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Accessibility
Prospective Cohort Study of Type 2 Diabetes and the Risk of Parkinson’s Disease

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OBJECTIVE — To evaluate the association between type 2 diabetes and newly reported Parkinson’s disease.

RESEARCH DESIGN AND METHODS — Our study included 21,841 participants in the Physicians’ Health Study, a cohort of U.S. male physicians. Diabetes and Parkinson’s disease were self-reported via questionnaire. We used time-varying Cox regression to calculate adjusted relative risk (RR) for Parkinson’s disease.

RESULTS — Over 23 years, 556 individuals with Parkinson’s disease were identified. Subjects with diabetes had an increased Parkinson’s disease risk (multivariable-adjusted RR 1.34 [95% CI 1.01–1.77]). The association remained significant after exclusion of those with known vascular disease. The diagnosis of diabetes was clustered around the diagnosis of Parkinson’s disease and was more apparent among men with short diabetes duration and those without complications from diabetes.

CONCLUSIONS — Results of this large prospective study in men do not suggest that diabetes is a preceding risk factor for Parkinson’s disease. Whether the positive association may be explained by ascertainment bias or a common underlying biological mechanism remains to be established.

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A positive association between diabetes and Parkinson’s disease has been found in some epidemiologic studies (1–4) but not in others (5–7). Diabetes might promote Parkinson’s disease through various pathways, including suppression of central dopamine levels, inflammation, oxidative stress, and cerebrovascular disease. We evaluated the relationship between type 2 diabetes and Parkinson’s disease in detail in a large prospective cohort.

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Type 2 diabetes and Parkinson’s disease risk

Table 1—RRs of Parkinson’s disease according to history of type 2 diabetes

| Participants (PD case subjects) | Person-years | RR (95% CI)* | Pinteraction |
|---------------------------------|--------------|--------------|--------------|
|                                 | Without diabetes | With diabetes | Without diabetes | With diabetes |                  |
| All participants                | 19,431 | 2,410 | 404,923 | 49,031 | 1.00 (ref.) | 1.34 (1.01–1.77) | 0.0002 |
| Baseline age (years)            |          |          |          |          |          |          |          |
| <55                             | 11,684 (149) | 1,247 (12) | 259,924 | 27,489 | 1.00 (ref.) | 1.12 (0.61–2.07) | 0.81 |
| 55–64                           | 5,140 (194) | 790 (26) | 103,743 | 15,937 | 1.00 (ref.) | 1.57 (1.04–2.38) | 0.14 |
| ≥65                             | 2,607 (155) | 373 (20) | 41,255 | 5,605 | 1.00 (ref.) | 1.25 (0.76–2.05) | 0.0002 |
| BMI                             |          |          |          |          |          |          |          |
| <25 kg/m²                       | 11,720 (289) | 858 (31) | 246,028 | 17,147 | 1.00 (ref.) | 1.88 (1.28–2.77) | 0.04 |
| 25 to <30 kg/m²                 | 7,097 (191) | 1,247 (25) | 147,109 | 25,713 | 1.00 (ref.) | 1.14 (0.75–1.72) | 0.0002 |
| ≥30 kg/m²                       | 614 (18) | 305 (2) | 11,786 | 6,171 | 1.00 (ref.) | 0.36 (0.08–1.59) | 0.81 |
| Diabetes with complications     | 19,431 (498) | 404,923 |          |          |          |          |          |
| No                              | 1,475 (33) | 30,981 | 1.00 (ref.) | 1.63 (1.14–2.33) | 0.61 |
| Yes                             | 935 (25) | 18,050 |          | 1.10 (0.74–1.64) | 0.0002 |
| Diabetes duration (years)       | 19,432 (498) | 404,931 |          |          |          |          |          |
| <5                              | 562 (22) | 11,048 | 1.00 (ref.) | 7.17 (4.59–11.20) | 0.0001 |
| 5–9                             | 631 (14) | 12,945 | 1.00 (ref.) | 2.03 (1.22–3.36) | 0.0001 |
| 10–14                           | 482 (7) | 9,921 | 1.00 (ref.) | 0.82 (0.42–1.60) | 0.61 |
| ≥15                             | 734 (15) | 15,109 | 1.00 (ref.) | 0.73 (0.45–1.18) | 0.0002 |
| Age at onset of diabetes (median)| 19,431 (498) | 404,923 |          |          |          |          |          |
| ≤63.7                           | 1,213 (22) | 24,654 | 1.00 (ref.) | 1.18 (0.78–1.79) | 0.0002 |
| >63.7                           | 1,197 (36) | 24,377 | 1.00 (ref.) | 1.49 (1.04–2.11) | 0.0002 |

Data are n (%) unless otherwise indicated. *Adjusted for the following baseline variables: age (continuous), smoking status (never, past, or current), alcohol use (rarely, weekly, or daily), BMI (<25 kg/m², 25 to <30 kg/m², or ≥30 kg/m²), physical activity vigorous enough to work up a sweat (>1–3 times/month or ≥1–3 times/month), hypertension (history of treatment or blood pressure >140 systolic or >90 diastolic), and cholesterol levels (history of treatment or total cholesterol >240). PD, Parkinson’s disease.

supplementary Fig. 1A, available in an online appendix at http://dx.doi.org/10.2337/dc08-0688). A similar clustering was not seen for the diagnosis of hypercholesterolemia (supplementary Fig. 1B).

**CONCLUSIONS** — In this large prospective study of men, a history of type 2 diabetes was associated with an increased risk of Parkinson’s disease. The association remained significant after adjustment for confounders and the exclusion of participants with known vascular disease. If diabetes causes Parkinson’s disease, one would expect increased duration and severity to increase Parkinson’s disease risk. However, we found the highest risk for Parkinson’s disease among individuals with uncomplicated or short-duration diabetes, regardless of baseline age. This was not explained by selective mortality among those with longer diabetes duration (data not shown). Diabetic individuals who developed Parkinson’s disease had a longer median time to first complication (17.0 vs. 15.4 years), consistent with decreased severity. Those with a normal BMI at baseline had the highest risk of Parkinson’s disease, suggesting a biological pathway other than obesity. Thus, our findings do not suggest that diabetes is a preceding risk factor for Parkinson’s disease.

Comparison of Parkinson’s disease risk between case and matched control subjects showed that the difference in risk was primarily due to a clustering of diabetes cases around the time of Parkinson’s disease identification (supplementary Fig. 1A). Thus, one explanation for the association may be detection bias from increased medical surveillance. However, when we examined the diagnosis of hypercholesterolemia, another condition diagnosed by a blood test, we did not observe a similar pattern (supplementary Fig. 1B).

Another possible explanation is that the development of Parkinson’s disease may influence diabetes risk. By the time Parkinson’s disease becomes clinically apparent, dopaminergic cell loss has reached 70–80% (10). Dopaminergic neurons help motivate feeding behavior when glucose levels are low. This feedback loop is mediated by insulin receptors in the substantia nigra, and postmortem studies of Parkinson’s disease show a loss of these receptors (11). Drugs that modulate central dopamine, such as bromocriptine, are known to affect peripheral glucose control. Changes in glucose control associated with loss of dopaminergic function might occur early in the course of Parkinson’s disease, perhaps even before neurological symptoms develop. If Parkinson’s disease were a cause of diabetes, one would expect an increased incidence after the diagnosis of Parkinson’s disease. However, the incidence dropped dramatically the year after Parkinson’s disease diagnosis (supplementary Fig. 1A). As over 25% of our Parkinson’s disease patients were aged ≥80 years at diagnosis, this might reflect decreased reporting from increased comorbidity and mortality. Parkinson’s disease treatment might also modulate diabetes risk.

In conclusion, results of this large prospective study in men do not suggest that diabetes is a preceding risk factor for Parkinson’s disease. The observed clustering of diabetes cases around the time of Parkinson’s disease diagnosis suggests as-
certainty bias or an underlying common biological mechanism. Future studies are warranted to further unveil this association.

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