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Circulating adhesion molecules after short-term exposure to particulate matter among welders

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Abstract

Background—Studies from several countries indicate that welders experience increased risk of mortality and morbidity from ischaemic heart disease. Although the underlying mechanisms are unclear, vascular responses to particulate matter contained in welding fumes may play a role. To investigate this, we studied the acute effects of welding fume exposure on the endothelial component of vascular function, as measured by circulating adhesion molecules involved in leukocyte adhesion (sICAM-1 and sVCAM-1) and coagulation (vWF).

Methods—A panel of 26 male welders was studied repeatedly across a 6 h work-shift on a high exposure welding day and/or a low exposure non-welding day. Personal PM_{2.5} exposure was measured throughout the work-shift. Blood samples were collected in the morning (baseline) prior to the exposure period, immediately after the exposure period, and the following morning. To account for the repeated measurements, we used linear mixed models to evaluate the effects of welding (binary) and PM_{2.5} (continuous) exposure on each blood marker, adjusting for baseline blood marker concentration, smoking, age and time of day.

Results—Welding and PM_{2.5} exposure were significantly associated with a decrease in sVCAM-1 in the afternoon and the following morning and an increase in vWF in the afternoon.

Conclusions—The data suggest that welding and short-term occupational exposure to PM_{2.5} may acutely affect the endothelial component of vascular function.

Welders experience an increased risk of mortality and morbidity due to ischaemic heart disease.^{1–4} While the reasons are unclear, fine particulate matter (mass median aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5})) contained in welding fume may play a role. Numerous air pollution studies associate PM_{2.5} exposures with adverse cardiovascular events including death,^{5–7} myocardial infarction,⁸ myocardial ischaemia⁹ and arrhythmia¹⁰ within hours to days of exposure. The mechanisms by which inhalation of PM_{2.5} leads to adverse

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cardiovascular responses is unclear, however a growing body of evidence suggests that short-term exposure elicits acute alterations in vascular function.^{11–18}

We previously reported that welding fume exposure and its PM_{2.5} component were associated with acute alterations in the augmentation index, a measure of vascular function that is correlated with arterial stiffness.¹⁹ In this current study, we use a repeated measures panel study design to investigate the short-term effect of exposure to welding fume on circulating adhesion molecules, including soluble inter-cellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), which are involved in leukocyte adhesion, and von Willebrand factor antigen (vWF:Ag), a pro-coagulatory molecule. Circulating levels of these proteins are often used as markers of endothelial cell activation and function, as these markers are released by endothelial cells into the circulation upon interaction with stimulating agents such as inflammatory cytokines. All three biological markers are increased in individuals with cardiovascular disease and predict future risk of adverse cardiovascular events and stroke to varying degrees.^{20,21} We hypothesised a priori that welding fume exposure would be associated with increases in circulating biomarkers related to endothelial function and that there would be positive exposure–response relationships with work-shift PM_{2.5} concentrations.

METHODS

The study population consisted of male boilermaker construction workers (“boilermakers”) recruited from a local union in Massachusetts whose membership is predominantly male. Boilermakers are responsible for building, installing, maintaining and repairing power-generating boilers. Recruitment was performed primarily among apprentices during regularly scheduled welding classes, although experienced journeymen were also invited to participate to increase the number of participants. A panel of 27 individuals was recruited into the study in the winter of 2006 over five weekends; however, one of the panel, an immune-compromised individual, was excluded from the study.

All data collection was conducted at the union hall and attached welding school which consisted of a large room outfitted with 10 welding booths that each measured approximately 16 square feet (39"×59") and 103" high. Each welding booth was covered by a curtain and was equipped with its own local exhaust ventilation. During classes, participants received instruction and trained in welding for approximately 6 h. The most common type of welding performed was manual metal arc welding on mild (manganese alloys) and stainless steel (chromium and nickel alloys) bases. As reviewed by Antonini, studies on welding fume particles have shown the particles to be ≤0.50 µm in diameter.²²

We monitored workers during winter (when there is less boilermaker work) to minimise welding fume and occupational PM_{2.5} exposure prior to the study. Ideally, participants would not have been exposed to welding fumes for at least 48 h prior to participating in the study; however, some worked or practiced welding the day before monitoring, but we did not exclude these individuals from the study. To assess potential carryover effects of previous exposures in the analyses, we collected information on exposure to welding fume the day prior to monitoring (yes/no) from each participant.

Boilermakers were also asked to participate on a separate day while performing office or bookwork at the union hall in a room adjacent to the welding room. Those who participated on these non-welding days provided a low-exposure comparison group which minimised potential confounding by between-person factors. For those who participated on both days, the order of exposure differed across participants, with some first monitored when welding, and others first monitored when not welding. In addition, the two monitoring days were

separated by at least 1 week. The Institutional Review Board of the Harvard School of Public Health approved the study protocol and all participants gave written informed consent.

Exposure assessment

Personal exposure to PM_{2.5} was measured throughout the course of the 6 h work-shift for all participants. Prior to the start of the welding or non-welding period, participants were given their personal air sampling equipment. The gravimetric particulate samplers were placed within the workers' breathing zone to measure exposure to PM_{2.5} throughout the work-shift or equivalent non-welding period. Study personnel periodically checked the samplers and pumps throughout the course of the day to ensure that the samplers were correctly worn in the breathing zone and that the air flow was not blocked. The gravimetric sample was collected onto a 37 mm polytetrafluoroethylene membrane filter (Gelman Laboratories, Ann Arbor, MI) using a KTL cyclone (GK2.05SH, BGI, Waltham, MA) with a 50% aerodynamic diameter cutpoint of 2.5 µm, used in line with a personal pump drawing 3.5 l/min of air. The polytetrafluoroethylene filter was encased in a cassette and placed downstream of the cyclone. The filters were weighed before and after sampling on a MT5 microbalance (Mettler-Toledo, Columbus, OH) after equilibrating for a minimum of 24 h in a temperature and humidity controlled room. The gravimetric PM_{2.5} mass concentration was calculated by dividing the mass collected on the filter by the sampled air volume. All samples were blank corrected. To account for differences in sampling times, PM_{2.5} concentrations were standardised to 8 h time weighted averages (TWA). One TWA PM_{2.5} concentration was assigned for each worker.

Collection and analysis of blood samples

Blood samples were collected by venous puncture prior to the start of exposure, immediately after, and the following morning. The samples from each draw were collected into tubes containing 3.2% sodium citrate (for vWF:Ag) and serum separator tubes (for sICAM-1 and sVCAM-1). Blood samples were centrifuged immediately and plasma samples were aliquoted into cryogenic storage tubes and kept on dry ice until transport back to the laboratory at the Harvard School of Public Health where they were stored in a -80°C freezer until analysis. Quantification of serum marker levels was conducted in-house approximately 2 months after blood collection using the enzyme-linked immunosorbent assay (ELISA) method with commercially available kits (R&D Systems, Minneapolis, MN (sICAM-1 and sVCAM-1) and American Diagnostica, Stamford, CT (vWF-Ag)). For the leukocyte adhesion molecules, we restricted the analysis to self-reported Caucasian individuals (thereby excluding one African-American participant), as the expression of ICAM-1 and VCAM-1 and therefore concentrations of their soluble forms have been reported to vary substantially by race and ethnicity.^{23,24}

All samples from each participant were analysed in duplicate and in one batch to avoid between-batch analytical variation. For each duplicate sample, any sample with a coefficient of variation >20% required that all samples from that participant be re-run until the coefficient of variation was ≤20%. The performance of the assays was monitored with standard quality control procedures including the analysis of blinded pooled samples. The intra- and inter-assay coefficients of variation were: 7.1% and 9.1% for sICAM-1; 5.3% and 9.0% for sVCAM-1; and 12.3% and 14.1% for vWF.

Collection of study population characteristics and other covariates

Information on demographics, medical history, medication usage, smoking history and occupational history was obtained using a self-administered modified standardised American Thoracic Society (ATS) questionnaire.²⁵ In addition, information on smoking

during the monitoring period was recorded on time activity sheets, as in previous studies of this population.²⁶ Information on respirator use during the monitoring period was also collected.

Statistical analysis

To account for the correlation of repeated measures within person, we constructed linear mixed models for each of the three blood markers to determine the effect of welding exposure (binary) on afternoon and next morning serum marker concentrations. In addition to accounting for the correlation of the repeated measurements, the mixed models accommodated the imbalances in the data which arose from some individuals participating on only the welding day or not returning for the next morning measurement.²⁷ We assumed that the data were missing at random, making the likelihood based inferences valid. To assess the exposure–response relationship, we also constructed separate models using the TWA work-shift PM_{2.5} concentrations (continuous) as the predictor. An autoregressive covariance matrix was chosen as the working covariance structure because it provided the lowest Akaike information criterion. Baseline blood marker concentration, taken prior to exposure measurements, was used as a predictor to control for individual factors that may influence blood marker levels. Age and smoking (yes/no) within the last 4 h of each afternoon and next morning blood draw were also controlled for in the models. In addition, to account for potential circadian variation in the blood markers, an indicator for time (next morning versus afternoon) was included in the models. To allow the effect of exposure to vary over time, we included an interaction term for weld (or PM_{2.5}) and time. Regression coefficients and 95% confidence intervals (CIs) for both the afternoon and the next morning blood marker levels were estimated from the models. For models evaluating the effect of continuous work-shift PM_{2.5} concentration, we performed additional subanalyses excluding individuals currently taking anti-hypertensive and lipid-lowering medications.

We also constructed models to account for the potential effects of welding exposure (yes/no) the day prior to monitoring by using indicator variables to reflect exposure conditions over the 2 days (ie, exposed the day prior to monitoring only, exposed the day of monitoring only, exposed both days, with the reference being unexposed on both days). In the model using PM_{2.5}, an indicator for exposure status the day prior to monitoring was used in the model as well as its interaction with PM_{2.5}. Residual plots and the distribution of the error terms were assessed to check the normality of the residuals and adequacy of model fits. Statistical significance for all testing was considered at the $\alpha = 0.05$ level. Analyses were performed with SAS v 9.1 (SAS Institute, Cary, NC).

RESULTS

The study population is described in table 1. Among the 26 participants, 25 participated on a welding day and 15 participated on a non-welding day, with 14 individuals participating on both a welding day and a non-welding day. A total of 40 post-shift afternoon and 34 next morning samples were collected in total.

Those who participated on both exposure days were comparable to those who participated on only 1 day in terms of age, number of years as boilermaker, smoking status, lipids, and all three baseline blood marker levels (data not presented). The median duration as a boilermaker was 5 years, suggesting that about half of the participants were apprentices and half were more experienced journeymen, given that the apprenticeship program for boilermakers typically lasts 4 years. The Spearman rank correlation coefficients were low for the biological markers: 0.12 ($p=0.57$) for sICAM-1 and sVCAM-1; -0.15 ($p=0.47$) for sICAM-1 and vWF; and 0.08 ($p=0.69$) for sVCAM-1 and vWF:Ag.

On a non-welding day, the average sampling time was 7.1 h (SD 1.2) and on a welding day, 6.7 h (SD 1.7). On a non-welding day, the median PM_{2.5} 8 h TWA exposure was 0.04 mg/m³ (range: 0.01–0.19 mg/m³) and on a welding day, 0.39 mg/m³ (range: 0.03–2.62 mg/m³). The overall median PM_{2.5} concentration among the 40 personal exposure samples was 0.39 mg/m³ (inter-quartile range: 0.05–0.58 mg/m³). None of the workers wore respirators while welding.

The associations between the leukocyte adhesion molecules and welding exposure are presented in table 2. The afternoon concentration of sVCAM-1 was lower on an exposed welding day versus a non-welding day and the difference was statistically significant. The lower sVCAM-1 concentration associated with welding exposure persisted the following morning, although the association was not as strong as compared to the previous afternoon, or statistically significant.

These results were supported when we examined the exposure–response relationship using work-shift PM_{2.5} and observed a decrease in the afternoon and next morning sVCAM-1 concentration with increasing exposure (table 3). As with the welding (yes/no) models, the next morning association between sVCAM-1 and PM_{2.5} was not as strong, or statistically significant, as compared with the association in the afternoon.

Some effect estimates associated with sICAM-1 were also negative, suggesting a decrease in relation to welding and increasing work-shift PM_{2.5}; however, the results were inconsistent for welding and PM_{2.5} and not statistically significant (tables 2 and 3). Welding fume exposure was associated with a statistically significant increase in vWF:Ag in the afternoon but not the following morning (table 2). Using the work-shift PM_{2.5} as the exposure variable, there was a marginally statistically significant increase in the afternoon level of vWF:Ag as the exposure concentration increased (table 3), while there was no significant change the next morning.

Among the 25 welding day participants, nine were exposed to welding fumes the day before monitoring, and among the 15 non-welding day participants, six were exposed the day before. All together, among the 40 person days of observation, 15 occurred 1 day after exposure to welding fumes. When we accounted for this previous day's exposure, we found that exposure over 2 days in a row resulted in an even greater decline in sVCAM-1 in the afternoon as compared to no exposure on either day ($p=0.003$) (fig 1). However, when we modelled an interaction term for previous day's exposure status and PM_{2.5}, there were no statistically significant differences in the effect of PM_{2.5} for any of the three markers according to welding status the day prior to monitoring (data not presented).

Exclusion of outlying residuals from the PM_{2.5} models did not appreciably change the results for each of the blood marker models. With regard to the exclusion of individuals taking anti-hypertensive and statin medications ($n=5$), the effect estimates for PM_{2.5} became stronger for all blood marker models and the association with next morning sVCAM-1 became statistically significant (sVCAM-1 decreased 31.4 ng/ml per inter-quartile range increase in PM_{2.5} concentration; 95% CI -60.5 to -2.4 ; $p=0.03$). Controlling for medication use in the models provided similar results although the effect of PM_{2.5} did not reach statistical significance for next morning sVCAM-1.

DISCUSSION

In this study of male boilermaker welders, short-term welding fume exposure was associated with changes in circulating markers related to endothelial function, a component of vascular function. Specifically, we observed an acute increase in vWF, a pro-coagulant, in the afternoon immediately after welding exposure, and a corresponding linear exposure–

response relationship between the work-shift PM_{2.5} concentrations and levels of vWF. We also observed a decrease in sVCAM-1, an endothelial leukocyte adhesion molecule, immediately after 6 h of welding exposure, which was contrary to our a priori hypothesis that levels would increase after exposure. A model based on work-shift PM_{2.5} concentrations also yielded an inverse exposure–response relationship with sVCAM-1, suggesting that the PM_{2.5} component of the welding fume was at least partially responsible for the inverse association we observed with binary welding exposure. Results from crude paired analysis of the crossover participants supported these findings (data not presented).

As a molecule involved in the adhesion of platelets, the positive association between PM_{2.5} exposure and vWF observed in this study suggests a pro-coagulant effect of PM_{2.5} exposure, which is consistent with findings from another small study of welding fume exposure.²⁸ Our findings for vWF are also consistent with a study of male highway patrol officers in which vehicular PM_{2.5} was associated with an increase in vWF.¹² Positive associations between vWF and ambient PM_{2.5} have also been observed among individuals with diabetes¹³¹⁷ and coronary heart disease.¹⁵ vWF is synthesised and stored in endothelial cells, and its release is indicative of stimulation of or damage to endothelial cells,²⁹ which may occur via interaction with proinflammatory cytokines.

We expected that the concentration of leukocyte adhesion molecules would increase with exposure, as such an association has been observed among individuals with diabetes and coronary artery disease.¹⁷³⁰ However, contrary to our expectation, sVCAM-1 decreased after welding exposure and an inverse relationship with PM_{2.5} concentrations was observed. The different direction of effect found in this study as compared to the previous studies may reflect differences in the underlying inflammatory state of the individuals studied. The unexpected relationship observed in these relatively young healthy boilermakers was also recently observed in a study of Mexico City children with high cumulative exposures to particulate air pollution. These children had significantly decreased levels of sVCAM-1 and sICAM-1 compared to children with substantially lower exposure to PM_{2.5}.³¹ The authors suggested that the observed down-regulation of adhesion molecules could be related to the anti-inflammatory effects of IL10, high concentrations of which were present in the Mexico City children. Interestingly, other pro-inflammatory cytokines were significantly higher in the exposed Mexico City children, which emphasises the complexity of the physiological and pathophysiological inflammatory and vascular responses to PM exposures.

Of note, using microarray gene expression techniques, we previously observed down-regulation of genes clustered into groups related to inflammatory responses, oxidative stress and intracellular signal transduction among boilermakers after exposure to welding fumes, which again points to the complexity of the biological pathways of response.³² Further research into the early biological responses to PM, including evaluation of responsible PM components, is needed to disentangle the complex mechanistic pathways.

We acknowledge that there are several limitations to this study, including the small sample size, which likely affected the precision of our estimates and may have precluded our ability to detect a statistically significant association with sICAM-1. Although the sample size was small, the panel study design with repeated measurements and the use of self-controls increased the efficiency of our sample size. We were still limited, however, in our ability to evaluate potential effect modification by factors such as duration as a boilermaker and smoking. It is possible that experience as a boilermaker, which would correspond to cumulative occupational PM_{2.5} exposure, may modify the associations between short-term PM_{2.5} exposure and acute effects on endothelial vascular health and that the inverse association observed between exposure and sVCAM-1 could be explained by an averaging of differential effects among apprentices and journeymen or smokers and nonsmokers.

However, we were not able to investigate these potential interactions due to our small sample size. It is unlikely that duration as a boilermaker (ie, apprentice versus journeyman) confounded our observations because each individual served as his own control due to the repeated measures study design, and thus factors that vary between persons were of minimal concern as potential confounders.

It is worth noting that the welders were exposed to particles from other sources such as grinding and cutting, which produces larger sized particles. However, the effects observed in this study were likely due to the PM_{2.5} contained in welding fume and not to the larger sized particles, as larger size fraction particles (eg, from welding slag, grinding dust and slagging dusts) are not likely to penetrate into the alveolar region of the lungs and be able to produce a systemic response. Moreover, the observed exposure–response relationship with PM_{2.5} suggests that the observed effects were due to PM_{2.5} and not larger particles, as larger size particles produced from activities other than those that generate PM_{2.5} are not likely to be correlated with PM_{2.5}. Only if PM_{2.5} and larger particles are correlated would this potentially account for all or some of the subclinical effects observed.

A limitation of greater concern was potential carryover effects from the occurrence of recent welding fume exposures prior to the start of monitoring. However, we found that the interpretation of our main analyses did not change after controlling for prior exposure, although there were suggestions of prolonged effects which we were not able to adequately study because of our limited sample size. The longer term effects of exposure should be further studied by monitoring workers over longer periods of time with detailed information on welding and PM_{2.5} exposures. In addition, although we controlled for time-varying smoking patterns, residual confounding by smoking cannot be ruled out, especially for the association between PM_{2.5} and vWF.³³ Further, lack of data on gaseous co-pollutants, a common concern in particulate air pollution studies, is another possible limitation of our study. However, a previous study in this cohort showed that concentrations of typical co-pollutants found in welding operations, O₃ and NO₂, were low and uncorrelated to the level of PM.³⁴ In general, concentrations of these gases are low in manual metal arc welding under a variety of operating conditions³⁵ and thus are not of major concern.

Our findings suggest that short-term occupational exposure to PM_{2.5} and welding fumes may acutely alter vascular health, specifically endothelial function, a component of vascular function, which over a working lifetime may cumulatively have an impact on long-term cardiovascular health. The interaction between duration of lifetime exposure to welding fumes and these alterations needs to be investigated for a clearer understanding of the biological mechanisms involved in the disproportionately poor cardiovascular health of welders. Additional larger studies, ideally with more repeated measures and biological markers of vascular function, are necessary to confirm these findings in other workers exposed to welding fumes and PM_{2.5}.

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Figure 1.

Adjusted mean (SE) blood marker concentrations by exposure status the day prior to and the day of monitoring. p Values obtained from mixed models and compare the mean concentration from each exposure scenario to the reference period (unexposed both days). The mean predicted level of sVCAM-1 was significantly lower in the afternoon after welding exposure on the day of monitoring only and after welding exposure 2 days in a row (A) versus being unexposed both days. No significant differences in the level of soluble vascular cell adhesion molecule-1 (sVCAM-1) were observed by exposure status the next morning (B). No significant differences in the level of soluble inter-cellular adhesion molecule-1 (sICAM-1) were observed by exposure status in the afternoon (C) or next morning (D). Levels of von Willebrand factor (vWF) were significantly higher in the afternoon after welding on the day of monitoring only (E). There were no differences in next morning vWF concentrations according to exposure status (F).

Table 1

Characteristics of male welders in the study population

Participants, n (%)	26 (100)
White, n (%)	24 (92.3)
Current smoker, n (%)	9 (34.6)
Age in years, mean (SD) (range)	40 (11) (24–60)
Median years as a boilermaker (range)	5 (<1–30)
Cardiopulmonary history, n (%)	
Chronic bronchitis	1 (4)
Asthma	1 (4)
High blood pressure	5 (19)
Myocardial infarction	1 (4)
Current medication usage, n (%)	
Anti-hypertensive medications	5 (19)
Statins *	3 (12)
Baseline blood marker levels, mean (SD) (range)	
sICAM-1 (ng/ml) [†]	285 (59) (210–430)
sVCAM-1 (ng/ml) [†]	596 (133) (409–874)
vWF:Ag (% normal)	92 (30) (35–151)

* Also taking anti-hypertensive medication;

[†] n = 25.

Table 2

Association between blood marker concentrations and welding exposure (yes/no) *

	Afternoon		Next morning	
	β Coefficient (95% CI)	p Value	β Coefficient (95% CI)	p Value
sVCAM-1 (ng/ml)	-62.4 (-105.0 to -19.9)	0.01	-36.9 (-82.4 to 8.6)	0.10
sICAM-1 (ng/ml)	-6.7 (-28.9 to 15.5)	0.52	0.6 (-28.6 to 29.8)	0.97
vWF:Ag (% normal)	8.1 (0.1 to 16.1)	0.05	-3.4 (-17.1 to 10.3)	0.60

* Models adjusted for baseline blood marker concentration, smoking within 4 h of blood draw, age and time.

Table 3

Association between blood marker concentrations and an inter-quartile range change in work-shift PM_{2.5} concentration (mg/m³)*

	Afternoon		Next morning	
	β Coefficient [†] (95% CI)	p Value	β Coefficient (95% CI)	p Value
sVCAM-1 (ng/ml)	-33.6 (-46.8 to -20.4)	<0.001	-25.8 (-54.5 to 2.9)	0.08
sICAM-1 (ng/ml)	2.7 (-3.0 to 8.4)	0.34	-2.1 (-8.5 to 4.4)	0.52
vWF:Ag (% normal)	3.8 (-20.2 to 7.7)	0.06	0.4 (-2.7 to 3.6)	0.78

* Models adjusted for baseline blood marker concentration, smoking within 4 h of blood draw, age and time.

[†] Effect estimate is for an inter-quartile range increase in PM_{2.5} (0.05 to 0.58 mg/m³).