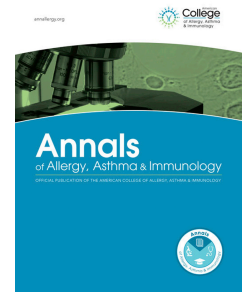


Accepted Manuscript

Effects of Indoor Particulate Matter Exposure on Daily Asthma Control

Syed Hussain, BSc, Sarah Parker, Karen Edwards, Joanne Finch, Antoine Jeanjean, PhD, Roland Leigh, PhD, Sherif Gonem, PhD



PII: S1081-1206(19)30538-1

DOI: <https://doi.org/10.1016/j.anai.2019.07.020>

Reference: ANAI 2966

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 6 March 2019

Revised Date: 17 July 2019

Accepted Date: 20 July 2019

Please cite this article as: Hussain S, Parker S, Edwards K, Finch J, Jeanjean A, Leigh R, Gonem S, Effects of Indoor Particulate Matter Exposure on Daily Asthma Control, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.07.020>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Effects of Indoor Particulate Matter Exposure on Daily Asthma Control

¹Syed Hussain BSc

¹Sarah Parker

¹Karen Edwards

¹Joanne Finch

^{2,3}Antoine Jeanjean PhD

^{2,3}Roland Leigh PhD

^{1,4}Sherif Gonem PhD

¹NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Groby Road, Leicester, United Kingdom

²Department of Physics and Astronomy, University of Leicester, Leicester, United Kingdom

³Earthsense, Exploration Drive, Leicester, United Kingdom

⁴Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham, United Kingdom

Address for correspondence:

Dr. Sherif Gonem

Department of Respiratory Medicine

Nottingham City Hospital

Hucknall Road, Nottingham. NG5 1PB, UK

Tel: 0044 115 969 1169

E-mail: sg330@le.ac.uk

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. This work was funded by an Academy of Medical Sciences Starter Grant, supported by the Academy of Medical Sciences, Wellcome Trust, Medical Research Council, British Heart Foundation, Arthritis Research UK, Royal College of Physicians and Diabetes UK, and by the Midlands Asthma and Allergy Research Association. SG was funded by an NIHR Clinical Lectureship. The authors thank the University of Leicester and EarthSense System Ltd for funding the development of the satellite dataset used in this study.

Clinical trial registration: not applicable

Key words: asthma, atopy, particulate matter, aeroallergen, indoor environment, home monitoring

Figures: 4

Tables: 2

Word count: 2878

Abbreviations

HDM	house dust mite
PM	particulate matter
PEF	peak expiratory flow
FeNO	fractional exhaled nitric oxide
ACQ	asthma control questionnaire
AQLQ	asthma quality of life questionnaire
FEV ₁	forced expiratory volume in one second

Introduction

Asthma is a chronic inflammatory airways disease that is initiated and maintained by a complex interaction between genes and the environment¹. Since most people in Europe and the United States spend the majority of their time indoors it is likely that indoor environmental exposures are at least as important as those encountered outdoors². Indoor particulate matter (PM) exposure can arise firstly through activities that involve combustion such as cooking and smoking, and secondly through inhalation of household dust, which contains a variety of aeroallergens such as the house dust mite (HDM) protein Der p1. Allergens derived from domestic animals such as Can f1 (from dogs) and Fel d1 (from cats) are carried on small particles ($< 5 \mu\text{m}$ diameter) which remain suspended in the air for a number of days, whereas HDM allergen is found primarily on larger particles ($> 5 \mu\text{m}$ diameter) which remain airborne for a shorter period following disturbance and may therefore be more difficult to detect unless continuous monitoring is used³⁻⁶.

Previous studies relating indoor PM exposure to asthma outcomes have mostly utilised cross-sectional measurements, and the few studies examining longitudinal relationships have focused on children with asthma⁷⁻¹². Overnight PM exposure may occur due to the carriage of respirable particles from bedding into the breathing zone via convection currents¹³. Temperature-controlled laminar airflow devices have been developed which reduce overnight PM exposure and their potential benefits are currently under investigation in patients with atopic asthma¹³⁻¹⁶.

We hypothesized that overnight particulate matter exposure is associated with day-to-day symptoms, lung function and airway inflammation in patients with asthma and HDM

sensitization. To test this hypothesis we undertook a prospective single-centre panel study, making use of commercially available indoor air quality monitors.

Methods

Participants

Twenty-eight patients with asthma who were sensitized to HDM were recruited from general respiratory and specialist clinics at Glenfield Hospital, Leicester. Asthma was diagnosed in a secondary or tertiary care setting according to British Thoracic Society guidelines¹⁷. HDM sensitization was established by positive skin prick test or raised HDM-specific immunoglobulin E levels in blood. Patients were seen at baseline in the stable state, with no changes having been made to their regular inhaled or oral asthma therapy within the preceding six weeks. All participants were never smokers or ex-smokers with less than 10 pack years' smoking history. Participants were excluded if they shared a home with a smoker or if they had irregular sleep patterns with frequent night shift working. The study was approved by the Leicestershire, Northamptonshire & Rutland Research Ethics Committee 1 (Reference number: 08/H0406/189), and all participants gave their written informed consent. Participants were recruited and studied on a rolling basis from June 2017 to March 2018.

Exposure measurements

Participants were provided with an indoor air quality monitor (Cair; NuWave Sensors, Dublin, Republic of Ireland) which was placed next to their bedside and continuously monitored concentrations of particulate matter (PM) in the surrounding ambient air. The Cair sensor has been previously validated against gold standard fixed PM monitors¹⁸.

Measurements of PM with a diameter $< 10\mu\text{m}$ (PM_{10}) and $< 2.5\mu\text{m}$ ($\text{PM}_{2.5}$) were recorded every minute in units of particles per cubic foot, and transmitted wirelessly to the study centre via a home hub. Participants were asked their usual bedtime and waking time, and mean $\text{PM}_{2.5}$ and PM_{10} concentrations were calculated for each participant day, both during the reported sleep period and during the 24-hour period starting from midnight.

Daily home monitoring

Participants were provided with an electronic symptom diary and peak expiratory flow (PEF) meter (Micro Diary; Carefusion, Basingstoke, UK) and a portable exhaled nitric oxide (FeNO) monitor (NOBreath; Bedfont, Maidstone, UK). The NOBreath unit has been validated against gold standard stationary monitors¹⁹, and we have previously shown that home FeNO measurements using NOBreath are repeatable and correlate with blood and sputum eosinophil counts²⁰. Participants used the Micro Diary unit once per day upon waking in the morning to rate the severity of their overnight asthma symptoms and their morning asthma symptoms, each using a visual analogue scale taking integer values from zero (no symptoms) to ten (severe symptoms). Participants undertook three PEF measurements using the same unit, and the best of the three readings was recorded. Two measurements of FeNO were made each morning using the NOBreath unit, at an exhalation rate of 50 ml/s. These were manually entered by patients into the Micro Diary since NOBreath does not have the facility for storing multiple test results. The average of the two daily readings was utilised in statistical analysis. Participants who utilised Ventolin as their primary reliever inhaler ($n = 15$) were provided with a sensor (Smartinhaler; Adherium, Auckland, New Zealand) which fitted onto the inhaler and recorded each instance of reliever inhaler use with an accurate date and time stamp.

Study visit schedule

Participants attended a baseline visit at which clinical and demographic details were recorded and the home monitoring equipment was introduced and explained. Participants were then followed up for a total of 12 weeks and attended study visits at 4-weekly intervals, at which time data were downloaded from the Micro Diary and Smart inhaler units. Participants also completed the Asthma Control Questionnaire (ACQ)²¹ and Asthma Quality of Life Questionnaire (AQLQ)²², and underwent spirometry. Spirometry was performed according to American Thoracic Society / European Respiratory Society guidelines²³ with predicted values calculated using Global Lung Initiative reference equations²⁴. Short and long-acting bronchodilators were withheld for 4 and 12 hours respectively before study visits.

Statistical analysis

Statistical analysis was performed using SPSS 24 (IBM, Armonk, New York, USA). Relationships between exposure and outcome variables were analysed using cross-correlation and linear mixed effects models.

Cross-correlation quantifies the degree to which the trends in two time series (in this case daily exposure and outcome variables) are related, either at the same time point (lag zero) or when one time series is shifted relative to the other (positive or negative lags). Positive cross-correlation values indicate time series that tend to move in the same direction, whereas negative values indicate time series moving in opposite directions. A cross-correlation of zero at a given lag indicates no relationship between the time series. Cross-correlation was used to assess the relationship between daily exposure and outcome variables in individual participants over a range of lag times (-7 to +7 days). Exposure variables were the average PM_{2.5} and PM₁₀ concentrations measured during the reported sleep period and during the

previous 24 hours. Outcome variables were PEF, FeNO, the sum of overnight and morning symptom scores, and daily reliever inhaler use (for participants in whom this was measured). Cross-correlation results were assessed individually, and were combined across the group to give the mean and 95% confidence interval cross-correlation at each lag time.

Linear mixed effects models were used to assess the longitudinal relationship between medium-term PM exposure and clinical outcomes measured at study visits. We modelled the relationship between average indoor PM_{2.5} and PM₁₀ during the 2 weeks prior to study visits and (i) forced expiratory volume in one second (FEV₁), (ii) ACQ-6 score, and (iii) AQLQ score. ACQ-6 refers to a validated version of the ACQ which does not incorporate the spirometry question²⁵. Clinical outcomes were entered as dependent variables in the model, with exposures specified as fixed effects. An autoregressive covariance structure was specified to account for the observed autocorrelation in the clinical time series.

In order to verify that indoor PM measurements were not reflective of outdoor air pollution levels, we compared 24-hour average PM_{2.5} and PM₁₀ readings measured using Cair with postcode-specific modelled air pollution levels based on satellite imaging data. Modelled PM_{2.5} and PM₁₀ estimates were produced by the Earth Observation Science Group at the University of Leicester with a spatial resolution of 1 km², as previously described²⁶. For each participant, cross-correlation was performed between indoor PM levels measured using Cair and modelled outdoor PM levels.

Statistical power calculation

The primary analysis was estimation of the effect of PM₁₀ exposure on PEF across the cohort, analysed using a linear mixed effects model. Calculation of statistical power was performed

by Dr. Matthew Richardson (University of Leicester) using a simulation approach, based upon an internal pilot comprising the first six participants in the study. A linear mixed effects model was fitted to the pilot data; the dependent variable was PEF and the independent variable was $\log_e(\text{PM}_{10})$. A random intercept for each subject was also included in the model. Estimates for the fixed effect intercept, variance of the random intercept and variance of the error term were obtained from the pilot sample. Values for PEF were then generated according to the regression equation derived from the pilot data, but allowing the regression coefficient for $\log_e(\text{PM}_{10})$ to vary. The random intercept for each subject was assumed to follow a normal distribution, and a normally distributed error term was included in the regression equation. The p-value for the regression coefficient of $\log_e(\text{PM}_{10})$ was obtained using 100 simulations, with sample size fixed at $n=28$. Based on the simulation results, it was estimated that this sample size would be sufficient to detect an effect size of $\log_e(\text{PM}_{10})$ on PEF (L/min) of approximately 5.5 units, (0.0032 units for the untransformed variable PM_{10}) with power=80% at the 5% significance level.

Results

Twenty-seven participants completed the study, with one participant withdrawing due to lack of time. Clinical and demographic characteristics of the participants are shown in Table 1. Participants were followed up for an average of 83 days, with a total of 2248 person-days of follow-up. The average missing data rate was 7.1% for Cair indoor PM monitoring and 21.4% for daily monitoring of PEF, FeNO and symptoms. Figure 1 shows an example time series of mean overnight $\text{PM}_{2.5}$ count. Figure 2 shows $\text{PM}_{2.5}$ levels measured over the 24-hour daily cycle averaged over 2089 person-days of observations. Particle counts peaked in the

morning, and to a lesser extent in the early evening. PM₁₀ counts displayed a similar biphasic pattern (supplementary eFigure 1). Cross-correlation analysis did not reveal a significant relationship between indoor PM counts and outdoor modelled PM levels (supplementary eFigure 2). There was significant day-to-day variability with regard to the exposure and outcome variables, with the exception of PEF. The mean coefficient of variation across the group for each variable was: PM₁₀ – 79%, PM_{2.5} – 60%, PEF – 9%, FeNO – 51%, total symptoms – 104%, reliever use – 51%.

Figures 3 and 4 show group-level cross-correlations between overnight PM counts measured using Cair and clinical outcomes. The group mean and 95% confidence interval of the cross correlations are shown for each lag time (days). A lag of zero refers to effects occurring on the same day; positive lags refer to changes in outcome preceded by changes in exposure; negative lags refer to changes in exposure preceded by changes in outcome. ‘Total symptoms’ refers to the sum of overnight and morning symptom scores; ‘Reliever use’ refers to the number of puffs of salbutamol inhaler used during the 24-hour period starting from midnight. We did not observe significant relationships between daily clinical outcomes and either overnight PM exposure (Figures 3 and 4) or 24-hour PM measurements (supplementary eFigures 3 and 4). A negative correlation of borderline significance was observed between total symptoms and both PM_{2.5} and PM₁₀ at a lag of zero days. We did not observe significant associations between 2-week average overnight exposures and clinical outcomes measured at study visits, as shown in Table 2.

Discussion

We undertook a panel study to test the hypothesis that levels of overnight PM exposure are associated with daily asthma control in patients with HDM sensitization. The hypothesis was plausible given the known ubiquity of the HDM allergen Der p1 in household dust, and the common perception of patients with atopic asthma that their symptoms are triggered by dust exposure. Despite using a range of outcome measures encompassing symptoms, lung function and airway inflammation, as well as a prolonged follow-up time of 12 weeks, we did not observe consistent relationships between PM exposure and clinical outcomes. The results are concordant with those of de Hartog *et al* who also did not observe significant associations between particulate matter exposure and PEF, FEV₁, or forced vital capacity²⁷, although in this study home exposure monitoring only took place for one week at each participant's home, thus limiting the opportunity to observe significant associations.

There are a number of possible explanations for the absence of an observed association between indoor PM levels and asthma control. Participants in our study were recruited in a stable state and their asthma treatment had been optimised in a secondary or tertiary care asthma clinic. Most participants were taking medium or high-dose inhaled corticosteroids and approximately one quarter were taking long-term oral corticosteroids. This treatment may have attenuated the underlying asthmatic response to PM exposure. We found that there was little day-to-day variability in PEF in our study population but there was significant variation in perceived symptoms and FeNO. Secondly, it is possible that the dose-response relationship between PM exposure and asthma outcomes is non-linear such that clinically significant improvements can only be seen if overnight PM exposure is almost eliminated, for instance by using a temperature-controlled laminar airflow device. Since our study was purely observational, it is likely that PM exposure levels remained moderate or high for most participants throughout the study period, without periods of very low exposure which may

have been associated with improved asthma outcomes. However, in general we did observe significant day-to-day variability in mean overnight PM levels, with levels typically varying threefold as exemplified in Figure 1. As would be expected, minute-by-minute PM levels varied to a much greater extent (typically by 3-4 orders of magnitude), presumably due to short periods of activity causing disturbance of dust from soft furnishings and carpets.

While our primary hypothesis focused on overnight exposure we also undertook supplementary analyses using 24-hour exposure, since some of our participants were retired and may have spent significant amounts of time in their homes during the day. In addition, it is likely that increased PM counts in the bedroom were associated with the presence of a person in the room causing disturbance of dust, although it cannot be guaranteed that this person was always the study participant. Nevertheless it is likely that study participants were exposed to the peak PM levels depicted in aggregate in Figure 2 since they are likely to have caused the disturbance of dust resulting in these peak levels. Consistent with this, the morning peak began at approximately 7am, a typical waking time, and extended into the late morning given the time it takes for dust to settle. Similarly the evening peak began at approximately 7pm, coinciding with people returning from work and entering their bedrooms to change clothes and prepare for the evening. In contrast, overnight exposure was relatively low.

A potential limitation of the study was that we measured indoor particulate matter but did not directly measure levels of Der p1 or other aeroallergens. Der p1 is known to be a constituent of house dust in the majority homes in the UK²⁸, and it is known that the composition of house dust does not vary significantly over short time periods within a given household²⁹. Therefore, day-to-day trends in particulate matter exposure are likely to mirror trends in Der

p1 exposure within each household, and our analysis methods were designed to compare trends in exposure and outcome variables rather than absolute values. Nevertheless, direct measurements of personal exposure to Der p1 and other aeroallergens may have yielded stronger associations with clinical outcomes, and novel methods such as those recently developed by Tovey *et al*³⁰ may allow such studies to be performed in future.

We utilised a portable PM monitor which had been specifically designed for residential use and had the advantage of excellent temporal resolution. The Cair monitor used a light-emitting diode to detect small (PM_{2.5} and large PM₁₀) particle counts. Although particle counts are not completely equivalent to gold-standard mass-based exposure measurements it has been shown that particle counts using devices similar to Cair usually follow a linear or quadratic relationship with mass measurements³¹. The Cair sensor has been subject to a formal evaluation by the Air Quality Sensor Performance Evaluation Center in the United States which found a linear relationship between Cair particle counts and mass measurements¹⁸.

We did not detect significant associations between indoor PM counts and modelled outdoor levels, suggesting that contamination from outdoor sources was unlikely to have been a major source of confounding. Previous studies have found that the infiltration factor (the fraction of outdoor particles that enter an indoor microenvironment and remain suspended) is approximately 0.6 for PM₁₀, and ranges between 0.4 and 0.8 for PM_{2.5}³². The infiltration factor depends on the air exchange rate, penetration efficiency and the particle deposition rate, all of which are heavily dependent on building construction. The lack of association between indoor and outdoor PM levels seen in our study may be related to the fact that most

of our participants resided in rural or suburban districts with a relatively low burden of outdoor air pollution.

In conclusion, we did not observe significant associations between indoor PM exposure and clinical outcomes in patients with asthma and HDM sensitization. Further studies directly measuring personal exposure to a range of aeroallergens throughout the day are needed to fully elucidate the relationship between allergen exposure and asthma clinical outcomes.

References

- 1) Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet*. 2018; 391(10122): 783-800.
- 2) Subramanian A, Khatri SB. The Exposome and Asthma. *Clin Chest Med*. 2019; 40(1): 107-123.
- 3) Custovic A, Green R, Fletcher A, Smith A, Pickering CA, Chapman MD, Woodcock A. Aerodynamic properties of the major dog allergen Can f 1: distribution in homes, concentration, and particle size of allergen in the air. *Am J Respir Crit Care Med*. 1997; 155(1): 94-8.
- 4) Custovic A, Simpson A, Pahdi H, Green RM, Chapman MD, Woodcock A. Distribution, aerodynamic characteristics, and removal of the major cat allergen Fel d 1 in British homes. *Thorax*. 1998; 53(1): 33-8.
- 5) Custovic A, Simpson B, Simpson A, Hallam C, Craven M, Woodcock A. Relationship between mite, cat, and dog allergens in reservoir dust and ambient air. *Allergy*. 1999; 54(6): 612-6.
- 6) Custovic A, Woodcock H, Craven M, Hassall R, Hadley E, Simpson A, Woodcock A. Dust mite allergens are carried on not only large particles. *Pediatr Allergy Immunol*. 1999; 10(4): 258-60.

- 7) Isiugo K, Jandarov R, Cox J, Ryan P, Newman N, Grinshpun SA, Indugula R, Vesper S, Reponen T. Indoor particulate matter and lung function in children. *Sci Total Environ.* 2019; 663: 408-417.
- 8) Holm SM, Balmes J, Gillette D, Hartin K, Seto E, Lindeman D, Polanco D, Fong E. Cooking behaviors are related to household particulate matter exposure in children with asthma in the urban East Bay Area of Northern California. *PLoS One.* 2018; 13(6): e0197199.
- 9) McCormack MC, Breyse PN, Matsui EC, Hansel NN, Peng RD, Curtin-Brosnan J, Williams DL, Wills-Karp M, Diette GB; Center for Childhood Asthma in the Urban Environment. Indoor particulate matter increases asthma morbidity in children with non-atopic and atopic asthma. *Ann Allergy Asthma Immunol.* 2011; 106(4): 308-15.
- 10) McCormack MC, Breyse PN, Matsui EC, Hansel NN, Williams D, Curtin-Brosnan J, Eggleston P, Diette GB; Center for Childhood Asthma in the Urban Environment. In-home particle concentrations and childhood asthma morbidity. *Environ Health Perspect.* 2009; 117(2): 294-8.
- 11) Delfino RJ, Quintana PJ, Floro J, Gastañaga VM, Samimi BS, Kleinman MT, Liu LJ, Bufalino C, Wu CF, McLaren CE. Association of FEV1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. *Environ Health Perspect.* 2004; 112(8): 932-41.

- 12) Trenga CA, Sullivan JH, Schildcrout JS, Shepherd KP, Shapiro GG, Liu LJ, Kaufman JD, Koenig JQ. Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study. *Chest*. 2006; 129(6): 1614-22.
- 13) Gore RB, Boyle RJ, Gore C, et al. Effect of a novel temperature-controlled laminar airflow device on personal breathing zone aeroallergen exposure. *Indoor Air*. 2015; 25(1): 36-44.
- 14) Pedroletti C, Millinger E, Dahlén B, Söderman P, Zetterström O. Clinical effects of purified air administered to the breathing zone in allergic asthma: A double-blind randomized cross-over trial. *Respir Med*. 2009; 103(9): 1313-9.
- 15) Boyle RJ, Pedroletti C, Wickman M, et al; 4A Study Group. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax*. 2012; 67(3): 215-21.
- 16) Storrar W, Fogg C, Brown T, et al. Temperature-controlled laminar airflow in severe asthma for exacerbation reduction (The LASER Trial): study protocol for a randomised controlled trial. *Trials*. 2016; 17: 15.
- 17) British Thoracic Society/Scottish Intercollegiate Guidelines Network, 2016. British Guideline on the Management of Asthma. Available from: <https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/>. Accessed 1st May 2018.

- 18) Air Quality Sensor Performance Evaluation Centre, 2017. Field evaluation of Cair. Available from: <http://www.aqmd.gov/aq-spec/evaluations/field>. Accessed 20th June 2018.
- 19) Pisi R, Aiello M, Tzani P, Marangio E, Olivieri D, Chetta A. Measurement of fractional exhaled nitric oxide by a new portable device: comparison with the standard technique. *J Asthma*. 2010; 47(7): 805-9.
- 20) Nanda CR, Singapuri A, Soares M, Monteiro W, Siddiqui S, Gonem S. Domiciliary exhaled nitric oxide and eosinophilic airway inflammation in adults with asthma. *Eur Respir J*. 2016; 48(1): 242-4.
- 21) Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999; 14(4): 902-7.
- 22) Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest*. 1999; 115(5): 1265-70.
- 23) Miller MR, Hankinson J, Brusasco V, et al; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005; 26(2): 319-338.
- 24) Quanjer PH, Stanojevic S, Cole TJ, et al. on behalf of the ERS Global Lung Function Initiative. (2012) Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. *Eur Respir J*. 2012; 40(6): 1324-1343.

- 25) Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med.* 2005; 99(5): 553-8.
- 26) Chambers L, Finch J, Edwards K, Jeanjean A, Leigh R, Gonem S. Effects of personal air pollution exposure on asthma symptoms, lung function and airway inflammation. *Clin Exp Allergy.* 2018; 48(7): 798-805.
- 27) de Hartog JJ, Ayres JG, Karakatsani A, et al. Lung function and indicators of exposure to indoor and outdoor particulate matter among asthma and COPD patients. *Occup Environ Med.* 2010; 67(1): 2-10.
- 28) Simpson A, Simpson B, Custovic A, Cain G, Craven M, Woodcock A. Household characteristics and mite allergen levels in Manchester, UK. *Clin Exp Allergy.* 2002; 32(10): 1413-9.
- 29) Antens CJ, Oldenwening M, Wolse A, Gehring U, Smit HA, Aalberse RC, Kerkhof M, Gerritsen J, de Jongste JC, Brunekreef B. Repeated measurements of mite and pet allergen levels in house dust over a time period of 8 years. *Clin Exp Allergy.* 2006; 36(12): 1525-31.
- 30) Tovey ER, Liu-Brennan D, Garden FL, Oliver BG, Perzanowski MS, Marks GB. Time-Based Measurement of Personal Mite Allergen Bioaerosol Exposure over 24 Hour Periods. *PLoS One.* 2016; 11(5): e0153414.

- 31) Dacunto PJ, Klepeis NE, Cheng K, Acevedo-Bolton V, Jiang R, Repace JL, Ott WR, Hildemann LM. Determining PM_{2.5} calibration curves for a low-cost particle monitor: common indoor residential aerosols. *Environ Sci: Processes Impacts*. 2015; 17: 1959.
- 32) Diapouli E, Chaloulakou A, Koutrakis P. Estimating the concentration of indoor particles of outdoor origin: a review. *J Air Waste Manag Assoc*. 2013; 63(10): 1113-29.

Figure legends

Figure 1: Daily time series of overnight mean $PM_{2.5}$ count in a single participant

Figure 2: Diurnal variation in $PM_{2.5}$ counts measured using Cair

Figure 3: Relationship between overnight $PM_{2.5}$ exposure and clinical outcomes

Figure 4: Relationship between overnight PM_{10} exposure and clinical outcomes

Table 1: Clinical and demographic characteristics

Age (years)	53.9 (14.3)
Sex	Female n=9 (33%) Male n=18 (67%)
Body mass index (kg/m ²)	29.8 (6.7)
Smoking status	Ex-smokers n=6 (22%) Never smokers n=21 (78%)
Age of onset of asthma (years)	12.7 (15.8)
Number of asthma exacerbations in the previous year	1 (0 – 2)
Regular inhaled corticosteroid use (n [%])	26 (96%)
Inhaled corticosteroid dose (beclometasone dipropionate equivalent [μ g])	650 (400 – 800)
Regular oral prednisolone use (n [%])	7 (26%)
Leukotriene receptor antagonist use (n [%])	9 (33%)
Oral theophylline use (n [%])	2 (7%)
Long-acting β_2 agonist use (n [%])	23 (85%)
Asthma Control Questionnaire-6 score*	1.6 (1.1)
Asthma Quality of Life Questionnaire score	5.4 (1.1)
Forced expiratory volume in one second (% predicted)	73.8 (25.7)
Forced vital capacity (% predicted)	87.3 (17.7)
Ratio of forced expiratory volume in one second to forced vital capacity (%)	66 (15)
Exhaled nitric oxide at a flow rate of 50ml/s (ppb)	18 (13 – 32.5)

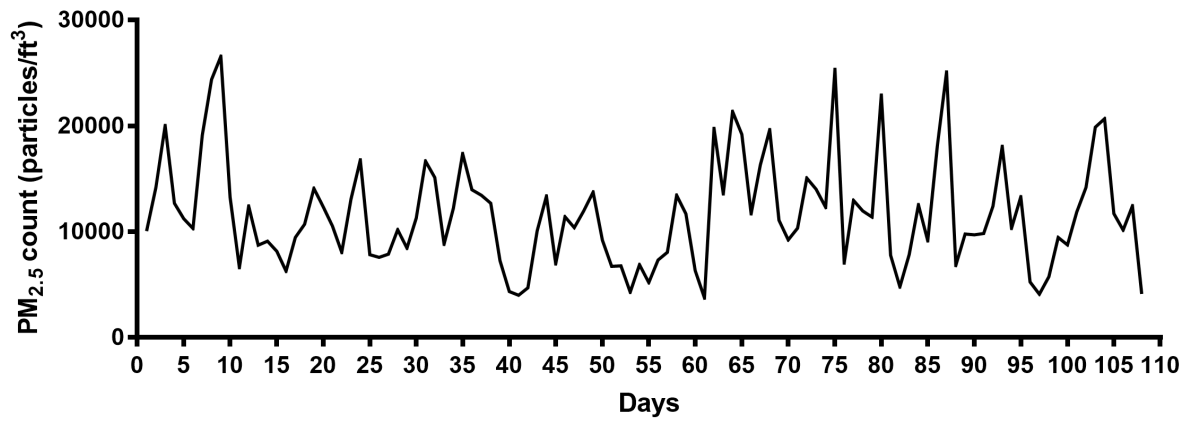
Data are expressed as n (%), mean (standard deviation) or median (interquartile range).

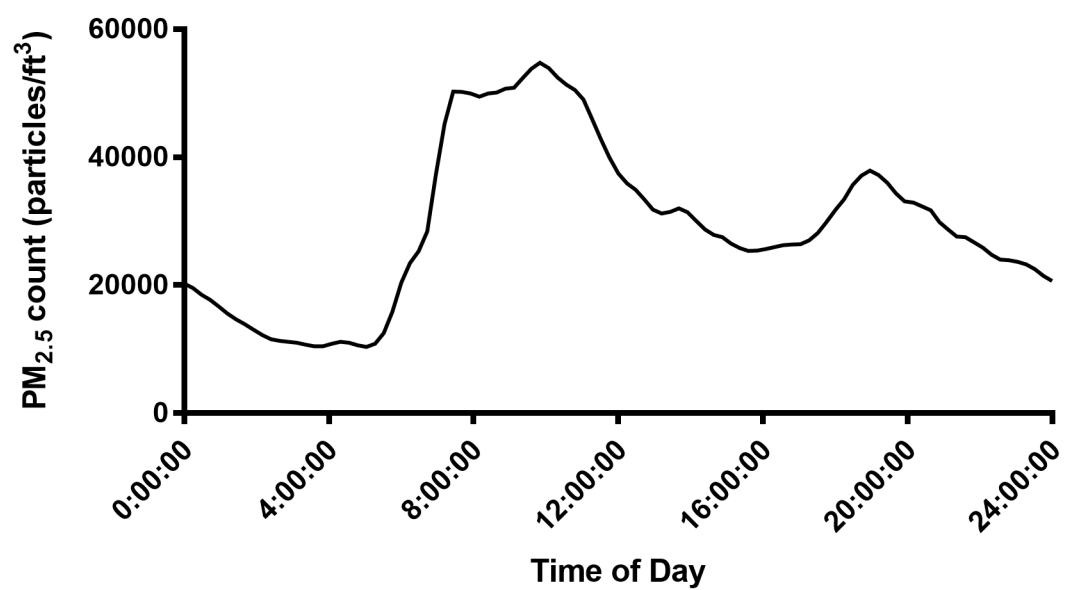
Table 2: Linear mixed models estimating fixed effects of airborne particulate matter exposure on daily clinical outcomes

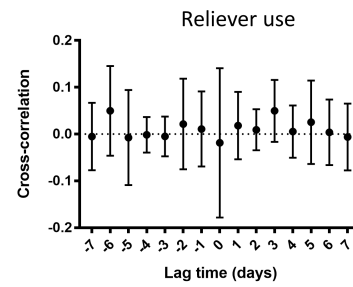
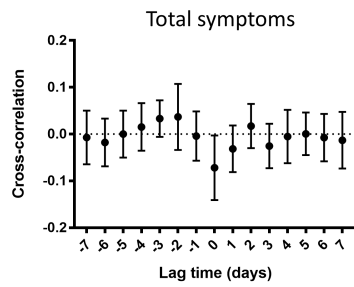
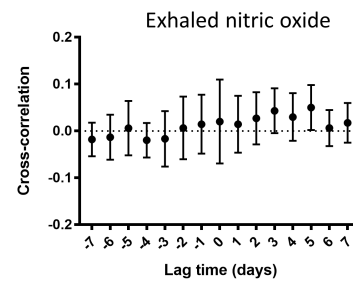
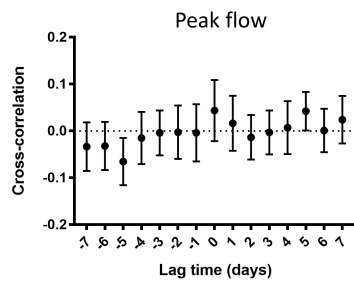
Outcome measure	Estimate of fixed effects (PM _{2.5})*	P value	Estimate of fixed effects (PM ₁₀)*	P value
Pre-bronchodilator FEV ₁ (% predicted)	0.00010	0.75	0.00094	0.78
Pre-bronchodilator FVC (% predicted)	0.00008	0.79	0.00044	0.89
Pre-bronchodilator FEV ₁ /FVC (% predicted)	0.00007	0.78	0.00115	0.67
Post-bronchodilator FEV ₁ (% predicted)	0.00012	0.42	0.00165	0.34
Post-bronchodilator FVC (% predicted)	0.00013	0.20	0.00164	0.16
Post-bronchodilator FEV ₁ /FVC (% predicted)	0.00003	0.78	0.00062	0.63
FEV ₁ bronchodilator reversibility (%)	-0.00004	0.78	-0.00033	0.82
FVC bronchodilator reversibility (%)	-0.00010	0.32	-0.00120	0.27
FEV ₁ /FVC bronchodilator reversibility (%)	0.00008	0.55	0.00010	0.47
ACQ-6 score	0.00001	0.25	0.00015	0.27
AQLQ score	-0.00001	0.28	-0.00013	0.31

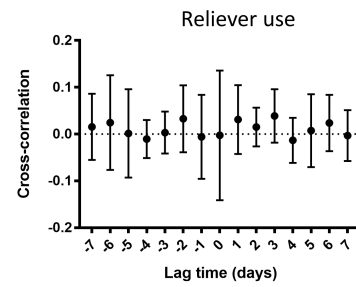
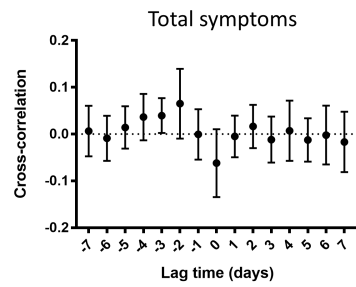
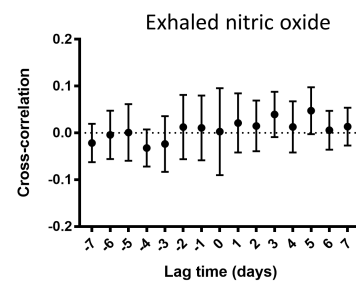
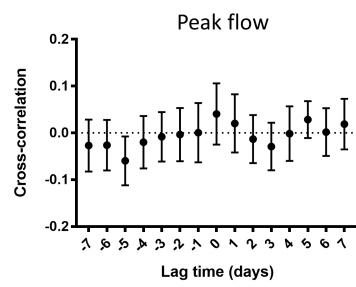
FEV₁ = forced expiratory volume in one second; FVC = forced expiratory volume; ACQ-6 = six-point Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire.

*Exposure variable measured in particles per cubic foot.







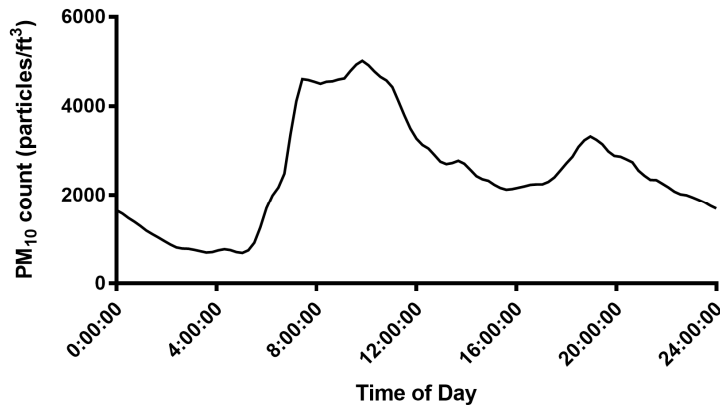


Acknowledgement

The authors gratefully acknowledge Dr. Matthew Richardson who performed the statistical power calculation for the study.

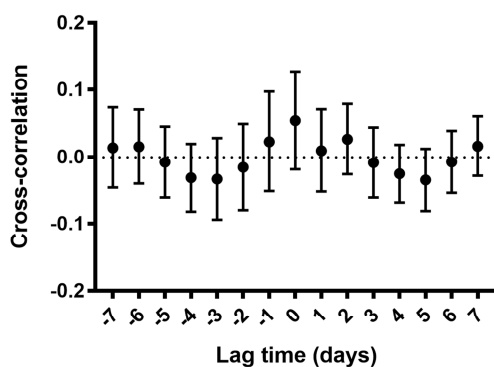
eFigure 1: Diurnal variation in PM₁₀ counts measured using Cair

Average PM₁₀ particle counts are shown during the 24-hour daily cycle over 2089 person-days of observations.

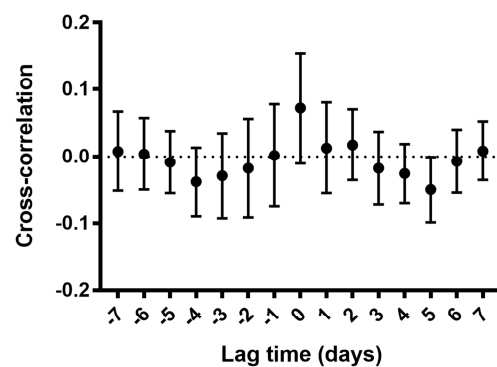
**eFigure 2: Association between modelled outdoor particulate matter levels and indoor levels measured using Cair**

Group-level cross-correlations are shown between modelled outdoor particulate matter (PM) levels and indoor PM counts measured using Cair. The group mean and 95% confidence interval of the cross correlation is shown for each lag time (days). A lag of zero refers to effects occurring on the same day; positive lags refer to changes in indoor PM levels preceded by changes in modelled outdoor levels; negative lags refer to changes in modelled outdoor PM levels preceded by changes in indoor levels. Panels A and B represent the associations for PM_{2.5} and PM₁₀ respectively.

A

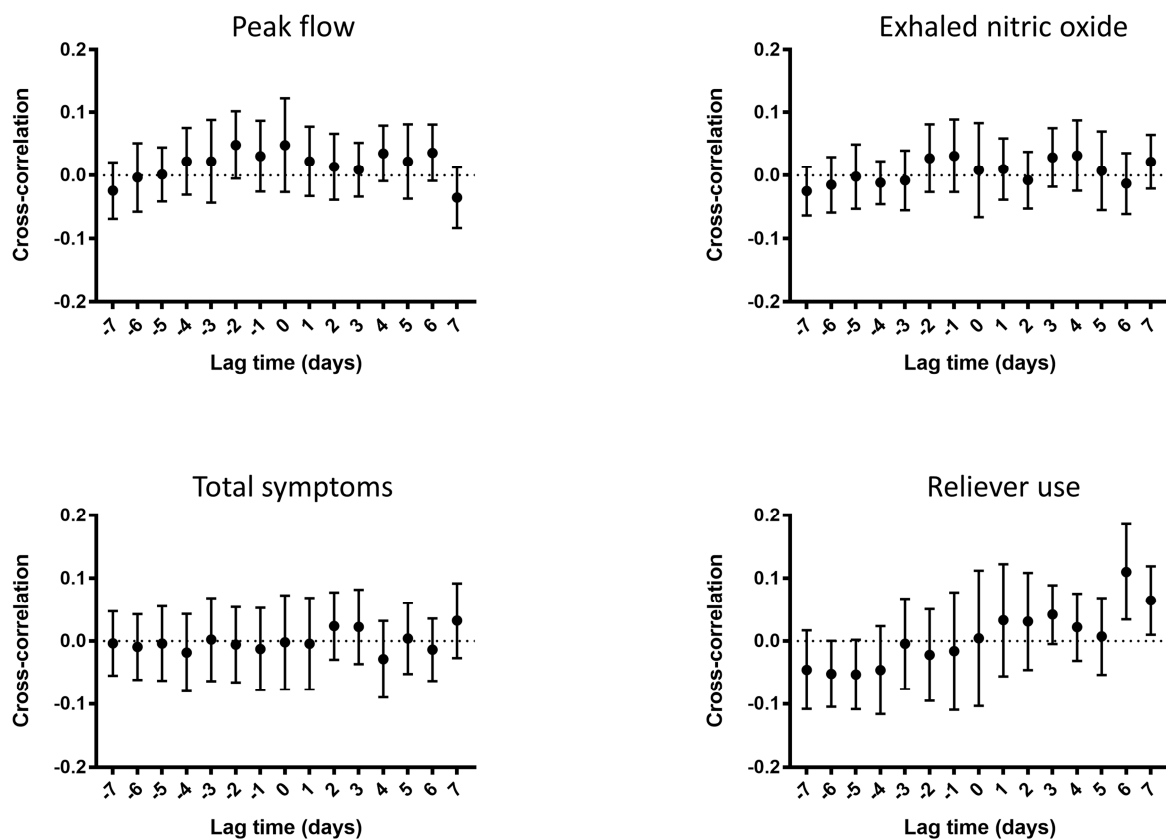


B



eFigure 3: Relationship between 24-hour PM_{2.5} exposure and clinical outcomes

Group-level cross-correlations are shown between 24-hour PM_{2.5} particle counts measured using Cair and clinical outcomes. The group mean and 95% confidence interval of the cross correlation is shown for each lag time (days). A lag of zero refers to effects occurring on the same day; positive lags refer to changes in outcome preceded by changes in exposure; negative lags refer to changes in exposure preceded by changes in outcome. Total symptoms refers to the sum of overnight and morning symptom scores; Reliever use refers to the number of puffs of salbutamol inhaler used during the 24-hour period starting from midnight.



eFigure 4: Relationship between 24-hour PM₁₀ exposure and clinical outcomes

Group-level cross-correlations are shown between 24-hour PM₁₀ particle counts measured using Cair and clinical outcomes. The group mean and 95% confidence interval of the cross correlation is shown for each lag time (days). A lag of zero refers to effects occurring on the same day; positive lags refer to changes in outcome preceded by changes in exposure; negative lags refer to changes in exposure preceded by changes in outcome. Total symptoms refers to the sum of overnight and morning symptom scores; Reliever use refers to the number of puffs of salbutamol inhaler used during the 24-hour period starting from midnight.

