Risk of Parkinson Disease Onset in Patients With Diabetes

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

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 [1.01–4.21]), followed by women aged 41–60 (2.05 [1.82–2.30]) and >60 years (1.65 [1.58–1.73]).

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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diabetic subjects aged 21–40 years (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 nondiabetic causes in diabetes) for all causes in 2000 and noted an overall adjusted HR of 1.37 (1.32–1.41).

**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. (3). Besides, animal and in vitro studies show a role for insulin in the regulation of brain dopaminergic activity. Insulin dysregulation and changes in insulin action have been of concern in the pathophysiology and clinical symptoms of PD (12). Furthermore, reduced expression of certain genes in type 2 diabetes is related to impaired mitochondrial oxidative pathway, while mitochondrial dysfunction has been suggested as a pathogenesis in PD (2,13). Our finding indicates a stronger association of diabetes with early onset PD (age <60 years), which is consistent with one recent study (2).

The limitation of this study is that we could not differentiate between type 1 and type 2 diabetes, despite the fact that type 1 diabetes constitutes only 1.8% of all diabetes in Taiwan (14). We limited the diabetic patients to those diagnosed after age 20 or older to further minimize this problem. In addition, because of a lack of complete information on subjects' lifestyle and environmental or occupational exposure, our study was unable to directly adjust for the potential confounding of those variables. The HR in diabetes was substantially decreased from 1.61 to 1.37 after adjusting for frequency of ambulatory care, suggesting major confounding by medical attention, which also may explain some of the remaining risk elevation.

During a 9-year study period, the diabetic patients in Taiwan experienced significantly increased risks of PD in both sexes and most ages; a stronger link between diabetes and young-onset PD deserves further investigation.

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

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Control group</th>
<th>Diabetic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subject (n)</td>
<td>Event (n)</td>
</tr>
<tr>
<td>Men</td>
<td>21–40</td>
<td>20,660</td>
</tr>
<tr>
<td></td>
<td>41–60</td>
<td>102,883</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>109,636</td>
</tr>
<tr>
<td>Total</td>
<td>233,179</td>
<td>290,120</td>
</tr>
<tr>
<td>Women</td>
<td>21–40</td>
<td>14,718</td>
</tr>
<tr>
<td></td>
<td>41–60</td>
<td>97,508</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>126,783</td>
</tr>
<tr>
<td>Total</td>
<td>239,009</td>
<td>312,652</td>
</tr>
<tr>
<td>Overall</td>
<td>472,188</td>
<td>603,416</td>
</tr>
</tbody>
</table>

*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 guarantor 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