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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. 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.

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 (NO_2), 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 NO_2 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, NO_2 = nitrogen dioxide.

INTRODUCTION

Acute and chronic air pollution exposure is associated with the risk of respiratory and cardiovascular morbidity and mortality.[1–4] 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.

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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	2194	21.5	2159	25.2	2258	28.9	3016	30.1	<0.0001	9627	26.3
14400–18300	1399	13.7	1452	17.0	1553	19.9	2017	20.2		6421	17.5
18301–21000	4541	44.4	2900	33.9	2018	25.8	2510	25.1		11969	32.7
21000	2088	20.4	2045	23.9	1996	25.5	2462	24.6		8591	23.5
Urbanization											
Highly urbanized	1636	16.0	1776	20.8	2660	34.0	4882	48.8	<0.0001	10954	29.9
Moderate urbanization	2957	28.9	3758	43.9	2147	27.4	2973	29.7		11835	32.3
Boomtown	1420	13.9	1294	15.1	1659	21.2	1403	14.0		5776	15.8
General town	2312	22.6	956	11.2	960	12.3	407	4.07		4635	12.7
Aging town	444	4.34	53	0.62	60	0.77	103	1.03		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 (TBNHI) 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 (NO_2) in 1998 to 2010 from 74 ambient air quality-monitoring stations, which were distributed over Taiwan. Two databases were linked by the insurant 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 NO_2 concentration (Q1: <6600.8, Q2: 6600.8–8339.2, Q3: 8339.3–9825.1, and Q4: >9825.1 ppb). 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, χ^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 NO_2 exposure, respectively. We categorized the CO and NO_2 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 CO 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 NO_2 exposure subjects was 62.3 years' old (SD = 8.84) (Table 2). Men were more likely exposed to lower NO_2 level, but more women undergoing estrogen supplement treatment were exposed to higher NO_2 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 NO_2exposure concentrations were more likely to have lower incomes and live in areas with higher urbanization.

The incidence for osteoporosis increased with CO and NO_2 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 NO_2 exposure concentration was 5% higher than those with highest NO_2 exposure concentration. In the multivariable Cox proportional hazard regression, the risk for osteoporosis increased with the CO and NO_2 exposure concentrations from 1.05 to 1.84 and from 1.35 to 1.60, respectively, compared with those exposed to the corresponding concentrations in Q1 level (Table 3). Regardless of sex, people with highest-level exposure to CO or NO_2 exhibited the highest risk for osteoporosis compared with those with lowest level.

TABLE 2. Comparison of Baseline Characteristics Among Quartiles of NO_2 Yearly Average

	Quartiles of NO_2 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
Estrogen supplement	1804	19.7	1920	21.6	1862	21.5	2218	22.5	<0.001	7804	21.3
Diabetic	1224	13.4	1177	13.2	1168	13.5	1303	13.2	0.947	4872	13.3
Hypertension	3957	43.3	3874	43.6	3592	41.4	4252	43.1	0.020	15675	42.9
Stroke	279	3.1	263	3.0	247	2.8	252	2.6	0.187	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	2098	23.0	2454	27.6	2646	30.5	3259	33.1	<0.001	10457	28.6
14400–18300	1086	11.9	1291	14.5	1500	17.3	1683	17.1		5560	15.2
18301–21000	4171	45.6	3082	34.7	2432	28.1	2266	23.0		11951	32.7
21000	1785	19.5	2066	23.2	2087	24.1	2649	26.9		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		11832	32.4
Boomtown	1122	12.3	1212	13.6	1926	22.2	1505	15.3		5765	15.8
General town	2303	25.2	1337	15.0	606	7.0	388	3.9		4634	12.7
Aging town	385	4.2	96	1.1	85	1.0	93	0.9		659	1.8
Agricultural town	851	9.3	402	4.5	175	2.0	114	1.2		1542	4.2
Remote town	378	4.1	591	6.6	135	1.6	85	0.9		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	PY	Incidence (/1000PY)	IRR	95% CI	aHR	95% CI
CO	Total	Q1	1324	97496	13.58	1.00		1.00	
		Q2	1092	81858	13.34	0.98	(0.91–1.07)	1.05	(0.97–1.14)
		Q3	1519	67703	22.44	1.62	(1.50–1.74)***	1.78	(1.65–1.92)***
		Q4	1937	87046	22.25	1.61	(1.50–1.72)***	1.84	(1.71–1.98)***
	Male	Q1	345	52899	6.52	1.00		1.00	
		Q2	269	44726	6.01	0.92	(0.79–1.08)	1.01	(0.86–1.19)
		Q3	354	35822	9.88	1.51	(1.30–1.75)***	1.77	(1.51–2.06)***
		Q4	397	45068	8.81	1.35	(1.17–1.56)***	1.71	(1.47–2.00)***
	Female	Q1	979	44597	21.95	1.00		1.00	
		Q2	823	37132	22.16	1.01	(0.92–1.11)	1.07	(0.97–1.18)
		Q3	1165	31881	35.54	1.61	(1.48–1.75)***	1.79	(1.64–1.96)***
		Q4	1540	41978	36.69	1.62	(1.50–1.76)***	1.89	(1.74–2.06)***
NO_2	Total	Q1	1242	86687	14.33	1.00		1.00	
		Q2	1510	80131	18.84	1.30	(1.21–1.40)***	1.35	(1.25–1.45)***
		Q3	1316	79706	16.51	1.14	(1.06–1.24)***	1.24	(1.15–1.35)***
		Q4	1781	87441	20.37	1.40	(1.31–1.51)***	1.60	(1.48–1.73)***
	Male	Q1	315	46563	6.76	1.00		1.00	
		Q2	351	44177	7.95	1.17	(1.01–1.37)*	1.20	(1.03–1.40)***
		Q3	327	41360	7.91	1.17	(1.00–1.36)	1.35	(1.15–1.59)***
		Q4	366	46362	7.89	1.17	(1.00–1.36)*	1.39	(1.18–1.64)***
	Female	Q1	927	40123	23.10	1.00		1.00	
		Q2	1159	35954	32.24	1.36	(1.25–1.49)***	1.40	(1.28–1.52)***
		Q3	989	38346	25.79	1.11	(1.01–1.21)*	1.22	(1.11–1.34)***
		Q4	1415	41078	34.45	1.46	(1.34–1.58)***	1.66	(1.52–1.82)***

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 NO_2 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.[9,20] A previous showed that a low concentration of CO (250 ppm)exposure would inhibit osteoclast genesis and decrease osteoclast-mediated bone erosion.[21] Similar results are shown in Table 2, although the CO concentration was a cumulative dose. Therefore, further study is warranted.

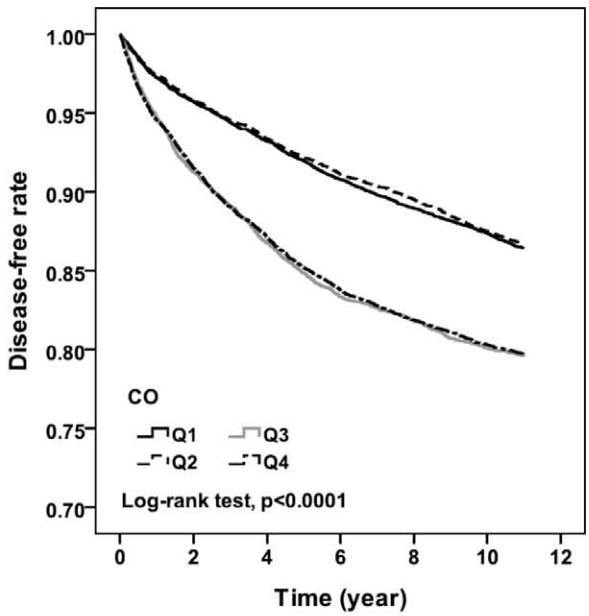
In other air studied related to air pollution, the investigators defined the active area of subjects based on geographic information system or insurance area.[22,23] In this study, we defined the active areas of the subjects according to the location of the clinics for most frequently sought treatment for AURTI. This definition method was used in our previous study.[17]

In addition to aging, estrogen deficiency is a critical factor for osteoporosis in women. However, osteoporosis etiology in elderly men was relatively unclear.[24] 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.[25–27] Second, cigarette smoke is the most important risk factor of COPD, and it also induces the osteoporosis.[28–32] In addition, alcohol consumption has consistently been recognized as a critical factor of osteoporosis.[33,34] 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 andurban.[35]

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,



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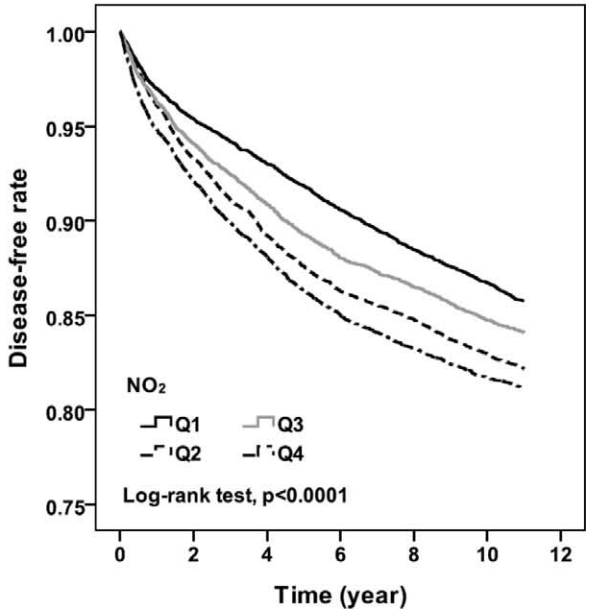

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FIGURE 1. The Kaplan–Meier curves of freedom for osteoporosis are separated by different pollutant concentrations.

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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