OPEN ACCESS

Original research

# Ambient heat exposure and COPD hospitalisations in England: a nationwide case-crossover study during 2007–2018

Garyfallos Konstantinoudis ,[1] Cosetta Minelli ,[2] Ana Maria Vicedo-Cabrera,[3,4] Joan Ballester,[5] Antonio Gasparrini,[6,7,8] Marta Blangiardo[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2021-218374).

[1]MRC Centre for Environment and Health, Imperial College London, London, UK
[2]NHLI, Imperial College London National Heart and Lung Institute, London, UK
[3]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[4]Oeschger Centre for Climate Change Research, University of Bern, Bern, Switzerland
[5]Climate and Health Program (CLIMA), Barcelona Institute for Global Health (ISGlobal), Barcelona, Spain
[6]Department of Public Health Environments and Society, London School of Hygiene & Tropical Medicine, London, UK
[7]Centre for Statistical Methodology, London School of Hygiene Tropical Medicine, London, UK
[8]Centre on Climate Change and Planetary Health, London School of Hygiene Tropical Medicine, London, UK

**Correspondence to**
Dr Garyfallos Konstantinoudis, Medicine, Imperial College London, London SW7 2BX, UK; g.konstantinoudis@imperial.ac.uk

Received 19 October 2021
Accepted 24 March 2022

Check for updates



**To cite:** Konstantinoudis G, Minelli C, Vicedo-Cabrera AM, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2021-218374

## ABSTRACT

**Background** There is emerging evidence suggesting a link between ambient heat exposure and chronic obstructive pulmonary disease (COPD) hospitalisations. Individual and contextual characteristics can affect population vulnerabilities to COPD hospitalisation due to heat exposure. This study quantifies the effect of ambient heat on COPD hospitalisations and examines population vulnerabilities by age, sex and contextual characteristics.

**Methods** Individual data on COPD hospitalisation at high geographical resolution (postcodes) during 2007–2018 in England was retrieved from the small area health statistics unit. Maximum temperature at 1 km ×1 km resolution was available from the UK Met Office. We employed a case-crossover study design and fitted Bayesian conditional Poisson regression models. We adjusted for relative humidity and national holidays, and examined effect modification by age, sex, green space, average temperature, deprivation and urbanicity.

**Results** After accounting for confounding, we found 1.47% (95% Credible Interval (CrI) 1.19% to 1.73%) increase in the hospitalisation risk for every 1°C increase in temperatures above 23.2°C (lags 0–2 days). We reported weak evidence of an effect modification by sex and age. We found a strong spatial determinant of the COPD hospitalisation risk due to heat exposure, which was alleviated when we accounted for contextual characteristics. 1851 (95% CrI 1 576 to 2 079) COPD hospitalisations were associated with temperatures above 23.2°C annually.

**Conclusion** Our study suggests that resources should be allocated to support the public health systems, for instance, through developing or expanding heat-health alerts, to challenge the increasing future heat-related COPD hospitalisation burden.

## Key messages

What is already known on this topic

- ► A handful of studies examine the effect of heat exposure on chronic obstructive pulmonary disease (COPD) hospitalisations, and the results are suggestive of a positive effect.

What this study adds

- ► We examine the effect of heat exposure on COPD hospitalisation using 12 years' worth of individual nationwide data in England. For every 1°C increase in summer temperatures higher than 23.2°C, the risk of COPD hospitalisation increases by 1.47%. We found weak evidence of an effect modification by age and sex, but strong in space, with populations in the North and in the South East of England being more vulnerable.

How this study might affect research, practice and/or policy

- ► Not only considering the rising temperatures but also future COPD prevalence and population ageing trends, the burden of heat exposure-related COPD hospitalisation is expected to increase. Our findings can be used as a guidance to policymakers, so resources are allocated to support the preparedness and resilience of public health systems.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the most prevalent chronic respiratory disease worldwide, with point prevalence varying from 1.56% in Sub-Saharan Africa to 6.09% in Central Europe, Eastern Europe and central Asia in 2007.[1] In England, COPD is a significant cause of morbidity and mortality, leading to 115 000 emergency admissions and 24 000 deaths per year.[2] The causes of acute exacerbation of COPD are established and include factors such as sex, age, COPD severity and comorbidities.[3] Environmental triggers of COPD hospitalisations such as air-pollution exposure have also been discussed extensively.[4] There is emerging evidence suggesting a link between heat exposure and COPD hospitalisation, either directly or through exacerbating the effects of factors such as ozone concentration that are associated with these events.[5]

Several previous studies have examined the effect of high temperatures on COPD hospitalisations, reporting higher rates with heat exposure[6–8] and heat waves.[9 10] The majority of these studies are based on aggregated data (at the city or regional level),[6 9–11] whereas only a few considered individual data.[7 8] Use of individual data allows investigation of possible effect modification by individual factors such as age and sex, and it avoids ecological bias arising when group-level associations do not reflect associations at the individual level.[12] Although previous studies have assessed the vulnerability related to individual factors, such as age and sex;[6 8] contextual characteristics, such as green space, average temperature, deprivation and urbanicity are still poorly characterised. Two of the previous studies have examined the spatial variation of the temperature effect on COPD hospitalisation, using, however, very coarse geographical resolution.[6 8]

In this nationwide study in England during 2007–2018, we investigated the effect of heat exposure on COPD hospital admissions using a semiecological framework. We took advantage of the individual data availability of the outcome and adopted a case-crossover study design that naturally accounts for time-constant variables at the individual patient level. Thus, we were able to account for factors like age, sex, comorbidities, deprivation as well as lifestyle characteristics such as physical activity through the study design. We also adjusted for time-varying confounders, such as air-pollution exposure and relative humidity and examined how the effect of temperature is modified by age, sex and in space. Last, we assessed the extent to which contextual characteristics, such as green space, deprivation, urbanicity and average temperature, contribute to the observed spatial variation of the effect of temperature.

## METHODS

### Study population

We included inpatient hospital admissions from COPD in England during 2007–2018 as retrieved from Hospital Episode Statistics data held by the UK Small Area Health Statistics Unit, provided by the Health and Social Care Information Centre. Age, postcode of residence at time of the hospitalisation and date of hospitalisation were available for each record. We focused only on admissions with acute exacerbation of COPD as primary diagnosis. We investigated the following diagnostic groups: J40–44 according to the International Classification of Disease V.10.[13] The analysis is restricted to June, July and August.

### Exposure

Daily minimum and maximum temperatures were available at 1 km×1 km resolution from the UK Met Office with methods described elsewhere.[14] In brief, the daily temperature in each grid cell was estimated based on inverse-distance-weighted interpolation of monitoring data, also accounting for latitude and longitude, elevation, coastal influence and proportion of urban land use. To assign daily temperature to health records, the postcode centroids of each patient were spatially linked to the 1 km×1 km grid cell, applying a 100 m fuzziness to the postcode location to fulfil governance requirements. We focused on daily maximum temperature, as we are interested in heat exposure, averaged over the day of hospitalisation and the preceding 2 days (lags 0–2 days) to estimate the cumulative health effects.[15–17]

### Covariates

We used hourly concentration of Ozone ($O_3$) and atmospheric particulate matter that has a diameter of less than 2.5 µm ($PM_{2.5}$), as retrieved from the unified model produced by the Met Office measured in $\mu g/m^3$.[18] The model outcome is then postprocessed to correct for bias using observational data.[18] For $O_3$, we calculated the daily mean of the 8 hours of maximum $O_3$, whereas for $PM_{2.5}$, the daily mean concentration. The geographical resolution of the air pollutants is 12 km×12 km for the years 2007–2011 and 2 km×2 km during 2012–2019. We adjusted for relative humidity (daily and at a 10 km×10 km grid) through a model that integrates Met Office data on daily observations from the meteorological stations and monthly nationwide data as retrieved from HadUK,[14] see online supplemental text S1.1. All covariates were included at lags 0–2 days, to match the exposure lags. $O_3$, $PM_{2.5}$ and relative humidity were included as linear terms in the model. We also accounted for the effect of national holidays through a dummy variable.

### Spatial effect modifiers

We selected these spatial effect modifiers based on consistency with the literature,[19] data availability in England and a priori hypotheses, see online supplemental text S1.3. As a measure of green space, we used the proportion of a region that is covered by green land such as woodland, agricultural land, grassland and other natural vegetated land as classified in the Land Cover Map 2015 (LCM V.15).[20]Deprivation is measured using the Index of Multiple Deprivation (IMD) 2015, as retrieved from the Ministry of Housing, Communities and Local Government.[21] We used the quintiles of IMD in our analysis. For these two modifiers, we selected the year 2015 as the most representative data point, among the ones available, for our study period. Urbanicity (predominantly rural, urban with significant rural and predominantly urban) is based on the Office for National Statistics classification in 2011 (the most recent year for which data was available at the time of analysis).[22] We also incorporated the average temperature during 2007–2018, as a measure of adaptation on higher temperatures.[23] Green space and average temperature were included as linear terms in the model. Due to power and computational considerations, all spatial effect modifiers were included at the lower tier local authority level (LTLA; online supplemental figure 1).

### Statistical methods

We used a time-stratified case-crossover design, commonly used for analysing the effect of transient exposures.[24 25] The temperature on the day of COPD hospitalisation (event day) is compared with the temperature on non-event days. In the case-crossover design, a case serves as its own control, thus, this design automatically controls for factors that do not vary or vary slowly over time, such as sex or deprivation. We selected non-event days on the same day of week and calendar month as the event day to avoid the overlap bias.[26] Thus, we could have maximum 4 non-event days per event day.

We modelled the effect of temperature on event compared with non-event days by specifying Bayesian hierarchical conditional Poisson models, with a fixed effect on the event/non-event day grouping.[19 27] We accounted for recurrent hospitalisations by adding a random effect on each patient. For the main analysis, we treated relative humidity and national holidays as confounders and, thus, adjusted for them, but we did not adjust for air pollutants because they were treated as mediators, see directed acyclic graph on online supplemental text S1.3.[28] As the effect of temperature on health is typically non-linear,[19] we used piecewise linear threshold models, to allow more flexible fits, but retain ease of interpretation. We considered nationwide thresholds, specified as the 50th, 55th …, 95th percentile of the daily temperatures. We selected the threshold based on the WAIC, a fully Bayesian estimate of predictive accuracy defined as the log pointwise posterior predictive density adjusted for overfitting by correcting for effective number of parameters, with smaller values indicating better fits.[29] We then ran additional models allowing the effect of heat exposure (temperatures above the threshold) to vary by sex (male and female), age (0–64, 65–74, 75+) and space (LTLA). We additionally included the air pollutants in these models to examine the sensitivity of the effect if the air pollutants were confounders. For the spatial effect modification, we used the Besag-York-Mollie prior that assumes local dependency among adjacent LTLAs.[30] We fitted this model with and without the spatial effect modifiers, while adjusting for confounders. The model is described in detail in the online supplemental text S1.2. Results are reported as medians and 95% CrI (CrI; 95% probability that the true values lie within this interval) of % increase in the hospitalisation risk for every 1°C increase in temperatures above the threshold[31]; additionally, we report posterior probabilities of a positive % increase. For the spatially varying risk, we also reported posterior probabilities that the % hospitalisation risk is larger than the average % hospitalisation risk.

### Population attributable fraction

To calculate the population attributable fraction, we extended[32] to incorporate the spatial dimension of the effect of heat exposure. We first calculated the cumulative heat exposure—COPD hospitalisation relative risk ($RR_s$) for the *s*th LTLA. We could then calculate the attributable fraction: $AF_s = (RR_s - 1)/RR_s$. Let $n_s$ be the number of hospitalisations at days above 23.2°C and $N_s$ the total number of hospitalisations, then $AF_s(n_s/N_s)$ is the population attributable fraction, that is, the number of COPD hospitalisations attributable to summer heat exposure. In our Bayesian formulation, we were able to propagate all the random variable-specific uncertainty in our estimates.

### Sensitivity analyses

We repeated the main analysis for the lags 0, 1 and 2 independently. We also used b-splines to model the temperature effect and examined the linearity assumption above the threshold.

All analyses are run in Numerical Inference for Hierarchical Models Using Bayesian and Likelihood Estimation.[33] The code for running the analysis is online available at https://github.com/gkonstantinoudis/COPDTempSVC.

## RESULTS

### Population

We retrieved 1 570 288 COPD hospital records during 2007–2018 in England. After removing the duplicated records, the ones with place of residence outside England, the ones not occurred in summer months and the ones for which we could not sample non-event days, we had 320 411 records available for the analysis (figure 1).

### Exposure, covariates and effect modifiers

The median maximum temperature across England has increased from 19.42°C in 2007 to 22.20°C in 2018 (online supplemental table S1). The median maximum temperature exposure is 20.91°C at lag 0 for event and 20.39°C non-event days, 20.97°C for event and 20.94°C for non-event days at lag 1, 20.92°C for event and 20.90°C for non-event days at lag 2°C and 20.93°C for event and 20.92°C for non-event days at lag 0–2 (online supplemental table S2). The distribution of the covariates across event and non-event days and the spatial distribution of the effect modifiers at the LTLA level is found in online supplemental table S2-5, and figure S2-5.

### WAIC analysis

In the model adjusted for relative humidity and national holidays, the 80th percentile of the temperature (23.2°C) was the threshold minimising the WAIC (online supplemental table S6). We found a 0.37% (95% CrI 0.09% to 0.65%) increase in the COPD hospitalisation risk for every 1°C increase in temperatures below 23.2°C (online supplemental table S6). In contrast, the effect above 23.2°C was higher, namely, 1.46% (95% CrI 1.19% to 1.71%) (online supplemental table S6). All subsequent analyses were conducted using the 80th percentile of the temperature as the threshold.

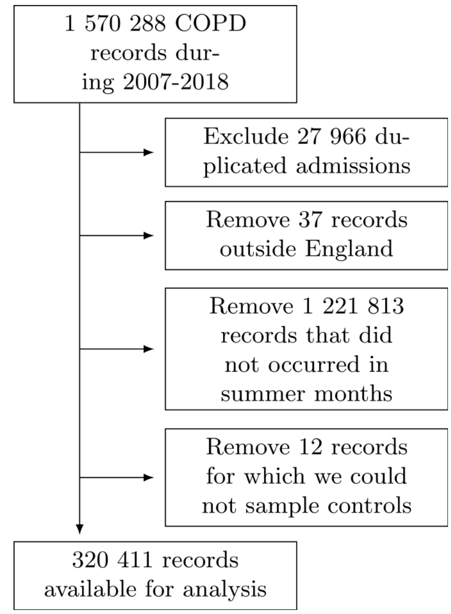



**Figure 1** Flowchart of COPD hospitalisations. COPD, chronic obstructive pulmonary disease.

### Age and sex effect modification

In the unadjusted models, the percentage of risk increase in hospitalisations for every 1°C increase above the threshold varies from 0.92% (95% CrI 0.25% to 1.63%) in women 64 years old or younger to 1.56% (95% CrI 0.94% to 2.20%) in women aged 65–74 (figure 2 and online supplemental table S6). After adjusting for relative humidity and national holidays, the effects are slightly higher varying from 1.14% (95% CrI 0.39% to 1.84%) in women 64 years old or younger to 1.75% (95% CrI 1.13% to 2.41%) in men 65–74 years old (Figure 2 and online supplemental table S7). Additionally adjusting for air pollution substantially reduces the observed effect (figure 2 and online supplemental table S7).

### Spatial effect modification

The spatial variation of the effect of heat exposure on COPD hospitalisations is shown in figure 3. The risk of COPD hospitalisation is less than 1.31% for every 1°C increase in heat exposure in South West, top left panel, figure 3. In contrast, populations in the South East are more vulnerable: the probability that the effect of heat exposure is larger than the national average estimate ranges between 0.6 and 1, top right panel (figure 3). After incorporating green space, deprivation, urbanicity and average temperature, the observed variation of the effect of temperature is slightly alleviated, bottom panels (figure 3).

We found weak evidence that populations in areas with higher proportions of green space, larger average temperature and higher level of urbanicity are more resilient to COPD hospitalisations due to heat exposure, table 1. If we increase an LTLA's proportion of green space by 1%, the spatial effect of the heat exposure changes by −1.46% (95% CrI −6.99% to 4.39%), table 1. For every 1°C increase in the average temperature per LTLA, the spatial effect of the heat exposure changes by −0.41% (95% CrI −1.49% to 0.71%), table 1. The spatial effect of heat

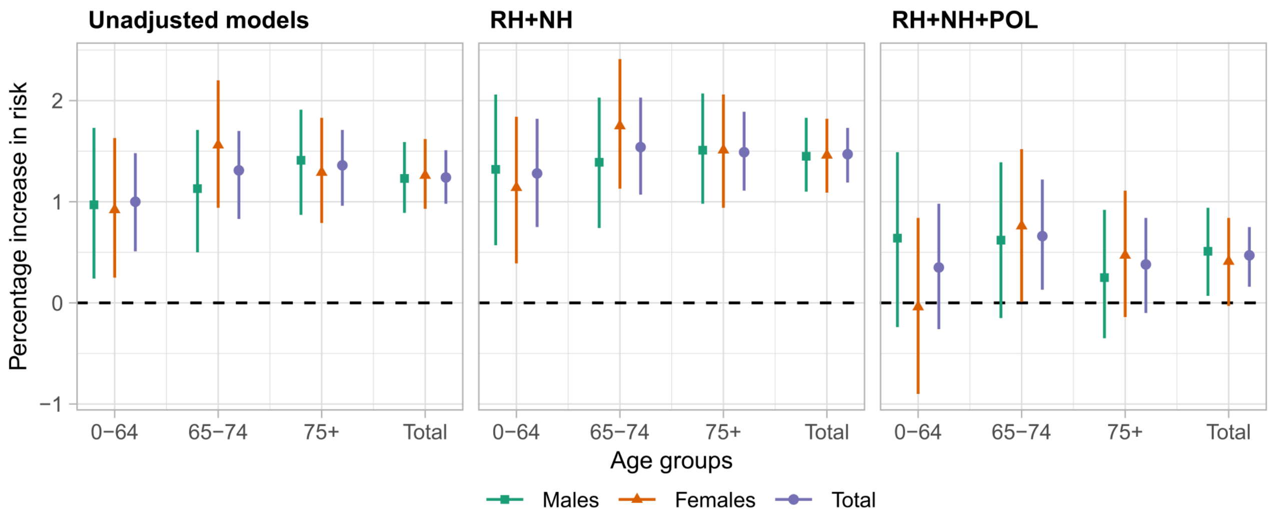



**Figure 2** Percentage risk of chronic obstructive pulmonary disease (COPD) hospitalisation for every 1°C increase in the temperatures above 23.2°C during the summer months between 2007 and 2018, for the unadjusted (left panel), the model adjusted for relative humidity (RH) and national holidays (NL) (mid panel) and the model additional adjusted for air pollution (POL) (right panel). Results are stratified by age (0–64, 65–74, 75+, total) and sex (male, female, total).

exposure in urban LTLAs with significant rural and predominantly urban LTLAs changes by −0.79% (95% CrI −3.10% to 1.51%) and −1.57% (95% CrI −4.16% to 0.96%), respectively, compared with predominantly rural LTLAs, table 1.

### Population attributable burden

We found that 1 851 (95% CrI 1 576 to 2 079) COPD hospitalisations were associated with temperatures above 23.2°C annually. This accounts for 7.8% (95% CrI 6.7% to 8.8%) of the total COPD hospitalisations during the summer months from 2007 to 2019. The proportion of COPD hospitalisations attributable to temperatures above the threshold has a clear spatial structure and is more than 8% in East Midlands, East of England, London and South East, while it is below 5% in the South West (figure 4).

### Sensitivity analysis

The lag with the highest influence was lag 1 with the risk of COPD hospitalisation being 1.37% (95% CrI 1.14% to 1.58%)

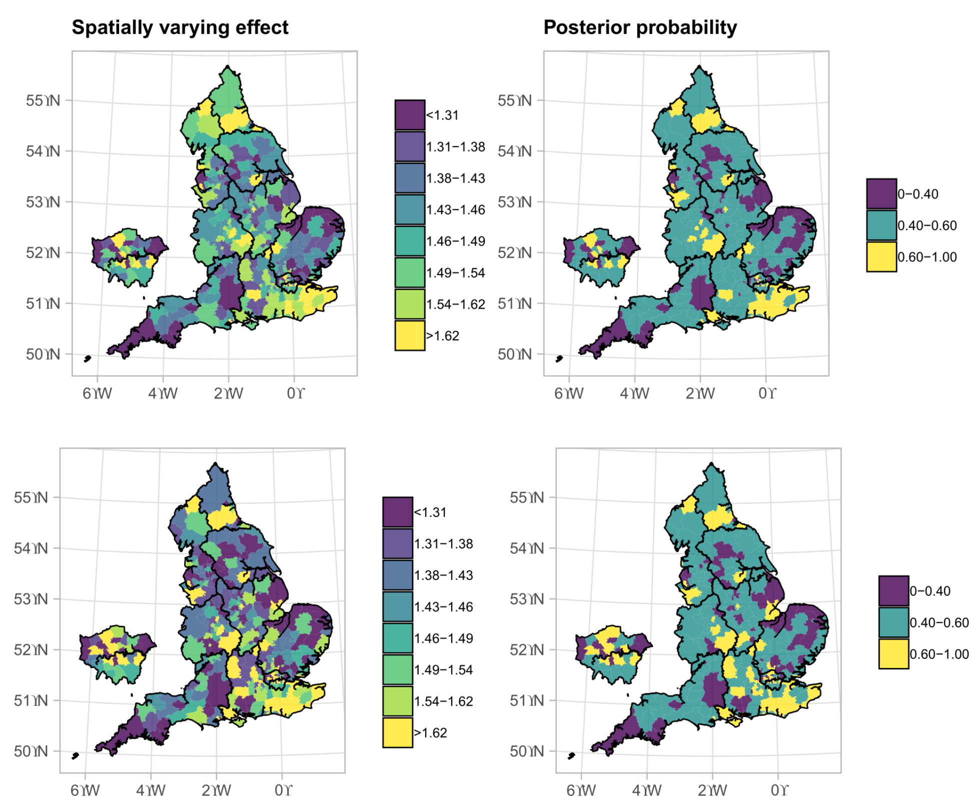



**Figure 3** Median spatial chronic obstructive pulmonary disease (COPD) hospitalisation risk for every 1°C increase in the temperatures above 23.2°C and posterior probability that the risk is larger than the overall risk in England during the summer months between 2007 and 2018. The top panels refer to the model without incorporating contextual characteristics, whereas the panels below otherwise. All models were fully adjusted.

**Table 1** Median, 95% credible intervals of the percentage change of the heat exposure-related spatial hospitalisation risk due to green space, average temperature, index of multiple deprivation and urbanicity and probability that this percentage change is higher than 0

| Effect modifier | Percentage change | Pr (% change >0)* |
|---|---|---|
| Green space† | −1.46 (−6.99 to 4.39) | 0.30 |
| Average temperature‡ | −0.41 (−1.49 to 0.71) | 0.22 |
| IMD§ | | |
| Q1 | * | |
| Q2 | 0.81 (−1.16 to 3.08) | 0.78 |
| Q3 | 1.57 (−0.76 to 4.06) | 0.91 |
| Q4 | 0.75 (−1.68 to 3.36) | 0.71 |
| Q5 | 1.62 (−1.31 to 4.49) | 0.85 |
| Predominantly rural | * | |
| Urban with significant rural | −0.79 (−3.10 to 1.51) | 0.25 |
| Predominantly urban | −1.57 (−4.16 to 0.96) | 0.12 |

*Posterior probability that the percentage change is larger than zero.
†Green space is the proportion of a region covered by green land such as woodland, agricultural land, grassland and other natural vegetated land.
‡The average temperature is the mean summer temperature per LTLA during 2007–2018°C.
§Index of multiple deprivation. IMD is calculated based on the following domains: (a) income, (b) employment, (c) education, skills and training, (d) health and disability, (e) crime, (f) barriers to housing and services and (g) living environment deprivation. Q1 denotes the most deprived areas, whereas Q5 the least deprived.
IMD, Index of Multiple Deprivation; LTLA, lower tier local authority.

for every 1°C increase in heat exposure. For lag 0 and lag 2, the point estimate was still positive, but lower in magnitude, 0.71% (95% CrI 0.50% to 0.93%) and 1.01% (95% CrI 0.78% to 1.24%), respectively, likely due to the correlation with temperatures at lag 1. The linearity assumption above the 23.2°C threshold looks reasonable (online supplemental figure S6).

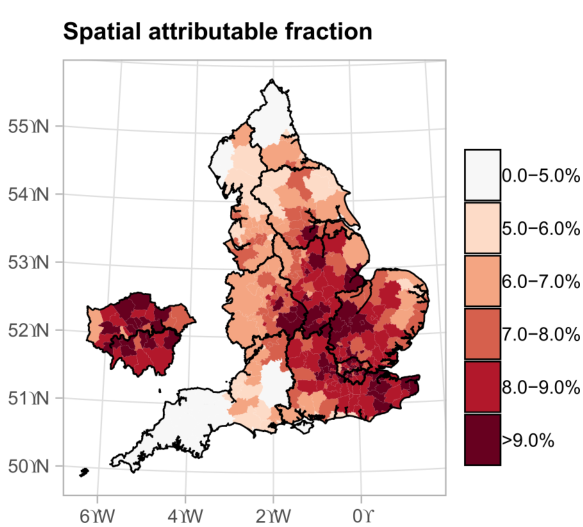



**Figure 4** The percentage of chronic obstructive pulmonary disease (COPD) hospitalisations by lower tier local authorities attributed to exposure to summer temperatures above 23.2°C during 2007–2018 in England. This effect assumes a causal relationship between heat exposure and COPD hospitalisation risk. The island on the left is a zoomed version of London.

## DISCUSSION

This is the first nationwide case-crossover study in England investigating the short-term effects of heat exposure on COPD hospitalisation. After accounting for confounding, the results indicate that for every 1°C increase in heat exposure the COPD hospitalisation risk increases by 1.47% (95% CrI 1.19% to 1.73%), with evidence that $PM_{2.5}$ and $O_3$ mediate this relationship. We found weak evidence of an effect modification by sex and age. The attributable burden of heat exposure has a clear spatial structure, with areas in East Midlands, East of England, London and South East affected the most. Assuming a causal relationship, 7.8% (95% CrI 6.7% to 8.8%) of COPD hospitalisations could be attributed to heat exposure during the summer months between 2007 and 2018.

The main strength of our study is the availability of postal codes, exploiting the highest spatial resolution available for linkage with the exposure and confounding factors. Such geographical resolution is expected to minimise misclassification, resulting from any spatial misalignment between the outcome and exposure/confounder. The availability of individual data for the outcome also minimises ecological bias,[12] while guaranteeing high statistical power due to the population-based nature of the study. We ascertained hospital records from NHS digital covering almost all hospitalisation occurred in the public sector in England during 2007–2018.

Our study has some limitations. First, residential temperature does not reflect the actual temperature exposure of an individual, as individuals are exposed to different temperatures in the course of the day. In addition to this, the outdoor temperature, as provided by Met Office, does not reflect the actual temperature exposure inside the house. Nevertheless, in line with most of the studies in this field and given the lack of more precise individual exposure data, we used residential temperature outdoors as a proxy for the individual exposure. To allow for flexible fits, we used a linear threshold model. More complex relationships may need multiple thresholds; however, the WAIC analysis suggested that the linearity assumption suffices. Although we adjusted for the main COPD hospitalisation environmental contributors, we could not evaluate other potential confounders (eg, seasonal allergies and pollen counts) due to the lack of available data. Additionally, exposure to other air pollutants, such as $NO_2$, $SO_2$, might also confound the observed relationship; we decided to adjust for $PM_{2.5}$ and $O_3$ as they seem to have a larger impact on COPD hospitalisation and to avoid potential collinearity with other pollutants.

Our results can be compared with studies examining COPD hospital admissions and ambient temperatures during the hottest months.[6 11 34 35] Our study is in line with a US study including 12.5 million participants that found a 4.7% (95% CrI 3.9% to 5.5%) increase in the COPD hospitalisation rate at lag 0 for every 5.6°C increase in the average daily temperature during May–September.[6] Our study is also in line with a case-crossover study in Brazil that reported a 5% (95% CrI 4% to 6%) increase in the hospitalisation odds for every 5°C increase in the average temperature (0–3 lags) during the 4 hottest months.[11] In contrast, a study in New York reported a 7.64% increase in the risk of COPD admissions for each 1°C increase in daily mean apparent temperature above 32°C.[35] A study in 12 European cities, reported a 4.5% (95% CrI 1.9 to 7.3) and 3.1% (95% CrI 0.8 to 5.5) increase in total respiratory admissions (the majority being COPD) in Mediterranean and North-Continental cities, respectively, for every for each 1°C increase in the maximum apparent temperature (lag 0–3 days) above the 90th percentile.[36] A study in Taiwan reported negative correlation between the average daily temperature and emergency admissions with COPD, but a 14% increase in the emergency COPD admissions when the diurnal temperature range is larger than 9.6°C.[34]

We found weak evidence of an effect modification by age and sex, but discrepancies in vulnerability in space. A previous study in Brazil reported higher COPD hospitalisation odds for women and the older people.[11] In the models adjusted for relative humidity and national holidays, in line with a previous study in the USA,[6] the age group 65–74 was the most vulnerable. Some spatial variability by regions or counties was also observed in previous studies in Brazil and the USA, potentially due to socioeconomic characteristics or exposure to higher average summer temperatures.[6,11] In our study, green space, average temperature, deprivation and urbanicity explained some of the observed variation in the observed spatial vulnerabilities, the evidence of an effect was, however, inconclusive.

Some discrepancies of our results compared with previous studies can have multiple explanations. Previous studies reporting higher effect estimates had available coarser geographical resolution (city or county level), leading to inadequate adjustment for confounding, as confounders, can vary in high geographical resolution.[11,34,36,37] Differences in the definition of the outcome can also lead to the discrepancies as previous studies have used the apparent temperature,[35,36] or diurnal temperature range,[34] while others, more in line with our approach, the daily mean.[6,11] Decisions regarding the selection of the temperature threshold, the warm-season months and the lags can also partly explain the observed difference in the effect estimates. Most previous studies adjusted for air pollution,[6,35,36] while we did not, as we assumed that air pollution is a mediator[28]; when we added air pollution to model the effect of heat exposure was much reduced.

Acute COPD episodes are associated not only with airways and systemic inflammation but also with cardiovascular comorbidity and may be triggered by exposures to heat.[36] Exposure to ambient heat can lead to heat dissipation through hyperventilation and may trigger dynamic hyperinflation and dyspnoea in patients with pre-existing COPD.[6,11] The higher risk of COPD hospitalisation in the 65–74 age group observed in our study could be explained by the inability of this frail population to dissipate excess heat through circulatory adjustment, and exposure to extreme temperatures increases their risk of developing pulmonary vascular resistance secondary to peripheral pooling of blood or hypovolemia.[36] In addition, older populations are of higher risk to have cardiovascular comorbidities, which are hypothesised to increase the risk of COPD hospitalisations associated with heat exposure. Nevertheless, such evidence is inconclusive.[36] We also reported a weak protective effect of higher average temperatures, arguing towards protective adaptation to heat, possibly related to differences in housing stock or behaviour during hot weather.[11] We observed weak evidence of increased resilience in populations in more deprived areas and in areas with higher degrees of urbanicity. Although this evidence is inconclusive, potential factors that could confound the observed effect include differences in demographics, for instance, ethnicity.

Previous studies examining future trends in COPD, population demographics and temperature changes have predicted a higher COPD prevalence, a raise in the average age of the population and increased global temperatures.[38–40] Resources should be allocated to support the preparedness and resilience of public health systems, for instance, through developing or expanding heat-health alerts, to challenge the increasing heat exposure-related COPD hospitalisation burden.

**Twitter** Garyfallos Konstantinoudis @konstantinoudis

**Acknowledgements** We thank Hima Daby, Gajanan Natu, Eric Johnson and Bethan Davies for their help with data acquisition, storage, preparation and governance. All authors acknowledge infrastructure support for the Department of Epidemiology and Biostatistics provided by the NIHR Imperial Biomedical Research Centre (BRC). Hospital Episode Statistics data are copyright © 2021, reused with the permission of NHS Digital. All rights reserved. The Hospital Episode Statistics data were obtained from NHS Digital.

**Contributors** GK and MB conceived the study. MB supervised the study. GK developed the initial study protocol and discussed it with MB, CM, AMV-C, JB and AG. GK developed the statistical model, prepared the covariate data and led the acquisition of hospitalisation data. MB validated the code. GK ran all the analysis and wrote the initial draft. All the authors contributed in modifying the paper and critically interpreting the results. All authors read and approved the final version for publication. GK is responsible for the overall content as the guarantor.

**Funding** GK is supported by an MRC Skills Development Fellowship [MR/T025352/1]. MB is supported by a National Institutes of Health, grant number [R01HD092580-01A1]. Infrastructure support for this research was provided by the National Institute for Health Research Imperial Biomedical Research Centre (BRC). AG is supported by the Medical Research Council-UK (Grant ID: MR/R013349/1), the Natural Environment Research Council UK (Grant ID: NE/R009384/1) and the European Union's Horizon 2020 Project Exhaustion (Grant ID: 820655). The work was partly supported by the MRC Centre for Environment and Health, which is funded by the Medical Research Council (MR/S019669/1, 2019-2024). JB gratefully acknowledges funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 865564 (European Research Council Consolidator Grant EARLY-ADAPT), support from the Spanish Ministry of Science and Innovation through the 'Centro de Excelencia Severo Ochoa 2019-2023' Program (CEX2018- 000806-S), and support from the Generalitat de Catalunya through the CERCA Program. The work of the UK Small Area Health Statistics Unit is overseen by Public Health England (PHE) and funded by PHE as part of the MRC-PHE Centre for Environment and Health also supported by the UK Medical Research Council, Grant number: MR/L01341X/1), and the National Institute for Health Research (NIHR) through its Health Protection Units (HPRUs) at Imperial College London in Environmental Exposures and Health and in Chemical and Radiation Threats and Hazards, and through Health Data Research UK (HDR UK). This paper does not necessarily reflect the views of Public Health England, the National Institute for Health Research or the Department of Health and Social Care.



**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the study, was covered by national research ethics approval from the London-South East Research Ethics Committee—reference 17/LO/0846. Data access to confidential patient information without consent was covered by the Health Research Authority—Confidentiality Advisory Group under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support')—HRA CAG reference: 20/CAG/0028.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** SAHSU does not have permission to supply data to third parties. For reproducibility purposes, we have simulated data and provided the code used for the analysis in https://github.com/gkonstantinoudis/COPDTempSVC.

**ORCID iDs**
Garyfallos Konstantinoudis http://orcid.org/0000-0001-7493-9334
Cosetta Minelli http://orcid.org/0000-0001-9166-3958

## REFERENCES

1 England N. *Overview of potential to reduce lives lost from chronic obstructive pulmonary disease (COPD)*. Department of Health, 2014.
2 SorianoJB, KendrickPJ, PaulsonKR, *et al*. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet Respir Med* 2020;8:585–96.
3 Alqahtani JS, Njoku CM, Bereznicki B, *et al*. Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis. *Eur Respir Rev* 2020;29. doi:10.1183/16000617.0166-2019. [Epub ahead of print: 30 Jun 2020].
4 DeVries R, Kriebel D, Sama S. Outdoor air pollution and COPD-Related emergency department visits, hospital admissions, and mortality: a meta-analysis. *COPD* 2017;14:113–21.
5 De Sario M, Katsouyanni K, Michelozzi P. Climate change, extreme weather events, air pollution and respiratory health in Europe. *Eur Respir J* 2013;42:826–43.
6 Anderson GB, Dominici F, Wang Y, *et al*. Heat-Related emergency hospitalizations for respiratory diseases in the Medicare population. *Am J Respir Crit Care Med* 2013;187:1098–103.
7 Astrom DO, Schifano P, Asta F. The effect of heat waves on mortality in susceptible groups: a cohort study of a Mediterranean and a northern European City. *Environ Health-Glob* 2015;14.
8 Zhao Q, Li S, Coelho MdeSZS, *et al*. Ambient heat and hospitalisation for COPD in Brazil: a nationwide case-crossover study. *Thorax* 2019;74:1031–6.
9 Bobb JF, Obermeyer Z, Wang Y, *et al*. Cause-Specific risk of hospital admission related to extreme heat in older adults. *JAMA* 2014;312:2659–67.
10 Monteiro A, Carvalho V, Oliveira T, *et al*. Excess mortality and morbidity during the July 2006 heat wave in Porto, Portugal. *Int J Biometeorol* 2013;57:155–67.
11 Zhang Y, Liu X, Kong D. Effects of ambient temperature on acute exacerbations of chronic obstructive pulmonary disease: results from a time-series analysis of 143318 hospitalizations (vol 15, PG 213, 2020). *Int J Chronic Obstr* 2021;16:2129–31.
12 Wakefield J. Ecologic studies revisited. *Annu Rev Public Health* 2008;29:75–90.
13 Rothnie KJ, Müllerová H, Thomas SL, *et al*. Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records. *Clin Epidemiol* 2016;8:771–82.
14 Hollis D, McCarthy M, Kendon M, *et al*. HadUK-Grid—A new UK dataset of gridded climate observations. *Geosci Data J* 2019;6:151–9.
15 Gasparrini A, Armstrong B, Kovats S, *et al*. The effect of high temperatures on cause-specific mortality in England and Wales. *Occup Environ Med* 2012;69:56–61.
16 Hajat S, Armstrong BG, Gouveia N, *et al*. Mortality displacement of heat-related deaths: a comparison of Delhi, São Paulo, and London. *Epidemiology* 2005;16:613–20.
17 Hajat S, Kovats RS, Lachowycz K. Heat-related and cold-related deaths in England and Wales: who is at risk? *Occup Environ Med* 2007;64:93–100.
18 Neal LS, Agnew P, Moseley S, *et al*. Application of a statistical post-processing technique to a gridded, operational, air quality forecast. *Atmos Environ* 2014;98:385–93.
19 Bennett JE, Blangiardo M, Fecht D, *et al*. Vulnerability to the mortality effects of warm temperature in the districts of England and Wales. *Nat Clim Chang* 2014;4:269–73.
20 Rowland C, Morton D, Carrasco Tornero L. Land cover MAP 2015 (1km percentage aggregate class, GB) 2017.
21 McLennan D, Noble S, Noble M. *The English indices of deprivation 2019: technical report*, 2019.
22 Statistics DR. *The 2011 rural-urban classification for output areas in England*. 2018.
23 Arbuthnott K, Hajat S, Heaviside C, *et al*. Changes in population susceptibility to heat and cold over time: assessing adaptation to climate change. *Environ Health* 2016;15 Suppl 1:33.
24 Lu Y, Zeger SL. On the equivalence of case-crossover and time series methods in environmental epidemiology. *Biostatistics* 2007;8:337–44.
25 Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 2017;185:1174–83.
26 Janes H, Sheppard L, Lumley T. Overlap bias in the case-crossover design, with application to air pollution exposures. *Stat Med* 2005;24:285–300.
27 Armstrong BG, Gasparrini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Med Res Methodol* 2014;14:122.
28 Buckley JP, Samet JM, Richardson DB. Commentary: does air pollution confound studies of temperature? *Epidemiology* 2014;25:242–5.
29 Watanabe S. Asymptotic equivalence of Bayes cross validation and widely applicable information criterion in singular learning theory. *J Mach Learn Res* 2010;11:3571–94.
30 Besag J, York J, Molli A. Bayesian image restoration, with two applications in spatial statistics. *Ann Inst Stat Math* 1991;43:1–20.
31 Navidi W, Weinhandl E. Risk set sampling for case-crossover designs. *Epidemiology* 2002;13:100–5.
32 Mansournia MA, Altman DG. Population attributable fraction. *BMJ* 2018;360:k757.
33 de Valpine P, Turek D, Paciorek CJ, *et al*. Programming with models: writing statistical algorithms for general model structures with NIMBLE. *J Comput Graph Stat* 2017;26:403–13.
34 Liang W-M, Liu W-P, Kuo H-W. Diurnal temperature range and emergency room admissions for chronic obstructive pulmonary disease in Taiwan. *Int J Biometeorol* 2009;53:17–23.
35 Lin S, Luo M, Walker RJ, *et al*. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. *Epidemiology* 2009;20:738–46.
36 Michelozzi P, Accetta G, De Sario M, *et al*. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. *Am J Respir Crit Care Med* 2009;179:383–9.
37 Konstantinoudis G, Padellini T, Bennett J, *et al*. Long-term exposure to air-pollution and COVID-19 mortality in England: a hierarchical spatial analysis. *Environ Int* 2021;146:106316.
38 Meehl GA, Stocker TF, Collins WD. *Global climate projections. Chapter 10*, 2007.
39 Nash A. *National population projections: 2018-based*. Office for National Statistics, 2019.
40 McLean S, Hoogendoorn M, Hoogenveen RT, *et al*. Projecting the COPD population and costs in England and Scotland: 2011 to 2030. *Sci Rep* 2016;6:31893.

# Online Supplement: "Ambient heat exposure and COPD hospitalisations in England: A nationwide case-crossover study during 2007-2018."

Garyfallos Konstantinoudis[1,*], Cosetta Minelli[2], Ana Maria Vicedo Cabrera[3,4], Joan Ballester[5], Antonio Gasparrini[6,7,8], and Marta Blangiardo[1]

[1] *MRC Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK*

[2] *National Heart and Lung Institute, Imperial College London, London, United Kingdom*

[3] *Institute of Social and Preventive Medicine, University of Bern, Switzerland*

[4] *Oeschger Center for Climate Change Research, University of Bern, Bern, Switzerland*

[5] *ISGlobal, Barcelona, Spain.*

[6] *Department of Public Health Environments and Society, London School of Hygiene Tropical Medicine, London, UK*

[7] *Centre for Statistical Methodology, London School of Hygiene Tropical Medicine, London, UK*

[8] *Centre on Climate Change and Planetary Health, London School of Hygiene Tropical Medicine, London, UK*

[*] Corresponding author. Email: g.konstantinoudis@imperial.ac.uk



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

# Contents



# List of Tables





Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

## List of Figures

# S1 Text

## S1.1 Modelling relative humidity

### S1.1.1 Model

Data on relative humidity in England during 1862-2019 is available nationwide from MetOffice through the HadUK-Grid product (`https://catalogue.ceda.ac.uk/`). The spatial resolution of HadUK-Grid can vary from 1km×1km to 60km×60km, nevertheless the highest temporal resolution available are months. MetOffice also provides daily data on relative humidity during 1853-2019 for each meteorological station through the Met Office Integrated Data Archive System (MIDAS) product (`https://catalogue.ceda.ac.uk/`). To retrieve daily relative humidity data nationwide and not only at the meteorological stations, we employ the following modelling framework:

Let $Y_{jkt}(s)$ be the arcsin transformation of the relative humidity from MIDAS and $X_{kt}(s)$ the nationwide relative humidity from HadUK-Grid in location $s$, day $j$, month $k$ and year $t$:

$$
\begin{aligned}
Y_{jkt}(s) &\sim \text{Normal}\big(\mu_{jkt}(s), \sigma_1\big) \\
\mu_{jkt}(s) &= \beta_0 + bX_{kt}(s) + \gamma_j + \omega_t + u(s) \\
\gamma_j &\sim \text{AR1}(\sigma_2, \rho) \\
\omega_t &\sim \text{Normal}(0, \sigma_3^2) \\
u(s) &\sim \text{GMRF}(\sigma_4, \phi) \\
\sigma_1, \sigma_2, \sigma_3, \phi, \rho &\sim \text{PCpriors} \\
\beta_0, b &\sim N(0, \delta)
\end{aligned} \tag{1}
$$

wheres $\mu_{jkt}(s)$ and $\sigma_1$ be the variables of the normal distribution, $\beta_0$ and $b$ the regression coefficients, $\gamma_j$ a random effect capturing the daily temporal trends, $\omega_t$ a random effect capturing the yearly trends, $u(s)$ the spatial autocorrelation term (based on the Stochastic Partial Differential Equation Approach [1]) and $\sigma_2, \sigma_3, \sigma_4, \rho,$ and $\phi$ the corresponding variance and correlation hyperparameters.

The specification of the PCpriors of the hyperparameter is the following: for $\sigma_1$ we specify that the probability of observing arcsin relative humidity larger than 10 is 0.10. Similarly for $\sigma_2$ and $\sigma_3$, we specify that the probability of observing arcsin relative humidity larger than 1 due to the temporal trends is 0.10. For the correlation parameter $\rho$ of the autoregressive process of order 1, we select a probability of 0.5 for correlations of 0.5 reflecting our lack of knowledge with respect to the correlation structure in the data. For the Gauss Markov Random Field



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

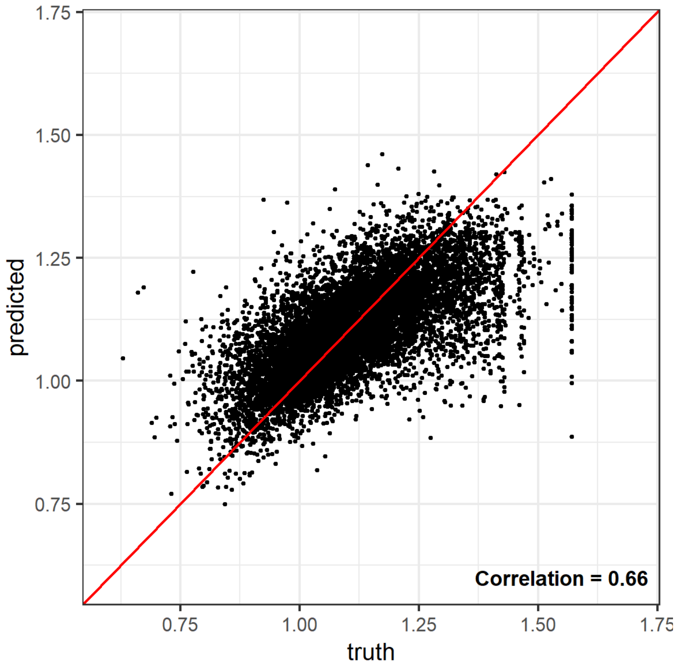



Figure 1.1. Predicted versus true values of the arcsin relative humidity for a sample of 10,000 values in the summer months during 2007-2018 in England.

(GMRF) term we select the standard deviation hyperparameter $\sigma_4$ as in the temporal case, whereas for the range parameter $\phi$ we select ranges larger that 10km with probability of 0.5. For more information about the PCpriors and their mathematical formulation see [2, 3]. Lastly, $\delta$ was fixed to 0.001 for the intercept, whereas to 0.1 for b.

#### S1.1.2 Cross-validation

We performed the following leave one out cross validation scheme: Let N be the total number of meteorological stations during 2007-2019, first we divided N randomly by 10 groups, and for each (out of the 10) step we excluded the entire time series of the group of the randomly sampled N/10 meteorological stations. Figure 1.1 shows the results of the cross validation, and in particular a scatterplot between the observed and predicted values. The correlation between truth and predicted is relatively high, ie 0.66, indicating that our model have good predictive ability.

#### S1.1.3 Results

Table 1.1 shows the results of Model 1, Figure 1.3 shows the mean of the daily median of relative humidity in 2013 for the 3 summer months. The maps show that areas around London had lower relative humidity during the summer months in 2013. The relative humidity seems to be consistently higher in South West during the

Table 1.1. Mean, standard deviation, median and 94% credible intervals of the intercept, the covariate and the hyperparameters of Model 1.

| Random variables | mean | sd | median | 2.5% | 97.5% |
|---|---|---|---|---|---|
| $\beta_0$ | 0.144 | 0.009 | 0.144 | 0.126 | 0.161 |
| b | 0.012 | 0.000 | 0.012 | 0.012 | 0.012 |
| $1/\sigma_1^2$ | 101 | 0.285 | 101 | 101 | 102 |
| $1/\sigma_2^2$ | 172 | 8.30 | 172.26 | 156.30 | 189 |
| $\rho$ | 0.386 | 0.028 | 0.384 | 0.332 | 0.440 |
| $1/\sigma_3^2$ | 68.1 | 26.3 | 63.8 | 29.8 | 131 |
| $1/\sigma_4^2$ | 0.063 | 0.007 | 0.063 | 0.052 | 0.079 |
| $\phi$ | 8,384 | 1,557 | 8,352 | 5,493 | 11,600 |

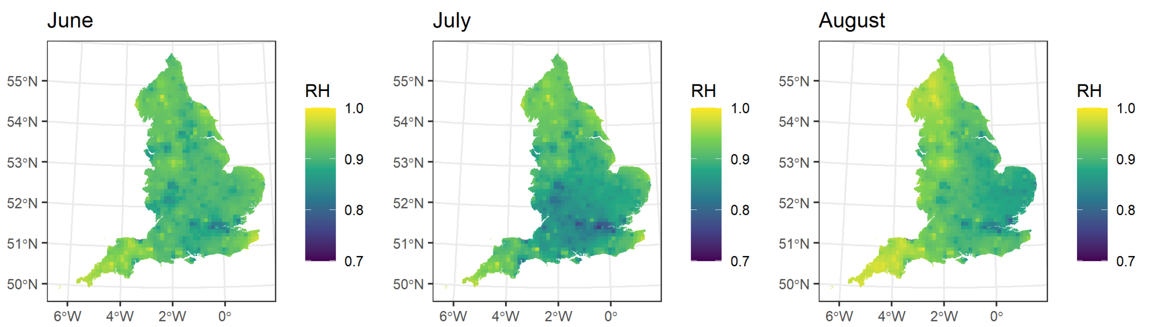



Figure 1.3. Maps of mean of median relative humidity by summer month in 2013.

summer 2013.

## S1.2 Statistical analysis

In this subsection we will introduce the mathematical notation of the models used in the main analysis.

### S1.2.1 WAIC analysis

Let $Y_{tjk}$ be the case-control identifier for the chronic obstructive pulmonary disease (COPD) hospitalisation for the event (case or control) at time $t$, in the $j$-th case-control group and $k$-th patient. Let also $X_1t$ be the temperature at $t$ event $Z_{1t}, Z_{2t})$ a vector denoting the different confounders (relative humidity and holiday) at the $t$-th time point. Then:

$$\begin{aligned}
Y_{tjk} &\sim \text{Poisson}(\mu_{itjk}) \\
\log(\mu_{tjk}) &= \alpha_1 I(X_{1t} < c_l) X_{1t} + \alpha_2 I(X_{1t} \geq c_l) X_{1t} + \sum_{m=1}^{2} \beta_m Z_{mt} + u_j + w_k \\
u_j &\sim N(0, 100) \\
w_k &\sim N(0, \sigma_1^2) \\
a_1, a_2, \beta_1, \ldots \beta_4 &\sim N(0, 1) \\
\sigma_1 &\sim \text{Gamma}(1, 2)
\end{aligned}$$

In the above equation, $a_1$ is the effect of temperatures lower than the threshold $c$, $a_2$ is the effect of temperatures higher or equal than the threshold $c$, $I(\cdot)$ an indicator function, $\beta_1$, $\beta_2$ the effects of the confounding, $u_j$ a fixed effect on the $j$-th case control group and $w_k$ a random effect to account for recurrent hospitalisations. The normal distributions read N(mean, variance). We ran the above model for the different temperature thresholds $c_l$ for $l = 1, 2, \ldots, 10$ representing the 50-th, 55-th, … 95-th percentiles of the temperature and computed the WAIC [4]. Removing the term $\sum_{m=1}^{2} \beta_m Z_{mi}$ and the corresponding priors of $\beta_1, \beta_2$ results in the unadjusted models.

### S1.2.2 Age-sex effect modification

Let $c_*$ be the temperature threshold that minimises the WAIC from Step 1. Expanding the indices of the above model results in the models for the age and sex effect modification. Let $g$ be the age-sex index representing individuals aged $0 - 64$, $65 - 74$ and $> 75$ years old or the total group and males, females or the total group.



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

The above model can be rewritten as follows:

$$\begin{aligned}
Y_{tjkg} &\sim \text{Poisson}(\mu_{tjkg}) \\
\log(\mu_{tjkg}) &= \alpha_1 I(X_{1tg} < c_*)X_{1tg} + \alpha_2 I(X_{1tg} \geq c_*)X_{1tg} + \sum_{m=1}^{2} \beta_m Z_{mtg} + u_j + w_k \\
u_j &\sim N(0, 100) \\
w_k &\sim N(0, \sigma_1^2) \\
a_1, a_2, \beta_1, \dots \beta_5 &\sim N(0, 1) \\
\sigma_1 &\sim \text{Gamma}(1, 2)
\end{aligned}$$

### S1.2.3 Spatial effect modification

On the third step of the analysis we let the coefficient of the temperature higher than $c_*$ vary by lower tier local authorities (LTLA). Let $H_{1i}, \dots, H_{8i})$ be the spatial effect modifiers representing the green space, the quintiles of deprivation, the urbanicity categories and the average temperature in the $s$-th LTLA. We can write:

$$\begin{aligned}
Y_{tjk} &\sim \text{Poisson}(\mu_{tjk}) \\
\log(\mu_{tjk}) &= \alpha_1 I(X_{1t} < c_*)X_{1t} + \alpha_{2s} I(X_{1t} \geq c_*)X_{1t} + \sum_{m=1}^{2} \beta_m Z_{mt} + u_j + w_k \\
\alpha_{2s} &= \alpha_2 + \sum_{q=1}^{8} \gamma_q H_{sq} + v_s + b_s \\
w_k &\sim N(0, \sigma_1^2) \\
v_s &\sim N(0, \sigma_2^2) \\
b_s | b_{-s} &\sim N\left(\frac{\sum_{s\sim r} w_{rs} b_s}{\sum_{s\sim r} w_{rs}}, \frac{\sigma_3^2}{\sum_{s\sim r} w_{rs}}\right) \\
u_j &\sim N(0, 100) \\
a_1, \beta_1, \dots \beta_4, \gamma_1, \dots, \gamma_8 &\sim N(0, 1) \\
a_2 &\sim N(0.0425, 0.0039^2) \\
\sigma_1, \sigma_2, \sigma_3 &\sim \text{Gamma}(1, 2).
\end{aligned}$$

$w_{rs}$ are neighborhood weights and are 1 when the $r$ and $s$ LTLAs are neighboring (we write $s \sim r$) and 0 otherwise, $\gamma_1, \dots, \gamma_8$ are the effects of the spatial effect modifiers and the $v_s + b_s$ the BYM prior [5]. Unstructured overdispersion is captured on $v_s$ and spatial autocorrelation on $b_s$. The hyperparameters $\sigma_2^2, \sigma_3^2$ are the variance



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

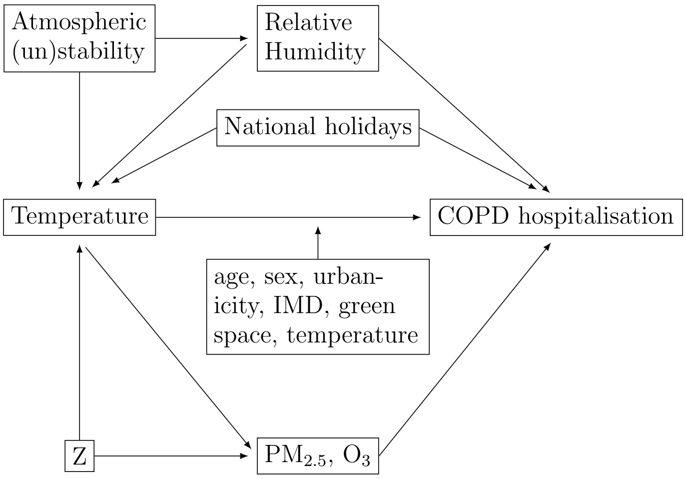
parameters of the unstructured and structured random effects. Removing the term $\sum_{q=1}^{8} \gamma_q H_{sq}$ and the corresponding priors of $\gamma_1, \ldots, \gamma_8$ results in the model without the adjustment for spatial effect modifiers, while allowing the effect of warm temperatures to vary in space.



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

### S1.3 Confounders/ Mediators/ Effect modifiers

Directed acyclic graph for the relationship between temperature and hospitalisations for chronic obstructive pulmonary disease (COPD).




- **Relative humidity**: Previous studies has reported an association between relative humidity and COPD hospitalisations [6]. Relative humidity and temperature are both affected by factors such as atmospheric (un)stability and climate dynamics. Nevertheless, (soil and air) humidity determines the fraction of radiation (coming from the Sun and absorbed mainly by the surface) that is transformed into latent and sensible heat. Latent heat is generated due to phase transition of water, e.g., evaporation. The remaining radiation is transformed into sensible heat, leading to temperature changes [7]. Thus, relative humidity is likely a confounder.

- **National holidays**: can affect individual behaviours with respect to seeking health care services but also through other behaviours that can affect the temperature. Thus, holidays can be a potential confounder [8].

- **Air-pollution**: Previous studies have reported an association between short term exposure to $PM_{2.5}$ and $O_3$, and COPD hospitalisations [9, 10]. Thus these air-pollutants are expected to be correlated with COPD hospitalisations. Although temperature and air-pollutants have their own causal factors, e.g. air pollution emissions, they are also likely to have a shared cause Z, an example could be the already mentioned atmospheric (un)stability and climate dynamics, and temperature to affect $PM_{2.5}$ and $O_3$ concentration [11]. Thus, $PM_{2.5}$ and $O_3$ are likely to be mediators.

- **Effect modifiers**: The effect of temperature on COPD hospitalisations can be modified by, among other



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

factors, age, sex, urbanicity, green space and average temperature. We selected these effect modifiers based on 1. consistency with the literature [8] and 2. Clear hypotheses about the mediation: We included age as the elderly have been reported to be more vulnerable, sex as differences can arise due to different lifestyle, occupational or biological factors, averaged temperature to account for potential adaptation to higher temperatures, urbanicity, to examine if urban heat island modifies the effect of temperature, and green space. Green space may reduce health risks in urban populations by removing air pollution, reducing noise, cooling temperature, enhancing physical activities, reducing psychological stress, and interaction with a clean environment [12]. 3. As the main interest of the current analysis was spatial effect modification, we did not include factors that vary significantly in time, such as air-pollution.



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Table S1: Mean, standard deviation (sd), median, interquartile range (IQR), min and max of maximum summer temperature [$^o$C] across England during 2007-2018.

| year | mean | sd | median | IQR | min | max |
|---|---|---|---|---|---|---|
| 2007 | 19.39 | 2.71 | 19.42 | 3.31 | 4.00 | 30.31 |
| 2008 | 19.63 | 2.90 | 19.39 | 3.47 | 6.35 | 30.20 |
| 2009 | 20.26 | 3.28 | 20.27 | 4.17 | 2.25 | 31.97 |
| 2010 | 20.49 | 3.25 | 20.38 | 4.28 | 6.41 | 32.83 |
| 2011 | 19.38 | 3.10 | 19.15 | 3.98 | 5.32 | 33.41 |
| 2012 | 19.05 | 3.42 | 18.89 | 4.27 | 2.83 | 33.05 |
| 2013 | 21.10 | 3.78 | 20.88 | 5.37 | 5.76 | 34.09 |
| 2014 | 20.63 | 3.16 | 20.53 | 4.33 | 6.38 | 32.30 |
| 2015 | 19.87 | 3.37 | 19.79 | 4.23 | 3.03 | 36.67 |
| 2016 | 20.46 | 3.36 | 20.31 | 4.09 | 5.26 | 34.21 |
| 2017 | 20.37 | 3.45 | 20.17 | 4.09 | 5.49 | 34.48 |
| 2018 | 22.42 | 3.98 | 22.20 | 5.86 | 4.98 | 35.66 |



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Table S2: Median and interquartile range (IQR) of the temperature [$^o$C], daily mean $PM_{2.5}$ [$\mu g/m^3$], daily mean of the 8 hours of maximum $O_3$ [$\mu g/m^3$] and relative humidity [%] across event, non-event days and the different lags preceding the hospitalisation event.

| | | Event days | | Non-event days | |
|---|---|---|---|---|---|
| Covariate | lag | Median | IQR | Median | IQR |
| Temperature | 0 | 20.91 | 4.17 | 20.93 | 4.13 |
| | 1 | 20.97 | 4.21 | 20.94 | 4.13 |
| | 2 | 20.92 | 4.23 | 20.90 | 4.15 |
| | 0-2 | 20.93 | 3.73 | 20.92 | 3.67 |
| $PM_{2.5}$ | 0 | 9.23 | 5.60 | 9.10 | 5.45 |
| | 1 | 9.25 | 5.57 | 9.07 | 5.38 |
| | 2 | 9.23 | 5.44 | 9.06 | 5.25 |
| | 0-2 | 9.24 | 4.54 | 9.08 | 4.38 |
| $O_3$ | 0 | 65.5 | 22.37 | 65.00 | 21.91 |
| | 1 | 66.08 | 22.68 | 65.37 | 21.82 |
| | 2 | 66.21 | 22.35 | 65.58 | 21.78 |
| | 0-2 | 65.94 | 19.45 | 65.31 | 18.81 |
| Relative humidity | 0 | 0.90 | 0.11 | 0.90 | 0.11 |
| | 1 | 0.90 | 0.11 | 0.90 | 0.11 |
| | 2 | 0.90 | 0.11 | 0.90 | 0.11 |
| | 0-2 | 0.90 | 0.08 | 0.90 | 0.08 |



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Table S3: Mean, standard deviation (sd), median, interquartile range (IQR), min and max of daily mean $PM_{2.5}$ $[\mu g/m^3]$ exposure across England during summers 2007-2018.

| year | mean | sd | median | IQR | min | max |
|---|---|---|---|---|---|---|
| 2007 | 8.71 | 5.51 | 7.47 | 5.13 | 0.10 | 76.97 |
| 2008 | 8.71 | 6.07 | 7.37 | 4.17 | 0.00 | 69.92 |
| 2009 | 8.81 | 4.55 | 7.48 | 4.14 | 1.15 | 62.24 |
| 2010 | 9.19 | 5.03 | 7.97 | 4.78 | 0.70 | 52.42 |
| 2011 | 9.20 | 4.50 | 8.03 | 4.41 | 0.87 | 71.39 |
| 2012 | 8.28 | 4.97 | 7.04 | 4.78 | 0.35 | 84.33 |
| 2013 | 10.42 | 7.12 | 8.20 | 8.26 | 0.00 | 75.41 |
| 2014 | 8.58 | 4.83 | 7.39 | 5.43 | 0.31 | 53.73 |
| 2015 | 7.86 | 4.88 | 6.75 | 5.79 | 0.03 | 44.60 |
| 2016 | 8.60 | 8.20 | 6.07 | 6.51 | 0.00 | 73.65 |
| 2017 | 8.05 | 6.04 | 6.20 | 6.20 | 0.00 | 65.88 |
| 2018 | 8.67 | 5.67 | 7.13 | 6.07 | 0.00 | 52.24 |



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Table S4: Mean, standard deviation (sd), median, interquartile range (IQR), min and max of daily mean of the 8 hours of maximum $O_3$ [$\mu g/m^3$] exposure across England during summers 2007-2018.

| year | mean | sd | median | IQR | min | max |
|---|---|---|---|---|---|---|
| 2007 | 70.15 | 18.75 | 67.33 | 18.59 | 5.99 | 198.68 |
| 2008 | 71.32 | 18.91 | 69.35 | 21.86 | 0.19 | 166.95 |
| 2009 | 69.10 | 20.51 | 64.09 | 22.77 | 3.09 | 180.97 |
| 2010 | 68.11 | 19.87 | 64.57 | 23.99 | 12.07 | 157.44 |
| 2011 | 67.02 | 16.06 | 65.18 | 18.66 | 7.75 | 145.45 |
| 2012 | 63.28 | 17.56 | 62.02 | 19.81 | 0.19 | 182.54 |
| 2013 | 71.60 | 19.99 | 69.04 | 23.01 | 0.00 | 186.98 |
| 2014 | 71.28 | 15.92 | 69.64 | 19.41 | 6.91 | 150.06 |
| 2015 | 71.69 | 17.33 | 69.33 | 21.35 | 2.09 | 177.66 |
| 2016 | 64.46 | 17.90 | 60.38 | 20.44 | 0.86 | 162.83 |
| 2017 | 63.17 | 17.04 | 60.39 | 18.88 | 12.31 | 246.06 |
| 2018 | 71.78 | 22.37 | 67.24 | 32.10 | 16.28 | 268.69 |



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Table S5: Mean, standard deviation (sd), median, interquartile range (IQR), min and max of daily median of relative humidity [%] exposure across England during summers 2007-2018.

| year | mean | sd | median | IQR | min | max |
|---|---|---|---|---|---|---|
| 2007 | 0.94 | 0.05 | 0.95 | 0.08 | 0.49 | 1.00 |
| 2008 | 0.93 | 0.06 | 0.95 | 0.09 | 0.51 | 1.00 |
| 2009 | 0.93 | 0.06 | 0.94 | 0.09 | 0.43 | 1.00 |
| 2010 | 0.91 | 0.07 | 0.93 | 0.12 | 0.46 | 1.00 |
| 2011 | 0.92 | 0.06 | 0.93 | 0.09 | 0.50 | 1.00 |
| 2012 | 0.96 | 0.05 | 0.97 | 0.06 | 0.54 | 1.00 |
| 2013 | 0.91 | 0.07 | 0.92 | 0.10 | 0.45 | 1.00 |
| 2014 | 0.91 | 0.06 | 0.91 | 0.09 | 0.50 | 1.00 |
| 2015 | 0.90 | 0.07 | 0.91 | 0.11 | 0.47 | 1.00 |
| 2016 | 0.94 | 0.06 | 0.95 | 0.08 | 0.50 | 1.00 |
| 2017 | 0.93 | 0.06 | 0.94 | 0.08 | 0.49 | 1.00 |
| 2018 | 0.88 | 0.09 | 0.90 | 0.14 | 0.37 | 1.00 |



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Table S6: Percentage hospitalisation risk of COPD for every 1$^o$C increase in summer temperature using the model adjusted for relative humidity and national holidays and the different temperature thresholds $c$.

| quantile | threshold $c$ ($^o$C) | WAIC | Effect bellow $c$ | Effect above $c$ |
|---|---|---|---|---|
| 50 | 20.6 | 2,257,389 | 0.12 (-0.22, 0.46) | 1.56 (1.26, 1.84) |
| 55 | 21.0 | 2,257,373 | 0.12 (-0.23, 0.48) | 1.56 (1.26, 1.86) |
| 60 | 21.3 | 2,257,371 | 0.16 (-0.21, 0.49) | 1.53 (1.24, 1.81) |
| 65 | 21.7 | 2,257,379 | 0.21 (-0.12, 0.57) | 1.50 (1.21, 1.78) |
| 70 | 22.1 | 2,257,333 | 0.22 (0.10, 0.55) | 1.49 (1.22, 1.77) |
| 75 | 22.6 | 2,257,331 | 0.37 (0.05, 0.65) | 1.42 (1.15, 1.68) |
| 80 | 23.2 | 2,257,273 | 0.37 (0.09, 0.65) | 1.46 (1.19, 1.71) |
| 85 | 23.8 | 2,257,330 | 0.44 (0.18, 0.70) | 1.46 (1.20, 1.72) |
| 90 | 24.9 | 2,257,440 | 0.62 (0.38, 0.86) | 1.39 (1.11, 1.66) |
| 95 | 26.5 | 2,257,351 | 0.72 (0.49, 0.93) | 1.50 (1.20, 1.82) |



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Table S7: Median and 95% credible intervals of the % risk COPD hospitalisation for every $1^o$ increase in warm temperatures by age group and sex. RH+NL refers to adjustment for relative humidity and national holidays, whereas RH+NL+POL for additional adjustment for $PM_{2.5}$ and $O_3$.

| Sex | Age group | Unadjusted models | RH+NL | RH+NL+POL |
|---|---|---|---|---|
| Males | 0-64 | 0.97 (0.24, 1.73) | 1.32 (0.57, 2.06) | 0.64 (-0.24, 1.49) |
| Females | 0-64 | 0.92 (0.25, 1.63) | 1.14 (0.39, 1.84) | -0.04 (-0.90, 0.84) |
| Total | 0-64 | 1.00 (0.51, 1.48) | 1.28 (0.75, 1.82) | 0.35 (-0.26, 0.98) |
| Males | 65-74 | 1.13 (0.50, 1.71) | 1.39 (0.74, 2.03) | 0.62 (-0.15, 1.39) |
| Females | 65-74 | 1.56 (0.94, 2.20) | 1.75 (1.13, 2.41) | 0.76 ( 0.01, 1.52) |
| Total | 65-74 | 1.31 (0.83, 1.70) | 1.54 (1.07, 2.03) | 0.66 ( 0.13, 1.22) |
| Males | >75 | 1.41 (0.87, 1.91) | 1.51 (0.98, 2.07) | 0.25 (-0.35, 0.92) |
| Females | >75 | 1.29 (0.79, 1.83) | 1.51 (0.94, 2.06) | 0.47 (-0.14, 1.11) |
| Total | >75 | 1.36 (0.96, 1.71) | 1.49 (1.11, 1.89) | 0.38 (-0.10, 0.84) |
| Males | Total | 1.23 (0.89, 1.59) | 1.45 (1.10, 1.83) | 0.51 ( 0.07, 0.94) |
| Females | Total | 1.26 (0.93, 1.62) | 1.46 (1.09, 1.82) | 0.41 (-0.03, 0.84) |
| Total | Total | 1.24 (0.98, 1.51) | 1.47 (1.19, 1.73) | 0.47 ( 0.16, 0.75) |



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Figure S1: Boundaries of the 326 Lower Tier Local Authorities of England in 2015 (median size: 208km$^2$).

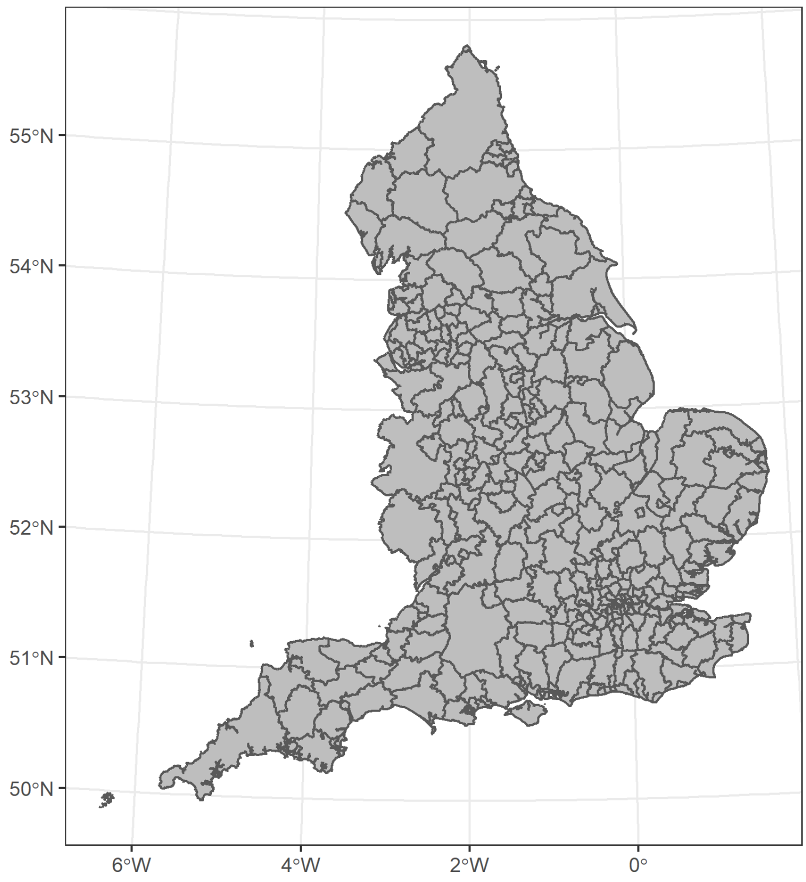
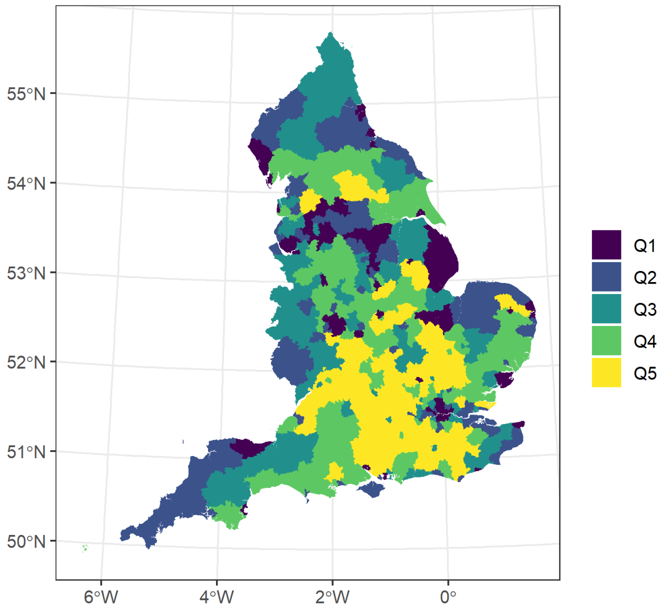


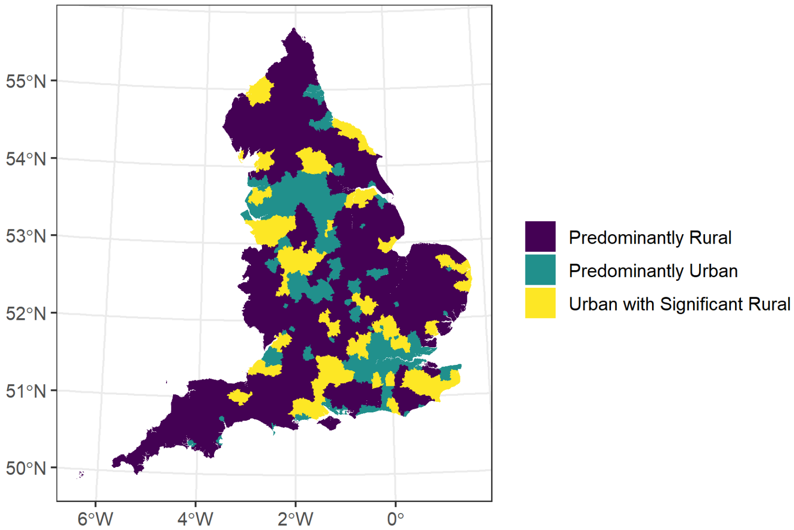
Figure S2: The spatial distribution of the index of multiple deprivation using quintiles in 2015 in England at the lower tier local authority level. Q1 indicates the most deprived areas.






Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

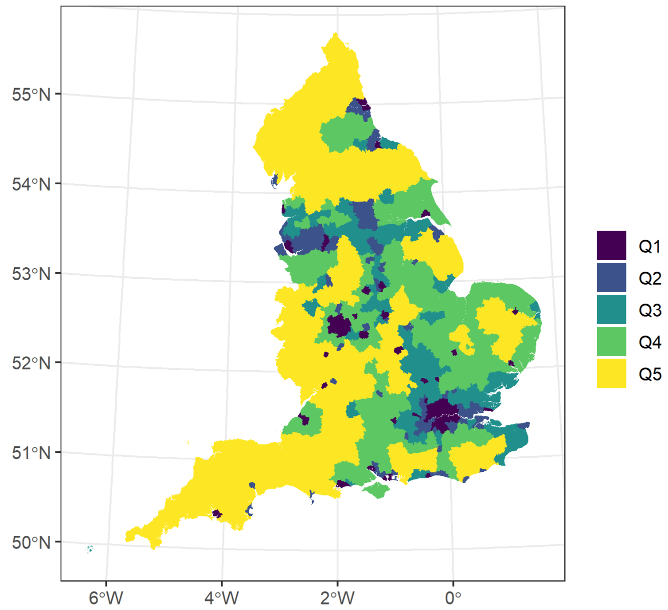
Figure S3: The spatial distribution of urbanicity in based on the Office for National Statistics classification in 2011 at the lower tier local authority level.






Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

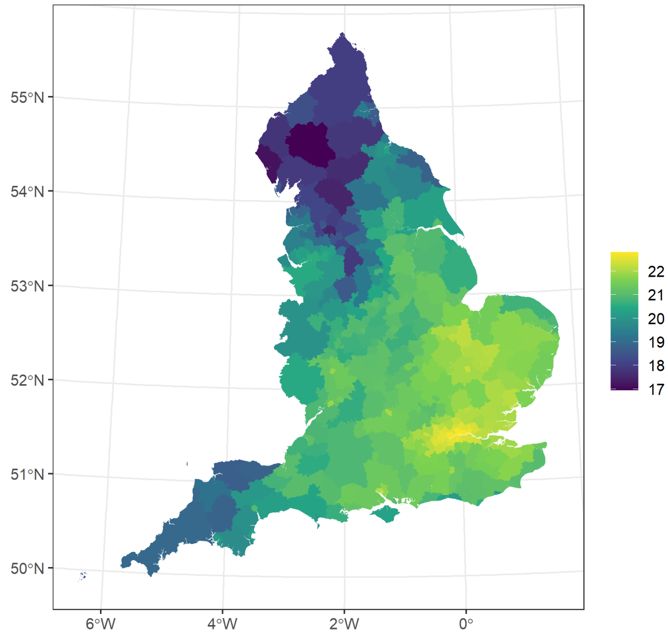
Figure S4: The quintiles of the spatial distribution of the proportion of a lower tier local authority that is covered by green land such as woodland, agricultural land, grassland and other natural vegetated land as classified in the Land Cover Map 2015.






Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

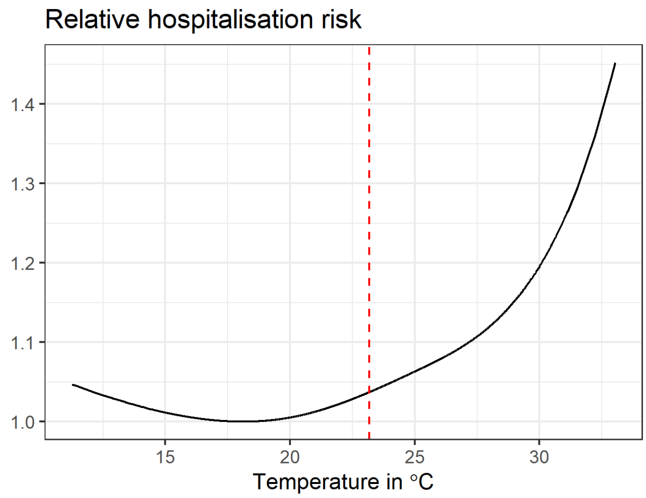
Figure S5: The spatial distribution of the average temperature [$^oC$] by lower tier local authority during 2007-2018 in England.






Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

Figure S6: Relative hospitalisation risk (relative to the risk at $18^oC$) using 3rd degree of b-splines at 3 knots and the model with total age and sex and adjusted for national holidays and relative humidity. The red dashed line indicated the threshold $c$ used throughout the study.






Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

# References

[1] Finn Lindgren, Håvard Rue, and Johan Lindström. An explicit link between gaussian fields and gaussian markov random fields: the stochastic partial differential equation approach. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 73(4):423–498, 2011.

[2] Sigrunn Holbek Sørbye and Håvard Rue. Penalised complexity priors for stationary autoregressive processes. *Journal of Time Series Analysis*, 38(6):923–935, 2017.

[3] Daniel Simpson, Håvard Rue, Andrea Riebler, Thiago G Martins, and Sigrunn H Sørbye. Penalising model component complexity: A principled, practical approach to constructing priors. *Statistical science*, pages 1–28, 2017.

[4] Andrew Gelman, Jessica Hwang, and Aki Vehtari. Understanding predictive information criteria for bayesian models. *Statistics and computing*, 24(6):997–1016, 2014.

[5] Julian Besag, Jeremy York, and Annie Mollié. Bayesian image restoration, with two applications in spatial statistics. *Annals of the institute of statistical mathematics*, 43(1):1–20, 1991.

[6] Jovan Javorac, Marija Jevtić, Dejan Živanović, Miroslav Ilić, Sanja Bijelović, and Nataša Dragić. What are the effects of meteorological factors on exacerbations of chronic obstructive pulmonary disease? *Atmosphere*, 12(4), 2021.

[7] Erich M Fischer, Sonia I Seneviratne, Pier Luigi Vidale, Daniel Lüthi, and Christoph Schär. Soil moisture–atmosphere interactions during the 2003 european summer heat wave. *Journal of Climate*, 20(20):5081–5099, 2007.

[8] James E Bennett, Marta Blangiardo, Daniela Fecht, Paul Elliott, and Majid Ezzati. Vulnerability to the mortality effects of warm temperature in the districts of england and wales. *Nature Climate Change*, 4(4):269–273, 2014.

[9] Man-Hui Li, Li-Chao Fan, Bei Mao, Jia-Wei Yang, Augustine MK Choi, Wei-Jun Cao, and Jin-Fu Xu. Short-term exposure to ambient fine particulate matter increases hospitalizations and mortality in copd: a systematic review and meta-analysis. *Chest*, 149(2):447–458, 2016.

[10] Hui Gao, Kan Wang, William W Au, Wensui Zhao, and Zhao-lin Xia. A systematic review and meta-analysis of short-term ambient ozone exposure and copd hospitalizations. *International journal of environmental research and public health*, 17(6):2130, 2020.



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374

[11] Jessie P Buckley, Jonathan M Samet, and David B Richardson. Commentary: Does air pollution confound studies of temperature? *Epidemiology*, 25(2):242–245, 2014.

[12] Iana Markevych, Julia Schoierer, Terry Hartig, Alexandra Chudnovsky, Perry Hystad, Angel M Dzhambov, Sjerp De Vries, Margarita Triguero-Mas, Michael Brauer, Mark J Nieuwenhuijsen, et al. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. *Environmental research*, 158:301–317, 2017.



Konstantinoudis G, *et al. Thorax* 2022;0:1–7. doi: 10.1136/thoraxjnl-2021-218374