Risk of Parkinson Disease Onset in Patients With Diabetes

A 9-year population-based cohort study with age and sex stratifications

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OBJECTIVE—We retrospectively assessed the age- and sex-specific incidence and relative risk of Parkinson disease (PD) in Taiwan’s diabetic population.

RESEARCH DESIGN AND METHODS—Study cohort included 603,416 diabetic patients and 472,188 nondiabetic control subjects. Incidence rate and relative risk of PD (ICD-9-CM 332.0) were evaluated.

RESULTS—The incidence of PD was 3.59 and 2.15 per 10,000 person-years for the diabetic and control group, respectively, representing a covariate adjusted hazard ratio (HR) of 1.61 (95% CI 1.56–1.66), which was substantially reduced to 1.37 (1.32–1.41) after adjusting for medical visits. Diabetes was associated with a significantly elevated risk of PD in all sex and age stratifications except in young women, with the highest HR noted for young men aged 21–40 years (2.10 [1.01–4.42]), followed by women aged 41–60 (2.05 [1.82–2.30]) and >60 years (1.63 [1.38–1.93]).

CONCLUSIONS—Diabetes is associated with an increased risk of PD onset in a Chinese population, and the relation is stronger in women and younger patients.

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A few recent studies raise the possibility of increased risk of Parkinson disease (PD) among diabetic patients (1–3). However, findings reported in prior studies are not consistent (4–7). Furthermore, large-scale population-based cohort studies with detailed age and sex stratifications in Asia are rare. The current study uses a national cohort retrieved from Taiwan’s National Health Insurance (NHI) database to retrospectively investigate the age- and sex-specific associations of diabetes with the risk of incident PD.

RESEARCH AND METHODS—Details of NHI claim data of Taiwan and methods of selection of diabetic and control groups were described previously (8,9). In brief, eligible study subjects were adult prevalent cases of diabetes with a diagnosis of diabetes (ICD-9 250 or A code 181) in 2000 (i.e., index date) who then experienced one or more diabetes diagnoses within the subsequent 12-month follow-up period. The first and last outpatient visits within 1 year had to be >30 days apart to avoid accidental inclusion of miscoded patients. The index date for subjects in the control group was the first date of enrollment to NHI. If their first date of enrollment was before 1 January 2000, the index date was set as 1 January 2000. The original study subjects consisted of 615,532 diabetic patients and 614,871 age- and sex-matched control subjects randomly selected from the registry of beneficiaries (8,9). Case subjects with a prior diagnosis of PD (ICD-9 332.xx, n = 2,977) or secondary Parkinsonism (n = 3,639) from 1 January 1997 to the index date were excluded. Case subjects aged <20 years were also excluded (n = 5,500). The same exclusion criteria were also applied to control subjects (PD, n = 1,699; secondary Parkinsonism, n = 1,398; age <20, n = 5,497). Control subjects treated for diabetes (ICD-9: 250.xx) during follow-up (i.e., 2000–2008) (n = 134,089) also were excluded to reduce the likelihood of disease misclassification. The final cohort consisted of 603,416 diabetic patients and 472,188 control subjects.

We identified the first diagnoses of PD (ICD-9: 332.0) from outpatient claims or hospitalization records from 2000 to 2008 as the study end point. Only those with end point onset 1 year after the index date were retrieved to establish the temporal link between diabetes and PD. All of the study subjects were followed from the index date to occurrence of end point, withdrawal from the NHI, or 31 December 2008, whichever date came first, and the later two dates were considered as censoring observations.

The age- and sex-specific incidence densities (IDs) were determined under Poisson assumption. Cox proportional hazards regression models were performed with adjustment for age, sex, geographic area, urbanization status, and comorbidities, including hypertension (ICD-9: 401–405), hyperlipidemia (ICD-9: 272), and cardiovascular disease (ICD-9: 410–414, 430–438). We also tested the interactive effects of diabetes with age or sex on risk of PD. We adjusted for geographic area to minimize the potential confounding by...
diabetic patients showed a significantly increased risk of PD with an adjusted hazard ratio (HR) of 1.61 (95% CI 1.56–1.66). The adjusted HR was significantly higher (β = 0.109657, P < 0.0001) in diabetic women (1.70 [1.63–1.77]) than in diabetic men (1.51 [1.44–1.57]). The interaction of diabetes with age was also statistically significant for both men (β = 0.18082, P = 0.0014) and women (β = 0.30550, P < 0.001). For men, the age-specific HR was highest in young diabetic subjects aged 21–40 years (2.10), then it declined to 1.60 and 1.49 for aged 41–60 and >60 years, respectively. The age-specific HR was lower for young women with diabetes (1.10) and was higher for middle-aged and older women with diabetes (2.05 and 1.65, respectively) (Table 1). To test the proportionality assumption of the Cox model, we performed stratified analysis according to the period of follow-up. The adjusted HR tended to be higher in earlier years (i.e., 2000–2004; 1.83 [1.75–1.91]) than in later years (i.e., 2005–2008; 1.44 [1.39–1.50]). We also calculated the HR for diabetic subjects whose dates of first-time ambulatory visit for diabetes were in 1997 or earlier, 1998–1999, or 2000 and observed an adjusted HR of 1.72 (1.66–1.77), 1.38 (1.32–1.44), and 1.25 (1.18–1.33), respectively.

To examine the potential bias arising from higher ambulatory care frequency in diabetic patients, we limited control subjects to those with ≥21 ambulatory visits (the average number of ambulatory visits for nondoniabetic causes in diabetes) for all causes in 2000 and noted an overall adjusted HR of 1.37 (1.32–1.41).

RESULTS—The overall ID for diabetic men and women was 3.34 and 3.82 per 10,000 patient-years, respectively, while the corresponding figures for control men and women were 2.12 and 2.18 per 10,000 patient-years. Irrespective of sex, the ID increased with age in both groups, with a dramatically high ID noted for those aged >65 years (Table 1).

Compared with control subjects, diabetic patients showed a significantly increased risk of PD with an adjusted hazard ratio (HR) of 1.61 (95% CI 1.56–1.66). The adjusted HR was significantly higher (β = 0.109657, P < 0.0001) in diabetic women (1.70 [1.63–1.77]) than in diabetic men (1.51 [1.44–1.57]). The interaction of diabetes with age was also statistically significant for both men (β = 0.18082, P = 0.0014) and women (β = 0.30550, P < 0.001). For men, the age-specific HR was highest in young diabetic subjects aged 21–40 years (2.10), then it declined to 1.60 and 1.49 for aged 41–60 and >60 years, respectively. The age-specific HR was lower for young women with diabetes (1.10) and was higher for middle-aged and older women with diabetes (2.05 and 1.65, respectively) (Table 1). To test the proportionality assumption of the Cox model, we performed stratified analysis according to the period of follow-up. The adjusted HR tended to be higher in earlier years (i.e., 2000–2004; 1.83 [1.75–1.91]) than in later years (i.e., 2005–2008; 1.44 [1.39–1.50]). We also calculated the HR for diabetic subjects whose dates of first-time ambulatory visit for diabetes were in 1997 or earlier, 1998–1999, or 2000 and observed an adjusted HR of 1.72 (1.66–1.77), 1.38 (1.32–1.44), and 1.25 (1.18–1.33), respectively.

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CONCLUSIONS—This retrospective study supports the putative link between diabetes and risk of PD (1–3). Our study provides additional information suggesting significant effect modifications by age and sex. We found a significantly higher HR of PD in diabetic women than in diabetic men. Moreover, young diabetic men aged 21–40 years or diabetic women aged 41–60 years are more vulnerable to the increased risk.

The association between diabetes and PD has not been fully illustrated. It is possible that chronic inflammation and oxidative stress noted in diabetes may also lead to higher risk of PD years later.

### Table 1—Overall and age- and sex-specific IDs and relative hazards of PD in the diabetic and control groups

| Variable* | Control group | Diabetic group | Diabetic group |
|-----------|---------------|----------------|----------------|
|           | Subject (n)   | Event (n) | ID (95% CI) per 10,000 patient-years‡ | Subject (n) | Event (n) | ID (95% CI) per 10,000 patient-years‡ | HR (95% CI) in association with diabetes | Adjusted HR§ (95% CI) in association with diabetes |
| Men       |               |           |                  |               |           |                  |                             |                                    |
| Age (years) |               |           |                  |               |           |                  |                             |                                    |
| 21–40     | 20,660        | 2         | 0.09 (0.05–0.14) | 21,310        | 4         | 0.22 (0.16–0.30) | 2.57 (1.42–4.67) | 2.10 (1.01–4.42) |
| 41–60     | 102,883       | 47        | 0.55 (0.50–0.60) | 128,217       | 108       | 1.06 (0.99–1.12) | 1.96 (1.76–2.18) | 1.60 (1.41–1.81) |
| >60       | 109,636       | 338       | 4.29 (4.15–4.44) | 140,593       | 599       | 6.41 (6.25–6.58) | 1.52 (1.46–1.59) | 1.49 (1.42–1.56) |
| Total     | 233,179       | 387       | 2.12 (2.06–2.19) | 290,120       | 711       | 3.34 (3.26–3.42) | 1.59 (1.53–1.65) | 1.51 (1.44–1.57) |
| Women     |               |           |                  |               |           |                  |                             |                                    |
| Age (years) |               |           |                  |               |           |                  |                             |                                    |
| 21–40     | 14,718        | 2         | 0.11 (0.06–0.19) | 14,881        | 3         | 0.22 (0.15–0.32) | 2.00 (1.05–3.79) | 1.10 (0.48–2.55) |
| 41–60     | 97,508        | 52        | 0.62 (0.56–0.67) | 125,561       | 156       | 1.51 (1.44–1.59) | 2.48 (2.25–2.74) | 2.05 (1.82–2.30) |
| >60       | 126,783       | 368       | 3.80 (3.67–3.92) | 172,210       | 743       | 6.18 (6.04–6.32) | 1.66 (1.59–1.72) | 1.65 (1.58–1.73) |
| Total     | 239,009       | 422       | 2.18 (2.11–2.24) | 312,652       | 902       | 3.82 (3.74–3.90) | 1.77 (1.71–1.84) | 1.70 (1.63–1.77) |
| Overall   | 472,188       | 809       | 2.15 (2.10–2.20) | 603,416       | 1,613     | 3.59 (3.53–3.64) | 1.69 (1.64–1.73) | 1.61 (1.56–1.66) |

*Inconsistency between total population and population summed for individual variable was the result of missing information. ‡Based on Poisson assumption. §Based on Cox proportional hazards regression with adjustment for age, sex, geographic area, urbanization status, hypertension, hyperlipidemia, and cardiovascular disease.
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Y.S. researched data and wrote the manuscript. Y.-H.C. analyzed data and drafted the results. H.-F.C. managed data, contributed to discussion, and reviewed and edited the manuscript. Y.-H.S. and H.-F.S. contributed to discussion and drafted the conclusion. C.-Y.L., the principal investigator, researched data and reviewed and edited the manuscript. C.-Y.L. is the guardian of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References
1. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson’s disease. Diabetes Care 2007;30:842–847
2. Schernhammer E, Hansen J, Rughjerg K, Wermuth L, Ritz B. Diabetes and the risk of developing Parkinson’s disease in Denmark. Diabetes Care 2011;34:1102–1108
3. Xu Q, Park Y, Huang X, et al. Diabetes and risk of Parkinson’s disease. Diabetes Care 2011;34:910–915
4. Draper JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G. Prospective cohort study of type 2 diabetes and the risk of Parkinson’s disease. Diabetes Care 2008;31:2003–2005
5. Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. Neurology 2007;69:1688–1695
6. Palacios N, Gao X, McCullough ML, et al. Obesity, diabetes, and risk of Parkinson’s disease. Mov Disord 2011;26:2253–2259
7. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Diabetes in patients with idiopathic Parkinson’s disease. Diabetes Care 2008;31:1808–1812
8. Chen HF, Chen P, Li CY. Risk of malignant neoplasms of liver and biliary tract in diabetic patients with different age and sex stratifications. Hepatology 2010;52:155–163
9. Chen HF, Chen P, Li CY. Risk of malignant neoplasm of the pancreas in relation to diabetes: a population-based study in Taiwan. Diabetes Care 2011;34:1177–1179
10. Tan HF, Tseng HF, Chang CK, Lin W, Hsiao SH. Accessibility assessment of the Health Care Improvement Program in rural Taiwan. J Rural Health 2005;21:372–377
11. Sanyal J, Chakraborty DP, Sarkar B, et al. Environmental and familial risk factors of Parkinson’s disease: case-control study. Can J Neurol Sci 2010;37:637–642
12. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004;3:169–178
13. Horan MP. Application of serial analysis of gene expression to the study of human genetic disease. Hum Genet 2009;126:605–614
14. Chuang LM, Tsai ST, Huang BY, Tai TY; DIABCARE (Taiwan) Study Group. The current state of diabetes management in Taiwan. Diabetes Res Clin Pract 2001;54 (Suppl. 1):S55–S65