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ORIGINAL ARTICLE

Incident ischemic heart disease and recent occupational exposure to particulate matter in an aluminum cohort

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Fine particulate matter ($PM_{2.5}$) in air pollution, primarily from combustion sources, is recognized as an important risk factor for cardiovascular events but studies of workplace $PM_{2.5}$ exposure are rare. We conducted a prospective study of exposure to $PM_{2.5}$ and incidence of ischemic heart disease (IHD) in a cohort of 11,966 US aluminum workers. Incident IHD was identified from medical claims data from 1998 to 2008. Quantitative metrics were developed for recent exposure (within the last year) and cumulative exposure; however, we emphasize recent exposure in the absence of interpretable work histories before follow-up. IHD was modestly associated with recent $PM_{2.5}$ overall. In analysis restricted to recent exposures estimated with the highest confidence, the hazard ratio (HR) increased to 1.78 (95% CI: 1.02, 3.11) in the second quartile and remained elevated. When the analysis was stratified by work process, the HR rose monotonically to 1.5 in both smelter and fabrication facilities, though exposure was almost an order of magnitude higher in smelters. The differential exposure–response may be due to differences in exposure composition or healthy worker survivor effect. These results are consistent with the air pollution and cigarette smoke literature; recent exposure to $PM_{2.5}$ in the workplace appears to increase the risk of IHD incidence.

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INTRODUCTION

Fine particulate matter ($PM_{2.5}$) in air pollution, primarily from combustion sources, is recognized as an important risk factor for cardiovascular events, including hypertension,[1] cardiac arrhythmia,[2] myocardial infarction,[3] and mortality.[4,5] Inhaled $PM_{2.5}$ (particles with an aerodynamic diameter of less than 2.5 μm) from active and passive[6] cigarette smoking is also associated with increased risk of cardiovascular disease.[7,8] The pathway has not been established; $PM_{2.5}$ may cause cardiovascular disease secondary to pulmonary inflammation or nanoparticles may pass through the lungs into the circulatory system to cause direct damage.[9] Exposure to high levels of $PM_{2.5}$ is thought to have an immediate (trigger) effect on cardiovascular events, but long-term exposure likely has a role as well.[10]

In a recent meta-analysis of cardiovascular mortality,[11] results from studies of ambient air pollution[5,12–16] and passive smoking[17,18] (<1 mg/day) and active cigarette smoking (>10 mg/day) were presented in a single graph by transforming the exposures into a common daily dose metric. Evident in the graph is a steep rise in relative risk at low exposures followed by a plateau over the high exposure range, with a wide gap between low and high $PM_{2.5}$ exposures. The range of $PM_{2.5}$ exposure experienced by industrial workers neatly covers the gap; however, the contribution to this literature from the occupational arena is limited. Historically, heart disease has not been an outcome of interest in occupational epidemiology.[19] Heart disease is a multi-factorial disease with well-established individual-level risk factors and occupational studies are often limited by the inability to control for potential confounders.[20]

In this report, we describe results from a prospective study of ischemic heart disease incidence (IHD) and $PM_{2.5}$ in a cohort of almost 12,000 actively employed aluminum production workers. The analysis is based on quantitative metrics of $PM_{2.5}$ generated from a variety of sources in aluminum smelting, fabrication, and refining facilities. We identified incident cases of IHD based on medical insurance claims in hourly workers. Smoking histories and data on other potential confounders were available from employment records and routine health exams. We focused on the association between IHD and recent occupational exposure to $PM_{2.5}$. Past exposure was given less attention due to limitations in available data. We stratified by manufacturing process to explore the role of composition and job placement practices.

METHODS

Cohort and Outcome Definition

Hourly workers enrolled in the primary insurance plan and employed for at least 2 years during follow-up in eight US aluminum facilities were considered for the cohort. Follow-up began on 1st January 1998 for six facilities and on 1st January 2005 for two facilities subsequently acquired by the company. Actively employed workers were followed for incidence of IHD identified from health insurance claims through 2009 or until they left work (whichever occurred first). Before 2003, all workers were assumed to use the primary insurance plan. This assumption is supported by the fact that 97% of workers filed at least one claim in this system during this period. After 2003, insurance options increased with the acquisition of new facilities and health insurance enrollment in the primary plan was tracked on a monthly basis.

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Health insurance claims for a relevant procedure (revascularization, angioplasty, or bypass), hospitalization for two or more days or a face-to-face visit with an ICD-9 code for IHD (410–414) comprised an IHD diagnosis. Admission codes only were recorded for hospitalization claims. Claims were available starting 1st January 1996 and a 2 year "wash-out" was used to exclude cohort members with prevalent disease. The date of IHD incidence was the earliest date of the first applicable claim. All cohort members were therefore at work for two disease-free years after 1st January 1996, before entering follow-up. For example, a worker hired on 1st January 1997 would enter follow-up on 1st January 1999 if no claims for heart disease had been filed during the two intermediate years.

Covariate Data Collection

Age, sex, race, and job grade data were available from employment records for all workers. In addition, smoking status, weight, and height information were maintained at occupational clinics located at each facility and were made available to researchers via chart abstraction. Chart availability varied by facility with some retaining all charts and others retaining only the charts of actively employed workers. Multiple imputation was used for missing smoking and body mass index (BMI) data.

Exposure Assessment

Workers in the eight study plants were primarily engaged in smelting aluminum or one of several fabricating processes involving aluminum and related products. The constituents of particulates in these divergent work environments, as well as the nature of the work environments generally, have been well characterized in the literature.[21] The exposure assessment for particulate matter relied on company industrial hygiene records as well as measurements collected by the research team in 2010 and 2011. Job title and department combinations in the company industrial hygiene database did not correspond to job titles as they appeared in the work history database. To compute individual exposure histories, we therefore aggregated similar jobs into distinct exposure groups within facilities and developed a mapping between the exposure and work history databases. This process incorporated changes in exposure caused by modifications in process or contaminant control (for example, new company exposure limits).

A job exposure matrix was first constructed for arithmetic mean total particulate matter (TPM) by distinct exposure group. The company had developed an industrial hygiene database of over 300,000 samples collected over the past 25 years. We included samples at the relevant facilities collected randomly for at least 70% of an employee's shift and analyzed using gravimetric methods.

To estimate $PM_{2.5}$, side-by-side personal size-selective sampling was conducted in 2010 and 2011 in eight facilities with the traditional closed face cassette paired with a personal modular impactor (PMI). The PMI measured airborne particles in three size ranges ($<2.5\,\mu$m ($PM_{2.5}$), 2.5–10.0 μm and $>10.0\,\mu$m). The percent $PM_{2.5}$ for each sample was calculated by dividing the concentration of $PM_{2.5}$ (from the PMI) by the concentration of paired TPM sample (cassette). The values within each distinct exposure group at each facility were averaged to obtain percent $PM_{2.5}$, which was multiplied by TPM to create $PM_{2.5}$ concentration in the job exposure matrix.

Details are provided in a separate manuscript by Noth et al.[22]

Exposure Variable Definitions

We partitioned exposure into two time-varying exposure windows: recent exposure (mg/m^3) in each year and cumulative exposure (mg/m^3-years). Recent exposure was the level of $PM_{2.5}$ estimated for the job held on 1st January of each year. Cumulative exposure was the sum of annual average exposures computed as a weighted average of exposure from all jobs held in each year. Company job codes were not readily translated into the distinct exposure groups before 1996. Thus, to extend cumulative exposure all the way back to start of employment for subjects hired before 1996, we assumed workers held the same job (with associated exposure) from hire up to 1996. Thus, estimates of cumulative exposure were less reliable than those for recent exposures, which only occurred during follow-up.

Respirator use was not considered other than to address extreme exposure values. For samples over 50 mg/m^3 a respirator protection factor was applied.[22] In a sensitivity analysis, we considered an alternative job exposure matrix in which no respirator adjustment was applied.

Given that TPM samples were collected as industrial hygiene monitoring data, not for research, jobs with potential for exposures greater than 30% of occupational exposure limits were targeted for sampling. Confidence scores were developed for exposure estimates in which higher confidence was assigned to estimates based on direct measurements rather than extrapolation algorithms (for more details, Noth et al.[22]). Some of the results presented here are restricted to recent exposures estimated by direct measurements.

Statistical Analysis

Cox proportional hazard models were fit to estimate the effects of recent exposure to $PM_{2.5}$ on IHD incidence. All Cox models used age in each year as the time metric. Sex, race (white/non-white), calendar year of follow-up, smoking status (ever/never), BMI, job grade (above/below median in each facility), and manufacturing process (smelter/fabrication/refinery/other) were included in all models to adjust for potential confounding. Models for recent $PM_{2.5}$ were additionally adjusted for cumulative exposure up until each year to control for potential confounding by exposure history. Variables plausibly on the causal pathway between exposure and IHD, such as hypertension, were not included in the models. Robust sandwich variance estimators were used to account for clustering across person-years belonging to the same person in all models.

Multiple imputation procedures in SAS were used to impute missing data for smoking status and BMI. Smoking was missing for 60% of workers and BMI was missing for 62%. The imputation proceeded in two steps, first continuous BMI was imputed using the EM algorithm to create a monotone missingness pattern, and then categorical smoking status was imputed using the logistic regression method. Case status, time since hire, hypertension, diabetes, obesity, employment termination, and all the variables used in the main models were used to impute missing information, as these variables were assumed to be sufficient to satisfy the missing at random assumption. Five imputed data sets were created and all subsequent model fits and inferences were calculated using the multivariate extension to Rubin's rules.[23]

Models included recent exposure to $PM_{2.5}$ defined as categorical variables. Results for recent $PM_{2.5}$ are presented with two strategies for choosing cut points: (1) cases were divided equally by quintiles of exposure and (2) cases were divided equally by quartiles of exposure above the reference level of 0.05 mg/m^3. The second strategy was guided by federal EPA air pollution standards; the 2006 daily standard for $PM_{2.5}$ was 0.035 mg/m^3. As industrial levels of $PM_{2.5}$ are higher than ambient levels and fewer exposure measurements were taken at the low levels, the lowest cut point we could set was 0.05 mg/m^3. To assess the possibility that uncertainty in low exposures might introduce bias, we conducted analyses restricted to exposures with high confidence scores.

Manufacturing process (smelter or fabrication) was considered as a potential effect measure modifier. To take advantage of the continuous exposure metric, we added a penalized spline function of recent $PM_{2.5}$ to stratified Cox models. Degrees of freedom were based on minimum Akaike's Information Criterion and biological plausibility. R software (R Development Core Team, Vienna, Austria) was used for the spline analysis and SAS software (SAS Institute, Cary, NC, USA) was used for all other analyses.

There was less emphasis on models for cumulative exposure; exposures were less reliable before 1996 and we could not feasibly restrict to higher confidence estimates. Pooled and stratified models, however, were also fit to estimate the effects of cumulative exposure to $PM_{2.5}$ on IHD incidence. Exposure was defined as a categorical variable with cases divided equally by quintiles of exposure. Smoking and BMI were imputed and controlled for as described above.

RESULTS

There were 697 IHD cases identified from a cohort of 11,966 aluminum workers. The IHD cases were more likely to be male, older and hired before the start of follow-up (Table 1). Most subjects worked in fabrication (69%); cases were slightly more likely to work in the smelters compared with the cohort as a whole. The median recent exposure was similar in the cohort and cases; however, median cumulative exposure was higher for cases, consistent with their older age and earlier hire dates.

The hazard ratios (HRs) for incident IHD were higher when the reference level was set at 0.05 mg/m^3, rather than quintiles, and

even higher still when exposures were restricted to those assessed with high confidence (Table 2). The exposure–response increased to a maximum of 1.78 (95% CI: 1.02, 3.11) though the pattern was non-monotonic. When cases were distributed evenly based on recent exposure quintiles, the HR was slightly elevated in the second category of exposure (1.28 (95% CI: 0.92, 1.63). HRs for higher categories of recent exposure remained modestly elevated and all confidence intervals included the null. When equal quintiles were based on exposure data restricted to high confidence, the risk of IHD increased by more than 20% in the highest exposure categories, though all confidence intervals included the null.

To examine effect measure modification, exposure–response was modeled as a smooth function of recent $PM_{2.5}$ exposure separately in fabrication and smelters. Stratification with splines avoids the selection of a common reference group—a particular challenge in this analysis, because $PM_{2.5}$ exposures in the smelters were several times higher than in fabrication. The splines also allow us to take advantage of the continuous data without parametric assumptions (Figure 1). Few women were employed in the smelters and so the entire stratified analysis was restricted to males. The HR for $PM_{2.5}$ and incident IHD rose in fabrication to 1.5 at 1.25 mg/m^3 and was statistically significant throughout most of the exposure range (Figure 2a). The exposure–response in the smelters was approximately linear and rose to an HR of 1.5 at 9 mg/m^3, but was only statistically significant around the mean (Figure 2b). This stratified analysis presents evidence that the association between recent $PM_{2.5}$ and IHD differs by manufacturing process.

In a sensitivity analysis, models with categorical exposure were fit in the each of the two work strata. In fabrication, the HR rose to 1.98 (95% CI: 1.06, 3.68) in the third exposure category and then dipped to 1.37 (95% CI: 0.74, 2.51) in the top category (>0.38 mg/m^3) compared with a reference group of ≤ 0.05 mg/m^3. In smelters, the HR rose from 1.13 (95% CI: 0.48, 2.65) in the first exposure category to 1.25 (95% CI: 0.52, 2.99) in the top category (>5.23 mg/m^3) compared with a reference group of ≤ 0.075 mg/m^3 (data not shown).

Table 1. Demographic characteristics of an aluminum manufacturing cohort in the United States 1998–2008.

	Cohort	*IHD cases*
No. of workers	11,966	697
Person-years	68,848	—
Male no. (%)	10,049 (84)	655 (94)
White no. (%)	9,919 (83)	591 (85)
Hired $\geq$follow-up no. (%)	3,665 (31)	81 (12)
Year of hire median (IQR)	1984 (1974–1996)	1977 (1970–1988)
Year of birth median (IQR)	1955 (1948–1962)	1948 (1944–1953)
Manufacturing process		
Smelter no. (%)	2194 (18)	152 (22)
Fabrication no. (%)	8290 (69)	449 (64)
Refinery no. (%)	960 (8)	56(8)
Other facility type no. (%)	522 (5)	40 (6)
Recent[a] PM (mg/m^3)		
$PM_{2.5}$ median (IQR)	0.29 (0.12–1.04)	0.26 (0.12–1.04)
Cumulative PM (mg/m^3-years)		
$PM_{2.5}$ median (IQR)	5.01 (1.74–18.41)	6.95 (2.39–26.46)

Abbreviations: IHD, ischemic heart disease; IQR, interquartile range; PM, particulate matter; $PM_{2.5}$, fine particulate matter.
[a]Recent exposure is defined as exposure within the last year.

Additional sensitivity analyses were conducted on a job exposure matrix in which no respirator adjustment was applied. The pooled and fabrication-specific results were unchanged. The spline in smelters remained linear, increased to a maximum HR of 1.4, and was statistically significant around the mean of exposure. However, without any respirator adjustment, the maximum exposure increased to 32 mg/m^3, thus the slope of the exposure–response curve was less steep than the slope presented in Figure 2b.

In contrast with recent exposure, there was no indication that cumulative $PM_{2.5}$ exposure increased IHD risk overall; all point estimates were below one (Table 3). When we stratified analyses of categorical cumulative exposure by manufacturing process, we observed HRs from 1.13 to 0.96 in fabrication and HRs from 0.86 to 0.77 in the smelters with all confidence intervals including the null (data not shown).

DISCUSSION

Results provide evidence that recent occupational exposure to $PM_{2.5}$ is associated with IHD incidence in a cohort of actively employed hourly workers. Increased risk of IHD was strongest at the relatively low $PM_{2.5}$ exposure levels found in the fabricating process. By contrast, we saw no evidence that cumulative $PM_{2.5}$ increases risk of IHD incidence, though the exposure estimates were less reliable and results more subject to survivor bias (as elaborated below). These findings are consistent with the literature on cardiovascular disease and ambient air pollution.

One striking feature of our $PM_{2.5}$ and IHD incidence results is the shape of the exposure–response curve in the pooled analysis. Risk peaked in the second category of exposure and leveled off in higher categories. This pattern was evident in the main analysis (Table 2) especially when the 0.05 mg/m^3 reference group was used. To help interpret these results, we address several factors: the reference group, workplace hire and retention practices, reliability of the exposure assessment, consistency across studies, and biological plausibility.

In choosing the lowest possible cut point for the reference group, we incorporated the wealth of existing knowledge and public health policy regarding ambient $PM_{2.5}$ exposure. The ideal cut point would have been 0.015 mg/m^3, the recent US EPA standard for annual ambient $PM_{2.5}$. In this occupational cohort, however, no cases were exposed at or below this level. We then considered 0.035 mg/m^3, the standard for daily ambient $PM_{2.5}$. The daily standard can be exceeded only 3 days a year in the ambient environment but offered a more realistic cut point in this industrial setting. However, only 13 cases were exposed at less than 0.035 mg/m^3 and none of the exposure estimates had high confidence scores. Thus, 0.05 mg/m^3 was determined to be the lowest level at which we had adequate power for categorical analysis. We also presented analysis based on a ''naïve'' reference group based on the 20th percentile of the cases. Despite the increased power in the ''naïve'' categorization, the HRs were attenuated likely due to increased baseline risk.

In categorical exposure models, there is a common reference group for all higher categories of exposure. However, the mean $PM_{2.5}$ is considerably lower in fabrication than in smelters with little overlap in levels. Thus, the reference group in the pooled models comprised mostly workers from fabrication whereas the higher categories comprised mostly workers from smelters. There are other relevant differences between smelters and fabrication jobs in addition to $PM_{2.5}$ exposure levels and constituents. First, jobs in smelters are the most physically demanding jobs in the aluminum industry. Some smelting jobs also involve exposure to high levels of heat that can be hazardous for workers with heart disease risk factors. As a result of these hazards, there is a heart disease risk factor screening program for placement and retention in many smelter jobs. Furthermore, ongoing screening occurs for

Table 2. Hazard ratios for ischemic heart disease.

All exposures					*Only exposures assessed with high confidence*				
Recent $PM_{2.5}$ (mg/m^3)	*No. of cases*	*Person-years*	*Hazard ratios[a]*	*95% Confidence interval*	*Recent $PM_{2.5}$ (mg/m^3)*	*No. of cases*	*Person-years*	*Hazard ratios[a]*	*95% Confidence interval*
Categories by quintiles of exposure among cases									
≤0.11	135	11,490	1		≤0.12	129	10,891	1	
>0.11–0.22	143	14,272	1.05	0.81, 1.35	>0.12–0.23	102	10,379	1.05	0.80, 1.39
>0.22–0.45	140	11,708	1.23	0.92, 1.63	>0.23–0.50	114	10,310	1.04	0.77, 1.41
>0.45–1.47	130	11,971	1.06	0.78, 1.45	>0.50–1.63	109	8,899	1.29	0.88, 1.88
>1.47	149	14,321	1.09	0.73, 1.62	>1.63	123	11,853	1.21	0.78, 1.88
Categories by quartiles of exposure among cases above reference level 0.05 mg/m^3									
≤0.05	61	6,151	1		≤0.05	15	1,452	1	
>0.05–0.16	156	13,770	1.26	0.92,1.71	>0.05–0.16	132	11,757	1.58	0.88, 2.63
>0.16–0.34	166	13,706	1.48	1.07, 2.05	>0.16–0.37	148	12,359	1.78	1.02, 3.11
>0.34–1.15	155	14,975	1.15	0.82, 1.63	>0.37–1.47	139	13,074	1.48	0.83, 2.66
>1.15	159	15,159	1.18	0.77, 1.82	>1.47	143	13,690	1.48	0.77, 2.85

Abbreviation: $PM_{2.5}$, fine particulate matter.
According to two categorizations of recent (within the last year) $PM_{2.5}$, each with all exposures and when restricted to exposures measured with high confidence, in an aluminum manufacturing cohort in the United States, 1998–2008.
[a]Hazard ratios adjusted for age, race, gender, calendar year, smoking, facility type, BMI, job grade, and past exposure.

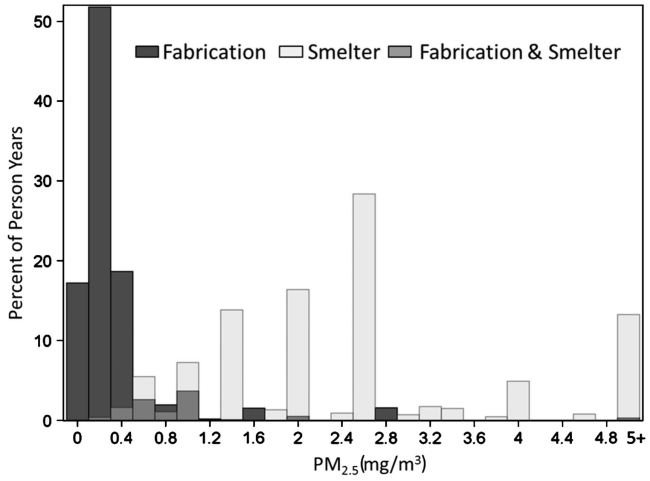

Figure 1. Percent of person-years in recent (within the last year) fine particulate matter ($PM_{2.5}$) exposure categories shown in overlapping distributions for fabrication and smelting processes in an aluminum manufacturing cohort followed from 1998 through 2008. (Exposures above 5 mg/m^3 lumped into top category).

almost all smelter workers in the context of mandatory respiratory fitness and work in hot environments. Thus, it is possible that the plateau in the highest two categories reflects a phenomenon analogous to the "healthy hire" effect that plagues occupational studies with external reference groups. If workers in the higher exposure categories (smelter workers) are screened and thus at less risk for heart disease than those in the reference group (fabrication workers), bias may occur even in our pooled internal analysis (Table 2) adjusting for baseline covariates.

In addition to selection bias, the plateau may also arise from misclassification of the highest exposures in the smelters. The presence of well-established risk factors for occupational asthma[24] and cancer[25] in the smelters has driven more widespread use of respiratory protection than in fabricating jobs. Had respirators been more completely accounted for in this analysis, the result would have been to reduce the value of smelter exposures on the high end, while very little would have changed on the low end. In fact, the exposure–response presented in Figure 2b was steeper than when we ignored the adjustment for values above 50 mg/m^3 in a sensitivity analysis. Future analyses will incorporate a more thorough evaluation of respirator use; it seems likely that such an adjustment will result in a steeper exposure–response for smelter workers.

To explore the impact of exposure misclassification on the steep increase in risk over lower exposure categories of our pooled analysis, we restricted our analysis to recent exposures estimated with a high confidence score. Despite a marked reduction of cases and person-years in the reference group, the shape of the exposure–response was robust and the HRs increased more sharply.

There are two sources of bias that might lead to attenuation of the HRs for cumulative exposure: left-truncation[26,27] and misclassification of exposure before the start of follow-up. Attenuation from left-truncation bias occurs if those who left work before the start of follow-up were more susceptible to the health effects of exposure than those who stayed to be included in the study. Ideally, we would restrict our analysis to workers hired after the start of follow-up, however, almost 70% of the cohort and 90% of the cases were already employed in 1996 when the study started. In addition, there was a lack of usable job histories before 1996. To estimate cumulative exposure before that time for workers who were already employed, we assumed that the job held at start of follow-up had been their job throughout their prior employment history. Furthermore, analyses for cumulative exposure included all exposures even those not measured with high confidence as there was no straight forward way to cumulate only the subset based on measurements. We therefore expected some attenuation and caution against over interpreting the absence of increased risk. The impact of past exposure on IHD risk in this setting remains an open question.

By using medical claims, we were able to identify incident IHD as well as conditions such as hypertension. The use of claims data has been found to be highly specific for hypertension in a validation study for this population.[28] However, the possibility remains that a worker without any diagnosis of IHD could have a fatal cardiac event without hospitalization. This rare scenario would result in misclassification of the outcome and would likely lead to attenuation.

The increased risk of IHD observed at low levels of recent exposure in this study is consistent with the existing $PM_{2.5}$ literature. The cardiovascular effects of ambient $PM_{2.5}$ and second hand smoke have been established at levels below our reference

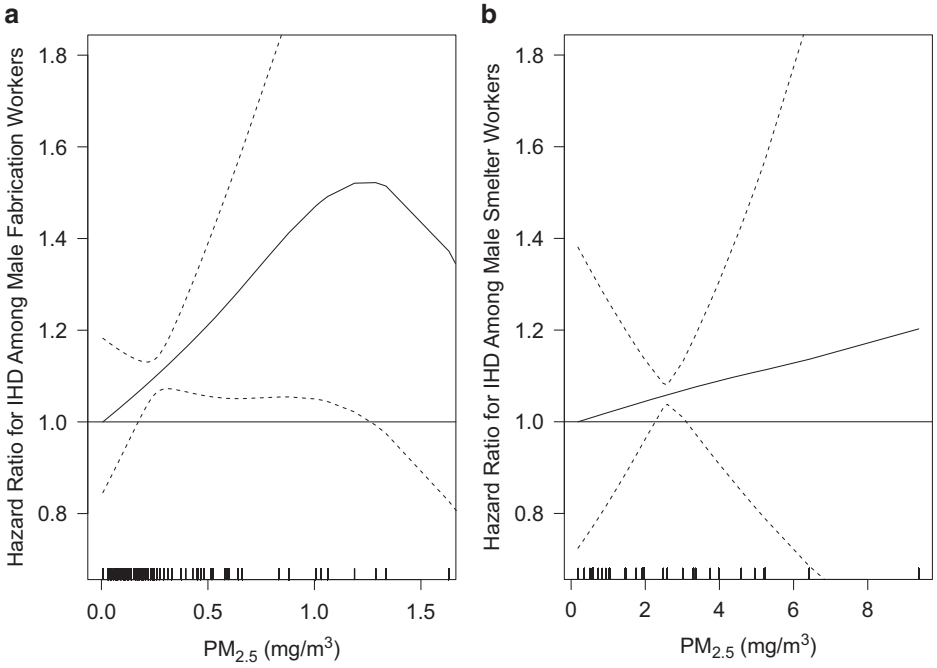

Figure 2. (**a**) Penalized spline of the adjusted hazard ratio for ischemic heart disease and recent (within the last year) fine particulate matter ($PM_{2.5}$) in a Cox model for males working in fabrication facilities in an aluminum manufacturing cohort in the United States, 1998–2008. Restricted to exposures measured with the highest confidence. Graph truncated at 97th percentile of exposure. (**b**) Penalized spline of the adjusted hazard ratio for ischemic heart disease and recent (within the last year) $PM_{2.5}$ in a Cox model for males in smelting facilities in an aluminum manufacturing cohort in the United States, 1998–2008. Restricted to exposures measured with the highest confidence.

Table 3. Hazard ratios for ischemic heart disease according to cumulative $PM_{2.5}$ (mg/m^3-years) in an aluminum manufacturing cohort in the United States, 1998–2008.

Cumulative $PM_{2.5}$	*No. of cases*	*Person-years*	*Hazard ratios*[a]	*95% Confidence interval*
$\leq$1.89	140	16,198	1	
>1.89–4.52	139	13,392	0.89	0.70, 1.12
>4.52–10.51	140	11,855	0.81	0.64, 1.03
>10.51–35.58	139	11,648	0.82	0.63, 1.07
>35.58	139	10,669	0.80	0.59, 1.07

Abbreviation: $PM_{2.5}$, fine particulate matter.
[a]Hazard ratios adjusted for age, race, gender, calendar year, smoking, BMI, job grade, and facility type.

cut point. In many US cities $PM_{2.5}$ in air pollution rarely rises above 0.03 mg/m^3 and second hand smoke ranges from 0.02 to 0.05 mg/m^3.[29–31]

In the heart disease and $PM_{2.5}$ research in occupational cohorts, internal comparisons are rare. Moreover, most studies lack detail in the exposure assessment and have limited data on potential confounders. A recent meta-analysis of four studies comparing high (or any) *versus* low (or no) PM exposure found an RR of 1.15 (95% CI: 1.06–1.14) for IHD mortality, although none of the studies included a minimally acceptable set of potential confounders.[20] Of particular interest, Burstyn et al.[32] report a monotonic exposure–response association for both recent and cumulative PAH (benzo(a)pyrene) exposure in male asphalt workers with a 60% increased risk of IHD mortality. Individual-level data for smoking were not available; however, sensitivity analyses suggested a 20–40% increase in risk under realistic scenarios of confounding by smoking. Since the meta-analysis, two relevant papers have been published. Costello et al.[33] reported increased risk of IHD mortality associated with exposure to respirable PM from straight metal-working fluids in a cohort of actively employed autoworkers. An increased risk of IHD mortality was associated with recent exposure to respirable PM before 1971 and with cumulative exposure to respirable PM after 1971, with no adjustment for smoking. The metal-working process among the autoworkers was similar to the fabrication manufacturing presented here; however, aluminum fabrication involves mostly water-based rather than oil-based (straight) fluids. Friesen et al.[34] reported on cumulative benzo(a)pyrene exposure in a male aluminum smelting workforce in Canada controlling for smoking status. When the cohort was restricted to actively employed workers, comparable to the smelter workers presented here, the HR for IHD mortality increased to two-fold in the highest category of cumulative exposure. Dust levels in the Canadian cohort were higher due to the time period and an older technology for smelting aluminum and no estimates for recent exposure were presented. To our knowledge, there is no occupational literature on recent exposure to respirable or fine PM and incident IHD adjusted for multiple potential confounders.

Data on many important covariates were available in this data set, however, we had to impute missing data for smoking and BMI. If the missing at random assumption was not met, then we may have residual confounding by these variables. Results presented here were similar to results from models run with a category for missingness for BMI and smoking, but slightly stronger than results unadjusted for BMI or smoking, especially in the smelters.

Three major pathophysiological pathways by which particulate matter may cause heart disease have been proposed.[35,36] First, upon entering the lungs, $PM_{2.5}$ may cause oxidative stress and systemic inflammatory response,[37–39] which can increase concentration of blood fibrinogen,[38,39] induce progression of atherosclerosis,[40,41] and activate cardiac myocytes and adipocytes.[36] Second, $PM_{2.5}$ could deposit in the upper airways and activate receptors linked to the autonomic nervous system

leading to a sympathetic upregulation and vagal withdrawal[36,42] as well as hypertension.[43] Third, components adsorbed on the surface of particles, or the ultrafine particles in the air mixture,[44–46] could cross the lung–blood barrier and interact directly with blood cells or the endothelium. We have neither measured the ultrafine component of the $PM_{2.5}$ nor taken account of the composition of the particles. In fabrication, PM is likely composed of water-based metal-working fluids (soluble or synthetic fluids).[33,47,48] In the smelters, the PM is likely composed of inorganic materials, that is, fluorides,[49] alumina dust, metals, and related fumes,[50] as well as coal tar pitch volatiles[34] in some areas. Given the apparent effect modification by manufacturing process (Figure 2a and b), composition of $PM_{2.5}$ may be as relevant to risk as concentration in this industrial setting.

Other heart disease risk factors, such as noise[51] and stress,[52] could vary by manufacturing process and may be responsible for some of the observed differences in risk.

We did not control for hypertension in our models, because it might be on the causal pathway between exposure and disease. Diagnosis of this condition might result in a decrease in exposure, via transferring jobs or reducing hours, thus including it in a person-year Cox model could introduce bias. We plan to apply marginal structural models to deal with time-varying confounding by this condition and to address censoring due to leaving work.[53]

CONCLUSION

This is the first report of incident IHD and recent $PM_{2.5}$ in an occupationally exposed US cohort of active aluminum production workers. We found evidence of increased risk of IHD even at the low end of the recent exposure range. The exposure–response was most striking when stratifying workers by manufacturing process. At the same recent exposure level, workers in the smelters have lower risk of IHD compared with the fabrication workers, possibly an unintended benefit of the workplace programs in place for heat and respiratory fitness. However, the risk does increase in both work environments, suggesting that composition of $PM_{2.5}$ may be etiologically relevant for cardiovascular risk.

CONFLICT OF INTEREST

Drs Costello, Brown, Noth and Eisen do not have any conflicts of interest to declare. Ms Cantley and Ms Tessier-Sherman receive salary support from Alcoa, Inc through contracts with Yale University. Dr Cullen receives salary support from Alcoa, Inc through contracts with Stanford University. Dr Hammond receives compensation as a member of the scientific advisory board for Alcoa, Inc and has also consulted on exposure assessment and received compensation.

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NIA Data Sharing: As an alternative to providing a de-identified data set to the public domain, we allow access for the purpose of re-analyses or appropriate "follow-on" analyses by any qualified investigator willing to sign a contractual covenant with the host Institution limiting use of data to a specific agreed upon purpose and observing the same restrictions as are limited in our contract with Alcoa, such as 60-day manuscript review for compliance purposes.

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