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Original Article

Characteristics of patients with endometrial hyperplasia under different air quality index conditions

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ABSTRACT

Objective: Air pollution has been widely recognized to pose a threat to health. Urban outdoor air pollution was listed as the 14th biggest risk factor for global deaths in 2004 in the Global Health Risks report published by the World Health Organization in 2009. Many past studies have indicated that exposure to environmental contaminants promotes changes in the internal mechanisms of diseases, including the infection of various systems in the body, hormonal changes, and vascular proliferation. These changes may be related to the severity of endometrial hyperplasia. Therefore, this study used the air quality monitoring data of the Environmental Protection Administration (EPA) to examine the effects of air pollutant concentration on patients with endometrial hyperplasia.

Materials and methods: This population-based nationwide study used data for 2002–2013 from the National Health Insurance Research Database of Taiwan. Patients who developed endometrial hyperplasia before 2002 were excluded. In total, 14,883 patients with endometrial hyperplasia were tracked. The exposure levels and air quality index (AQI) values in this study were based on the taiwan air quality monitoring network data collected by the EPA from 2000 to 2013. The data were further divided into the good air quality group (AQI $\leq$ 50) and poor air quality group (AQI > 50). The study used linear regression model to estimate the correlation linking air pollutant concentration with endometrial hyperplasia.

Results: The results indicated that, in comparison to endometrial hyperplasia patients who were exposed to air with good quality, those exposed to air with poor quality had a higher average age ($p < 0.001$) and higher proportion of living in southern Taiwan ($p < 0.001$), as well as higher rates of diabetes ($p < 0.001$), hyperlipidemia ($p < 0.001$), hypertension, cerebrovascular diseases ($p = 0.024$), cerebral vascular accidents ($p = 0.024$), and chronic kidney disease ($p < 0.001$).

Conclusion: The patients with endometrial hyperplasia in poor AQI area had severe comorbidity. Thus, attention must be paid to the improvement of air quality and the implementation of preventive measures against contaminants.

Introduction

Air pollution has been widely recognized to pose a threat to health. Urban outdoor air pollution was listed as the 14th biggest risk factor for global deaths in 2004 in the Global Health Risks report published by the World Health Organization in 2009 [1]. The influence of air pollution on health is determined by many factors.

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In addition to the concentration and chemical characteristics of air pollutants, other factors include an individual's age, general health status, and duration of exposure to the pollutants, as well as climate conditions and the distance between the individual and the emission source. People who frequently engage in outdoor work or activities have a higher chance of being affected by air pollution. In general, the health risks of pollutants are lower in the case of short-term contact [1]. Many studies have indicated that air pollution has vast and deep effects on human health. Apart from respiratory tract diseases, it increases the risk of coronary arteriosclerosis, cardiac failure, stroke, insulin resistance, diabetes, and obesity. The American Heart Association (AHA) has declared that the particulate matter (PM) in air increases the risk of and mortality due to cardiovascular diseases. Exposure to a $PM_{2.5}$ environment for several hours or weeks triggers cardiovascular diseases and may even cause death, whereas long-term exposure to such an environment reduces life expectancy [2]. The European Study of Cohorts for Air Pollution Effects (ESCAPE) analyzed the long-term effects of air pollution in Europe and found that long-term exposure to $PM_{2.5}$ concentration increases the risk of death despite being within the permissible limits [3].

Endometrial hyperplasia refers to an excessive number and density of endometrial cells and a deviation in their shape as observed via a microscope. The endometrium is filled with endometrial cells to the degree that pathological changes occur in the cells, resulting in the increased density of the entire tissue [4,5]. Endometrial hyperplasia develops when estrogenic hormones stimulate the endometrium over a long period of time and there is a lack of progesterone protection. Endometrial hyperplasia is a type of hyperplasia and one of the symptoms of polycystic ovary syndrome [6–8]. If not properly treated, it may lead to endometrial cancer. In recent years, the incidence rates of endometrial cancer, breast cancer, and lung cancer among women in Taiwan have rapidly increased. A possible cause of lung cancer is the severe air pollution in Taiwan, whereas endometrial cancer and breast cancer may be related to diet westernization, obesity, and long-term exposure to endocrine disrupter substance. Many past studies have indicated that exposure to environmental contaminants promotes changes in the internal mechanisms of diseases, including the infection of various systems in the body, hormonal changes, and vascular proliferation [9–11]. Many studies have focused on the effects of air pollutants on the respiratory tract and cardiovascular diseases, while few studies have discussed the influence of air pollution on patients with endometrial hyperplasia. This study is the first exploratory research into the differences among endometrial hyperplasia patients under different air quality conditions.

Material and methods

Air pollution data collected

This study utilized air pollution data collected from 2000 to 2013. The air quality monitoring data released by the Environmental Protection Administration (EPA) of the Executive Yuan were summarized, standardized, and ordered. The average concentration values for each year were calculated based on the air quality index (AQI) values reported by the EPA. The AQI includes seven index pollutants (O_3-1hr, O_3-8hr, $PM_{2.5}$, PM_{10}, CO-8hr, SO_2, and NO_2) and is divided into seven levels (Table 1). The health effects of the AQI include six degrees, namely, good, moderate, unhealthy for sensitive groups, unhealthy, very unhealthy, and hazardous. The harmfulness of the air quality is indicated by different colors (Table 1). In this study, yearly statistical data were input into software for calculations and the average concentrations of pollutants served as a basis of exposure concentrations. Air quality monitoring data collected from Taiwan were divided into the good air quality group (AQI $\leq$ 50) and poor air quality group (AQI > 50) based on the AQI values.

Study population

The study area in this study included all of Taiwan, and the research participants were selected based on the 2000 to 2013 insurance data obtained from the National Health Insurance database. The Longitudinal Health Insurance Database (LHID) 2000 contains all the original claim data of 1,000,000 individuals randomly sampled from the year 2000. The Registry for Beneficiaries of the NHIRD, maintains the registration data of person who was a beneficiary in National Health Insurance program from 2000 to 2013. There was no significant difference in the gender distribution ($\chi 2 = 1.74$, df = 1, p = 0.187) between the patients in the LHID2000 and the original NHIRD. In the present study, we used LHID2000 to analyze the relationship between endometrial hyperplasia and air quality index.

The participants were patients with endometrial hyperplasia (ICD-9-CM code: 621.3), although any patients who developed endometrial hyperplasia before 2002, who had a history of intimal hyperplasia, or who were under 20 years old were excluded. In total, 14,883 patients were tracked in this study. Based on the position of

Table 1
AQI pollutant concentration values, comparison and health effects.

Air quality index (AQI)								
AQI	O_3 (ppm) 8-h average	O_3 (ppm) hour average	$PM_{2.5}$ (μg/m^3) 24-h average	PM_{10} (μg/m^3) 24-h average	CO (ppm) 8-h average	SO_2 (ppb) hourly average	NO_2 (ppb) hourly average	Effects on human body health
Good 0 ~ 50	0.000–0.054	–	0.0–15.4	0–54	0–4.4	0–35	0–53	Good air quality; low or no pollution.
Moderate 51 ~ 100	0.055–0.070	–	15.5–35.4	55–125	4.5–9.4	36–75	54–100	Moderate air quality; slight effects on few representatives of sensitive groups.
Unhealthy for sensitive groups 101 ~ 150	0.071–0.085	0.125–0.164	35.5–54.4	126–254	9.5–12.4	76–185	101–360	Air pollutants affect health of people in sensitive groups but do not have a significant effect on general public.
Unhealthy 151 ~ 200	0.086–0.105	0.165–0.204	54.5–150.4	255–354	12.5–15.4	186–304	361–649	Influence on health of all people and particularly strong influence on health of people in sensitive groups.
Very unhealthy 201 ~ 300	0.106–0.200	0.205–0.404	150.5–250.4	355–424	15.5–30.4	305–604	650–1249	Health warning: severe effects on health of all people.
Hazardous 301 ~ 500		0.405–0.604	250.5–500.4	425–604	30.5–50.4	605–1004	1250–2049	Critical health hazard; all people are affected.

the insuring agency in the air quality monitoring network, patients were divided into a good air quality group (AQI ≤ 50) and a poor air quality group (AQI > 50). Patients were compared to identify differences in their basic characteristics and the incidence of comorbidities. The incidence of comorbidities was defined based on the new diagnoses of the patients from 2002 to 2013 (Fig. 1).

Data sources

In this population-based retrospective study, data were obtained from Taiwan's National Health Insurance Research Database (NHIRD). In March 1995, the Taiwanese government implemented the National Health Insurance (NHI) program, which provides general health insurance coverage to almost the entire Taiwanese population. The NHI program provides health care to Taiwanese residents through contracted services with 97% of the hospitals and clinics in Taiwan. The database of this program contains registration files and original claims data for reimbursement, which are maintained by the National Health Research Institute (NHRI) and have been provided to scientists for research purposes since 2000.

Statistics

Charlson comorbidity index (CCI) is used by Charlson et al. [12] to collect data from the review of medical records, to control the causes and severity of major admissions, and to explore the relationship between comorbidity and death within 1 year by survival analysis. And give 19 types of comorbid weights according to the relative risk of correction. If the relative risk is 1.2 or more or less than 1.5, the weight is 1; 1.5 or more, or less than 2.5, the weight is 2; 2.5 or more, or less than 3.5, the weight is 3; in addition, the relative risk of the two types of comorbidities is greater than 6, giving a weight of 6. Adding the patient's comorbid weights, such as dementia and diabetes, with a total score of 2, with the total score of each patient representing the comorbid condition, controlled in the study and the subsequent studies have also analyzed the types of comorbidities in each category. This article uses eight types of comorbidity weights (Chronic pulmonary disease, Diabetes, Hypertension, Cerebrovascular disease, Cerebral vascular accident, Chronic kidney disease, Coronary heart disease, Liver cirrhosis and Hyperlipidemia) as a comorbidity analysis.

Student's *t*-test was used to compare the mean age and Charlson comorbidity index between AQI ≤ 50 and AQI > 50 groups. And Chi-square test was used to compare categorized age, Charlson comorbidity index, comorbidity, monthly income and insured region in Taiwan between AQI ≤ 50 and AQI > 50 groups. Forward stepwise logistic regression was further used to evaluate the odd ratios between AQI ≤ 50 and AQI > 50 groups. Statistical analyses were performed using SPSS 16.0 and Excel 2010. All statistical tests and p values were two-sided, and the level of significance was set to <0.05 (*).

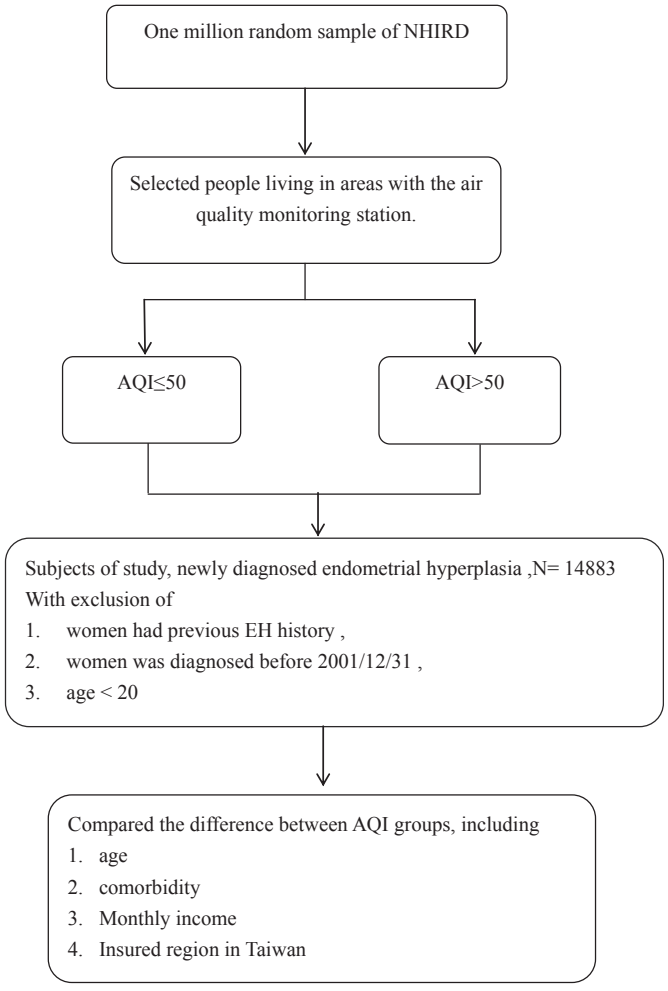

Fig. 1. Study flow chart of endometrial hyperplasia from the 1-million random sample of the National Health Insurance Research Database (NHIRD) from 2000 to 2013 in Taiwan.

Results

This study investigated the differences in the characteristics of endometrial hyperplasia patients exposed to air of different quality levels. This study investigated the differences in the characteristics of endometrial hyperplasia patients exposed to air of different quality levels.The medical illness of each patient was based on the Charlson's Comorbidity Index score (CCIS), which is widely used for risk adjustment in administrative claims data sets [12]. According to each participant's inpatient diagnosis, we calculated the CCI scores as the comorbidity measure. A weight was assigned in each indicated diagnosis and added together to provide a total CCI score. In CCI score, sixteen kinds of different comorbidity were classified in different categories. Participants with the comorbidity was calculated weighted 1, such as myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, peptic ulcer disease, mild liver disease and diabetes mellitus. Moderate to severe chronic kidney disease, hemiplegia, diabetes with end-organ damage, leukemia, tumor of any type and malignant lymphoma were weighted 2. Participants with moderate to severe liver disease was weighted 3. Acquired immune deficiency syndrome (AIDS) and metastatic solid tumor were weighted 6^{12}. As seen from Table 2, the average age of the 14,883 participants with endometrial hyperplasia was 52.4 years, with a standard deviation of 21 years. The average age in the AQI > 50 group of 7844 endometrial hyperplasia patients was 54.1 years, with a standard deviation of 20.9 years. The average age in the AQI ≤ 50 group of 7039 endometrial hyperplasia patients was 50.6 years, with a standard deviation of 20.9 years. The results indicated that the patients exposed to AQI > 50 had a significantly higher average age (AQI≤50 = 50.6 years; AQI>50 = 54.1 years, $p < 0.001$) and included a higher proportion of patients aged 50 years and older ($p < 0.001$) than those exposed to AQI ≤ 50. The patients exposed to AQI > 50 also showed a significantly higher Charlson comorbidity index (CCI) than those exposed to AQI ≤ 50 ($p < 0.001$).

Table 2
Differences in characteristics of endometrial hyperplasia patients under different air quality conditions.

Variable	AQI ≤ 50 (n = 7039)		AQI > 50 (n = 7844)		Total (n = 14,883)		*p*[a] value
	mean	SD	mean	SD	mean	SD	
age	50.6	20.9	54.1	20.9	52.4	21.0	<0.001[b]
Charlson comorbidity index	1.3	1.9	1.4	2.0	1.4	2.0	<0.001[b]
	n	%	n	%	n	%	
age							<0.001
20–29	1534	21.8	1297	16.5	2831	19.0	
30–39	1099	15.6	1091	13.9	2190	14.7	
40–49	1093	15.5	1166	14.9	2259	15.2	
50–59	878	12.5	1187	15.1	2065	13.9	
60-69	673	9.6	864	11.0	1537	10.3	
>=70	1762	25.0	2239	28.5	4001	26.9	
Charlson comorbidity index							<0.001
0	3693	52.5	3873	49.4	7566	50.8	
1	1228	17.4	1343	17.1	2571	17.3	
2	692	9.8	846	10.8	1538	10.3	
≥3	1426	20.3	1782	22.7	3208	21.6	
Comorbidity							
Chronic pulmonary disease	1450	20.6	1604	20.4	3054	20.5	0.823
Diabetes	987	14.0	1409	18.0	2396	16.1	<0.001
Hypertension	2084	29.6	2821	36.0	4905	33.0	<0.001
Cerebrovascular disease	1258	17.9	1515	19.3	2773	18.6	0.024
Cerebral vascular accident	1258	17.9	1515	19.3	2773	18.6	0.024
Chronic kidney disease	254	3.6	410	5.2	664	4.5	<0.001
Coronary heart disease	890	12.6	913	11.6	1803	12.1	0.063
Liver cirrhosis	655	9.3	639	8.1	1294	8.7	0.013
Hyperlipidemia	344	4.9	557	7.1	901	6.1	<0.001
Monthly income (TWD)							<0.001
<20,000	2321	33.0	2064	26.3	4385	29.5	
20,000–40000	3311	47.0	4345	55.4	7656	51.4	
40,000–60000	997	14.2	1015	12.9	2012	13.5	
≥60,000	410	5.8	420	5.4	830	5.6	
Insured region in Taiwan							0.003
Northern	3197	45.4	3372	43.0	6569	44.1	
Middle	1554	22.1	1820	23.2	3374	22.7	
Southern	1995	28.3	2368	30.2	4363	29.3	
Eastern and outlying islands	293	4.2	284	3.6	577	3.9	

[a] Based on the Chi-square test.
[b] Based on the Student *t*-test.

Further analyses of the comorbidities of the endometrial hyperplasia patients revealed that the incidences of diabetes (18.0%, $p < 0.001$), hypertension (36.0%, $p < 0.001$), cerebrovascular diseases and cerebral vascular accidents (19.3%, $p = 0.024$), chronic kidney disease (5.2%, $p < 0.001$), and hyperlipidemia (7.1%, $p < 0.001$) were significantly higher in the participants exposed to AQI > 50 than in those exposed to AQI ≤ 50. However, the incidence of liver cirrhosis in this group was found to be lower (8.1%, $p = 0.013$) (Table 2).

Significantly fewer people had a monthly income of >NT$40000 among the participants exposed to AQI > 50, as compared to those exposed to AQI ≤ 50 ($p < 0.001$). A significantly greater proportion of the participants exposed to AQI > 50 had insurance addresses based in central and southern Taiwan, while a significantly greater proportion of the participants exposed to AQI ≤ 50 had insurance addresses based in northern Taiwan ($p = 0.003$) (Table 2).

In this analyzed cohort, endometrial hyperplasia patients who exposure to poor air quality implicated to have a higher average age and more severe comorbidity, and furthermore a stepwise logistic regression analysis was used to evaluate whether higher average age acted as confounding factor to result in severe comorbidity. In Table 3, we found that exposure to poor air quality associated with higher average age with an increased trend of odd ratio, and similarly exposure to poor air quality also associated with more severe comorbidity with an increased trend of odd ratio. In detail, endometrial hyperplasia patients who exposed to higher poor air quality (AQI > 50) had a 1.170-fold risk to suffer with moderate comorbidity (Charlson comorbidity index = 2, $p = 0.005$) and a 1.188-fold risk to suffer with severe comorbidity (Charlson comorbidity index ≥3, $p < 0.001$) whilst compared to who were diagnosed without any comorbidity (Charlson comorbidity index = 0). Besides, it also implicated there is no obvious interaction between average and Charlson comorbidity index, that is, they were not functioned as confounding factors to each other.

Discussion

Endometrial hyperplasia is caused by the excessive growth of cells in the endometrium and is defined as the abnormal growth of endometrial and stromal cells. Some experts suggest that endometrial hyperplasia is a precancerous pathology or indication of endometrial cancer. Endometrial hyperplasia can occur at any age and, if not treated in time, lead to cancer. It results in the long-term thickening of the endometrium and increases the possibility of endometrial cancer developing. The most prominent symptoms of endometrial hyperplasia include abnormal menstrual periods and bleeding. Endometrial hyperplasia is particularly likely to develop in postmenopausal women. Other high-risk factors include obesity, diet westernization, polycystic ovary syndrome, oversupply of estrogens, and the taking of tamoxifen for breast cancer.Depending on its tissue pattern, endometrial hyperplasia can be simple, complex, simple atypical, or complex atypical. The risk of developing endometrial cancer is different for each of the four types (1% for simple, 3% for complex, 8% for simple atypical, and 29% for complex atypical). Therefore, abnormal endometrial growth must be treated in time in order to prevent the development of

Table 3
Logistic regression analysis of AQI, age and Charlson comorbidity index.

Subject characteristics	AQI ≤ 50 (n = 7039)	AQI > 50 (n = 7844)	OR (95%CI)	p[a]
age				
20–29	1534	1297	1 (ref)	
30–39	1099	1091	1.174 (1.050–1.313)	0.005
40–49	1093	1166	1.262 (1.129–1.410)	<0.001
50–59	878	1187	1.599 (1.426–1.793)	<0.001
60-69	673	864	1.518 (1.340–1.721)	<0.001
> = 70	1762	2239	1.503 (1.364–1.656)	<0.001
Charlson comorbidity index				
0	3693	3873	1 (ref)	
1	1228	1343	1.045 (0.955–1.143)	0.342
2	692	846	1.170 (1.048–1.307)	0.005
≥3	1426	1782	1.188 (1.093–1.291)	<0.001

Abbrev: OR: odds ratio, 95% CI: 95% confidence interval.
[a] Based on the forward stepwise logistic regression model, with statistical significance ($p < 0.05$) was shown in boldfaced.

endometrial cancer. Similar to uterine fibroids, endometrial hyperplasia requires the avoidance of dietary risk factors and of exposure to endocrine disrupter substance. From this analysis, it can be found that endometrial hyperplasia does not occur only in women who are traditionally cognitively postmenopausal, but in all age groups. Interestingly, in areas with AQI ≤ 50, patients with endometrial hyperplasia in this age group of 20–29 years old are more than other age groups. In the other two groups (AQI ≤ 50 vs AQI > 50), it can be observed that the endometrium of AQI ≤ 50 is more proliferating under 50 years of age, while the endometrium of AQI > 50 is more than 50 years old (Table 2).

Air pollution exposure, including transportation-related exhaust gases (diesel and non-diesel), can be measured in terms of PM. A smaller PM, such as ≤2.5 μm PM ($PM_{2.5}$), can infiltrate the bloodstream, deposit in tissues, and promote inflammation in parts of the body or the entire body [13,14]. Many laboratory studies have confirmed that air pollutants stimulate the activity of estrogens and androgens [15–18]. Many past studies have also indicated that exposure to environmental contaminants promotes changes in the internal mechanisms of diseases, including the infection of various systems in the body, hormonal changes, and vascular proliferation [9–11]. Therefore, exposure to air pollution is to a certain degree linked to endometrial hyperplasia. Air pollution exposure has been found to be related to the incidence rates of diabetes, hypertension, cerebrovascular diseases, and cerebral vascular accidents. According to past research, air pollutants have a complex composition and contain many endocrine disrupter substances that can spread to the entire body through the cardiovascular system and affect organs. Many past studies have indicated that exposure to environmental contaminants promotes changes in the internal mechanisms of diseases, including infections of various systems in the body, hormonal changes, and vascular proliferation [2,19–21]. In this study, it was found that endometrial hyperplasia patients exposed to higher concentrations of air pollutants demonstrated significantly higher incidences of comorbidities. The results corresponded to those of the aforementioned European survey, which showed that, even when the concentration of air pollutants was within the permissible limits, long-term exposure to air pollutants still increased the risk of death and diseases, especially in groups sensitive to air pollution [3]. The results of this study demonstrated that a higher proportion of endometrial hyperplasia patients exposed to AQI > 50 lived in central and southern Taiwan. Hence, central and southern Taiwan have poorer AQI and more patients with endometrial hyperplasia, and more attention must be paid to the influence of air pollution on endometrial hyperplasia patients in these regions.

This study was the first exploratory study to investigate the characteristics of endometrial hyperplasia patients exposed to different AQI levels. The results can provide a reference for future research on air pollution in relation to the mechanisms and incidences of endometrial hyperplasia and endometrial cancer.

However, certain limitations of this study should be mentioned. First, essential data, including detailed demographic and lifestyle information such as smoking habits, alcohol consumption, body mass index, and family history of systemic diseases which are risk factors, are missing from the NHIRD. Second, the quality of evidence from a retrospective cohort study is generally lower than that of randomized trials because patients in the cohort study could have many biases that must be adjusted for confounding variables. Despite our meticulous study design with adequate control of confounding factors, the bias could limit this study if unmeasured or unknown confounders were present. Third, because all beneficiaries listed on the NHIRD are protected by anonymity, we could not obtain individual clinical, imaging, pathological, and laboratory data.

Conclusion

This study demonstrated that exposure to air of different quality levels had a significant effect on patients with endometrial hyperplasia, particularly on the incidence of related comorbidities. The results indicated that the incidence rates of diabetes, hypertension, cerebrovascular diseases, cerebral vascular accidents, chronic kidney disease, and hyperlipidemia were significantly higher in endometrial hyperplasia patients exposed to air with poorer AQI. These patients also had a significantly higher CCI, and their insurance addresses were primarily based in central and southern Taiwan. Thus, poor air quality was found to increase the risk of comorbidities in patients with endometrial hyperplasia. In view of the results, attention must be paid to the risk of comorbidities in endometrial hyperplasia patients exposed to poor AQI, the improvement of air quality, and the prevention of pollutants in order to protect the health of the Taiwanese people. This study was the first exploratory study to investigate the characteristics of endometrial hyperplasia patients exposed to different AQI levels. The results can provide a reference for future research on air pollution in relation to the mechanisms and incidences of endometrial hyperplasia and endometrial cancer.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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