

## ORIGINAL RESEARCH

# Accelerated lung function decline in an aluminium manufacturing industry cohort exposed to PM<sub>2.5</sub>: an application of the parametric g-formula

Andreas M Neophytou <sup>1,2</sup>, Sadie Costello,<sup>2</sup> Sally Picciotto,<sup>2</sup> Elizabeth M Noth,<sup>2</sup> Sa Liu,<sup>2,3</sup> Liza Lutzker,<sup>2</sup> John R Balmes,<sup>2</sup> Katharine Hammond,<sup>2</sup> Mark R Cullen,<sup>4</sup> Ellen A Eisen<sup>2</sup>

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<sup>1</sup>Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, Colorado, USA

<sup>2</sup>School of Public Health, Division of Environmental Health Sciences, University of California Berkeley, Berkeley, California, USA

<sup>3</sup>School of Health Sciences, Purdue University, West Lafayette, Indiana, USA

<sup>4</sup>Department of Internal Medicine, Stanford University School of Medicine, Stanford, California, USA

## Correspondence to

Dr Andreas M Neophytou, Environmental and Radiological Health Sciences, Colorado State University, Fort Collins, CO 80523, USA; [andreas.neophytou@colostate.edu](mailto:andreas.neophytou@colostate.edu)

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## 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<sub>2.5</sub>) while adjusting for the healthy worker survivor effect.

**Methods** Analyses were performed in a cohort of 6485 hourly male workers in an aluminium manufacturing company in the USA, followed between 1996 and 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.

**Results** A counterfactual scenario envisioning a limit on exposure equivalent to the 10th percentile of the observed exposure distribution of 0.05 mg/m<sup>3</sup> was associated with an improvement in forced expiratory volume in one second (FEV<sub>1</sub>) equivalent to 37.6 mL (95% CI 13.6 to 61.6) after 10 years of follow-up when compared with 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<sub>1</sub> 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<sub>2.5</sub> exposure in the aluminium 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.<sup>1–4</sup> The American Thoracic Society has reported that at least 15% of both asthma and COPD in the general population are work-related,<sup>1</sup> while a recent European study attributed over 20% of COPD incidence, to a set of occupational exposures.<sup>5</sup> These reports indicate the considerable burden of respiratory disease attributable

## 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 aluminium 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.

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.<sup>6–8</sup>

Previous studies of occupational exposures to particles from combustion sources, metals and mine dust have shown associations with obstructive airways outcomes.<sup>9–11</sup> Evidence regarding the relationship of occupational dust exposures and lung function has been accumulating over the past decades, including reports from longitudinal studies.<sup>12–14</sup> 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<sup>15–17</sup> indicates the need for intervention measures in this particular industrial sector.<sup>18</sup> 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.<sup>19</sup> This type of bias is not adequately addressed by traditional regression approaches for longitudinal data or approaches such as generalised estimating equations,<sup>20</sup> which have typically been used in the existing literature.

In the current study, we assess the relationship between decline in lung function (forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC)) over time and exposure to particulate matter with aerodynamic diameter 2.5 µm or less (PM<sub>2.5</sub>) in the American Manufacturing Cohort, a dynamic cohort of workers in the US aluminium industry.<sup>21</sup> 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<sub>1</sub> 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 eight US facilities of the same aluminium manufacturing company, with available PM<sub>2.5</sub> exposure and spirometry data. The population giving rise to the sample in the current study is described in more detail elsewhere.<sup>21 22</sup> 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 1 January 1996 and 31 December 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 1 January 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 31 December 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 programme, 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.<sup>23</sup> FEV<sub>1</sub> 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 V. 5.0, Verscend

Technologies, Waltham, Massachusetts) 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<sub>2.5</sub> in this cohort,<sup>22</sup> and it was also significantly associated with FEV<sub>1</sub> and FVC in this dataset (online supplementary table S1).

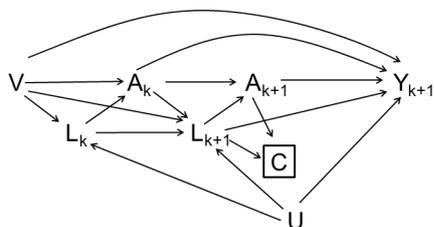
### Exposure assessment

Average annual PM<sub>2.5</sub> concentrations (in mg/m<sup>3</sup>) were assigned to distinct exposure groups within each facility to create a job-exposure matrix. The exposure assessment has been described in detail elsewhere.<sup>24</sup> 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<sub>2.5</sub> collected by our research team in 2010–2011. The % of TPM that was composed of PM<sub>2.5</sub> was determined from colocated TPM and PM<sub>2.5</sub> measurements and was used to derive model estimates for PM<sub>2.5</sub> for distinct exposure groups that lacked PM<sub>2.5</sub> 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<sup>25</sup> and with a respirator protection factor reflective of respirator use under actual conditions in the workplace.<sup>26</sup>

### Statistical analyses

We applied the parametric g-formula to assess the effects that hypothetical interventions to reduce PM<sub>2.5</sub> exposure would have on lung function as measured by FEV<sub>1</sub> 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<sub>1</sub> 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<sup>3</sup> in 0.5 mg/m<sup>3</sup> 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 25th (0.14 mg/m<sup>3</sup>) and 75th (0.51 mg/m<sup>3</sup>) percentiles of the observed exposure distribution were assessed to explore potential effects equivalent to an IQR 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 10th, 25th, 50th and 75th percentiles of the observed distribution of PM<sub>2.5</sub> exposures). Predicted FEV<sub>1</sub> and FVC values under these interventions were compared with 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.*<sup>27</sup> Briefly, the process involved fitting parametric models for the outcome (linear regression model for height-standardised FEV<sub>1</sub> 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<sub>2.5</sub> exposure). Models were fit pooled on the person-year level, conditional on covariate histories (past risk score and PM<sub>2.5</sub> exposures) and the following baseline covariates: age and calendar time (both as



**Figure 1** Directed acyclic graph depicting the assumed relationships between baseline covariates (V), PM<sub>2.5</sub> 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. PM<sub>2.5</sub>, particulate matter with aerodynamic diameter 2.5 µm or less.

cubic spline functions), indicator variable for race (white versus 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 online 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 pseudosample, 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 (ie, 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 pseudoworker or until they were predicted to be censored due to death or termination of employment. The counterfactual average FEV<sub>1</sub> 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<sub>1</sub> and FVC, we also generated estimates of per cent predicted FEV<sub>1</sub> and FVC values for each individual based on the reference equations described by Hankinson *et al.*<sup>28</sup>

The entire above process was repeated in 200 bootstrap samples and the SD of the estimates from the bootstrap samples was used as an estimate of the SE,<sup>29</sup> which was then used to generate 95% CI. In a sensitivity analysis, we also estimated the predicted FEV<sub>1</sub> 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, V. 9.4 (SAS Institute, Cary, North Carolina, USA).

**Table 1** Demographic characteristics of a cohort of workers in the US aluminium 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 (years)		7.8 (4.6)	
Prevalent hires	4770 (73.6)		
Total tenure (years)†		21.8 (12.8)	
Risk score*		0.79 (0.85)	
FEV <sub>1</sub> (L)*		3.8 (0.7)	
Per cent predicted FEV <sub>1</sub> *		93.7 (13.7)	
FVC (L)*		4.9 (0.9)	
Per cent 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.

FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity.

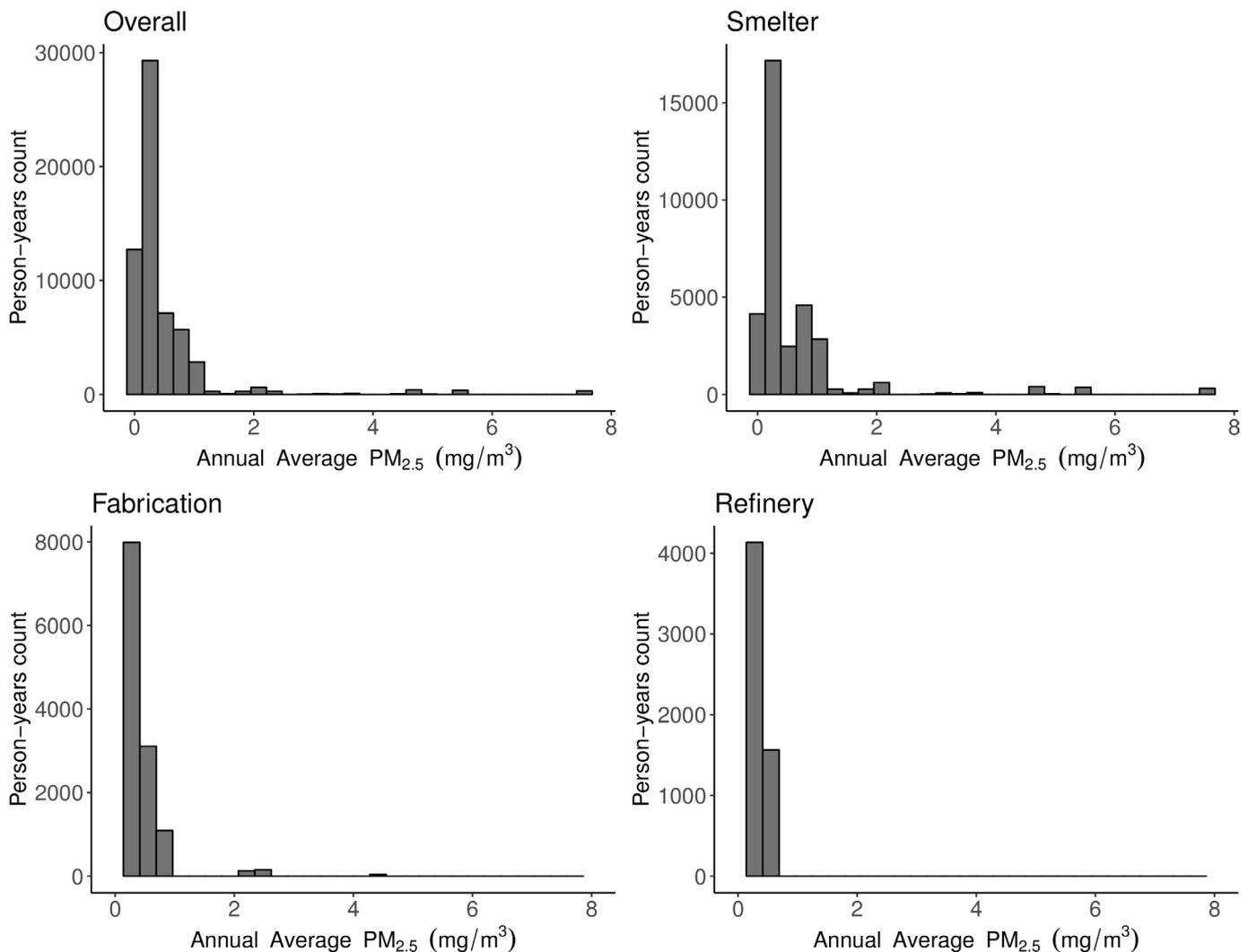
## RESULTS

Demographic characteristics of the study population are summarised 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 per cent predicted FEV<sub>1</sub> at baseline was 93.7% (median of 93.9% and an IQR of 85.2%–102.7%), while the corresponding numbers for FVC were 94.0% (median of 93.9% and an IQR of 85.8%–101.9%).

[Figure 2](#) illustrates observed PM<sub>2.5</sub> 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 with other facility types with higher exposures on average (mean (SD) of 0.64 (1.05) mg/m<sup>3</sup>, compared with 0.27 (0.37) mg/m<sup>3</sup> and 0.32 (0.10) mg/m<sup>3</sup> for fabrication and refinery, respectively).

Estimates for counterfactual FEV<sub>1</sub> and FVC under 11 scenarios where workers are always exposed to increasing levels of PM<sub>2.5</sub> (range 0–5 mg/m<sup>3</sup>) along with Loess smoothing curves are summarised in [figure 3](#), overall ([figure 3A and B](#) for FEV<sub>1</sub> and FVC respectively) and by facility type ([figure 3C and D](#) for FEV<sub>1</sub> and FVC, respectively). Results indicate a steeper relative decline in smelting facilities compared with fabrication. The overall additional mean decrease in FEV<sub>1</sub>/height<sup>2</sup> after 10 years if all workers were exposed at 0.51 mg/m<sup>3</sup> PM<sub>2.5</sub> (corresponding to the 75th percentile of the overall exposure distribution) compared with exposure at 0.14 mg/m<sup>3</sup> (the 25th percentile) was 12.5 mL/m<sup>2</sup> (95% CI –24.6 to 0.4), which would be equivalent to an additional loss of 40.5 mL (95% CI –79.6 to 1.4) in FEV<sub>1</sub> for a 1.8 m tall man.

[Table 2](#) summarises the estimates of mean FEV<sub>1</sub> and FVC under hypothetical interventions of a series of exposure limits as well as corresponding per cent predicted values after 10 years



**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 US aluminium industry with spirometry testing followed between 1996 and 2013. Distributions presented for all workers overall (top left) and clockwise by facility type (smelter, refinery and fabrication).  $PM_{2.5}$ , particulate matter with aerodynamic diameter 2.5  $\mu\text{m}$  or less.

of follow-up. The counterfactual change in  $FEV_1$  after 10 years under a hypothetical intervention setting a limit at 0.05  $\text{mg}/\text{m}^3$  (corresponding to the 10th percentile of the overall exposure distribution) compared with the natural course was an improvement of 11.6 mL (95% CI 4.2 to 19.0), which would be equivalent to an improvement of 37.6 mL (95% CI 13.6 to 63.6) in  $FEV_1$  for a 1.8 m tall man. The observed mean predicted  $FEV_1$  at baseline was 93.7% compared with 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 with the observed of 91.9%.

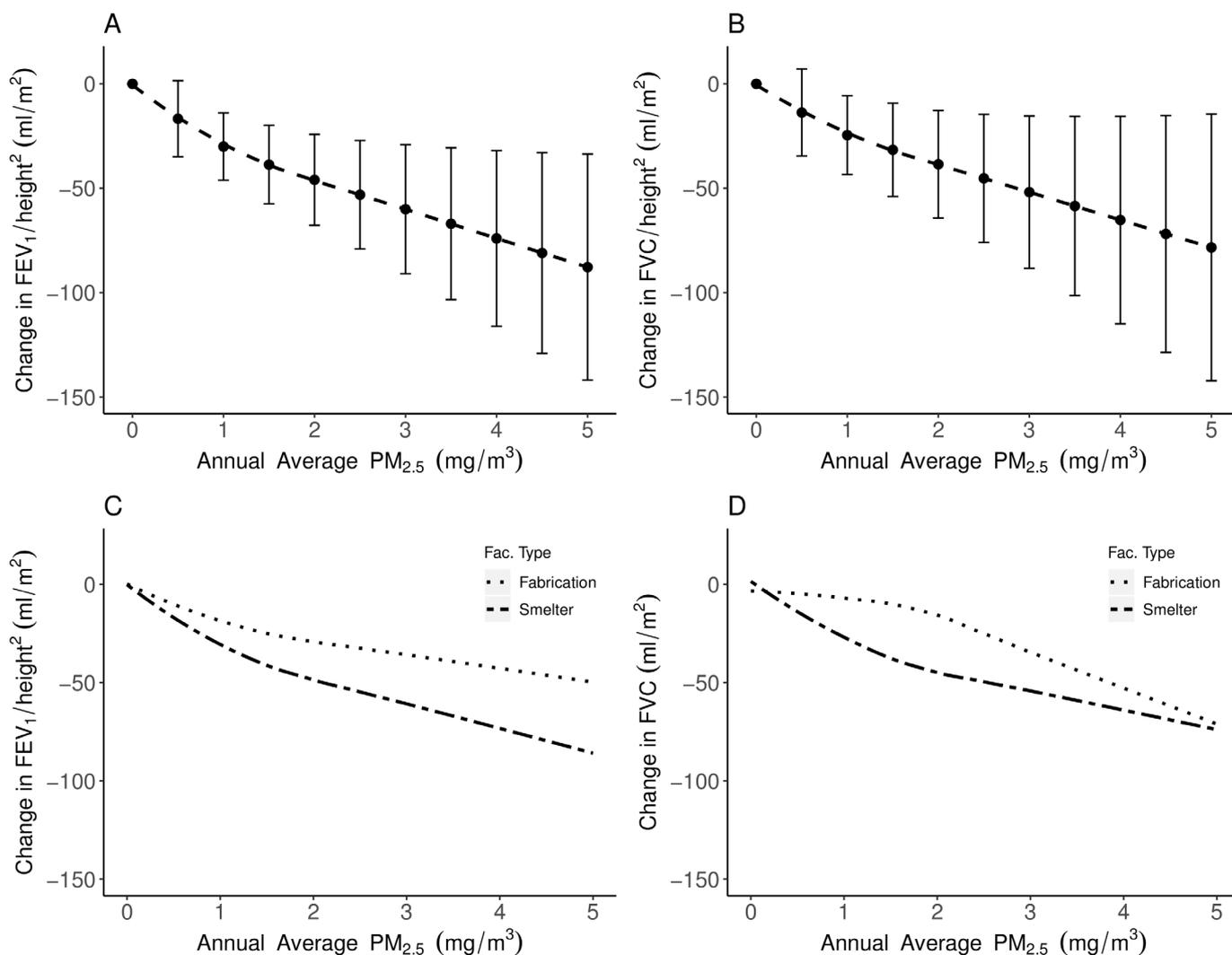
Results from a sensitivity analysis using multiple imputation for missing smoking data at baseline were very similar (online supplemental table S2), while results assuming no workers were censored after 10 years, yielded stronger associations with exposure (online supplemental table S3).

## DISCUSSION

We observed a reduction in lung function associated with increasing occupational  $PM_{2.5}$  exposures in a cohort of active US aluminium 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 1.8 m tall man over 10 years, compared with 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 with the expected decline with age (based on the Hankinson reference values for a 1.8 m tall man<sup>28</sup>). 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 aluminium 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



**Figure 3** Change (and 95% CIs) in average predicted FEV<sub>1</sub> (standardised by height squared, mL/m<sup>2</sup>) (A) and FVC (B) corresponding to hypothetical interventions where all workers are exposed to increasing exposure concentrations, compared with always unexposed. Change (and 95% CIs) in average predicted FEV<sub>1</sub> (C) and FVC (D) corresponding to the same hypothetical interventions where workers are exposed to increasing exposure concentrations are also presented by facility type. FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; PM<sub>2.5</sub>, particulate matter with aerodynamic diameter 2.5 µm or less.

respiratory outcomes, including excess COPD mortality, have been previously reported in the industry.<sup>30–33</sup> Although potroom exposures occurring in smelting facilities are reported to be especially harmful to respiratory health,<sup>32 34 35</sup> other exposures in smelters may also lead to adverse outcomes.<sup>36</sup>

PM in aluminium 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

**Table 2** Predicted FEV<sub>1</sub> and FVC after 10 years of follow-up under hypothetical interventions with a limit on exposure, and change (with 95% CI) compared with the observed natural course

Intervention*	FEV <sub>1</sub>				FVC			
	FEV <sub>1</sub> /height <sup>2</sup> (mL/m <sup>2</sup> )	Per cent predicted†	ΔFEV <sub>1</sub> /height <sup>2</sup> (mL/m <sup>2</sup> )	95% CI	FVC/height <sup>2</sup> (mL/m <sup>2</sup> )	Per cent predicted*	ΔFVC/height <sup>2</sup> (mL/m <sup>2</sup> )	95% CI
Natural course	1121.6	91.9	Referent	Referent	1449.2	92.0	Referent	Referent
PM <sub>2.5</sub> ≤ 0.51 mg/m <sup>3</sup>	1126.1	92.4	4.5	0.8 to 8.2	1453.0	92.3	3.8	-0.7 to 8.2
PM <sub>2.5</sub> ≤ 0.33 mg/m <sup>3</sup>	1130.5	92.7	8.9	3.9 to 13.9	1457.4	92.5	8.2	2.3 to 14.1
PM <sub>2.5</sub> ≤ 0.14 mg/m <sup>3</sup>	1131.9	92.8	10.3	4.1 to 16.5	1458.1	92.5	8.9	1.7 to 16.1
PM <sub>2.5</sub> ≤ 0.05 mg/m <sup>3</sup>	1133.2	92.9	11.6	4.2 to 19.0	1458.9	92.6	9.7	1.2 to 18.2
PM <sub>2.5</sub> = 0 mg/m <sup>3</sup>	1135.5	93.1	13.9	2.8 to 25.0	1459.5	92.6	10.3	-2.4 to 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<sub>1</sub> and FVC under each intervention are based on percentages estimated using equations by Hankinson *et al* (1999).<sup>28</sup> FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; PM<sub>2.5</sub>, particulate matter with aerodynamic diameter 2.5 µm or less.

concentration compared with 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<sub>2.5</sub> 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<sup>37</sup> and also shown to be affected by previous exposure in this cohort.<sup>22</sup> 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,<sup>38</sup> 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 hypothesised interventions (such as the equivalent of the 10th percentile of the observed distribution at 0.05 mg/m<sup>3</sup>) with their use alone. It should also be noted that general occupational PM<sub>2.5</sub> exposures per se are not directly regulated in the USA, 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 does have a permissible exposure limit for 'particulates not otherwise regulated' of 15 mg/m<sup>3</sup> for total dust and 5 mg/m<sup>3</sup> for the respirable fraction (defined as the subfraction of inhaled particles that penetrates into the alveolar region of the lung).<sup>39</sup> 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 hypothesised, and 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 (ie, 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 and so on), so quantitative analyses were limited to PM<sub>2.5</sub>. Last, 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<sub>2.5</sub> exposure in a US aluminium manufacturing cohort. Our results indicate an acceleration of lung function decline associated with higher PM<sub>2.5</sub> 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.

**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 KH 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.

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**Data availability statement** 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.

#### ORCID iD

Andreas M Neophytou <http://orcid.org/0000-0001-7327-5361>

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