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Incident Ischemic Heart Disease After Long-Term Occupational Exposure to Fine Particulate Matter: Accounting for 2 Forms of Survivor Bias

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Little is known about the heart disease risks associated with occupational, rather than traffic-related, exposure to particulate matter with aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$). We examined long-term exposure to $PM_{2.5}$ in cohorts of aluminum smelters and fabrication workers in the United States who were followed for incident ischemic heart disease from 1998 to 2012, and we addressed 2 forms of survivor bias. Left truncation bias was addressed by restricting analyses to the subcohort hired after the start of follow up. Healthy worker survivor bias, which is characterized by time-varying confounding that is affected by prior exposure, was documented only in the smelters and required the use of marginal structural Cox models. When comparing always-exposed participants above the 10th percentile of annual exposure with those below, the hazard ratios were 1.67 (95% confidence interval (CI): 1.11, 2.52) and 3.95 (95% CI: 0.87, 18.00) in the full and restricted subcohorts of smelter workers, respectively. In the fabrication stratum, hazard ratios based on conditional Cox models were 0.98 (95% CI: 0.94, 1.02) and 1.17 (95% CI: 1.00, 1.37) per 1 mg/m^3-year in the full and restricted subcohorts, respectively. Long-term exposure to occupational $PM_{2.5}$ was associated with a higher risk of ischemic heart disease among aluminum manufacturing workers, particularly in smelters, after adjustment for survivor bias.

epidemiologic methods; occupational epidemiology; survivor bias

Abbreviations: BMI, body mass index; CI, confidence interval; IHD, ischemic heart disease; MSM, marginal structural model; $PM_{2.5}$, particulate matter with aerodynamic diameter of less than 2.5 μm.

Particulate matter with aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) is recognized as a major contributing factor to the global burden of heart disease. Most of the literature on $PM_{2.5}$ and cardiovascular disease deals primarily with ambient air pollution or cigarette smoking, with more limited evidence on associations with occupational exposures from industrial sources (1, 2). Results from the majority of the air pollution studies corroborate the fact that recent (hours to days) exposure to $PM_{2.5}$ is associated with the risk of cardiovascular events among susceptible people (3–6). There is mounting evidence that longer-term exposure to ambient air pollution also elevates the risk for cardiovascular morbidity and mortality, although exposure is usually measured only in the most recent 1–5 years (7). In contrast, in studies of occupational exposures, investigators often have access to employment records that allow us to characterize long-term exposure over a working lifetime. Thus, it may be possible to assess the risk of ischemic heart disease (IHD) from truly long-term exposure. The populations exposed to occupational $PM_{2.5}$ differ from those exposed to more general sources in terms of underlying health status, age, and other factors that might modify the association between $PM_{2.5}$ and IHD. Moreover, although in most occupational studies investigators have detailed exposure information, they do not have information on important potential confounders, such as smoking and body mass index (BMI), let alone measures of underlying cardiovascular health.

To address these research gaps, we studied heart disease in a large cohort of actively employed aluminum production workers for whom extensive data on health status were available from company personnel records, medical claims databases, and occupational medical records. In a previous study in this cohort, we demonstrated a positive association between

IHD incidence and recent exposure to $PM_{2.5}$ but a protective association with cumulative exposure (8). We hypothesized that the association with cumulative exposure was downwardly biased because of survivor bias, specifically employment termination due to changes in health status caused by prior exposure. Since this finding, we have documented evidence of this bias among workers employed in smelting but not among workers in the fabrication processes (9), necessitating the use of g-methods in the smelter stratum. G-methods are well equipped to adjust for time-varying confounding affected by prior exposure that occurs during follow up.

Left truncation bias (10) is another form of survivor bias in which otherwise eligible workers do not remain observable for a later start of follow up. Those who left work prior to the start of follow up may have been more susceptible to exposure-related IHD. Including only those who remained at work until the start of follow up can result in a downward bias, especially when studying associations between health and long-term exposure. Analyses restricted to workers hired closer to the start of follow up have shown steeper exposure-response curves in other cohorts (11, 12).

In the present study, we address the association between long-term exposure to $PM_{2.5}$ in the aluminum fabrication and smelting processes and the risk of IHD. We restricted analyses by date of hire to address left truncation bias in both work processes and applied a g-method to address time-varying confounding affected by prior exposure in the smelters. In addition, we illustrate the use of nested cohort restrictions to reduce left truncation bias in both types of work processes.

METHODS

Study population, outcome assessment, and covariate information

We conducted our analysis using data from hourly workers at 11 US facilities of a single aluminum company. To be eligible, workers had to be employed, to be enrolled in the primary insurance plan, and to have had no claims for IHD for at least 2 years during follow up. This 2-year washout period was implemented to exclude potential prevalent cases of IHD. Follow up began on January 1, 1996, for workers at most facilities and on January 1, 2003, for workers at the 2 facilities acquired by the company at a later date. All workers were assumed to have used the primary insurance plan before 2003, an assumption supported by the fact that 97% of workers filed at least 1 claim in this system between 1996 and 2003. After 2003, insurance options increased, and enrollment in the primary plan was tracked on a monthly basis.

Most jobs clearly fit into 1 of 2 categories: jobs that involved smelter processes versus those that involved fabrication processes. However, workers with jobs that required tasks in both environments, for example, electricians and janitorial staff, were included in the smelter stratum. Subcohorts within each type of work process were further restricted based on the number of years before the start of follow up that the workers had been hired, starting with the full cohort then creating subgroups of those hired 25, 10, and 0 years prior.

Incident cases of IHD were identified from health insurance claims through 2012 or until the date of termination of active employment, whichever occurred first. IHD case patients were defined as subjects with insurance claims for relevant procedures (codes are provided in Appendix 1) or for a face-to-face outpatient visit to a health care provider with a code for IHD, as well as those who had been hospitalized for 2 or more days and whose medical records showed a code for admission for IHD (*International Classification of Diseases, Ninth Revision* codes 410–414) or death from IHD (identified by *International Classification of Diseases, Ninth Revision*, codes 410–414 or *International Classification of Diseases, Tenth Revision*, codes I20–I25). Deaths due to IHD were identified from the National Death Index (National Center for Health Statistics, Hyattsville, Maryland).

Information was available on age, sex, race, and job grade through employment records. Data on smoking status, height, and weight were collected at occupational health clinics located at each of the facilities, and availability varied by facility. We had access to a time-varying health "risk score" that was derived using a third-party algorithm to predict future health expenditures for insurance purposes (13). As described in detail previously (9), this variable was the time-varying proxy for overall health status in analysis in the smelter stratum and was included as a covariate in the fabrication stratum.

Exposure assessment

Average annual $PM_{2.5}$ concentrations (in milligrams per cubic meter) were assigned to distinct exposure groups within each facility to create a job exposure matrix (14). The estimates were based on more than 8,000 industrial hygiene samples collected over 25 years by the company, as well as measurements collected by our research team in 2010–2011. Exposure estimates for each job-year were classified as "high confidence" if estimates were based on direct measurements rather than extrapolation. All analyses presented here are restricted to exposures measured with high confidence to reduce bias from exposure misclassification (8). Annual averages were calculated and then summed to create the cumulative exposure metric; cumulative exposure was treated as continuous in the fabrication stratum. In contrast, long-term exposure is dichotomized at the 10th percentile of the distribution of annual $PM_{2.5}$ across person-time in the smelter stratum.

Statistical analysis

Fabrication stratum. Cox proportional hazards regression models were fitted to estimate hazard ratios for cumulative $PM_{2.5}$ exposure (mg/m^3-year) and incident IHD among the workers engaged in aluminum fabrication processes. To maximize model flexibility, we added a penalized spline function of cumulative $PM_{2.5}$ exposure. Degrees of freedom were based on minimum Akaike's information criterion and biological plausibility. Attained age was used as the time scale, and models were stratified so that baseline hazards were allowed to vary by calendar time. Models also included covariates for sex, race, job grade (above or below the median for each facility), smoking status (current, ever, or never), facility, risk score (deciles), and BMI value. The models predicted the risk of IHD as a function of exposure cumulated during follow-up adjusted for exposure cumulated before follow

Table 1. Characteristics of an Aluminum Manufacturing Cohort by Processing Type in the United States, 1998–2012

Characteristic	No. of Years Prior to Start of Follow-Up Participants Were Hired							
	Full Cohort		≤25		≤10		0	
	No.	Median	No.	Median	No.	Median	No.	Median
Fabrication Cohort								
All subjects	7,805		7,759		5,125		3,003	
No. of cases	554		550		270		134	
Person-years	49,786		49,578		30,631		15,206	
Male sex	5,965		5,920		3,664		2,221	
White race	6,057		6,016		3,851		2,135	
Birth year		1957		1957		1961		1964
Hire year		1989		1989		1995		1998
Age, years		53		53		51		50
Cumulative exposure to $PM_{2.5}$ during follow up[a]		0.90 (0.37, 2.28)		0.90 (0.37, 2.28)		0.85 (0.36, 2.20)		0.81 (0.33, 2.13)
Smelter Cohort								
All subjects	5,472		4,375		2,666		1,900	
No. of cases	411		282		114		64	
Person-years	37,145		30,600		16,974		10,508	
Male sex	5,230		4,133		2,490		1,777	
White race	4,754		3,768		2,251		1,568	
Birth year		1953		1955		1963		1966
Hire year		1980		1989		1997		2000
Age, years		55		53		51		51
Annual exposure to $PM_{2.5}$ during follow up[b]		1.78 (0.72, 2.59)		1.78 (1.03, 2.59)		1.96 (1.28, 2.59)		1.96 (1.28, 2.59)

Abbreviation: $PM_{2.5}$, particulate matter with aerodynamic diameter of less than 2.5 μm.
[a] Units are mg/m^3-years. The parenthetical values are the 25th and 75th percentiles for cumulative exposure to $PM_{2.5}$ during follow up.
[b] Units are mg/m^3. The parenthetical values are the 25th and 75th percentiles for annual exposure to $PM_{2.5}$ during follow up.

up, including exposure cumulated during the wash-out period. Models were restricted to people who ever had high-confidence exposure values; thus, the cumulative exposure metrics could include annual exposure estimates that were not classified as high confidence.

Multiple imputation was used to impute missing data for smoking (33% missing), BMI (20% missing), and risk score (13% missing). Given the sources of the data, it was plausible to assume that the data were missing at random after accounting for case status and the variables included in the main analytical models. A 2-stage imputation process was implemented in which BMI and risk score were imputed first using the expectation-maximization algorithm (15) and smoking status was subsequently imputed using logistic regression.

Smelter stratum. Marginal structural models (MSMs) with inverse probability weights were used to estimate the hazard ratio for the association of everyone being always exposed to levels above (versus below) the 10th percentile of $PM_{2.5}$ exposure and incident IHD among smelter workers. Pooled logistic models for the exposure were fitted to determine the inverse probability weights. The models included covariates for age, sex, race, smoking status, BMI, job grade, and facility, as well as cumulative exposure prior to the start of follow up. Risk score estimation was based on data from the past year and thus chronologically preceded exposure in each person-year. Estimation of inverse probability weights has been described in detail elsewhere (16). Briefly, the weights for each subject at a given time point are proportional to the inverse of the model-derived probability that each subject had his or her own actual exposure history at a given time. These probabilities were estimated as the product of the model-derived probability of a subject receiving his or her own exposure in each year using predicted values from the logistic models described above, resulting in subject-specific, time-dependent weights (per person-year). Stabilized weights were estimated to minimize variability and extreme weight values (17). The risk score variable was entered in the model for the weight denominator, whereas all other variables were entered in both the numerator and denominator models.

Cox models with robust variance estimation were then fitted using the pseudo-population created by the inverse probability

weights in which the pathway of exposure to outcome is no longer confounded by intermediate health status. As in the models for fabrication workers, attained age was the time scale, and the rest of the covariates listed above (with the exception of risk score) were also included in the models. Missing data on smoking and BMI, but not risk score, were imputed as described above. Models were restricted to person-years with high-confidence exposure values to avoid a scenario in which potentially influential weights due to extrapolated exposure could be carried over into future person-years. Sensitivity analyses were done on the smaller subsets of smelter and fabrication workers for whom exposure was measured with high confidence in all years.

R software, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria), was used for the spline analysis, and SAS, software version 9.4 (SAS Institute, Inc., Cary, North Carolina), was used for preparing the data sets, for the multiple imputation procedure, and for the MSMs.

RESULTS

Characteristics of the fabrication and smelter workers by the number of years prior to the start of follow up that they were hired are presented in Table 1. There were 554 cases of IHD identified in the full cohort of 7,805 fabrication workers. There were 550, 270, and 134 cases of IHD identified in the subcohorts hired 25, 10, and 0 years prior to the start of follow up, respectively. Compared with the fabrication workers, there were fewer smelter workers, and they were more likely to be male and white. There were 411 IHD cases identified in the full cohort of 5,472 smelter workers. There were 282, 114, and 64 cases of IHD identified in the subcohorts hired 25, 10, and 0 years prior to the start of follow up, respectively. When stratifying by time since hire, we found that decreasing number of years before the start of follow up was associated with increases in the percentage of participants who were younger, female, and nonwhite, so that each subcohort of time before start of follow up was younger and had more female and nonwhite participants than the one before it.

The hazard ratios for the association of cumulative $PM_{2.5}$ exposure with IHD in the fabrication facilities were less than 1 in the full cohort and the subcohort hired 25 years before the start of follow up (Figure 1). The hazard ratio for IHD in the subcohorts hired within 10 and 0 years prior to the start of follow-up rose to 1.08 and 1.42 at 2.0 mg/m^3-years, respectively (Table 2). The hazard ratio for IHD was statistically significant over the upper ranges of exposure for the subcohorts hired 10 and 0 years prior to the start of follow up but not for the full cohort or the subcohort hired within 25 years of the start of follow up.

Compared with those always exposed to $PM_{2.5}$ levels below the 10th percentile of exposure, smelters who were always exposed to levels above the 10th percentile had a higher risk of IHD in MSMs in which we accounted for time-varying confounding that was affected by prior exposure (Table 3). The hazard ratio for IHD in the full cohort was 1.67; in the subcohorts restricted to workers hired 25 years, 10 years, and 0 years prior to the start of follow up, the hazard ratios were 1.75, 3.18, and 3.95, respectively. The confidence intervals excluded 1 for all but the smallest subcohort that comprised workers hired after the start of follow up.

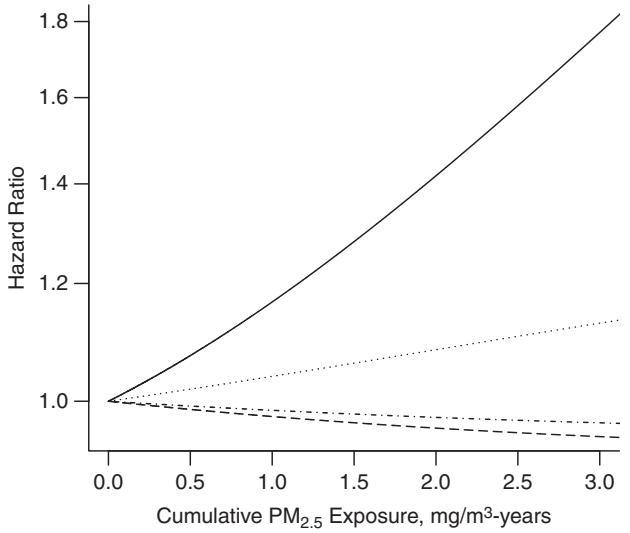

Figure 1. Hazard ratios for incident ischemic heart disease and cumulative exposure to particulate matter with aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) in an aluminum fabrication cohort and subcohorts by number of years hired prior to follow up in the United States, 1998–2012. The solid line represents participants hired 0 years prior to the start of follow up, the dotted line represents participants hired 10 years prior to the start of follow up, the dash-dotted line represents participants hired 25 years prior to the start of follow up, and the dashed line represents the full cohort.

Results from the smelter strata were robust in a sensitivity analyses restricted to the smaller subset of workers who had high-confidence exposures in every year; the hazard ratios were slightly higher and the confidence intervals included 1 for the 2 subcohorts hired 10 and 0 years before the start of follow up. Results from the fabrication workers were less robust to the same sensitivity analysis: Results were unchanged for the full cohort and the subcohorts of participants hired 25 and 10 years prior to the start of follow up. However the model failed to converge for the subcohort hired after the start of follow up.

DISCUSSION

In this occupational cohort of aluminum fabrication and smelter workers, there was evidence of an association between elevated IHD risk and long-term $PM_{2.5}$ exposure after adjustment for survivor bias. In both strata of exposure, the hazard ratios increased with each successive restriction of the number of years the participants could have been hired prior to follow up, indicating that the hazard ratios in the full cohort analyses were attenuated by left truncation bias. The risk of IHD from long-term $PM_{2.5}$ exposure was stronger overall among the smelter workers. Although the hazard ratios reported for the 2 analyses are not directly comparable, given the differences in the exposure metrics and the conditional versus marginal nature of the 2 analyses, the hazard ratios from the smelter stratum demonstrated overall stronger associations.

The average exposure is an order of magnitude higher among the smelters, and the composition of particulate matter differs by process (8). The aluminum fabrication industry uses primarily

Table 2. Hazard Ratios for Ischemic Heart Disease at 3 Levels of Cumulative Exposure to Particulate Matter With Aerodynamic Diameter of Less Than 2.5 μm in an Aluminum Fabrication Cohort and Subcohorts in the United States, 1998–2012

Cohort by No. of Years Prior to Follow up Hired	No. of Cases	$PM_{2.5}$ Exposure, mg/m^3-year					
		0.5		1.0		2.0	
		HR	95% CI	HR	95% CI	HR	95% CI
0	134	1.08	0.78, 1.49	1.17	1.00, 1.37	1.42	1.07, 1.89
≤10	270	1.02	0.92, 1.13	1.04	0.98, 1.10	1.08	1.02, 1.15
≤25	550	0.99	0.93, 1.07	0.99	0.95, 1.03	0.98	0.95, 1.01
Full cohort	554	0.99	0.92, 1.07	0.98	0.94, 1.02	0.96	0.92, 1.00

Abbreviations: CI, confidence interval; HR, hazard ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm.

water-based metalworking fluids that are contaminated with endotoxin, biocides, nitrosamines, metals, and other potentially toxic substances (18) that may lead to lung and systemic inflammation. Particulate matter to which the smelters are exposed is likely composed of inorganic materials, that is, fluorides (19), alumina dust, metals, and related fumes (20), as well as coal tar pitch volatiles (21). On entering the lungs, fine particulate matter may cause a systemic inflammatory response (22–24), which can induce the progression of atherosclerosis (25, 26) and activate cardiac myocytes and adipocytes (27).

In addition to exposure differences, we previously reported that health status was associated with past exposure and predicted both subsequent exposure and IHD among smelter, but not fabrication, workers (9). MSMs and inverse probability weighting were used in the smelters to handle the type of healthy worker survivor effect evident in that stratum. MSMs are one of several g-methods that have been developed to address time-varying confounders affected by prior exposure (16, 17, 28, 29). Assuming correct models, no unmeasured confounding, and positivity, MSMs can provide consistent estimates of average causal effects of exposure (30).

Survivor bias from worker attrition due to time-varying confounding affected by prior exposure can be conceived of in 3 parts, depending on when the attrition occurs in relation to follow up. In studies in which prevalent hires are included, if workers become ill from the exposure and leave work prior to the start of follow up and are thus not included in the cohort, the source of the bias is left truncation. If workers in the cohort become ill from exposure and leave work but are still followed for the outcome, the bias becomes healthy worker survivor bias. If workers in the cohort become ill from exposure and leave work but follow up is dependent on active employment, then the bias is exposure-dependent right censoring.

Although the underlying mechanism is the same, different analytic methods are needed to address the 3 aspects of survivor bias. Cohort restriction can address left truncation bias, g-methods account for healthy worker survivor bias, and censoring weights can account for exposure-dependent right censoring. In the present article, we addressed left truncation bias and healthy worker survivor bias. Censoring weights did not change the hazard ratios in this cohort (9).

To completely eliminate left truncation bias one would, ideally, study an inception cohort—a group of workers followed from their very first day at work. In reality, study design and statistical power considerations may prohibit analysis of an inception cohort. For example, this cohort study design included a 2-year washout period to remove prevalent cases of IHD, and therefore all workers, even those hired after the start of follow up, had to survive for 2 years without IHD. Thus, there is likely residual left truncation bias in our most restrictive analyses. In addition, we must consider the "bias-variance trade-off." Stricter restrictions by hire date may reduce bias; however, they also result in smaller cohorts and increased variance. Fortunately, our results suggest that restriction by hire date reduces the magnitude of left truncation bias, even if restriction to an inception cohort is not feasible.

Although not a bias, the heterogeneity of the workforce in each work process type influences the interpretation of the results presented here. The heterogeneity extends to differences between subcohorts within each stratum of work process as well. Participants in the subcohorts hired after the start of follow up were younger and somewhat less likely to be white men than were participants in the larger subcohorts. Thus, the increased IHD risk from long-term $PM_{2.5}$ exposure in the smaller subcohorts might not have been seen in the larger

Table 3. Hazard Ratios Comparing Always Exposed Participants Above and Below the 10th Percentile of Annual Exposure in an Aluminum Smelter Cohort and Subcohorts in the United States, 1998–2012

Cohort by Years Prior to Follow Up Hired	10th Percentile of $PM_{2.5}$, mg/m^3-year	HR[a]	95% CI	IPW Range[b]
0	0.49	3.95	0.87, 18.00	0.38–2.87
≤10	0.49	3.18	1.17, 8.68	0.34–3.81
≤25	0.28	1.75	1.04, 2.96	0.25–2.72
Full cohort	0.26	1.67	1.11, 2.52	0.23–3.11

Abbreviations: CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; $PM_{2.5}$, particulate matter with an aerodynamic diameter of less than 2.5 μm.

[a] Results from a marginal structural Cox model that controlled for cumulative exposure up to baseline.

[b] Stabilized weights with a mean of 1 were applied.

subcohorts had they been followed for IHD for whole duration of their employment.

Previous analyses in this cohort demonstrated that including workers who always had "low-confidence" exposure estimates reduced the hazard ratio for IHD (8). Corporate industrial hygienists collect exposure measurements more frequently in areas in which high exposures are expected (14). Thus, when we restricted our analyses to exposure estimates that were based on measured exposure data, subjects with high exposures were preferentially selected into our cohort. If workers with low-confidence exposure estimates were different from the rest of the population with respect to unmeasured factors prognostic of IHD, then the restriction could result in selection bias. That said, we are certain that the restriction reduced exposure misclassification, whereas there is no reason to believe that the confidence measure is associated with unmeasured prognostic factors. Therefore, our analysis restricted to workers for whom exposure was estimated with high confidence was likely to generate less biased results than was an analysis of the full cohort.

There are relatively few occupational studies on heart disease and long-term exposure to respirable particulate matter aside from our own. Our prior work in this cohort has included exposure-response models based on a standard Cox analysis in which we pooled smelter and fabrication workers, as well as 2 different g-methods stratified by work process. We found no increased risk of IHD with increased cumulative $PM_{2.5}$ exposure in a naive analysis in which we pooled across work type and without adjustment for survivor bias (8). When we applied a Cox MSM to data from the smelter cohort, we found that compared with workers always exposed to $PM_{2.5}$ levels below the 10th percentile of exposure, those always exposed to levels above the 10th percentile had a hazard ratio for IHD of 1.98 (95% confidence interval (CI): 1.18, 3.32); when we applied a standard Cox model to data from the fabrication cohort, the hazard ratio was 1.34 (95% CI: 0.98, 1.83) (9). Results based on an application of the targeted minimum loss estimation method to estimate the difference in marginal cumulative risk of IHD in the cohorts when comparing the counterfactual outcomes if participants were always exposed above or below the 10th percentile cutpoint were consistent. After adjustment for time-varying confounding affected by prior exposure, the reported risk ratios after 15 years of accumulating exposure were 1.77 (95% CI: 1.03, 3.06) in the smelters and 1.45 (95% CI: 1.13, 1.86) in the fabricators (31). Each of the g-methods applied by our group answer different questions and rely on specific assumptions. Neophytou et al. (9) and Brown et al. (31) both used a dichotomized exposure and adjusted for healthy worker survivor bias but not left truncation bias. In the present analysis, we took advantage of the strength of the quantitative exposure metric in the fabrication stratum and explored the use of nested cohort restrictions to reduce left truncation bias.

The association between occupational exposure to particulate matter and IHD has been reported in 2 other cohorts of aluminum smelter workers and also in metal fabrication workers. An increased risk of IHD mortality was reported with increased benzo[a]pyrene exposure among Canadian aluminum smelter workers (21); however, no association of cardiovascular death was found with coal tar pitch volatiles, fluoride, or inhalable dust in Australian prebake smelters (32). Neither of these studies adjusted for survivor bias. In a study of metalworking fluid and IHD in a cohort of autoworkers, all of whom were hired after the start of follow up, g-estimation resulted in higher hazard ratios for IHD in relation to both oil (33) and water-based (34) metalworking fluids compared with those estimated using standard Cox models.

Survivor bias from worker attrition can operate in a variety of ways depending on when during follow up it occurs, and different methods are needed to account for the bias. In the present cohort, evidence of time-varying confounding affected by prior exposure was only observed in the smelters; however, left truncation bias appeared to be operational in both types of work processes. Long-term exposure to occupational $PM_{2.5}$ was associated with an increased risk of IHD among aluminum manufacturing workers, particularly in smelters, after adjustment for survivor bias.

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Note on National Institute of Aging data sharing: As an alternative to providing a deidentified data set to the public domain, we allow access for the purpose of reanalyses or appropriate "follow-on" analyses to any qualified investigator willing to sign a contractual covenant with the host institution limiting the use of data to a specific agreed-upon purpose and observing the same restrictions as are set forth in our contract with Alcoa, Inc., such as 60-day manuscript review for compliance purposes.

Conflict of interest: M.R.C. receives salary support from Alcoa, Inc. (Pittsburgh, Pennsylvania) through contracts with Stanford University (Stanford, California). S.K.H. has received compensation as a member of the scientific advisory board for Alcoa, Inc., in the past. She has also consulted for Alcoa, Inc., and received compensation. The other authors report no conflicts.

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(Appendix follows)

Appendix Table 1. Procedure Codes Used in the Identification of Cases of Ischemic Heart Disease From an Administrative Database

Code	Definition
33510	Coronary artery bypass, vein only; single coronary venous graft
33511	Coronary artery bypass, vein only; 2 coronary venous grafts
33512	Coronary artery bypass, vein only; 3 coronary venous grafts
33513	Coronary artery bypass, vein only; 4 coronary venous grafts
33514	Coronary artery bypass, vein only; 5 coronary venous grafts
33516	Coronary artery bypass, vein only; 6 or more coronary venous grafts
33517	Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft
33518	Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts
33519	Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts
33521	Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts
33522	Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts
33523	Coronary artery bypass, using venous graft(s) and arterial graft(s); 6 or more venous grafts
33533	Coronary artery bypass, artery only; single coronary arterial graft
33534	Coronary artery bypass, artery only; 2 coronary arterial grafts
33535	Coronary artery bypass, artery only; 3 coronary arterial grafts
33536	Coronary artery bypass, artery only; 4 or more coronary arterial grafts
33542	Myocardial resection (e.g., ventricular aneurysmectomy)
33545	Repair of postinfarction ventricular septal defect, with or without myocardial resection
33548	Surgical ventricular restoration procedure, includes prosthetic patch, when performed (e.g., ventricular remodeling, surgical ventricular restoration, surgical anterior ventricular endocardial restoration, Dor procedure)
92975	Thrombolysis, coronary; by intracoronary infusion, including selective coronary angiography
92977	Thrombolysis, coronary; by intravenous infusion
92980	Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel
92982	Percutaneous transluminal coronary balloon angioplasty; single vessel
92995	Percutaneous transluminal coronary atherectomy, by mechanical or other method, with or without balloon angioplasty; single vessel
33140	Transmyocardial laser revascularization, by thoracotomy
33141	Transmyocardial laser revascularization, by thoracotomy; performed at the time of other open cardiac procedure(s)