Supplementary file

Protocol - Protocol for research using THIN

Table S1. - Patient characteristics insulin cohort

Table S2. - Results analysis insulin cohort

STROBE Checklist - Checklist of items that should be included in reports of cohort studies.

Title of the study

Differential Risk of Parkinson's disease in Diabetes Mellitus Type II patients according to diabetes treatments.

Background

Several studies have been published exploring the potential of repurposing antidiabetic drugs to treat neurodegenerative diseases such as Parkinson's disease (PD). Three types of antidiabetic drugs are of particular interest with regard to their potential protective effect against PD: Glitazones, dipeptidyl peptidase-4 (DPP4) inhibitors & glucagon-like peptide-1 (GLP-1) receptor agonists.

PPARɣ agonist antidiabetic glitazone drugs (pioglitazone and rosiglitazone) were first introduced in 1999. Several observational studies found strong evidence of a protective effect of glitazones on the risk of PD in individuals with diabetes, whilst other studies found no such effect (1-3). The results of the first clinical trial in which the potential of pioglitazone as PD treatment was investigated were negative(4). This can partly be explained by the short duration of the trial, 44 weeks, as any beneficial effects may take longer to show.

Dipeptidyl peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists ultimately result in increased GLP1 receptor stimulation, which in turn increases insulin levels. The first DPP4 inhibitor, sitagliptin, and the first GLP-1 receptor agonist, exanatide, were introduced in 2006. A small Scandinavian study found a lower risk of PD among patients treated with dipeptidyl peptidase-4 (DPP4) inhibitors (5). The point estimate for the risk of PD in patients on GLP-1 receptor agonists was less than 1 (i.e. protective) however the small sample size meant that confidence intervals were large and this could not be interpreted as evidence of a protective effect. Positive Phase 2 results of using exenatide in PD patients have been published(6, 7). Multiple other trials of GLP-1 receptor agonists and DPP4 inhibitors are being planned/set up.

The findings of all these studies are interesting in the light of the growing disease burden of PD and the absence of any treatment to change the disease trajectory of PD(8). Parkinson's disease is a degenerative neurological disease primarily characterised by nerve cell death in the substantia nigra and a consequent deficit in the amount of dopamine available in the central nervous system. People with PD gradually develop movement-related symptoms, including tremor, bradykinesia and rigidity. The pathophysiological causes of PD are complex, and are thought to involve oxidative stress, mitochondrial and proteasomal dysfunction and neuroinflammation(9). The lifetime risk of being diagnosed with Parkinson's in the UK is 2.7% and the prevalence is expected to rise by 18% in the next 7 years(8). The overall UK incidence of PD diagnosis for people over 50 years is 84 per 100,000 person years (95 % CI 82-85)(10).

While there are consistent associations between Diabetes Mellitus (DM) and PD risk in large cohort studies(11), there has been very little work exploring the epidemiological associations between DM, different types of antidiabetic drugs and PD risk. We hypothesise that patients with diabetes have a higher risk of Parkinson's disease than non-diabetes patients. We further hypothesise that this risk will be variable according to their diabetes treatment regime.

Our comparative study will be of great value in clinical practice when presented with a choice of oral pharmacological treatment options for diabetes. Assuming similar primary treatment results, comparing treatments that may have secondary benefits (protection against PD) will be of relevance in the decision making process of both clinicians and patients.

Purpose

Aim

The current proposal is to perform a population-based study to assess the effect of diabetes on the risk of Parkinson's disease, and to investigate if this risk is modified according to three different diabetes medications.

Objectives

- To estimate the incidence rate ratio for Parkinson's disease in people with diabetes, comparing individuals diagnosed with diabetes to people without diabetes.
- To compare the risk of PD in individuals treated with or GLP-1 receptor agonists or DPP4 inhibitors or glitazones to people treated with agents other than GLP-1 receptor agonists, DPP4 inhibitors and glitazones.

Data source

THIN offers an ideal source of observational data to examine the association between diabetes and the use of antidiabetic medications and PD onset in a large population. Preliminary exploration of the THIN database reveals;

1. Number of Type 2 DM patients in the THIN database: N=498642

2. Number of patients on following drug treatments:
a) GLP1 agonists (Exenatide, Liraglutide, Lixisenatide): N=21072
b) DPP4 inhibitors (sitagliptin, Saxagliptin, Valdagliptin): N=42689
c) Thiozolidinediones (Pioglitazone, Rosiglitazone): N=69588

A previous study using UK primary health care record found 175 incident PD cases in a population of 45,000 glitazone users. The cohort of users of GLP-1 agonists is small, but with an average follow-up time of 5 years, we expect to find around 40-100 PD cases exposed to GLP1 agonists and between 120-200 cases exposed to DPP-4 inhibiters during the study period.

Methods

Study design

We will conduct a retrospective cohort study comparing the rate of PD diagnosis in people treated with one of three specific types of antidiabetic drugs, compared with people being treated with other antidiabetic drugs.

Study population

We propose to identify a cohort of adults (18+) diagnosed with DM type II between 2006 and 2018. This cohort will be further divided into individuals prescribed GLP-1 agonists, DPP-4 inhibitors and/or glitazones and compared to users of other types of antidiabetic drugs. Individuals with a DM2 diagnosis will be identified by the corresponding Medcode using the medical files (see Appendix 1). DM medication exposure (see Appendix 2) will be defined as at least two consecutive prescriptions for a DM drug after the current practice registration date, the first recorded diagnosis of DM or the date from which the practice's data recording is of sufficient quality and completeness, whichever was latest. Every patient will be followed from the first date for a prescription of an antidiabetic drug (indexdate) onwards.

Study variables

Exposure

There will be six specific exposure groups of interest, as outlined below:
1a) Individuals prescribed GLP-1 agonists as monotherapy or in combination with sulfonylureas or biguanides
1b) Individuals prescribed GLP-1 agonists in combination with insulin
2a) Individuals prescribed DPP-4 inhibitors as monotherapy or in combination with sulfonylureas or biguanides)
2b) Individuals prescribed DPP-4 inhibitors in combination with insulin
3a) Individuals prescribed glitazones as monotherapy or in combination with sulfonylureas or biguanides
3b) Individuals prescribed glitazones in combination with insulin
Drug propensity scores will be calculated for the individuals in the exposure groups as outlined above.

Selection of comparison groups:

To address the first objective we will compare the proportion of individuals with a PD diagnosis in those with and without DM type 2 (healthy population). This will be a crude comparison, stratified by age and gender.

To address the second objective, comparator groups will be selected using inverse weighting based on propensity scores. Individuals in Groups 1a, 2a and 3a will be compared to individuals prescribed sulfonylureas or biguanides (both as mono- or oral combination therapy). Individuals in Groups 1b, 2b and 3b will be compared to individuals prescribed insulin (as monotherapy or in combination with sulfonylureas or biguanides).

Primary outcome of interest: The outcome for this study is the first recording of a diagnosis of PD, as identified from medical files, using the medcode list in Appendix 3.

Exclusion criteria: Patients with PD prior to any DM diagnosis will be excluded as will patients diagnosed with PD due to known causes (see Appendix 3).

Analysis
Statistical method

We will calculate propensity scores using a logistic regression model which will include all of the confounding variables as described in the next paragraph.

We will measure a hazard ratio for the association between DM and incident PD using stratified Cox proportional hazards models to compare time to diagnosis of Parkinson disease in the propensity score-weighted populations. We will estimate the treatment effect in the entire population using inverse probability treatment weighting (IPTW) after imputing missing values for the following variables: smoking, alcohol use and body mass index. Using multiple imputation we will perform a propensity score analysis in each imputed dataset and combine these treatment effect estimates to obtain an overall estimate (12).

The primary analysis will follow all patients from their index date until the earliest of a PD record, transfer out/death, or last data collection extract from practice, and their exposure will remain as defined at the index date.

Sensitivity analyses will be as follows:

- Our primary analysis is an 'intention to treat' analysis, in which the exposure status remains the same regardless of any changes in medication use. We will censor patients upon discontinuation of the index medication to take into account cessation of therapy. We will introduce a 180 days gradual shift from full exposure to an entirely unexposed state, allowing for potential delayed use of medication.
- To examine any potential duration-response associations we will identify patients with continuous use of the index drug for a minimum duration of: 3 months, 6 months, 9 months, 1 year, 2 years and 3 years or more.
- A stratified analysis will be conducted to look separately at the association between PD and the most commonly used individual drugs (pioglitazone, rosiglitazone, sitagliptin and liraglutide).
- A sensitivity analysis will be conducted using a stricter definition of PD in which at least two prescriptions for an anti-PD drug will be required in addition to a Read code indicating PD.
- Users of antidiabetic agents will be limited to those aged 40 and older and, in a separate analysis, will be restricted to non-smokers.
- GLP1 agonists reduce PD risk partly via a metabolic action that includes reduction in BMI, therefore we will run a sensitivity analysis in which BMI will be removed from the propensity score and, in a separate analysis, added to the model as a confounder.

Confounding variables

Covariates to be included in the Propensity Scores will be:

- Smoking status (measured using the medical and additional health files)
- Hormone Replacement Therapy (HRT) (any recorded prescriptions in the therapy files)
- Head trauma (measured by using the medical files)
- Age and sex (determined using the patient files)
- Calcium channel blocker use (any recorded prescriptions in the therapy files)
- Diabetes itself has been shown to be possibly associated with PD: Length of time between diabetes diagnosis and index date, and HbA1c level at index date will be determined and explored for possible confounding properties. In addition, the effect of time updated HbA1c levels will be explored (using additional health files).
- Comorbid conditions: Cardiovascular or renal disease and potential diabetic complications (e.g., retinopathy, neuropathy using medical files)
- Prescriptions for cardiovascular and renal disease (using therapy files)

Other covariates that have not been shown to be associated with PD will also be explored in case of possible confounding, and will include:

- Alcohol consumption (measured using the additional health and medical files)
- Body mass index (using the additional health files)
- Calendar year (using therapy files)

Limitations

The onset of PD in the context of the current study refers to the first recorded clinical diagnosis of PD in THIN. Patients are likely to have experienced symptoms before the date of their clinical

diagnosis. Diagnoses of PD in UK primary care have a positive predictive value of 90%(13, 14) and so a small degree of misclassification amongst outcomes is expected. However, this is likely to be non-differential with respect to DM treatment status and would be expected to bias results towards the null. In addition, missing cases of PD are likely to be rare in our study population, given that the prevalence of PD is low in the general population.

We will not be able to rule out unknown or unmeasured differences between the treatment and comparison groups. However, by using propensity scores we will be able to adjust for measured confounding and unmeasured confounding due to underlying indication.

Another limitation of our study will be potential exposure misclassification. As with all studies using electronic prescription databases, we will not be able to confirm whether patients picked up and used their prescriptions as intended. Again, any misclassification of exposure is likely to occur to a similar degree in both the treatment and control groups.

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Appendix 1. Diabetes Medcodes

Medcode				
Cyu2.00	66AI.00	C106y00	C10FB00	C109B11
Cyu2000	66AJ.00	C105y00	C109012	C10FB11
Cyu2300	66AJz00	C10yy00	C10F000	C109011
C10N100	13L4.11	C104y00	C10F600	C10F011
C10..00	66A3.00	C10zy00	C109612	C10F611
C10D.00	66A5.00	L180600	C10F400	C109611
C102z00	66AV.00	L180X00	C109412	C109411
C101z00	66A4.00	L180700	C10F900	C10F411
C103z00	66As.00	C10N.00	C109912	C10F911
C106z00	66AL.00	C10N000	C109.13	C109911
C100z00	1434	C10G.00	C10F.11	C108z00
C105z00	C109J11	C10G000	C109711	66AJ.11
C10yz00	C109J00	C109.12	C10F711	
C107z00	C109J12	C10F.00	C109G11	
C10zz00	C10M.00	C10F700	C10FG11	
C107.11	C10A.00	C109712	C109E11	
C102.00	C10A000	C109G12	C10FE11	
C101.00	C10A100	C10FG00	C109511	
C103.00	C10A500	C109E12	C10F511	
C104z00	C100111	C10FE00	C109D11	
C106.00	C10D.11	C10FQ00	C10FD11	
C106.12	C109.11	C10F500	C10FN11	
C100.00	C107400	C109512	C10FP11	
C105.00	C109E00	C10FR00	C109A11	
C10y.00	C100112	C10FD00	C10FA11	
C107.00	C109.00	C109D12	C10F311	
C106.13	C109700	C10FN00	C109C11	
C104.00	C109G00	C10FP00	C10FC11	
C10z.00	C109500	C10FA00	C109211	
C106100	C109D00	C10F300	C10F211	
C105100	C109A00	C109312	C109H11	
C10z100	C109C00	C10FC00	C10FH11	
C100100	C109B00	C109C12	C109111	
C102100	C109400	C109212	C10F111	
C101100	C109300	C10F200	C109F11	
C103100	C109200	C109H12	C10FF11	
C104100	C109100	C10FH00	C10FM11	
C107200	C109000	C10F100	C10FL11	
C10y100	C109600	C109112	C109B11	
C107100	C109900	C109F12	C10FB11	
C107000	C103y00	C10FF00	C109011	
C107.12	C101y00	C10FM00	C10F011	
66AK.00	C108y00	C10FL00	C10F611	

Appendix 2 – Diabetes Drugcodes:

Drugcode		
Glitazones	*DDP-4*	*GLP-1*
88528998	31126978	39144978
88523998	78729978	53433978
88528996	78730978	53434978
88523996	78727978	53431978
87180998	78728978	53432978
87179998	78725978	84693998
87771998	78726978	84696998
87770998	78723978	55150978
87166998	78724978	55151978
87165998	54906979	81305998
87774998	54907979	81307998
87772998	54904979	84694998
85622998	54905979	84697998
85624998	81159998	55818978
85625998	81160998	55819978
91880990	82068998	55842978
92237998	83401998	82793998
92238998	53006979	82794998
47709978	53007979	52041979
82196978	53004979	52043979
92237997	53005979	52044979
92238997	81513998	52042979
87884998	81514998	52039979
87885998	82573998	52040979
87775998	82575998	
87182998	84639998	
87773998	84640998	
89763998	59373979	
90048998	59374979	
87181998	59371979	
89763997	59372979	
90048997	84008998	
89763996	84010998	
90048996	84009998	
	84011998	
	84338998	
	84341998	

Appendix 3 –PD Medcodes

Include		Exclude	
Medcode	**Medterm**	**Medcode**	**Medterm**
F12z.00	Parkinson's disease NOS	F121.00	Parkinsonism secondary to drugs
F130300	Parkinsonism with orthostatic hypotension	F121.11	Drug induced parkinsonism
F12..00	Parkinson's disease	F123.00	Postencephalitic parkinsonism
F120.00	Paralysis agitans	F124.00	Vascular parkinsonism
Eu02300	[X]Dementia in Parkinson's disease	F12W.00	Secondary parkinsonism due to other external agents
297A.00	O/E - Parkinsonian tremor	F12X.00	Secondary parkinsonism, unspecified
2987.00	O/E -Parkinson flexion posture	Fyu2200	[X]Parkinsonism in diseases classified elsewhere
2987.11	O/E - Parkinson posture	A94y100	Syphilitic parkinsonism
2994.00	O/E-festination-Parkinson gait	Fyu2900	[X]Secondary parkinsonism, unspecified
2994.11	O/E - Parkinson gait	Fyu2100	[X]Other secondary parkinsonism
F11x900	Cerebral degeneration in Parkinson's disease		

* THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA

Table S1. Patient characteristics insulin cohort

	Control medication (*N*=10,504)	Glitazones or DPP4 (*N*=3,175)	GLP-1 (*N*=2004)	Glitazones (*N*=929)	DPP-4 (*N*=2,246)
Age, mean (SD)	59.75 (15.52)	62.20 (14.67)	56.31 (11.43)	58.16 (13.5)	63.51 (15.13)
Gender, male (%)	5689 (54.16)	1592 (50.14)	889 (44.36)	490 (52.74)	1102 (49.07)
Smoking (%)					
Current* smoker	1879 (17.97)	367 (11.57)	133 (6.64)	133 (14.32)	234 (10.42)
Ex-smoker	3713 (35.52)	1227 (38.68)	1094 (54.59)	345 (37.14)	882 (39.27)
Non-smoker	4862 (46.51)	1578 (49.75)	776 (38.72)	450 (48.44)	1128 (50.22)
Drinking status					
Current drinker	5120 (52.53)	1415 (46.67)	902 (45.01)	425 (45.75)	990 (44.08)
Ex-drinker	636 (6.53)	273 (9.00)	189 (9.43)	62 (6.67)	211 (9.39)
Non-drinker	3025 (31.04)	1172 (38.65)	722 (36.03)	328 (35.31)	844 (37.58)
Excessive drinker	965 (9.90)	172 (5.67)	108 (5.39)	57 (6.14)	115 (5.12)
BMI, kg/m2 (%)					
<18.5	61 (0.59)	8 (0.26)	3 (0.15)	2 (0.22)	6 (0.27)
18.5-24.9	1760 (17.05)	357 (11.41)	29 (1.45)	84 (9.04)	273 (12.15)
25-29.9	3848 (37.28)	940 (30.04)	252 (12.57)	296 (31.86)	644 (28.67)
≥30	4653 (45.08)	1824 (58.29)	1660 (82.83)	539 (58.02)	1285 (57.21)
Hba1c_level, mean (SD)	8.90 (4.29)	9.23 (4.16)	9.36 (3.97)	9.53 (4.49)	9.11 (4.01)
Medical diagnoses (%)					
Head injury	729 (4.08)	182 (5.73)	100 (4.99)	58 (6.24)	124 (5.52)
Cerebrovascular disease	914 (8.70)	358 (11.28)	154 (7.68)	66 (7.10)	292 (13.00)
Heart failure	711 (6.77)	286 (9.01)	155 (7.73)	35 (3.77)	251 (11.18)
Myocardial Infarction	1072 (10.21)	739 (13.83)	226 (11.28)	107 (11.52)	332 (14.78)
Renal disease	1268 (12.07)	1035 (32.60)	489 (24.4)	214 (23.04)	821 (36.55)
Arrhythmias	935 (8.90)	338 (10.65)	159 (7.93)	45 (4.84)	293 (13.05)
Hypertension	5110 (48.65)	1930 (60.79)	1266 (63.17)	526 (56.62)	1404 (62.51)
Calcium Channel Inhibitor use (%)					
Current user for < 1 year	326 (3.10)	244 (7.69)	57 (2.84)	48 (5.17)	196 (8.73)
Current user for > 1 year	2330 (22.18)	696 (21.92)	530 (26.45)	220 (23.68)	476 (21.19)
Past user	140 (1.33)	71 (2.24)	254 (12.67)	9 (0.97)	62 (2.76)
Non-user	7708 (73.38)	2164 (68.16)	1163 (58.03)	652 (70.18)	1512 (67.32)
Hormone Replace Therapy use (%)					
Current user for < 1 year	41 (0.39)	10 (0.31)	5 (17.24)	3 (0.32)	7 (0.31)
Current user for > 1 year	97 (0.92)	14 (0.44)	24 (1.20)	6 (0.65)	8 (0.36)
Past user	11 (0.10)	1 (0.03)	200 (9.98)	0.00	1 (0.04)
Non-user	10355 (98.58)	3150 (99.21)	1775 (88.57)	920 (99.03)	2230 (99.29)
Diabetes duration (year), mean (SD)	6.00 (7.76)	11.73 (8.62)	11.63 (7.27)	10.56 (7.13)	12.22 (9.13)

DPP-4= dipeptidyl peptidase-4 inhibitors; GLP-1= glucagon-like peptide-1 receptor agonists; BMI= Body Mass Index; HbA1c=haemoglobin A1c

Table S2. Results analysis insulin cohort

Type of analysis	Group	Crude HR (95% CI)	Adjusted HR (95% CI)	p value
Primary analysis	Other anti-diabetic exposed group	1	1	
	Glitazones & DPP4	1.20 (0.53-2.73)	1.66 (0.96-2.90)	0.07
	GLP-mimetics*	0.50 (0.12-2.12)	0.85 (0.37-1.94)	0.70
	GTZ*	0.78 (0.19-3.21)	0.92 (0.18-4.76)	0.93
	DPP-4 inhibitors*	1.57 (0.60-4.10)	0.81 (0.36-1.86)	0.62

***<5 patients were diagnosed with PD**