

The associations between air quality and the number of hospital admissions for acute pain and sickle-cell disease in an urban environment

Deborah Yallop,¹ Edward R. Duncan,¹ Elizabeth Norris,² Gary W. Fuller,² Nikki Thomas,¹ Joan Walters,³ Moira C. Dick,³ Susan E. Height,³ Swee L. Thein¹ and David C. Rees³

¹Department of Haematology, King's College London School of Medicine at Guy's, King's College and St Thomas' Hospitals, King's College Hospital, ²Environmental Research Group, King's College London, and ³Department of Paediatric Haematology, King's College London School of Medicine at Guy's, King's College and St Thomas' Hospitals, King's College Hospital, Denmark Hill, London, UK

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Correspondence: Dr David C. Rees, Department of Paediatric Haematology, King's College Hospital, Denmark Hill, SE5 9RS London, UK. E-mail: david.rees@kcl.ac.uk

Summary

The clinical severity of sickle-cell disease (SCD) is dependent on genetic and environmental variables. Environmental factors have been poorly studied. We have investigated possible links between air pollution and acute pain in SCD. We retrospectively studied the numbers of daily admissions with acute sickle-cell pain to King's College Hospital, London, in relation to local daily air quality measurements. We analysed 1047 admissions over 1400 d (1st January 1998–31st October 2001). Time series analysis was performed using the cross-correlation function (CCF). CCF showed a significant association between increased numbers of admissions and low levels of nitric oxide (NO), low levels of carbon monoxide (CO) and high levels of ozone (O₃). There was no association with sulphur dioxide (SO₂), nitrogen dioxide or PM₁₀ (dust). The significant results were further examined using quartile analysis. This confirmed that high levels of O₃ and low levels of CO were associated with increased numbers of hospital admissions. Low NO levels were also associated with increased admissions but did not reach statistical significance on quartile analysis. Our study suggests air quality has a significant effect on acute pain in SCD and that patients should be counselled accordingly. The potential beneficial effect of CO and NO is intriguing and requires further investigation.

Keywords: sickle-cell disease, air pollution, ozone, carbon monoxide, nitric oxide.

Acute pain in sickle-cell disease and air pollution

Sickle-cell disease (SCD) is characterised by episodes of acute pain that are thought to be caused by vaso-occlusion. Vaso-occlusion is caused by a complex series of processes that are initiated by the deoxygenation and polymerisation of haemoglobin S (HbS). Several other factors have been identified as important in the pathology of SCD, including abnormal expression of adhesion molecules, red cell dehydration and functional nitric oxide (NO) deficiency (Stuart & Nagel, 2004). The average rate of acute painful crisis requiring hospital attendance is 0.8/year/person, but this varies very widely, with 30–40% of patients having no painful episodes per year and 1% having more than six episodes/year (Platt *et al*, 1991). The reason for this variability is not known, but is thought to involve a large number of environmental and genetic factors.

Environmental factors have been poorly studied. We previously demonstrated windy weather and low humidity were associated with increased hospital admissions (Jones *et al*, 2005). The impact of environmental factors on health is a major public health issue. Air pollution has been consistently correlated with poor health, particularly in respiratory disease. The European Union financed the APHEA-1 (Air Pollution and Health – A European Approach) project 'Short term effects of air pollution on health: A European Approach using epidemiological time series data'. Over 14 years, this study collated data on more than 25 million people, looking into mortality from natural causes, cardiovascular and respiratory diseases in association with air pollutant levels. The existence of an association between daily variations in the levels of urban air pollution and adverse health effects was established (Spix *et al*, 1998). No studies to our

knowledge have correlated measurements of air quality and morbidity in SCD.

Methods

King's College Hospital (KCH) is a teaching hospital in South East London, UK. A population of approximately 900 patients have a diagnosis of SCD. Patients are admitted following assessment in the Day Unit (adults, Monday–Friday 09:00–17:00) or accident and emergency (paediatrics and adults at all other times). The study used data from the 1400 days between 1st January 1998 and 31st October 2001 collected prospectively by specialist nurses as part of the routine data collection on all sickle-cell admissions. The number of daily admissions varied from zero to five. Admissions were included in the study if the patient had a diagnosis of SCD (HbSS, HbSC, HbS/ β^0 -thalassaemia, HbS/ β^+ thalassaemia, HbS/HbD^{Punjab}), was admitted for at least one night and the principal reason for the hospital admission was acute pain.

Air quality data was collected by the London Air Quality Network (<http://www.londonair.org.uk>) at three sites: Southwark (2.9 km from KCH) [carbon monoxide (CO), NO, ozone (O_3), sulphur dioxide (SO_2)], Croydon (10-km away) (PM_{10} , O_3) and Eltham (9.5-km away) [nitrogen dioxide (NO_2)]. All these collection sites were away from main roads and positioned to measure background air pollution. PM_{10} was measured by tapered element oscillating micro-balance. Air quality was measured every 15 min and the daily average was calculated and used in analyses.

Statistical analysis was performed using techniques for time series analysis. Patterns of admission to hospital were initially analysed using graphs of the cross-correlation function (CCF), where the observations of one series were correlated with the observations of another series at various lags and leads (Chatfield, 2000) [Statistical Package for the Social Sciences (SPSS) software; SPSS Inc., Chicago, IL, USA]. This showed whether there was any correlation between the measured parameter, such as O_3 , and the number of admissions on that day (day 0) and also on subsequent days (days +1, +2 etc). A significant correlation was shown by the CCF exceeding 0.05. For example, if a high level of O_3 caused increased admissions for three days, this would show as the CCF exceeding 0.05 on days 0, +1 and +2. Any significant results on CCF analysis were further studied using quartile analysis, in which the 1400 days of the study were divided into quartiles for the different parameters, and the mean number of admissions per day in each of these quartiles compared by Mann–Whitney *U*-test and ANOVA (SPSS).

Results

There were 1047 admissions with acute pain over the 1400-day study period (756 adult and 291 paediatric). These admissions were made up of 331 different patients. Eighty per cent of patients were admitted on fewer than five occasions, 12% between five and 10 times, and 8% more than 10 times. These

same admissions have previously been analysed with regard to the effects of climate (Jones *et al*, 2005).

Cross-correlation function analysis showed a significant effect of O_3 , CO and NO on admissions to hospital with acute pain and SCD. Levels of SO_2 , NO_2 and PM_{10} had no association with sickle admissions by CCF analysis and were not studied further.

Cross-correlation function analysis of O_3 levels gave a value of 0.067 on the day of analysis (day 0) (values >0.05 were considered significant). Quartile analysis confirmed this relationship, showing a significant increase in hospital admissions associated with high O_3 levels [one-way analysis of variance (ANOVA), $P = 0.039$] (Fig 1). The effect was relatively small but statistically significant, with 55% of admissions occurring on days in the highest two quartiles for O_3 , and 45% in the lowest two. This trend was present at both geographical sites at which O_3 levels were measured. O_3 levels are known to increase in summer, and this pattern was seen in our study; this seasonal trend mirrored, and may explain, the trend towards more hospital admissions during the summer months (Fig 2).

Carbon monoxide levels were inversely correlated with frequency of admissions. Low levels of CO resulted in statistically increased numbers of admissions, both on CCF (CCF = 0.064 on day 0) and quartile analysis (one-way ANOVA, $P = 0.042$) (Fig 3). Again the effect was relatively small, with 54% of admissions occurring in the two quartiles with the lowest CO levels.

Similarly, low NO levels were linked to more admissions on CCF analysis (CCF –0.063 on day 0, –0.051 on day +1); this pattern was present on quartile analysis but did not reach statistical significance (one-way ANOVA, $P = 0.158$). Fifty-three per cent of admissions occurred in the two quartiles with the lowest NO levels (Fig 4).

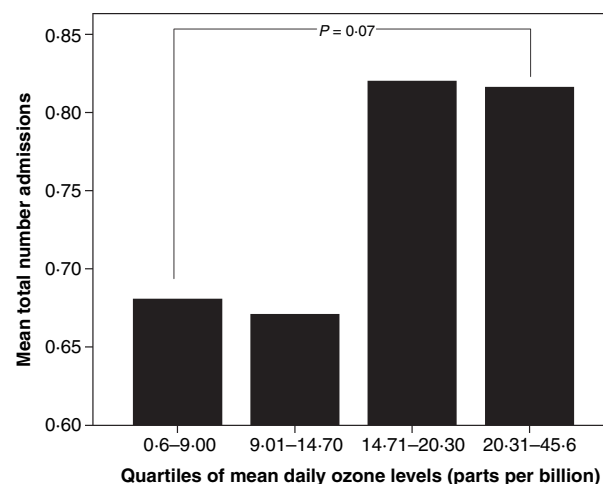


Fig 1. Bar graph showing the mean number of admissions for the different quartiles of background O_3 levels measured in Southwark. *P*-value is shown for a comparison of means of the first and fourth quartile (Mann–Whitney *U*-test). The trend towards increasing admissions with increasing O_3 levels is significant with ANOVA ($P = 0.039$).

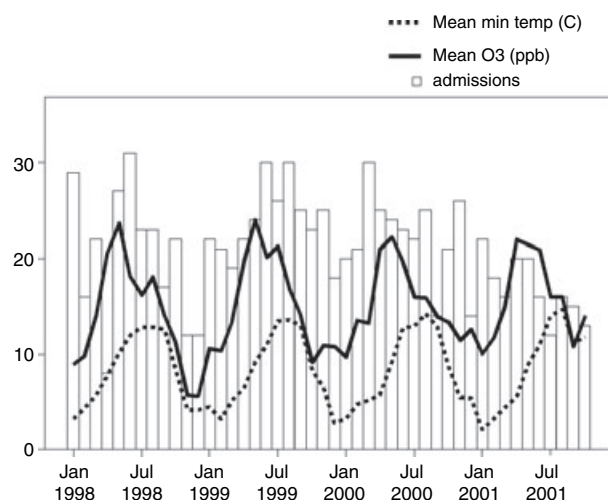


Fig 2. Summary of monthly data over period of study. Bars show total admissions with acute pain caused by sickle-cell disease for each month. The average monthly minimum temperature ($^{\circ}\text{C}$) is shown by a broken line, and the average monthly background O_3 concentration (parts per billion, ppb) is shown by the continuous line.

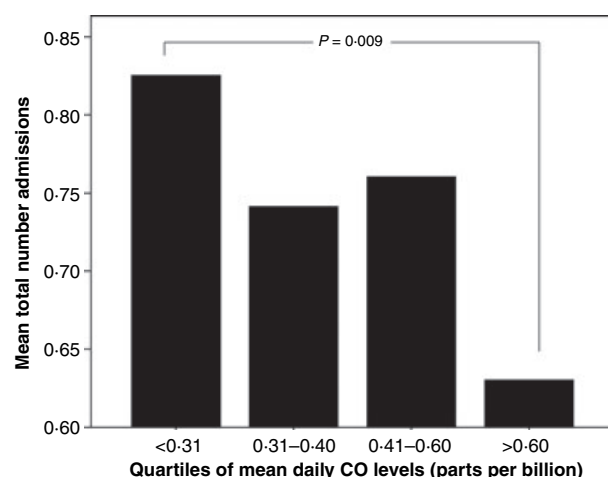


Fig 3. Bar graph showing the mean number of admissions for the different quartiles of background CO levels measured in Southwark. P -value is shown for a comparison of means of the first and fourth quartile (Mann-Whitney U -test). The trend towards increasing admissions with increasing O_3 levels is significant with ANOVA ($P = 0.042$).

Discussion

This study recorded O_3 , CO, NO, NO_2 , SO_2 and PM_{10} as measures of air pollution. To our knowledge, this is the first study to investigate, in detail, the effects of local air quality on the frequency of sickle-cell admissions with acute pain.

A significant relationship was found between high O_3 levels and increased numbers of sickle-cell admissions with pain. The adverse effects of high O_3 levels may explain the paradoxical increase in summer admissions in London shown in our previous study (Jones *et al*, 2005), and possibly other cities. Tropospheric O_3 is a secondary pollutant formed in the

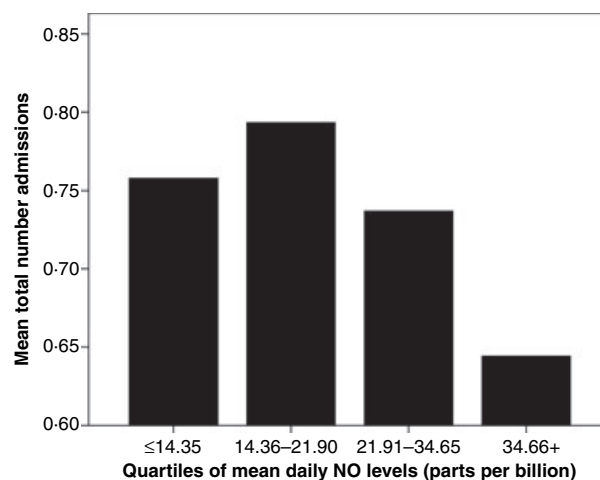


Fig 4. Bar graph showing the mean number of admissions for the different quartiles of background NO levels measured in Southwark.

atmosphere from reactions between primary pollutants emitted from combustion and industrial processes. Peak levels of O_3 occur on hot sunny days when these reactions are favoured. High levels of urban O_3 have been linked to several harmful effects, including reduced lung function, increased respiratory symptoms, exacerbation of asthma and death (Bell *et al*, 2006). It is possible that O_3 could precipitate acute pain through its respiratory effects. There is increasing evidence of a temporal link between asthma and episodes of acute pain in children with SCD (Glassberg *et al*, 2006). Similarly, O_3 has been strongly implicated in asthma exacerbations; for example, Friedman *et al* (2001) demonstrated reduced acute exacerbations of asthma in association with reduced traffic and O_3 levels during the Atlanta Olympics in 1996. It is therefore possible that O_3 levels could be linked to acute pain in SCD through asthma. Similarly, O_3 could act as a marker of poor air quality, and the relationship with acute pain could arise because of another unstudied air pollutant.

This study also showed that high CO levels were associated with fewer admissions for acute pain. Many previous studies have highlighted the negative effect of increased CO levels on health (Curtis *et al*, 2006). It has been linked to increased admissions with exacerbation of respiratory diseases and acute coronary events. The present study showed that high levels of CO may be protective against acute pain in SCD. An interesting explanation for this result is that high levels of atmospheric CO form increased amounts of sickle carboxyhaemoglobin, which does not polymerise. The rate of haemoglobin S (HbS) polymerisation is known to be critically dependent on the concentration of deoxyHbS. The increase in carboxyhaemoglobin associated with higher atmospheric levels of CO might dilute the deoxyHbS sufficiently to be of clinical benefit. This was investigated in the 1970s by studying the effect of CO on red cell survival *in vivo*. CO, at concentrations of 1000–2000 parts per million (ppm), was administered to two sickle-cell patients. In both there was significant prolon-

gation of red cell survival, suggesting a potential therapeutic benefit from CO (Beutler, 1975). More recently, CO was shown to inhibit stasis in the blood of transgenic sickle mice (Belcher *et al*, 2006) and therapeutic applications have been explored in other areas, including lung disease (Ryter & Choi, 2006). Because of the anonymous nature of this study, we do not have information on smoking, which is a major determinant of carboxyhaemoglobin levels. Heavy smokers exhale CO in concentrations of up to 20 ppm (Groman *et al*, 2000), compared with the highest background levels in this study of 2.9 parts per billion (ppb). However, it is safe to assume that smoking rates did not vary significantly with air quality, and it is unlikely that smoking artefactually created the effect of CO on hospital admission.

Similarly, increasing NO levels were linked to decreased admissions with acute pain. NO is known to be central to the pathophysiology of SCD. It was suggested that impaired bioavailability of NO in SCD is due in part to the scavenging of NO by cell free plasma haemoglobin (Reiter *et al*, 2002). This has led to the investigation of the benefits of NO therapy in SCD (Weiner *et al*, 2003). Initial studies suggest that NO acts as a vasodilator, decreases pulmonary artery pressure, inactivates free plasma haemoglobin, and ameliorates ischaemia-reperfusion injuries. It is unknown what effect the levels of atmospheric NO have *in vivo*. In our study, the highest average NO on any 1 day was 259 ppb, although considerably higher peak levels may have been achieved on this day. This is 100 times lower than levels in therapeutic studies, which typically use 40 ppm, although it is possible that atmospheric variation in NO levels might result in subtle clinical effects.

This and our previous study on weather and acute pain (Jones *et al*, 2005) have identified a number of inter-related environmental factors that are associated with complications of SCD. High O₃ levels correlate with low NO, low CO, increased wind speeds and low humidity; all these factors were also linked to increased admissions with acute pain but it was not possible, from this sort of association study, to determine which are the primary factors. Overall the strongest statistical association was with mean O₃ concentration, and the links between asthma, SCD and O₃ add to the plausibility of this relationship. Exposure to cold is a well-established precipitant of SCD (Redwood *et al*, 1976), and it seems possible that the lack of seasonality in SCD admissions in our patients and other urban studies (Seeler, 1973; Slovis *et al*, 1986; Kehinde *et al*, 1987) is partly caused by air pollution. The damaging effect of cold weather is reduced by warm clothing and central heating, whilst the potential benefits of warm weather are countered by the poorer air quality. Although the strongest effect is seen with the secondary pollutant, O₃, the potential adverse effects of low atmospheric CO and NO levels are intriguing and of pathological and therapeutic importance. Further studies are needed to clarify the links between these factors and pain, including measurements of carboxyhaemoglobin, NO metabolites and respiratory function when patients are admitted with acute pain.

Worldwide, air pollution is estimated to cause 800 000 premature deaths annually (Cohen *et al*, 2005). The average adult inhales 20 m³ of air per day (Berne *et al*, 1998), which, in towns and cities, inevitably contains a large number of chemicals. Patients with SCD in developed countries primarily reside in these urban areas and are vulnerable to the adverse effects of many of these pollutants. Air quality may be one of the environmental factors that contribute to the phenotypic variability of SCD. Further studies investigating the impact of air quality on SCD are warranted. Based on this study, it may be sensible to warn patients with SCD that acute pain is more likely to occur on days with high levels of O₃, and that it may be sensible to avoid areas with poor air quality.

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