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Accessibility
Short-term metal particulate exposures decrease cardiac acceleration and deceleration capacities in welders: a repeated-measures panel study

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ABSTRACT

Objective Acceleration (AC) and deceleration (DC) capacities measure heart rate variability during speeding up and slowing down of the heart, respectively. We investigated associations between AC and DC with occupational short-term metal PM2.5 exposures.

Methods A panel of 48 male welders had particulate matter less than 2.5 microns in diameter (PM2.5) exposure measurements over 4–6 h repeated over 5 sampling periods between January 2010 and June 2012. We simultaneously obtained continuous recordings of digital ECG using a Holter monitor. We analysed ECG data in the time domain to obtain hourly AC and DC.

Linear mixed models were used to assess the associations between hourly PM2.5 exposure and each of hourly AC and DC, controlling for age, smoking status, active smoking, exposure to secondhand smoke, season/time of day when ECG reading was obtained and baseline AC or DC. We also ran lagged exposure response models for each successive hour up to 3 h after onset of exposure.

Results Mean (SD) shift PM2.5 exposure during welding was 0.47 (0.43) mg/m³. Significant exposure–response associations were found for AC and DC with increased PM2.5 exposure. In our adjusted models without any lag between exposure and response, a 1 mg/m³ increase of PM2.5 was associated with a decrease of 1.46 (95% CI 1.00 to 1.92) ms in AC and a decrease of 1.00 (95% CI 0.53 to 1.46) ms in DC. The effect of PM2.5 on AC and DC was maximal immediately postexposure and lasted 1 h following exposure.

Conclusions There are short-term effects of metal particulates on AC and DC.

INTRODUCTION

Short-term and long-term particulate exposures have been shown to have adverse effect on cardiovascular outcomes.1–4 One of the mechanisms involved is through affection of the autonomic nervous system, which has been measured traditionally using heart rate variability (HRV).5–7 Air pollution studies have consistently shown a decrease in HRV with exposure to PM2.5.8 9 A decrease in HRV has also been linked to an increase in adverse cardiovascular outcomes.10–13

Whereas there is ubiquitous exposure to particulates in ambient air, occupational exposure to particulates is usually greater. For example, welders have been shown to have been exposed to about 24 times the level of ambient PM2.5 exposure levels.14 15 Furthermore, an exposure-related decrease in HRV has been demonstrated among these welders.16

Although previous research suggests that there is a significant exposure–response relationship with increasing exposures to metal PM2.5 producing increasing cardiac autonomic dysfunction (reduced HRV), this was evaluated using HRV as the index of autonomic dysfunction, which has limitations. HRV fails to account for the heart rate, and is therefore prone to missclassification.17 Current mechanistic research using HRV cannot clarify if a decrease in HRV means a decrease in accelerations and/or decrease in decelerations of the heart rate.

Acceleration capacity (AC) is a measure of the responsiveness of the heart to speed up when stimulated, and it is known to be under both autonomic (sympathetic) and non-autonomic control.11 12 Deceleration capacity (DC), on the other hand, describes the behaviour of the heart when the heart rate is slowing, and it reflects a measure of parasympathetic modulation of the heart.18 While there have been no population-level studies yet to measure the normal range levels of AC and DC in the healthy general population, most studies of patients with postmyocardial infarction have reported baseline levels of magnitude 7.0–8.0 ms for both AC and DC in their respective scales.19–21

What this paper adds

▸ Heart rate variability (HRV) has been the widely used outcome in cardiac autonomic research but has been critiqued for its potential of misclassification with changing heart rates.

▸ Short-term metal PM2.5 exposure decreases HRV, but the specific effects on accelerations and decelerations are unknown.

▸ This paper shows that there are decreases in both cardiac accelerations and decelerations.

▸ The decreases in acceleration and deceleration capacities persist up to 1 h even after exposure ceases.

▸ Targeted interventions should aim at reducing particulate exposure and mitigating effects on both cardiac acceleration and deceleration capacities.
In 2006, Bauer et al. described the phase-rectified signal averaging (PRSA) method for calculating the cardiac AC and DC, which are measures of the responsiveness of the heart, like HRV. These have the advantage over HRV of parsing the Holter data into accelerations and decelerations while also accounting for the heart rate, and have been demonstrated to be more predictive of morbidity and mortality among patients with postmyocardial infarction than traditional HRV. Therefore, using sensitive indices—AC and DC—this study aims to investigate the potential for cardiac autonomic dysfunction from metal PM exposure. We hypothesised that metal-rich PM exposure would decrease both AC and DC.

**METHODS**

**Participant recruitment**

We recruited a convenience sample of 72 male boilermakers based on outreach to the union membership with an overall participation rate of 93% during five sampling periods between January 2010 and June 2012 from the boilermaker union in Quincy, Massachusetts. These boilermakers were part of an ongoing ‘Harvard Boilermakers’ Cohort’ initiated in 1999 to study the cardiopulmonary effects of particulates. The ‘Harvard Boilermakers’ Cohort’ was a coalition of different smaller panel studies that were conducted at different sampling periods to answer specific research questions including the effect of secondhand smoke and metal particulates on cardiopulmonary effects. Participants were mostly monitored on consecutive non-welding and welding days during each sampling period. Although we had recruited 72 boilermakers, we restricted our study to 52 participants who were only monitored on welding days. We were only able to record simultaneous PM, and digital ECG on non-welding days for 20 participants, poor-quality ECG data in 2 participants, and failed ECG data retrieval in 2 other participants. We analysed data from 48 boilermakers (our final sample) on only welding days for our study. They constituted 67% of the participants in the existing cohort whom we were able to obtain PM exposure from during welding shift, as well as record continuous digital ECG recording during welding shifts recruited within sampling periods between 2010 and 2012. We conducted our study during winter or summer when 75% (36) of the study participants had not actively welded 2 weeks prior to our data collection. The other 25% (12) had welded between 3 and 10 days before our sampling (weld) day. The Institutional Review Board at the Harvard T. H. Chan School of Public Health approved the study protocol. The study participants at the union welding school using personal DustTrak Aerosol Monitor (TSI, Inc., St. Paul, Minnesota, USA) for processing and analysis. Holter recordings were then down-loaded and sent to the Cardiovascular Epidemiology Research Unit (CVERU) of Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) for processing and analysis. Holter recordings were uploaded into the GE MARS ECG analysis system, which automatically scans recordings for areas of noise and groups heartbeats as normal or arrhythmic. Trained technicians blinded to the exposure status of the participant from whom the ECG reading was obtained verified the automated scans as correct or changed them to the appropriate designation. The data were then exported for analysis using the Physionet toolkit. To remove artefacts from the data, they used only beats with a distance between two consecutive R waves on the electrocardiogram (RR) interval within 5% difference of adjacent beats. They used an automated process described by Bauer et al. to create 5 min segments with anchors for the PRSA method of computing the AC and DC. In brief, to compute the DC, this involves identifying heartbeat intervals longer than the preceding interval as anchors (for AC, beats shorter than preceding beats were anchors). Overlapping segments of interval data were then automatically generated from the ECG such that all segments are aligned at the anchors in the centre and averaged. The PRSA method then quantifies the signals within aligned segments using the Haar wavelet analysis with a scale of 2 by a computer processing of the ECG with visual and digital outputs. Thus, AC and DC were calculated separately as a quarter of the difference between two sums, that is, the sum of the averaged anchor points RR intervals (X̄) with the succeeding RR intervals (X̄) and the sum of the two averaged RR intervals preceding anchor points (X̄–2, X̄–1).
Using the digital ECG data in the time domain, we computed the average AC and average DC for each simultaneous hour of PM\(_{2.5}\) exposure and monitoring by taking the mean of the 12 adjacent 5 min segments of the ECG within each hour of the day using the automated output.

Data analysis

We calculated summary measures of potential covariates, and percentiles of our exposure and outcome to further understand their distribution. Potential covariates that we considered include: age, race, smoking status (smoker/non-smoker), actively smoking during work (yes/no) and secondhand smoke exposure (exposed/not exposed), time of day when ECG was obtained, season of study, previous weld exposure (last weld day), chronic effects of welding (years of boilermaker), actively welding (yes/no), presence of heart problems, and baseline cardiac autonomic function (baseline AC or DC for AC and DC models, respectively). Secondhand smoke exposure was defined as being exposed to smoke from other nearby workers smoking during our sampling. We then explored the inter-relationships between them by using Spearman’s correlations for continuous variables and t tests for binary variables. In order not to have missed any inter-relationships between potential covariates with our exposure/outcome, we used \(\alpha=0.10\) level for these correlations and t tests between covariates and outcome/exposure.

For our model without any lag between exposure and response, we used linear mixed models to assess the associations between hourly PM\(_{2.5}\) as a continuous measure and simultaneously measured hourly AC, and a separate model for PM\(_{2.5}\) and DC. Furthermore, we used a backward method of model selection using a p value of 0.2 each for staying in the model to select our final model. We compared models using the log likelihood ratio test. We considered controlling for age, smoking status, last weld day (unmeasured acute weld exposure), number of years as a boilermaker (chronic effects), baseline AC or DC (for AC or DC models respectively), and time of day and season when ECG reading was obtained. Our final model included age, baseline AC or DC, smoking status, active smoking, secondhand smoke exposure, time of day and season of ECG. For the lagged models, we used linear mixed models to assess the associations between hourly PM\(_{2.5}\) and lagged hourly AC or DC at 1, 2 and 3 h lags. A lag was defined as the time period between exposure (metal-rich PM\(_{2.5}\)) and its response (AC or DC). Therefore, a ‘1 hour’ lag model was evaluating the effect of PM\(_{2.5}\) at a time point on AC or DC level ‘1 hour’ later. Statistical significance was assessed at \(\alpha=0.05\) level in two-sided tests for our final model. All analyses were performed using PROC MIXED in SAS V9.4 (Cary, North Carolina, USA).

RESULTS

We successfully collected 892 person-hours of weld day PM\(_{2.5}\) and 1392 person-hours of weld day ECG from 48 participants during a median of three work shifts per participant of 4–6 h duration, all males with a mean age of 40 years and had been boilermakers for a median of 4 years (range 0.25–21 years). The study population included 19 (40%) smokers (Table 1).

Five of these 48 participants reported heart problems and possible heart-related problems. Of these five, one reported arrhythmia, one reported sinus (sinoatrial node) problems, one reported angina in the past year, one reported mitral valve prolapse with murmur and one reported hypertension for which he was taking a \(\beta\)-blocker. No other participant reported the use of \(\beta\)-blockers or ACE inhibitor drug use. Less than half (38%) of the baseline ECG were taken in the morning, and each participant had PM\(_{2.5}\) measurements taken in 2–5 typical work shifts of 4–6 h.

The mean number of years as a boilermaker was 9 years (range 1–35 years). The mean PM\(_{2.5}\) during the work shift for participants measured was 0.47 mg/m\(^3\) (range 0.01–1.40 mg/m\(^3\)). The mean (range) baseline AC was –7.1 ms (–2.1 to –22.6) on the negative scale (Table 2). The mean (range) baseline DC was 8.8 ms (3.3–22.4).

Spearman’s correlations coefficients (and p value) for correlation between potential covariates and PM\(_{2.5}\) or baseline measures of AC and DC were mostly statistically non-significant. However, season of the year and active smoking were correlated with AC and/or DC, but not with PM\(_{2.5}\). Among the other covariates considered, age was neither correlated with PM\(_{2.5}\) exposure nor with the baseline AC or DC. The number of years as a boilermaker and last weld day were only moderately correlated with PM\(_{2.5}\) exposure but not with baseline AC or DC. There were no differences in categories of other covariates in terms of measures of shift PM\(_{2.5}\), baseline AC and DC.

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>N</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
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<td>100</td>
</tr>
<tr>
<td>Caucasian</td>
<td>42</td>
<td>88</td>
</tr>
<tr>
<td>Smoking status (current smoker)*</td>
<td>19</td>
<td>40</td>
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<tr>
<td>Other characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of ECG (AM)†</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>Season of ECG (Winter)‡</td>
<td>33</td>
<td>69</td>
</tr>
<tr>
<td>Heart problems§</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start of study 2010 (years)</td>
<td>40</td>
</tr>
<tr>
<td>Number of years as a boilermakers (years)</td>
<td>9</td>
</tr>
<tr>
<td>Last weld day before study (days)</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 1: Demographics and characteristics for the 48 study participants

<table>
<thead>
<tr>
<th>Baseline and hourly levels of metal PM(_{2.5}) (mg/m(^3)), acceleration (AC) and deceleration (DC) capacities of the heart (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>PM(_{2.5}) (mg/m(^3))†</td>
</tr>
<tr>
<td>AC (ms)†</td>
</tr>
<tr>
<td>DC (ms)</td>
</tr>
</tbody>
</table>

Bold values indicate significant associations (p<0.05).

Table 2: Baseline and hourly levels of metal PM\(_{2.5}\) (mg/m\(^3\)), acceleration (AC) and deceleration (DC) capacities of the heart (ms)
The linear mixed models analyses for our model without any lag revealed that PM$_{2.5}$ levels were associated with a decrease in AC and DC after adjusting for age, smoking status, active smoking, secondhand smoke exposure and baseline AC or DC (tables 3 and 4).

When we introduced lags by the hour between PM$_{2.5}$ exposure and AC or DC, there were associations between metal PM$_{2.5}$ exposure and lagged responses in AC and DC at 1 h postexposure. These were consistent with or without adjustment for PM$_{2.5}$ exposure in the previous hour(s). When we excluded the five participants with heart problems, the results were consistent. A sensitivity analysis that excluded the 12 participants who had welded within 2 weeks before our study showed qualitatively similar results (table 5).

**DISCUSSION**

The goal of this study was to investigate the associations between AC and DC with acute metal-rich PM$_{2.5}$ exposures. Consistent with our hypothesis, metallic PM$_{2.5}$ exposure was associated with AC and DC. We found significant exposure-response relationships between increasing short-term metallic PM$_{2.5}$ exposure producing decreasing AC and DC. These associations were qualitatively consistent with or without adjustment for PM$_{2.5}$ exposure in the previous hour(s). There may therefore be a reduction in the capacity of the heart to accelerate and decelerate over time with acute insults from these exposures. These data imply that there may be changes in parasympathetic control, sympathetic modulation and/or non-autonomic control of the heart with acute exposure to particulates. Few studies have documented associations between particulate exposures and HRV in the short term. $^2$ $^5$ $^7$ $^9$ $^{26}$ Yet, fewer studies have observed associations between short-term fine particulate exposure and DC. $^{18}$ This study is the first to our knowledge to demonstrate declines in AC following acute metal-rich particulate exposures among healthy welders.

We cannot directly compare our study results with those of prior studies due to the differences in exposure characteristics and study population. We did find declines in DC slightly greater than declines reported following short-term PM$_{2.5}$ exposures among post-myocardial infarction patients. $^{18}$ In addition, we observed declines in AC among welders who are not acutely ischaemic which has never been reported. This result highlights the possibility of differences in effect among our study population (active healthy welders) compared with other studies (patients with postmyocardial infarction) that were mostly conducted in clinical settings. Furthermore, the different constituents of the particulate exposures may have varying effects on the electrical activity of the heart. While organic and elemental carbons have been implicated as suspects, metals have also been shown to play a role. $^{14}$ $^{18}$ $^{27}$ Welders are exposed to metal-rich fumes, and this may be responsible for the effects on AC we found in this study.

Only five of the study participants reported known or possible heart problems. There was no difference in quality of results in the sensitivity analyses that excluded these five participants. This suggests that the effects of particulates in chronic ischaemic heart conditions and healthy persons are qualitatively similar.

We found significant effects with both the AC and DC, as well as lagged responses between PM$_{2.5}$ and DC. We would

### Table 3  Main effect of PM$_{2.5}$ (mg/m$^3$) on acceleration capacity (AC; ms) and deceleration capacity (DC; ms) without adjustment for hourly pre-exposures from the linear mixed effect response-lagged models with 48 participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AC* (95% CI)</th>
<th>DC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lag</td>
<td>1.46 (1.00 to 1.92)</td>
<td>−1.00 (−0.53 to −1.46)</td>
</tr>
<tr>
<td>1 h lag†</td>
<td>0.73 (0.26 to 1.20)</td>
<td>−0.40 (0.08 to −0.87)</td>
</tr>
<tr>
<td>2 h lag†</td>
<td>−0.29 (−0.83 to 0.24)</td>
<td>0.65 (1.22 to 0.07)</td>
</tr>
<tr>
<td>3 h lag†</td>
<td>−0.34 (−0.92 to 0.25)</td>
<td>0.52 (1.15 to −0.12)</td>
</tr>
</tbody>
</table>

Bold values indicate significant associations (p<0.05). Models are adjusted for age, smoking status, active smoking, secondhand smoke exposure, time of day and season of ECG reading, and baseline AC or DC.

*AC is measured on a negative scale; therefore, a 1 mg/m$^3$ increase in PM$_{2.5}$ results in a decrease in AC by 1.46 ms (on a negative scale) for the association without any lag.

†Lagged models adjust for exposure time points before the lags. For example, a 1 h lag model also adjusts for PM$_{2.5}$ measurements in the preceding hour before the exposure time point of interest.

### Table 4  Main effect of PM$_{2.5}$ (mg/m$^3$) on acceleration capacity (AC; ms) and deceleration capacity (DC; ms) with adjustment for hourly pre-exposures from the linear mixed effect response-lagged models with 48 participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AC* (95% CI)</th>
<th>DC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lag</td>
<td>1.46 (1.00 to 1.92)</td>
<td>−1.00 (−0.53 to −1.46)</td>
</tr>
<tr>
<td>1 h lag†</td>
<td>0.81 (0.30 to 1.32)</td>
<td>−0.70 (−0.14 to −1.26)</td>
</tr>
<tr>
<td>2 h lag†</td>
<td>1.00 (0.13 to 1.87)</td>
<td>−0.45 (0.52 to −1.42)</td>
</tr>
<tr>
<td>3 h lag†</td>
<td>0.41 (−1.65 to 2.46)</td>
<td>−0.12 (2.48 to −2.71)</td>
</tr>
</tbody>
</table>

Bold values indicate significant associations (p<0.05). Models are adjusted for age, smoking status, active smoking, secondhand smoke exposure, time of day and season of ECG reading, and baseline AC or DC.

*AC is measured on a negative scale; therefore, a 1 mg/m$^3$ increase in PM$_{2.5}$ results in a decrease in AC by 1.46 ms (on a negative scale) for the association without any lag.

†Lagged models adjust for exposure time points before the lags. For example, a 1 h lag model also adjusts for PM$_{2.5}$ measurements in the preceding hour before the exposure time point of interest.
therefore hypothesise that during acute exposure to particulates, there is a blunting of the autonomic response of the heart to the activation of both parasympathetic and sympathetic nervous system influences to regulate the response of the heart, as well as the interplay of non-autonomic control (cytokines and inflammatory mediators) which may be playing a major role in the lagged responses of AC and DC to exposure of metal particulates. We found the effects on AC and DC lasted up to 1–2 h postexposure. We doubt the sustenance of autonomic effects up to this time, and we would hypothesise that non-autonomic influences may begin to play a role at this time. If this hypothesis is correct, then our results are not completely consistent with previous knowledge that AC is influenced by both autonomic control and inflammatory stimuli, and that DC which is mainly under autonomic control,\textsuperscript{17} since we found that sustained effects of PM$_{2.5}$ exposure affect both AC and DC. This discrepancy may be explained by AC and DC being antagonistically opposed to each other. There may be greater sensitivity on AC by acute insults as the effect on AC remains until 2 h following the insult.

DC has been shown to be predictor of mortality following acute myocardial infarction, even among patients with preserved AC, as there is a rapid decline in the parasympathetic innervation of the heart following ischaemia.\textsuperscript{17} We did observe declines in the DC among these healthy welders as only one of them had had an ischaemic event within the last year of the study. However, the clinical usefulness of a decline in the DC of the heart of healthy persons is unknown. Even more so, the significance of declines in AC in both ischaemic/non-ischaemic hearts is uncertain. This may be due to the multifactorial influences on the AC.

Short-term metal particulates have effect on the AC and DC lasting 1 h postexposure. This is similar to the early phase of the multiphasic response of HRV to particulates which showed a sustained effect on HRV up to 3 h.\textsuperscript{8} However, our study results did not show a sustained effect on AC and DC up to 3 h postexposure. This may be as a result of misclassification of HRV with respect to accelerations and decelerations. Additionally, the declines in HRV (15 ms per 1 mg/m$^3$ PM$_{2.5}$) observed in similar study population were 10-fold greater than the declines observed in AC and DC.\textsuperscript{16} Thus, HRV may be differentially misclassifying effect of PM$_{2.5}$ exposure on cardiac automaticity with respect to both accelerations and decelerations.

There was no difference between mean hourly AC and DC compared with baseline. This may be the result of averaging over few hours after PM$_{2.5}$ exposure ceases to have effect on AC and DC. This result suggests that the heart may be adapting its response to the continuous exposure of fine particulate. This is further supported by the intermediate decline in AC at the ‘1 h lag’ compared with the ‘no lag’ and ‘2 h lag’ indicating some attempt of the heart at recovery (table 4). Excluding study participants who had welded within 2 weeks before our study did not significantly alter the results of our study. This suggests that there may not be a significant cardiac sensitisation on re-exposure to metallic PM$_{2.5}$ following a washout period.

Based on our study results, reducing exposure would be a major goal of health promotion for these workers. The use of personal protective equipment such as a respirator has been shown to reduce exposures to particulates and improve HRV.\textsuperscript{20} Our study has its strengths and limitations. Importantly, we captured ECG recordings digitally that were parsed into phases of accelerations and decelerations accounting for differences in heart rate. Our results are therefore not confounded by heart rate. We also adjusted for confounding by potential confounders. We used repeated continuous shift PM$_{2.5}$ measured using DustTrak Aerosol Monitor. We were also able to account for previous welding exposure by restricting most of our study population to those who had not welded 2 weeks prior to our study, and considered adjusting for prior uncaptured PM$_{2.5}$ exposure using ‘last weld day’ in our models. PM$_{2.5}$ exposure measurements were obtained in comparable work settings at the union hall\textsuperscript{3} and may reflect what their typical exposures would have been if they were followed up at their work places, which would be challenging to do. There is a potential for selection bias in our study as we were only able to retrieve weld day data for 67% of our participants. However, there were no differences in baseline characteristics of the welders whom we were not able to retrieve their records and those in our study. We also followed up study participants for only 3 h following onset of exposure. The specific component of PM$_{2.5}$ exposure causing the declines in AC and DC would require further study. Therefore, the results of this study will only be generalisable to similar occupational settings with rich metallic PM$_{2.5}$ exposure.

In conclusion, metal-rich occupational PM$_{2.5}$ exposure is associated with a reduction in AC and DC lasting up to 1 h after exposure has ceased. This suggests that there may be more pathways other than a direct autonomic effect of particulates on AC and DC that sustain the acute cardiac response following metallic PM$_{2.5}$ exposure up to 1 h following exposure.\textsuperscript{15} An investigation of the non-autonomic control of cardiac AC and DC is needed. The specific component of PM$_{2.5}$ exposure causing the declines in AC and DC would require further study. In addition, targeted interventions should aim at reducing particulate exposure and mitigating effects on both cardiac AC and DC.

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Contributors
DCC, JMC and SCF drafted data collection tools. PEU, along with a team of others supervised by DCC collected data. MAM supervised the algorithm designed research methods. PEU wrote the statistical analysis plan under supervision of DCC. In addition, PEU cleaned and analysed the data, and drafted and revised the paper with inputs from all co-authors and supervision from DCC, CL and XL. DCC is the guarantor.

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Competing interests
None declared.

Patient consent
Obtained.

Ethics approval

Provenance and peer review
Not commissioned; externally peer reviewed.

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