Investigating the Relationship Between Type 2 Diabetes and Parkinson's Disease Using Electronic Medical Records in the GoDARTS Bioresource

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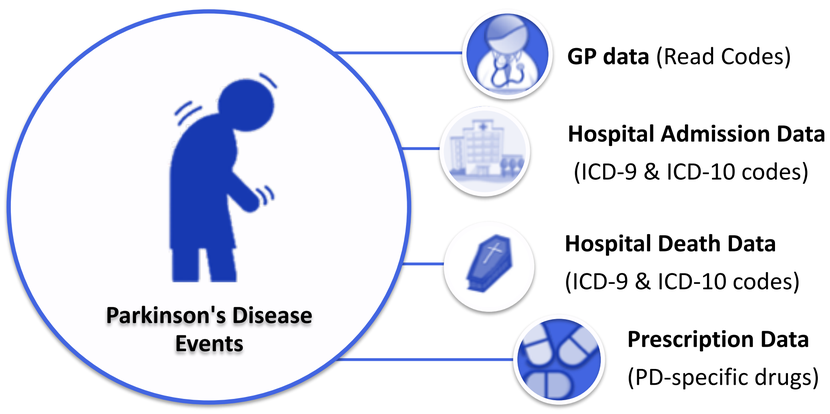
Introduction

Type 2 Diabetes (T2D) and **Parkinson's Disease (PD)** are both increasing in incidence, and thus, so is their associated healthcare burden. Previous studies have suggested that **T2D may increase the risk of developing PD**[1] but others have found no or an inverse association[2,3].

- Better understanding of the link between the two conditions may enable the implementation of preventative lifestyle and/or clinical interventions.
- Insulin resistance is characteristic of T2D, and through associated pathological mechanisms (e.g. hyperglycaemia, amyloid aggregation, inflammation, mitochondrial dysfunction) results in decreased pancreatic beta-cell function[4].
- **Insulin resistance-related mechanisms have been suggested to also be involved in the development and progression of PD**[5], resulting in reduced function and loss of dopaminergic neurones of the substantia nigra[4].
- GoDARTS comprises a large study of T2D case and control subjects with longitudinal follow-up in electronic medical records (EMR)[6]. The large amount of data available within GoDARTS makes it a useful resource to investigate the link between T2D and PD.
- It may be that other genetic and lifestyle factors are implicated in both T2D and PD. As the leading cause of death in T2D patients is cardio-vascular disease (CVD), we investigated the impact of various CVD risk factors.

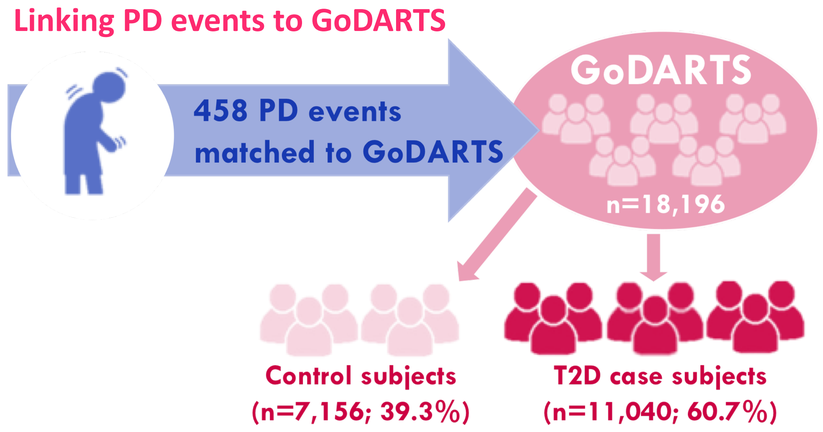
Methods

Adjudication of PD from the EMR



458 PD events were identified from the above data sources.

Linking PD events to GoDARTS



This prospective case-control designed study used the GoDARTS bioresource to determine the risk of T2D status for incident PD that accounted for competing risk of death. Cause-specific and sub-distributional hazards were used to compare hazards of PD. Age and sex were included in all models.

Individuals were followed up from 45 years of age, until the earliest PD event recorded in the EMR. Censoring was the earliest date of non-PD death, or the end of available EMR data. Individuals with evidence of PD prior to entry date were excluded from the analysis.

We then used the T2D cohort to examine differences in characteristics between subjects with or without a PD event. We also considered a genome-wide polygenic risk score for CVD (CVDprs) to see whether genetic factors influencing CVD outcomes were important in PD.

Results 1: Case-control population characteristics

	Control subjects	T2D case subjects	Overall
Age, mean (SD), years	**60.5** (13.3)*	**64.6** (12.3)*	63.0 (12.8)
Female, n (%)	3,673 (**51.3**)†	4,839 (**43.8**)†	8,512 (46.8)
Total PD events, n (%)	133 (**1.9**)†	325 (**2.9**)†	458 (2.5)
Total time, years (% total)	5.2 (38.5)	8.4 (61.5)	13.6
Rate (95% CI)	**25.2** (21.3-29.9)‡	**38.8** (34.8-43.3)‡	33.6 (30.7-36.9)

Table 1: Crude incidence rates of Parkinson's Disease (PD) by Type 2 Diabetes (T2D) status

*Total time and rate = per 100,000 person-years. *P<0.001, t test. †P<0.001, Chi-square test. ‡P<0.0001, Mantel-Haenszel estimate, controlling for age. SD = standard deviation; CI = confidence interval.*

T2D subjects developed PD at a significantly greater rate than controls (38.8 vs 25.2; p<0.001). The overall incidence rate was 33.6 per 100,000 person-years.

Results 2: Impact of T2D status on incident Parkinson's Disease

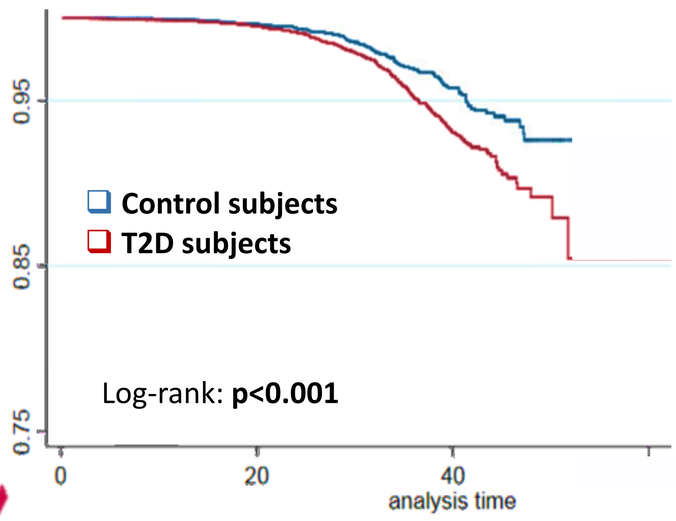
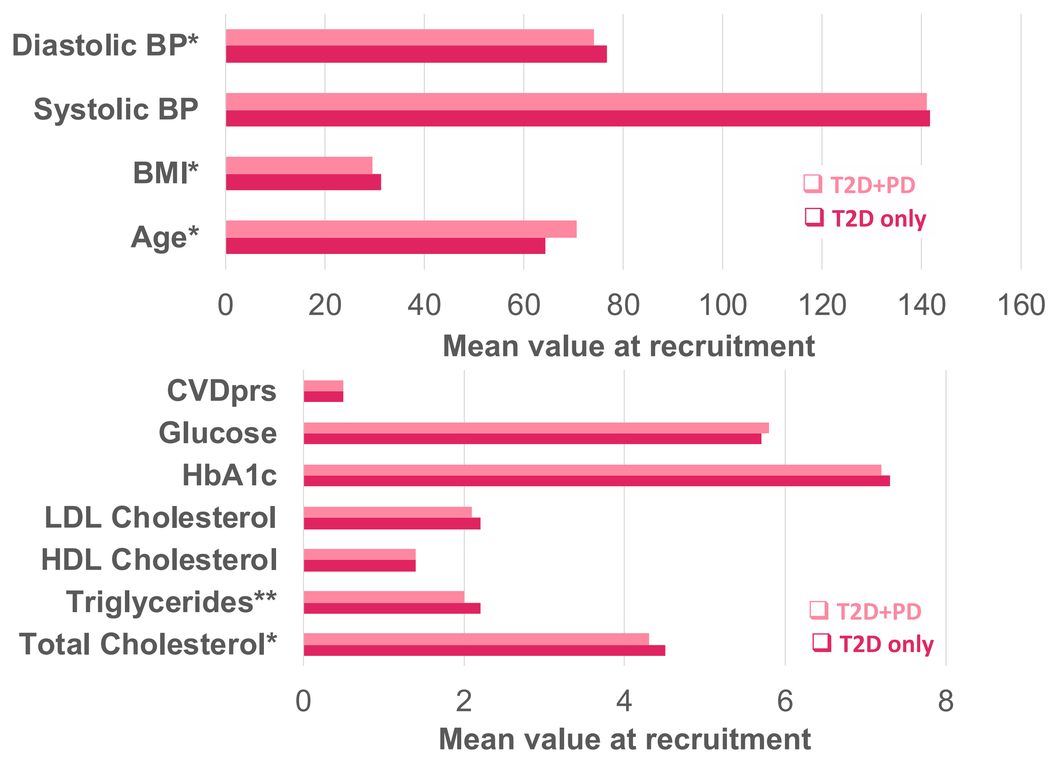


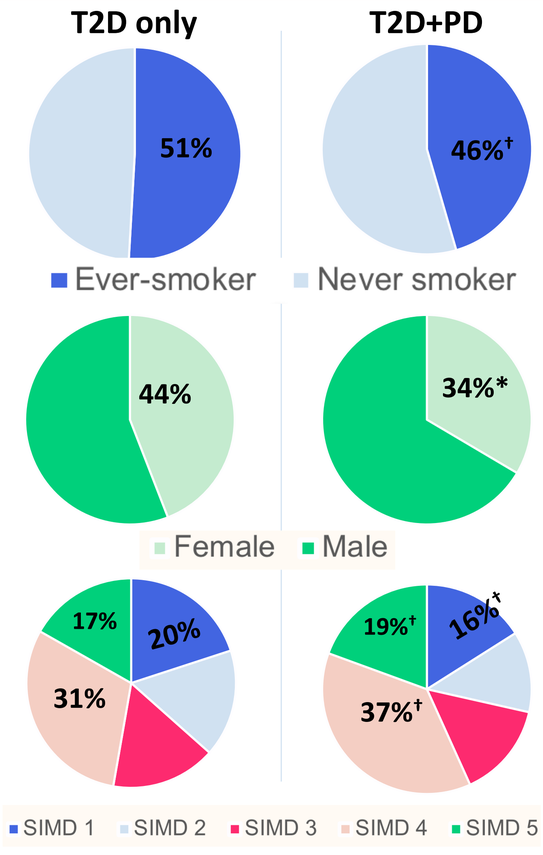
Figure 1: Kaplan-Meier survival functions
(adjusted from 45 years of age)

	csHR			sdHR		
	HR	95%CI	P	HR	95%CI	P
T2D	**1.40**	1.14-1.73	1.17 x10^{-3}	**1.18**	0.96-1.45	0.11
Age	**0.97**	0.96-0.99	2.89 x10^{-5}	**1.01**	1.00-1.02	8.20 x10^{-3}
Female	**0.51**	0.42-0.62	3.85 x10^{-11}	**0.55**	0.45-0.67	3.64 x10^{-9}

Table 2: Hazard Ratio (HR) of PD by T2D status
csHR= cause-specific HR; sdHR= subdistribution HR

Results 3: Different characteristics in T2D patients with or without a PD event





*t-test, p<0.001; **t-test, p<0.05; †Chi-square test, p<0.05; BMI = body mass index; CVDprs = CVD polygenic risk score; SIMD = Scottish Index of Multiple Deprivation*

Conclusions

- **In GoDARTS, T2D is associated with an increased risk of PD (csHR=1.40, p=0.0011)**, however, this association is weakened when accounting for competing risks (sdHR=1.18, p=0.11).
- Parkinson's UK (2015) reported an incidence rate of 33.4 per 100,000 person-years in people aged 45 years and above[7]. The likeness of this value and the incidence rate obtained from our study highlights the accuracy and potential value of bioresources linked to EMR to study PD.
- The negative association of CVD risk factors (e.g. raised triglycerides and total cholesterol levels, high BMI, smokers) with PD amongst T2D subjects indicates that the **association between T2D and PD may be better explained by pathogenic mechanisms implicated in insulin resistance and hyperglycaemia**, than mechanisms related to CVD risk.
- **T2D subjects with particular characteristics may be more susceptible to PD than others.** Continuing research into the phenotypic subtypes of T2D will enable us to stratify the risk of disease progression in specific T2D subtypes, as well as determine their susceptibility to neurodegenerative conditions.
- **Further establishing the link between T2D and PD will help us implement preventative interventions and focus of developing new treatments that take advantage of the pathologic mechanisms common to both.**

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