Air Pollution Exposure and Osteoporosis among Retired Workers with Chronic Obstructive Pulmonary Disease

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whether people with corticosteroids usage were most at risk for air pollution effects on incident osteoporpsis.

Materials and Methods

Ethics approval

The study protocol was approved by the Ethics Committee of the Chang-Gung Memorial Hospital and all participants gave written informed-consent before taking part in the study.

Study design and participants

This epidemiological study was designed to monitor changes in yearly air pollutants concentrations and collect health data simultaneously in study participants in general environments. Seventy retired workers with COPD were recruited from the pulmonary outpatient unit of Shuang-Ho Hospital, which is the largest hospital with 1580 beds in New Taipei City from 1 January 2010 to 31 December 2012. The population in New Taipei City, which is situated in northern Taiwan and covers an area of about 2052 km^2, was zapproximately 3.96 million in 2014. Participants who met the following conditions were recruited: (a) diagnosed as having COPD based on clinical evaluation and by pulmonary function test, showing irreversible airflow obstruction and with a FEV1/FVC ratio <70% of predicted value. The classification of COPD severity followed the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [10]. (b) No subject had an acute exacerbation or received therapy with oral corticosteroids for 3 months prior to the study, and all the subjects continued with a stable regimen of medications throughout the study.

Study procedures and measurements

Each participant was interviewed, face-to-face, to evaluate the risk profile, data were collected on age, sex, smoking, inhaled corticosteroids (ICS) usage, degree of spirometric obstruction measured in forced expiratory volume in 1 second (FEV1), exercise capacity as defined by the distance covered in the 6-minute walk test body mass index (BMI), and bone mineral density (BMD).

Lung function parameters were assessed using the Vitalograph Spirotac V™; postbronchodilator forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were measured, and FEV1/FVC was calculated. All included participants had an FEV1/FVC of <70%. The six-minute walk test (6MWT) was carried out according to the American Thoracic Society (ATS) guidelines. The scale has been validated [11] and shown to be reliable [12] for evaluating exercise capacity of participants with COPD. All participants were instructed to walk as far as possible but were allowed to stop and rest during the test [13] Weight and height were measured according to standard methods. Body weight was measured to the nearest 0.1 kg with subjects standing barefoot with light indoor clothing. Height was measured to the nearest 0.1 cm. BMI was calculated according to kg/m^2.

To identify participants at risk of osteoporosis, BMD at the hip, femoral neck and lumbar spine was using a dual-energy X-ray bone densitometry. For categorization, we followed the criteria defined by the WHO [14]. Normal BMD was considered when the values were, at most, less than one standard deviation (SD) from the average healthy young adult reference (T-score). Osteopenia was defined when the T-score was between -1 and -2.5 and osteoporosis if it was less than or equal to -2.5 in any of the explored territories.

Environmental data

Twenty-five monitoring stations operated by the Taiwan Environmental Protection Administration throughout northern Taiwan measured air pollutants and weather data daily. Daily concentrations of particulate matter with aerodynamic diameters <10 μm (PM10), ozone (O_3), NO_2, sulfur dioxide (SO_2), carbon monoxide (CO), and temperature were used to represent 70 participants' air pollution exposure by assigning each of them to the nearest station within 10 km of their residence. Participants were also assigned exposure values equal to the weighted average of all monitors in their area of residence if there was more than one station within 10 km of their residence, with weights proportional to the inverse of the square of the distance between their residence and the monitor.

All daily air pollution and weather data were matched with the interview date of health data collection for each participant. The environmental data averaged by 365 days before the interview date were used to estimate yearly air pollution effects on the risk of osteoporosis.

Statistical analyses

We applied generalized additive models to examine the associations between long-term air pollution exposure and osteoporosis risk. The exposure variables were PM10, PM2.5, O_3, NO_2, SO_2, and CO on 1-year average, and the outcome variable was incident osteoporosis (Yes vs. No). Each regression model included age, sex, BMI, current smoker (Yes vs. No), drinking (Yes vs. No), inhaled corticosteroids usage (Yes vs. No), 6MWD, GOLD. The models also adjusted for smooth function terms as fit by penalized cubic regression spline to reflect possible nonlinear effects of interview date and yearly temperature. Effect modification by ICS usage (Yes versus No) was explored by including interaction terms between long-term air pollution effects and effect modifier. All statistical analyses were performed using R Statistical Software, version 2.4.1.

Results

The age range of the 70 retired workers varied widely (65 to 87 years); 88.6% of the participants were non-smokers; 78.6% of them were using steroids. Only 15 participants had no osteoporosis. Median BMI and 6MWT were 23.2 kg/m^2 and 379.1 m, respectively (Table 1).

Variables
Sex, no (%)
Female

Range	16.1-33.9
6MWD, m	
Mean ± SD	379.1 ± 111.7
Range	78-546
Current smoking, no (%)	
No	62 (88.6)
Yes	8 (11.4)
Drinking, no (%)	
No	53 (75.7)
Yes	17 (24.3)
Osteoporosis, no (%)	
No	15 (21.4)
Yes	55 (78.6)
Inhaled corticosteroids, no (%)	
No	7 (10)
Yes	63 (90)
GOLD, no (%)	
Mild (FEV1≥ 80%)	2 (2.9)
Moderate (50% ≤FEV1 80%)	24 (34.3)
Severe (30% ≤FEV1<50%)	30 (42.9)
Very severe (FEV1<30%)	14 (20)

6MWD, six-minute walk distance; GOLD, global initiative for chronic obstructive lung disease; FEV1, forced expiratory volume in 1 second.

Discussion

This is the first study to demonstrate that long-term exposure (1-year) to NO_2 was associated with increased risk of osteoporosis among retired workers with COPD. Our finding provides epidemiological evidence to support the hypothesized mechanisms of air pollution effects on osteoporosis risk through inflammatory responses. Previous findings of epidemiological [15] and toxicological [16] studies on NO_2 demonstrate that pulmonary inflammation is a possible mechanism to explain the association between short-term exposure to NO_2 and cardiovascular effects. Long-term exposure to air pollution has been reported to be associated with elevated interleukin 6 (IL-6), neutrophils [17] and C-reactive protein (CRP) [18,19] in previous studies. Recently, Calderón-Garcidueñas et al found that 6-year-old children in highly polluted city had significantly higher concentrations of IL-6, monocytes, and higher risk of low bone mass and osteoporosis compared to city with low air pollution levels [9]. It has been reported that inflammatory cytokines can enhance bone resorption and then result in systemic bone loss [20]. The biological mechanisms linking inflammatory responses with bone detrimental effect can be through the activation of p38 mitogen-activated protein kinase pathways [21] or NFκB and the stress activated protein kinase/c-Jun NH2-terminal kinase activity [22]. Taken overall, long-term exposure to air pollution may increase the risk of osteoporosis among vulnerable population such as children and people with COPD through pollution-related inflammatory effects.

The present study found no effects of PM10, O_3, SO_2 or CO on increasing risk of osteoporosis among participants with COPD. The possibility of this finding was that it was caused by the different spatial representativeness of air monitoring stations for NO_2 and other air pollutants [23]. We correlated yearly concentrations of PM10, NO_2, O_3, SO_2 and CO measured at one air monitoring station with those measured at 9 air monitoring stations and found that NO2 had the highest correlation coefficients (r=0.87) compared to PM10 (r=0.57), O_3 (r=0.72), SO_2, (r=0.42) and CO (0.55). It is possible that PM10, O_3, SO_2 and CO measured at the air monitoring station may not properly represent participants' long-term air pollution exposures. The association of incident osteoporosis with PM10, O_3, SO_2 and CO may be biased towards the null due to misclassification [24]. However, the association between NO_2 exposure and the risk of osteoporosis may be overestimated because we used air monitoring station data to represent participants' personal exposures rather than personal monitoring data. These participants' personal NO_2 exposures might be higher than the NO_2 concentrations measured in air monitoring stations because participants' breathing zones were closer to the emission sources, such as gas stoves and vehicles' tail-pipes, than air monitoring stations' sampling inlets [25].

Another interesting finding of this study was that ICS usage seemed to modify the effect of NO_2 exposure on the increased risk of osteoporosis: greater effect was observed among participants with COPD taking ICS as compared to those without taking it. ICS, particularly when combined with long-acting beta2-agonist, improves lung function and health status and reduces exacerbations in moderate to very severe COPD [26]. However its adverse effects, such as pneumonia and impairment in bone health, have long been a concern. Although the impact of ICS on bone density and fracture rate in prospective trials is controversial [27,28], a recent meta-analysis did show a modest but statistically significant increased likelihood of such risk [29]. The present study further heightens this concern when long-term occupational or environmental exposure to air pollution is taken into consideration.

There are several limitations of our study should be noted. First, the limited number of participants we recruited in this study may not be sufficient to fully control for individual differences in health outcome in our generalized additive models. Second, we cannot rule out the possibility of unmeasured confounders even though we have adjusted for several individual-level confounders. Third, the present study did not measure markers that are related to bone metabolism, such as osteocalcin [30] and pro-inflammatory cytokines [31]. Such markers should be analyzed in the future to understand the possible mechanisms underlying the association with NO_2.

Conclusions

Our finding generally supports the hypothesis that long-term exposures to NO_2 can lead to increased risk of osteoporosis among retired workers with COPD. Steroids usage can modify the effect of NO_2 on osteoporosis risk.

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