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Risk of respiratory hospital admission associated with modelled concentrations of *Aspergillus fumigatus* from composting facilities in England

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ABSTRACT

Bioaerosols have been associated with adverse respiratory-related health effects and are emitted in elevated concentrations from composting facilities. We used modelled *Aspergillus fumigatus* concentrations, a good indicator for bioaerosol emissions, to assess associations with respiratory-related hospital admissions. Mean daily *Aspergillus fumigatus* concentrations were estimated for each composting site for first full year of permit issue from 2005 onwards to 2014 for Census Output Areas (COAs) within 4 km of 76 composting facilities in England, as previously described (Williams et al., 2019). We fitted a hierarchical generalized mixed model to examine the risk of hospital admission with a primary diagnosis of (i) any respiratory condition, (ii) respiratory infections, (iii) asthma, (iv) COPD, (v) diseases due to organic dust, and (vi) Cystic Fibrosis, in relation to quartiles of *Aspergillus fumigatus* concentrations. Models included a random intercept for each COA to account for over-dispersion, nested within composting facility, on which a random intercept was fitted to account for clustering of the data, with adjustments for age, sex, ethnicity, deprivation, tobacco sales (smoking proxy) and traffic load (as a proxy for traffic-related air pollution). We included 249,748 respiratory-related and 3163 Cystic Fibrosis hospital admissions in 9606 COAs with a population-weighted centroid within 4 km of the 76 included composting facilities. After adjustment for confounders, no statistically significant effect was observed for any respiratory-related (Relative Risk (RR) = 0.99; 95% Confidence Interval (CI) 0.96–1.01) or for Cystic Fibrosis (RR = 1.01; 95% CI 0.56–1.83) hospital admissions for COAs in the highest quartile of exposure. Similar results were observed across all respiratory disease sub-groups. This study does not provide evidence for increased risks of respiratory-related hospitalisations for those living near composting facilities. However, given the limitations in the dispersion modelling, risks cannot be completely ruled out. Hospital admissions represent severe respiratory episodes, so further study would be needed to investigate whether bioaerosols emitted from composting facilities have impacts on less severe episodes or respiratory symptoms.

1. Introduction

Biological air pollution (bioaerosols) is a complex mixture of airborne fungal, bacterial and pollen species, cellular constituents, and particulate matter which can be viable or non-viable (Douwes et al., 2003; Pearson et al., 2015). Bioaerosols are ubiquitous in the

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Abbreviations

AIC	Akaike information criterion
CI	Confidence Interval
COA	Census Output Area
COPD	Chronic Obstructive Pulmonary Disease
EU	European Union
GP	General Practitioner
HES	Hospital Episode Statistics
ICD	International Classifications of Diseases
NHS	National Health Service
ONS	Office for National Statistics
PHE	Public Health England
PM	Particulate Matter
RR	Relative Risk
SAHSU	Small Area Health Statistics Unit

environment but are emitted in elevated quantities (up to nine orders of magnitude above background) during large scale composting, particularly when the compost is handled or agitated (e.g. shredded, turned or screened) (Pearson et al., 2015; Robertson et al., 2019; Taha et al., 2006; Wery, 2014). The number of large scale composting facilities (that require a permit to operate) in England has increased by over 150% in the last ten years (Environment Agency, 2018) as a result of European Union (EU) directives to divert waste from landfill (EU Landfill directive 1999/31/EC) (The Council of the European Union, 1999).

Bioaerosols emitted from composting facilities are typically less than 3 μm in diameter (Feeney et al., 2018; Gales et al., 2015; Gutarowska et al., 2015; O'Connor et al., 2015; Pahari et al., 2016; Tamer Vestlund et al., 2014) and are, therefore, respirable (Byeon et al., 2008; Chiang et al., 2003; Wery, 2014). A well-described and common component of bioaerosols is *Aspergillus fumigatus*, a pathogenic fungus that can trigger inflammatory, immunological, and allergic responses when inhaled (Lacey and Dutkiewicz, 1994; Pearson et al., 2015; Swan et al., 2003; Sykes et al., 2007; Wery, 2014). Its abundance and pathogenic characteristics makes it a good indicator for bioaerosol emissions in epidemiological studies (see Appendix A for a more detailed justification).

To date, there have been a limited number of studies examining the health effects of bioaerosols from composting facilities in community settings, as highlighted in a systematic review (Pearson et al., 2015), and subsequent update (Robertson et al., 2019). These studies have mostly relied on self-reported health symptoms, and/or proximity indicators as a proxy measure for estimating bioaerosol exposure, providing mixed results regarding the health effects of bioaerosol emissions. Douglas et al. (2016) conducted a national small area ecological study, which examined risk of respiratory-related hospital admission in relation to distance from composting facilities in England between 2008 and 2010. The authors did not find clear evidence for an increased risk of respiratory-related hospital admission in communities living beyond 250 m of facilities yet did find a small non-statistically significant ($p = 0.054$) association with total respiratory admissions when using distance as a continuous proxy measure for exposure. Distance is a common, yet rather simple, exposure proxy used in epidemiological studies when more sophisticated measures are not available. However, it ignores the influence of other factors in the dispersion patterns and may lead to exposure misclassification (Hodgson et al., 2007). In this case, the dispersion of bioaerosols in the nearby areas is likely to be affected by, albeit not limited to, emission rates at each composting facility, wind direction and ambient temperature. Therefore, epidemiological studies would benefit from more comprehensive estimates of bioaerosol exposure, using more sophisticated tools such as dispersion models. Recently (Williams et al., 2019), developed the first application of a dispersion model, Atmospheric Dispersion Modelling System (ADMS), to estimate *Aspergillus fumigatus* concentrations from large scale composting facilities on a national scale for use in epidemiological studies. This provides an improved exposure measure as it accounts for wind direction, ambient temperature and composting facility characteristics, among other factors relevant to bioaerosol dispersion.

The purpose of this epidemiological study was to, for the first time, apply these national dispersion model estimates of *Aspergillus fumigatus* concentrations from composting facilities in an epidemiological study. The dispersion model estimates provide a more sophisticated method of assessing community exposure to *Aspergillus fumigatus* emitted from composting facilities, improving upon previous studies that have relied on proximity proxies, e.g. Douglas et al. (2016), that do not take account of wind direction and other factors and therefore resulting in exposure misclassification. Moreover, instead of relying upon subjective health outcome data collected from questionnaires as per previous studies, this epidemiological study utilises objectively collected health data, reducing recall bias.

Therefore, the aim of this study was to investigate, on a national scale, whether estimated concentrations of *Aspergillus fumigatus* emitted from large scale composting facilities are associated with respiratory-related hospital admissions, in England, between 2005 and 2014.

2. Materials and methods

2.1. Composting facility selection

Data on composting facilities were obtained from the Environment Agency (EA) and contained information on all composting facilities that had a valid permit to operate at the end of 2014 ($n = 313$, Appendix B Fig. B1). A facility requires a permit to operate if they store or treat > 60 tonnes of compost at any one time (GOV.UK, 2014). The data contained detailed information of each facility, including the date when the permit was awarded, composting activity type (e.g. open windrow, in-vessel, etc.) and the facility address. For each composting facility, the date of the permit was taken as the operational starting date. Facility addresses were used to locate composting facilities and delimit the perimeter of the outdoor composting activity component using Google Earth Pro, as previously described (Williams et al., 2019). Duplicated composting facilities ($n = 22$) or those with no outdoor component ($n = 36$) or lacking geographical information ($n = 38$) were excluded. Of those with an outdoor component, only fully open windrow facilities were considered ($n = 173$), as emissions are completely uncontained and therefore, assumed to have the most impact on the surrounding community. We included 76 composting facilities in the main analysis (Fig. 1) due to further criteria applied because of the characteristics and format of the exposure data (see 2.3. Exposure Data).

2.2. Study population

All Census Output Areas (COAs) (average of 300 inhabitants) with a population-weighted centroid (obtained from Office of National Statistics (ONS) (ONS, 2019)) within 4 km of a composting facility were included, to ensure that areas with background levels of bioaerosols were included as a control, based on previous findings (Douglas et al., 2016; Williams et al., 2019). Population weighted centroids, as opposed to geometric centroids, were used as these account for population distribution within the COA and thus, better capture population exposure. COAs that were within 4 km of multiple composting facilities ($n = 4331$) were assigned to the nearest one.

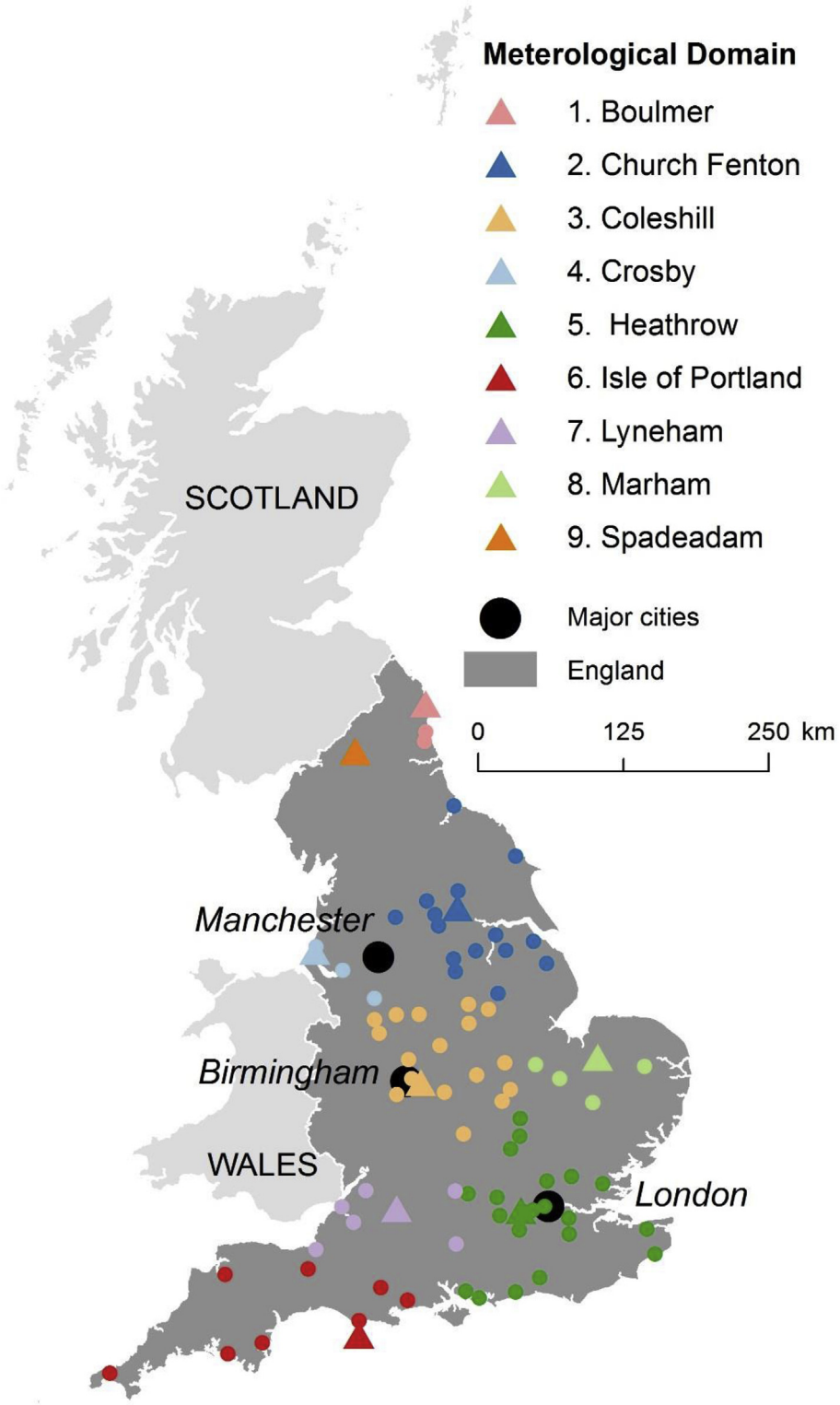

Fig. 1. Locations of the permitted open windrow composting facilities included in the study (coloured circles) and meteorological stations assigned to each composting facility (coloured triangles). Major cities are indicated (black circles).

2.3. Exposure data

For this epidemiological study, we used the output of a novel application of a dispersion model to estimate *Aspergillus fumigatus* concentrations from large scale composting facilities on a national scale developed by (Williams et al., 2019). In brief, the model uses ADMS, a well-validated Gaussian-based atmospheric dispersion model (CERC, 2018) to predict daily ground-level concentrations of *Aspergillus fumigatus* at residential postcode centroids (average 12 households) within 4 km of composting facilities operating between 2005 and 2014. The dispersion model accounted for variation in meteorological conditions, including ambient temperature, and reflected seasonal changes in Aspergillus fumigatus emissions. Although it was not possible to fully assess the model performance using existing measured bioaerosol data

(which was not fit for purpose), we did base model inputs on the best available data, including results from a recent model validation study (Douglas et al., 2017), as fully described and discussed in Williams et al. (2019). Postcodes within 4 km of more than one composting facility were modelled considering the combined emission of all the composting facilities involved.

ADMS is designed to simulate dispersion of more standard air pollutants (e.g. particulate matter (PM), nitrogen oxides (NOx), sulphur dioxide (SO_2), etc.). Previous evidence shows that *Aspergillus fumigatus* has a diameter of typically < 3 μm (Feeney et al., 2018; Gales et al., 2015; Gutarowska et al., 2015; O'Connor et al., 2015; Pahari et al., 2016; Tamer Vestlund et al., 2014) (Appendix A). Therefore, we modelled PM with a diameter less than 2.5 μm ($PM_{2.5}$) as a proxy for *Aspergillus fumigatus* emissions, which is considered a relevant indicator of

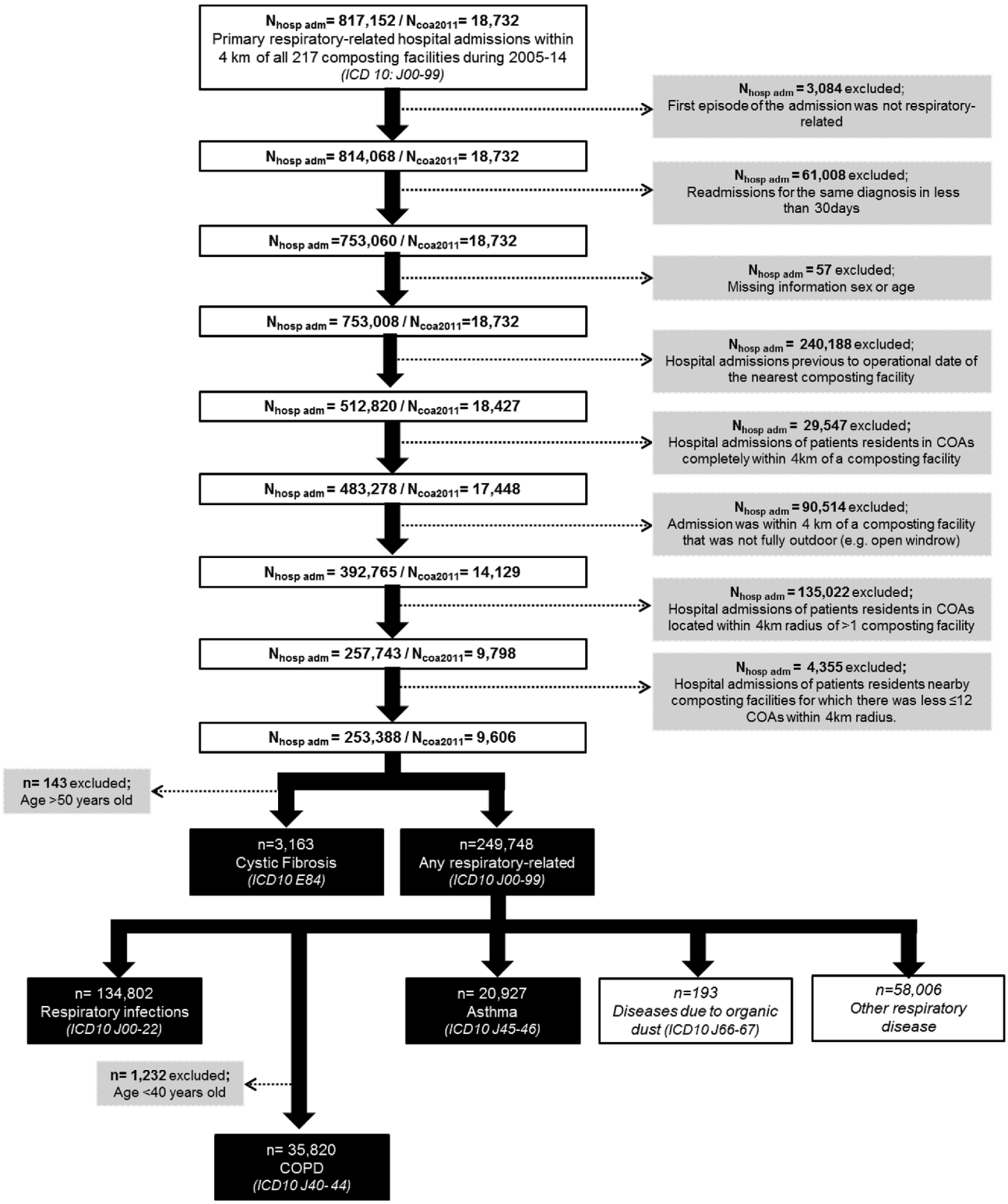

Fig. 2. Data cleaning flowchart of the hospital admissions data used in the study analysis. The exclusions are shaded in light grey. The outcomes investigated, and for which results are presented, are shaded in black.

bioaerosols (Lacey and Dutkiewicz, 1994; Pankhurst et al., 2011; Pearson et al., 2015; Swan et al., 2003; Sykes et al., 2007; Wery, 2014; Williams et al. 2013, 2019), as discussed in Appendix A. Model input parameters relevant to *Aspergillus fumigatus* dispersion were included in the model (e.g. exit velocity and temperature) as well as meteorological information (e.g. ambient temperature, wind direction and speed). Composting facilities were assigned to a meteorological station based on their spatial proximity and climate representativeness of the area (Fig. 1). More information on the dispersion model specifications can be found in Williams et al. (2019).

2.3.1. Harmonising exposure data

Exposure, health, population and confounder data were available at different geographical levels and consequently harmonised to COAs (using 2011 census boundaries), the highest spatial unit at which all data were available. For the exposure data, each COA was assigned the modelled estimates from the nearest composting facility. Composting facilities with COAs within 4 km of other composing facilities were excluded from the main analyses (Appendix B, Fig. B1.) to avoid overestimating the exposure (as the model accounted for the combined emission, rather than the one from the nearest composting facility only).

Daily average postcode-level *Aspergillus fumigatus* concentrations were spatially aggregated to COAs using a postcode-weighted approach (Appendix C). As dispersion modelling was conducted at postcode level, some COAs that had a population-weighted centroid within 4 km of a composting facility did not have *Aspergillus fumigatus* concentrations modelled for all of the postcodes (as they would be outside the 4 km area) (n = 979). Only COAs with all postcodes modelled were included in the main analysis.

Daily *Aspergillus fumigatus* concentrations were temporally aggregated to obtain a mean daily concentration for each COA over the entire operational period covering the nearest full year from 2005 onwards that the composting facility was awarded permission to the end of the study period in 2014 (details in Appendix C). These were categorised into quartiles relative to each composting facility to highlight the spatial gradient of bioaerosols concentrations at each individual facility (so the upper quartile for facility A may be similar to the lower quartile for facility B, for example). This was done to manage the high variability in modelled concentrations observed and to account for baseline exposure differences at facility level, as the exact emission rates were not available. This allowed us to assess whether, given a composting facility, there is a different risk of respiratory-related hospitalisation for COAs that have higher versus lower concentrations of *Aspergillus fumigatus*, without looking at the absolute concentrations. Thirty-one of the 107 composting facilities were excluded as there were < 12 COAs within 4 km of the facility, a threshold set to meaningfully categorize the exposure into quartiles) (Appendix B, Fig. B1.).

2.4. Health data

Data on hospital admissions between 2005 and 2014 for the selected COAs were obtained from the Hospital Episode Statistics (HES) national dataset held by the UK Small Area Health Statistics Unit (SAHSU), provided by National Health Service (NHS) Digital. The HES inpatient dataset is a comprehensive administrative dataset that records all hospital admissions at NHS and NHS–funded hospitals and facilities in England. On admission to hospital, a period of care is opened, termed 'episode'. One unique admission may be given several episodes if the patient was attended by multiple consultants, with the first episode of care relating to the primary cause of hospitalisation. Each episode contains a primary diagnosis field and up to 19 secondary diagnosis fields. Only the primary diagnosis of the first episode was considered for each admission. Diagnostic codes included in this study, as defined by the International Classification of Disease, 10th edition (ICD-10) (WHO, 2010), were as follows: (i) all respiratory-related diseases (ICD-10: J00-99), (ii) respiratory infections (ICD10: J00-22), (iii) asthma (ICD10: J45-46), and (iv) chronic obstructive pulmonary disease (COPD) (ICD10: J40- 44). We also analysed hospital admissions of Cystic Fibrosis (ICD10: E84) as patients with this condition are susceptible to infections caused by *Aspergillus fumigatus* exposure. For example, allergic bronchopulmonary aspergillosis occurs in approximately 10% of Cystic Fibrosis patients (Burgel et al., 2016; Garczewska et al., 2016). Disease due to organic dust (ICD10: J66-67) were also investigated, yet results are not presented due to too few cases (n = 193 over the 10-year period).

To summarise, our outcome is the sum of primary first episode hospitalizations with any of the above diagnostic codes at COA level. Hospital admissions with the same primary diagnosis occurring within 30 days were considered as a readmission and only the first admission was kept (n = 61,008); this is because readmissions within 30 days are likely to represent complications from the initial condition, rather than a new health effect resulting from re-exposure (NHS Digital, 2019). Hospital admissions were also excluded if data on sex and age were missing (n = 57) or if the admission date was prior to the opening date of the closest composting facility (n = 240,188). If a facility started operating mid-year, all admissions for that year were excluded. Fig. 2 summarises the data cleaning process. In the main analysis, hospital admissions from people of all ages were included with the exception of COPD and Cystic Fibrosis. The common age of onset for COPD onset is over 65 years old, with early COPD onset occurring around 40–50 years old (Abramson et al., 2014; Kobayashi et al., 2017). Survival for Cystic Fibrosis patients is currently approximately 50 years (Keogh et al., 2018). Therefore, we excluded any case of COPD and of Cystic Fibrosis hospitalisation registered in patients aged < 40 years and > 50 years old, respectively, as this is likely reflecting extreme cases or coding and diagnostic errors.

2.5. Confounder data

Area level deprivation was captured through the Carstairs index, a composite measure of deprivation consisting of four deprivation indicators (i.e. unemployment, household overcrowding, no car ownership and social class (Carstairs and Morris, 1989)). Carstairs deprivation scores were computed using input data from the 2011 census, standardized across England at COA level and categorised into quintile groups for the analysis.

Weekly tobacco expenditure data (pounds spent per week) for COAs, used as a proxy for tobacco smoking, were obtained from CACI Ltd (CACI, 2014) for 2014. Data were estimated per person aged ≥16 years using data population information from the 2011 census, resulting in pounds spent per week on tobacco per person aged ≥16 years per COA. Tobacco expenditure was used as a continuous variable.

Each COA was classified as rural or urban as there may be more natural sources of *Aspergillus fumigatus* and other fungi in rural settings. Areas were classified according to the 2011 Rural-Urban Classification provided by (ONS, 2018), which is based on population density and accessibility.

Traffic-related air pollution such as $PM_{2.5}$ and NO_2, have been shown to be positively associated with respiratory hospitalisations (Lipfert, 2017) and could confound our results. We used annual average daily traffic load data from 2013 (vehicles per day × m) from major roads within 150 m of each postcode (measured as the product of traffic intensity and the length of major road fragments within a 150 m buffer) as a proxy for traffic-related air pollution, similarly to Lanki et al. (2015). Major roads where defined as those with > 10,000 vehicles based on work by Morley and Gulliver (2016). Total estimates per postcode were aggregated to COA level as a proxy of air pollution exposure from major roads.

2.6. Statistical analysis

We examined the association between the number of respiratory-related hospital admissions and the modelled concentration of *Aspergillus fumigatus* categorised into quartiles relative to each composting facility. We fitted a generalized mixed model, assuming a Poisson distribution for the COA-level number of hospital admissions. Expected counts were estimated using age- and sex-specific rates derived from the entire study population and applied to the age- and sex-specific population estimates of each COA, available from the Office for National Statistics (ONS). We fitted a model with no adjustment for area-level confounders (Model 1) and a model (Model 2) fully adjusted for COA level: rural/urban classification, deprivation (Carstairs quintiles), tobacco expenditure, and road-traffic load index. The equation for Model 2 is provided in Appendix D Eq. (D.1.). For both models, we included a random intercept for each composting facility to allow for differences in baseline rates, and a nested random intercept for each COA to account for over dispersion. Analyses were conducted separately for each health event (i.e. all respiratory-related disease, respiratory infections, asthma, COPD, and Cystic Fibrosis).

All analyses were conducted in STATA version 13 (StataCorp, 2013).

2.7. Sensitivity analyses

Several sensitivity analyses were conducted to understand potential uncertainties introduced during the data handling (Appendix E, Table E1 and Fig. E1.). A sensitivity analysis was conducted including facilities that were in-vessel but had an outdoor composting component (n = 94) (sensitivity analysis 1). To assess the impact of excluding composting facilities with overlapping 4 km buffers, we conducted a sensitivity analysis where we included them (sensitivity analysis 2). The effect of the coverage rate of the postcodes modelled within each COA under study, was assessed through sensitivity analysis 3 and 4 were we applied less restrictive criteria and included any COA which had modelled concentrations for at least 75% of its postcodes, for both open windrow composting facilities only and for all facilities with an outdoor composting component, respectively. We also looked at health effects on vulnerable groups including children (aged ≤19 years old) and the elderly (aged ≥65 years old) (sensitivity analyses 5 and 6, respectively). Finally, we limited the analyses to composting facilities located in rural and urban areas only (sensitivity analyses 7 and 8, respectively).

In addition, during the data exploration, we observed some variability in the exposure distribution between meteorological stations and composting facilities. Therefore, we explored additional models by (i) adding an overarching random intercept for meteorological station; (ii) adding a random slope for meteorological station, and (iii) adding a random slope for composting facility, always holding for the hierarchical random nested intercept structure of COA within composting facility. However, based on the Akaike Information Criterion (AIC) there was not enough evidence that the fit of the model improved (data not shown). Therefore, the most parsimonious model was used (Model 2, Appendix D Eq. (D.1).

3. Results

Overall, 76 large scale open windrow composting facilities were included in the study (Fig. 1). Postcode-level modelled estimates of *Aspergillus fumigatus* concentrations were obtained and aggregated spatially and temporally. A total of 9606 COAs with a population-weighted centroid within 4 km of the composting facility were included

Table 1
Total and percentage of hospital admissions overall and by exposure quartiles in the study area.

	Overall		Exposure quartiles							
			Q1 - Least exposed		Q2		Q3		Q4 - Most exposed	
	n	%	n	%	n	%	n	%	n	%
Hospital admissions[a]										
All respiratory (ICD 10, J00-J99)	249,748		60,659	24.3	64,994	26.0	64,123	25.7	59,972	24.0
Respiratory infections only (ICD 10, J00-J22)	134,802		32,776	24.3	35,241	26.1	34,473	25.6	32,312	24.0
Asthma only (ICD 10, J45-J46)	20,927		5206	24.9	5700	27.2	5374	25.7	4647	22.2
COPD only (ICD 10, J40-J44)	35,820		8480	23.7	9470	26.4	9331	26.0	8539	23.8
Disease due to organic dust (ICD 10, J66-J67)	193		61	31.6	50	25.9	50	25.9	32	16.6
Cystic Fibrosis (ICD 10, E84)	3163		848	26.8	827	26.1	715	22.6	773	24.4
Number of hospital admissions by age group (years)[b]										
0–19 years	74,465	29.4	18,405	29.9	19,517	29.7	18,985	29.3	17,558	28.9
20–39 years	35,215	13.9	8608	14.0	9356	14.2	9134	14.1	8117	13.4
40–64 years	39,977	15.8	9938	16.2	10,000	15.2	10,315	15.9	9724	16.0
≥65 years	103,254	40.8	24,556	39.9	26,948	40.9	26,404	40.7	25,346	41.7
Sex[b]										
Male	129,117	51.1	31,417	51.1	33,398	50.7	33,214	51.2	31,088	51.2
Female	123,794	48.9	30,090	48.9	32,423	49.3	31,624	48.8	29,657	48.8
Carstairs deprivation quintile[b,c]										
Q1- Least deprived	31,946	12.6	8114	13.2	6459	9.8	7191	11.1	10,182	16.8
Q2	40,553	16.0	10,066	16.4	9170	13.9	9123	14.1	12,194	20.1
Q3	45,965	18.2	10,736	17.5	12,182	18.5	11,861	18.3	11,186	18.4
Q4	56,186	22.2	11,136	18.1	14,812	22.5	16,739	25.8	13,499	22.2
Q5 - Most deprived	78,261	30.9	21,455	34.9	23,198	35.2	19,924	30.7	13,684	22.5
Number of people living in[b]										
Rural areas	28,782	11.4	7524	12.2	5498	8.4	5673	8.7	10,087	16.6
Urban area	224,129	88.6	53,983	87.8	60,323	91.6	59,165	91.3	50,658	83.4
Mean (SD) tobacco expenditure (£ spent per week per person aged ≥16 years per COA)[b, c]	7.6	(2.7)	7.5	(2.7)	7.8	(2.6)	7.7	(2.7)	7.2	(2.9)
Mean (SD) traffic load (vehicles per day per m)[b,c,d]	1.5	(0.7)	1.5	(0.7)	1.5	(0.7)	1.5	(0.7)	1.6	(0.8)

[a] – Percentages given over overall admissions (i.e. across rows).
[b] – Information given for all respiratory-related hospital admissions.
[c] – At COA level.
[d] – Traffic load as proxy for traffic air pollution within 150 m

in the analyses, after excluding COAs with incomplete coverage of modelled postcodes (Appendix E, Table E1.). Results from the dispersion modelling have been described elsewhere (Williams et al., 2019). There was a total of 249,748 primary non-repeat first-episode respiratory-related hospital admissions over the study period and 3163 Cystic Fibrosis hospital admissions (Table 1, Fig. 2). Population characteristics of the hospital admissions included in the main analyses, overall and per exposure quartile, are provided in Table 1.

The most common causes of hospitalisation were respiratory infections (n = 134,802) followed by COPD (n = 35,820) and asthma (n = 20,927) (Table 1, Fig. 2). There were no noteworthy differences in the occurrence of both overall and disease-specific hospitalisations across exposure quartiles except for disease due to organic dust which showed a lower occurrence in the most exposed quartile (16.6%) (Table 1). The most common ages for hospitalisation was ≥65 years (40.8%), followed by ≤ 19 years (29.4%) with similar age distribution within each exposure quartile. There were slightly more males hospitalised overall (51.1%) and across exposure quartiles. Hospitalisations were mainly from persons living in deprived areas (i.e. Carstairs quintile 4 and 5) always representing more than 50% of all hospitalisations, both overall and by exposure quartiles. Most of the hospital admissions occurred in urban areas (88.6%, Table 1) where most of the population reside (87.2%, Appendix F). The mean (SD) weekly expenditure in tobacco among population aged ≥16 years old was 7.6 (2.7), with similar values across exposure quartiles. Likewise, mean (SD) traffic load showed similar values across exposure groups to those found for the overall study population (1.5 (0.7)). Descriptive statistics of the general population living in the study area are provided in Appendix F Table F1.

Table 2 shows the results for the association between disease-specific hospital admissions and quartiles of exposure. The results from the basic adjusted model (Model 1) showed a slight protective effect across all health outcomes in areas with the highest concentrations of *Aspergillus fumigatus*. However, after models were fully adjusted (Model 2), this effect was noticeably reduced and lost statistical significance. Of the adjustment variables, area level deprivation quintiles and rural classification were those explaining most of the variability (data not shown). For all respiratory diseases and respiratory infections, we observed a non-significant relative risk (RR) of 0.99 (95%CI: 0.96–1.01) and 0.98 (95%CI: 0.95–1.00), respectively, for COAs in the highest compared to the lowest quartile of exposure. For COPD the protective effect disappeared completely, yet after adjustment the association remained non-significant (RR = 1.01 (95%CI: 0.96–1.08). For asthma, the magnitude of the protective effect for the highest exposed areas was reduced and became statistically non-significant (RR = 0.97 (95%CI = 0.91; 1.04)).

Similar results were observed across all sensitivity analyses (Appendix G).

4. Discussion

This is the first study that has examined associations between modelled *Aspergillus fumigatus* concentrations and respiratory-related hospital admissions, using a small area ecological study design. We did not find any significant associations, neither overall nor in sub-analysis focusing on specific respiratory subgroups such as asthma.

4.1. Comparison with other studies

In our previous study assessing the risk of hospitalisation for respiratory-related health outcomes in relation to proximity to large scale composting facilities (as a proxy for bioaerosol exposure) (Douglas et al., 2016), we found a small non-statistically significant association with total respiratory admissions when using a continuous measure of distance in those living within 2.5 km of a facility. Here, using a more sophisticated exposure measure (which accounts for important factors influencing bioaerosol dispersion patterns, e.g. meteorological conditions, emission characteristics) and extending our study area to 4 km, we found no statistically significant effects.

Only six other community health studies have been conducted to date (Aatamila et al., 2011; Browne et al., 2001; Douglas et al., 2016; Herr et al. 2003a, 2003b; Kramer et al., 1989; Liu et al., 2011), and provide mixed evidence as to whether bioaerosol exposure from composting facilities results in increased respiratory-related symptoms and disease. Some studies showed significant increased risks of respiratory symptoms (e.g. cough with phlegm, wheeze etc.) (Aatamila et al., 2011; Herr et al., 2003b) or somatic complaints (Aatamila et al., 2011; Herr et al. 2003a, 2003b), and one suggested induced pro-inflammatory responses (Liu et al., 2011). However, two studies found no significant associations with respiratory symptoms and disease (Browne et al., 2001; Kramer et al., 1989). The majority of these studies relied on self-reported health data; were conducted over short timescales; relied on simple proxies of exposure measure (e.g. exposed vs non exposed or proximity to composting facility), and concerned a small number of facilities or small areas, and therefore are prone to bias (Pearson et al., 2015).

Table 2
Relative risk (95% confidence intervals) of hospital admission for any respiratory-related disease, asthma, COPD, cystic fibrosis and respiratory infections associated with quartiles of modelled concentrations of Aspergillus fumigatus.

	Model 1[a]			Model 2[b,c]		
	RR	95%CI	p-value	RR	95%CI	p-value
Any respiratory related disease (ICD-10, J00-J99)						
Q1 - Least exposed	1			1		
Q2	1.00	(0.98,1.03)	0.81	0.99	(0.97,1.01)	0.35
Q3	1.02	(0.99,1.04)	0.22	1.00	(0.98,1.02)	0.95
Q4 - Most exposed	0.94	(0.92,0.97)	< 0.005	0.99	(0.96,1.01)	0.21
Asthma (ICD-10, J45-J46)						
Q1 - Least exposed	1					
Q2	1.04	(0.97,1.11)	0.27	1.01	(0.95,1.08)	0.67
Q3	1.02	(0.96,1.09)	0.50	1.00	(0.94,1.07)	0.88
Q4 - Most exposed	0.91	(0.85,0.97)	< 0.005	0.97	(0.91,1.04)	0.42
COPD (ICD-10, J40-J44)						
Q1 - Least exposed	1					
Q2	1.04	(0.97,1.12)	0.27	1.00	(0.94,1.06)	0.95
Q3	1.04	(0.97,1.12)	0.22	1.01	(0.95,1.07)	0.85
Q4 - Most exposed	0.91	(0.85,0.98)	0.01	1.01	(0.96,1.08)	0.65
Respiratory infections (ICD-10, J00-J22)						
Q1 - Least exposed	1			1		
Q2	1.00	(0.97,1.02)	0.84	0.98	(0.96,1.01)	0.17
Q3	1.01	(0.98,1.04)	0.59	0.99	(0.97,1.02)	0.57
Q4 - Most exposed	0.94	(0.92,0.97)	< 0.005	0.98	(0.95,1.00)	0.07
Cystic Fibrosis (ICD-10, E84)						
Q1 - Least exposed	1		1			
Q2	1.11	(0.62,1.98)	0.72	1.10	(0.62,1.96)	0.74
Q3	0.93	(0.51,1.68)	0.81	0.92	(0.51,1.67)	0.78
Q4 - Most exposed	1.03	(0.57,1.87)	0.92	1.01	(0.56,1.83)	0.98

[a] Model 1, Model with random intercept composting facility || random intercept COA.

[b] Model 2, fully-adjusted model including Carstairs deprivation quintile + rural/urban + tobacco sales + index for proximity to major road + random intercept composting facility || random intercept COA.

[c] Not all confounders were available for all COAs (n = 2) and thus, were excluded from Model 2.

4.2. Exposure assessment

Strengths of the study are its national scale and use of modelled exposure to improve on use of distance as a proxy for exposure. Although model inputs were based on the latest evidence from the *Aspergillus fumigatus* modelling literature (Douglas et al., 2017; Williams et al., 2019), we did not directly measure bioaerosols. Due to limitations in the dispersion modelling approach, the estimated concentrations could not be considered as a quantitative estimate of *Aspergillus fumigatus* exposure, but could be used to provide a qualitative estimate (as previously described (Williams et al., 2019)). Therefore, we considered that the estimated concentrations were not appropriate to conduct a time-series study of daily predicted concentrations of *Aspergillus fumigatus*. Instead, we averaged the modelled outputs to produce a relative indicator of bioaerosol exposure gradient. It is likely that there will be peaks and troughs in *Aspergillus fumigatus* exposure, which may impact on any health response. We were also unable to account for natural variation in bioaerosol concentrations; there is currently limited knowledge on background bioaerosol variation temporally and spatially, particularly at genera/species level (Pearson et al., 2015; Robertson et al., 2019). However, we were able to somewhat account for background levels of air pollution, by using a road-traffic load index. We also, included a random intercept in our statistical model which allowed us to account for differences in baseline rates between composting facilities.

Despite the above limitations, this is an improvement to other commonly used bioaerosol exposure measures such as distance (Douglas et al., 2016). We were able to investigate this by comparing the spatial distribution of distance, wind-weighted distance and the average modelled concentrations of *Aspergillus fumigatus* (Appendix H, Section H.1.). Modelled concentrations of *Aspergillus fumigatus* showed a less patched and more complex spatial distribution. This was highly influenced by meteorology, which is consistent with previous evidence on the influence of these factors in bioaerosol dispersion. In addition, we tested the consistency of our results against the use of distance and wind-weighted distance (Appendix H, Section H.2 and H.3, respectively). Results using distance as a proxy showed some protective effects, particularly for asthma and COPD. When using wind-weighted distance, which adds an additional layer of complexity to the exposure assessment by accounting for wind direction, the effects were diluted. This reduction was even more obvious when using modelled concentrations of *Aspergillus fumigatus*. This suggests that our exposure assessment method is capturing some exposure dispersion patterns not fully described by these simpler proxies, adding to the body of literature highlighting the limitations of using distance proxies for epidemiological studies (Hodgson et al., 2007).

We focused on *Aspergillus fumigatus*, a pathogenic, well-studied bioaerosol component, which is known to be emitted from composting facilities in elevated concentrations (Pearson et al., 2015) as a proxy for bioaerosols more generally. *Aspergillus fumigatus* has been used as a proxy for bioaerosols in previous studies (Douglas et al., 2017), but this field would benefit from more research looking at the validity of using *Aspergillus fumigatus* as a proxy to describe spatial patterns of bioaerosol dispersion and more importantly, exploring multi-component exposure measures to better capture bioaerosol dispersion properties.

4.3. Health outcome data

We used objectively collected hospital admissions data, an improvement on subjective self-reported questionnaire data which has been frequently used in previous community health studies (Pearson et al., 2015). It was difficult to fully evaluate the impacts of *Aspergillus fumigatus* exposure on Cystic Fibrosis sufferers due to small numbers. We may have underestimated true effects, due to our inclusion criteria. If a composting facility started operating mid-year, we did not consider any hospital admissions for the entire calendar year. This would have resulted in the possible exclusion of cases immediately after the facility began operation, when emissions may be higher or more variable as the facility establishes its management processes and best-practises. In addition, by using hospitalisation data we are only capturing severe health outcomes and thus, milder health effects are not being contemplated here (probably dealt with at a primary health care or emergency department unit or at home if minor). We used the NHS standard definition of readmission being within 30 days or index admission. However, this may vary by disease.

4.4. Results interpretation

Hospital admissions represent more severe respiratory episodes. Therefore, our results showing no significant associations between modelled *Aspergillus fumigatus* exposure and respiratory-related hospitalisation suggest that bioaerosols are unlikely to have a severe impact on respiratory disease. However, given the limitations in the dispersion modelling, risks cannot be completely ruled out. We cannot rule out an impact on less severe symptoms managed without admission to hospital (e.g. home managed, as outpatients, or with General Practitioners (GPs)). Patients with existing chronic diseases are also more likely to be closely monitored and thus, complications of their health status may be detected and addressed at early stages, avoiding severe complications and thus, hospitalisation.

We cannot rule out residual confounding. Additionally, people living in most exposed areas may take medication in response to mild symptoms triggered by the exposure itself which would avoid their condition to worsen and thus, lead to hospitalisation (Silverwood et al., 2018). Also, it has been suggested that sustained exposure to bioaerosol emissions over time may act as a selection pressure to improve the immune system (i.e. the biodiversity hypothesis (von Hertzen et al., 2011), an extension of the hygiene hypothesis (Strachan, 1989)). Our results could potentially reflect the establishment of an immune tolerance to bioaerosols in higher exposed areas.

This study is a cross-sectional ecological study, and thus, results apply to areas and not individuals, and do not inform on longer-term trends of disease. We were unable to account for migration in and out of areas, individual-level factors (such as personal exposure, medical history, presence of indoor mould, building quality and insulation, etc.) or investigate seasonal patterns.

4.5. Future considerations

Future studies should consider individual-level exposure and health outcomes over longer time periods, making use of emerging work improving on measurement and modelling of bioaerosols emissions from composting facilities. Multiple health-effects should be explored, using objective health measurements (e.g. lung function, inflammatory markers, changes in the respiratory microbiome), alongside subjective symptom diaries and questionnaires. It is essential for these measurements to be conducted longitudinally at regular intervals (ideally in real-time), to capture peaks and troughs in exposure and subsequent health impacts. Indoor bioaerosol exposure should also not be ignored, as outdoor bioaerosols may enter and colonise nearby buildings, which is not currently well understood. Moreover, indoor exposure may be an important confounder, as people working or living in damp buildings are more likely to be exposed to fungi, which can cause several respiratory conditions (European Lung Foundation. Mould, 2017).

5. Conclusions

We conducted a national small-area cross sectional study of health effects of estimated *Aspergillus fumigatus* emissions from large scale composting facilities. Results did not show any increased risk of all types of respiratory-related conditions together, respiratory infections, asthma, COPD, or Cystic Fibrosis hospital admissions in areas with

higher exposure of *Aspergillus fumigatus*. This suggests that large scale composting facilities do not influence severe respiratory disease prevalence in surrounding communities. However, this needs confirmation, ideally with time-resolved exposure estimates to explore whether daily or weekly spikes in exposure are associated with health impacts. Given the study design, we also cannot comment on potential effects on less severe respiratory disease or symptoms suggested in some previous research, nor on potential for short-term impacts of intermittent high bioaerosol emissions.

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Ethics

The study uses SAHSU data, obtained from NHS Digital and Office for National Statistics. The study was covered by national research ethics approval from the London-South East Research Ethics Committee - reference 17/LO/0846. Data access was covered by the Health Research Authority - Confidentiality Advisory Group under section 251 of the National Health Service Act 2006 and the Health Service (Control of Patient Information) Regulations 2002 - HRA CAG reference: 14/CAG/1039.

CRediT authorship contribution statement

Aina Roca-Barcelo: Data curation, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Philippa Douglas:** Data curation, Methodology, Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition, Project administration, Software. **Daniela Fecht:** Resources, Data curation, Methodology, Writing - review & editing. **Anna Freni Sterrantino:** Methodology, Formal analysis, Software, Validation, Writing - review & editing. **Ben Williams:** Resources, Data curation, Methodology, Writing - review & editing, Software, Validation. **Marta Blangiardo:** Methodology, Software, Validation, Writing - review & editing. **John Gulliver:** Methodology, Writing - review & editing. **Enda T. Hayes:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition. **Anna L. Hansell:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition, Methodology.

Declaration of competing interest

None.

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Supplementary data

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