this to systematically occur in our models, seems unlikely. Satellite derived UVA measures may be overestimated under high aerosol loadings (e.g., when the PM2.5 count is high), this may mean our model, because we adjust for PM2.5, underestimates the association between actual UVA exposure and COVID19 deaths. There could be misclassification of deaths and rates of infection are estimated within the model and with indirect measures. However, any resulting measurement errors seem unlikely to be correlated with spatial variation in UVA and therefore biasing. The random effect in our models will incorporate differences between socially and politically distinct regions (States, Local Authorities and Municipalities) that might induce a spurious relationship between UVA and mortality. The replication of the findings across three countries with very different health systems, economic and political structures, pandemic situations and climates suggest a robust finding.

Conclusions

This study is observational and therefore any causal interpretation needs to be taken with caution. However, if the relationship identified proves to be causal, it suggests that optimising sun exposure may be a possible public health intervention. Given that the effect appears independent of a vitamin D pathway, it suggests possible new COVID-19 therapies and the importance of exploring the role of circulating NO.

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Figure 1: Average daily mean UVA (KJ/m^2) Jan-April [a] USA [b] England [c] Italy. The UVA-colour scale differs between countries. Counties, in the USA, that were excluded from the study because they had monthly mean UVvitd of over 165 KJ/m2 are shown in grey.

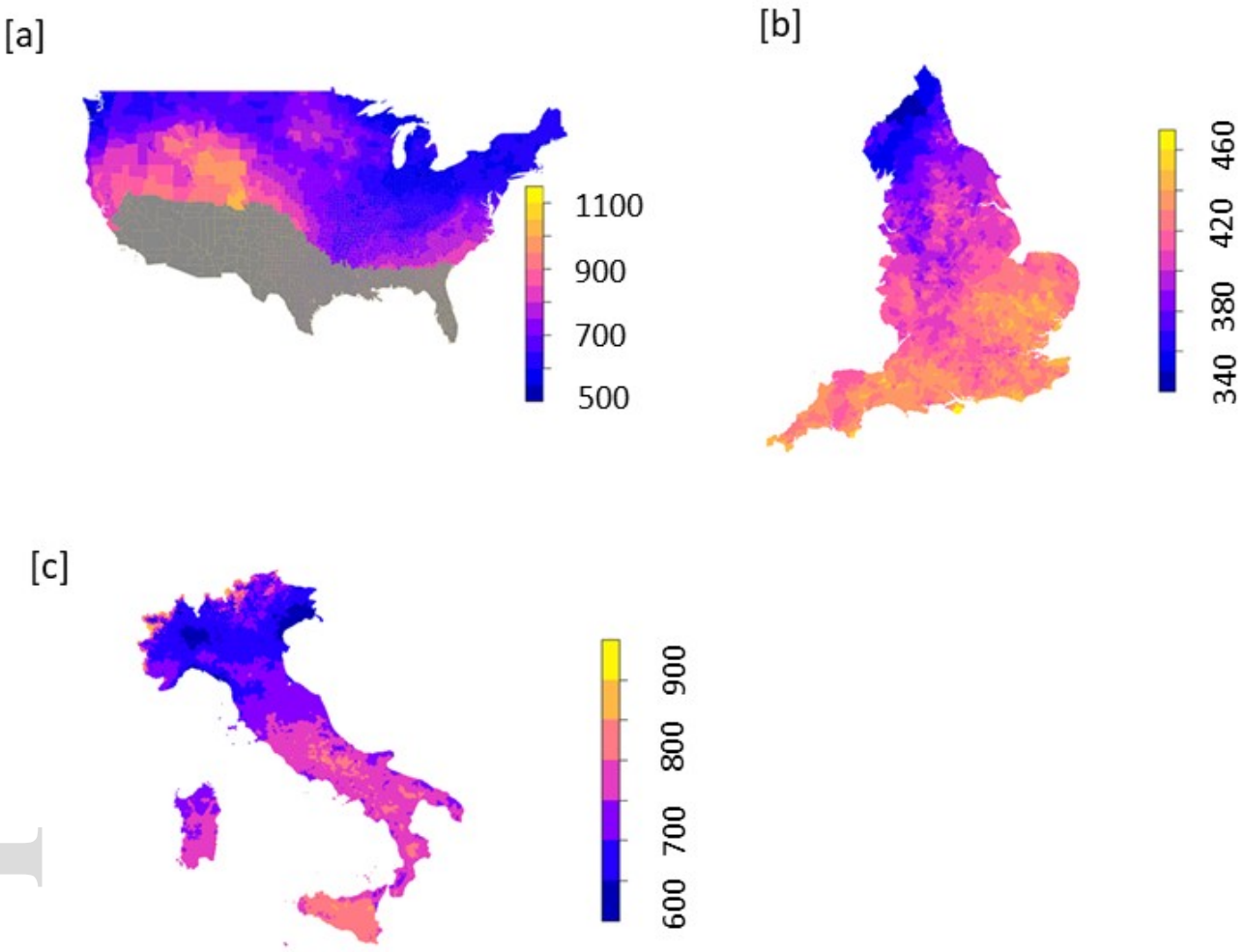

Figure 2: Predicted COVID-19 rates of deaths at selected levels of UVA in the [a] USA [b] England [c] Italy, given the model random effect, at the mean level of all other covariates. The predicted risks reflects the pandemic situation (ie infection levels) in each country at the time of the study.

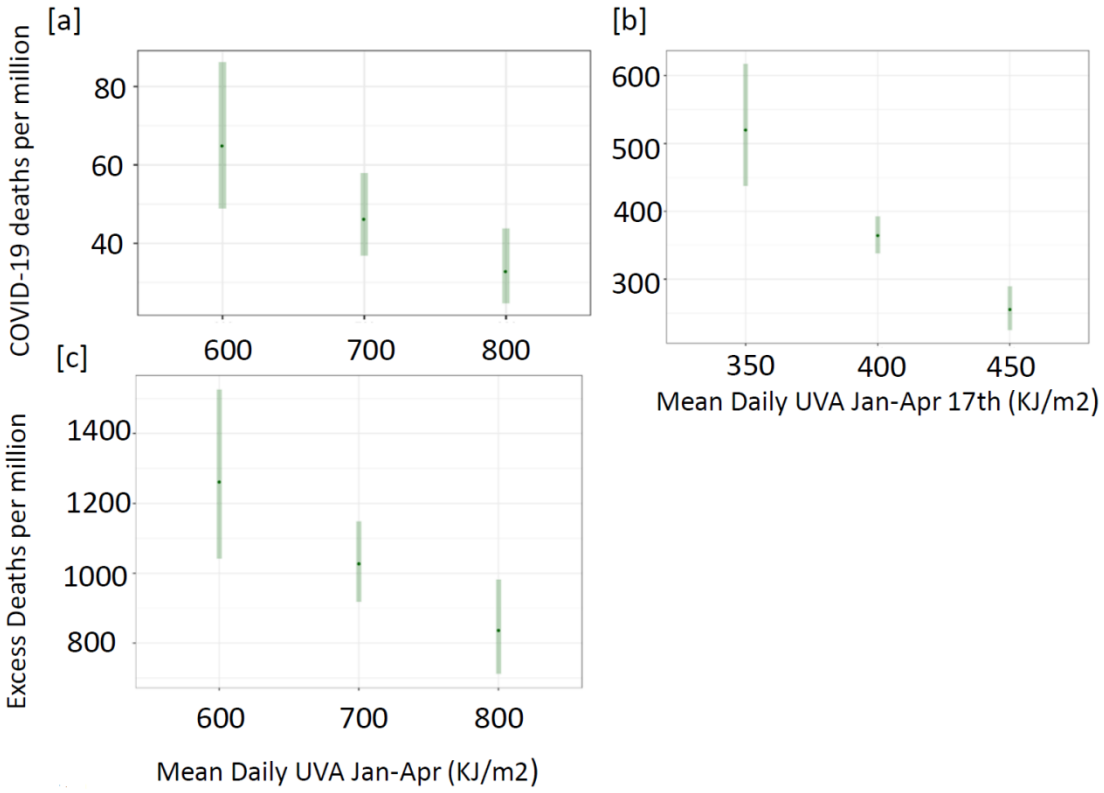

Table 1a: Zero Inflated Negative Binomial models for the USA, England and Italy showing the change in COVID-19 Mortality Risk Ratio per 100 KJ/m^2 increase in UVA

Model *	Geographic Units of analysis	Random effect	Deaths	Adjusted MRR (95% CI) per 100 KJ/m^2 increase in UVA	Adjusted Intraclass-correlation coefficient (ICC)
USA	Counties (N=2,474)	State (N=46)	62,219 (COVID-19 deaths)	0.71 (0.60-0.85)	0.042
England	England MSOAs (N=6,724)	Upper Tier Local Authority (UTLA) level (N=150)	19,315 (COVID-19 deaths)	0.49 (0.38-0.64)	0.231
Italy	Municipalities (N=6,775)	Province (N=104)	46,095 (excess deaths)	0.81 (0.71-0.93)	0.068

* Adjusted for the variables in table 1b

Table 1b: Models adjusted for these variables.

Model	Negative Binomial Model adjusted for	Zero-Inflated Model adjusted for
USA	County level: $PM_{2.5}$; UV_{vitd}, winter temperature; winter humidity, Percentage of residents: 65+; Black, Hispanic; deprivation score; urban/rural. State level: proportion of positive COVID-19 cases.	County level: Percentage of residents: 65+; Black, Hispanic; deprivation score; urban/rural. State level: proportion of positive COVID-19 cases
England	MSOAs level: $PM_{2.5}$, long term winter temperature; Percentage of residents: aged 80+, aged 65-79, Black, Indian, Pakistani/Bangladeshi, Chinese, in care homes, in higher education; income, deprivation score. UTLA level: number of days since a local authority had 10 confirmed cases.)	MSOAs level: Percentage of residents: aged 80+, aged 65-79, Black, Indian, Pakistani/Bangladeshi, Chinese, in care homes, in higher education, using public transport (bus, train, tube); income deprivation score; population density. UTLA Level: number of days since a local authority had 10 confirmed cases
Italy	Municipalities level: $PM_{2.5}$, long term winter temperature; Number of foreign born; Percentage of residents: aged 65+, aged 85+; population density; municipality area, deprivation score; Province level: Total cases in province	Municipalities level: Number of foreign born; Percentage of residents: aged 65+, aged 85+; population density; municipality area, deprivation score. Province level: Total cases in province

Table 2: Mortality Risk Ratios per 100 KJ/m2 increase in mean daily UVA – pooled estimate from random effects model.