Epidemiology of Parkinson's disease and comorbidities in the prodromal phase

PhD thesis

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The incidence of PD has increased at the fastest rate in the last decades. Incidence and prevalence rates of PD vary greatly. Estimates of the incidence of PD over 40 years of age in females is 37/100 000/year, in males 61/100 000/year. The worldwide prevalence of PD is approximately 0.3 percent in the general population of 40 years of age and older. A systematic review estimated a global prevalence of 6.1 million people with PD in the year 2016. PD is the fastest growing source of disability due to neurologic disorders, based on estimations by 2040 there will be over 17 million patients with PD.

Previous estimates three decades ago based on door-to-door survey in a district of the capital city estimated that around 12 300 people may live with PD in Hungary, and a European review reported 21 thousand people in Hungary with PD. However, epidemiological statistics of PD in the region are outdated and need revision.

Generally there are two main designs for frequency estimation of PD: case finding studies, in which hospital, general practice or pharmacy records are searched for diagnosed cases, often in combination; and door-to-door surveys in which the studied population is screened for the presence of the disease using the same, standardized diagnostic criteria. The most reliable method is a door-to-door survey, however it requires greater effort and expense than case finding studies. Identifying a population of patients with PD with appropriate algorithms used from healthcare administrative databases and pharmacy data is a potentially practical, inexpensive strategy to develop large population based epidemiologic and health service studies.

When the first symptoms of PD appear, the majority (up to 60-80%) of the substantia nigra neurons are already lost. This assumes the existence of a preclinical state of several decades. This is called the prodromal phase, which precedes the onset of motor symptoms and manifests in non-motor symptoms that are considered to be early signs of neurodegeneration.

In recent years, many studies have focused on the detection of the prodromal phase, since it is believed that at this stage, appropriate neuroprotective treatment may prevent or delay the onset of PD.

Multimorbidity is common in PD patients. Various studies have shown that around 80% of PD patients have five or more comorbid diseases at the same time. There are few data on internal diseases prior to the diagnosis of PD, on the other hand there are many non-motor conditions which have been associated with an increased risk for developing PD. Studies in this regard are contradictory, but there is evidence that in patients with diabetes mellitus (DM) and hypercholesterolemia the risk is increased for developing PD.

The association between restless legs syndrome (RLS) and PD has been extensively studied on the basis that dopaminergic hypofunction in the central nervous system is present in both diseases and it has been suggested that RLS is a possible preclinical marker of PD. However, there is still insufficient evidence to support an identical pathophysiologic mechanism for both the diseases.

In PD, in addition to the typical motor symptoms, nonmotor symptoms may occur, neuropsychiatric manifestations often being the most common. The prevalence of neuropsychiatric symptoms (NPS) in early, untreated PD patients is up to 56%. NPS are identifed to be integral to PD throughout the course of the disease, often developing in the early, untreated stages, before the onset of classical motor symptoms of PD, suggesting that neurophysiological impairments that cause NPS may already develop in the initial phases of PD. The occurrence of NPS in PD patients may frequently be related to potentially additive mechanisms, including psychological reactions to disability, psychiatric symptoms caused by structural brain damage, and adverse effects of dopamine replacement therapy. This pathophysiological heterogeneity poses a challenge to the clinician. The main limitation of investigating these symptoms is that NPS are influenced by dopamine replacement therapy and often are hardly differentiated from each other because of symptom overlaps.

2. Objectives

Epidemiological statistics of PD in Hungary are outdated and need revision. We calculated the incidence and prevalence rates of PD in Hungary with a multiple validated method, covering the whole population.

We also aimed to analyse the prodromal/untreated phase of PD, the period before PD diagnosis. Previous studies had conflicting results investigating the association between internal diseases and PD, our objective was to to assess the prevalence of the most common metabolic, circulatory, and gastrointestinal disorders prior to the diagnosis of PD. The onset and characteristics of NPS in drug naïve patients before the diagnosis of PD are still not well studied, further examination of patients in the premotor, untreated phase is needed to better understand NPS which are linked to the disease pathology itself. Therefore our objective was to explore retrospectively also the prevalence of NPS before the diagnosis of PD that we compared to a control group, patients with ischemic cerebrovascular lesion (ICL). Given that previous studies about RLS and PD reported contradictory results, we examined in a historic prospective cohort study the association of RLS with the development of incident PD in a large group of US veterans. Based on previous findings, we hypothesized that RLS is associated with higher risk of development of incident PD

3. Methods

In the framework of the Hungarian National Brain Research Program the NEUROHUN 2004–2016 database was created from medical and medication reports submitted for reimbursement purposes. The NEUROHUN database can be devided in two parts: data between 2004-2013 containing information from neurological specialist care only, data between 2004-2016 containing information from all specialist care without general practitioner care data. PD and other diseases were analysed from the database of the National Health Insurance Fund from all hospitals, outpatient services and pharmacies throughout Hungary using using the International Classification of Diseases (ICD-10) or pharmacy records. Primary as well as secondary diagnoses were considered simultaneously during data analysis. The original patient identifier codes were anonymized and encrypted identifiers were used, data analysis between different databases was possible with record linkage. All personal data protection regulations

were followed, and the Ethics Committee of Semmelweis University, Budapest, Hungary approved the study (Approval No: SE TUKEB 88/2015).

Determination of PD incidence and prevalence: There are two independent databases that we linked: the database of the neurological patient care system (2004-20013), and the pharmacy database of medication refills (available from 2010). Record linkage between the clinical and pharmacy databases was possible by applying the encrypted individual identifier. The study was divided in four phases. Case identification in the first phase was followed by 3 steps of case certification. For case identification, all individuals were selected from the neurological care system, who used either the inpatient or the outpatient neurological service at least once during this period and had a primary or secondary diagnosis of PD (ICD-10, G20). In the second phase, case certification was performed in the clinical database. The following criteria had to be fulfilled for a patient to be considered to have PD in the year of evaluation: to receive G20 diagnosis in the neurology care system in at least 2 years during the 10-year period regardless of the diagnosis type (i.e., primary/admitting diagnosis or secondary diagnosis). We calculated crude and age-standardized incidence and prevalence rates of PD in Hungary for each year of the period 2010–2012. In the third phase, validation of the clinical diagnosis criteria of PD on a smaller subsample was performed. Firstly, we made an IT validation of data by cross-checking the database of the national neurological patient care system (NEUROHUN) and the local integrated hospital healthcare IT system (MedSol) of Semmelweis University, Budapest and vice versa, by choosing a 2 months period for examination: November–December, 2012. Finally, in the same period we retrieved the individual patient healthcare documents of all inpatients (N = 31) and 19 consecutive outpatients with a clinical diagnosis of PD, checked if they appear at least in 2 years with G20 diagnosis code in the large database and we made sure that PD diagnosis is accurate and clinically supported based on final hospital discharge reports. In the fourth phase, to achieve a more conservative case certification, we counted those who fulfill the clinical diagnosis criteria of PD and also refilled an antiparkinson drug (APD) prescription in the year of interest. APDs are coded N04 in accordance with the Anatomical Therapeutic Chemical Classification (ATC) system.

Analysis of internal diseases and NPS: we used the database of all specialist care between 2004 and 2016. For the definition of PD patients we used the previously mentioned 2-year rule, but starting only from year 2015. We analysed the most common diagnosis types from the following diagnosis groups in the period before PD diagnosis: endocrine, nutritional and metabolic diseases (E00-E90), diseases of the circulatory system (I00-I99), diseases of the digestive system (K00-K93). NPS were analysed also by ICD-10, codes F00-F99, before the first diagnosis of PD. For the control group we chose all patients with at least one ICL diagnosis (ICD-10, codes I63 or I64).

Analysis of RLS and PD association: The study was approved by the institutional review committees of the Memphis and Long Beach Veterans Affairs (VA) Medical Centers. We identified RLS and PD from the VA Inpatient and Outpatient Medical SAS Datasets using ICD-9 diagnostic codes. Those veterans were selected who did not have a PD diagnosis prior to RLS diagnosis. The final cohort included 3 481 506 patients, of which 3 423 031 patients were without RLS and 58 475 patients had prevalent RLS. Using this cohort, we created a propensity score-matched cohort of 50 441 patients in each group using 1:1 matching. We defined incident PD as our outcome of interest. RLS was defined by the presence of a relevant ICD-9 code at baseline, and incident PD was defined as a new ICD-9 code for PD during the follow-up period. Patients with an existing diagnosis of PD before or within 60 days of the diagnosis of RLS were excluded.

Statistical analysis:

The crude incidence and prevalence rates were standardized to the European standard population of 2013 with 95% confidence intervals (CI 95%) using a binominal distribution.

Internal diseases and NPS prior to PD diagnosis were analyzed by basic descriptive statistical methods. For associations between the PD and ICL group we used chi-squared test and logistic regression analysis.

For RLS and PD association we generated summary statistics using proportions, means ± SD, or medians (interquartile ranges). We compared continuous variables with the Student's t test or the Mann–Whitney U test, as appropriate. The associations between

prevalent RLS and incident PD were assessed using the Kaplan–Meier method, and Cox proportional hazard models. We applied a propensity score matching method to account for baseline differences in clinical and demographic characteristics between those with and without RLS. We used logistic regression to determine characteristics associated with RLS, which we then used to calculate propensity scores. The propensity score was calculated from the following variables: gender, age, race/ethnicity, marital status, income, baseline eGFR, comorbidities at baseline baseline neuroleptic usage, and body mass index. Statistical analyses were performed using Stata MP version 12 (Stata Corporation, College Station, Texas).

4. Results

Estimating the number of possible PD patients over 10 years: During 2004-2013 there were overall 96 874 patients admitted to hospitals or had outpatient visits at a neurological specialist care at least once with PD as a primary or secondary diagnosis.

Validating the clinical diagnosis criteria of PD on a smaller subsample: in the period of Nov.–Dec. 2012 out of 60 inpatients with G20 in any diagnosis position in the hospital records 59 appeared also in the national database. The one missing patient from the national database was due to a reporting error from the hospital. All of the 31 inpatients in the national database with G20 appearing at least in 2 years in the national database with one of these appearances in the period of Nov.–Dec. 2012 were present in the local hospital records. Out of 224 outpatients with G20 in the hospital records 223 appeared in the national database. The one missing patient had no patient ID in the hospital records. All of the 224 outpatients with G20 appearing at least in 2 years in the national database with one of these appearances in the period of Nov.–Dec. 2012 were present in the hospital records.

Reviewing final hospital discharge reports we found that out of 31 inpatients 26 (84%) had clinically supported PD. The other 5 patients had a final clinical diagnosis of other secondary parkinsonian syndrome. Out of 19 outpatients 18 (94%) had clinically supported PD. One patient had other not defined secondary parkinsonian syndrome.

Estimating the number of patients with clinically consistent PD diagnosis for the period of 2010–2012: overall 46 383 patients fulfilled our criteria for PD diagnosis

between 2010 and 2012. Incidence and prevalence rates for this period are presented in **Table 1.**

Table 1. Incidence (new patients per 100,000 inhabitants/year) and prevalence (number of patients per 100,000 inhabitants) of PD in Hungary between 2010 and 2012.

Year	Crude incidence	Crude prevalence	Standardized incidence*	Standardized prevalence*
2010	53	394	59	458
2011	50	406	57	473
2012	46	414	52	483
95% CI overall for 3 years	45-53	392-416	51-60	456-485

* Age standardization was performed using the 2013 European standard population

Linking the clinically consistent PD cases with APD medication refill: the number of patients who refilled an N04 ATC medication are presented in **Figure 1**, sorted by diagnosis distribution. The refill rate among those PD patients who also appeared at a neurology service in the same year was 0.80, whereas the refill rate of all living PD patients was 0.72.
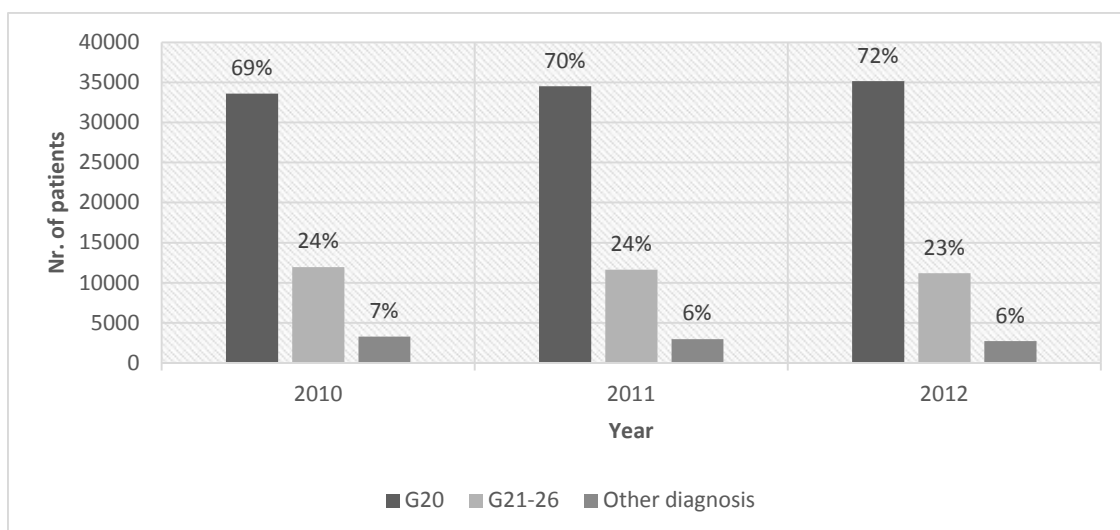

Figure 1. Refill of N04 ATC drugs: with G20 diagnosis, with G21–26 diagnosis and with other diagnosis codes between 2010 and 2012.

Occurence of internal diseases before the diagnosis of PD: there were 5209 patients who had their first PD diagnosis in 2015 than in 2016 also, ergo fullfilment of 2-year diagnostic criteria was met (**Table 2.**). Occurrence of internal disease was examined retrospectively until 2004, starting from 2015, year of the first PD diagnosis.

Table 2. First two most common internal diseases based on ICD categories.

ICD code	ICD name	Prevalence N=5209 (100%)
E78	Disorders of lipoprotein metabolism and other lipidemias	2156 (41%)
E11	Type 2 diabetes mellitus	1675 (32%)
I10	Essential (primary) hypertension	4618 (89%)
I25	Chronic ischemic heart disease	2641 (51%)
K21	Gastro-esophageal reflux disease	1478 (28%)
K80	Cholelithiasis	1286 (25%)

NPS in the premotor phase of PD: the number of patients between 2004 and 2016 with at least one PD diagnosis (G20) in the specialist healthcare service (outpatient and inpatient) was 130 773. Fulfillment of the minimum 2-year PD diagnosis criteria was present in 79 795 patients, this was the cohort for further analysis. The mean ± SD age of this group was 73 ± 9 years, 48% were male. Of the 79 795, 59 403 (74.4%) patients had at least one mental and behavioral disorder (F00-F99) anytime during the examined 13 year period. The number of patients who had their F00-F99 diagnosis before the first PD diagnosis was 26 645 (33.3%). Out of the 26 645 patients 19 774 (24.7%) had their F00-F99 diagnosis in specialized psychiatric care (outpatient/inpatient) established at least once.

The control group between 2004 and 2016 with at least one ICL diagnosis (I63 or I64) and without PD diagnosis in the neurological service (outpatient/inpatient) consisted of 783 843 patients. The mean ± SD age of this group was 69 ± 12 years, 45% were male. 437 139 (55.7%) patients with ICL had at least one F00-F99 diagnosis during the studied 13 years. Of those, 232 083 (29.6%) had their psychiatric diagnosis before the diagnosis of ICL, and 157 091 (20%) had their F00-F99 diagnosis established in psychiatric care at least once. Of the PD patients 33.3% whereas of those with ICL 29.6% had a psychiatric diagnosis before the first appearance of PD or ICL (p<0.001). The higher rate of NPS in PD compared to ICL remained significant after controlling for age and gender in logistic regression analysis (p<0.01 for age, gender and diagnosis

type). In the PD group where psychiatric diagnosis appeared before PD diagnosis, in descending order Mood disorders (F30-F39: 16%), Organic, including symptomatic, mental disorders (F00-F09: 16%), Neurotic, stress-related and somatoform disorders (F40-F48: 14%) and Schizophrenia, schizotypal and delusional disorders (F20-F29: 5%) were the most common diagnosis categories, compared with only 12% ($p < 0.001$), 9% ($p < 0.001$), 12% ($p < 0.001$) and 2% ($p < 0.001$) in the ICL group in the same categories.

Association between RLS and incident PD cases: The mean ± SD age of the cohort at baseline was 60 ± 14 years, 93% were male, 78% and 17% of patients were white and black, respectively, 44% were unmarried, 24% of the patients were diabetic, and the mean baseline eGFR was 84 ± 16 ml/min/1.73m2.

Incident PD in the Propensity-Matched Cohort: the median follow-up time was 8.1 years (IQR: 7.2–8.5 years) in the propensity-matched cohort. There were 253 incident PD events (0.25%, incidence rate 3.35 [2.96–3.79]/10 000 patient-years) in the propensity-matched cohort. There were 68 incident PD events (0.13%, incidence rate 1.87 [1.48–2.37]/10 000 patient-years) in the RLS-negative group, and 185 incident PD events (0.37%, incidence rate 4.72 [4.09–5.45]/10 000 patient-years) in the RLS positive group. Prevalent RLS was associated with a more than twofold higher risk of incident PD (hazard ratio [HR]: 2.57, 95% confidence interval [CI]: 1.95–3.39) compared to RLS-negative patients (**Figure 2.**). Similar results were found in almost all subgroups (**Figure 3.**).
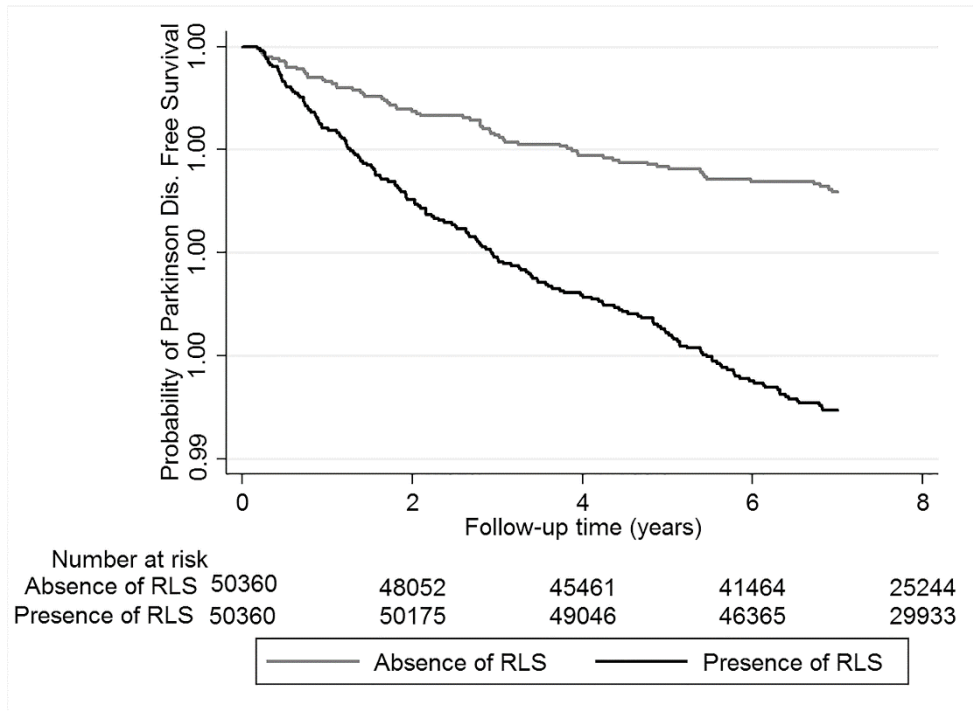
Figure 2. Kaplan–Meier curves of incident PD in patients with and without RLS in the propensity-matched cohort.

Incidence and prevalence of PD in Hungary: our aim was to estimate the number of those with PD in Hungary and to validate prevalence and incidence rates by comparing two independent national healthcare databases. We found that incidence and prevalence estimates of PD were considerably higher than previous reports, suggesting that in the years 2010–2012 in Hungary there were around 40,000 patients with PD. If we consider only those 72% who refilled APD medication, the number was still considerably higher than previous estimates. The refill rate was higher (80%) among PD patients who received regular neurological care. We found similar results in numerous studies using similar methodologies worldwide in terms of incidence, prevalence, and APD refill rates.

Overall, the use of large healthcare adminisitrative databases for epidemiological analysis not unique after all, in case of PD, more accurate estimates can be obtained using appropriate, rigorous identification and case finding criteria (appearance over several years, consideration of all types of diagnosis, specific drug refill).
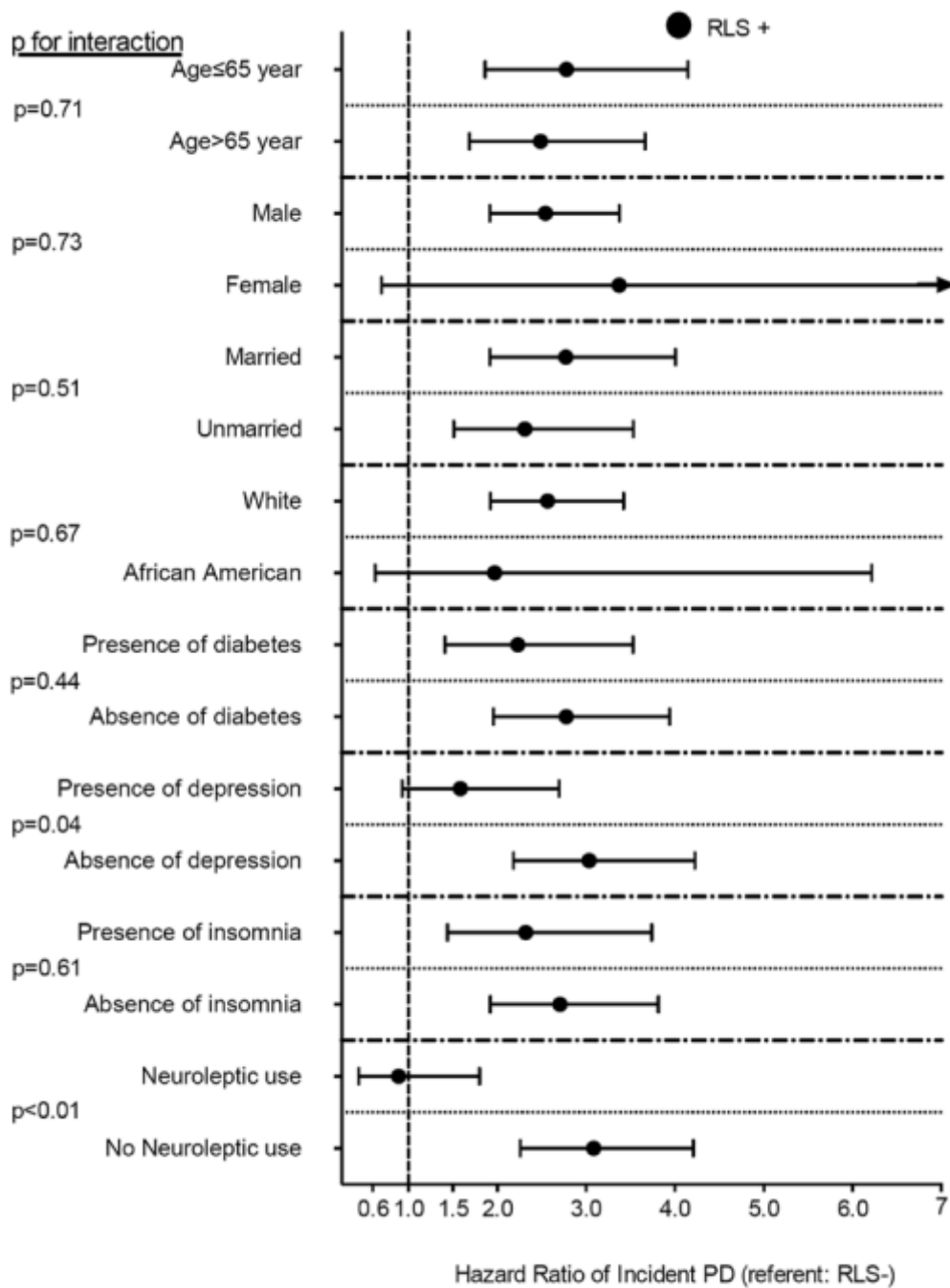
Figure 3. Association between RLS and incident PD in different subgroups of patients in the propensity-matched cohort.

Differentiating PD, especially at disease onset, from parkinsonism is often difficult. Therefore it is a challenge to create a valid approach for correctly identifying patients with PD or parkinsonism from administrative databases. Additionally, identifying a population of patients with PD from administrative databases represents a complicated issue for several other reasons which affect our study as well: PD is a clinical diagnosis

and it is definitively identified only by brain pathological findings, therefore the degree of clinical uncertainty always remains present. However, accuracy of the clinical diagnosis is likely to become more assured over time as clinical data accumulates therefore we used the 2 year diagnostic criteria. PD diagnoses used in the study are not made by direct contact with the patients but by reliability on physicians/specialists reports prepared essentially for financial purposes. N04 ATC drugs are not specific and unique medications for PD as they are also used for other conditions and the diagnosis could be specified wrong on the prescription for a N04 ATC medication.

The possibility of misclassification error should be considered as an important source of research bias using health administrative databases and threatens the validity of study results. Additionally, patients not presenting in the neurological care system, undiagnosed patients, patients who have not yet been commenced on antiparkinsonian therapy, or those who do not refill the prescribed medication due to disadvantaged socioeconomic conditions result in further underestimation of the number of patients with PD.

Occurence of internal diseases in the premotor phase of PD: the analysis showed that out of metabolic diseases lipidemia and diabetes mellitus, out of circulatory diseases hypertension and ischemic heart disease and out of the gastrointestinal diseases gastroesophageal reflux disease and gallstones were the first two most common diseases. Since only the prevalence of diagnoses has been examined, causal relationship between PD and the listed conditions cannot be deducted. It highlights a possible association and draws attention to the need for further investigations.

NPS in the premotor phase of PD: our aim was to estimate the prevalence of psychiatric disorders before the diagnosis of PD. Our primary findings were that several psychiatric diseases (mood disorders, cognitive impairment, anxiety disorders, schizophrenia) were more common in PD patients before PD diagnosis compared to our control group, patients with ICL. If we consider only those diagnoses that were established by psychiatric care, the numbers are still significantly higher in PD than in the control group. Our findings indicate that 16% of diagnoses in our total PD sample are from the Organic, including symptomatic, mental disorders group (F00-09), most of which were different types of dementias, showing evidence of cognitive dysfunction. In

comparison, only 9% of those with ICL were diagnoses from the F00-09 group. It was previously demonstrated that the prevalence of cognitive impairment is high even in newly diagnosed PD patients, it is associated with extensive atrophy and greater percentage of cortical thinning, older age at disease onset is an important determinant of cognitive dysfunction and up to 80% of all PD patients will eventually develop dementia. Our results support these findings because in our PD sample the average age in the year of the appearance of the first PD diagnosis in our database was relatively high, 73 years.

We found significant difference also in the Schizophrenia, schizotypal and delusional disorders (F20–F29) category, where schizophrenia diagnosis (F20) was the most common. In the PD group there was a more than twofold higher prevalence (5%) compared to the control group (2%). The exact association between schizophrenia and PD remains to be elucidated, because there are still just a few studies with inconclusive data which examined the connection between the two diseases. The role of dopamine and dopaminergic pathways that play crucial role in both PD and schizophrenia is well-known. Current data assume that negative and cognitive symptoms in schizophrenia anticipate the onset of positive symptoms, decreased dopamine may be responsible for these, suggesting that schizophrenia may essentially represent a hypodopaminergic disorder after all. On the other hand a few studies have proposed the idea that parkinsonism in schizophrenia may not be just the consequence of neuroleptic exposure but it could be also related to the clinical spectrum and might represent the motor side of schizophrenia manifesting in the late phase of disease course.

In the Mood (affective) disorders (F30–F39) category the diagnosis rate was higher in the PD sample (16%) and it was significantly larger than in the ICL group (12%). The most frequent disorder before PD diagnosis was, not surprisingly the depressive episode in both PD and ICL groups. Depressive symptoms predating PD can have diverse etiologies, although the exact pathomechanism is still unknown. Neurobiological factors, changes in brain structure and neuronal systems (dopaminergic, noradrenergic, and serotonergic) that are associated with the underlying neurodegenerative processes in PD play an important role in the early stages, later on mood reaction to the progressive disability and PD itself, psychosocial factors or pain could also have roles in the appearance of depressive symptoms. Our prevalence values correlate favorably with

previous findings and further support the idea of depression being a non-motor symptom already present before the diagnosis of PD.

Another group which showed significant difference was the Neurotic, stress-related and somatoform disorders (F40–F48) category, before PD diagnosis being present in 14%, while before ICL only in 12%, anxiety disorders being the most common in this category. The etiology of anxiety in PD is also multifactorial. Our study provides further evidence on anxiety disorders having a high prevalence before PD diagnosis.

Association between RLS and PD: In a large cohort of US veterans, we examined the association between RLS and the development of incident PD. Our findings confirm that prevalent RLS is associated with higher risk of incident PD during 8 years of follow-up. In our study, the explanation for the observed association between RLS and PD is unclear. Since the cause of RLS remains unknown and the absolute incidence of PD in patients with RLS is very low, it is difficult to postulate a common pathophysiological background for the two diseases, although the response to dopaminergic agents in both the conditions may suggest this. To the best of our knowledge, there were only two recent studies (a cross-sectional and a prospective longitudinal study) including mostly men, which concluded that RLS was associated with a higher prevalence of PD across all age-groups and that RLS was an early clinical feature of PD, not a risk factor. The findings of these cross-sectional studies support our results, namely, that there is an association between RLS and PD. It remains unclear if the observed associations are explained by a pathological link leading from RLS to PD, versus both diseases having a common root. It is important to note that in our study, the estimated risk of incident PD events in the RLS group is relativel small, suggesting that the connection between the two diseases may not be very strong and/or specific. In contrast, other diseases such as idiopathic rapid eye movement (REM) sleep behavior disorder have stronger effects. Limitations previously mentioned about the use of ICD codes also apply in this study. We were unable to assess the associations between the severity of RLS and PD. We also have no data about the treatment of RLS. In addition, we did not have data regarding usage of dopamine agonists or levodopa. The study population consisted mostly of male and elderly US veterans. Hence, the results may not be accurately representative of other populations such as women, younger patients or non-US patients.

5. Conclusions:

Incidence and prevalence of PD in Hungary: the NEUROHUN database with proper case identification and case certification methodology can be appropriate to evaluate clinical, epidemiological, and organizational features of PD in Hungary. The higher incidence and prevalence values than previously estimated, reflect the growing burden of PD on the Hungarian health care system. The database has the potential to estimate quality of care, cost of care, follow-up and prevalence of PD or other specific neurological conditions in Hungary.

Occurence of internal diseases in the premotor phase of PD: our study raised the possibility of a link between dyslipidemias, diabetes mellitus, hypertension, ischemic heart disease, gastooesophagial reflux, gallstones and PD. In patients with the above mentioned conditions might be useful to look for classic symptoms of PD, thereby facilitating early diagnosis and proper treatment. In addition, our study draws attention to the high prevalence of comorbidities in PD.

NPS in the premotor phase of PD: we determined that a range of psychiatric illnesses have elevated prevalence before the first diagnosis of PD compared to ICL. This study may reflect neurotransmitter changes in the early phase of PD and highlights the importance of early, routine screening for highly prevalent, often under-diagnosed and under-treated NPS in PD patients to initiate optimal treatment.

Association between RLS and PD: in a large cohort of US veterans, we found that prevalent RLS is associated with higher risk of incident PD during 8 years of follow-up. Our results suggest that RLS could be an early clinical feature of incident PD.

Publications:

In the topic of the present thesis:

1./ Szatmari S Jr, Bereczki D, Fornadi K, Kalantar-Zadeh K, Kovesdy CP, Molnar MZ. (2017) Association of restless legs syndrome with incident Parkinson's disease. Sleep, 40: 2.

2./ Szatmari S, Illigens BM-W, Siepmann T, Pinter A, Takats A, Bereczki D. (2017) Neuropsychiatric symptoms in untreated parkinson's disease. Neuropsychiatr Dis Treat, 13.

3./ Szatmari Jr S, Ajtay A, Balint M, Takats A, Oberfrank F, Bereczki D. (2019) Linking individual patient data to estimate incidence and prevalence of Parkinson's disease by comparing reports of neurological services and pharmacy prescription refills at a nationwide level. Front Neurol, 10: 640.

4./ ifj. Szatmári Sz, Ajtay A, Oberfrank F, Bereczki D. (2019) Belgyógyászati betegségek előfordulása a Parkinson-kór premotoros szakaszában egy teljes lakosságot lefedő adatbázis elemzése alapján. Bulletin of medical sciences/Orvostudományi Értesítő, 92: 35-41.

5./ közlésre benyújtva: PLoS One: Szatmari Jr S, Ajtay A, Oberfrank F, Bereczki D: The prevalence of psychiatric symptoms before the diagnosis of Parkinson's disease in a nationwide cohort: a comparison to patients with cerebral infarction.

Other publications:

-Pinter A, Szatmari Jr S, Horvath T, Penzlin A, Barlinn K, Siepmann M, Siepmann T: (2019) Cardiac dysautonomia in depression – heart rate variability biofeedback as a potential add-on therapy. Neuropsychiatr Dis Treat, 15: 1287–1310.

-Siepmann T, Pintér A, Buchmann SJ, Stibal L, Arndt M, Kubasch AS, Kubasch ML, Penzlin AI, Frenz E, Zago W, Horváth T, Szatmári S Jr, Bereczki D, Takáts A, Ziemssen T, Lipp A, Freeman R, Reichmann H, Barlinn K, Illigens BM. (2017) Cutaneous Autonomic Pilomotor Testing to Unveil the Role of Neuropathy Progression in Early Parkinson's Disease (CAPTURE PD): Protocol for a Multicenter Study. Front Neurol, 8: 212.

-ifj. Szatmári Sz, Bajkó Z, Szász J. (2015) A szubsztitúciós terápia bevezetésének sajátosságai a marosvásárhelyi ideggyógyászati klinikák Parkinson kóros betegeinél. Bulletin of medical sciences/Orvostudományi értesítő, 88: 103-107.