Diabetes and the Risk of Developing Parkinson's Disease in Denmark

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OBJECTIVE—Insulin contributes to normal brain function. Previous studies have suggested associations between midlife diabetes and neurodegenerative diseases, including Parkinson's disease. Using Danish population registers, we investigated whether a history of diabetes or the use of antidiabetes drugs was associated with Parkinson's disease.

RESEARCH DESIGN AND METHODS—From the nationwide Danish Hospital Register hospital records, we identified 1,931 patients with a first-time diagnosis of Parkinson's disease between 2001 and 2006. We randomly selected 9,651 population control subjects from the Central Population Registry and density matched them by birth year and sex. Pharmacy records comprising all antidiabetes and anti-Parkinson drug prescriptions in Denmark were available. Odds ratios (ORs) were estimated by logistic regression models.

RESULTS—Having diabetes, as defined by one or more hospitalizations and/or outpatient visits for the condition, was associated with a 36% increased risk of developing Parkinson's disease (OR 1.36 [95% CI 1.08–1.71]). Similarly, diabetes defined by the use of any antidiabetes medications was associated with a 35% increased Parkinson's disease risk (1.35 [1.10–1.65]). When diabetes was defined as the use of oral antidiabetes medications, effect estimates were stronger in women (2.92 [1.34–6.36]), whereas when diabetes was defined as any antidiabetes drug prescription, patients with early-onset Parkinson's disease were at highest risk (i.e., Parkinson's disease diagnosed before the age of 60 years; 3.07 [1.65–5.70]).

CONCLUSIONS—We found that a diagnosis of, or treatment received for, diabetes was significantly associated with an increased risk of developing Parkinson's disease, especially younger-onset Parkinson's disease. Our results suggest a common pathophysiologic pathway between the two diseases. Future studies should take age at Parkinson's disease onset into account.

P arkinson's disease is one of the most common aging-related neurodegenerative diseases, characterized by a progressive loss of dopamine-producing substantia nigra cells. The loss of dopamine and brain circuitry's compensatory actions lead to a broad spectrum of motor and nonmotor features, including muscle rigidity, slowing of physical movement, sensory dysfunction, behavioral abnormalities, autonomic impairment, and sleep disturbances (1), all of which have a dramatic impact on quality of life in these elderly patients.

Some preliminary evidence emerged that midlife occurrence of adult-onset diabetes may result in neurodegenerative diseases, including Parkinson's disease (2). Whether this association might in part be explained by common pathophysiologic pathways currently is unknown (e.g., the *GIGYF2* gene involved in both IGF and insulin-signaling pathways recently has been identified as the *PARK11* gene, but current literature does not provide strong support for its role in Parkinson's disease). Nevertheless, it is well known that insulin plays an important role in

normal brain function, and insulin resistance may lead to neurodegenerative disease, as suggested by a large study (3) that reported a higher incidence of Alzheimer's disease in men who developed diabetes in midlife, particularly those without the apolipoprotein Eε4 allele known to increase the risk of Alzheimer's disease.

A number of previous observational studies (2,4–16) have evaluated the association between diabetes and Parkinson's disease and provided mixed results ranging from protective to no or positive associations. The aim of this specific analysis was to examine whether a history of diabetes and, as such, insulin resistance is linked to Parkinson's disease. Adding to previous literature, ours is the first and largest study to examine whether the type of treatment with antidiabetes drugs differentially affects the risk of developing Parkinson's disease. Our investigation was based on a large population-based case-control study in Denmark, using information on Parkinson's disease from the National Danish Hospital Register and documenting antidiabetes and anti-Parkinson's prescriptions on an individual level using a nationwide prescription database.

RESEARCH DESIGN AND METHODS

—Denmark's National Health Service provides free and equal access to health care for the entire population. Health services–related events are recorded in national databases, including the Danish Hospital Register and the Danish prescription database. Information from both registries can be linked to each other by the use of the unique 10-digit Central Population Registry number applied to all residents in Denmark.

We conducted a population-based case-control study. Parkinson's disease cases were ascertained from the computerized Danish Hospital Register, with all hospitalizations with Parkinson's disease diagnoses registered since 1977 and all clinic visits, including outpatient clinics, since 1995. Individual information on the date of death, disappearance, or emigration was obtained from the Central Population Registry. We identified 82,140 subjects (13,695 patients with Parkinson's

disease and 68,445 individuals without Parkinson's disease) in the Danish Hospital Register in the period 1986–2006 who 1) had a valid Central Population Registry number, 2) were aged >35 years at the time of diagnosis, and 3) had not emigrated from Denmark. However, to allow for long enough lag times between diabetes and Parkinson's disease, only individuals who were registered for the first time with a primary diagnosis of Parkinson's disease (ICD-10 code G20) between January 2001 and December 2006 (or had no previous hospitalization) were considered for inclusion as case subjects in our analyses. To more accurately define the "earliest date of a Parkinson's disease diagnosis," we dated the primary Parkinson's disease diagnoses back to either the first hospital or outpatient record that ever mentioned Parkinson's disease or the first prescription of Parkinson's disease medications (Anatomical Therapeutic Chemical [ATC] code N04B) since inception of the Danish Prescription Database (1995), whichever came first. Patients with Parkinson's disease whose backdated diagnosis date fell into the period prior to 2001 were excluded, leaving 2,188 patients with Parkinson's disease. Of these, we further excluded patients with Parkinson's disease who had never received a Parkinson's disease drug prescription (257 case subjects). To more efficiently control for confounding by the two most important risk factors for Parkinson's disease, we then individually matched five randomly selected control subjects (i.e., individuals without Parkinson's disease at the index date) from the Central Population Registry by sex and year of birth to each case subject, using incidence-density sampling (17). The date of Parkinson's disease diagnosis served as the index date for control selection. This left a total of 1,931 case subjects with Parkinson's disease and 9,651 control subjects for our primary analyses. In secondary analyses, to further examine the potential for disease misclassification, we excluded Parkinson's disease case subjects diagnosed with any type of dementia (both Alzheimer's type and unspecified for ICD-8 codes 29009–29011, 29018–29019, and 29309 and for ICD-10 codes F00.x, F03, and G30) or cerebrovascular disease (ICD-8 codes 430–438 and ICD-10 codes I60–I69 and G45–G46) in the 2 years preceding their Parkinson's disease diagnosis (135 case subjects) and case subjects who used neuroleptics (ATC codes N05AA, N05AB, N05AC, N05AD, N05AF, and N05AG)

in the 6 months preceding Parkinson's disease diagnosis (194 case subjects). Finally, we obtained a full history of hospitalization backdating to 1977 for all case and control subjects and calculated the Charlson comorbidity score, a weighted index of 19 medical conditions (18), with a lag-time of 5 years prior to index date as an indicator of baseline morbidity. The study protocol was approved by the Danish Data Protection Agency (no. 2002-41-2112) and the University of California Los Angeles Human Subject Review Board.

Assessment of diabetes diagnosis and antidiabetes drug use

Information on whether Parkinson's disease case and control subjects had a diabetes diagnosis prior to the index date was extracted by use of the Central Population Registry number from the National Danish Hospital Register using the ICD codes for diabetes (249 and 250.x for ICD-8 and E10–E14 for ICD-10). Because ICD misclassification of insulin-dependent diabetes (also known as type 1 diabetes, ICD-8 code 249 and ICD-10 code E10) and non–insulin-dependent diabetes (also known as type 2 diabetes, ICD-8 code 250 and ICD-10 codes E11–E14) is prevalent (19,20), and because of inconsistencies in diabetes codes between ICD-8 and ICD-10, we chose not to present stratified analyses by subtype of diabetes.

Since 1 January 1995, the Danish Prescription Database has received data on all dispensed prescriptions from pharmacies in Denmark, including the individual's Central Population Registry number, drug type by ATC code, and prescription dispensing date. Use of antidiabetes drugs by study subjects prior to the index date was extracted from this database, including ATC groups A10A (insulins and analogs), A10B (oral blood glucose–lowering drugs, including sulfonylureas [e.g., gliclazide] and biguanides [e.g., metformin]), and A10x (other drugs used in diabetes). We defined antidiabetes drug use as any filling of one or more prescriptions during the relevant period prior to the index date; nonusers never filled a single prescription. We also categorized study participants into insulin users versus oral diabetes medication users according to ATC code.

Statistical analysis

We used unconditional logistic regression to calculate odds ratios (ORs) and 95% CIs for diabetes, while adjusting for age

(continuous), sex, and chronic obstructive pulmonary disease (COPD; as a proxy for heavy smoking) diagnosis (ICD-8 codes 490.00, 491.00, 491.01, and 491.03 and ICD-10 code J44) identified in the Danish Hospital Register. Comorbidities registered before the index date (using the Charlson index) were based on ICD codes for 19 chronic disease categories recorded in the hospital records, including diabetes (18). Parameter estimates changed by <10% when controlling for the Charlson index in multivariate models, so it was excluded from additional analyses.

To further preclude the possibility of having included prevalent cases, for our primary analyses, we advanced (lagged) the index date for antidiabetes drug prescriptions or diagnosis of diabetes (using ICD codes) by 2 years (i.e., we excluded all first treatments and diagnoses of diabetes within a 2-year period prior to the index date). In addition, we performed nonlagged and 5-year-lagged analyses of Parkinson's disease. We lagged COPD by 5 years to capture the general health status of subjects prior to the index date. In secondary analyses, we stratified by age at first diagnosis (aged ≤60 and >60 years) and sex. In sensitivity analyses aimed at reducing Parkinson's disease misclassification, we excluded case subjects (and their matched control subjects) and all control subjects diagnosed with dementia or cerebrovascular disease 2 years prior to Parkinson's disease diagnosis of the index case.

RESULTS—Case subjects and their control subjects combined were on average 72.2 years of age (SD 10.2) at the index date. We identified more male than female subjects with a diagnosis of Parkinson's disease. Five years prior to the index date, case subjects had less COPD than control subjects, although this difference was not statistically significant (Table 1). At the index date, 6.4% of our study population had received a prescription for any type of oral antidiabetes medication or insulin; antidiabetes drug prescriptions included oral blood glucose–lowering drugs, including sulfonylureas (e.g., gliclazide [43.4%]) and biguanides (e.g., metformin [25.3%]) as well as insulin (26.6%), and 53% of subjects had received more than one type of antidiabetes prescription. The median length of time for receiving prescriptions for oral antidiabetes medication since 1995 and prior to the index date was 5.5 years for

Table 1—Characteristics of the Danish study population, 2001–2006

	Parkinson's disease case subjects	Control subjects
n	1,931	9,651
Age (years)	72.2 ± 10.5	72.2 ± 10.5
Sex		
Female	810 (41.9)	4,048 (41.9)
Male	1,121 (58.1)	5,603 (58.1)
Birth year		
1900–1909	3 (0.2)	15 (0.2)
1910–1919	254 (13.2)	1,269 (13.2)
1920–1929	737 (38.2)	3,684 (38.2)
1930–1939	568 (29.4)	2,840 (29.4)
1940–1949	266 (13.8)	1,329 (13.8)
1950–1959	73 (3.8)	364 (3.8)
1960–1969	30 (1.5)	150 (1.5)
Age-group (years)		
30–40	15 (0.8)	68 (0.7)
41–50	59 (3.1)	298 (3.1)
51–60	183 (9.5)	921 (9.5)
61–70	438 (22.7)	2,190 (22.7)
71–80	753 (39.0)	3,769 (39.1)
81–90	455 (23.6)	2,279 (23.6)
>90	28 (1.5)	126 (1.3)
Charlson index*		
0	1,454 (75.3)	7,365 (76.3)
1	251 (13.0)	1,245 (12.9)
≥2	226 (11.7)	1,041 (10.8)
COPD*		
No	1,910 (98.9)	9,448 (97.9)
Yes	21 (1.1)	203 (2.1)

Data are n (%) or means ± SD. *Five-year lag: variables are ascertained 5 years prior to the index date or date of Parkinson's disease diagnosis; COPD is a proxy for heavy smoking; Charlson comorbidity score is a weighted index of 19 medical conditions.

case subjects and 5.2 years for control subjects and for insulin was 6.0 years among the case subjects versus 4.9 years in the control subjects.

In our main logistic regression analyses using a 2-year lag and relying on diabetes diagnoses based on ICD codes, we estimated an overall 36% increase in the risk of developing Parkinson's disease (95% CI 1.08–1.71) among those with diabetes (data not shown). In stratified analyses (with a 2-year lag), associations were slightly stronger in women (OR 1.50 [95% CI 1.02–2.22]) than in men (1.29 [0.97–1.72]) and mainly seen in all patients with early-onset Parkinson's disease (i.e., aged <60 years at Parkinson's disease diagnosis; 2.68 [1.04–6.91]) compared with those with late-onset Parkinson's disease (i.e., aged ≥60 years at Parkinson's disease diagnosis; 1.16 [0.85–1.57]).

Relying on antidiabetes drug use to identify participants with diabetes, we found strikingly similar associations,

suggesting a positive association for Parkinson's disease for those who had ever used antidiabetes drugs >2 years prior to Parkinson's disease onset (OR 1.35 [95% CI 1.10–1.65]) (Table 2). In analyses based on 0-year and 5-year lags instead, our risk estimates were comparable in size (0-year lag: 1.21 [1.00–1.47]; 5-year lag: 1.35 [1.07–1.72]). Overall, these associations were somewhat stronger for users of oral diabetes medication than for insulin users (OR 1.37 vs. 1.22) (see Table 2).

In stratified analyses (with a 2-year lag), risk estimates differed for men and women and also for those younger (aged <60 years) or older (aged ≥60 years) at diagnosis/index date, whereas the risk of developing Parkinson's disease associated with the use of any type of antidiabetes drug was very similar for men and women (men: OR 1.33 [95% CI 1.03–1.72]; women: 1.38 [0.99–1.92]); among those using oral diabetes medication, only women were at higher risk of

developing Parkinson's disease (men: 0.74 [0.37–1.50]; women: 2.92 [1.34–6.36]). By contrast, men with diabetes who use insulin experienced a 48% higher risk of developing Parkinson's disease (1.48 [1.13–1.95]), whereas the risk was slightly lower in women (1.20 [0.83–1.74]). Similar to our ICD code–based results, when stratifying by age at onset of Parkinson's disease (aged <60 years vs. ≥60 years at onset), the risk of Parkinson's disease was much higher among patients with diabetes using antidiabetes drugs in early onset (3.07 [1.65–5.70]) than in late-onset Parkinson's disease (1.24 [0.99–1.53]). On closer examination, this difference tended to be largely attributed to insulin use, as opposed to the use of oral antidiabetes medications: for early-onset Parkinson's disease (albeit based on two cases only), the risk associated with insulin use was 3.74 (1.89–7.38) and 1.32 (0.28–6.26) for use of oral antidiabetes medication, whereas these risks were 1.24 (0.98–1.57) and 1.21 (0.71–2.06), respectively, for late-onset Parkinson's disease. Generally, these associations tended to be attenuated in 0-lag analyses and slightly stronger in the 5-year lag analyses (data not shown). When we further stratified by sex, albeit based on small case numbers, we found these associations particularly for oral antidiabetes medications (we did not have enough power to examine this for insulin use), again stronger for early-onset Parkinson's disease, regardless of sex.

In sensitivity analyses, we excluded Parkinson's disease patients and control subjects diagnosed with dementia or cerebrovascular diseases 2 years prior to the index date, but the risk estimates changed only minimally (data not shown). Similarly, excluding case subjects with neuroleptic use within 6 months prior to Parkinson's disease diagnoses did not alter our findings substantially (OR for any use of antidiabetic drugs 1.26 [95% CI 1.01–1.56]).

CONCLUSIONS—We identified all case subjects with a primary diagnosis of Parkinson's disease in Denmark from hospital and outpatient clinic records between 2001 and 2006. In our analyses, both ICD code–based hospital and outpatient clinic reports of diagnoses of diabetes (which does not allow us to distinguish between type 1 and type 2 diabetes), as well as the use of antidiabetes drugs (which, to some degree, allows us to distinguish between type 1 and type 2

Table 2—*Association between diabetes (2-year lag, i.e., diabetes was present at least 2 years prior to the index date) and Parkinson's disease**

	Case subjects (n = 1,931)	Control subjects (n = 9,651)	Adjusted model 1	Adjusted model 2
Overall				
No diabetes	1,805	9,169	1.0	1.0
Diabetes	126	482	1.33 (1.09–1.63)	1.35 (1.10–1.65)
Men				
No diabetes	1,042	5,298	1.0	1.0
Diabetes	79	305	1.32 (1.02–1.70)	1.33 (1.03–1.72)
Women				
No diabetes	763	3,871	1.0	1.0
Diabetes	47	177	1.35 (0.97–1.88)	1.38 (0.99–1.92)
Early-onset Parkinson's disease (aged <60 years at Parkinson's disease diagnosis)				
No diabetes	240	1,257	1.0	1.0
Diabetes	17	29	3.09 (1.67–5.73)	3.07 (1.65–5.70)
Late-onset Parkinson's disease (aged ≥60 years at Parkinson's disease diagnosis)				
No diabetes	1,565	7,912	1.0	1.0
Diabetes	109	453	1.22 (0.98–1.51)	1.24 (0.99–1.53)
Analyses by type of antidiabetes drug prescription				
Overall				
No antidiabetes drug prescription	1,805	9,169	1.0	1.0
Insulin prescription	19	81	1.19 (0.72–1.97)	1.22 (0.74–2.02)
Oral antidiabetes drug prescription	107	401	1.36 (1.09–1.69)	1.37 (1.10–1.71)
Men				
No antidiabetes drug prescription	1,042	5,298	1.0	1.0
Insulin prescription	9	63	1.47 (1.12–1.94)	1.48 (1.13–1.95)
Oral antidiabetes drug prescription	70	242	0.73 (0.36–1.47)	0.74 (0.37–1.50)
Women				
No antidiabetes drug prescription	763	3,871	1.0	1.0
Insulin prescription	10	18	1.18 (0.82–1.70)	1.20 (0.83–1.74)
Oral antidiabetes drug prescription	37	159	2.82 (1.30–6.13)	2.92 (1.34–6.36)
Early-onset Parkinson's disease (aged <60 years at Parkinson's disease diagnosis)				
No antidiabetes drug prescription	240	1,257	1.0	1.0
Insulin prescription	2	8	3.77 (1.91–7.43)	3.74 (1.89–7.38)
Oral antidiabetes drug prescription	15	21	1.32 (0.28–6.25)	1.32 (0.28–6.26)
Late-onset Parkinson's disease (aged ≥60 years at Parkinson's disease diagnosis)				
No antidiabetes drug prescription	1,565	7,912	1.0	1.0
Insulin prescription	17	73	1.22 (0.97–1.55)	1.24 (0.98–1.57)
Oral antidiabetes drug prescription	92	380	1.18 (0.69–2.00)	1.21 (0.71–2.06)

Data are n or OR (95% CI). Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and COPD (lagged 5 years). *Diagnosis of diabetes based on any prescription of antidiabetes drugs (ATC codes).

diabetes, as individuals using oral diabetes medications only are likely to have type 2 diabetes), were positively associated with Parkinson's disease. These associations became stronger with longer lag times and showed differences in subgroup analyses (i.e., the associations were markedly stronger for early-onset Parkinson's disease, particularly for insulin use, vs. the risk for early-onset diabetes and was more modest when oral antidiabetes drugs were used to treat diabetes).

Among female subjects, oral antidiabetes drugs were more strongly associated with overall risk of Parkinson's disease than among men, and oral antidiabetes drugs also appeared to drive the association with early-onset diabetes in men.

Observational studies that previously examined associations between diabetes and Parkinson's disease have produced mixed results. Although most of the published epidemiologic studies reported a positive association between diabetes

and Parkinson's disease (2,9,10,13) or Parkinsonian signs (5) and drug-induced Parkinsonism (4), some studies reported no association (6,11) and others even inverse associations (7,12).

A cross-sectional study of 791 patients with Parkinsonism that had linked U.S. National Survey data of 24,831 elderly to 1.9 million Medicare claims found that those with Parkinsonism had a 50% (men) to 70% (women) higher risk of concurrent diabetes (13). In a selected

group of 1,030 U.S. elderly subjects without a diagnosis of Parkinson's disease, diabetes was found to be associated with a more severe score of global Parkinsonian signs, which was used to determine the degree of motor dysfunction (5). Similar to our results, these researchers also found the association of diabetes with Parkinsonian signs to be similar among men and women but stronger in younger compared with older patients (5).

By contrast, in a case-control study of 490 Parkinson's disease patients derived from a neurologist's private-practice database, the prevalence of diabetes was found to be similar in those with and without Parkinson's disease (12.9 vs. 12.1%) (11). Three small case-control studies of 352 (12), 318 (7), and 178 (14) newly diagnosed patients with Parkinson's disease reported inverse associations with diabetes prior to Parkinson's disease (OR 0.52 for men with diabetes vs. OR 0.80 for women with diabetes in the first, OR 0.40 in the second, and OR 0.30 in the third study). Moreover, a study based on the U.K. General Practice Research Database reported the diabetes prevalence to be similar in patients with and without Parkinson's disease and the risk of developing diabetes to be lower in Parkinson's disease patients (6). In the most recent retrospective study, a hospital-based case-control study conducted in Japan (16) and comprising 250 new-onset Parkinson's disease (within 6 years of diagnosis), a decreased risk of Parkinson's disease was observed among individuals with a history of diabetes (OR 0.38 [95% CI 0.17–0.79]). This risk did not vary by sex; however, neither was age at onset of Parkinson's disease nor type of medication used taken into account in this retrospective analysis.

The few prospective studies that evaluated associations between diabetes and Parkinson's disease published to date tended to report positive associations between the two conditions. In a prospective study of 51,552 Finnish men and women, a diabetes diagnosis at baseline was associated with an 85% increased risk of developing Parkinson's disease (9). Based on data from two large prospective cohorts, the Nurses' Health Study cohort and the Health Professionals Follow-up Study (15), the relative risk for developing Parkinson's disease was 1.12 (95% CI 0.69–1.81) among those with a baseline history of diabetes. The most detailed study to date was conducted by Driver et al. (8), who used data from a large male prospective cohort, the Physicians' Health Study. The authors describe an overall increased risk of Parkinson's disease associated with diabetes (1.34 [1.01–1.77]), a relative risk strikingly similar in magnitude to our own findings. However, in contrast to our own results, they reported that most of the excess diabetes risk occurred in the year prior to and the year of Parkinson's disease diagnosis and speculated that this positive association may therefore either be driven by surveillance bias or by a common underlying biologic mechanism causing both diseases and yet to be determined. In our study, we excluded both first diabetes diagnoses based on ICD codes as well as antidiabetes drug use by up to 5 years prior to index date and found that associations tended to become stronger with such lagging, especially when using antidiabetes medications to identify diabetic case subjects.

In a previous publication based on the same Danish dataset, we explored associations between autoimmune diseases, including insulin-dependent diabetes defined by ICD-8 code 249 and Parkinson's disease risk during a longer period of observation (1986–2006) (21). On the basis of ICD codes alone, we observed a higher risk of Parkinson's disease (OR 1.6 [95% CI 1.02–2.5]) only in women, whereas no association was apparent among men using insulin (0.8 [0.5–1.2]) when lagging the diabetes diagnoses by 5 years. Differences in the present results are likely attributed to the different types of diabetes included in the studies (only insulin-dependent diabetes in the previous study and both insulin and non–insulin dependent diabetes in this study) and possibly also our use of a more refined Parkinson's disease definition based on a combination of Parkinson's disease ICD codes and Parkinson's disease drug prescriptions in the current study.

Insulin has been implicated in Alzheimer's disease risk. Whether this is primarily a result of vessel damage caused by long-term elevated blood glucose levels as the primary mechanism behind these associations is currently unknown. However, given that Parkinson's disease is not primarily a vascular disease, we speculate that an association between diabetes and Parkinson's disease, as found in our study, could suggest a different pathway, especially because the associations seemed to be stronger in younger-onset Parkinson's disease (i.e., patients less likely to be affected by cerebrovascular disease). One such pathway might be related to vitamin D levels, which have been implicated in both diseases (i.e., it has been suggested that Vitamin D lowers both the risk of Parkinson's disease and type 2 diabetes) (22–24).

We found substantial differences in estimated effect size between diabetes and Parkinson's disease by age at onset of Parkinson's disease, although this difference is based on small numbers of patients with early onset. Only one previous study, examining the association between diabetes and Parkinsonian signs, was able to address this, and they too report the association between diabetes with Parkinsonian signs to be stronger in younger compared with older patients (5). Although there also were differences for insulin users versus oral diabetes medication users in relation to Parkinson's disease by sex and age at onset, statistical power issues limited our ability to explore these substrata in greater detail. Overall, the stronger associations with early-onset Parkinson's disease are suggestive of a common genetic origin and might serve as an explanation as to why previous studies were contradictory, as they were not able to stratify according to early- or late-onset Parkinson's disease.

Recently, an intriguing hypothesis emerged that may link Parkinson's disease and diabetes via the mitochondrial dysfunction pathway. Mitochondrial dysfunction has long been suggested as a pathway in Parkinson's disease. Neurons in the substantia nigra (Parkinson's disease) as well as pancreatic islet β-cells (affected in diabetes) have been described as cells with low respiratory capacity/low mitochondrial capacity and therefore have a greater sensitivity to defects or impairments in mitochondrial respiratory chain enzymes than other cells with higher respiratory capacity. Thus, both cell types (substantia nigra and islet β-cells) are more vulnerable to defects or toxins that further diminish the capacity to generate ATP when the mitochondrial genome accumulates genetic lesions during aging. In a study comparing 64 Japanese centenarians to 61 patients with Parkinson's disease (25), Tanaka (25) found a by-far-greater frequency of deleterious mitochondrial variants and a much greater variety of amino acid replacements among Parkinson's disease patients; in contrast, such variations were absent in centenarians. Given the above-mentioned bioenergetic similarity of substantia nigra and pancreatic islet β-cells in terms of their ability to respond

to mitochondrial impairment, this could provide a pathogenetic link between Parkinson's disease and diabetes.

Strengths of our study are that control subjects were selected at random from a population registry and did not have to volunteer information for our study, thus avoiding bias attributed to selective nonparticipation. We required that all Parkinson's disease case subjects had been admitted at least once with a primary diagnosis of Parkinson's disease, and, whenever possible, we dated diagnoses back to the likely earliest diagnosis (e.g., a first prescription of Parkinson's disease medications).

Limitations include some disease misclassification because primary Parkinson's disease diagnoses were identified from hospital records that may have included some cases of nonidiopathic Parkinsonism. Sensitivity analyses in which we excluded Parkinson's disease case subjects with prior diagnoses of dementia and cerebrovascular diseases in the 2 years before Parkinson's disease diagnosis, and Parkinson's disease case subjects with neuroleptic use in the 6 months preceding diagnosis suggested the bias to be minimal. We might have selected less healthy Parkinson's disease case subjects more likely to be hospitalized than Danish Parkinson's disease patients seen exclusively by private practitioners without ever attending a specialty clinic before 2007. The slightly higher Charlson index and greater number of cardiovascular disease drug prescriptions among our study's Parkinson's disease patients compared with control subjects 2 years prior to and at the index date (data not shown) supports, albeit only modestly, the possibility for such a selection bias. However, differences in general health status were not evident 5 years prior to Parkinson's disease diagnosis/index date. The universal coverage of most health care expenses in Denmark, including partial reimbursement of costs for prescribed drugs, makes it less likely that antidiabetes drug prescriptions or Parkinson's disease diagnoses were influenced by factors determining access to care. In addition, we may have missed diabetes case subjects who never took any antidiabetes drugs; however, results from ICD-based diabetes diagnoses were very similar to those based on antidiabetes drug use. We were unable to fully control for smoking, known for its strong negative association with Parkinson's disease, although our adjustment for COPD as a proxy for heavy smoking may have, at least partly, controlled for smoking.

In summary, evidence is accruing for an association between diabetes and Parkinson's disease. Whether this association is causal or a result of a common pathophysiologic pathway still needs to be determined, although a common biologic pathway appears to be the most plausible explanation at this point. Future studies of the association between diabetes and Parkinson's disease should take age at onset of Parkinson's disease into account.

References

1. Pfeiffer RF. Non-motor parkinsonism. Parkinsonism Relat Disord 2007;13(Suppl. 3): S211–S220
2. Sandyk R. The relationship between diabetes mellitus and Parkinson's disease. Int J Neurosci 1993;69:125–130
3. Rönnemaa T. Intensive glycemic control and macrovascular disease in type 2 diabetes: a report on the 44th Annual EASD Meeting, Rome, Italy, September 2008. Rev Diabet Stud 2008;5:180–183
4. Ma HI, Kim JH, Chu MK, et al. Diabetes mellitus and drug-induced Parkinsonism: a case-control study. J Neurol Sci 2009; 284:140–143
5. Arvanitakis Z, Wilson RS, Bienias JL, Bennett DA. Diabetes and parkinsonian signs in older persons. Alzheimer Dis Assoc Disord 2007;21:144–149
6. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Diabetes in patients with idiopathic Parkinson's disease. Diabetes Care 2008;31:1808–1812
7. D'Amelio M, Ragonese P, Callari G, et al. Diabetes preceding Parkinson's disease onset: a case-control study. Parkinsonism Relat Disord 2009;15:660–664
8. Driver 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
9. 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
10. Lipman IJ, Boykin ME, Flora RE. Glucose intolerance in Parkinson's disease. J Chronic Dis 1974;27:573–579
11. Nataraj A, Rajput AH. Parkinson's disease, stroke, and related epidemiology. Mov Disord 2005;20:1476–1480
12. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. Diabetes, smoking, and other medical conditions in relation to Parkinson's disease risk. Parkinsonism Relat Disord 2006;12:185–189
13. Pressley JC, Louis ED, Tang MX, et al. The impact of comorbid disease and injuries on resource use and expenditures in parkinsonism. Neurology 2003;60: 87–93
14. Scigliano G, Musicco M, Soliveri P, Piccolo I, Ronchetti G, Girotti F. Reduced risk factors for vascular disorders in Parkinson disease patients: a case-control study. Stroke 2006;37:1184–1188
15. Simon KC, Chen H, Schwarzschild M, Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. Neurology 2007;69:1688–1695
16. Miyake Y, Tanaka K, Fukushima W, et al. Case-control study of risk of Parkinson's disease in relation to hypertension, hypercholesterolemia, and diabetes in Japan. J Neurol Sci 2010;293:82–86
17. Ritz B, Rhodes SL, Qian L, Schernhammer E, Olsen JH, Friis S. L-type calcium channel blockers and Parkinson disease in Denmark. Ann Neurol 2010;67:600–606
18. Charlson ME, Sax FL, MacKenzie CR, Braham RL, Fields SD, Douglas RG Jr. Morbidity during hospitalization: can we predict it? J Chronic Dis 1987;40:705–712
19. Elks ML, Sawyer JW Jr. Misunderstanding in the classification of diabetes mellitus: what's in a name? West J Med 1993;159: 44–49
20. Svensson J, Marinelli K, Eising S; Danish Childhood Diabetes Register; National Discharge Register. Comparison of registration of data from the Danish Childhood Diabetes Register and The National Discharge Register. Ugeskr Laeger 2007;169: 122–125
21. Rugbjerg K, Friis S, Ritz B, Schernhammer ES, Korbo L, Olsen JH. Autoimmune disease and risk for Parkinson disease: a population-based case-control study. Neurology 2009;73:1462–1468

22. Knekt P, Laaksonen M, Mattila C, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology 2008; 19:666–671

23. Littorin B, Blom P, Schölin A, et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). Diabetologia 2006;49: 2847–2852

24. Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care 2006;29:650–656

25. Tanaka M. Mitochondrial genotypes and cytochrome b variants associated with longevity or Parkinson's disease. J Neurol 2002;249(Suppl. 2):II11–II18