HHS Public Access

Author manuscript

Occup Environ Med. Author manuscript; available in PMC 2020 December 29.

Published in final edited form as:

Occup Environ Med. 2019 December ; 76(12): 888–894. doi:10.1136/oemed-2019-105908.

Accelerated lung function decline in an aluminum manufacturing industry cohort exposed to $PM_{2.5}$: an application of the parametric g-formula.

Andreas M. Neophytou[1,2], **Sadie Costello**[2], **Sally Picciotto**[2], **Elizabeth M. Noth**[2], **Sa Liu**[2,3], **Liza Lutzker**[2], **John R. Balmes**[2], **S. Katharine Hammond**[2], **Mark R. Cullen**[4], **Ellen A. Eisen**[2]

[1]Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO, USA

[2]School of Public Health, Division of Environmental Health Sciences, University of California, Berkeley, Berkeley, CA, USA

[3]School of Health Sciences, Purdue University, West Lafayette, IN, USA

[4]Department of Internal Medicine, Stanford School of Medicine, Stanford University, Stanford, CA, USA

Abstract

Objective: Occupational dust exposure has been associated with accelerated lung function decline, which in turn is associated with overall morbidity and mortality. In the current study we assess potential benefits on lung function of hypothetical interventions that would reduce occupational exposure to fine particulate matter ($PM_{2.5}$), while adjusting for the healthy worker survivor effect.

Methods: Analyses were performed in a cohort of 6485 hourly male workers in an aluminum manufacturing company in the U.S., followed between 1996-2013. We used the parametric g-formula to assess lung function decline over time under hypothetical interventions, while also addressing time-varying confounding by underlying health status, using a composite risk score based on health insurance claims.

Correspondence to: Dr. Andreas M. Neophytou, Department of Environmental and Radiological Health Sciences, 1681 Campus Delivery, Fort Collins CO, 80523, USA, Andreas.Neophytou@colostate.edu.

Contributors: AMN was responsible for data analyses and manuscript preparation. SC, SP and JRB assisted with interpretation of findings and critically reviewed the manuscript. EMN, SL and SKH participated in data collection and assessment, as well as critically reviewing the manuscript. LL assisted with data management and critically reviewing the manuscript. MRC initiated the original study and critically reviewed the manuscript. EAE and AMN devised the concept of the current study and critically reviewed the manuscript.

Note on National Institute of Aging 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 to any qualified investigator willing to sign a contractual covenant with the host institution limiting the use of data without direct PHI/PII identifiers, in accordance to HIPAA regulations, and with a 15-day manuscript review for compliance purposes. For access to the data, interested parties can contact the study PI, Dr. Mark Cullen, at mrcullen@stanford.edu.

Conflicts of interest

SKH has received compensation as a member of the scientific advisory board for Alcoa, Inc. (Pittsburgh, Pennsylvania), and for consulting for Alcoa, Inc. in the past. MRC has received salary support from Alcoa, Inc. through contracts with Stanford University (Stanford, California). All other authors declare no conflict of interest.

Results: A counterfactual scenario envisioning a limit on exposure equivalent to the 10th percentile of the observed exposure distribution of 0.05 mg/m^3 was associated with an improvement in forced expiratory volume in one second (FEV_1) equivalent to 37.6 ml (95% CI: 13.6, 61.6) for after 10 years of follow-up when compared to the observed. Assuming a linear decrease and (from NHANES reference values) a 20 ml decrease per year for a 1.8 m-tall man as they age, this 37.6 ml FEV_1 loss over 10 years associated with observed exposure would translate to approximately a 19% increase to the already expected loss per year from age alone.

Conclusions: Our results indicate that occupational $PM_{2.5}$ exposure in the aluminum industry accelerates lung function decline over age. Reduction in exposure may mitigate accelerated loss of lung function over time in the industry.

Introduction

Occupational exposure to dust has been associated with adverse respiratory outcomes, including asthma, chronic obstructive pulmonary disease (COPD), declining lung function, and respiratory symptoms.[1–4] The American Thoracic Society has reported that at least 15% of both asthma and COPD in the general population are work-related,[1] while a recent European study attributed over 20% of COPD incidence, to a set of occupational exposures.[5] These reports indicate the considerable burden of respiratory disease attributable to occupational exposures, as well as the need for potential intervention measures and adequate surveillance to protect workers' respiratory health. In occupational studies of the risk of respiratory disease, accelerated loss of lung function can be an informative outcome and a useful measure for surveillance, as it is predictive of future chronic disease and mortality.[6–8]

Previous studies of occupational exposures to particles from combustion sources, metals and mine dust have shown associations with obstructive airways outcomes.[9–11] Evidence regarding the relationship of occupational dust exposures and lung function has been accumulating over the past decades, including reports from longitudinal studies.[12–14] With respect to exposures related to metal smelting in particular, evidence of adverse effects on lung function in a study of various metal smelters in Norway[15–17] indicates the need for intervention measures in this particular industrial sector.[18] However, even longitudinal occupational studies are subject to healthy worker survivor bias in the form of time-varying confounding affected by prior exposure, which could lead to downward bias in the assessment of exposure-outcome relationships.[19] This type of bias is not adequately addressed by traditional regression approaches for longitudinal data or approaches such as generalized estimating equations,[20] which have typically been utilized in the existing literature.

In the current study we assess the relationship between decline in lung function (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)) over time and exposure to particulate matter with aerodynamic diameter 2.5 micrometers or less ($PM_{2.5}$) in the American Manufacturing Cohort (AMC), a dynamic cohort of workers in the U.S. aluminum industry.[21] We leverage a dataset rich in individual-level characteristics, not typically available in occupational cohorts, and apply the parametric g-formula in order to

address confounding and healthy worker survivor bias. We estimate counterfactual FEV_1 and FVC trajectories under different hypothetical interventions to reduce exposure, to assess the potential effects of such interventions on worker respiratory health.

Methods

Study Population

The study was based on a sample of actively employed hourly workers at 8 U.S. facilities of the same aluminum manufacturing company, with available $PM_{2.5}$ exposure and spirometry data. The population giving rise to the sample in the current study is described in more detail elsewhere.[21,22] Briefly, to be eligible, workers had to be enrolled in the company's primary insurance plan and be actively employed for at least a year during the follow-up period, between January 1st 1996 and December 31st 2013, as well as have at least two lung function measurements during this period. Follow-up for this analysis began with first lung function test occurring at or after January 1st 1996, and ended when participants were no longer actively employed (either because of termination of employment or death) or administrative end of follow-up on December 31st 2013. Only 6.2% of workers satisfying these criteria were women and given the large differences in the outcome distribution by sex, we restricted analyses to men. The study sample based on the aforementioned inclusion criteria was 6485 actively employed male workers.

Outcome and covariate information

As part of a company medical surveillance program, spirometry was performed at least once every 3 years for employees exposed to respiratory toxicants, with the frequency of testing varying by facility and over time, resulting in an unbalanced longitudinal dataset. Spirometry was performed with OMI Sensormedic 1022 spirometers (dry rolling seal spirometers) according to American Thoracic Society standards.[23] FEV_1 and FVC were the outcomes of interest in this study. Information was also available on age, sex, race, and job grade (indicator for whether the job held was above or below the median employer-assigned job grade in each facility) 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. In addition to this information, we also had access to a time-varying health risk score, derived using a third-party algorithm (DXCG Intelligence v5.0, Verscend Technologies, Inc., Waltham, MA) to predict future health expenditures for insurance purposes. This variable is associated with a variety of health outcomes and was used as a proxy for overall health status in our analysis. It is also associated with past and future exposure to $PM_{2.5}$ in this cohort,[22] and it was also significantly associated with FEV_1 and FVC in this dataset (supplemental table S1).

Exposure assessment

Average annual $PM_{2.5}$ concentrations (in mg/m^3) were assigned to distinct exposure groups within each facility to create a job-exposure matrix. The exposure assessment has been described in detail elsewhere.[24] Briefly, the estimates were based on more than 8000 industrial hygiene personal samples for total particulate matter (TPM) collected over 25 years by the company, as well as personal samples of both TPM and $PM_{2.5}$ collected by our

research team in 2010-2011. The % of TPM that was composed of $PM_{2.5}$ was determined from co-located TPM and $PM_{2.5}$ measurements and was used to derive model estimates for $PM_{2.5}$ for distinct exposure groups that lacked $PM_{2.5}$ measurements. Personal exposures were assigned based on the job held at the beginning of each year. Exposures in the job-exposure matrix were also adjusted for time-varying trends in exposure[25] and with a respirator protection factor reflective of respirator use under actual conditions in the workplace.[26]

Statistical Analyses

We applied the parametric g-formula to assess the effects that hypothetical interventions to reduce $PM_{2.5}$ exposure would have on lung function as measured by FEV_1 and FVC (in separate analyses) over time. We considered two types of interventions. The first series of interventions set exposures at fixed values for all-workers and time points; FEV_1 and FVC values were predicted after 10 years of follow-up under these different exposure scenarios to explore potential exposure-response relationships. We assessed 11 interventions in which all workers were continuously exposed at each concentration between 0 and 5 mg/m^3 in 0.5 mg/m^3 increments. These interventions were assessed in the entire analytical sample and also separately in fabrication and smelter facilities. Additionally, interventions where everyone was exposed to values equivalent to the 25^{th} (0.14 mg/m^3) and 75^{th} (0.51 mg/m^3) percentiles of the observed exposure distribution were assessed to explore potential effects equivalent to an interquartile range increase in exposure. We also considered another series of interventions where a hypothetical limit on exposure was introduced. Limits were chosen based on values of the observed distribution of exposure (specifically, setting limits at the values corresponding to the 10^{th}, 25^{th}, 50^{th} and 75^{th} percentiles of the observed distribution of $PM_{2.5}$ exposures). Predicted FEV_1 and FVC values under these interventions were compared to the natural course (simulation of what actually happened) after 10 years of follow-up in order to assess any potential improvements in lung function.

The approach for the parametric g-formula is described in greater detail in general terms by Taubman *et al.*.[27] Briefly, the process involved fitting parametric models for the outcome (linear regression model for height-standardized FEV_1 or FVC) and each time-varying covariate (pooled logistic model for censoring due to death or termination employment, and linear models for log-transformed values of both risk score and $PM_{2.5}$ exposure). Models were fit pooled on the person-year level, conditional on covariate histories (past risk score and $PM_{2.5}$ exposures) and the following baseline covariates: age and calendar time (both as cubic spline functions), indicator variable for race (white vs. non-white), and categorical variables for smoking (ever, never or missing), individual facility and facility type (smelter, fabrication or refinery). More details on the parametric models are included in the supplemental material, while the assumed relationships between all variables are depicted in Figure 1.

Subsequently, a large Monte-Carlo sample was generated based on the observed distributions of the baseline covariates (N=50,000, sampled with replacement from the observed data at baseline). In this pseudo-sample we simulated exposure, covariate, and outcome values in each year of follow-up using the parameters of the models for the

exposure and covariates, under the natural course and each intervention of interest. For the natural course (i.e. what we predict would have happened under no intervention, like the scenario that gave rise to the observed data) the simulation used model-predicted values for the exposure and time-varying covariates to predict the outcome. For hypothetical interventions in which everyone's exposure was assigned to a fixed value, exposures were simply assigned that value at all time points. Under hypothetical interventions in which maximum limits of exposure were introduced, exposure values were predicted from the exposure model and then replaced with the limit specified by the intervention only if they exceeded the limit; otherwise they remained unchanged. For both types of interventions, the assigned values were then used to predict subsequent values of time-varying covariates and the outcome.

The simulation continued for 10 years for each pseudo-worker, or until they were predicted to be censored due to death or termination of employment. The counterfactual average FEV_1 or FVC under each intervention is thus estimated among those predicted to be actively employed after 10 years of follow-up. Using the estimates of predicted counterfactual FEV_1 and FVC we also generated estimates of percent predicted FEV_1 and FVC values for each individual based on the reference equations described by Hankinson *et al.*[28].

The entire above process was repeated in 200 bootstrap samples and the standard deviation (SD) of the estimates from the bootstrap samples was used as an estimate of the standard error,[29] which was then used to generate 95% confidence intervals (CI). In a sensitivity analysis we also estimated the predicted FEV_1 and FVC values under interventions from 50 multiply imputed datasets (proc mi procedure in SAS) in which smoking (missing for approximately 33% of participants) was imputed at baseline conditional on observed exposure, outcome and covariate values. We also repeated analyses with censoring set to zero for all workers, so they were simulated to be actively employed for 10 years. All analyses were carried out using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Demographic characteristics of the study population are summarized in Table 1. Briefly, the cohort was predominantly white (86%) with a mean age at baseline was 43.6 years. The number of spirometry measures per participant varied from 2 to 16 with a median of 3. The overall mean percent predicted FEV_1 at baseline was 93.7% (median of 93.9% and an interquartile range of 85.2%, 102.7%), while the corresponding numbers for FVC were 94.0% (median of 93.9% and an interquartile range of 85.8%, 101.9%).

Figure 2 illustrates observed $PM_{2.5}$ exposure distributions for the person-time in our study sample, overall and by facility type. There was a wider range of exposures in smelters compared to other facility types with higher exposures on average (mean (SD) of 0.64 (1.05) mg/m^3, compared to 0.27 (0.37) mg/m^3 and 0.32 (0.10) mg/m^3 for fabrication and refinery, respectively).

Estimates for counterfactual FEV_1 and FVC under 11 scenarios where workers are always exposed to increasing levels of $PM_{2.5}$ (range 0-5 mg/m^3) along with loess smoothing curves

are summarized in Figure 3, overall (Figures 3A & 3B for FEV_1 and FVC respectively) and by facility type (Figures 3C & 3D for FEV_1 and FVC respectively). Results indicate a steeper relative decline in smelting facilities compared to fabrication. The overall additional mean decrease in FEV_1/height^2 after 10 years if all workers were exposed at 0.51 mg/m^3 $PM_{2.5}$, (corresponding to the 75th percentile of the overall exposure distribution) compared to exposure at 0.14 mg/m^3 (the 25th percentile) was 12.5 ml/m^2 (95% CI: −24.6, −0.4), which would be equivalent to an additional loss of 40.5 ml (95% CI: −79.6, −1.4) in FEV_1 for a1.8m tall man.

Table 2 summarizes the estimates of mean FEV_1 and FVC under hypothetical interventions of a series of exposure limits as well as corresponding percent predicted values after 10 years of follow-up. The counterfactual change in FEV_1 after 10 years under a hypothetical intervention setting a limit at 0.05 mg/m^3 (corresponding to the 10th percentile of the overall exposure distribution) compared to the natural course was an improvement of 11.6 ml (95% CI: 4.2, 19.0), which would be equivalent to an improvement of 37.6 ml (95% CI: 13.6, 63.6) in FEV_1 for a 1.8m-tall man. The observed mean predicted FEV_1 at baseline was 93.7% compared to 91.9% after 10 years of follow-up. Mean FEV_1 values would have remained to 93.1% of predicted after 10 years under an intervention of always unexposed, compared to the observed of 91.9%.

Results from a sensitivity analysis using multiple imputation for missing smoking data at baseline were very similar (Supplemental Table S2), while results assuming no workers were censored after 10 years, yielded stronger associations with exposure (Supplemental Table S3).

Discussion

We observed a reduction in lung function associated with increasing occupational $PM_{2.5}$ exposures in a cohort of active U.S. aluminum industry workers. Our estimates of counterfactual lung function parameters under hypothetical interventions to reduce exposure also indicate that such interventions may benefit worker respiratory health in this industry and ameliorate the accelerated decline in lung function associated with exposure. Observed $PM_{2.5}$ exposures were associated with an average 37.6 ml additional decline for a 1.8m tall man over 10 years, compared to a hypothetical intervention with an exposure limit set at the 10th percentile of the observed exposure distribution. Assuming a linear trend over time, this decline would be equivalent to an approximately 20% greater loss compared to the expected decline with age (based on the Hankinson reference values for a 1.8m tall man[28]). Over the course of a 30-year working life, this would translate to a fast-forwarding of lung function decline by 5-6 years by the time of retirement. In general, our findings in a dynamic population are likely to translate to larger effects under ‘worst case scenario’ exposures persisting in a fixed population over the course of a long working life. Furthermore, greater than the reported *average* declines associated with exposure in an individual worker with already compromised lung function, may prove clinically significant.

Workers in this aluminum manufacturing cohort are exposed to particulate matter (PM) from combustion sources as well as metalworking fluids and metal dusts during several stages in

the manufacturing process, with high exposures particularly in smelting facilities. Decreased lung function and other adverse respiratory outcomes, including excess COPD mortality, have been previously reported in the industry.[30–33] Although potroom exposures occurring in smelting facilities are reported to be especially harmful to respiratory health, [32,34,35] other exposures in smelters may also lead to adverse outcomes.[36]

PM in aluminum smelting is composed of inorganic materials such as fluorides and metals, as well as organic materials such as coal tar volatiles. PM in fabrication facilities is composed of water-based soluble and synthetic metalworking fluids, as well as metal dust. Particulate exposures in smelters are also higher in concentration compared to fabrication. Results stratified by facility type indicated differences in rates of the decline in lung function (steeper declines in smelters compare to fabrication) even at lower exposure concentrations, suggesting that $PM_{2.5}$ composition may also be a determinant of lung function decline in this industry.

Our study applies the parametric g-formula to account for time-varying confounding affected by prior exposure in the form of healthy worker survivor bias, a trademark of most occupational studies, while accounting for potential non-linearities in the exposure-response relationship. We used a time-varying health risk score variable as an overall marker of health status, previously associated with various adverse health outcomes,[37] and also shown to be affected by previous exposure in this cohort.[22] This variable was also highly predictive of lung function in this cohort. Within a counterfactual framework and under assumptions listed below, the method allowed us to assess lung function trajectories under hypothetical interventions, in an effort to generate population average estimates that could be observed in a real-world intervention scenario. We assessed the effects of hypothetical interventions to reduce exposures in a population with varying exposures and durations of employment, as would be expected in a real-world working population.

The feasibility of any workplace intervention of interest is bounded by what can be achieved by technology in the form of engineering control and personal protective equipment. Specific NIOSH approved respirators can filter up to 99.97% of airborne particles,[38] but effectiveness is subject to compliance and other conditions. Furthermore, oversized equipment may hinder worker's movement, vision and hearing, thereby compromising productivity and potentially increasing risk of workplace injury. Engineering controls would not share these limitations, but it would also be difficult to achieve some of the lower limits in the hypothesized interventions (such as the equivalent of the 10^{th} percentile of the observed distribution at 0.05 mg/m^3) with their use alone. It should also be noted that general occupational $PM_{2.5}$ exposures per se are not directly regulated in the U.S., while Environmental Protection Agency standards for ambient exposures are far lower than exposures observed in this population. In the absence of extensive risk assessment and cost-benefit analyses and lack of any regulatory standards applicable for this population and exposure distribution, we based counterfactual intervention limits on selected percentiles of the observed distribution of exposure. The Occupational Safety and Health Administration (OSHA) does have a Permissible Exposure Limit (PEL) for "particulates not otherwise regulated" of 15 mg/m^3 for total dust, and 5 mg/m^3 for the respirable fraction (defined as the sub fraction of inhaled particles that penetrates into the alveolar region of the lung).[39]

Although these standards apply to exposures with different particle size definitions, our results suggest adverse effects at levels well below these standards. We also assessed interventions where all workers were exposed at a series of exposure levels within the observed range of exposures to generate an exposure-response-like curve. We did not observe any evidence of a threshold of exposure effects, with a steeper slope in decline with increasing exposures appearing at the lower parts of the observed exposure distribution (Figure 3). Although based on current practice and control technology it may be challenging to achieve some of the interventions we hypothesized, our analysis suggests adverse effects at levels well below the current US occupational exposure limits, and reduction in exposure will benefit workers' health in the industry.

Causal interpretation of our findings is subject to assumptions such as conditional exchangeability (no unmeasured confounding). A limitation of our study potentially related to this assumption was the lack of complete data on smoking. Another assumption we have to rely on is that of correct model specification, and a general limitation of the parametric g-formula is the number of parametric models required, making this a strong assumption. It should also be noted that interventions where everyone was unexposed suffer from non-positivity and were based on extrapolation from the models, as there was no observed unexposed person-time. This intervention is also considered infeasible, as there will always be some particulate exposure in this occupational setting. Results under these interventions, however, are useful as they allow the estimation of the magnitude of risk attributable to the exposure in the observed population. Near-violations of positivity may also have occurred for interventions in which all workers are exposed at the same level at higher values of exposure where person-time was scarcer in the data. Likewise, interventions setting all workers' exposures at the same level (especially at higher levels) would not take place in a real-world scenario, but assessment of these interventions allowed for investigating effects at increasing levels of exposure within the observed range. These interventions are also more akin a 'worst-case scenario' risk assessment typically employed in regulatory frameworks.

Hypothetical interventions in this study only affected exposure after beginning of follow-up, with any exposure accrued prior to beginning of follow-up remaining unchanged. We lacked the power to assess intervention effects among only newly hired workers not previously exposed, but this group may experience an even greater reduction in lung function decline, since their entire history of exposure would be intervened on. The length of observed follow-up time also prevented us from examining population average effects over a greater time window (i.e. simulating the duration of a full working life). We also lacked quantitative data on specific respiratory toxicants prevalent in the industry (such as polycyclic aromatic hydrocarbons, fluorides, metals, metalworking fluids, welding fumes, etc.), so quantitative analyses were limited to $PM_{2.5}$. Lastly, the absence of post-bronchodilator data prevented us from assessing COPD as an outcome based on spirometric data.

In summary, we estimated counterfactual lung function trajectories over time under hypothetical interventions to reduce occupational $PM_{2.5}$ exposure in a U.S. aluminum manufacturing cohort. Our results indicate an acceleration of lung function decline associated with higher $PM_{2.5}$ exposures in this cohort, particularly in smelters, adjusting for

healthy worker survivor bias. We also provide evidence that interventions to reduce exposures are likely to ameliorate adverse effects on lung function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This study was supported by the National Institutes of Health, Institute of Aging (R01-AG026291), the Centers for Disease Control and Prevention, National Institute of Occupational Safety and Health (R01 OH009939).

References

1. Balmes J, Becklake M, Blanc P, et al. American thoracic society statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003;167:787–97. [PubMed: 12598220]
2. Blanc PD, Iribarren C, Trupin L, et al. Occupational exposures and the risk of COPD: Dusty trades revisited. Thorax 2009;64:6–12. [PubMed: 18678700]
3. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693–718. [PubMed: 20802169]
4. Omland Ø, Würtz ET, Aasen TB, et al. Occupational chronic obstructive pulmonary disease: a systematic literature review. Scand J Work Environ Health 2014;40:19–35. [PubMed: 24220056]
5. Lytras T, Kogevinas M, Kromhout H, et al. Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. Thorax 2018;73:1008–15. [PubMed: 29574416]
6. Hole DJ, Watt GCM, Davey-Smith G, et al. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. BMJ 1996;313:711–5. [PubMed: 8819439]
7. Mannino DM, Reichert MM, Davis KJ. Lung function decline and outcomes in an adult population. Am J Respir Crit Care Med 2006;173:985–90. [PubMed: 16439715]
8. Lange P, Celli B, Agustí A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. N Engl J Med 2015;373:111–22. [PubMed: 26154786]
9. Hauser R, Eisen EA, Pothier L, et al. Spirometric abnormalities associated with chronic bronchitis, asthma, and airway hyperresponsiveness among boilermaker construction workers. Chest 2002;121:2052–60. [PubMed: 12065377]
10. Alif SM, Dharmage SC, Benke G, et al. Occupational exposures to solvents and metals are associated with fixed airflow obstruction. Scand J Work Environ Heal 2017;43:595–603.
11. Kuempel ED, Wheeler MW, Smith RJ, et al. Contributions of dust exposure and cigarette smoking to emphysema severity in coal miners in the United States. Am J Respir Crit Care Med 2009;180:257–64. [PubMed: 19423717]
12. Eisen EA, Wegman DH, Louis TA, et al. Healthy worker effect in a longitudinal study of one-second forced expiratory volume (FEV1) and chronic exposure to granite dust. Int J Epidemiol 1995;24:1154–61. [PubMed: 8824857]
13. Hochgatterer K, Moshammer H, Haluza D. Dust is in the air: Effects of occupational exposure to mineral dust on lung function in a 9-year study. Lung 2013;191:257–63. [PubMed: 23568145]
14. Liao S-Y, Lin X, Christiani DC. Occupational exposures and longitudinal lung function decline. Am J Ind Med 2015;58:14–20. [PubMed: 25384732]
15. Søyseth V, Johnsen HL, Benth JŠ, et al. Production of Silicon Metal and Alloys Is Associated With Accelerated Decline in Lung Function. J Occup Environ Med 2007;49:1020–6. [PubMed: 17848858]

16. Johnsen HL, Hetland SM, Benth JŠ, et al. Dust exposure assessed by a job exposure matrix is associated with increased annual decline in FEV1: A 5-year prospective study of employees in Norwegian smelters. Am J Respir Crit Care Med 2010;181:1234–40. [PubMed: 20203247]
17. Søyseth V, HL J, MD B, et al. Prevalence of airflow limitation among employees in Norwegian smelters: a longitudinal study. Occup Env Med 2011;68:24–9. [PubMed: 20798007]
18. Hnizdo E Lung function loss associated with occupational dust exposure in metal smelting. Am J Respir Crit Care Med 2010;181:1162–3. [PubMed: 20535848]
19. Eisen EA, Robins JM, Picciotto S. Healthy worker effect In: El-Shaarawi AH, Piegorsch W, eds. Encyclopedia of Environmetrics. Chichester, United Kingdom: : John Wiley & Sons, Ltd 2012 1269–72.
20. Robins JM, Hu F, Neuhaus JM. Estimation of the causal effect of a time-varying exposure on the marginal mean of a repeated binary outcome. J Am Stat Assoc 1999;94:706–7.
21. Elser H, Neophytou AM, Tribett E, et al. Cohort Profile: The American Manufacturing Cohort (AMC) study. Int J Epidemiol 2019;:[Epub ahead of print].
22. Neophytou AM, Costello S, Brown DM, et al. Marginal Structural Models in Occupational Epidemiology: Application in a Study of Ischemic Heart Disease Incidence and PM2.5 in the US Aluminum Industry. Am J Epidemiol 2014;180:608–15. [PubMed: 25125691]
23. American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995;152:1107–36. [PubMed: 7663792]
24. Noth EM, Dixon-Ernst C, Liu S, et al. Development of a job-exposure matrix for exposure to total and fine particulate matter in the aluminum industry. J Expo Sci Environ Epidemiol 2013;24:89–99. [PubMed: 24022670]
25. Noth E, Liu S, Cullen M, et al. Approaches to developing exposure estimates that reflect temporal trends in total particulate matter in aluminium smelters. Occup Environ Med 2014;71:A14 LP–A14.
26. Liu S, Noth E, Eisen E, et al. Respirator use and its impact on particulate matter exposure in aluminum manufacturing facilities. Scand J Work Environ Health 2018;44:547–54. [PubMed: 29870045]
27. Taubman SL, Robins JM, Mittleman MA, et al. Intervening on risk factors for coronary heart disease: An application of the parametric g-formula. Int J Epidemiol 2009;38:1599–611. [PubMed: 19389875]
28. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–87. [PubMed: 9872837]
29. Efron B, Tibshirani RJ. An Introduction to the Bootstrap. Boca Raton, FL: : Chapman & Hall/CRC 1993.
30. Field GB. Pulmonary function in aluminium smelters. Thorax 1984;39:743–51. [PubMed: 6495242]
31. Barnard CG, McBride DI, Firth HM, et al. Assessing individual employee risk factors for occupational asthma in primary aluminium smelting. Occup Environ Med 2004;61:604–8. [PubMed: 15208376]
32. Søyseth V, Henneberger PK, Einvik G, et al. Annual decline in forced expiratory volume is steeper in aluminum potroom workers than in workers without exposure to potroom fumes. Am J Ind Med 2016;59:322–9. [PubMed: 26853811]
33. Gibbs GW, Sevigny M. Mortality and cancer experience of Quebec aluminum reduction plant workers. Part 3: Monitoring the mortality of workers first employed after January 1, 1950. J Occup Environ Med 2007;49:1269–87. [PubMed: 17993932]
34. Donoghue AM, Frisch N, Ison M, et al. Occupational Asthma in the Aluminum Smelters of Australia and New Zealand : 1991 – 2006. Am J Ind Med 2010;231:224–31.
35. Abramson MJ, Benke GP, Cui J, et al. Is potroom asthma due more to sulphur dioxide than fluoride? An inception cohort study in the Australian aluminium industry. Occup Environ Med 2010;67:679–85. [PubMed: 20798006]
36. Oliphant RC, Sharpe K, Smith MM, et al. A longitudinal study of lung function in non-asthmatic workers in an aluminum smelter. Int J Occup Environ Health 1997;3:13–9. [PubMed: 9891096]

37. Hamad R, Modrek S, Kubo J, et al. Using “Big Data” to Capture Overall Health Status: Properties and Predictive Value of a Claims-Based Health Risk Score. PLoS One 2015;10.

38. NIOSH. Guide to the selection and use of particulate respirators. Cincinnati, OH U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH): 1996 https://www.cdc.gov/niosh/docs/96-101/default.html%0D

39. Occupational Safety & Health Administration [OSHA]. Chemical Sampling Information. 2012https://www.osha.gov/dts/chemicalsampling/data/CH_259640.html

Key messages

What is already known about this subject?

Occupational dust exposure is known to be harmful for workers' respiratory health. However previous studies may have been subject to healthy worker survivor bias, thus underestimating effects, while studies assessing benefits of potential regulatory interventions have not been extensively carried out.

What are the new findings

We leverage a dataset rich in covariates and quantitative exposure assessment and assess the effects of hypothetical interventions on exposure while adjusting for healthy worker survivor bias. Harmful exposure effects are seen even at lower levels of the observed exposure distribution, at different facility types in the aluminum industry.

How might this impact on policy or clinical practice in the foreseeable future?

We examine an occupational exposure over a wide range of concentrations, including those within current regulatory standards. Our results indicate that regulatory interventions resulting in lower exposures will likely benefit workers' respiratory health.

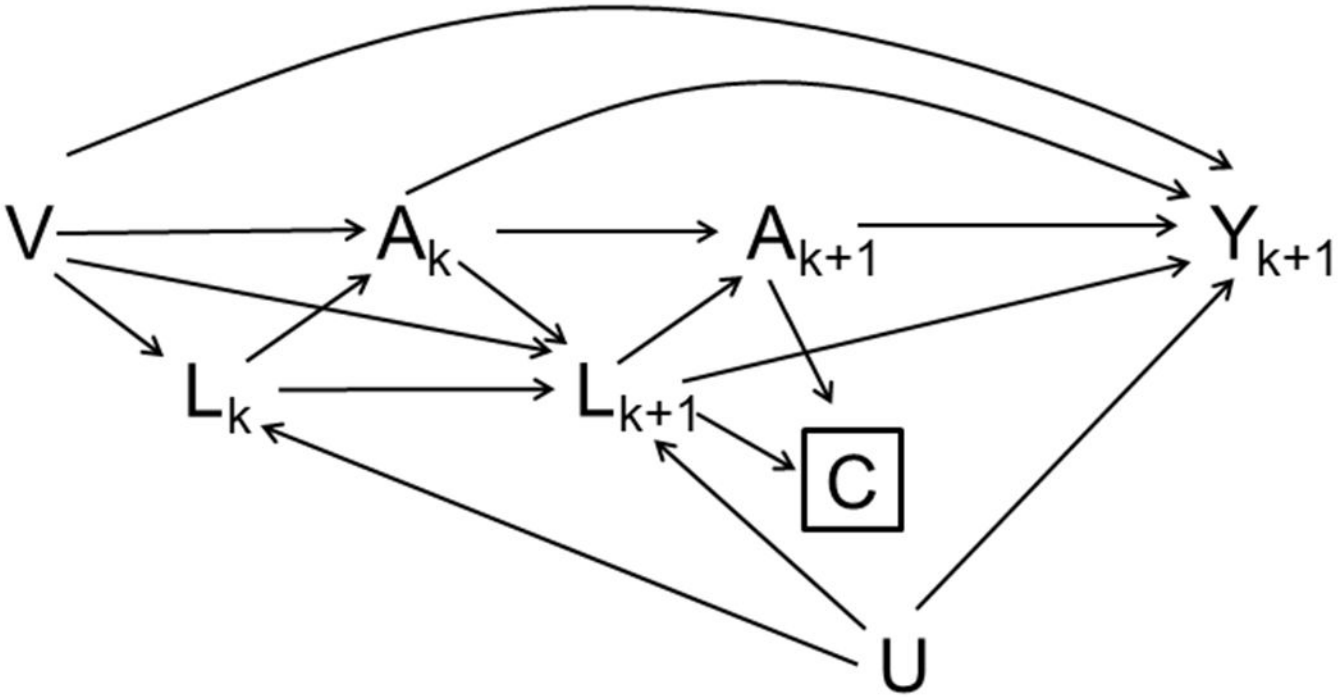

Figure 1:
Directed acyclic graph depicting the assumed relationships between baseline covariates (V), $PM_{2.5}$ exposure (A), health status (L), censoring through termination of active employment or death (C), and lung function (Y). Unmeasured covariates are represented by U while subscripts (k) denote different time points for time-varying covariates.

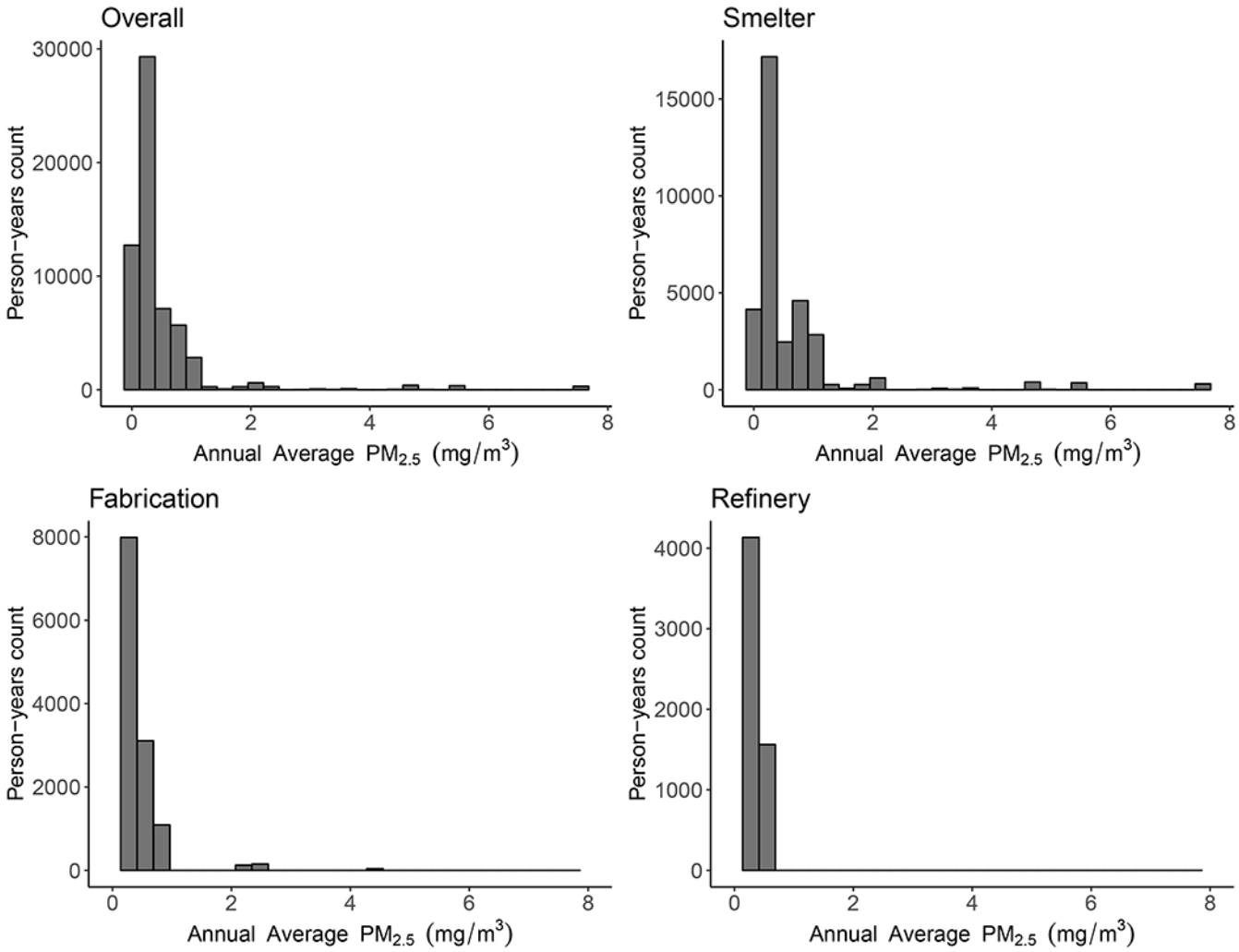

Figure 2:

Annual average $PM_{2.5}$ exposure distributions by person-year count in a study sample of 6485 hourly workers (56,903 person-years) in a U.S. aluminum industry with spirometry testing followed between 1996-2013. Distributions presented for all workers overall (top left) and clockwise by facility type (smelter, refinery and fabrication).

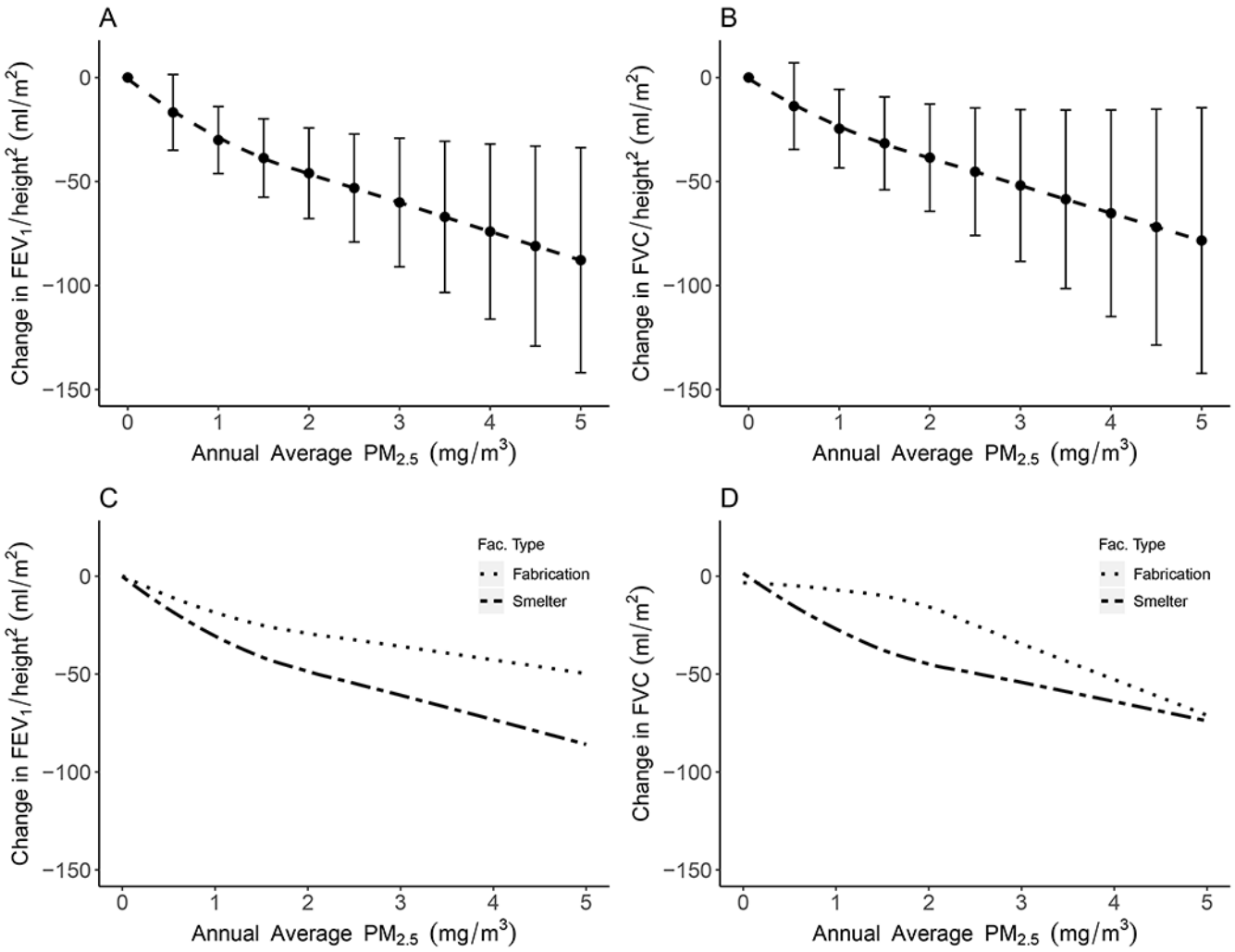

Figure 3:

Change (and 95% CIs) in average predicted FEV_1 (standardized by height squared, ml/m^2) (Figure 3A) and FVC (Figure 3B) corresponding to hypothetical interventions where all workers are exposed to increasing exposure concentrations, compared to always unexposed. Change (and 95% CIs) in average predicted FEV_1 (Figure 3C) and FVC (Figure 3D) corresponding to the same hypothetical interventions where workers are exposed to increasing exposure concentrations are also presented by facility type.

Table 1:

Demographic characteristics of a cohort of workers in the U.S. aluminum manufacturing cohort (n=6485) followed between 1996 and 2013.

Characteristic	N (%)	Mean (SD)	Median (range)
White	5574 (86.0)		
Facility type			
Smelter	3712 (57.2)		
Fabrication	1931 (29.8)		
Refinery	842 (13.0)		
Smoking status			
Ever	2569 (39.6)		
Never	1798 (27.8)		
Missing	2118 (32.6)		
Age (years)*		43.6 (9.9)	
Follow-up time		7.8 (4.6)	
Prevalent hires	4770 (73.6)		
Total tenure**		21.8 (12.8)	
Risk score*		0.79 (0.85)	
FEV_1 (L)*		3.8 (0.7)	
Percent predicted FEV_1*		93.7 (13.7)	
FVC (L)*		4.9 (0.9)	
Percent predicted FVC*		94.0 (12.8)	
Number of Spirometry measures per participant			3 (2, 16)

*At baseline

**Including years of employment prior to beginning of follow-up for those hired before 1996

Table 2:

Predicted FEV_1 and FVC after 10 years of follow-up under hypothetical interventions with a limit on exposure, and change (with 95% CI) compared to the observed natural course.

	FEV_1				FVC			
Intervention*	**FEV_1/height^2 (ml/m^2)**	**Percent Predicted****	**ΔFEV_1/height^2 (ml/m^2)**	**95 % CI**	**FVC/height^2 (ml/m^2)**	**Percent Predicted***	**ΔVC/height^2 (ml/m^2)**	**95 % CI**
Natural Course	1121.6	91.9	Referent	Referent	1449.2	92.0	Referent	Referent
$PM_{2.5}$≤0.51 mg/m^3	1126.1	92.4	4.5	0.8, 8.2	1453.0	92.3	3.8	−0.7, 8.2
$PM_{2.5}$≤0.33 mg/m^3	1130.5	92.7	8.9	3.9, 13.9	1457.4	92.5	8.2	2.3, 14.1
$PM_{2.5}$≤0.14 mg/m^3	1131.9	92.8	10.3	4.1, 16.5	1458.1	92.5	8.9	1.7, 16.1
$PM_{2.5}$≤0.05 mg/m^3	1133.2	92.9	11.6	4.2, 19.0	1458.9	92.6	9.7	1.2, 18.2
$PM_{2.5}$=0 mg/m^3	1135.5	93.1	13.9	2.8, 25.0	1459.5	92.6	10.3	−2.4, 23.0

*Limits corresponding to the 75th, 50th, 25th and 10th percentile of the observed exposure distribution as well as an intervention of 0 exposure.

**Percentage of predicted values for each of the counterfactual values of FEV_1 and FVC under each intervention are based on percentages estimated using equations by Hankinson et al. (1999).