

# Ultraviolet A Radiation and COVID-19 Deaths in the USA with replication studies in England and Italy

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## **Abstract**

### **Objectives**

To determine whether UVA exposure might be associated with COVID-19 deaths

### **Design**

Ecological regression, with replication in two other countries and pooled estimation

### **Setting**

2,474 counties of the contiguous USA, 6,755 municipalities in Italy, 6,274 small areas in England. Only small areas in their 'Vitamin D winter' (monthly mean  $UV_{vitd}$  of under 165 KJ/m<sup>2</sup>) from Jan to April 2020.

### **Participants**

The 'at-risk' population is the total small area population, with measures to incorporate spatial infection into the model. The model is adjusted for potential confounders including long-term winter temperature and humidity.

### **Main outcome measures**

We derive UVA measures for each area from remote sensed data and estimate their relationship with COVID-19 mortality with a random effect for States, in a multilevel zero-inflated negative binomial model. In the USA and England death certificates had to record COVID-19. In Italy excess deaths in 2020 over expected from 2015-19.

### **Data sources**

Satellite derived mean daily UVA dataset from Japan Aerospace Exploration Agency. Data on deaths compiled by Center for Disease Control (USA), Office for National Statistics (England) and Italian Institute of Statistics.

### **Results**

Daily mean UVA (January-April 2020) varied between 450 to 1,000 KJ/m<sup>2</sup> across the three countries. Our fully adjusted model showed an inverse correlation between UVA and COVID-19 mortality with a Mortality Risk Ratio (MRR) of 0.71 (0.60 to 0.85) per 100KJ/m<sup>2</sup> increase UVA in the USA, 0.81 (0.71 to 0.93) in Italy and 0.49 (0.38 to 0.64) in England. Pooled MRR was 0.68 (0.52 to 0.88).

### **Conclusions**

Our analysis, replicated in 3 independent national datasets, suggests ambient UVA exposure is associated with lower COVID-19 specific mortality. This effect is independent of vitamin D, as it occurred at irradiances below that likely to induce significant cutaneous vitamin D3 synthesis. Causal interpretations must be made cautiously in observational studies. Nonetheless this study suggests strategies for reduction of COVID-19 mortality.

## Introduction

Seasonality<sup>1</sup> and variation in temperature<sup>2</sup>, humidity<sup>3</sup> and UV radiation<sup>4</sup> are related to the incidence of several infectious diseases. COVID-19 arose less than 6 months ago, and it is thus not possible to describe seasonal variation. Nonetheless, spatial variation in levels of environmental UV in the early pandemic allows its relationship with COVID-19 mortality to be modelled. We have previously described a novel nitric oxide driven, vitamin D independent, mechanism<sup>5</sup> by which sunlight can lower blood pressure, and at the population level we have shown that UV is associated with lower blood pressure<sup>6</sup> and a reduced incidence of myocardial infarctions<sup>7</sup>. The same UV driven mechanism may also cause seasonal variation in development of diabetes and metabolic syndrome<sup>8</sup>. Given the apparent greater severity of illness and risk of death amongst those with these conditions<sup>9 10</sup> and the importance of season, we explore whether ambient UVA exposure is associated with COVID-19 deaths across the USA and replicate this analysis in independent data sets from England and Italy.

## Methods

### *Study Setting and Participants*

We use an ecological regression model of COVID-19 deaths across USA counties (N=2,472), English Middle Layer Super Output Areas (MSOA's) (N=6,724) and excess deaths in Italian municipalities (N=6,775). We only include counties that were experiencing levels of UV too low (monthly mean UVvitd of under 165 KJ/m<sup>2</sup>) to be inducing significant levels of cutaneous vitamin D<sub>3</sub> synthesis during the study period ('UV vitamin D winter') (Supplementary figure 3). USA COVID-19 deaths were drawn from data compiled by the Center for Systems Science and Engineering at Johns Hopkins University. Data were from the period up to the 30<sup>th</sup> of April. These data are derived from death certificates, with information on cause and circumstances of death recorded, collected by the Center for Disease Control and Prevention (CDC). A COVID-19 death represents a case where the practitioner suspected that COVID-19 played a role in the death, even if it was not directly attributable to the death. English COVID-19 deaths were drawn from data compiled by the Office for National Statistics (<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvedcovid19bylocalareasanddeprivation/deathsoccurringbetween1marchand17april>). Data were from the period from 1<sup>st</sup> of March to the 17<sup>th</sup> of April. To be included in this dataset COVID-19 had to be mentioned on the death certificate, with a delay of usually five days between occurrence and registration. Italian excess deaths were drawn from ISTAT (Italian Institute of Statistics) (<https://www.istat.it/it/archivio/240401>) for a sample of municipalities (7,270/7,904; 92%). Data were for the period 1<sup>st</sup> of March to 30<sup>th</sup> of April for 2015-2019 and 2020. These data included all deaths registered in an integrated database, consisting of the registry source (Anagrafe Nazionale della Popolazione Residente; ANPR, and municipalities) with the Tax Register. We classified excess deaths as the positive difference in deaths between 2020 and 2015-19, with negatives recorded as zero.

### *Ambient UV data*

We derive mean daily UVA for each study – USA (1<sup>st</sup> of Jan – 30<sup>th</sup> of April); England (1<sup>st</sup> of Jan – 17<sup>th</sup> of April) and Italy (1<sup>st</sup> of Jan – 30<sup>th</sup> of April). 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<sup>11</sup>. 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. These data are available to download at a 5km by 5km spatial resolution. UVA data were aggregated for USA counties, English MSOA's and Italian municipalities and expressed as mean daily KJ/m<sup>2</sup>.

The long term UV<sub>vitd</sub> dataset (30-year monthly average) was developed by the National Center for Atmospheric Research (NCAR) using the Tropospheric Ultraviolet and visible (TUV) radiation model<sup>12</sup>. This model uses the Total Ozone Mapping Spectrometer (TOMS) on board several satellites (Nimbus-7, Meteor-3 and Earth Probe) to account for atmospheric ozone and climatological cloudiness (defined by TOMS reflectivity at 380 nm). Mean monthly values at a 1° (latitude) by 1.25° (longitude) spatial resolution were available for the period 1979-2000. UV<sub>vitd</sub> data were aggregated for US counties and expressed in mean monthly KJ/m<sup>2</sup>. 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<sup>2</sup>. It also corresponds approximately to the 37°N parallel; Holick suggests that people living North of this latitude will not receive sufficient UV for vitamin D synthesis in the winter<sup>13</sup>.

### *Covariates*

A number of demographic, socioeconomic deprivation, long term environment exposures and variables to measure infection susceptibility were adjusted for in the analysis in case they were spatially associated with both UVA exposure and risk of COVID-19 mortality.

#### *Demographic*

We used data on county percentage of older residents ( $\geq$  age 65), percentage of Hispanic residents and percentage of Black residents for the USA. We used data from ONS mid-year population estimates of 2018 on percentage of residents who were: aged 80 or over, aged 65-79, the 2011 census on living in care homes, Black, Indian, Pakistani/Bangladeshi and Chinese in England. We used data from ISTAT on number of foreign born residents and the percentage of residents: aged 65 and above and aged 85 and above, for Italy. Older age and BAME ethnicity are associated with higher risk of COVID-19 death, possibly due to higher prevalence of comorbidities, including hypertension, heart disease and respiratory diseases<sup>10</sup>.

#### *Socioeconomic Deprivation*

Socioeconomic deprivation was defined in the USA by the first principal component score from A Principle Component Analysis of the following county variables: percentage in poverty, median house value, median house income, percentage owner occupied and percent of population with less than a high school education. We reversed the direction of percentage in poverty and percent of population with less than a high school education so that higher score represented higher affluence. To capture socioeconomic deprivation in England we used percentage of residents who were under 21 did not enter higher education and the income deprivation score indicating of percentage of people who received benefit due to low income (<https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019>). For our Italian study, we used the Italian Deprivation index, calculated by ISFOL (research Italian institute on work and social policies), which considers income, education, living conditions, unemployment and household composition. It is hypothesised that whilst affluent citizens were more likely to get COVID-19 in the early stages of the pandemic, poorer citizens are increasingly at higher risk of infection due to essential working and death due to pre-existing health conditions<sup>14</sup>.

#### Long term environment

Long term PM<sub>2.5</sub> (2000-2016) data at a 0.01° by 0.01° resolution were modelled using satellite and monitored PM<sub>2.5</sub> station data<sup>15</sup>. We used these data for both the USA and Italy. In England long term 2014-2018 PM<sub>2.5</sub> at a 1km by 1km resolution was modelled using monitored PM<sub>2.5</sub> station data (<https://uk-air.defra.gov.uk/data/pcm-data>). Higher PM<sub>2.5</sub> is linked with a range of respiratory and cardiovascular disease and shown to increase COVID mortality rate in other analyses<sup>16</sup>. Long term mean monthly winter temperature (Dec-Feb) at a 4km by 4km resolution for 2000-2016, was modelled using satellite data<sup>17</sup> 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 Met Office weather stations for England (<http://data.ceda.ac.uk/badc/ukmo-hadobs/data/insitu/MOHC/HadOBS/HadUK-Grid/v1.0.1.0/1km/tas/mon-30y/v20190808>). 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 ([https://developers.google.com/earth-engine/datasets/catalog/OpenLandMap\\_CLM\\_CLM\\_LST\\_MOD11A2-DAY\\_M\\_v01](https://developers.google.com/earth-engine/datasets/catalog/OpenLandMap_CLM_CLM_LST_MOD11A2-DAY_M_v01)). Variation in temperature was recently associated with COVID-19<sup>18</sup> mortality.

#### Viral exposure

Viral exposure was modelled through county 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 30<sup>th</sup> of April (<https://github.com/pcm-dpc/COVID-19/tree/master/dati-province>). 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. Therefore the infections susceptibility measures adjust the models for the population 'at-risk'.

### *Statistical Analysis*

We estimate, in a multilevel zero-inflated negative binomial model (using the glmmTMB package), the relationship between ambient UVA and COVID-19 deaths (21<sup>st</sup> January-April 30<sup>th</sup>), with a state level (N=46) level random effect. The 'at-risk' population is the total county population, with the [1] state level random effect, [2] a measure of the proportion of population tested positive for COVID-19 at the state level and [3] measures of infection susceptibility (county population density and urban-rural status), used to incorporate viral exposure into the model (in effect 'correcting' the at risk population to be the exposed population not the entire population). The model is adjusted at the county level for: percentage of older residents ( $\geq$  age 65), Hispanic and Black residents; socioeconomic deprivation and long term modelled 2000-2016 PM<sub>2.5</sub>, long term mean winter temperature (Dec-Feb) and long term mean winter humidity (Dec-Feb) to remove any potential confounding by spatially associated risk factors.

Our first replication of the USA model was to investigate the relationship between ambient UVA and COVID-19 deaths in England (1<sup>st</sup> of March to 17<sup>th</sup> of April), with UTLA (N=150) level random effect. The 'at risk' population is the total MSOA population, with the [1] UTLA level random effect, [2] number of days since a local authority had 10 confirmed cases UTLA level and [3] measures of infection susceptibility (MSOA population density, population using public transport – bus, train and tube). The model is adjusted at the MSOA level for: Long term PM<sub>2.5</sub>, long term winter temperature, Percentage of residents: aged 80+, aged 65-79, Black, Indian, Pakistani/Bangladeshi, Chinese, in care homes, in higher education and income deprivation score.

Our second replication of the USA model was to investigate the relationship between ambient UVA and excess deaths in Italy (1<sup>st</sup> of March to 30<sup>th</sup> of April), with Province (N=104) level random effect. The 'at risk' population is the total municipality population, with the [1] province level random effect, [2] number of tests for COVID-19 cases at the Province level and [3] measures of infection susceptibility (municipality population density and area). The model is adjusted at the municipality level for: Long term PM<sub>2.5</sub>, long term winter temperature, Number of foreign born, Percentage of residents: aged 65+, aged 85+ and deprivation.

Effect estimates were presented as mortality rate ratios with 95% confidence intervals. We predicted the number of deaths per million population at suitable levels of UVA by calculating the marginal means in the 'emmeans' package. To understand the average true effect of UVA on COVID-19 related death in all similar countries to those included, we used a random effects model as part of the 'metafor' package to calculate a cross county pooled estimate of the MRR.

All analyses were undertaken in R 3.6.1.

### **Data and code availability**

The data and to reproduce the current study is held at [https://github.com/markocherrie/COVID19\\_UVA](https://github.com/markocherrie/COVID19_UVA).

## Results

Daily mean UVA (January-April 2020) varied between 450-1,000 KJ/m<sup>2</sup> across the three countries, with lower average levels experienced across England (Figure 1 a,b,c). Our fully adjusted model shows reductions in Mortality Risk Ratios (MRR) of 0.71 in the USA per 100 increase in UVA (KJ/m<sup>2</sup>) (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 with a pooled estimate of 0.68 (Figure 2d). This represents a halving of the average risk of death across the lower and narrower range of UVA experienced across England and across the higher and wider range across Italy and the USA (Figure 2 a,b,c).

## Discussion

Our analysis suggests that higher ambient UVA exposure is associated with lower COVID-19 specific mortality. This effect was independent of temperature and UV within the vitamin D action spectrum. Relatively higher UVA, across a country experiencing lower average levels of UVA during and immediately preceding the pandemic (England), is associated with greater falls in mortality risk compared to countries (Italy and the USA) with a higher average level suggesting an exposure tolerance effect.

There has been considerable debate around the possible role of Vitamin D supplementation for prevention of COVID-19, but to date the data do not support this intervention<sup>19</sup>. We have been able to show a possible benefit from UV at wavelengths that do not cause synthesis of vitamin D. This suggests that explanations for seasonal and geographic variations in COVID-19 prevalence<sup>20</sup> need to consider mechanisms other than just vitamin D.

Seasonal variations in disease incidence can be caused by environmental, behavioural, and immunological factors with the relative importance of these varying by location and disease. UV may have a direct effect on the viability of SARS-CoV2 virus in airborne droplets and on fomites, thus reducing both infection rates, and also the size of inoculum in those becoming infected, with correspondingly reduced disease severity<sup>21 22</sup>. UVA radiation photo-releases nitric oxide (NO) from stores in the skin whence it is mobilised to the systemic circulation, causing vasodilation and reduction in blood pressure<sup>5</sup>, offering cardiovascular and metabolic benefits from UV exposure<sup>5 8</sup>. As cardio-metabolic disease and possibly hypertension<sup>23</sup> increase the risk of death from COVID-19, any UV driven improvements in these risk factors would be expected to reduce mortality<sup>24</sup>. Nitric oxide may also have a specific effect on COVID-19. It inhibits replication of SARS CoV<sup>25</sup>, probably by S-nitrosating the spike protein, thus preventing the post translational palmitoylation of the spike protein, required for fusion with its cognate angiotensin converting enzyme 2 receptor(ACE2R).<sup>26</sup> The spike protein of SARS CoV is highly homologous to that of SARS CoV2<sup>27 28</sup> suggesting that NO may similarly limit binding to ACE2R by SARS CoV2 with reduction in disease transmission and severity. Endothelial damage, with reduced homeostatic endothelial NO synthase activity may underlie widespread organ involvement<sup>29</sup>. This would be mitigated by photochemical NO production.

There are several weaknesses in this study. UVA and covariates are measured at the small area level not as individual level exposures, there could be misclassification of deaths and infection was only 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. Importantly we replicate the finding across three countries with very different health systems and economic and social structures, pandemic situations and measure COVID-19 related deaths in two different ways.

The study was 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 in particular the importance of exploring the role of circulating NO.

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#### **Ethics declaration**

Competing interests

RW is a director of Relaxsol (company making sunscreen).

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Figure 1a: Daily mean UVA ( $\text{KJ}/\text{m}^2$ ) in the contiguous USA between Jan-Apr 30<sup>th</sup> 2020.

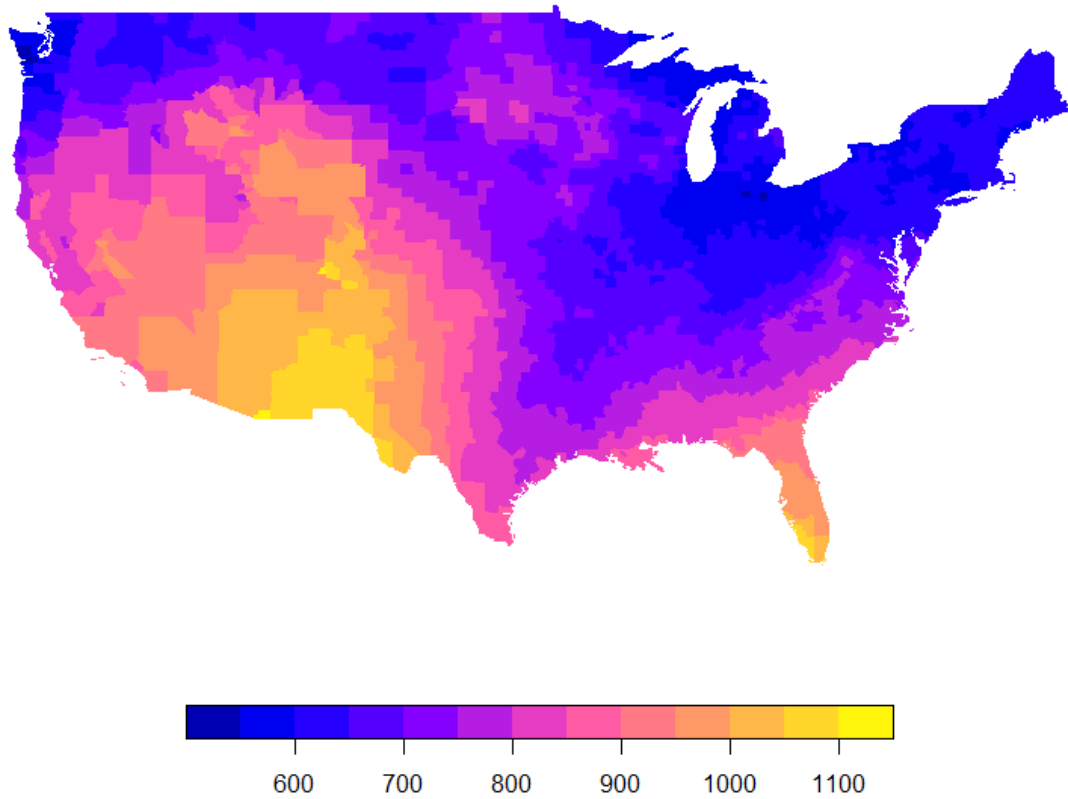


Figure 1b: Daily mean UVA ( $\text{KJ}/\text{m}^2$ ) in England between Jan 1<sup>st</sup> -Apr 17<sup>th</sup> 2020

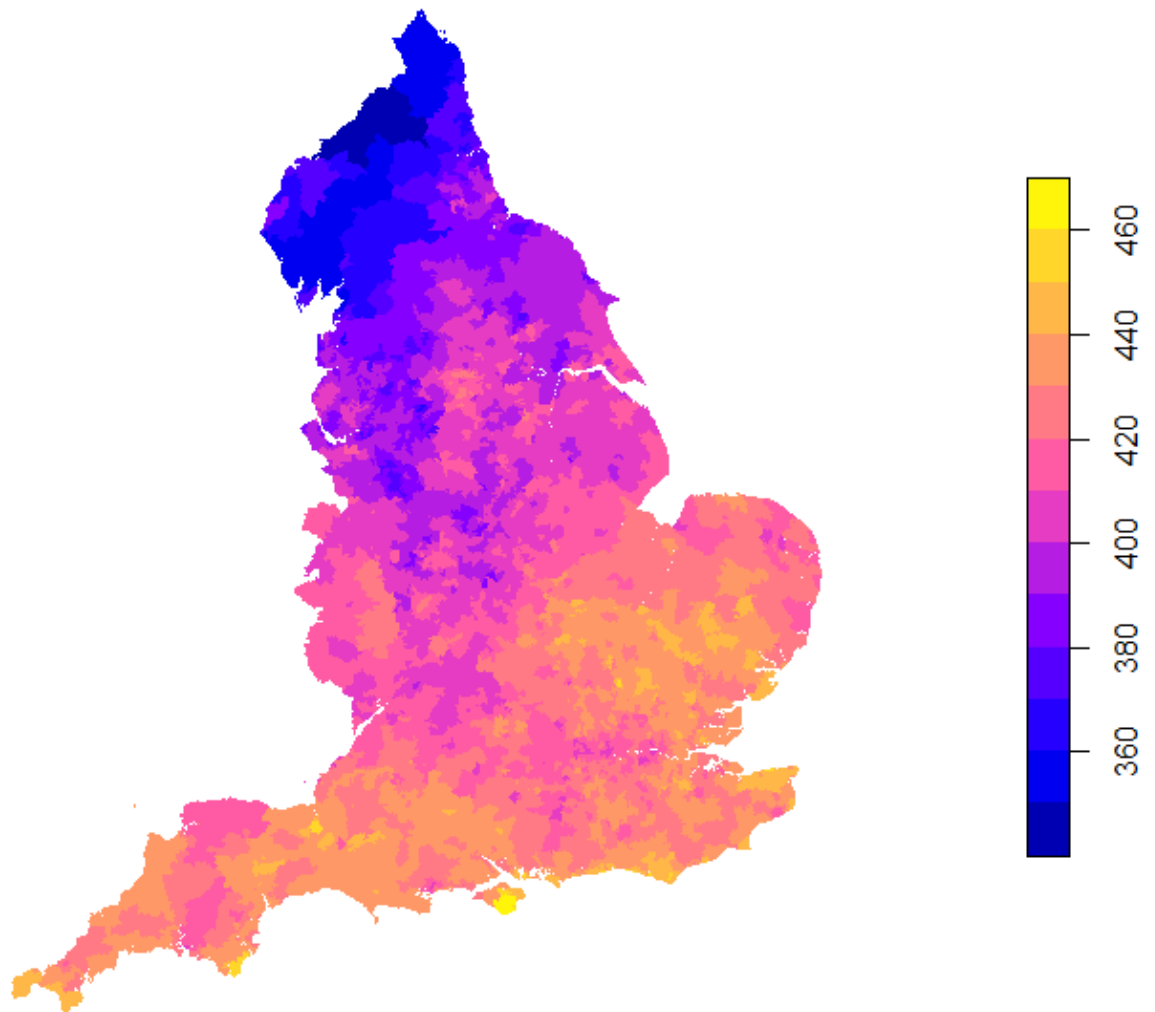


Figure 1c: Daily mean UVA ( $\text{KJ}/\text{m}^2$ ) in the Italy between Jan 1<sup>st</sup> - Apr 30<sup>th</sup> 2020

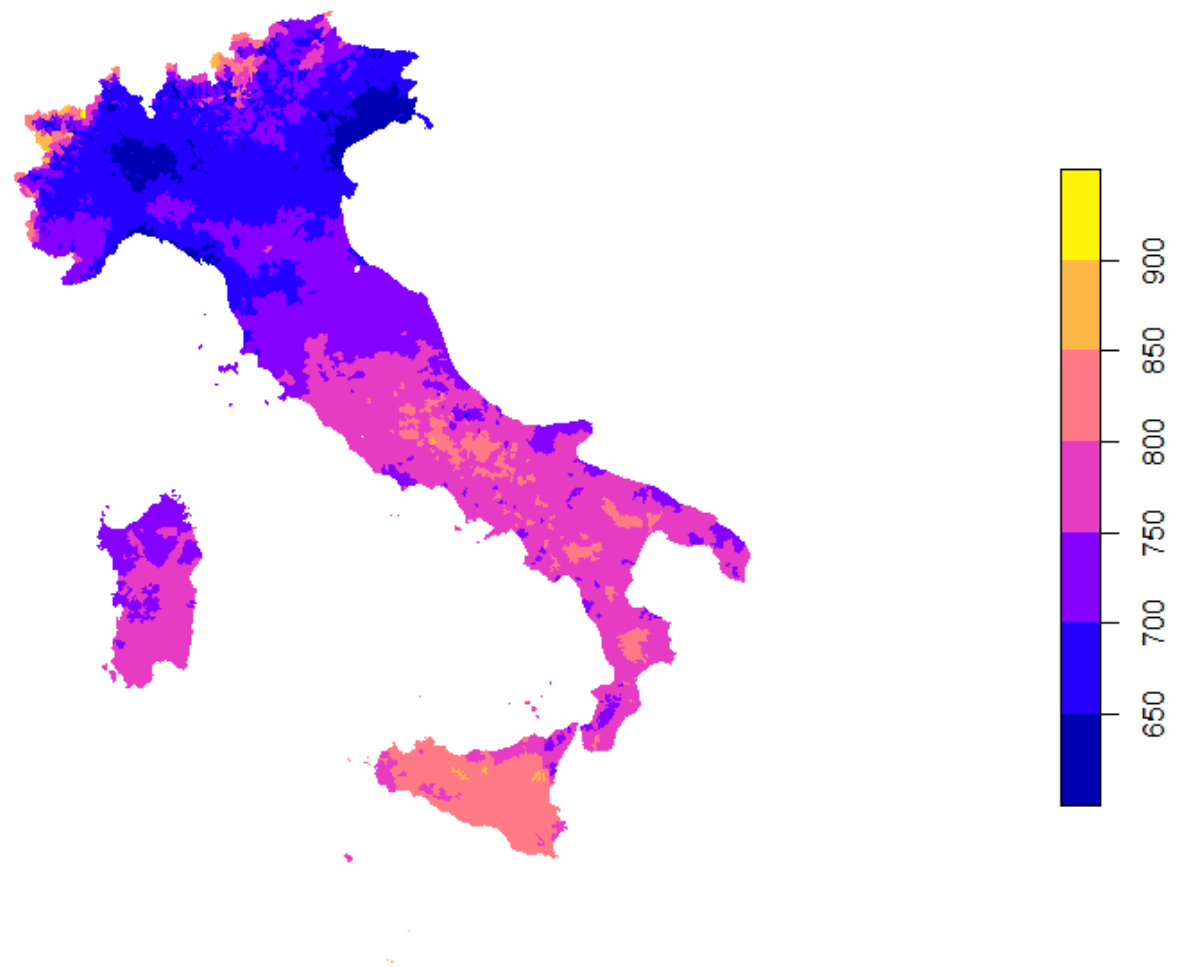


Table 1: Model estimates for the relationship between UVA and covid-19 death

Sample	Negative Binomial Model (adjusted for)	Zero-Inflated Model	Estimated MRR  (95% CI)
USA Counties (N=2,474)	Average UVA Jan-Apr 30 <sup>th</sup> per 100 KJ/m <sup>2</sup> $\bar{x}$ = 696 KJ/m <sup>2</sup> , SD = 83  (Long term: PM <sub>2.5</sub> ; UV <sub>vitd</sub> , winter temperature; winter humidity, Percentage of residents: 65+; Black, Hispanic; deprivation score; urban/rural; state proportion of positive COVID-19 cases)	Percentage of residents: 65+; Black, Hispanic; deprivation score; urban/rural; state proportion of positive COVID-19 cases	0.71  (0.60-0.85)
England MSOAs (N=6,724)	Average UVA Jan-Apr 17 <sup>th</sup> per 100 KJ/m <sup>2</sup> $\bar{x}$ = 412 KJ/m <sup>2</sup> , SD = 18  (Long term: PM <sub>2.5</sub> , 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; Upper Tier Local Authority (UTLA) number of days since a local authority had 10 confirmed cases.)	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 number of days since a local authority had 10 confirmed cases	0.49  (0.38-0.64)
Italy Municipalities (N=6,775)	Average UVA Jan-Apr 30 <sup>th</sup> per 100 KJ/m <sup>2</sup> $\bar{x}$ = 717 KJ/m <sup>2</sup> , SD = 52;  (Long term: PM <sub>2.5</sub> , long term winter temperature; Number of foreign born; Percentage of residents: aged 65+, aged 85+; population density; municipality area, deprivation score; total cases in province)	Number of foreign born; Percentage of residents: aged 65+, aged 85+; population density; municipality area, deprivation score; total cases in province	0.81  (0.71-0.93)

Figure 2a: Predicted COVID-19 deaths by experienced ambient UVA exposure in the contiguous USA

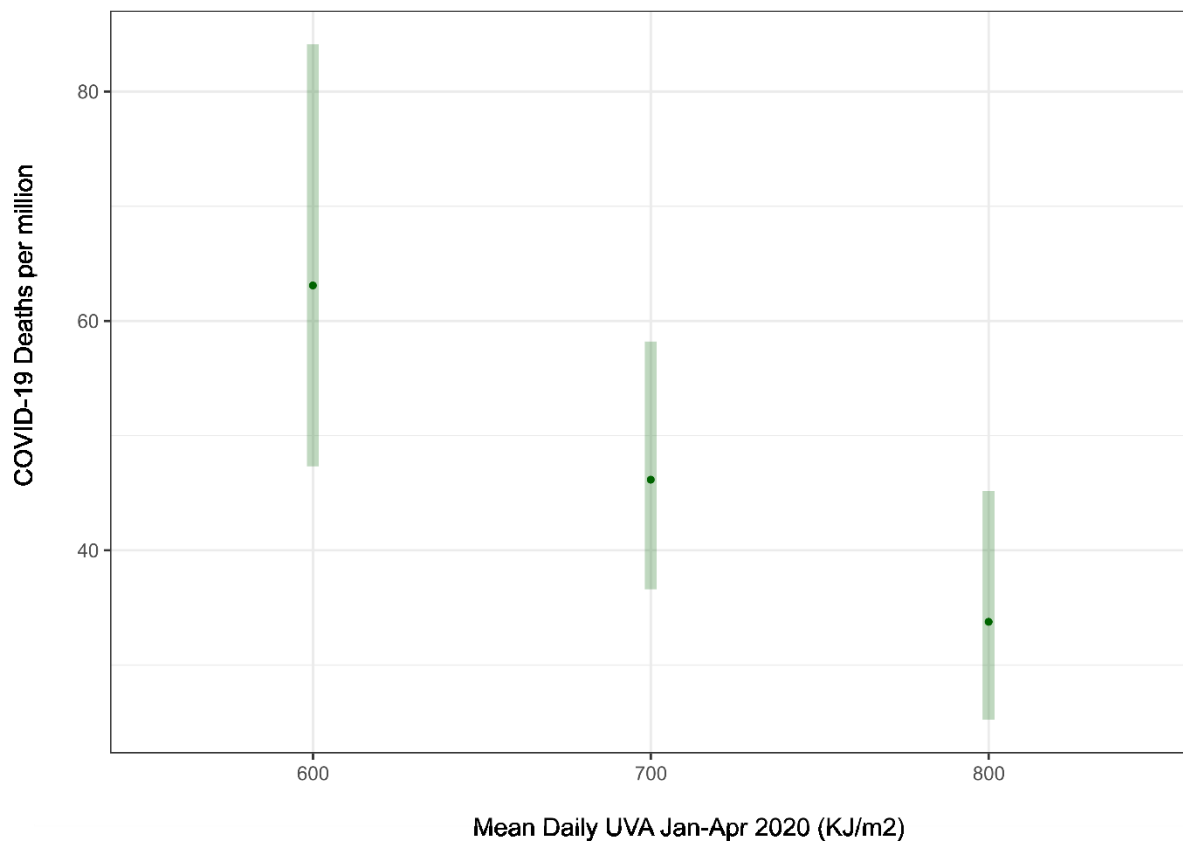


Figure 2b: Predicted COVID-19 deaths by experienced ambient UVA exposure in England



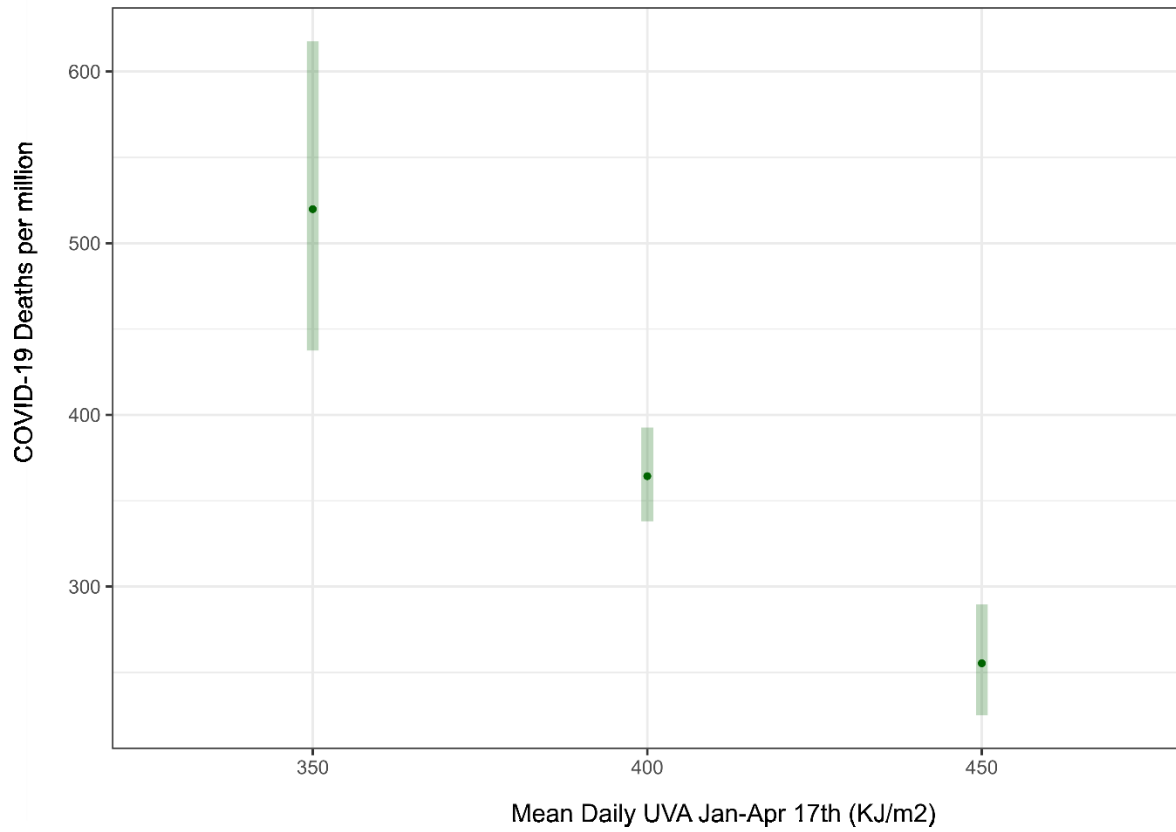


Figure 2c: Predicted excess deaths by experienced ambient UVA exposure in the Italy

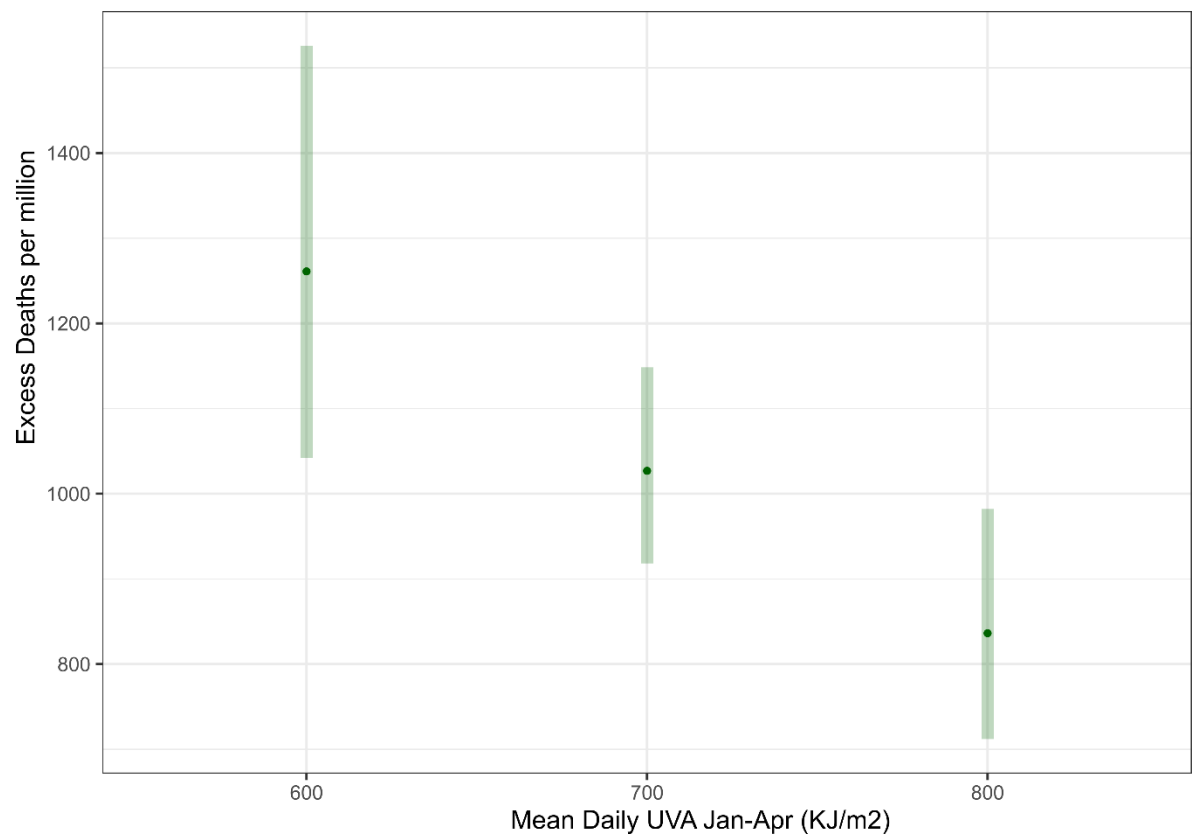


Figure 2d: Forrest plot of estimates for Mortality Rate Ratio per 100 KJ/m² increase in mean daily UVA

