Association between coarse particulate matter ($PM_{10\text{-}2.5}$) and nasopharyngeal carcinoma among Taiwanese men

Hsu-Chih Huang,[1,2] Disline Manli Tantoh,[3,4] Shu-Yi Hsu,[4] Oswald Ndi Nfor,[4] Cheau-Feng Lin Frank,[2,5] Chia-Chi Lung,[4] Chien-Chang Ho,[6] Chih-Yi Chen,[1,2] Yung-Po Liaw [3,4]

[1]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
[2]Division of Thoracic Surgery, Department of Surgery, Chung Shan Medical University Hospital, Taichung, Taiwan
[3]Department of Medical Imaging, Chung Shan Medical University Hospital, Taichung, Taiwan
[4]Department of Public Health and Institute of Public Health, Chung Shan Medical University, Taichung, Taiwan
[5]School of Medicine, Chung Shan Medical University, Taichung, Taiwan
[6]Department of Physical Education, Fu Jen Catholic University, New Taipei, Taiwan

Correspondence to
Professor Yung-Po Liaw, Department of Public Health and Institute of Public Health, Chung Shan Medical University, Taichung 40201, Taiwan; Liawyp@csmu.edu.tw
Professor Chih-Yi Chen; cshy1566@csh.org.tw

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ABSTRACT

The nasopharyngeal tract traps mainly coarse particles in inhaled air. Soluble carcinogenic compounds, endotoxins, and trace metals contained in these particles are potential causes of inflammation and oxidative stress which could enhance carcinogenesis. The aim of this study was to determine the association between coarse particulate matter ($PM_{10\text{-}2.5}$) and nasopharyngeal cancer (NPC). A total of 521,098 men (355 cases and 520,743 non-cases), aged ≥40 years were included in this study. Data were retrieved from the Taiwan Cancer Registry, the Adult Preventive Medical Services Database, and the Air Quality Monitoring Database. $PM_{10\text{-}2.5}$ was significantly associated with a higher risk of NPC after adjusting for SO_2, NOx, O_3, age, body mass index, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia. With $PM_{10\text{-}2.5}<20.44$ µg/m^3 as the reference, the ORs and 95% CIs were 1.47; 1.03–2.11, 1.34; 0.94–1.91, and 1.68; 1.16–2.44 for $20.44 \le PM_{10\text{-}2.5} < 24.08$, $24.08 \le PM_{10\text{-}2.5} < 29.27$, and $PM_{10\text{-}2.5} \ge 29.27$ µg/m^3, respectively. $PM_{10\text{-}2.5}$ remained significantly associated with a higher risk of NPC after further adjustments were made for the aforementioned covariates and $PM_{2.5}$. The ORs; 95% CIs were 1.42; 0.96 to 2.12, 1.41; 0.94 to 2.10, and 1.71; 1.10 to 2.66 for $20.44 \le PM_{10\text{-}2.5} < 24.08$, $24.08 \le PM_{10\text{-}2.5} < 29.27$, and $PM_{10\text{-}2.5} \ge 29.27$ µg/m^3, respectively. In conclusion, $PM_{10\text{-}2.5}$ was significantly associated with a higher risk of NPC in Taiwanese men.

Significance of this study

What is already known about this subject?

- The nasopharyngeal tract traps mainly coarse particles in inhaled air whose sizes range between 5 and 10 um.
- The coarse fraction of particulate matter ($PM_{10\text{-}2.5}$) could trigger inflammation and cancer development in the nasopharynx.
- It has been shown to be a predictor of increased mortality and hospital admissions for respiratory and cardiovascular diseases.

What are the new findings?

- $PM_{10\text{-}2.5}$ was significantly associated with a higher risk of nasopharyngeal cancer.
- The association of $PM_{2.5}$ with nasopharyngeal cancer was not significant.
- PM_{10} was significantly associated with a higher risk of nasopharyngeal cancer.

How might these results change the focus of research or clinical practice?

- These findings highlight the relationship between coarse particulate matter and nasopharyngeal cancer, which has not been widely reported in previous literature.

INTRODUCTION

Air pollution is associated with an increased risk of cancers of the upper aerodigestive tract including oral, lung, and nasopharyngeal carcinoma among others.[1–3] The International Agency for Research on Cancer (IARC) classifies air pollutants especially particulate matter (PM) as group 1 carcinogens.[4]

Typically, particles with an aerodynamic diameter less than 2.5 µm ($PM_{2.5}$ or fine PM) can be deposited right into the lung alveoli, while those with aerodynamic diameter below 10 µm (PM_{10}) do not penetrate right into the lung alveoli.[5–7] However, they can be deposited in the upper respiratory tract.[8] So far, less work has been done with regard to the health effects of particles with an aerodynamic diameter between 2.5 and 10 µm ($PM_{10\text{-}2.5}$ or coarse PM) compared with $PM_{2.5}$ and PM_{10}.[5 6 8–10]

Nasopharyngeal cancer (NPC) is among the cancers that are most common in the head and neck regions.[11] It is potentially curable when diagnosed at an early stage.[11] Some risk factors for NPC include age, Epstein-Barr virus, family history, tobacco smoke, alcohol consumption, dietary habits, and occupational wood dust.[11–14] Generally, the risk in men doubles or triples that in women.[11–13 15] For instance, in 2012, more than 86,500 cases of NPC were reported in the world.[11 16] The standardized incidence per 100,000 was 1.2 (1.7 in men and 0.7 in women).[11] Moreover, about 50,831

NPC-related deaths were reported and the standardized mortality rate per 100,000 was 0.7 (1.0 in men and 0.4 in women).[11] NPC is also more common in East and Southeast Asia.[11 16 17] For instance, in 2012, about 71% of new cases were reported in East and Southeast Asia.[16] Taiwan is one of the Southeast Asian countries with a higher incidence of NPC.[11 12 18] According to the 2008 Taiwan Cancer Registry (TCR) reports, NPC was the 10th incident cancer and the 9th cause of mortality among Taiwanese men.[19] The age-adjusted incidence and mortality rates per 100,000 were 8.29 and 4.5, respectively.[19]

The coarse fraction of PM ($PM_{10\text{-}2.5}$) has been shown to be a predictor of increased mortality and hospital admissions for respiratory and cardiovascular diseases.[9 10 20] Moreover, it is associated with proinflammatory and cytotoxic effects[21] which are believed to promote tumorigenesis.

To our knowledge, there is limited research on the relationship between NPC and outdoor air pollution, especially coarse PM. In a study conducted in Taiwan, exposure to higher levels of NO_2 and $PM_{2.5}$ was found to be significantly associated with a higher risk of NPC. However, only three pollutants (SO_2, NO_2, and $PM_{2.5}$) were included in the analyses.[18] The aim of this study was to determine the association between coarse PM ($PM_{10\text{-}2.5}$) and NPC among Taiwanese men aged ≥40 years.

MATERIALS AND METHODS

Study participants

Initially, a total of 1,207,827 male participants were considered for the current study. However, 686,729 of them were excluded for the following reasons: (1) younger than 40 years (n=12,664); (2) diagnosed with NPC before 2009 (n=216); (3) lived in townships without air quality monitoring stations (n=642,787); and 4) incomplete data (n=31,062). The final study participants included 521,098 men (355 cases and 520,743 non-cases of NPC) who lived in 71 townships with air quality monitoring stations. Data were retrieved from three databases which were linked using participants' identification and household registration numbers that were protected for privacy reasons. The databases included the Air Quality Monitoring Database (AQMD), the TCR, and the Adult Preventive Medical Services Database (APMSD).

Datasets and measures

The air quality data were retrieved from the AQMD, Taiwan. The Air Quality Monitoring Network of the Environmental Protection Administration (EPA), Taiwan has been monitoring air quality in Taiwan since 1993.[22] This network contains fully automated air quality monitoring stations which provide daily concentrations of $PM_{2.5}$, PM_{10}, sulfur dioxide (SO_2), NOx (nitrogen monoxide (NO) and nitrogen dioxide (NO_2)), carbon monoxide (CO), and ozone (O_3).[23] The instruments used for measuring the various pollutants are stated elsewhere.[24] Even though air quality monitoring has been taking place in Taiwan since 1993, $PM_{2.5}$ data are available only from 2006 while PM_{10} data are available only from 1998. In our study, the participants' exposure data were assumed to be those obtained from the air quality monitoring stations found in townships where their household registration was done. A total of 71 townships had air quality monitoring stations. Mean annual concentrations (from 2006 to 2008) of air pollutants including $PM_{2.5}$, PM_{10}, $PM_{10\text{-}2.5}$, sulfur dioxide (SO_2), NOx, carbon monoxide (CO), and ozone (O_3) were used. Data on household registration, age, body mass index (BMI), smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia were retrieved from the APMSD (2012–2013). The National Health Insurance Administration, Taiwan began providing free adult preventive medical services to adults aged 40 years and above since 1996.[2 25] However, valid electronic records of users of these services were set up only in 2012.[2] The free adult preventive care services are provided once in 3 years for adults aged 40–64 years and once per year for those aged 65 years and above.[25] Data are collected through physical examinations (eg, height and weight), questionnaires (eg, age, betel nut chewing, exercise, disease history, smoking and drinking status) as well as blood and urine tests.[2 25] Data on NPC from 2009 to 2013 were collected from the TCR using the International Classification of Diseases for Oncology, third edition (ICD-O-3) code C11.

Statistical analysis

Concentrations of $PM_{10\text{-}2.5}$ were calculated by subtracting the measured concentrations of $PM_{2.5}$ from those of PM_{10}. Concentrations of PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ were stratified into quartiles. Quartiles were used because different concentrations of air pollutants might have different impacts on the risk of NPC. Furthermore, there was no information regarding the threshold of air pollution levels in NPC. For collinearity among pollutants, a variance influence factor (VIF) >10 was set as a cut-off value. Pollutants whose VIFs were >10 were not included in the regression models. The categorical variables were compared using the χ^2 test while the correlation among air pollutants was determined using Pearson correlation analysis. The association between PM (PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$) and nasopharyngeal carcinoma was determined using logistic regression. Covariates included SO_2, NOx, O_3, age, BMI, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia. The regression results were presented in four models. In models 1, 2, and 3, adjustments were made for SO_2, NOx, O_3, age, BMI, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia. In model 4, adjustments were made for $PM_{2.5}$, SO_2, NOx, O_3, age, BMI, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia. The SAS 9.4 software (SAS Institute, Cary, North Carolina, USA) was used to perform all the statistical analyses.

RESULTS

The mean annual concentrations of the air pollutants from 2006 to 2008 were 0.61 ppm for CO, 34.35, 59.71, and 25.37 µg/m^3 for $PM_{2.5}$, PM_{10}, and $PM_{10\text{-}2.5}$, respectively, and 5.06, 29.25, and 27.74 ppb for SO_2, NOx and O_3, respectively (table 1). Pearson correlation coefficients among the air pollutants are presented in table 2. Because CO was strongly correlated (VIF >10) with NOx (table not shown), it was not included in the regression models. The descriptive statistics of the study participants are shown in table 3. There

Table 1 Concentrations of air pollutants in Taiwan (2006–2008)

Air pollutants	Mean	SD	Min.	Q1	Median	Q3	Max.	Range
$PM_{2.5}$ (μg/m^3)	34.35	7.89	13.45	30.42	32.71	40.35	51.39	37.93
PM_{10} (μg/m^3)	59.71	13.51	26.82	50.66	58.89	70.23	89.72	62.90
$PM_{10\text{-}2.5}$ (μg/m^3)	25.37	6.79	12.62	20.44	24.08	29.27	43.13	30.51
SO_2 (ppb)	5.06	2.07	1.86	3.65	4.63	5.81	12.38	10.52
NOx (ppb)	29.25	14.48	4.32	20.50	27.25	32.80	81.76	77.44
CO (ppm)	0.61	0.22	0.15	0.47	0.57	0.71	1.34	1.19
O_3 (ppb)	27.74	4.01	16.42	25.71	27.64	30.19	44.96	28.54

Max, Maximum; Min, Minimum.

were significant differences ($p<0.05$) between the NPC and non-NPC cases in relation to PM_{10} $PM_{10\text{-}2.5}$, NOx, age, BMI, and alcohol drinking. The associations between PM (PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$) and NPC are shown in table 4. Only PM_{10} and $PM_{10\text{-}2.5}$ were significantly associated with a higher risk of NPC after adjusting for SO_2, NOx, O_3, age, BMI, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia (table 4, models 1, 2, and 3). For PM_{10} (reference: $PM_{10}<50.66$ μg/m^3), the ORs; 95% CIs were 1.31; 0.91 to 1.88, 1.52; 1.09 to 2.13, and 1.52; 1.03 to 2.23 for $50.66\leq PM_{10}<58.89$, $58.89\leq PM_{10}<70.23$, and $PM_{10}\geq 70.23$ μg/m^3, respectively (table 4, model 1). For $PM_{2.5}$ (reference: $PM_{2.5}<30.42$ μg/m^3), the ORs; 95% CIs were 0.69; 0.46 to 1.04, 1.09; 0.75 to 1.57, and 1.08; 0.75 to 1.55 for $30.42\leq PM_{2.5}<32.71$, $32.71\leq PM_{2.5}<40.35$, and $PM_{2.5}\geq 40.35$ μg/m^3, respectively (table 4, model 2). For $PM_{10\text{-}2.5}$ (reference: $PM_{10\text{-}2.5}<20.44$ μg/m^3), the ORs; 95% CIs were 1.47; 1.03 to 2.11, 1.34; 0.94 to 1.91, and 1.68; 1.16 to 2.44 for $20.44\leq PM_{10\text{-}2.5}<24.08$, $24.08\leq PM_{10\text{-}2.5}<29.27$, and $PM_{10\text{-}2.5}\geq 29.27$ μg/m^3, respectively (table 4, model 3). After excluding PM_{10} to avoid collinearity, $PM_{10\text{-}2.5}$ remained significantly associated with a higher risk of NPC after adjustments were made for $PM_{2.5}$, SO_2, NOx, O_3, age, BMI, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia. The ORs; 95% CIs were 1.42; 0.96 to 2.12, 1.41; 0.94 to 2.10, and 1.71; 1.10 to 2.66 for $20.44\leq PM_{10\text{-}2.5}<24.08$, $24.08\leq PM_{10\text{-}2.5}<29.27$, and $PM_{10\text{-}2.5}\geq 29.27$ μg/m^3, respectively (table 4, model 4).

DISCUSSION

In the current study, $PM_{10\text{-}2.5}$ was significantly associated with a higher risk of nasopharyngeal carcinoma after adjusting for age, BMI, smoking, and alcohol drinking among others. However, the association with $PM_{2.5}$ was not significant. It is worth mentioning that the association between NPC and outdoor air pollution, especially PM, has not been extensively investigated. To date, only one study has assessed the risk of NPC among Taiwanese adults exposed to air pollution.[18] However, $PM_{10\text{-}2.5}$ was not considered in the analysis.[18] Therefore, to our knowledge, this is the first study that has shown a significant association between $PM_{10\text{-}2.5}$ and NPC.

In the study conducted in Taiwan, $PM_{2.5}$ was significantly associated with an increased risk of NPC in Taiwanese adults.[18] However, the association between coarse PM and NPC was not assessed in that study.[18] In our current study, NPC was significantly associated with $PM_{10\text{-}2.5}$ but not $PM_{2.5}$. Fine PM ($PM_{2.5}$) and coarse PM ($PM_{10\text{-}2.5}$) vary in terms of size and deposition in the body.[26] This could account for their different impacts on NPC as observed in the current study. Fine particles which are smaller in diameter could be deposited right into the bronchioles and alveoli.[26] As such, they may not be trapped in the nasopharynx. These might explain why fine PM ($PM_{2.5}$) and NPC were not significantly associated in the current study. The nasopharyngeal tract traps mainly coarse particles in inhaled air whose sizes range between 5 and 10 um.[12 27] These particles contain endotoxins, soluble carcinogenic compounds, and trace metals which could trigger immune responses like inflammation and oxidative stress.[28 29] PM-induced immune responses in the nasopharynx could induce DNA damage and DNA adducts which could subsequently enhance predisposition to cancer.[29–31]

A limitation of this study is that information on important factors like socioeconomic status, family disease history, urbanization among others were not available to be included in the analysis. We did not also have information on participants who moved out of a township between 2006 and 2008. As a result, we could not determine the risk of NPC among such individuals. However, we believe that this might have resulted in a non-differential outcome

Table 2 Pearson correlation coefficients among air pollutants

Air pollutants	$PM_{2.5}$	PM_{10}	$PM_{10\text{-}2.5}$	SO_2	NOx	CO	O_3
$PM_{2.5}$	1.00	0.93*	0.69*	0.50*	0.10*	0.09*	<0.01
PM_{10}	–	1.00	0.91*	0.54*	0.09*	0.08*	0.05*
$PM_{10\text{-}2.5}$	–	–	1.00	0.50*	0.05*	0.06*	0.11*
SO_2	–	–	–	1.00	0.35*	0.33*	–0.18*
NOx	–	–	–	–	1.00	0.95*	–0.67*
CO	–	–	–	–	–	1.00	–0.66*
O_3	–	–	–	–	–	–	1.00

*P<0.05.

Table 3 Descriptive data of the participants

Variables	Non-nasopharyngeal carcinoma cases (n=520,743)	Nasopharyngeal carcinoma cases (n=355)	P value
$PM_{2.5}$ (μg/m^3)			
$PM_{2.5}$<30.42	165,634 (31.81%)	110 (30.99%)	0.260
30.42≤$PM_{2.5}$<32.71	87,233 (16.75%)	47 (13.24%)	
32.71≤$PM_{2.5}$<40.35	142,273 (27.32%)	104 (29.3%)	
$PM_{2.5}$≥40.35	125,603 (24.12%)	94 (26.48%)	
PM_{10} (μg/m^3)			
PM_{10}<50.66	130,770 (25.11%)	64 (18.03%)	0.019*
50.66≤PM_{10}<58.89	118,457 (22.75%)	84 (23.66%)	
58.89≤PM_{10}<70.23	146,439 (28.12%)	113 (31.83%)	
PM_{10}≥70.23	125,077 (24.02%)	94 (26.48%)	
$PM_{10\text{-}2.5}$ (μg/m^3)			
$PM_{10\text{-}2.5}$<20.44	122,658 (23.55%)	59 (16.62%)	0.018*
20.44≤$PM_{10\text{-}2.5}$<24.08	138,620 (26.62%)	103 (29.01%)	
24.08≤$PM_{10\text{-}2.5}$<29.27	126,679 (24.33%)	89 (25.07%)	
$PM_{10\text{-}2.5}$≥29.27	132,786 (25.5%)	104 (29.3%)	
SO_2 (ppb)			
SO_2<3.65	131,457 (25.24%)	76 (21.41%)	0.151
3.65≤SO_2<4.63	124,313 (23.87%)	77 (21.69%)	
4.63≤SO_2<5.81	133,527 (25.64%)	102 (28.73%)	
SO_2≥5.81	131,446 (25.24%)	100 (28.17%)	
NOx (ppb)			
NOx<20.50	127,602 (24.5%)	73 (20.56%)	0.047*
20.50≤NOx<27.25	130,325 (25.03%)	91 (25.63%)	
27.25≤NOx<32.80	134,522 (25.83%)	83 (23.38%)	
NOx≥32.80	128,294 (24.64%)	108 (30.42%)	
O_3 (ppb)			
O_3<25.71	128,955 (24.76%)	93 (26.2%)	0.300
25.71≤O_3<27.64	124,633 (23.93%)	97 (27.32%)	
27.64≤O_3<30.19	139,920 (26.87%)	88 (24.79%)	
O_3≥30.19	127,235 (24.43%)	77 (21.69%)	
CO (ppm)			
CO<0.47	125,976 (24.19%)	77 (21.69%)	0.111
0.47≤CO<0.57	125,414 (24.08%)	86 (24.23%)	
0.57≤CO<0.71	138,495 (26.6%)	84 (23.66%)	
CO≥0.71	130,858 (25.13%)	108 (30.42%)	
Age (years)			
30≤Age<40	115,635 (22.21%)	80 (22.54%)	<0.001*
40≤Age<50	139,232 (26.74%)	119 (33.52%)	
50≤Age<60	121,312 (23.3%)	99 (27.89%)	
60≤Age<70	144,564 (27.76%)	57 (16.06%)	
BMI (Kg/m^2)			
BMI<18.5	12,853 (2.47%)	12 (3.38%)	0.025*
18.5≤BMI<24	193,008 (37.06%)	155 (43.66%)	
24≤BMI<27	179,161 (34.40%)	113 (31.83%)	
BMI≥27	135,721 (26.06%)	75 (21.13%)	
Smoking			
Never	395,746 (76.00%)	283 (79.72%)	0.218
Occasional	24,675 (4.74%)	19 (5.35%)	
Average <1 pack/day	67,793 (13.02%)	35 (9.86%)	
Average >1 pack/day	32,529 (6.25%)	18 (5.07%)	
Drinking			
Never	375,072 (72.03%)	279 (78.59%)	0.022*
Occasional	117,233 (22.51%)	62 (17.46%)	
Frequent	28,438 (5.46%)	14 (3.94%)	
Betel chewing			

Continued

Table 3 Continued

Variables	Non-nasopharyngeal carcinoma cases (n=520,743)	Nasopharyngeal carcinoma cases (n=355)	P value
Never	481,688 (92.50%)	333 (93.80%)	0.444
Occasional	24,553 (4.71%)	16 (4.51%)	
Frequent	14,502 (2.78%)	6 (1.69%)	
Exercise			
No	263,320 (50.57%)	193 (54.37%)	0.358
<150 min/week	180,540 (34.67%)	114 (32.11%)	
>150 min/week	76,883 (14.76%)	48 (13.52%)	
Hypertension			
No	375,652 (72.14%)	265 (74.65%)	0.292
Yes	145,091 (27.86%)	90 (25.35%)	
Diabetes			
No	461,197 (88.57%)	317 (89.30%)	0.665
Yes	59,546 (11.43%)	38 (10.70%)	
Hyperlipidemia			
No	489,383 (93.98%)	337 (94.93%)	0.451
Yes	31,360 (6.02%)	18 (5.07%)	

*P<0.05.

classification error which might have led to an underestimation of the NPC risk. Notwithstanding, our findings still indicate that the actual effect could have been significant at the last quartile of $PM_{10\text{-}2.5}$. In addition, average concentrations of atmospheric pollutants measured by fixed monitoring stations were assumed to be the participants' exposure data. This assumption might not be completely correct as the participants might have spent time both indoors and outdoors. Moreover, the ambient air concentrations registered by the fixed monitoring stations may differ as one moves away from those stations. This might have influenced the results. However, no algorithms have been validated to determine an individual's exposure to pollutants and, therefore, it is not very feasible to estimate individual exposures to air pollution.[32] As such, measurements from nearby monitoring stations are usually used as proxies for individual exposure estimates.[32] Even though this method is prone to exposure misclassification, exposure classification error might have been minimized in our study as both the cases and non-cases of NPC are believed to have been non-differentially misclassified. Furthermore, data on some covariates were only available in the APMSD (2012–2013). As such, we considered the APMSD (2012–2013) covariate data as our baseline data. Measuring covariates after the exposure may result in biased results. However, in Taiwan, the air pollution exposure pattern in the past years has been constant.[2] Moreover, the levels of air pollutants between 2006–2008 and 2012–2013 were highly correlated (table not shown). This implies that the exposure data in 2006–2008 might not have been too different from those in 2012 and 2013. Therefore, the bias resulting from using the exposure data from 2006 to 2008 and covariates from 2012 to 2013 might have been minimized.

In conclusion, coarse PM ($PM_{10\text{-}2.5}$) was significantly associated with a higher risk of NPC in Taiwanese men in the current study. To support these findings, more studies are warranted.

Table 4 Association of nasopharyngeal carcinoma with PM_{10}, $PM_{2.5}$, and $PM_{10\text{-}2.5}$ in Taiwanese men

	Model 1			Model 2			Model 3			Model 4		
Variables	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
PM_{10}												
PM_{10}<50.66	1.00	–	–	–	–	–	–	–	–			
50.66≤PM_{10}<58.89	1.31	0.91 to 1.88	0.145	–	–	–	–	–	–			
58.89≤PM_{10}<70.23	1.52	1.09 to 2.13	0.015*	–	–	–	–	–	–			
PM_{10}≥70.23	1.52	1.03 to 2.23	0.034*	–	–	–	–	–	–			
$PM_{2.5}$												
$PM_{2.5}$<30.42	–	–	–	1.00	–	–	–	–	–	1.00	–	
30.42≤$PM_{2.5}$<32.71	–	–	–	0.69	0.46 to 1.04	0.075	–	–	–	0.70	0.46 to 1.07	0.103
32.71≤$PM_{2.5}$<40.35	–	–	–	1.09	0.75 to 1.57	0.665	–	–	–	0.86	0.56 to 1.31	0.476
$PM_{2.5}$≥40.35	–	–	–	1.08	0.75 to 1.55	0.686	–	–	–	0.87	0.58 to 1.31	0.492
$PM_{10\text{-}2.5}$												
$PM_{10\text{-}2.5}$<20.44	–	–	–	–	–	–	1.00	–	–	1.00	–	–
20.44≤$PM_{10\text{-}2.5}$<24.08	–	–	–	–	–	–	1.47	1.03 to 2.11	0.036*	1.42	0.96 to 2.12	0.082
24.08≤$PM_{10\text{-}2.5}$<29.27	–	–	–	–	–	–	1.34	0.94 to 1.91	0.109	1.41	0.94 to 2.10	0.097
$PM_{10\text{-}2.5}$≥29.27	–	–	–	–	–	–	1.68	1.16 to 2.44	0.006*	1.71	1.10 to 2.66	0.018*
SO_2												
SO_2<3.65	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
3.65≤SO_2<4.63	0.93	0.65 to 1.34	0.706	1.16	0.77 to 1.74	0.468	0.89	0.62 to 1.28	0.526	1.01	0.66 to 1.55	0.965
4.63≤SO_2<5.81	1.03	0.67 to 1.60	0.880	1.15	0.75 to 1.76	0.524	0.99	0.65 to 1.50	0.945	1.00	0.65 to 1.54	0.995
SO_2≥5.81	1.17	0.73 to 1.88	0.511	1.43	0.89 to 2.32	0.143	1.18	0.73 to 1.91	0.506	1.26	0.75 to 2.13	0.381
NOx												
NOx<20.50	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
20.50≤NOx<27.25	0.98	0.66 to 1.46	0.925	1.07	0.72 to 1.58	0.753	1.09	0.73 to 1.65	0.670	1.13	0.75 to 1.72	0.561
27.25≤NOx<32.80	0.70	0.40 to 1.22	0.209	0.70	0.41 to 1.19	0.184	0.73	0.41 to 1.32	0.301	0.72	0.40 to 1.30	0.276
NOx≥32.80	0.94	0.51 to 1.71	0.834	0.91	0.51 to 1.63	0.752	0.94	0.51 to 1.74	0.841	0.92	0.50 to 1.69	0.777
O_3												
O_3<25.71	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
25.71≤O_3<27.64	1.13	0.81 to 1.57	0.466	1.14	0.77 to 1.68	0.513	1.10	0.81 to 1.49	0.555	1.03	0.69 to 1.56	0.878
27.64≤O_3<30.19	0.83	0.54 to 1.28	0.400	0.74	0.47 to 1.17	0.197	0.72	0.49 to 1.08	0.109	0.65	0.40 to 1.04	0.075
O_3≥30.19	0.77	0.46 to 1.29	0.317	0.70	0.41 to 1.20	0.197	0.72	0.44 to 1.19	0.197	0.64	0.37 to 1.11	0.111

Models 1, 2 and 3: Adjusted for SO_2, NOx, O_3, age, BMI, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia.
Model 4: Adjusted for $PM_{2.5}$, SO_2, NOx, O_3, age, BMI, smoking, alcohol drinking, betel nut chewing, exercise, hypertension, diabetes, and hyperlipidemia.
*P<0.05.

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ORCID iD
Yung-Po Liaw http://orcid.org/0000-0003-2046-4964

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