Blood leukocyte count as a systemic inflammatory biomarker associated with a more rapid spirometric decline in a large cohort of iron and steel industry workers

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Research

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Abstract

Objective: Iron and steel industry workers are exposed to high levels of inhalable dust particles that contain various elements, including metals, and cause occupational lung diseases. We aim to assess the relationship between occupational dust exposure, systemic inflammation, and spirometric decline in a cohort of Chinese iron and steelworkers.

Methods: We studied 7,513 workers who participated in a Health Surveillance program at Wugang Institute for Occupational Health between 2008 and 2017. Time-weighted exposure intensity (TWEI) of dust was quantified based on self-reported dust exposure history, the experience of occupational hygienists, and historical data of dust exposures for workers with certain job titles. A linear mixed-effects model was used for association analyses.

Results: The average annual change of lung function was -50.78 ml/year in forced expiratory volume in 1 second (FEV1) and -34.36 ml/year in forced vital capacity (FVC) in males, and -39.06 ml/year in FEV1 and -26.66 ml/year in FVC in females. Higher TWEI prior to baseline was associated with lower longitudinal measurements of FEV1 and FVC but not with their declines. Higher WBC and its differential at baseline were associated with lower longitudinal measurements and a more rapid decline of FEV1 and FVC in a dose-dependent monotonically increasing manner. Moreover, the elevations of WBC and its differential post-baseline were also associated with a more rapid decline of FEV1 and FVC.

Conclusions: Our findings strongly support the important role of systemic inflammation in affecting the temporal change of lung function in iron and steel industry workers.

Key Messages

1. What is the key question?

Cohort members with high levels of WBC counts and differential had lower longitudinal measurements and a more rapid decline of FEV1 and FVC in workers in a dose-dependent increasing manner.

2. What is the bottom line?

Preliminary studies suggest that Occupational exposure to inhalable dust in the iron and steel industry has been shown to compromise lung function and increasing the risk of chronic airflow obstruction in exposed workers.

3. Why read on?

Increasing blood leukocytes may serve as a systematic inflammatory biomarker that can predict the increased decline in FEV1 and FVC after exposure to steel dust. Therefore, pay attention to reduce systematic inflammatory will decrease the vulnerability to a disease of respiratory such as COPD and thereby contribute to reducing the large burden of morbidity and mortality associated with this disease.

Introduction

The iron and steel industry as a fundamental component of modern industrial infrastructure for the entire human society has employed millions of workers who were exposed to many chemical and physical hazards, workplace activities, or conditions [1]. Workers are exposed to high levels of inhalable dust particles containing various elements such as metals, silica, carbon, polycyclic aromatic hydrocarbon, which caused chronic occupational diseases such as chronic obstructive pulmonary disease (COPD)[2-5]. The International Agency for Research on Cancer has classified iron and steel founding processes as Group 1 human carcinogens based on sufficient human data for lung cancer [6]. Cross-sectional studies have established strong associations between dust exposure and pulmonary symptoms and lung function impairment in iron and steelworkers [1, 7, 8]. However, the effect of dust exposure on lung function decline is inadequately studied.

White blood cell (WBC) counts and its subsets (i.e., neutrophils, lymphocytes, monocytes, eosinophils, and basophils) are established systemic inflammatory markers and have been identified to be associated with the development of abnormal FEV1 and airflow obstruction in occupational cohorts or general populations [9-14]. For example, after the September 11, 2001 World Trade Center attacks, rescue and recovery workers were exposed to a high level of dust mixture and were later found to have high rates of airway injury, including excessive loss of lung function, airflow obstruction, and airway hyper-reactivity [15]. Elevated blood neutrophil and eosinophil concentrations were independently associated with an accelerated FEV1 decline (64 mL/year or more), a well-established risk factor for COPD development [15]. Mechanisms underlying the associations observed may involve increased lung tissue damage due to the release of destructive enzymes or highly reactive oxygen species from neutrophils [16-19] or the generation of eosinophilia/Th2 inflammation in airways [12, 20].

Few studies have evaluated the associations between WBC counts and longitudinal changes of lung function in iron and steelworkers. We hypothesized baseline WBC as a systemic inflammatory biomarker is associated with both a lower and a more rapid decline in lung function in a cohort of 7,513 iron and steelworkers. We also assessed the elevation of WBC counts post-baseline and the longitudinal change of spirometry. Our findings may support the important role of systemic inflammation in affecting the temporal change of lung function in iron and steelworkers.

Methods

A detailed description is available in supplemental materials.

Study subjects

This longitudinal study was conducted on 7,575 workers who were employed at Wuyang Iron and Steel Company Limited (Hangang Group in Henan, China) and were required to participate in the Worker Health Surveillance program at the Wugang Institute for Occupational Health between 2008 and 2017. This company has been using the electric arc furnace technique to manufacture steel from scrap or direct reduced iron, melted by electric arcs, and mainly has steel making, continuous casting, rolling, and oxygen-making plants. According to the Reports of Occupational Hazard Control Assessment conducted by Henan Institute of Occupational Medicine in 2006 and 2007, inhalable dust and noise are the two occupational hazards that have samples exceeding the national standards (the permissible concentration time-weighted average of 8 mg/m^3 for inhalable dust and 85 dB(A) for noise in China). This cohort was dynamic with workers entering and leaving the cohort at different times. In general, individual participants in this program received medical assessments every other year with medical surveillance workouts recommended by the China Ministry of Health. The de-identified data were obtained from the Wugang Institute for Occupational Health. The Research Ethics Committee of the Qingdao University School of Medicine approved the study protocol with a waiver of subject consent (QYFYWZLL25933).

Occupational Dust Exposure Assessment

Employment history including occupation, length of employment, and occupational dust exposure (yes or no) for three consecutive jobs or positions were self-reported at study entry. Because no cohort members were newly employed at the baseline visit, we focused on detailed employment history including plant, workshop, and post at the Wuyang Iron and Steel Company prior to baseline visit to quantify occupational dust exposure. All study subjects belonged to 79 workshops from seven plants. Based on the percentage of subjects reporting dust exposure, consultation with occupational hygienists, historical personal air sampling data in 2006 and 2007 (Table E1), and epidemiological consideration of sample size within each exposure category, the workshops were classified into low (n=43, person-posts=4034), medium (n=20, person-posts=3816), and high (n=16, person-posts=2562) exposure categories to maximize the statistical power of the study. We calculated time-weighted exposure intensity (TWEI) using the sum of exposure unit (coded as 0, 1, 2 for low, medium, and high) years divided by total years prior to the baseline of dust exposure for each individual.

Lung function paraments

Prebronchodilator spirometry was performed every other year by a certified technician using a portable calibrated electronic spirometer (CHESTGRAPH HI-701, Japan) in accordance with the American Thoracic Society (ATS)/European Respiratory Society standards(ERS) at base and follow-up [21]. The spirometer was checked each study day for leaks by a calibrated syringe. Persons were in the standing position and a nose clip was used. After two or more practice blows FEV1 and FVC were determined as the highest value from the results of measurements. Standing height and body weight were measured and recorded at each test occasion. Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio were used in this study. Percent predicted values were calculated using the equations for Asian adults supplied in the user's manual.

Complete blood count with differential

Peripheral venous blood samples were drawn from the antecubital veins of patients after overnight fasting. The blood samples were put into lithium heparin-containing tubes to avoid pseudo thrombocytopenia. The number of red blood cells, white blood cells (WBC), and platelets, and WBC differential counts (i.e., neutrophils, lymphocytes, monocytes, basophils, and eosinophils) were measured by a hematology analyzer (Sysmex. XS-500ix, China). Absolute cell counts were used in the analyses.

Data Analysis

Sixty-two workers with airflow obstruction (defined as FEV1/FVC <0.7) at baseline (n=20) or without spirometry data (n=42) were excluded from this study, leaving 7,513 workers with at least one spirometry measurement for data analyses. The sample size evolution for different analyses was summarized in Figure E2. A prudent analytical plan was developed to analyze the relationship among dust exposure, WBC count, and longitudinal spirometric decline with a careful assessment of important covariates, dose-response relationship, potential confounding effects, and sex stratification by linear mixed model. Models were constructed with time-weighted exposure intensity of dust and time as fixed factors and subject (intercept) as a random factor, respectively. All data analyses were conducted in male and female workers separately because of the division of labor by sex in heavy industry with females more likely to conduct less physical intensive assignments with less exposure to occupational hazards (Table 1). Data analyses were performed using SAS version 9.4 (site 70239492).

Results

Demographics of study subjects

This study included 6,188 male and 1,325 female workers with an average age of 34.5 years at study entry (Table 1). Workers reported occupational dust exposure at the Wuyang Iron and Steel Company for about 13 years, concordant with the fact that the Company was the first employer for most cohort members. The median follow-up duration in the cohort (TIC) was six years, which allowed for three to four spirometry measurements. In total, 25,164 prebronchodilator spirometry measurements were obtained from 7,513 workers. The average percent predicted values of FEV1 and FVC at baseline were over 100%. Airflow obstruction was identified in 22 subjects during follow-up evaluations, resulting in an incidence of 2.9 cases per 1000 person-years.

Occupational dust exposure

Median inhalable dust concentrations (8-hour time-weighted average [TWA]) for workshops classified in medium and high exposure categories were 0.91-1.45 and 7.45-10.35 mg/m^3, respectively between 2006 and 2007. Ninety percent of dust mass was non-silica (potentially as metal dust). Size distribution analysis found over 80% of particles had sizes less than 5 μm. No occupational monitoring data was available for the low exposure category. However, PM2.5 levels ranged from 33-108 μg/m^3 in non-heating seasons and 73-203 μg/m^3 in heating seasons in the national air quality monitoring stations closest to Wugang city (about 30 miles away) between 2013 and 2017. The entire company sits in a small valley, which is 5 km long and 1.9 km wide with north and west sides surrounded by mountains, thus the entire company area could be polluted by industrial dust. The median TWEI was 1.0 units for male workers and 0.19 units for female workers, supporting male workers having much higher occupational dust exposure.

Occupational dust exposure and spirometry

The average annual change of FEV1, FVC, and FEV1/FVC ratio during follow-up were 50.78 ml, 34.36 ml, and 0.49 in males (Table 2, model 1) and 39.06 ml, 26.66 ml, and 0.50 in female (Table E2, model 1), respectively. Higher TWEI prior to baseline was associated with lower longitudinal measurements of FEV1 and FVC in either sex and with females more vulnerable to the adverse effect of occupational dust exposure (e.g., -21.76 ml in males versus -41.96 ml in females for FEV1 and -28.71 ml in males versus -36.67 ml in females for FVC, per unit increase of TWEI, Table 2 and Table E2, model 1), but no effect on FEV1/FVC ratio. The most probable reason for lower spirometry in workers with higher past occupational dust exposure may be because of their more rapid initial decline of lung function or inadequate ongoing lung growth and development after the initiation of exposure. However, occupational dust exposure prior to baseline was associated with a slower annual decline of FEV1 and FVC in either sex (Table 2 and Table E2, model 2), and a more rapid decline of FEV1/FVC ratio in males. We hypothesized a slower decline of FEV1 and FVC associated with higher TWEI could be due to the “healthy worker effect” that in this case, certain worker characteristics could mediate such associations. Univariate analyses identified workers with higher TWEI were younger and taller, and had shorter years of dust exposure for either sex at baseline (Table E3). Age and years of dust exposure were highly correlated with Spearman correlation coefficients >0.93 for either sex and could not be the factors mediating the observed associations because occupational dust exposure history and its interaction with TIC had been included in the model (Table 2 and Table E2). Taller workers had a slower decline of FEV1 and FVC and a faster decline of FEV1/FVC ratio for either sex and inclusion of interaction term of height and TIC in model 2 completely nullified the significance of interaction term of TWEI and TIC (Table E4 and 5), suggesting that height may be the healthy worker characteristic that mediates the association between higher TWEI and slower decline of spirometry. Moreover, the inclusion of any additional interaction terms with TIC (e.g., smoking status, HGB, packyears, and BMI) had no impact on the estimate and significance for the interaction term of TWEI and TIC (data not shown).

Occupational dust exposure and longitudinal data of WBC count and its differential

Current smokers, packyears and years of dust exposure in males (Table 3), and BMI in either sex (Table 3 and Table E6) were each associated with higher WBC count and all differential cell counts (neutrophils, lymphocytes and mid-range absolute counts), consistent with the fact that cigarette smoking, higher BMI, and years of dust exposure increased systemic inflammation. However, age and TIC were associated with lower levels of WBC count and most differential counts in either sex, suggesting aging may reduce general immunity. Interestingly, there was no evidence to support TWEI was associated with increased WBC count and differential cell counts in either sex. In opposite, TWEI was associated with lower lymphocyte count in males (Table 3) and with lower mid-range absolute count (MID) count in either sex (Table 3 and Table E6). Self-reported exposure to toxic gases (e.g., carbon monoxide, nitrogen monoxide and dioxide, and benzene and its derivatives) was not associated with WBC count and its differential (data not shown).

Associations of WBC count and its differential with a spirometric decline

Higher baseline WBC count and differential (neutrophil and lymphocyte) counts were associated with lower longitudinal measurements and a more rapid decline of FEV1 and FVC in male workers only (Table 4). The MID count was similarly associated with a more rapid decline of FEV1 and FVC in male workers only (Table 4). Lymphocyte count was associated with lower longitudinal measurements of FEV1 and FVC but not with a decline in females (Table 4). We further stratified workers into quartiles of WBC count or differential counts to characterize the dose-response relationship with longitudinal lung function measurements and their declines (Table E7). Increasing WBC count and differential (neutrophil and lymphocyte count) were monotonically associated with lower longitudinal measurements and a more rapid decline of FEV1 and FVC in males only (Table E7 and Figure E1). MID was monotonically associated with a more rapid decline of FEV1 and FVC in male workers only (Table E7 and Figure E1). Lymphocyte count was associated with lower longitudinal measurements of FEV1 and FVC in a dose-response relation in females (Table E7).

We further tested whether elevation of WBC count and its differential post-baseline as an indicator for the elevation of systemic inflammation over time was associated with a more rapid decline of lung function. Change in WBC and its differential for each visit relative to baseline level were calculated and were included in the linear mixed-effects (LME) models together with its interaction of TIC. Interestingly, the elevation of WBC and its differential (e.g., neutrophil and MID) was associated with a more rapid decline of FEV1 and FVC in either sex (Table 5). Moreover, the magnitude of association seems to be more robust in female than male workers. Elevation of lymphocyte count was associated with a more rapid FEV1 decline in male workers only which resulted in a more rapid decline of FEV1/FVC ratio.

Sensitivity analyses

We are concerned that the associations between occupational dust exposure or WBC count and differential and lung function decline could be potentially confounded by cigarette smoking. Three-way interaction terms including current smoker × TWEI × TIC or current smoker × WBC × TIC with two-way interaction terms and main effects were included in the LME models. None of these three-way interaction terms were statistically significant (data are not shown). We also repeated the main analyses in subjects (n=6735) with two or more visits, findings similar to that seen in the entire 7513 workers were identified (data not shown).

Discussion

In this longitudinal cohort of 7,513 workers, occupational exposure to inhalable particles containing metal elements prior to baseline evaluation was inversely associated with longitudinal measurements of FEV1 and FVC over a follow-up period of 10 years. We also observed that cohort members with high levels of baseline WBC counts and differential had lower longitudinal measurements and a more rapid decline of FEV1 and FVC in male workers in a dose-dependent increasing manner. Moreover, the elevation of WBC counts and its differential count post-baseline as an indicator of increased systemic inflammation was associated with a more rapid decline of FEV1 and FVC in either sex. Finally, sex disparity of the effects of dust exposure or WBC on lung function was identified with stronger adverse effects of dust exposure or change of WBC seen in females as well as stronger effects of baseline WBC seen in males. The mechanisms underlying the sex disparity may be attributed to differences in dust exposure level [22], inherited differences in lung structure [23], or differences in sex hormones regulating lung homeostasis upon the challenge of dust exposure.

Occupational exposure to inhalable dust in the iron and steel industry has been shown to compromise lung function and increasing the risk of chronic airflow obstruction in exposed workers [1, 24-26]. In this study, the decline rates of FEV1 and FVC are much faster than those observed in current and former cigarette smokers from a NM, USA-based Lovelace Smokers cohort with a median packyears of 36.0 and relatively healthy lung function, but comparable to those seen in smokers from Pittsburgh Lung Screening Study cohort with a median packyears of 59 and much-compromised lung function [27] from Lung Health Study with all participants having mild to moderate airway obstruction [28], supporting the adverse effects of occupational dust exposure on the age-related decline of spirometry. A case-control study from New York City firefighters has shown that inhalable dust could remain in the lungs and be pro-inflammatory for up to 10 months after cessation of fire smoke exposure [29, 30]. However, we did not see an accelerated FEV1 and FVC decline associated with dust exposure prior to baseline. This finding was not altered even when dust exposure calculated up to each physical examination date was included in the model. Such patterns of results were supported by a most recent study in which prior airborne occupational exposures (e.g., biological dust, mineral dust, gases/fumes, insecticides, herbicides, fungicides, aromatic, chlorinated, other solvents, and metals) were associated with lower lung function measurements but not with annual decline using the Lifelines Cohort Study [31]. This could explain by that most workers in our study have been working at a job title with occupational exposures for more than a decade prior to the baseline visit, thus workers may already develop resistance or saturation, a state of indifference or non-reactivity towards a substance that would normally be expected to excite a more exaggerated health effect[31]. A second explanation is that workers who are sensitive to dust-induced health effects could have switched their job with lower dust exposure or the pre-employment selection criteria could select subjects who are less likely to be affected by occupational dust exposure on lung function decline. Indeed, we do find workers at positions with higher dust exposure tend to be taller than workers from other positions and height is associated with better lung function and greater resilience for age-related lung function decline.

Higher WBC and its differential at baseline were associated with lower longitudinal measurements of lung function and a higher decline rate of FEV1 and FVC among the male workers. Besides, this association is independent of occupational dust exposure. Furthermore, although in average WBC and its differential declined over time, the elevation of WBC and its differential post-baseline was associated with a more rapid decline of FEV1 and FVC in either sex as well. These findings strongly support our hypothesis that elevated systemic inflammatory markers predict a more rapid decline of lung function in workers[32-34]. However, the temporal relationship between baseline WBC and its differential and subsequent lung function change and the compelling dose-response relationship does not directly support a causal relationship between systemic inflammation and lung function impairment. Instead, it may reflect a latent condition that workers with higher systemic inflammation are more vulnerable to dust exposure-induced health effects. The lack of a positive correlation between TWEI and WBC and its differential also suggested this latent condition is more reflective of individual predisposition rather than an acquired trait due to chronic dust exposure. The magnitude of associations of lung function or its decline with WBC and its differential is very comparable and this does not support a more dominant effect of certain leucocytes. Thus, all these suggest systemic inflammation as a holistic readout of individual predisposition that well predicts the severity of pulmonary toxicity caused by dust exposure containing metals in workers[34, 35].

This study benefits greatly from a large sample size, high-quality data for longitudinal measurements of lung spirometry and WBC, and a long follow-up period that together contribute to sufficient statistical power and a more precise assessment of the magnitude of associations. However, this study does have limitations. Because of the lack of reliable occupational monitoring data for all years except 2006 and 2007, for many job posts, and the low exposure category, the job-exposure matrix could not be established for studied subjects. Second, we do not have the resources to assess what has happened in the first ten years of employment of the enrolled workers. A cohort with careful and repeated assessment of occupational exposure would help to disentangle the relationship between dust exposure, systemic inflammation, and the initial decline of lung function.

Conclusion

In conclusion, we have shown that previous occupational exposure to inhalable dust-containing metals resulted in a reduction in FEV1 and FVC. Higher WBC and its differential at baseline or elevation post-baseline were associated with a more rapid decline of FEV1 and FVC. Future studies should focus on a more quantitative assessment of occupational exposure and its constituents, a cohort of new employees to detect early changes of health effects after exposure initiation, and novel local and systemic inflammation biomarkers [36].

List Of Abbreviations

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity

COPD: chronic obstructive pulmonary disease

WBC: White blood cell

NEU: neutrophilicgranulocyte

LYM: lymphocyte

MID: mid-range absolute count

BMI: body mass index

TWEI: time-weighted exposure intensity

ATS: American Thoracic Society

ERS: European Respiratory Society standards

TIC: time in cohort

TWA: time-weighted average

LME: the linear mixed-effects

SE: standard error of mean

M: mean

SD: standard deviation

Q: quartile

Declarations

Ethics approval and consent to participate

The Research Ethics Committee of the Qingdao University School of Medicine approved the study protocol with a waiver of subject consent (QYFYWZLL25933, 16Sep2020).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests

Authors' contributions

YZ and SL conceived of and designed the study; NK, HW, YL, and HZ performed the data collection and data input; NK conducted the data analyses, tabulated and interpreted the results, and drafted the first version of the manuscript; GC, HZ, and SY were occupational hygienists; SY was the certified pulmonary technician and conducted all spirometry; JL, XC, and TW assist with SAS programming; XL and JT edited the first version of the manuscript; AS, YZ, and SL critically edited the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of study subjects by sex

Variable	Male			Female			P [a]
	n	M ± SD	Median (Q1, Q3)	n	M ± SD	Median (Q1, Q3)	
Age (yr)	6188	34.4 ± 9.2	34 (26, 42)	1325	34.7 ± 7.6	35 (29, 40)	0.014
Han Ethnic (n, %)	6188	6129, 99.1		1325	1312, 99.0		0.972
Height (cm)	6110	171.5 ± 5.5	171 (168, 175)	1295	160.1 ± 5.2	160 (156, 164)	<0.001
BMI (kg/m^2)	6110	24.5 ± 3.6	24.38 (21.9, 26.9)	1295	22.3 ± 3.1	21.87 (20.03, 23.88)	<0.001
Current smoker (n, %)	6188	3034, 49.0		1325	0, 0		NC
Packyears	3034	11.0 ± 10.4	7.5 (3.0, 18.0)	0	NA	NA	NC
Years of dust exposure (yr)	6188	12.6 ± 9.7	10.5 (3.3, 20.8)	1325	13.5 ± 8.2	13.9 (5.3, 19.9)	<0.001
Time in cohort (yr)	6188	5.4 ± 2.8	6.00 (3.9, 8.1)	1325	5.3 ± 2.6	6.0 (3.9, 7.9)	0.184
TWEI	6188	0.93 ± 0.74	1.00 (0.00, 1.5)	1325	0.64 ± 0.74	0.19 (0.00, 1.00)	<0.001
NO. of spirometry (n)	6188	3.5 ± 1.4	4 (2, 5)	1325	3.4 ± 1.2	3 (2, 4)	0.004
Spirometry							
FEV1 (ml)	6188	3838.6 ± 622.5	3800 (3410, 4240)	1325	2828.7 ± 440.2	2800 (2520, 3090)	<0.001
FEV1% predicted (%)	6105	102.2 ± 14.3	100.7 (92.0, 111.0)	1295	101.5 ± 14.6	100.0 (90.9, 109.9)	0.098
FVC (ml)	6188	4211.4 ± 623.0	4150 (3730, 4650)	1325	3101.5 ± 467.6	3060 (2750, 3400)	<0.001
FVC% predicted (%)	6105	103.1 ± 14.2	101.5 (92.5, 112.3)	1295	106.0 ± 14.7	104.4 (94.9, 115.4)	<0.001
FEV1/FVC (%)	6188	91.3 ± 6.2	91.3 (87.0, 96.5)	1325	91.3 ± 5.9	91.2 (87.5, 95.9)	0.702
White blood cell count							
WBC (10^9 cells per L)	5949	6.23 ± 1.63	6.0 (5.1, 7.1)	1290	5.31 ± 1.41	5.1 (4.3, 6.1)	<0.001
NEU (10^9 cells per L)	5945	4.00 ± 1.35	3.8 (3.1, 4.7)	1287	3.43 ± 1.13	3.3 (2.6, 4.0)	<0.001
LYM (10^9 cells per L)	5945	21.97 ± 0.54	1.9 (1.6, 2.3)	1287	1.67 ± 0.51	1.6 (1.4, 1.9)	<0.001
MID (10^9 cells per L)	5945	0.26 ± 0.14	0.2 (0.2, 0.3)	1287	0.21 ± 0.11	0.2 (0.1, 0.3)	<0.001
HGB (g/L)	5035	149.35 ± 12.43	150 (141, 158)	1174	123.86 ± 13.16	124 (117, 133)	0.194

Definition of abbreviations: M = mean; SD = standard deviation; Q = quartile; BMI = body mass index; TWEI = time-weighted exposure intensity; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; WBC = white blood count; NEU = neutrophilicgranulocyte; LYM = lymphocyte; MID = mid-range absolute count

[a] T-test for all variables between sexes except for ethnicity which used c^2 Test.

Table 2. The effect of dust exposure on spirometry in male workers using linear mixed-effects model (n = 6100)

Variable	FEV1 (ml/s)						FVC (ml)						FEV1/F
	Model 1			Model 2			Model 1			Model 2			Model
	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β
Intercept	-1263	172.2	<0.001	-1400.4	103.1	<0.001	-2269.7	178.7	<0.001	-2100.1	114.8	<0.001	107.63
Age (yr)	-22.85	1.6	<0.001	-7.76	1.0	<0.001	-21.38	1.7	<0.001	-9.19	1.1	<0.001	-0.10
Current smoker	15.37	10.3	0.135	-3.13	7.3	0.668	18.87	11.3	0.095	2.15	8.2	0.794	-0.07
Packyears (py)	-2.02	0.7	0.004	-0.77	0.5	0.100	-1.87	0.8	0.013	-0.9	0.5	0.086	-0.01
BMI (kg/m^2)	-10.52	1.5	<0.001	-0.62	0.9	0.473	-10.85	1.5	<0.001	-2.88	1.0	0.003	-0.02
Height (cm)	35.89	1.0	<0.001	13.95	0.6	<0.001	43.82	1.0	<0.001	19.74	0.7	<0.001	-0.08
TIC (yr)	-50.78	0.8	<0.001	199.38	5.6	<0.001	-34.36	1.0	<0.001	259.77	6.5	<0.001	-0.49
$Spirometry_{base}$ (ml)				0.80	0.007	<0.001				0.77	0.007	<0.001	
$Spirometry_{base}$ (ml) * TIC				-0.06	0.001	<0.001				-0.07	0.001	<0.001	
TWEI	-21.76	7.3	0.003	-22.04	5.4	<0.001	-28.71	7.6	<0.001	-20.53	6.1	<0.001	0.07
TWEI * TIC				2.00	1.0	0.052				3.78	1.2	0.002	
Years of dust exposure (yr)	-1.31	1.5	0.383	3.12	0.9	<0.001	-2.22	1.6	0.155	4.27	1.0	<0.001	0.02
Years of dust exposure * TIC				-1.43	0.1	<0.001				-1.79	0.1	<0.001	

Definition of abbreviations: SE = standard error of mean; BMI = body mass index; TIC = time in cohort; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; TWEI = time-weighted exposure intensity

Table 3. The effect of dust exposure on white blood cell count and its differential in male workers using linear mixed-effects model (n = 6100)

Variable	WBC (10^9 cells per L)			NEU (10^9 cells per L)			LYM (10^9 cells per L)			MTD (10^9 cells per L)		
	β	SE	P	β	SE	P	β	SE	P	β	SE	P
Intercept	7.0064	0.567	<0.001	4.5810	0.457	<0.001	2.1658	0.197	<0.001	0.2124	0.037	<0.001
Age (yr)	-0.0284	0.005	<0.001	-0.0156	0.004	<0.001	-0.0126	0.002	<0.001	-0.0004	0.000	0.236
Current smoker	0.2943	0.035	<0.001	0.2174	0.030	<0.001	0.0862	0.012	<0.001	0.0137	0.003	<0.001
Packyears (py)	0.0227	0.002	<0.001	0.0178	0.002	<0.001	0.0045	0.001	<0.001	0.0010	0.0002	<0.001
BMI (kg/m^2)	0.0758	0.005	<0.001	0.0552	0.004	<0.001	0.0188	0.002	<0.001	0.0023	0.0003	<0.001
Height (m)	-0.0124	0.003	<0.001	-0.0103	0.003	<0.001	-0.0019	0.001	0.083	-0.0001	0.0002	0.686
TIC (yr)	-0.0409	0.003	<0.001	-0.0250	0.002	<0.001	-0.0099	0.001	<0.001	-0.0053	0.0003	<0.001
TWEI	-0.0108	0.024	0.653	0.0270	0.019	0.164	-0.0312	0.008	<0.001	-0.0075	0.002	<0.001
Years of dust exposure (yr)	0.0175	0.005	<0.001	0.0121	0.004	0.003	0.0045	0.002	0.008	0.0008	0.000	0.018

Definition of abbreviations: TWEI = time-weighted exposure intensity; BMI = body mass index; TIC = time in cohort; WBC = white blood count; NEU = neutrophilicgranulocyte; LYM = lymphocyte; MTD: mid-range absolute count including monocytes, eosinophils and basophils; SE = standard error of mean

Table 4. The sex-specific effect of white blood cell count and its differential count (analyzed as continuous variables) at baseline on spirometry using linear mixed-effects model [a]

Variable	Model [b]	FEV1 (ml/s)						FVC (ml)						FEV1/FVC (%)		
		Male (n = 5949)			Female (n = 1290)			Male (n = 5949)			Female (n = 1290)			Male (n = 5949)		
		β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P
WBC	1	-38.09	6.4	<0.001	-11.88	10.3	0.249	-37.29	6.7	<0.001	-12.65	11.0	0.249	-0.14	0.1	0.(
WBC * TIC	2	-4.33	0.9	<0.001	1.24	1.7	0.455	-4.62	1.1	<0.001	1.31	1.9	0.490	-0.02	0.01	0.1
NEU	1	-33.04	6.1	<0.001	-6.62	9.9	0.504	-31.50	6.4	<0.001	-5.89	10.5	0.576	-0.13	0.1	0.(
NEU * TIC	2	-3.46	0.9	<0.001	1.23	1.6	0.436	-3.58	1.0	<0.001	1.47	1.8	0.417	-0.02	0.01	0.(
LYM	1	-30.30	6.7	<0.001	-17.55	7.9	0.026	-30.33	7.0	<0.001	-17.46	8.4	0.037	-0.10	0.1	0.2
LYM * TIC	2	-3.96	1.0	<0.001	0.20	1.3	0.880	-4.53	1.1	<0.001	0.06	1.5	0.970	-0.002	0.01	0.8
MID	1	3.80	3.7	0.300	11.63	14.1	0.410	0.88	3.8	0.817	4.61	15.0	0.759	0.06	0.0	0.1
MID * TIC	2	-1.54	0.5	0.003	-1.03	2.3	0.647	-1.18	0.6	0.046	-1.94	2.6	0.452	-0.01	0.007	0.(

Definition of abbreviations: WBC = white blood count; NEU = neutrophilicgranulocyte; LYM = lymphocyte; MID = mid-range absolute count including monocytes, eosinophils and basophils; SE = standard error of mean; TIC = time in cohort

[a] β and standard error of mean was calculated using the interquartile range of WBC count and its differential at baseline as the unit of change. Inter-quartile ranges in male workers: WBC: $2.0*10^9$/L; NEU: $1.6*10^9$/L; LYM: $0.7*10^9$/L; MID: $0.1*10^9$/L. Inter-quartile ranges in female workers: WBC: $1.8*10^9$/L; NEU: $1.4*10^9$/L; LYM: $0.5*10^9$/L; MID: $0.2*10^9$/L.

[b] Model 1 assessed the associations of longitudinal lung function measurements as the outcome with baseline WBC and its differential with adjustment for age, smoking status (male only), packyears (male only), height, BMI, TIC, TWEI, and years of dust exposure. Model 2 assessed the effects of baseline WBC and its differential on lung function decline and used longitudinal lung function measurements as the outcome. In addition to all covariates adjusted in model 1, model 2 also included baseline spirometry and baseline WBC and its differential and interaction terms of TIC with TWEI, baseline spirometry, years of dust exposure, and baseline WBC and its differential. A negative β of the interaction term between TIC and baseline WBC in model 2 indicated that higher baseline WBC was associated with a more rapid decline of lung function.

Table 5. The effect of the increase of white blood cell count and its differential post-baseline on lung function decline assessed using a linear mixed-effects model

Variable [a]	FEV1 (ml/s)						FVC (ml)						FEV1/FVC (%)			
	Male (n = 5864)			Female (n = 1260)			Male (n = 5864)			Female (n = 1260)			Male (n = 5864)			Fe
	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β
Change of WBC *TIC	-0.90	0.2	<.0001	-1.18	0.3	<.0001	-0.80	0.2	<.0001	-1.34	0.4	<.0001	-0.004	0.002	0.050	0.(
Change of NEU * TIC	-0.71	0.2	<.0001	-0.96	0.3	0.001	-0.75	0.2	<.0001	-0.99	0.3	0.004	-0.001	0.002	0.455	-0.
Change of LYM *TIC	-0.43	0.2	0.006	-0.24	0.3	0.448	-0.05	0.2	0.790	-0.49	0.4	0.177	-0.009	0.002	<.0001	0.(
Change of MID * TIC	-1.03	0.1	<.0001	-1.37	0.3	<.0001	-1.14	0.1	<.0001	-1.62	0.3	<.0001	-0.0003	0.002	0.834	0.(

Definition of abbreviations: WBC = white blood count; NEU = neutrophilicgranulocyte; LYM = lymphocyte; MID = mid-range absolute count including monocytes, eosinophils and basophils; SE = standard error of mean; TIC = time in cohort

[a] Delta change was calculated as values of WBC and its differential for each non-baseline visit minus baseline value for each individual and was included in the model for assessing its association with lung function decline. The model used longitudinal lung function measurements as the outcome and included age, smoking status (male only), packyears (male only), height, BMI, TIC, TWEI, years of dust exposure, baseline spirometry, baseline WBC and its differential, delta change of WBC and its differential, and interaction terms of TIC with TWEI, baseline spirometry, years of dust exposure, baseline WBC and its differential, and delta change of WBC and its differential. A negative β of the interaction term between TIC and delta change of WBC indicated that an increase in WBC post-baseline was associated with a more rapid decline of lung function. β and standard error of the mean was calculated using the interquartile range as the unit of change. Inter-quartile ranges for delta changes were calculated based on the distribution of annual changes of WBC (i.e., last WBC – baseline WBC /

TIC) and its differential in cohort members with positive delta change values (n = 2211, 2360, 2235, and 1355 for WBC, NEU, LYM, and MID, respectively). WBC: $0.187*10^9$/L; NEU: $0.150*10^9$/L; LYM: $0.060*10^9$/L; MID: $0.014*10^9$/L. The inter-quartile range values were not sex-specific because we want to quantitatively compare the magnitude of associations between sexes.

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