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Nonsteroidal Antiinflammatory Drugs Modify the Effect of Short-Term Air Pollution on Lung Function

To the Editor:

Air pollution, especially fine particulate matter (PM $<2.5 \mu\text{m}$ [PM_{2.5}]), has been recognized as a major public health concern worldwide (1). Previous epidemiological studies demonstrated that short-term PM exposure can trigger acute respiratory events, including the decline of lung function (e.g., FEV₁ and FVC) (2). The activation of systemic inflammatory response is a widely accepted mechanism for the acute effect of PM exposure (1). Nonsteroidal antiinflammatory drugs (NSAIDs) are one of the most commonly prescribed medications for pain and inflammation. Previous studies revealed that daily use of aspirin, a common NSAID, was associated with a reduced risk of chronic obstructive pulmonary disease (3) and a significantly slower progression of emphysema over 10 years (4). Therefore, we hypothesized that the use of NSAIDs may be associated with a smaller decrease in lung function under short-term ambient PM exposure and tested this hypothesis in the longitudinal data of the Normative Aging Study (NAS).

Methods

Established in 1963, the NAS is a cohort of 2,280 male veterans from the Greater Boston area, where air pollution data have been collected since 1995 (5). Participants have been reevaluated every 3–5 years with use of on-site physical examinations and questionnaires, and they have provided detailed information about lifestyle and demographic factors at each visit. Spirometry was assessed with subjects in the standing position, wearing a noseclip, and using a 10-L, water-filled, survey-recording spirometer and an Eagle II minicomputer (Eagle Computer). Standard methods were used to obtain FVC (in L), FEV₁ (in L), percentage of vital capacity (FEV₁/FVC), and maximal midexpiratory flow rate (in L/s, calculated as the average flow rate between 25% and 75% of FVC) (6). All values were corrected to body temperature and pressure saturated with water vapor. Smoking status and pack-years were assessed at the time of pulmonary function testing. Usage of NSAIDs (“no”/“yes”) at each visit was recorded and further

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classified into four groups based on aspirin use (“no”/“yes, nonaspirin NSAIDs only”/“yes, aspirin only”/“yes, aspirin + nonaspirin NSAIDs”). We focused on short-term PM_{2.5} (μg/m³) and black carbon (BC; μg/m³) levels measured on the day of the visit and mean values at 7, 14, 21, and 28 days before each visit. Both concentrations were measured at the Harvard University supersite, which is approximately 1 km from the examination center. Because the study participants lived in the Greater Boston area within a median distance of 20 km from the examination center, we assumed that the ambient air pollutant concentrations could serve as surrogates of the levels of PM at the home addresses of the NAS participants. This study included 3,220 medical visits of 1,078 white participants between 1995 and 2012 with available data of lung function, PM exposures, and NSAID use. The Department of Veterans Affairs Boston Healthcare System approved the NAS, and written informed consent was obtained from each subject.

The primary analysis model was a time-varying linear mixed-effects regression model with random participant-specific intercepts (via PROC MIXED), accounting for the correlation of repeated measures. The model had the main effect terms of PM exposure (PM_{2.5} or BC) and NSAID (aspirin) use, as well as their interaction term “PM exposure × NSAID (aspirin) use,” which was used to test whether the effect of PM exposure on each lung function measurement was modified by NSAID (aspirin) use. We further adjusted for age, height, body mass index, smoking status, pack-years, alcohol intake, systolic blood pressure, hypertension, stroke, coronary heart disease, season of study visits, and corresponding ambient temperature (°C) and relative humidity (%). Corticosteroid usage was also adjusted to exclude the confounding from chronic lung conditions (e.g., asthma and chronic bronchitis). The main effect term of PM_{2.5} concentration was also controlled for in the BC models. Subgroup analyses stratified by NSAID (aspirin) use were then performed to yield the estimates, which were reported as changes in lung function per interquartile range (IQR) increase in PM exposures. In addition, we performed four sensitivity analyses to validate our primary findings. SAS 9.4 software (SAS Institute) was used to perform all data cleaning and analyses. A two-sided *P* value less than 0.05 was considered statistically significant.

Results

The average age of participants at the time of visits was 72.8 ± 7.6 years (Table 1). More than 64% of the visits were by former smokers, and 31% were by never smokers. Most of the observations were from obese or overweight participants and participants who consumed less than two drinks per day. Average FVC and FEV₁ were 3.42 ± 0.69 L and 2.54 ± 0.59 L, respectively. More than 75% of the visits were by participants who received NSAIDs, and most of them (57.8%) used aspirin only. Only about 5% of the visits were by men who used corticosteroids. The 28-day average exposure was 10.85 ± 3.23 μg/m³ (IQR, 4.18) for PM_{2.5} and 0.93 ± 0.36 μg/m³ (IQR, 0.44) for BC. At each exposure window, PM_{2.5} and BC levels were highly correlated (*P* < 0.0001).

Increased PM_{2.5} and BC levels were associated with decreased FVC and FEV₁, and these effects were attenuated among individuals who received NSAIDs (Figure 1). Specifically, an IQR of higher 28-day average concentration of each pollutant was

Table 1. Characteristics of the 1,078 Men Participating in 3,220 Visits in the Normative Aging Study (1995–2012)

Characteristics	Data (N = 3,220)
Age, yr	72.8 (7.6)
FVC, L	3.42 (0.69)
FEV ₁ , L	2.54 (0.59)
FEV ₁ /FVC, %	74.2 (7.8)
MMEF, 25–75%, L/min	236.2 (105.1)
Systolic blood pressure, mm Hg	132.1 (18.0)
Smoking status	
Current smoker	157 (4.9%)
Former smoker	2,057 (64.1%)
Never smoker	993 (31.0%)
Body mass index	
Underweight or normal weight, <25.0 kg/m ²	715 (22.2%)
Overweight, ≥25 to <30 kg/m ²	1,672 (51.9%)
Obese, ≥30.0 kg/m ²	833 (25.9%)
Alcohol consumption (2+ drinks per day)	635 (19.7%)
Major diseases	
Hypertension	2,323 (72.1%)
Stroke	220 (6.8%)
Coronary heart disease	1,007 (31.3%)
Season of the study visit	
Spring (March–May)	803 (24.9%)
Summer (June–August)	927 (28.8%)
Fall (September–November)	925 (28.7%)
Winter (December–February)	565 (17.6%)
Use of NSAIDs	2,426 (75.3%)
Use of aspirin	
Aspirin only	1,862 (57.8%)
Nonaspirin NSAIDs only	373 (11.6%)
Aspirin + nonaspirin NSAIDs	191 (5.9%)
Use of corticosteroids	168 (5.2%)

Definition of abbreviations: MMEF = maximal midexpiratory flow rate;

NSAIDs = nonsteroidal antiinflammatory drugs.

Data are expressed as mean values (SD) for continuous variables and *n* (%) for categorical variables.

associated with lower FVC (PM_{2.5} [−0.097 L; 95% confidence interval (CI), −0.148 to −0.046]; BC [−0.062 L; 95% CI, −0.115 to −0.009]) and FEV₁ (PM_{2.5} [−0.083 L; 95% CI, −0.128 to −0.038]; BC [−0.064 L; 95% CI, −0.109 to −0.019]) in participants not receiving NSAIDs. Among those who used NSAIDs, effects of the same increase in PM concentrations on lung function were attenuated (FVC for PM_{2.5} [−0.058 L; 95% CI, −0.089 to −0.027]; FVC for BC [−0.034 L; 95% CI, −0.063 to −0.005]; FEV₁ for PM_{2.5} [−0.048 L; 95% CI, −0.075 to −0.021]; FEV₁ for BC [−0.053 L; 95% CI, −0.078 to −0.028]). *P* values of corresponding interaction terms (NSAID use × PM exposures) for each relationship were 0.026 (PM_{2.5}–FVC), 0.048 (BC–FVC), 0.043 (PM_{2.5}–FEV₁), and 0.152 (BC–FEV₁), respectively. However, we did not observe strong modifying effects of NSAIDs when examining the relationships between PM exposure and FEV₁/FVC or maximal midexpiratory flow rate, though the directions of modifying effects were consistent with what we observed for FVC and FEV₁.

When looking specifically at aspirin use, subgroups of “nonaspirin NSAIDs only” or “aspirin + nonaspirin NSAIDs” did not show any significant effects on the change of lung function, potentially owing to the relatively small sample size (nonaspirin NSAIDs only, 373; aspirin + nonaspirin NSAIDs, 191). Although

Figure 1. Associations of (A–H) fine particulate matter ($PM_{<2.5} \mu m$ [$PM_{2.5}$]) and (I–P) black carbon with lung function measurements in the exposure window of 28 days, stratified by use of nonsteroidal antiinflammatory drugs and aspirin. All models were adjusted for age (yr), body mass index (underweight or normal weight/overweight/obese), smoking status (current/former/never smoker), alcohol intake (less than two drinks per day or two or more drinks per day), systolic blood pressure, hypertension, stroke, coronary heart disease, season of the study visits (spring/summer/fall/winter), corresponding ambient temperature ($^{\circ}C$), relative humidity (%), and the use corticosteroids (no/yes). $PM_{2.5}$ concentration was also controlled for in the black carbon models. Dots represent point estimates; corresponding lines represent 95% confidence levels. * $P < 0.05$ for interaction term “PM exposure $\times$ NSAID (aspirin) use.” IQR = interquartile range; MMEF = maximal midexpiratory flow rate.

not significant, the FVC and FEV₁ in the “aspirin + nonaspirin NSAIDs” group were still higher than the measures from participants not receiving any NSAIDs, and such patterns were in line with the findings from the subgroup analyses based on NSAID use. The “aspirin-only” group showed trends similar to those of subjects who used any NSAIDs when compared with participants who did not use any NSAIDs. Together with the limited sample size of both the “nonaspirin NSAIDs only” and “aspirin + nonaspirin NSAIDs” subgroups, this may suggest that, in this study, the robust modifying effect of NSAID use was driven mainly by aspirin use.

Four sensitivity analyses further validated the reliability of our primary findings. We also tested the main effects of NSAID (aspirin) use on lung function in the whole population and among the subgroups based on the tertiles of the PM exposures in each exposure window (data not shown). However, we did not find any significant hits.

Discussion

This longitudinal study demonstrates that the use of NSAIDs, especially aspirin, was robustly associated with smaller decreases of FVC and FEV₁ under short-term PM exposure. To the best of our knowledge, this is the first study on the subclinical preventive effects of NSAIDs against the adverse effects of air pollution on lung function. Because we did not find any significant main effect of NSAID (aspirin) use on lung function as reported in the previous study (4), we suggest that NSAID (aspirin) use may mainly affect the negative associations between PM exposures and lung function as an effect modifier. The modifying effect indicates that NSAIDs may mitigate the inflammation induced by PM exposures. Previous studies have shown that two PM inhalation-related inflammatory markers, IL-6 and C-reactive protein (7, 8), when persistently elevated, may indicate a systemic inflammatory phenotype of chronic obstructive pulmonary disease and can be attenuated by aspirin (9, 10). Altogether, the potential alleviation of PM-related inflammation after taking NSAIDs may suggest specific biological mechanisms that still need to be investigated in further studies.

This study has several limitations. NSAID use was ascertained through self-reports and thus may be subject to recall bias and measurement error. NSAID dose and duration were unavailable, and therefore a dose–response analysis was not applicable. Also, as indicated by the sensitivity analysis using a distributed lag model, the estimated effects of PM concentrations on lung function in the primary analysis may be potentially biased by the acute effects of PM exposures—without, however, changing the overall patterns observed in the analyses. Furthermore, although the overall sample size was relatively large, some of the nonsignificant results may be attributable to limited statistical power within the relatively smaller subgroups. This specifically restricted our capacity to fully understand the effect of nonaspirin on the PM–lung function relationship in this study. In addition, multiple comparisons may also potentially induce findings by chance, but we observed consistencies of the significant associations between certain exposures and lung function stratified by NSAID use across each time window and different subgroups in the sensitivity analyses. This may indicate that our findings were not incidental. Last, participants in this study were

older white men, which limits the generalizability of our results to other racial/ethnic groups and to women.

Although massive efforts have been made by governments and regulatory agencies to abate PM emissions, exposure peaks with adverse clinical consequences are still frequent. Our study indicates that NSAIDs may mitigate the acute respiratory effects of PM exposure on aging individuals. Larger prospective studies and randomized clinical trials are highly warranted to further validate our findings and confirm the effectiveness of NSAIDs.

Supplemental methods and results are available upon request. ■

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Silica Exposure and Connective Tissue Disease: An Underrecognized Association in Three Australian Artificial Stone Workers

To the Editor:

We write from Australia, where an emerging epidemic of rapidly progressive silicosis is occurring, caused by occupational exposure to respirable crystalline silica (RCS) generated during the cutting of “artificial stone” benchtops (or countertops). Artificial (or engineered) stone is a product with a high RCS content—between 80% and 90%—and has been widely used for kitchen benchtops over the last 15 years. As of July 25, 2019, 137 cases of artificial stone silicosis, including 9 cases of progressive massive fibrosis, had been described in Queensland alone, and more than 40 cases had been reported in other Australian states (1). There had been at least five deaths nationally. These patients present late, with few respiratory symptoms, and ideally should be detected by surveillance programs. However, surveillance is rarely implemented despite existing legislative provisions, nor are appropriate precautions taken against dust inhalation. There is also limited appreciation of the fact that RCS exposure, with or without silicosis, is associated with autoantibody-positive connective tissue disease (CTD), predominantly systemic sclerosis (SSc). Here, to highlight this issue, we report three cases of men exposed to silica from cutting artificial stone benchtops.

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Clinical details, including positive autoantibody levels, are presented in Table 1, and occupational histories are presented below to illustrate typical exposures.

Case 1

A 45-year-old male had a 15-year history of installing artificial stone kitchen benchtops and stonemasonry. He was referred with exertional dyspnea, arthropathy, sclerodactyly, and Raynaud's phenomenon. He received a diagnosis of silicosis with progressive massive fibrosis. He described very high dust exposure while cutting and grinding artificial stone daily without the use of water suppression, respiratory personal protective equipment, or local exhaust ventilation. He was unemployed for 18 months because of his medical condition. He was considered for lung transplantation but was considered unsuitable and recently died in hospital.

Case 2

A 47-year-old male with a 23-year history of dry-cutting marble blocks with a power saw and installing artificial stone benchtops, monument work, and tombstones was referred with progressive exertional dyspnea and arthropathy. He was diagnosed with pulmonary fibrosis and SSc. He always wore a paper mask while working, but usually dry-cut stone without the use of water suppression or local exhaust ventilation. He had been forced to retire because of his medical condition and is currently being considered for lung transplantation.

Case 3

A 53-year-old male with a 20-year history of dry-cutting marble, granite, and artificial stone benchtops was referred with dyspnea and sicca symptoms. Investigations revealed silicosis with progressive massive fibrosis and pulmonary hypertension. He wore a mask, but dry-cut stone without the use of water suppression or local exhaust ventilation. He underwent successful bilateral single sequential lung transplantation (see Figure 1).

Discussion

Silicosis is an entirely preventable disease that can be controlled by stopping RCS inhalation through workplace precautions such as water suppression, respiratory personal protective equipment (including masks), and local exhaust ventilation (2). Nonetheless, silicosis remains an endemic disease worldwide. There has been a resurgence of this disease recently, reaching epidemic status, with silicosis outbreaks caused by occupational exposure to RCS during the cutting of artificial stone benchtops reported in Israel (3) and most recently in Australia, where the index case was first described in 2017 (4, 5). A few cases of artificial stone silicosis have also been reported in the United States (6) and Europe, and it is highly likely that further cases will be discovered.

The association between silica exposure and CTD development has been documented for over 100 years. Erasmus reported a high risk of scleroderma in South African gold miners (7), and the association between silica exposure and CTD, especially SSc, was subsequently confirmed in many publications. There is now a convincing body of evidence pointing to a causal association between silica and CTD (8–10).

Although recent silicosis outbreaks have been reported as associated with CTD (3), a lack of awareness among