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Type 2 diabetes and the risk of Parkinson's disease

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Objective- The aim of this study was to evaluate whether type 2 diabetes at baseline is a risk factor for Parkinson's disease.
Research design and methods- We prospectively followed 51 552 Finnish men and women of 25 to 74 years of age without a history of Parkinson's disease at baseline. History of diabetes and other study parameters were determined at baseline using standardized measurements. Ascertainment of the Parkinson's disease status was based on the nationwide Social Insurance Institution's Drug Register data. Hazards ratios of incident Parkinson's disease associated with the history of type 2 diabetes were estimated.
Result- During a mean follow up period of 18.0 years, 324 men and 309 women developed incident Parkinson's disease. Age-and study year-adjusted hazard ratios of incident Parkinson's disease among subjects with type 2 diabetes, compared to those without it, were 1.80 (95% CI 1.03-3.15) in men, 1.93 (95% CI 1.05-3.53) in women, and 1.85 (95% CI 1.23-2.80) in men and women combined (adjusted also for sex), respectively. Further adjustment for body mass index, systolic blood pressure, total cholesterol, education, leisure time physical activity, smoking, alcohol drinking, coffee and tea consumption affected the results only slightly. The multivariate adjusted association between type 2 diabetes and the risk of Parkinson's disease was also confirmed in stratified subgroup analysis.
Conclusion- These data suggest that type 2 diabetes is associated with an increased risk of Parkinson's disease. Surveillance bias might account for higher rates in diabetes. The mechanism behind this association between diabetes and Parkinson's disease is not known.

Type 2 diabetes is one of the fastest growing public health problems worldwide (1), and it is associated with multiple complications. Epidemiological studies have indicated that patients with type 2 diabetes present an excess risk of coronary heart disease compared with those without diabetes (2; 3). Evidence from prospective epidemiological studies has identified type 2 diabetes as an independent risk factor for multiple hyperglycaemia-induced complications virtually in all organs, including neurodegenerative diseases such diabetic neuropathy (4), stroke (5-8), dementia (9-11), and Alzheimer's disease (9-11). However, little is known about the association between diabetes and the risk of Parkinson's disease. Only a few cross-sectional studies and two case-control studies have examined the prevalence of diabetes among patients with Parkinson's disease (12-15), and no prospective epidemiological studies have thus far addressed this association. Recently, animal and in vitro studies have shown that insulin dysregulation and changes in insulin action have been concerned in the pathophysiology and clinical symptoms of Parkinson's disease (16). The aim of this study was to examine whether type 2 diabetes at baseline is a risk factor for Parkinson's disease in a large population-based prospective cohort of Finnish men and women.

Research design and methods

Participants

Six independent cross-sectional population surveys were carried out in five geographic areas of Finland in 1972, 1977, 1982, 1987, 1992 and 1997 (17). In 1972 and 1977, a randomly selected sample making up 6.6% of the population born between 1913 and 1947 was drawn. Since 1982, the sample was stratified by area, gender and 10-year age group according to the World Health Organization MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol (18). The subjects included in the six surveys were 25 to 64 years of age, and the 1997 survey also included subjects aged 65 to 74 years. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the six surveys was 53 166. The participation rate varied by year from 74% to 88% (17). After excluding 123 subjects due to prevalent Parkinson's disease at baseline, 112 subjects due to prevalent type 1 diabetes at baseline or during follow-up, and 1379 subjects due to incomplete data on any variables required, the present analyses comprises 25 168 men and 26 384 women. The participants gave an informed consent (verbal 1972-1992 and signed 1997). These surveys were conducted according to the ethical rules of the National Public Health Institute and the investigations were performed in accordance with the Declaration of Helsinki.

Assessment of type 2 diabetes at baseline

Assessment of the history of type 2 diabetes was based on self-reporting and on the data of two nationwide registers. The National Hospital Discharge Register data included hospital discharge diagnoses since 1968. Data on diabetes medication were ascertained from the National Social Insurance Institution's Register on special reimbursement for anti-diabetic drugs from 1964. Anti-diabetic drugs prescribed by a physician are free of charge in Finland and are subject to approval of a physician of the Institution who reviews each case history. The physician confirms the diagnosis of diabetes applying the WHO criteria: one or more classic symptoms plus a fasting plasma glucose level ≥7.8 mmol/l (≥7.0 mmol/l from 1998) or the oral glucose tolerance test ≥11.1 mmol/l; at least 1 raised plasma glucose concentrations on a fasting plasma glucose level ≥7.8 mmol/l (≥7.0 mmol/l from 1998) or the oral glucose tolerance test ≥11.1 mmol/l in the absence of symptoms; or treatment with a hypoglycemic drug (oral antidiabetic agents or insulin) (19; 20). All patients receiving free medication were entered into a register maintained by the Social Insurance Institution. Subjects who reported having diabetes on the questionnaire, or who had had a hospital discharge with a diagnosis of diabetes, or the approval for free-of-charge medication for diabetes before the baseline survey, were classified as having the history of diabetes at baseline.

Diagnosis of Parkinson's disease

Ascertainment of the Parkinson's disease status was based on the National Social Insurance Institution's Register on special reimbursement for Parkinson's disease drugs during 1964 through December 31, 2002. Similarly to diabetic patients, all patients diagnosed with Parkinson's disease are entitled for free-of-charge drugs. According to the criteria set by the Institution the diagnosis is based on medical history, clinical examination (tremor, bradykinesia, stiffness etc) and other relevant diagnostic methods. The diagnosis needs to be done by a consultant (usually a specialist in neurology). Intention tremor or essential tremor does not justify for special reimbursement according to the criteria. Tremor caused by neuroleptic drugs justified for reimbursement exceptionally. A detailed written statement from the physician in charge of the treatment verifying the clinical course and the diagnostic facts is needed in order to obtain the right to this special reimbursement. The statement is submitted to the Institution and reviewed by the Institution's specialist. Thus, the patient is included in the register only if the diagnosis is agreed independently by two specialist physicians. It is possible that some mild cases of Parkinson's disease have not been qualified for the special reimbursement of drugs. All patients receiving free-of-charge medication are entered into a register maintained by the Social Insurance Institution. The National Social Insurance Institution's Register data were linked to the risk factor data using the unique ID-numbers assigned to every resident of Finland. Follow-up of each cohort member continued until the date of the diagnosis of Parkinson's disease, death, or December 31, 2002. This diagnosed method has been used in several studies in Finland (21).

Covariates

A self-administered questionnaire was sent to the participants to be completed at home. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits, and alcohol, coffee and tea consumption. Education level, measured as the total number of school years, was divided into birth cohort specific tertiles. A detailed description of the questions about leisure time physical activity has been presented elsewhere (22-29). Self-reported leisure time physical activity was classified into three categories: low, moderate, or high. Based on the questionnaire data, the participants were classified as never, ex- and current-smokers. Current smokers were further categorized according to the amount of cigarettes smoked daily (1-9, 10-19, or ≥20 cigarettes per day). Coffee consumption was categorized into five categories: none, 1-2 cups, 3-4 cups, 5-6 cups, and ≥7 cups per day (29; 30). Tea consumption was categorized into three categories: none, 1-2 cups, and ≥3 cups per day because only a few persons drank tea. Since questions on alcohol consumption were different between the first two surveys (1972 and 1977) and the later surveys, alcohol consumption was categorized into two categories: yes and no.

At the study site, nurses specially trained for survey methodology measured height, weight, and blood pressure using the standardized protocol according to the WHO MONICA project (18). Blood pressure was measured with a standard sphygmomanometer from the right arm of the participant who was seated for 5 minutes before the measurement. Height was measured without shoes and weight was measured with light clothing. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. After blood pressure measurement, a venous blood specimen was drawn. Serum total cholesterol concentration was determined in the same laboratory for all surveys; Lieberman Burchard method was used in 1972 and 1977, and an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany) since 1982. Because the enzymatic method gave 2.4% lower values than the Lieberman Burchard method, 1972 and 1977 values were corrected by this percentage.

Statistical analyses

Sex-specific differences in risk factors based on the history of type 2 diabetes were tested using analysis of variance or logistic

regression after adjustment for age and study year. The association between the history of type 2 diabetes and the risk of Parkinson's disease was analyzed by using Cox proportional hazards models. All analyses were adjusted for age, study year, BMI, systolic blood pressure, total cholesterol, education, leisure time physical activity, smoking, alcohol drinking, coffee and tea drinking. Since the interactions between sex and the history of type 2 diabetes on the risk of Parkinson's disease were not statistically significant, data for men and women were combined in some analyses. To avoid the potential bias due to early diagnosis of Parkinson's disease or early mortality with a potential subclinical disease, additional analyses were carried out excluding the subjects who were diagnosed with Parkinson's disease or those who died from any cause during the first five years of follow-up. Finally, to assess the potential effect of secondary Parkinsonism or vascular Parkinsonism, additional sensitivity analyses were conducted after excluding subjects, who had stroke or coronary heart disease or who used neuroleptic drugs either at baseline or during the follow-up. Statistical significance was considered to be $P<0.05$. All statistical analyses were performed with SPSS for Windows 14.0 (SPSS Inc, Chicago, III).

Results

At baseline, 591 men and 507 women were identified as having a history of type 2 diabetes. General characteristics of the study population are presented in Table 1. Men and women with the history of type 2 diabetes were older, their BMI and baseline systolic blood pressure were higher, and they had lower levels of serum total cholesterol, were less often alcohol drinkers, less often smokers, and more physically inactive than those without diabetes.

During a mean follow up period of 18.0 years, 324 men and 309 women developed incident Parkinson's disease. The average ages at the time of diagnosis were 64.3 years in men and 65.8 years in women. Age-and study year-adjusted hazard ratios of incident Parkinson's disease in persons with type 2 diabetes, compared with persons without it, were 1.80 (95% CI 1.03-3.15) in men, 1.93 (95% CI 1.05-3.53) in women, and 1.85 (95% CI 1.23-2.80) in men and women combined (adjusted also for sex), respectively (Table 2). Further adjustment for BMI, systolic blood pressure, total cholesterol, education, leisure time physical activity, smoking, alcohol drinking, coffee and tea consumption affected the results only slightly.

After exclusion of participants who were diagnosed with Parkinson's disease during the first five years of follow-up or who died during this period (n=1341), sex- and multivariate-adjusted hazard ratio of Parkinson's disease in persons with type 2 diabetes, compared with persons without it, was 1.88 (95% CI 1.19-2.99). After exclusion of participants who were diagnosed with stroke at baseline and during follow-up (n=3049), sex- and multivariate-adjusted type 2 diabetes associated hazard ratio of Parkinson's disease was 2.00 (95% CI 1.29-3.11). After further exclusion of participants who were diagnosed with coronary heart disease at baseline (n=1150), sex- and multivariate-adjusted type 2 diabetes associated hazard ratio of Parkinson's disease was 1.94 (95% CI 1.21-3.11). Moreover, after exclusion of participants who used neuroleptic medications at baseline or during follow-up (n=1817), sex- and multivariate-adjusted type 2 diabetes associated hazard ratio of Parkinson's disease was 1.92 (95% CI 1.21-3.06).

Table 3 shows the association of type 2 diabetes with the risk of Parkinson's disease in different subgroups. Sex- and multivariate-adjusted direct association between the history of type 2 diabetes and the risk of Parkinson's disease was present in smokers. The association was strongest in diabetic patients aged 25-44 years and statistically significant also in those aged 45-54 years at baseline. There were no significant interactions between age and diabetes on risk of Parkinson's disease.

Conclusions

In this large prospective study, the type 2 diabetes was associated with an increased risk of Parkinson's disease among Finnish men and women. This association was independent of the known modifying factors such as the smoking status, coffee and alcohol drinking, and body weight. The multivariate-adjusted association was present both in subjects aged 25-44 years and 45-54 years, and in smokers.

The present study is, to our knowledge, the first large prospective study to find out that type 2 diabetes is a risk factor of Parkinson's disease. In one longitudinal study examining the association of diabetes at baseline with the progression of parkinsonian-like signs, the investigators observed that diabetes was associated with worsening rigidity and gait but was not associated with an increased risk of bradykinesia or tremor (31). The presence of stroke did not substantially affect the association of diabetes with rigidity but reduced the association of diabetes with gait (31). Until now, only a few cross-sectional studies and two case-control studies have examined the prevalence of diabetes among patients with Parkinson's disease. It has been reported in one review by Sandyk (12), that over half of patients with Parkinson's disease have abnormal glucose tolerance. In a national survey of 24 831 U.S. elderly adults, the investigators found that the prevalence of diabetes among adults with Parkinson's disease was higher compared with people without Parkinson's disease (13). In two case-control studies, the prevalence of diabetes among patients with Parkinson's disease was lower compared with control group (14; 15). A moderately reduced risk of Parkinson's disease was associated with diabetes among men but not women in one case-control study (14). In another case-control study, diabetes was significantly associated with a reduced risk of Parkinson's disease in the univariate analysis but not in the multivariate analysis (15). Several reasons for the inconsistency of these two case-control studies with our study can be considered. First, potential recall bias, in the case of Parkinson's disease, could be substantial because patients often experience cognitive decline and tend to gradually change their lifestyles prior to the diagnoses. It has been shown that patients with Parkinson's disease often will develop dementia, but in their paper all patients with Parkinson's disease were newly diagnosed and authors did not report any cases of dementia among patients with Parkinson's disease (14; 15). In the present study, we also have no information about the dementia and Alzheimer's disease. Second, the risk effect of diabetes on Parkinson's disease could be diminished in a case-control study due to survival bias associated with high mortality among diabetic patients. Third, the authors did not differentiate between type 1 and type 2 diabetes in one case-control study (14). Fourth, there is a possibility for a reverse causality, i.e. that the development of Parkinson's disease may influence risk factors for diabetes as seen to happen for other chronic diseases such as Alzheimer's disease (32; 33). Finally, they did not measure some important factors which are associated with both type 2 diabetes and Parkinson's disease, such as coffee and alcohol consumption, BMI, serum lipids, physical activity, etc (14; 15).

Even though the mechanism of the association between the history of type 2 diabetes and the risk of Parkinson's disease is poorly understood, several putative mechanisms can be proposed. Animal and in vitro studies have shown a role for insulin in the regulation of brain dopanergic activity. Insulin and dopamine may exert reciprocal regulation (16). Recently, insulin dysregulation and changes in insulin action has been concerned in the pathophysiology and clinical symptoms of Parkinson's disease (16).

Several lifestyle factors are associated both with the risk of type 2 diabetes and Parkinson's disease. Cigarette smoking increases the risk of type 2 diabetes, where as some studies have suggested an inverse association between cigarette smoking and the risk of Parkinson's disease (34). Coffee drinking (caffeine) is known to reduce the risk of Parkinson's disease (34). Although total alcohol intake has been found no association with the risk of Parkinson's disease in the Health Professionals Follow-up Study and the Nurses' Health Study,

the combined analysis of these two studies found that beer drinkers had a 30% lower incidence of Parkinson's disease than non-beer drinkers (35). A significantly inverse association between leisure time physical activity and the risk of Parkinson's disease has been found among men in the Health Professionals Follow-up Study but not among women in the Nurses' Health Study (36). In the present study, Finnish men and women with the history of type 2 diabetes were less often alcohol drinkers, less often smokers, and were less active than people without diabetes. However, there were no differences in coffee consumption between Finnish subjects with and without type 2 diabetes. In our study we took into account the possible effect of all lifestyle factors by adjusting for baseline habits of tea consumption, coffee and alcohol consumption, smoking, and leisure time physical activity in the data analyses.

It could also be hypothesized that diabetes might increase the risk of Parkinson's disease partly through excess body weight. A statistically significant direct association between triceps skinfold thickness and the risk of Parkinson's disease has been found in the Honolulu Heart Program including 7990 Japanese-American men in Hawaii (37). We have demonstrated that excess weight, defined as a BMI of 23 or more, is associated with an elevated risk of Parkinson's disease in the same study population (21). In the present study, Finnish men and women with the history of type 2 diabetes had a significant higher baseline BMI than those without diabetes. However, we found that the association between the history of type 2 diabetes and the risk of Parkinson's disease was independent of baseline BMI. The relative risk of Parkinson's disease was the lowest among the baseline oldest subjects in whom the prevalence of Parkinson's disease is the highest. Dose the risk of Parkinson's disease depend on the length of exposure for diabetes? One explanation could be that lifestyle or other possible factors such as insulin dysregulation may need a longer period to show their effects on the dopaminergic system.

There are several strengths and limitations in our study. The study was population-based, and was based on a large number of men and women from a homogeneous population. The mean follow-up, 18.0 years, was long. The sample included the largest number of patients with Parkinson's disease reported in any prospective study to date; thus statistical power in our study was high. Cerebrovascular disorders, coronary heart disease and certain drugs are among the important causes of secondary parkinsonism and vascular Parkinsonism (38-40). Exclusion of subjects with stroke or coronary heart disease or those who used neuroleptic drugs did not attenuate the association between type 2 diabetes and the Parkinson's disease risk. The main limitations of our study included the absence of information in surveillance of diabetic patients from non-diabetic patients during the follow-up. Second, since we did not carry out either fasting glucose measurement or a glucose tolerance test at the baseline, we have missed some cases of asymptomatic or diet-treated diabetes. Third, we did not have data on the severity and duration of diabetes, glucose control and the type of drugs used for the treatment of diabetes. Fourth, because our data allowed for only a dichotomized measure of alcohol consumption in our sample, we may not have been able to control fully for the effect of this variable on the risk of Parkinson's disease. Fifth, patients with type 2 diabetes are more prone to other diseases and are therefore likely to be in contact with the health care system more often than people without diabetes. Increased surveillance of patients with diabetes for other medical conditions, including neurologic disorders like Parkinson's disease, could also have contributed to higher rates than among patients without diabetes, who tend to be under less intense, long-term medical scrutiny. This could result in ascertainment bias. However, we think this is less likely in Parkinson's disease, because Parkinson's disease symptoms are clearly defined, and likely to bring a subject to the attention of the medical system. It could also be the case that diabetes associated co-morbidities exacerbate Parkinson's disease symptoms, so that diabetic patients with Parkinson's disease are

more likely to reach the threshold at which they qualify for special reimbursement of drugs, and thus be included in our sample. Sixth, we can not completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured factors. Finally, we can neither exclude a shared environmental nor genetic background of diabetes and the risk of Parkinson's disease.

In conclusion, our study demonstrated that type 2 diabetes was associated with an elevated risk of Parkinson's disease among men and women independently of other potential confounding factors. The biological mechanisms behind the association of type 2 diabetes with the risk of Parkinson's disease are, however, not understood at the present. Further studies to replicate our findings in other populations should be acknowledged.

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Table 1- Baseline characteristics according to history of type 2 diabetes

	Men			Women		
Characteristic	No diabetes	Diabetes	P Value	No diabetes	Diabetes	P Value
n	24 577	591		25 877	507	
Age (years)	44.4 ± 11.5	53.3 ± 10.6	<0.001	44.5 ± 11.3	52.9 ± 11.0	<0.001
Body mass index (kg/m^2)	26.3 ± 3.7	27.6 ± 4.4	<0.001	26.0 ± 4.7	28.4 ± 6.0	<0.001
Systolic blood pressure (mmHg)	143 ± 19	148 ± 23	<0.001	139 ± 23	145 ± 25	<0.001
Diastolic blood pressure (mmHg)	88 ± 12	88 ± 14	0.641	84 ± 12	85 ± 13	0.014
Serum total cholesterol (mmol/l)	6.2 ± 1.3	6.0 ± 1.4	<0.001	6.1 ± 1.3	6.0 ± 1.4	0.014
Education (years)	9.1 ± 3.9	9.1 ± 4.0	0.947	9.5 ± 3.9	8.9 ± 3.8	<0.001
Coffee consumption (cups/day)	5.3 ± 3.2	5.1 ± 3.1	0.171	4.6 ± 2.5	4.5 ± 2.4	0.134
Tea consumption (cups/day)	0.8 ± 1.4	0.7 ± 1.4	0.309	0.8 ± 1.2	0.7 ± 1.2	0.163
Alcohol drinker (%)	64.9	56.2	<0.001	35.2	22.7	<0.001
Low leisure time physical activity (%)	28.9	36.2	<0.001	38.2	47.9	<0.001
Current smoker (%)	42.5	34.7	<0.001	17.2	13.6	0.034

Data are means ± SD unless otherwise indicated and are adjusted for age and study year.

Table 2- Hazard ratio of Parkinson's disease according to history of type 2 diabetes

	Numbers of participants	Numbers of cases	Person-years	Hazard ratio (95% confidence interval)			
				Adjustment for age and study year	Multivariate adjustment*	Multivariate adjustment†	Multivariate adjustment‡
Men							
No prior diabetes	24,577	311	428,052	1.00	1.00	1.00	1.00
Prior diabetes	591	13	7125	1.80 (1.03-3.15)	1.78 (1.01-3.12)	1.79 (1.02-3.13)	1.78 (1.01-3.12)
Women							
No prior diabetes	25,877	298	485,518	1.00	1.00	1.00	1.00
Prior diabetes	507	11	7042	1.93 (1.05-3.53)	1.93 (1.05-3.54)	1.90 (1.04-3.49)	1.91 (1.04-3.52)
Men and women combined§							
No prior diabetes	50,454	609	913,570	1.00	1.00	1.00	1.00
Prior diabetes	1098	24	14,167	1.85 (1.23-2.80)	1.85 (1.22-2.79)	1.83 (1.21-2.76)	1.83 (1.21-2.76)

*Adjusted for age, study year, body mass index (<23, 23-24.9, 25-26,9, 27-29,9, and ≥30), systolic blood pressure, cholesterol, education, and leisure time physical activity (low, moderate, and high).
†Adjusted for age, study year, cigarette smoking (never, past, and current smoking of 1-9, 10-19 or ≥20 cigarettes/day), coffee consumption (none, 1-2, 3-4, 5-6, and ≥7 cups/day), tea consumption (none, 1-2, and ≥3 cups/day), and alcohol consumption (yes and no).
‡Adjusted for age, study year, body mass index (<23, 23-24.9, 25-26,9, 27-29,9, and ≥30), systolic blood pressure, cholesterol, education, leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-9, 10-19 or ≥20 cigarettes/day), coffee consumption (none, 1-2, 3-4, 5-6, and ≥7 cups/day), tea consumption (none, 1-2, and ≥3 cups/day), and alcohol consumption (yes and no).
§Also adjusted for sex.

Table 3- Hazard ratio of Parkinson's disease according to history of type 2 diabetes mellitus among various subpopulations

	Numbers of participants		Numbers of cases		Person-years		Hazard ratio (95% confidence interval)	
	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes
Age at baseline (years)								
25-44	25 391	217	162	4	508 691	3853	1.00	3.45 (1.27-9.37)
45-54	13 355	267	223	9	242 241	3896	1.00	2.88 (1.47-5.66)
55-74	11 708	614	224	11	162 637	6418	1.00	1.26 (0.68-2.32)
Smoking								
Never	27 466	574	373	13	519 144	7583	1.00	1.70 (0.98-2.98)
Ever or current	22 988	524	236	11	394 425	6584	1.00	1.94 (1.05-5.59)

Adjusted for age, sex, study year, body mass index (<23, 23-24.9, 25-26,9, 27-29,9, and ≥30), systolic blood pressure, cholesterol, education, leisure time physical activity (low, moderate, and high), cigarette smoking (never, past, and current smoking of 1-9, 10-19 or ≥20 cigarettes/d; except in smoking status analysis), coffee consumption (none, 1-2, 3-4, 5-6, and ≥7 cups/d), tea consumption (none, 1-2, and ≥3 cups/d), and alcohol consumption (yes and no).