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SYSTEMATIC REVIEW AND META-ANALYSIS

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Risk of Parkinson Disease in Diabetes Mellitus: An Updated Meta-Analysis of Population-Based Cohort Studies

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Abstract: Previous meta-analysis has identified the associations between diabetes mellitus (DM) and the risk of Parkinson disease (PD). However, the results are still debatable. The purpose of this study is to perform an updated meta-analysis to investigate the up-to-date pooling evidence based on published population-based cohort studies and assess the association between DM and the risk of PD.

Electronic database including Pubmed and Embase were searched to identify cohort studies published before October, 2015. Studies were selected if they reported the risk estimates for PD associated with DM. We pooled the adjusted effect estimates using random-effects meta-analysis. Funnel plot, Begg, or Egger test as well as Duval and Tweedie trim-and-fill approach were applied to assess publication bias.

A total of 7 population-based cohort studies, representing 1,761,632 individuals were included in the meta-analysis. The pooled adjusted relative risk (RR) of PD associated with DM was 1.38 (95% CI 1.18–1.62, $P < 0.001$). An effect was consistent in female (RR 1.50 95% CI 1.07–2.11, $P = 0.019$) and in male (RR 1.40, 95% CI 1.17–1.67). The association was similar when stratified by study quality, research region, study design, sample size, published year, diabetes duration, and baseline age. The trim-and-fill approach confirmed the robustness of the result (RR 1.31, 95% CI 1.09–1.57, $P = 0.015$).

Our findings based on population-based cohort studies indicate that diabetes is associated with increased PD risk by about 38%. More large-scale prospective studies are warranted to further clarify this association and its mechanism.

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Abbreviations: CI = confidence interval, DM = diabetes mellitus, GLP-1 = glucagon like peptide-1, HR = hazard ratio, NOS = Newcastle–Ottawa scale, OR = odds ratio, PD = Parkinson disease, RR = relative risk.

INTRODUCTION

Diabetes mellitus (DM) has been and will continue to be one of the most common chronic diseases globally, which adds a tremendous burden to health care systems.[1] As an age-related neurodegenerative disease, Parkinson disease (PD) shares similar pathophysiological with DM in that both conditions are involved in similar protein misfolding, peripheral and central insulin signaling, and some shared cytotoxic processes.[2,3] PD and diabetes share similar genetic and environmental factors caused by dysregulation in common pathways. Detrimental environmental exposure, genetic susceptibility, and lifestyle factors may cause mitochondrial and endoplasmic reticulum malfunction, inflammatory response, and metabolic disorder, which contribute to neurodegenerative diseases (such as PD) and/or diabetes.[3] Diabetes can involve multiple systems or organs, such as diabetic neuropathy and Alzheimer disease.[4–6] Nevertheless, evidence from epidemiological studies has not definitely identified whether preexisting DM has direct relationship with the risk of developing PD.

A previous meta-analysis by Cereda et al[7] indicated that DM was a risk factor for the future development of PD based on four prospective studies. However, when involved 14 case–control studies, Lu et al[8] did not find the relationship between DM and risk of PD, which was also reported by Cereda et al[7] when pooling the results of 5 case–control studies. Due to the interstudy heterogeneity, the seemingly contradictory results add little evidence to the true relationship between DM and risk of developing PD.[9–31] Therefore, the purpose of our study is to conduct an updated meta-analysis of the available population-based cohort studies to estimate the impact of preexisting of DM on the risk of developing PD.

METHODS

Search Strategy

We searched Pubmed and Embase from inception up to October 2015 with no language limitations using the following search terms: ''diabetes mellitus,'' diabet∗ which were combined with the Boolean logical operator AND with studies identified with the terms ''Parkinson disease,'' Parkinson∗. The reference lists of all primary selected relevant articles and several previously published reviews and meta-analyses were also scrutinized to identify additional relevant studies on this topic (detailed see supplementary Table 1, http://links.lww.com/MD/A937).

Eligibility Criteria

We selected observational cohort studies with prospective or retrospective study design that investigated the association of

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XJY and TL were responsible for the study design; XJY wrote and implemented the protocol under the guidance of TL; XJY, HHL, and TL screened the studies and extracted data; XJY and TL analyzed the data and provided statistical guidance; XJY and TL drafted the manuscript; XJY, PZ, LC, and TL contributed to the interpretation of results and subsequent revisions; LC and TL revised the study data for inclusion in the review; XJY and TL are guarantors; and the final version of the manuscript was approved by all of the authors.
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DM exposure with PD. The inclusion criteria of this study were the studies that reported odds ratios (ORs)/relative risks (RRs)/hazard ratios (HRs) for PD risk in diabetic patients compared with that in nondiabetic patients, or to provide indirect raw data to allow for calculation of the risk estimates. Studies had to define diabetes and PD using self-reported questionnaires or with the criteria based on the International Classification of Diseases, 10th revision. Studies were excluded with case–control study design, if no relevant relative ratio or HR was reported, or if the participants of the same cohort were published more than twice. Studies were also excluded for those without sufficient data for analysis or those without original data such as comments, letters, reviews, and meta-analyses. Institutional review board approval and patient consent were not applied to this meta-analysis of observational studies.

Data Extraction and Quality Assessment

Eligible articles were screened and reviewed independently by 2 investigators (XJY and HHL), and data were extracted into a standardized a Microsoft Excel spreadsheet. Any discrepancies were resolved by discussion or by a senior investigator (TL), until consensus was reached. The following items were extracted for each study: first author, publication year, research country, study name, study design, number of participants, age at baseline, PD and DM diagnostic criteria, risk estimates for PD, adjusted variables, and analytical method.

The methodological quality of observational cohort studies was assessed using the Newcastle–Ottawa scale (NOS) by 2 investigators independently (XJY and HHL).[32] According to this scale, 3 domains were scored concerning selection and comparability of study cohorts, and ascertainment of the outcome of interest, with a score range of 0 to 9.

Statistical Analysis

We used the DerSimonian and Laird random effects model to calculate pooled estimates and corresponding 95% confidence interval (CI).[33] As the prevalence of PD was relatively rare, ORs were considered approximations of RRs or HRs. Adjusted risk estimates (ORs/RRs/HRs) reported in studies were chosen for analysis to account for confounding variables. The interstudy heterogeneity was tested by the Cochran Q and I^2 statistic with an I^2 value more than 50% representing significant heterogeneity.[34] We also conducted sensitivity analyses by excluding 1 study at a time and reanalyzing the remaining studies to examine whether the results altered substantially by any individual study. We used the method through visual inspection of the funnel plot symmetry and Begg regression as well as Egger linear regression test to assess the potential of publication bias.[35] In addition, Duval nonparametric trim-and-fill procedure was used to assess the possible influence of publication bias.[36] The statistical analyses were performed using Stata 12.0 (Stata Corporation, College Station, TX).

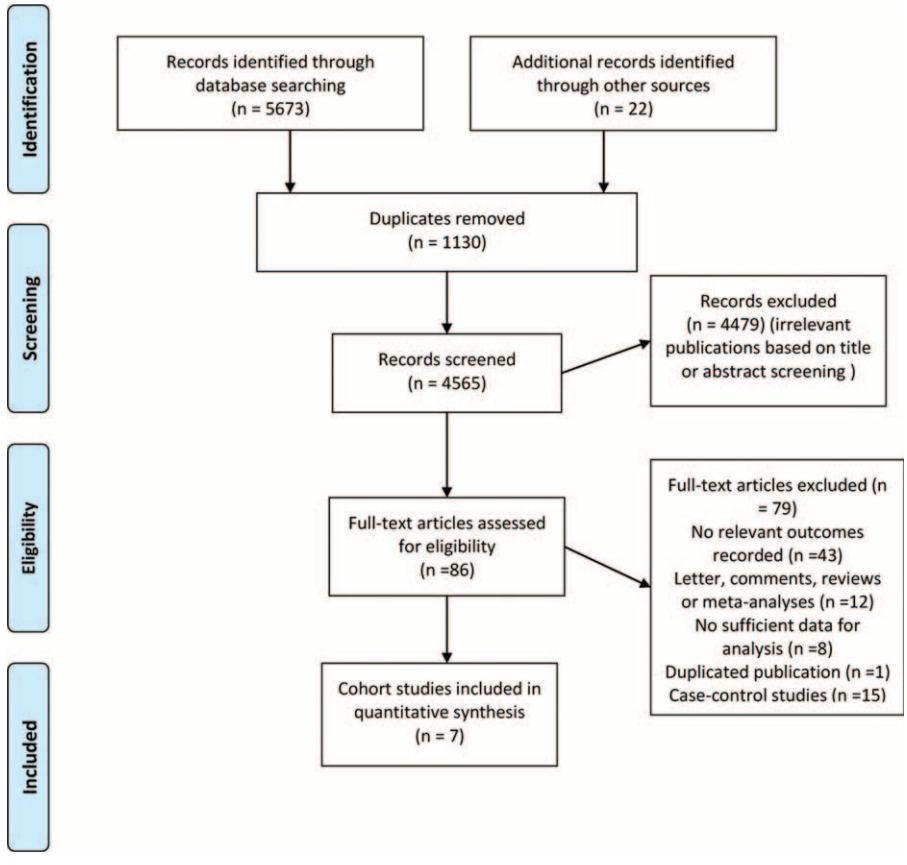

FIGURE 1. Flowchart of study selection.

TABLE 1. Baseline Characteristics of Included Studies in the Meta-Analysis

First Author	Publication Year	Country	Study Name	Study Design	No of Participants	Age at Baseline, years	PD Diagnostic Criteria	DM Diagnostic Criteria	Risk (OR/RR/HR, 95%CI) for PD	Adjusted Variables	Analytical Method
De Pablo-Fernández	2014	Spain	NEDICES cohort (population based)	Prospective	4998	NR	UK PD Society Brain Bank diagnostic criteria	Self-reported questionnaire	OR = 2.07; 95% CI 0.94–4.59; DM > 10 year: OR = 3.52; 95% CI 1.22–10.17	Demographics, cardiovascular risk factors, prevalent chronic diseases, and therapies potentially causing parkinsonism	Multivariate
Sun	2012	China (Taiwan)	NHI cohort (population based)	Retrospective	1,075,604 (603,416 diabetic patients and 472,188 control)	>20	ICD-9: 332	ICD-9: 250 or A code 181	HR = 1.61 95% CI 1.56–1.66; men: HR = 1.51; 95% CI 1.44–1.57; women: HR = 1.70; 95% CI 1.63–1.77	Age, sex, geographic area, urbanization status, and comorbidities, including hypertension, hyperlipidemia, and cardiovascular disease	Multivariate
Xu	2011	USA	NIH-AARP Diet and Health study	Prospective	288,662 (21,611 diabetic patients and 267,051 control)	50–71	Neurologist diagnosis	Self-administered questionnaire	OR = 1.41 95% CI 1.20–1.66	Age, sex, race, education, smoking, coffee, BMI, and physical activity	Multivariate
Palacios	2011	USA	CPS-II Nutrition cohort	Prospective	147,096	≥18	Medical record review	Self-administered questionnaire	RR = 1.00 95% CI 0.75–1.34; men: RR = 0.98; 95% CI 0.66–1.46; women: RR = 1.02 95% CI 0.66–1.56	Age, smoking, alcohol intake, caffeine intake, caloric intake, dairy intake, pesticide exposure, education and physical activity, BMI	Multivariate
Driver	2008	USA	The Physicians' Health Study cohort	Prospective	21,841	40–84	Self-reported questionnaires	Self-reported questionnaires	Men: RR = 1.34 95% CI 1.01–1.77	Age, smoking, alcohol use, BMI, physical activity, hypertension, and high serum cholesterol	Multivariate
Simon	2007	USA	NHS cohort and HPFS cohort	Prospective	171,879	Women: 30–55; men: 40–75	Neurologist diagnosis	Self-reported history	RR = 1.04 95% CI 0.74–1.46	Age, sex, and Smoking, BMI, physical activity, alcohol, caffeine and energy intake, and comorbidities	Multivariate
Hu	2007	Finland	The Finland Nationwide cohort	Prospective	51,552	Women: mean 65.8; men: mean 64.3	Neurologist diagnosis	Self-reporting and two nationwide registers.	RR = 1.83; 95% CI 1.21–2.76; men: RR = 1.78; 95% CI 1.01–3.12; women: RR = 1.91; 95% CI 1.04–3.52	Age, sex, smoking, BMI, alcohol use, coffee and tea consumption, education, physical activity, systolic blood pressure, and total cholesterol	Multivariate

AARP = American Association of Retired Persons, BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, HPFS = the Health Professionals Follow-up Study, HR = hazard ratio, ICD = International Classification of Diseases, NR = not reported, NEDICES = the Neurological Disorders in Central Spain, NHI = Taiwan National Health Insurance, NHS = the Nurses Health Study, NIH = the National Institutes of Health, OR = odds ratio, PD = Parkinson disease, RR = relative risk.

We set a P value less than 0.05 indicating statistical significance.

RESULTS

Study Characteristics

Figure 1 illustrates the detailed study selection process. In summary, 86 references were initially identified through reading titles or abstracts from 4565 records. After full text review, 79 articles were excluded for multiple reasons (details were provided in Table 2, http://links.lww.com/MD/A937), and only 7 articles were deemed suitable and satisfied the inclusion criteria.[23–25,27,29–31] Table 1 provides the detailed baseline characteristics of each study that met our inclusion criteria. All 7 studies were cohort studies (6 prospective and 1 retrospective) published between 2007 and 2014 in English peer-reviewed journals. A total of 1,761,632 individuals were included in this study with a median sample size of 147,096 (range, 4998–1,075,604). Four studies were conducted in USA,[24,27,29,31] 2 in Europe,[23,25] and 1 in China (Taiwan).[30] Based on NOS, 6 studies were assigned as higher score[24,25,27,29–31] and 1 as lower score[23] (Table 3). The

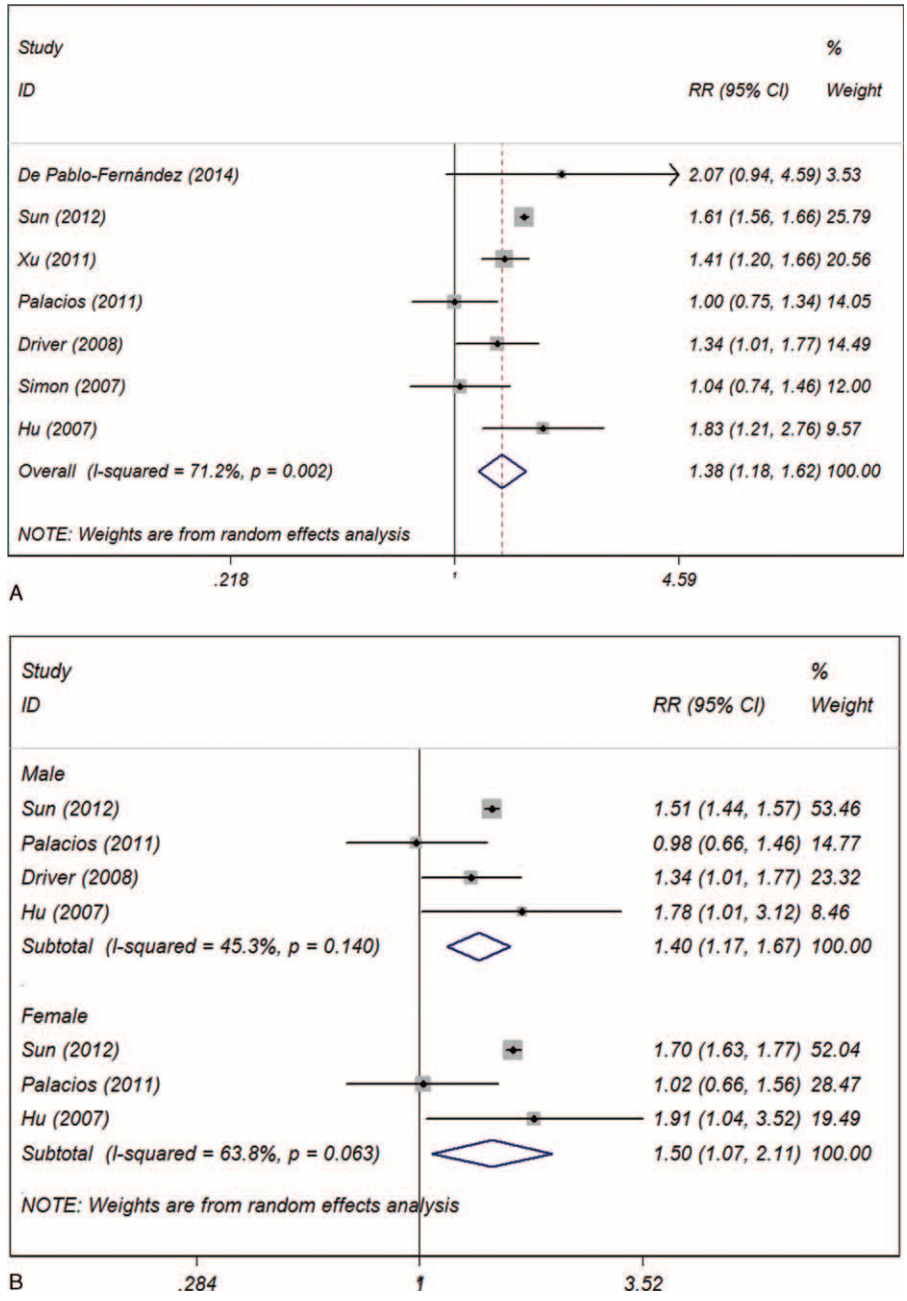

FIGURE 2. (A) Forest plot for risk of Parkinson disease in diabetic patients. (B) Forest plot for risk of Parkinson disease in diabetic patients by different genders.

confirmation of PD was based on self-reported questionnaires in 1 study[24] and neurological diagnosis based on International Classification of Diseases in 6 studies.[23,25,27,29–31]

Risk of PD in Patients With DM

Pooled analysis of 7 studies showed a significant association between DM and risk of developing PD, RR 1.38 (95 % CI 1.18–1.62, $P < 0.001$, $I^2 = 71.2\%$) compared with nondiabetic patients (Figure 2A). Although substantial statistical heterogeneity was noted in the meta-analysis, almost all of the 7 included studies showed a similar direction of effect, thus demonstrating that some of the heterogeneity mainly attribute to variation in the magnitude of the estimated risk instead of the direction. No evident publication bias was identified when examining for funnel plot asymmetry by Egger test ($P = 0.147$) or Begg test ($P = 0.764$). However, due to the limited number of included studies, we should interprete it with caution. We then applied the trim and fill method to conduct the sensitivity analysis and the result indicated 2 missing studies in the funnel plot (Figure 3). However, imputing these 2 hypothesized studies did not largely alter the original pooled estimate (RR 1.31 95% CI 1.09–1.57, $P = 0.015$). Furthermore, sensitivity analysis by omitting 1 study at a time and recalculating the pooled estimate, the results of that still showed significant association between DM and risk of PD (data no shown) (Figure 4).

Subgroup Analyses

Four studies[24,25,27,30] investigating on the prevalence of PD by gender were identified, with a pooled RR of 1.50 (95 % CI 1.07–2.11, $P = 0.019$, $I^2 = 63.8\%$) in female and 1.40 (95 % CI 1.17–1.67, $P < 0.001$, $I^2 = 45.3\%$) in male (Figure 2B). The results indicated DM was a significant risk factor of developing PD in both males and females, but no significant difference was observed in PD prevalence between males and females ($P = 0.72$). Four studies[24,25,30,31] investigated whether poor or fair health status (such as stroke, heart disease, cancers, etc.) could influence the combined estimates. The results showed that DM was still associated with significant increased risk of PD (pooled RR 1.45, 95% CI 1.20–1.74) when pooling the estimates from studies that excluded individuals with poor or fair health status (Table 3).

We also assessed the impact of study quality (high quality vs low quality), research country involved (USA vs Europe vs Asia), study design (prospective vs retrospective), sample size

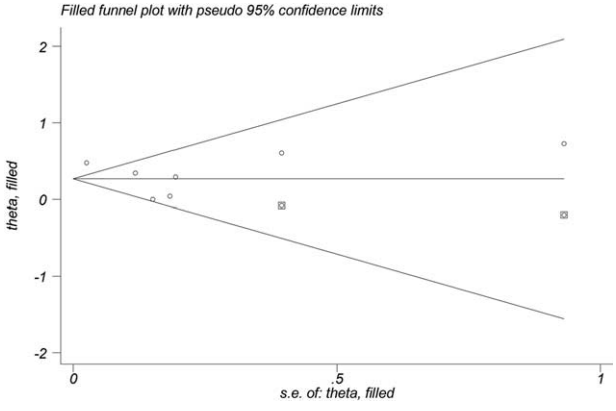

FIGURE 3. Trimmed and filled funnel plot of diabetes and Parkinson disease.

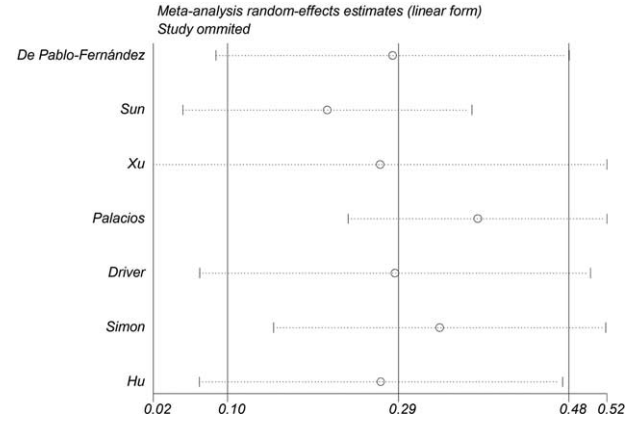

FIGURE 4. Sensitivity analysis using a random-effect model by omitting 1 study at a time and pooling the other included studies.

(≥100,000 vs <100,000), and published year (before 2010 vs after 2010). Regardless of the above-mentioned factors, an almost consistent positive relationship between DM and the prevalence of PD still existed (Table 2). We further conducted subgroup analyses by diabetes duration, age, body mass index, smoking status, and other available relevant factors. The results are presented in Table 3. We note that patients with diabetes whose baseline age more than 40 years old, body mass index less than 25 kg/m^2, and who were ever or current smokers had significant higher risk of PD. We also find that patients with DM duration less than 10 years tended to have a significant higher risk of PD (RR 2.33, 95% CI 1.25–4.34) than those with DM duration more than 10 years (RR 1.28, 95% CI 0.95–1.72).

DISCUSSION

In this comprehensive updated meta-analysis based on 7 observational cohort studies analyzing the impact of diabetes on the risk of PD in over 1,761,000 individuals, we noted that, compared to nondiabetic patients, patients with diabetes were associated with a 38% increase in the risk of developing PD, with an increased risk of 50% and 40% in female and in male, respectively. This effect persisted on analysis stratified by study quality, research country, study design, sample size, or published year. The trim and fill method and sensitivity analysis also confirmed the robustness of the association.

Our findings of the current meta-analysis are in line with those of a previous review of observational studies. Based on 4 cohort studies, Cereda et al also concluded that preexisting diabetes was a risk factor for future PD (RR 1.37, 95% CI 1.21–1.55). The mechanisms of the potential roles of diabetes in developing PD are not fully demonstrated. It has been proposed that diabetes might initiate PD through various intrinsic pathways. First, both diabetes and PD involve similar systemic chronic inflammation,[37,38] which plays an pivotal role in the occurrence and development of those diseases. Second, oxidative stress, abnormal central dopamine levels, and mitochondria dysfunction can be noted in both of these 2 age-related chronic diseases.[39–42] Furthermore, in vitro studies also show that insulin has some potential role in regulating brain dopaminergic activity.[43] Interestingly, other studies proposed that DM is associated with more severe cognitive or postural impairment in PD patients likely through some of the nondisease-specific neurodegeneration mechanisms.[44,45] Based on

TABLE 2. Subgroup Analyses in Subset of Included Studies According to Baseline Characteristics

	RR	95%CI	Heterogeneity, %	*P*	No. of Included Studies
Total	1.38	1.18–1.62	71.2	<0.001	7.
Study quality					
NOS score > 6	1.36	1.15–1.61	75.5	<0.001	6
NOS score ≤ 6	2.07	0.94–4.59	–	–	1
Research region					
USA	1.22	1.02–1.46	47.1	0.026	4
Europe	1.88	1.30–2.71	0	0.001	2
Asia	1.61	1.56–1.66	–	–	1
Study design					
Prospective	1.31	1.10–1.57	48.5	0.003	6
Retrospective	1.61	1.56–1.66	–	–	1
Sample size					
≥100,000	1.30	1.05–1.61	83.8	0.017	5
<100,000	1.53	1.21–1.94	6.4	<0.001	2
Published year					
Before 2010	1.34	1.01–1.79	53.6	0.046	3
After 2010	1.41	1.15–1.72	76.8	0.001	4
Gender					
Female	1.50	1.07–2.11	63.8	0.019	3
Male	1.40	1.17–1.67	45.3	<0.001	4

CI = confidence interval, NOS = Newcastle–Ottawa scale, RR = relative risk.

these mechanisms, several potential targets for therapeutical interventions in neurodegenerative disorders have been developed. Insulin and glucagon like peptide-1 (GLP-1) (known as an insulinotropic hormone) play a pivotal role in maintaining homeostasis and regulating glucose levels. Besides the intracephalic autocrine function, they also contribute to the regulation of neuronal excitability, metabolism, and apoptosis. The blood glucose-lowering effects of GLP-1 are limited by dipeptidyl peptidase 4 which degrades GLP-1. Recently, some drugs have been developed for the treatment of type-2 diabetes, which can also slow the rapid inactivation of GLP-1 through dipeptidyl peptidase 4 inhibition thus exerting a neuroprotective effect. This effect is likely to be a promising approach for the treatment of PD.[46]

The strengths of this meta-analysis include the comprehensive and reproducible search of the major databases and

TABLE 3. Subgroup Analyses According to Some of the Selected Baseline Characteristics

	RR	95%CI	Heterogeneity, %	*P*	No. of Included Studies
Overall					
All participants	1.38	1.18–1.62	71.2	<0.001	7
Excluding poor health status	1.59	1.50–1.69	6.2	<0.001	4
Diabetes duration, years					
>10	1.28	0.95–1.72	80.2	0.099	5
≤10	2.33	1.25–4.34	96.4	0.008	3
Baseline age, years					
<40	1.61	0.98–2.64	38.1	0.058	3
41–60	2.05	1.50–2.25	70.9	<0.001	3
>60	1.55	1.41–1.70	71.9	<0.001	3
Body mass index					
<25 kg/m^2	1.88	1.28–2.77	–	–	1
25 to <30 kg/m^2	1.14	0.75–1.72	–	–	1
≥30 kg/m^2	0.36	0.08–1.59	–	–	1
Smoking					
Never	1.70	0.98–2.98	–	–	1
Ever or current	1.94	1.05–5.59	–	–	1

CI = confidence interval, RR = relative risk.

thoroughly assessment of the effects of diabetes on risk of developing PD based on high quality population-based cohort studies. Compared with the recently published meta-analysis by Lu et al[8] involving case–control studies, this study had a much larger sample size (the largest ever published on this topic) and mainly included high quality population-based cohort studies (6 of 7 with an NOS score of 8 or 9), a sample size of more than 1,761,000 provided the most powerful and comprehensive synthesis of the evidence so far concerning the association between the preexisting DM and risk of PD. Moreover, stratified analyses on the study characteristics were conducted across studies, and generally consistent result was obtained, despite the existence of heterogeneity to some degree. Finally, we formally assessed and rated the study quality or risk of bias for all the included studies using a commonly used scale for cohort studies, and some other approaches, such as trim and fill method, were applied to assess the publication bias.

Several potential limitations should also be addressed. First, there were relatively small number of published studies available for pooling. Therefore, limited subgroup analyses could be conducted to explore possible reasons for heterogeneity for the insufficient power to detect heterogeneity when fewer studies were involved in the analysis. Due to the unavailability of the information in some included studies such as the identification of cases of Parkinsonism or vascular type, not idiopathic PD, sensitivity analyses could not be fully performed and identification bias did exist. Second, as the inherent limitations of observational studies, there was probability of publication bias. Although we scrutinized several major sources to search for all potential relevant studies to minimize publication bias, unpublished gray literature was not included, which might result in the possibility of missing some unpublished data with negative results. However, we applied the trim and filled method to detect this bias and the result was consistent with the original analysis, still showing significant evidence on the relationship between preexsisting DM and risk of developing PD. Additionally, differences in the baseline characteristics of each study could also account for the interstudy heterogeneity. The summary results only show variations among the included studies rather than among individual patient. For example, we had no detailed data concerning the DM duration of each patient and the medication history for diabetes. Thus, more detailed meta-analysis could only be conducted if individual patient data could be obtained.

In conclusion, with this meta-analysis, we have attempted to clarify the association between preexisting diabetes and risk of developing PD. We found that compared with nondiabetic individuals, those with diabetes appear to have a significant high incidence of PD. In view of the interstudy heterogeneity, we advocate large-scale prospective studies to elucidate the robustness of the association. Besides, further biological studies should be conducted to demonstrate the potential mechanisms.

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