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Association between chronic obstructive pulmonary disease and PM2.5 in Taiwanese nonsmokers

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in the world. Not much is known regarding the influence of non-smoking-related risk factors on COPD in Taiwan. We examined the relationship between exposure to particulate matter < 2.5 μm ($PM_{2.5}$) and COPD among nonsmokers in Taiwan.

Methods: This population-based study involved 3941 nonsmoking Taiwanese adults who were recruited in the Taiwan Biobank project between 2008 and 2015. Air pollution data between 2006 and 2011 were obtained from the air quality monitoring database (AQMD). COPD was the outcome of interest and was identified using the National health insurance Research Database (NHIRD). The data were analyzed using multiple logistic regression models.

Results: Compared with the lowest quartile ($PM_{2.5}$ = 29.38), exposure to $PM_{2.5}$ in the highest quartile (> 38.98 μg/m^3) was significantly associated with COPD (OR, 1.29; CI 1.01–1.65) after multivariate adjustments. However, exposures to concentrations of 32.07–38.98 μg/m^3 (OR, 1.12 CI 0.88–1.44) and 29.38–32.07 μg/m^3 (OR, 1.09 CI 0.84–1.41) showed positive but non-significant associations. However, the test for trend was significant (Ptrend = 0.043). The ORs for exposure to sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO) and NOx (nitrogen monoxide (NO were not significant.

Conclusions: Based on our data, exposure to $PM_{2.5}$ at concentrations greater than 38.98 μg/m^3 increased susceptibility to COPD among Taiwanese nonsmokers. Combatting COPD would involve integrating tobacco control and pollution management strategies.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructive lung disease characterized by long-term breathing problems and poor airflow. It is the fourth leading cause of death worldwide (Rabe et al., 2007) with an estimated prevalence of 6.1% in Taiwan (Cheng et al., 2015). It is the 7th most common cause of death in Taiwan (Hsiao et al., 2015; Wei et al., 2017). By and large, tobacco smoking is a common risk factor for COPD (Cheng et al., 2015). Besides smoking, air pollution has also been associated with increased rates of COPD exacerbations and emergency hospital admissions (Anderson et al., 1997; Ko et al., 2007). Associations between COPD and air pollution have been widely reported (Lee et al., 2007; Moore et al., 2016; Tian et al., 2014; Yang and Chen, 2007).

Single nucleotide polymorphisms (SNP) have also been associated with respiratory phenotypes (Holloway et al., 2012). Genetic association studies have identified SNPs that raise COPD and lung cancer risk (Xiao et al., 2017; Young et al., 2009). Findings from a previous review

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suggested that genetic factors can influence the mechanisms of lung injury caused by air pollutants (Xiao et al., 2017). Lung cancer is one of the comorbidities in COPD. Both conditions are caused by an interaction between genetic susceptibility and environmental influences (Ziółkowska-Suchanek et al., 2015). Several microRNAs in the blood of COPD patients have been linked to lung cancer (Keller et al., 2018). To date, gene polymorphisms have been widely investigated in lung cancer. However, not much is known about the genetic components that may affect the development of COPD, especially in Taiwan. Rs4488809, a variant located on chromosome 3q28 in the TP63 locus has been consistently associated with non-small cell lung cancer (NSCLC). An interaction was also found between this variant and household air pollution on lung cancer risk (Hosgood et al., 2015).

Particulate matter < 2.5 μm ($PM_{2.5}$) is one of the air pollutants that are of particular concerns to respiratory health (DeVries et al., 2016). It is a major risk factor for common and complex diseases in Taiwan. About 7.5% (4 million) of deaths registered in 2016 were linked to $PM_{2.5}$ (Guo et al., 2018). Individuals with pre-existing lung diseases are said to be more vulnerable. Exposure to $PM_{2.5}$ has been associated with immune disorders in mice, hence aggravating COPD (Zhang et al., 2018). The prevalence of COPD among Taiwanese adults remains relatively high even though that of smoking has decreased steadily over the years. Most of the studies investigating the relationship between air pollution and COPD in Taiwan have recruited samples mainly from the National Health Insurance Research databases (NHIRD). Such investigations have not ruled out smokers. Moreover, single nucleotide polymorphisms were not considered in the study.

However, based on a recent study, most people with COPD have never smoked (Shen et al., 2016). Considering that lung cancer is a comorbidity in COPD and that little is known on the genetic components affecting COPD in Taiwan, we included a lung-cancer associated variant (TP63 rs4488809) in the model and assessed the relationship between $PM_{2.5}$ and COPD among nonsmokers.

2. Methods

2.1. Data source

The study data were obtained from three data sources: 1) Taiwan biobank (which contained phenotypic and genotypic data for 2008–2015). 2) The National Health Insurance Research Database (NHIRD, with data available for 2000–2015). These databases were linked and information about COPD was obtained using personal identification numbers. 3) The Air Quality Monitoring Database (AQMD, data available from 2006 to 2011) provided by the environmental protection agency (EPA). The Institutional Review Board of Chung Shan Medical University approved this study.

2.2. Air pollution exposure and confounders

In 1998, fully automated air quality monitoring stations were set up by the Environmental Protection Agency in Taiwan. These stations supply daily readings of the concentrations of air pollutants that are saved in the Air Quality Monitoring Database (AQMD).

Air pollution data used in this study were collected from the 77 air quality-monitoring stations situated in 74 municipalities. The measurement period was from 2006 to 2011. Every municipality had a monitoring station except 3 which had two stations each. Air pollution exposure was estimated based on the municipality of residence. The daily readings (measurements) taken at each monitoring station represented the level of exposure for each participant residing in that zone. The annual average concentrations of $PM_{2.5}$ including the other pollutants (SO_2, O_3, CO, NOx, and NO_2) were determined.

2.3. Study participants

Our initial recruitment included 12,374 Taiwan Biobank participants. After excluding current and former smokers (n = 3266), people with no air pollution data in their place of residence (n = 5156), as well as people with incomplete information (n = 11), 1406 men and 2535 women were included in the final analysis.

Patients were defined as having COPD if they had either two-outpatient visits or one-time hospitalization with reported International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) 490, 491, 492, 494, and 496 codes. The diagnostic period was from 2000 to 2015. Alcohol drinkers were defined as persons who reported drinking more than 150 ml of alcohol per week during the six months prior to health examination. Physical activity included any amount of exercise activity at least 3 times a week and lasting for at least 30 min each time. A secondhand smoker was defined as someone who was currently exposed to smoke from other people for at least 5 min.

2.4. Statistical analysis

Chi-square and t-tests were used to compare the differences between discrete and continuous variables. Logistic regression analysis was used to investigate the effects of $PM_{2.5}$ on COPD. $PM_{2.5}$ was used in quartiles because it was the main variable of interest. In addition, it is a group 1 carcinogen, which has also been linked to a significant amount of lung diseases. Adjustments were made for sex, age, education, alcohol drinking, physical activity body mass index (BMI), secondhand smoke, and FEV1/FVC. We also examined the TP63 variant (rs4488809) among COPD patients. This variant was selected because of its previous association with lung cancer as well as its interaction with air pollution. SNP genotyping was performed at the National Center for Genome Medicine in Academia Sinica using the Axiom-Taiwan Biobank Array Plate (Affymetrix, Santa Clara, CA, USA). SNPs were excluded if they deviated from the Hardy-Weinberg equilibrium or if the minor allele frequency (MAF) was less than 0.05. The odds ratios (ORs) with their 95% confidence intervals were estimated. Statistical analyses were performed using the statistical analysis system (SAS) software (version 9.4) and PLINK.

3. Results

Basic characteristics of study participants are shown in Table 1. Of the 3941 nonsmokers recruited, 791 had COPD. The mean ages were significantly different between patients with and without COPD. Table 2 shows the association of COPD with $PM_{2.5}$. Exposure to PM2.5 greater than 38.98 $\mu g/m^3$ was significantly associated with COPD (OR, 1.29; CI 1.01–1.65). However, exposures to concentrations of 32.07–38.98 $\mu g/m^3$ (OR, 1.12 CI 0.88–1.44) and 29.38–32.07 $\mu g/m^3$ (OR, 1.09 CI 0.84–1.41) were not significant. Nonetheless, the test for trend was significant (Ptrend = 0.043). Table 3 shows the association between COPD and TP63 variant (rs4488809). The T allele was the risk allele. Compared with the CC genotype, the OR for COPD was 1.23 (CI 1.01–1.50) for the CT genotype and 1.26 (CI 1.00–1.58) for the TT genotype. Table 4 shows the association between $PM_{2.5}$ and COPD, with TP63 rs4488809 included in the model. Including TP63 variant into the model did not have an impact on the association between exposure to $PM_{2.5}$ and COPD. The OR was 1.29 (CI 1.01–1.65) for $PM_{2.5}$ greater than 38.98 $\mu g/m^3$, 1.13 (CI 0.88–1.45) for PM2.5 ranging from 32.07 to 38.98 $\mu g/m^3$, and 1.09 (CI 0.84–1.42) for exposures ranging from 29.38 to 32.07 $\mu g/m^3$. The ORs for exposure to SO_2, O_3, CO, and NOx were not significant.

4. Discussion

It is worthy to note that this is the first study to merge the NHIRD, Taiwan Biobank and EPA to determine the relationship between $PM_{2.5}$

Table 1
Demographic characteristics of study participants.

	Control n	(n = 3150)%	COPD n	(n = 791)%	P value	
$PM_{2.5}$ (μg/m^3)[a]					0.852	
$PM_{2.5} \leq Q1$	730	23.17	177	22.38		
$Q1 < PM_{2.5} \leq Q2$	978	31.05	238	30.09		
$Q2 < PM_{2.5} \leq Q3$	643	20.41	167	21.11		
$PM_{2.5} > Q3$	799	25.37	209	26.42		
Other pollutants (mean, SD)						
SO_2(ppb)	4.34	1.60	4.23	1.46	0.063	
O_3 (ppb)	27.96	3.46	27.99	3.42	0.798	
CO(ppm)	0.56	0.20	0.54	0.19	0.126	
NO_x (ppb)	26.03	11.81	25.37	11.01	0.138	
TP63(rs4488809)					0.061	
CC	867	27.52	185	23.39		
CT	1491	47.33	399	50.44		
TT	792	25.14	207	26.17		
Age (mean, SD)	48.09	10.89	53.80	10.87	< .0001	*
Sex					0.630	
Female	2032	64.51	503	63.59		
Male	1118	35.49	288	36.41		
Education					< .0001	*
Elementary school	139	4.41	82	10.37		
Junior and Senior high school	1082	34.35	286	36.16		
University above	1929	61.24	423	53.48		
Alcohol drinker					0.798	
Never	3018	95.81	761	96.21		
Former	30	0.95	8	1.01		
Current	102	3.24	22	2.78		
Physical activity					0.001	*
No	1809	57.43	403	50.95		
Yes	1341	42.57	388	49.05		
BMI					0.032	*
BMI < 18.5	119	3.78	19	2.4		
18.5 ≤ BMI < 24	1686	53.52	399	50.44		
24 ≤ BMI < 27	804	25.52	235	29.71		
BMI ≥ 27	541	17.17	138	17.45		
Secondhand smoke					0.274	
No	2843	90.25	724	91.53		
Yes	307	9.75	67	8.47		
FEV1/FVC (mean, SD)	71.17	18.98	72.34	17.41	0.098	

[a] Quartile of PM2.5: Q1 = 29.3838, Q2 = 32.0705, Q3 = 38.9754.

and COPD. In addition, the TP63 rs4488809 variant and secondhand smoke were included in the model. Based on our findings, exposure to $PM_{2.5}$ at concentrations greater than 38.98 μg/m^3 was associated with increased susceptibility to COPD among non-smokers in Taiwan. Lower $PM_{2.5}$ quartiles (that is, levels below 38.98 μg/m^3) did not show significant associations with COPD. There has been an increasing interest in the role of particulate matter (PM) in the development of COPD (Jo et al., 2018). Compared with PM_{10}, $PM_{2.5}$ is a stronger risk factor for cardiopulmonary morbidity and mortality. Based on a previous review, an increase in $PM_{2.5}$ of 10 μg/m^3 was associated with a 2.5% increased risk of COPD-related emergency department (DeVries et al., 2017). In the same study, ambient concentrations of NO_2 and SO_2 were also found to be positively associated with COPD morbidity and mortality. However, in our study, both particles showed no significant associations. Similar findings have been previously reported (Schikowski et al., 2014). Recently in Korea, COPD-related visits increased significantly in the $PM_{2.5}$ area of Chungcheon (Jo et al., 2018). Based on a current study involving Taiwanese adults aged 20 years and older, long-term exposure to ambient $PM_{2.5}$ has resulted in an increased incidence of COPD and a decline in lung function (Guo et al., 2018). Other studies have found positive but non-significant results on the association between COPD and ambient $PM_{2.5}$ (Lepeule et al., 2012; Schikowski et al., 2014). In another study, an unexpected negative association was found but was attributed to the complex air chemistry of low concentration of PM in the area concerned (DeVries et al., 2016).

Female nonsmokers are more predisposed to COPD than men (Han et al., 2007). This has been associated with sexual dimorphism. In our study, 61.4% of cases with COPD were women. The mean age of male participants was 49.62 years while that of women was 48.72 years. Indian women were found to have an earlier age of onset of COPD compared to men (Walia et al., 2016). So far, studies investigating the relationship between COPD and air pollution in Taiwan have focused on data collected from the NHIRD. However, the database is limited in that it does not contain lifestyle information such as smoking.

As mentioned above, TP63 rs4488809 is one of the variants that have been associated with lung cancer, one of the comorbidities in COPD. The addition of this variant into the model did not alter the effect PM2.5 had on COPD. However, the TT and CT genotypes appeared to increase the risk of COPD. This is an indication that this SNP is likely to be among those polymorphic variants that affect both COPD and lung cancer incidence. More studies would help to clarify these associations.

Even though most of the COPD cases have been attributed to smoking, a noticeable proportion of cases (ranging from 22.9% in the UK to 69% in India) are reported to be nonsmokers (Walia et al., 2016). Less is known regarding the influence of non-smoking-related risk factors on COPD in Taiwan. In this study, we excluded current and former smokers and adjusted for second-hand smoke in the model. This enabled us to appreciate the extent to which $PM_{2.5}$ might affect COPD. However, our study is limited in that individual breathing data were not available in the database. Exposure misclassification may not be ruled out; however, such misclassification would be considered non-differential. In addition, information on the actual distance between each participant's residence and the air quality monitoring station was not available.

In conclusion, we have attempted to show an association between

Table 2
Overall association between $PM_{2.5}$ and COPD in nonsmoking Taiwanese adults.

Characteristic	OR	95% CI			P value	
$PM_{2.5}$ (μg/m³)[a]						
$PM_{2.5} \leq Q1$	ref					
$Q1 < PM_{2.5} \leq Q2$	1.09	0.84	–	1.41	0.517	
$Q2 < PM_{2.5} \leq Q3$	1.12	0.88	–	1.44	0.357	
$PM_{2.5} > Q3$	1.29	1.01	–	1.65	0.043	*
P for trend					0.043	*
SO_2 (ppb)	0.97	0.91	–	1.04	0.405	
O_3 (ppb)	0.98	0.95	–	1.02	0.345	
CO (ppm)	0.51	0.14	–	1.87	0.312	
NO_x (ppb)	1.00	0.98	–	1.03	0.874	
Sex						
Female	ref					
Male	1.06	0.89	–	1.27	0.523	
Age	1.05	1.04	–	1.06	< .0001	*
Education						
Elementary school	ref					
Junior and Senior high school	0.69	0.51	–	0.95	0.023	*
University above	0.77	0.55	–	1.06	0.107	
Secondhand smoke						
No	ref					
Yes	0.99	0.75	–	1.33	0.967	
Alcohol drinker						
Never	ref					
Former	0.89	0.40	–	1.99	0.777	
Current	0.85	0.52	–	1.38	0.506	
Physical activity						
No	ref					
Yes	0.86	0.72	–	1.02	0.085	
BMI (kg/m²)						
BMI < 18.5	0.81	0.48	–	1.34	0.405	
18.5 ≤ BMI < 24	ref					
24 ≤ BMI < 27	1.09	0.90	–	1.32	0.366	
BMI ≥ 27	1.09	0.87	–	1.36	0.474	
FEV1/FVC	1.00	1.00	–	1.01	0.188	

[a] Quartile of PM2.5: Q1 = 29.3838, Q2 = 32.0705, Q3 = 38.9754.

Table 3
Association of TP63 rs4488809 with COPD in nonsmoking Taiwanese adults.

Characteristic	OR	95% CI			P value	
TP63 (rs4488809)						
CC	ref					
CT	1.23	1.01	–	1.50	0.039	*
TT	1.26	1.00	–	1.58	0.046	*
P for trend					0.047	*
Sex						
Female	ref					
Male	1.08	0.90	–	1.29	0.414	
Age	1.05	1.04	–	1.06	< .0001	*
Education						
Elementary school	ref					
Junior and Senior high school	0.66	0.49	–	0.91	0.010	*
University above	0.71	0.52	–	0.98	0.036	*
Secondhand smoke						
No	ref					
Yes	0.99	0.74	–	1.32	0.951	
Alcohol drinker						
Never	ref					
Former	0.90	0.41	–	2.01	0.802	
Current	0.84	0.52	–	1.38	0.494	
Physical activity						
No	ref					
Yes	0.87	0.74	–	1.04	0.124	
BMI (kg/m²)						
BMI < 18.5	0.81	0.49	–	1.35	0.423	
18.5 ≤ BMI < 24	ref					
24 ≤ BMI < 27	1.10	0.91	–	1.33	0.316	
BMI ≥ 27	1.08	0.86	–	1.36	0.493	
FEV1/FVC	1.00	1.00	–	1.01	0.092	

[a]Quartile of PM2.5: Q1 = 29.3838, Q2 = 32.0705, Q3 = 38.9754.

Table 4
Association of $PM_{2.5}$ with COPD in never smokers, with TP63 rs4488809 included in the model.

Characteristic	Genotype model					
	OR	95% CI			P value	
$PM_{2.5}$ (μg/m³)[a]						
$PM_{2.5} \leq Q1$	ref					
$Q1 < PM_{2.5} \leq Q2$	1.09	0.84	–	1.42	0.516	
$Q2 < PM_{2.5} \leq Q3$	1.13	0.88	–	1.45	0.330	
$PM_{2.5} > Q3$	1.29	1.01	–	1.65	0.045	*
P for trend					0.042	*
TP63(rs4488809)						
CC	ref					
CT	1.23	1.01	–	1.50	0.042	*
TT	1.25	1.00	–	1.57	0.050	*
P for trend					0.049	*
SO_2 (ppb)	0.98	0.92	–	1.04	0.430	
O_3 (ppb)	0.98	0.95	–	1.02	0.331	
CO (ppm)	0.52	0.14	–	1.90	0.325	
NO_x (ppb)	1.00	0.98	–	1.03	0.898	
Sex						
Female	ref					
Male	1.06	0.89	–	1.27	0.504	
Age	1.05	1.04	–	1.06	< .0001	*
Education						
Elementary school	ref					
Junior and Senior high school	0.69	0.50	–	0.95	0.022	*
University above	0.76	0.55	–	1.05	0.100	
Secondhand smoke						
No	ref					
Yes	0.99	0.74	–	1.32	0.955	
Alcohol drinker						
Never	ref					
Former	0.88	0.39	–	1.97	0.756	
Current	0.85	0.52	–	1.39	0.520	
Physical activity						
No	ref					
Yes	0.86	0.73	–	1.02	0.092	
BMI (kg/m²)						
BMI < 18.5	0.81	0.49	–	1.35	0.419	
18.5 ≤ BMI < 24	ref					
24 ≤ BMI < 27	1.09	0.90	–	1.32	0.369	
BMI ≥ 27	1.08	0.86	–	1.36	0.504	
FEV1/FVC	1.00	1.00	–	1.01	0.196	

[a] Quartile of PM2.5: Q1 = 29.3838, Q2 = 32.0705, Q3 = 38.9754.

$PM_{2.5}$ and the development of COPD. Based on these findings, combatting COPD would involve integrating tobacco control and pollution management strategies.

Declaration of interest

None.

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Appendix A. Supplementary data

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