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A comparison between early presentation of Alzheimer's disease, Parkinson's disease and dementia with Lewy Bodies in routine primary care and UK Biobank data.

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Abstract

Background Understanding the shared and specific clinical manifestations of neurodegenerative diseases in the prodromal phase is key to understanding their complexity and specific pathophysiologies.

Methods Using the longitudinal THIN database in the UK, we contrasted clinical characteristics from individuals with a final diagnosis of Parkinson's disease (PD), Alzheimer's disease (AD), dementia with Lewy Bodies (DLB), and controls without neurodegenerative disorders. We tested the association (OR) of each neurodegenerative disorder for a selected list of symptoms including motor, autonomic, and neuropsychiatric features, as well as broad families of treatments (laxatives, antihypertensives, statins, benzodiazepines and neuroleptics). We subsequently tested whether the association were different between disorders, in recognition that the difference may indicate possible disease-specific effects. We investigated three prediagnosis time periods (0 to 5 years, 5 to 10 years and 10 to 15 years) to separate risk factors from prodromes/comorbidities. Analyses were corrected for age and sex and associations were presented as odds ratios (OR). We replicated the main findings in the UK Biobank (UKB).

Findings Firstly, we used 28,222 patients with PD, 20,214 with AD, 4,682 with DLB and 20,214 controls, from the THIN UK Database. Neurodegenerative disorders were significantly associated with the presence of multiple clinical characteristics before their diagnosis including memory problems, tremor, confusion, hallucinations, constipation, sleep disorders, anxiety, depression, falls, hypotension, urinary tract disorders and abnormal weight loss, and less frequent use of agents acting on the renin–angiotensin–aldosterone system and selective beta-2-adrenoreceptor agonists. Benzodiazepines and serotonin reuptake inhibitors consumption was more frequent in individuals who later developed all three diseases while antidiabetic medication consumption was lower in both future AD and PD patients. By contrast, the use of statins was significantly different across diseases at the prediagnosis stage, with lower usage in patients who later developed PD (OR = 0.78 (0.75,0.82)) and higher usage in patients who developed DLB (OR = 1.38 (1.27,1.51)), while association with AD was not significant (OR = 0.98 (0.93-1.02)). We replicated different usage of statins in PD and AD using the UKB (OR PD vs. AD = 0.77 (0.63, 0.94)) and performed sensitivity analyses further controlling for SES, BMI or APOE status.

Interpretation In addition to a range of non-motor features, benzodiazepines and serotonin reuptake inhibitor use was increased in individuals at a pre-diagnosis stage of neurodegenerative diseases, while agents acting on the renin–angiotensin–aldosterone system and selective beta-2-adrenoreceptor agonists were less prescribed. In contrast, statin usage was differentially associated with the three neurodegenerative diseases, suggesting that they may play a differential role in neurodegenerative diseases.

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Introduction

Neurodegenerative diseases represent one of the main public health issues in western societies. In 2019, about 57 million individuals were living with dementia worldwide.¹ Alzheimer's disease (AD) accounts for 60-70% of dementia cases (29 million) and represents the first cause of dementia while dementia related to synucleinopathies (Parkinson's disease dementia and dementia with Lewy bodies) are the second most common neurodegenerative cause of dementia.² Parkinson's disease (PD) is the second cause of neurodegenerative disease, estimated worldwide to affect 6.1 million individuals in 2016.³ There is currently no cure for neurodegenerative disorders and treatments can only temporarily reduce the symptoms. Prevention policies have thus become a major challenge. Primary prevention focuses on actionable risk factors, while secondary prevention aims to slow down disease progression with very early therapeutic interventions, ideally at the pre-symptomatic stage. Key to the implementation of such prevention measures is the identification of modifiable risk factors and patients in the earliest disease stages.

All these neurodegenerative diseases are known to have a very long preclinical stage. For AD, accumulation of amyloid can precede a clinical diagnosis of dementia by up to 20 years.⁴ Synucleinopathies, including PD and DLB, also have a long prodromal stage as demonstrated by isolated REM sleep behavioural disorders which can precede symptomatic PD or DLB by 10 years or more⁵. The first dysautonomic signs have been estimated to start as early as 15 years before motor symptoms in PD.^{6,7}

Analyses on general practitioners (GP) databases have already led to the identification of disease-specific prodromal symptoms of PD and AD as well as risk factors in the primary care data^{8,9} However, it is unknown how the prodromal features and risk factors of these disorders differ. Overall, cross-disorder analyses focusing on shared and specific associations with neurodegenerative diseases are rare.¹⁰

We undertook cross-disorder analyses in order to identify prediagnostic associations and risk factors of the most common neurodegenerative conditions (AD, PD and DLB), using data collected by general practitioners over a long time window (up to 15 years of follow-up). We sought to identify disorders and drug prescriptions associated with AD, PD and DLB, as well as those that are specific to each condition. We relied on the Health Improvement Network UK primary care for discovery and the UK Biobank (UKB) for selected replication.

Methods

Study design and participants

THIN database

We used The Health Improvement Network (THIN®) database,¹¹ a large European standardized database of anonymized and non-extrapolated Electronic Medical Records collected at the physicians' level by the company Cegedim and coded using the International Classification of Diseases, 10th Revision (ICD-10) codes. The THIN database complies with all the current European data protection laws (General Data Protection Regulation (GDPR)) and adheres to the Observational Medical Outcomes Partnership (OMOP) model. Data were collected in 400 general practices, representing around 6% of the UK population, which have been selected to join the "THIN quality data recording scheme" using the Vision practice

management software.⁹ Several reports have shown that electronically coded diagnoses in this database are representative of the UK general practice population in terms of demographics and type of consultation.^{11,12} For each patient and visit, we obtained, the diagnosis and prescription established during the visit, as well as all ongoing prescriptions and associated diagnoses. To preserve data anonymity, educational level, geographical location and socio-economical status (SES) data were not provided.

We defined our neurological cases based on ICD10 codes given by the general practitioners of the THIN database recorded between January 1996 and April 2020. For the neurodegenerative disorders of interest, AD cases corresponded to codes F00 and G30, PD to code G20 and dementia with Lewy Bodies to code G31.8 (and READ code Eu025, to exclude frontotemporal dementia). We extracted all DLB patients in the database, and a random subsample of patients with AD or with PD, with at least 2 years of follow-up in the database. We defined age at onset as the age at the first record coded with AD, PD or DLB diagnosis. Controls were screened for any history of Alzheimer's disease (F00 et G30), Parkinson's disease (G20), frontotemporal dementia (G31.0 and G31.8), dementia with Lewy Bodies (G31.8), Huntington's disease (G10), or multiple sclerosis (G35). We had access to 20,214 controls matched with AD cases on sex and age +/- 1 year at last record in the database from a precedent study which was specific to AD.¹³

UK Biobank replication sample

For replication, we used the UKB, a large population-based cohort which consists in 502,492 unselected volunteers from the UK, recruited between 2006 to 2010, of which 487,409 underwent genotyping and extensive phenotyping.¹⁴ Phenotypic data of interest include age (field ID), sex (field ID 31), Body Mass Index (field ID 21001), townsend deprivation index (measure of socioeconomic status (SES)) (field ID 189) which is based on participants residential postcode and the age they completed full time education (field ID 845). Cholesterol data was measured from blood collected in the baseline visit (cholesterol level field ID 30690, HDL level field ID 30760, LDL level field ID 30780). Of note, the UK Biobank is not considered to be representative of the general UK population as females, healthy individuals and inhabitants of high SES areas are over-represented.¹⁵ Informed consent was obtained from all participants registered in the UK Biobank.

In the UKB, we included the 1,005 patients with a reported diagnosis of AD, the 2,268 patients with PD, and the 2,732 patients with a report of dementia (Table 3). The clinical outcomes (Parkinson's field ID 42030, Alzheimer's field ID 42020, all dementia field ID 42018) including AD were generated by the UKB (category 42), by crossing UKB baseline self-reports with linked hospital admissions and death register data. Details about the algorithms are available at https://biobank.ndph.ox.ac.uk/ukb/docs/alg_outcome_pdp.pdf and https://biobank.ndph.ox.ac.uk/ukb/docs/alg_outcome_dementia.pdf. We excluded from further analysis the 69 patients who had records of both AD and PD diagnoses. (see eTable 5 and eTable 6 for statistics on this population). Finally, we only considered patients with at least one UKB visit before a diagnosis of neurodegenerative disease.

Health conditions and prescriptions of drugs of interest

We considered symptoms previously reported to be associated with one of these neurodegenerative diseases in the literature and likely to be coded by a GP. We included in the analysis memory problems, tremor, confusion, hallucinations, sleep disorders, constipation, anxiety, depression, falls, hypotension, urinary tract disorders and abnormal weight loss. We

used the READ codes and the International Classification of Diseases, 10th Revision (ICD10) to extract health conditions (the mapping is provided in eTable 14). We also conducted analysis on a preselected list of classes of medications previously reported to be associated with one of the neurodegenerative diseases, including all classes of anti-hypertensive medications, laxatives, statins, and medications used for neurological disorders, including treatments against depression, anxiety, and psychosis (eTable 15). We relied on the Anatomical Therapeutic Chemical (ATC) Classification System^{16,17} available directly in the THIN database. In the UKB, we used the medication-use data collected by trained nurses during interviews. The UKB classifies medications into 6,745 categories of which 1,809 were reported by 10 or more people.¹⁶ We mapped the medication categories into ATC codes (1,752 over 1,809 were mapped) as previously done in a genetic analysis of the UKB.¹⁶

Statistical analysis

We first used the THIN database to estimate the association (odd-ratios) between the preselected list of health conditions or medication classes and each specific neurodegenerative disorder. We estimated the odds ratios using a logistic regression corrected for sex and age at index date. We reported the OR estimates for different time windows prior to the neurodegenerative onset: (0 - 5] years, (5 - 10] years, and (10-15] years, in order to show their progression over time. The index date for each AD-control pair was defined as the first date of AD diagnosis of the corresponding patient with AD. The index date for PD and DLB was defined as age of onset. We corrected for multiple comparison using Bonferroni corrections. This led to using a significance threshold of $p < 0.004$ ($p=0.05$ with Bonferroni correction for 12 potential exposures, 2-tailed test). All analyses were conducted using the StatsModel library in Python. Next, we compared the OR between the three neurodegenerative disorders (PD vs. AD, DLB vs. AD and DLB vs. PD). Analyses were corrected for age at diagnosis and sex.

In the UKB, we compared the AD and PD groups to replicate the significant results for all classes of health conditions medications considered in the THIN study. The wealth of data available in the UKB allowed to further control for possible confounders that were not available in the THIN database. We used logistic models and controlled for sex, assessment center, age at diagnosis, age at entry in the cohort, and also for the townsend deprivation index, body mass index and education level (age at completed full-time education), which were not available in the THIN study. In a sensitivity analysis, we also contrasted PD patients with the group of patients with a report of dementia. When testing associations of PD, AD or all field dementia with the class of lipid-modifying agents, we further corrected for Apolipoprotein E (APOE) status (carriers of at least one epsilon 4 variant). We finally compared the associations with cholesterol, the LDL and HDL levels between PD and AD patients corrected for age at diagnosis, age at first visit, sex, center, BMI, education level and townsend deprivation index.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication. All authors had access to all the data and FM, LG and TN ensured data quality.

Results

In the THIN database, our full initial analytical cohort included 20,214 patients with a final diagnosis of AD, 28,222 patients with a diagnosis of PD, 4,682 patients with a diagnosis of DLB and 20,214 control patients. Table 1 describes the characteristics of the different populations. The median age at diagnosis was younger for PD (77 (70-83) years) than for DLB (80 (74-85) years) and AD patients (82 (76-87) years) and for controls (82 (76-87) years). There were more men than women in the PD and DLB cohorts (sex ratio of 57%) and the opposite in the AD and controls cohorts (sex ratio of 31%). 13,625 AD patients, 14,539 PD patients, 2,279 DLB patients and 10,205 controls had data available for more than 10 years before diagnosis. Demographic characteristics were similar between the different retrospective follow-up intervals (0 to 5, 10 or 15 years before diagnosis, see eTable1).

All conditions were more frequent than in controls in all three neurodegenerative diseases during the period 0-5 years before diagnosis (Figure 1). The prevalence of tremor, sleep disorders, constipation, anxiety and urinary tract disorders was higher in PD and DLB than in controls up to 15 years prior diagnosis, and anxiety and depression only for DLB (eTable2). The pre-diagnosis profile of the 12 health conditions investigated in the THIN study in AD, PD, DLB and controls over time are shown in Figure 2 (for details, see eTable3). Drug prescriptions in the 5 years prior to the diagnosis of neurodegenerative diseases are shown in Figure 2 and Table 2. Treatments against depression, anxiety and constipation were all more frequently prescribed in individuals with a later diagnosis of AD, PD and DLB. A higher frequency of benzodiazepines and serotonin reuptake inhibitors prescription was observed in the years preceding the diagnosis of all three diseases. Lower antidiabetic medications use, including insulins, biguanids, sulfonylureas and DDP4 inhibitors, was observed before the diagnosis of AD and PD. A lower prescription of agents acting on the renin–angiotensin–aldosterone system and selective beta-2-adrenoreceptor agonists was significantly observed before the diagnosis of the three diseases when compared to controls.

Cross disorder analyses

The odds of the 12 health conditions before diagnosis was different when comparing between diseases (eTable 3). In the 5 years prior to diagnosis, memory problems were more frequent in AD compared to PD and DLB patients, while the constipation was more common before PD and DLB onset than before AD onset (respective OR 1.45 and 2.08 against AD). When comparing PD and DLB, we found that tremor was more frequent in the years preceding PD diagnosis, whereas memory troubles, confusion, hallucinations, constipation, falls and depression were more frequent before the diagnosis of DLB.

Laxatives were used more frequently prior to diagnosis of PD and DLB than of AD, in line with the higher prevalence of constipation in these conditions. Neuroleptics were more frequently prescribed before DLB than AD and PD diagnoses, in accordance with their greater association with hallucination and confusion. Two drug groups showed a differential association across diseases compared to controls. A higher beta-blocker agents prescription rate was observed in the years prior to PD and DLB diagnoses compared with AD patients. A higher prescription of statins were significantly observed in the years prior to the DLB diagnosis while the opposite was observed prior to PD diagnosis, when compared with AD.

We used the UKB database to replicate the comparison in terms of medication usage between AD and PD. The demographic characteristics of the 1,005 patients with AD and the 2,268 patients with PD included in the analysis are described in Table 3. In this dataset, 60% of AD patients were either E3/E4 or E4/E4 compared to 26% in the PD cohort and 25% in the full UKB cohort (eTable 5). The results concerning the association with drugs are shown in Table 4. In this database, a lower prescription of statins was also observed in the years prior to diagnosis of PD as compared to AD (OR = 0.77, p= 0.01). As for the THIN database, there was no significant difference between AD and PD patients regarding agents acting on the renin–angiotensin–aldosterone system. When PD patients were compared with dementia cases (including vascular dementia and AD), prescriptions of all families of anti-hypertensors (calcium channel blockers, diuretics, beta blockers and agents acting on renin–angiotensin–aldosterone system) and statins (Table 4) were higher in individuals with subsequent dementia.

We found that a higher prescription of statins was significantly associated with increased BMI, lower age at diagnosis and lower age at first visit in both the AD and PD cohorts but not significantly associated with any APOE genotypes (eTable11). Finally, we compared the levels of LDL and HDL between PD and AD patients. We do not know if the analyses were performed under medication or not. There was no significant difference (eTable12), but the number of patients who had a blood sample before their diagnosis was very small (88 PD, 91 AD).

Discussion

In this large cross-disorder analysis, we compared the prodromal symptoms and drug prescription before the diagnosis of three of the main neurodegenerative diseases (AD, PD and DLB). Our results complement previous approaches which tested separately a range of prodromal features on PD⁹ or AD⁸, observable at the GP level. By contrasting AD with PD and DLB, we found cardinal motor or non-motor symptoms of each diseases to be more frequent than in controls at least 5 years before diagnosis: memory problems for AD, tremor for PD and hallucination, confusion, movement disorders and memory problems for DLB. We also observed that GP reported more falls in future DLB patients than in AD and PD patients in adequation with the McKeith 2017 criteria for DLB.¹⁸ We also found a robust association between all three neurological disorders and constipation in accordance with previous studies,¹⁹ even though the association was stronger for PD and DLB than for AD. More generally, we showed that all neurological disorders present more autonomic dysfunction in primary care compared to controls, including constipation, urinary disorders and hypotension years before diagnosis, with a stronger association for PD and DLB than for AD. These autonomic dysfunctions might be used by GP in the future to better anticipate a neurodegenerative disease. This result may support the hypothesis that neurodegenerative diseases pathological mechanisms affect the periphery before spreading into the brain.²⁰

We also investigated drug use and found a lower prescription of all the main antihypertensors families, including agents acting on the renin–angiotensin–aldosterone system (for all three diseases), calcium channel blockers (for AD and PD) and diuretics (for AD and DLB), in accordance with previous epidemiological studies showing an inverse association between antihypertensive drugs and AD, PD or DLB.²¹ These results may support the hypothesis that vascular diseases are a risk factor of neurodegenerative diseases²¹, a frequent comorbid condition of these diseases and that decreasing cardiovascular risks by prescribing antihypertensive drugs would help to decrease the risk of developing all neurodegenerative diseases. Alternatively, some of these drugs may have unspecific neuroprotective effects,²² as

antidiabetics drugs that were less prescribed in the years preceding all three diseases.²³ The design of this study did not allow us to distinguish between these two possibilities. The difference observed on beta-blocker agents which were more prescribed in individuals who later developed PD and DLB compared to AD or controls, confirms previous similar results and may be explained by their use to relieve tremor.²⁴ The lower risk of developing PD with the use of Beta-2-adrenoreceptors and the higher risk with using beta-blocker agents may also be consistent with the current assumption that β 2-adrenoreceptor is a regulator of the α -synuclein gene (*SNCA*).²⁵ Benzodiazepines usage have been repeatedly linked to a higher risk of dementia²⁶, and benzodiazepines were indeed more prescribed in the years preceding with all three diseases. Of note, all three diseases were also associated with increased rates of anxiety and sleep disorders. As above, the design of the study did not allow us to distinguish between a direct effect of benzodiazepines on risk of dementia or the consequence of the need to treat prodromal anxiety. Our observed association of benzodiazepines with PD and DLB suggests that this association is not specific to AD.

More surprisingly, we found a lower prescription of statins in years before the diagnosis of PD compared to dementia-related disorders (AD, DLB). These differences remained significant when adjusting for potential confounding variable such as APOE status, BMI, education level and townsend deprivation status, and in the replication (UKB) dataset. This observation could have several explanations. First, since statins are prescribed in secondary prevention of cardiovascular diseases, it may result of higher vascular comorbidities in the AD and DLB groups.²⁷ However, lipid lowering therapies intake was similar between AD and controls. Moreover we observed that anti-hypertensors were similarly prescribed in the three diseases, which suggests that the three populations may have similar vascular risk factors. Secondly, AD participants were screened out for vascular dementia in the UKB.. Another explanation would be that subjects treated with lipid lowering therapies are at lower risk to develop PD. Indeed, higher cholesterol levels have been associated with a lower risk of PD,^{28,29} including a recent mendelian randomization analysis suggesting that this association could be causal.³⁰ Finally, lipid lowering agents may have a protective effect on PD as supported by a study showing that the Mediterranean diet adherence is associated with a reduced risk of prodromal PD,³¹ even though similar studies also exist in AD.³² A recent randomized controlled trial of simvastatin for delay of disease progression in PD was negative,³³ indicating that the association might not be causal. Another assumption would be that PD induces a global hypermetabolism and thus fat burning, which could indirectly lower cholesterol levels and thus a lower use of statins. The mechanisms by which lipid lowering therapies may be protective against PD remains to be understood.

This study is to our knowledge the largest addressing on the same database the prodromal phase of the three neurodegenerative diseases allowing to compare their clinical profile and treatment prescriptions as observed by general practitioners. Another notable strength of this study is the replication on the UK Biobank, with consistent results obtained for the two analysis. Our work has also several limitations. First, in the THIN database, the diagnosis of neurodegenerative diseases was made by general practitioners, which may result in a delayed diagnosis, explaining why we can observe diseases' specific symptoms before their diagnosis. In the UKB database, diseases have to be detected during an hospitalisation or mentioned in death registers. Second, the frontiers of each complex neurodegenerative disease may not be defined perfectly, the zero one distinction being a simplification with respect to disorders heterogeneity³⁴ and distinction between developing a dementia with Lewy Bodies or having at the same time PD and AD might be difficult to do in practice. However, the differences observed in the prodromal stage of DLB patients, show that DLB is not simply the addition of the symptoms of AD and PD at the GP

level. Finally, in the THIN analysis, controls were matched with the AD population, which was older and had a higher proportion of female patients than the PD and DLB cohorts, and we may therefore have underestimated associations particularly in the younger PD population. AD patients in the UKB might also not be representative of the general patient population as they are still relatively young.

Conclusion

Our results highlight the long-term clinical prodromal phase of neurodegenerative diseases, and therefore could enable more efficient primary and secondary prevention measures. To the best of our knowledge, this is the first study showing a difference in terms of statins use in the years preceding AD, DLB, and PD diagnoses. Our results suggest that there may be a differential role of lipid lowering therapies in the prodromal phase of neurodegenerative diseases. Further studies are needed to confirm this results and to better understand the relationship between cholesterol levels and the risk of neurodegenerative diseases.

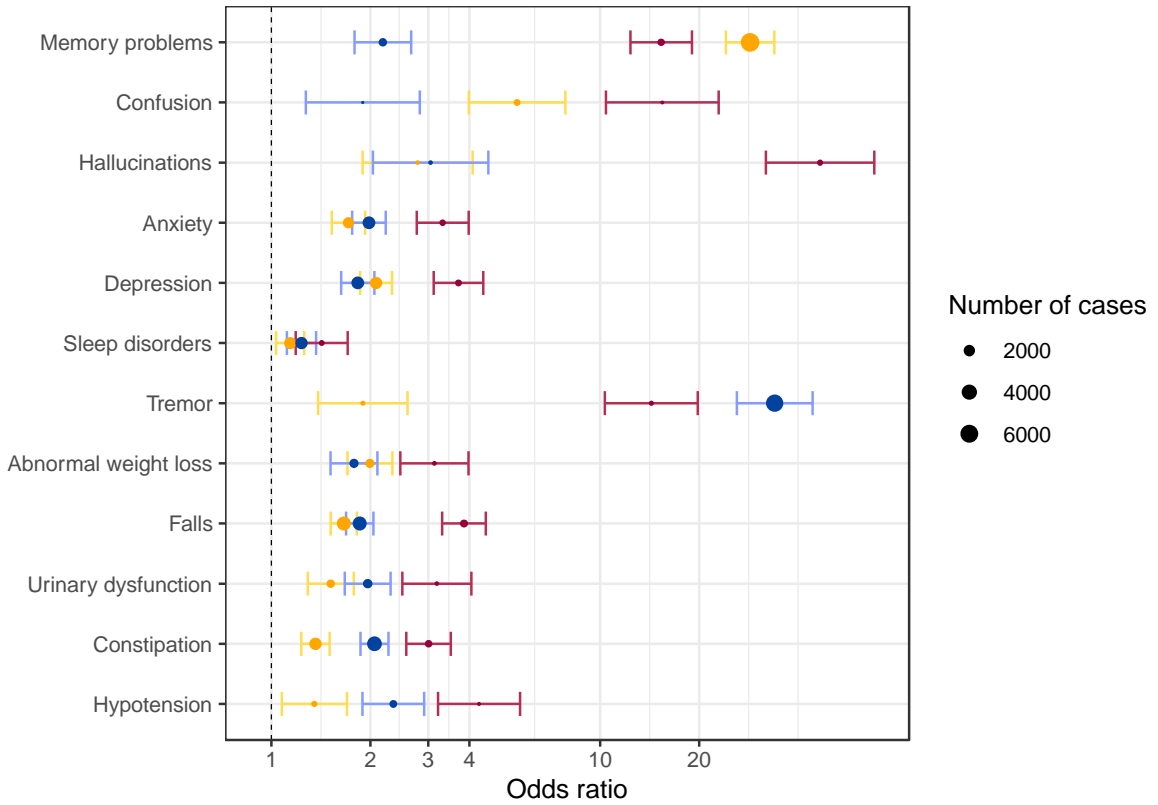
	Total				With >=5 years of retrospective data			
	Alzheimer's disease (n=20214)	Parkinson's disease (n=28222)	Dementia with Lewy Bodies (n=4682)	Controls (n=20214)	Alzheimer's disease (n=17871)	Parkinson's disease (n=22281)	Dementia with Lewy Bodies (n=2712)	Controls (n=15361)
Sex: Women	14106 (69%)	12332 (43%)	2050 (43%)	14106 (69%)	12531 (70%)	9532 (42%)	1156 (42%)	10624 (69%)
Men	6108 (31%)	15890 (57%)	2632 (57%)	6108 (31%)	5340 (30%)	12749 (58%)	1556 (58%)	4737 (31%)
Birth year	1926 (1921-1933)	1929 (1921-1938)	1932 (1926-1938)	1925 (1918-1933)	1927 (1921-1933)	1931 (1923-1940)	1932 (1927-1939)	1927 (1920-1934)
Age at index date	82 (76-87)	77 (70-83)	80 (74-85)	82 (76-87)	82 (76-87)	77 (70-83)	79 (74-84)	82 (76-87)
Person-years of data available before index date	13 (8-18)	10 (6-16)	10 (1-18)	10 (5-17)	14 (10-18)	12 (9-18)	17 (12-21)	13 (9-18)
Number of visits per year	7 (4-11)	7 (4-12)	10 (6-17)	7 (3-11)	7 (4-10)	7 (4-11)	7 (4-11)	7 (4-11)

Table 1 : Characteristics of patients with Alzheimer's disease, with Parkinson's disease, with Dementia with Lewy Bodies and controls. The data shown are numbers (%) and medians (IQR).

	Alzheimer's disease		Parkinson's disease		Dementia with Lewy Bodies		Parkinson's disease against Alzheimer's disease	
	OR (95%CI)	p value (corr. p value)	OR (95%CI)	p value (corr. p value)	OR (95%CI)	p value (corr. p value)	OR (95%CI)	p value (corr. p value)
Diuretics	0.74 (0.71,0.77)	<0.001 (<0.001)	0.93 (0.89,0.97)	0.002 (0.035)	0.85 (0.78,0.93)	<0.001 (0.006)	1.25 (1.2,1.31)	<0.001 (<0.001)
Beta-blocker agents	0.86 (0.82,0.9)	<0.001 (<0.001)	1.14 (1.08,1.19)	<0.001 (<0.001)	1.21 (1.11,1.33)	<0.001 (0.001)	1.32 (1.26,1.38)	<0.001 (<0.001)
Calcium-channel blockers	0.77 (0.73,0.81)	<0.001 (<0.001)	0.77 (0.73,0.81)	<0.001 (<0.001)	0.93 (0.85,1.02)	0.144 (2.441)	1.01 (0.96,1.07)	0.566 (9.624)
Agent acting on angiotensin system	0.71 (0.68,0.74)	<0.001 (<0.001)	0.73 (0.7,0.77)	<0.001 (<0.001)	0.8 (0.73,0.87)	<0.001 (<0.001)	1.05 (1.0,1.1)	0.049 (0.826)
Statins	0.98 (0.93,1.02)	0.304 (5.175)	0.78 (0.75,0.82)	<0.001 (<0.001)	1.38 (1.27,1.51)	<0.001 (<0.001)	0.82 (0.78,0.86)	<0.001 (<0.001)
Fibrates	0.83 (0.65,1.07)	0.151 (2.565)	0.81 (0.64,1.04)	0.094 (1.591)	0.64 (0.37,1.1)	0.104 (1.776)	0.97 (0.76,1.23)	0.789 (13.421)
Other lipid modifying agents	0.83 (0.7,0.99)	0.041 (0.699)	0.82 (0.69,0.98)	0.026 (0.449)	1.05 (0.75,1.45)	0.792 (13.457)	0.95 (0.8,1.14)	0.579 (9.842)
Insulins and analogues	0.72 (0.61,0.85)	<0.001 (0.002)	0.74 (0.63,0.87)	<0.001 (0.004)	1.04 (0.78,1.37)	0.807 (13.721)	1.02 (0.86,1.21)	0.828 (14.079)
Biguanides	0.77 (0.71,0.84)	<0.001 (<0.001)	0.77 (0.7,0.83)	<0.001 (<0.001)	0.89 (0.76,1.05)	0.161 (2.736)	0.99 (0.91,1.08)	0.848 (14.417)
Sulfonylureas	0.76 (0.69,0.84)	<0.001 (<0.001)	0.83 (0.75,0.91)	<0.001 (0.001)	0.64 (0.52,0.79)	<0.001 (<0.001)	1.06 (0.96,1.17)	0.234 (3.985)
DDP4 inhibitors	0.62 (0.48,0.79)	<0.001 (0.002)	0.54 (0.42,0.68)	<0.001 (<0.001)	0.86 (0.57,1.3)	0.466 (7.919)	0.93 (0.72,1.21)	0.582 (9.891)
GLP-1 inhibitors	0.69 (0.36,1.34)	0.276 (4.691)	0.67 (0.36,1.22)	0.191 (3.251)	1.36 (0.53,3.5)	0.518 (8.814)	1.01 (0.53,1.94)	0.967 (16.439)
Laxatives	1.25 (1.19,1.31)	<0.001 (<0.001)	1.85 (1.76,1.95)	<0.001 (<0.001)	3.9 (3.57,4.26)	<0.001 (<0.001)	1.46 (1.39,1.53)	<0.001 (<0.001)
Serotonin inhibitors	1.84 (1.76,1.93)	<0.001 (<0.001)	1.83 (1.74,1.92)	<0.001 (<0.001)	3.85 (3.52,4.2)	<0.001 (<0.001)	0.95 (0.91,0.99)	0.029 (0.493)
Dopamin antagonists	2.42 (1.95,3.0)	<0.001 (<0.001)	2.18 (1.73,2.74)	<0.001 (<0.001)	4.25 (3.12,5.79)	<0.001 (<0.001)	0.79 (0.66,0.94)	0.006 (0.11)
Benzodiazepines	1.3 (1.22,1.39)	<0.001 (<0.001)	1.61 (1.5,1.72)	<0.001 (<0.001)	2.7 (2.43,3.01)	<0.001 (<0.001)	1.22 (1.15,1.29)	<0.001 (<0.001)
Selective beta-2-adrenoreceptor agonists	0.74 (0.7,0.78)	<0.001 (<0.001)	0.71 (0.67,0.75)	<0.001 (<0.001)	0.83 (0.74,0.93)	0.001 (0.022)	0.95 (0.89,1.01)	0.091 (1.54)

Table 2: Odds ratios corresponding to Alzheimer's disease, Parkinson's disease and Dementia with Lewy Bodies and to the comparison between Parkinson's and Alzheimer's disease (0-5] years before a first diagnosis. Odds ratios are corrected for age at diagnosis and sex. P values are corrected for multiple comparisons.

Associations with health conditions (0–5 years to diagnosis)



Associations with medication classes (0–5 years to diagnosis)

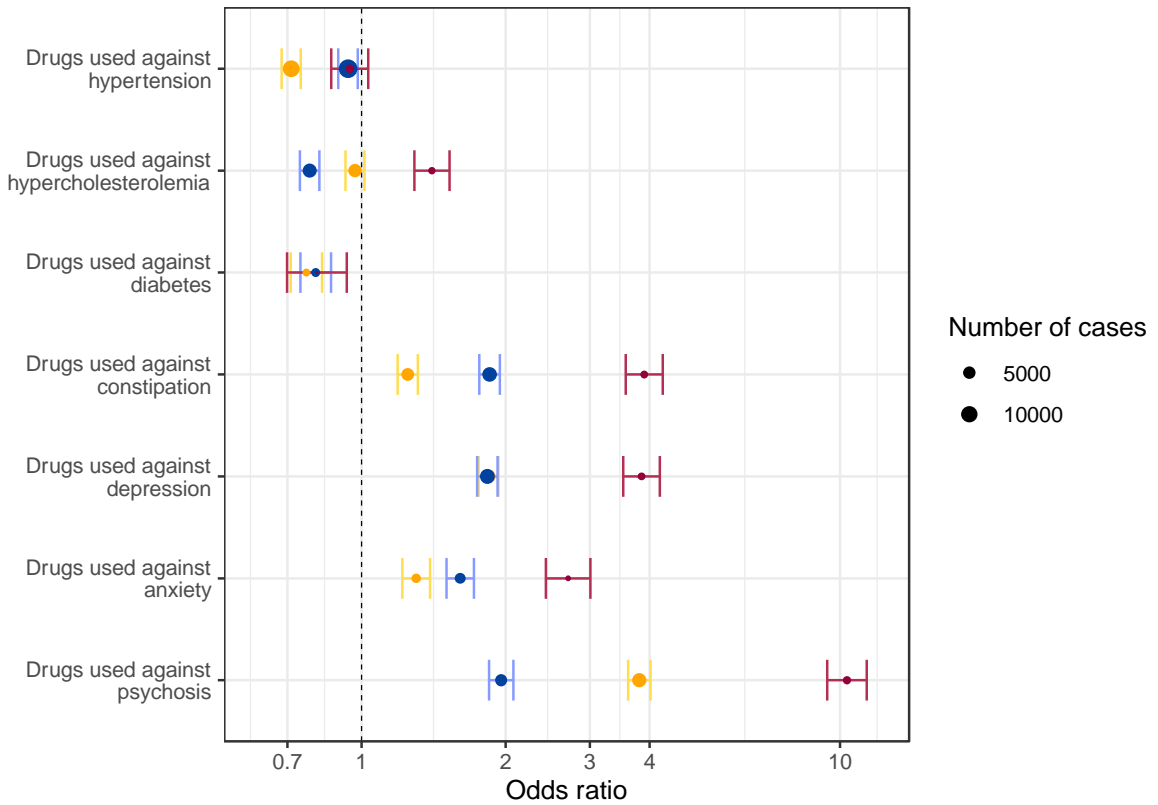


Figure 1: **Disease specific odds ratio of multiple health conditions and classes of medications for Alzheimer's disease (yellow), Parkinson's disease (blue) and Lewy-bodies dementia (red) compared to controls.** Odds ratios are corrected for sex and age at diagnosis. Odds ratios are computed in the time period

between (0-5] years before a first diagnosis of the corresponding neurodegenerative disease. Confidence intervals are corrected for multiple comparisons.

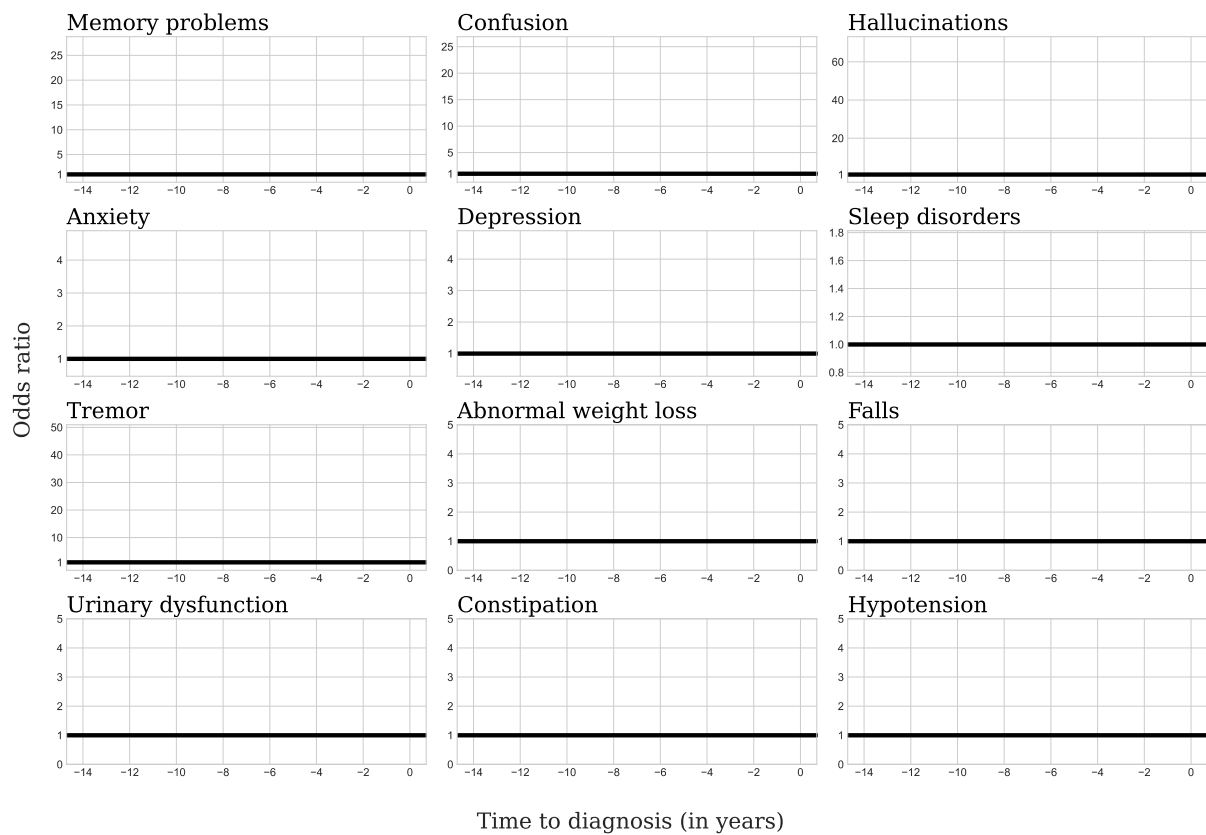


Figure 2 : Disease specific odds ratio of mutple health conditions for Alzheimer's disease (yellow), Parkinson's disease (blue) and Lewy-bodies dementia (red) compared to controls. Odds ratios are corrected for sex and age at diagnosis. The x-axis corresponds to the time (in years) before diagnosis. In the statistical analysis, we report odds ratios computed for following time period in years : [15,10), [10,5) and [5, diagnosis). Y-axis shows the odds ratio.

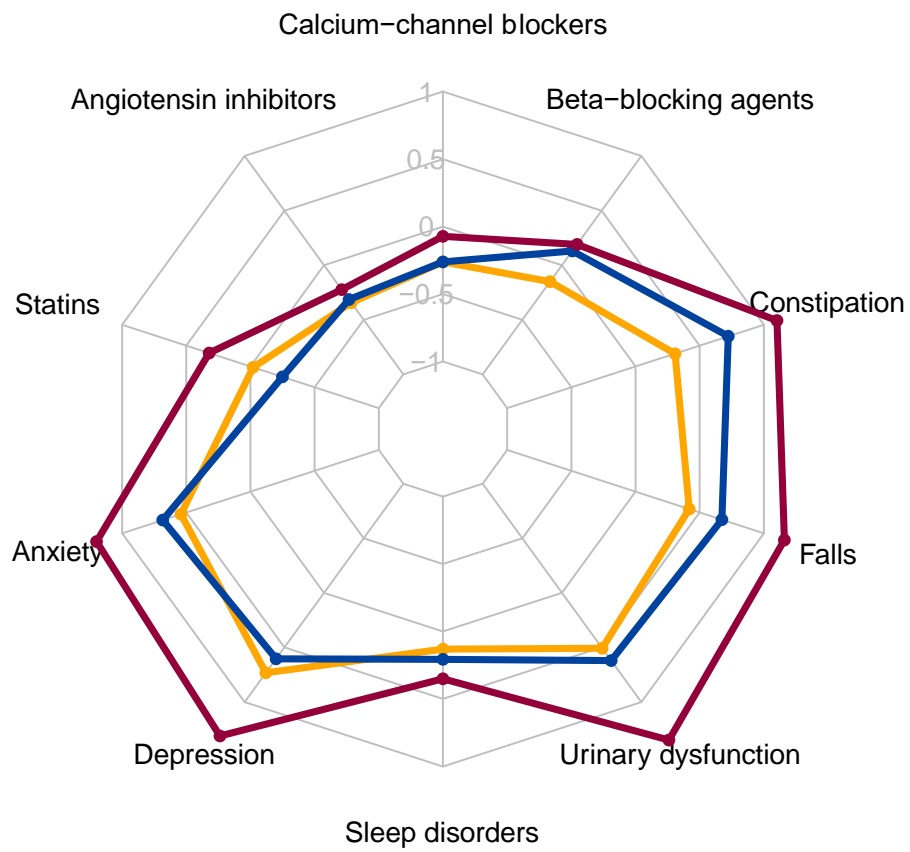


Figure 3 : Disease specific log odds ratio of various health conditions and drug prescriptions in the five years prior to diagnosis of Alzheimer's disease (yellow), Parkinson's disease (blue) and Lewy-bodies dementia (red) compared to controls. Log-transformed odds ratios are corrected for sex and age at diagnosis.

	All				With at least one visit before diagnosis	
	Total UK Biobank	All dementias	Alzheimer	Parkinson	Alzheimer	Parkinson
Total	502492	2732	1005	2268	920	1272
Women (n, %)	273377 (54%)	1216 (44%)	491 (48%)	879 (38%)	465 (50%)	505 (39%)
Men (n, %)	229115 (46%)	1516 (56%)	514 (52%)	1389 (62%)	455 (50%)	767 (61%)
BMI	26.86 (24.23-29.98)	27.24 (24.41-30.3)	26.75 (23.96-29.54)	27.25 (24.7-30.16)	26.66 (23.79-29.37)	27.38 (24.75-30.26)
Education level	16 (15-17)	15 (15-16)	15 (15-16)	16 (15-17)	15 (15-16)	16 (15-17)
Townsend deprivation	-2.14 (-3.64-0.55)	-1.67 (-3.46-1.71)	-1.99 (-3.62-1.31)	-2.29 (-3.71-0.7)	-2.02 (-3.64-1.24)	-2.17 (-3.67-0.88)
Year of birth	1950 (1945-1958)	1943 (1940-1946)	1942 (1940-1946)	1944 (1941-1948)	1942 (1940-1946)	1944 (1941-1948)
Age at first visit	58 (51-64)	66 (62-68)	66 (63-68)	64 (60-67)	66 (63-68)	65 (61-68)
Age at diagnosis		71 (67-74)	72 (68-74)	65 (58-71)	72 (69-74)	70 (66-73)

Table 3 : Characteristics of patients with any types of dementia, Alzheimer’s disease and Parkinson's disease in the UK Biobank. The data shown are numbers (%) or medians (IQR).

	Parkinson against Alzheimer		Parkinson against all dementia	
	OR (95% CI)	pvalue	OR (95% CI)	pvalue
Diuretics	0.88 (0.67, 1.14)	0.324	0.85 (0.68, 1.07)	0.169
Beta-blocker agents	0.88 (0.68, 1.13)	0.309	0.78 (0.62, 0.97)	0.028
Calcium-channel blockers	0.84 (0.64, 1.09)	0.18	0.69 (0.55, 0.87)	0.001
Agent acting on angiotensin system	0.93 (0.76, 1.16)	0.534	0.74 (0.62, 0.89)	0.001
Statins	0.77 (0.63, 0.94)	0.01	0.73 (0.62, 0.86)	<0.001
Fibrates	0.47 (0.16, 1.33)	0.154	0.54 (0.21, 1.36)	0.19
Other lipid modifying agents	1.08 (0.75, 1.56)	0.679	1.02 (0.75, 1.38)	0.921
Insulins and analogues	0.59 (0.35, 1.0)	0.051	0.49 (0.31, 0.77)	0.002
Biguanides	0.78 (0.53, 1.15)	0.213	0.61 (0.44, 0.85)	0.003
Sulfonylureas	1.21 (0.67, 2.17)	0.525	0.75 (0.47, 1.2)	0.232
Laxatives	1.31 (0.85, 2.03)	0.228	1.08 (0.75, 1.55)	0.688
Serotonin reuptake inhibitors	0.81 (0.63, 1.04)	0.094	0.88 (0.71, 1.09)	0.245
Benzodiazepines	1.08 (0.49, 2.35)	0.855	0.95 (0.51, 1.77)	0.881
Selective beta-2-adrenoreceptor agonists	0.83 (0.6, 1.15)	0.258	0.82 (0.62, 1.09)	0.172

Table 4 : Odds ratios corresponding to the comparison between Parkinson and Alzheimer and between Parkinson and all dementias with the visits happened before a first diagnosis of the corresponding neurodegenerative disorders. Odds ratios are corrected for age at diagnosis, age at first visit, sex, center, BMI, education level and townsend deprivation index.

Contributors

TN, BCD, AS, JCC and SD conceived and designed the study. FM, LG, BCD, and ADB extracted the data. FM, LG and TN ensured data quality and TN, BCD, ADB, AS, JCC and SD analysed the data. TN and BCD generated the figures. TN, BCD, ADB, FM, LG, BL, NV, AS, SD and JCC interpreted the results and contributed to the writing of the final version of the manuscript. All authors agreed with the results and conclusions and approved the final draft.

Competing interest

FM, LG and BE are full time employees of Cegedim. Other authors declare no competing interests.

Data sharing statement

The data used in the preparation of the article are available from the Cegedim company upon reasonable request.

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Ethics committee approval

Approval was sorted before carrying out this study (and for the use of datasets). The study was a retrospective analysis of secondary anonymised patient data only. For the UK THIN database, data is only available to researchers carrying out approved medical research. Ethical approval was granted by the NHS South-East Multicentre Research Ethics Committee in 2003 (ref: 03/01/073) for establishment of the THIN database, and it was updated in 2011. A further update and approval was granted in 2020 by the NHS South Central, Oxford C Research Ethics Committee (Ref: 20/SC/0011). Researchers willing to replicate the results should address a request to the Cegedim company (info@the-health-improvement-network.co.uk). Informed consent was obtained from all UKB participants. Procedures are controlled by a dedicated Ethics and Guidance Council (http://www.UK_Biobank.ac.uk/ethics), with the Ethics and Governance Framework available at http://www.UK_Biobank.ac.uk/wp-content/uploads/2011/05/EGF20082.pdf. IRB approval was also obtained from the North West Multi-centre Research Ethics Committee. This research has been conducted using the UK Biobank Resource under Application Number 53185.

Patient and Public involvement

We plan to disseminate the results of our research to the public and relevant patient community through the current publication and its related press release as well as presentations at scientific conferences.

The lead authors (AS, SD, JCC) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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