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Household coal combustion, indoor air pollutants, and circulating immunologic/inflammatory markers in rural China

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ABSTRACT

The study aim was to investigate whether household bituminous ("smoky") coal use and personal exposure to combustion emissions were associated with immunologic/inflammatory marker levels. A cross-sectional study of healthy never-smoking women from rural Xuanwei and Fuyuan, China was conducted, which included 80 smoky coal and 14 anthracite ("smokeless") coal users. Personal exposure to fine particulate matter ($PM_{2.5}$) and benzo[a]pyrene (BaP) was assessed using portable devices, while 67 circulating plasma immunologic/inflammatory markers were measured using multiplex bead-based assays. Multivariable linear regression models were employed to estimate associations between smoky coal versus smokeless coal use, indoor air pollutants, and immunologic/inflammatory markers. Six markers were altered among smoky coal users compared to smokeless coal, including significantly decreased interferon-inducible T-cell alpha chemoattractant (CXCL11/I-TAC), and increased serum amyloid P component (SAP). CXCL11/I-TAC was previously found to be reduced in workers exposed to high levels of diesel engine exhaust, which exhibits similar constituents as coal combustion emissions. Further, there was evidence that elevated $PM_{2.5}$ and BaP exposure was associated with significantly diminished levels of the serum amyloid A (SAA); however, the false discovery rates (FDRs) were >0.2 after accounting for multiple comparisons. Inflammatory processes may thus mediate the carcinogenic effects attributed to smoky coal emissions.

KEYWORDS

Smoky coal; combustion; indoor air pollution; immunologic inflammatory markers

Introduction

Combustion of bituminous ("smoky") coal for heating and cooking has led to hazardous levels of indoor air pollutants in households in Xuanwei and Fuyuan, rural counties of southwestern China that have the highest rates of lung cancer among never-smoking women in the country (Downward et al. 2014b; Lan et al. 2008; Mumford et al. 1987; Shen et al. 2009). Lifetime smoky coal use was previously found to be associated with a nearly 100-fold increased risk of lung cancer mortality compared to lifetime anthracite ("smokeless") coal use in Xuanwei and Fuyuan (Barone-Adesi et al. 2012). The suspected genotoxic components of smoky coal including fine particulate matter ($PM_{2.5}$) and polycyclic aromatic hydrocarbons (PAHs) were reported to promote local and systemic inflammation, lipid peroxidation of cellular membranes, and oxidative damage to the genome (Alshaarawy et al. 2013; Farmer et al. 2003; Hajat et al. 2015; Liu et al. 2008; Li et al. 2017 Sorensen et al. 2003; Wei et al. 2009; Wu et al. 2016). Although significant research has been directed towards characterizing the etiology underlying this relationship (Hosgood et al. 2008; Hu et al. 2014; Keohavong et al. 2005; Lan et al. 2002, 1993, 2001; Lan and He 2004; Seow et al. 2014), the biological mechanisms by which these household air pollutants exert their carcinogenic effects remain unclear.

Chronic inflammation is one of many established predisposing factors of carcinogenesis (Lee and Lawrence 2018; Malkinson et al. 2000;

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Supplemental data for this article can be accessed on the publisher's website.

O'Byrne and Dalgleish 2001; Shiels et al. 2015, 2013). Certain circulating levels of immunologic/inflammatory markers are reflective of inflammation and were noted to be altered in response to local and systemic tissue damage, in addition to disease states (Brenner et al. 2014; Kim et al. 2018; Lee and Lawrence 2018; Raulf et al. 2016). In addition, altered levels of some circulating immunologic/inflammatory markers were found to be associated with future enhanced risk of lung cancer (Shiels et al. 2015, 2013, 2017). Further, an occupational study of men exposed to diesel engine exhaust emissions, which possesses common components similar to coal emissions, demonstrated altered levels of nine immunologic/inflammatory markers that were previously linked to increased lung cancer risk in an investigation of never-smoking women (Bassig et al. 2017; Shiels et al. 2017).

Previously in China, coal combustion emissions were shown to be related to impaired immune responses (Jin et al. 2002; Zhang and Smith 2007). Further, components of coal combustion emissions including $PM_{2.5}$ were demonstrated to be associated with altered immune responses (Granum and Lovik 2002; Williams et al. 2011; Zhao et al. 2013), while carcinogenic PAHs were demonstrated to suppress the immune system in animal studies (Burchiel and Luster 2001; Davila et al. 1995). Circulating levels of immunologic/inflammatory biomarkers are reflective of an immune response, both directly and indirectly. However, whether certain immunologic/inflammatory markers are influenced by smoky coal combustion emissions and components of indoor air pollution was not comprehensively investigated in humans. As an initial step towards understanding the impact of smoky coal combustion emissions on immune/inflammatory responses, a cross-sectional molecular epidemiologic study of disease-free, never-smoking women from Xuanwei and Fuyuan, China was conducted. The aim of this study was to investigate smoky versus smokeless coal use, as well as personal exposure to $PM_{2.5}$ and benzo[a]pyrene (BaP; a surrogate for other PAH species), in relation to circulating levels of 67 immunologic/inflammatory markers, which are proxies for various immunologic/inflammatory activities.

Materials and methods

Study population

The Xuanwei Exposure Assessment Study was previously described in detail (Hu et al. 2014). Briefly, this cross-sectional study of healthy never-smoking women from Xuanwei and Fuyuan was conducted to characterize indoor exposure to key components of coal combustion products to provide data for a companion case–control study (Wong et al. 2019). Disease-free female heads-of-household were recruited from 30 villages across Xuanwei and portions of neighboring Fuyuan. Up to five households were selected in each village based upon having a stove that used solid fuel; the residence was more than 10 years old; the same cooking or heating equipment was utilized for the past 5 years; and presence of a never-smoking healthy woman aged 20 – 80 years who was primarily responsible for cooking. During the screening and enrollment phase, the women were asked to report their personal medical history on questionnaires for chronic bronchitis, asthma, tuberculosis, emphysema, pneumonia, benign or malignant tumors, and other conditions. Women who reported any occurrence of these medical conditions were excluded. Data were collected during two time-periods. In the first visit, 148 participants were recruited from August 2008 to February 2009. In the second visit, 53 of the initial participants from 16 villages were re-sampled and 15 additional women recruited from March to June 2009.

Two trained interviewers collected information on household, demographic, and anthropometric characteristics. Activities including cooking, heating, and fuel use during the sampling periods were assessed employing activity questionnaires. Information on fuel types utilized for cooking and heating were also collected. Self-reported fuel type was confirmed via geochemical analysis of collected fuel samples (Downward et al. 2014a). The first assessment of 80 smoky and 14 smokeless coal users was analyzed. Two sequential personal 24-hr air measurements were collected. Whole blood was obtained on the second day after the air measurements.

Personal exposure assessment: $PM_{2.5}$ and PAHs

Personal $PM_{2.5}$ measurements across 24-hr were collected on pre-weighed 37 mm Teflon filters using portable devices with an aerodynamic cutoff of 2.5 μm (Model BGI, GK2.05SH) at a flow rate of 3.5 L/min (±20%) as previously described by Hu et al. (2014). The pump was packed in a hip bag and the portable device attached near the breathing zone of each participant. The sampling bag was placed next to the women's bed while sleeping. All exposed filters were individually placed in Petri slides, sealed in plastic bags, and stored at −80°C before post-weighing. Particulate mass was determined by pre- and post-weighing of the filters in duplicate. $PM_{2.5}$ concentrations ($\mu g/m^3$) were calculated by dividing weights by total volume of air drawn through filters. Approximately 10% of households were randomly selected to have duplicate $PM_{2.5}$ measurements to assess reproducibility. The coefficient of variation (CV) for the $PM_{2.5}$ measurements was 13%.

Further, particle-bound PAHs including fluoranthene (FLT), pyrene (PYR), benzo[a]anthracene (BaA), chrysene (CHR), benzo[b]fluoranthene (BbF), benzo[k]flouranthene (BkF), benzo[a]pyrene (BaP, a surrogate for other highly correlated PAHs), dibenz-(ah)anthracene (DBA), benzo[ghi]perylene (BPE), and indeno(1,2,3-cd)pyrene (IPY) were assessed in addition to gas-phase PAHs including fluorine (FLU), naphthalene (NAP), acenaphthylene (ANY), and phenanthrene (PHE). Particle-bound PAHs (ng/m^3) were collected with 37 mm Teflon filters in portable devices, while personal gas phase PAHs were measured with XAD-2 sorbent tubes at a median airflow rate of 63 mL/min, as previously described (Downward et al. 2014b). PAH species were identified using gas chromatograph connected to a mass spectrometer (Shimadzu QP2010 plus) (Downward et al. 2014b). The CVs for the PAH readings from 13 duplicate samples were 25.6% (FLT), 28.3% (PYR), 20.8% (BaA), 7.6% (CHR), 22.1%(BbF),21.3% (BkF), 25.4% (BaP), 32.4% (IPY), 41.5% (DBA), 25% (BPE), 17.6% (NAP), 30.4%(ANY), 29.3% (FLU), and 46.9% (PHE).

Outcome: immunologic/inflammatory marker panel

Circulating levels of 67 immunologic/inflammatory markers (pg/ml) were measured in plasma from whole blood samples. Markers were measured employing multiplex Luminex bead-based assays (Millipore Inc., Billerica, MA), which were tested for sensitivity and reproducibility previously by Chaturvedi et al. (2011). The intraclass correlations (ICC), CVs, and percentage of samples below the lower limit of quantification (LLOQ) are presented in Supplementary Table 1. Concentrations were calculated using either a four- or five-parameter standard curve. The assay consisted of six panels of immunologic/inflammatory markers including cytokines, chemokines, soluble receptors, and acute phase markers. Samples were determined in singlets except for the high sensitivity cytokine panel, in which plasma samples were measured in duplicate and averaged to calculate the concentration of each marker. Blinded duplicates within each batch and a pooled plasma sample across batches were included to assess assay reproducibility across batches. Markers with high proportions below the LLOQ including IL-33 (82%), thymic stromal lymphopoietin (TSLP) (97%), and interferon type 1 (IFN1) (45%) were excluded from the analyses. Measurements below the LLOQ were assigned a value of ½ the LLOQ. CCL20/MIP3a was measured on two panels and had similar CVs and ICC; thus, only data from the high sensitivity panel were analyzed.

Statistical analysis

The distribution and normality of continuous variables were assessed using histograms and Shapiro–Wilks tests, respectively. $PM_{2.5}$, BaP, and immunologic/inflammatory marker levels were natural log-transformed to approximate normal distributions. Correlations between $PM_{2.5}$ and PAH species were reflected by Spearman's rank correlation coefficient.

Several independent sets of analyses were conducted using separate multivariable linear regression models for each of the 63 immunologic/inflammatory markers as outcomes. First, the associations were assessed for smoky coal versus smokeless coal adjusting for age. Second, the associations were estimated with personal $PM_{2.5}$ exposure adjusting for age, body mass index (BMI), and fuel type. Third, the associations with BaP were assessed adjusting for age, BMI, and fuel

type. Fourth, associations were determined with $PM_{2.5}$ and BaP restricted to smoky coal users while adjusting for age and BMI.

False discovery rates (FDR) were employed to account for the inflated family-wise error rate from multiple testing. Results with p-values <0.05 and FDR <0.2 were considered statistically significant. All analyses were conducted using SAS v9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Study population characteristics

A cross-sectional analysis of 80 smoky and 14 smokeless coal users was conducted. The mean ages were 55 (15.4 SD) and 58 (12.2 SD) years at their initial visit, respectively. In addition, the average BMI of the smoky coal and smokeless coal users was 22 (3.4 SD) and 22 (3.3 SD), respectively. Among smoky coal users, 59% of women were from Xuanwei, while 93% of smokeless coal users originated from Fuyuan.

Correlation between air pollutants

Personal $PM_{2.5}$ was moderately correlated with BaP and other PAHs (Supplementary Table 2). BaP was significantly correlated with most PAH-species including BPE, BaA, BbF, BkF, CHR, DBA, FLT, IPY, and PYR; while moderately correlated with ANY, FLU, NAP, and PHE. Taking these observations into consideration, BaP was deemed as an appropriate surrogate for other PAHs.

Associations between smoky coal versus smokeless coal use and immunologic/inflammatory marker levels

Six markers were markedly altered in smoky coal users compared to smokeless coal users (Table 1). Most notably, interferon-inducible T-cell alpha chemoattractant (CXCL11/I-TAC) was significantly decreased, while acute phase response plasma protein serum amyloid P component (SAP) was significantly elevated. Further, there was evidence that epithelial-derived neutrophil-activating peptide 78 (ENA-78), granulocyte chemotactic protein 2 (CXCL6/GCP2), tumor necrosis factor alpha (TNF-α), and thymus and activation regulated chemokine (CCL17/TARC) levels were markedly reduced among smoky coal users after accounting for multiple comparisons. The other markers with non-significant associations are shown in Supplementary Table 3.

Associations between personal exposure to $PM_{2.5}$ and BaP and immunologic/inflammatory marker levels

Overall and among smoky coal users, there was evidence that increased $PM_{2.5}$ and BaP was associated with decreased levels of acute phase response protein serum amyloid A (SAA) (Table 2). Further, there was evidence that elevated $PM_{2.5}$ exposure was associated with lowered soluble interleukin-4 receptor (sIL-4R) and monocyte chemoattractant protein (CCL13/MCP-4) levels (Table 2). However, the FDRs for the relationships were >0.2 after accounting for multiple comparisons. The other non-significant markers are presented in Supplementary Table 4.

Discussion

Household combustion of carcinogenic smoky coal was significantly associated with altered levels of two immunologic/inflammatory markers, namely CXCL11/I-TAC and SAP, compared to smokeless coal. Further, there was evidence that increased $PM_{2.5}$ and BaP exposure was associated with reduced SAA levels. In addition, there was some indication that elevated $PM_{2.5}$ may be related to lower CCL13/MCP-4 and sIL-4R levels. However, the relationships with $PM_{2.5}$ and BaP were not significant after accounting for multiple comparisons. Taken together, combustion emissions from smoky coal may induce immunologic/inflammatory responses of greater magnitude compared to those derived from smokeless coal.

CXCL11/I-TAC was the most notably altered marker when comparing smoky to smokeless coal and was also reduced in relation to increasing exposure to diesel engine exhaust, an established carcinogen (IARC Working Group on the Evaluation of Carcinogenic Risks 2014; Silverman 2018), in agreement with a previous molecular epidemiologic study (Bassig et al. 2017). This overlap suggests that combustion emission components common to both smoky coal and diesel

Table 1. Notable Comparisons of Circulating Immunologic/Inflammatory Marker Concentrations Among Coal Users in Xuanwei and Fuyuan, China.

Immunologic / Inflammatory Marker	Smoky Coal, Median, n = 80	25th Pctl	75th Pctl	Smokeless Coal, Median, n = 14	25th Pctl	75th Pctl	Crude Median Difference, Smoky vs. Smokeless Coal, pg/ml	β-estimate, Smoky vs. Smokeless Coal	95% CI Lower	95% CI Upper	p-value	FDR
CXCL11/I-TAC	40.4	30.8	73.8	67.6	51.6	137.3	−27.2	−0.51	−0.87	−0.15	0.01	0.20
SAP	3.8E+07	3.0E+07	4.7E+07	3.0E+07	2.8E+07	3.5E+07	7.6E+06	0.25	0.07	0.43	0.01	0.20
CXCL5/ENA78	704.5	443.7	985.4	1172.3	800.1	1352.1	−467.9	−0.38	−0.68	−0.08	0.01	0.27
CXCL6/GCP2	38.9	24.6	61.4	50.5	42.9	110.4	−11.5	−0.41	−0.76	−0.06	0.02	0.33
TNF-α	16.4	13.2	19.9	19.8	16.4	23.0	−3.4	−0.18	−0.35	−0.01	0.04	0.40
CCL17/TARC	21.9	14.7	40.8	36.6	25.5	59.8	−14.7	−0.44	−0.85	−0.02	0.04	0.40

*Immunologic/inflammatory markers with $p < 0.05$ were considered noteworthy. Linear regression models were adjusted for age. β-estimates reflect the average difference in the marker levels (ln pg/ml) between smoky and smokeless coal users. Immunologic/inflammatory markers were natural log transformed. Abbreviations: false discovery rate (FDR), confidence intervals (CI)

Table 2. Notable Associations between $PM_{2.5}$, BaP, and Immunologic/Inflammatory Marker Concentrations Among Coal Users in Xuanwei and Fuyuan, China.

Immunologic /Inflammatory Marker	β-estimate	95% CI Lower	95% CI Upper	p-value	FDR	Immunologic /Inflammatory Marker	β-estimate	95% CI Lower	95% CI Upper	p-value	FDR
I) $PM_{2.5}$, Among All Coal Users, n = 94						II) $PM_{2.5}$, Among Smoky Coal Users, n = 80					
SAA	−0.62	−1.20	−0.04	0.04	0.72	SAA	−0.72	−1.41	−0.04	0.04	0.80
sIL-4R	−0.13	−0.24	−0.02	0.02	0.72	sIL-4R	−0.12	−0.25	0.00	0.05	0.80
CCL13/MCP-4	−0.20	−0.37	−0.03	0.02	0.72	MDC	0.14	0.00	0.28	0.05	0.80
sVEGFR3	−0.20	−0.42	0.01	0.06	0.72	sVEGFR3	−0.25	−0.51	0.00	0.05	0.80
III) BaP, Among All Coal Users, n = 94						IV) BaP, Among Smoky Coal Users, n = 80					
SAA	−0.44	−0.75	−0.13	0.01	0.38	SAA	−0.47	−0.82	−0.13	0.01	0.53
CCL19/MIP-3b	0.11	0.01	0.22	0.03	0.62	sIL-4R	−0.06	−0.13	0.00	0.05	0.82
MDC	0.08	0.01	0.15	0.02	0.62	MDC	0.07	0.00	0.14	0.06	0.82
CXCL12a-b/SDF-1a-b	0.06	0.00	0.12	0.05	0.75	CCL19/MIP-3b	0.10	−0.01	0.22	0.07	0.82

*Immunologic/inflammatory markers with $p < 0.05$ among smoky and smokeless coal users were considered notable. I and III) Linear regression models were adjusted for age, BMI, and coal type. II and IV) Linear regression models were adjusted for age and BMI. β-estimates reflect the incremental change in the marker levels (ln pg/ml) per unit increase in $PM_{2.5}$ (ln μg/m^3) or BaP (ln ng/m^3) exposure level. Abbreviations: false discovery rate (FDR), confidence intervals (CI)

engine exhaust may influence immunologic/inflammatory parameters. CXCL11/I-TAC is a small cytokine of the CXC chemokine family that is induced by interferons and highly expressed in white blood cells (Cole et al. 1998). CXCL11/I-TAC are key molecules involved in white blood cell trafficking, migration, recruitment, and activation during immune/inflammatory response. More specifically, CXCL11/I-TAC displays potent chemoattractant activity for interleukin (IL)-2–activated T cells, but not for unstimulated T cells, neutrophils, or monocytes (Cole et al. 1998). Further, CXCL11/I-TAC counteract the responses mediated by many other inflammatory chemokines that act not only through the CCR3 receptor, but also CCR5 (Petkovic et al. 2004).

SAP was found to be increased among smoky coal users compared to smokeless coal users. SAP is an acute phase glycoprotein of the highly conserved pentraxin family that shares substantial structural similarity with C-reactive protein (CRP) (Pepys et al. 1980). Similar to CRP, SAP exhibits calcium-dependent binding to pathogens and several different molecules including bacterial lipopolysaccharides (LPS; endotoxins) during immune response (de Haas et al. 1998; Srinivasan et al. 1994). However, the biological role of SAP in cancer risk and human health at large remains poorly characterized (Yuste et al. 2007).

The results for CXCL11/I-TAC and SAP suggest that smoky coal emissions may alter recruitment of certain immune cells during innate and cell-mediated inflammatory response to affected tissues, impair immunosurveillance of precancerous cells, and promote certain pro-inflammatory responses. However, the role of these markers in carcinogenesis and consequences of decreased circulating levels are currently unclear. Previously, Shiels et al. (2017) did not detect significant associations between CXCL11/I-TAC, SAP, and incident lung cancer risk in a cohort study of Chinese women. However, these observations may be attributed to issues related to statistical power, as well as measuring immunologic/inflammatory markers at etiologically relevant time-windows for lung carcinogenesis (White, Hunt, and Casso 1998).

Increased $PM_{2.5}$ and BaP concentrations were associated with reduced serum amyloid A (SAA) levels; however, the findings were not significant after accounting for multiple comparisons. Similar to SAP, SAA is an acute phase protein produced by the liver that is regulated by various inflammatory cytokines during both acute and chronic inflammation (Liu 2012). In addition, evidence indicates that CCL13/MCP-4 was diminished in relation to increased personal exposure to $PM_{2.5}$ but was not significant after accounting for multiple comparisons. CCL13/MCP-4 is a chemoattractant for macrophages, leukocytes, immature dendritic cells, and T-cells (Garcia-Zepeda et al. 1996; Mendez-Enriquez and Garcia-Zepeda 2013). The lack of significant associations for these markers might be attributed to limited statistical power. Taken together with the findings for smoky versus smokeless coal, the lack of significant results for $PM_{2.5}$ and PAHs does not imply that these substances are not important carcinogenic components of smoky coal. Rather, other constituents of smoky coal may contribute to the overall carcinogenicity.

Previous studies found correlations between air pollutants and altered immunologic/inflammatory marker levels (Carosino et al. 2015; Holz et al. 2018). With respect to PM, Pope et al. (2016) noted in Provo, Utah that $PM_{2.5}$ exposure was associated with decreased circulating levels of pro-angiogenic growth factors such as epidermal growth factor (EGF), increased levels of anti-angiogenic (i.e. TNF-α) and proinflammatory cytokines including CCL2/MCP2, MIP1α/β, Interleukins-6 (IL6), and IL1β), and markers of endothelial adhesion such as sICAM1 and sVCAM1. Further, Hajat et al. (2015) reported that long-term ambient $PM_{2.5}$ exposure was associated with elevated IL6 concentrations in the Multi-ethnic Study of Atherosclerosis (MESA). In addition, a study in Beijing, China demonstrated that exposure to $PM_{2.5}$ constituents from ambient air pollution was associated with altered immunologic/inflammatory markers including sVCAM1 (Wu et al. 2016). Differences in altered markers among these investigations may be attributed to variations in study design, statistical power, and composition of $PM_{2.5}$. Although few studies examined PAHs, elevated urinary biomarkers of exposures were found to be correlated with increased CRP, brain-derived neurotrophic factor, and activated leukocyte cell

adhesion molecule levels (Alshaarawy et al. 2013; Yang et al. 2016a).

This study had notable strengths. First, the study of non-smoking women mitigated confounding by active cigarette smoking and gender. Second, the participants were exposed to very high levels of indoor air pollution, which enhances the chances of observing a biological effect. Third, the study employed personal air monitoring, which is more accurate and precise compared with area monitors, reducing exposure misclassification. Lastly, the blood samples were collected after air monitoring, which establishes temporality between exposure and outcome.

This study had several limitations. First, the sample size was small; therefore, one could not discount the possibility of chance findings. Second, the cross-sectional nature of the analyses could not capture trajectories in immunologic/inflammatory marker levels. However, reverse causation was unlikely given that marker levels could not feasibly affect coal use, as this was primarily determined by the residential distance to coal sources. Third, there was limited covariate data; therefore, both unmeasured (e.g., secondhand smoke exposure levels) and residual (e.g., outdoor air pollution exposure levels) confounding are possibilities.

In summary, evidence indicated that household combustion of carcinogenic smoky coal was associated with altered levels of multiple immunologic/inflammatory markers compared to smokeless coal. Coal combustion emissions may decrease recruitment of certain immune cells to inflamed tissues, impair immunosurveillance of pre-cancerous cells, and/or promote certain pro-inflammatory responses. The altered markers have yet to be firmly linked to other environmental air pollutants or increased lung cancer risk in human studies. As such, the previously established relations between smoky coal exposure and elevated lung cancer risk in Xuanwei may be potentially mediated through other factors unrelated to these or other immunologic/inflammatory markers. Findings from this investigation may shed light into potential biological mechanisms by which coal combustion and indoor air pollutants influence lung cancer development. However, given the biological complexity of immune response and limitations of the study, caution is recommended when interpreting the findings. Each marker exerts multiple roles in different states of inflammation and may operate as activators or repressors of specific targets. A comprehensive network analysis of longitudinal, repeated marker measurements and continuous exposure monitoring would be required to better understand the immune/inflammatory response to coal combustion emissions.

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Declaration of Interest Statement

We declare no conflicts of interest.

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Statement of Author Contributions

Jason Y.Y. Wong conducted statistical analysis and composed the manuscript. Bryan A. Bassig, Wei Hu, Wei Jie Seow, and Bu-Tian Ji conducted analysis and edited the manuscript. Meredith S. Shiels and Allan Hildesheim provided extensive consultation on immunologic/inflammatory markers and edited the manuscript. Wei Hu managed the study data. George S. Downward and Roel Vermeulen conducted the air pollution exposure assessment and edited the manuscript. Yunchao Huang, Kaiyun Yang, Jihua Li, Jun He, and Ying Chen provided medical/clinical expertise on lung cancer, recruited study participants, and edited the manuscript. Qing Lan and Nathaniel Rothman designed and supervised all aspects of the study.

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