Associations of PM$_{2.5}$ with Chronic Obstructive Pulmonary Disease in Shipyard Workers: A Cohort Study

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**ABSTRACT**

The association between lung deposition of particulate matter with an aerodynamic diameter less than 2.5 µm (PM$_{2.5}$) from welding fumes and lung function is unclear. We conducted a cohort study with a follow-up of 4 years in 115 shipyard workers to investigate the incidence rate of chronic obstructive pulmonary disease (COPD), and to evaluate the effects of welding fume PM$_{2.5}$ deposition on fractional exhaled nitric oxide (FeNO), lung function, and blood pressure using generalized estimating equation models. Personal exposure to welding fumes was measured, and deposition fractions of inhaled welding fume PM$_{2.5}$ in lung regions were estimated using multiple-path particle dosimetry. We observed the overall incidence rate of COPD to be 2.51 cases per 100 person-years. The incidence rate was higher in welding workers than in office workers and higher in non-smokers compared to smokers. We observed that a 1-µg m$^{-3}$ increase in PM$_{2.5}$ deposition in lung regions (total lung, and head and nasal, tracheobronchial, and alveolar regions) was associated with decreases ($β$ coefficients) in FeNO, FVC, FEV$_{1}$, PEF, FEF$_{25\%-75\%}$, FEF$_{25\%}$, and FEF$_{50\%}$ (all $p < 0.05$). We observed that a 1-µg m$^{-3}$ increase in PM$_{2.5}$ deposition in lung regions (total lung, and head and nasal, tracheobronchial, and alveolar regions) was associated with decreases ($β$ coefficients) in FeNO, FVC, FEV$_{1}$, PEF, FEF$_{25\%-75\%}$, FEF$_{25\%}$, and FEF$_{50\%}$ (all $p < 0.05$). We observed
that the absolute values of β coefficients decreased as follows: alveolar > head and nasal > tracheobronchial > total lung regions. Higher incidence rates of COPD were observed in non-smokers and welders, which associated with lung function declines due to PM$_{2.5}$ exposure. Pulmonary effects by welding fume PM$_{2.5}$ in occupational settings is an urgent occupational issue for worker health protection.

**Keywords:** Air pollution, Alveoli, COPD, Particulate matter, Welding fume

### ABBREVIATION LIST

- FEF$_{25\%}$, forced expiratory flow (FEF) during 25% of the forced vital capacity; FEF$_{50\%}$, FEF during 50% of the forced vital capacity; FEF$_{75\%}$, FEF during 75% of the forced vital capacity; FEF$_{25\%-75\%}$, FEF between 25% and 75% of the forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; PM$_{2.5}$, particulate matter (PM) less than 2.5 µm in aerodynamic diameter.

### 1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterized by poorly reversible airflow limitations associated with increased inflammatory responses to noxious particles or gases in the respiratory tract (Vestbo et al., 2013). In 2019, the World Health Organization estimated that COPD ranked third in global causes of mortality (WHO, 2020). Smoking is considered a major risk factor for COPD. Nevertheless, according to the American Thoracic Society (ATS), occupational-related COPD cases contribute to approximately 15% of total COPD (Melville et al., 2010). Occupational exposures to gases, vapors, dust, and welding fumes, notably in non-smokers, could result in a 1.32-fold increased risk of COPD mortality (95% confidence interval (CI): 1.18–1.47) (Torén and Järvholm, 2014).

Chronic exposure to metal fumes, which contain numerous metals such as zinc, manganese, copper, cadmium, nickel, and aluminum, may cause serious health problems, especially in welding workers (Lai et al., 2021). Welders are regarded as a population at risk for COPD due to high levels of metal fume particulate matter less than 2.5 µm in aerodynamic diameter (PM$_{2.5}$) in their breathing zone. Notably, previous studies showed that exposure to welding fumes was associated with declines in lung function in welders (Christensen et al., 2008). It was reported that the prevalence of COPD in welding workers was approximately 15.2% (Koh et al., 2015; Minov et al., 2015). Moreover, the prevalence of COPD in welding workers was higher than in office workers ($p < 0.05$) (Minov et al., 2015). Despite the high burden of COPD in welding workers, the welding-related incidence rate of COPD is still unavailable.

Multiple-path particle dosimetry (MPPD) is a computational algorithm to estimate PM deposition in lung regions (Asgharian et al., 2001). Specifically, an MPPD study demonstrated that coarse particles are mostly deposited in the head and nasal region, whereas ultrafine particles are deposited in deeper parts of the airway (i.e., the tracheobronchial and alveolar regions) (Manojkumar et al., 2018). Another MPPD study found that PM deposition was higher during the haze period compared to the non-haze period (Behera et al., 2015). However, associations between PM deposition of welding fume PM$_{2.5}$ in lung regions and respiratory health are poorly understood.

Shipyards are major sources of exposure to welding fumes as determined in previous studies (Jeong et al., 2016; Chuang et al., 2018; Su et al., 2019). Our previous findings demonstrated that exposure to metal fume PM$_{2.5}$ increased systemic oxidative stress and inflammation in shipyard workers (Lai et al., 2016). In this study, a cohort study was conducted with a follow-up of 4 years in a shipyard. The objective of this study was to examine the incidence rate of COPD, and to evaluate the effects of welding fume PM$_{2.5}$ on lung function and blood pressure in these workers.
2. METHODS

2.1 Study Subjects
To examine the effects of welding fumes on workers in a shipyard located in northern Taiwan, a dynamic cohort study was conducted from 2014 to 2017. There were 115 subjects in total enrolled in the study. Exclusion criteria for subjects were being aged younger than 20 or older than 70 years, having comorbidities (diabetes mellitus, heart failure, or coronary artery disease), and having experienced exacerbations within 1 month prior to the study. Data on the smoking status (non-smoker, ex-smoker, or current smoker) and the use of personal protective masks were collected. Tungsten inert gas (TIG) welding was the main welding method used at the shipyard (Lai et al., 2016). Welding rods used in the present study mainly contained manganese, silicon, nickel, chromium, and molybdenum (Lin and Pan, 2012). The Ethics Committee of the Joint Institutional Review Board of Tri-Service General Hospital (IRB no. 1-102-05-013) approved the study protocol. All subjects obtained oral and written information and provided informed consent prior to inclusion. The methods were performed according to approved guidelines.

2.2 Personal PM$_{2.5}$ Exposure
The individual exposure assessment for PM$_{2.5}$ was conducted for each participant as previously demonstrated (Chuang et al., 2018). Briefly, individual exposure to welding fume PM$_{2.5}$ was obtained from a whole working day. Consecutive 8-h personal welding fume PM$_{2.5}$ sampling was performed (09:00–17:00, Monday) by a model 200 Personal Environmental Monitor (PEM) equipped with an AirChek® XR5000 air sampling pump (SKC, Eighty-Four, PA, USA) at a flow rate of 2 L min$^{-1}$. Next, PM$_{2.5}$ was collected onto Teflon filter substrates (37 mm, pore size: 2-µm, Pall, Ann Arbor, MI, USA) within the breathing zone. We measured the personal exposure to welding fume PM$_{2.5}$ once per year (the same month) for 4 years.

2.3 MPPD Model
Deposition fractions of inhaled welding fume PM$_{2.5}$ in the human lungs (i.e., total lung, head and nasal, tracheobronchial, and alveolar regions) were estimated using the MPPD computational model (MPPD vers. 3.04 for Windows, Applied Research Associates, Albuquerque, NM, USA) as previously reported (Asgharian et al., 2001). Briefly, deposition fractions were estimated for 3300 ml of functional residual capacity. The upper respiratory tract volume was predicted to be 50 mL. We assumed a tidal volume of 625 mL, a respiratory rate of 12 breaths min$^{-1}$, and an inspiratory to expiratory ratio of 1:2 with no pause between inhalation and exhalation. PM$_{2.5}$ deposition, which was assumed to enter the lungs via the nasal airway, was estimated to have various diameter sizes (0.01–1 µm).

2.4 Fractional Exhaled Nitric Oxide (FeNO) Measurement
A handheld FeNO device (NObreath, Bedfont Scientific, Kent, UK) was employed to quantify FeNO in accordance with ATS guidelines (ATS, 2003). The method of FeNO detection was previously described (Fan et al., 2018). FeNO was measured at the beginning of the day following the previous day of exposure (Tuesday morning; post-exposure). FeNO measurements in each subject were conducted in triplicate. Values were averaged as the response.

2.5 Lung Function
Spirometry was conducted on shipyard workers in accordance with the ATS/European Respiratory Society guidelines on Tuesday morning (1 day post-exposure) (Miller et al., 2005). The tests were conducted by a licensed respiratory therapist. Lung function parameters included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV$_1$), the FEV$_1$/FVC ratio, peak expiratory flow (PEF), forced expiratory flow (FEF) between 25% and 75% of the FVC (FEF$_{25\%}-_{75\%}$), FEF during 25% of the FVC (FEF$_{25\%}$), FEF during 50% of the FVC (FEF$_{50\%}$), and FEF during 75% of the FVC (FEF$_{75\%}$). COPD was determined based on the post-bronchodilator FEV$_1$/FVC < 0.70 according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Vestbo et al., 2013).
2.6 Statistical Analysis

Tests of normality were used to identify if the data had a normal distribution. To minimize the influence of outliers, extreme values outside the 1 and 99 percentiles were replaced by a winsorization method (Tsai et al., 2012). Incidence rates of COPD were determined by dividing the number of incident cases by the total person-years of subjects at risk and are expressed per 100 person-years. Generalized estimating equation (GEE) models were employed to investigate associations of PM$_{2.5}$ with FeNO, lung function, and blood pressure in the overall subject group, healthy subject group (FEV$_1$/FVC ratio $\geq$ 70%), and COPD group (FEV$_1$/FVC ratio $<$ 70%). These associations were expressed as regression coefficients (β) multiplied by the interquartile range (IQR) of welding fume PM$_{2.5}$ levels. These models were adjusted for the test year, age, work type (office or welding), working duration, and smoking status. To examine associations (β coefficients) of PM$_{2.5}$ deposition in lung regions with FeNO, lung function, and blood pressure in the overall subject group, GEE models were employed. These models were adjusted for test year, age, work type (office or welding), working duration, smoking status, and COPD. We also adjusted for protective mask use in these models (Supplementary Material Fig. S1 and Fig. S2). Two-sided $p$ values of $<$ 0.05 were considered statistically significant. Data analyses were conducted by SPSS vers. 22 for Windows statistical software (SPSS, Chicago, IL, USA).

3 RESULTS AND DISCUSSION

3.1 Characteristics of the Study Cohort

To better understand the chronic impacts of welding fume PM$_{2.5}$ in shipyard workers, a cohort study was performed. The characteristics of 115 subjects in our study cohort are summarized in Table 1. The total follow-up time of the subjects was 239 cases per 100 person-years. Overall, subjects had a mean age of 47.1 ± standard deviation (SD) 12.1 years, and 94.9% were men. The average body-mass index (BMI) was 25.35 ± 3.45 kg m$^{-2}$. For the smoking status, 34.2% of the workers were current smokers, 18.5% were ex-smokers, and 47.3% were non-smokers. Welding workers comprised 73.5% of subjects and office workers comprised 26.5%. Their average working duration was 22.9 ± 16.1 years. Their average FeNO was 14.85 ± 12.12 ppb. In terms of lung function, subjects had a mean FVC of 3.77 ± 0.50 L, a mean FEV$_1$ of 3.22 ± 0.57 L, and FEV$_1$/FVC ratio of 76.24% ± 5.36%. Mean values of the PEF, FEF$_{25-75}$%, FEF$_{50}$%, and FEF$_{75}$% were 8.42 ± 0.82, 3.98 ± 0.71, 7.62 ± 0.68, 5.02 ± 0.72, and 2.28 ± 1.08 L s$^{-1}$, respectively. The mean systolic pressure was 132.86 ± 18.97 mmHg, and the mean diastolic pressure was 80.04 ± 12.64 mmHg.

The percentage of protective mask use in shipyard workers was 79.7%. The average personal exposure concentration to welding fume PM$_{2.5}$ was 999.38 ± 1168.93 µg m$^{-3}$, whereas the IQR value was 1309.03 µg m$^{-3}$. As depicted in Table 2, the deposition levels of PM$_{2.5}$ in the total lung, head and nasal, tracheobronchial, and alveolar regions were 941.51 ± 1101.25, 363.17 ± 424.79, 377.46 ± 441.51, and 200.77 ± 234.84 µg m$^{-3}$, respectively.

Since most of the metal fume particles were less than 2.5 µm, we opted to use welding fume PM$_{2.5}$ as the exposure assessment. We found that the average individual exposure to welding fume PM$_{2.5}$ was 999.38 µg m$^{-3}$, which was lower than the U.S. Occupational Safety and Health Administration permissible exposure limits of 5 mg m$^{-3}$, averaged over an 8-hour period, for respirable fraction particles not specifically regulated (NIOSH, 2011; CDC, 2018; NIOSH, 2018; Lai et al., 2021). Nevertheless, PM$_{2.5}$ concentrations in this study were higher than in our previous studies which reported that welding fume PM$_{2.5}$ levels ranged 716–755 µg m$^{-3}$ (Lai et al., 2016; Lai et al., 2021). We observed associations between welding fumes and adverse health effects by cross-sectional studies (Koh et al., 2015; Li et al., 2015); however, the long-term impacts on respiratory health among the workers remain unclear.

3.2 Incidence Rate of COPD

Six subjects developed COPD during the 4-year follow-up period. As observed in Table 3, the overall incidence rate of COPD was 2.51 cases per 100 person-years. The incidence rate of COPD in current smokers and ex-smokers (1.41 cases per 100 person-years) was lower than in non-smoking workers (4.12 cases per 100 person-years). Furthermore, the incidence rate of COPD in welding workers (2.96 cases per 100 person-years) was higher than that in office workers
Table 1. Characteristics of cohort subjects in the shipyard.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>115</td>
</tr>
<tr>
<td>Person-years</td>
<td>239</td>
</tr>
<tr>
<td>Male (%)</td>
<td>94.9</td>
</tr>
<tr>
<td>Age (years) ± standard deviation (SD)</td>
<td>47.1 ± 12.1</td>
</tr>
<tr>
<td>Body-mass index (kg m(^{-2})) ± SD</td>
<td>25.35 ± 3.45</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>34.2</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>18.5</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>47.3</td>
</tr>
<tr>
<td>Working duration (years) ± SD</td>
<td>22.9 ± 16.1</td>
</tr>
<tr>
<td>FeNO (ppb) ± SD</td>
<td>14.85 ± 12.12</td>
</tr>
<tr>
<td>Work type (%)</td>
<td></td>
</tr>
<tr>
<td>Welding worker</td>
<td>73.5</td>
</tr>
<tr>
<td>Office worker</td>
<td>26.5</td>
</tr>
<tr>
<td>Lung function ± SD</td>
<td></td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.77 ± 0.50</td>
</tr>
<tr>
<td>FEV(_1) (L)</td>
<td>3.22 ± 0.57</td>
</tr>
<tr>
<td>FEV(_1)/FVC (%)</td>
<td>76.24 ± 5.36</td>
</tr>
<tr>
<td>Peak expiratory flow (L s(^{-1}))</td>
<td>8.42 ± 0.82</td>
</tr>
<tr>
<td>FEF(_{25%-75%}) (L s(^{-1}))</td>
<td>3.98 ± 0.71</td>
</tr>
<tr>
<td>FEF(_{25%}) (L s(^{-1}))</td>
<td>7.62 ± 0.68</td>
</tr>
<tr>
<td>FEF(_{50%}) (L s(^{-1}))</td>
<td>5.02 ± 0.72</td>
</tr>
<tr>
<td>FEF(_{75%}) (L s(^{-1}))</td>
<td>2.28 ± 1.08</td>
</tr>
<tr>
<td>Blood pressure ± SD</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>132.86 ± 18.97</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.04 ± 12.64</td>
</tr>
<tr>
<td>Personal protective mask (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79.7</td>
</tr>
<tr>
<td>No</td>
<td>20.3</td>
</tr>
<tr>
<td>PM(_{2.5}) (µg m(^{-3})) ± SD</td>
<td>999.38 ± 1168.93</td>
</tr>
<tr>
<td>Interquartile range (µg m(^{-3}))</td>
<td>1309.03</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; FEV\(_1\), forced expiratory volume in 1 s; FEF\(_{25\%-75\%}\), forced expiratory flow (FEF) at 25%–75% of FVC; FEF\(_{25\%}\), FEF at 25% of FVC; FEF\(_{50\%}\), FEF at 50% of FVC; FEF\(_{75\%}\), FEF at 75% of FVC; PM\(_{2.5}\), particulate matter less than 2.5 µm in aerodynamic diameter; BP, blood pressure.

Table 2. Particulate matter with an aerodynamic diameter less than 2.5 µm (PM\(_{2.5}\)) deposition in the total lung, head and nasal, tracheobronchial, and alveolar regions.

<table>
<thead>
<tr>
<th>Respiratory tract region</th>
<th>Concentration, µg m(^{-3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung region</td>
<td>941.51 ± 1101.25</td>
</tr>
<tr>
<td>Head and nasal region</td>
<td>363.17 ± 424.79</td>
</tr>
<tr>
<td>Tracheobronchial region</td>
<td>377.46 ± 441.51</td>
</tr>
<tr>
<td>Alveolar region</td>
<td>200.77 ± 234.84</td>
</tr>
</tbody>
</table>

(1.43 cases per 100 person-years). The incidence rate of COPD in workers who used protective masks was 2.51 cases per 100 person-years, whereas the incidence rate of COPD in workers who did not use protective masks was 2.50 cases per 100 person-years.

Previous studies reported that the incidence rate of COPD in the general population ranged 2.6–9.2 cases per 1000 person-years (García Rodríguez et al., 2009; van Durme et al., 2009). Specifically, a prospective cohort involving subjects aged ≥ 55 years based on a Rotterdam study reported that the overall incidence rate of COPD was 9.2 cases per 1000 person-years (95% CI: 8.5–10.0) (van Durme et al., 2009). Another cohort including subjects aged 40–89 years reported...
Table 3. Incidence rates for overall, smoking-specific, work type-specific, and protective mask-specific chronic obstructive pulmonary disease (COPD) per 100 person-years in the study cohort.

<table>
<thead>
<tr>
<th>COPD cases (%)</th>
<th>12.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD incidence rate per 100 person-years</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>2.51</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Current and ex-smokers</td>
<td>1.41</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>4.12</td>
</tr>
<tr>
<td>Work type</td>
<td></td>
</tr>
<tr>
<td>Welding</td>
<td>2.96</td>
</tr>
<tr>
<td>Office</td>
<td>1.43</td>
</tr>
<tr>
<td>Personal protective mask</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.51</td>
</tr>
<tr>
<td>No</td>
<td>2.50</td>
</tr>
</tbody>
</table>

that the incidence rate of COPD was 2.6 cases per 1000 person-years (95% CI: 2.5–2.7) (García Rodríguez et al., 2009). Meanwhile, a cohort including young adults aged 20–44 years showed that the incidence rate of COPD was 2.8 cases per 1000 person-years (95% CI: 2.3–3.3) (de Marco et al., 2007). The results suggested that the COPD incidence rate in shipyard workers was higher than in the general population. Previous studies also demonstrated the association of welding fume exposure with lung function decline and increased risk of COPD (Christensen et al., 2008; Koh et al., 2015; Grahn et al., 2021). Next, we observed the COPD incidence rate was higher in welding workers than in office workers. In a study including non-smoking workers aged 37–59 years, the prevalence of COPD in welding workers was higher than in office workers (p < 0.05) (Minov et al., 2015). Furthermore, a case-control study found that welders had a 6.4-increased odds (95% CI: 1.6–25.5) of developing COPD compared to office workers (Mastrangelo et al., 2003). The present study demonstrated that the incidence rate of COPD was higher in non-smokers than in smokers. This finding suggests that exposure to welding fume PM2.5 could be associated with higher risk of COPD in non-smoking welders than in smoking welders. Previous studies also reported the associations of welding fumes with declining lung function and COPD in non-smoking welders (Koh et al., 2015; Minov et al., 2015). We found that incidence rates of COPD in workers with protective masks and those without protective masks were similar. It was reported that protective mask use was positively associated with FVC (β = 0.263; p < 0.05) (Hamzah et al., 2016).

3.3 Associations of PM2.5 with FeNO and Lung Function

Associations of PM2.5 with FeNO and lung function in the overall subject group, healthy group, and COPD group are demonstrated in Fig. 1. In the overall subject group, we observed that one IQR (1309.03-µg m⁻³) increase in welding fume PM2.5 was associated with a 1.618-ppb decrease in FeNO, a 0.115-L decrease in FVC, a 0.091-L decrease in FEV₁, a 0.520% increase in the FEV₁/FVC ratio, a 0.259-L s⁻¹ decrease in PEF, a 0.096-L s⁻¹ decrease in FEF₂₅%–₇₅%, a 0.215-L s⁻¹ decrease in FEF₂₅%, and a 0.114-L s⁻¹ decrease in FEF₅₀%. In the healthy subject group, we found that one IQR (1450.80-µg m⁻³) increase in welding fume PM2.5 was associated with a 1.925-ppb decrease in FeNO, a 0.121-L decrease in FVC, a 0.102-L decrease in FEV₁, a 0.404% increase in the FEV₁/FVC ratio, a 0.283-L s⁻¹ decrease in PEF, a 0.110-L s⁻¹ decrease in FEF₂₅%–₇₅%, a 0.232-L s⁻¹ decrease in FEF₂₅%, and a 0.124-L s⁻¹ decrease in FEF₅₀%. In the COPD subject group, we observed no significant associations of welding fume PM2.5 with FeNO or lung function.

FeNO is a sensitive noninvasive marker of eosinophilic airway inflammation and asthma (Verini et al., 2010; Riise et al., 2011; Schneider et al., 2013). It was reported that each IQR increase in personal exposure to PM2.5 resulted in a 12.8% increase (95% CI: 5.5%–20.7%) in FeNO (Fan et al., 2018).
Fig. 1. Associations of particulate matter with an aerodynamic diameter less than 2.5 µm (PM$_{2.5}$) with fractional exhaled nitric oxide (FeNO), lung function, and blood pressure in overall cohort subjects, healthy subjects, and chronic obstructive pulmonary disease (COPD) subjects. Data are presented as regression coefficients multiplied by an interquartile range (IQR) increase in PM$_{2.5}$ with the 95% confidence interval (CI). Generalized estimating equations were adjusted for test year, age, work type (office or welding), working duration, and smoking status. Values in bold characters with red color were deemed statistically significant (*$p$ < 0.05).
However, the effects of welding fumes on FeNO are still unclear. Previous studies reported that the association between welding fume PM$_{2.5}$ exposure and FeNO was insignificant (Lehnert et al., 2011; Järvelä et al., 2013; Lai et al., 2021). Moreover, various associated factors could lead to a decrease in FeNO levels such as smoking, physical exercise, and sputum induction (Gabriele et al., 2005; Abba, 2009). Therefore, this association observed in shipyard workers needs further investigation in future studies.

Next, we found that an increase in the IQR of welding fume PM$_{2.5}$ was associated with declines in FVC, FEV$_1$, and PEF in the overall subject group and healthy subject group. This was consistent with previous studies showing declines in FVC, FEV$_1$, and PEF in welders compared to a control group (Meo et al., 2003). It was also reported that FVC, FEV$_1$, and FEF$_{25\%-75\%}$ decreased over the years of welding (Kilburn and Warshaw, 1989; Humerfelt et al., 1993). Together, the reduced FVC, FEV$_1$, and PEF in our study could suggest impairment of pulmonary function in welders. Next, we found that an increase in the IQR of PM$_{2.5}$ was associated with declines in FEF$_{25\%-75\%}$, FEF$_{50\%}$, and FEF$_{50\%}$ in the overall subject group and healthy subject group. Our results were also in line with previous findings which demonstrated that welders had lower levels of FEF$_{25\%-75\%}$ than office workers ($p < 0.05$) (Chuang et al., 2018). A reduction in FEF$_{25\%-75\%}$ with normal FEV$_1$, FVC, and FEV$_1$/FVC could be a sensitive marker of small and distal airway obstruction (Marseglia et al., 2007; Raji et al., 2018). Impaired FEF$_{25\%-75\%}$ was thus employed to detect early stages of obstructive airway disease (asthma and COPD) (Riley et al., 2015; Kwon et al., 2020). It was also reported that exposure to high levels of welding fumes resulted in 3.8-fold increased odds (95% CI: 1.03–16.02) of COPD compared to exposure to low levels of welding fumes (Koh et al., 2015). Furthermore, occupational exposure to dust and fume was associated with an increased mortality of COPD (Torén and Järvelom, 2014). It was reported that exposure to welding fumes could lead to increases in oxidative stress biomarkers (i.e., H$_2$O$_2$ and 8-hydroxy-8-deoxyguanosine (OHdG)) (Graczyk et al., 2016; Lee et al., 2013). These reactive oxygen species (ROS) were associated with reduced lung function (i.e., FEV$_1$ and FVC) (Schünemann et al., 1997; Ochs-Balcom et al., 2005) and COPD (Montuschi et al., 2000; Kinnula et al., 2007). However, a positive association was observed between welding fume PM$_{2.5}$ and the FEV$_1$/FVC ratio in subjects. This could have been due to a decrease in the magnitude of FVC compared to FEV$_1$ (Barreiro and Perillo, 2004; Johnson and Theurer, 2014). Previous studies also demonstrated an annual increase of the FEV$_1$/FVC ratio after exposure to welding fumes (Mur et al., 1989; Szram et al., 2013). Meanwhile, another study reported no significant association between exposure to welding fumes and the FEV$_1$/FVC ratio (Christensen et al., 2008). This association thus needs to be clarified in future works. Together, our findings imply that exposure to chronic welding fume PM$_{2.5}$ could lead to reduced lung function, small airway obstruction, and COPD.

### 3.4 Associations of PM$_{2.5}$ Deposition with FeNO and Lung Function

Particle deposition in lung regions is vital for understanding the mechanism of declining lung function. As depicted in Fig. 2, we observed that a 1-μg m$^{-3}$ increase in welding fume PM$_{2.5}$ deposition in lung regions (i.e., the total lung region, the head and nasal region, the tracheobronchial region, and the alveolar region) was associated with decreases in FeNO, FVC, FEV$_1$, PEF, FEF$_{25\%-75\%}$, FEF$_{50\%}$, and FEF$_{50\%}$, and was associated with an increase in the FEV$_1$/FVC ratio ($\beta$ coefficients). Importantly, we found that the absolute values of $\beta$ coefficients decreased in the following order: alveolar > head and nasal > tracheobronchial > total lung region. Therefore, our results suggested that metal fume PM$_{2.5}$ deposition in the alveolar region was associated with the higher risk of COPD compared to other lung regions. This was consistent with our previous study which reported significant associations of PM$_{2.5}$ deposition in the alveolar region of the lung lobes with emphysema severity and COPD (Tung et al., 2021). Furthermore, a previous study demonstrated that cigarette smoke particles are mostly deposited in the alveolar region (Sahu et al., 2013). It was reported that deposition fractions of cigarette smoke in the head and nasal, tracheobronchial, and alveolar regions were 0.163, 0.152, and 0.298, respectively (Sahu et al., 2013). The alveolar region plays an important role in the toxicological effects of inhaled welding fumes due to its permeability (Fröhlich and Salar-Bezhadi, 2014). Welding fumes can affect the alveolar epithelium through endocytosis, oxidative stress, and proinflammatory mechanisms (Suri and Grigg, 2016; Yan et al., 2016; Wang et al., 2020). Furthermore, mitochondrial ROS can lead to alveolar smooth muscle...
Fig. 2. Associations (β coefficient) of particulate matter with an aerodynamic diameter less than 2.5 µm (PM$_{2.5}$) deposition in total lung, head and nasal, tracheobronchial, and alveolar regions with forced exhaled nitric oxide (FeNO), lung function, and blood pressure in overall cohort subjects. Generalized estimating equations were adjusted for test year, age, work type (office or welding), working duration, smoking status, and chronic obstructive pulmonary disease (COPD). Values in bold characters with red color were deemed statistically significant (* p < 0.05).
proliferation, contraction, and remodeling (Sutcliffe et al., 2012; Wiegman et al., 2015; Pan et al., 2019). Together, our findings showed that PM$_{2.5}$ deposition in lung regions, especially in the alveolar region, was associated with a lung function decline and an increased risk of COPD.

The main strength of our study is the occupational cohort of shipyard workers, with a follow-up time of 4 years, in which we examined the decline in lung function over the study duration. A limitation of our study is its small sample size. Moreover, the metal components of the welding fumes were not identified in our study. We did not account for other gaseous air pollutants (i.e., nitrogen dioxide, carbon monoxide, and volatile organic compounds) in this study. Other risk factors for COPD, such as nutrition and genetics, should be studied in future work. Age-related changes in lung function with PM$_{2.5}$ deposition in lungs were not measured in this study and could have impacted the statistical data. PM$_{2.5}$ personal exposure may be partially originated from other emission sources. The authors wish to thank Ms. Yi-Syuan Lin, A-Chuan Ho, Shih-Ting Huang, Kai-Wei Cheng, and Mr. Huan-Wun Chen for technical assistance with this research.

4 CONCLUSIONS

This is the first study reporting the incidence rate of COPD in shipyard workers. We observed that the overall incidence rate of COPD in the shipyard cohort was approximately 2.51 cases per 100 person-years. Higher incidence rates of COPD were observed in non-smokers and welders, which was associated with decreases in FeNO and lung function decline after exposure to welding fume PM$_{2.5}$. Pulmonary effects by PM$_{2.5}$ exposure in occupational settings is an urgent issue for worker health protection.

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DISCLAIMER

The authors have no relevant financial or non-financial interests to disclose.

SUPPLEMENTARY MATERIAL

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