

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

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Abstract

Background: While effects of occupational and environmental air pollution exposure on inflammation-related cardiopulmonary impairment are well documented, the association linking long-term air pollution exposure and osteoporosis risk is still unclear. The aim of this study was to investigate effects of long-term air pollution exposure on the risk of osteoporosis in people with chronic obstructive pulmonary disease (COPD).

Methods: We collected 70 retired workers' data from the pulmonary outpatient unit of a medical center in Taiwan and air pollution data from the Taiwan Environmental Protection Administration. Associations of 1-year averaged criteria air pollutants [particulate matter with aerodynamic diameters <10 µm (PM₁₀), ozone (O₃), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), and carbon monoxide (CO)] with the risk of osteoporosis were explored by generalized additive models. Effect modification by inhaled corticosteroids (ICS) usage was also assessed in the model.

Results: After controlling for age, sex, body mass index, current smoking, drinking, ICS usage, six-minute walk distance, global initiative for chronic obstructive and smooth functions of interview date and yearly temperature, we observed that increased 1-year averaged NO₂ was significantly associated with 45% higher odds of osteoporosis (odds ratio=1.451 [95% confidence interval=1.124 to 1.778]). Retired workers with ICS usage showed 44% higher odds of osteoporosis associated with increased NO₂.

Conclusions: The risk of developing osteoporosis among retired workers with COPD was positively associated with long-term exposure to 1-year averaged NO₂. ICS usage can modify the effect of NO₂ on osteoporosis risk.

Keywords: Air pollution; Long-term exposure; Osteoporosis; Chronic obstructive pulmonary disease

Introduction

Occupational and environmental exposure to air pollution has been documented as a risk factor for cardiopulmonary effects [1,2]. The presence of preexisting chronic respiratory diseases may also increase cardiopulmonary mortality risk [3]. The World Health Organization (WHO) has predicted that chronic obstructive pulmonary disease (COPD) will be the third leading cause worldwide by 2030 [4]. COPD can be worsened by air pollution exposure [5]. It has been reported that exposure to air pollution such as particulate matter (PM) [6] and nitrogen dioxide (NO₂) [7] is associated with COPD exacerbations, hospitalizations and mortality.

The association between COPD and osteoporosis has been documented in previous study. COPD-related systemic inflammation and the use of systemic corticosteroids can increase bone destruction risk [8]. A recent epidemiological study investigated the bone mineral density in 20 6-year-old children with a lifetime residency in Mexico versus a control group with 15 children from a city with air pollution levels below the USA National Ambient Air Quality Standards. The results showed increased risk of low bone mass and osteoporosis in response to air pollution exposure [9].

Since epidemiological evidence linking air pollution exposure to osteoporosis among people with preexisting lung diseases is still limited. We hypothesized that long-term exposure to air pollutants increased the risk of osteoporosis among people with chronic obstructive pulmonary disease (COPD). We further investigated

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

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 km², was approximately 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/m².

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 (O₃), NO₂, sulfur dioxide (SO₂), 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, O₃, NO₂, SO₂, 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/m² and 379.1 m, respectively (Table 1).

Variables	
Sex, no (%)	
Female	2 (2.9)
Male	68 (97.1)
Age, years	
Mean ± SD	75.2 ± 5.5
Range	66-87
Body mass index, kg/m ²	
Mean ± SD	23.2 ± 3.6

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.	

Table 1: Basic characteristics of 70 study participants with chronic obstructive pulmonary disease (COPD).

Air pollution and temperature measurements are shown in Table 2.

	Mean ± SD	N	Range
PM10, µg/m ³	43.8 ± 8.1	70	24.5-63.1
NO ₂ , ppb	19.5 ± 4.9	70	4.8-39.8
O ₃ , ppb	23.1 ± 8.0	70	4.8-34.6
SO ₂ , ppb	3.7 ± 1.6	70	1.2-7.0
CO, ppm	0.87 ± 0.3	70	0.5-2.0
Temperature, °C	21.5 ± 3.0	70	12.5-29.4
PM10, particulate matter less than 10 µm in aerodynamic diameter; NO ₂ , nitrogen dioxide; SO ₂ , sulfur dioxide; CO, carbon monoxide			

Table 2: Summary statistics of 1-year averaged air pollutants and temperature levels during study period

The mean levels for PM10, NO₂, O₃, SO₂ and CO for 1-year average time periods were 43.8 µg/m³, 19.5 ppb, 23.1 ppb, 3.7 ppb, and 0.9 ppm, respectively.

Table 3 shows increase in osteoporosis risk for 1-unit increase in air pollution on 1-year average, as estimated using generalized additive modelling. We observed associations of osteoporosis risk with increased NO₂ on 1-year average after adjustment for age, sex, body mass index, current smoking, drinking, steroids usage, 6MWD, GOLD and smooth functions of visit date and yearly temperature. For an unit increase in NO₂, we found 45% higher odds of osteoporosis (odds ratio=1.451 [95% confidence interval=1.124 to 1.778]). No significant association of incident osteoporosis was observed with PM10, O₃, SO₂, and CO.

Air pollutant	Osteoporosis*
PM10 (µg/m ³)	1.012 (0.949, 1.079)
NO ₂ (ppb)	1.451 (1.124, 1.778)
O ₃ (ppb)	0.960 (0.893, 1.032)
SO ₂ (ppb)	1.147 (0.848, 1.553)
CO (ppm)	0.672 (0.203, 3.285)
PM10, particulate matter less than 10 µm in aerodynamic diameter; NO ₂ , nitrogen dioxide; SO ₂ , sulfur dioxide; CO, carbon monoxide.	
* All models adjusting for age, sex, body mass index, current smoking, drinking, inhaled corticosteroids usage, six-minute walk distance, global initiative for chronic obstructive and smooth function of interview date and yearly temperature.	

Table 3: Estimated odds ratios (95% CI) for the risk of osteoporosis with 1-unit increase in 1-year averaged among participants with chronic obstructive pulmonary disease.

Table 4 suggests effect modification of NO₂ according to and ICS usage (Yes vs. No). Participants with ICS usage showed 44% higher odds of osteoporosis associated with increased NO₂, whereas participants without using ICS showed no significant increase in osteoporosis. We also found effect modification of NO₂ on osteoporosis risk by current smoking (Yes vs. No) or overweight (BMI 25 vs. BMI <25) (data not shown). There was no effect modification by sex or drink in this study.

	1-year averaged NO ₂ *
Inhaled corticosteroids usage	
Yes	1.443 (1.026, 1.860)†
No	1.147 (0.993, 1.301)
P for interaction	0.034
NO ₂ , nitrogen dioxide.	
*All models adjusting for age, sex, body mass index, current smoking, drinking, six-minute walk distance, global initiative for chronic obstructive and smooth function of interview date and yearly temperature. †p<0.05.	

Table 4: Effect modification of association of osteoporosis with 1-year averaged NO₂ by steroids usage.

Discussion

This is the first study to demonstrate that long-term exposure (1-year) to NO₂ 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 NO₂ demonstrate that pulmonary inflammation is a possible mechanism to explain the association between short-term exposure to NO₂ 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, O₃, SO₂ 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 NO₂ and other air pollutants [23]. We correlated yearly concentrations of PM₁₀, NO₂, O₃, SO₂ 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), O₃ (r=0.72), SO₂ (r=0.42) and CO (0.55). It is possible that PM₁₀, O₃, SO₂ 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, O₃, SO₂ and CO may be biased towards the null due to misclassification [24]. However, the association between NO₂ 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 NO₂ exposures might be higher than the NO₂ 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 NO₂ 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 NO₂.

Conclusions

Our finding generally supports the hypothesis that long-term exposures to NO₂ can lead to increased risk of osteoporosis among retired workers with COPD. Steroids usage can modify the effect of NO₂ on osteoporosis risk.

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