Exposure to Air pollution Increases the Risk of Osteoporosis
A Nationwide Longitudinal Study

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Abstract: Several studies have indicated that air pollution induces systemic as well as tissue-specific inflammation. Chronic inflammatory diseases such as rheumatoid arthritis and chronic obstructive pulmonary disease reduce bone mineral density (BMD), leading to increased release of immune cells from the bone marrow. Therefore, the association between air pollution and osteoporosis remains poorly defined. Therefore, we conducted this population-based retrospective cohort study to evaluate the risk of osteoporosis in Taiwanese residents exposed to air pollution.

We combined 2 nationwide databases in this study. The National Health Insurance Research Database of Taiwan was available from 2000 to 2010. Detailed daily data on air pollution were collected by Taiwan Environmental Protection Agency (EPA) from 1998 to 2010. We calculated the yearly average concentrations of air pollutants from the study start to the date of osteoporosis occurrence, or withdrawal from the NHI program, or December 31, 2010. The yearly average concentrations of air pollutants were categorized into quartiles, and the risks of osteoporosis were evaluated among 4 stages of air pollutants. Among Q1, Q2, Q3, and Q4 of pollutants in all subjects, the adjusted hazard ratios (HRs) of osteoporosis in Q2, Q3, and Q4 were compared with Q1. For carbon monoxide (CO), the adjusted HRs were 1.05 (95% confidence interval [CI], 0.97–1.14), 1.78 (95% CI, 1.65–1.92), and 1.84 (95% CI, 1.71–1.98), respectively. For nitrogen dioxide (NO2), the adjusted HRs were 1.35 (95% CI, 1.25–1.45), 1.24 (95% CI, 1.15–1.35), and 1.60 (95% CI, 1.48–1.73), respectively, in all subjects.

The findings of the present study show that CO and NO2 exposure is associated with an increased risk of osteoporosis in the Taiwanese population.

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Abbreviations: BMD = bone mineral density, CIs = confidence intervals, CO = carbon monoxide, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HRs = hazard ratios, HT = hypertension, ICD-9-CM = International Classification of Diseases, IHD = ischemic heart disease, IRR = incidence rate ratio, NHIRD = National Health Insurance Research Database, Ninth Revision = Clinical Modification, NO2 = nitrogen dioxide.

INTRODUCTION

A cute and chronic air pollution exposure is associated with the risk of respiratory and cardiovascular morbidity and mortality.1–14 Several studies have indicated that air pollution also induces systemic as well as tissue-specific inflammation.5,6 Chronic inflammatory diseases such as rheumatoid arthritis and chronic obstructive pulmonary disease reduce bone mineral density (BMD), leading to increased release of immune cells from the bone marrow.7,8 A Mexican study suggested that children exposed to air pollution had higher interleukin 6 (IL-6) concentrations than unexposed children, but exhibited no significant change in BMD.9 The associations between cigarette smoking and BMD or bone mineral content are also well established.10–14 A study conducted in Oslo revealed a significant association between air pollution and BMD in men aged 75 to 76 years.15 Another study on elderly men from Oslo suggested that the reduction in BMD was associated with exposure to particulate matter.16 However, the association between air pollution and osteoporosis remains poorly defined. Therefore, we conducted this population-based retrospective cohort study to evaluate the risk of osteoporosis in Taiwanese residents exposed to air pollution.
TABLE 1. Comparison of Baseline Characteristics Among Quartiles of CO Yearly Average

| Quartiles of CO yearly average | Q1 (n = 10222) | Q2 (n = 8556) | Q3 (n = 7825) | Q4 (n = 10005) | p | Total (n = 36608) |
|--------------------------------|---------------|---------------|---------------|----------------|---|------------------|
| Age, y, mean ± SD              | 62.6 ± 8.55   | 62.1 ± 8.77   | 62.3 ± 9.5    | 62.2 ± 9.01    | <0.0001 | 62.3 ± 8.84      |
| Male                           | 5362 52.5     | 4498 52.6     | 3855 49.3     | 4823 48.2      | <0.0001 | 18538 50.6       |
| Estrogen supplement            | 2021 19.8     | 1717 20.1     | 1782 22.8     | 2295 22.9      | <0.0001 | 7815 21.4        |
| Diabetic                       | 1344 13.2     | 1123 13.1     | 1052 13.4     | 1360 13.6      | 0.73    | 4879 13.3        |
| Hypertension                   | 4427 43.3     | 3556 41.6     | 3437 43.9     | 4285 42.8      | 0.02    | 15705 42.9       |
| Stroke                         | 316 3.09      | 223 2.61      | 229 2.93      | 274 2.74       | 0.20    | 1042 2.85        |
| COPD                           | 3870 37.9     | 2976 34.8     | 2832 36.2     | 3436 34.3      | <0.0001 | 13114 35.8       |
| Alcoholism                     | 18 0.18       | 18 0.21       | 17 0.22       | 23 0.23        | 0.86    | 76 0.21          |
| Ischemic heart disease         | 2134 20.9     | 1609 18.8     | 1612 20.6     | 1947 19.5      | 0.001   | 7302 20.0        |
| Hyperlipidemia                 | 2171 21.2     | 1715 20.0     | 1574 20.1     | 2135 21.3      | 0.044   | 7595 20.8        |
| Insurance fee                  | 14400 14.0    | 14400–18300   | 18301–21000   | 21000          |        |                  |
| Urbanization                   | 1399 13.7     | 1452 17.0     | 1659 21.2     | 2017 20.2      | 0.0001 | 6421 17.5        |
| Highly urbanized               | 2194 21.5     | 2159 25.2     | 2258 28.9     | 3016 30.1      | <0.0001 | 9627 26.3        |
| Moderate urbanization          | 2957 28.9     | 3758 43.9     | 2147 27.4     | 2973 29.7      | 0.0001 | 11835 32.3       |
| Boomtown                       | 1420 13.9     | 1294 15.1     | 1659 21.2     | 1403 14.0      | 0.0001 | 5776 15.8        |
| General town                   | 2312 22.6     | 956 11.2      | 960 12.3      | 407 4.07       | 4632   | 12.7             |
| Aging town                     | 444 4.34      | 53 0.62       | 60 0.77       | 103 1.03       | 0.0001 | 660 1.80         |
| Agricultural town              | 899 8.79      | 356 4.16      | 165 2.11      | 138 1.38       | 1558   | 4.26             |
| Remote town                    | 554 5.42      | 363 4.24      | 174 2.22      | 99 0.99        | 1190   | 3.25             |

COPD = chronic obstructive pulmonary disease, SD = standard deviation.

MATERIALS AND METHODS

Data Source

This retrospective cohort study was used the Longitudinal Health Insurance Database (LHID) and Taiwan Air Quality Monitoring Database (TAQMD). LHID contained 1 million insurant randomly selected from the original 2000 Registry for beneficiaries joining in the Taiwan National Health Insurance program. This program was set up by Taiwan Bureau of National Health Insurance (TBNIH) in March 1995 and covered over 99% Taiwan residents. LHID included all medical records from the start of 1996 to the end of 2010. The identification of insurant was re-coded before it had been released to researchers because of the Personal Information Protection Act. This study was also approved by the Institutional Review Board of China Medical University, Taiwan. To identify the disease in LHID was according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

TAQMD was set up by Taiwan Environmental Protection Administration Executive Yuan and included daily concentrations of carbon monoxide (CO) and nitrogen dioxide (NO2) in 1998 to 2010 from 74 ambient air quality-monitoring stations, which were distributed over Taiwan. Two databases were linked by the insuring living area and the air quality-monitoring stations location. The living area for the insured persons was defined based on the sought treatment for acute upper respiratory tract infection (AURTI) (ICD-9-CM code 460).

Study Subject, Exposure Measurement, and Comorbidity

We selected people living in areas with the air quality-monitoring stations in this study. Patients with osteoporosis history before the year of 2000 were excluded and they were followed from the start of 2000 to the date for osteoporosis development. People without osteoporosis development were followed to the date for withdrew from the program or the end of 2011.17 The yearly average pollutants’ concentrations for each study subject were calculated from 1998 until the end of observation year. Air pollutant concentrations were grouped into 4 levels based on quartile: CO concentration (Q1: <200.9, Q2: 200.9–248.4, Q3: 248.5–295.9, and Q4: >295.9 ppm) and NO2 concentration (Q1: <6600.8, Q2: 6600.8–8339.2, Q3: 8339.3–9825.1, and Q4: >9825.1 ppm). Comorbidity contained diabetes mellitus (DM, ICD-9-CM code 250), ischemic heart disease (IHD, ICD-9-CM codes 410–414), hypertension (HT, ICD-9-CM codes 401–405), chronic obstructive pulmonary disease (COPD, ICD-9-CM codes 490–496), alcoholism (ICD-9-CM codes 303, 305.0, and V113), hyperlipidemia (ICD-9-CM code 272), and estrogen supplement in women.

Statistical Analysis

To test the distributed difference for sex, insurance fee (<14,400, 14,400–18,300, 18,301–21,000, and >21,000 New Taiwan Dollar), urbanization, and comorbidity among air pollutant concentration levels, $\chi^2$ test was used. One-way analysis of variance (ANOVA) test was used to test the different of mean age among different air pollutant concentration levels. The
incidence of osteoporosis (per 1000 person-years) was counted in different air pollutant concentration levels. Cox proportional hazard regression was used to estimate the hazard ratios (HRs) and 95% confidence interval (CIs) for osteoporosis in Q2–Q4 level for air pollutant concentration compared the lowest one (Q1). Multivariable model was adjusted for age, sex, insurance fee, urbanization, and comorbidity. Kaplan–Meier analysis was used to plot the osteoporosis-free rate curve and log-rank test was used to test the difference among air pollutant concentration levels. All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC) and the Statistical Package for the Social Science (Version 15.1; SPSS Inc, Chicago, IL). All statistical tests were considered statistically significant when 2-tailed P values were <0.05.

RESULTS

According to the location of the Taiwan air quality monitoring station, we collected the data of 36,608 and 36,561 patients without osteoporosis history under conditions of CO and NO2 exposure, respectively. We categorized the CO and NO2 concentrations into 4 levels based on quartiles, ranging from Q1 (the lowest concentration) to Q4 (the highest concentration). The mean age in CO-exposed patients was 62.3 years (SD = 8.84) (Table 1). The proportion of men and women were similar (50.6% vs 49.4%). Women receiving estrogen supplements were more likely exposed to higher NO2 level. More patients with hypertension were exposed to Q3 level, more patients with COPD and IHD were exposed to the lowest level, and more hyperlipidemia patients were exposed to the highest level. In the Q4 group, more people had lower incomes and lived areas with higher urbanization.

The mean age in the NO2 exposure subjects was 62.3 years’ old (SD = 8.84) (Table 2). Men were more likely exposed to lower NO2 level, but more women undergoing estrogen supplement treatment were exposed to higher NO2 level. More patients with hypertension and ISD were exposed to Q2 level, those with COPD were exposed to lowest level, and those with hyperlipidemia were exposed to highest level. People with highest NO2 exposure concentrations were more likely to have lower incomes and live in areas with higher urbanization.

The incidence for osteoporosis increased with CO and NO2 exposure concentration, increasing from 13.58 to 22.25 and from 14.33 to 20.37 per 1000 person-years, respectively (Table 3). After 11 follow-up years, the osteoporosis-free rate for people living in areas with lower CO concentration (Q1 and Q2) was approximately 6.5% higher than those living areas with higher CO concentration (Q3 and Q4) (Figure 1). The osteoporosis-free rate among people with the lowest NO2 exposure concentration was 5% higher than those with highest NO2 exposure concentration. In the multivariable Cox proportional hazard regression, the risk for osteoporosis increased with the corresponding concentrations in Q1 level (Table 3). Regardless of sex, people with highest-level exposure to CO or NO2 exhibited the highest risk for osteoporosis compared with those with lowest level.

### TABLE 2. Comparison of Baseline Characteristics Among Quartiles of NO2 Yearly Average

|           | Q1 (n = 9140) | Q2 (n = 8894) | Q3 (n = 8668) | Q4 (n = 9859) | P       | Total (n = 36561) |
|-----------|---------------|---------------|---------------|---------------|---------|------------------|
| Age, y, mean ± SD | 62.75 ± 8.63  | 62.52 ± 8.87  | 61.84 ± 8.83  | 62.16 ± 8.98  | <0.001  | 62.32 ± 8.84     |
| Male      | 4743 (51.9%)  | 4592 (51.6%)  | 4306 (49.7%)  | 4878 (49.5%)  | <0.001  | 18519 (50.7%)    |
| Diabetic  | 1804 (19.7%)  | 1920 (21.6%)  | 1862 (21.5%)  | 2218 (22.5%)  | <0.001  | 7804 (21.3%)     |
| Hypertension | 1224 (13.4%) | 1177 (13.2%)  | 1168 (13.5%)  | 1303 (13.2%)  | 0.947   | 15675 (42.9%)    |
| Stroke    | 279 (3.1%)    | 263 (3.0%)    | 247 (2.8%)    | 252 (2.6%)    | 0.174   | 1041 (2.8%)      |
| COPD      | 3405 (37.3%)  | 3252 (36.6%)  | 3014 (34.8%)  | 3415 (34.6%)  | <0.001  | 13086 (35.8%)    |
| Alcoholism| 18 (0.2%)     | 19 (0.2%)     | 20 (0.2%)     | 19 (0.2%)     | 0.941   | 76 (0.2%)        |
| Ischemic heart disease | 1889 (20.7%) | 1880 (21.1%)  | 1601 (18.5%)  | 1923 (19.5%)  | <0.001  | 7293 (19.9%)     |
| Hyperlipidemia | 1920 (21.0%) | 1832 (20.6%)  | 1699 (19.6%)  | 2138 (21.7%)  | 0.005   | 7589 (20.8%)     |
| Insurance fee | 14400         | 2454 (27.6%)  | 2646 (30.5%)  | 3259 (33.1%)  | <0.001  | 10457 (28.6%)    |
| Moderate urbanization | 14400–18300   | 1291 (14.5%)  | 1300 (17.3%)  | 1683 (17.1%)  | 0.556   | 5560 (15.2%)     |
| General town | 18301–21000   | 3082 (34.7%)  | 2432 (28.1%)  | 2266 (23.0%)  | <0.001  | 11951 (32.7%)    |
| 21000      | 1785 (19.5%)  | 2066 (23.2%)  | 2087 (24.1%)  | 2649 (26.9%)  | 0.857   | 8587 (23.5%)     |
| Urbanization | Highly urbanized | 1564 (17.1%)  | 1831 (20.6%)  | 2372 (27.4%)  | 5173 (52.5%) | <0.001  | 10940 (29.9%)    |
| Moderate urbanization | 2537 (27.8%) | 3425 (38.5%)  | 3369 (38.9%)  | 2501 (25.4%)  | 0.001   | 11832 (32.4%)    |
| Boomtown   | 1122 (12.3%)  | 1212 (13.6%)  | 1926 (22.2%)  | 1505 (15.3%)  | 0.576   | 5765 (15.8%)     |
| General town | 2203 (25.2%)  | 1337 (15.0%)  | 606 (7.0%)    | 388 (3.9%)    | 0.463   | 4634 (12.7%)     |
| Aging town | 385 (4.2%)    | 96 (1.1%)     | 85 (1.0%)     | 93 (0.9%)     | 0.659   | 659 (1.8%)       |
| Agricultural town | 851 (9.3%)   | 402 (4.5%)   | 175 (2.0%)    | 114 (1.2%)    | 0.542   | 1542 (4.2%)      |
| Remote town | 378 (4.1%)    | 591 (6.6%)    | 135 (1.6%)    | 85 (0.9%)     | 0.118   | 1189 (3.3%)      |

COPD = chronic obstructive pulmonary disease, SD = standard deviation.
TABLE 3. Comparisons of Difference Osteoporosis Incidences and Associated Hazard Ratios Among 4 Levels of Air Pollutants by Sex Stratification

| Osteoporosis | Incidence (1/1000PY) | IRR  | 95% CI   | aHR   | 95% CI   |
|--------------|----------------------|------|----------|-------|----------|
| CO Total     | 1324                 | 13.58| 1.00     | (0.91–1.07) | 1.05     | (0.97–1.14) |
| Male         | 1092                 | 13.34| 0.98     | (0.79–1.08) | 1.01     | (0.86–1.19) |
| Female       | 1316                 | 35.54| 1.61     | (1.50–1.72) | 1.84     | (1.71–1.98) |

CI = confidence interval, IRR = incidence rate ratio, PY = person-years, aHR = adjusted hazard ratio.

*p < 0.05, **p < 0.01, ***p < 0.001.

DISCUSSION

The major findings of this study were the positive associations between risk of osteoporosis and concentrations of air pollutants in both men and women. Several previous studies have indicated that exposure to air pollutants such as NO₂ might induce systemic inflammation.18,19 In bone metabolism, systemic inflammation regulates immune responses and has osteoclastic effects through increased bone-resorption by IL-6. A previous showed that a low concentration of CO (250 ppm) exposure would inhibit osteoclast genesis and decrease osteoclast-mediated bone erosion. Similar results are shown in Table 2, although the CO concentration was a cumulative dose. Therefore, further study is warranted.

In other air studied related to air pollution, the investigators defined the active area of subjects based on geographic information system or insurance area. In this study, we defined the active area of subjects according to the location of the clinics for most frequently sought treatment for AURTI. This definition method was used in our previous study. In addition to aging, estrogen deficiency is a critical factor for osteoporosis in women. However, osteoporosis etiology in elderly men was relatively unclear. Therefore, we performed a statistical analysis stratified by sex, and considered the effect of estrogen supplements in women.

There were several reasons for COPD adjustment. First, osteoporosis has been one of the most common comorbidities in COPD. Second, cigarette smoke is the most important risk factor of COPD, and it also induces the osteoporosis. In addition, alcohol consumption has consistently been recognized as a critical factor of osteoporosis. Because of the lack of information on healthy behaviors in NHIRD, we considered COPD and alcoholism instead of cigarette smoke and alcohol consumption in the Cox proportional hazard regression. Furthermore, we used urbanization as a covariate in multivariate analysis model in accordance with the suggestion about the bone mineral density of residents was significant difference between rural and urban.53 We observed conflicting results regarding the subjects in the Q4 group who did not have the highest prevalence of comorbidity in Tables 1 and 3. It was more likely consistent with the age distribution. The highest prevalence of comorbidities appeared in areas with the highest air pollution level and oldest subjects.

This retrospective population-based cohort study combined 2 nationwide databases. Although the difference in urbanization level among towns throughout Taiwan was considered, potential bias may have resulted from defining the active area according to the location of medical institutions where residents sought AURTI treatment. Although we rejected residents with no medical record related to AURTI between 2000 and 2010, healthy residents are more likely to be exposed to the lowest level of air pollution. This might lead to the underestimation of osteoporosis risk. We have adjusted many covariates, such as age, sex, urbanization, hyperlipidemia, estrogen supplement usage in women, cerebrovascular disease,
and cardiovascular disease. However, because of the various causes of osteoporosis and the limitation of the NHIRD, it was not feasible to consider all of the confounders, such as diet, exercise, related medication, endocrine disease, and gastrointestinal disease, that are likely to be associated with osteoporosis occurrence.

In summary, we observed an increasing trend in the relationship between air pollutant stage and the risk of osteoporosis in both men and women. Exposure to the highest level of air pollutants might increase 39% to 89% risk of osteoporosis. Despite the research limitations, the findings were considered reliable and worthy for conducting further studies.

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FIGURE 1. The Kaplan–Meier curves of freedom for osteoporosis are separated by different pollutant concentrations.
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