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Associations between environmental factors and hospital admissions for sickle cell disease

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Abstract

Sickle cell disease is an increasing global health burden. This inherited disease is characterised by a remarkable phenotypic heterogeneity, which can only partly be explained by genetic factors. Environmental factors are likely to play an important role but studies of their impact on disease severity are limited and their results are often inconsistent. This study investigated associations between a range of environmental factors and hospital admissions of young patients with sickle cell disease in London and in Paris between 2008 and 2012. Specific analyses were conducted for sub-groups of patients with different genotypes and for the main reasons of admissions. Generalized additive models and distributed lag non-linear models were used to assess the magnitude of the associations and to calculate relative risks. Some environmental factors significantly influence the numbers of hospital admissions of children with sickle cell disease, although the associations identified are complicated. Our study suggests that meteorological factors are more likely to be associated with hospital admissions for sickle cell disease than air pollutants. It confirms previous reports of risks associated with wind speed (risk ratio: 1.06/standard deviation [95% confidence interval: 1.00-1.12]) and also with rainfall (1.06/standard deviation [1.01-1.12]). Maximum atmospheric pressure was found to be a protective factor (0.93/standard deviation [0.88-0.99]). Weak or no associations were found with temperature. Divergent associations were identified for different genotypes or reasons of admissions, which could partly explain the lack of consistency in earlier studies. Advice to patients with sickle cell disease usually includes avoiding a range of environmental conditions that are believed to trigger acute complications, including extreme temperatures and high altitudes. Scientific evidence to support such advice is limited and sometimes confusing. This study shows that environmental factors do explain some of the variations in rates of admission to hospital with acute symptoms in sickle cell disease, but the associations are complex, and likely to be specific to different environments and the individual's exposure to them.

Furthermore, this study highlights the need for prospective studies with large numbers of patients and standardised protocols across Europe.

Introduction

The clinical severity of sickle cell disease (SCD) is extremely variable.[1] Genetic and genome wide association studies have so far only explained a small fraction of this phenotypic variability.[2-4] Investigations of the impact of environmental factors, including meteorological factors and air quality, on the severity of the disease conducted across a range of countries have provided inconsistent results partly because of i) the use of potentially inaccurate coded data (e.g. ICD 10) rather than specific hospital records; ii) the intricate relationships between weather and air quality exposure variables; and iii) the use of different modelling approaches to assess such interactions.[5-9] Furthermore, the impact of environmental factors on different types of SCD (HbSS *vs* HbSC) and on the specific clinical complications leading to hospital admissions has not been previously reported (i.e. all genotypes and clinical complications are typically lumped together).

The costs of care for SCD patients are high and increasing.[10] For the year 2010–2011, it was estimated that the total costs of hospitalisations for SCD crisis (as a primary diagnosis) added up to more than £18,000,000 in England.[11] In London, the highest hospital admission rates are seen among males in their 40s, a demographic group in which rates increased from 7.6 to 26.8 per 100,000 between 2001 and 2009.[12] The vast majority of patients with SCD in the UK and in France live in capital cities (68% in London, 70% in Paris area).[13] Identifying environmental factors triggering clinical complications in urban settings could therefore lead to better patient care, which could result in improved quality of life for patients with SCD and their relatives, as well as in reductions in hospital admissions and health care costs.

We investigated the associations between weather, air quality, and daily hospital admissions for pain, fever and acute chest syndrome (ACS) of young patients known to have SCD, over a five-year

period in London and Paris using generalized additive models (GAM) and distributed lag non-linear models (DLNM), adjusted for long-term trends and day of the week. We then compare our results with those of previous studies and discuss the direct impact that these results could have on the prevention of hospital admissions for SCD.

Methods

Data sources

We extracted anonymised daily hospital admission records from 1 January 2008 to 31 December 2012 for patients with sickle cell disease (SCD) under the age of eighteen-year-old at the time of admission living within a radius of ten kilometres from each of the following hospitals: Kings College Hospital (Camberwell), Evelina Children's Hospital (Lambeth) and Royal London Hospital (Whitechapel) in London; and the Necker Hospital for Sick Children (15th arrondissement) in Paris (Supplementary Figure 1). Recorded reasons for hospital admissions were pain, fever, acute chest syndrome (ACS) and other. Information on the genotype of patients, either HbSS or HbSC, was available for the three hospitals in London, but not in Paris. Outcome data were collected by inspection of specific databases of SCD patients and admissions at each hospital to optimise accuracy. Too few admissions of patients with HbS β-thalassemia, a third common form of SCD, were available to be included in the study.

Official meteorological data of daily rainfall (mm); air temperature (°C), relative humidity (%), wind speed (m/s) and atmospheric pressure (hPa) were extracted from the British Atmospheric Data Centre (BADC, http://badc.nerc.ac.uk/view/badc.nerc.ac.uk__ATOM__dataent_ukmo-midas) for several monitoring stations, including Heathrow (51°28'13"N, 0°27'02"W, code 708, the reference station in London) and St James Park (51°30'17"N, 0°07'52"W, code 697, the nearest station to the three hospitals). Measurements were highly consistent across different monitoring stations and, as a result, only data from Heathrow were included in the final analyses. Based on these preliminary analyses (not shown), data were purchased from Météo France only for one meteorological station, Paris Montsouris (48°49'18"N, 2°20'12"E). A composite index of temperature and relative humidity was calculated as a measure of apparent (or "feels like") temperature using the following equations:[14, 15]

Equation 1: $\square\square \approx \square - \left(\frac{100 - \square\square}{5}\right)$

Equation 2: $\square\square = -2.653 + (0.994 \times \square) + \left(0.0153 \times \square\square^2\right)$

where $\square\square$ is the dew point temperature in °C; $\square\square$ is the relative humidity; $\square\square$ is the apparent temperature in °C; $\square$ is the ambient temperature in °C. Lawrence's simple approximation is fairly accurate for relative humidity values above 50%, which matches conditions in London and Paris.

In addition, a "wind chill" index was also included as a composite index of temperature and wind speed (Equation 3):[16]

Equation 3: $\square_{\square\square} = 13.12 + 0.6215 \times \square_{\square} - 11.37 \times \square^{0.16} + 0.3965 \times \square_{\square} \times \square^{0.16}$

where $\square_{\square\square}$ is the wind chill index; $\square_{\square}$ is the air temperature in degrees Celsius (°C); and $\square$ is the wind speed at standard anemometer height (10 meters), in kilometres per hour (km/h).

Daily mean concentrations of carbon monoxide (CO, mg/m^3), nitrogen oxides (NO_X = NO + NO_2; µg/m^3), sulphur dioxide (SO_2, µg/m^3), ozone (O_3, µg/m^3), particle matter in two size ranges (< 10 µm or PM_{10}; and < 2.5 µm, both expressed in µg/m^3), black carbon (µg/m^3) and particle number (N/cm^3) were extracted from the London Air Quality Network (http://www.londonair.org.uk/); the DEFRA Black Carbon (https://uk-air.defra.gov.uk/networks/network-info?view=ukbsn) and the DEFRA Particle Numbers and Concentrations Networks (https://uk-air.defra.gov.uk/networks/network-info?view=particle) for London; and from the AirParif Network (http://www.airparif.asso.fr/en/) for Paris. Because all monitoring stations do not record all the above pollutants for the entire period of time of the study, missing records were present in the time-series. We therefore kept only data from the most complete monitoring stations (i.e. records available for at least 80% of days during the study period) and filled the gaps using an expectation–maximization imputation algorithm for multivariate normal time-series implemented in the *mnimput* function of the *mtsdi* R package. Missing values were therefore estimated by accounting for both correlation between time-series (i.e. from other monitoring stations) and time structure of the series itself (Supplementary Code 1). Air pollutant concentrations were normalised using a log transformation. To assess the error in imputed values, cross-validation based on a left-out sample of 100 daily records was conducted and

the root mean squared error (RMSE) and normalised root mean square error (NRMSE) were calculated (Supplementary Table 1). Separate analyses were run for monitoring stations categorised as "background" and "roadside" sites in London in order to identify potential associations with specific pollution caused by traffic.

Descriptive statistics of hospital admissions (outcome) and environmental variables (exposure) in each of the study settings are shown in Table 1 and Table 2, respectively. Standardised z-score meteorological and air pollution data (Equation 4) were used in the time-series analyses in order to generate relative risks per one standard deviation (SD) increase. Statistical differences between admission rates per year, season, month and day of the week were identified by ANOVAs with Tukey's honestly significant difference (HSD) test.

Equation 4: $\square = \frac{\square - \mu}{\square}$

where x is the exposure record, μ is the mean of the exposure records over the study period, and σ is the standard deviation of the exposure records over the study period.

Data analysis

First, we explored the relationships between the different outcome and standardised exposure variables using quasi-poisson generalized additive models (GAM). We used flexible thin-plate regression splines with shrinkage for long-term trends, seasonality, effects of the year, month and day of the week, and tested for weekend effects.

Second, two standard methods commonly used to assess the relationship between an exposure variable and a health outcome in time-series analyses were implemented: the distributed lag non-linear models (DLNMs) and aggregated case-crossover study (ACC). DLNMs is a flexible modelling framework to describe potential associations with non-linear and delayed effects in time-series data[17]. ACC provides an efficient framework for evaluating associations between transient exposures and the onset of rare acute events, when exposure measurements are not available for each individual[18] In a DLNM, seasonality, long-term trends and confounding by other time-varying factors

(e.g. temperature) are typically corrected by fitting flexible spline functions of the different covariates. While delayed exposure effects can be explored for a specific lag, the DLNM offers the advantage of considering all lags considered together. While various maximum lags (up to 3 weeks) were tested, a lag of one week was considered the most relevant, biologically. The standard analysis of aggregated case-crossover studies is by conditional logistic regression on a time-series dataset, in which each case day (a day with at least one hospital admission for SCD) is matched to all the other days within a given time window (e.g. one month). Relatively short time windows avoid long-term or seasonal effects, accounted for by strata, Fourier series or splines in DLNMs. Various levels of constraints can be added by matching case and control days for a given covariate (e.g. temperature within 1°C) or a combination of covariates (e.g. temperature within 1°C and day of the week). While both methods have been previously used individually to assess environmental influences on SCD hospital admissions,[8, 9] the consistency of results between them has not been previously investigated.

Third, based on the results from single-exposure models, we explored multiple-exposure GAMs for combined lags of 0 and 1. The different combinations of exposure variables used are shown in Supplementary Table 5.

Finally, sensitivity analyses were performed throughout the whole model selection by i) exploring a full range of measurements (e.g. NO, NO_X, NO_2 in turn) from several individual monitoring stations and average values; ii) checking the consistency of the results across different methods; and iii) selecting the best-performing model based on objective criteria (Generalized Cross Validation (GCV), Bayesian Information Criteria (BIC) or Akaike Information Criterion (AIC)). All the analyses were performed with R 3.2.4 and full scripts of the code used are provided in the Supplementary Material and available on request.

The study was discussed with the local research ethics committees, and formal ethical approval was not deemed necessary. All analysed data were fully anonymised. The research was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Results

Over the five-year study period, 1,887 and 346 hospital admissions for SCD (HbSS and HbSC only) were recorded in London and Paris, respectively. The proportions of HbSS and HbSC in London, and the reasons for admissions in London and Paris are shown in Table 1. The average daily number of SCD admissions was 1.03 in London (across the three hospitals) and 0.19 in Paris (1 hospital), with maximums of 5 and 4 per day, respectively. Although individual patient's data were not analysed as part of this study, it is worth noting that some patients may have been admitted several times over the study period.

Average daily hospital admissions of SCD patients revealed differences in temporal patterns (yearly, monthly, daily and per season) between cities, genotypes and reasons for admissions (Table 3 and Figure 3). Average daily hospital admissions in London significantly increased from 0.52/day in 2008 to 0.98/day in 2009 (ANOVA, P=0.001) before stabilizing around 0.85 admissions per day, probably reflecting increasing patient numbers over that time period. No statistically significant difference was observed between years in Paris. In London, admission rates were significantly greater in autumn than in spring (P=0.045), while in Paris, there were fewest admissions in summer (P=0.029). Hospital admissions, particularly for pain, were lower during weekends, both in London (P<0.0001) and Paris (P=0.042). In London, there were significantly more admissions of SCD patients on Mondays compared to Saturdays (P<0.0001), although the peak of admissions of HbSS patients for pain was observed on Tuesday.

GAMs testing for associations between environmental factors and hospital admissions for SCD in London revealed relative risks per one standard deviation increase of 1.06 [95% confidence interval (CI): 1.01-1.12] for rainfall, and 0.93 [0.88-0.99] for maximum atmospheric pressure (Figure 1 and Supplementary Table 2). Specific GAMs looking at genotypes and reasons for admissions suggested that the former association was mostly seen in HbSS patients admitted for pain (1.07 [1.01-1.14]). The latter association was strongest in SCD patients with fever (0.84 [0.75-0.95]). Further

associations were found in HbSS patients with pain and maximum wind speed (1.09 [1.02-1.16]); with fever and CO (1.14 [1.01-1.30]), and with other complications and $PM_{2.5}$ (1.22 [1.02-1.46]). Similar results were obtained when looking only at "background" or "roadside" monitoring stations (results not shown). No specific associations were identified for HbSC patients, possibly due to the smaller numbers. In Paris, we found relative risks of 0.75 [0.57-0.99] for patients with pain in relation to minimum temperature.

DLNMs, which account for lag effects, only supported associations with rainfall (1.06 [1.01-1.12]) at lag 0 in London (Figure 2 and Supplementary Table 3). An association with black carbon at lag 6 was also found (1.08 [1.02-1.16]). A similar effect of wind speed was found in Paris for a lag of 3 days (1.08 [1.02-1.13]). In addition, an association was found with CO at lag 6 (1.14 [1.00-1.29]). For HbSC, significant associations with maximum pressure (0.66 [0.52-0.83] at lag 0) and maximum relative humidity (0.91 [0.84-1.00] at lag 3, 0.88 [0.79-0.99] at lag 4) were found (Supplementary Figure 2). Statistically significant associations often differed when comparing the main reasons for hospital admission (Supplementary Figure 3). For example, maximum temperature was a risk factor at lags 1 & 2 for ACS but not for fever or pain, while maximum pressure appeared protective at lag 0 for pain and fever but not for ACS.

In London, the results of multiple-exposure GAMs support an association between admissions for pain for patients with HbSS, and rainfall and maximum wind speed, while maximum pressure appeared protective for HbSS patients with fever (Supplementary Table 5). No statistically significant associations were found in multiple-exposure analyses for Paris. These results were consistent with the findings of single-exposure GAMs. A summary of the convergence and divergence of associations identified in London and Paris is presented in Table 4.

Discussion

A better understanding of the environmental factors triggering clinical complications in patients with SCD could allow healthcare professionals to give more accurate information to patients about the risks associated with certain conditions, facilitating behavioural changes to avoid clinical complications and hospital admission. Evidence generated so far about the influence of meteorological factors and pollutants on symptoms in SCD often presented discordant results, which are difficult to translate into health policies and patient advice. This is partly because previous studies were mostly small, combining reasons for admissions and not distinguishing between different types of SCD, in addition to the variability of climate effects in different countries. Perhaps the most consistently quoted effect is the increase in episodes of acute pain associated with cold weather. Using high-quality hospital records from London and Paris, combined with rigorous time-series analysis methods, our results do not support strong associations between hospital admissions for SCD and temperature. This might be related to the urban environment in high-income countries, in which the effects of temperature changes may be countered by access to warm clothes and heated buildings. Environmental factors that consistently appeared significant throughout our analyses were rainfall, wind speed and atmospheric pressure. Wind speed has been identified in several previous studies in urban settings, and is emerging as one of the most important meteorological factors[13]. Rainfall has not been consistently linked to increased hospital admissions, but emerges as an important factor, particular precipitating pain in children with HbSS. Both high wind speed and rainfall have the effect of causing rapid skin cooling, which has been implicated as a cause of vaso-occlusive pain in physiological experiments[19], and might be the mechanism of action in this case. While standard composite indices used in this study (i.e. apparent temperature and wind chill) did not reveal statistically significant associations, the development of a novel specific composite index allowing to predict the risk of hospitalization in SCD based on the above results would warrant further investigation.

We also identified a clear weekend effect, in both London and Paris, which is relevant in the broader context of healthcare provision.[20] Lower admissions during weekends, particularly for pain, may arise from many different social and logistical issues, but are unlikely to be primarily related to environmental factors. Perhaps the most plausible explanation is that parents were able to stay at home and look after their children at the weekends, whereas this becomes much harder during the working week. It does suggest that improved community support for families with sick children may be effective at reducing hospital admissions. Although patients included in this study were managed by hematologists familiar with SCD, delaying seeking healthcare could also reflect the distress of facing common misconceptions (e.g. lack of tolerance to pain, drug addiction) previously reported among medical staff and of longer waiting times compared to other complications (e.g. long bone fracture) previously reported in emergency departments.[21]

To the best of our knowledge, this study is the largest to use accurate hospital-based registers of patients with SCD with data specifically collected for this study. Other large studies have relied on coded data generated for routine administrative purposes, which are often associated with misclassification errors. We also analysed the different types of SCD separately, as there is considerable evidence that the pathophysiology of HbSS and HbSC disease is significantly different.[22] Furthermore, we focused on young children to avoid a series of confounding factors involved at older ages (e.g. smoking, occupational exposure, comorbidities) and used rigorous statistical methods, which revealed mostly consistent results for the main associations identified. Conducting separate analyses for each genotype and reason for admission revealed important differences, which could partly explain the inconsistency of previous results. Despite focusing on a five-year period, the number of admissions in Paris and the number of admissions of HbSC patients in London remained relatively limited, which led to large confidence intervals, potentially masking some associations.

Extreme temperatures are believed to trigger acute vaso-occlusive complications in patients with SCD. This is reflected in advice given to patients, but we could not find consistent support for such an association in our study, although increasing minimum temperature was associated with significant reduction in admissions for acute pain in Paris (RR 0.75, 0.57 – 0.99) (Supplementary Table 2). Instead, we found significant associations with maximum wind speed, which have previously been reported for London.[6] In contrast to an earlier, smaller study in London, we did not find significant association between increased numbers of SCD admissions and low concentrations of nitrogen oxides (NO_x), low concentrations of carbon monoxide (CO) and high concentrations of ozone (O_3).[7]

A recent study of 17,710 emergency hospital admissions (EHA) of SCD patients in Paris concluded that most weather conditions and air pollutants assessed were correlated to each other and influenced the rate of EHA in SCD over a lag period of one week.[8] CO concentrations, day-to-day mean temperature drop and higher wind speed were associated with increased risks in a multiple-exposure analysis. Contrary to our study, the authors did not find a weekend effect, which might be due to their focus on emergency admissions. Despite using a much larger number of admissions, they were partly based on ICD codes, included all types of SCD and all reasons for admission, and covered a much broader age range (2 to 70 year-old). These findings may differ from ours because risk factors for acute complications may be very different in children than adults; additionally, children are known to spend most of their time close to home, exposed to the same environment, whereas adults often work far from home and are potentially exposed to several different environments each day.

Another recent study assessing the association between air pollution and emergency visits of children with SCD in Sao Paulo, Brazil, found remarkably high increases in relation to PM_{10}, NO_2, CO and O_3.[9] We could not find consistent risks associated with pollutants in this study, particularly of the magnitude described in Brazil. While both studies tested for lag effects, the Brazilian study looked at up to four day lags while we tested for effects up to one week. The levels of exposure to pollution

and environmental co-factors are very different in Brazil (e.g. NO_2 = 104.59µg/m^3±48.56; $T°_{min}$ = 15.23°C±3.40) compared to London (NO_2 = 56.18µg/m^3±16.84; $T°_{min}$ = 7.73°C ±5.19) and Paris (NO_2 = 35.76 µg/m^3±13.00; $T°_{min}$ = 9.04°C ±5.79), and it is perhaps unsurprising that the findings are different.

Environmental factors are important determinants of acute complications in children with SCD, but these effects are complex and differ significantly with geography and city design, even between apparently similar cities such as London and Paris. Better understanding of these factors in different geographic settings is important to allow patients and families to be given accurate information on how to reduce the risk of acute complications. This approach is particularly important in a chronic disease, such as SCD, for which there are few effective therapeutic options. Although the precise mechanism by which wind speed could trigger complications in SCD is not clear, it represents the environmental factors that is most consistently identified in association studies in European cities.

Further studies are needed to accurately define environmental effects in SCD. These are particularly relevant in some cities in sub-Saharan Africa and India, where pollution levels and patient numbers are very high[23], and are likely to become more relevant as global warming and air pollution increase. Future studies need to consider the different types of SCD separately, and also consider how these may change with the age of the patient. Other important questions on environmental effects which need to be answered include the role of the home environment and the long-term effects of exposure to air pollutants.[13] Due to the range of complications associated with SCD and to differences in exposures between patients living in urban environments, monitoring the exposure of large number of patients through personal devices (e.g mobile phone apps or personal monitors) might be particularly informative. Environmental factors in SCD are particularly important to understand because they can be manipulated relatively easily and cheaply with simple advice, unlike genetic causes of variation. Increased knowledge in this area will also be valuable for public health

services, to understand when more patients will be admitted to hospital, and what housing requirements are important for families with SCD.

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Author contributions

FBP, GWF and DCR were responsible for the study concept and design. ST, VB, AF, VG, BI, PT, MdM were involved in data acquisition. All authors were involved in analysis and interpretation of data. FBP and DCR drafted the manuscript, and all authors revised it critically for important intellectual content. FBP and DCR had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Tables

Table 1. Summary statistics of SCD admission data (outcome) in London and Paris between 1st January 2008 and 31st December 2012

City	Hospital	Average age	M/F ratio	Reason for admission	Number of admissions				
					SCD	SS	%	SC	%
London	King's College Hospital	8	1.76	All	471	439	*93%*	32	*7%*
				Pain		283	*60%*	16	*3%*
				Fever		62	*13%*	6	*1%*
				ACS		47	*10%*	3	*1%*
				Other		47	*10%*	7	*1%*
	Royal London Hospital	10	1.00	All	445	403	*91%*	42	*9%*
				Pain		258	*58%*	30	*7%*
				Fever		77	*17%*	12	*3%*
				ACS		25	*6%*	0	*0%*
				Other		43	*10%*	0	*0%*
	Evelina London Hospital	6	0.78	All	558	510	*91%*	48	*9%*
				Pain		318	*57%*	29	*5%*
				Fever		129	*23%*	14	*3%*
				ACS		32	*6%*	1	*0%*
				Other		29	*5%*	4	*1%*
	Total	8	1.19	All	1474	1352	*92%*	122	*8%*
				Pain		859	*58%*	75	*5%*
				Fever		268	*18%*	32	*2%*
				ACS		104	*7%*	4	*0%*
				Other		119	*8%*	11	*1%*
Paris	Necker Hospital	8	1.09	All	347	347	*100%*		
				Pain		201	*58%*		
				Fever		51	*15%*		
				ACS		12	*3%*		
				Other		83	*24%*		

Table 2. Summary statistics of the meteorological and air quality parameters (exposure) in London and Paris between 1st January 2008 and 31st December 2012.

		London				Paris			
		Mean	S.D.	Min	Max	Mean	S.D.	Min	Max
Weather	Rainfall (mm)	1.69	3.64	0.00	31.80	1.60	3.68	0.00	43.10
	maximum Temperature (˚C)	14.91	6.42	-0.70	31.00	16.34	7.74	-3.90	38.40
	Minimum temperature (˚C)	7.72	5.19	-9.40	19.70	9.03	5.79	-8.90	22.60
	Maximum wind speed (m/s)	21.26	6.89	5.00	51.00	10.71	3.64	3.10	33.80
	Maximum pressure (hpa)	1,017.89	9.74	984.60	1,043.60	1,016.30	9.14	974.60	1,041.50
	Maximum relative humidity (%)	91.33	5.95	64.10	100.00	85.92	8.45	49.00	99.00
Air quality	CO (µg/m³)	0.37	0.12	0.17	1.58	0.62	0.18	0.25	1.92
	NO2 (µg/m³)	56.18	16.81	16.52	122.32	35.75	12.98	8.46	99.99
	NOX (µg/m³)	126.31	56.49	24.41	537.97	68.33	36.85	18.24	387.95
	O3 (µg/m³)	31.57	16.13	1.09	92.35	45.15	19.76	1.33	134.52
	SO2 (µg/m³)	3.47	1.89	0.52	30.35	/	/	/	/
	PM10 (µg/m³)	28.62	10.77	9.35	96.38	30.14	13.22	7.13	131.87
	PM2.5 (µg/m³)	16.65	10.90	3.29	84.76	20.35	12.05	3.92	119.82
	Black carbon (µg/m³)	5.57	2.25	0.91	16.08	/	/	/	/
	Particle number (µg/m³)	23,919.06	7,457.71	6,890.75	60,832.66	/	/	/	/

Table 3. Effects of day of the week, weekend, season and year on admissions for sickle cell disease in Paris and London between 1st January 2008 and 31st December 2012, based on ANOVA's. Minimum and maximum values are highlighted in green and red, respectively, for columns in which a statistically significant difference was found (P<0.05).

			Average daily admissions												
	London										Paris				
	N	All	SS					SC			SS				
			All	Pain	Fever	ACS	Other	All	Pain	Fever	N	All	Pain	Fever	Other
Day of the week															
Monday	253	0.969	0.881	0.556	0.188	0.050	0.088	0.088	0.556	0.188	57	0.218	0.123	0.034	0.061
Tuesday	245	0.939	0.851	0.598	0.138	0.065	0.050	0.088	0.598	0.138	61	0.234	0.146	0.031	0.046
Wednesday	201	0.770	0.709	0.467	0.107	0.069	0.065	0.061	0.467	0.107	52	0.199	0.115	0.027	0.050
Thursday	210	0.805	0.751	0.452	0.149	0.050	0.100	0.054	0.452	0.149	54	0.207	0.130	0.019	0.054
Friday	226	0.866	0.797	0.460	0.192	0.069	0.077	0.069	0.460	0.192	42	0.161	0.088	0.027	0.038
Saturday	163	0.625	0.571	0.356	0.123	0.061	0.031	0.054	0.356	0.123	36	0.138	0.077	0.031	0.023
Sunday	174	0.667	0.613	0.402	0.130	0.034	0.046	0.054	0.402	0.130	45	0.172	0.092	0.027	0.046
P-value		**<0.0001**	**<0.0001**	**0.001**	0.116	0.644	**0.026**	0.508	0.922	0.354		0.202	0.227	0.978	0.574
Weekend															
Working days	1135	0.870	0.798	0.507	0.155	0.061	0.076	0.072	0.507	0.155	266	0.204	0.120	0.028	0.050
Weekend	337	0.646	0.592	0.379	0.126	0.048	0.038	0.054	0.379	0.126	81	0.155	0.084	0.029	0.034
P-value		**<0.0001**	**<0.0001**	**0.001**	0.169	0.320	**0.005**	0.186	0.717	0.056		**0.042**	**0.046**	0.899	0.181
Season															
Spring	328	0.713	0.659	0.450	0.126	0.043	0.039	0.054	0.450	0.126	82	0.178	0.117	0.022	0.035
Summer	360	0.783	0.713	0.404	0.172	0.048	0.089	0.070	0.404	0.172	69	0.150	0.070	0.026	0.043
Autumn	402	0.884	0.811	0.488	0.171	0.066	0.086	0.073	0.488	0.171	109	0.240	0.143	0.035	0.053
Winter	382	0.845	0.774	0.540	0.117	0.071	0.046	0.071	0.540	0.117	87	0.192	0.111	0.029	0.051

P-value		**0.045**	0.062	**0.029**	0.063	0.254	**0.003**	0.719	0.812	**0.017**		**0.029**	**0.015**	0.700	0.599
Year															
2008	190	0.519	0.475	0.328	0.074	0.044	0.030	0.044	0.328	0.074	84	0.230	0.128	0.033	0.060
2009	353	0.967	0.901	0.545	0.208	0.071	0.077	0.066	0.545	0.208	80	0.219	0.121	0.033	0.049
2010	320	0.877	0.808	0.501	0.167	0.058	0.082	0.068	0.501	0.167	47	0.129	0.077	0.008	0.036
2011	297	0.814	0.759	0.474	0.151	0.060	0.074	0.055	0.474	0.151	69	0.189	0.110	0.030	0.049
2012	312	0.852	0.751	0.503	0.134	0.052	0.063	0.101	0.503	0.134	67	0.183	0.115	0.036	0.033
P-value		**0.001**	**0.007**	**0.017**	0.339	0.893	0.140	**0.019**	0.331	0.235		0.107	0.506	0.925	0.135

Table 4. Summary of the congruence and divergence of statistically significant associations between environmental factors and hospital admissions for sickle cell anemia (SS) in London and Paris between 1st January 2008 and 31st December 2012. Red indicates risk factors, while green indicates protective factors for the following reasons of admissions: all, pain, fever, acute chest syndrome (ACS) or other. Main associations are shown in **bold**.

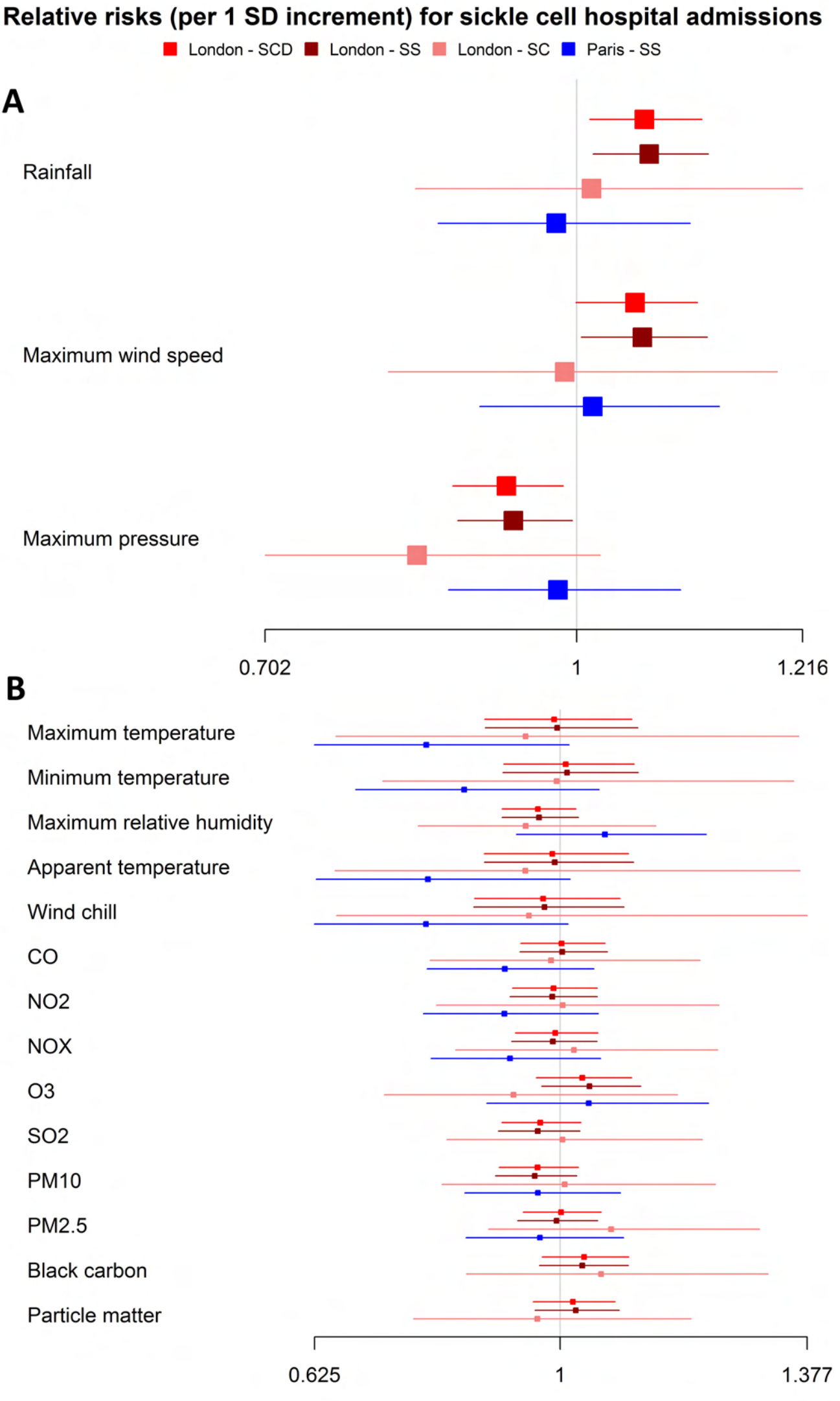
	Factor	London (n = 1,474)	Paris (n = 347)
Temporal patterns	Day of the week	Higher on Mondays, lower on Sundays	No differences
	Weekend	Lower during weekends	
	Season	Higher in Autumn	
		Lower in Spring	Lower in Summer
	Year	Lower in 2008, higher in 2009	No differences
Meteorological factors	Rainfall	***All, Pain*** & ***Fever***	No differences
	Min Temperature	No differences	*Pain*
	Max Temperature	*ACS*	
	Wind speed	***All*** & ***Pain***	
	Atmospheric pressure	***All*** & ***Pain***	No differences
	Relative humidity	*ACS*	No differences
Air quality factors	Carbon monoxide	*Fever*	*All*
	Ozone	*Fever*	No differences
	$PM_{2.5}$	*Pain* & *Other*	No differences
	PM_{10}	*ACS*	No differences
	Black carbon	*All, Pain*	No data
	Particle number	*Pain*	No data

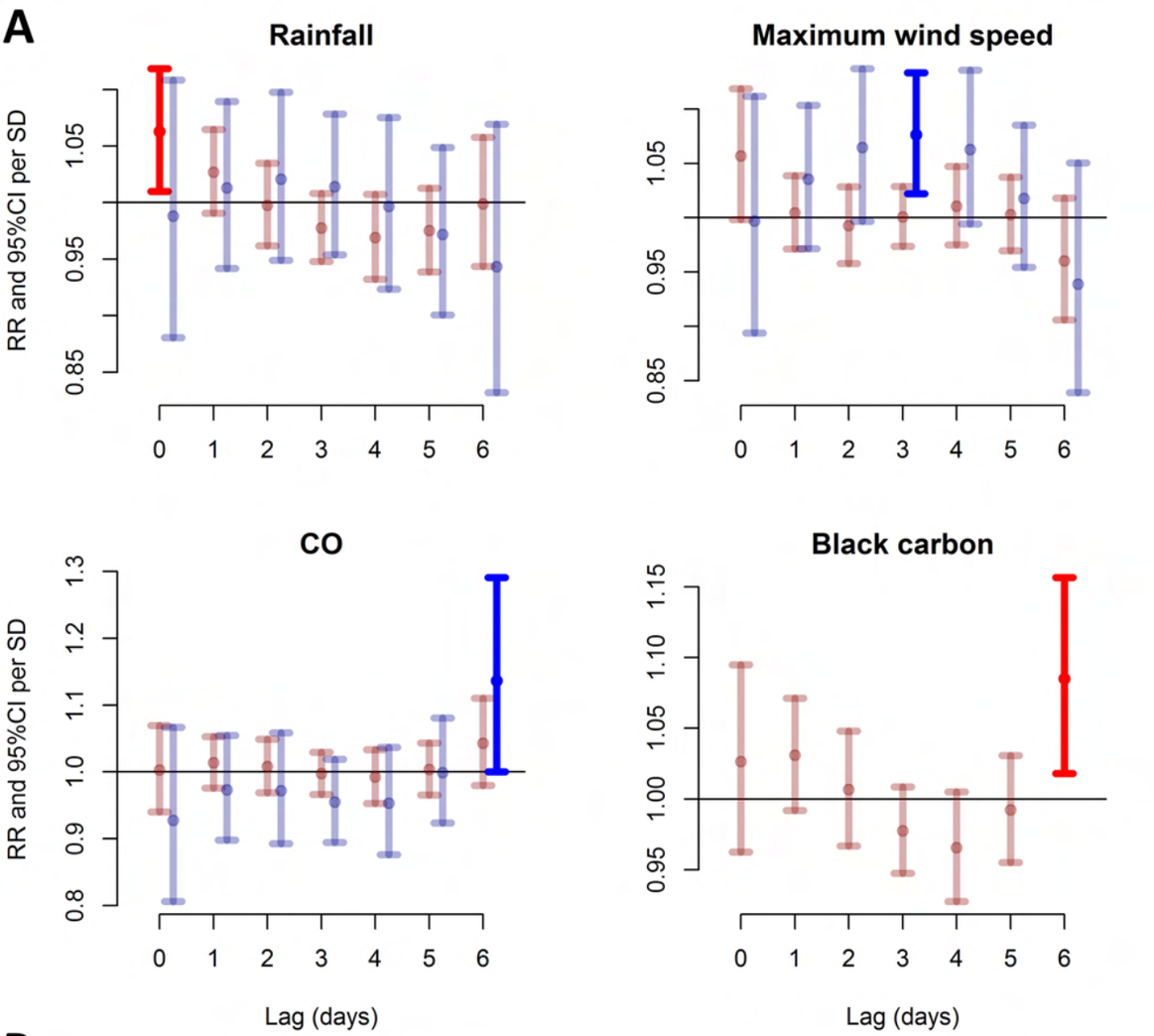
Figures

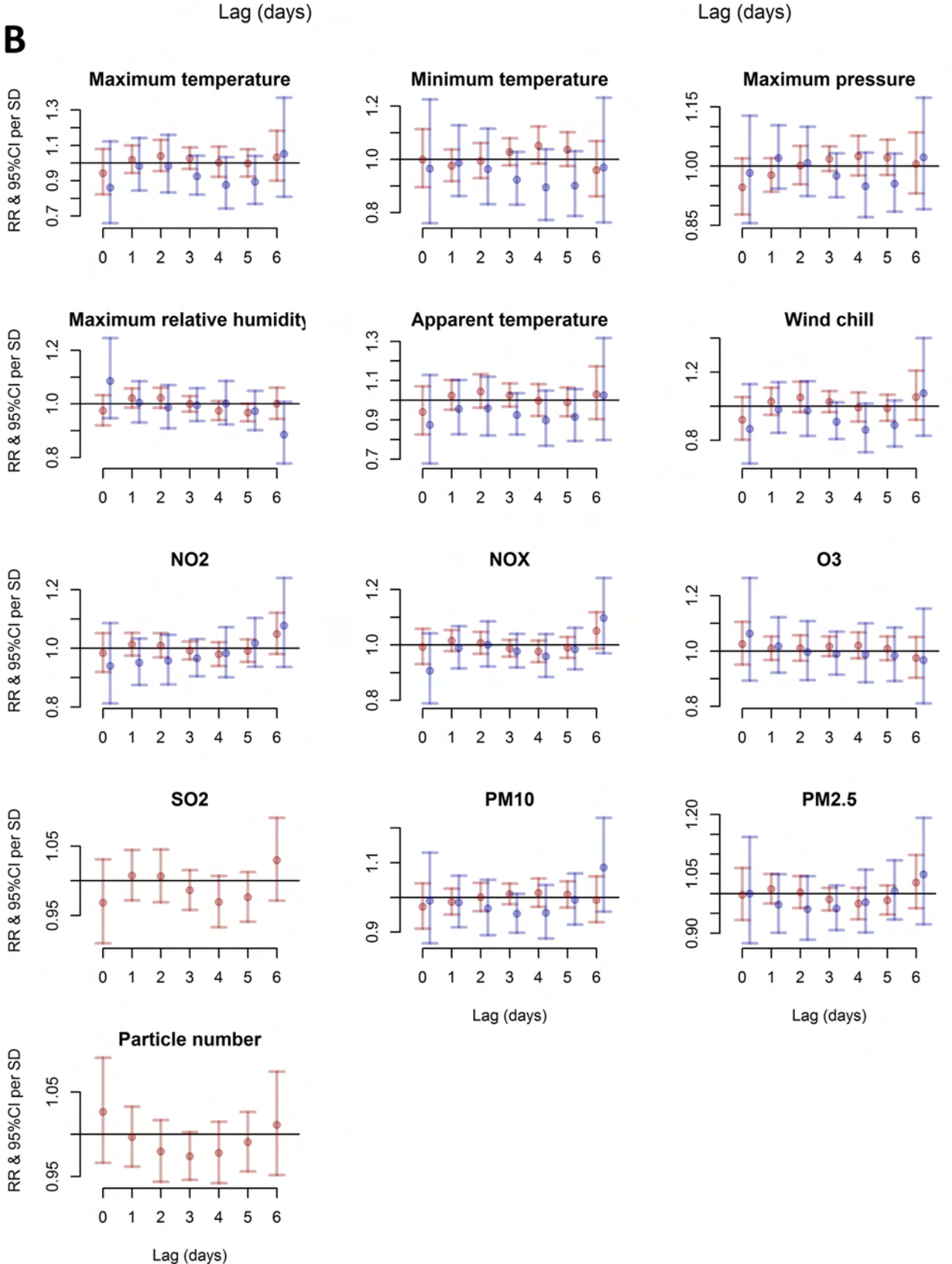
Figure 1. Forest plot of the association at lags 0 and 1 between environmental factors, including weather and air pollution, and hospital admissions for sickle cell disease (SCD) in London and Paris, based on generalised additive models (GAM) corrected for long-term trends and weekend effect. Panel A shows variables with statistically significant associations, while Panel B shows those with non-statistically significant associations.

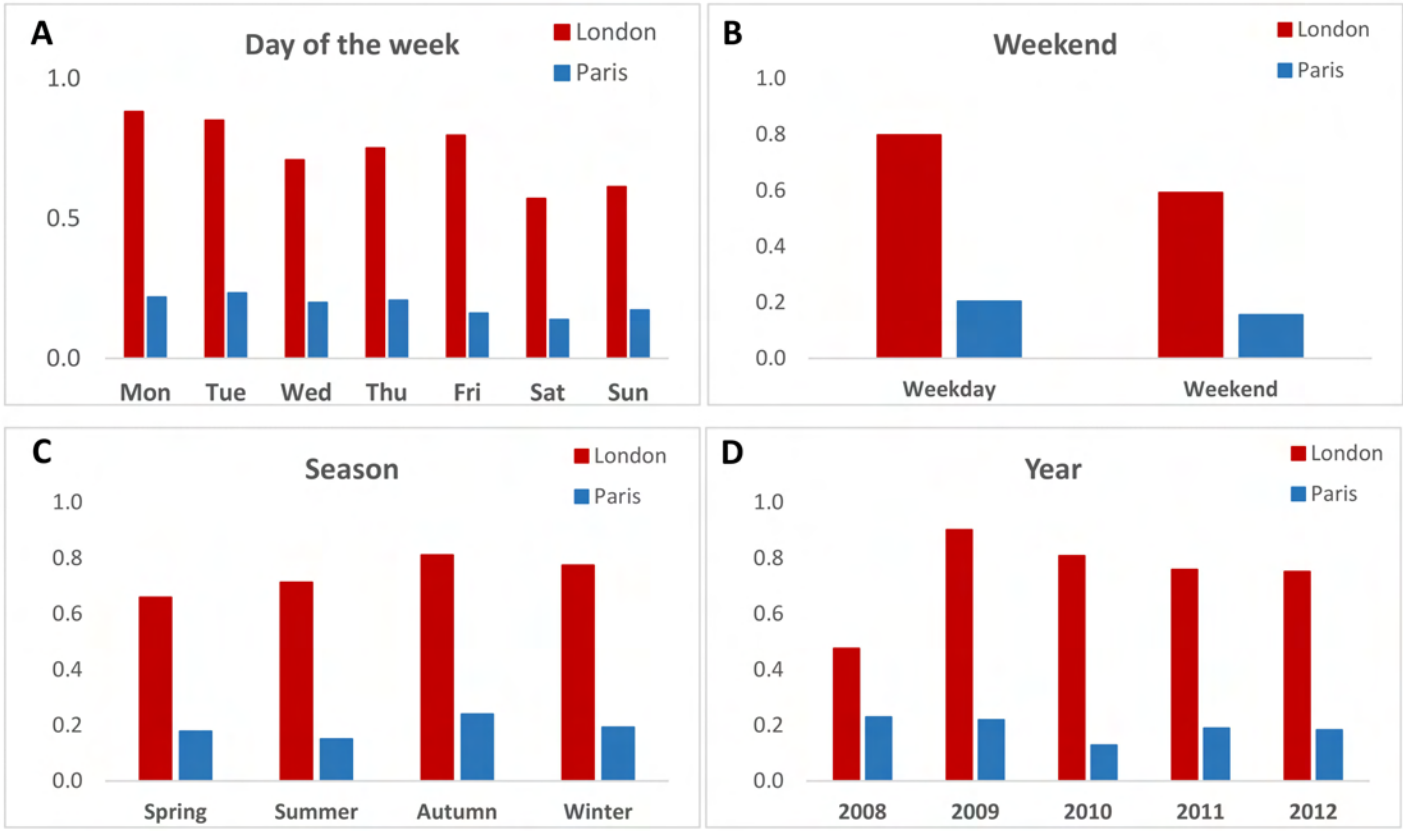
Figure 2. Lag plots of relative risks (RR) and 95% confidence intervals (CI) per standard deviation (SD) increase in 15 exposure variables (6 for meteorological conditions and 9 for air quality) based on distributed lag non-linear models (DLNM) with all lags (0-15 days) modelled together using a polynomial constraint for sickle cell anemia (HbSS) admissions in London (red) and Paris (blue) between 1st January 2008 and 31st December 2012. Panel A shows variables with statistically significant associations, while Panel B shows those with non-statistically significant associations. Statistically significant risks are shown in a brighter red or blue for London and Paris, respectively. Data on black carbon and particle number were not available for Paris.

Figure 3. Average daily admissions for sickle cell anemia per day of the week (A), weekday/weekend (B), season (C) and year (D) in three hospitals in London (red) and one hospital in Paris (blue) between 1st January 2008 and 31st December 2012. The number of * indicates the level of statistical significance (***: $p<0.001$, *: $p<0.05$).


Relative risks (per 1 SD increment) for sickle cell hospital admissions
London - SCD
London - SS
London - SC
Paris - SS
A
Rainfall
Maximum wind speed
Maximum pressure
0.702
1
1.216
B
Maximum temperature
Minimum temperature
Maximum relative humidity
Apparent temperature
Wind chill
CO
NO2
NOX
O3
SO2
PM10
PM2.5
Black carbon
Particle matter
0.625
1
1.377


A
Rainfall
Maximum wind speed
CO
Black carbon
RR and 95%CI per SD
Lag (days)

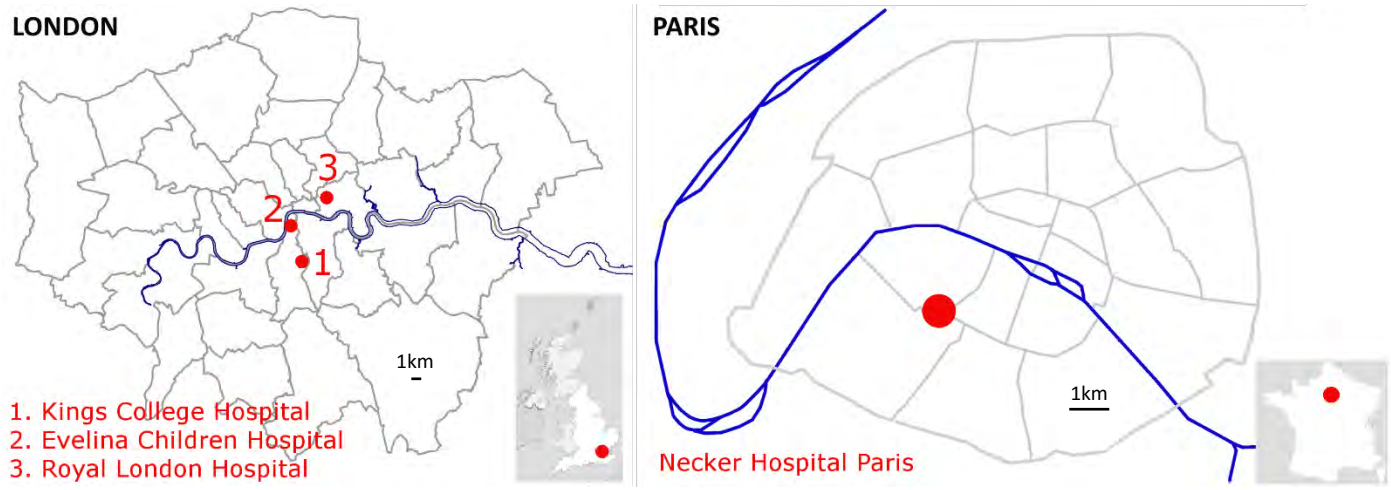

B
Maximum temperature
Minimum temperature
Maximum pressure
Maximum relative humidity
Apparent temperature
Wind chill
NO2
NOX
O3
SO2
PM10
PM2.5
Particle number
RR & 95%CI per SD
Lag (days)


A
Day of the week
London
Paris
1.0
0.5
0.0
Mon
Tue
Wed
Thu
Fri
Sat
Sun
B
Weekend
London
Paris
1.0
0.8
0.6
0.4
0.2
0.0
Weekday
Weekend
C
Season
London
Paris
1.0
0.8
0.6
0.4
0.2
0.0
Spring
Summer
Autumn
Winter
D
Year
London
Paris
1.0
0.8
0.6
0.4
0.2
0.0
2008
2009
2010
2011
2012

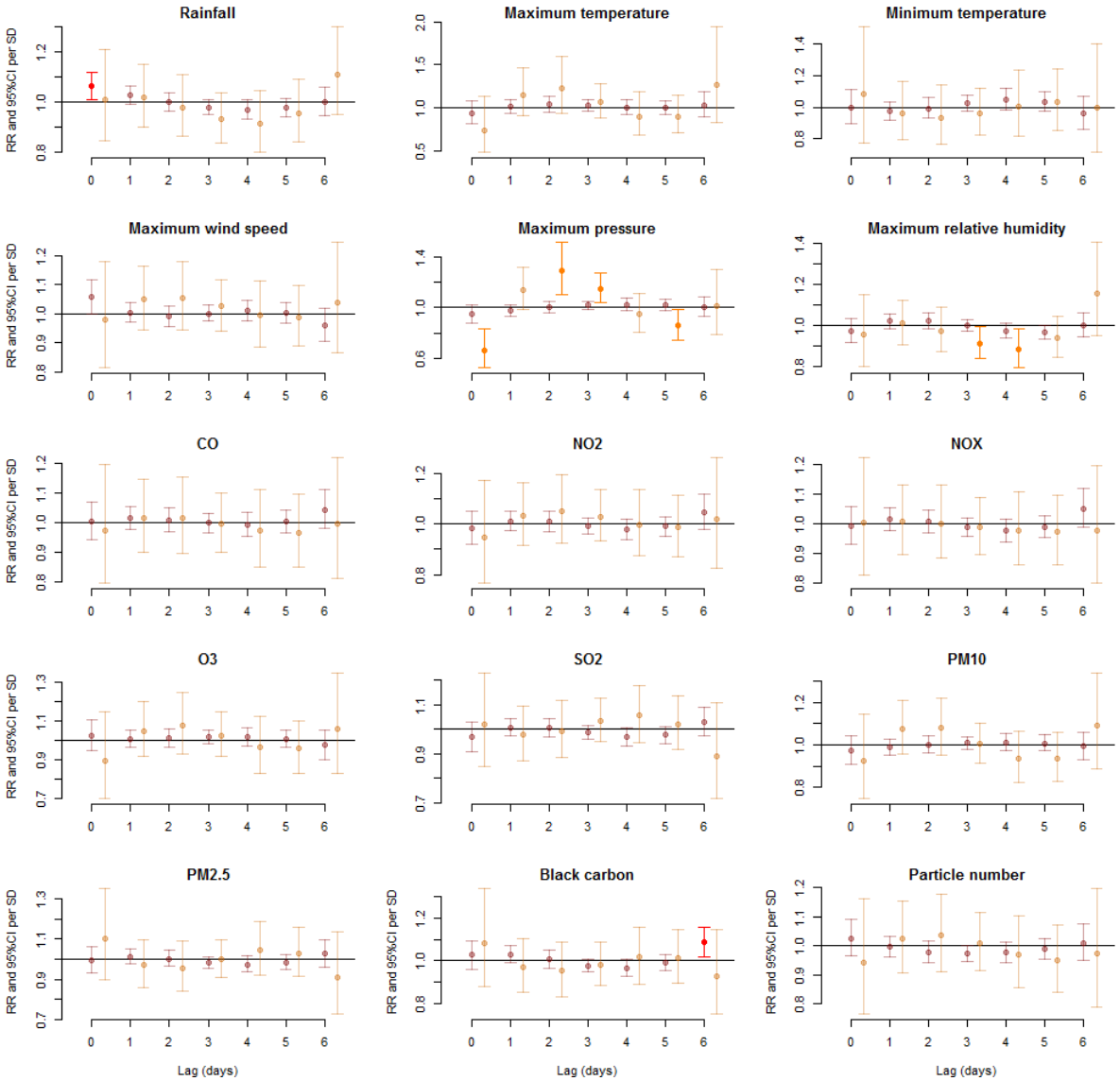
Associations between environmental factors and hospital admissions for sickle cell disease – Supplementary Information

Frédéric B. Piel, Sanjay Tewari, Valentine Brousse, Antonis Analitis, Anna Font, Stephan Menzel, Subarna Chakravorty, Swee Lay Thein, Baba Inusa, Paul Telfer, Marianne de Montalembert, Gary W. Fuller, Klea Katsouyanni & David C. Rees

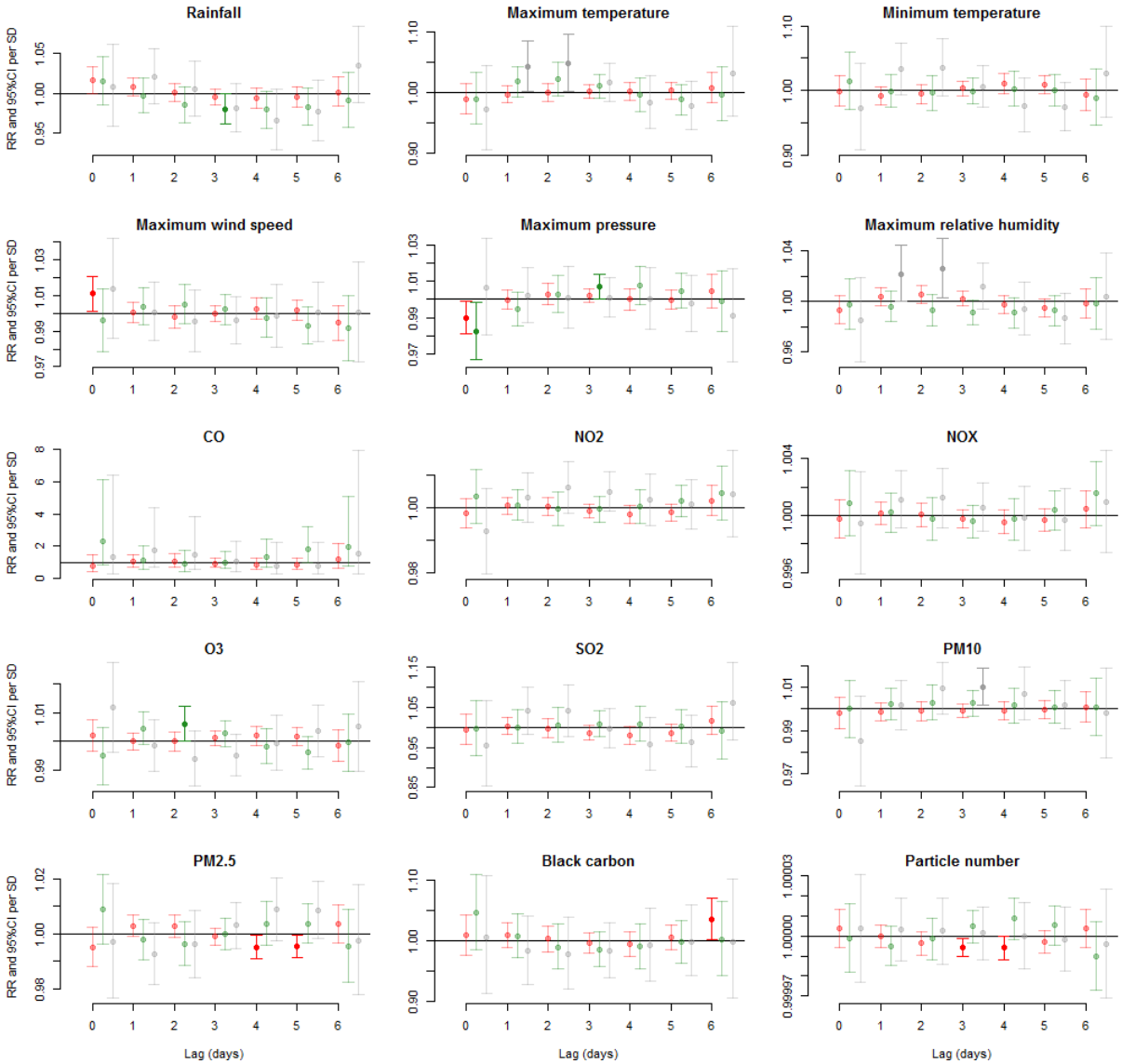
Supplementary Figure 1. Map of the hospitals included in this study, in London (left) and Paris (right).



Supplementary Figure 2. Lag plots of relative risks (RR) and 95% confidence intervals (CI) per standard deviation (SD) increase in 15 exposure variables (6 for meteorological conditions and 9 for air quality) based on distributed lag non-linear models (DLNM) with all lags (0-6 days) modelled together using a polynomial constraint for HbSS (red) and HbSC (orange) hospital admissions in London between 1st January 2008 and 31st December 2012. Statistically significant risks are shown in brighter colours.



Supplementary Figure 3. Lag plots of relative risks (RR) and 95% confidence intervals (CI) per standard deviation (SD) increase in 15 exposure variables (6 for meteorological conditions and 9 for air quality) based on distributed lag non-linear models (DLNM) with all lags (0-6 days) modelled together using a polynomial constraint for sickle cell disease hospital admissions in London for pain (red), fever (green) and acute chest syndrome (grey) between 1st January 2008 and 31st December 2012. Statistically significant risks are shown in brighter colours.



Supplementary Table 1. Number of monitoring stations with more than 80% of records available, root mean squared error (RMSE) and normalised root mean square error (NRMSE) associated with the expectation–maximization imputation algorithm for multiple-exposure normal time-series, based on cross-validation using a left-out sample of 100 daily records, in London and Paris over the 5-year study period (1st January 2008 – 31st December 2012).

			CO	NO2	NOX	O3	SO2	PM10	PM2.5
London	Background	# of stations included	3 (out of 10)	9 (out of 37)	9 (out of 37)	5 (out of 20)	3 (out of 16)	0 (out of 0)	0 (out of 0)
		RMSE (%)	0.09	6.13	14.43	4.95	1.8	NA	NA
		NRMSE (%)	7.32	7.02	5.85	5.96	15.09	NA	NA
	Roadside	# of stations included	4 (out of 11)	21 (out of 76)	21 (out of 76)	6 (out of 13)	2 (out of 15)	16 (out of 71)	1 (out of 12)
		RMSE (%)	0.13	8.78	32.04	5.54	2.84	4.75	NA
		NRMSE (%)	14.37	7.77	6.65	7.00	16.47	7.41	NA
Paris		# of stations included	4 (out of 10)	32 (out of 46)	31 (out of 45)	19 (out of 29)	0 (out of 11)	13 (out of 29)	4 (out of 8)
		RMSE (%)	160.9	6.00	16.03	4.28	NA	3.61	3.57
		NRMSE (%)	11.46	8.75	9.2	4.77	NA	4.04	5.53

Supplementary Table 2. Relative risks (RR) and 95% confidence intervals (CI) from the generalized additive models (GAM) for sickle cell disease admissions and various environmental factors in London and Paris between 1st January 2008 and 31st December 2012. Exposure factors associated to increased/reduced relative risks are shown in red/blue, respectively. The number of admissions falling into each subgroup is shown as N. ACS = Acute chest syndrome.

City	Genotype	Exposure variable	Reason for admission														
			All			Pain			Fever			ACS			Other		
			RR	CI Low	CI Up	RR	CI Low	CI Up	RR	CI Low	CI Up	RR	CI Low	CI Up	RR	CI Low	CI Up
London	SCD	N	1472			934			300			108			130		
		Rainfall	1.06	1.01	1.12	1.07	1.01	1.14	1.05	0.95	1.18	1.02	0.84	1.23	1.08	0.92	1.26
		Maximum temperature	0.99	0.88	1.11	0.95	0.83	1.09	1.08	0.85	1.38	1.17	0.79	1.73	0.93	0.65	1.35
		Minimum temperature	1.01	0.91	1.11	0.98	0.87	1.10	1.06	0.85	1.31	1.02	0.73	1.43	1.07	0.78	1.48
		Maximum wind speed	1.06	1.00	1.12	1.08	1.01	1.16	0.98	0.87	1.11	1.05	0.87	1.27	1.03	0.86	1.24
		Maximum pressure	0.93	0.88	0.99	0.93	0.87	1.00	0.84	0.75	0.95	1.07	0.88	1.31	1.08	0.88	1.31
		Maximum relative humidity	0.97	0.91	1.02	0.96	0.90	1.03	0.95	0.84	1.08	0.96	0.78	1.18	1.04	0.86	1.26
		CO	1.00	0.94	1.07	0.96	0.89	1.04	1.12	0.99	1.26	1.09	0.89	1.32	0.93	0.73	1.18
		NO_2	0.99	0.93	1.06	0.97	0.90	1.05	1.08	0.94	1.24	0.97	0.77	1.21	0.97	0.78	1.20
		NO_X	0.99	0.93	1.06	0.98	0.90	1.05	1.05	0.92	1.20	1.03	0.84	1.27	0.94	0.75	1.17
		O_3	1.03	0.96	1.11	1.05	0.97	1.14	0.98	0.84	1.15	1.13	0.89	1.43	0.96	0.76	1.22
		SO_2	0.97	0.91	1.03	0.98	0.92	1.06	0.99	0.86	1.13	0.94	0.75	1.17	0.83	0.64	1.06
		PM_{10}	0.97	0.91	1.03	0.96	0.89	1.03	1.04	0.91	1.19	0.91	0.73	1.14	0.93	0.75	1.17
		$PM_{2.5}$	1.00	0.94	1.06	0.96	0.90	1.03	1.08	0.95	1.22	0.92	0.74	1.14	1.22	1.02	1.46
		Black carbon	1.04	0.97	1.10	1.03	0.95	1.11	1.09	0.95	1.25	1.01	0.81	1.26	1.03	0.84	1.26
		Particle number	1.02	0.96	1.08	1.03	0.96	1.11	0.98	0.86	1.12	1.03	0.83	1.27	1.03	0.85	1.25
	HbSS	N	1350			859			268			104			119		
		Rainfall	1.07	1.02	1.13	1.07	1.00	1.14	1.06	0.95	1.19	1.04	0.86	1.25	1.10	0.95	1.29
		Maximum temperature	1.00	0.89	1.12	0.93	0.81	1.07	1.12	0.87	1.45	1.26	0.84	1.88	0.97	0.66	1.42
		Minimum temperature	1.01	0.91	1.12	0.97	0.86	1.09	1.07	0.85	1.35	1.08	0.76	1.51	1.12	0.80	1.57
		Maximum wind speed	1.06	1.00	1.12	1.09	1.02	1.16	0.98	0.86	1.11	1.07	0.89	1.30	1.06	0.88	1.27
		Maximum pressure	0.94	0.89	1.00	0.93	0.87	1.00	0.86	0.76	0.98	1.09	0.89	1.33	1.06	0.86	1.30
		Maximum relative humidity	0.97	0.91	1.03	0.96	0.90	1.04	0.95	0.83	1.08	0.97	0.79	1.20	1.04	0.85	1.27
		CO	1.00	0.94	1.07	0.96	0.89	1.05	1.14	1.01	1.30	1.07	0.88	1.32	0.90	0.70	1.16
		NO_2	0.99	0.92	1.06	0.97	0.90	1.06	1.07	0.92	1.24	0.95	0.75	1.20	0.96	0.77	1.21
		NO_X	0.99	0.93	1.06	0.98	0.90	1.06	1.06	0.91	1.22	1.01	0.82	1.26	0.92	0.73	1.17
		O_3	1.04	0.97	1.12	1.05	0.97	1.15	0.99	0.84	1.17	1.17	0.91	1.49	0.98	0.77	1.26
		SO_2	0.97	0.91	1.03	0.98	0.91	1.06	0.98	0.85	1.14	0.94	0.75	1.18	0.85	0.66	1.09
		PM_{10}	0.96	0.90	1.03	0.95	0.88	1.03	1.05	0.91	1.21	0.90	0.72	1.13	0.92	0.72	1.17
		$PM_{2.5}$	0.99	0.94	1.06	0.95	0.88	1.02	1.09	0.95	1.24	0.93	0.75	1.16	1.24	1.03	1.49
		Black carbon	1.03	0.97	1.10	1.03	0.95	1.12	1.07	0.93	1.24	0.98	0.78	1.23	1.03	0.84	1.27
		Particle number	1.02	0.96	1.09	1.03	0.96	1.12	1.00	0.87	1.15	1.01	0.81	1.25	1.02	0.84	1.25
	HbSC	N	122			75			32			4			11		
		Rainfall	1.01	0.85	1.22	1.09	0.89	1.33	0.95	0.66	1.39	/	/	/	/	/	/
		Maximum temperature	0.95	0.66	1.36	1.17	0.74	1.84	0.83	0.38	1.84	/	/	/	/	/	/
		Minimum temperature	0.99	0.73	1.36	1.13	0.76	1.70	0.95	0.52	1.72	/	/	/	/	/	/
		Maximum wind speed	0.99	0.82	1.19	1.03	0.81	1.30	0.97	0.67	1.39	/	/	/	/	/	/
		Maximum pressure	0.85	0.70	1.02	0.88	0.69	1.11	0.75	0.52	1.08	/	/	/	/	/	/
		Maximum relative humidity	0.95	0.78	1.15	0.94	0.74	1.19	0.93	0.62	1.40	/	/	/	/	/	/
		CO	0.99	0.80	1.21	0.95	0.71	1.26	1.01	0.69	1.46	/	/	/	/	/	/
		NO_2	1.00	0.81	1.24	0.91	0.69	1.20	1.25	0.84	1.86	/	/	/	/	/	/
		NO_X	1.02	0.84	1.24	0.98	0.75	1.28	1.07	0.77	1.49	/	/	/	/	/	/
		O_3	0.93	0.73	1.18	1.01	0.76	1.36	0.82	0.49	1.36	/	/	/	/	/	/
		SO_2	1.00	0.83	1.22	1.04	0.82	1.30	1.13	0.80	1.59	/	/	/	/	/	/
		PM_{10}	1.01	0.82	1.24	1.03	0.80	1.32	1.05	0.68	1.64	/	/	/	/	/	/
		$PM_{2.5}$	1.08	0.89	1.30	1.14	0.91	1.43	1.09	0.72	1.65	/	/	/	/	/	/
		Black carbon	1.06	0.86	1.32	0.97	0.74	1.28	1.24	0.85	1.83	/	/	/	/	/	/
		Particle number	0.96	0.78	1.20	0.97	0.74	1.28	0.83	0.55	1.26	/	/	/	/	/	/
Paris	HbSS	N	347			201			51			12			83		
		Rainfall	0.98	0.87	1.11	1.02	0.88	1.19	0.64	0.37	1.11	/	/	/	1.02	0.82	1.27
		Maximum temperature	0.80	0.62	1.01	0.75	0.55	1.02	0.94	0.50	1.77	/	/	/	0.84	0.52	1.36
		Minimum temperature	0.85	0.69	1.06	0.75	0.57	0.99	0.93	0.53	1.63	/	/	/	0.96	0.63	1.45
		Maximum wind speed	1.02	0.91	1.14	1.01	0.88	1.17	0.99	0.75	1.32	/	/	/	1.01	0.81	1.27
		Maximum pressure	0.98	0.88	1.10	0.94	0.81	1.08	1.12	0.84	1.50	/	/	/	1.12	0.89	1.40
		Maximum relative humidity	1.07	0.93	1.22	1.11	0.93	1.32	0.87	0.63	1.21	/	/	/	0.98	0.75	1.28
		CO	0.92	0.80	1.05	0.93	0.78	1.11	1.05	0.77	1.43	/	/	/	0.81	0.61	1.09
		NO_2	0.92	0.79	1.06	0.96	0.79	1.15	1.09	0.77	1.55	/	/	/	0.77	0.57	1.05
		NO_x	0.92	0.80	1.06	0.95	0.80	1.13	1.01	0.74	1.39				0.85	0.63	1.13
		O_3	1.04	0.89	1.23	1.02	0.82	1.25	1.34	0.90	1.99	/	/	/	1.07	0.78	1.48
		PM_{10}	0.97	0.85	1.09	1.03	0.89	1.20	1.09	0.82	1.43	/	/	/	0.78	0.59	1.03
		$PM_{2.5}$	0.97	0.86	1.10	1.05	0.90	1.22	1.04	0.78	1.38	/	/	/	0.77	0.58	1.02

Supplementary Table 3. Relative risks (RR) from the distributed lag non-linear models (DLNM) for sickle cell disease admissions and various environmental factors, at lags up to 6 days, in London and Paris between 1st January 2008 and 31st December 2012. Statistically significant RRs are highlighted in bold. Exposure factors associated to increased/reduced relative risks are shown in red/blue, respectively.

City	Exposure	Lag (days)						
		0	1	2	3	4	5	6
London	Rainfall	**1.06**	1.03	1.00	0.98	0.97	0.98	1.00
	Maximum temperature	0.94	1.02	1.04	1.03	1.00	1.00	1.03
	Minimum temperature	1.00	0.98	0.99	1.03	1.05	1.04	0.96
	Maximum wind speed	1.06	1.00	0.99	1.00	1.01	1.00	0.96
	Maximum pressure	0.95	0.98	1.00	1.02	1.03	1.02	1.01
	Maximum relative humidity	0.97	1.02	1.02	1.00	0.97	0.97	1.00
	CO	1.00	1.01	1.01	1.00	0.99	1.00	1.04
	NO_2	0.98	1.01	1.01	0.99	0.98	0.99	1.05
	NO_X	0.99	1.01	1.01	0.99	0.98	0.99	1.05
	O_3	1.03	1.01	1.01	1.02	1.02	1.01	0.97
	SO_2	0.97	1.01	1.01	0.99	0.97	0.98	1.03
	PM_{10}	0.97	0.99	1.00	1.01	1.01	1.01	0.99
	$PM_{2.5}$	1.00	1.01	1.00	0.99	0.97	0.98	1.03
	Black carbon	1.03	1.03	1.01	0.98	0.97	0.99	**1.08**
	Particle number	1.03	1.00	0.98	0.97	0.98	0.99	1.01
Paris	Rainfall	0.99	1.01	1.02	1.01	1.00	0.97	0.94
	Maximum temperature	0.86	0.98	0.98	0.92	0.88	0.89	1.05
	Minimum temperature	0.97	0.99	0.96	0.92	0.89	0.90	0.97
	Maximum wind speed	1.00	1.04	1.06	**1.08**	1.06	1.02	0.94
	Maximum pressure	0.98	1.02	1.01	0.98	0.95	0.95	1.02
	Maximum relative humidity	1.09	1.00	0.99	1.00	1.00	0.97	0.88
	CO	0.93	0.97	0.97	0.95	0.95	1.00	**1.14**
	NO_2	0.94	0.95	0.96	0.97	0.98	1.02	1.08
	NO_x	0.91	0.99	1.00	0.98	0.96	0.98	1.10
	O_3	1.06	1.02	1.00	0.99	0.99	0.98	0.97
	PM_{10}	0.99	0.99	0.97	0.95	0.96	0.99	1.09
	$PM_{2.5}$	1.00	0.97	0.96	0.96	0.98	1.01	1.05

Supplementary Table 4. Relative risks and 95% confidence intervals from the time-series case-crossover generalized additive models (GAM) for sickle cell disease admissions and various environmental factors in London and Paris between 1st January 2008 and 31st December 2012. Exposure factors associated to increased/reduced relative risks are shown in red/blue, respectively. The number of admissions falling into each subgroup is shown as N. ACS = Acute chest syndrome.

			Reason for admission													
			ALL			PAIN			FEVER			ACS			OTHER		
City	Genotype	Exposure variable	RR	Min	Max	RR	Min	Max	RR	Min	Max	RR	Min	Max	RR	Min	Max
London	SS	N	1350			859			268			104			119		
		Rainfall	1.10	1.03	1.17	1.12	1.04	1.21	1.04	0.91	1.19	1.10	0.86	1.41	1.12	0.91	1.38
		Maximum temperature	0.93	0.81	1.06	0.84	0.71	0.99	1.19	0.88	1.61	1.19	0.75	1.90	0.88	0.56	1.38
		Minimum temperature	0.99	0.88	1.11	0.94	0.81	1.08	1.14	0.88	1.48	1.03	0.68	1.58	1.03	0.70	1.52
		Maximum wind speed	1.07	1.00	1.15	1.10	1.01	1.19	0.94	0.81	1.09	1.12	0.88	1.43	1.18	0.94	1.49
		Maximum pressure	0.91	0.84	0.97	0.90	0.82	0.98	0.87	0.74	1.02	0.96	0.76	1.22	0.99	0.76	1.29
		Maximum relative humidity	0.96	0.89	1.03	0.96	0.88	1.05	0.97	0.82	1.14	0.96	0.75	1.23	0.94	0.72	1.21
		CO	0.99	0.91	1.07	0.95	0.85	1.05	1.08	0.93	1.25	1.20	0.93	1.54	0.79	0.56	1.11
		NO_2	0.96	0.88	1.05	0.95	0.86	1.06	1.02	0.84	1.23	1.02	0.75	1.38	0.87	0.66	1.15
		NO_x	0.97	0.90	1.06	0.96	0.87	1.06	1.01	0.85	1.21	1.20	0.91	1.58	0.82	0.62	1.09
		O_3	1.07	0.98	1.18	1.09	0.98	1.21	0.99	0.80	1.22	1.15	0.83	1.58	1.11	0.82	1.49
		SO_2	0.95	0.88	1.03	0.97	0.89	1.06	0.95	0.78	1.16	1.00	0.79	1.26	0.78	0.58	1.05
		PM_{10}	0.95	0.87	1.03	0.91	0.82	1.01	1.12	0.93	1.35	0.97	0.71	1.32	0.86	0.65	1.14
		$PM_{2.5}$	0.99	0.92	1.06	0.93	0.85	1.02	1.15	0.97	1.37	0.94	0.73	1.21	1.15	0.92	1.45
		Black carbon	1.03	0.95	1.11	1.01	0.92	1.12	1.06	0.89	1.27	0.92	0.68	1.24	1.10	0.85	1.43
		Particle matter	0.96	0.89	1.04	0.96	0.87	1.06	0.94	0.79	1.12	1.02	0.77	1.34	0.93	0.71	1.22
	SC	N	122			75			32			4			11		
		Rainfall	1.04	0.83	1.32	1.13	0.87	1.46	1.02	0.57	1.82	/	/	/	/	/	/
		Maximum temperature	0.86	0.55	1.35	1.00	0.57	1.75	1.04	0.40	2.71	/	/	/	/	/	/
		Minimum temperature	1.05	0.71	1.56	1.20	0.73	1.99	1.14	0.53	2.46	/	/	/	/	/	/
		Maximum wind speed	0.98	0.78	1.24	0.99	0.74	1.33	1.08	0.70	1.67	/	/	/	/	/	/
		Maximum pressure	0.87	0.68	1.10	0.88	0.65	1.19	0.80	0.51	1.27	/	/	/	/	/	/
		Maximum relative humidity	0.95	0.75	1.21	0.94	0.70	1.25	1.00	0.61	1.64	/	/	/	/	/	/
		CO	0.88	0.67	1.17	0.88	0.60	1.30	0.77	0.44	1.35	/	/	/	/	/	/
		NO_2	0.82	0.62	1.10	0.76	0.53	1.10	0.94	0.53	1.68	/	/	/	/	/	/
		NO_x	0.89	0.68	1.16	0.90	0.63	1.27	0.80	0.48	1.35	/	/	/	/	/	/
		O_3	0.94	0.69	1.27	0.97	0.67	1.40	1.05	0.52	2.13	/	/	/	/	/	/
		SO_2	0.86	0.64	1.15	0.93	0.66	1.32	0.85	0.48	1.51	/	/	/	/	/	/
		PM_{10}	0.81	0.60	1.08	0.83	0.58	1.18	0.64	0.32	1.27	/	/	/	/	/	/
		$PM_{2.5}$	1.08	0.84	1.39	1.12	0.83	1.52	1.26	0.68	2.34	/	/	/	/	/	/
		Black carbon	1.00	0.77	1.31	0.89	0.63	1.26	1.04	0.64	1.67	/	/	/	/	/	/
		Particle matter	0.85	0.65	1.13	0.82	0.58	1.15	0.69	0.38	1.26	/	/	/	/	/	/
Paris	SS	N	347			201			51			12			83		
		Rainfall	0.99	0.87	1.14	1.01	0.85	1.20	0.77	0.42	1.39	/	/	/	1.01	0.79	1.28
		Maximum temperature	0.94	0.71	1.24	0.94	0.66	1.35	0.96	0.46	2.01	/	/	/	0.88	0.50	1.55
		Minimum temperature	0.83	0.65	1.06	0.80	0.58	1.10	0.71	0.38	1.35	/	/	/	0.90	0.56	1.45
		Maximum wind speed	0.99	0.86	1.13	1.00	0.83	1.21	1.09	0.76	1.57	/	/	/	0.92	0.70	1.22
		Mean pressure	1.02	0.89	1.17	1.01	0.84	1.21	1.05	0.77	1.43	/	/	/	1.08	0.83	1.42
		Maximum relative humidity	1.05	0.89	1.23	1.08	0.87	1.34	1.00	0.66	1.51	/	/	/	0.93	0.66	1.29
		CO	0.89	0.75	1.05	0.92	0.73	1.17	1.07	0.68	1.68	/	/	/	0.80	0.57	1.13
		NO_2	0.90	0.75	1.07	0.94	0.74	1.18	1.06	0.68	1.65	/	/	/	0.79	0.55	1.14
		NO_x	0.90	0.76	1.07	0.95	0.76	1.20	0.96	0.63	1.47	/	/	/	0.85	0.61	1.19
		O_3	1.04	0.86	1.26	1.06	0.82	1.38	1.19	0.79	1.80	/	/	/	0.99	0.66	1.49
		PM_{10}	1.00	0.87	1.16	1.13	0.93	1.37	1.07	0.71	1.63	/	/	/	0.79	0.57	1.10
		$PM_{2.5}$	1.02	0.88	1.18	1.16	0.95	1.41	1.04	0.69	1.57	/	/	/	0.79	0.57	1.10

Supplementary Table 5. Relative risks and 95% confidence intervals from multiple-exposure generalized additive models (GAM) for sickle cell anemia (HbSS) admissions and selected environmental factors (based on results from single-exposure models) in London and Paris between 1st January 2008 and 31st December 2012. Exposure factors associated to increased/reduced relative risks are shown in red/blue, respectively. The number of admissions falling into each subgroup is shown as N. ACS = Acute chest syndrome.

City	Genotype	Exposure variable (lags 0 & 1)	Reason for admission														
			ALL			PAIN			FEVER			ACS			OTHER		
			RR	Min	Max	RR	Min	Max	RR	Min	Max	RR	Min	Max	RR	Min	Max
London	SS	N	1350			859			268			104			119		
		Rainfall + Ozone	1.07	1.01	1.13	1.07	1.00	1.14	1.07	0.95	1.20	1.02	0.84	1.25	1.09	0.93	1.28
		Rainfall + CO	1.07	1.01	1.13	1.07	1.00	1.14	1.08	0.96	1.20	1.03	0.85	1.25	1.09	0.93	1.27
		Rainfall + $PM_{2.5}$	1.07	1.02	1.13	1.07	1.01	1.14	1.07	0.96	1.20	1.02	0.84	1.24	1.11	0.95	1.29
		Maximum wind speed + Ozone	1.08	1.00	1.17	1.13	1.02	1.24	0.98	0.82	1.17	0.95	0.72	1.26	1.09	0.84	1.40
		Maximum wind speed + CO	1.08	1.01	1.16	1.11	1.02	1.21	1.03	0.88	1.20	1.07	0.84	1.35	1.00	0.79	1.26
		Maximum wind speed + PM2.5	1.09	1.02	1.17	1.14	1.05	1.24	0.96	0.82	1.12	1.01	0.80	1.27	1.15	0.92	1.43
		Mean pressure + Ozone	0.91	0.82	1.00	0.93	0.82	1.05	0.73	0.59	0.91	1.14	0.80	1.62	1.08	0.77	1.52
		Mean pressure + CO	0.91	0.82	1.00	0.92	0.82	1.04	0.73	0.59	0.90	1.10	0.77	1.56	1.11	0.79	1.56
		Mean pressure + PM2.5	0.90	0.81	0.99	0.92	0.81	1.03	0.73	0.59	0.91	1.12	0.79	1.59	1.03	0.73	1.45
Paris	SS	N	347			201			51			12			83		
		Rainfall + Ozone	0.97	0.86	1.10	1.01	0.87	1.18	0.59	0.33	1.05	/	/	/	1.01	0.81	1.26
		Rainfall + CO	0.96	0.85	1.09	1.01	0.86	1.18	0.62	0.35	1.09	/	/	/	1.00	0.80	1.25
		Rainfall + $PM_{2.5}$	0.96	0.85	1.09	1.02	0.88	1.19	0.58	0.32	1.06	/	/	/	0.98	0.77	1.24
		Maximum wind speed + Ozone	1.01	0.87	1.16	1.07	0.89	1.28	0.80	0.56	1.15	/	/	/	0.91	0.69	1.20
		Maximum wind speed + CO	0.96	0.83	1.11	1.01	0.84	1.22	0.92	0.63	1.33	/	/	/	0.83	0.62	1.12
		Maximum wind speed + PM2.5	0.98	0.86	1.12	1.06	0.90	1.26	0.90	0.63	1.28	/	/	/	0.81	0.61	1.08
		Mean pressure + Ozone	0.91	0.75	1.11	0.85	0.67	1.08	1.22	0.73	2.02	/	/	/	1.15	0.78	1.69
		Mean pressure + CO	0.94	0.78	1.14	0.88	0.69	1.12	1.17	0.71	1.93	/	/	/	1.21	0.82	1.78
		Mean pressure + PM2.5	0.94	0.78	1.14	0.84	0.66	1.08	1.18	0.71	1.97	/	/	/	1.31	0.89	1.93

Supplementary Code 1. Expectation–maximization imputation for multiple-exposure normal time-series of concentrations of air pollutants in London and Paris.

```
# Change variable name accordingly
# Options: "background" or "road"
mytype <- "background"
# Options: "CO, "NO2", "NOX", "O3", "SO2" (and "PM10", "PM25" if "road")
myvar <- "NOX"

# Set Dir as the directory containing the input files
mydata <- read.table(paste(Dir,mytype,"DailyConcentrations_2008to2014_",myvar,".CSV",sep=""), header=T,
sep=",")
# Use only data for the study period (2008-2012)
mydata <- mydata[1:1827,]

mydata2 <- data.frame(mydata[,1])
colname <- "date"
j=1
f="~"
# Identify columns for which missing data for less than 20% of days
for (i in c(2:ncol(mydata))){
  if (sum(is.na(mydata[,i]))<(0.2*nrow(mydata))){
    mydata2 <- cbind(mydata2,mydata[,i])
    colname <- c(colname, paste(myvar,colnames(mydata[i]),sep="_"))
    if (j==1) f <- paste(f,myvar,"_",colnames(mydata[i]),sep="") else f <-
paste(f,"+",myvar,"_",colnames(mydata[i]),sep="")
    j=j+1
    }
}
colnames(mydata2)<-colname

# Fill in the gaps
library (mtsdi)
i <- mnimput(as.formula(f), mydata2, eps=1e-3 ,ts = TRUE ,method="spline", log = FALSE,
sp.control=list(df=rep(7,ncol(mydata2)-1)))
Var.nogap <- predict(i)
# Save the output
write.table(Var.nogap, paste(Dir,mytype,"_",myvar,"_nogap.csv",sep=""))

### Sensitivity analysis

# Replace some measurements with NAs, independently for each column
mydata3 <- na.omit(mydata2)
mydata4 <- mydata3
N <- 100
inds <- matrix(NA,ncol=N,nrow=ncol(mydata3)-1)
for (i in c(2:ncol(mydata3))){
  inds[i-1,] <- round(runif(N,1,nrow(mydata3)))
  mydata4[,i][inds[i-1,]] <- NA
}
i4 <- mnimput(as.formula(f), mydata4, eps=1e-3,ts = TRUE, method = "spline", log = TRUE, sp.control =
list(df=rep(7,ncol(mydata2)-1)))
Var.nogap4 <- predict(i4)

### Assess prediction performance
```

```
library(Hmisc)
# Function that returns Root Mean Squared Error
rmse <- function(error) [21]

myrmse <- rep(0,ncol(Var.nogap4))
mynrmse <- rep(0,ncol(Var.nogap4))

for (j in c(1:(ncol(mydata3)-1))){
  mypred <- Var.nogap4[,j][inds[j,]]
  myobs <- mydata3[,j+1][inds[j,]]
  mycor <- rcorr(mypred,myobs)
  error <- myobs - mypred
  myrmse[j] <- rmse(error)
  mynrmse[j] <- rmse(error)/(max(myobs)-min(myobs))*100
}
```

Supplementary Code 2. GAM models and plots

```
################################################################################
# Code used by Piel et al (2016) Associations between environmental factors and hospital admissions for sickle cell disease
# Last updated: 25 October 2016
# Author: Fred B. Piel
################################################################################

library(mgcv)
library(Epi)
library(forestplot)
library(splines)

setwd("path")
mydata <- read.table("data file", sep=",", header=T)

## Tested for "Road air pollution data

#mydata <- mydata[1:1827,]
mydata$time <- seq(nrow(mydata))

### Calculate RR, CIs and P-values for London (SCD, SS, SC) and Paris (SS)
mymodel <- matrix(NA, nrow = 17, ncol=16)
colnames(mymodel) <-
c("SCD","SCD.CI.low","SCD.CI.high","SCD.p","SS","SS.CI.low","SS.CI.high","SS.p","SC","SC.CI.low","SC.CI.high","SC.p","Paris","Paris.CI.low","Paris.CI.high","Paris.p")
rownames(mymodel) <- c("Rainfall", "Maximum temperature","Minimum temperature","Maximum wind speed","Maximum pressure","Maximum relative humidity","Apparent temperature","Wind chill",
                       "CO","NO2","NOX","O3","SO2","PM10","PM2.5","Black carbon","Particle matter")
mymodel <- as.data.frame(mymodel)
y <- 1

# Fill in the data frame for London - SCD, SS, SC
for (j in c(68:70)){
  k <- 1
  for (i in c(37:53)){
    myexpo1 <- mydata[,i]
    #myexpolag <- cbind(myexpo1, lag(myexpo1,1))
    myoutcome <- mydata[,j]
    mygam1 <- gam(myoutcome ~ myexpo1 + ns(time,df=20) + as.factor(WeekDay),
data=mydata,family=quasipoisson)
    eff1 <- ci.lin(mygam1,subset="y",Exp=T)
    mymodel[k,c(y,y+1,y+2,y+3)] <- eff1[1,c(5:7,4)]
    k <- k+1
  }
y <- y+4
}

# Fill in the data frame for Paris - SS
j <- 83
k <- 1
for (i in c(54:67)){
  myexpo2 <- mydata[,i]
  myoutcome <- mydata[,j]
```

```
  mygam2 <- gam(myoutcome ~ myexpo2 + ns(time,df=20) + as.factor(WeekDay),
data=mydata,family=quasipoisson)
  eff2 <- ci.lin(mygam2,subset="y",Exp=T)
  mymodel[k,c(y,y+1,y+2,y+3)] <- eff2[1,c(5:7,4)]
  if (i == 65) k <- k+2
  else k <- k+1
}
mymodel

# Save the table of GAM results
library(xlsx)
write.xlsx(mymodel, "GAM results 20161025.xlsx")

################################################################################

### Create a forest plot from the above
mymodel2 <- cbind(rownames(mymodel),mymodel[,1:15])
# Using log if large range of values
#mymodel2 <- cbind(rownames(mymodel),log(mymodel[,1:15]))

### Panel A
mymodelA <- mymodel2[c(1,4:5),]
#png(filename = paste("GAM",colnames(mydata[j]),".png"))
forestplot(mean=cbind(mymodelA$SCD, mymodelA$SS, mymodelA$SC, mymodelA$Paris),
        lower=cbind(mymodelA$SCD.CI.low, mymodelA$SS.CI.low, mymodelA$SC.CI.low,
mymodelA$Paris.CI.low),
        upper=cbind(mymodelA$SCD.CI.high, mymodelA$SS.CI.high, mymodelA$SC.CI.high,
mymodelA$Paris.CI.high),
        labeltext=paste(mymodelA[,1]),
        is.summary=c(F, rep(FALSE, times=nrow(mymodelA))),
        txt_gp = fpTxtGp(label = gpar(fontfamily="", cex=1), ticks = gpar(fontfamily="", cex=1)),
        legend=c("London - SCD","London - SS","London - SC","Paris - SS"),
        zero=1,
        boxsize=0.1,
        new_page=T,
        # Change the "1" in the middle to "0" if using log above.
        xticks=c(round(min(mymodelA[,c(3,7,11,15)], na.rm=T),3),1,round(max(mymodelA[,c(4,8,12,16)],
na.rm=T),3)),
        # Tricky to highlight significant variables - TO WORK ON
        col=fpColors(box=c("red","darkred","light coral","blue"),line=c("red","darkred","light coral","blue")),
        title="Relative risks (per 1 SD increment) for sickle cell hospital admissions")
#dev.off()

### Panel B
mymodelB <- cbind(rownames(mymodel[c(2:3,6:17),]), mymodel[c(2:3,6:17),])
forestplot(mean=cbind(mymodelB$SCD, mymodelB$SS, mymodelB$SC, mymodelB$Paris),
        lower=cbind(mymodelB$SCD.CI.low, mymodelB$SS.CI.low, mymodelB$SC.CI.low,
mymodelB$Paris.CI.low),
        upper=cbind(mymodelB$SCD.CI.high, mymodelB$SS.CI.high, mymodelB$SC.CI.high,
mymodelB$Paris.CI.high),
        labeltext=paste(mymodelB[,1]),
        is.summary=c(F, rep(FALSE, times=nrow(mymodelB))),
        txt_gp = fpTxtGp(label = gpar(fontfamily="", cex=1), ticks = gpar(fontfamily="", cex=1)),
        zero=1,
        boxsize=0.1,
        new_page=T,
        # Change the "1" in the middle to "0" if using log above.
```

```
        xticks=c(round(min(mymodelB[,c(3,7,11,15)], na.rm=T),3),1,round(max(mymodelB[,c(4,8,12,16)],
na.rm=T),3)),
        col=fpColors(box=c("red","darkred","light coral","blue"),line=c("red","darkred","light coral","blue")))
```

Supplementary Code 3. DLNM models and plots

```
################################################################################
# Code used by Piel et al (2016) Associations between environmental factors and hospital admissions for sickle cell disease
# Last updated: 25 October 2016
# Author: Fred B. Piel
################################################################################

library(dlnm)
library(splines)
library(foreign)
library(tsModel)
library(mgcv)

# LOAD THE DATA INTO THE SESSION
setwd("path")
mydata <- read.table("data file", sep=",", header=T)

mydata$time <- seq(nrow(mydata))

################################################################################
# London and Paris plots all on the same figure
################################################################################
par(mfrow=c(4,4), mar=(c(4,5,1.5,1)))
myvar <- c("Rainfall", "Maximum temperature","Minimum temperature","Maximum wind speed","Maximum pressure","Maximum relative humidity","Apparent temperature","CO","NO2","NOX","O3","SO2","PM10","PM2.5","Black carbon","Particle number")
nlag <- 6
mydlnm.table <- as.data.frame(matrix(NA, nrow = 17*(nlag+1), ncol=8))
colnames(mydlnm.table) <- c("Exposure", "Lag","RR_LON","ci.low_LON","ci.hi_LON",
"RR_PAR","ci.low_PAR","ci.hi_PAR")
mydlnm.table[,1] <- c(rep("Rainfall",(nlag+1)), rep("Maximum temperature",(nlag+1)), rep("Minimum temperature",(nlag+1)), rep("Maximum wind speed",(nlag+1)), rep("Maximum pressure",(nlag+1)), rep("Maximum relative humidity",(nlag+1)), rep("Apparent temperature",(nlag+1)), rep("Wind chill",(nlag+1)), rep("CO",(nlag+1)),rep("NO2",(nlag+1)),rep("NOX",(nlag+1)),rep("O3",(nlag+1)),rep("SO2",(nlag+1)),rep("PM10",(nlag+1)),rep("PM2.5",(nlag+1)),rep("Black carbon",(nlag+1)),rep("Particle number",(nlag+1)))
x <- "lag0"
for (i in c(1:nlag)){
  x <- c(x,paste("lag",i,sep=""))
  }
mydlnm.table[,2] <- rep(x,17)

k <- 1
xx <- 1
for (i in c(37:52)){
  # For London - 16 exposure variables
  myexpo1 <- mydata[,i]
  cb1<-crossbasis(myexpo1, lag=nlag, argvar=list(fun="lin"), arglag=list(fun="poly",degree=3))
  #cb11<-crossbasis(mydata$London_Max_Temp, lag=nlag, argvar=list(fun="lin",cen=FALSE),
arglag=list(fun="poly",degree=3))
  mydlnm1 <- gam(mydata$LON_SS ~ cb1 + ns(time,df=20) + WeekDay,family=quasipoisson(), data=mydata)
  pred1 <- crosspred(cb1,mydlnm1,at=1)
  j=0
  if (i %in% c(37:47)) j = i+16
```

```
  if (i %in% c(49:50)) j = i+15

  if (i %in% c(37:47,49:50)){
    # For Paris - 12 exposure variables
    myexpo2 <- mydata[,j]
    cb2<-crossbasis(myexpo2, lag=nlag, argvar=list(fun="lin"), arglag=list(fun="poly",degree=3))
    mydlnm2 <- gam(mydata$Paris_SS ~ cb2 + ns(time,df=20) + WeekDay,family=quasipoisson(), data=mydata)
    pred2 <- crosspred(cb2,mydlnm2,at=1)
    tablag <- cbind(with(pred1,t(rbind(matRRfit,matRRlow,matRRhigh))),
with(pred2,t(rbind(matRRfit,matRRlow,matRRhigh))))
    colnames(tablag) <- c("RR_LON","ci.low_LON","ci.hi_LON", "RR_PAR","ci.low_PAR","ci.hi_PAR")
    # Different types for x- and y-axis labels depending on position
    if (k %in% c(1,5,9)) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="RR and 95%CI per SD")
      }
    else if (k %in% c(2:4,6:8,10:12)) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="")
    }
    else if (k == 13) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="Lag (days)",ylab="RR and 95%CI per SD")
    }
    else if (k == 14) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="Lag (days)",ylab="")
    }
    abline(h=1)
    # London - Red
    arrows(0:nlag,tablag[,2],0:nlag,tablag[,3],length=0.05,angle=90,code=3,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
    points(0:nlag,tablag[,1],pch=19,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
    # Paris - Blue
    arrows(0.25:(nlag+.25),tablag[,5],0.25:(nlag+.25),tablag[,6],length=0.05,angle=90,code=3,
col=ifelse(xor(pred2$matRRhigh<1,pred2$matRRlow>1),"#0000FF","#00008050"))
    points(0.25:(nlag+.25),tablag[,4],pch=19,
col=ifelse(xor(pred2$matRRhigh<1,pred2$matRRlow>1),"#0000FF","#00008050"))
    mydlnm.table[xx:(xx+(nlag)),3:8] <- tablag
  } else {
    # London only - 4 exposure variables: Feel temp, SO2, Black carbon and particle number
    tablag <- with(pred1,t(rbind(matRRfit,matRRlow,matRRhigh)))
    colnames(tablag) <- c("RR_LON","ci.low_LON","ci.hi_LON")
    # Different types for x- and y-axis labels depending on position
    if (k %in% c(15,16)) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="Lag (days)",ylab="")
    }
    else if (k == 12){
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="")
    }
    abline(h=1)
    # London - Red
    arrows(0:nlag,tablag[,2],0:nlag,tablag[,3],length=0.05,angle=90,code=3,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
```

```
   points(0:nlag,tablag[,1],pch=19,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
   mydlnm.table[xx:(xx+(nlag)),3:5] <- tablag
  }
 k <- k+1
 xx <- xx+(nlag+1)
}

# Save the table of DLNM results
library(xlsx)
write.xlsx(mydlnm.table, "DLNM results - 7 lags - 20161017.xlsx")

################################################################################
### 2-panel plots
################################################################################
# Panel 1 - Significant results
par(mfrow=c(2,2), mar=(c(4,5,1.5,1)))
myvar <- c("Rainfall", "Maximum wind speed","CO","Black carbon")
nlag <- 6
mydlnm.table <- as.data.frame(matrix(NA, nrow = length(myvar)*(nlag+1), ncol=8))
colnames(mydlnm.table) <- c("Exposure", "Lag","RR_LON","ci.low_LON","ci.hi_LON",
"RR_PAR","ci.low_PAR","ci.hi_PAR")
mydlnm.table[,1] <- c(rep("Rainfall",(nlag+1)), rep("Maximum wind speed",(nlag+1)), rep("CO",(nlag+1)),
rep("Black carbon",(nlag+1)))
x <- "lag0"
for (i in c(1:nlag)){
 x <- c(x,paste("lag",i,sep=""))
}
mydlnm.table[,2] <- rep(x,length(myvar))

k <- 1
xx <- 1
for (i in c(37,40,45,52)){
 # For London - 4 significant exposure variables
 myexpo1 <- mydata[,i]
 cb1<-crossbasis(myexpo1, lag=nlag, argvar=list(fun="lin"), arglag=list(fun="poly",degree=3))
 #cb11<-crossbasis(mydata$London_Max_Temp, lag=nlag, argvar=list(fun="lin",cen=FALSE),
arglag=list(fun="poly",degree=3))
 mydlnm1 <- gam(mydata$LON_SS ~ cb1 + ns(time,df=20) + WeekDay,family=quasipoisson(), data=mydata)
 pred1 <- crosspred(cb1,mydlnm1,at=1)
 j=0
 if (i %in% c(37:48)) j = i+17
 if (i %in% c(50:51)) j = i+16

 if (i %in% c(37:48,50:51)){
  # For Paris - 3 exposure variables
  myexpo2 <- mydata[,j]
  cb2<-crossbasis(myexpo2, lag=nlag, argvar=list(fun="lin"), arglag=list(fun="poly",degree=3))
  mydlnm2 <- gam(mydata$Paris_SS ~ cb2 + ns(time,df=20) + WeekDay,family=quasipoisson(), data=mydata)
  pred2 <- crosspred(cb2,mydlnm2,at=1)
  tablag <- cbind(with(pred1,t(rbind(matRRfit,matRRlow,matRRhigh))),
with(pred2,t(rbind(matRRfit,matRRlow,matRRhigh))))
  colnames(tablag) <- c("RR_LON","ci.low_LON","ci.hi_LON", "RR_PAR","ci.low_PAR","ci.hi_PAR")
  # Different types for x- and y-axis labels depending on position
  if (k == 1) {
    plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="RR and 95%CI per SD")
```

```
   }
   else if (k == 2) {
    plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="")
   }
   else if (k == 3) {
    plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="Lag (days)",ylab="RR and 95%CI per SD")
   }
   abline(h=1)
   # London - Red

arrows(0:nlag,tablag[,2],0:nlag,tablag[,3],length=0.05,angle=90,code=3,lwd=4,col=ifelse(xor(pred1$matRRhigh
<1,pred1$matRRlow>1),"#FF0000","#80000050"))
   points(0:nlag,tablag[,1],pch=19,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
   # Paris - Blue

arrows(0.25:(nlag+.25),tablag[,5],0.25:(nlag+.25),tablag[,6],length=0.05,angle=90,code=3,lwd=4,col=ifelse(xor(
pred2$matRRhigh<1,pred2$matRRlow>1),"#0000FF","#00008050"))
   points(0.25:(nlag+.25),tablag[,4],pch=19,
col=ifelse(xor(pred2$matRRhigh<1,pred2$matRRlow>1),"#0000FF","#00008050"))
   mydlnm.table[xx:(xx+(nlag)),3:8] <- tablag
  } else {
   # London only - 1 exposure variables: Black carbon
   tablag <- with(pred1,t(rbind(matRRfit,matRRlow,matRRhigh)))
   colnames(tablag) <- c("RR_LON","ci.low_LON","ci.hi_LON")
   # Different types for x- and y-axis labels depending on position
   if (k == 4) {
    plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="Lag (days)",ylab="")
   }
   #else if (k == 12){
   #  plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="")
   #}
   abline(h=1)
   # London - Red

arrows(0:nlag,tablag[,2],0:nlag,tablag[,3],length=0.05,angle=90,code=3,lwd=4,col=ifelse(xor(pred1$matRRhigh
<1,pred1$matRRlow>1),"#FF0000","#80000050"))
   points(0:nlag,tablag[,1],pch=19,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
   mydlnm.table[xx:(xx+(nlag)),3:5] <- tablag
  }
  k <- k+1
  xx <- xx+(nlag+1)
}

# Panel 2 - Non significant associations
########################################
par(mfrow=c(5,3), mar=(c(4,5,1.5,0.3)))
myvar <- c("Maximum temperature","Minimum temperature","Maximum pressure","Maximum relative
humidity","Apparent temperature","Wind chill","NO2","NOX","O3","SO2","PM10","PM2.5","Particle number")
nlag <- 6
mydlnm.table <- as.data.frame(matrix(NA, nrow = length(myvar)*(nlag+1), ncol=8))
```

```
colnames(mydlnm.table) <- c("Exposure", "Lag","RR_LON","ci.low_LON","ci.hi_LON",
"RR_PAR","ci.low_PAR","ci.hi_PAR")
mydlnm.table[,1] <- c(rep("Maximum temperature",(nlag+1)), rep("Minimum temperature",(nlag+1)),
rep("Maximum pressure",(nlag+1)), rep("Maximum relative humidity",(nlag+1)), rep("Apparent
temperature",(nlag+1)), rep("Wind chill",(nlag+1)),
rep("NO2",(nlag+1)),rep("NOX",(nlag+1)),rep("O3",(nlag+1)),rep("SO2",(nlag+1)),rep("PM10",(nlag+1)),rep("P
M2.5",(nlag+1)),rep("Particle number",(nlag+1)))
x <- "lag0"
for (i in c(1:nlag)){
  x <- c(x,paste("lag",i,sep=""))
}
mydlnm.table[,2] <- rep(x,length(myvar))

k <- 1
xx <- 1
for (i in c(38:39,41:44,46:51,53)){
  # For London - 13 exposure variables
  myexpo1 <- mydata[,i]
  cb1<-crossbasis(myexpo1, lag=nlag, argvar=list(fun="lin"), arglag=list(fun="poly",degree=3))
  #cb11<-crossbasis(mydata$London_Max_Temp, lag=nlag, argvar=list(fun="lin",cen=FALSE),
arglag=list(fun="poly",degree=3))
  mydlnm1 <- gam(mydata$LON_SS ~ cb1 + ns(time,df=20) + WeekDay,family=quasipoisson(), data=mydata)
  pred1 <- crosspred(cb1,mydlnm1,at=1)
  j=0
  if (i %in% c(37:48)) j = i+17
  if (i %in% c(50:51)) j = i+16

  if (i %in% c(38:39,41:44,46:48,50:51)){
    # For Paris - 11 exposure variables
    myexpo2 <- mydata[,j]
    cb2<-crossbasis(myexpo2, lag=nlag, argvar=list(fun="lin"), arglag=list(fun="poly",degree=3))
    mydlnm2 <- gam(mydata$Paris_SS ~ cb2 + ns(time,df=20) + WeekDay,family=quasipoisson(), data=mydata)
    pred2 <- crosspred(cb2,mydlnm2,at=1)
    tablag <- cbind(with(pred1,t(rbind(matRRfit,matRRlow,matRRhigh))),
with(pred2,t(rbind(matRRfit,matRRlow,matRRhigh))))
    colnames(tablag) <- c("RR_LON","ci.low_LON","ci.hi_LON", "RR_PAR","ci.low_PAR","ci.hi_PAR")
    # Different types for x- and y-axis labels depending on position
    if (k %in% c(1,4,7)) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="RR & 95%CI per SD",cex=1.5)
    }
    else if (k %in% c(2:3,5:6,8:9)) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="", cex=1.5)
    }
    else if (k %in% c(11:12)) {
      plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="Lag (days)",ylab="")
    }
    abline(h=1)
    # London - Red
    arrows(0:nlag,tablag[,2],0:nlag,tablag[,3],length=0.05,angle=90,code=3, lwd=2,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
    points(0:nlag,tablag[,1],pch=19,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
    # Paris - Blue
```

```
arrows(0.25:(nlag+.25),tablag[,5],0.25:(nlag+.25),tablag[,6],length=0.05,angle=90,code=3,lwd=2,col=ifelse(xor(
pred2$matRRhigh<1,pred2$matRRlow>1),"#0000FF","#00008050"))
   points(0.25:(nlag+.25),tablag[,4],pch=19,
col=ifelse(xor(pred2$matRRhigh<1,pred2$matRRlow>1),"#0000FF","#00008050"))
   mydlnm.table[xx:(xx+(nlag)),3:8] <- tablag
  } else {
   # London only - 4 exposure variables: SO2 and particle number
   tablag <- with(pred1,t(rbind(matRRfit,matRRlow,matRRhigh)))
   colnames(tablag) <- c("RR_LON","ci.low_LON","ci.hi_LON")
   # Different types for x- and y-axis labels depending on position
   if (k == 10) {
    plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="",ylab="RR & 95%CI per SD")
   }
   else if (k == 13){
    plot(-0.5:(nlag+.5),-0.5:(nlag+.5),type="n", bty="n", ylim=c(min(tablag),max(tablag)), main= myvar[k],
xlab="Lag (days)",ylab="RR & 95%CI per SD")
   }
   abline(h=1)
   # London - Red
   arrows(0:nlag,tablag[,2],0:nlag,tablag[,3],length=0.05,angle=90,code=3, lwd=2,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
   points(0:nlag,tablag[,1],pch=19,
col=ifelse(xor(pred1$matRRhigh<1,pred1$matRRlow>1),"#FF0000","#80000050"))
   mydlnm.table[xx:(xx+(nlag)),3:5] <- tablag
  }
  k <- k+1
  xx <- xx+(nlag+1)
}
```