

# Diabetes and Risk of Parkinson's Disease

## A systematic review and meta-analysis

EMANUELE CEREDA, MD, PHD<sup>1,2</sup>  
 MICHELA BARICHELLA, MD<sup>2</sup>  
 CARLO PEDROLI, MD<sup>3</sup>  
 CATHERINE KLERSY, MD, MSC<sup>4</sup>

ERICA CASSANI, MD<sup>2</sup>  
 RICCARDO CACCIALANZA, MD<sup>1</sup>  
 GIANNI PEZZOLI, MD<sup>2</sup>

**OBJECTIVE**—Diabetes has been associated with chronic neurodegeneration. We performed a systematic review and meta-analysis to assess the relationship between pre-existing diabetes and Parkinson's disease (PD).

**RESEARCH DESIGN AND METHODS**—Original articles in English published up to 10 May 2011 were searched for in electronic databases (PubMed, Embase, and Scopus) and by reviewing references of eligible articles. Prospective cohort and case-control studies providing risk and precision estimates relating to pre-existing diabetes and PD were considered eligible.

**RESULTS**—Nine studies/1,947 citations (cohort,  $N = 4$ ; case-control,  $N = 5$ ) fulfilled inclusion criteria for meta-analysis. In prospective studies, the onset of diabetes before onset of PD was found to be a risk factor for future PD (relative risk [RR] = 1.37 [95%CI 1.21–1.55];  $P < 0.0001$ ). This association was confirmed by secondary analyses based on estimates derived after the exclusion of participants who had vascular disease at baseline and/or who developed vascular disease during follow-up (RR = 1.34 [1.14–1.58];  $P < 0.001$ ) and by sensitivity analyses addressing the association with diabetes at baseline or during follow-up. However, the association found for case-control studies was not significant (odds ratio [OR] 0.75 [95%CI 0.50–1.11];  $P = 0.835$ ). Sensitivity analysis based on estimates adjusted for BMI confirmed the lack of a relationship between PD and diabetes (OR 0.56 [0.28–1.15];  $P = 0.089$ ).

**CONCLUSIONS**—Although data from cohort studies suggest that diabetes is a risk factor for PD, there is no conclusive evidence on this association. Further prospective studies focused on putative pathogenic pathways and taking a broad range of confounders into account is required to clarify this relationship.

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**P**arkinson's disease (PD) is a progressive and disabling motor disorder in which typical symptoms (bradykinesia, resting tremor, rigidity, and postural instability) are mainly a result of a reduction in dopaminergic activity of the substantia nigra in the midbrain. It is the second most common chronic neurodegenerative disease of aging people with an approximate ratio of 1:800–1,000 in subjects aged over 60 years (1,2). PD is regarded mainly as a sporadic

disorder. In the last 30 years, research on its pathogenesis has identified several potential contributing factors, suggesting that it is of multifactorial origin. Besides a number of genetic mutations, nutritional and metabolic factors appear to be involved (2–4). The relationship between diabetes and PD has been the subject of several studies that have yielded conflicting results (5–8). Along with this, various disease-related mechanisms have been suggested that are

involved in both the promotion of PD and protection against it (9,10).

Because information on the etiology of PD may improve clinical practice in terms of both prevention and treatment, the aim of this study was to systematically review the published literature relating to the role of diabetes as a risk factor for PD.

### RESEARCH DESIGN AND METHODS

The review and meta-analysis procedures were planned, conducted, and reported following the PRISMA guidelines (11).

### Literature search and study inclusion criteria

A literature search for all English language manuscripts published up to 10 May 2011 and focused on the relationship between diabetes and PD was performed independently by E.Ce. and C.P. Queried databases were as follows: PubMed (accessed 10 May 2011), Scopus (accessed 21 April 2011), and Embase (accessed 21 April 2011).

The search strategy included terms (free text and/or MeSH terms adapted to the requirements of each database) for diabetes (diabetes mellitus, diabetes mellitus type-2, diabetes mellitus type-1, glucose intolerance, and insulin resistance), and PD. We also searched the references of included articles for potential additional reports. Searching queries are listed in the Supplementary Data.

Both prospective (cohort) and case-control original studies investigating the role of diabetes as a risk factor for PD were potentially eligible for inclusion. Manuscripts were initially selected on the basis of the title and abstract. To be included in the quantitative analyses (meta-analysis), articles had to report at least a risk (relative risk [RR], or odds ratio [OR]) and a precision estimate (95% CI) relating pre-existing diabetes to subsequent incident PD or enough data to calculate them.

Thereafter, selected studies were assessed for quality (risk of bias) according to the following items: 1) for cohort studies, the systematic lack of case identification or bias in case ascertainment (for PD) and 2) for case-control studies, the exclusion of

From the <sup>1</sup>Nutrition and Dietetics Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; the <sup>2</sup>Parkinson Institute–Istituti Clinici di Perfezionamento, Milan, Italy; the <sup>3</sup>Dietetic and Clinical Nutrition Unit, Trento Hospital, Trento, Italy; and the <sup>4</sup>Biometry and Clinical Epidemiology Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

Corresponding author: Emanuele Cereda, e.cereda@smatteo.pv.it.

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Table 1—List and features of the prospective cohort studies included in quantitative analyses

Source [reference]	Cohort and features (nation)	Follow-up (years)	Age at inclusion (years)	Age at diagnosis of PD (years)	Risk of PD (95% CI)	Adjustment variables	Findings	Potential estimation bias
Hu et al. 2007 [6]	51,552 subjects without PD, and type 1 diabetes (Finland)	18.0 [mean]	25–74 [range]	Women: 65.8 Men: 64.3 [mean]	1.83 (1.21–2.76)	Age, sex, smoking, BMI, alcohol use, coffee and tea consumption, education, physical activity, systolic blood pressure, and total cholesterol (baseline)	Type 2 diabetes was associated with an increased risk of PD. In sensitivity analysis (exclusion of those who had vascular diseases at baseline or who developed stroke during follow-up [N = 47,353]) risk of PD was 1.94 [1.21–3.11].	Only baseline self-reported diabetes and confounders were included in risk analyses. Surveillance bias might account for higher rates in diabetes. Finally, as a result of case ascertainment procedure, it could not be excluded that few cases (mild untreated PD patients) were lost to identification.
Simon et al. 2007 [5]	171,879 subjects without prevalent stroke and PD at baseline (121,046 women [Nurses' Health Study] and 50,833 men [Health Professionals Follow-up Study]); participants developing stroke before PD onset were censored throughout the follow-up (U.S.)	Women: 22.9 Men: 12.6 [mean]	Women: 30–55 Men: 40–75 [range]	Women: 63.5 Men: 69.7 [mean]	1.04 (0.74–1.46)	Age, sex, and smoking. The adjustment for multiple updated (every 2 years) covariates [BMI, physical activity, alcohol, caffeine and energy intake, and comorbidities] produced similar results (data not shown)	Preceding diabetes (both type 1 and type 2) was not related to increased risk of PD. The association of baseline diabetes was also nonsignificant (RR = 1.12 [0.69–1.81]).	Data on diabetes were self-reported.

Table 1—Continued

Source [reference]	Cohort and features (nation)	Follow-up (years)	Age at inclusion (years)	Age at diagnosis of PD (years)	Risk of PD (95% CI)	Adjustment variables	Findings	Potential estimation bias
Driver et al. 2008 [12]	21,841 male subjects free of cancer, vascular disease, dementia, and PD enrolled in the Physicians' Health Study (U.S.)	23.1 [median]	40–84 [range]	73.1 [median]	1.34 (1.01–1.77)	Age, smoking, alcohol use, BMI, physical activity, hypertension, and high serum cholesterol (updated yearly)	Updated history type 2 diabetes was associated with increased risk of PD. Sensitivity analyses showed that PD was more associated with short duration and uncomplicated diabetes, and low BMI. In sensitivity analysis (exclusion of those developing vascular disease during the follow-up [N = 16,423]) risk of PD was 1.46 [1.00–2.13].	Data on diabetes and PD were self-reported. The increased risk for those with shorter duration of diabetes could be explained by detection bias from increased medical surveillance.
Xu et al. 2011 [13]	288,662 subjects without prevalent PD enrolled in the National Institutes of Health-AARP Diet and Health Study (U.S.)	15 [mean]	50–71 [range]	66.7 [7.3] (mean [SD])	1.41 (1.20–1.66)	Age, sex, race, BMI, physical activity, smoking, coffee intake, and education	Preceding diabetes (both type 1 and type 2) was associated with an increased risk of PD. In sensitivity analysis (exclusion of those with stroke, heart disease, cancer and poor/fair health [N = 215,723]) risk of PD was 1.34 [1.06–1.69].	Data on diabetes were self-reported. Only baseline diabetes and confounders were included in risk analyses. The increased risk of PD could be partly explained by detection bias from increased medical surveillance in diabetic participants.

Table 2—List and features of case-control studies included in qualitative analyses

Source [reference]	Ethnicity	PD (N)	Age at inclusion (years)*	Prevalence of diabetes (%)	Control subjects (N) and matching variables	OR** (95%CI) for cases	Adjustment variables	Potential estimation bias and other observations
Leibson et al. 2006 [14]	U.S. (Olmsted County; Minnesota)	197 incident cases	70 (11)	9.1	197 subjects matched for age ( $\pm 1$ year), sex, and geographical location	0.7 (0.4–1.4)	None	Presence of other neurologic disease (e.g., stroke or dementia) was not an exclusion criterion. A trend toward a higher prevalence of stroke and dementia was present in the PD group. BMI was not included among the potential confounders and adjusting variables.
Powers et al. 2006 [15]	U.S. (Group Health Cooperative database; Washington)	352 newly diagnosed cases of idiopathic PD without cognitive impairment	69 [35–88]	7.4	484 subjects matched for age (in decades), sex, year of enrollment, and geographical location	0.62 (0.32–1.01)	Age, ethnicity, education, and smoking habit	Medical conditions were self-reported. BMI was not included among potential confounders and adjusting variables.
Scigliano et al. 2006 [16]	Italy	157 newly diagnosed cases (duration of PD <6 months) of idiopathic PD	58.1 (11.4)	3.4	533 subjects matched for age ( $\pm 3$ years) and sex	0.30 (0.13–0.72)	Age and sex	Control subjects were recruited in a hospital setting, and a higher prevalence of vascular risk factors (diabetes, hypertension, or dyslipidemia) might have occurred. BMI, although similar in both groups, was not included among potential confounders and adjusting variables. Finally, in stepwise multivariable analysis, diabetes was no longer associated with reduced risk of PD.

Table 2—Continued

Source [reference]	Ethnicity	PD (N)	Age at inclusion (years)*	Prevalence of diabetes (%)	Control subjects (N) and matching variables	OR** (95%CI) for cases	Adjustment variables	Potential estimation bias and other observations
Becker et al. 2008 [7]	U.K. (General Practice Research Database)	3,637 new drug-free cases of PD (90% with an age at onset >60 years)	Not reported (90% aged >60 years)	8.0%	3,637 subjects matched for age (same year of birth), sex, and general practice	0.95 (0.80–1.14)	BMI, smoking, and multiple comorbidities (several neurologic disorders, hypertension, cardiovascular diseases, and dyslipidemia)	Detection bias deriving from increased medical surveillance related to some medical conditions could not be excluded at all.
D'Amelio et al. 2009 [8]	Italy (Italian region of Sicily)	318 newly diagnosed cases	66.7 (-)	4.1	318 subjects matched for age ( $\pm 2$ year) and sex	0.4 (0.2–0.8)	Age, sex, education, BMI, occupational status, alcohol and coffee consumption, and smoking habit	Ascertainment of diabetes was based on self-reported data.
Miyake et al. 2010 [17]	Japan (Osaka, Kyoto, and Wakayama Prefectures)	249 cases with a disease duration < 9 years	68.5 (8.6)	4.0	368 in-patients and out-patients not individually or in larger groups, matched to cases	0.38 (0.17–0.79)	Age, sex, smoking, area of residence, BMI, education, leisure-time exercise, intake of energy, cholesterol, vitamin E, alcohol and coffee, and the dietary glycemic index	Ascertainment of diabetes was based on self-reported data. Although control subjects were recruited in a hospital setting, and higher rates of comorbidities could be expected, prevalence of diabetes was comparable with that of the general population in the same area. Moreover, PD cases were thinner ( $P = 0.01$ ) and older ( $P = 0.006$ ), but multivariable models accounted for the effect of these confounders.

Table 2—Continued

Source [reference]	Ethnicity	PD (N)	Age at inclusion (years)*	Prevalence of diabetes (%)	Control subjects (N) and matching variables	OR** (95%CI) for cases	Adjustment variables	Potential estimation bias and other observations
Schemhammer et al. 2011 [18]	Denmark	1,931 PD cases admitted to hospital with a first-time diagnosis and identified through the nationwide Danish Hospital Register	72.2 (10.5)	6.5	9,651 free-living individuals (5 for any case) selected from the Central Population Registry, matched for age (same year of birth) and sex	1.36 (1.08–1.71)	Age, sex, and chronic obstructive pulmonary disease (lagged 5 years as surrogates of smoking)	Although cases were identified through the Danish Hospital registry, only those who were registered for the first time with a primary diagnosis of PD were included. This criterion should have significantly reduced the risk of higher rates of vascular factors (diabetes, hypertension, or dyslipidemia) in hospitalized patients. However, BMI was not included among potential confounders and adjusting variables. In sensitivity analysis performed after the exclusion of cases and control subjects diagnosed with dementia or cerebrovascular disease 2 years before the indexing, risk estimates were changed only minimally. Finally, in analyses restricted to PD cases aged >60 years at diagnosis, diabetes was no longer associated with increased risk of PD (OR = 1.16 [0.85–1.57]).

\*Data are presented as median [range] or as mean (SD); \*\*OR (95% CI) for the association between PD and preceding diabetes.

secondary causes of parkinsonism (inclusion bias) and/or adequate comparability (selection bias) between PD cases and control subjects.

**Data extraction and analyses**

Titles, abstracts, and articles were reviewed independently by two authors, E.Ce. and R.C. Abstracted data included study population characteristics, risk and precision estimates, adjustment variables, and potential for bias. Fully adjusted estimates were preferably included and analyzed. Results from sensitivity analyses, particularly those taking the potential confounding by concomitant vascular diseases into account, were also collected. Any discrepancies in data extraction were resolved by discussion with a third reviewer (C.P.). Authors of investigations were also contacted for further information as necessary.

Data from prospective cohort and case-control studies were analyzed separately. Potential sources of heterogeneity between studies were assessed using Cochran's Q and I<sup>2</sup> statistics. To compensate for potential between-study heterogeneity, we calculated a pooled RR or OR using a random-effect model (DerSimonian-Laird method); otherwise, we used fixed effect models. Sensitivity analyses were also considered, and specific criteria were provided along with the results. Forrest plots were used to summarize results, and funnel plots were used to assess publication bias. The prevalence of diabetes in case-control studies included/not included in this meta-analysis was computed, together with 95% CI, and compared by means of a loglinear model. Frequency weights for study size were used.

All analyses were performed using STATA 11 (StataCorp, College Station, TX), establishing the level of significance at a two-tailed P value of <0.05.

**RESULTS**—The literature search yielded 1,947 citations (electronic databases, N = 1,824; reviewing of references, N = 123), of which 48 were thoroughly assessed for eligibility. Of these, 11 (cohort, N = 4; case-control, N = 7) (5–8,12–18) were included in the present systematic review of diabetes as a risk factor for PD. Descriptive data and main results from these studies are presented in Table 1 (cohort) and Table 2 (case-control). In particular, we excluded 13 case-control studies, mainly because the authors did not evaluate incident cases of PD (Supplementary Data). In these studies (for available data), the mean prevalence of

diabetes in idiopathic PD was 12.4% (95% CI 12.2–12.7%; range, 6.5–16.2%).

Finally, out of the 11 studies initially included for qualitative assessment, 9 (cohort, N = 4; case-control studies, N = 5) met the additional inclusion criteria for meta-analysis.

**Prospective cohort studies**

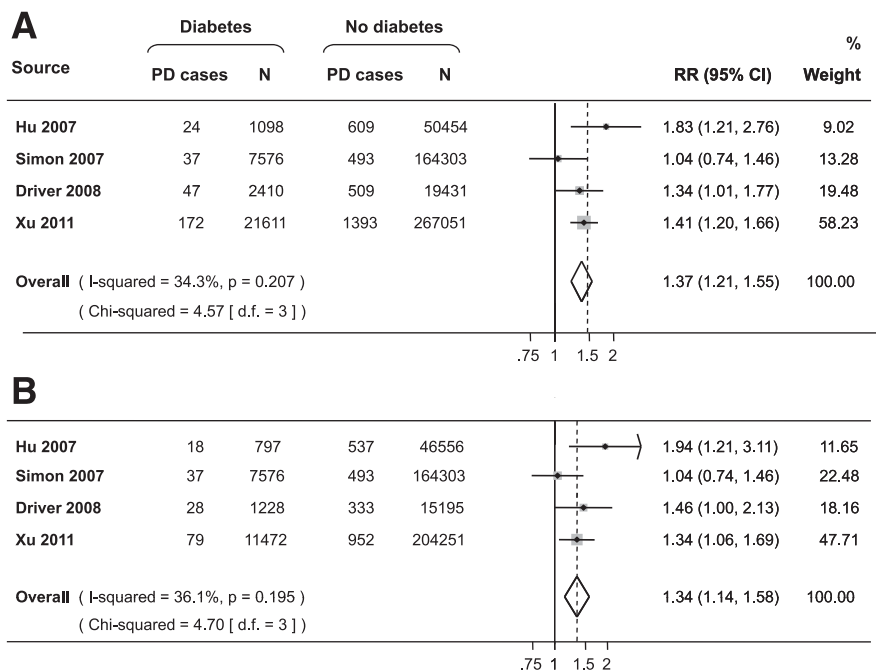
Among the cohort studies reviewed (Table 1), two addressed the risk associated with both type 1 and type 2 diabetes (with type 2 diabetes accounting for >90% of cases) (6,13) and two estimated the risk of type 2 diabetes (5,12). Simon et al. found that the risk of PD was similar, independently of diabetes status (5), whereas the other studies reported a significant risk of PD for participants with pre-existing diabetes (6,12,13). In all cohorts a positive history of diabetes was based on self-reported doctor-diagnosed diabetes either alone or confirmed through the use of national registers.

In the primary analysis (Fig. 1; plot A), based on fully adjusted estimates, the pooled risk for diabetes was 1.37 [95% CI 1.21–1.55] (z = 5.01; P < 0.0001) with limited variation attributable to study heterogeneity (I<sup>2</sup> = 34.3%; P = 0.207). Because cerebrovascular disorders and coronary heart disease were among the important causes of secondary parkinsonism

(vascular) (19), a secondary analysis was carried out, based on the estimates obtained through sensitivity analyses performed after the exclusion of participants who had vascular disorders at baseline or who had had a stroke during follow-up (Fig. 1; plot B). The association remained significant also in this analysis (RR = 1.34 [1.14–1.58]; z = 3.58, P < 0.001) with a similar variation attributable to study heterogeneity (I<sup>2</sup> = 36.1%; P = 0.195). The exclusion of the only study performed out of the U.S. area brought similar findings (RR = 1.28 [1.08–1.52]; z = 2.81, P = 0.005; heterogeneity, I<sup>2</sup> = 2.3%, P = 0.359). Finally, sensitivity analyses for the risk associated with diabetes at baseline and diabetes that developed during follow-up were also considered. For baseline diabetes the RR was 1.38 [1.14–1.68] (z = 3.32, P = 0.001; heterogeneity, I<sup>2</sup> = 28.1%, P = 0.249). However, for diabetes during follow-up the relationship approached significance (RR = 1.21 [0.94–1.56] (z = 1.48, P = 0.139; heterogeneity, I<sup>2</sup> = 41.5%, P = 0.191).

**Case-control studies**

About half of the case-control studies (Table 2) included in qualitative assessment consistently concluded that preceding diabetes was inversely associated with PD (8,16,17). In one study this association



**Figure 1**—Meta-analysis and pooled RRs of PD in diabetic participants from prospective cohort studies (Forrest plot A [A], association found for fully adjusted estimates; Forrest plot B [B], association found for fully adjusted estimates obtained after the exclusion of participants who had vascular disease at baseline and/or who developed them during the follow-up). d.f., degrees of freedom.

was marginally significant (15), whereas in another a trend toward a lower prevalence of diabetes in PD patients was described (14). Only Becker et al. (7) and Schernhammer et al. (18) found that in cases the prevalence of diabetes was similar to or even higher than control subjects. It is noteworthy that these investigations were also the ones with the largest populations. The prevalence of diabetes in PD populations was mildly heterogeneous, ranging between 3.4 and 9.1% (weighted mean 9.5% [95% CI 9.0–9.9%]; for excluded case-control studies, RR = 1.62 [95% CI 1.54–1.70],  $P < 0.001$ ). Ascertainment was frequently based on self-reported data (8,15,17). A distinction between type 1 and type 2 diabetes was made only in one study (16), but it is likely that most cases refer to the latter. With the exception of one case (14), adjusted ORs were available.

According to quality assessment procedures, we excluded the data of two studies (14,16) from quantitative synthesis. In the study by Leibson et al. (14), the presence of other neurologic diseases (e.g., stroke or dementia) was not an exclusion criterion. A trend toward a higher prevalence of stroke and dementia was present in the PD group, and it is

reasonable to think that secondary forms of parkinsonism (vascular) may have been included. Moreover, only crude ORs were provided. In the study by Scigliano et al. (16), control subjects were recruited in a hospital setting, and the particularly high prevalence of vascular risk factors (diabetes, hypertension, or dyslipidemia) was recognized as source of estimation bias. Therefore, the meta-analysis was based on five studies (Fig. 2). When compared with matched control subjects, PD patients at diagnosis were characterized by a similar prevalence of diabetes: OR = 0.75 [95% CI 0.50–1.11] ( $z = 0.21$ ;  $P = 0.835$ ) with a high variation in risk attributable to study heterogeneity ( $I^2 = 82.3\%$ ,  $P < 0.001$ ). The sensitivity analysis including studies providing estimates adjusted for BMI, an important confounder of the effect of diabetes, confirmed the lack of association with PD (OR = 0.56 [0.28–1.15];  $z = 1.70$ ;  $P = 0.089$ ;  $I^2 = 80.5\%$ ,  $P = 0.006$ ).

For both the study designs considered it was not possible to calculate sex-specific estimates of risk.

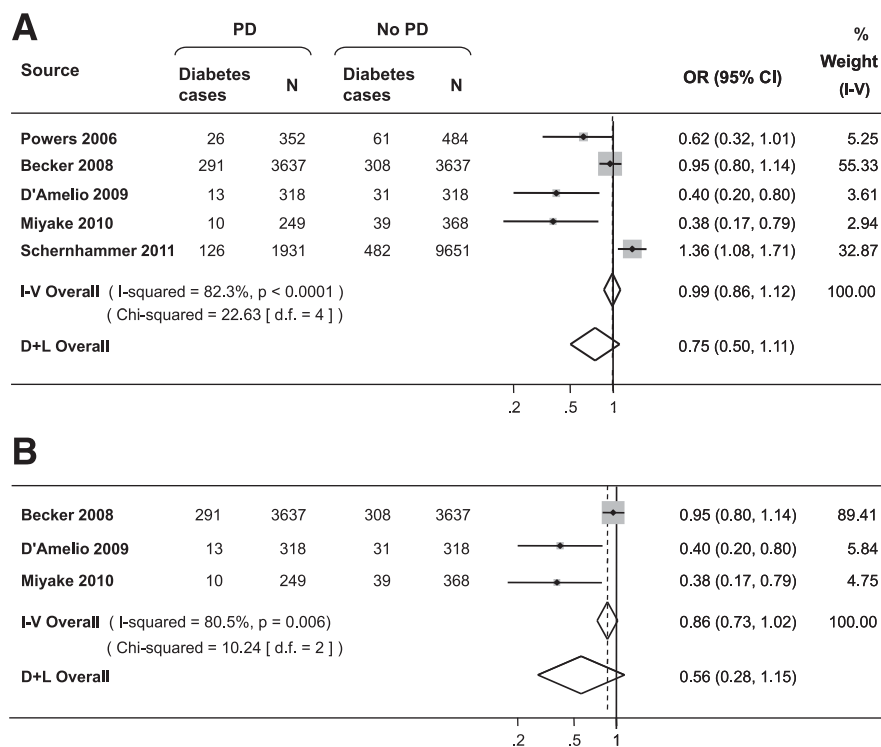
**CONCLUSIONS**—According to this meta-analysis diabetes appears to be a risk factor for PD. Higher weight was given to

the evidence derived from prospective investigations. In etiologic epidemiology the use of cohort studies is preferable, because it enables researchers to formulate a cause-effect hypothesis. However, the incidence of PD is low and shifted toward advanced age; large populations and a long follow-up are required for adequately powered risk analyses and, up to now, only one study has investigated a large number of cases (13). Thus the evidence collected is still limited. In this perspective, case-control studies could gain value and, since they have the advantage of being less expensive and time-consuming, enable the collection of a larger mass of data. However, they suffer mainly from recall (risk factors and duration of exposure) and inclusion (for both case subjects and control subjects) bias and only associations, not real causal relationships, can be inferred.

Heterogeneity among the studies retrieved and limitations of the literature search deserve comment and should be taken into account for a correct interpretation of the results. Although we used strict inclusion criteria and performed sensitivity analyses, several residuals of confounding and estimation bias could be present.

Diabetes is a metabolic disorder contributing to both large and small vessel diseases (20), and we were not sure that the study populations were confined to idiopathic PD. Although vascular parkinsonism possibly relating to major vascular disorders was generally taken into account during the recruitment phase or through adjusted analyses, the exclusion of parkinsonism related to microvascular complications should probably be based also on imaging techniques (21), even when the diagnosis of PD is made by a neurologist or a specialist in movement disorders. Nevertheless, sensitivity analyses confirmed the role of diabetes as a risk factor for future PD.

The lack of an established mechanism linking diabetes to PD is a major limitation for the interpretation of our findings. Recent studies have shown that, independently of hyperglycemia, which is mainly responsible for endothelial dysfunction (20), distinct pathologic pathways may contribute to neurodegeneration. Regarding PD, this hypothesis appears to be supported by the various associations found between PD and diabetes duration. Both insulin deficiency and insulin resistance with compensatory hyperinsulinemia might play a role (22–24). Insulin can act as a growth factor in the brain and can



**Figure 2**—Forrest plot (pooled OR) for the association between pre-existing diabetes and PD in case-control studies: plot A (A), primary analysis (all studies); plot B (B), sensitivity analysis (studies providing estimates adjusted for BMI). I-V, inverse variance fixed-effect model; D+L, DerSimonian-Laird random-effect model; d.f., degrees of freedom.



reduce oxidative stress. Insulin resistance has been shown to result in decreased insulin transport into the brain (9,10). Insulin receptors are densely represented in the substantia nigra and insulin increases dopamine transporter mRNA in the substantia nigra. It also regulates dopamine concentrations in the brain (9,10). During the natural history of diabetes, both changes in insulin secretion and in insulin activity may occur and have never been investigated in terms of the risk of PD. However, both insulin resistance and PD may be consequences of the aging process (1,2,25), and the clustering of PD and diabetes with age observed by Driver et al. (12) could also suggest the existence of common pathogenic processes leading first to diabetes and then to PD. In the Physicians' Health Study, the prevalence of diabetes, despite being similar to that reported by Simon et al. (5) at study entry (~2%), was more than twice as high at the end of the follow-up (11 vs. 4.5%). Similarly, also the age at PD diagnosis appeared to be higher as well as the prevalence of PD (2.5%; about eightfold higher than in the other cohorts included in the meta-analysis). However, the increased risk for those with diabetes of shorter duration may also be explained by detection bias as a result of increased medical surveillance (12). Recently this clustering with age was not confirmed by the other prospective investigation reporting an increased risk of PD in diabetic subjects (13). In the cohort followed by Xu et al. (13) only a history of diabetes longer than 10 years was significantly associated with PD risk. However, only diabetes at baseline was included in the analyses, and differences in monitoring of diabetic and nondiabetic patients during follow-up could have contributed to estimation bias (13). It is noteworthy that the prevalence of PD at the end of follow-up was similar to that reported by Simon et al. (0.3 vs. 0.5%) (5), whereas the prevalence of diabetes at baseline was about 3.5-fold higher than in the other cohorts (7.4 vs. ~2%) (5,6,12).

Other pathogenic mechanisms shared by diabetes and PD involve the inflammatory and mitochondrial dysfunction pathways. The contribution of chronic low-grade inflammation to the development of insulin resistance is generally accepted (26). Similarly, recent research has indicated that neuroinflammation plays a role in the pathogenesis of PD (27,28). Furthermore, recent studies support the hypothesis that the link between the two diseases may be the bioenergetic similarity of the midbrain substantia nigra

and the pancreatic islet  $\beta$ -cells. In particular, the higher vulnerability to oxidative stress and toxins may result in lower respiratory capacity (ATP production) and cellular vitality (9,10).

Looking at prospective studies other limitations should be taken into account. First, no information on glucose control and related management was considered during the follow-up. Data from the literature suggest that insulin and insulin-sensitizers, such as thiazolidinediones, could be a viable therapeutic approach to the treatment of neurodegenerative disorders, since they would also improve systemic low-grade inflammation (10). Second, most of the information collected was self-reported, and recall bias cannot be excluded with advancing age, particularly in the presence of concomitant deterioration in cognitive status. This applies at least to diabetes since blood glucose was not measured in prospective studies. Third, changes in the initial diagnosis of parkinsonism may also occur (29). Fourth, the potential confounding effect of other cardiovascular risk factors frequently clustered with diabetes within the spectrum of the metabolic syndrome has been considered only to some extent. Although their role still needs to be elucidated as a result of inconsistent evidence, some investigators have suggested that hypertension and high blood cholesterol are associated with an increased risk of PD (30,31). Conversely, high serum urate has been reported to be a protective factor (32,33) as well as the use of statins (34). Finally, among the several specific food items investigated (antioxidants, macronutrients, dairy products, etc.) (35), only the effect of caffeine and alcohol intake was taken into account. In regard to this, it should also be mentioned that the consumption of some foods could alternatively increase the risk of PD and reduce that of diabetes, as is the case for dairy products (36,37).

From a diagnostic point of view case-control studies probably offer some advantages, at least in terms of an accurate diagnosis of idiopathic PD. However, PD itself may influence the risk of diabetes, thus confounding the association. At least two factors should be considered. First, PD is associated with generalized sympathetic denervation (38,39), a condition that appears to contribute to reduced metabolic activity within adipose tissue and to an improved cardiometabolic profile (15,40). However, the timing of these effects is unclear, and only one study

among those reviewed provided enough information on the length of diabetes history (8). Second, although some studies have reported that body weight does not change before the onset of PD, a recent literature overview reported that weight loss, above all in terms of adipose tissue, commonly occurs (3). This would be a continuous process, starting several years before the diagnosis, to which both reduced calorie intake and increased energy expenditure, secondary to motor symptoms, can contribute (3). Although BMI has been considered among the potential confounders, this parameter, together with weight loss, should probably be taken into account during control selection and inclusion. Finally, survival bias as a result of high mortality among diabetic patients could contribute to the inverse relationship between diabetes and PD in case-control studies.

### Conclusion and perspectives

Literature analysis suggests that the etiologic role of diabetes in the development of PD requires further prospective investigation. In future cohort studies attention should be paid to putative pathogenic pathways, such as abnormal insulin production, insulin resistance, therapies for glucose control as well as inflammation and other cardiovascular risk factors that frequently cluster with diabetes within the spectrum of the metabolic syndrome. Nonetheless, case ascertainment should probably include the use of neuro-imaging techniques.

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E.Ce. contributed to literature review, data extraction, and manuscript drafting. E.Ce. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.B. contributed to literature review and critique. C.P. contributed to literature review and data extraction. C.K. contributed to data analysis. E.Ca. contributed to data extraction. R.C. contributed to literature review and critique. G.P. provided supervision and contributed to review and critique. All authors significantly contributed to the work and approved the manuscript for submission.

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