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Long-Term Exposure to Air Pollution and the Occurrence of Metabolic Syndrome and Its Components in Taiwan

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Background: Metabolic syndrome (MetS), a major contributor to cardiovascular and metabolic diseases, has been linked with exposure to air pollution. However, the relationship between air pollutants and the five components of MetS [abdominal obesity, elevated triglyceride, decreased high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and elevated fasting blood glucose levels], has not been clearly described.

Objective: We examined the association between long-term exposure to air pollutants and the occurrence of MetS and its components by using a longitudinal cohort in Taiwan.

Methods: The MJ Health Research Foundation is a medical institute that conducts regular physical examinations. The development of MetS, based on a health examination and the medical history of an MJ cohort of 93,771 participants who were enrolled between 2006 and 2016 and had two or more examinations, was compared with estimated exposure to air pollutants in the year prior to health examination. The exposure levels to fine particulate matter [PM with an aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$)] and nitrogen dioxide (NO_2) in the participants' residential areas were estimated using a hybrid Kriging/land-use regression (LUR) model executed using the XGBoost algorithm and a hybrid Kriging/LUR model, respectively. Cox regression with time-dependent covariates was conducted to estimate the effects of annual air pollutant exposure on the risk of MetS and its components.

Results: During the average follow-up period of 3.4 y, the incidence of MetS was 38.1/1,000 person-years. After mutual adjustment and adjustments for potential covariates, the results indicated that every 10-$\mu g/m^3$ increase in annual $PM_{2.5}$ concentration was associated with an increased risk of abdominal obesity [adjusted hazard ratio (aHR) = 1.07; 95% confidence interval (CI): 1.01, 1.14], hypertriglyceridemia (aHR = 1.17; 95% CI: 1.11, 1.23), low HDL-C (aHR = 1.09; 95% CI: 1.02, 1.17), hypertension (aHR = 1.15; 95% CI: 1.09, 1.21), and elevated fasting blood glucose (aHR = 1.15; 95% CI: 1.10, 1.20). Furthermore, $PM_{2.5}$ and NO_2 may increase the risk of developing MetS among people who already "have" some components of MetS.

Discussion: Our findings suggest that in apparently healthy adults undergoing physical examination, exposure to $PM_{2.5}$ and NO_2 might be associated with the occurrence of MetS and its components. https://doi.org/10.1289/EHP10611

Introduction

In the 2017 Global Burden of Disease Study, cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) accounted for 31.8% (17.8 million) and 1.8% (1 million), respectively, of all-cause global deaths for that year.[1] Metabolic syndrome (MetS), a cluster of modifiable components—namely abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure (BP)—is regarded as an indicator of CVD and T2DM development and as a contributor to all-cause mortality.[2,3] Therefore, the identification of MetS can help in the prevention of the onset of the aforementioned diseases.

Traditional risk factors for MetS include older age, the male sex, low socioeconomic status, and poor lifestyle habits.[2] In addition, increasing bodies of epidemiological evidence from Asia,[4–6] Europe,[7–9] and the United States[10,11] demonstrate that ambient air pollution may contribute to an increased risk of MetS and its components. A meta-analysis of cohort studies revealed that every 5-$\mu g/m^3$ annual increment of fine particulate matter [PM with an aerodynamic diameter of $\leq$2.5 μm ($PM_{2.5}$)] was associated with a 4% higher risk of MetS.[12] Overall, the population-attributable risk of MetS associated with long-term $PM_{2.5}$ exposure was estimated to be 12.28%.[12]

To control air pollution and prevent its destructive effect on health, legislation has been promulgated in several countries, including in the United States,[13] the European Union member states,[14] China,[15] and Taiwan.[16] Notably, a quasi-experimental study revealed that the adverse effects of $PM_{2.5}$ on dyslipidemia was mitigated after the implementation of the Air Pollution Prevention and Control Action Plan in China.[17]

However, longitudinal studies evaluating the effects of gradually decreasing concentrations of ambient air pollutants are limited. Studies using a time-dependent Cox regression analysis revealed that $PM_{2.5}$ exposure was associated with a higher risk of MetS and its components.[11,18] Similarly, traffic-related air pollutants were reported to be associated with MetS-related outcomes, such as T2DM.[19] Therefore, exploring the long-term health effects of nitrogen dioxide (NO_2), an indicator of traffic-related emissions,[20] is also valuable. Accordingly, the purpose of this study was to execute a time-dependent Cox regression analysis to assess the effects of long-term exposure to $PM_{2.5}$ and NO_2 on the incidence of MetS and its components in a cohort selected from the MJ Health Research Foundation.

Methods

Study Population

The study population was a cohort selected from the database of the MJ Health Research Foundation in Taiwan, which has been built up as a cohort to collect individuals' characteristics, life style,

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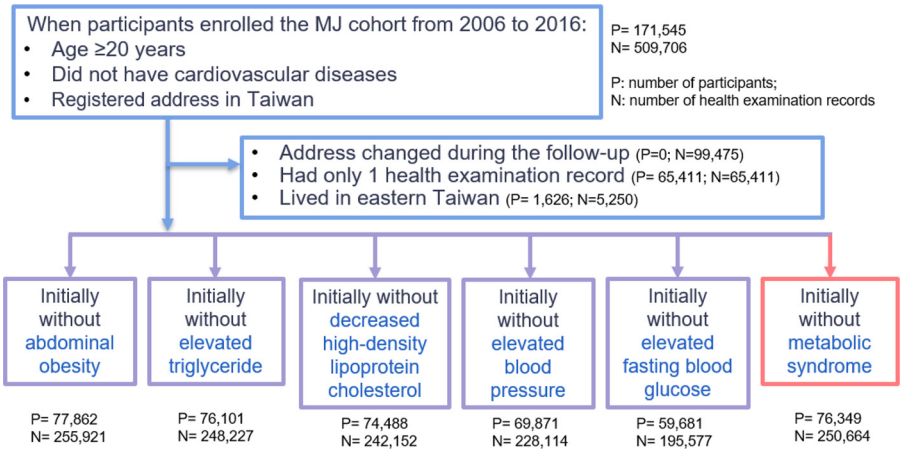

Figure 1. Flowchart of data selection from the MJ database from 2006 to 2016. The MJ database is a longitudinal, population-based health research cohort, comprising data (questionnaire, physical examination, and blood tests) from apparently healthy individuals seeking physical examination services at a private health care firm in Taiwan (MJ Health Management Institution).[22] Many participants contributed data from multiple visits. At each visit, behavioral and lifestyle information was obtained via questionnaire, and anthropometric and biological data were obtained via the physical examination.[23] Only the air pollutants of the participant's first address were included for the analysis to avoid potential mixing of early and delayed effects. For participants who changed address, only health records before they moved were used for analysis. Therefore, in the first exclusion process, despite 99,475 records being removed, no participant was removed.

and health status through a health screening program to help researchers investigate the relationships between chronic diseases and modifiable risk factors.[21–23] The MJ Health Database is a longitudinal, population-based health research cohort, comprising data (questionnaire, physical examination, and blood tests) from apparently healthy individuals seeking physical examination services at a private health care firm in Taiwan (MJ Health Management Institution).[22] Individuals were enrolled beginning in 1994 and data is collected on an ongoing basis with, at present, no termination date. Many participants contributed data from multiple visits. At each visit, behavioral and lifestyle information was obtained via questionnaire, and anthropometric and biological data were obtained via the physical examination. Informed consent was collected before physical examination, and only health data with authorization from the MJ participants were available for research purposes.[23] The study protocol was approved by the research ethics committee of the National Taiwan University Hospital (No. 202002093RIND).

Approximately half of the MJ participants paid for themselves or family members to have the health examination, and the other half received the examination as part of their employment benefits. Participants' records were censored if they did not persistently take the physical examination, or if their companies (for those participating as part of their employment benefits) did not renew the contract with MJ and therefore subsequent data collection was not possible.

Our selection pool comprised 171,545 participants who provided deidentified health examination records for the period between 2006 and 2016, were ≥20 years of age at the time of enrollment, did not have CVD, and had a registered address in Taiwan. To observe the occurrence of MetS and its components, we excluded 65,411 participants who took only one health examination for inappropriateness to the follow-up study design. Furthermore, because air quality monitoring stations are not as dense in eastern Taiwan as they are in the western regions of the island, 1,626 participants who lived in the east (∼0.6% of the cohort) were excluded. Only the air pollutants of the participant's first address were included for the analysis to avoid potential mixing of early and delayed effects. Thus, for participants who changed address, health records before they moved were used for analysis. After excluding records after a changed address, those who had only one health examination record, or those who lived in eastern Taiwan, we categorized the remaining participants into six groups according to their baseline condition as follows: *a*) without abdominal obesity, *b*) with normal triglyceride (TG) levels, *c*) with normal high-density lipoprotein cholesterol (HDL-C) levels, *d*) with normal BP levels, *e*) with normal fasting blood glucose (FBG) levels, and *f*) without MetS. Criteria for each of these groups is described in the section "Definition of MetS and Its Components." Thus, the final cohort comprised 77,862, 76,101, 74,488, 69,871, 59,681, and 76,349 participants in the above six groups. Such categorization allowed the participants to be included in more than one group (Table S1). Figure 1 illustrates the flowchart of the data selection process.

Exposure Assessment

According to the "Air Quality Annual Report of R.O.C. (Taiwan), 2015,"[24] yearly distributions of $PM_{2.5}$ and NO_2 gradually decreased from 33.5 to 22.1 $\mu g/m^3$ and from 18.75 to 14.21 ppb, respectively, from 2006 to 2016. For $PM_{2.5}$, the southwestern region is situated on the leeside of the mountains and under the effect of monsoonal flow, where ambient PM combines with local anthropogenic emissions from industries, and consequently, $PM_{2.5}$ concentrations increase from the northern to southern part of western Taiwan.[25] For NO_2, primary emission from vehicles, there were ∼21.5 million registered motor vehicles in Taiwan, 39.6%, 27.2%, 30.6%, and 2.6% in northern, central, southern, and eastern Taiwan, respectively.[26] Compared with similar areas in these four regions, NO_2 concentrations were higher in northern and southern regions, followed by central and eastern regions (Table S2). The regions correspond to administrative units and are considered to have slight cultural differences. Roughly, the southern region is tropical, including five cities/counties, and the central and northern are subtropical, including five and six cities/counties, respectively. Western Taiwan is essentially the combination of the northern, central, and southern regions (Figure S1).

The average annual concentrations of $PM_{2.5}$ and NO_2 for the year prior to the health examination were recorded at the township level according to each participant's address and used as surrogates for long-term exposure. The original daily concentrations of pollutants were measured continuously and reported hourly—$PM_{2.5}$ by

the β-ray attenuation method and tapered element oscillating microbalance technology, and NO_2 by chemiluminescence[24]—from 73 fixed air quality monitoring stations, included 68 from western and 5 from eastern Taiwan.[27] Given that residents of the eastern coast represented a very small (0.6%) proportion of MJ examinees and that the monitoring stations were not as dense in eastern Taiwan, the decision was made to exclude eastern coast participants. Estimations of $PM_{2.5}$ and NO_2 from 2005 to 2015 were modeled from the 68 monitoring stations from the western coast of Taiwan. Modeling was performed as previously described.[27,28] Daily concentrations of $PM_{2.5}$ and NO_2 at monitoring stations were obtained from the Taiwan Environmental Protection Administration air quality database and were then aggregated into annual averages for modeling. Interpolated $PM_{2.5}$ and NO_2 values were generated via a leave-one-out ordinary Kriging model, as explanatory variables in the stepwise land-use regression (LUR).[27,28] For $PM_{2.5}$, predictors included geospatial variables [i.e., distance to the nearest airport, forest, farmland, and Normalized Difference Vegetation Index (NDVI) within circular buffers], meteorological variables (i.e., temperature, relative humidity, wind speed, wind direction, precipitation, and ultraviolet index), and copollutants [i.e., sulfur dioxide (SO_2), ozone (O_3), and NO_2]. At a 50×50 m grid resolution, the hybrid Kriging/LUR with the XGBoost algorithm model showed the adjusted R^2 of 10-fold cross-validation was 0.93.[27] For NO_2, predictors included geospatial variables (i.e., agriculture, forest, transportation, water, building, public facilities, recreation, mining or salt production, industrial parks, incinerator chimneys and powerplants, Chinese restaurants, temples, funeral facilities, crematoria, and NDVI), meteorological variable (i.e., temperature), and copollutants [i.e., SO_2, O_3, and PM with an aerodynamic diameter of ≤ 10 μm (PM_{10})]. The developed hybrid Kriging/LUR model with a 250×250 m grid resolution showed the adjusted R^2 of 10-fold cross-validation was 0.88.[28]

Definition of MetS and Its Components

The definition of MetS applied in this study was based on a joint scientific statement from the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute.[29] The criteria for the clinical diagnosis of MetS were the presence of three or more of the following components for Asian individuals: *a*) having a waist circumference of ≥90 cm in men and ≥80 cm in women, *b*) having a TG level of ≥150 mg/dL or receiving drug treatment for hypertriglyceridemia, *c*) having an HDL-C level of <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females or receiving drug treatment for decreased HDL-C, *d*) having a systolic BP level of ≥130 or diastolic BP level of ≥85 mmHg or receiving drug treatment for hypertension, and *e*) having an FBG level of ≥100 mg/dL or receiving drug treatment for hyperglycemia.[29] The same criteria were used individually to classify change in each component (negative to positive) for the other cohorts as well.

In health examinations by MJ Health Research Foundation, measurements of waist circumference and BP were standardized according to the recommendations by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan. The measurements for FBG, TG, and HDL-C were conducted using a Toshiba C-8000.[30]

In the present study, time of incident MetS and its components was defined as the first detection of such conditions by examination, which included interview and blood collection. Participants who had moved from their first address, were lost to follow-up (i.e., did not continue to participate in the health examination), or had not developed MetS or its components by 31 December 2016 were regarded as right-censored data in our study.

Covariates

MetS has been associated with age, smoking, heavy carbohydrate intake, and physical inactivity and negatively associated with moderate alcohol intake (women only), education level,[2] and marital satisfaction (in women).[31] In addition, it has been related to poor sleep quality,[32] and either short sleep or long sleep duration.[33] We included these variables as covariates for analysis, except for carbohydrate intake which was unavailable in MJ data set. We thus included fried food consumption and processed food consumption as covariates in the present study.

Individual characteristics included as covariates were age, sex, baseline body mass index (BMI), marital status, education level, sleeping time per day, smoking habits, alcohol drinking habits, fried and processed food consumption, and regular exercise. Body weight and height were examined by experienced nurses during examination. BMI was calculated by dividing body weight (in kilograms) by squared height (in meters squared), whereas the other covariates were collected at each health examination via self-administered questionnaire.[23] In addition, because of established cultural differences, as well as differences in concentrations of $PM_{2.5}$ and NO_2 among northern, central, and southern Taiwan, region of residence was included as a covariate as well.

Marital status was classified as single/divorced/separated/widowed and married/cohabiting; and education level was categorized as junior high school and below, general and vocational high school, college, and master's degree and above. Sleeping time per day was categorized into the following groups: <6, 6–8, and >8 h. Smoking habits were classified as never smoking/former smoking, secondhand smoke exposure, and frequent smoking/daily smoking; alcohol drinking habits were divided into never drinking/former drinking, occasional drinking, and frequent drinking/daily drinking. Fried and processed food consumption was classified as none, little, or ≤1 portion/wk; 2–3 portions/wk; and ≥4 portions/wk. Regular exercise was classified as none, little or <1 h weekly; 1–4 h weekly or once per 2–3 d; ≥5 h weekly or daily. Moreover, in sensitivity analyses, age was divided into the following categories: ≤44, 45–64, and ≥65 y, and baseline BMI was divided into <18.5, 18.5–24, and ≥24 kg/m^2.

Statistical Analysis

In previous longitudinal studies with lower to higher annual $PM_{2.5}$ concentrations, the effects of increases in $PM_{2.5}$ on MetS and its components changed from statistically nonsignificant[8,34,35] to significant detrimental.[4,36–41] Because the effect of ambient air pollutants on health may have decreased over time as a result of decreasing pollutant concentrations during the follow-up period, we performed a time-dependent Cox regression analysis to estimate the effects of long-term exposure to $PM_{2.5}$ and NO_2 on the incidence of abdominal obesity, elevated TG, reduced HDL-C, elevated BP, elevated FBG, and MetS. The terms elevated and reduced refer to values above and below the standard reference range as defined in the "Definition of MetS and Its Components" section. The advantage of a time-dependent Cox regression analysis is that it allows hazard ratios (HRs) to be separated into distinct time windows,[42] making it suitable for this study given that concentrations of ambient air pollutants in Taiwan have gradually decreased.[24] In the present study, the time-varying average of $PM_{2.5}$ and NO_2 are on the yearly scale. Spearman correlation coefficients were used to examine the correlation between $PM_{2.5}$ and NO_2.

The study models were adjusted for the aforementioned covariates, except for baseline BMI, with a time-varying method as well. Missing information on covariates were represented by the

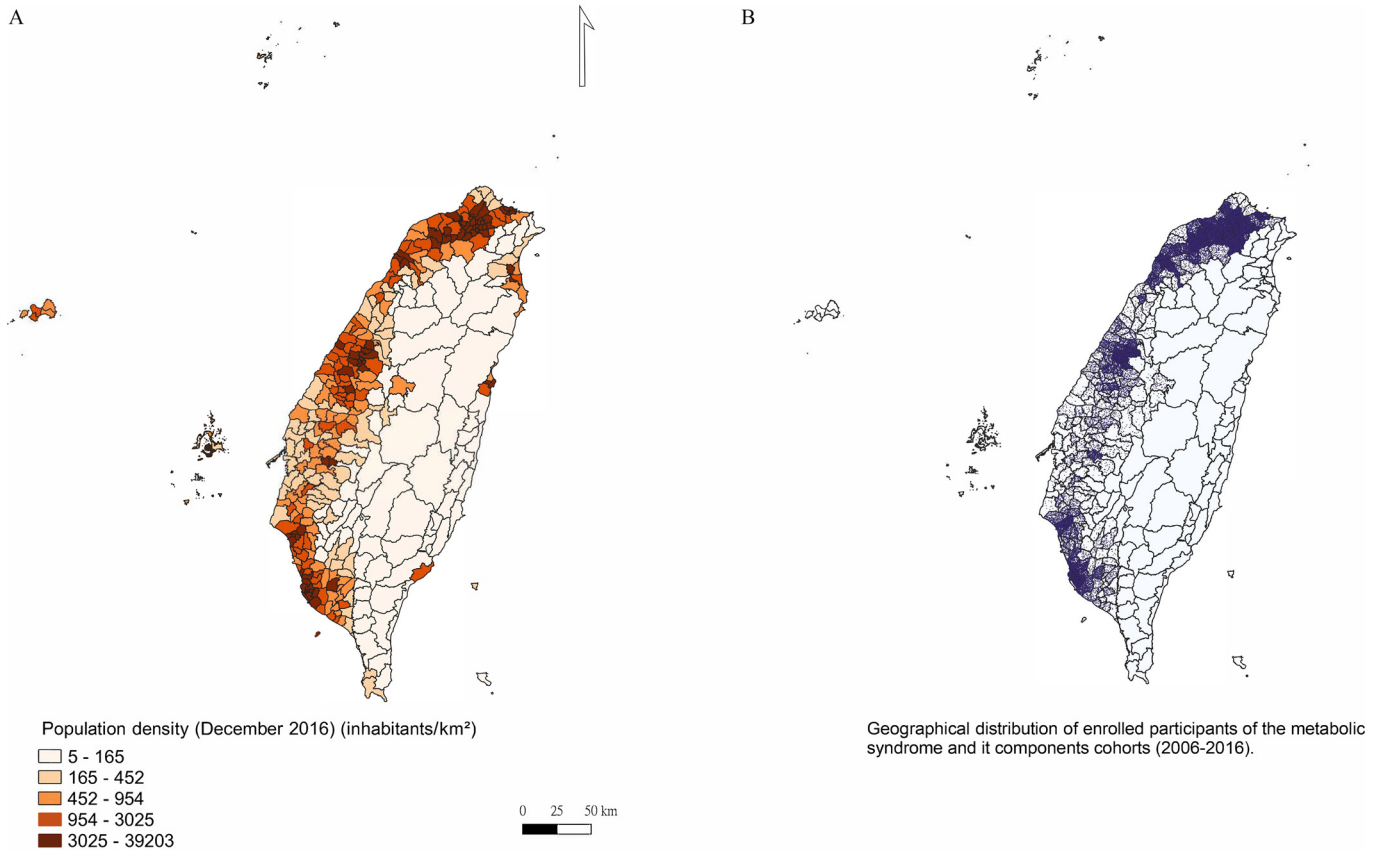

Figure 2. Geographical distributions of population density in Taiwan ($N = 23{,}539{,}816$), and the participants of the metabolic syndrome and its components cohorts ($N = 93{,}771$). The area of Taiwan is $\sim 36{,}000\,km^2$,[44] with a population of 23.5 million people.[45] (A) Population density. (B) General distribution of enrolled participants; each dot represents one participant. The small, outlined areas represent townships. This figure was created using the QGIS Desktop software (version 3.22; Open Source Geospatial Foundation).

previous value available for each participant, contributing an additional $\sim 3\%$ of the valid data for analysis.

To assess the robustness of the outcomes, we performed sensitivity analyses, and adjusted for additional covariates. First, we included not only characteristics' covariates but also baseline waist circumference, TG, HDL-C, BP, and FBG for additional adjustment in each cohort under the consideration that an individual's baseline status may affect the incidence of MetS and its components. Although some articles included BMI as a covariate in the model,[18,43] BMI could be associated with air pollution as well; thus, the model without baseline BMI was examined (Table S3). Second, in previous studies, the effects of noise (which is highly associated with traffic-related nitrogen oxides) on MetS and its components were inconsistent.[10,35] In addition, sleeping time has been found to be associated with traffic noise,[44] so adjusting for sleeping time with NO_2 might have been an overadjustment. Considering the lack of traffic noise information, we examined the effects without sleeping time in our study (Table S4). Third, owing to the varied prevalence of MetS across age and sex,[2] we performed sensitivity analyses by age and sex stratification. The potential modification effects were examined by adding interaction terms of age, sex, and the air pollutants into the time-dependent Cox regression models.

The area of Taiwan is $\sim 36{,}000\,km^2$,[45] with a population of 23.5 million people.[46] To illustrate the population density and the distribution of our study participants, Figure 2 was created using the QGIS Desktop software (version 3.22; Open Source Geospatial Foundation). All the statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc.). We considered $p < 0.05$ as indicating statistical significance for a two-tailed test.

Results

Figure 2 shows the geographical distributions of the overall study participants ($N = 93{,}771$), which could be similar to the population density in Taiwan ($N = 23{,}539{,}816$). Table 1 presents the baseline characteristics of the study population, which was divided into six cohorts: without abdominal obesity, with normal TG, with normal HDL-C, with normal BP, with normal FBG, and without MetS. Most of the participants (66.1%–74.9%) were ≤ 44 years of age at the time of enrollment, and the male and female distributions in the population were similar. In terms of BMI, 58.0%–65.9% of the participants were within the normal range ($18.5–24\,kg/m^2$). More than 60% of the participants were married or cohabiting and had a college-level education or higher. Approximately 80% of the participants were never smokers or former smokers, and 84.3%–87.1% of them were never alcohol drinkers or former drinkers. Furthermore, $>70\%$ of the participants slept 6–8 h/d, and nearly half did no, little or <1 h weekly regular exercise. Regarding fried and processed food consumption, $\sim 30\%$ and 60% of the participants consumed none and little or ≤ 1 portion per week, respectively. Most of the participants (68.7%–71.9%) lived in northern Taiwan. Overall, there were 93,771 participants enrolled in the six cohorts: 5.1% ($n = 4{,}766$) in only one cohort, and 36.9% ($n = 34{,}572$) in all six cohorts (Table S1). The annual concentration of $PM_{2.5}$ was

Table 1. Baseline characteristics [*n* (%) or mean ± SD] of the MJ Health Database study population between 2006 and 2016, Taiwan.

Variable	Cohort without abdominal obesity ($N = 77,862$)	Cohort with normal TG ($N = 76,101$)	Cohort with normal HDL-C ($N = 74,488$)	Cohort with normal BP ($N = 69,871$)	Cohort with normal FBG ($N = 59,681$)	Cohort without MetS ($N = 76,349$)
Already diagnosed with MetS						
No	69,970 (93.6)	68,633 (93.5)	67,163 (90.2)	63,061 (94.1)	54,903 (96.0)	76,349 (100)
Yes	4,765 (6.4)	4,771 (6.5)	7,266 (9.8)	3,930 (5.9)	2,287 (4.0)	0 (0)
Missing	3,127	2,697	59	2,880	2,490	0
Enrolled age (y)	40.2 ± 11.6	40.3 ± 12.0	41.1 ± 12.1	39.0 ± 10.6	38.6 ± 11.0	40.1 ± 11.6
≤44	53,821 (69.1)	52,354 (68.8)	49,209 (66.1)	51,388 (73.5)	44,694 (74.9)	53,006 (69.4)
45–64	21,206 (27.2)	20,488 (26.9)	21,821 (29.3)	16,963 (24.3)	13,324 (22.3)	20,594 (27.0)
≥65	2,835 (3.6)	3,259 (4.3)	3,458 (4.6)	1,520 (2.2)	1,663 (2.8)	2,749 (3.6)
Sex						
Male	37,055 (47.6)	33,623 (44.2)	37,469 (50.3)	31,064 (44.5)	25,145 (42.1)	35,573 (46.6)
Female	40,807 (52.4)	42,478 (55.8)	37,019 (49.7)	38,807 (55.5)	34,536 (57.9)	40,766 (53.4)
Body mass index (kg/m^2)	22.1 ± 2.7	22.6 ± 3.4	22.9 ± 3.5	22.5 ± 3.3	22.4 ± 3.3	22.4 ± 3.1
<18.5	6,891 (8.9)	6,773 (8.9)	6,130 (8.2)	6,461 (9.2)	6,033 (10.1)	6,518 (8.5)
18.5–24	51,311 (65.9)	46,206 (60.7)	43,187 (58.0)	42,900 (61.4)	37,041 (62.1)	47,820 (62.6)
≥24	19,643 (25.2)	23,103 (30.4)	25,152 (33.8)	20,504 (29.3)	16,593 (27.8)	22,004 (28.8)
Missing[a]	17	19	19	6	14	7
Marital status						
Single/divorced/separated/widowed	26,155 (33.8)	26,324 (34.8)	24,659 (33.3)	24,031 (34.6)	22,003 (37.1)	25,670 (33.8)
Married/cohabitating	51,227 (66.2)	49,307 (65.2)	49,457 (66.7)	45,411 (65.4)	37,315 (62.9)	50,325 (66.2)
Missing[a]	480	470	372	429	363	354
Education level						
Junior high school and below	8,748 (11.3)	9,373 (12.4)	9,616 (12.9)	6,405 (9.2)	5,736 (9.6)	8,696 (11.4)
General and vocational high school	14,822 (19.1)	14,237 (18.8)	13,809 (18.6)	13,816 (18.9)	11,057 (18.6)	14,312 (18.8)
College	43,004 (55.4)	41,637 (54.9)	40,188 (54.1)	39,950 (57.4)	34,220 (57.5)	42,185 (55.4)
Master's degree and above	11,001 (14.2)	10,572 (14.0)	10,682 (14.4)	10,063 (14.5)	8,450 (14.2)	10,975 (14.4)
Missing[a]	287	282	193	267	218	181
Smoking habits						
Never smoking/former smoking	60,882 (78.4)	60,732 (80.1)	58,107 (78.2)	54,083 (77.6)	46,807 (78.7)	60,056 (78.8)
Secondhand smoke exposure	3,290 (4.2)	3,411 (4.5)	3,196 (4.3)	3,022 (4.3)	2,623 (4.4)	3,294 (4.3)
Frequent smoking/daily smoking	13,447 (17.3)	11,722 (15.5)	13,035 (17.5)	12,545 (18.0)	10,060 (16.9)	12,857 (16.9)
Missing[a]	243	236	150	221	191	142
Alcohol drinking habits[b]						
Never drinking/former drinking	66,801 (86.3)	66,154 (87.4)	62,822 (84.7)	60,452 (87.0)	51,990 (87.6)	65,718 (86.4)
Occasional drinking	7,316 (9.4)	6,750 (8.9)	7,667 (10.3)	6,484 (9.3)	5,231 (8.8)	7,213 (9.5)
Frequent drinking/daily drinking	3,322 (4.3)	2,774 (3.7)	3,677 (5.0)	2,553 (3.7)	2,148 (3.6)	3,108 (4.1)
Missing[a]	423	423	322	382	312	310
Sleeping time per day (h)						
<6	16,751 (21.6)	16,946 (22.3)	16,706 (22.5)	15,027 (21.6)	12,939 (21.8)	16,713 (21.9)
6–8	56,114 (72.3)	54,328 (71.6)	53,112 (71.5)	50,300 (72.2)	42,810 (72.0)	54,801 (71.9)
>8	4,731 (6.1)	4,560 (6.0)	4,491 (6.0)	4,298 (6.2)	3,733 (6.3)	4,647 (6.1)
Missing[a]	266	267	179	246	199	161
Regular exercise						
None, little or <1 h weekly	35,252 (49.6)	34,312 (49.7)	33,498 (49.3)	33,239 (52.1)	28,042 (51.4)	34,779 (49.9)
1–4 h weekly or once per 2–3 d	26,581 (37.4)	25,678 (37.2)	24,962 (36.8)	23,412 (36.7)	20,249 (37.1)	26,001 (37.3)
≥5 h weekly or daily	9,195 (12.9)	9,047 (13.1)	9,428 (13.9)	7,126 (11.2)	6,219 (11.4)	8,985 (12.9)
Missing[a]	6,834	7,064	6,600	6,094	5,171	6,584
Fried food consumption per week (portions)						
None, little or ≤1	22,525 (29.0)	21,849 (28.8)	21,370 (28.8)	19,233 (27.6)	16,376 (27.5)	21,904 (28.8)
2–3	40,811 (52.6)	39,706 (52.4)	38,849 (52.3)	36,876 (53.0)	31,493 (52.9)	40,015 (52.5)
≥4	14,252 (18.4)	14,267 (18.8)	14,072 (18.9)	13,504 (19.4)	11,610 (19.5)	14,251 (18.7)
Missing[a]	274	279	197	258	202	179
Processed food consumption per week (portions)						
None, little or ≤1	48,818 (62.9)	47,402 (62.5)	45,996 (61.9)	43,233 (62.1)	36,854 (62.0)	47,669 (62.6)
2–3	25,588 (33.0)	25,255 (33.3)	25,064 (33.7)	23,411 (33.6)	20,093 (33.8)	25,364 (33.3)
≥4	3,175 (4.1)	3,161 (4.2)	3,226 (4.3)	2,964 (4.3)	2,529 (4.3)	3,150 (4.1)
Missing[a]	281	283	202	263	205	184
Region						
North[c]	54,142 (69.5)	54,215 (71.2)	51,167 (68.7)	50,234 (71.9)	41,235 (69.1)	53,446 (70.0)
Central[d]	10,178 (13.1)	9,553 (12.6)	10,352 (13.9)	8,868 (12.7)	8,722 (14.6)	10,153 (13.3)
South[e]	13,542 (17.4)	12,333 (16.2)	12,969 (17.4)	10,769 (15.4)	9,724 (16.3)	12,750 (16.7)

Note: The criteria for the clinical diagnosis of MetS were the presence of any three or more of the following components for Asian individuals *a*) having a waist circumference of ≥90 cm in men and ≥80 cm in women, *b*) having a TG level of ≥150 mg/dL or receiving drug treatment for hypertriglyceridemia, *c*) having an HDL-C level of <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females or receiving drug treatment for decreased HDL-C, *d*) having a systolic BP level of ≥130 or diastolic BP level of ≥85 mmHg or receiving drug treatment for hypertension, and *e*) having an FBG level of ≥100 mg/dL or receiving drug treatment for hyperglycemia.[29] The same criteria were used individually to classify change in each component (event to happen) for the other cohorts as well. BP, blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; SD, standard deviation; TG, triglyceride.

[a]Missing information on covariates were initially represented by the previous value available of each participant. Participants without available value for representation were not eligible for data analysis depending on the covariates included in the models in Table 3 and Tables S3 and S4.

[b]Never drinking/former drinking: teetotaler, abstainer, or drank less than once weekly; occasional drinking: drank once or twice weekly; frequent drinking/daily drinking: drank more than three times weekly.

[c]The northern region included Taipei, New Taipei, Keelung, Hsinchu, and Taoyuan Cities and Hsinchu County.

[d]The central region included Taichung City and Miaoli, Changhua, Nantou, and Yunlin Counties.

[e]The southern region included Kaohsiung, Tainan, and Chiayi Cities and Chiayi and Pingtung Counties.

revealed to be mildly correlated with NO_2 in the six cohorts in whole Taiwan, with Spearman correlation coefficients ranging from 0.249 to 0.291 (all $p < 0.001$; Table S5).

Table 2 presents the results obtained for the three regions (northern, central, and southern Taiwan). Participants living in the southern region had the highest annual exposure concentration of $PM_{2.5}$, and those in the northern and southern regions had the highest exposure concentration of NO_2. During the exposure period of 2005 to 2015, the data shows a gradual decreasing trend, with fluctuation in the annual average concentrations of $PM_{2.5}$ and NO_2 (Figure S2; the complete data set is included as Excel Table S1). Over the period of 2005–2015, based on the residences of the participants in the cohorts of MetS and its components, $PM_{2.5}$ decreased by 5.93–7.20 $\mu g/m^3$ and NO_2 decreased by 4.04–5.33 ppb, respectively. For our longitudinal analysis (Table 2), we included 77,862 participants who were initially free of abdominal obesity; the average incidence of abdominal obesity was 31.95/1,000 person-years over a mean ± standard deviation (SD) follow-up period of 3.5 ± 2.3 y, and the incidence was lowest in southern Taiwan (23.11/1,000 person-years). Among the participants with normal TG at baseline, the average incidence of elevated TG was 50.01/1,000 person-years, ranging from 49.46 (south) to 52.16 (central). For those with initially normal HDL-C, the average incidence of reduced HDL-C was 28.89/1,000 person-years, ranging from 23.22 (north) to 44.32 (south). The average incidence of elevated BP in the normal BP cohort was 56.81, ranging from 55.25 (south) to 63.31 (central). The average incidence of elevated FBG in the normal FBG cohort was 112.77/1,000 person-years, with the lowest rate being in central Taiwan (88.09) and the highest being in the north (123.12). Among the cohort without MetS, MetS occurred after 3.4 ± 2.3 y of follow-up, with an average incidence of 38.07/1,000 person-years and the lowest rate occurring in the southern region (36.39) and the highest rate occurring in the central region (40.73). A total of 84.0% ($n = 78,786$) participants did not have incident any component of MetS by the end of follow-up, whereas 0.1% ($n = 58$) had incident all the five components (Table S1).

Table 3 presents the results of our time-dependent Cox regression analysis performed to assess the effects of two pollutants simultaneously on the HRs of developing abdominal obesity, elevated TG, reduced HDL-C, elevated BP, elevated FBG, and MetS. In Model 1—with adjustments for age, sex, marital status, education level, sleeping time per day, smoking habits, alcohol drinking habits, and fried and processed food consumption—every 10-$\mu g/m^3$ increase in $PM_{2.5}$ concentration in the year prior to the health examination significantly enhanced the HRs for all five components of MetS (i.e., abdominal obesity; TG, BP, or FBG above reference range; and HDL-C below reference range), and 10-ppb increase in NO_2 concentration enhanced the HR for FBG above reference range. In Model 2, which included an additional adjustment for regular exercise, the results were similar to Model 1. In Model 3, which additionally adjusted for baseline status (waist circumference, TG, HDL-C, systolic and diastolic BP, and FBG for each cohort) and baseline BMI, and the association of $PM_{2.5}$ remained significant; however, the association of NO_2 with FBG became statistically nonsignificant. Every 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with an increased risk for abdominal obesity [adjusted hazard ratio (aHR) = 1.07; 95% confidence interval (CI): 1.01, 1.14], elevated TG (aHR = 1.17; 95% CI: 1.11, 1.23), reduced HDL-C (aHR = 1.09; 95% CI: 1.02, 1.17), elevated BP (aHR = 1.15; 95% CI: 1.09, 1.21), and elevated FBG (aHR = 1.15; 95% CI: 1.10, 1.20). As for the incidence of MetS, we present the results of participants who had none or some (1–2) components of MetS at baseline. For the participants initially without any component of MetS, we found no association between exposure to higher $PM_{2.5}$ (aHR = 0.99; 95% CI: 0.89, 1.12) and NO_2 (aHR = 0.88; 95% CI: 0.76, 1.03) and increased risk of MetS incidence. For those with one component of MetS, a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 12% greater risk of MetS (aHR = 1.12; 95% CI: 1.04, 1.20). For those had two components of MetS, every 10-$\mu g/m^3$ increase in $PM_{2.5}$ and every 10-ppb increase in NO_2 was associated with a 14% (aHR = 1.14; 95% CI: 1.07, 1.22) and a 10% (aHR = 1.10; 95% CI: 1.03, 1.18) increased risk for MetS incidence, respectively.

Tables S3 and S4 present models without baseline BMI and without sleeping time, respectively. The associations between $PM_{2.5}$, NO_2, MetS, and its components were similar to the findings in Table 3.

Figure S3 presents the potential modification effects of age and sex by adding the interaction terms in stratified analyses. Such findings were similar to our major results in Table 3. For sex, positive associations between $PM_{2.5}$, elevated TG, reduced HDL-C, elevated BP, elevated FBG, and from initially having one or more components of MetS were found in both male and female participants. In addition, the association between $PM_{2.5}$ and abdominal obesity was significant in male (aHR = 1.15; 95% CI: 1.07, 1.23) but not in female (aHR = 0.98; 95% CI: 0.91, 1.06, $p_{Interaction} = 0.000$); the association of $PM_{2.5}$ with elevated BP was more prominent in female (aHR = 1.22; 95% CI: 1.14, 1.30) than male (aHR = 1.12; 95% CI: 1.06, 1.18, $p_{Interaction} = 0.003$). For age, positive associations between $PM_{2.5}$, elevated TG, elevated BP, and elevated FBG were found in all age subgroups (≤44, 45–64, ≥65 years of age). In the abdominal obesity cohort, participants ≤44 years of age had higher risk (aHR = 1.10; 95% CI: 1.03, 1.18) when exposed to increased $PM_{2.5}$ than participants ≥65 years of age (aHR = 0.93; 95% CI: 0.80, 1.07, $p_{Interaction} = 0.017$). No significant modification effect of age or sex subgroup in the associations between NO_2, MetS, and its components was observed. The complete data set is included as Excel Table S2.

Discussion

Primary Findings

By using a time-dependent Cox regression analysis to consider the gradually changing concentrations of $PM_{2.5}$ and NO_2 in cohorts of 59,681–77,862 participants from the MJ Health Database with a follow-up period of 3.0–3.5 y, we observed associations between long-term $PM_{2.5}$ and NO_2 exposure and incidence of abdominal obesity, elevated TG, reduced HDL-C, elevated BP, elevated FBG, and MetS. An additional exposure to 10 $\mu g/m^3$ of $PM_{2.5}$ annually was associated with an increased risk of abdominal obesity (7%), hypertriglyceridemia (17%), reduced HDL-C (9%), hypertension (15%), and elevated FBG (15%). The associations between $PM_{2.5}$ and incident MetS and its components remained robust when additionally adjusting for either baseline BMI (Table S3) or sleeping time (Table S4). In the sensitivity analyses, the association between $PM_{2.5}$ and abdominal obesity was significant in male and ≤44-y-old participants, whereas the association of $PM_{2.5}$ with elevated BP was more prominent in female participants. For age subgroups (≤44, 45–64, ≥65 y), no interactions were observed between $PM_{2.5}$, elevated TG, elevated BP, and elevated FBG (Figure S3). In addition, the effects of long-term $PM_{2.5}$ and NO_2 exposure were particularly pronounced in participants who had some components of MetS at baseline (abdominal obesity, high TG levels, low HDL-C levels, high BP levels, and high FBG levels). For participants who had had one or two components of MetS, every 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with 12% and 14% risk of MetS incidence, respectively. For those who already had two components of MetS, every 10-ppb increase in NO_2 was associated with a 10% risk of MetS incidence.

Table 2. Summary statistics of concentrations of air pollutants (2005–2015) and incidence of metabolic syndrome and its components in the MJ Health Research cohort by region between 2006 and 2016, Taiwan.

Statistics	Cohort without abdominal obesity ($N = 77,862$)	Cohort with normal TG ($N = 76,101$)	Cohort with normal HDL-C ($N = 74,488$)	Cohort with normal BP ($N = 69,871$)	Cohort with normal FBG ($N = 59,681$)	Cohort without MetS ($N = 76,349$)
1-y average concentration for the year before health check-up (mean ± SD)						
$PM_{2.5}$ ($\mu g/m^3$)						
North	27.67 ± 4.65	27.71 ± 4.66	27.49 ± 4.72	27.74 ± 4.67	27.93 ± 4.61	27.61 ± 4.68
Central	33.97 ± 3.81	34.00 ± 3.84	33.98 ± 3.81	34.06 ± 3.82	34.19 ± 3.77	33.99 ± 3.82
South	42.77 ± 4.03	42.82 ± 4.05	42.73 ± 4.05	42.86 ± 4.00	42.89 ± 3.99	42.76 ± 4.04
Total	31.30 ± 7.33	31.05 ± 7.22	31.18 ± 7.37	30.94 ± 7.13	31.48 ± 7.13	31.13 ± 7.28
NO_2 (ppb)						
North	20.41 ± 5.06	20.48 ± 5.08	20.35 ± 5.13	20.48 ± 5.05	20.63 ± 5.03	20.42 ± 5.11
Central	15.86 ± 2.85	15.82 ± 2.89	15.79 ± 2.89	16.00 ± 2.81	15.99 ± 2.87	15.81 ± 2.87
South	20.35 ± 4.69	20.38 ± 4.72	20.24 ± 4.80	20.60 ± 4.55	20.54 ± 4.66	20.35 ± 4.69
Total	19.78 ± 5.00	19.86 ± 5.04	19.65 ± 5.07	19.91 ± 4.98	19.86 ± 4.98	19.76 ± 5.04
Participants with event [n (%)][a]	8,632 (11.1%)	12,643 (16.6%)	7,266 (9.8%)	13,055 (18.7%)	20,541 (34.5%)	9,898 (13.0%)
Follow-up period (y)	3.5 ± 2.3	3.3 ± 2.2	3.4 ± 2.2	3.0 ± 2.0	3.1 ± 2.1	3.4 ± 2.3
Incidence rate (per 1,000 person-years)[b]						
North	34.23	49.74	23.22	55.93	123.12	37.94
Central	32.28	52.16	36.16	63.31	88.09	40.73
South	23.11	49.46	44.32	55.25	95.31	36.39
Total	31.95	50.01	28.89	56.81	112.77	38.07

Note: BP, blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter (PM with an aerodynamic diameter of ≤2.5 μm); SD, standard deviation; TG, triglyceride.

[a]Event referred to occurrence of MetS and components. For cohort without abdominal obesity, event meant having a waist circumference of ≥90 cm in men and ≥80 cm in women. For cohort with normal TG, event meant having a TG level of ≥150 mg/dL or receiving drug treatment for hypertriglyceridemia. For cohort with normal HDL-C, event meant having an HDL-C level of <40 mg/dL (1.0 mmol/L) in males and <50 mg/dL (1.3 mmol/L) in females or receiving drug treatment for decreased HDL-C. For cohort with normal BP, event meant having a systolic BP level of ≥130 or diastolic BP level of ≥85 mmHg or receiving drug treatment for hypertension. For, cohort with normal FBG, event meant having an FBG level of ≥100 mg/dL or receiving drug treatment for hyperglycemia. For cohort without MetS, event meant the presence of any three or more of the above components.

[b]Incidence rate was calculated by dividing the number of events by total per 1,000 person-years for each cohort.

Related Literature

In 14 May 2012, Taiwan tightened the air quality standards of 24-h and yearly average $PM_{2.5}$ concentrations to 35 and 15 $\mu g/m^3$, respectively, as well as 24-h and yearly average NO_2 concentrations to 100 and 30 ppb, respectively.[16] In the present study, which included exposure data for the period from 2005 to 2015, although the annual average concentration of $PM_{2.5}$ (based on each participant's address) was ~30 $\mu g/m^3$, the concentration decreased gradually over time, as did that of NO_2. Therefore, the changes in air pollutant concentrations must be carefully considered when examining their effects on MetS and its components, and time-dependent Cox regression analysis may be appropriate for the present study.

In other countries with comparatively lower annual $PM_{2.5}$ concentrations (median ≤20 $\mu g/m^3$), longitudinal studies using linear regression, logistic regression, or generalized estimating equations have revealed that the effects of increases in $PM_{2.5}$ exposure on MetS and its components were statistically nonsignificant, namely, in Germany[8,35] and Southern California.[34] However, when $PM_{2.5}$ exposure was used as a time-dependent variable, an annual median value of 26.7 $\mu g/m^3$ was demonstrated to be associated with higher risks of abdominal obesity, hypertriglyceridemia, reduced HDL-C, hypertension, hyperglycemia, and MetS from the National Health Insurance Service-National Health Screening Cohort in Korea,[18] which is consistent with our findings. Moreover, people living in regions with high annual concentrations of $PM_{2.5}$ (median ≥55 $\mu g/m^3$) in China have been reported to be at higher risk of abdominal obesity from 31 China provinces,[4] reduced HDL-C,[36] and MetS[41] from the Henan Rural Cohort study, elevated BP among rural and urban regions,[37–39] and elevated FBG among an elderly population.[40]

In comparatively lower annual concentrations (mean <20 ppb) of NO_2 (an indicator of traffic-related emissions), exposure was reported to be associated with elevated total cholesterol and low-density lipoprotein but not with reduced HDL-C, elevated FBG among young adults from the Southern California Children's Health Study,[34] or with MetS from the population-based survey in Augsburg, Germany.[35] In studies where annual average concentrations were higher (20–30 ppb), NO_2 exposure was associated with increased BP among older adults in Taiwan[5] but not with elevated FBG among Taiwanese[5] and Mexican Americans.[47] When NO_2 annual average concentration was >30 ppb, an increased risk of MetS was reported in Germany[8] and China.[41] However, association between NO_2 concentrations and hypertension was inconsistent.[38,39] In our study, the effect of NO_2 on elevated FBG remained significant (Table 3, Model 1 and 2) before baseline status were added for additional adjustment. Therefore, we could not exclude the possibility of an existing impact of NO_2 on baseline BMI and FBG before the study enrollment. The inconsistency in findings between previous studies and the present study could be partly attributable to the differences in NO_2 concentrations, the study methodology, and analysis.

Possible Mechanisms

Exposure to PM was associated with DNA hypomethylation, and PM-induced reactive oxygen species and elevated cytokine levels has been reported to elicit systemic inflammation in murine and human studies.[48] In healthy young adults, high exposure to $PM_{2.5}$ was found to relate to changes in DNA methylation in genes involved in glucose and lipid metabolism, inflammation, oxidative stress, platelet activation, and cell survival and apoptosis.[49] In a study with nonsmoking participants, $PM_{2.5}$ exposure was found to be associated with autonomic nervous system imbalance, as well as with impaired endothelial function 24 h after exposure. Both were regarded to be relevant to hypertension.[50] As for the potential mechanisms of the observed effects of NO_2, inhaled NO_2 oxidized antioxidants within the epithelial lining fluid and triggered extracellular damage and oxidative stress,[51] which can inhibit glucose metabolism in rodents.[52] Korean[6] and German[53] populations exposed to ambient NO_2 concentrations were found to have

Table 3. Associations [aHR (95% CI)] of $PM_{2.5}$ and NO_2 with metabolic syndrome and its components among participants of the MJ Health Research cohort in Taiwan between 2006 and 2016.

	Model 1[a]		Model 2[b]		Model 3[c]	
MetS and its components	$PM_{2.5}$	NO_2	$PM_{2.5}$	NO_2	$PM_{2.5}$	NO_2
Development of abdominal obesity in the no abdominal obesity cohort	($n = 76{,}960$; $e = 8{,}555$)		($n = 70{,}729$; $e = 7{,}705$)		($n = 70{,}589$; $e = 7{,}698$)	
	1.15 (1.01, 1.12)	1.06 (0.99, 1.12)	1.08 (1.02, 1.15)	1.01 (0.95, 1.07)	1.07 (1.01, 1.14)	0.97 (0.92, 1.03)
Development of reduced HDL-C in the normal HDL-C cohort	($n = 75{,}210$; $e = 12{,}542$)		($n = 68{,}733$; $e = 11{,}373$)		($n = 68{,}727$; $e = 11{,}372$)	
	1.16 (1.10, 1.22)	1.03 (0.99, 1.08)	1.17 (1.11, 1.23)	1.02 (0.97, 1.07)	1.17 (1.11, 1.23)	0.99 (0.94, 1.03)
Development of elevated TG in the normal TG cohort	($n = 73{,}707$; $e = 7{,}210$)		($n = 67{,}592$; $e = 6{,}490$)		($n = 67{,}587$; $e = 6{,}489$)	
	1.10 (1.02, 1.18)	1.01 (0.95, 1.07)	1.12 (1.04, 1.20)	1.00 (0.94, 1.07)	1.09 (1.02, 1.17)	0.94 (0.88, 1.01)
Development of elevated BP in the normal BP cohort	($n = 69{,}075$; $e = 12{,}965$)		($n = 63{,}514$; $e = 11{,}772$)		($n = 63{,}510$; $e = 11{,}771$)	
	1.18 (1.12, 1.24)	1.03 (0.98, 1.08)	1.18 (1.12, 1.24)	1.01 (0.97, 1.06)	1.15 (1.09, 1.21)	1.04 (0.99, 1.10)
Development of elevated FBG in the normal FBG cohort	($n = 59{,}681$; $e = 20{,}549$)		($n = 54{,}274$; $e = 18{,}615$)		($n = 54{,}269$; $e = 18{,}614$)	
	1.11 (1.06, 1.15)	1.07 (1.03, 1.11)	1.11 (1.06, 1.16)	1.06 (1.02, 1.10)	1.15 (1.10, 1.20)	1.03 (0.99, 1.07)
Development of MetS based on the number of MetS components exhibited at baseline	($n = 75{,}596$; $e = 9{,}818$)		($n = 69{,}460$; $e = 8{,}850$)		($n = 69{,}456$; $e = 8{,}848$)	
0	($n = 34{,}285$; $e = 897$)		($n = 31{,}788$; $e = 824$)		($n = 31{,}787$; $e = 824$)	
	0.99 (0.89, 1.11)	0.87 (0.75, 1.01)	0.99 (0.89, 1.11)	0.87 (0.75, 1.01)	0.99 (0.89, 1.12)	0.88 (0.76, 1.03)
1	($n = 25{,}277$; $e = 3{,}175$)		($n = 23{,}137$; $e = 2{,}858$)		($n = 23{,}134$; $e = 2{,}856$)	
	1.12 (1.04, 1.20)	1.02 (0.94, 1.11)	1.12 (1.04, 1.21)	1.02 (0.94, 1.11)	1.12 (1.04, 1.20)	1.01 (0.93, 1.10)
2	($n = 16{,}034$; $e = 5{,}746$)		($n = 14{,}535$; $e = 5{,}168$)		($n = 14{,}535$; $e = 5{,}168$)	
	1.12 (1.05, 1.19)	1.13 (1.06, 1.21)	1.12 (1.05, 1.19)	1.14 (1.06, 1.21)	1.14 (1.07, 1.22)	1.10 (1.03, 1.18)

Note: All estimates were calculated for every 10-$\mu g/m^3$ increase in $PM_{2.5}$ and every 10-ppb increase in NO_2 in the annual average concentrations, two-pollutant model, determined using time-dependent Cox regression. Missing information on covariates were initially represented by the previous value available of each participant. Participants without available value for representation were not eligible for data analysis depending on the covariates in the models, leading to different eligible numbers of participants in different models. The terms elevated and reduced refer to above and below normal reference range, respectively. aHR, adjusted hazard ratio; CI, confidence interval; BP, blood pressure; *e*, number of participants with the incident outcome; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; *n*, number of participants without missing variables in each model; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter (PM with an aerodynamic diameter of ≤ 2.5 μm); TG, triglyceride.

[a]Adjusted by age, sex, marital status (single/divorced/separation/widowed, married/cohabitating), education level (junior high school and below, general and vocational high school, college, master's degree and above), smoking habits (never smoking/former smoking, secondhand smoke exposure, frequent smoking/daily smoking), alcohol drinking habits (never drinking/former drinking, occasional drinking, frequent drinking/daily drinking), sleeping time per day (<6, 6–8, >8 h), fried food consumption (none, little or ≤1 portion weekly, 2–3 portions weekly, ≥4 portions weekly), processed food consumption (none, little or ≤1 portion weekly, 2–3 portions weekly, ≥4 portions weekly), and region (north, central, south).

[b]Additionally adjusted for the covariates from Model 1 and exercise (none, little or <1 h weekly, 1–4 h weekly or once per 2–3 d; ≥5 h weekly or daily).

[c]Additionally adjusted for the covariates from Model 2, baseline body mass index (<18.5, 18.5–24, ≥24 kg/m^2), and the initial status—baseline waist circumference for abdominal obesity cohort, baseline TG for elevated TG cohort, baseline HDL-C for reduced HDL-C cohort, baseline systolic BP and baseline diastolic BP for elevated BP cohort, baseline FBG for elevated FBG cohort.

impaired glucose metabolism, an important component of MetS. These mechanisms may support our findings.

Limitations and Strengths

Although we used a prospective cohort and rigorous exposure assessment of air pollutants, our study has some limitations. First, in this study, exposure assessment was based on the estimated concentration in the township the participant gave as their residence in the questionnaire. Personal habits, work exposure, commute, indoor/outdoor differences, and microenvironments render potential deviations in these measurements from the true exposure. However, these deviations tend to be in a random misclassification manner, thus causing the observed relationship between outcomes and exposure to be biased toward the null hypothesis. On the other hand, the outcomes measurements are also subject to measurement error. Given that those health care workers performing the health examination were unaware of the study hypothesis, bias is unlikely. Despite the efforts of standardization in questionnaire, equipment, and measurements,[30,54] misclassification could not totally be avoided. Again, these misclassifications likely weaken the observed association. Therefore, the observed relationship likely underestimates the true effects. Second, the participants who changed address during the follow-up were excluded because their exposure could not be attributed to an exact level within the time period. This potentially induced selection bias to the study. However, moving has not been reported as a risk or protective factor for MetS. Third, the surrounding vegetation (greenness) in the participants' residential areas was not directly included in the study models, neither was participants' occupation. Some researchers have reported a negative association between MetS-related components and residential surrounding greenness,[55–57] but the protective effect was inconsistent with that in urban regions.[35,58] Exposure to annual concentrations of $PM_{2.5}$ and NO_2 was estimated at the township level, and green space was regarded as an explanatory predictor in the modeling procedure.[27,28] In addition, data on real exposure to greenness for urban residents were unavailable. Accordingly, greenness was not adjusted for in this study. On the other hand, although some occupations have been reported to be associated with incident MetS,[59] the MJ health questionnaire changed options of the occupational items during our research period, and the categories could not objectively present workers' intensity of labor. Therefore, we did not include occupation as a covariate. Fourth, the incidence was based on the month of the participants took the health examination. Therefore, a time lag between the actual incidence of MetS and its components and the health examination existed, and the short-term effects of $PM_{2.5}$ and NO_2 exposure on MetS and its components were not achievable.

Regardless of these limitations, in Table 3, our study used time-dependent analysis to examine the health effects of $PM_{2.5}$ and NO_2 exposure, and found that exposure to $PM_{2.5}$ was associated with the occurrence the components of MetS. The sensitivity analyses by age and sex stratifications showed that the association between $PM_{2.5}$ and abdominal obesity was significant in the male and ≤44-y-old groups, and the association between $PM_{2.5}$ and elevated BP was more prominent in the female group. Furthermore, the results of incident MetS indicates people who already had components of MetS could be vulnerable to the development of MetS when exposed to increased $PM_{2.5}$ and NO_2 concentrations. Our results generally support the hypothesis that long-term exposure to $PM_{2.5}$ and NO_2 are associated with increased risk of MetS and its components. Strategies aimed at improving air quality and using personal protective equipment might reduce the risks, especially for people who already have some components of MetS.

Conclusions

Our findings suggest that exposure to high levels of $PM_{2.5}$ ($\sim 15\ \mu g/m^3$ above Taiwan's current air quality standards)[16] was associated with increased risk of abdominal obesity, hypertriglyceridemia, reduced HDL-C, elevated BP, and elevated FBG. Moreover, we also observed that exposure to $PM_{2.5}$ and NO_2 were associated with the risk of developing MetS among people who already had some components of MetS. Additional studies are required to confirm the consistency of the effects of $PM_{2.5}$ and NO_2 exposure at different exposure ranges.

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