Introduction

Parkinson’s disease (PD) is the second most common chronic neurodegenerative disorder after Alzheimer disease, and affects more than 1% of the elderly population worldwide [1]. Recent literature suggested that diabetes mellitus (DM) has been associated with PD, and they have shared similar pathogenic pathways [2,3]. Genetic and environmental factors cause dysregulation in common pathways that lead to neurodegeneration and diabetes [2]. Moreover, insulin and dopamine may exert reciprocal regulation between PD and diabetes [3]. However, the relationship between diabetes and PD was inconsistent with several epidemiological studies, ranging from a positive association to a null, or even inverse association [4–12].

A recent systematic review and meta-analysis on the risk of PD associated with diabetes has been published by Cereda et al. [13], and its conclusion suggested that diabetes was a risk factor for PD according to data from 4 cohort studies. However, no association was found between diabetes and PD based on data from 5 case-control studies. An update of risk estimates from 5 cohort studies was also conducted by Cereda et al. [14], suggesting that diabetes may be considered a risk factor for future PD. However, there was little evidence on this association because of the significant heterogeneity between studies [15]. Thus we conducted an updated systematic review, which incorporated more recent case-control studies, to further determine whether prior onset of diabetes contributes to the risk of PD.

Research Design and Methods

We performed a systematic review of the published literature based on the guidelines for reporting of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [16]. Results are reported according to the recently published PRISMA guidelines [17].

Eligibility criteria

We included those studies that met all of the following criteria: (1) reported separately relevant risk statistics for PD by antecedent diagnosis or characterization of diabetes based on case-control studies. An update of risk estimates from 5 cohort studies was found between diabetes and PD based on data from 5 case-control studies, to further determine whether prior onset of diabetes contributes to the risk of PD. However, there was little evidence on this association because of the significant heterogeneity between studies [15]. Thus we conducted an updated systematic review, which incorporated more recent case-control studies, to further determine whether prior onset of diabetes contributes to the risk of PD.

Methods: Seven databases were searched to identify case-control studies that evaluated the association between diabetes and PD. The methodological quality of included studies was assessed using Newcastle-Ottawa scale. All data were analyzed using Review Manager 5.1 software. Subgroup analyses were also adopted, according to stratification on gender, geographic location, source of the control group, smoking, anti-diabetes drug prescription and duration of DM.

Results: Fourteen studies fulfilled inclusion criteria for meta-analysis, yielding a total of 21395 PD patients and 84579 control subjects. Individuals with diabetes were found to have a negative association with future PD (OR 0.75; 95% CI 0.58–0.98) in spite of significant heterogeneity. In subgroup analyses, the negative correlation was still found in studies from North America, non-PD control groups from general population, never smoking individuals, and DM ascertainment based on questionnaire or self-report. Stratification of gender and DM duration showed no significant association. No association was also found in European and Asian individuals, hospital-based controls, ever smoking subjects, DM assessment by medical record or physician diagnosis, and insulin prescription for DM.

Conclusion: Evidence from case-control studies suggested that diabetic individuals may have a decreased incidence of PD despite significant heterogeneity. More researches are warranted to clarify an understanding of the association between diabetes and risk of PD.
Diabetes and Risk of Parkinson’s Disease

Search methods
A computerized literature search was conducted using PubMed, Web of Science, Scopus, Google Scholar, Chinese National Knowledge Infrastructure (CNKI), VIP Journals Database and Wanfang database until May 2013 for studies of the association between diabetes and PD (see also Appendix S1). We also hand-searched bibliographies of retrieved papers for additional references, and contacted experts in the field for any unpublished studies. The researches and studies included were not limited by publication date, country, or language.

Data collection and analysis
Selection of studies. Two review authors (LL, FDL) independently performed the data extraction on study characteristics, including the first author’s last name, publication year, source of study, characteristics (age, sex, geographical location etc.), diagnoses of cases, method of ascertainment of diabetes, sample size, variables adjusted in the analysis, and the risk estimates with corresponding 95% CIs, into a standardized data extraction form. We extracted the OR or RR estimate that was adjusted for the exposure or provided sufficient information to calculate them.

Results of meta-analyses
We conducted a primary meta-analysis with all the 14 identified studies that reported results on diabetes and PD incidence. The ORs with 95% confidence intervals (CIs). Heterogeneity among studies was estimated using Cochran’s Q test (reported with a x2-value and P-value) and I2 statistic [19,20]. For the Q test, a P-value of less than 0.1 was used as an indication for the presence of heterogeneity. For the I2 statistic, as a measure of the proportion of total variation in estimates, is due to heterogeneity rather than chance, I2 values of greater than 50% were considered to denote substantial heterogeneity.

Publication bias was detected graphically using a funnel plot of a trial’s effect size against the standard error. A two-tailed P value of less than 0.05 was considered to be statistically significant.

Results
Study selection
We identified 242 literatures, of which 55 were considered to be of potential value and the full text was retrieved for detailed evaluation. Thirty-one of these 55 articles were subsequently excluded from the systematic review, of which 7 studies used Parkinsonism as outcome, 10 papers possessed uncompleted data that could not fulfill analysis, 5 exerted multiple publications, and the rest 9 studies provided no information on whether the onset of diabetes preceded the onset of PD. Thus, a total of 14 articles, which met the inclusion and exclusion criteria, were used in this systematic review. The screening process was summarized in a flow diagram (Figure 1).

Study characteristics
This systematic review identified 105974 subjects, and most of the studies pointed out the specific male and female number in both PD patients and control subjects, with the exception of 3 studies for no information on gender [9,21,22]. The total number of PD cases in the included studies was 21395. Of these cases, 615 (2.9%) were diabetes. These cases were compared with 84579 non-PD individuals in the general population and hospital setting, of whom 1336 (1.6%) were diabetes. Four studies were conducted in North America [22–25], 7 in Europe [8,10–12,21,26,27], and the rest 3 in Asia [9,28,29]. Study size ranged from 140 to 82140 participants. PD was identified with register-based sources in all studies. Six studies ascertained diabetes with physician diagnosis or medical record [10,12,22,23,26,27], 7 with by self-report or constructed questionnaire [8,9,11,24,25,28,29], and the study of Skeie et al. [21] with no mention. The majority of studies showed that the median ages at the onset of PD were over 60 years, with no description in 2 studies [9,25]. None of the included studies differentiated types of diabetes distinctly, although Scigliano et al. noted that about 97% DM in cases and controls were type 2 diabetes [27]. Potential confounders were controlled in most of the studies, except in Kessler’s study, where the confounders adjusted for were not indicated clearly. The detail characteristic of the included studies was listed (Table 1). The quality of included studies was moderate or good, varying from five to eight points (Table 2).

Results of meta-analyses
We conducted a primary meta-analysis with all the 14 identified studies that reported results on diabetes and PD incidence. The
pooled summary OR was 0.75 (95% CI 0.58–0.98) in a random-effect model for PD patients, compared with non-PD individuals (Figure 2). There was significant heterogeneity among these studies ($Q = 52.68, P < 0.00001, I^2 = 75\%$). To further elicit the association between diabetes and the risk of PD, subgroup analyses were adopted, according to stratification on gender, geographic location, source of the control group, smoking, anti-diabetes drug prescription and duration of DM (Table 3). There was no significant difference between cases and controls for the prevalence of DM in men and women separately [11,23–26]. No statistical significance was found in subgroup analyses by DM duration [12,23] and insulin prescription of DM [23,26] (Table 3). Oral anti-diabetes drug appeared to increase PD risk in Schernhammer’s study (OR 1.37; 95% CI 1.10–1.71) [26]. Half of the included studies using general population-based controls reported inverse pooled estimate (OR 0.63; 95% CI 0.40–0.99) [8–10,24,27–29], while the other hospital-based controls reported no significant association (OR 0.88; 95% CI 0.62–1.25) [11,21–25,26]. A slightly intensified negative correlation was found between diabetes and the developing of PD in North America (OR 0.61; 95% CI 0.45–0.83) [22–25], whereas no significant association in Europe (OR 0.94; 95% CI 0.69–1.28) [8,10–12,21,26,27] and Asia (OR 0.54; 95% CI 0.23–1.27) [9,28,29].

Two studies showed that never smoking firmly strengthened the inverse association (OR 0.37; 95% CI 0.21–0.66), versus no significant difference in ever smoking individuals (OR 0.67; 95% CI 0.40–1.13) [11,24] (Table 4).

In sensitivity analyses, we excluded PD patients and control subjects diagnosed with dementia or cerebrovascular disease prior to the index date. No significant difference was observed in the association with diabetes and PD incidence (OR 0.73; 95% CI 0.48–1.12) [8,11,12,23,25,28,29]. We investigated the impact of DM assessment on the estimate of odds risk as well. Except one study with no mention of DM assessment method [21], the negative correlation was stronger in studies that identified DM through self-report or questionnaire (OR 0.57; 95% CI 0.39–0.85) [8,9,11,24,25,28,29] than physician diagnosis or relevant criterion in medical record (OR 0.92; 95% CI 0.70–1.21) [10,12,22,23,26,27] (Table 3). When we removed one study at a time and analyzed the rest of studies, the ORs altered only minimally. The ORs ranged from 0.73 (95% CI 0.52–1.01) after excluding the study by Becker et al. whose study carried the most weight [10] to 0.73 (95% CI 0.56–0.95) after excluding the study by Ho et al. whose study carried the least weight) [28]. In general, stratification of the studies by quality-associated variables did not obviously reduce the heterogeneity of effect estimates.
## Table 1. Characteristics of the included studies.

| Study | Study period | Resource | Location | Number of case (PD) subjects (M/F) | Mean age at onset PD (mean duration) | Number of prior DM in cases | Number of control subjects (M/F) | Source of the control | Number of DM in controls | Definition of PD | DM assessment | OR (95% CI) for cases | Adjustment variables |
|-------|--------------|----------|----------|-----------------------------------|-------------------------------------|-----------------------------|-----------------------------|----------------------------|-----------------------|----------------|-------------|----------------------|----------------------|
| Skeie et al., 2013 [21] | 2004–2006 | Norwegian ParkWest study | Norway | 212 (-) | 67.3 ± 9.8 (6) | 18 | 175 (-) | General population | 8 | Gel criteria | Not stated | 1.94 (0.82–4.57) | Age, sex |
| Savica et al., 2012 [23] | 1976–1995 | Rochester Epidemiology Project | U.S. | 196 (121/75) | 71 (2–73 years) | 13 | 196 (121/75) | General population | 17 | Diagnostic criteria | DM or use of glucose-lowering medications | 0.77 (0.37–1.57) | Age, sex |
| Schernhammer et al., 2011 [26] | 2001–2006 | Danish Hospital/Denmark Register | Denmark | 1931 (1121/810) | 72.2± 12.0 (-) | 126 | 9651 (5603/4048) | General population | 482 | ICD-10 code G20, ATC code N04B | ICD codes and ATC NO-4B | 1.36 (1.08–1.71) | Age, sex, and COPD |
| Miyake et al., 2010 [29] | 2006–2008 | 11 hospitals in Japan | Japan | 249 (93/156) | 68.5± 8.6 (within 6 years) | 10 | 368 (141/227) | Hospital setting | 39 | UK PD Society Brain Bank clinical diagnostic criteria | self-administered questionnaires | 0.38 (0.17–0.79) | Age, sex, smoking, area of residence, BMI, education, leisure-time exercise, dietary intake of energy, cholesterol, vitamin E, alcohol and coffee, and the dietary glycemic index |
| Rugbjerg et al., 2009–2006 | 1986–2006 | Danish Hospital/Denmark Register | Denmark | 13695 (7423/6272) | 73.0 (-) | 48 | 68445 (37101/31344) | General population | 223 | ICD-8 code 342 | Medical record | 1.1 (0.8–1.5) | Age, sex |
| D’Amelio et al., -2009 [11] | - | Neurological Department, Palermo | Italy | 318 (153/165)60.8 (59 years) | 13 | 318 (153/165) | General population | 31 | 2 out of 4 cardinal signs, progressive course, good response to anti-parkinsonian drugs | Semistructured questionnaire | 0.4 (0.2–0.8) | Age, sex, education, BMI, occupational status, alcohol and coffee consumption, and smoking habit |
| Becker et al., 2008 [10] | 1994–2005 | General Practice Research Database, UK | U.K. | 3637 (2167/1470) | 90% aged >60 years (-) | 291 | 3637 (2167/1470) | Hospital setting | 308 | OXIMIS codes | Antidiabetes- drug use or diet recommendation in the medical record | 0.95 (0.80–1.14) | Age, sex, BMI, smoking, diuretics, β-blockers, systemic steroids, and comorbidities |
| Scigliano et al., 1970–1987 | 2006 [27] | C. Besta Neurological Institute, Milan | Italy | 178 (92/86) | 58.1 ± 11.4 (16 months) | 6 | 534 (276/258) | Hospital setting | 58 | 2 out of 4 cardinal signs, good response to L-DOPA | Discharge diagnosis | 0.30 (0.13–0.72) | Age and sex |
| Powers et al., 1992–2005 | 2006 [24] | Group Health Cooperative database, Washington | U.S. | 352 (217/135)69 (-) | 26 | 484 (298/186) | Hospital setting | 61 | Neurologist diagnosed, 2 out of 4 cardinal signs | Structured questionnaire | 0.62 (0.38–1.01) | Age, ethnicity, education, and smoking habit |
| Leibson et al., 1976–1995 | 2006 [22] | Olmsted County, Minnesota | U.S. | 197 (-) | 70 ± 11 (-) | 18 | 197 (-) | General population | 24 | REP diagnostic index, diagnostic criteria | ICD-9-CM | 0.7 (0.4–1.4) | Age, sex |
| Herishanu et al., 2001 [9] | 1989–1995 | PD clinic of Soroka University Medical Centre | southern Israel | 93 (-) | - | 11 | 93 (-) | Hospital setting | 26 | 2 out of 4 cardinal signs, progressive course, good response to L-DOPA | Structured questionnaire (T2DM) | 0.35 (0.15–0.75) | Age, sex |
Table 1. Cont.

| Study period          | Resource Location                  | Number of cases (M/F) | Number of control subjects (M/F) | Number of DM cases (M/F) | Mean age at PD onset (years) | Number of DM cases in PD subjects | Number of prior DM cases in control subjects | Number of DM in PD subjects | Number of DM in control subjects | DM assessment of PD | Definition of PD | Number of prior DM cases in PD controls | Number of prior DM cases in control controls | OR (95% CI) | Adjusted variables |
|------------------------|------------------------------------|-----------------------|-------------------------------|-------------------------|-----------------------------|---------------------------------|---------------------------------|----------------|----------------|---------------------------------|---------------------------------|----------------|-------------------|----------------|
| 1989–1990              | General hospitals in Caceres, Spain| 74 (33/41)            | 148 (66/82)                   | 15                       | 64.4 (61-67.3)              | 105 (33/72)                     | 105 (33/72)                     | 16             | 105 (33/72)            | Hospital setting                  | Diagnostic criteria               | 1.6 (0.5-5.1) |
| 1992–1999              | 10 Old Age Homes in Shatin and Tai Po, Hong Kong | 35 (11/24) | 105 (33/72) | 105 (33/72) | 65–87 (26) | 105 (33/72) | 105 (33/72) | 6 | 105 (33/72) | Hospital setting | Diagnostic criteria | 1.6 (0.5-5.1) |
| 1992                    | Gestational diabetes mellitus in Rochester, U.S. | 228 (123/105) | 228 (123/105) | 228 (123/105) | 65–79 (50) | 120 (62/58) | 120 (62/58) | 12 | 120 (62/58) | General population | Physician-diagnosed PD | 29 |

Limitations
This review has several limitations which should be addressed. First, all included case-control studies in the meta-analysis were relied on diagnostic criteria of primary studies included to identify idiopathic PD, regardless of chronic health status. However, diabetes patients are often comorbid with one or more chronic conditions and is also an important risk factor for cardiovascular disease with vascular parkinsonism. We have conduct sensitivity analysis by excluding participants with vascular type parkinsonism, and the results showed that no significant difference was observed in the association with diabetes and PD incidence. Since internationally accepted diagnostic criteria are not yet available, the responsibility of microvascular complications could not be assessed.
| Study                          | Case definition adequate | Representativeness of the cases | Selection of controls | Definition of controls | Comparability based on design analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate | Total scores |
|-------------------------------|--------------------------|--------------------------------|-----------------------|------------------------|---------------------------------------|---------------------------|--------------------------------------------------|-----------------|-------------|
| Skeie et al., 2013 [21]       | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 5           |
| Savica et al., 2012 [23]      | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 8           |
| Schernhammer et al., 2011 [26]| ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 8           |
| Miyake et al., 2010 [29]      | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 5           |
| Rugbjerg et al., 2009 [12]    | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 7           |
| D'Amelio et al., 2009 [11]    | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 7           |
| Becker et al., 2008 [10]      | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 7           |
| Scigliano et al., 2006 [27]   | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 6           |
| Powers et al., 2006 [24]      | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 5           |
| Leibson et al., 2006 [22]     | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 7           |
| Herishanu et al., 2001 [9]    | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 6           |
| Morano et al., 1994 [8]       | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 6           |
| Ho et al., 1989 [28]          | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 6           |
| Kesler, 1972                  | ★★                       | ★                              | ★                     | ★                      | ★                                    | ★                         | ★                                 | ★               | 5           |

doi:10.1371/journal.pone.0085781.t002

Table 2. Newcastle-Ottawa Scale (NOS) assessment of the quality of the studies.
Confounders consideration

An overestimate of the relationship between DM and risk of PD. Publication bias may have resulted in analysis of published data, because of small studies with null results. Finally, the possibility of publication bias is inherent in any meta-analysis of observational studies. We cannot exclude the possibility of potential confounding by various variables that may be associated with the exposure. Fourth, 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. Finally, the possibility of publication bias is inherent in any meta-analysis of published data, because of small studies with null results. Publication bias may have resulted in an overestimate of the relationship between DM and risk of PD.

Confounders consideration

Our finding of a lower risk of PD associated with DM raises questions as to the possible broad range of confounders across studies that may require more consideration to clarify this relationship. Firstly, two out of 14 included studies [12,23] took into account the duration of diabetes with the cutoff of 10 years in the analyses for an increase of PD risk, and both indicated that no associations were found in cases and controls among diabetics. Although prospective studies are less prone to recall and selection biases, the results of two cohort studies are warranted further to unveil the real association between the duration of diabetes and PD risk. Secondly, coffee and caffeine have been linked to both diabetes and PD. Inversely, Xu et al. [7] found higher PD risk (RR 1.75) among diabetics who had diabetes for more than 10 years of the disease; however this finding may undermine the potential ascertainment bias, reverse causality, or common mechanisms that underlie both diabetes and PD. Inversely, Xu et al. [7] found higher PD risk (RR 1.75) among diabetics who had diabetes for more than 10 years of the disease; however this finding may undermine the potential ascertainment bias, reverse causality, or common mechanisms that underlie both diabetes and PD. Inversely, Xu et al. [7] found higher PD risk (RR 1.75) among diabetics who had diabetes for more than 10 years of the disease; however this finding may undermine the potential ascertainment bias, reverse causality, or common mechanisms that underlie both diabetes and PD. Inversely, Xu et al. [7] found higher PD risk (RR 1.75) among diabetics who had diabetes for more than 10 years of the disease; however this finding may undermine the potential ascertainment bias, reverse causality, or common mechanisms that underlie both diabetes and PD. Inversely, Xu et al. [7] found higher PD risk (RR 1.75) among diabetics who had diabetes for more than 10 years of the disease; however this finding may undermine the potential ascertainment bias, reverse causality, or common mechanisms that underlie both diabetes and PD. Inversely, Xu et al. [7] found higher PD risk (RR 1.75) among diabetics who had diabetes for more than 10 years of the disease; however this finding may undermine the potential ascertainment bias, reverse causality, or common mechanisms that underlie both diabetes and PD. Inversely, Xu et al. [7] found higher PD risk (RR 1.75) among diabetics who had diabetes for more than 10 years of the disease; however this finding may undermine the potential ascertainment bias, reverse causality, or common mechanisms that underlie both diabetes and PD.
### Table 3. Univariate analysis: association between Parkinson’s disease (PD) and diabetes preceding PD onset.

| Study                          | Cases            | Controls       | OR (95% CI) P   |
|-------------------------------|------------------|----------------|-----------------|
|                               | Diabetes/tot. %  | Diabetes/tot. %|                 |
| Savica et al., 2012 [23]     | 13/196 6.6       | 17/196 8.7     | 0.67 (0.31–1.48) 0.32 |
| Gender                        | Male 7/121 5.8   | 12/121 9.9     | 0.57 (0.21–1.56) 0.28 |
|                               | Female 6/75 8.0  | 5/75 6.7       | 1.05 (0.28–3.86) 0.95 |
| DM duration                   | 0–9 years before index 5/196 2.6 | 9/196 4.6 | 0.51 (0.17–1.57) 0.24 |
|                               | ≥10 years before index 8/196 4.1 | 8/196 4.1 | 0.88 (0.30–2.54) 0.81 |
| Schernhammer et al., 2011All individuals [26] | 126/1931 6.5 | 482/9651 5.0 | 1.35 (1.10–1.65) - |
| Gender                        | Male 79/1121 7.0 | 305/5603 5.4 | 1.33 (1.03–1.72) - |
|                               | Female 47/810 5.8 | 177/4048 4.4 | 1.38 (0.99–1.92) - |
| Age at PD onset               | <60 17/257 6.6  | 29/1286 2.3   | 3.07 (1.65–5.70) - |
|                               | ≥60 109/1674 6.5 | 453/8365 5.4 | 1.24 (0.99–1.53) - |
| Antidiabetes drug prescription | Insulin prescription 19/1931 1.0 | 81/9651 0.8 | 1.22 (0.74–2.02) - |
|                               | Oral antidiabetes drug 107/1931 5.5 | 401/9651 4.1 | 1.37 (1.10–1.71) - |
| Rugbjerg et al., 2009 [12]   | All individuals 48/13695 0.4 | 223/68445 0.3 | 1.1 (0.8–1.5) - |
| DM duration                   | 5–9 years 31/13695 0.2 | 161/68445 0.2 | 1.0 (0.7–1.4) - |
|                               | 10–14 years 15/13695 0.1 | 51/68445 0.1 | 1.5 (0.8–2.6) - |
|                               | ≥15 years 2/13695 0.0 | 11/68445 0.0 | 0.9 (0.2–4.2) - |
| D’Amello et al., 2009 [11]   | All individuals 13/318 4.1 | 31/318 9.8 | 0.4 (0.2–0.8) 0.007 |
| Gender                        | Male 8/153 5.2 | 17/153 11.1 | 0.4 (0.2–1.0) 0.05 |
|                               | Female 5/165 3.0 | 14/165 8.5 | 0.4 (0.1–1.0) 0.05 |
| Age at interview              | <66.7 8/180 4.5 | 17/178 9.6 | 0.4 (0.1–1.0) 0.05 |
|                               | ≥66.7 5/138 3.6 | 14/140 10.0 | 0.4 (0.2–1.0) 0.05 |
| Age at PD onset               | <60.8 2/140 1.4 | 8/143 5.6 | 0.2 (0.1–1.1) 0.07 |
|                               | ≥60.8 11/178 6.2 | 23/175 13.1 | 0.5 (0.2–1.0) 0.04 |
| BMI                           | <26.1 4/179 2.2 | 9/173 5.2 | 0.4 (0.1–1.3) 0.1 |
|                               | ≥26.1 9/139 6.5 | 22/145 15.2 | 0.4 (0.2–0.9) 0.03 |
| Smoking                       | Ever 6/126 4.8 | 14/138 10.1 | 0.3 (0.1–0.9) 0.02 |
|                               | Never 7/192 3.7 | 17/180 9.4 | 0.5 (0.2–1.2) 0.1 |
| Alcohol                       | Ever 8/155 5.2 | 19/165 11.5 | 0.5 (0.2–1.1) 0.07 |
|                               | Never 5/163 3.1 | 12/153 7.8 | 0.4 (0.1–1.0) 0.06 |
1.34; 95% CI 0.75–2.39), but not in men (OR 0.99; 95% CI 0.63–1.53). Breast cancer in women showed no association with PD, and prostate cancer risk was associated with a slightly reduced PD risk (OR 0.77; 95% CI 0.33–1.79). No consistent association with other cancers were observed. Leibson et al. [22] found that PD with age at onset under 70 years was associated with increased likelihood of being assigned a diagnosis of all type of cancer; however, because of limitations in statistical power, the 95% confidence intervals were wide. However, no study focused on an association between cancer and PD among diabetics. Fifthly, two included studies showed that increased BMI had no significant association with PD onset [10,23], while BMI was commonly recognized as a major anthropometric obesity indicator that have a substantial association with future diabetes risk [42,43]. Conversely, D’Amelio et al. [11] reported that diabetes patients with a BMI of $26.1$ kg/m² have a negative association with PD incidence (OR 0.4; 95% CI 0.2–0.9), but no significant difference with a BMI of $\geq 26.1$ kg/m² (OR 0.4; 95% CI 0.1–1.3). Was PD in fact inversely associated with diabetes for a possible effect of BMI? Obesity paradox in diabetes mellitus was also found in

Table 3. Cont.

| Study                          | Cases                              | Controls                           | OR (95% CI)   | P      |
|--------------------------------|------------------------------------|------------------------------------|---------------|--------|
|                                | Diabetes/tot. %                    | Diabetes/tot. %                    |               |        |
| Powers et al., 2006 [24]       | Ever 12/267 4.5                    | 28/296 9.5                         | 0.5 (0.2–0.9) | 0.03   |
|                                | Never 1/51 2.0                     | 3/22 13.6                          | 0.2 (0.1–1.5) | 0.1    |
|                                | Gender                             |                                    |               |        |
|                                | Male 16/217 7.4                    | 43/298 14.4                         | 0.52 (0.28–0.97) | -    |
|                                | Female 10/135 7.4                  | 18/286 6.3                         | 0.80 (0.35–1.83) | -    |
| Smoking                        | Ever 16/155 10.3                   | 36/285 12.6                         | 0.80 (0.43–1.49) | -    |
|                                | Never 10/197 5.1                   | 25/199 12.6                         | 0.37 (0.17–0.80) | -    |
| Leibson et al., 2006 [22]     | All individuals 18/197 9.1         | 24/197 12.2                         | 0.7 (0.4–1.4) | -      |

Table 4. Subgroup analysis of the association between diabetes mellitus (DM) and Parkinson’s disease.

| Category of variables | Variables of study characteristics | Number of studies | OR (95% CI)   | $i^2$ | P-value heterogeneity |
|-----------------------|-----------------------------------|-------------------|---------------|------|----------------------|
| Gender                | Male                              | 5                 | 0.71 (0.40–1.23) | 74%  | 0.004                |
|                       | Female                            | 5                 | 0.79 (0.41–1.49) | 68%  | 0.01                 |
| Geographic location   | Europe                            | 7                 | 0.94 (0.69–1.28) | 77%  | 0.0002               |
|                       | North America (U.S.)              | 4                 | 0.61 (0.45–0.83) | 0    | 0.85                 |
|                       | Asia                              | 3                 | 0.54 (0.23–1.27) | 68%  | 0.04                 |
| Source of the control | Hospital setting                  | 7                 | 0.88 (0.62–1.25) | 72%  | 0.002                |
|                       | General population                | 7                 | 0.63 (0.40–0.99) | 75%  | 0.0004               |
| DM duration           | $<10$ years                       | 2                 | 0.90 (0.63–1.30) | 0    | 0.34                 |
|                       | $\geq 10$ years                   | 2                 | 1.27 (0.79–2.05) | 0    | 0.59                 |
| Antidiabetes drug     | Insulin prescription              | 2                 | 1.18 (0.74–1.89) | 0    | 0.93                 |
| Smoking               | Ever                              | 2                 | 0.67 (0.40–1.13) | 0    | 0.33                 |
|                       | Never                             | 2                 | 0.37 (0.21–0.66) | 0    | 0.97                 |
| DM assessment         | Medical record                    | 6                 | 0.92 (0.70–1.21) | 72%  | 0.003                |
|                       | Questionnaire                     | 7                 | 0.57 (0.39–0.85) | 54%  | 0.04                 |
mortality. Adults who are normal weight at the time of incident diabetes have higher mortality than adults who are overweight or obese [44]. Diabetes induced by the metabolic stress of obesity may be a fundamentally different problem from diabetes that develops in the absence of the stress of obesity among PD patients. Mechanisms to explain negative association between PD with comorbid diabetes and obesity are unknown.

Public Health Implication

The incidence rate of PD among diabetes patients increased with age and was dramatically high in patients aged >65 years [1,31], as age confirmed a proverbial effect modifier of increasing PD prevalence. Although age was not stratified by subgroups in the present review, the mean age of PD onset was over 60 years. Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α, encoded by PPARGC1) was identified as a potential therapeutic target for early intervention in PD patients with diabetes[45,46], and glucagon-like peptide-1 (GLP-1) and its analogues could also be possible treatments for cognitive deficits in individuals with neurodegenerative disorders [47,48]. This meta-analysis suggested that insulin prescription of DM may not have much impact on the relationship between diabetes and risk of PD, whereas oral anti-diabetes drug appeared to increase PD risk.

Biological Plausibility

The possible mechanisms underlying the association of diabetes with a decreased PD risk are the mutual pathophysiological interactions. First, the coexistence of dopaminergic neurons and insulin receptors in the substantia nigra suggested a direct association between the two diseases [49]. Second, sirtuins, an evolutionarily conserved class of seven proteins (SIRT 1–7) regulating a variety of cellular functions such as genome maintenance, longevity, and metabolism [50], possesses antagonizing effect on a target’s activity despite having the same molecular target [51]. SIRT1 activators will exert their activity protecting individuals from diabetes [51], while inhibition of SIRT2 would protect dopaminergic cell against death both in vitro and in a drosophila model of PD [52]. Third, genetic susceptibility, lifestyle choices, and exposure to toxic environmental factors may lead to mitochondrial dysfunction [3,53], endoplasmic reticulum (ER) stress [54,55], inflammation [56–58], impaired glucose tolerance/insulin resistance[3,52,59], and metabolic dysregulation [60]. The dysregulation of these pathways may ultimately lead to neurodegenerative disease and/or diabetes [2,3]. In the subgroup analysis according to geography location, we found that an inverse association between diabetes and the prevalence of PD in U.S. population, but discordant results obtained in Asia and Europe. This heterogeneity of results across populations with different ancestry boosts the possibility of a genetic influence. However, the biological mechanism behind the association of and PD risk and diabetic patients is far not clear.

Conclusions

Diabetic individuals had a decreased incidence of PD despite heterogeneity in study design, geographic area, assessment of exposure and outcome, and control of potential confounders. More researches, both epidemiological and mechanistic, are warranted to clarify an understanding of the association between diabetes and risk of PD.

Supporting Information

Appendix S1 Search strategies. (DOC)

Appendix S2 PRISMA checklist. (DOC)

Author Contributions

Conceived and designed the experiments: GQZ. Performed the experiments: LL, HQL, AJL, JHL. Analyzed the data: LL, DLF, HQL, AJL, JHL. Contributed reagents/materials/analysis tools: LL, DLF. Wrote the paper: LL, DLF, GQZ.
30. Shapiro S (1997) Is meta-analysis a valid approach to the evaluation of small studies? J Clin Epidemiol 50: 223–229.
31. Sun Y, Chang YH, Chen HF, Su YH, Su HF, et al. (2012) Risk of Parkinson disease onset in patients with diabetes: a 24-year population-based cohort study with age and sex stratifications. Diabetes Care 35: 1002–1009.
32. Scheuing N, Best F, Dapp A, Drehsang P, Feli HP, et al. (2013) Multicentre analysis of 178,992 type 2 diabetes patients revealed better metabolic control despite higher rates of hypertension, stroke, dementia and repeated inpatient care in patients with comorbid Parkinson’s disease. Parkinsonism Relat Disord 19: 687–692.
33. Cereda E, Barichella M, Cassani E, Caccialanza R, Pezzoli G (2012) Clinical features of Parkinson disease when onset of diabetes came first: A case-control study. Neurology 78:1507–1514.
34. Qi H, Li S (2013) Dose-response meta-analysis on coffee, tea and caffeine consumption risk of Parkinson’s disease. Geriatr Gerontol Int: 10.1111/ggi.12123.
35. Jiang X, Zhang D, Jiang W (2013) Coffee and caffeine intake and incidence of type 2 diabetes mellitus: a meta-analysis of prospective studies. Eur J Nutr. [Epub ahead of print].
36. Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernandez-Crehuet Navajas R (2009) Smoking and Parkinson’s disease: systematic review of case-control studies. Parkinsonism Relat Disord 15: 660–664.
37. Willi C, Bodenmann P, Gahl WA, Fares PD, Cornuz J (2007) Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 298: 2654–2664.
38. Fagerhol MH, Linson PM (2009) Smoking and diabetes—the double health hazard! Prim Care Diabetes 3: 205–209.
39. Tomstad S (2009) Cigarette smoking, smoking cessation, and diabetes. Diabetes Res Clin Pract 85: 4–13.
40. Chai Y, Giovannucci E, Lee JE (2012) Glycemic index and glycemic load in relation to risk of diabetes-related cancers: a meta-analysis. Br J Nutr 108: 1934–1947.
41. Rughberg K, Friis S, Jensen LB, Bjerregaard N, Eriksen IE, et al. (2009) Reduced risk factors for vascular disorders in Parkinson disease patients: a case-control study. Stroke 40: 1184–1189.
42. Kodama S, Horikawa C, Fukushima H, Irie Y, Hirasawa R, et al. (2012) Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratios: a meta-analysis. Am J Epidemiol 176: 959–969.
43. Biggs ML, Mokhail KL, Luchsinger JA, Iliff JH, Carnethon MR, et al. (2010) Association between adiposity in midlife and older age and risk of diabetes in older adults. JAMA 303: 2594–2592.
44. Carnethon MR, De Chavez J, Biggs ML, Lewis CE, Pankow JS, et al. (2012) Association of weight status with mortality in adults with incident diabetes. JAMA 308: 591–599.
45. Zheng B, Liao Z, Lucassen JJ, Loensak KA, Roeder BK, et al. (2010) PGC-1alpha, a potential therapeutic target for early intervention in Parkinson’s disease. Sci Transl Med 2: 52ra73.
46. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, et al. (2003) PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat Genet 34: 267–273.
47. McIntyre RS, Powell AM, Kaidanovich-Beilin O, Soczynska JK, Alsuwaidan M, et al. (2013) The neuroprotective effects of GLP-1: possible treatments for cognitive deficits in individuals with mood disorders. Behav Brain Res 237: 164–171.
48. McClean PL, Gaul VA, Harriott P, Holcher C (2010) Glucagon-like peptide-1 analogues enhance synaptic plasticity in the brain: a link between diabetes and Alzheimer’s disease. Eur J Pharmacol 630: 158–162.
49. Young JW, Livingston JN, Moss AM (1991) Insulin receptors in the central nervous system: localisation, signalling mechanisms and functional aspects. Prog Neurobiol 36: 341–362.
50. Milne JC, Denu JM (2008) The Sirtuin family: therapeutic targets to treat diseases of aging. Curr Opin Chem Biol 12: 111–117.
51. Dilibin A, Kelly JW (2007) Medicine. The yin-yang of sirtuins. Science 317: 461–462.
52. Outeiro TF, Kontopoulos E, Altman SM, Karasev I, Strathern KE, et al. (2007) Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson’s disease. Neurobiol Dis 29: 377–386.
53. Unger JW, Livingston JN, Moss AM (1991) Insulin receptors in the central nervous system: localisation, signalling mechanisms and functional aspects. Prog Neurobiol 36: 341–362.
54. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, et al. (2000) Prevalence of Parkinson’s disease in Europe: A collaborative study of population-based cohorts. Neurology 54: 1169–1173.
55. Santos RX, Carvalho C, Carbonato SF, de Carvalho AC, de Souza M, et al. (2009) Sirtuin 2 mediates the protective effects of resveratrol against α-synuclein-induced toxicity. Brain Res 1288: 99–109.
56. Scigliano G, Musico M, Soliveri P, Piccolo I, Ronchetti G, et al. (2006) Decreased risk factors for vascular disorders in Parkinson disease patients: a case-control study. Stroke 37: 1184–1189.
57. Do SC, Joo JY, Lee CM (1989) Epidemiologic study of Parkinson’s disease in Korea. Hong. Neurology 39: 1314–1318.
58. Miyake Y, Tanaka K, Fukushina W, Sasaki S, Kiyohara C, et al. (2010) Case-control study of risk of Parkinson’s disease in relation to hyperglycemia, hypercholesterolemia, and diabetes in Japan. J Neurol Sci 289: 82–96.
59. Shapira S (1997) Is meta-analysis a valid approach to the evaluation of small effects in observational studies? J Clin Epidemiol 50: 223–229.
58. Song IJ, Kim JS, Chung SW, Lee KS (2009) Is there an association between the level of high-sensitivity C-reactive protein and idiopathic Parkinson’s disease? A comparison of Parkinson’s disease patients, disease controls and healthy individuals. Eur Neurol 62: 99–104.

59. Peila R, Rodriguez BL, White LR, Launer LJ (2004) Fasting insulin and incident dementia in an elderly population of Japanese-American men. Neurology 63: 220–223.

60. Vincent A, Briggs L, Chatwin GF, Emery E, Tomlins R, et al. (2012) Parkin-induced defects in neurophysiology and locomotion are generated by metabolic dysfunction and not oxidative stress. Hum Mol Genet 21: 1760–1769.