ARTICLE

# Association between diabetes and subsequent Parkinson disease

## A record-linkage cohort study

Eduardo De Pablo-Fernandez, MD, Raph Goldacre, MSc, Julia Pakpoor, BM BCh, Alastair J. Noyce, MRCP, PhD,* and Thomas T. Warner, FRCP, PhD*

**Correspondence**
Prof. Warner
t.warner@ucl.ac.uk

## Abstract

### Objective
To investigate the association between type 2 diabetes mellitus (T2DM) and subsequent Parkinson disease (PD).

### Methods
Linked English national Hospital Episode Statistics and mortality data (1999–2011) were used to conduct a retrospective cohort study. A cohort of individuals admitted for hospital care with a coded diagnosis of T2DM was constructed, and compared to a reference cohort. Subsequent PD risk was estimated using Cox regression models. Individuals with a coded diagnosis of cerebrovascular disease, vascular parkinsonism, drug-induced parkinsonism, and normal pressure hydrocephalus were excluded from the analysis.

### Results
A total of 2,017,115 individuals entered the T2DM cohort and 6,173,208 entered the reference cohort. There were significantly elevated rates of PD following T2DM (hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.29–1.35; $p < 0.001$). The relative increase was greater in those with complicated T2DM (HR 1.49, 95% CI 1.42–1.56) and when comparing younger individuals (HR 3.81, 95% CI 2.84–5.11 in age group 25–44 years).

### Conclusions
We report an increased rate of subsequent PD following T2DM in this large cohort study. These findings may reflect shared genetic predisposition and/or disrupted shared pathogenic pathways with potential clinical and therapeutic implications.

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## Glossary

**CI** = confidence interval; **HES** = Hospital Episode Statistics; **HR** = hazard ratio; **ICD-10** = *International Classification of Diseases, Tenth Revision*; **PD** = Parkinson disease; **T2DM** = type 2 diabetes mellitus.

An association between diabetes mellitus and future risk of Parkinson disease (PD) has been postulated although evidence remains equivocal.[1,2] Cohort studies have shown conflicting results, but a meta-analysis reported an increased pooled relative risk of developing PD after diabetes mellitus.[2] We aimed to use national record-linkage to evaluate whether preexistent type 2 diabetes mellitus (T2DM) was associated with subsequent PD in a large hospital cohort.

## Methods

### Population and data

A retrospective cohort study was conducted using data from English national Hospital Episode Statistics (HES) and mortality data (January 1999 to December 2011). HES records incorporate every episode of day-case (admission without overnight stay) or inpatient care (at least 1 overnight stay) in all National Health Service hospitals in England. A cohort of individuals with T2DM (exposed cohort) was constructed by identifying for each individual the earliest known episode of day-case or inpatient admission in which T2DM was coded (ICD-10 code E11) in any diagnostic position within the study period. A reference cohort comprised all individuals without a coded diagnosis of T2DM admitted for a range of minor medical and surgical procedures (see table footnote). Individuals were excluded if they had record of PD (ICD-10 code G20) dated either before or at the same time as the earliest known T2DM record or, in the unexposed cohort, their admission for their reference condition. Exposed and reference cohorts were then searched for any subsequent hospital admission with a diagnosis of PD.

Individuals with a code for ischemic cerebral infarction (ICD-10 code I63), vascular parkinsonism (ICD-10 code G21.4), drug-induced secondary parkinsonism (ICD-10 code G21.1), or normal pressure hydrocephalus (ICD-10 code G91.2) recorded at any time were excluded from both cohorts.

### Statistical analysis

Date of entry was the date of the first recorded episode of hospital admission coded for T2DM or any reference condition. Date of first hospital admission coded for PD in any position (ICD-10 code G20), or death, or date of end of data collection (whichever occurred first) constituted the date of exit.

Multivariable Cox proportional hazard regression models were used to estimate the risk of a subsequent diagnosis of PD. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated and adjusted for age, sex, calendar year of cohort entry, region of residence, and patients' quintile of Index of Multiple Deprivation score (a measure of area-level deprivation). Subgroup analyses were subsequently conducted to assess whether the HRs differed by age group, by length of follow-up, or by the presence of T2DM-related complications (see table footnote).

### Standard protocol approvals, registrations, and patient consents

The construction, maintenance, and analysis of the dataset for research were approved by the Central and South Bristol Research Ethics Committee (04/Q2006/176).

### Data availability

All data were obtained from National Health System Digital (formerly the Health and Social Care Information Centre) and the Office for National Statistics. Onward sharing of deidentified individual-level data is prohibited by the data sharing agreements with these data providers, but such data may be available from the data providers directly. Aggregated summary data may be available from the corresponding author where the data requested are considered appropriate and relevant to this study.

## Results

A total of 2,017,115 individuals entered the T2DM cohort and 6,173,208 people entered the reference cohort. Results showed an overall higher rate of subsequent PD in the T2DM cohort with an adjusted HR of 1.32 (95% CI 1.29–1.35). Subgroup analysis revealed a substantially higher relative rate in younger individuals and those with complicated T2DM (table). In the T2DM cohort aged 25–44, 58 of 130,728 people had subsequent PD, compared with 280 of 2,559,693 in the reference cohort. For those over 75 years, these figures were 7,371 out of 664,709, and 10,105 out of 752,104, respectively. The following sensitivity analyses were performed but none of them materially affected the point estimate and a significant association remained (table): (1) to assess the potential possibility of surveillance bias and reverse causality, those with an interval between the earliest record of T2DM and PD <1 year were excluded; (2) to evaluate potential outcome misclassification, patients with a diagnosis of schizophrenia or other psychotic disorders (ICD 10 code F20–29), other forms of secondary parkinsonism (ICD-10 codes G21 and G22), degenerative diseases of the basal ganglia (ICD-10 code G23), essential tremor (ICD-10 code G25.0), and drug-induced and other forms of tremor (ICD-10 codes G25.1 and G25.2) were excluded; and (3) to mitigate surveillance bias, results were also controlled by total number of admissions per individual.

## Discussion

Our results support an increased risk of PD in patients with previous T2DM. The magnitude of association was higher in

**Table** HRs and associated 95% CIs in the exposed T2DM cohort compared with the reference cohort[a]

|  | PD observed | HR | 95% CI | p Value |
|---|---|---|---|---|
| **T2DM cohort (N = 2,017,115)** | 14,252 | 1.32 | 1.29–1.35 | <0.001 |
| **Age group** |  |  |  |  |
| 25–44 y (n = 130,728) | 58 | 3.81 | 2.84–5.11 | <0.001 |
| 45–64 y (n = 650,387) | 1,711 | 1.71 | 1.61–1.81 | <0.001 |
| 65–74 y (n = 571,291) | 5,112 | 1.40 | 1.35–1.45 | <0.001 |
| ≥75 y (n = 664,709) | 7,371 | 1.18 | 1.14–1.21 | <0.001 |
| **Sex** |  |  |  |  |
| Men (n = 1,068,269) | 8,713 | 1.27 | 1.23–1.30 | <0.001 |
| Women (n = 948,846) | 5,539 | 1.42 | 1.37–1.47 | <0.001 |
| **T2DM-PD coded admission time interval, y** |  |  |  |  |
| <1 | 3,030 | 1.44 | 1.37–1.52 | <0.001 |
| >1 | 11,222 | 1.29 | 1.26–1.33 | <0.001 |
| 1–4 | 6,958 | 1.30 | 1.26–1.34 | <0.001 |
| 5–9 | 3,737 | 1.28 | 1.23–1.33 | <0.001 |
| ≥10 | 527 | 1.32 | 1.19–1.46 | <0.001 |
| **T2DM-related complications[b]** |  |  |  |  |
| Complicated T2DM (n = 180,593) | 1,824 | 1.49 | 1.42–1.56 | <0.001 |
| Uncomplicated T2DM (n = 1,836,522) | 12,428 | 1.30 | 1.27–1.33 | <0.001 |
| **Controlling by total no. of admissions per individual** |  | 1.31 | 1.28–1.34 | <0.001 |

Abbreviations: CI = confidence interval; HR = hazard ratio; ICD-10 = *International Classification of Diseases, Tenth Revision*; PD = Parkinson disease; T2DM = type 2 diabetes mellitus.
[a] Conditions used in the reference cohort included any of the following: otitis, varicose veins, hemorrhoids, upper respiratory tract infections, nasal polyps, tonsillectomy, teeth disorders, inguinal hernia, nail diseases, sebaceous cyst, internal derangement of knee, bunions, contraceptive management, dislocations/sprains/strains, bruising, gallbladder disease, appendectomy, hip replacement, knee replacement.
[b] Complicated T2DM was defined by the presence of a hospital episode coded for diabetic neuropathy (ICD-10 code G63.2), diabetic nephropathy (N08.3), or diabetic retinopathy (H36.0).

individuals with T2DM who were younger or had T2DM complications. The main strengths of this study are the large size of the HES database with stratification of relative risks by age group, sex, and T2DM complications, the cohort design, and the ability to exclude patients with cerebrovascular disease, and drug-induced and vascular parkinsonisms. HES dataset includes all National Health Service hospitals in England and, because health care is free to access, it is considered to be representative of the entire population, and results are likely generalizable.

Previous cohort studies have shown a positive[3,4] or no association[5] between preexisting T2DM and PD. The magnitude of association in our study is similar to the pooled estimate from a meta-analysis that included 5 studies with a total population of 681,000 (HR 1.26, 95% CI 1.03–1.55),[2] although the size of our study is far greater, with tight CIs around the point estimate. There was significant heterogeneity in the studies included in the previous meta-analysis ($I^2$ = 60.2%; $p$ = 0.039), which would have affected precision, and

is likely attributable to differences in study design (hospital-based as in our study, health/professional registries,[3] or population-based[4,5]), study population (results differ between Europe[4] and mainland United States[5]), ascertainment of PD and T2DM (self-reported, drug/medical registries, or physician-confirmed diagnosis), and adjustment for confounding factors.

The magnitude of risk in our study was greater in younger individuals whereby genetic factors may relatively exert more of an effect, and more than 400 genes, previously identified through genome-wide association studies, have been closely linked to both conditions using integrative network analysis.[6] However, the association in elderly patients may be the consequence of disrupted insulin signaling secondary to additional lifestyle and environmental factors causing cumulative pathogenic brain changes. This is supported by the higher risk among those with complicated T2DM in our cohort, and those with long T2DM disease duration (>10 years) reported in previous studies.[3,7] Whether attributable to

genetic predisposition, environmental factors, or both, disrupted brain insulin signaling could lead to shared dysregulated cellular pathways including neuroinflammation (microglia activation, production of proinflammatory cytokines), mitochondrial dysfunction, and increased oxidative stress ultimately promoting synuclein aggregation and contributing to the development of PD.[8]

Restoration of brain insulin signaling could have neuroprotective effects and antidiabetic drugs are currently being repurposed as potential PD treatments.[8] A recent double-blind trial involving 62 patients with PD randomly assigned to placebo or exenatide 2-mg weekly injections showed positive and persistent effects on motor symptoms measured by section 3 of the Movement Disorder Society–Unified Parkinson's Disease Rating Scale.[9] Whether the effect is secondary to symptomatic benefit or neuroprotection remains unclear.

Limitations of the study include lack of clinical information for PD ascertainment beyond routinely collected data. However, in England, PD diagnosis is based on recommendations by national clinical guidelines and it is common clinical practice for patients with suspected diagnosis to be referred untreated to a movement disorder specialist for diagnosis confirmation.[10] In addition, individuals with cerebrovascular disease, secondary parkinsonism, and other movement disorders that could potentially be misdiagnosed as PD were excluded to reduce potential diagnostic misclassification. The study used routinely collected data, and we were unable to adjust for other potential confounders such as antidiabetic medication or smoking. Because this is a hospital-based study, potential selection bias cannot be ruled out (although this is mitigated by using a hospital-based reference cohort), and individuals included in the T2DM cohort may represent the more severe spectrum of disease. Moreover, the study uses prevalent T2DM cases based on first recorded hospital diagnosis and is not a follow-up from first point of onset.

This national record-linkage cohort study suggests an increased risk of PD in patients with T2DM. Our results support the link between these 2 conditions, which may be the result of genetic predisposition and/or disrupted shared pathogenic pathways with potential clinical and therapeutic implications.

## Author contributions

E.D.P.-F., A.J.N., and T.T.W. proposed the study. E.D.P.-F. and J.P. wrote the first draft of the manuscript. R.G. and J.P. designed and conducted the analysis. R.G. is the guarantor of the study. All authors contributed to the interpretation of the data and edited the manuscript for important intellectual content.

## Disclosure

E. De Pablo-Fernandez, R. Goldacre, and J. Pakpoor report no disclosures relevant to the manuscript. A. Noyce has received grants from Parkinson's UK, Élan/Prothena Pharmaceuticals, GE Healthcare; advisory board membership for myHealthPal; honoraria from Office Octopus, Henry Stewart Talks, and Britannia Pharmaceuticals Ltd., all outside of the submitted work. T. Warner receives research support from Brain Research Trust, Cure Huntington's Disease Initiative, Medical Research Council, and Corticobasal Degeneration Solutions. Go to Neurology.org/N for full disclosures.

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