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Original Research Article

Long-term exposure to air-pollution and COVID-19 mortality in England: a hierarchical spatial analysis

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Summary

Background Recent studies suggested a link between long-term exposure to air-pollution and COVID-19 mortality. However, due to their ecological design, based on large spatial units, they neglect the strong localised air-pollution patterns, and potentially lead to inadequate confounding adjustment. We investigated the effect of long-term exposure to NO_2 and $PM_{2·5}$ on COVID-19 deaths up to June 30, 2020 in England using high geographical resolution.

Methods We included 38 573 COVID-19 deaths up to June 30, 2020 at the Lower Layer Super Output Area level in England (n=32 844 small areas). We retrieved averaged NO_2 and $PM_{2·5}$ concentration during 2014-2018 from the Pollution Climate Mapping. We used Bayesian hierarchical models to quantify the effect of air-pollution while adjusting for a series of confounding and spatial autocorrelation.

Findings We find a 0·5% (95% credible interval: -0·2%-1·2%) and 1·4% (-2·1%-5·1%) increase in COVID-19 mortality rate for every 1$\mu g/m^3$ increase in NO_2 and $PM_{2·5}$ respectively, after adjusting for confounding and spatial autocorrelation. This corresponds to a posterior probability of a positive effect of 0·93 and 0·78 respectively. The spatial relative risk at LSOA level revealed strong patterns, similar for the different pollutants. This potentially captures the spread of the disease during the first wave of the epidemic.

Interpretation Our study provides some evidence of an effect of long-term NO_2 exposure on COVID-19 mortality, while the effect of $PM_{2·5}$ remains more uncertain.

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Introduction

As of 30th of June 2020, COVID-19 has caused more than 500 000 deaths globally, with an estimated case fatality of 1-4%.[1] The UK is one of the countries most affected, with the an estimated 49 200 (44 700-53 300) more deaths than it would be expected from mid-February to 8th May 2020 had the pandemic not taken place.[2] Established risk factors of COVID-19 mortality include age, sex and ethnicity.[3] Previous studies have observed a correlation between pre-existing conditions such as stroke, hypertension and diabetes.[4,5] Long-term exposure to air-pollution has been hypothesised to worsen COVID-19 prognosis: either directly, as it can suppress early immune responses to the infection,[6] or indirectly, as it can increase the risk of stroke, hypertension and other pre-existing conditions.[7,8]

Little is known about the effect of long-term exposure to air-pollution on COVID-19 mortality and evidence so far relies on ecological studies based on large areas. A study in the US, at county level, reported an 8% (95% confidence intervals: 2%-15%) increase in the COVID-19 death rate, for an increase of 1$\mu g/m^3$ in the long-term exposure to $PM_{2\cdot5}$ (atmospheric particulate matter that has a diameter of less than 2·5 micrometers).[6] Another study in the US, at county level, examined the long-term effect of NO_2, $PM_{2\cdot5}$ and O_3 on COVID-19 case fatality (proportion of deaths among infected) and mortality rate and reported a 7·1% (1·2%-13·4%) and 11·2% (3·4%-19·5%) increase per 4·5ppb increase in NO_2 for case fatality and mortality rate respectively.[9] The same study reported weak evidence of an association between COVID-19 case fatality or mortality with long term exposure to $PM_{2\cdot5}$ and O_3. A study in the Netherlands using municipalities reported that every unit increase in the long-term exposure to $PM_{2\cdot5}$, NO_2 and SO_2 was associated with 0·35, 2·3 and 1·8 additional COVID-19 deaths respectively.[10] A study in England reported a significant association between long-term exposure to NO_2, NO and O_3 and COVID-19 deaths at Lower Tier Local Authorities (LTLA).[11]

Several methodological shortcomings limit the interpretability of previous studies:

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1) They were based on data aggregated on large spatial units and thus suffer from ecological fallacy (grouped levels association do not reflect individual ones).[12]

2) Air pollution is characterised by high spatial variability, making the availability of mortality data at the same high spatial resolution crucial. In addition, a coarse geographical resolution might lead to inadequate adjustment for confounders, when these are available at higher resolution.

3) Most previous studies assessed cumulative deaths until mid or end of April and thus the generalisability of the results is limited to the early stages of the epidemic.[6,9,11] Only one study had data available up to 5th June 2020 capturing almost the entire first wave.[10]

In this nationwide study in England, we investigated the effect of long-term exposure to air pollution on COVID-19 mortality during the entire first wave of the epidemic, after accounting for confounding and spatial autocorrelation. We focused on exposure to NO_2 and $PM_{2·5}$. We downscaled the LTLA geographical information to the Lower Layer Super Output Area (LSOA) to alleviate the effect of ecological bias and exploit the variability of the exposure at high geographical resolution. We hypothesise that long-term exposure to these compounds worsens the prognosis of COVID-19 patients, as exposure to pollution can suppress early immune responses to the infection, leading to later increases in inflammation[6] and as it can affect the onset of pre-existing conditions.[13-16]

Methods

Study population

We included all COVID-19 deaths up to June 30, 2020 in England as retrieved from Public Health England (PHE). For each death, PHE records individual data on age, sex and ethnicity, as well as the LTLA of the residential address. Information for the general population about age and sex is available from the Office of National Statistics (ONS) for 2018, whereas ethnicity is obtained from the 2011 census at the LSOA level.

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We downscaled the LTLA geographical information to the LSOA level using census based weights to match the age, sex and ethnic composition of the deaths in each LTLA with that of the corresponding LSOAs. For more information about the downscaling procedure see Supplementary Material S1.1.

Exposure

We considered exposure to NO_2 and $PM_{2·5}$ as indicators of air pollution. We selected these pollutants because: 1) they reflect different sources of air-pollution (NO_2 reflects traffic related air-pollution, whereas $PM_{2·5}$ is a combination of traffic and non-traffic sources), 2) they were considered in previous studies[6,9-11] and 3) they are responsible for the highest number of years of life lost compared to other pollutants in Europe.[17] We retrieved NO_2 and $PM_{2·5}$ concentration in England from the Pollution Climate Mapping (PCM; https://uk-air.defra.gov.uk/). The PCM produces annual estimates during 2001-2018 for NO_2 and 2002-2018 for $PM_{2·5}$ at 1x1km resolution for the UK. The PCM model is calibrated using monitoring stations across the nation and has high predictive accuracy, R^2 =0·88 for NO_2 and R^2 = 0·63 for $PM_{2·5}$.[18] We defined long-term exposure to these compounds as the mean of the past 5 years for which data was available, i.e. 2014-2018. We weighted the exposure using a combination of population estimates available from the fourth version of Gridded Population of the World (GPW) collection at 1x1km grid as of 2020[19] and from ONS at LSOA level as of 2018. For more information about the population weights see Supplementary Material S1.2.

Confounders

We considered confounders related with meteorology, socio-demographics, disease spread, healthcare provision and health related variables (Table 1). As meteorological confounders, we considered temperature and relative humidity and calculated the mean for March-June 2018 as this is the latest year with data available at 1x1km grid retrieved from the MetOffice. We weighted temperature and relative humidity using the population weights calculated for the air-pollution exposure. As socio-demographical confounders we considered age, sex,

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ethnicity, deprivation, urbanicity, population density and occupation. Information on age (2018), sex (2018), ethnicity (2011), urbanicity (2011) and population density (2018) was available at the LSOA level from ONS. To adjust for deprivation, we used quintiles of the index of multiple deprivation at LSOA level in 2011 (Ministry of Housing, Communities and Local Government), excluding the dimension related to air quality. We used estimates of occupational exposures to COVID-19, as calculated by ONS, to adjust for high risk exposure to COVID-19, defined as those with a score higher than 80/100 (corresponding to at least >1 per week exposed to someone infected, Supplementary Material S1.3 and Table S1). To account for disease progression, we used the number of days since the 1st reported case and the number of positive cases in each LTLA (as of 30th of June, as retrieved from PHE). For healthcare provision, we used the number of intensive care unit beds per population, in February 2020 per NHS trust, as retrieved by NHS. Last, as health-related variables, we considered smoking and obesity prevalence at the GP practice level during 2018-2019, as retrieved by PHE (Supplementary Material S1.3).

Statistical methods

We specified Bayesian hierarchical Poisson log-linear models to investigate the association of COVID-19 deaths and NO_2 and $PM_{2·5}$ independently. Spatial autocorrelation was modelled using a re-parametrisation of the Besag-York-Mollié conditional autoregressive prior distribution.[20,21] We fitted four models including: 1) each pollutant (model 1), 2) each pollutant and the spatial autocorrelation term (model 2), 3) each pollutant and all confounders (model 3) and 4) each pollutant, the spatial autocorrelation term and all confounders (model 4). All models were adjusted for age, sex and ethnicity using indirect standardisation. In order to propagate the uncertainty resulted from the sampling we used for the downscaling (Supplementary Material S1.1), we fitted the models over 100 downscaled samples and then performed Bayesian model averaging to combine the estimates.[22] We report results as posterior median of mortality relative risk for every 1μg/m^3 increase in the air-pollutants, 95%

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credibility intervals (CrI) and posterior probability that the estimated effect is positive. We also report posterior median of spatial mortality relative risks (exponential of the spatial autocorrelation term) and posterior probabilities that the spatial relative risks are larger than 1. The full model and prior specifications are given in the Supplementary Material S1.4.

All models are fitted in INLA.[23] Data and code are available on github (https://github.com/gkonstantinoudis/COVID19AirpollutionEn).

Sensitivity analyses

We performed a series of sensitivity analyses. First, we repeated the main analyses using data at the LTLA level with all exposures and confounding weighted by population. Second, we examined if there is a differential effect of long-term exposure to air-pollution at the early stages of the epidemic, considering the lockdown (23rd of March 2020) as a landmark. Third, we assessed the correlation between the latent field of the full model (model 4) with that of the model excluding or including only covariates indicating disease spread (i.e. number of tested positive cases and days since first reported cases). Fourth, we categorised pollutants into quintiles to allow more flexible fits. Fifth, we repeated the analysis using suspected cases as the outcome.

Results

Study Population

We identified 38 573 COVID-19 deaths with a laboratory confirmed test in England between 2nd March and 30th June (Figure 1). The age, sex and ethnicity distribution of the deaths follows patterns reported previously (Supplementary Material Tables S2-3).

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Exposure

Figure 2 shows the population weighted air-pollutants at LSOA level in England. We observe that the localised variation of NO_2, for instance due to the highways, is adequately captured at the spatial resolution of the LSOAs. The mean of NO_2 is 16·17μg/m^3 and it varies from 2·99μg/m^3 in highly rural areas to 50·69μg/m^3 in the big urban centres (Figure 2). The mean of $PM_{2·5}$ is 9·84μg/m^3 with a smaller variation, 5·14-14·22 μg/m^3 (Figure 2).

Confounders

Plots and maps of the confounders can be found in Supplementary Material, Figures S1-11.

NO_2

We observe a 2·6% (95%CrI: 2·4%-2·7%) increase in the COVID-19 mortality rate for every 1μg/m^3 increase in the long-term exposure to NO_2, based on model 1 (Figure 3 & Supplementary Material Table S4). There is still evidence of an effect, albeit smaller, once we adjust for spatial autocorrelation or confounders, with increases in the long-term exposure to NO_2 of, respectively, 1·3% (0·8% - 1·8%), 1·8% (1·5% - 2·1%) for every 1μg/m^3. When we adjust for both autocorrelation and confounders the evidence is less strong, with estimates of 0·5% (-0·2% - 1·2%) for every 1μg/m^3 (Figure 3 & Supplementary Material Table S4) and posterior probability of a positive effect reaching 0·93. The spatial relative risk in England varies from 0·24 (0·08-0·69) to 2·09 (1·30-3·11) in model 2 and from 0·30 (0·10-0·84) to 1·87 (1·18-2·93) in model 4, implying that the confounders explain very little of the observed variation (Figure 3). The variation is more pronounced in the cities and suburban areas (with posterior probability higher than 1; Figure 3).

$PM_{2·5}$

We observe a 4·4% (3·7%-5·1%) increase in the mortality rate for every 1μg/m^3 increase in the long-term exposure to $PM_{2·5}$, based on model 1 (Figure 3 & Supplementary Material Table S5). When we adjust for spatial autocorrelation the effect increases slightly but the credibility intervals are wider, 5·4% (2·5%-8·4%), whereas it is similar when we adjust for confounding

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4·9% (3·7%-6·2%) (Figure 3 & Supplementary Material Table S5). The effect is weak when we account for confounders and spatial autocorrelation 1·4% (-2·1%-5·1%) (Figure 3 & Supplementary Material Table S5). The posterior probability of a positive effect is lower than observed for NO_2, and equal to 0·78. The spatial relative risk follows similar patterns as the one reported in the models for NO_2, with the posterior median relative risk varying from 0·24 (0·12-0·46) to 2·26 (1·32-3·85) in model 2 and from 0·30 (0·15-0·57) to 1·90 (1·14-3·17) in model 4 (Supplementary Material Figure S12).

Sensitivity Analyses

When LTLAs are the main geographical unit for analysis, the results are consistent, but higher in magnitude, potentially due to inadequate covariate and spatial autocorrelation adjustment due to the coarse geographical resolution (Supplementary Material Tables S6-7, Figures S13-14). Restricting the study period to March 23, 2020 (N=698) also results in similar estimates for both pollutants, however the uncertainty is higher (Supplementary Material Tables S8-9, Figures S15-16). The latent field of model 4, with NO_2 as the pollutant, is similar to the latent fields of the models with and without the disease progression variables, with a correlation coefficient of 0·94 and 0·93 respectively (Supplementary Material Figure S17). The use of quintiles of the pollutants justifies the linearity assumption (Supplementary Material Figure S18). Finally, the results are consistent, but the evidence weaker, when suspected COVID-19 deaths are used instead (Supplementary Material Tables S10-11, Figures S19-20).

Post-hoc analysis

In a post-hoc analysis we investigated if the evidence of an effect of NO_2 on COVID-19 mortality can be attributed to pre-existing conditions. We selected hypertension, chronic obstructive pulmonary disease (COPD) and diabetes, because of 1) indications of previous literature that they increase the COVID-19 mortality risk,[4,5] 2) previous literature that suggest an effect with long-term exposure NO_2[14-16] and 3) data availability. We retrieved prevalence data for these pre-existing conditions from PHE available at the GP practice level during

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2018-2019 (https://fingertips.phe.org.uk/), Supplementary Material Figures S21-23. The effect of NO_2 remain similar, 0·6% (-0·1% - 1·3%) with the posterior probability being 0·94 whereas the spatial relative risk highlights the same geographical locations, Supplementary Material Figure S24.

Discussion

Main findings

This is the first nationwide study in England investigating the effect of long-term exposure to NO_2 and $PM_{2·5}$ during 2014-2018 on COVID-19 mortality at LSOA level. The unadjusted models indicate that for every 1μg/m^3 increase in the long-term exposure to NO_2 and $PM_{2·5}$ the COVID-19 mortality rates increase. After considering the effect of confounding and spatial autocorrelation the evidence is less strong for NO_2, while for $PM_{2.5}$ there is larger uncertainty. The spatial relative risk has strong spatial patterns, identical for the different pollutants, potentially highlighting the effect of disease spread.

Comparison with previous studies focusing on NO_2

Our study is comparable with three previous studies in the US, England and the Netherlands assessing the long-term effect of NO_2 in COVID-19 mortality. The study in the US focused on deaths reported by April 29, 2020, using 3 122 counties. For the exposure, they calculated the mean of daily concentrations during 2010-2016 as modelled by a previously described ensemble machine learning model (R^2=0·79).[25] They reported a 7·1% (1·2%-13·4%) increase in mortality per 4·5ppb (1ppb=1·25μg/m^3) increase in NO_2 after adjusting for confounders and spatial autocorrelation[9] (that is approximately 1·3% increase per 1 μg/m^3). The study in England, with partly overlapping data as in our analysis, also reported a significant association between NO_2 and COVID-19 mortality ($p<0·05$). For the analysis they focused on COVID-19 deaths reported in England up to April 10, 2020, used 317 LTLAs, and did not account for spatial autocorrelation.[11] The study in the Netherlands using 335 municipalities and mean exposure during 2015-2019 reported 0·35 (0·04-0·66) additional COVID-19 deaths

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for every 1μg/m^3 increase in NO_2 after adjusting for confounders and certain spatial controls, such as transmission beyond the Dutch national borders[10]. Since the mean number of deaths in their sample is 16·86, the above estimate translates to a 2·0% increase in the COVID-19 mortality for every 1μg/m^3 increase in NO_2.

Comparison with previous studies focusing on $PM_{2·5}$

Our study is comparable with previous studies assessing the long-term effect of $PM_{2·5}$ on COVID-19 mortality. The aforementioned study in the US also assessed the effect of $PM_{2·5}$ on COVID-19 mortality.[9] Their exposure model was previously validated having an R^2 = 0·89 for the annual estimates.[26] The evidence for $PM_{2·5}$ was weak, namely 10·8% (-1·1-24·1%) per 3·4μg/m^3 increase in $PM_{2·5}$ concentration (that is approximately 3·2% increase per 1 μg/m^3) after adjusting for confounding and spatial autocorrelation. Our study comes in contrast with another study in the US that used deaths reported until April 22nd, 2020 and counties as the geographical unit.[6] For the exposure, they used previously validated monthly $PM_{2·5}$ concentrations (R^2 = 0·70)[27] and averaged them during 2000 and 2016. After adjusting for confounding but not for spatial autocorrelation, they found an 8% (2%-15%) increase in the COVID-19 death rate for an increase of 1μg/m^3 in $PM_{2·5}$ concentration. Our study comes also in contrast with the study in the Netherlands that reported 2·3 (1·3-3·0) additional COVID-19 deaths for an increase of 1μg/m^3 in the averaged long-term $PM_{2·5}$ concentration.[10] Having a mean number of deaths equal to 16·86, the above estimate translates to a 13·6% increase in the COVID-19 mortality rate for an increase of 1μg/m^3 in $PM_{2·5}$ concentration.

Strengths and Limitations

Our study is the first study that examines the association between long-term exposure to NO_2 and $PM_{2·5}$ at very high geographical precision. The spatial unit of our analysis is LSOAs, for which there are 32 844 in England (~130 000km^2), whereas previous studies have used 317 LTLAs in England, counties in the US (3 122 in an area ~9·8 million km^2) and municipalities in the Netherlands (334 in an area ~41 500km^2). Such high-resolution allows capturing the

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localised geographical patterns of the pollutants but also ensures adequate confounding and spatial autocorrelation adjustment. Our study also covers, so far, the largest temporal window of the epidemic (capturing the entire first wave, Figure S25 Supplementary Material), while most previous studies focused on the early to mid-stages of the first wave. This ensures better generalisability of the results. We also adjusted for spatial autocorrelation, which was found to be a crucial component in the model. Not accounting for spatial autocorrelation, when spatial autocorrelation is present, is expected to give rise to narrower credible intervals and false positive effects.[28]

Our study has also some limitations. The downscaling procedure will likely inflate the reported credible intervals. However, this naturally reflects the uncertainty of the place of residence resulted from the downscaling approach. Although we consider small areas, the study is still an ecological one and thus the reported effects do not reflect individual associations.[12] Case fatality might have been a more appropriate metric for the analysis, since disease spread is accounted for in the denominator. Nevertheless, given the asymptomatic infections and the fact that number of reported infections is not a random sample of the general population, the number of COVID-19 cases per LTLA is not reliable at this stage. However, part of the disease spread was captured in the spatial autocorrelation term. We did not account for population mobility during 2014-2018, and assumed constant residence and thus levels of exposure to air-pollution. We also could not account for non-residential air-pollution exposure.

Interpretation

Compared to the previous studies, our results are the smallest in magnitude, likely because of the high geographical precision that allows more accurate confounding and spatial autocorrelation adjustment. In addition, we report the weakest evidence of an effect, which could be due to lack of power and individual exposure data. Nevertheless, as for NO_2 we find a high posterior probability of an effect on mortality, we argue that a potential explanation

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might be the mediation effect of pre-existing conditions. While in our analysis the inclusion of area-level prevalence of hypertension, diabetes and COPD did not change the results, the ecological nature of the pre-existing conditions data does not allow us to account for the mediation effect at the individual level. None of the previous studies have accounted for pre-existing conditions. Similarly, the weak, but positive, effect observed for $PM_{2\cdot5}$ could be an attribute to pre-existing conditions, or even disease spread, as recent studies have suggested that $PM_{2\cdot5}$ can proliferate COVID-19 transmission.[29]

Our analysis captured strong spatial autocorrelation. The observed pattern could reflect residual variation from a potential inadequate covariate adjustment (including disease spread), spatial variation of pre-existing conditions, other unknown spatial confounders or a combination from all above. In a sensitivity analysis, we observed that the factors associated with disease transmission left the latent field unchanged (Supplementary Material Figure S17), as did the inclusion of hypertension, diabetes and COPD (Supplementary Material Figure S24). When we restricted the analysis to the pre-lockdown period, the latent field for both pollutants captured London and Birmingham, i.e. the cities with the first outbreaks. Considering the above, and the fact that COVID-19 is an infectious disease, we believe that large variation of Figure 4 is likely due to disease spread, which is not adequately captured in the disease progression covariates.

Conclusion

Overall, this study provides some evidence of an association between averaged exposure during 2014-2018 to NO_2 and COVID-19 mortality, while the role of $PM_{2\cdot5}$ remains more uncertain.

Contributors

Conceptualisation: G.K., T.P., M.B.; Methodology: G.K., T.P., M.B.; Formal analysis: G.K., T.P.; Validation: G.K., T.P., J.B., B.D., M.E., and M.B.; Writing-original draft: G.K.;

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Writing-review and editing: G.K., T.P., J.B., B.D., M.E., and M.B.; Resources: G.K., M.B., M.E.; Supervision: M.B. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Ethical approval

Only aggregated count data were used in this analysis; no individual data were used.

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Tables

Table 1. Data sources used in the analysis

Confounders	Source	Spatial Resolution	Temporal Resolution	Type
Temperature	MetOffice https://www.metoffice.gov.uk/	1km^2	Mar-June 2018	continuous
Relative humidity	MetOffice https://www.metoffice.gov.uk/	1km^2	Mar-June 2018	continuous
Index of Multiple Deprivation	Ministry of Housing, Communities and Local Government https://www.gov.uk/	Lower layer super output area	2011	rank (quintiles)
Urbanicity	Office of National Statistics https://www.ons.gov.uk/	Lower layer super output area	2011	urban/rural
Days since 1st reported case	Public Health England	Lower tier local authority	Until 30th June	continuous
Number of positive cases	Public Health England	Lower tier local authority	Until 30th June	discrete (counts)
Population density	Office of National Statistics https://www.ons.gov.uk/	Lower layer super output area	2018	continuous (log transformed)
Number of intensive care unit beds	National Health Service https://www.england.nhs.uk/	National Health Service trust	February 2019	continuous (per population)
Smoking	Public Health England https://fingertips.phe.org.uk/	General practitioner catchment area	2018-2019	continuous (prevalence)
Obesity	Public Health England https://fingertips.phe.org.uk/	General practitioner catchment area	2018-2019	continuous (prevalence)
High Risk Occupation	Office of National Statistics https://www.ons.gov.uk/	Middle layer super output area	2011	continuous (prevalence)

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Figures

Fig 1. Flowchart of the COVID-19 deaths.

Fig 2. Population weighted exposure per LSOA.

Fig 3. Density strips for the posterior of COVID-19 mortality relative risk with $1\mu g/m^3$ increase in NO_2 (top panel) and $PM_{2\cdot5}$ (botom panel) averaged long-term exposure.

Fig 4. Median posterior spatial relative risk (exponential of the spatial autocorrelation term) and posterior probability that the spatial relative risk is larger than 1 for the models with NO_2 and a spatial autocorrelation term and the fully adjusted NO_2 model.

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Fig 1.

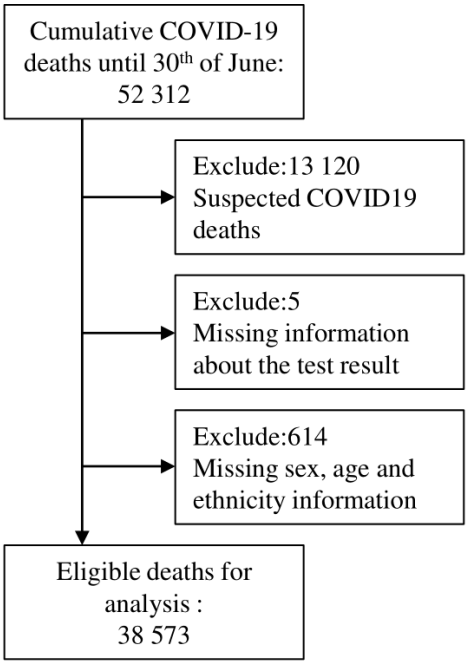

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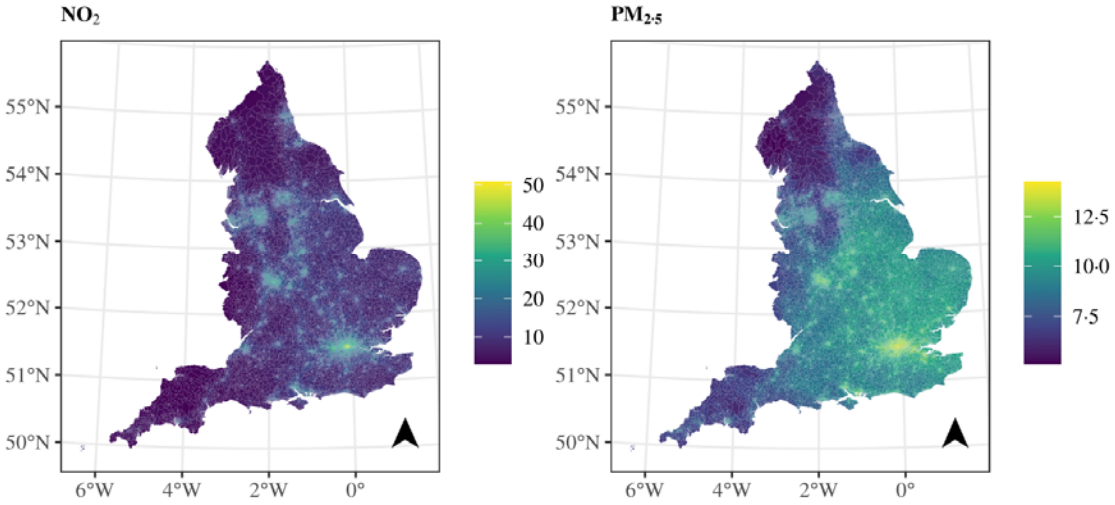
Fig 2.



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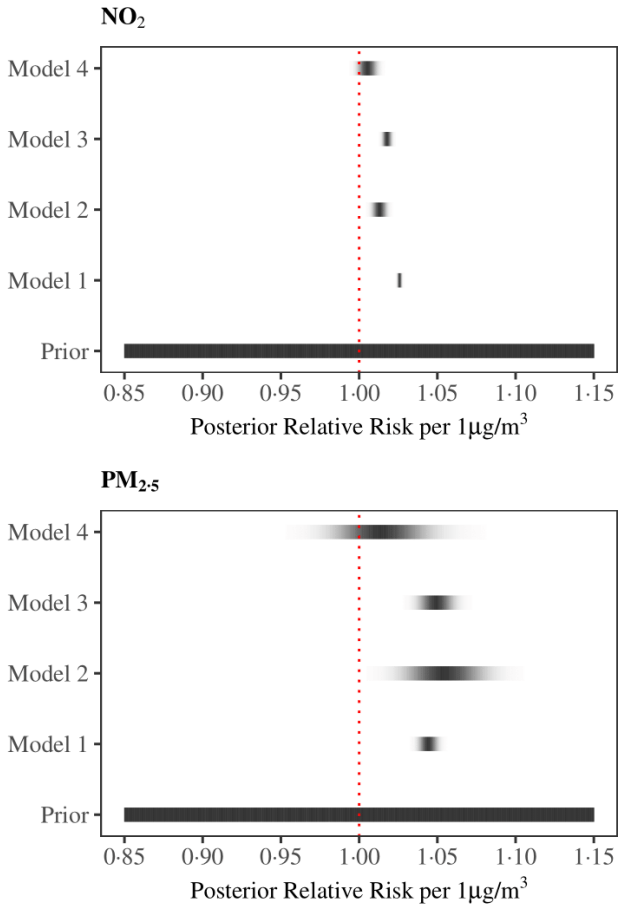
1 **Fig 3.**



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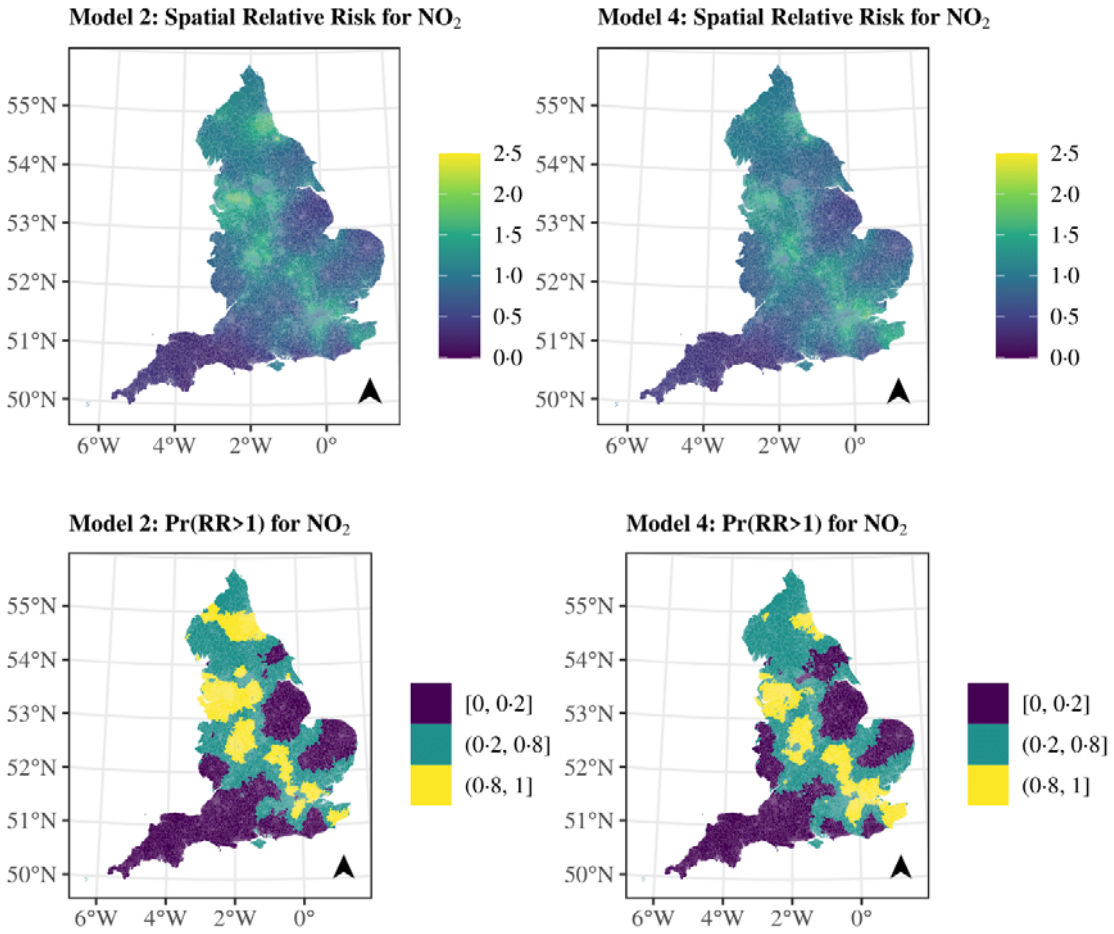
1 **Fig 4.**



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