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Risk of developing Parkinson's disease among patients with asthma: a nationwide longitudinal study

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Abstract

Background: A cross-sectional retrospective study suggested a link between allergic diseases and Parkinson's disease. However, the temporal association between asthma and Parkinson's disease remains unknown.

Methods: From the Taiwan National Health Insurance Research Database, 10 455 patients who were diagnosed with asthma between 1998 and 2008 and aged ≥45 years and 41 820 age- and sex-matched controls were selected for our study and observed until the end of 2011. Those who developed Parkinson's disease during the follow-up period were identified. We also examined the asthma severity, as indicated by the frequency of admission (times per year) for asthma exacerbation, and the risk of subsequent Parkinson's disease.

Results: Patients with asthma had an increased risk of developing Parkinson's disease (hazard ratio [HR]: 3.10, 95% confidence interval [CI]: 2.20–4.36) after we adjusted for demographic data, health system use, medical comorbidities, and medication use. Sensitivity tests yielded consistent findings after we excluded observations on the first year (HR: 2.90, 95% CI: 2.04–4.13) and first 3 years (HR: 2.46, 95% CI: 1.64–3.69). Patients with asthma who had more frequent admissions (times per year) during the follow-up period exhibited a greater risk of subsequent Parkinson's disease (>2: HR: 16.42, 95% CI: 5.88–45.91; 1-2: 12.69, 95% CI: 5.03–31.71; 0-1: HR: 2.92, 95% CI: 1.91–4.49).

Conclusion: Patients with asthma had an elevated risk of developing Parkinson's disease later in life, and we observed a dose-dependent relationship between greater asthma severity and a higher risk of subsequent Parkinson's disease.

Parkinson's disease is the second most common neurodegenerative disorder among people older than 65 years of age (1–4). The incidence of Parkinson's disease rises steeply with age, from 17.4 per 100 000 person-years between 50 and 59 years of age to 93.1 per 100 000 person-years between 70 and 79 years, with a lifetime prevalence of developing the disease of 1−5% (2). The characteristic symptoms of Parkinson's disease include bradykinesia, resting tremor, gait imbalance, muscular rigidity, postural instability, slowing of physical movements, and autonomic dysfunction, which are caused by a progressive degeneration and loss of dopaminergic cells in the substantia nigra (1–4). However, the etiology of Parkinson's disease remains unknown, except that several rare genetic mutations were found in a small percentage of younger onset cases (2).

A growing body of evidence supports the association between allergic diseases and related chronic inflammatory process and the development of neurodegenerative disorders, such as Alzheimer's disease (5–7). However, previous studies regarding the relationship between allergic diseases and

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Parkinson's disease have been limited (8). Bower et al. (8) examined 196 patients with Parkinson's disease and 196 controls to explore the disease prevalence of immediate-type hypersensitivity (allergic rhinitis and asthma) and found that patients with Parkinson's disease had a higher prevalence of comorbid allergic rhinitis (12.8% *vs* 5.1%) and asthma (9.7% *vs* 5.6%) than those in the control group did. In addition, they suggested that Parkinson's disease is associated with an elevated risk of allergic rhinitis (odds ratio [OR]: 2.9, 95% confidence interval [CI]: 1.3–6.4) and asthma (OR: 1.8, 95% CI: 0.8–3.9) (8). However, several limitations in the Bower et al. study included a small sample size, a cross-sectional study design, and a lack of adjustment for other medical comorbidities in the regression model, preventing it from clarifying the temporal and independent association between asthma and Parkinson's disease.

In our study, using the Taiwan National Health Insurance Research Database (NHIRD), a large sample size, and a longitudinal follow-up study design, we investigated the temporal association between asthma and the risk of subsequent Parkinson's disease. We hypothesized that patients with asthma had an elevated risk of developing Parkinson's disease later in life.

Methods

Data source

Taiwan's National Health Insurance is a mandatory universal health insurance program that was inaugurated in 1995 and covers up to 99% of the country's 23 million residents (http://nhird.nhri.org.tw/). The NHIRD is administered by the National Health Research Institute and provides comprehensive patient information, such as demographic data, clinical visit dates, and disease diagnoses. All identities are encrypted to ensure patient privacy. The diagnostic codes used are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in numerous epidemiologic studies in Taiwan (9–12).

Inclusion criteria for patients with asthma and the control group

Patients aged older than 45 years who were diagnosed with asthma (ICD-9-CM code: 493) by pulmonologists or rheumatologists on the basis of clinical judgment or the pulmonary function test between January 1, 1998, and December 31, 2008, and who had no history of Parkinson's disease (ICD-9-CM code: 332) before enrollment were included as the asthma cohort. To construct an age-, sex-, and date of enrollment-matched (1 : 4) control cohort, patients, who were not included in the asthma cohort, had not been diagnosed with asthma at any time and had not been diagnosed with Parkinson's disease before enrollment was randomly selected from the same database. Cases of Parkinson's disease (ICD-9-CM code: 332.0) diagnosed by board-certified neurologists were identified during the follow-up period and followed until December 31, 2011, or the date of death. Because of the high comorbidity of other allergic diseases with asthma, we assessed the comorbid effects of allergic diseases, namely allergic rhinitis (ICD-9-CM code: 477) and atopic dermatitis (ICD-9-CM codes: 691, 691.8), on the risk of developing Parkinson's disease. Other medical comorbidities recorded in the database during the follow-up period were also assessed as confounding factors; these included depressive disorder, alcohol-related disorders, substance use disorders, dementia, hypertension, dyslipidemia, diabetes mellitus, renal diseases, ischemic heart diseases, cerebrovascular diseases, chronic respiratory diseases, and head injury. The inhaled steroid, inhaled beta-agonist agents, xanthine derivative agents, antihistamine agents, and health system use (number of medical consultations per year) were included in the analyses and adjusted for their confounding effects. Furthermore, the frequency of asthma clinics visiting (times per year) or of admission (times per year) for asthma exacerbation was assessed and regarded as the disease severity of asthma in our study. All diagnoses were given at least twice by physicians between the enrollment and the event onset (Parkinson's disease), the study end, or the date of death to achieve diagnostic validity. The level of urbanization (level 1 to level 5; level 1: most urbanized; level 5: least urbanized) was also assessed (13).

Statistical analysis

For between-group comparisons, the independent *t*-test was used for continuous variables and Pearson's chi-squared test was used for nominal variables, where appropriate. The Cox regression model was used to investigate the hazard ratios (HRs) with 95% CIs of developing Parkinson's disease after adjustment for demographic data, medical comorbidities, medication use, and health system use. Sensitivity tests were performed to validate the findings after we excluded observations on the first year and the first 3 years. A subanalysis stratified according age group (age <65 years and age ≥ 65 years) was performed to investigate the risk of developing Parkinson's disease in both subgroups. We also investigated the disease severity of asthma indicated by the frequency of asthma clinics visiting or of admission for asthma exacerbation and the risk of subsequent Parkinson's disease. All data processing and statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc.) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC, USA).

Results

In total, 10 455 patients with asthma and 41 820 age- and sex- matched controls were included in our study; the mean age was 59.79 ± 9.48 years, and female patients were predominant (58.7% *vs* 41.3%). During the follow-up period, patients with asthma had a higher incidence of developing Parkinson's disease (1.47 *vs* 0.49 per 1000 person-years, $P < 0.001$) and an earlier onset of Parkinson's disease

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diagnosis (72.28 ± 7.67 *vs* 74.65 ± 7.07 years, $P = 0.007$) than did the controls (Table 1). Among all patients with asthma, 92.0% visited asthma clinics 0–5 times per year, 5.6% visited 5–10 times per year, and 2.4% visited over 10 times per year; 96.6% were admitted to hospital for asthma exacerbation 0–1 times per year, 2.3% were admitted 1–2 times per year, and only 1.1% of patients exhibited an admission frequency of over two times per year (Table 1). In addition, a higher prevalence of allergic comorbidities, psychiatric comorbidities, and other medical comorbidities,

Table 1 Demographic data and incidence of Parkinson's disease of patients with asthma and the control group

	Patients with asthma (n = 10455)	Controls (n = 41820)	P-value
Age at diagnosis of asthma/enrollment (years, SD, *n*, %)	59.79 (9.48)	59.79 (9.48)	
<65 years	7335 (70.2)	29340 (70.2)	
≥65 years	3120 (29.8)	12480 (29.8)	
Sex (M, %)	4319 (41.3)	17276 (41.3)	
The frequency of admission (times per year) for asthma exacerbation (*n*, %)			
0–1	10097 (96.6)	–	
1–2	244 (2.3)	–	
>2	114 (1.1)	–	
The frequency of asthma clinics visiting (times per year) (*n*, %)			
0–5	9616 (92.0)	–	
5–10	588 (5.6)	–	
>10	251 (2.4)	–	
Parkinson's disease (*n*, 1000 person-year)	123 (1.47)	165 (0.49)	<0.001
Age at diagnosis (years, SD)	72.28 (7.67)	74.65 (7.07)	0.007
Duration between asthma/enrollment and diagnosis (years, SD; *n*, %)	5.23 (3.27)	6.57 (3.10)	<0.001
<1 year	6 (4.9)	3 (1.8)	
1–3 years	35 (28.5)	24 (14.5)	
>3 years	82 (66.7)	138 (83.6)	
Comorbidities during the whole follow-up (*n*, %)			
Atopic dermatitis	133 (1.3)	365 (0.9)	<0.001
Allergic rhinitis	3256 (31.1)	4003 (9.6)	<0.001
Depressive disorder	811 (7.8)	1828 (4.4)	<0.001
Alcohol-related disorders	87 (0.8)	277 (0.7)	0.063
Substance use disorders	15 (0.1)	49 (0.1)	0.531
Dementia	516 (4.9)	1570 (3.8)	<0.001
Hypertension	5903 (56.5)	19807 (47.4)	<0.001
Dyslipidemia	3493 (33.4)	11598 (27.7)	<0.001
Diabetes mellitus	2751 (26.3)	9204 (22.0)	<0.001
Renal diseases	631 (6.0)	1992 (4.8)	<0.001
Ischemic heart diseases	1345 (12.9)	3331 (8.0)	<0.001
Cerebrovascular diseases	1410 (13.5)	4304 (10.3)	<0.001
Chronic respiratory diseases	3551 (34.0)	1431 (3.4)	<0.001
Head injury	530 (5.1)	1505 (3.6)	<0.001
Medication use during the whole follow-up (*n*, %)			
Inhaled steroid use	6673 (63.8)	738 (1.8)	<0.001
Inhaled beta-agonist use	6532 (62.5)	3359 (8.0)	<0.001
Xanthine derivative use	5092 (48.7)	1517 (3.6)	<0.001
Antihistamine agent use	9366 (89.6)	24121 (57.7)	<0.001
Level of urbanization (*n*, %)			
1 (most urbanized)	3062 (29.3)	12001 (28.7)	0.001
2	3133 (30.0)	12155 (29.1)	
3	1628 (15.6)	6249 (14.9)	
4	1502 (14.4)	6431 (15.4)	
5 (most rural)	1130 (10.8)	4984 (11.9)	
Income-related insured amount			
≤15 840 NTD/month	5598 (53.5)	22043 (52.7)	0.004
15 841–25 000 NTD/month	3006 (28.8)	12691 (30.3)	
≥25 001 NTD/month	1851 (17.7)	7086 (16.9)	
Health system use (number of consultations/year)	21.24 (22.16)	14.51 (17.62)	<0.001

SD, standard deviation; NTD, New Taiwan Dollar.

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namely atopic dermatitis (1.3% *vs* 0.9%, $P < 0.001$), allergic rhinitis (31.1% *vs* 9.6%, $P < 0.001$), depressive disorder (7.8% *vs* 4.4%, $P < 0.001$), dementia (4.9% *vs* 3.8%, $P < 0.001$), hypertension (56.5% *vs* 47.4%, $P < 0.001$), dyslipidemia (33.4% *vs* 27.7%, $P < 0.001$), diabetes mellitus (26.3% *vs* 22.0%, $P < 0.001$), renal diseases (6.0% *vs* 4.8%, $P < 0.001$), ischemic heart diseases (12.9% *vs* 8.0%, $P < 0.001$), cerebrovascular diseases (13.5% *vs* 10.3%, $P < 0.001$), chronic respiratory diseases (34.0% *vs* 3.4%, $P < 0.001$), and head injury (5.1% *vs* 3.6%, $P < 0.001$), was noted in the asthma cohort compared with the control cohort (Table 1). Patients with asthma exhibited a higher rate of health system use ($P < 0.001$), resided in regions that are more urbanized ($P = 0.001$), and had a lower income ($P = 0.004$) (Table 1). The frequencies of medical comorbidities and medication uses in patients with Parkinson's disease from the study and control groups are shown in Table 2. Patients with Parkinson's disease and asthma had a higher prevalence of cerebrovascular diseases (39.0% *vs* 23.0%, $P = 0.004$) and chronic respiratory diseases (39.0% *vs* 6.7%, $P < 0.001$) compared to those with Parkinson's disease only (Table 2).

Kaplan–Meier survival analyses with a log-rank test demonstrated a dose-dependent association ($P < 0.001$) between asthma disease severity and the risk of developing Parkinson's disease later in life among patients with asthma

Table 2 Demographic data and clinical characteristics of patients with Parkinson's disease with or without asthma

	Asthma and Parkinson's disease ($n = 123$)	Parkinson's disease alone ($n = 165$)	*P*-value
Age at diagnosis of asthma/enrollment (years, SD, *n*, %)	67.09 (7.80)	68.04 (7.08)	0.280
Sex (M, %)	55 (44.7)	68 (41.2)	0.630
The frequency of admission (times per year) for asthma exacerbation (*n*, %)			
0–1	107 (87.0)	–	
1–2	8 (6.5)	–	
2	8 (6.5)	–	
The frequency of asthma clinics visiting (times per year) (*n*, %)			
0–5	95 (77.2)	–	
5–10	15 (12.2)	–	
>10	13 (10.6)	–	
Comorbidities during the whole follow-up (*n*, %)			
Atopic dermatitis	2 (1.6)	0 (0)	0.182
Allergic rhinitis	39 (31.7)	35 (21.2)	0.056
Depressive disorder	18 (14.6)	21 (12.7)	0.728
Alcohol-related disorders	2 (1.6)	0 (0)	0.182
Substance use disorders	–	–	–
Dementia	19 (15.4)	20 (12.1)	0.487
Hypertension	86 (69.9)	127 (77.0)	0.222
Dyslipidemia	38 (30.9)	55 (33.3)	0.703
Diabetes mellitus	34 (27.6)	56 (33.9)	0.304
Renal diseases	12 (9.8)	12 (7.3)	0.520
Ischemic heart diseases	28 (22.8)	34 (20.6)	0.667
Cerebrovascular diseases	48 (39.0)	38 (23.0)	0.004
Chronic respiratory diseases	48 (39.0)	11 (6.7)	<0.001
Head injury	13 (10.6)	12 (7.3)	0.398
Medication use during the whole follow-up (*n*, %)			
Inhaled steroid use	76 (61.8)	4 (2.4)	<0.001
Inhaled beta-agonist use	84 (68.3)	25 (15.2)	<0.001
Xanthine derivative use	69 (56.1)	14 (8.5)	<0.001
Antihistamine agent use	118 (95.9)	123 (74.5)	<0.001
Level of urbanization (*n*, %)			
1 (most urbanized)	37 (30.1)	43 (26.1)	0.081
2	45 (36.6)	48 (29.1)	
3	19 (15.4)	20 (12.1)	
4	14 (11.4)	31 (18.8)	
5 (most rural)	8 (6.5)	23 (13.9)	
Income-related insured amount			
≤15 840 NTD/month	96 (78.0)	109 (66.1)	0.079
15 841–25 000 NTD/month	24 (19.5)	48 (29.1)	
≥25 001 NTD/month	3 (2.4)	8 (4.8)	
Health system use (number of consultations/year)	25.97 (18.27)	23.67 (19.26)	0.303

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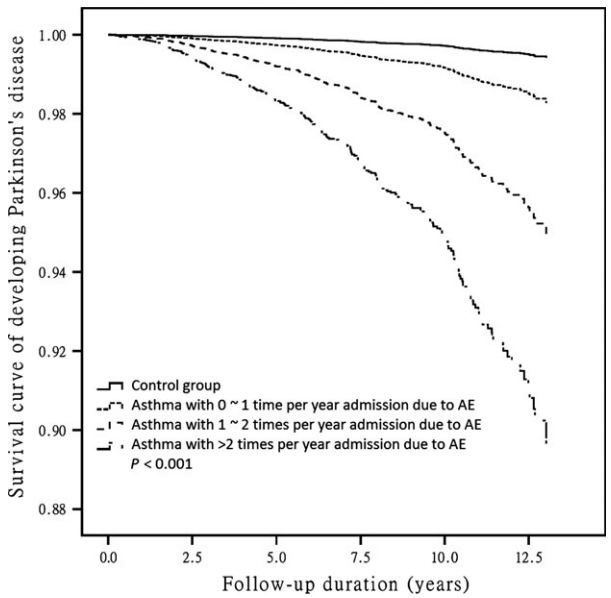

Figure 1 Survival curve of developing Parkinson's disease among patients with asthma and control group. AE, asthma exacerbation.

and the control group (Fig. 1). The Cox regression model with adjustment for demographic data, medical comorbidities, medication use, and health system use showed that patients with asthma had a higher risk of developing Parkinson's disease (HR: 3.10, 95% CI: 2.20–4.36) later in life than did those in the control group (Table 3). In patients who had a greater asthma severity, as indicated by the frequency of asthma clinics visiting or of admission (times per year) for asthma exacerbation, the likelihood of subsequent Parkinson's disease development increased in a dose-dependent manner relative to that of the control group (asthma clinics visiting: >10: HR: 18.88, 95% CI: 9.44–37.79; 5–10: HR: 9.11, 95% CI: 4.64–17.87; 0–5: HR: 3.05, 95% CI: 2.16–4.32; admission for asthma exacerbation: >2: HR: 16.42, 95% CI: 5.88–45.91; 1–2: 12.69, 95% CI: 5.03–31.71; 0–1: HR: 2.92, 95% CI: 1.91–4.49) (Table 4). Sensitivity analyses yielded consistent findings after we excluded observations on the first year (HR: 2.90, 95% CI: 2.04–4.13) and first 3 years (HR: 2.46, 95% CI: 1.64–3.69) (Table 5). Furthermore, when stratified according to age, both patients with asthma in midlife (<65 years) (HR: 3.51, 95% CI: 1.95–6.31) and those with asthma in old age (≥65 years) (HR: 2.95, 95% CI: 1.93–4.50) were prone to developing Parkinson's disease later in life (Table 3).

Finally, our results showed that depressive disorder (HR: 2.05, 95% CI: 1.44–2.92), cerebrovascular diseases (HR: 1.61, 95% CI: 1.23–2.11), and antihistamine agent use (HR: 1.45, 95% CI: 1.04–2.04) were associated with an elevated risk of subsequent Parkinson's disease (Table 3). A slightly trend association between allergic rhinitis and the risk of Parkin-

Table 3 Multivariable Cox regression analysis of developing Parkinson's disease of patients with asthma and the control group

	<65 years HR (95% CI)	≥65 years HR (95% CI)	Total HR (95% CI)
	Parkinson's disease[†]		
Asthma, presence *vs* absence	**3.51 (1.95–6.31)**	**2.95 (1.93–4.50)**	**3.10 (2.20–4.36)**
Comorbidities, presence *vs* absence			
Atopic dermatitis	0.73 (0.10–5.24)	0.42 (0.06–3.00)	0.54 (0.13–2.15)
Allergic rhinitis	1.26 (0.76–2.07)	1.31 (0.93–1.86)	1.29 (0.97–1.72)
Depressive disorder	1.70 (0.88–3.23)	**2.22 (1.46–3.39)**	**2.05 (1.44–2.92)**
Alcohol-related disorders	1.39 (0.19–10.16)	1.05 (0.15–7.53)	1.23 (0.31–4.96)
Substance use disorders	–	–	–
Dementia	0.98 (0.38–2.54)	1.18 (0.80–1.75)	1.15 (0.80–1.65)
Hypertension	0.95 (0.59–1.53)	1.32 (0.91–1.90)	1.22 (0.92–1.64)
Dyslipidemia	0.90 (0.57–1.42)	0.67 (0.48–1.03)	0.77 (0.80–1.01)
Diabetes mellitus	1.12 (0.69–1.78)	0.86 (0.62–1.18)	0.95 (0.73–1.24)
Renal diseases	0.84 (0.36–1.97)	0.93 (0.56–1.52)	0.92 (0.60–1.41)
Ischemic heart diseases	1.27 (0.70–2.28)	1.18 (0.84–1.67)	1.20 (0.89–1.62)
Cerebrovascular diseases	**2.17 (1.29–3.45)**	**1.47 (1.07–2.02)**	**1.61 (1.23–2.11)**
Chronic respiratory diseases	1.00 (0.53–1.87)	0.73 (0.48–1.10)	0.78 (0.55–1.10)
Head injury	0.86 (0.31–2.36)	1.57 (0.98–2.49)	1.38 (0.91–2.10)
Medication use, presence *vs* absence			
Inhaled steroid use	0.86 (0.44–1.69)	0.83 (0.53–1.30)	0.83 (0.57–1.21)
Inhaled beta-agonist use	0.61 (0.32–1.14)	1.14 (0.79–1.65)	0.97 (0.70–1.33)
Xanthine derivative use	1.13 (0.60–2.15)	0.73 (0.47–1.12)	0.83 (0.58–1.18)
Antihistamine agent use	1.72 (0.92–3.19)	1.32 (0.89–1.99)	**1.45 (1.04–2.04)**

[†]Adjusted by demographic data, health system use, medical comorbidities, and medication use.
HR, hazard ratio; CI, confidence interval; NA, not available.
Bold type indicates the statistical significance.

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Table 4 Asthma severity and risk of developing Parkinson's disease†

Asthma severity‡	HR	CI
Nonasthma controls	1	–
The frequency of admission (times per year) for asthma exacerbation		
0–1	**2.92**	**1.91–4.49**
1–2	**12.69**	**5.03–31.71**
>2	**16.42**	**5.88–45.91**
The frequency of asthma clinics visiting (times per year)		
0–5	**3.05**	**2.16–4.32**
5–10	**9.11**	**4.64–17.87**
>10	**18.88**	**9.44–37.79**

†adjusted by demographic data, health system use, medical comorbidities, and medication use.
‡The frequency of admission (times per year) for asthma exacerbation as the indicator of asthma severity.
HR, hazard ratio; CI, confidence interval; NA, not available.
Bold type indicates the statistical significance.

Table 5 Sensitivity test for the risk of developing Parkinson's disease of patients with asthma and the control group

	Total	>1 year	>3 years
	HR (95% CI)	HR (95% CI)	HR (95% CI)
	Parkinson's disease†		
Asthma, presence *vs* absence	**3.10 (2.20–4.36)**	**2.90 (2.04–4.13)**	**2.46 (1.64–3.69)**

†Adjusted by demographic data, health system use, medical comorbidities, and medication use.
HR, hazard ratio; CI, confidence interval.
Bold type indicates the statistical significance.

son's disease was also noted (HR: 1.29, 95% CI: 0.97–1.72) (Table 3).

Discussion

Our study results support the study hypothesis that patients who had asthma in midlife and those who had asthma in old age were associated with an increased risk of developing Parkinson's disease later in life after we adjusted for demographic data, medical and psychiatric comorbidities, medication use, and health system use. In addition, patients with asthma had an earlier onset of Parkinson's disease than did the controls. The results also indicated a dose-dependent association between greater asthma severity and a higher risk of subsequent Parkinson's disease.

From a clinical perspective, several studies have suggested a potential relationship between asthma and Parkinson's disease (8, 14, 15). Hoffman et al. (15) reported a case of elderly adults with Parkinson's disease and severe asthma who lived in nursing homes and required inhaled steroids for asthma exacerbation. As previously mentioned, only one retrospective case–control study has suggested a biological link between allergic diseases and subsequent Parkinson's disease (8). Bower et al. determined that the frequency of diseases of immediate-type hypersensitivity (asthma and allergic rhinitis) was significantly higher in patients with Parkinson's disease than in controls (OR: 1.8, 95% CI: 1.1–3.1) (8). They also found that patients who had an earlier onset (≤71 years) of Parkinson's disease had a higher likelihood of having a comorbid allergic disease (OR: 2.6, 95% CI: 1.2–5.5) and that this association between allergic diseases and Parkinson's disease remained significant when allergic rhinitis was considered separately, but was not significant when asthma was considered separately (8). Barbeau et al. revealed that the urinary excretion of dopamine was extremely low in many patients with asthma (14). Compatible with previous findings, the results of our study, which used the largest sample size and a longitudinal design, supported a dose-dependent temporal association between asthma and Parkinson's disease after we adjusted for demographic data, other allergic diseases, medical comorbidities, medication use, and health system use. Greater asthma severity was associated with a higher risk of developing Parkinson's disease later in life. Furthermore, asthma in both midlife and old age was associated with an elevated risk of subsequent Parkinson's disease.

From a neurobiological perspective, asthma-related immunological dysregulation and disturbance may explain the association between asthma and neurodegenerative disorders, such as Parkinson's disease (16–19). The early phase of allergic responses of asthma is predominantly mediated by Th_2 cytokines; specifically, interleukin (IL)-1 and IL-6 drive IgE production by promoting immunoglobulin class switch recombination in B cells. Allergic responses are then mediated by a cascade of pro-inflammatory agents, including Th_1 immunoactive cytokines (i.e., IL-2, IL-3, tumor necrosis factor-α [TNF-α]) and chemokines, which are also released sequentially in the late phase of allergic responses (16, 19). A growing body of evidence has shown that these pro-inflammatory cytokines play a crucial role in the pathophysiology of Parkinson's disease and suggests that dysregulation of the inflammatory pathway may affect the central nervous system and be involved in the pathophysiological mechanisms of neurodegenerative disorder (7, 8, 17, 18, 20–22). Mogi et al. revealed that the levels of IL-1β, IL-6, and TNF-α in the striatum and the level of TNF-α in the cerebrospinal fluid were higher in patients with Parkinson's disease than in the control group (21, 22). Reale et al. found that patients with Parkinson's disease had an elevated concentration of IL-1β and TNF-α in the plasma compared with controls, and the cytokine levels were significantly correlated with the disease severity and stage of Parkinson's disease (23). Furthermore, Pott Godoy et al. used an animal model of Parkinson's disease to investigate low-grade inflammation in the disease course of Parkinson's disease and determined that both increased levels of central and systemic IL-1 exacerbated neurodegeneration and the motor symptoms of Parkinson's disease (18). Moreover, evidence has indicated that oversecreted pro-inflammatory cytokines during an allergic response pene-

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trate the blood–brain barrier and activate abnormal neuroimmune mechanisms involving specific neural circuits related to motor and emotional modulation (24–26). Asthma-related neuroimmune changes, in a vicious cycle, require time to impair the specific brain function and neural circuitry involved in motor function and mood, possibly explaining the sequential development of asthma and, subsequently, Parkinson's disease. Considering the aforementioned evidence, we hypothesized that the long-term inflammation caused by asthma-related allergic responses may contribute to the development of neurodegenerative disorders, such as Parkinson's disease (16, 18, 21–23). Further study is required to determine the mechanisms underlying the relationship between asthma and Parkinson's disease.

Consistent with the finding of Bower et al., our results supported a slightly trend association between allergic rhinitis and Parkinson's disease (8). We also found that antihistamine agent use was related to an elevated risk of developing Parkinson's disease after adjusting for demographic data, medical comorbidities, medication use, and health system use. Antihistamine agents were widely used in treating allergic diseases, but the link between antihistamine agent use and the risk of Parkinson's disease was unclear. Several case report studies have demonstrated that Parkinson's disease was induced by flunarizine or cinnarizine having histamine H_1-receptor blocking activity (27, 28). Furthermore, a growing body of evidence suggested a potential role of histamine in the regulation of substantia nigra dopaminergic system and in the pathophysiology of Parkinson's disease (29–31). These results may inspire researchers to elucidate the role of allergic diseases and antihistamine agent use in the development and clinical progress of neurodegenerative disorders and to further clarify whether prompt intervention for allergic diseases reduces the risk of subsequent Parkinson's disease.

Finally, our results showed that depressive disorder and cerebrovascular diseases are related to an elevated risk of Parkinson's disease; this finding is compatible with previous findings (12, 32, 33). Shen et al. reported that patients with depressive disorder had an elevated likelihood (HR: 3.24, 95% CI: 2.36–4.44) of developing Parkinson's disease later in life compared with those without depression (12). Papapetropoulos et al. reported that patients with Parkinson's disease exhibited a high prevalence of stroke (12%) and suggested that cerebrovascular disease affects the risk of Parkinson's disease (33). Aleyasin et al. reported that Parkinson's disease and stroke may share some common genes (i.e., DJ-1 [PARK7]) related to oxidative stress and long-term inflammation (32).

This study had some limitations. First, the incidence of Parkinson's disease may have been underestimated because only people who sought medical consultation or treatment were enrolled in our study. However, those enrolled in our study were diagnosed by board-certified neurologists; thus, the diagnoses were valid. Second, although we have adjusted for the health system use in the regression model in our study, early Parkinson's disease may demonstrate an abnormal response to hypoxia; thus, asthma exacerbation may result in an earlier diagnosis of the disease. Further clinical follow-up study would be required to clarify this issue and to reduce this potential identification bias. Third, this longitudinal observation was in fact retrospective, as no control visits or examinations were accomplished. Further prospective study would be required to validate our finding. Fourth, the NHIRD did not provide certain information, such as disease duration of asthma, missed working days due to asthma, smoking history, family history, personal lifestyle, and environmental factors. Without this information, we were unable to examine the influence of these factors on the risk of Parkinson's disease.

In conclusion, both middle-aged and elderly adults with asthma had an elevated risk of developing Parkinson's disease later in life after we adjusted for demographic data, medical comorbidities, medication use, and health system use. Greater asthma severity was associated with a higher susceptibility to developing Parkinson's disease. Further study is required to validate our findings and investigate the pathophysiology underlying the relationship between asthma and Parkinson's disease.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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All authors have no financial relationships relevant to this article to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The univariable Cox regression analyses of developing Parkinson's disease of patients with asthma and the control group.

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Supplementary table 1. The univariable Cox regression analyses of developing Parkinson's disease of patients with asthma and the control group

	Parkinson's disease	
	HR	95%CI
Asthma, presence vs. absence	**2.74**	**2.16~3.46**
Atopic dermatitis, presence vs. absence	0.64	0.16~2.58
Allergic rhinitis, presence vs. absence	**1.82**	**1.39~2.38**
Depressive disorder, presence vs. absence	**2.59**	**1.85~3.64**
Alcohol-related disorders, presence vs. absence	1.49	0.37~6.00
Substance use disorders, presence vs. absence	-	-
Dementia, presence vs. absence	**1.58**	**1.12~2.23**
Hypertension, presence vs. absence	**1.42**	**1.08~1.87**
Dyslipidemia, presence vs. absence	0.89	0.69~1.15
Diabetes mellitus, presence vs. absence	1.03	0.80~1.33
Renal diseases, presence vs. absence	1.02	0.67~1.55
Ischemic heart diseases, presence vs. absence	**1.44**	**1.08~1.92**
Cerebrovascular diseases, presence vs. absence	**1.85**	**1.43~2.39**
Chronic respiratory diseases, presence vs. absence	**1.51**	**1.12~2.02**
Head injury, presence vs. absence	**1.76**	**1.17~2.66**

*: adjusted by demographic data and health system use.

HR: hazard ratio; CI: confidence interval.

Bold type indicates the statistical significance.