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ORIGINAL ARTICLE

Fractional exhaled NO in a metalworking occupational cohort

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Abstract

Purpose Secondary metalworking carries exposure to relatively heavy levels of respirable particulate. We investigated the extent to which metalworking is associated with increased exhaled nitric oxide (FeNO), an established inflammatory biomarker.

Methods We studied 80 metalworking factory employees in Kazakhstan. Informed by industrial hygiene data, we categorized them into three groups: (1) machine operators (41%); (2) welders or assemblers (33%); and (3) all others, including administrative and ancillary staff (26%). Participants completed questionnaires covering occupational history, smoking, home particulate sources, respiratory symptoms, and comorbidities. We measured exhaled carbon monoxide (CO), exhaled fractional nitric oxide (FeNO), and spirometric function. We used mixed-effects modeling to test the associations of occupational group with FeNO, adjusted for covariates.

Results The median age was 51.5 (interquartile range 20.5) years; 7% were women. Occupational group ($p < 0.01$), daily current cigarette smoking intensity ($p < 0.05$), and age ($p < 0.05$), each was statistically associated with FeNO. Welders, or assemblers (Group 2), who had intermediate particulate exposure, manifested significantly higher exhaled FeNO compared to machinists (Group 1, with the highest particulate exposure) and all others (Groups 3, the lowest particulate): adjusted Group 2 mean 44.8 ppb (95% confidence interval (CI) 33.8–55.9) vs. Group 1 24.6 ppb (95% 20.5–28.7) and Group 3, 24.3 ppb (95% CI 17.7–30.9). Secondhand smoking and height were not associated with FeNO.

Conclusion In a metalworking industrial cohort, welders/assemblers manifested significantly higher levels of FeNO. This may reflect respiratory tract inflammation associated with airborne exposures specific to this group.

Keywords Welding · Assembling · Inflammation · Occupational · Exhaled nitric oxide · Mixed-effects model

Introduction

Workplace exposure to respirable particulates (solids and aerosols) is associated with cardiopulmonary morbidity (Christensen et al. 2008; Meza et al. 2013; Picciotto et al. 2016; Andersson et al. 2019, 2020). Inflammatory processes are believed to mediate such particulate-related adverse effects. Because these disease endpoints are poorly reversible, early identification of inflammatory changes could be central to preventive action. Inflammatory biomarkers, however, are infrequently assessed among workers at potential risk from particulate exposures (van Kampen et al. 2019).

Secondary metalworking is an industry in which exposure to relatively heavy levels of respirable particulate is well recognized (Reh et al. 2005; Insley et al. 2019). In addition to primary metal constituents, metalworking particulates may also contain byproducts of various manufacturing processes, including flame cutting, brazing, and welding (Insley et al. 2019). These byproducts typically include pro-inflammatory reactive metal oxides.

We undertook this investigation to ascertain the extent to which metalworking exposure is associated with increased exhaled nitric oxide (FeNO), an established biomarker of respiratory tract inflammation. We hypothesized that among metalworkers experiencing respiratory particulate exposure across a range of intensity, those engaged in welding would manifest increased exhaled FeNO, even taking into account

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overall particulate levels as well as other factors, especially cigarette smoking, a known modifier of exhaled FeNO.

Materials and methods

Study venue

We studied the employees of a metalworking plant located in Almaty, Kazakhstan. The facility, which employed actively approximately 100 at the time of this investigation, produces metal containment tanks, equipment for oil and gas industry, metal parts for industrial vehicles, and various other metal products. The workload is not constant, but rather varies depending on the orders placed for which the staff is recalled to the workplace. The overall footprint of the metal workshops is approximately 1000 m^3 located under one roof, with free communication among various stations separated only by partitions. The roof is 9 m in height, with sufficient space for cranes to operate overhead. Common exhaust ventilation is provided by a number of ceiling fans providing air movement out of the building and into the ambient environment. A communicating building houses ancillary and managerial staff.

The feedstock is comprised of mild steel, higher nickel content steel, and stainless steel. Galvanized steel and hard metal (tungsten carbide cobalt) are not worked in this facility. Metalworking processes include: welding, machining, assembling, and metal coatings application (primary paints only; epoxide coatings are not used). A subset of workers is engaged in argon plasma arc cutting, although those workers did not participate in the current study. Ancillary and management tasks include administration, human resources, labor safety, engineering, accounting, cleaning, and security. Work shifts are all daytime, typically 8 h in duration.

Participation and questionnaire

We surveyed study participants using a structured self-administered questionnaire in Russian or Kazakh. The survey instrument included items covering demographics, cigarette smoke exposures, home particulate sources, respiratory symptoms, and comorbidity, and a detailed occupational history from the current and all preceding lifetime positions (including work duration in years, length of work shift in hours, and days per week worked, along with the frequency of personal protection equipment use). We used questionnaire data to classify smokers as never, former, or current cigarette users and to quantify the number of cigarettes smoked per day among current smokers. We also characterized study participants with or without current secondhand smoke (SHS) at work or at home. Based on items on home heating and cooking, we dichotomized between those with coal or wood vs. natural gas for home heating and natural gas vs. wood for cooking.

We assessed respiratory symptoms using items from the COPD Assessment Test (CAT), which consists of eight questions with a response range for each from 0 to 5, yielding an overall score 0–40 (Jones et al. 2009). We also asked the MRC battery assessing dyspnea yielding a score of 0–4 (Bestall et al. 1999). To assess possible asthma, we included two yes or no items from the Fresh Air study (Cragg et al. 2016): (1) Have you ever had wheezing (especially when exhaling)? (2) Do you ever happen to wake up because of wheezing in the morning or at night? In addition, we also asked “Compared to your peers, are you more dyspneic?” (yes or no), We further assessed specific diagnoses ever received from a health care provider: chronic bronchitis, chronic obstructive pulmonary disease (COPD), bronchial asthma, and allergic rhinitis.

Exposure data

We exploited personal breathing zone particulate matter $(PM)_{2.5}$ exposure data obtained though sampling that had been carried out in a previously published industrial hygiene investigation for those engaged in arc cutting, machining, assembling, and welding (Vinnikov and Tulekov 2021) and, for the current analysis, additional exposure data for administrative and other ancillary positions, most of whom were not regularly on the factory floor. For both the previous and the latter industrial hygiene assessments, we collected 8-h full work shift samples from randomly selected subsets of workers of the occupational groups as noted, within the factory. These included machine operating, assembling, and welding included in this study and plasma arc cutters who, as noted above, did not participate in the current study. Sampling relied on portable battery-operated PM monitors with $PM_{2.5}$ impactors worn by workers on a waist belt. The sampling tube was connected to a particulate impactor, with the intake in the breathing zone of a worker. We used a direct reading apparatus, TSI SidePak AM520 (TSI, USA), which used light-scattering technology to calculate the mass concentration of PM, which passed through an impactor with a calibrated speed via in internal pump set at 1.7 l/min. Data were logged every minute, and the average (or time-weighted 1-min average), median, and geometric mean concentrations were available for the analysis.

Carbon monoxide measurement

We used a portable Smokerlizer piCO (Bedfont, UK) to measure exhaled carbon monoxide (CO) to help confirm self-reported smoking status in all subjects. They were asked to hold breath for 15 s after a deep inhalation, and then to exhale in the device through a disposable mouthpiece.

Current daily smokers are expected to have exhaled CO 10 parts per million (ppm) or more. Never- or ex-smokers have readings below 10 ppm.

Nitric oxide measurement

To measure the fraction of exhaled NO (FeNO) measurement, we calibrated and used a portable NOBreath (Bedfont, UK) device with disposable mouthpieces, which operated as an electrochemical sensor and measured FeNO in parts per billion (ppb). Two measurements were obtained from each subject with an interval between exhalations 3 and 5 min, and the mean of these two was recorded. All measurements were performed in a medical examination room at the work site. Participants were asked to refrain from smoking for at least 2 h prior to the test. In accordance with ATS recommendations, FeNO was measured after inhalation through the mouth and with exhalation rate 50 ml/s between the 6th and the 10th seconds of exhalation (Dweik et al. 2011). All FeNO measurements were performed prior to spirometry.

Spirometry

Expiratory spirometry was performed in a medical examination room at the plant after FeNO measurement using MAS-2S spirometer (Belintelmed, Belarus). Three reproducible maneuvers (difference below 150 ml) of vital capacity (VC) followed by three reproducible maneuvers of forced VC (FVC) were obtained. We performed bronchodilation with three doses of salbutamol with a metered dose inhaler and repeated FVC maneuvers after 15 min in those who had forced expiratory volume in 1 s (FEV_1)/FVC below 0.7 or FEV_1 below 80% predicted at baseline. We applied Global Lung Function Initiative (GLI)-2012 reference equations in this study (Quanjer et al. 2012). Subjects with post-bronchodilator FEV_1/FVC below 0.7 were considered as having bronchial obstruction and were excluded from the cohort. Of 81 subjects who underwent examination, one foreman was excluded because of post-bronchodilator obstruction with FEV_1/FVC 61% (lower limit of normality (LLN) 66%).

Statistical analysis

The primary end-point in this analysis was FeNO as a continuous variable. We tested the normality of the distributions of FeNO and other key variables, observing non-normal distributions in all. We therefore applied non-parametric tests to analyze these data. We used Mann–Whitney *U* test for pairwise comparisons; the Kruskal–Wallis test for comparisons of three or more groups; and Spearman rank correlation to test the association between exhaled CO and FeNO. Differences between dichotomous variables were tested with the Chi-square test. For continuous variables, we present data as medians with their corresponding interquartile range (IQR), or as numeric counts and percentages for dichotomous variables.

Based on the visual inspection, communication with the plant manager, and further informed by our previous (Vinnikov and Tulekov 2021), and current industrial hygiene data, we tentatively categorized the employees into three groups. The first group consisted of machine operators; the second, welders, and assemblers (who also performed welding as part of their typical work routine); and the third, all other occupations, dominated by administrative and other ancillary personnel. We tested the differences in the normalized particulate levels among the three occupational groups using analysis of variance (ANOVA). We also tested particulate levels as an independent variable in relation to FeNO using linear regression analysis.

We applied mixed-effects model to test the association of an occupational group with FeNO, also considering smoking, age, sex, and height as covariates in such model. The choice of covariates was guided by the previously published epidemiological studies (Karrasch et al. 2011; Torén et al. 2017). Smoking was treated as a categorical variable, grouped into non-smokers; daily smokers smoking up to ten cigarettes a day; or daily smokers smoking more than ten cigarettes a day. In a sensitivity analysis, we re-estimated the model excluding females (and dropping sex as a covariable). We treated height as a continuous variable in the main model, but in an additional analysis, we stratified subjects into three groups: those below or equal to the 25th percentile of height; those within the interquartile range (IQR); or those above 75th percentile for height. For both fixed effect predictors (occupational group and smoking group), we report *F* values with the corresponding *p* values for the predictor as a whole, as well as for each pairwise comparison of the groups within each of two tested predictors. Mixed-effects model are adjusted for all included covariates; we report Bonferroni adjusted *p* values for pairwise comparisons between occupational groups and smoking categories. All tests were run in NCSS 2020 (Utah, USA).

Results

We analyzed data for 80 study participants. The median age was 51.5 (IQR 20.5) years; six (7%) were women; and height ranged from 155 to 192 cm, with a median of 170 cm. Although age and height did not differ statistically by occupational group, all but one of the females was in the group of "others" ($p < 0.05$) (Table 1). Sixty-one percent of study participants were current smokers, with a median intensity of 5.5 (IQR 20) cigarettes per day, while 60 (75%) reported exposure to SHS at home or at work. Welders/assemblers manifested a greater number of years at work, but this group

Table 1 Demographic, occupational, smoking status, comorbidities, and FeNO overall and among three occupational groups

Study participant characteristics	Occupational group				P
	All $n=80$	Machine operators $n=33$ (41%)	Welders/ assemblers $n=26$ (33%)	Others $n=21$ (26%)	
Men, *n* (%)	74 (93)	32 (97)	26 (100)	16 (76)	<0.01
Age in years, median (IQR)	51.5 (20.5)	49 (22)	54 (19)	52 (21.5)	0.61
Height, cm (IQR)	170 (8.8)	169 (7)	172 (8.8)	168 (12)	0.18
Work duration, years mean (SD) or median (IQR)	11 (14)	11 (8)	17.5 (27.3)	9 (14.5)	0.049
Smoking status, *n* (%)					0.38
Never-smoker	13 (16)	5 (15)	5 (19)	3 (14)	
Ex-smoker	18 (23)	4 (12)	8 (31)	6 (29)	
Current smoker	49 (61)	24 (73)	13 (50)	12 (57)	
Cigarettes per day (current smokers)	15 (11)	17.5 (10)	10 (15)	20 (10)	0.11
Exhaled CO, ppm	6 (10.8)	7 (10.5)	5.5 (12.5)	3 (8.5)	0.10
Exposure to secondhand smoke, *N* (%)	60 (75)	26 (79)	22 (85)	12 (57)	0.08
CAT score (0–40), median (IQR)	5.5 (7)	6 (7.5)	4 (7.5)	6 (9.5)	0.84
mMRC score (0–4), median (IQR)	0 (0)	0 (0)	0 (0)	0 (0.5)	0.38
Ever-wheezing, *N* (%)	11 (14)	6 (18)	2 (8)	3 (14)	0.51
Seasonal allergy, *N* (%)	13 (16)	5 (15)	3 (12)	5 (24)	0.52
Diagnosed chronic bronchitis, *N* (%)	17 (21)	4 (12)	8 (31)	5 (24)	0.21
Diagnosed allergic rhinitis, *N* (%)	2 (3)	1 (3)	0 (0)	1 (5)	0.28
Spirometry, post-bronchodilator					
FEV_1, % predicted, mean ± SD	92.9 ± 15.0	90.4 ± 13.7	94.3 ± 16.0	94.9 ± 16.1	0.51
FEV_1, % predicted, range	57–128	65–124	57–128	64–119	–
FVC, % predicted, mean ± SD	92.3 ± 14.8	88.9 ± 13.2	93.2 ± 14.8	96.4 ± 16.7	0.21
FVC, % predicted, range	52–135	66–118	52–120	70–135	–
FEV_1/FVC, mean ± SD	80.7 ± 7.0	81.9 ± 7.2	80.6 ± 6.5	79.0 ± 7.1	0.37
FEV_1/FVC, range	67–99	67–98	70–95	68–99	–
Exhaled NO, ppb	25 (22.3)	25 (15)	43.5 (49.3)	22 (16)	<0.01

All data except post-bronchodilator spirometry are presented as medians with interquartile ranges. *p* values from Kruskal–Wallis test or χ^2 test

CAT COPD Assessment Test, ranges from 0 to 40, FEV_1 forced expiratory flow in one second, *FVC* forced vital capacity, *SD* standard deviation

was similar to the others in smoking status, exposure to SHS, and in exhaled CO (Table 1). Work duration in the current job did differ statistically among the groups, with the longest duration among welders/assemblers, even though the median age did not differ statistically among the three occupational groups, as previously noted above.

Respiratory complaints, assessed with the CAT instrument, were infrequent in the overall group (median 5.5; IQR 7), as well as in all three occupational groups. The mMRC score did not differ among the groups either. Fourteen percent of workers reported wheezing at some time in their lifetime (no participant reported a current diagnosis of asthma). Chronic bronchitis, however, was more common, being reported by 17 (21%). The prevalence of chronic bronchitis did not differ statistically among the three occupational groups ($p=0.21$). Although 16% reported seasonal allergy, only two reported a diagnosis of allergic rhinitis.

The median FeNO among all study participants by occupational group is included in Table 1 and shown in Fig. 1. The highest median FeNO was manifested in welders/assemblers; 43.5 (IQR 49.3) ppb), and lower and similar in the other two groups of machine operators and "others" (25 and 22 ppb, respectively; $p<0.01$ for three-way comparison).

Of 79 $PM_{2.5}$ personal 8-h samples collected at the plant, the median was 0.604 (IQR 0.470) mg/m^3. There was a wide range in observed concentrations, from 0.125 to 1.354 mg/m^3. The greatest median was observed in the group of machine operators (0.866 (IQR 0.313) mg/m^3), with the group of welders/assemblers (0.604 (IQR 0.400) mg/m^3) somewhat lower, and all others, the lowest [0.286 (IQR 0.221) mg/m^3]. These differences in $PM_{2.5}$ differed statistically among the three groups (Kruskal–Wallis $p<0.001$). The median sampling value by group was not statistically associated with individual FeNO values (regression model beta coefficient 95% CI − 28.4 to 15.7).

Cigarette smoking intensity per day (treated as a zero value for non-smokers) was statistically associated with FeNO, with an inverse association (beta − 0.65; 95% CI

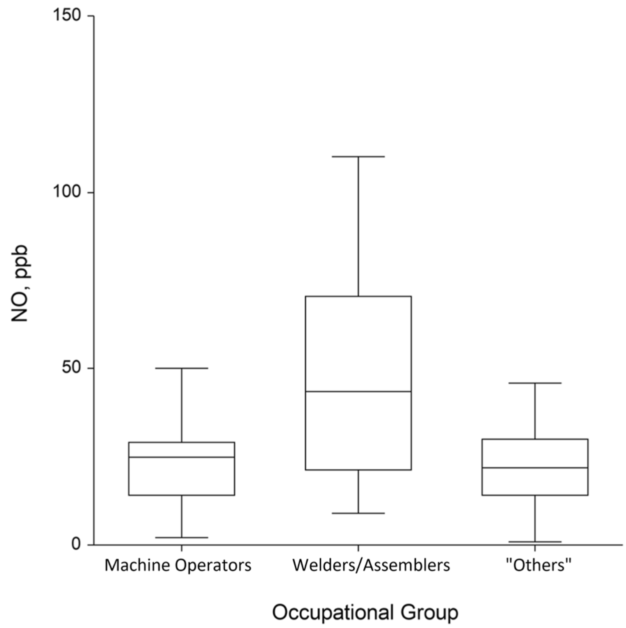

Fig. 1 Medians with the interquartile levels of NO in each of three occupational groups. Occupational Group 1 are machine operators; Group 2 are welders/assemblers; Group 3 includes all others ($p < 0.01$ for three-way comparison)

− 1.15 to − 0.15, $p = 0.01$) in the entire group. Limiting the analysis to current smokers only, the association was more negative (beta − 1.33; − 2.04 to − 0.63, $p < 0.001$). Exhaled CO, however, was not statistically associated with FeNO, either among all subjects ($r^2 = 0.07$; 95% CI − 0.15 to 0.29, $p = 0.53$) or among smokers only ($r^2 = 0.05$; 95% CI − 0.24 to 0.32, $p = 0.76$).

In a mixed-effects model including height, age, and sex, occupational group (machine operators, welders/assemblers, others) ($F = 6.12$; $p < 0.01$), number of smoked cigarettes (0, > 0 and up to 10; > 10) ($F = 3.39$, $p < 0.05$), and age ($F = 5.95$, $p < 0.05$) were each statistically associated with FeNO values (Table 2). In pairwise comparisons of each occupational group, welders/assemblers manifested significantly higher FeNO compared to machine operators and "others": adjusted welders/assemblers mean 43.5 ppb (95% CI 30.8–56.3 ppb) vs. machine operators 23.3 ppb (95% 15.7–31.0 ppb) and "others" 23.5 ppb (95% CI 15.8–31.2). We found no statistical differences in comparisons between machine operators and the "others" employee category. In addition, those smoking 0–10 cigarettes a day also higher FeNO compared to heavier smokers: 35.8 ppb (95% CI 26.9–44.7 ppb) vs. 24.9 ppb; (95% CI 16.1–33.7 ppb) There was no statistical difference comparing FeNO among non-smokers with light smokers (> 0–10 cigarettes a day) or heavier smokers (> 10 per day).

To test whether the concentration of women in the group of "others" accounted for the observed results, we

Table 2 Statistically significant pairwise comparisons of groups in mixed effect models, also adjusted for age, sex, and height

Fixed effects	*F* value	Bonferroni adjusted *p* value
Occupational group overall	6.12	NA
Machine operators vs. welders/assemblers	12.1	0.004
Welders vs. "others"	9.8	0.01
Smoking categories overall	3.39	NA
Lighter vs. heavier smokers	6.77	0.036

Models also include age and height as continuous predictors and sex as a fixed effect. There were no statistical differences between machine operators and the "others" employee category (row not shown)

re-estimated the mixed-effects model among men only (and without sex as a covariate). The results for occupation did not change substantively: among the three groups, $F = 6.04$, $p < 0.01$ and in pairwise comparisons of each occupational group, welders/assemblers manifested significantly higher FeNO compared to machine operators or to others) (adjusted welders/assemblers mean, 44.9 ppb (95% CI 33.8–56.0 ppb) vs. machine operators, 24.7 ppb (95% CI 20.3–29.0 ppb) and "others", 24.9 ppb (95% CI 16.2–33.6). The difference in FeNO among the three categories of smoking intensity was less pronounced ($F = 2.96$, $p = 0.06$) when women were excluded.

To test whether SHS was associated with FeNO, we re-estimated the mixed-effects model including SHS and found no statistical association for that covariate. We also failed to observe a statistical association of height with FeNO ($F = 0.34$, $p = 0.56$) in mixed-effects modeling. Similarly, we observed no statistical association of height, categorized into three groups, and FeNO ($F = 0.24$; $p = 0.79$).

Discussion

In this study of 80 employees of a metalworking plant in Almaty, with mean lung function within the normal range lung, we observed significant differences in FeNO among three occupational groups, with the highest values among welders/assemblers, even after adjusting for smoking and age. Despite the FeNO elevation among welders/assemblers, neither respiratory symptoms nor comorbid conditions differed statistically among the occupational groups. Nor was this biomarker of inflammation accounted for by $PM_{2.5}$, which was highest among machinists, not the welders/assemblers. This dissociation suggests that either gaseous pollutants or the chemical specificity of the particulate, not simply its bulk, may be critical in driving inflammation. The observation of elevated FeNO is consistent with the known composition and pro-inflammatory potential of welding-generated metal fumes and gases.

Endogenous NO is produced from arginine with NO-synthase (NOS). In healthy subjects, FeNO falls within the range of predicted values (Torén et al. 2017), but does vary in relation to smoking, age, height, infection, and atopy (Karrasch et al. 2011; Nerpin et al. 2019). The median value of FeNO in a population sample in Germany was 13.9 ppb (Karrasch et al. 2011), quite close to the U.S. sample, the latter with a 5th–95th percentile in the adult population of 3.5–39 ppb (See and Christiani 2013). A wide range of medical conditions may affect FeNO, dominated by bronchial asthma, in which this biomarker can be used as an indicator of inflammation intensity and response to inhaled corticosteroid treatment (Quirce et al. 2000; Stewart and Katial 2007; Donohue and Jain 2013; Kim et al. 2014). Because elevated FeNO may not only be a manifestation of occupational exposures, but also may reflect a variety of clinical conditions, elevated FeNO values in the occupational cohorts should be considered in its potential clinical context.

In occupational settings, FeNO has been described as a marker of respiratory inflammation, albeit infrequently, presumably due to the working environment. Of note, FeNO has been studied among welders specifically in two relevant investigations (Järvelä et al. 2013; Kauppi et al. 2015). In the first study, FeNO did not change statistically after a working day in 20 welders from 20.0 to 19.4 ppb, but a number of blood inflammatory markers did (blood leukocytes and neutrophils) (Järvelä et al. 2013). Similarly, leukocytes, neutrophils, and platelets increased after a welding challenge test, but no statistically significant change in FeNO was recorded in another simulated exposure to with mild and stainless steel in welders ($N=7$), sheet metal workers ($N=7$), a single assembler, and a single metal worker (Kauppi et al. 2015). The FeNO was 25 ppb at baseline, 25 ppb after mild steel exposure, and 28 ppb after stainless steel exposure. Nonetheless, there was a 30% rise in FeNO in five welders after exposure to mild steel and in two participants after stainless steel. Exposure to metal particulate in relation to FeNO among fly ash exposed boilermakers (who also performed welding, metal burning, and grinding) has also been reported (Kim et al. 2003). In that study of 34 workers, metal particulate was negatively associated with FeNO; the overall levels of FeNO were close to the machinists in our cohort, and substantially lower than the welder/assemblers we studied.

Other studies, but not of welders, have found occupational associations with elevated FeNO. Occupational groups found to have elevated FeNO include aluminum pot-room workers (Lund et al. 2000) and underground tunnel workers (Ulvestad et al. 2001). A 40% increase of FeNO was found in shoe and leather workers by the end of a shift (Maniscalco et al. 2004). Negative FeNO studies, which are as frequent, have included petroleum refinery workers (Meo et al. 2015), those working with engineered nanomaterials (Iavicoli et al. 2020), cement-exposed apprentices (Carlsten et al. 2007), and among those working at the World Trade Center disaster site (Mauer et al. 2011). Since many occupational exposures are inflammatory in nature, elevated FeNO in selected occupational groups is plausible, but as summarized above, has not been consistently observed. Occupational asthma, where elevated FeNO has been repeatedly documented, has proved to be an exception (Lemiere 2007; Sastre et al. 2013; Merget et al. 2015).

Most known predictors of FeNO have been accounted for in our analysis. Consistent with other population-based studies, smoking showed significant associations with FeNO in our analysis. We observed no statistical relationship to height, however, as might have been expected. The relatively small sample size of our cohort may explain this and additional deviations in our findings from those of other studies. Light smoking was associated with an increase in exhaled NO, whereas heavier smoking yielded low levels of FeNO, reflecting a U-shape relationship. Occupational studies of FeNO as a marker of inflammation that involve smokers are not always consistent in showing elevated FeNO, because smoking may downregulate NOS. Therefore, such studies should employ stratification of smoking (Malinovschi et al. 2012; Olin 2012) or use a mixed-effects model, as we did in the current report. Because all measurements were completed in the workplace, other non-occupational exposures occurring acutely prior to the examination should not have come into play. Nonetheless, we cannot exclude a contribution of other exposures or long-term smoking contributing to ongoing, chronic inflammation manifested in altered FeNO values. We do note the relatively low prevalence of self-reported chronic bronchitis in this cohort, which may reflect various factors. One factor may be a "healthy survivor effect," but we did not collect data on that potential phenomenon and it would be overly speculative to invoke that as a presumed explanation.

For the current analysis, we had the benefit of a set of personal exposure data of fine PM, which is a relative strength of this study. These sampling data, although sufficient to characterize exposure groups, did not extend to all study participants and required generalized assignment of a median value to all members of each group. Another advantage of the current study is the measurement of spirometry and the confirmation the mean findings fell within normal limits for the cohort as a whole and there was no statistical difference in lung function among the three occupational groups studied. Nonetheless, the overall values for FEV_1 and FVC were only 93–94% predicted, rather than being closer to 100%. This may be attributable to a paucity of Central Asian normative spirometry data (Vinnikov et al. 2018). We also should note that we were not able to successfully recruit the subset of plasma arc cutters in the factory, who we know from previous study had markedly elevated particulate exposure (geometric mean of average concentrations 1.73 mg/m^3, maximal 1-min concentration 8.55 mg/m^3) (Vinnikov and Tulekov 2021). Another limitation of our investigation is the relatively small sample size, dictated by the small workload in production sites such as this in Kazakhstan. Although this could lead to failure to identify true differences, the relatively narrow confidence intervals, as well as the statistical significance for the important differences that we did observe, argue against low study power as a substantial limitation. We addressed the potential limitation of multiple comparisons leading to false rejection of the null hypothesis by the judicious use of a Bonferroni adjustment, although we acknowledge that this a conservative approach. Nonetheless, our cohort is comparable in size or larger to other workplace studies of exhaled FeNO.

Our cohort size is also counterbalanced by our relatively high proportion of current workers participating (80 out of approximately 100, excepting the aforementioned plasma arc cutters of whom only three, however, were actively working at the time of the study). In addition, we did not consider ethnicity of workers (Asian vs. non-Asian) which might have controlled for some unmeasured confounders. Our study was restricted to one location in only one city in Central Asia, limiting generalizability. The cross-sectional study design precludes causal conclusions. Typical occupational exposures in the study site did not include solvents or chemical irritants that may have an association with FeNO. Although such exposures were not included in our study questionnaire, we acknowledge that this omission could lead to missed, occult chemical factors. Finally, and perhaps most importantly, we did not measure gaseous pollutants nor do we have data on chemical composition of the particulate among the three occupational groups we studied. Such data could help explain the dissociation between the observed $PM_{2.5}$ values and FeNO.

Conclusions

In this study of nearly all the active employees in a metalworking plant in Almaty, categorized into machinists, welders/assemblers, and other occupations, we observed statistically higher FeNO levels among the welders/assemblers, even after adjustment for cofactors. Further research is needed to shed light to the etiology of this inflammatory biomarker elevation in welders/assemblers, in particular more detailed industrial hygiene characterization of their working environment and additional characterization of biomarkers in additional to FeNO, such as induced sputum or exhaled particles.

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Author contributions DV planned the study, performed the analysis, and drafted the manuscript. ZhT recruited patients, drafted the manuscript, and approved the final version. PDB performed the analysis, drafted and revised the manuscript, and approved the final version.

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Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study was approved by the local Committee on Bioethics of the School of Public Health of al-Farabi Kazakh National University.

Consent to participate Every participant signed an informed written consent to participate. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication Not applicable.

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