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Environmental Influences on Daily Emergency Admissions in Sickle-Cell Disease Patients

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Abstract: Previous reports have suggested a role for weather conditions and air pollution on the variability of sickle cell disease (SCD) severity, but large-scale comprehensive epidemiological studies are lacking.

In order to evaluate the influence of air pollution and climatic factors on emergency hospital admissions (EHA) in SCD patients, we conducted an 8-year observational retrospective study in 22 French university hospitals in Paris conurbation, using distributed lag non-linear models, a methodology able to flexibly describe simultaneously non-linear and delayed associations, with a multivariable approach.

During the 2922 days of the study, there were 17,710 EHA, with a mean daily number of 6.1 ± 2.8. Most environmental factors were significantly correlated to each other. The risk of EHA was significantly associated with higher values of nitrogen dioxide, atmospheric particulate matters, and daily mean wind speed; and with lower values of carbon monoxide, ozone, sulfur dioxide, daily temperature (minimal, maximal, mean, and range), day-to-day mean temperature change, daily bright sunshine, and occurrence of storm. There was a lag effect for 12 of 15 environmental factors influencing hospitalization rate. Multivariate analysis identified carbon monoxide, day-to-day temperature change, and mean wind speed, along with calendar factors (weekend, summer season, and year) as independent factors associated with EHA.

In conclusion, most weather conditions and air pollutants assessed were correlated to each other and influenced the rate of EHA in SCD patients. In multivariate analysis, lower carbon monoxide concentrations, day-to-day mean temperature drop and higher wind speed were associated with increased risk of EHA.

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Abbreviations: ACS = acute chest syndrome, EHA = emergency hospital admissions, SCD = sickle cell disease, VOC = vaso-occlusive painful crises.

INTRODUCTION

Sickle cell disease (SCD) is one of the most common severe inherited disorders in the world. It is characterised by recurrent vaso-occlusive painful crises (VOCs), which are the most common reasons for patient's emergency admissions. Although its pathophysiology is still unclear, many factors are known or suspected to precipitate VOC, including dehydration, hypoxemia, pregnancy, infections, and surgery. VOCs may be complicated by respiratory symptoms defining the acute chest syndrome (ACS). The pathophysiology of ACS is also complex, and may include pulmonary fat embolism[1] secondary to bone marrow necrosis during VOC, pulmonary artery thrombosis[2] and/or in situ lung capillary vaso-occlusion.

Erythrocyte sickling is enhanced by lower temperatures and physiological studies have demonstrated a link between skin cooling and vaso-occlusion.[3–5] Previous epidemiological studies exploring the influence of weather conditions and air pollution on the variability of SCD severity yielded mixed results.[6–11] However, all these studies used a univariate methodology. Because meteorological factors and pollution factors frequently display between-group and within-group interrelation, the use of a multivariable approach may be crucial in this setting. In addition, environmental stressors may have non-linear effects and their impact may appear with some latency, and persist for some time after exposure (lag effect).[12,13] None of the previous studies assessed the time structure of the effects analyzed.

Our objective was to evaluate the influence of air quality and weather on the incidence of emergency department admissions for VOC and chest disease in patients with homozygous SCD in an urban environment (Paris conurbation). We used distributed lag non-linear models (*dlnm*), a methodology able to flexibly describe simultaneously non-linear and delayed associations, with a multivariable approach.

METHODS

Patients

The study was retrospectively performed using data collected during an 8-year period (2922 days) from January 1, 2004 to December 31, 2011 in 22 hospitals from the Assistance Publique-Hôpitaux de Paris (the public hospital network of Paris conurbation) (Figure 1). Using billing record discharge summaries, we included all emergency department visits for VOCs or chest disease in SCD patients (SS, SC, or S-thalassemia genotype) aged from 2 to 70 years. Chest disease was

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FIGURE 1. Paris conurbation map with the public hospital network (H) and monitoring stations for meteorological (black circles) and air quality (white circles) data.

defined as any new-onset lower acute respiratory tract disease that was compatible with ACS[14] with the exclusion of other formally defined diagnoses like trauma, cardiogenic pulmonary oedema, or pneumothorax. We used the chest disease terminology instead of ACS because the latest diagnosis is not formally defined in the International Classification of Diseases 10 and was not available in billing record discharge summaries. Ethical approval was not required as per French legislation on observational retrospective studies on already collected data.

Meteorological and Air Quality Data

Meteorological and air quality data were obtained for the same period from the French meteorology agency (Meteo France, https://public.meteofrance.com/public/accueil) and the Paris conurbation air quality agency (AirParif, http://www.airparif. asso.fr/telechargement/telechargement-station). We averaged hourly recorded data from 7 synoptic meteorological stations within the Paris conurbation to compute the following variables: daily minimal temperature (°C), daily maximal temperature (°C), daily mean temperature (°C), daily temperature range (°C), day-to-day mean temperature change (°C, calculated as the difference between mean temperature of the day and mean temperature of the previous day), daily rainfall (mm), daily relative humidity (%), daily bright sunshine (%), daily mean wind speed (m/s), daily maximal wind speed (m/s) and occurrence of a storm (yes or no). We also averaged hourly recorded data from 13 to 50 synoptic air pollution stations within the Paris conurbation to compute the daily mean concentrations ($\mu g/m^3$) of the following compounds: carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and atmospheric particulate matters with aerodynamic diameter smaller than 10 μm (PM_{10}) or 2.5 μm ($PM_{2.5}$).

Statistical Analysis

The data were analyzed using SPSS Base 13 (SPSS Inc, Chicago, IL) and R 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed as percentages and continuous data were expressed as mean ± standard deviation. We used the chi-square or Fisher exact test to compare categorical variables between groups and the Student *T* test to compare continuous variables. Correlations were tested using the Spearman's method.

To assess the effects of daily meteorological and air quality measurements on daily counts of hospital emergency admissions, we used the *dlnm* package implemented within the statistical software R.[15] This procedure can simultaneously represent non-

TABLE 1. Descriptive Statistics of Environmental Factors

Variable	Mean	Standard Deviation	Minimum	Percentile 25	Percentile 50	Percentile 75	Maximum
Air pollutants							
CO ($\mu g/m^3$)	744.6	295.5	185.2	515.1	696.9	929.7	2716.2
NO_2 ($\mu g/m^3$)	40.7	13.6	10.6	30.5	39.5	49.9	130.6
O_3 ($\mu g/m^3$)	43.7	20.9	1.1	28.3	44.1	57.6	134.5
SO_2 ($\mu g/m^3$)	3.8	3.5	0.0	1.31	2.8	5.2	30.6
PM_{10} ($\mu g/m^3$)	27.7	12.5	6.5	19.5	24.8	32.6	138.1
$PM_{2.5}$ ($\mu g/m^3$)	19.3	11.2	4.3	11.9	16.4	23.1	130.1
Meteorological variables							
Daily rainfall (mm)	1.7	3.4	0.0	0.0	0.1	1.7	35.5
Daily minimal temperature (°C)	7.9	5.9	−11.8	3.5	8.3	12.7	21.9
Daily maximal temperature (°C)	15.9	7.8	−4.3	10.0	16.4	21.9	36.8
Daily mean temperature (°C)	11.7	6.7	−6.1	6.6	12.1	17.0	28.1
Daily temperature range (°C)	8.0	3.7	0.7	5.2	7.6	10.7	19.7
Day-to-day mean temperature change (°C)	0.0	2.1	−8.8	−1.3	0.1	1.4	8.6
Daily mean wind speed (m/s)	3.5	1.4	0.7	2.5	3.2	4.2	10.1
Daily maximal wind speed (m/s)	10.9	3.6	3.6	8.3	10.3	12.8	31.9
Daily relative humidity (%)	75.8	11.6	38.9	67.6	77.4	84.9	97.9
Daily bright sunshine (%)	36.5	31.2	0.0	6.7	30.2	63.8	96.5

CO = carbon monoxide, NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = atmospheric particulate matters with aerodyamic diameter smaller than 10 μm, $PM_{2.5}$ = atmospheric particulate matters with aerodyamic diameter smaller than 2.5 μm, SO_2 = sulfur dioxide.

TABLE 2. Matrix of Correlation Coefficients Between Environmental Factors

	CO	NO_2	O_3	SO_2	PM_{10}	PM_{25}	Rain	$Temp_{min}$	$Temp_{max}$	$Temp_{mean}$	$Temp_{range}$	$Wind_{mean}$	$Wind_{max}$	Hum	Sun	$Temp_{change}$	Storm
CO																	
NO_2	0.41*																
O_3	−0.26*	−0.43*															
SO_2	0.64*	0.58*	−0.38*														
PM_{10}	0.25*	0.49*	−0.17*	0.23*													
PM_{25}	0.29*	0.51*	−0.26*	0.27*	0.96*												
Rain	−0.11*	−0.08*	0.07	−0.11*	−0.22*	−0.18*											
$Temp_{min}$	−0.23*	−0.41*	0.55*	−0.46*	−0.26*	−0.34*	0.12*										
$Temp_{max}$	−0.16*	−0.32*	0.62*	−0.41*	−0.08	−0.20*	0.02*	0.89*									
$Temp_{mean}$	−0.19*	−0.37*	0.61*	−0.44*	−0.16*	−0.27*	0.05*	0.95*	0.98*								
$Temp_{range}$	0.03	−0.01†	0.42*	−0.11*	0.24*	0.12*	−0.15*	0.27*	0.68*	0.55*							
$Wind_{mean}$	−0.33*	−0.24*	0.08*	−0.10*	−0.40*	−0.39*	0.22*	−0.02	−0.17*	−0.11*	−0.32*						
$Wind_{max}$	−0.35*	−0.26*	0.19*	−0.19*	−0.41*	−0.43*	0.34*	0.10*	−0.01	0.03†	−0.19*	0.88*					
Hum	0.20*	0.18*	−0.59*	0.18*	−0.09*	0.05	0.26*	−0.36*	−0.61*	−0.53*	−0.71*	0.07*	0.01†				
Sun	0.04	0.02	0.27*	−0.04	0.28*	0.18*	−0.29*	0.07*	0.40*	0.27*	0.73*	−0.24*	−0.21*	−0.69*			
$Temp_{change}$	0.07*	0.12*	−0.13*	0.12*	0.08*	0.06*	−0.06*	0.02†	0.18*	0.15*	0.35*	−0.04*	−0.06*	−0.13*	0.08*		
Storm	−0.12	−0.24	0.25†	−0.19*	−0.12*	−0.14*	0.03	0.31*	0.30*	0.31*	0.13*	−0.01	0.05	−0.15	0.03	−0.04*	

* Correlation is significant at the 0.01 level.

† Correlation is significant at the 0.05 level.

CO = carbon monoxide, Hum = daily relative humidity, NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = atmospheric particulate matters with aerodyamic diameter smaller than 10 μm, $PM_{2.5}$ = atmo-atmospheric particulate matters with aerodyamic diameter smaller than 2.5 μm, Rain = daily rainfall, SO_2 = sulfur dioxide, Storm = occurrence of a storm during the 7 preceding days, Sun = daily bright sunshine, $Temp_{max}$ = daily maximal temperature, $Temp_{mean}$ = daily mean temperature, $Temp_{min}$ = daily minimal temperature, $Temp_{range}$ = daily temperature range, $Wind_{max}$ = daily maximal wind speed, $Wind_{mean}$ = daily mean wind speed.

linear exposure–response dependencies and delayed effects.[16] The relationship with environmental factors was modeled through a generalized linear model with Poisson family, a natural cubic spline and boundary knots located at the range of the observed values.

We estimated associations between environmental variables and emergency hospital admissions (EHAs) for various single-day lags. For example, a lag of 3 days corresponds to the association between environmental variables in a given day and the risk of hospital admission 3 days later. The lagged effect was specified from lag1 to lag7. Lag0 (unlagged, which refers to the association between environmental variables in a given day and hospital admission in the same day), was excluded in order to avoid the bias of analyzing environmental data recorded during hours following the index hospitalization. Mean values of environmental factors were used as reference values to calculate the relative risks. The specification for the degrees of freedom (*df*) in each dimension was chosen so as to minimize the quasi-Akaike Information Criterion. In order to be able to capture non-linear effects and their time structure while keeping the model on the ground of parcimony, we tested *df* 1 to 2 in space dimension and in time dimension. The influence of year on emergency admissions was also assessed using *dlnm*. Wilcoxon rank sum test with continuity correction was used to assess the effects of weekend, summer season (from July 1 to August 31), and occurrence of storm during the preceding week on emergency admissions.

To evaluate independent factors associated with emergency admissions, significant univariate risk factors were examined using stepwise multivariate analysis. Among significant univariate factors that were closely related with a correlation coefficient >0.80 (minimal temperature, maximal temperature, and mean temperature for temperatures; PM_{10} and $PM_{2.5}$ for particulate matters), only the most clinically pertinent and straightforwardly interpretable for decision making purposes (daily mean temperature and PM_{10}) were entered into the multivariate model in order to minimize the effect of colinearity. Thus, the 15 variables entered into the multivariable analysis were: daily mean temperature, daily temperature range, day-to-day mean temperature change, daily relative humidity, daily mean wind speed, daily bright sunshine, occurrence of a storm, daily mean concentrations of CO, NO_2, O_3, SO_2, and PM_{10}, weekend, holiday, and year. Two-sided P values <0.05 were considered signicant. Univariate analyses were repeated in the 2 subgroups defined by age up to 18 or 18 years and over.

RESULTS

Study Population and Environmental Factors

During the 2922 days of the study, there were 17,710 emergency admissions for VOC or chest disease, involving a total of 4426 patients. The mean daily number of emergency admissions was 6.1 ± 2.8 (from 0 to 19), mean hospital length of stay was 4.8 ± 4.8 days, and mean patient age was 19.3 ± 11.3 years. Table 1 shows the descriptive statistics for weather conditions and air quality. There were 265 (9.1%) days with storm occurrence during the study period. Table 2 shows the matrix of correlation coefficients between environmental factors. Almost all meteorological variables and air pollutants correlated closely to each other.

Determinants of EHAs

Table 3 shows the *dlnm* univariate analysis of the relation between environmental factors and EHAs. Higher values of

TABLE 3. Univariate Analysis of the Relation Between Environmental and Hospital Admissions

			Estimate (*P* Value) of *dlnm*	
Variable	***df*var**	**Knot**	**Space Dimension**	**Time Dimension**
Air polluants				
CO ($\mu g/m^3$)	2	696.8	−0.35 ($<10^{-15}$); −0.29 ($<10^{-4}$)	0.34 ($<10^{-5}$); −0.26 (0.02)
NO_2 ($\mu g/m^3$)	2	39.4	0.06 (0.02); −0.02 (0.71)	0.18 ($<10^{-3}$); −0.08 (0.44)
O_3 ($\mu g/m^3$)	1	–	−0.04 ($<10^{-4}$)	–
SO_2 ($\mu g/m^3$)	2	2.8	−0.19 ($<10^{-14}$); 0.05 (0.48)	0.07 (0.29); −0.15 (0.21)
PM_{10} ($\mu g/m^3$)	2	24.8	0.19 ($<10^{-10}$); −0.08 (0.27)	0.20 ($<10^{-3}$); −0.25 (0.02)
$PM_{2.5}$ ($\mu g/m^3$)	2	16.3	0.15 ($<10^{-5}$); −0.11 (0.18)	0.07 (0.20); −0.26 (0.03)
Meteorological factors				
Daily rainfall (mm)	2	1.6	−0.03 (0.65)	−0.14 (0.07)
Daily minimal temperature (°C)	2	7.9	0.01 (0.84); −0.09 ($<10^{-10}$)	0.15 (0.12); 0.07 (0.13)
Daily maximal temperature (°C)	2	16.4	−0.04 (0.11); −0.11 ($<10^{-10}$)	0.20 (0.02); 0.17 ($<10^{-3}$)
Daily mean temperature (°C)	2	12.1	−0.03 (0.30); −0.10 ($<10^{-12}$)	0.21 (0.01); 0.16 ($<10^{-3}$)
Daily temperature range (°C)	2	7.6	−0.10 ($<10^{-3}$); −0.03 (0.29)	0.02 (0.68); 0.12 (<0.01)
Day-to-day mean temperature change (°C)	2	0.1	−0.46 ($<10^{-4}$); −0.18 (<0.01)	−0.07 (0.53); 0.12 (0.02)
Daily relative humidity (%)	2	77.4	−0.08 (0.049); 0.05 ($<10^{-4}$)	−0.30 ($<10^{-4}$); 0.02 (0.54)
Daily bright sunshine (%)	2	30.2	−0.06 (<0.01); 0.01 (0.56)	−0.03 (0.23); 0.04 (0.04)
Daily mean wind speed (m/s)	2	3.24	0.01 (0.69); 0.06 (0.01)	–
Daily maximal wind speed (m/s)	1	–	0.04 (0.25)	−0.11 (0.04)

dlnm = distributed lag non-linear models; the degree of freedom in space dimension (dfvar) and in time dimension (dflag) were chosen as to minimize the quasi-Akaike Information Criterion; in space dimension, there is one estimate if dfvar = 1 (from minimal value to maximal value) and 2 estimates if dfvar = 2 (the first from minimal value to central knot and the second from central knot to maximal value); in time dimension, there is no estimate if dflag = 1 and 1 estimate if dflag = 2, CO = carbon monoxide, Hum = daily relative humidity, NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = atmospheric particulate matters with aerodynamic diameter smaller than 10 μm, $PM_{2.5}$ = atmospheric particulate matters with aerodynamic diameter smaller than 2.5 μm, Rain = daily rainfall, SO_2 = sulfur dioxide, Sun = daily bright sunshine, $Temp_{max}$ = daily maximal temperature, $Temp_{mean}$ = daily mean temperature, $Temp_{min}$ = daily minimal temperature, $Temp_{range}$ = daily temperature range, $Wind_{max}$ = daily maximal wind speed, $Wind_{mean}$ = daily mean wind speed.

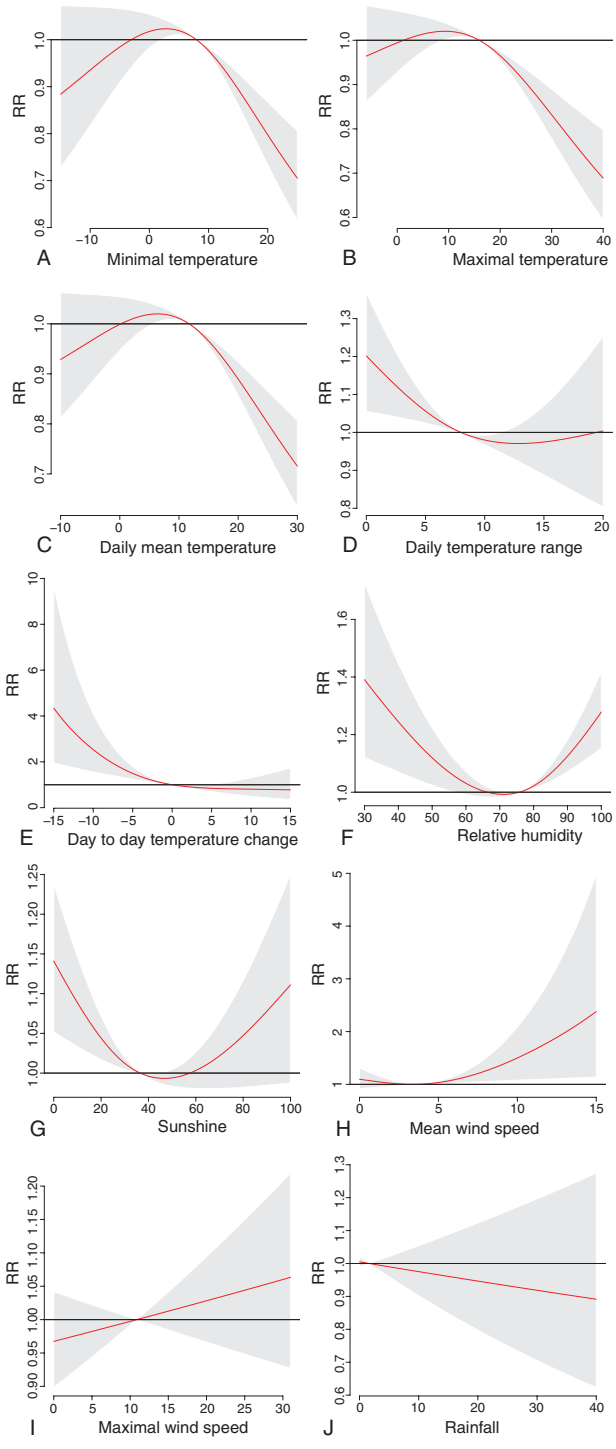

FIGURE 2. Overall effect with relative risk (red line) and 95% confidence interval (grey area) for associations between the number of daily emergency admissions in sickle cell disease patients and daily minimal temperature (panel A), daily maximal temperature (panel B), daily mean temperature (panel C), daily temperature range (panel D), day-to-day mean temperature change (panel E), daily relative humidity (panel F), daily bright sunshine (panel G), daily mean wind speed (panel H), daily maximal wind speed (panel I), and daily rainfall (panel J).

NO_2, $PM_{2.5}$, PM_{10}, and daily mean wind speed; and lower values of CO, O_3, SO_2, daily minimal temperature, daily maximal temperature, daily mean temperature, daily temperature range, day-to-day mean temperature change, daily bright sunshine and occurrence of storm were significantly related with the risk of EHAs while the association with daily relative humidity was U shaped (Figures 2 and 3). *Dlnm* evidenced a lag effect for 12 of 15 significant environmental factors, with a short-term effect (before lag3) for CO (lower values), SO_2, minimal, maximal, and mean temperatures; and a delayed effect (after lag3) for CO (higher values), NO_2, PM_{10}, $PM_{2.5}$, daily temperature range day-to-day mean temperature change, humidity, and sunshine (Table 3, see Supplemental Digital Content Figure SDC1 to Figure SDC16, http://links.lww.com/MD/A95). The number of EHAs increased with year of admission (*dlnm* estimate of 0.07, $P < 10^{-15}$) and was significantly lower during the summer season as compared the rest of the year and during weekends as compared to weekdays ($P < 10^{-10}$ for both comparisons, Figure 4). Multivariate analysis identified lower values of CO (*dlnm* estimate of -0.18, $P < 10^{-3}$), day-to-day temperature drops (*dlnm* estimate of -0.30, $P < 0.01$), higher values of mean wind speed (*dlnm* estimate of 0.05, $P = 0.03$), weekend (*dlnm* estimate of -0.13, $P < 10^{-11}$), summer season (*dlnm* estimate of -0.15, $P < 10^{-8}$), and increasing year (*dlnm* estimate of 0.05, $P < 10^{-12}$) as independent factors associated with EHAs (Table 4); all these factors were also significantly related with the risk of EHAs in the subgroup of 1953 children (<18 years old, 8054 admissions) and in the subgroup of 2473 adults (9656 admissions) except for mean wind speed in children.

DISCUSSION

We found that the majority of air pollutants and environmental factors were correlated to each other and influenced EHAs in SCD patients, over a lag period of 1 week. Multivariate analysis identified day-to-day temperature drop, increased mean wind speed and decreased CO concentration as independent factors associated with a higher risk of EHAs, while controlling for calendar factors.

Meteorological Factors

In the present study, a decrease in all daily temperatures (minimal, maximal, mean and range) and a drop in day-to-day mean temperature were associated with a higher risk of hospitalization. These results are in accordance with previous studies reporting that seasonally colder temperatures may exacerbate sickle cell-related pain.[17–21] Patients with SCD exhibit hypersensitivity to thermal stimuli[22] and often report cooler weather or exposure to cold as the most important precipitating factor for VOC.[6,7,23] This effect is not likely to be mediated by direct sickling, because lowering of the temperature reduces HbS polymerization in vitro.[24,25] In addition, VOC and ACS are poorly related to indices of chronic hemolysis.[26] The reflex constriction of superficial blood vessels in response to skin cooling is enhanced in SCD as compared to normal individuals.[5] This vasoconstrictor reflex is even stronger in SCD patients who are more prone to painful crises.[3] Serjeant and Chalmers[27] hypothesized that this vasoconstriction may be associated with diversion of blood (''vascular steal'') away from active bone marrow and may cause avascular necrosis and precipitate VOC. This hypothesis is corroborated by radioisotope scanning evidence of impaired blood flow in the bone marrow during a painful crisis and biopsies of sites of maximal tenderness

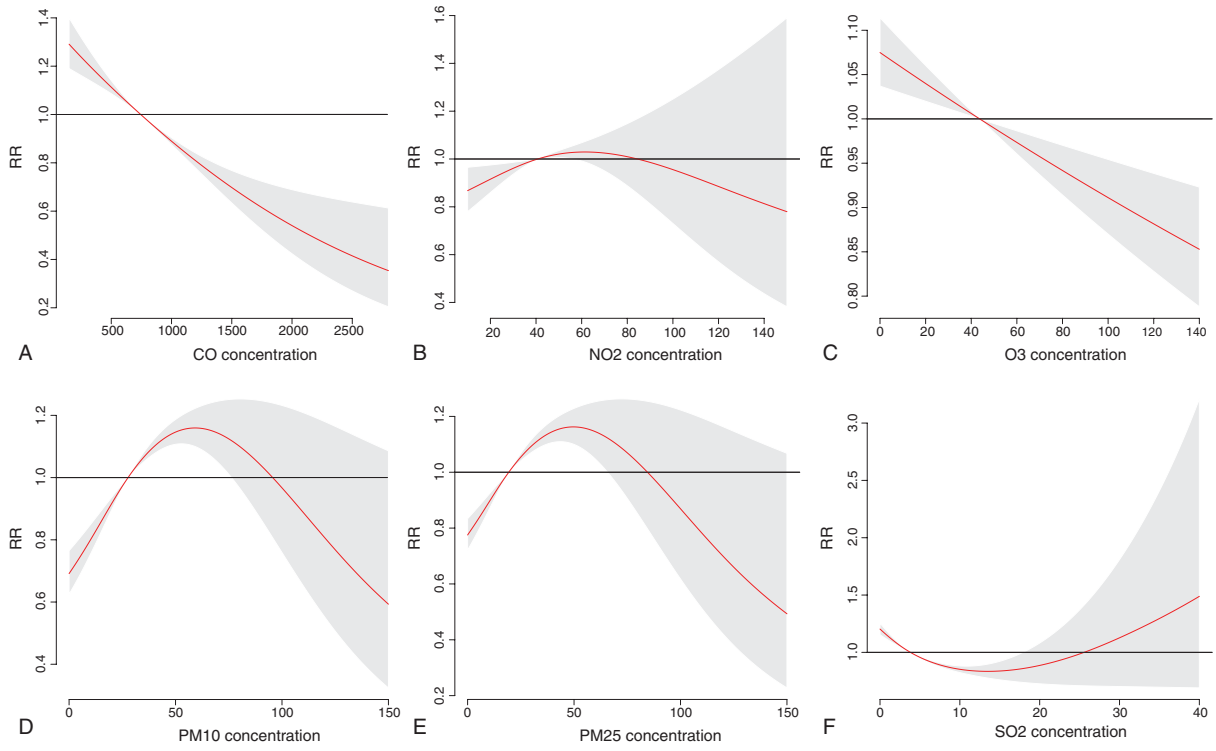

FIGURE 3. Overall effect with relative risk (red line) and 95% confidence interval (grey area) for associations between the number of daily emergency admissions in sickle cell disease patients and daily mean concentrations of carbon monoxide (panel A), nitrogen dioxide (panel B), ozone (panel C), atmospheric particulate matters with aerodynamic diameter smaller than 10 μm (panel D) or 2.5 μm (panel E), and sulfur dioxide (panel F). CO = carbon monoxide, NO_2 = nitrogen dioxide, O_3 = ozone, PM_{10} = atmospheric particulate matters with aerodyamic diameter smaller than 10 μm, $PM_{2.5}$ = atmospheric particulate matters with aerodyamic diameter smaller than 2.5 μm, SO_2 = sulfur dioxide.

yielding necrotic marrow.[28] Increased wind speed and low humidity are both likely to accelerate skin cooling. Convection and sweat evaporation are 2 main mechanisms of human body heat loss. The rate of convective cooling increases with higher wind speed and low atmospheric humidity accelerates evaporative cooling. In our study, high wind speed and low humidity were associated with increased admissions of SCD patients, as previously reported in other areas of temperate climate.[29,30] However, in our study, the relation linking relative humidity to admission risk was significant only by univariate analysis and displayed a U shape, with an increase in hospital admission with higher humidity after a knot around 70% of relative humidity. A similar positive association between relative humidity and hospitalization rate in SCD patients was previously reported.[17,21]

Air Pollutants

The association between daily variations in the levels of urban air pollution and adverse health effects has been established in the general population.[31] Most patients with SCD in developed countries live in urban areas with variable and often poor air quality. In our study, an increased admission risk was associated with higher levels of NO_2, PM_{10}, and $PM_{2.5}$ and lower levels of CO, O_3, and NO_2. These findings differ from those of a previous smaller report[32] except for the protective association of CO. CO was the only air pollutant (negatively) associated with hospital admission by multivariate analysis in our cohort. CO binds to hemoglobin with an affinity over 200 times that of O_2 to form carboxyhaemoglobin (HbCO), which increases the affinity of other binding sites for O_2 and shifts the oxygen dissociation curve to the left. This reduces the level of deoxyHbS and the tendency for HbS to polymerise.[33] CO also inhibits vasoconstriction and platelet aggregation.[34] Inhaled CO reduces inflammation, leucocytosis,[35] and vasoocclusion[36] in murine models of SCD. CO administration to SCD patients induced a significant prolongation of red cell survival.[37] Altogether, these findings suggest CO may be beneficial to patients having SCD.

Calendar Factors

dlnm showed a progressive yearly increase in admission rate during the study period, which persisted in multivariate analysis. This increase may be explained by the progressive increase in cohorts of patients treated for SCD in Paris conurbation during the same period. Weekend and summer season were associated with lower admission rate by multivariate analysis. The difference in hospitalization rate between weekend and weekdays has been reported in other settings like myocardial infarction.[38] This difference may be attributable to a lifestyle change between weekdays and weekends and/or to an attempt by some patients to delay hospital admission until Monday because of the leisurely pace of life on weekends. The decreased incidence during summer season is likely related to higher temperatures and/or traveling outside the Paris conurbation during that holiday period.

Clinical Implications

Education of both SCD patients and their families about how to avoid crises may lead to a decrease in their number and severity.[39] Our findings may help health care providers and

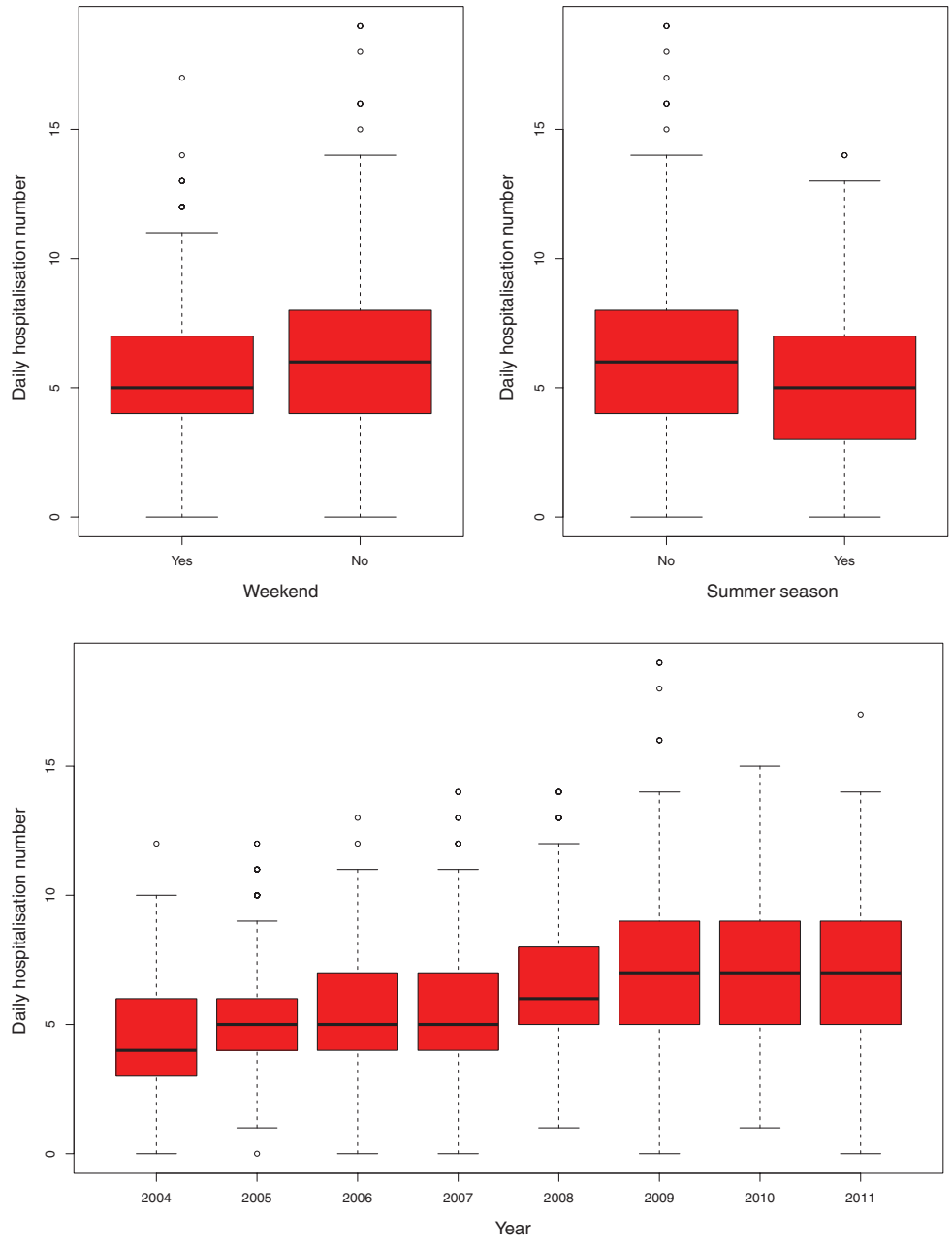

FIGURE 4. Box and Whisker plots of the number of daily emergency admissions in sickle cell disease patients according to weekend (panel A), summer season (panel B), and year of the study (panel C).

patients to adopt preventive measures to avoid hospitalizations. Our report reinforces general recommendation provided to SCD patients, such as to avoid cold, to wear warm clothes outside in cold weather and inside of air-conditioned rooms, and not to swim in cold water.[40] Increased wind speed and day-to-day temperature drop (but not mean daily temperature) were the 2 meteorological factors selected by our multivariable model as modifiers of the risk of emergency hospitalization. Permanently low temperatures may dictate clothing choices and time spent outdoors whereas day-to-day unanticipated falls in temperature may specifically expose SCD patients to outdoor cooling. Patients with SCD should be particularly careful in case of anticipated temperature drop or windy weather. Concerning air pollution, further clinical studies are needed to explore the potential for inhaled CO to alleviate VOC and/or ACS.

Study Strengths and Limitations

Our study is the first multicentric study in SCD patients with a very large sample size spanning several years, with concurrent daily environmental and clinical data, adjusted to calendar data, and using an analytic approach able to capture time structure and non-linear effects in a multivariable analysis. The multivariable approach was necessary given that almost all

TABLE 4. Multivariate Analysis of the Relation Between Environmental and Calendar Factors and Hospital Admissions

Variable	Estimate (*P* Value) of the *dlnm*	
	Space Dimension	Time Dimension
Air polluants		
Carbon monoxide ($\mu g/m^3$)	−0.18 ($<10^{-3}$); −0.10 (0.27)	0.23 (0.06); −0.06 (0.65)
Meteorological factors		
Day-to-day mean temperature change (°C)	−0.30 (<0.01); −0.21 ($<10^{-3}$)	−0.15 (0.17); 0.10 (0.09)
Daily mean wind speed (m/s)	0.05 (0.03); 0.03 (0.25)	–
Calendar		
Year	0.05 ($<10^{-12}$)	–
Summer holidays	−0.15 ($<10^{-8}$)	–
Weekends	−0.13 ($<10^{-11}$)	–

dlnm = distributed lag non-linear models; the degree of freedom in space dimension (dfvar) and in time dimension (dflag) were chosen as to minimize the quasi-Akaike Information Criterion; in space dimension, there is one estimate if dfvar = 1 (from minimal value to maximal value) and 2 estimates if dfvar = 2 (the first from minimal value to central knot and the second from central knot to maximal value); in time dimension, there is no estimate if dflag = 1 and 1 estimate if dflag = 2.

environmental factors variables were observed to correlate. In addition, a lag effect is virtually inevitable in SCD patients, who usually attempt to manage pain at home prior to seeking medical care. The association with the risk of hospital admission by *dlnm* was delayed (starting after lag3 to lag4) for CO (higher values), NO_2, PM_{10}, $PM_{2.5}$, daily temperature range, day-to-day temperature change, daily relative humidity, and daily bright sunshine.

Our study has several limitations. First, it was performed in an urban environment with a temperate climate and our findings may not be extrapolated to other climates. We could not evaluate the extent to which patients might have mitigated environmental factors (eg, by using warm clothing, indoor air conditioning and/or heating), which may lessen the strength of associations between some climate factors and hospitalizations. On the same line, we did not have information about smoking habits, which is a major determinant of HbCO levels and could influence the association between atmospheric CO and hospital admissions. Second, we only studied patients presenting to the emergency department, and some painful crises may have been managed at home, inducing a selection bias. In addition, the chest disease terminology used in the present report may not perfectly overlap ACS because the latest diagnosis is not formally defined in the International Classification of Diseases 10. Third, we did not analyze barometric pressures, but Paris conurbation is a relatively flat region and none of the sites had unusually high elevation that would be associated with consistently low barometric pressures. Similarly, we could not compute perceived temperature because wind measurements were made at a standard height of 33 feet, which do not correspond with the wind experienced by patients, as friction attenuates wind speed closer to the ground. Last, we could not explore the role of several patient characteristics on the influence of environmental factors on hospital admissions.

In conclusion, the majority of weather conditions and air pollutants assessed were correlated to each other and influenced the rate of EHA in SCD patients. In multivariate analysis, weekdays, non-summer seasons, lower CO concentrations, day-to-day mean temperature drop and higher wind speed were associated with an increased risk of EHA.

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