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ORIGINAL ARTICLE

Time trends in the prevalence and incidence of Parkinson's disease in Taiwan: A nationwide, population-based study

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Background/purpose: Identifying trends in the prevalence and incidence of Parkinson's disease (PD) may yield information that supports public health goals. Our aim was to evaluate time-trend changes in the prevalence and incidence of PD in Taiwan between 2004 and 2011.
Methods: This retrospective, nationwide, longitudinal study used the Taiwan National Health Insurance Research Database to identify patients with PD from 2004 to 2011 based on having ICD-9-CM diagnostic codes, which were assigned by neurologists, and being prescribed PD medication. Annual incidence and prevalence were calculated, and time-trend analyses were estimated assuming a Poisson distribution.
Results: Over the study period, 19,302 patients in 2004 and 41,606 patients in 2011 fulfilling the study criteria for PD were included in the analysis. The average age-standardized prevalence of PD per 100,000 of population was 84.8 in 2004 and 147.7 in 2011, with a 7.9% yearly increase. Increasing prevalence trends of PD were statistically significant ($p < 0.001$) in all age groups, with the steepest rate among those aged ≥ 80 years. In contrast, the average age-standardized incidence of PD decreased steadily from 35.3 per 100,000 in 2005 to 28.8 per 100,000 in 2011. The incidence rate was higher in men than in women, and increased with age.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.
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Conclusion: We identified an increasing trend in the annual prevalence rates of PD from 2004 to 2011; however, the substantial decline in the incidence of PD suggests that some major environmental risk factors for PD were removed from this population during this time period.

Introduction

Parkinson's disease (PD), a disorder of complex etiology including both genetic and environmental factors, is one of the most common neurodegenerative diseases.[1] The past decade has been characterized by a remarkable acceleration in the identification of genetic variants linked to a minority of PD cases;[2] however, penetrance is often incomplete. This observation suggests the importance of environmental risk factors, including exposure to certain agricultural chemicals that have also been associated with an increased risk of PD.[3]

Given that the population worldwide has aged dramatically in the past decade, the impact of PD on global society is a major concern. A key to unravelling the etiology of PD is to investigate its occurrence and distribution within communities and globally. Time trends in the incidence and prevalence of PD may help to generate new etiologic hypotheses and enable public health systems to project the future burden of these disabling conditions and plan medical services based on these projections.

Previous studies comparing prevalence rates across different regions have had conflicting results.[4-7] A recent meta-analysis of prevalence studies reported a stable prevalence rate in the UK in recent decades,[8] and a similar stable trend of the prevalence of PD was also observed in a US county over a 15-year period.[9] However, no population-based large-scale analyses have been published on the incidence and prevalence of PD over time in Asia. We therefore conducted time-trend analyses of the prevalence and incidence of PD in Taiwan from 2004 to 2011, comparing the sexes and different age groups, and report the findings in the context of previous results for Taiwan and western countries.

Methods

Data source

The Taiwanese government launched the National Health Insurance (NHI) program in March 1995, which covered >99% of the total population by the end of 2008.[10] The NHI Research Database was developed at the National Health Research Institute, with linked data from demographic and enrollment records, hospital claims, ambulatory care visits, and pharmacy-dispensing claims from hospitals, outpatient clinics, and community pharmacies. Every individual in Taiwan has a unique personal identification number. Data on patient identities are scrambled cryptographically by the National Health Research Institutes to protect patient privacy.

Our study was approved by the Research Ethics Committee of National Taiwan University Hospital. No informed consent from participants was required because the data were analyzed anonymously. We analyzed data from 2004 to 2011.

Study population

We searched the entire population in the Taiwan National Health Insurance Database from 2004–2011 to identify any outpatient visitor or hospitalized individual with PD as one of the diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification; ICD-9-CM code: 332.0). Patients were classified as having PD and included in the analysis if they had at least one hospital admission or one neurologist outpatient visit using the PD diagnostic code, and if they received PD medication (including levodopa, carbidopa, bromocriptine mesylate, pergolide mesylate, amantadine, anticholinergics, selegiline, cabergoline, ropinirole, or pramipexole; Anatomical Therapeutic Chemical Classification System, N04) in any of the calendar years. To improve the diagnostic accuracy and to exclude patients with possible secondary parkinsonism, patients who had had a diagnosis of dementia, cerebrovascular diseases, head trauma, or psychotic disorders at the time of, or 1 year before the diagnosis of PD were excluded.

Incident and prevalent case ascertainment

An incident case was ascertained after confirming that the patient met the criteria for PD in the claims database with a minimum of 1 year. As a result, we could only identify incident cases after 2005. The hospital admission date or the first date of an outpatient visit that met our definition of PD, whichever came first, was used as the date of the incident event. Patients were classified as prevalent cases if they met the criteria for PD in each year of the study, but were not incident cases. Because no death records are in the database, we assumed that patients with PD had an unknown vital status if there was no claim for any health service in the database for >1 year, and they were not counted as prevalent cases after the date of the last record.

Statistical analysis

We calculated the annual incidence and prevalence of PD from 2004 to 2011 by dividing the number of patients by the

mid-year Taiwanese population of that year. The 95% confidence intervals were not calculated because we analyzed data from the whole nation without sampling. The age- and gender-specific annual estimates were calculated for groups aged < 50 years, 50–59 years, 60–69 years, 70–79 years, and ≥ 80 years. Age-adjusted, sex-specific estimates were directly standardized by applying the age-specific rates to those of the population in 2005. Results are further presented as graphs stratified by sex and age. Poisson regression adjusted by age was used to analyze each year's trend of the prevalence and incidence of PD. Calendar year, as the continuous variable, was used in the model for linear trend, and an interaction term with sex cross-product year was used to test the difference in trends between men and women. For results indicating significant trends in each year, the percent change in incidence and prevalence at

the end of the study period (2011) was compared to that at the beginning of the study (2004).

Results

A total of 19,302 patients in 2004 and 41,606 patients in 2011 fulfilled study criteria for PD and were included in the analysis. The average age-standardized prevalence of PD per 100,000 of population was 84.8 in 2004 and 147.7 in 2011, accounting for a 7.9% increase each year. Figure 1A shows that the annual standardized prevalence steadily increased for both men and women during the study period. Table 1 summarizes the age- and sex-specific annual prevalence of PD. A higher annual prevalence was observed in the older age groups in both men and women, with a
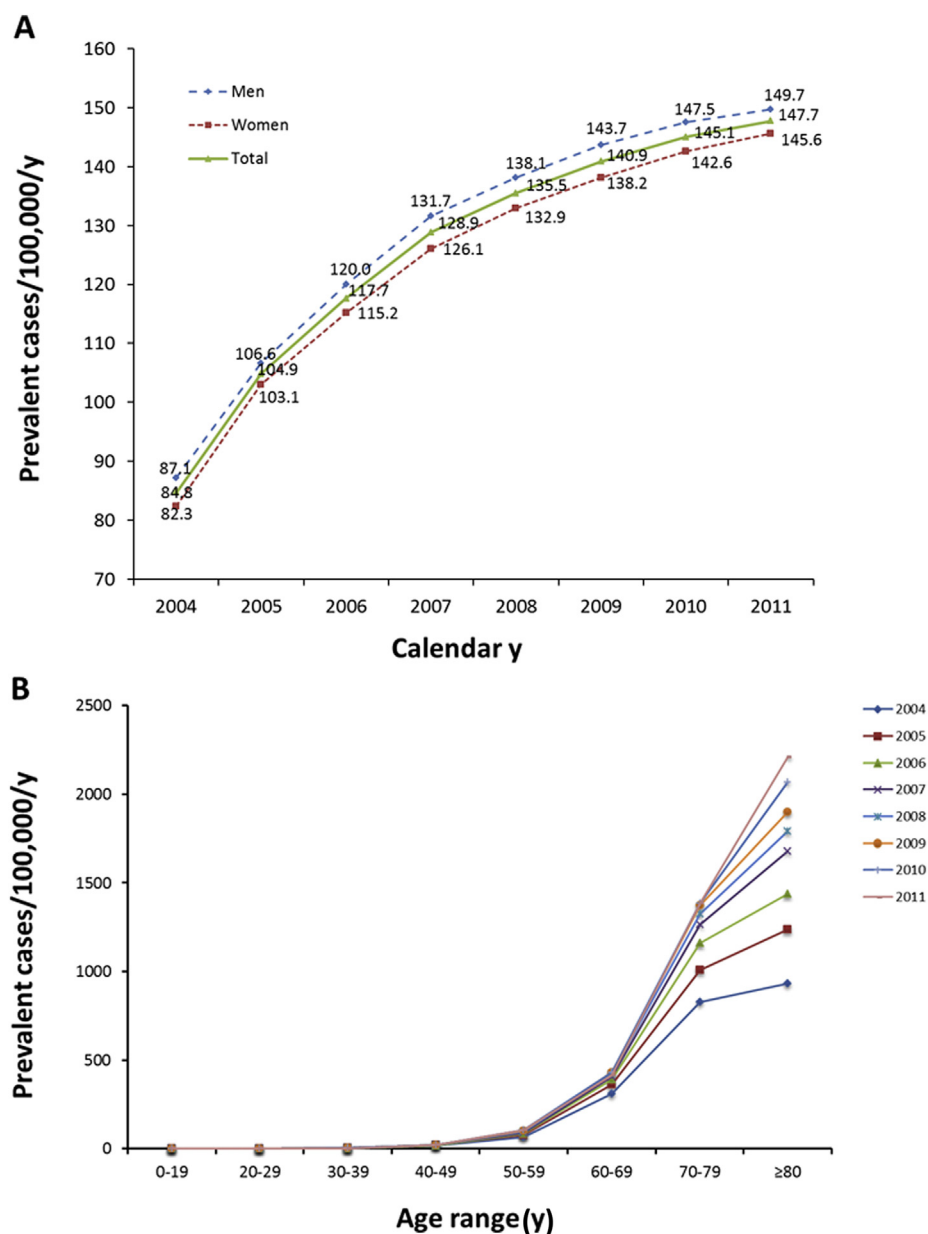

Figure 1 Time trends in the average prevalence (prevalent cases per 100,000 people) of Parkinson's disease by (A) sex and (B) age between 2004 and 2011.

Table 1   Prevalence of Parkinson's disease in Taiwan from 2004 to 2011 (per 100,000 of population).

Year	2004	2005	2006	2007	2008	2009	2010	2011	p
Prevalent cases	19,302	23,875	27,604	31,176	33,904	36,618	39,256	41,606	
Crude prevalence rate	84.8	104.9	120.7	135.8	147.2	158.4	169.5	179.1	
Standardized prevalence rate	84.8	104.8	117.7	128.9	135.5	140.9	145.1	147.7	< 0.001
Age group (y)									
50–59	63.0	73.8	79.5	86.5	90.7	93.5	94.8	96.8	< 0.001
60–69	303.3	360.5	392.8	417.9	426.6	432.3	429.5	410.4	< 0.001
70–79	814.6	1007.5	1142.1	1235.1	1300.8	1347.3	1379.5	1406.0	< 0.001
≥80	857.8	1145.4	1342.1	1562.4	1690.4	1809.8	1953.6	2076.6	< 0.001
Sex									
Men	87.1	106.6	120.0	131.7	138.1	143.7	147.5	149.7	< 0.001
Women	82.3	103.1	115.2	126.1	132.9	138.2	142.6	145.6	< 0.001

slightly higher prevalence in men. Although all increasing trends for prevalence of PD were statistically significant in each age group ($p < 0.001$), the highest increasing rate was observed in those aged ≥ 80 years (Figure 1B). From 2004 to 2011, the annual prevalence increased in that group by 19.5% (from 1932.6 to 2207.0 per 100,000) among men and by 21.3% (from 783.0 to 1948.0 per 100,000) among women, followed by a 9.62% increase (from 829.1 to 1387.3 per 100,000) among men and 11.1% increase (from 799.2 to 1421.9 per 100,000) among women in the 70–79-year age group; by 4.8% (from 309.6 to 414.3 per 100,000) among men and 5.3% (from 297.4 to 406.7 per 100,000) among women in the 60–69-year age group; and by 8.2% (from 67.3 to 105.9 per 100,000) among men and 7.1% (from 58.7 to 87.9 per 100,000) among women in the 50–59-year age group.

The number of annual incident cases of PD decreased from 8297 in 2005 to 8031 in 2011. We found that the average age-standardized incidence rate of PD per 100,000 decreased from 35.3 in 2005 to 28.8 in 2011. Table 2 summarizes age- and sex-specific annual incidence rates of PD, showing that higher incidence rates were observed in older age groups in both men and women, with a slightly higher incidence in men, especially those aged ≥ 80 years; however, women aged 60–69 years had a higher incidence compared with men. As depicted in Figure 2A, in contrast with the increasing trends for prevalence, a significant decrease in the incidence rate of PD was observed for both men and women. The most obvious tendency for decreasing

incidence was in the 60–69-year age group in both sexes (4.5% for men and 5.0% for women).

Discussion

To the best of our knowledge, this is the first study to assess the time trends of PD incidence and prevalence in an Asian population. We found an increased trend in the age-/sex-standardized annual prevalence rates of PD over the past 8 years. The prevalence was slightly higher in men than in women and increased steadily with age. Notably, our results showed that the incidence of PD decreased gradually throughout the study period, although the incidence rate was higher in men than in women and increased with age.

We observed a gradual increase in PD prevalence throughout the study period. Similar results have also been reported for Japan, Israel, and France in the past decade (Figure 3A).[11–13] Although our prevalence rate was lower than those in Israel and France,[12,13] it was comparable with that of Japan.[11] Both changes over time in the incidence of PD and the length of survival of individuals with PD affect the prevalence of PD. Because the incidence rate showed a decreased trend, we speculate that the increasing prevalence of PD over time may come from an increase in the general aging population in Taiwan.[14] Taiwan has become an aging society since 1993, when the percentage of the population aged > 65 years reached 7% and increased

Table 2   Incidence of Parkinson's disease in Taiwan from 2005 to 2011 (per 100,000 of population).

| Year	2004	2005	2006	2007	2008	2009	2010	2011	p
Incident cases									
Crude incidence rate	—	35.3	33.6	33.9	32.6	33.4	34.4	34.7	
Standardized incidence rate	—	35.3	32.7	32.2	30.1	29.8	29.6	28.8	< 0.001
Age group (y)									
50–59	—	22.7	21.3	21.5	20.9	20.8	20.4	19.8	0.006
60–69	—	119.2	104.7	105.4	97.0	95.6	89.8	85.1	< 0.001
70–79	—	338.3	318.7	305.2	292.6	288.8	285.0	275.2	< 0.001
≥80	—	402.0	385.9	382.3	344.3	345.6	365.2	364.1	< 0.001
Sex									
Men	—	35.3	33.2	33.1	30.3	30.4	30.0	29.2	< 0.001
Women	—	35.3	32.2	31.2	29.8	29.3	29.3	28.3	< 0.001
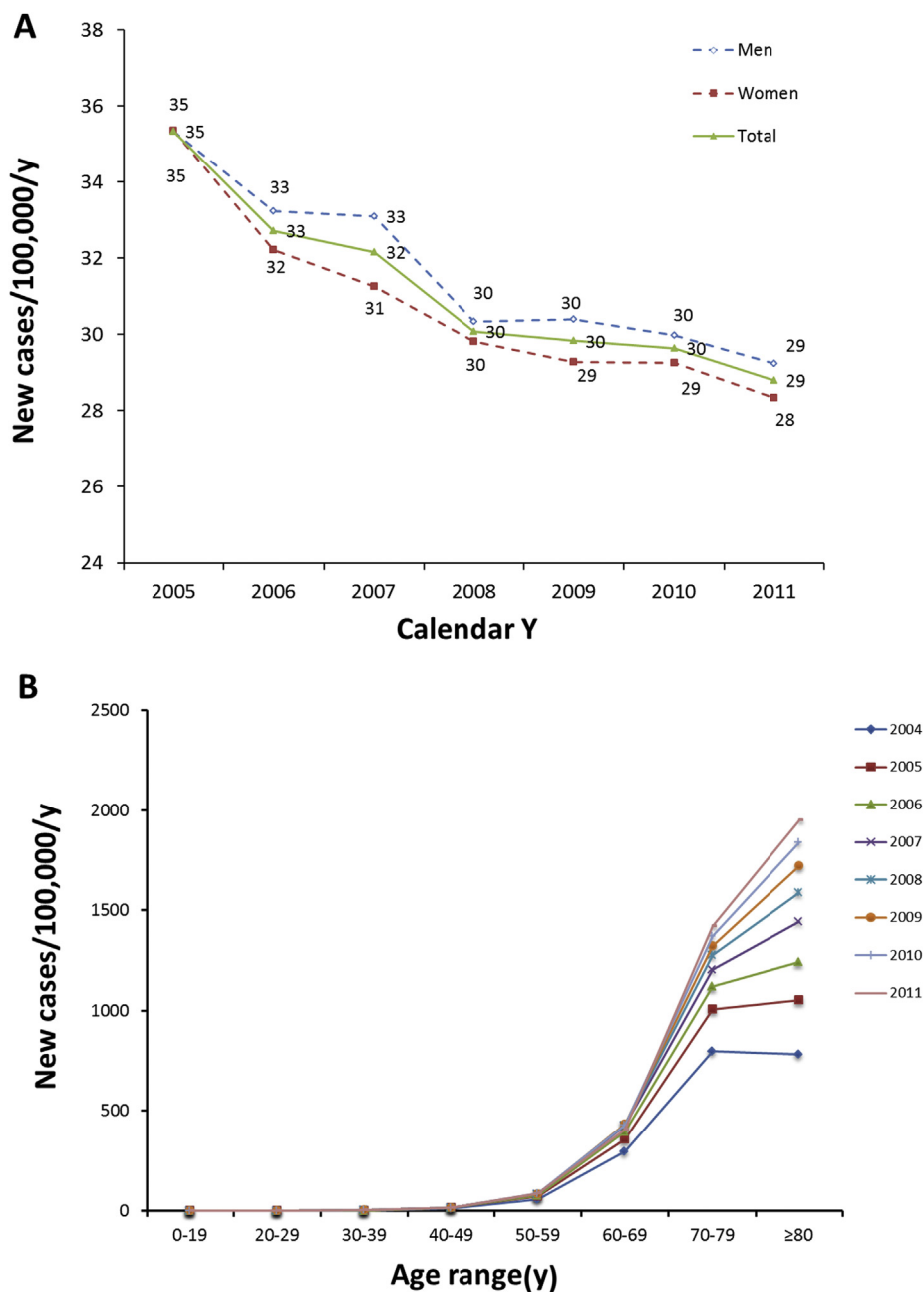
Figure 2 Time trends in the average incidence (new cases per 100,000 people) of Parkinson's disease by (A) sex and (B) age between 2004 and 2011.

rapidly to 10.2% by the end of 2007.[14] Data from England and Wales showed decreasing mortality rates from PD in both men and women from 1993 to 2006, largely because of improvements in treatments for PD and general medical care.[15,16]

Our results suggest the multidisciplinary approach to managing patients with PD, combining pharmacological treatment with non-pharmacological interventions which has proven beneficial in recent years, has been successful.[17] The findings also show that the prevalence of PD increases with age, and steeply increases after 60 years of age (Figure 1B), which is compatible with the fact that PD is a progressive, disabling, neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra of the brain.[18]

Additionally, our data were consistent with findings from previous studies conducted in rural areas of Taiwan, Kinmen, and Ilan; studies from North America/Europe; and one recent study from China (Table 3). An exception is the 70–79-year age group, which had a higher prevalence in our study compared with previous findings. Our national trends are, however, comparatively lower than those reported for an urban city in Taiwan.[4] We hypothesize that the convenience of medical access and higher socioeconomic status, along with better drug adherence in urban areas, may partly explain these urban–rural differences in PD prevalence.[19] These observations suggest a distribution
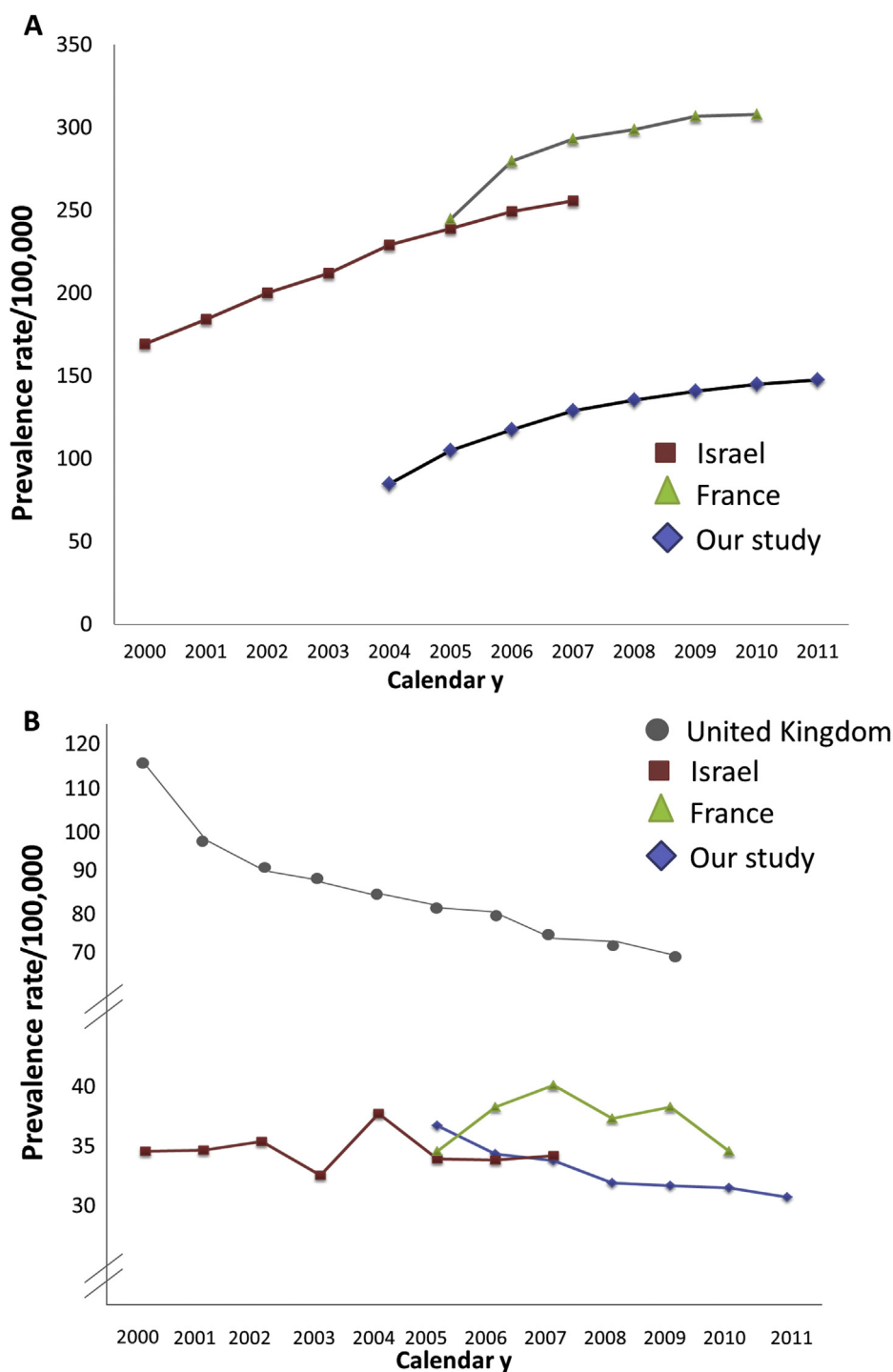
A

B

Figure 3 Comparison of the time-trend changes in the average age-specific (A) prevalence and (B) incidence rates of PD between Taiwan, France [12], Israel [13] and the UK [8].

heterogeneity of PD, even though the genetic background is similar, and further emphasize the importance of nation-wide study designs, as in the current work.

In contrast with the findings of an increased trend in the prevalence of PD, we observed a decreased trend in the incidence of PD. Similar trends have been reported in the UK between 1999 and 2009 (Figure 3B), although the average annual incidence rate was higher than in our

population (84 per 100,000/y vs. 31 per 100,000/y).[15] There was a downward trend in the incidence of PD in the UK study, with adjusted incidence rates declining by approximately 6% every calendar year during the study period.[15] Previous studies of time trends of the incidence of PD in Olmsted County in the US, however, suggested a stable trend in the incidence of PD between 1976 and 1990.[9] Studies conducted in France (2005 and 2010)[12]

Table 3 Comparison of the prevalence of Parkinson's disease by local geographic regions within Taiwan and China (per 100,000 of population).

Geographic regions	<50 y	50−59 y	60−69 y	70−79 y	≥80 y
Rural areas in Taiwan					
Kinmen[6]	NA	273	535	565	1839
Ilan[5]	38	123	547	820	2198
Urban areas in Taiwan					
Keelung[4]	NA	121	687	1838	4328
Nationwide study in Taiwan					
Current study (2011)	20 (CI)	97 (CI)	410 (CI)	1406 (CI)	2077 (CI)
China[28]	NA	133	422	825	1663
Other Asian countries[22]	NA	88 (39−201)	376 (166−848)	646 (320−1345)	1418 (612−3285)
North America/Europe[29]	NA	113 (49−261)	540 (373−781)	1602 (1219−2105)	2953 (1936−4503)

CI = confidence interval; NA = not applicable.

and Israel (1998 and 2008)[13] using a database study design also demonstrated relatively stable trends in the incidence of PD in recent decades (Figure 3B), although the incidence rate was comparable to that identified in our study.

We hypothesize that because the genetic background of our population did not change much over the past decade, the most probable reason for the decreasing incidence rate of PD may be lifestyle changes due to urbanization and industrialization of society during this time period.[19−21] Lifestyle changes, with more tap water use rather than well water, working environment changes with a decreased population working in agriculture, and dietary changes, with an increased consumption of caffeine-containing drinks, could all potentially contribute to this decreasing trend in the incidence of PD in our population.[20,22]

Not surprisingly, our results showed a sex difference in PD incidence rates, with more new cases in men than women. Our findings are consistent with previous studies and a recent systematic review.[23−25] Possible reasons for this divergence between men and women include the neuroprotective effects of estrogen, a higher frequency of exposure to toxins and minor head trauma in men, and recessive susceptibility genes on the X chromosome.[23,24]

Our study has the following strengths. Firstly, we used nationwide data and had a large sample size, which emphasizes the prevalence and incidence trends over an 8-year time period. We used a strict definition to define patients diagnosed with PD (ICD-9 332.0 diagnosed by neurologists and at least one PD treatment agent taken at the same time), which made the statistical analysis more accurate and reliable. Secondly, the NHI program in Taiwan provides continuing universal coverage for the entire population in Taiwan, which avoids selection bias. Thirdly, NHI datasets were used, which eliminated the need to minimize the number of partients in the cohorts lost to follow up. Finally, a large sample of geographically-dispersed patients was easily obtained, which avoided regional differences in estimations. However, our study also has some limitations. The major limitation was that despite analyzing healthcare records from a representative, national dataset, our diagnosis of PD was based on the diagnostic code from the NHI database; therefore, we could not distinguish between primary and secondary parkinsonism. However, we

excluded patients who had ever had diagnoses of dementia, cerebrovascular diseases, head trauma, or psychotic disorders at the time of, or 1 year before, the diagnosis of PD, to exclude the possibility of enrolling patients with diffuse Lewy body disease, vascular parkinsonism, and secondary parkinsonism related to intracranial hemorrhage or neuroleptic use. We were unable to review the medical records of all defined PD patients because all the medical information from the national NHI database was de-identified due to ethical requirements. Therefore, we had no clinical data regarding neuroimaging examinations or the duration of and treatment response to PD medications in the defined PD patients, which hampered our ability to perform a nationwide validation study. Therefore, to evaluate the accuracy of the diagnostic criteria for PD in our study, we performed a hospital-based validation study using the medical records of patients who were consecutively diagnosed with PD from 2002 to 2010 and who received long-term follow up at National Taiwan University Hospital, a tertiary referral center in Taiwan. A movement disorder specialist (CHL) evaluated the medical records of these patients. PD was clinically diagnosed according to the United Kingdom Brain Bank criteria.[26] A total of 1985 PD patients were confirmed by critical medical record review. Among these clinically confirmed patients, 1883 (94.8%) were identified using the diagnostic criteria in the main study (based on ICD-9-CM code and medication history), suggesting that the diagnostic sensitivity of our study criteria is acceptable.[27] Because prospective incidence studies of PD are difficult and costly to perform and, thus, many have important limitations,[28,29] the analysis of this database allowed us to examine a very large sample of population-based information, reflecting clinical practice in Taiwan over 8 years, and to study the results over time. Additionally, because the death record is not included in the National Health Research Institute database, we assigned an unknown vital status to patients for whom there was no claim for any health service in the database for >1 year. We may have underestimated the actual death rate in 2011 and therefore may have overestimated the prevalence of PD in 2011.

The results of our study show temporal trends in the incidence and prevalence of PD in Taiwan over the past 8 years. An accurate estimate of the disease burden is a

necessary first step in efforts to mitigate the effects of a projected wave of PD on public health economies. Future longer-term follow-up studies examining genetic or environmental exposures, individual characteristics (e.g., smoking), and carefully established PD diagnoses are required for a better understanding of the relationship between environmental and genetic risk factors for PD and to guide future planning for resources and community costs of this disease.

Acknowledgments

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