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The effects of exposure to air pollution on the development of uterine fibroids

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ABSTRACT

Background: Air pollution may cause specific genetic or epigenetic abnormalities and lead to the development of uterine fibroids (UFs). However, there have been limited studies evaluating the relationship between air pollutant exposure and the development of UFs.
Methods: We conducted a 10-year cohort-based case-control study in Taiwan from 2001 to 2010 using National Health Institute Research Database (NHIRD) to assess the association between air pollution and the UFs development among Taiwanese women. The case group consisted of 11,028 women newly diagnosed with UFs during the study period and the control group was 44,112 women aged 25–45 years using density sampling with a 1:4 matching on the date of birth from 224,675 women in 2001–2010. The average age of onset was 36 ± 4.37 years old. Daily concentrations of $PM_{2.5}$ were estimated by linear mixed-effects model integrating aerosol optical depth (AOD) and meteorological variables; daily concentrations of O_3, CO, NO_2 and SO_2 were calculated by the Inverse Distance Weighting (IDW). The annual cumulative exposure to air pollutants during the study period was calculated corresponding to residential zip codes.
Results: In the conditional logistic regression adjusting for confounders, the adjusted odds ratio (aOR) for UFs per 10 $\mu g/m^3$ increase in $PM_{2.5}$ was 1.105 (95% confidence interval: 1.069, 1.141), per 10 ppb increase in O_3 was 1.075 (95% confidence interval: 1.039, 1.113), respectively.
Conclusions: Our study suggests that exposure to $PM_{2.5}$ and O_3 may increase the risk of developing UFs. Further studies are needed to confirm this novel finding.

1. Introduction

Uterine fibroids (UFs), the benign tumors and generally known as uterine leiomyoma, are the most frequently occurring tumors and neoplasms of the reproductive tract in women in Taiwan. Marino et al. (2004) examined the association of menstrual cycle characteristics with UFs in women and reported that UFs commonly occurred in reproductive-aged women with the incidence approximately up to 60%. Chao et al. (2005) examined the rate of inappropriate hysterectomy and found that UFs (46.2%) was the major indication for hysterectomy, following by cancer or premalignant conditions (22.2%), pelvic relaxation (12.6%) and endometriosis (9.9%) in Taiwan. UFs accounted for the largest percentage of hysterectomy not only in Taiwan (46.2%), but also in the U.S. (40.7%), Italy (41%), South Africa (23%), and India (27.9%) (Ho et al., 2015).

Air pollution may play an important role in environmental problems around the world. Mounting epidemiologic studies showed significant associations between air pollution and numerous women's health problems. Hooper et al. (2018) conducted a cohort study of women in the U.S. and investigated the relationship between long-term exposure to air pollutants (NO_2 and PM) and chronic bronchitis. They found that PM exposure was associated with the prevalence of chronic bronchitis, particularly for the women who smoke. Merklinger-Gruchala et al. (2017) attempted to examine if air pollutants such as PM_{10}, SO_2, CO and NO_X were related to the women's reproductive health and even influenced the length or phases of menstrual cycle. PM_{10}, SO_2, and CO per 1 g/m3 increase resulted in a decrease of the length of the luteal phase −0.02 day in PM_{10} ($p = 0.03$), 0.1 day in SO_2 ($p = 0.02$) and

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0.52 day in CO ($p = 0.06$). They finally indicated that air pollution might cause female fertility problems. Coogan et al. (2012) evaluated the risk of incident hypertension with the exposure to fine particulate matter ($PM_{2.5}$) in Los Angeles. They concluded that the risk of hypertension (HTN) was associated with traffic-related pollutants. Boynton-Jarrett et al. (2005) further reported a positive relationship between elevated blood pressure and the risk of UFs. Not only HTN, but also $PM_{2.5}$ plays a critical role in contributing to global cardiovascular (CV) disability and mortality. Weichenthal et al. (2014) investigated the association between $PM_{2.5}$ and CV mortality in the United States. They reported that CV mortality may increase by a relative 10% (per 10 μg/m^3) during long-term exposure to $PM_{2.5}$. Similar results were also found in the nationwide study in Canada. An increase of ischemic heart disease deaths was significantly associated with an interquartile increase of $PM_{2.5}$ (6.2μg/m3). And the exposure level was lower (mean = 8.7 μg/m^3) than that found in previous studies (Crouse et al., 2012).

To the best of our knowledge, there was only one study investigating the association between air pollution and the development of UFs. Mahalingaiah et al. (2014) conducted a prospective cohort study of 85,251 female nurses aged 25–42 years in the United States. They found that cumulative average concentrations of $PM_{2.5}$ were associated with an increased risk of UFs. The cumulative average concentrations of $PM_{2.5}$ were 15.2 μg/m^3, much lower than those in Taiwan (33.93 μg/m^3). Therefore, we conducted a 10-year cohort-based case-control study at the area with high $PM_{2.5}$ concentrations (approximately three times higher than the criteria recommended by the WHO) to assess the effects of long-term exposure to $PM_{2.5}$, O_3, CO, NO_2 and SO_2 on the development of UFs among Taiwanese women.

2. Methods

2.1. Study population

We utilized the Longitudinal Health Insurance Database 2000 (LHID 2000), which includes 1,000,000 beneficiaries randomly sampled from the National Health Institute Research Database (NHIRD). NHIRD, a single-payer National Health Insurance program, covers 99.9% of the 23 million residents in Taiwan. This nationally representative sample was provided by the National Health Research Institutes (NHRI) authorized by the Ministry of Health and Welfare of Taiwan. All personal identification numbers were anonymized to protect the privacy of subjects. Therefore, we don't have to obtain informed consents from the sampled beneficiaries. Our study was approved by the Institute Review Board of China Medical University Hospital ((CMU-REC-101-012) and also in conformity with the Helsinki Declaration.

2.2. Study design

We conducted a cohort-based case-control study from 2001 to 2010 to investigate the effects of air pollution exposure to the risk of UFs. First, we excluded 513,670 males, 417 people with missing or incorrect information on gender, 16 people with missing or incorrect information on residential zip codes, 3,637 people without exposure data, and 7,716 people diagnosed with UFs before the beginning of follow-up date on January 1, 2001. The study population included 224,675 women aged 25–45 years free of UFs at baseline (January 1, 2001). Eleven thousand and one hundred nine participants withdrew during the study period. The follow-up rate was 95% (213,566/224,675). To increase the study efficiency, we conducted a density matching on the date of birth (e.g. age) (Pearce, 2016). The controls were chosen simultaneously as the day the case was newly diagnosed. Finally, we identified new UFs cases (n = 11,028) during the study period, and the control subjects (n = 44,112) were selected randomly from the beneficiaries not diagnosed with UFs in the ratio of 1: 4 (case: control) from the source population (N = 224,675 women). (Fig. 1). The average age of women with newly diagnosed UFs was 36 years (standard deviation ± 4.37). The design enabled us to verify an appropriate temporality between the hypothesized air pollution exposure and the development of UFs and to eliminate the possibility that the presence of UFs would influence the assessment of exposure (e.g., seasonal variation and the length of exposure).

2.3. Definition of outcome

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) is a criterion for clinical physicians to diagnose patients. The disease diagnostic codes are considered reliable because the reimbursement process is reviewed rigorously and professionally by the National Health Insurance Administration (NHIA). In our study, we followed up ambulatory care expenditures by visits and inpatient expenditures by admissions from the National Health Institute Research Database (NHIRD) from 2001 to 2010. We defined ICD-9-CM code 218.0, 218.1, 218.2, and 218.9 as the cases of UFs when each code appears in medical records at least twice based on ultrasound physician diagnoses. The newly diagnosed cases during the follow-up period were defined as the diagnostic codes first appearing in the registration data.

2.4. Exposure assessment

We obtained hourly concentrations of air pollutants from Taiwan Environmental Protection Administration (TEPA). There are 73 monitoring stations throughout Taiwan. At present, there is no evidence to indicate the effects of the duration of exposure to air pollution on the development of UFs. Therefore, we used the average exposure over 2-year and 4-year periods before the diagnosis of UFs to estimate the association between air pollutants and UFs in order to compare our results with the findings from Mahalingaiah et al. (2014).

We used the Inverse Distance Weighting (IDW) to estimate daily concentrations of O_3, CO, NO_2 and SO_2 (Lee et al., 2018). We further incorporated aerosol optical depth (AOD), meteorological variables and land use data in the linear mixed-effect model to speculate daily concentrations of $PM_{2.5}$ over Taiwan. More details can refer to the Jung et al.'s study (Jung et al., 2017). We subsequently integrated daily concentrations of air pollutants corresponding to residential zip codes to calculate 2-year and 4-year average exposure before the diagnosis of UFs from 2000 to 2010. The average spatial resolution of residential zip codes in Taiwan was typically corresponded to one block face in urban areas (17 ± 8.56 km^2) with high population density, but was larger in rural areas (154 ± 104.39 km^2) with low population density.

2.5. Covariates

Social economic status (SES) was divided into four groups (≤25th: ≤ 15,840; 25th-50th: 15,840–21,000; 50th-75th: 21,000–30,300 and > 75th: > 30,300 NTD) according to the interquartile range (IQR). Co-morbidities included parity with a diagnosis-related group (DRG) code 0373A, 0371A, 0373B, 0373C, hypertension (HTN) with an ICD-9-CM code 401–405 and hormones intake, considered as potential confounding factors of UFs. Because breast cancer may lead to the enlargement and growth of UFs when undergoing hormones therapy, we also took breast cancer (BC) with an ICD-9-CM code 174 into account as a covariate of UFs (Flake et al., 2003). In addition, smoke records were not available in the NDIRH. An estimated 95% of COPD cases were attributed to smoking in the developed countries (Barnes et al., 2003). A Taiwanese study also indicated that 82.9% cases of COPD were caused due to smoking (Cheng et al., 2015). Therefore, we used chronic obstructive pulmonary disease (COPD) as a substitute with an ICD-9-CM code 490 for smoke information. Cases of co-morbidities –breast cancer and hypertension were identified with two consistent diagnoses.

Estrogen and progesterone are two major hormones in women's bodies. Estrogen is related to increased risks of endometrial cancer;

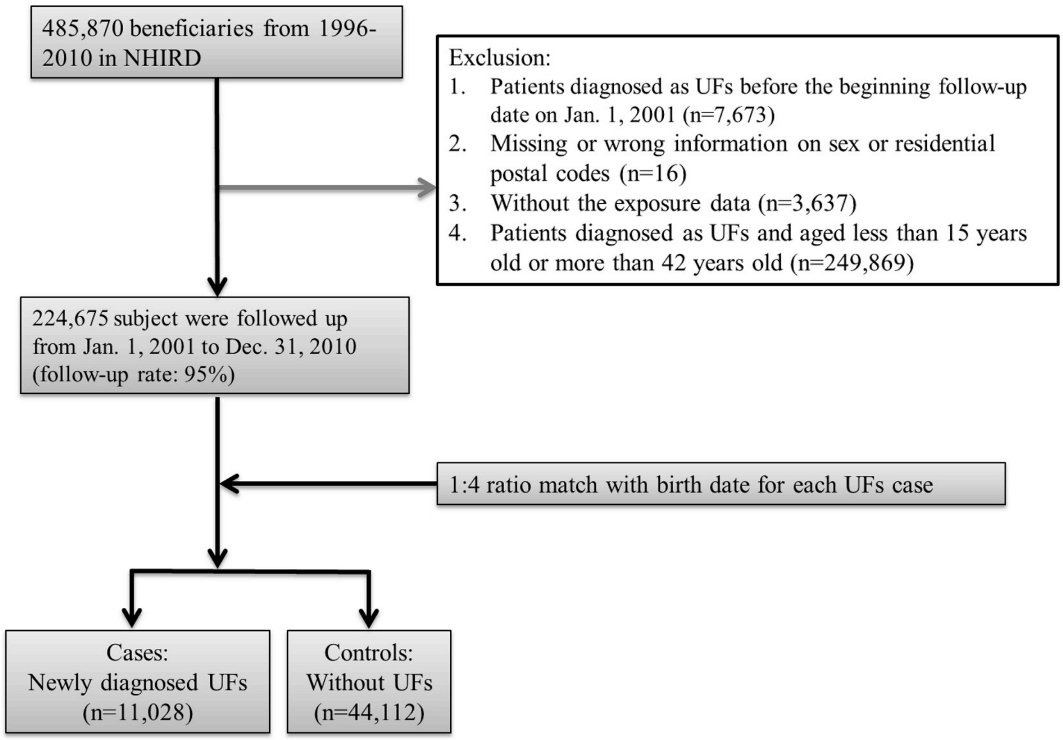

Fig. 1. Study flow diagram of cohort-base case-control study.

conversely, the use of progesterone is to negate the risk from taking estrogen. Therefore, the women with an intact uterus should be prescribed sufficient progesterone as they use estrogen. With the exception of women who do not have a uterus or have the extensive endometriosis history should not be prescribed progesterone with estrogen (North American Menopause Society, 2012). We followed Reed et al. 's suggestion and defined the woman who had used estrogen or progestin for at least 3 months (around 90 days) as an ever-user because uterine fibroids could undergo the growth when hormones were introduced within about 90 days (Reed et al., 2004).

2.6. Statistical analysis

We investigated the association between air pollution exposure and UFs by using conditional logistic regression. The effect estimations were presented as odds ratios (ORs) per 10 $\mu g/m^3$ unit changes for $PM_{2.5}$, 10 ppb for O_3, 100 ppb for CO, 10 ppb NO_2, and 1 ppb for SO_2 with the 95% confidence intervals (CI). The potential confounders (SES, COPD, HTN and hormones taking) were defined as determinants of UFs and associated with air pollution concentrations and further incorporated into models. In order to determine whether or not exposure time windows could influence UFs, we assessed the association between different exposure periods (2-year, and 4-year exposure periods before the diagnosis of UFs) and the development of UFs. We further performed the distributed lag nonlinear model (dlnm package in the R program) to investigate the exposure-response relationships between air pollutants and UFs. The functions of curve fitting for exposure-response relationships (b-spline or natural cubic, and degree of freedom from 4 to 9) were determined by the minimum Akaike information criterion (AIC).

3. Results

3.1. Characteristics of study population

The final study population consisted of 11,028 cases and 44,112 controls. Table 1 presents demographic characteristics of the study population. The odds ratios (ORs) of UFs were higher in groups with highest social economic status (OR = 1.62; 95% CI: 1.52–1.72), COPD (OR = 1.40; 95% CI: 1.30–1.51), and HTN (OR = 1.46; 95% CI: 1.30–1.64). In contrast, parity was negatively associated with UFs. The risk of UFs for the parous women was 0.87 (95% CI: 0.83, 0.91) lower than the nulliparae. With regard to hormones intake, we found that the use of estrogen and progesterone was associated with increased risks of developing UFs. The risk of UFs for the women who had hormones prescription experience longer than 90 days was higher than those without hormones prescription experience. (OR = 2.60; 95% CI: 2.33, 2.92). Concerning different types of hormones, we found that the women who had used both estrogen and progesterone might face the highest risk (OR = 2.47; 95% CI: 2.33, 2.61) of developing UFs. We controlled these potential confounding factors in the multiple conditional logistic regression.

3.2. Air pollution

Table 2 shows distributions of mean concentrations in 3 exposure averages. We found that the means of air pollutants over 2-year average exposure before the onset of UFs were the lowest of all. At each exposure period, the mean and median levels within single pollutant were similar (Table 2). Table 3 shows the association between different air pollutants and UFs over the cumulative exposure period. The concentrations of NO_2 and CO were highly correlated (0.94) indicating the main source of traffic-related air pollutants or the vegetation burning activities. The concentration of O_3 was negatively correlated with CO (0.57) and NO2 (0.53), but positively with $PM_{2.5}$ (0.61) (Table 3). In the multiple-pollutant modelling, we were able to control for one stationary fossil fuel pollutant (SO_2) or one of traffic-related pollutants (NO_2 or CO) at a time as a potential confounder when evaluation the effect of $PM_{2.5}$ or O_3.

3.3. Air pollution and uterine fibroids

Table 4 indicates the association between air pollutants and UFs in

Table 1
Demographic distributions of all population (n = 55,140) during 2001–2010.

	Case N (%)	Control N (%)	OR (95%CI)	p-value
total	11,028 (100)	44,112 (100)		
Age (average age of onset: 36.00 ± 4.37 years old)				
≤35 years old	4,133 (37.48)	16,532 (37.48)		
> 35 years old	6,895 (62.52)	27,580 (62.52)		
Social Economic Status				
1 (≤15,840 NTD)	2,229 (20.21)	11,959 (27.11)	reference	
2 (15,840–21,000 NTD)	3,946 (35.78)	15,604 (35.37)	1.36 (1.28–1.44)	0.6522
3 (21,000–30,300 NTD)	1,699 (15.41)	6,081 (13.79)	1.50 (1.40–1.61)	< 0.0001
4 (≤30,300 NTD)	3,154 (28.60)	10,468 (23.73)	1.62 (1.52–1.72)	< 0.0001
Breast Cancer				
No	10,977 (99.54)	43,959 (99.65)	reference	
Yes	51 (0.46)	153 (0.35)	1.34 (0.97–1.84)	0.0741
Chronic Obstructive Pulmonary Disease				
No	9,995 (90.63)	41,072 (93.11)	reference	
Yes	1,033 (9.37)	3,040 (6.89)	1.40 (1.30–1.51)	< 0.0001
Hypertension				
No	10,607 (96.18)	42,937 (97.34)	reference	
Yes	421 (3.82)	1,175 (2.66)	1.46 (1.30–1.64)	< 0.0001
Parity				
0 birth	7,225 (65.52)	27,552 (62.47)	reference	
≧1 birth	3,803 (34.48)	16,560 (37.53)	0.87 (0.83–0.91)	< 0.0001
Hormones Intake				
Total days of prescription				
No	4,157 (37.69)	23,410 (53.07)	Reference	
< 90 days	6,386 (57.91)	19,620 (44.48)	1.88 (1.80–1.97)	< 0.0001
≧ 90 days	485 (4.40)	1,082 (2.45)	2.60 (2.33–2.92)	< 0.0001
Different types of hormones				
No	4,157 (16.71)	23,410 (27.91)	Reference	
Yes (E or P)	6,871 (83.29)	20,702 (72.09)	2.23 (2.13–2.33)	< 0.0001
E	3,901	10,769	2.43 (2.30–2.56)	< 0.0001
P	6,460	19,470	2.23 (2.13–2.34)	< 0.0001
E and P	3,490	9,537	2.47 (2.33–2.61)	< 0.0001

N: number; 95% CI: confidence interval; E: Estrogen; P: Progesterone.

Table 2
Distribution of air pollutant concentrations over different exposure periods.

Pollution (unit)	Mean ± SD	Max	Min	Q1	Median	Q3	IQR
2-year average before the onset of UFs							
$PM_{2.5}$ (μg/m^3)	33.87 ± 7.18	52.45	13.29	29.66	33.12	39.38	9.72
O_3 (ppb)	42.05 ± 6.97	61.54	26.11	36.05	41.18	48.04	11.99
CO (ppm)	0.68 ± 0.22	2.14	0.15	0.53	0.66	0.79	0.26
NO_2 (ppb)	22.04 ± 5.31	38.93	1.30	18.33	22.19	25.68	7.34
SO_2 (ppb)	4.59 ± 1.82	12.98	0.24	3.52	4.17	5.15	1.63
4-year average before the onset of UFs							
$PM_{2.5}$ (μg/m^3)	33.95 ± 7.19	51.79	13.36	29.88	32.76	39.36	9.48
O_3 (ppb)	42.00 ± 6.85	58.66	26.66	35.93	41.37	47.89	11.96
CO (ppm)	0.68 ± 0.20	1.93	0.16	0.53	0.65	0.78	0.25
NO_2 (ppb)	22.11 ± 5.23	37.23	1.64	18.37	22.30	25.74	7.37
SO_2 (ppb)	4.65 ± 1.76	11.47	0.31	3.60	4.27	5.10	1.50

Table 3
The Spearman's correlation coefficient of air pollutants over a cumulative exposure period.

Spearman Correlation Coefficients					
	$PM_{2.5}$	O_3	CO	NO_2	SO_2
$PM_{2.5}$	1	0.61*	−0.07*	−0.02*	0.24*
O_3		1	−0.57*	−0.53*	0.08*
CO			1	0.94*	0.25*
NO_2				1	0.37*
SO_2					1

$PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; O_3, ozone; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide.
*$p < 0.0001$.

Table 4
Odds ratios and 95% confidence intervals for the associations between single air pollutant and UFs over different exposure periods.

Pollution (unit)	OR (95% CI)	Adjusted OR (95% CI)
2-year average (n = 48,755)		
$PM_{2.5}$ (10 μg/m^3)	1.097 (1.064–1.132)	1.088 (1.054–1.123)
O_3 (10 ppb)	1.067 (1.033–1.102)	1.064 (1.029–1.100)
CO (100 ppb)	1.010 (1.000–1.021)	1.012 (1.001–1.023)
NO_2 (10 ppb)	1.040 (0.997–1.086)	1.040 (0.995–1.087)
SO_2 (1 ppb)	1.007 (0.994–1.020)	1.004 (0.992–1.017)
4-year average (n = 36,275)		
$PM_{2.5}$ (10 μg/m^3)	1.082 (1.043–1.121)	1.079 (1.040–1.120)
O_3 (10 ppb)	1.068 (1.028–1.109)	1.071 (1.030–1.114)
CO (100 ppb)	1.006 (0.993–1.019)	1.007 (0.993–1.020)
NO_2 (10 ppb)	1.021 (0.971–1.073)	1.018 (0.967–1.071)
SO_2 (1 ppb)	1.000 (0.986–1.015)	1.000 (0.986–1.016)

$PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm; O_3, ozone; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide.
Adjusted ORs were adjusted for SES, COPD, HTN, and hormones intake.

the single pollutant model. The risks of UFs were significantly associated with the 2-year average, and 4-year average of $PM_{2.5}$ and O_3. The adjusted odds ratios (aORs) of UFs was 1.088 for $PM_{2.5}$ (95% CI: 1.054, 1.123) and 1.064 for O_3 (95% CI: 1.029, 1.100) respectively in 2-year average exposure. Moreover, the risk of UFs in 2-year average exposure before the onset of UFs was slightly higher than 4-year average exposure (aOR = 1.079; 95% CI: 1.040, 1.120) when exposure to $PM_{2.5}$, but the result was opposite to O_3 (aOR = 1.071; 95% CI: 1.030, 1.114) (Table 4).

We further examined the exposure-response relationships of $PM_{2.5}$ and O_3 focusing on 4-years average exposure (Figs. 2–3). For the distributed lag nonlinear model of $PM_{2.5}$, the best AIC was obtained with b-spline at the degree of freedom of 9 (AIC = 22670). The exposure-

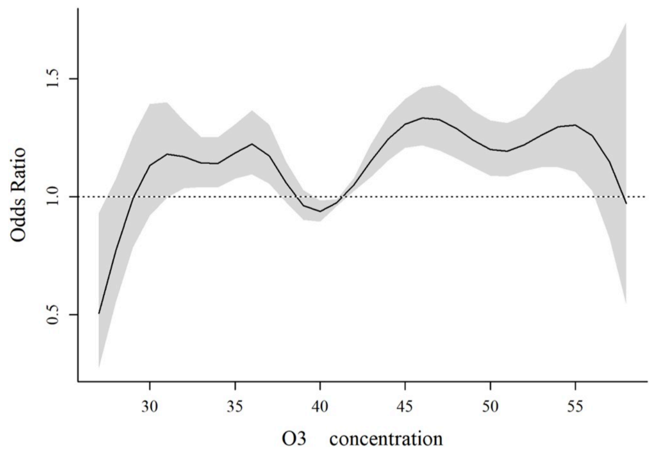

Fig. 2. Adjusted odds ratio (OR) with 95% confidence interval (grey area) of UFs with a 1 ppb increase in O_3 in 4 year average exposure by a conditional logistic regression combined with a distributed lag non-linear model. The model was adjusted for SES, COPD, HTN, and hormones taking. The exposure-response relation was set as b-spline with degree of freedom of 9 (AIC = 22659.05), setting equally-spaced knots without intercept and with a centering value set at 41.37 ppb (Q2).

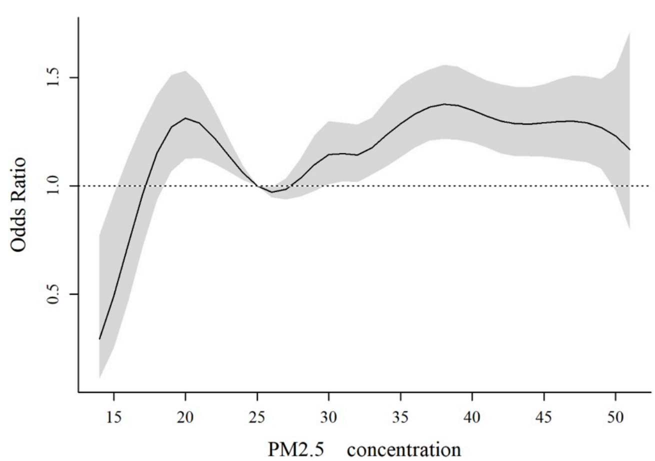

Fig. 3. Adjusted odds ratio (OR) with 95% confidence interval (grey area) of UFs with a 1 μg/m^3 increase in $PM_{2.5}$ in 4 year average exposure by a conditional logistic regression combined with a distributed lag non-linear model. The model was adjusted for SES, COPD, HTN, and hormones taking. The exposure-response relation was set as b-spline with degree of freedom of 9 (AIC = 22670), setting equally-spaced knots without intercept and with a centering value set at 25 μg/m^3 based on the WHO 24-hr mean standard.

response pattern of $PM_{2.5}$ showed that the ORs of UFs increased gradually between 19 and 24 μg/m^3 (ORs ranged from 1.061 to 1.312), and it dramatically increased when exposure to $PM_{2.5}$ above 30 μg/m^3 (Fig. 2). For the distributed lag nonlinear model of O_3, the best AIC was obtained with b-spline at the degree of freedom of 9 (AIC = 22659). The exposure-response relationship of O_3 is nonlinear. The ORs of UFs were statistical significant and positive at exposure to O_3 between 32 and 37 ppb, the maximum OR of UFs occurred at O_3 concentration of 42 ppb (Fig. 3).

Because urban air pollution constitutes a complex mixture of several components, we further consider multiple-pollutant models when we focused on cumulative exposure category. In the two-pollutant model, addition of either NO_2 (1.103, 1.068–1.140) or SO_2 (1.114, 1.076–1.154) did not change the effect estimate for $PM_{2.5}$ substantially (Fig. 4). In the three-pollutant model, the estimates for $PM_{2.5}$ were 1.123 (95% CI 1.083–1.164) and 1.121 (95% CI 1.081–1.161) respectively when (CO and SO_2) or (NO_2 and SO_2) were added and showed statistical significances (Fig. 5). The adjusted odds ratio for 10 ppb change in O_3 was 1.133 (95% CI 1.087–1.1824) and the estimates changed little when a second or third pollutant was added.

4. Discussion

In the present study, we found associations between exposure to air pollutants and the risk of UFs. In the average exposure over 2-year and 4-year periods before the onset of UFs, our results showed that exposure to $PM_{2.5}$ or O_3 was significantly associated with an increased odds ratio of the development of UFs. Mahalingaiah et al. (2014) found a modest risk of exposure to $PM_{2.5}$ in the cumulative exposure period, yielding adjusted odd ratio of 1.11 (95% CI: 1.03, 1.19), but not for the average exposure to PM2.5 over two years and four years. In our study, we found a significant positively association between the women with 2-year and four-year exposure to PM2.5 and the development of UFs. With regard to different results, it could be explained that the concentrations of $PM_{2.5}$ in our study were much higher than those in the Nurses' Health Study in the United States. Therefore, we suspected the exposure time window of UFs could be much shorter when women were exposed to higher levels of $PM_{2.5.}$

As for exposure-response relationships, the ORs of UFs increased gradually between 19 and 24 μg/m^3 $PM_{2.5}$ exposure and increased dramatically at exposure to $PM_{2.5}$ greater than 30 μg/m^3. In addition, the ORs of UFs were significantly positive at exposure to O_3 between 32 and 37 ppb and sharply increased over 42 ppb.

Cigarette smoking may be also an important risk factor for UFs. Dragomir et al. (2010) conducted a cross-sectional study to compare the risk factor for uterine fibroids subtypes among premenopausal women and indicated increased risks of diffuse UFs in smokers (Dragomir et al., 2010). Because smoke records were not available in NHIRD, we substituted chronic obstructive pulmonary disease (COPD) for smoke information (Barnes et al., 2003). Additionally, a positive association between hypertension and UFs was found in our study which is consistent with previous studies (Faerstein et al., 2001; Takeda et al., 2008).

Our results also showed that the risk for the women who used hormones longer than 90 days was significantly higher than those who never used. We also found that women who took either estrogen or progesterone were more likely to develop UFs. Flake et al. (2003) conducted systematic reviews and concluded that either estrogen or progesterone was a critical factor for stimulating the growth of uterine fibroids. In the rat model, both estrogen and progesterone were main hormones for promoting the growth of fibroids (Moravek and Bulun, 2015; Moravek et al., 2014; Rein, 2000).

Although the pathogenesis of UFs is still unclear, the subset of human myometrial cells has been proved to have similar characteristics with stem cells. Under normal condition, somatic stem cells (SSC) divide into transit amplifying (TA) cells first. Then TA cells divide a limited number of times until mature tissues are formed. Under increased pressure, such as HTN, cells may potentially differentiate into UF progenitor/clonal cells. A stem cell may become tumor-initiating cells (TICs) by the stimulus of $PM_{2.5}$ or $O_{3,}$ which might cause specific genetic or epigenetic abnormalities and finally developed into a uterine fibroid (Yang et al., 2016). The other possible pathogenesis of UFs was that $PM_{2.5}$ or O_3 may interact with innate immune system and cause innate immune responses. Saxon and Diaz-Sanchez (2005) proposed that particulate pollutants and gaseous pollutants can act on the upper and lower airways and aggravate cellular inflammation. We speculated that $PM_{2.5}$ may penetrate into lungs and diffuse into other organs such as kidneys, livers, hearts, and even suffuse the uterus (Takenaka et al., 2001). Then, it may further influence the uterus directly. Additionally, when exposed to O_3, pollutants would also be inhaled into lungs and subsequently cause the release of pro-inflammatory mediators which can result in the chronic lung inflammation (Bayram et al., 2001;

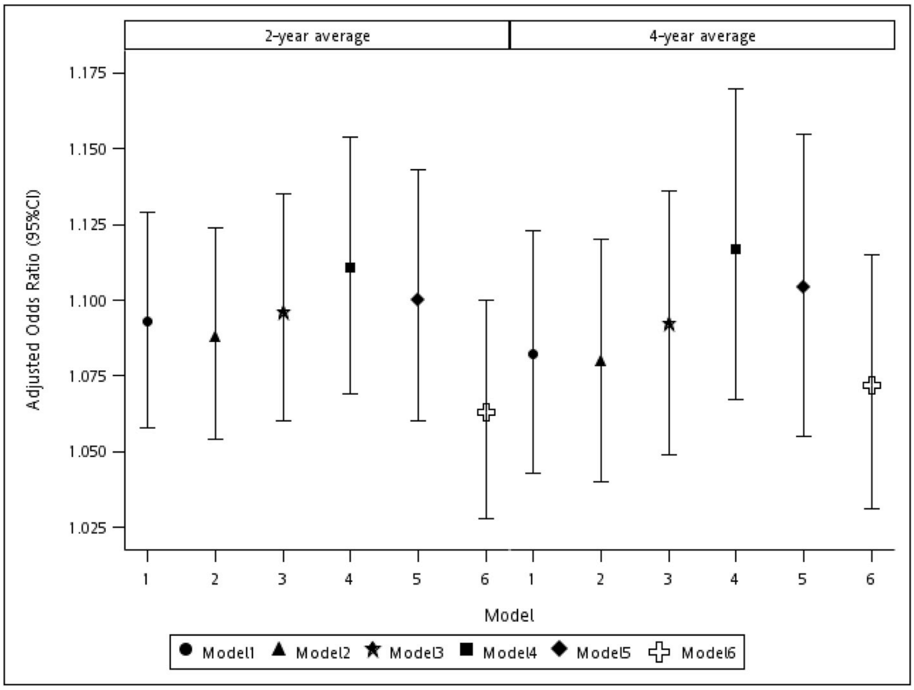

Fig. 4. Association between air pollution and different exposure periods from multipollutant models, 2000–2010. Unit changes: 10 μg/m^3 for particulate matter with aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$); 10 ppb for ozone (O_3) and nitrogen dioxide (NO_2); 100 ppb for carbon monoxide (CO); and 1 ppb for sulfur dioxide (SO_2). All models were adjusted for SES, COPD, HTN, and hormones taking. Model 1 included $PM_{2.5}$ and CO. Model 2 included $PM_{2.5}$ and NO_2. Model 3 included $PM_{2.5}$ and SO_2. Model 4 included O_3 and CO. Model 5 included O_3 and NO_2. Model 6 included O_3 and SO_2.

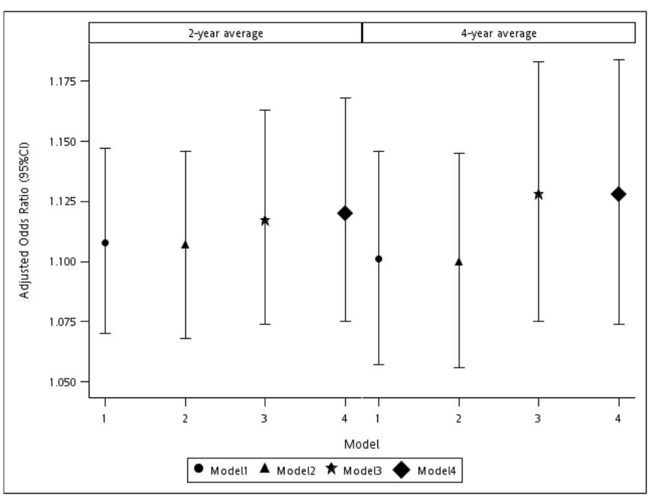

Fig. 5. Association between air pollution and different exposure periods from multipollutant models, 2000–2010. Unit changes: 10 μg/m^3 for particulate matter with aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$); 10 ppb for ozone (O_3) and nitrogen dioxide (NO_2); 100 ppb for carbon monoxide (CO); and 1 ppb for sulfur dioxide (SO_2). All models were adjusted for SES, COPD, HTN, and hormones taking. Model 1 included $PM_{2.5}$, CO and SO_2. Model 2 included $PM_{2.5}$, NO_2 and SO_2. Model 3 included O_3, CO and SO_2. Model 4 included O_3, NO_2 and SO_2.

Tamagawa and van Eeden, 2006). Then, O_3 may go through the blood-brain barrier (Banks et al., 2002) and join the circulation of peripheral organs to affect the inflammatory response of peripheral innate immune cells (Block and Calderón-Garcidueñas, 2009; Tracey, 2009). The inflammatory response further leads to chronic inflammation. After that, a conductive microenvironment is established to initiate the fibrinogenesis and tumorigenesis finally results in UFs (Chegini, 2010; Saxon and Diaz-Sanchez, 2005).

Although our exposure assessment was assigned from the UFs diagnosis corresponding to residential zip codes rather than addresses, a previous study reported that when using the municipal level of exposure as a proxy for individual level of exposure results in smaller effect estimates than using individual level of exposure assessment (Navidi and Lurmann, 1995). A plausible source of information bias is that women may change residential location during the study period, which will result in exposure misclassification. Similar impacts of random migration on cases and controls might introduce non-differential misclassification and decrease the accuracy of exposure assessment. It would most likely result in underestimation of air pollution effects rather than introducing a bias in associations.

There are several strengths in our study. First, the entire study population from the NHIRD providing a sufficient database and covering over 99% residents in Taiwan was large enough for us to estimate relationships between the women exposed to air pollutants and the development of UFs. Second, a nested case-control design was used in the present study. Comparing with the traditional case-control study, this study design was able to avoid the recall bias and verify an appropriate temporality between the hypothesized air pollution exposure and the development of UFs. Third, applying the density matching approach on the basis of the date of birth, we could control the confounding effects of age and ensure that each woman in the same matched groups would have the same duration of exposure to $PM_{2.5}$ and O_3. Fourth, several studies reported that race was a possible confounding factor with regard to the relationship between air pollution and UFs. The previous four registry studies indicated that the risk of UFs for black women was two to threefold higher than white women (Baird et al., 2003; Boynton-Jarrett et al., 2005; Marshall et al., 1997; Templeman et al., 2009). However, because of the Han ethnic homogeneity in Taiwan, race may not be an issue in our study.

Our study also has some notable limitations. First, we obtained air pollution data from monitoring stations and estimated air pollutant concentrations corresponding to their residential zip codes. This may lead to non-differential misclassification of exposure because we were not be able to consider living activities and residential movement during the study as well as indoor air pollution Furthermore, the diagnosis date was not a real onset of UFs, which could also enhance the probability of exposure misclassification of UFs. Second, the bias in diagnosis may occur as we used ICD-9-CM code to identify the cases. To improve the accuracy, the cases were defined as those with at least two ICD 9 based diagnoses in our study.

5. Conclusion

Our study suggests that women aged 25–45 years with higher long-term exposure to PM2.5 and/or O3 have an increased chance of developing UFs. However, further studies are still needed to confirm or repeat our novel findings.

Competing financial interest declaration

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The authors declare they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.02.004.

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