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Original Article

Effects of fine particulate matter and NOx and their interaction on the admission rate for major depressive disorder—A population-based study

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Purpose: Few studies have analyzed the association between ambient temperature/air pollutants and inpatient admissions for major depressive disorder (MDD). The aim of this population-based study was to investigate the association between inpatient admissions due to MDD and ambient temperature/air pollutants over a period of 7 years.
Methods: Among 185,689 patients identified from the Psychiatric Inpatient Medical Claim dataset of Taiwan from 2000 to 2005, 41,312 MDD patients were included in this study. Any psychiatric hospitalization of these patients from January 1, 2006 to September 30, 2012 was recorded. Meteorological and air pollutant data were collected from the databases of the Central Weather Bureau and Environmental Protection Administration, respectively.
Results: Females had higher odds of MDD admission. Admission rates proportionally increased with elevated ambient temperature, $PM_{2.5}$ levels, and NO_x levels for same-day, 7-day lagged, and 14-day lagged exposures. Higher NO_x was positively associated with admission rate. Compared with lower levels of $PM_{2.5}$, higher levels of $PM_{2.5}$ had a protective effect on MDD admissions for 7-day and 14-day lagged exposures. There was a positive relationship between the interactions of both high levels of $PM_{2.5}$ and NO_x and MDD admissions after controlling for other factors.
Conclusion: More research is needed to identify potential environmental risks to decrease MDD admissions.

Keywords: Major Depressive Disorder. Temperature. $PM_{2.5}$, NO_x

1. Introduction

According to the World Health Organization (WHO), the lifetime prevalence of major depressive disorder (MDD) is approximately 10%. In 2012, around 350 million people experienced depression. MDD may become the principal cause of disability worldwide by 2030 [34]. During the World Mental Health Survey conducted in 17 countries, an average of 1 in 20 people reported having an episode of depression in the previous year [34]. In Taiwan, the

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prevalence of probable common mental disorders (including nonpsychotic, depressive, and anxiety disorders) was 23.8% in 2010, double that in 1990 [11]. MDD has been suggested to have multifactorial etiologies, involving genetic, biological, environmental, and psychological factors [2]. In terms of environment-related risk factors, the impact of air pollution on MDD has rarely been discussed. Although air pollution has been implicated in numerous health outcomes, particularly cardiovascular and respiratory diseases [8, 33], its effects on major depressive episodes have been underexplored and the results of studies that have been conducted have been inconclusive.

Air pollution is caused by particulate matter (PM), gaseous pollutants, and metallic and organic compounds. Ambient air pollution has been correlated with emergency department visits for depressive disorder and suicide attempts [3, 17, 31]. Moreover, daily emergency visits for depression have been positively correlated with PM in the cold winter period in Canada [17] and $PM_{2.5}$ has been demonstrated to be associated with higher depressive scores during colder months. However, no significant seasonal pattern in hospital admissions for depression has been found in Brazil, a subtropical area [16]. Although the pathophysiological mechanisms linking $PM_{2.5}$ and depression remain unknown, MohanKumar et al. found that air pollutants, specifically PM, induce inflammation and oxidative stress in the brain, potentially contributing to depression [23]. Unlike high-latitude countries, Taiwan, located at between 21°45′ N and 25°56′ N, has typically subtropical weather. It is usually hot and humid all year round, with vague demarcation between the seasons. In recent years, air pollution in Taiwan has worsened, with increasing concentrations of $PM_{2.5}$. Furthermore, rather than local sources, such as motor vehicles and power plants, the largest single source of $PM_{2.5}$ in Taiwan is long-range air pollution from neighboring China [12]. Therefore, it is necessary to urgently investigate the effects of $PM_{2.5}$ on MDD in Taiwan.

Other than $PM_{2.5}$, air pollutants include nitrogen dioxide and nitric oxide, which together are referred to as oxides of nitrogen (NO_x). NO_x gases react to form smog and acid rain and are central to the generation of PM and ground-level ozone, both of which are associated with adverse health effects [10]. Vert et al. have found that the rate of depression increases two-fold for each 10 $\mu g/m^3$ increase in nitric oxide level [32]. Although $PM_{2.5}$ and NO_x have been implicated in the pathogenesis of MDD, the effects of the interaction between $PM_{2.5}$ and NO_x on MDD have rarely been discussed.

In this study, we investigated the association between ambient temperature/air pollutants and MDD-related inpatient admissions in subtropical Taiwan. We used a nationwide database to test the hypothesis that inpatient admissions for MDD correlate with ambient temperature/ambient air pollutants over a 7-year period. The effects of the interaction of NO_x and $PM_{2.5}$ on MDD admission rate were also investigated.

2. Methods

2.1. Study population

Taiwan's National Health Insurance Program (NHIP), established in 1995, is a single-payer compulsory social insurance system, which regulates the disbursement of health care funds and promises equal access to health care for all citizens, including psychiatric patients. The study data were retrieved from the Psychiatric Inpatient Medical Claim (PIMC) dataset, a subset of the National Health Insurance Research Database (NHIRD), which contains inpatient expenditures, ambulatory care expenditures, details of ambulatory care, and inpatient orders, in addition to a registry of beneficiaries from 2000 to 2012. We defined cases with MDD (*International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes: 296.2 and 296.3) as having two or more outpatient diagnoses or one inpatient diagnosis of MDD. Then, we extracted diagnostic code information from the PIMC dataset according to the ICD-9-CM codes. Of 185,689 patients from the PIMC dataset from 2000 to 2005, 41,312 patients diagnosed with MDD were included in this study. Any psychiatric admission (target event) of these patients from January 1, 2006 to September 30, 2012 was noted. The Institutional Review Board of Chung Shan Medical University Hospital, Taiwan approved this study (IRB No. CS2-14035). All authors had access to the study data and reviewed the final

manuscript.

2.2. Meteorological parameters

Meteorological parameters (monthly mean ambient temperature, temperature increase compared with the previous month, rainfall, and sunlight) were collected from the database of the Central Weather Bureau in Taiwan (http://www.cwb.gov.tw/ Retrieved July 30, 2011). Data from six weather stations (in northwestern, midwestern, southwestern, northeastern, mideastern, and southeastern areas, respectively) were averaged to represent the monthly meteorological parameters of Taiwan. As Taiwan is a small island, with a total land mass of slightly over 36,188 km^2, we used only a monthly mean value for climatic data to explore the association with admission rate for MDD. Daily meteorological measurements were obtained from the average of 24-h readings of ambient temperature. NO_x and $PM_{2.5}$ data from 76 monitoring stations were obtained from the Environmental Protection Administration of Taiwan from 2005 to 2012.

2.3. Statistical analysis

Demographic and meteorological characteristics of MDD admissions were converted to observed person-days. The dependent variables were the numbers of psychiatric admissions during the study period from January 2006 to September 2012. Monthly admission rates per 100,000 people for major depressive episodes were calculated. As the effects of climatic conditions on admissions may not be immediate, different time lags for the effects of air pollutants and meteorological factors were modeled: same-day (i.e., 0-day lagged), 7-day lagged, and 14-day lagged exposures. Poisson analysis was performed on psychiatric admissions and adjusted for intercorrelations (age, sex, ambient temperature, $PM_{2.5}$, and NO_x). Furthermore, we tested the interaction between $PM_{2.5}$ and NO_x after controlling for other variables. All analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Table 1 presents the demographic and meteorological data for observed person-days of MDD admission. Females had higher odds of MDD admission. Admission rates proportionally increased with increases in ambient temperature, $PM_{2.5}$ levels, and NO_x levels for same-day, 7-day lagged, and 14-day lagged exposures. The median values (interquartile ranges) for ambient temperature, $PM_{2.5}$, and NO_x were 24.8 (19.9-28.1), 29.4 (21.6-40.4) and 22.8 (19.4-27.9), respectively.

Table 2 presents the results of the Poisson regression model for the relationship between the meteorological data and the admission rate after adjusting for age, sex, ambient temperature, $PM_{2.5}$, and NO_x when appropriate. The adjusted relative risk (aRR) of the admission rate significantly increased among insured patients aged <20 years, 20–40 years, and 40–64 years when compared with patients aged >65 years for same-day, 7-day lagged, and 14-day lagged exposures. Males had a significantly lower admission rate than females (aRR: 0.69 for all three exposure times). Using 20–25 °C as a reference, lower temperature (< 20 °C) resulted in a significantly lower risk of admission, whereas higher temperatures (25–30 °C and >30 °C) resulted in an increased risk of admission. Compared with low $PM_{2.5}$ concentrations (<20 μg/m^3), high $PM_{2.5}$ concentrations (≥60 μg/m^3) were negatively associated with MDD admission for 7-day and 14-day lagged exposures but not for same-day exposure. Higher NO_x level (>20 ppb) was positively associated with the admission rate when compared with lower NO_x level (< 10 ppb). We further explored the interaction between NO_x and $PM_{2.5}$ (Figure 1). NO_x > 30 ppb was associated with a higher risk of admission only when $PM_{2.5}$ was >60 μg/m^3 (aRR: 2.31, 95% CI: 1.30–4.10; aRR: 2.42, 95% CI: 1.26–4.66; aRR: 2.13, 95% CI: 1.19–3.83, respectively, for the three exposure times).

4. Discussion

In this population-based study, the correlation between MDD admissions and meteorological factors, including ambient temperature, NO_x, and $PM_{2.5}$, and the interaction between NO_x and $PM_{2.5}$ were examined. Admission rates increased among females and insured adults aged <20 years and

40–65 years, as well as in the presence of elevated ambient temperature and increased $PM_{2.5}$ and NO_x levels. Regarding the interaction between $PM_{2.5}$ and NO_x levels, our data demonstrated that higher $PM_{2.5}$ (≥60 μg/m^3) is inversely correlated with MDD admission. However, this trend was reversed if NO_x also increased (≥30 ppb).

Ambient temperature change has been suspected to exacerbate mental and behavioral disorders [22]. Studies from both developed and developing nations have indicated an increase in hospital admissions during periods of high ambient temperature among individuals with psychological disorders [13, 29]. High-temperature exposure may be associated with the occurrence of depressive disorder [7, 27].

In Taiwan, which generally has a hot and humid

Table 1. Admission rates of patients with major depressive disorder

	Lag 0 days			Lag 7 days			Lag 14 days		
	Observed person-days	Admission		Observed person-days	Admission		Observed person-days	Admission	
		Event	Rate†		Event	Rate†		Event	Rate†
Age									
<20	487643	127	2.6	487608	126	2.6	487573	123	2.5
20-40	39630746	6505	1.6	39538714	6450	1.6	39446591	6413	1.6
40-65	40895883	12603	3.1	40777934	12540	3.1	40659938	12491	3.1
≧65	13424262	1719	1.3	13387644	1704	1.3	13350979	1694	1.3
Gender									
Female	49203373	13251	2.7	49072587	13173	2.7	48941719	13121	2.7
Male	45235161	7703	1.7	45119313	7647	1.7	45003362	7600	1.7
Ambient temperature (°C)									
<20	24118989	5014	2.1	24118989	5155	2.1	24118989	5001	2.1
20-25	24473804	5788	2.4	24403362	5577	2.3	24403362	5709	2.3
25-30	42142446	9236	2.2	41966254	9186	2.2	41719435	9109	2.2
>30	3703295	916	2.5	3703295	902	2.4	3703295	902	2.4
$PM_{2.5}$ (μg/m^3)									
<20	18064886	3726	2.1	18064886	3843	2.1	18064886	3900	2.2
20-40	51701958	11407	2.2	51490545	11388	2.2	51384792	11286	2.2
40-60	21308505	5012	2.4	21273284	4774	2.2	21132218	4716	2.2
≧60	3363185	809	2.4	3363185	815	2.4	3363185	819	2.4
NO_x (ppb)									
<10	342571	34	1.0	342571	50	1.5	342571	49	1.4
10-20	27394622	4486	1.6	27147988	4589	1.7	27112739	4537	1.7
20-30	49602226	11915	2.4	49602226	11817	2.4	49390656	11750	2.4
≧30	17099115	4519	2.6	17099115	4364	2.6	17099115	4385	2.6

†per 10000 person-days.

subtropical climate, a retrospective population-based study using the nationwide Longitudinal Health Insurance Database revealed that the risk for MDD is higher among residents of regions with an average temperature of >23 °C [5]. This is consistent with our result that higher temperature exposure (median 24.8 °C for our cohort) is associated with MDD incidence.

Climatic variables have been found to modulate biological correlates that may be related to depression, such as plasma tryptophan and serotonin availability [21, 25], platelet serotonin levels [20], and brain serotonin turnover [18]. Climatic variables may partially explain the exacerbations of mood or psychotic symptoms in MDD.

$PM_{2.5}$ is one of the most dangerous and fervently

Table 2. Poisson regression analysis for the relationship between air pollution and major depressive disorder

	Lag 0 days				Lag 7 days				Lag 14 days			
		95% C.I.				95% C.I.				95% C.I.		
	aRR	Lower	Upper	p-value	aRR	Lower	Upper	p-value	aRR	Lower	Upper	p-value
Age												
≥65	1				1				1			
<20	1.86	1.55	2.22	<0.001	1.87	1.56	2.24	<0.001	1.82	1.52	2.19	<0.001
20-40	1.36	1.29	1.43	<0.001	1.36	1.29	1.43	<0.001	1.36	1.29	1.43	<0.001
40-65	2.38	2.27	2.51	<0.001	2.39	2.28	2.52	<0.001	2.40	2.28	2.52	<0.001
Sex												
Female	1				1				1			
Male	0.69	0.67	0.71	<0.001	0.69	0.67	0.71	<0.001	0.69	0.67	0.71	<0.001
Ambient temperature (°C)												
20-25	1				1				1			
<20	0.87	0.84	0.91	<0.001	0.93	0.89	0.96	<0.001	0.88	0.84	0.91	<0.001
25-30	1.16	1.12	1.21	<0.001	1.15	1.11	1.20	<0.001	1.12	1.08	1.16	<0.001
>30	1.50	1.39	1.62	<0.001	1.44	1.34	1.56	<0.001	1.41	1.31	1.52	<0.001
$PM_{2.5}$ (μg/m^3)												
<20	1				1				1			
20-40	1.05	0.98	1.12	0.153	1.06	1.00	1.13	0.065	1.02	0.96	1.09	0.439
40-60	1.09	0.95	1.24	0.212	0.99	0.86	1.13	0.836	1.04	0.91	1.19	0.565
≧60	0.61	0.36	1.04	0.069	0.42	0.23	0.79	0.007	0.54	0.31	0.93	0.027
NO_x (ppb)												
<10	1				1				1			
10-20	1.60	1.14	2.25	0.007	1.12	0.85	1.49	0.429	1.15	0.87	1.53	0.335
20-30	2.73	1.94	3.83	<0.001	1.87	1.41	2.48	<0.001	1.96	1.48	2.61	<0.001
≧30	2.42	1.63	3.60	<0.001	2.09	1.50	2.92	<0.001	1.93	1.37	2.72	<0.001

†Adjusted for age, sex, ambient temperature, $PM_{2.5}$, and NO_x.

discussed sources of air pollution. Although $PM_{2.5}$ was not highly related to MDD admissions in our study, NO_x was found to proportionally increase the odds of MDD admission. It is possible that our study outcome is MDD admission for conditions that are more severe than just depressive mood. Previous findings on the effects of air pollution on MDD have been inconclusive. Some studies have demonstrated a positive association between air pollution and depression [1, 9], while other studies have reported no association [9]. Higher concentrations of $PM_{2.5}$ and NO_x have been found to be significantly associated

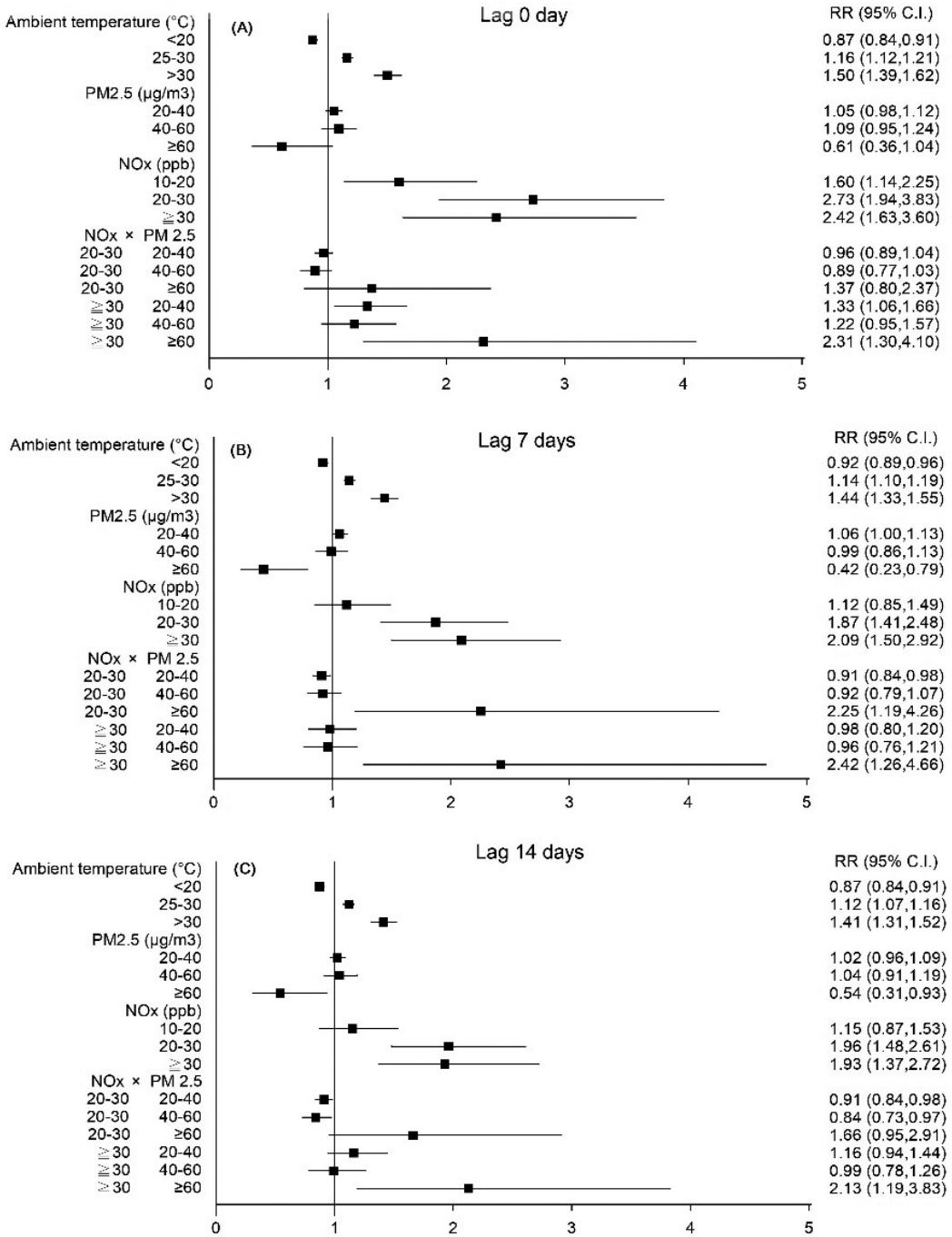

Figure 1. Forest plot of interactions of PM2.5 and NOx with MDD admissions.

with a higher incidence of depressive symptoms in older women [1]. From a meta-analysis of 22 studies, among ambient air pollutants, only short-term exposure to NO_2 has been found in association with increased odds of depression [9].

Exposure to PM air pollution may induce or exacerbate depression through increased oxidative stress and systemic inflammation [14, 17, 30] or through promotion or aggravation of chronic diseases [3, 26]. However, the interaction between NO_x and $PM_{2.5}$ has been unclear, and how this interaction may affect MDD has rarely been discussed.

During the COVID-19 lockdown period in China in 2020, most businesses were closed, with reduced emissions of primary air pollutants, including NOx, resulting in marked decreases in $PM_{2.5}$ concentration [28]. Although the cause is unknown, the atmospheric concentration of $PM_{2.5}$ has been reported to be highly correlated with ozone formation and other atmospheric oxidants [15] [19]. There have been increasing numbers of reports on the adverse effects of air pollution on the brain [4]. Biophysical and meteorological factors may affect the concentrations of cerebral neurotransmitters, causing mental or behavioral changes [6]. PM and NO_x have strong inflammatory effects [24] and can increase the risk of depression by altering the functioning of the central nervous system through a proinflammatory response pathway. This may partially explain our finding that the combination of high $PM_{2.5}$ and NO_x is associated with MDD admissions.

Our study has several strengths. The study data were extracted from a nationwide database spanning 12 years, sample size was large, and selection bias was minimized. In addition, no such study has been undertaken in Taiwan, an island with no significant seasonal variations. We modeled three time lags (same-day exposure, 7-day lagged exposure, and 14-day lagged exposure) for meteorological factors and air pollutants to explore their effects on MDD.

The main limitation of this study was the assessment of air pollution exposure using data from a monitoring station to serve as a proxy for personal exposure, which might have led to exposure measurement errors. To protect patient confidentiality, the residential sites of our psychiatric patients could not be retrieved, and we could not explore the associations in different locations in Taiwan.

However, we averaged the meteorological data and air quality data from 76 monitoring stations and adjusted for several covariates to represent general levels of exposure. Information regarding family history, medication adherence, and life events, which are potential risk factors for MDD, were also unavailable from the NHIRD.

5. Conclusion

We found that females, insured adults aged <20 years and 40–65 years, elevated ambient temperature, and increased $PM_{2.5}$ and NO_x levels are associated with MDD admission. Interaction was noted for both high $PM_{2.5}$ and NO_x levels. The findings of our study may be used to identify potentially modifiable environmental risk factors for MDD. Interventions aimed at reducing exposure to or harmful sequelae from environmental triggers of MDD can prevent or mitigate disease progression.

Declaration of Competing Interests

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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Author Contributions

Po-Chung Ju: conceptualization, methodology, writing - original draft, writing - review & editing, funding acquisition. Ming-Hong Hsieh: conceptualization, methodology, formal analysis,

writing - review & editing, funding acquisition. Jong-Yi Wang: conceptualization, methodology, writing - review & editing. Yu-Hsun Wang: methodology, analysis, investigation, writing - review & editing. Jeng-Yuan Chiou: methodology, investigation, writing - review & editing. Cheng-Chen Chang: conceptualization, methodology, investigation, formal analysis, writing - review & editing, supervision.

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