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To my family

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ABSTRACT

Parkinson's disease (PD) is mainly a late-life neurodegenerative movement disorder. The prevalence of PD is increasing rapidly in the world. It is typically associated with an early and progressive loss of dopaminergic neurons in the substantia nigra. However, it also affects several other neurotransmitter systems making it a multisystem progressive disease. The clinical presentation of PD is variable with respect to both motor and non-motor symptoms. As the cardinal motor signs (rest tremor, rigidity, bradykinesia and postural instability) appear in a patient, substantial damage of dopaminergic neurons has already occurred. In turn, some of the non-motor symptoms, such as constipation, psychiatric problems and sleep problems, may occur several years before motor symptoms in the prodromal phase of PD.

PD is a progressive disorder that is associated with increased mortality. Although current pharmacotherapies and device-aided therapies of PD induce clear effects on the quality of life, there is a lack of evidence of which treatments could alter the course of the disease. This thesis investigated patient characteristic-, comorbidity-, and treatment-related prognostic factors of PD patients.

The results demonstrated improved survival of Finnish male PD patients in recent years without a similar change in female PD patients. This will further increase the male-to-female ratio in PD prevalence. The results also showed that a previously diagnosed hyperdopaminergic schizophrenia spectrum disorder increases the risk of hypodopaminergic PD later in life. In line with previous evidence, we observed that psychosis/hallucination-, cognition-, and constipation-related problems in the early course of PD are related to worse survival of PD patients. Moreover, we found a possible novel link between pain in the prediagnostic period of PD and mortality within the first five years after diagnosis. Furthermore, the results demonstrated that the outcome of deep brain stimulation (DBS) treatment in monogenic PD patients depends on the mutated gene. The outcome of DBS seems to be excellent in patients with *LRRK2* p.G2019S mutations and good in patients with *PRKN* mutations whereas it appears less favourable in patients with *LRRK2* p.R1441G mutations. Moreover, marked progression of cognitive and neuropsychiatric symptoms in PD patients with *SNCA*, *GBA* and *LRRK2* p.T2013S mutations may diminish the overall benefit of DBS in these monogenic PD patients.

KEYWORDS: Parkinson's disease, dopamine, prognosis, mortality, genetic, deep brain stimulation, comorbidity, schizophrenia, data mining, electronical health records

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TIIVISTELMÄ

Parkinsonin tauti on pääasiassa myöhemmällä iällä ilmaantuva neurodegeneratiivinen liikehäiriö, joka on nopeimmin yleistyvä neurologinen sairaus maailmassa. Parkinsonin taudissa keskiaivojen mustatumakkeen dopaminergiset hermosolut tuhoutuvat. Tauti aiheuttaa muutoksia muissakin välittäjäainejärjestelmissä, joten sitä voidaan pitää etenevänä systeemisairautena. Parkinsonin taudin kliininen oirekuva koostuu motoristen ja ei-motoristen oireiden kokonaisuudesta. Mustatumakkeen dopaminergisissä hermosoluissa on todettavissa jo merkittävä vaurio, kun potilaalle ilmaantuu motorisia oireita. Joitakin ei-motorisia oireita, kuten ummetusta ja unihäiriöitä, voi kuitenkin ilmaantua useita vuosia aiemmin niin sanotussa Parkinsonin taudin prodromaalivaiheessa.

Parkinsonin tauti on etenevä sairaus, johon liittyy lisääntynyt kuolleisuus terveisiin verrokkihenkilöihin nähden. Nykyisten lääke- ja laitehoitojen avulla saadaan vaikutettua positiivisesti potilaiden elämänlaatuun, mutta taudin etenemistä hidastavaa tai pysäyttävää hoitomuotoa ei ole vielä saatavilla. Tässä väitöskirjassa tutkittiin potilaiden ilmiasuun, yhteissairastavuuteen ja hoitoon liittyviä ennusteellisia tekijöitä Parkinsonin taudissa.

Tulokset osoittivat, että Suomessa diagnosoitujen Parkinson-potilaiden elinajanennuste on kasvanut miehillä naisia enemmän, mikä tulee kasvattamaan jo nyt yliedustettua miesten osuutta Parkinson-potilaissa. Tulokset osoittivat myös, että potilaalla aiemmin diagnosoitu hyperdopaminerginen skitsofrenia lisää myöhemmin kehittyvän hypodopaminergisen Parkinsonin taudin riskiä. Aiempia tutkimustuloksia vastaten havaitsimme taudin alkuvaiheessa esiintyvien psykoosi-, kognitio- ja ummetusoireiden liittyvän huonompaan ennusteeseen Parkinsonin taudissa. Lisäksi havaitsimme ennen diagnoosia esiintyvän kipuoireiston mahdollisen yhteyden korkeampaan kuolleisuuteen viiden vuoden sisällä Parkinson-diagnoosin asettamisesta. Tulokset osoittivat myös, että syväaivostimulaation vaste perinnöllisessä Parkinsonin taudissa riippuu taudinaiheuttajamutaatiosta. Hoitovaste vaikuttaa olevan erinomainen potilailla, joilla on *LRRK2*-geenin p.G2019S-mutaatio tai *PRKN*-geenin mutaatio mutta huono potilailla, joilla on *LRRK2*-geenin p.R1441G-mutaatio. Kognitiivisten ja neuropsykiatristen oireiden merkittävä eteneminen voi heikentää syväaivostimulaation vastetta potilailla, joilla on *LRRK2*-geenin p.T2013S-mutaatio tai *SNCA*- tai *GBA*-geenien mutaatio.

AVAINSANAT: Parkinsonin tauti, dopamiini, ennuste, kuolleisuus, perinnöllinen, syväaivostimulaatio, yhteissairastavuus, skitsofrenia, tekstinlouhinta, sähköinen potilastietojärjestelmä

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Abbreviations

5-HT	5-hydroxytryptamine
AD	Alzheimer's disease
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
CI	Confidence interval
CSAI	Continuous subcutaneous apomorphine infusion
DA	Dopamine
DAs	Dopamine agonist
DaT SPECT	Dopamine transporter single-photon emission computed tomography
DBS	Deep brain stimulation
DIP	Drug-induced parkinsonism
DLB	Dementia with Lewy bodies
EHRs	Electronic health records
EIF4G1	Eukaryotic translation initiation factor 4-gamma 1
FBS	Frontal behavioural-spatial syndrome
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GBA	Glucocerebrosidase
GPi	Globus pallidus interna
HR	Hazard ratio
ICD	Impulse control disorder
L-dopa	Levodopa
LCIG	Levodopa-carbidopa intestinal gel
LECIG	Levodopa-entacapone-carbidopa intestinal gel
LRRK2	Leucine-rich repeat kinase 2
MAO-B	Monoamine oxidase B
MCI	Mild cognitive impairment
MDS	The International Parkinson and Movement Disorder Society
MRgFUS	Magnetic resonance-guided focused ultrasound
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy

MSA-C	Cerebellar variant of MSA
MSA-P	Parkinsonian variant of MSA
naPPA	Nonfluent/agrammatic variant of primary progressive aphasia
NMDA	N-methyl-D-aspartate
NMS	Non-motor symptom
OR	Odds ratio
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PEG-J	Percutaneous gastrojejunostomy tube
PIGD	Postural instability gait disorder
PINK1	Phosphatase and tensin homolog-induced putative kinase 1
PRKN	Parkin
PSP	Progressive supranuclear palsy
PSP-RS	Richardson's syndrome
PSPS	Progressive supranuclear palsy syndrome
QoL	Quality of life
RBD	Rapid eye movement sleep behaviour disorders
REM	Rapid eye movement
RLS	Restless leg syndrome
rTMS	Repetitive transcranial stimulation
SCD	Schizophrenia spectrum disorder
SCZ	Schizophrenia
SN	Substantia nigra
SNCA	Synuclein alpha
SSNRI	Selective serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STN	Subthalamic nucleus
TCA	Tricyclic antidepressant
VIM	Ventral intermediate nucleus
VP	Vascular parkinsonism
VPS35	Vacuolar protein sorting 35

List of Original Publications

This thesis is based on the following four original publications, which are referred to in the text by Roman numerals I-IV:

I Kuusimäki T, Korpela J, Pekkonen E, Martikainen MH, Antonini A, Kaasinen V. Deep brain stimulation for monogenic Parkinson's disease: a systematic review. J Neurol. 2020 Apr;267(4):883–897.

II Kuusimäki T, Kurki S, Sipilä JOT, Salminen-Mankonen H, Carpén O, Kaasinen V. Sex-Dependent Improvement in Survival of Parkinson's Disease Patients. Mov Disord Clin Pract. 2020 Apr 27;7(5):516–520.

III Kuusimäki T, Al-Abdulrasul H, Kurki S, Hietala J, Hartikainen S, Koponen M, Tolppanen AM, Kaasinen V. Increased risk of Parkinson's disease in patients with schizophrenia spectrum disorders. Mov Disord. (E-pub 2021 Jan 6).

IV Kuusimäki T, Sainio J, Kurki S, Vahlberg T, Kaasinen V. Prediagnostic expressions in health records predict mortality in Parkinson's disease: A proof-of-concept study. [Manuscript].

1 Introduction

Parkinson's disease (PD) is a complex neurodegenerative disease that progressively affects more and more people worldwide (Armstrong & Okun, 2020; Ray Dorsey et al., 2018). PD is typically idiopathic, but 5–10% of patients have been reported to carry a monogenic mutation causing the disease (Deng et al., 2018; Kouli et al., 2018). There are several environmental and behavioural factors, such as pesticide exposure and high consumption of dairy products, which have been recognised to increase the risk of developing PD (Armstrong & Okun, 2020; Ascherio & Schwarzschild, 2016), as well as patient-related factors, like male gender and higher age (Ascherio & Schwarzschild, 2016; Kalia & Lang, 2015). PD manifests in patients as a diverse entity of motor symptoms and non-motor symptoms (NMSs) (Kalia & Lang, 2015). From the very beginning, the clinical features of PD were described in 1817 by English physician, Dr James Parkinson, when he reported six individuals in his work, "An Essay on the Shaking Palsy" (Parkinson, 2002). Dr. Parkinson recognised rest tremor, festinating gait and stooped posture as the characteristic features of the syndrome, which he named "Shaking Palsy". Further, over fifty years later, rigidity was identified as an additional clinical feature of the syndrome by French neurologist, Dr Jean-Martin Charcot, who renamed the disease "PD" (J. A. Obeso et al., 2017). Besides PD's classical motor signs of bradykinesia, rest tremor, rigidity and postural instability, a great variety of NMSs, such as hyposmia, constipation, depression, psychosis, sleep disorders and impulse control disorders (ICDs), are observed in PD patients (Armstrong & Okun, 2020; Kalia & Lang, 2015). Some NMSs can manifest for several years before motor symptoms appear during the so-called prodromal phase of PD, while some NMSs manifest dominantly in more advanced stages of the disease (Armstrong & Okun, 2020; Schapira et al., 2017). In recent years, there has been increasing interest in this prodromal phase of PD, considering aims to develop disease-modifying or neuroprotective therapies for PD.

The clinical diagnostics of PD are based on the medical history and physical examination of the patient (Armstrong & Okun, 2020). Several different criteria for clinical diagnostics of PD have been proposed (Armstrong & Okun, 2020), the UK Brain Bank Criteria (Hughes et al., 1992) and the more recent International

Parkinson and Movement Disorder Society (MDS) criteria (Postuma et al., 2015) being the most prevalent. However, many other syndromes may have partially overlapping phenotypes with PD, leading to misdiagnosis, especially in the early stage of the disease. The accuracy of clinical PD diagnoses have been reported to vary between 75% and 95% in different studies (Postuma et al., 2015).

The pharmacological treatment for motor symptoms of PD aims to increase intracerebral dopamine (DA) concentration and to stimulate DA receptors (Armstrong & Okun, 2020). As the motor symptoms cannot be sufficiently managed with oral treatment optimization, device-aided therapies should be considered for PD patients. The primary pharmacotherapy for early and moderate PD has remained mostly unaltered for the past two decades in developed countries (Armstrong & Okun, 2020; Pahwa & Lyons, 2014; Rascol et al., 2011), and the greatest improvements in PD treatment have recently been documented with device-aided therapies in advanced patients. However, there is no confident evidence of neuroprotectivity from any drug nor device-aided therapy (Armstrong & Okun, 2020; Dijk et al., 2020; Hayes, 2019).

The objective of this thesis was to investigate prognostic factors in PD patients. We focused on patient characteristic-, treatment-, and comorbidity-related issues of PD patients.

2 Review of the Literature

2.1 Epidemiology of Parkinson's disease

PD is the fastest growing neurological disorder worldwide (Ray Dorsey et al., 2018) and is reported to be the second most common neurodegenerative disease after Alzheimer's disease (AD) (Armstrong & Okun, 2020; Ascherio & Schwarzschild, 2016). In 2016, there were over 6 million patients with PD diagnosis globally, 2.4 times more than in 1990 (Armstrong & Okun, 2020; Ray Dorsey et al., 2018). This remarkable increase is thought to result from improved diagnostics of PD, ageing population, increasing life expectancy, and possibly growing exposure to environmental risk factors (Armstrong & Okun, 2020; Ray Dorsey et al., 2018). PD is associated with increased mortality as, on average, survival is reduced by approximately 5% every year in followed cohorts (Macleod et al., 2014). As a late-life neurodegenerative disease, PD epidemiology is affected by general factors that increase or decrease life expectancy.

A lifetime risk of developing PD is estimated to be around 1.5% (Lees et al, 2009). The risk is a bit higher in men than in women, and according to Elbaz and colleagues, the lifetime risk of developing PD is 2% for men and 1.3% for women in individuals aged 40 years in the USA (Elbaz et al., 2002). The male-to-female incidence ratio varies from 1.3 to 2.0 in different studies (Ascherio & Schwarzschild, 2016; Cerri et al., 2019), and the ratio has been suggested to increase with age (Kaasinen et al, 2015). PD is quite rare among people under the age of 50 years, and the incidence increases remarkably with age, being highest at around 80 years (Ascherio & Schwarzschild, 2016). The annual median age-standardized incidence of PD in high-income countries is reported to be 14/100 000 people in the total population, but it is 160/100 000 in people aged 65 years or older (Hirtz et al., 2007). The prevalence of PD in industrialised countries is estimated to be 0.3% (Hayes, 2019). Geographically, the age-adjusted prevalence of PD seems to be lower in Africa than in Europe, Asia and the Americas (Ascherio & Schwarzschild, 2016; Okubadejo et al., 2006; Zhang et al., 2005). The results of PD incidence by ethnicity are inconsistent. One study from the USA reported that the incidence of PD is higher among black people compared to white people (Mayeux et al., 1995), while another US-based study reported a higher incidence in white people than in black people

(Wright Willis et al., 2010). In turn, Van Den Eeden et al. stated that age- and sex-adjusted incidence of PD is highest among Hispanic people, followed by non-Hispanic white people, Asian people and black people (Van Den Eeden et al., 2003).

2.2 Risk factors of Parkinson's disease

PD is a multifactorial disease, and although most PD cases are idiopathic, there are several environmental and behavioural factors that influence the risk of developing PD (Armstrong & Okun, 2020; Kalia & Lang, 2015). The most robust risk factors for the development of PD are reported to be age, gender and ethnicity (Ascherio & Schwarzschild, 2016; Kalia & Lang, 2015). Indeed, it is well known that the prevalence and incidence of PD increases remarkably with age, and it is more common in males than in females (Ascherio & Schwarzschild, 2016). In one study, the incidence of PD in the USA is reported to be highest in people of Hispanic ethnic origin, followed by non-Hispanic Whites, Asians, and Blacks (Van Den Eeden et al., 2003). However, as explained above, there are fluctuations in reported PD incidences by ethnicity. Age, gender and ethnicity are non-modifiable risk factors; thus, the effect of these factors cannot be changed by modifying the lifestyle.

Noyce and colleagues have published a meta-analysis investigating 30 different potential risk factors for PD (Noyce et al., 2012). Pesticide exposure, traumatic brain injury, rural living, use of β-blockers, agricultural occupation and drinking well water were identified as risk factors for developing PD. Corresponding risk factors for PD have also been observed also in several other studies (Ascherio & Schwarzschild, 2016; Kalia & Lang, 2015). For instance, exposure to pesticides during work on plantations has been shown to increase the PD risk; relative risk for PD was reported to be 1.9 times greater for individuals who have worked 20 or more years on a plantation compared to individuals who have not worked on plantations (Petrovitch et al., 2002). The increased risk of PD after pesticide exposure may be explained by actions which can cause oxidative stress or impact to the mitochondrial respiratory chain (Ascherio & Schwarzschild, 2016). Head injuries may lead to consequences which are related to increased incidence of PD, such as damage to the blood–brain barrier, long-lasting brain inflammation, disruption of mitochondrial function and alpha-synuclein accumulation in the brain (Marras et al., 2014). The risk of PD seems to increase soon after traumatic brain injury but gradually decreases over time (Ascherio & Schwarzschild, 2016). Fang et al. have reported a relative risk of 3.34 within one year after head injury leading to hospitalisation and, remarkably, a decreased relative risk of 1.28 one to four years after head injury (Fang et al., 2012). It is hypothesised that an early increase in PD risk after head injuries is probably explained by more frequent falls and head injuries in individuals with early PD (Ascherio & Schwarzschild, 2016). On the contrary, Noyce and colleagues reported

that tobacco smoking, coffee drinking, use of non-steroidal anti-inflammatory drugs, use of calcium channel blockers and alcohol consumption were linked to decreased risk of developing PD (Noyce et al., 2012). A low risk of PD among tobacco smokers has also been observed in several other studies (Ascherio & Schwarzschild, 2016; Kalia & Lang, 2015), and the risk has been reported to decrease up to 70% with increasing duration of smoking (Thacker et al., 2007). It has been hypothesised that the negative association between PD and tobacco smoking could be due to a decreased responsiveness to nicotine during the prodromal phase of PD (Ascherio & Schwarzschild, 2016; Kalia & Lang, 2015). Caffeine is an adenosine receptor antagonist whose neuroprotective effect is well documented in experimental models of PD (Xu et al., 2010). Coffee and, in some studies, tea consumption are linked to decreased risk of PD (Ascherio & Schwarzschild, 2016). Among coffee drinkers, the association is more robust in males than in females (Liu et al., 2012). Urate is a potent antioxidant, and previous cellular and animal studies have shown that it can protect against degeneration of dopaminergic neurons (X. Chen et al., 2013). The results of a previously published meta-analysis showed lower PD risk among patients with higher plasma urate levels (Weisskopf et al., 2007). The negative correlation between alcohol consumption and PD is shown in previous studies (Ascherio & Schwarzschild, 2016), and the descendent effect on the PD risk is probably related to the urate-elevating effects of alcoholic beverages (Yamamoto et al., 2005).

In addition, there are several other factors associated with developing PD. High milk and dairy consumption are associated with increased risk of PD possibly due to urate-lowering effects of dairy products (Ascherio & Schwarzschild, 2016). The relative risk of PD has been reported to be 1.6 in individuals with the highest dairy intake compared to individuals with the lowest (H. Chen et al., 2007). Methamphetamine is an abused and highly addictive stimulant drug that binds to the presynaptic DA transporters and increases extracellular DA concentrations, which has been shown in experimental animals to lead to similar damage of DA neurons in the substantia nigra (SN) to that seen in PD patients (Guilarte et al., 2003). Consequently, the use of methamphetamine is reported to be one of the risk factors for developing PD (Ascherio & Schwarzschild, 2016). The increased risk of PD is robustly documented among patients with melanoma (Ascherio & Schwarzschild, 2016). Olsen et al. reported a 44% increased risk of developing PD in patients with melanoma (Olsen et al., 2006), and further, increased risk of melanoma has been reported among patients with early PD (Constantinescu et al., 2014). Studies of body mass index and diabetes mellitus effects on the risk of PD show inconsistent results (Ascherio & Schwarzschild, 2016). However, a recently published study reported that being underweight and diabetes mellitus are risk factors for developing PD (Jeong et al., 2020). Jeong and colleagues showed that the adjusted hazard ratio (HR) was 1.28 (95% confidence interval (CI): 1.21–1.36) in the underweight group versus

the normal group, whereas the adjusted HR was 0.88 (95% CI: 0.88–0.93) in the obese group, and 0.77 (95% CI: 0.72–0.82) in the severely obese group. Several gastrointestinal manifestations are also associated with the risk of developing PD. For instance, constipation (Adams-Carr et al., 2016), irritable bowel syndrome (Lai et al., 2014), and inflammatory bowel disease (Weimers et al., 2019) are related to a higher risk of PD. Alterations of gut microbiota composition are also observed in PD patients (Scheperjans et al., 2015). Moreover, in a recently published study, exposure to certain oral antibiotics (especially macrolides and lincosamides) were associated with elevated risk of PD (Mertsalmi et al., 2020). There have also been identified various genetic risk loci and variants for sporadic PD (Deng et al., 2018; Nalls et al., 2014). Thus, the combined effect of environmental, behavioural and genetic factors together with patient characteristics influence the overall risk of developing PD (**Figure 1**).

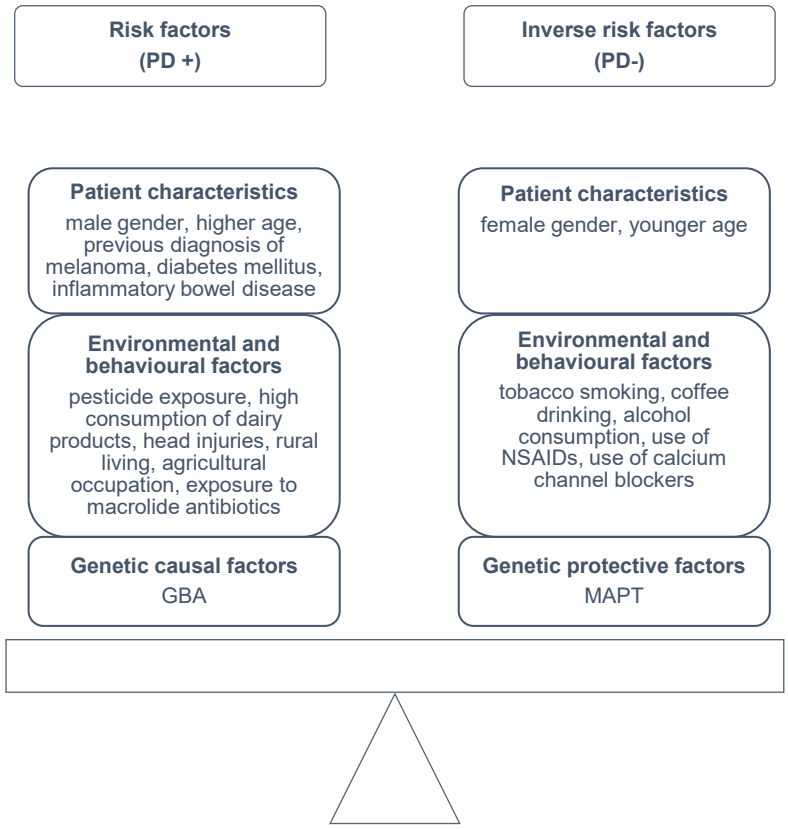

Figure 1. Examples of risk factors for the development of Parkinson's disease. The figure was modified from the figure in Ascherio & Schwarzschild, 2016. NSAID = Non-steroidal anti-inflammatory drug.

2.3 Genetics of Parkinson's disease

Approximately 15% of PD patients have a positive family history, and 5–10% of PD patients have a monogenic form of the disease with Mendelian inheritance (Deng et al., 2018; Kouli et al., 2018). There are many gene mutations with both dominant and recessive inheritance patterns, which appear to be associated with PD or parkinsonism (Deng et al., 2018; Puschmann, 2013). Currently, researchers have identified at least 23 loci and 19 disease-causing genes, which are designated as PD-causing genes by the HUGO Gene Nomenclature Committee (**Table 1**) (Deng et al., 2018). Furthermore, several studies have reported genetic risk-increasing factors for PD (Deng et al., 2018), and, for instance, polymorphism in mitochondrial DNA-encoded complex I genes has been associated with increased risk for PD (J. Autere et al., 2004). However, the incidence of monogenic PD in Finland remains uncertain as findings on disease-causing gene mutations are scarce in Finnish PD studies (J. M. Autere et al., 2002; Eerola et al., 2002; Hernandez et al., 2012).

Autosomal dominant PD is most frequently linked to mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene (Deng et al., 2018; Ramirez et al., 2016) and also to mutations, e.g. in synuclein alpha (*SNCA*), vacuolar protein sorting 35 (*VPS35*) and eukaryotic translation initiation factor 4-gamma 1 (*EIF4G1*) genes in more rare cases (Deng et al., 2018; Puschmann, 2013). Parkin (*PRKN*) mutations are the most common genetic cause of autosomal recessive PD, and in prevalence, they are followed by mutations in the phosphatase and tensin homolog-induced putative kinase 1 (*PINK1*) gene (Deng et al., 2018; Puschmann, 2013). Both homozygous and heterozygous glucocerebrosidase (*GBA*) mutations are shown to predispose to PD and are currently considered the most important genetic risk factors (Zhao et al., 2016).

In general, genetic PD occurs more commonly at a younger age of onset; however, the clinical manifestations vary depending on the gene and the specific mutations (Kasten et al., 2017). *LRRK2* mutation is the most common genetic cause of PD (Deng et al., 2018), and the clinical phenotype of *LRRK2*-associated PD tends to be more benign than that of the general PD population (Healy et al., 2008). PD patients with *PRKN* mutations are characterised as being young or very young at onset, but they have a lower risk for NMSs such as cognitive decline (Puschmann, 2013). In contrast, *SNCA* patients tend to develop severe autonomic dysfunction, speech problems, cognitive decline and neuropsychiatric problems (Puschmann, 2013). The phenotype of *GBA* mutation carriers is usually also more severe than that of idiopathic PD patients: earlier age at onset, more aggressive progression of motor symptoms, greater cognitive decline, more severe autonomic dysfunction and more prevalent psychiatric complications (Deng et al., 2018). Further, medication effects may vary between different mutations. For instance, PD patients with *PRKN* mutations typically are especially prone to dyskinesias induced by levodopa (L-

dopa), whereas those with *LRRK2* mutations tend to show a normal long-term benefit for L-dopa (Healy et al., 2008; Puschmann, 2013). The effects of other antiparkinsonian drugs, such as rasagiline, may also be modulated by the genotype (Masellis et al., 2016). Moreover, the effect of deep brain stimulation (DBS) seems to vary depending on the specific PD-causing mutation (Artusi et al., 2019; de Oliveira et al., 2019; Kuusimäki et al., 2020; Rizzone et al., 2019). There have been reports of positive motor outcome of DBS in most genetic forms of PD, but complications such as motor and neuropsychiatric problems vary between different mutations.

Table 1. Disease-causing genes of Parkinson's disease. The table was modified from the table in Deng et al., 2018.

HGNC approved gene symbol	Full gene name approved by HGNC	Locus	Inheritance	Disease onset
SNCA	Synuclein alpha	PARK1	AD	Usually early-onset
PARK3	Parkinson disease 3	PARK3	AD	Late-onset
UCHL1	Ubiquitin C-terminal hydrolase L1	PARK5	AD	Early-onset, late-onset
LRRK2	Leucine rich repeat kinase 2	PARK8	AD	Late-onset
GIGYF2	GRB10 interacting GYF protein 2	PARK11	AD	Late-onset
HTRA2	HtrA serine peptidase 2	PARK13	AD	Usually late-onset
VPS35	VPS35, retromer complex component	PARK17	AD	Late-onset
EIF4G1	Eukaryotic translation initiation factor 4 gamma 1	PARK18	AD	Late-onset
TMEM230	Transmembrane protein 230	PARK21	AD	Usually late-onset
CHCHD2	Coiled-coil-helix-coiled-coil-helix domain containing 2	PARK22	AD	Usually late-onset

RIC3	RIC3 acetylcholine receptor chaperone		AD	Usually late-onset
PRKN	Parkin RBR E3 ubiquitin protein ligase	PARK2	AR	Early-onset
PINK1	PTEN induced putative kinase 1	PARK6	AR	Early-onset
PARK7	Parkinsonism associated deglycase	PARK7	AR	Early-onset
ATP13A2	ATPase 13A2	PARK9	AR	Early-onset
PLA2G6	Phospholipase A2 group VI	PARK14	AR	Early-onset
FBXO7	F-box protein 7	PARK15	AR	Early-onset
DNAJC6	DnaJ heat shock protein family member C6	PARK19	AR	Early-onset
SYNJ1	Synaptojanin 1	PARK20	AR	Early-onset
VPS13C	Vacuolar protein sorting 13 homolog C	PARK23	AR	Early-onset
PARK12	Parkinson disease 12	PARK12	X-linked	Late-onset
PARK10	Parkinson disease 10	PARK10	Unclear	Late-onset
PARK 16	Parkinson disease 16	PARK16	Unclear	Late-onset

* AD = Autosomal dominant, AR = Autosomal recessive, HGNC = HUGO Gene Nomenclature Committee.

2.4 Clinical features and diagnostics of Parkinson's disease

PD is a complex neurodegenerative disease associated with a variety of motor symptoms and NMSs (Armstrong & Okun, 2020; Kalia & Lang, 2015). The main pathological feature of idiopathic PD is the damage of dopaminergic neurons in the SN pars compacta, especially in its ventrolateral tier (Kalia & Lang, 2015). Dopaminergic neuronal loss also occurs widely in other regions of the brain, and PD pathology also involves neurotransmitters other than DA, including dysfunction of serotonin, acetylcholine, glutamate and norepinephrine systems (Dickson, 2018; Kalia & Lang, 2015). Another hallmark of the neuropathology of PD is the Lewy pathology that affects both the central and peripheral nervous systems (Dickson,

2018). Misfolded proteins, mainly consisting of alpha-synuclein, form insoluble aggregates that accumulate in cell bodies (called Lewy bodies) and neuron processes (called Lewy neurites) (Dickson, 2018; Kalia & Lang, 2015; Schapira & Jenner, 2011). The most known hypothesis about the beginning and progression of sporadic PD is called the Braak hypothesis (Braak et al., 2003a). The first theory proposed that unknown pathogens in the gut could initiate the pathological process of sporadic PD (Braak et al., 2003b). This was followed by the dual-hit hypothesis, suggesting that sporadic PD starts in two different locations: in the neurons of the nasal cavity and in the neurons of the gut (C. H. Hawkes et al., 2007; C. H. Hawkes et al., 2009). According to the Braak hypothesis (Braak et al., 2003a), the neuropathological process in PD starts in the medulla and olfactory tract and then proceeds to the SN pars compacta and to other midbrain and basal forebrain structures, and in advanced stages of PD, the process further progresses to cerebral cortices. Although the loss of dopaminergic neurons and the Lewy pathology are obviously seen in patients with idiopathic PD, the relationship of these two cellular pathologies and the ultimate aetiology of PD remain elusive (J. A. Obeso et al., 2017).

2.4.1 Motor symptoms

Motor symptoms of PD usually occur when approximately half of the neurons in the caudal SN are pathologically affected (Fearnley & Lees, 1991). The phenotype of PD concerns four classical motor signs: bradykinesia, rest tremor, rigidity and postural instability (Kalia & Lang, 2015). However, manifestation of clinical motor features varies between PD patients. Bradykinesia is seen as a rule in all PD patients, with tremor and rigidity in most, while postural instability is usually more dominant in more advanced stages of the disease (J. A. Obeso et al., 2017).

Several different methods, including motor signs, nonmotor features and rates of progression, have been used to divide PD into different subtypes (J. A. Obeso et al., 2017). The most distinguished distribution is the division to tremor-dominant and non-tremor-dominant subtypes based on the dominant motor features of PD (Kalia & Lang, 2015; Marras & Lang, 2013; J. A. Obeso et al., 2017). The latter subtype is subdivided further to akinetic-rigid syndrome and to postural instability gait disorder (PIGD) (Kalia & Lang, 2015). Tremor-dominant PD is typically associated with better prognosis and slower progression of the disease than non-tremor-dominant PD (Kalia & Lang, 2015). It is also hypothesised that the aetiology and pathogenesis may be separate between different subtypes of PD (Kalia & Lang, 2015; Marras & Lang, 2013).

In clinical practice, bradykinesia comprehends the slowness of movements, decreased movement amplitude and dysrhythmia, which can be seen, for example, in repetitive finger tapping. Bradykinesia is often used synonymously with the terms

"akinesia" and "hypokinesia"; although bradykinesia technically refers to the slowness of movements, akinesia refers to poverty or absence of spontaneous movements, and hypokinesia refers to the decreased amplitude of movements (Berardell et al., 2001). Bradykinesia is thought to primarily result from a failure of basal ganglia output to reinforce the cortical mechanisms that prepare and execute the commands to move (Berardelli et al., 2001). Factors such as rigidity and muscle weakness secondarily influence bradykinesia. In addition to bradykinesia in limbs, the symptom can be detected also in the face, voice and axial domains (Erro & Stamelou, 2017). Tremor refers to involuntary rhythmical and oscillatory movement of a body part and can be classified as rest, postural or kinetic tremor (Bhatia et al., 2018). Classical PD tremors emerge at rest and at a frequency of 4–6 Hz (Armstrong & Okun, 2020). However, PD patients can also suffer other types of tremor besides the tremor-at-rest (Hallett, 2012). Especially in later stages of the disease, tremor can be re-emergent, meaning it can be seen in action after a short pause when a body part is transitioned from rest to posture (Mark & Günther, 2010). In addition, distinct postural tremor, essential tremor and dystonic tremor are reported in patients with PD (Hallett, 2012; Pasquini et al., 2018). A recent review outlined that the response of rest tremor to dopaminergic medications is often unsatisfactory, addressing that DA deficiency alone does not explain the tremor severity (Pasquini et al., 2018). Some studies have reported that rest tremor might relate to systems other than dopaminergic ones, for instance serotonergic neuronal dysfunction of raphe nuclei (Qamhawi et al., 2015) or dysfunction of the noradrenergic locus coeruleus (Isaias et al., 2012). Rigidity refers to stiffness of muscles and is detected as involuntary resistance to passive movements of a joint (Armstrong & Okun, 2020). It is detected when a patient is relaxed, and the examiner manipulates the limbs and neck. PD patients' rigidity is typically characterised as lead-pipe resistance and is often combined with the cogwheel phenomenon (Postuma et al., 2015). In PD, rigidity usually increases especially when the contralateral limb is activated (Hong et al., 2007). Moreover, PD patients usually suffer from gait and axial disturbances, which are observed as difficulties in maintaining or changing postures when walking or standing (Armstrong & Okun, 2020; Postuma et al., 2015). Postural instability is usually more prominent in advanced stages of the disease (J. A. Obeso et al., 2017) and can indicate other forms of parkinsonism if it is already clearly seen in the early course of the disease (Postuma et al., 2015). The typical first appearances of gait and axial disturbances are stooped posture, shortened stride and reduced arm swing when walking (Erro & Stamelou, 2017). These symptoms tend to worsen as the disease progress and can lead to frequent falls in patients with advanced PD (Erro & Stamelou, 2017). The gradual strengthening of the stooped posture can eventually lead to camptocormia (Doherty et al., 2011) or so-called Pisa syndrome (Tinazzi et al., 2015), which often presents in later-stage PD.

Motor complications, often called L-dopa-related problems, appear as the disease progresses (Kalia & Lang, 2015). PD patients suffer from worsening motor symptoms before the next L-dopa dose (so-called wearing-off phenomenon), unpredictable off-periods, off-phase dystonia or delayed response to the L-dopa dose (so-called delayed-on) (Erro & Stamelou, 2017; Kalia & Lang, 2015; Postuma et al., 2015). In addition to these hypodopaminergic problems, patients can also suffer from L-dopa-induced dyskinesias, which can occur when the concentration of L-dopa is at its highest (so-called peak dyskinesias) or when the concentration rises or falls (so-called diphasic dyskinesias) (Erro & Stamelou, 2017; Kalia & Lang, 2015; Postuma et al., 2015).

2.4.2 Non-motor symptoms

Non-motor features of PD are a common and diverse group of symptoms that have a remarkable influence on the quality of life (QoL) of PD patients. Some of these symptoms, like hyposmia and sleep disorders, can precede several years before the motor symptoms appear (Armstrong & Okun, 2020). The neuropathology of PD NMSs extends to central and autonomic nervous systems and includes the dysfunction of both dopaminergic and non-dopaminergic pathways (Schapira et al., 2017). The manifestation of NMSs during the course of PD is illustrated in **Figure 2**.

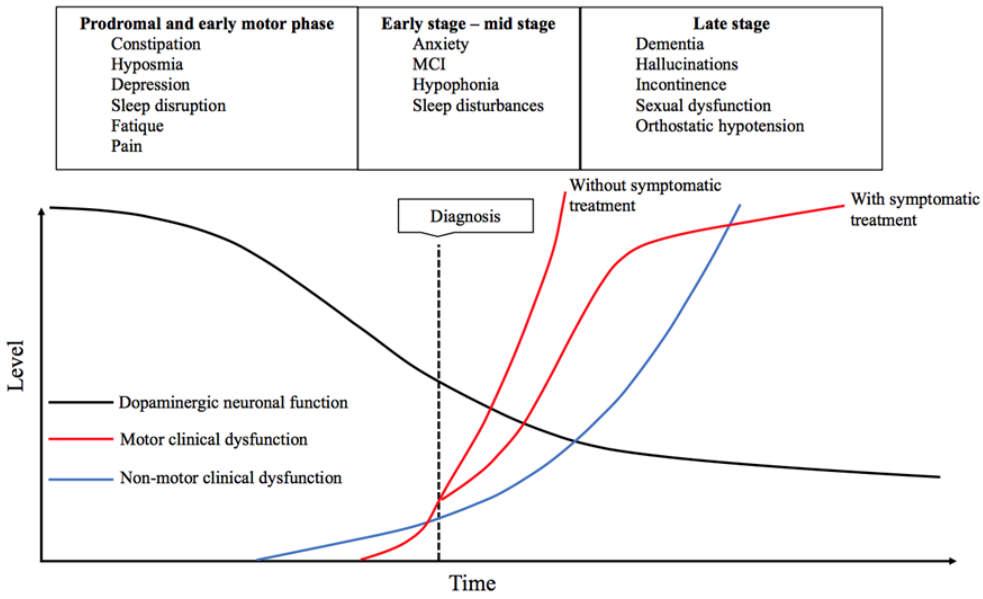

Figure 2. Some non-motor symptoms of Parkinson's disease and their appearance over the disease course. The figure was modified from the figure in Schapira et al, 2017. MCI = Mild cognitive impairment.

2.4.2.1 Neuropsychiatric symptoms

2.4.2.1.1 Depression

Depression is a common symptom in patients with PD and its prevalence is higher among PD patients compared to healthy controls (Larsen et al., 2017). It has been estimated that approximately 35% of PD patients suffer from clinically relevant depression (Reijnders et al., 2008). Depression is usually thought to be milder in PD patients compared to people without PD (Schapira et al., 2017). It can occur in all disease stages of PD, although it is often observed in the prodromal phase of the disease (Schapira et al., 2017). In addition, PD depression can occur due to psychological stress caused by PD-related disability (Even & Weintraub, 2012). Duration of the disease, complexity of motor symptoms, appearance of motor complications and dosage of dopaminergic medication have been shown to influence PD depression (N. N. W. Dissanayaka et al., 2011; A. H. V. Schapira et al., 2017). Further, other NMSs, including cognitive decline, dementia, anxiety and sleep disturbances, increase the risk of PD depression (Santangelo et al., 2014).

The neuropathology of PD depression is multifactorial. As in PD pathophysiology, DA is also the main factor in the pathophysiology of PD depression. Dysfunction of dopaminergic pathways in limbic and frontal areas are crucial in PD-related depression (Castrioto et al., 2016). In a PET study, Remy et al. have shown that DA transporter availability is decreased in the striatum and limbic brain regions in PD patients with depression compared to those without depression (Remy et al., 2005). In addition, a recently published study showed that degeneration of dopaminergic neurons is significantly more prominent in Lewy body spectrum disease patients with comorbid depression compared to patients without depression (Saari et al., 2021). Imaging studies have also shown loss of white matter in corticolimbic regions, which are associated with dopaminergic regulation of mood and motivation (Schapira et al., 2017). Depression usually deepens during off-periods and can respond to dopamine agonist (DAs) therapy (Bxarone et al., 2010; Seppi et al., 2019) supporting that DA is one of the main factors in PD depression. In addition, dysfunctions of noradrenergic, serotonergic and cholinergic systems are linked to neuropathology of PD depression (Frisina et al., 2009; A. H. V. Schapira et al., 2017).

In a recent review, Seppi and colleagues published recommendations for treatment of NMSs of PD (Seppi et al., 2019). Medication options for PD depression include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), DAs and monoamine oxidase B (MAO-B) inhibitors. The best evidence on the efficacy of PD-related depression treatment seems to be for pramipexole (DAs) and venlafaxine

(SSNRI). Nonpharmacological interventions include repetitive transcranial stimulation (rTMS) and cognitive-behavioural therapy.

2.4.2.1.2 Anxiety

PD patients suffer frequently from anxiety, and it is often underdiagnosed among them (N. N. W. Dissanayaka et al., 2014). PD-related anxiety disorders manifest as panic attacks, social phobias or generalised anxiety, affecting as much as 60% of PD patients (Schapira et al., 2017). Anxiety commonly coexists with depression in PD, but, it can also appear as an isolated symptom (Schapira et al., 2017). Female gender, younger age at onset of PD, advanced stage of PD and previous history of anxiety predispose to the development of this neuropsychiatric manifestation of PD (N. N. W. Dissanayaka et al., 2014; Lin et al., 2015). Anxiety is considered one of the prodromal markers of PD (Postuma & Berg, 2019), but anxiety disorders can occur at any stage of the disease (Pfeiffer, 2016). The severity of anxiety typically increases with motor fluctuation, and the most pronounced symptoms are linked to off- and freezing periods when DA levels are low (Schapira et al., 2017).

Damage of both nigrostriatal and extra-nigrostriatal pathways are linked to pathophysiology of anxiety in PD (Schapira et al., 2017; Wen et al., 2016). Functional imaging studies have revealed an inverse correlation between dopaminergic density in the caudate and putamen with the severity of anxiety in PD, but there was no consistent correlation between dopaminergic density of the thalamus and anxiety (Wen et al., 2016). There are no published randomised clinical trials for treating anxiety in PD (Armstrong & Okun, 2020; Seppi et al., 2019).

2.4.2.1.3 Hallucinations and psychosis

PD psychosis refers to illusions, hallucinations and delusions experienced by PD patients (Ffytche & Aarsland, 2017). Psychotic symptoms occur in approximately 40% of PD patients and typically present in the advanced stage of the disease (Armstrong & Okun, 2020; Ffytche & Aarsland, 2017). It has been reported that these symptoms are more common among patients with a non-tremor-dominant clinical subtype of PD (Reijnders et al., 2009). The first psychotic symptoms appearing in PD are typically illusions, passage hallucinations (moving figures or objectives in the visual field) or presence hallucinations (feeling that someone is in the same room) (Ffytche & Aarsland, 2017). As the disease progresses, these minor hallucinations are followed by formed hallucinations and, finally, delusions (Ffytche & Aarsland, 2017). PD-related hallucinations are mainly visual hallucinations, such as animals or people. Other types of hallucinations (auditory, tactile and olfactory)

and delusions are more rare and are usually seen in later course of the illness (Ffytche & Aarsland, 2017).

Hallucinations in PD are associated with the presence of Lewy bodies in the amygdala and cortical structures, decreased 5-hydroxytryptamine (5-HT) levels in the forebrain and diminished cortical cholinergic transmission (Schapira et al., 2017). Moreover, Jaakkola and her colleagues have previously shown that DA transporter binding of the ventral striatum is lower in PD patients who suffer from visual hallucinations compared to PD patients without visual hallucinations (Jaakkola et al., 2017). PD patients may also have comorbid diseases which cause psychotic symptoms. For instance, there are two previously published studies which pointed to a possible increased risk of PD in patients with schizophrenia (SCZ) (Gabilondo et al., 2017; Smith et al., 2013). Increased risk of developing PD has also been reported in patients with bipolar disorder (Faustino et al., 2020; Huang et al., 2019).

Dopaminergic medications, especially L-dopa and DAs, can induce psychotic symptoms (Kalia & Lang, 2015). The first choice in the treatment of psychotic symptoms in PD patients is to reduce the dose of antiparkinsonian drugs, but adequate reduction of antiparkinsonian medications is not always possible because it can cause manifestation of PD motor symptoms (Schapira et al., 2017). Consequently, adding an antipsychotic agent is often necessary, and PD-related psychotic symptoms are typically treated with DA antagonists and atypical 5-HT-based antipsychotics (Schapira et al., 2017). Quetiapine, pimavanserin and clozapine are reported to be first-line choices in the treatment of PD psychosis in a recent review (Seppi et al., 2019).

2.4.2.1.4 Impulse control disorders

ICDs in PD include eating and sexual behaviours, pathological gambling, and compulsive buying, whereas related disorders include punding (repetitive, purposeless behaviours), DA dysregulation syndrome (compulsive medication overuse), and hobbyism (e.g., compulsive Internet use) (Weintraub & Mamikonyan, 2019). Overall, ICDs tend to emerge equally in males and females, but compulsive sexual behaviours are reported to be more common in males, whereas compulsive shopping and binge eating disorders appear more frequently in females (Weintraub et al., 2010). It has been shown that ICDs and related disorders have remarkable adverse effects on QoL, interpersonal relationships, and caregiver burden, and are associated with psychiatric comorbidity in PD (Jaakkola et al., 2014; Weintraub, 2019; Weintraub & Mamikonyan, 2019). Several factors, such as personal or familial history of alcoholism or gambling, and cigarette smoking, are associated with increased risk of developing ICDs (Weintraub, 2019). ICDs seem to be

underrecognised and undermanaged in clinical practice, probably due to embarrassment and limited awareness associated with the disorders and the inability to suspect the association between symptoms and PD medications (Weintraub et al., 2010).

In a study by Bastiaens et al., 39% of patients treated with DAs were reported to develop ICDs within 4 years after treatment initiation (Bastiaens et al., 2013). Another study observed a cumulative ICD prevalence of 8.5% after using rotigotine in a 24-hour patch formulation (Antonini et al., 2016a). In a large cross-sectional DOMINION study, 13.6% of PD patients were reported to suffer from ICDs, and 29% of them simultaneously experienced two or more types of ICDs (gambling in 5.0%, compulsive sexual behaviour in 3.5%, compulsive shopping in 5.7%, and binge eating disorder in 4.3%) (Weintraub et al., 2010). Several other studies, for instance from Finland, Germany and Spain, have reported corresponding rates of ICDs compared to results of the DOMINION study (Weintraub, 2019). Weintraub and his colleagues also reported that ICDs were significantly more common among those treated with DAs compared to patients without DAs therapy (17.1% versus 6.9%). Furthermore, ICDs were identified in 17.7% of patients using DAs with L-dopa, in 14.0% of patients using DAs without L-dopa, and in 7.2% of patients using only L-dopa. In the DOMINION study, there was no detected significant difference in the prevalence of ICDs between patients treated with pramipexole and patients treated with ropinirole (17.7% versus 15.5%), and the study did not observe a dose-response relationship between DAs use and ICDs. However, there is a hypothesis that distinct D3:D2 receptor binding selectivity of DAs may influence the DAs' potential to cause ICDs (Seeman, 2015). Some studies have also reported dose-related (Bastiaens et al., 2013) and treatment duration–related (Antonini et al., 2016a) connections between DAs and ICDs. In addition, the use of L-dopa, amantadine, and MAO-B inhibitors are reported to be associated with ICDs (Weintraub, 2019; Weintraub & Mamikonyan, 2019). The hypothesis that ICDs may be a disease manifestation of PD has been proposed and subsequently reversed, as there was no observed difference in reported ICDs between non-treated PD patients and healthy controls, and ICDs have also been shown to associate with DAs therapy in the treatment of diseases other than PD, such as fibromyalgia (Weintraub, 2019).

The most common way to treat ICDs in PD is to reduce or discontinue DAs while increasing the dose of L-dopa (Weintraub, 2019; Weintraub & Mamikonyan, 2019). However, some patients struggle to stop using DAs due to withdrawal symptoms (Armstrong & Okun, 2020). Pharmacological treatment options for ICDs are restricted, but cognitive-behavioural therapy has been shown as likely efficacious in treating ICDs (Seppi et al., 2019).

2.4.2.1.5 Cognitive decline and dementia

Problems in cognitive functions are common among PD patients, as up to 83% of PD patients may suffer from some level of cognitive dysfunction during the course of the disease course (Schapira et al., 2017). Cognitive impairment is usually considered to be associated with more advanced stages of PD, but 15–20% of patients have been reported to have mild cognitive impairment (MCI) already at the time of PD diagnosis (Aarsland, 2016). PD patients with the non-tremor-dominant phenotype are more prone to develop cognitive problems compared to patients who have tremor-dominant PD (Schapira et al., 2017). Some PD-causing gene mutations, such as *SNCA* mutations, are also associated with increased risk of cognitive problems (Puschmann, 2013). Cognitive decline commonly worsens as PD progresses, and a period of PD-MCI usually precedes dementia (Aarsland, 2016). Clinical characteristics such as higher age, more severe motor symptoms, and amnestic MCI are linked to shorter time of PD dementia (PDD) development (Aarsland, 2016). Nevertheless, there is also a "dual syndrome hypothesis": cognitive deficits related to temporal and posterior lesions, such as recognition memory, are associated with subsequent dementia, whereas deficits like executive dysfunction linked to frontostriatal lesions are more stable (Williams-Gray et al., 2007). The limbic and cortical Lewy body pathology is considered the main factor in the pathophysiology of cognitive decline in PD (Walker et al., 2015). However, AD-type amyloid-beta plaques are also observed in patients with PDD, and furthermore, tau-based inclusions may also be present (Aarsland, 2016). Dysfunction in several neurotransmitter pathways, such as dopaminergic, cholinergic and glutaminergic dysfunction, has been reported in PDD (Aarsland, 2016).

It is important to separate MCI and dementia from each other; cognitive impairment is the main factor in both conditions, but in dementia, cognitive decline is accompanied by significant problems in activities of daily living and in independent functions. Further, it may be difficult to distinguish whether the specific cause of cognitive problems is, for instance, PDD, dementia with Lewy bodies (DLB) or AD dementia (Walker et al., 2015). The clinical diagnostic criteria for PDD were published by the MDS in 2007 (Emre et al., 2007). In PDD, there is typically a period of motor symptoms without remarkable cognitive problems at first, and significant cognitive decline occurs at least one year after the diagnosis of PD (Walker et al., 2015). However, there is individual fluctuation at the time of developing cognitive impairment and dementia among PD patients (Kempster et al., 2010). The deficits in executive, visuospatial and attentional functions with relatively less severe memory impairment are usually the main features of the early cognitive profile in PD (Schapira et al., 2017). These typical symptoms differ from the clinical picture of MCI caused by AD (Aarsland, 2016). As the disease progresses, cognitive decline is usually rapid in patients with PDD (Kempster et al.,

2010), and behavioural symptoms such as hallucinations and agitation are quite common in advanced stages of the disease (Aarsland, 2016). Rivastigmine is the only acetylcholinesterase inhibitor that has been shown to be clinically useful in the treatment of PDD, while donepezil and galantamine are characterised as possibly useful (Seppi et al., 2019). There is insufficient evidence on the efficacy of N-methyl-D-aspartate (NMDA) receptor antagonist memantine in the treatment of PDD (Seppi et al., 2019).

2.4.2.2 Sleep disorders

Sleep disorders are common among PD patients and have a remarkable negative impact on QoL of PD patients (Schapira et al., 2017). They may begin appearing in the premotor phase of the disease, but their prevalence and severity tend to increase as the illness progresses (Falup-Pecurariu & Diaconu, 2017). Sleep disturbances in PD can be divided into disturbances during sleep and disturbances during wakefulness; nocturnal disorders include insomnia, rapid eye movement sleep behaviour disorders (RBD), nonrapid eye movement parasomnias, restless leg syndrome (RLS), periodic limb movements, and sleep-disordered breathing, whereas diurnal disorders include excessive daytime sleepiness and sudden onset of sleep (Falup-Pecurariu & Diaconu, 2017). There are multiple factors associated with the development of sleep disorders in PD, such as degeneration of central sleep regulation centres in the brainstem and thalamocortical pathways, the influence of drugs on sleep structure, and sleep fragmentation due to multiple factors (Braak & Del Tredici, 2008). Moreover, other NMSs (such as nocturia and hallucinations) and motor symptoms (such as dyskinesias or wearing-off phenomena during the night) of PD patients may amplify sleep disturbances (Schapira et al., 2017).

A significant proportion of PD patients suffer from sleep disturbances in some point of the disease course, and prevalence estimates of PD-related sleep disorders have varied from 40% to 98% (Falup-Pecurariu & Diaconu, 2017). Sleep disturbances are also common in the general population, but several studies have indicated that sleep disorders are much more common in PD patients than in healthy controls (Falup-Pecurariu & Diaconu, 2017). For instance, Kumar et al. reported sleep disorders in 42% of PD patients and in 12% of healthy controls (Kumar et al., 2002). They also showed that sleep problems correlate with increased severity of the disease. In addition, associations of sleep disturbances with scores from the Unified Parkinson's Disease Rating Scale Part III, L-dopa dose, rigidity score and bradykinesia score were observed via multiple logistic regression analyses.

The most common sleep disorders in PD are RBD, excessive daytime sleepiness, insomnia and RLS (Chahine et al., 2017). The distinctive feature of RBD is a lack of normal motor atonia during rapid eye movement (REM) sleep,

which leads to disruptive motor behaviour. Typically, vocalisations (e.g. shouting) and abnormal movements (e.g. arm/leg jerks or falling out of bed) are reported by bed partners of PD patients suffering from RBD. Physical movements while dreaming may be very vivid and predispose the patient and bed partner to injuries. RBD is neuropathologically associated with degeneration of lower brainstem nuclei, including pedunculopontine and subcoeruleal nucleus (Chahine et al., 2017). RBD is one of the main clinical predictors of developing PD, and it is linked to a PD phenotype characterised by more severe autonomic dysfunction, gait impairment and dementia (Kalia & Lang, 2015). Some PD patients suffer from RBD throughout the disease, but one study has reported resolution of RBD within four years in about a third of PD patients (Gjerstad et al., 2008). Pharmacological treatment options for RBD include clonazepam and melatonin (Seppi et al., 2019). However, the use of SSRIs, SSNRIs and TCAs can worsen RBD, and these potential aggravators should be removed before initiating pharmacotherapy for RBD (Seppi et al., 2019).

Excessive daytime sleepiness is a common and multifactorial symptom occurring in PD patients. If it is severe enough, it can cause sudden-onset sleep episodes, causing impaired social functioning and accident risk when driving. In turn, insomnia refers to trouble falling and/or staying asleep, which causes sleep fragmentation. It is divided into sleep onset and sleep maintenance insomnia, both of which are common in PD (Chahine et al., 2017). Insomnia can be disease-related or drug-related (too little or too much dopaminergic therapy) (Schapira et al., 2017). Several factors impact PD patients' insomnia: PD medications (e.g. DAs and selegiline), motor symptoms (e.g. wearing-off and impaired bed mobility), other NMSs (e.g. pain), psychiatric comorbidity (e.g. depression and anxiety) and other sleep disorders (e.g. RBD and RLS) (Chahine et al., 2017). RLS refers to uncomfortable sensations in the legs and an urge to move the legs during inactivity. PD seems to be a risk factor for RLS, and a diagnosis of RLS may be early manifestation of PD (Chahine et al., 2017). There are no specific recommendations for the treatment of RLS specifically in PD patients, but the effectiveness of L-dopa and DAs has been shown in the general treatment of RLS (Chahine et al., 2017).

2.4.2.3 Autonomic dysfunction

The peripheral autonomic nervous system includes the sympathetic (cholinergic and noradrenergic), parasympathetic and enteric nervous systems, which are extensively exposed to the Lewy pathology in PD (Kaufmann & Goldstein, 2013). Impairment of a specific component of the autonomic nervous system leads to distinctive signs and symptoms of autonomic dysfunction; sympathetic cholinergic failure can cause

e.g. decreased sweating; sympathetic noradrenergic failure can manifest e.g. as orthostatic hypotension; parasympathetic cholinergic failure can induce e.g. constipation, urinary retention and erectile failure; and enteric nervous system dysfunction can cause e.g. constipation and delayed gastric emptying (Kaufmann & Goldstein, 2013; Leclair-Visonneau et al., 2018).

The classical dysautonomic features of PD include bladder dysfunction, gastrointestinal disorders, cardiovascular complications, and sexual dysfunction (Chaudhuri & Schapira, 2009; Schapira et al., 2017). Autonomic symptoms are frequent in patients with PD and may appear in all PD stages but usually strengthen as the disease progresses (Schapira et al., 2017). Moreover, dysautonomic dysfunction can be one of the earliest prodromal symptoms of PD, occurring several years before onset of motor symptoms (Berg et al., 2015). Older age at the time of PD diagnosis, male sex, poor L-dopa response and PIGD phenotype are associated with increased risk of developing autonomic symptoms in patients with PD (De Pablo-Fernandez et al., 2017). Dysautonomic symptoms occurring in the early stages of PD are also linked to shorter survival in PD patients (De Pablo-Fernandez et al., 2017). In addition, some PD-related genetic mutations, such as *SNCA* mutations, predispose to autonomic problems (Puschmann, 2013).

2.4.2.4 Pain

A remarkable number of PD patients suffer from pain, making it a significant NMS of PD. PD patients experience more pain than age-matched controls and can suffer from several types of pain simultaneously (Antonini et al., 2018a). In addition, PD patients may have painful comorbidities which further aggravate negative sensations (Antonini et al., 2018a). Although all kinds of pain negatively impact QoL for PD patients, it tends to be underreported and undertreated (Schapira et al., 2017). In the DoPaMiP study, 61.8% of PD patients were reported to suffer from at least one form of chronic pain (Nègre-Pagès et al., 2008). However, reported prevalence rates of pain in PD patients vary from 30% to 85% in different epidemiological studies (Chaudhuri et al., 2015; Nègre-Pagès et al., 2008). The big variety of these results may be at least partly explained by differences in defining different pain types, lack of accurate outcome measures, and patient-related differences in experiencing pain.

The aetiology of pain in PD is multifactorial. It has been shown that loss of dopaminergic input to the basal ganglia modifies sensory perception and changes pain thresholds in PD (Schapira et al., 2017). In addition, DA modulates the sensation of pain outside the basal ganglia, such as in the spinal cord and the thalamus, and other neurotransmitter pathways are also involved in developing pain in PD (Chaudhuri & Schapira, 2009). Several different proposals for the

classification criteria for PD-related pain have been represented (Schapira et al., 2017). Chaudhuri and Schapira have proposed the classification of pain in PD to musculoskeletal pain, PD-related chronic pain (central or visceral pain), fluctuation-related pain (dyskinetic, off-period dystonia-related, and off-period generalised pain), nocturnal pain (e.g. nocturnal akinesia-related pain), orofacial pain, and peripheral limb or abdominal pain (Chaudhuri & Schapira, 2009). Additionally, Chaudhuri and his colleagues published the first PD-specific pain scale for clinical use (the King's PD Pain Scale) in 2015 (Chaudhuri et al., 2015).

2.4.3 Diagnosis

The clinical diagnostics of PD are based on the medical history and physical examination of the patient (Armstrong & Okun, 2020). The specificity of clinical PD diagnosis has varied between 75% and 95% in different studies (Postuma et al., 2015), and diagnosis can be verified only at autopsy (Rizzo et al., 2016). Misdiagnosis can be caused by some other neurodegenerative parkinsonism (e.g. multiple system atrophy (MSA)), secondary parkinsonism (e.g. drug-induced parkinsonism (DIP) or frontotemporal lobar degeneration (FTLD)) or illness without true progressive parkinsonian disorder (e.g. essential tremor) (Hughes et al., 1992; Postuma et al., 2015). Several different criteria for clinical diagnosis of PD have been proposed (Calne et al., 1992; Gelb et al., 1999; Gibb & Lees, 1988; Litvan et al., 2003), but the most used criteria has been the UK Brain Bank criteria from the Parkinson's Disease Society Brain Bank (**Table 2a**) (Hughes et al., 1992; Postuma et al., 2015).

The steps of the diagnostic process of PD according to the UK Brain Bank criteria fall into three categories (Hughes et al., 1992; Kalia & Lang, 2015). The first step is to point out the motor signs of parkinsonism: bradykinesia with at least one other classical motor sign (rigidity, rest tremor or postural instability that is not caused by visual, vestibular, cerebellar or proprioceptive dysfunction). The second step includes considering the possible exclusion criteria for PD, such as sustained remission, repeated strokes with stepwise progression of parkinsonism and early signs of dementia or autonomic dysfunction. The last step encompasses features that support the diagnosis of PD. These positive criteria include unilateral symptom onset, progressive course of the illness, positive response to L-dopa and appearance of L-dopa-induced dyskinesias.

Table 2a. Clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank. The table was modified from the table in Kalia et al., 2015.

Step 1: Diagnosis of parkinsonian syndrome	
	Bradykinesia + one or more of the following features:
	Muscular rigidity
	4–6 Hz rest tremor
	Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2: Exclusion criteria for PD (one or more of the following features suggest an alternate diagnosis)	
	History of repeated strokes with stepwise progression of parkinsonian features
	History of repeated head injuries
	History of definite encephalitis
	Neuroleptic treatment at onset of symptoms
	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure
	Negative response to large doses of L-dopa
	More than one affected relative
	Sustained remission
	Strictly unilateral features after 3 years
	Early severe autonomic involvement
	Early severe dementia with disturbances of memory, language, and praxis
	Oculogyric crises
	Supranuclear gaze palsy
	Babinski sign
	Cerebellar signs
	Presence of a cerebral tumour or communicating hydrocephalus on CT scan or MRI
Step 3: Supportive prospective positive criteria for PD (three or more features are required for diagnosis of definite PD)	
	Unilateral onset
	Rest tremor present
	Progressive disorder
	Persisting asymmetry affecting the side of onset most
	Excellent response (70-100%) to L-dopa
	Severe L-dopa-induced chorea
	L-dopa response for 5 years or more
	Clinical course of 10 years or more

* CT = Computed tomography, L-dopa = Levodopa, MRI = Magnetic resonance imaging.

MDS has reviewed and updated the diagnostic criteria for PD in 2015 (Postuma et al., 2015). The motor manifestations of parkinsonism are still the core of PD diagnostics in the new criteria, which distribute the diagnosis of PD to clinically established and clinically probable PD. The diagnosis of clinically established PD requires that the patient have bradykinesia with rest tremor and/or rigidity combined with at least two supportive factors and the absence of red flags and exclusion criteria. The diagnosis of clinically probable PD also requires typical motor characteristics of parkinsonism and at least two supportive criteria but allows, at most, two red flags which must be counterbalanced by supportive factors. As mentioned above, NMSs are present in most PD patients, and some of these, such as hyposmia, have been noticed in the new criteria, which are presented in **Table 2b**. Moreover, NMSs can dominate in the prodromal phase of PD, and research criteria for diagnosis of prodromal PD have also been published (Berg et al., 2015).

Table 2b. Diagnosis of Parkinson's disease by MDS criteria. The table was modified from the tables in Postuma et al., 2015.

Essential criteria	
	Bradykinesia + rest tremor and/or rigidity
Clinically established PD	
	Absence of absolute exclusion criteria
	At least two supportive criteria
	No red flags
Clinically propable PD	
	Absence of absolute exclusion criteria
	Presence of red flags counterbalanced by supportive criteria
Absolute exclusion criteria	
	Unequivocal cerebellar abnormalities
	Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
	Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia within the first five years of the disease
	Parkinsonian features restricted to the lower limbs for more than 3 years
	Treatment with a DA receptor antagonist or a DA-depleting agent in a dose and time-course consistent with DIP
	Absence of observable response to high-dose L-dopa despite at least moderate severity of disease
	Unequivocal cortical sensory loss, clear limb apraxia, or progressive aphasia
	Normal functional neuroimaging of the presynaptic dopaminergic system

	An alternative condition known to produce parkinsonism
Red flags	
	Rapid progression of gait impairment within 5 years of motor onset
	A compelete absence of progression of motor symptoms over 5 or more years unless stability is related to treatment
	Early bulbar dysfunction or severe dysphagia within first 5 years
	Inspiratory respiratory dysfunction
	Severe autonomic failure such as orthostatic hypotension or severe urinary retention or urinary incontinence in the first 5 years of disease
	Recurrent falls because of impaired balance within 3 years of onset
	Disproportionate anterocollis or contractures of hand or feet within first 10 years
	Absence of any of the common nonmotor features despite 5 years disease duration
	Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia
	Bilateral symmetric parkinsonism
Supportive criteria	
	Clear and dramatic beneficial response to dopaminergic therapy
	Presence of L-dopa-induced dyskinesia
	Rest tremor of a limb
	Presence of olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

* DA = Dopamine, DIP = Drug-induced parkinsonism, L-dopa = Levodopa, MIBG = Metaiodobenzylguanidine.

PD cannot be diagnosed directly with imaging techniques, but magnetic resonance imaging (MRI) is especially helpful in diagnosing other diseases causing parkinsonism, such as vascular parkinsonism (VP) (Armstrong & Okun, 2020). DA transporter single-photon emission computed tomography (DaT SPECT) can be used to support the diagnosis of idiopathic PD or to differentiate PD from illnesses without true progressive parkinsonian disorder, such as essential tremor (Armstrong & Okun, 2020). DaT SPECT shows presynaptic DA neuronal dysfunction that is seen in PD and other neurodegenerative forms of parkinsonism (J. A. Obeso et al., 2017; Postuma et al., 2015). The imaging study is associated with high sensitivity and specificity (from 98% to 100%) in detecting nigrostriatal cell loss in individuals with neurodegenerative parkinsonism (Suwijn et al., 2015), but it cannot distinguish idiopathic PD from neurodegenerative parkinsonism, such as MSA or progressive supranuclear palsy (PSP) (Armstrong & Okun, 2020).

2.4.4 Differential diagnostics

2.4.4.1 Atypical parkinsonism

2.4.4.1.1 Progressive supranuclear palsy

PSP is a tauopathy with unknown aetiology (Hayes, 2019). The course of the disease is progressive, and there is no current effective treatment, leading to an estimated mean survival of nine years from the onset of symptoms (Rajput & Rajput, 2001). PSP affects men more than women (Rajput & Rajput, 2001). It is presumably underdiagnosed, and clinical diagnosis of PSP is not always possible during a patient's lifetime (Hayes, 2019). Confirmed diagnosis of PSP requires suitable clinical features of the disease and neuropathological confirmation at autopsy (I. Litvan et al., 1996). Recently, new criteria for the diagnosis of PSP were published by MDS (Höglinger et al., 2017). These new criteria determine the disease course to the presymptomatic, suggestive, and fully symptomatic phases of PSP. The symptomatic phase of PSP is further divided into different subtypes according to the dominant clinical features of the illness. The classical phenotype of PSP is called Richardson's syndrome (PSP-RS), which is associated with symptoms like unsteady gait, repeated falls, bradykinesia, mild personality changes (e.g. apathy), cognitive slowing, speech problems (e.g. slow and hypophonic speech), dysphagia and eye movement problems (Boxer et al., 2017). The hallmark of clinical diagnosis of PSP-RS is a vertical supranuclear gaze palsy that can develop a few years after disease onset (Boxer et al., 2017). In addition, multiple clinical variants of PSP are recognised; PSP-parkinsonism, PSP-corticobasal syndrome, PSP-speech language, PSP with frontal presentation, PSP with predominant cerebellar ataxia and PSP with mixed pathology (Boxer et al., 2017).

The hallmark of PSP neuropathology is the wideapread existence of neurofibrillary tangles and/or neurophil threads (which contain abnormally phosphorylated tau protein) in the neurons of the central nervous system (Boxer et al., 2017; Rajput & Rajput, 2001). Anatomic sides that are usually affected include the pallidum, SN, subthalamic nucleus (STN), locus coeruleus, periaqueductal grey matter, midbrain tectum and pontine nuclei (Rajput & Rajput, 2001). Several neurotransmitter systems, such as dopaminergic, cholinergic and GABAergic systems, are affected (Rajput & Rajput, 2001). The distribution of neuropathology is usually distinctive between patients and correlates to signs and symptoms of PSP patients (Rajput & Rajput, 2001). For instance, PSP with frontal presentation is connected to a more prominent cortical tau pathology than PSP-parkinsonism, in which the brainstem is more affected (Boxer et al., 2017).

Atrophy of the midbrain and superior cerebellar peduncles, as seen in MRI, can be helpful in differentiating PSP-RS from other forms of parkinsonian syndromes

(Boxer et al., 2017). Significant midbrain atrophy with sparing of pons seen in the sagittal plane via MRI is the so-called hummingbird sign (**Figure 3**); it is the so-called morning glory sign on axial imaging (**Figure 4**) (Boxer et al., 2017). These signs have high specificity for PSP but lower sensitivity (Massey et al., 2012). The best specificity and sensitivity of imaging markers is reported to be the pons-to-midbrain ratio (Boxer et al., 2017).

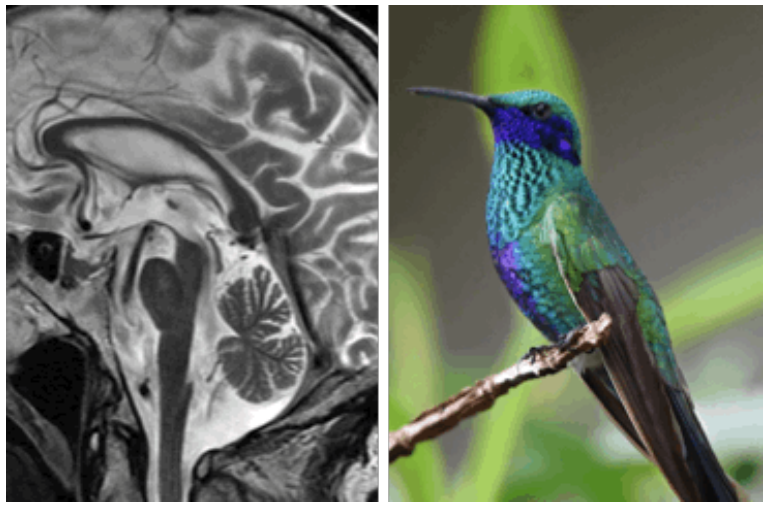

Figure 3. Hummingbird sign in the sagittal plane on MRI. Left side figure: Case courtesy of Dr Prashant Gupta, Radiopaedia.org, rID/ 18863. Right side figure: Case courtesy of Assoc Prof Craig Hacking, Radiopaedia.org, rID/ 76531.

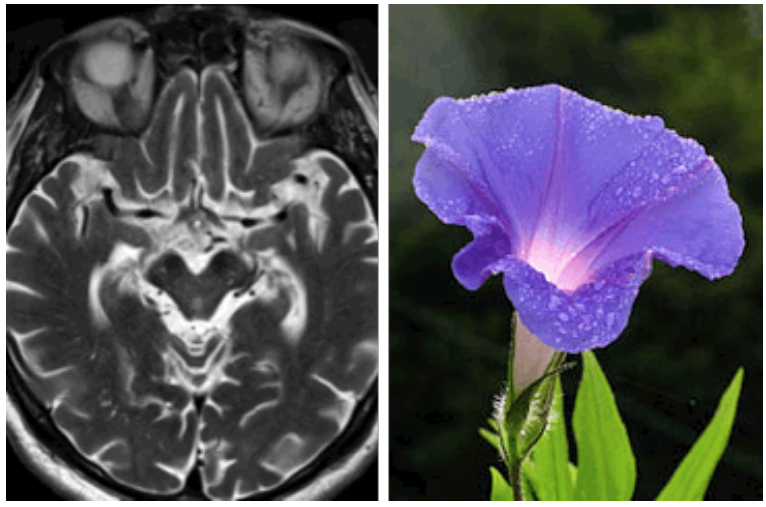

Figure 4. Morning glory sign on axial plane on MRI. Left side figure: Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID/ 48610. Right side figure: Case courtesy of Dr Ian Bickle, Radiopaedia.org, rID/ 51577.

2.4.4.1.2 Multiple system atrophy

MSA is a fatal and rapidly progressive neurodegenerative illness with no effective treatment, and it usually leads to death within nine years from symptom onset (Hayes, 2019; Miki et al., 2019). MSA belongs to a group of alpha-synucleinopathies, and the inclusion of filamentous alpha-synuclein is seen mainly in oligodendrocytes but also in nerve cells (Schweighauser et al., 2020). As the name of the disease suggests, it is associated with the degeneration of several regions of the central nervous system: cerebellum, brainstem, basal ganglia and spinal cord (Miki et al., 2019).

The main clinical features of MSA are severe autonomic dysfunction combined with cerebellar ataxia and/or parkinsonism that responds poorly to L-dopa (Hayes, 2019). Based on the clinical phenotype, the disease is classified to parkinsonian (MSA-P: related to striatonigral degeneration) and cerebellar variants (MSA-C: related to olivopontocerebellar atrophy) (Miki et al., 2019). The criteria for diagnostics of MSA were reviewed in 2008 (Gilman et al., 2008); a definite diagnosis of MSA requires neuropathological confirmation of alpha-synuclein-positive glial cytoplasmic inclusions with neuronal loss in striatonigral or olivopontocerebellar regions, whereas probable and possible MSA can be clinically diagnosed. There are two imaging signs on MRI which are related to MSA with high specificity but lower sensitivity: a hot cross bun sign on the axial plane via MRI (**Figure 5**) and a middle cerebellar sign seen as T2 hyperintensity on MRI in this specific area (Massey et al., 2012).

The clinical diagnostics of MSA are challenging; for instance, patients with PD, DLB or PSP may be misdiagnosed as having MSA (Miki et al., 2019). Miki and colleagues published a study which aimed to identify the diagnostic pitfalls of MSA. The study group reviewed 203 patients who were clinically diagnosed with MSA (Miki et al., 2019) and found that 160 out of 203 patients (78.8%) had a pathologically confirmed diagnosis of MSA. The remaining 43 patients had other diagnoses, mainly PSP or Lewy body disease. Inter alia, they reported that orthostatic hypotension and urinary incontinence with the requirement for urinary catheters increased the odds of MSA versus Lewy body disease or PSP based on several logistic regression analyses. Moreover, it seemed that autonomic dysfunction within three years from symptom onset can separate MSA from PSP.

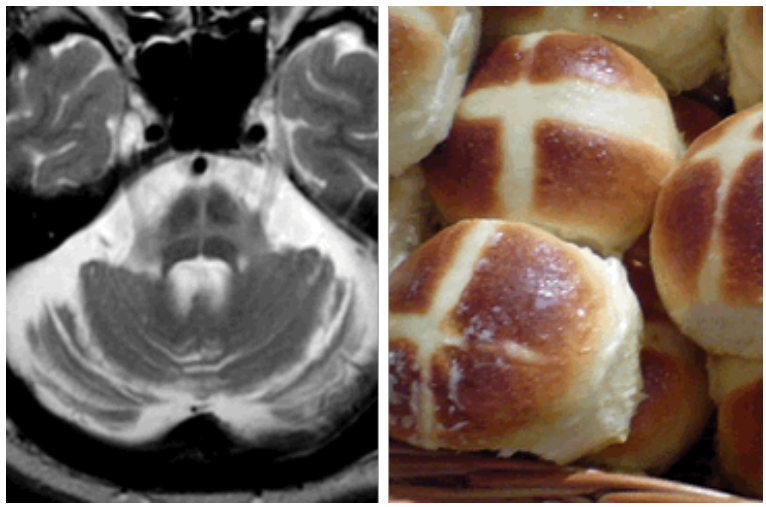

Figure 5. Hot cross bun sign on the axial plane on MRI. Left side figure: Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID/ 5465. Right side figure: Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID/ 13007.

2.4.4.1.3 Corticobasal degeneration

Corticobasal degeneration (CBD) is a relatively rare and progressive degenerative neurological disease affecting both men and women equally (Saranza et al., 2019). Treatment of CBD is symptomatic; the disease is associated with poor prognosis, and the mean disease duration from onset of the symptoms to death is reported to be 6.6 years (Ling et al., 2010). The major factor in the pathogenesis of CBD is the tau dysfunction, the formation of tau filaments and tau protein deposits in different cell types (Saranza et al., 2019). A typical macroscopic finding of CBD is asymmetric cortical atrophy in the superior frontal or parietal parasagittal regions, but sometimes, the pre- and postcentral regions may be affected, and in rare cases, the occipital lobe may be affected (Saranza et al., 2019). Histopathologically, neuronal loss and gliosis are seen in atrophic cortical and subcortical areas, and swollen neurons (so-called ballooned achromatic neurons) are seen in affected cortical areas (Saranza et al., 2019).

The clinical picture of CBD is plural and consists of motor and cognitive features (Ling et al., 2010; Saranza et al., 2019). The classical motor features of CBD are asymmetric L-dopa unresponsive rigidity and bradykinesia, clumsiness of one hand, postural instability, limb dystonia, myoclonus and mixed-type tremor (Saranza et al., 2019). Cognitive dysfunction typically appears as general cognitive impairment, behavioural changes and limb apraxia (Armstrong et al., 2013). The alien limb phenomena (unintentional limb movements interfering with normal tasks, the sensation that a limb is foreign or has a will of its own) is often linked to CBD, but

Armstrong et al. reported that it occurred in only 30% of compiled CBD cases (Armstrong et al., 2013). CBD patients may also have abnormal eye movements, speech abnormalities and pyramidal dysfunction observed as hyperreflexia (Saranza et al., 2019). The phenotype of CBD can closely resemble the clinical picture of other neurological disorders, such as PSP, AD or PD, which can lead to misdiagnoses (Ling et al., 2010).

The diagnostic criteria for CBD were reviewed in 2013 (Armstrong et al., 2013). Armstrong and colleagues proposed two diagnostic classifications for CBD: clinical research criteria for probable sporadic CBD and for possible CBD. In addition, the new criteria separate four different phenotypes of the disease: corticobasal syndrome (CBS), frontal behavioural-spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (naPPA), and progressive supranuclear palsy syndrome (PSPS). These variant forms of CBD emerge on the basis of the dominant clinical features: asymmetric movement disorders combined with lateralised higher cortical features in CBS, postural instability, oculomotor dysfunction and symmetric parkinsonism in PSPS; impaired comprehension and apraxia of speech in naPPA; and behavioural changes, impairment of memory and visuospatial problems in FBS (Armstrong et al., 2013; Saranza et al., 2019).

2.4.4.1.4 Frontotemporal lobar degeneration

The term FTLD refers to a pathologically confirmed case of frontotemporal dementia (FTD) (Deutschländer et al., 2018). FTLD includes various clinical forms: behavioural variant FTD, semantic variant primary progressive aphasia, non-fluent agrammatic variant primary progressive aphasia, logopenic variant primary progressive aphasia and FTD associated with motor neuron disease (Bang et al., 2015; Deleon & Miller, 2018; Deutschländer et al., 2018; Dickson, 2018; Mann & Snowden, 2017). Histopathologic and genetic features of FTLD are also heterogeneous (Mann & Snowden, 2017). The main histological findings include pathology in tau, TDP-43 and FUS proteins (Mann & Snowden, 2017). Due to underlying tau pathology, the above-described PSP and CBD are also currently classified as FTD-related disorders (Deutschländer et al., 2018). Three major genes associated with FTLD are *MAPT*, *GRN* and *C9orf72* (Deutschländer et al., 2018; Mann & Snowden, 2017).

FTD principally affects the frontal and temporal lobes of the brain (Bang et al., 2015; Deutschländer et al., 2018). The most relevant radiological finding is atrophy in the frontal and temporal lobes with relative preservation of the posterior areas (Deutschländer et al., 2018). Symptoms of FTD patients vary from behavioural disturbances to different language disorders, and some patients also suffer from motor neuron disorders or associated parkinsonism (Deutschländer et al., 2018).

Signs of parkinsonism usually appear in FTD patients as the disease progresses (Bang et al., 2015). However, Le Ber and her colleagues reported that early parkinsonism is an accompanying feature of the disease in slightly under 20% of patients with FTD (Le Ber et al., 2006). Parkinsonism was detected most often in patients with behavioural variant FTD and in patients with non-fluent variant primary progressive aphasia (Le Ber et al., 2006).

2.4.4.2 Dementia with Lewy bodies

Lewy body dementias include two separate clinical syndromes which differ in the sequence of dementia onset; the condition in which dementia occurs before, cotemporally or within one year of onset of parkinsonism is called DLB, and if cognitive problems start one year or more after conventional parkinsonism, the situation is referred to as PDD (Walker et al., 2015). DLB is an age-related disease and is more common in males than in females (Walker et al., 2015). Of all dementia cases, 7.6% were reported to have DLB in a population-based study from Spain (Tola-Arribas et al., 2013). However, highly variable estimates of the prevalence and incidence of DLB have been reported, and it is probably under-diagnosed in clinical practice (Walker et al., 2015).

DLB pathology is associated with the appearance of Lewy bodies in the striatum and widely in the cortical neurons with a relative paucity of the neurofibrillary tangles and amyloid plaques associated with AD (Hayes, 2019; Walker et al., 2015). The clinical diagnostic criteria were reviewed and proposed for DLB in 2017 (McKeith et al., 2017). DLB patients present with a wide range of motor, cognitive, neuropsychiatric, sleep and autonomic symptoms, but the typical clinical features of DLB are parkinsonian symptoms, dementia, hallucinations and delusions generally fluctuating with periods of lucidity (Hayes, 2019; McKeith et al., 2017; Walker et al., 2015). Cognitive problems are usually seen as deficits on tests of attention, executive function and visuospatial ability (McKeith et al., 2017). Supportive factors include, for instance, REM sleep disorder, sensitivity to antipsychotics, severe autonomic dysfunction, repeated falls, non-visual hallucinations, and low DA transporter uptake in the basal ganglia seen in DaT SPECT (McKeith et al., 2017; Walker et al., 2015). The treatment of DLB is a challenging task; benefits for one domain may cause deterioration in another domain (Taylor et al., 2020). For example, motor symptoms are reported in up to 85% of DLB patients, and up to a third of these patients are reported to experience alleviation of motor symptoms with L-dopa therapy that often causes adverse effects such as psychotic symptoms, postural hypotension and sedation in DLB patients (Taylor et al., 2020). Therefore, the interdisciplinary approach should be considered to accomplish the best therapeutic gains.

2.4.4.3 Secondary parkinsonism

Secondary or symptomatic parkinsonism indicates a parkinsonism syndrome without detectable aggregation of misfolded proteins and is caused by a specific factor that insults the function of the nigrostriatal dopaminergic system (Höllerhage, 2019). The most common causes of secondary parkinsonism are reported to be drugs and vascular lesions (Fleury et al., 2018; Savica et al., 2017). Chronic traumatic encephalopathy, brain tumours, infectious and metabolic diseases, environmental toxins and street drugs are more uncommon causes of secondary parkinsonism (Höllerhage, 2019).

The incidence and prevalence of DIP is higher among older people, and it affects more females than males (Savica et al., 2017). It has been hypothesised that the increased risk of DIP in older people is due to increased vulnerability of the dopaminergic system to additional insults induced by the natural decline of dopaminergic neurons in SN with advancing age (Höllerhage, 2019). Antipsychotic medications that are commonly used in the treatment of SCZ and psychosis are most robustly associated with the development of neurological adverse effects manifested as DIP. The use of first-generation antipsychotics or so-called typical antipsychotics are reported to affiliate with higher risk of DIP compared to typical antipsychotics (Factor et al., 2019). However, antipsychotic drugs are not the only medicines that can cause DIP. All drugs blocking DA D2 receptors can cause it. A recent review also reported other drug groups that can be related to movement disorder, including calcium channel blockers, antidepressants (especially SSRIs), some antiepileptics and mood stabilisers (Friedman, 2020).

DIP generally develops subacutely over days to months after beginning the drug or after increasing the dose of the drug (Factor et al., 2019). It is worth noting that parkinsonism can also develop in a patient who has used DA receptor antagonists for decades due to the development of true idiopathic PD or increased susceptibility to DIP of the ageing brain as explained above (Factor et al., 2019). There is no difference in the clinical picture of DIP after using typical or atypical antipsychotics (Munhoz et al., 2017). It is challenging and sometimes even impossible to make a clinical distinction between DIP and idiopathic PD based on patients' clinical features. However, features supporting the diagnosis of DIP include subacute onset of symmetrical parkinsonism, absence of tremor, presence of tardive dyskinesia, absence of hyposmia, sleep disorders and urinary symptoms, and presence of only two or fewer cardinal features of PD (Factor et al., 2019).

It has been reported that symptoms associated with DIP typically resolve after the reduction or removal of the offending agent over the course of weeks to months (Aronson, 1985; Ayd, 1961; Wilson et al., 1987). In a group of 48 patients with DIP, it took an average of seven weeks for symptom resolution, but 11% of patients had symptoms persisting beyond 18 months (Stephen & Williamson, 1984). Alvarez and Evidente have stated that most cases remit within four months after stopping the causative drugs (Alvarez & Evidente, 2008). However, a recent review reported that

it can take several months or even years for DIP to resolve after the initiating drug is stopped (Factor et al., 2019). Several studies have revealed high sensitivity and specificity of DaT SPECT in distinguishing DIP from PD (Factor et al., 2019).

VP is parkinsonism caused by brain confluent white matter lesions and lacunar infarcts insulting thalamocortical projections (Höllerhage, 2019; Korczyn, 2015). The classical clinical picture of VP is symmetrical lower body parkinsonism with pronounced gait disorder and gradually developing cognitive deficiency and incontinence as the disease progresses (Höllerhage, 2019). A more uncommon type of VP consists of unilateral parkinsonian signs with acute or subacute onset due to infarcts of the striatum affecting putaminopallido-thalamic loops (Wenning et al., 2011). In the latter type, dopaminergic medication may be helpful (Korczyn, 2015).

2.5 Treatment of Parkinson's disease

2.5.1 Medical treatment

The foundation of pharmacological treatment for PD motor symptoms is DA replacement therapy that aims to increase intracerebral DA concentration and stimulate DA receptors: L-dopa preparations, DAs and MAO-B inhibitors are commonly used (Armstrong & Okun, 2020). Anticholinergic agents are used less frequently in younger patients with prominent tremor, but these drugs are often associated with potential adverse effects, particularly relating to cognition (Armstrong & Okun, 2020).

Several studies have reported the effectiveness of MAO-B inhibitors (Allain et al., 1993; Olanow et al., 2009; Pålhagen et al., 1998; Siderowf et al., 2002), DAs (Adler et al., 1997; Blindeauer, 2003; Shannon et al., 1997; Watts et al., 2007) and L-dopa (Fahn et al., 2004; Hauser et al., 2009) in the earlier stages of PD, but the effects of antiparkinsonian medications on PD mortality remain speculative, and there is no confident evidence of the neuroprotective effect of any drug (Armstrong & Okun, 2020; Hayes, 2019). The optimal time to initiate PD medication is considered together with the patient, usually when the symptoms affect their QoL (Armstrong & Okun, 2020). L-dopa was previously avoided in the treatment of early stages of PD, but in recent years, in line with new evidence, the traditional view of early pharmacotherapy has started to shift from delayed L-dopa at advanced stages of PD to earlier initiation of low-dose therapy for improved QoL (Cilia et al., 2014; Gray et al., 2014; Schapira & Olanow, 2008). Otherwise, the primary pharmacotherapy for early and moderate PD has remained mostly unaltered for the past two decades in developed countries (Armstrong & Okun, 2020; Pahwa & Lyons, 2014; Rascol et al., 2011).

MAO-B inhibitors (selegiline, rasagiline, safinamide) and DAs (pramipexole, ropinirole, rotigotine) are related to less effective symptom relief but lower risk of

dyskinesias than L-dopa, and these drugs are often used as monotherapy in the early course of PD, especially in younger patients (Armstrong & Okun, 2020; Connolly & Lang, 2014). L-dopa therapy or combination therapy with drugs from multiple classes is needed as the disease proceeds, causing more severe disability for PD patients (Connolly & Lang, 2014). DAs stimulate DA receptors in the central nervous system, and they are associated with increased risk of hallucinations, delusions, hypotension, somnolence and ICDs, potentially due to decreased specificity in the way they stimulate dopaminergic receptors (Armstrong & Okun, 2020; Hayes, 2019). The risk of hallucinations and hypotension is particularly high among elderly PD patients (Hayes, 2019), so the treatment of elderly PD patients usually starts directly with L-dopa (Armstrong & Okun, 2020; Hayes, 2019). ICDs are common adverse effects related to DAs; as much as over 40% of PD patients with oral DAs have been reported to suffer from ICDs (Armstrong & Okun, 2020). Furthermore, 15–20% of patients who stop using the DAs develop withdrawal symptoms, such as irritability, anxiety, pain and drug cravings (Armstrong & Okun, 2020), and DAs cannot always be discontinued despite side effects like ICDs.

L-dopa is a precursor of DA, which can pass the blood–brain barrier and is reported to still have the greatest symptomatic effect in the treatment of PD (Armstrong & Okun, 2020; Connolly & Lang, 2014; Hayes, 2019). L-dopa is usually paired with DOPA-decarboxylase inhibitor (carbidopa or benserazide), which blocks the peripheral metabolism of L-dopa, increasing the central nervous system bioavailability and reducing peripheral adverse effects. Every PD patient requires L-dopa therapy at some point during their illness (Armstrong & Okun, 2020). In addition, patients typically need more frequent and higher doses of L-dopa as the disease progresses because the brain loses its ability to store additional DA for later us; patients lose their long-duration response to dopaminergic medication, and their short-duration response decreases due to disease-related pathophysiologic changes in the brain (Armstrong & Okun, 2020). L-dopa therapy is associated with both hypodopaminergic (wearing-off phenomenon, unpredictable off-periods and delayed-on) and hyperdopaminergic motor complications (dyskinesias) (Postuma et al., 2015). It has been reported that the use of L-dopa doses higher than 600 mg/day or more than 5–6 mg/kg predisposes to development of motor complications 3–5 years after treatment initiation (Antonini & Nitu, 2018). The main purpose of the treatment of hypodopaminergic problems is to prolong DA effect by inhibiting the breakdown of L-dopa and DA; clinical ways of achieving this include increasing the dosage of dopaminergic medications, adding another dopaminergic medication to the treatment, dividing L-dopa dosage into smaller but more frequent doses (so-called L-dopa dose fractionation), and adding a catechol-O-methyltransferase inhibitor (entacapone or tolcapone) or MAO-B inhibitor to treatment (Connolly & Lang, 2014). In addition, inhaled L-dopa and subcutaneous apomorphine can be used to accomplish faster medication response (Armstrong &

Okun, 2020). Dyskinesias are treated by reducing dopaminergic medications or adding amantadine (NMDA receptor antagonist) (immediate-release and extended-release preparations) (Armstrong & Okun, 2020; Fox et al., 2018). In addition, the atypical neuroleptic clozapine has been reported to be useful in the treatment of dyskinesias (Fox et al., 2018).

2.5.2 Device-aided therapies

Device-aided therapies include DBS, L-dopa-carbidopa intestinal gel (LCIG) infusion, L-dopa-entacapone-carbidopa intestinal gel (LECIG) infusion and continuous subcutaneous apomorphine infusion (CSAI). These treatment options should be considered for PD patients once the motor complications cannot be adequately managed with oral treatment optimisation (Antonini et al., 2018b). The selection of the most optimal device-aided therapy for every PD patient is based on patient-specific factors (such as dominant motor features, cognitive and psychiatric status), device-specific factors (such as adverse effect profile, ease of use and acceptability to the patient and family), country-specific factors (availability in the patient's country) and financial costs (Marsili et al., 2020). Although device-aided therapies induce clear effects on symptoms and QoL in PD, there is a lack of current evidence for neuroprotective nature (Dijk et al., 2020). Thus far, there are no published evidence-based guidelines to direct concordant clinical decisions among device-aided therapies in PD. Indicators to recognise suspected advanced PD is presented in **Table 3a**, clinical profiles indicating good candidates for device-aided therapies in **Table 3b** and main contraindications for device-aided therapies in **Table 3c**.

Table 3a. The most important clinical features indicating advanced Parkinson's disease. The table was modified from the tables in Antonini et al., 2018c.

Motor symptoms	Non-motor symptoms	Functional impacts
Moderate motor fluctuations	Mild dementia	Repeated falls
Off-symptoms at least 2 hours of the waking day	Non-transitory troublesome hallucinations	Need of help in ADLs at least some of the time
Dyskinesias at least 1 hour of the day	Moderate level of psychosis	Unable to perform complex tasks at least some of the time
Moderate dyskinesias	NMS fluctuations	Moderate impairad mobility
Troublesome dysphagia	Moderate nighttime sleep disturbances	
Oral L-dopa dose at least 5 times a day		

* ADLs = Activities of Daily Living, L-dopa = Levodopa, NMS = Non-motor symptom.

Table 3b. Characteristics affecting the selection of suitable device-aided therapy. The table was modified from the tables in Antonini et al., 2018c.

Characteristics	DBS	LCIG	CSAI
Good L-dopa response	++	+++	++
L-dopa resistant tremor	+++	-	-
Troublesome dyskinesia	++	++	+
Dystonia induced pain	+	+	+
Good cogtivine function	++	++	++
Nighttime sleep disturbances	+	+	+
Impulse control disorders	+	+	-
Troublesome hallucinations	-	-	-
Depression	-	+	+
Apathy	-	+	+
Anxiety	+	+	-
Dysarthria	-	-	-
Repeated falls	-	-	+
Limitation with ADLs	-	+	+
Younger age (<70 years)	++	++	++
Patient own values	++	+	-
Lack of caregiver support	+	-	-

* ADLs = Activities of Daily Living, L-dopa = Levodopa.

Table 3c. Contraindications for device-aided therapies. The table was modified from the tables in Antonini et al., 2018c.

Characteristics	DBS	LCIG	CSAI
Motor symptoms			
Dysphagia	+	-	-
Freezing of gait during off-time	+	-	-
Non-motor symptoms			
Dysarthria	++	-	-
Non transitory psychosis	++	+	+++
Severe dementia	+++	++	+++
Moderate dementia	+++	+	++
Mild dementia	+++	-	-
Impulse control disorders	+	+	++
Depression	+++	+	+
Troublesome hallucinations	++	+	+
Functional impairment			
Repeated falls	++	+	+
Patient characteristic			
Older age (>70 years)	++	-	-
Patient fear of side effects	+	+	+
Living in a nursing home	+	+	-
Lack of caregiver support	+	+	+
Access to a hospital or treatment center	+	+	+
Patient expectations	+	+	+

2.5.2.1 Deep brain stimulation

In DBS therapy, unilateral or bilateral leads are surgically placed transcranially into the deep brain nuclei, and the leads are attached to a battery located in the patient's chest. DBS-induced high-frequency stimulation is directed to the target nuclei, and stimulation parameters are optimised regularly in follow-up visits. DBS treatment is indicated in PD patients who suffer from L-dopa responsive motor complications without satisfactory response from medical treatment (Fox et al., 2018). Exclusion criteria include older age (over 70 years), remarkable cognitive impairment, dementia, non-drug-related hallucinations, treatment-resistant severe depression and extensive vascular lesions seen in MRI (Parkinson's disease: Current Care Guidelines, 2019). The best efficacy from DBS has been observed on tremor, dyskinesias and duration/severity of off-periods (Marsili et al., 2020; Nagao & Patel, 2019). According to present-day knowledge, the benefit of symptom control through DBS surpasses that of optimal medical treatment in patients with motor fluctuations and dyskinesias, and it is a relatively safe treatment option for motor complications of idiopathic PD (Antonini et al., 2018b; Obeso et al., 2001; Schuepbach et al., 2013). Complications related to DBS treatment are rare and usually related to the procedure (such as wound infection, intracerebral haemorrhage, lead malposition/migration, and lead or extension fractures) (Nagao & Patel, 2019).

Several controlled studies have demonstrated that DBS provides better motor, nonmotor and QoL outcomes compared to medical treatment alone for patients with advanced PD (Antonini et al., 2018b; Deuschl et al., 2006; Obeso et al., 2001; Weaver et al., 2009). Initially, patients who underwent DBS surgery had mean disease duration of PD for over 10 years (Krack et al., 2019). However, the efficacy of DBS has also been shown in the earlier stages of PD (Krack et al., 2019). The EARLYSTIM study, published in 2013, included younger PD patients who had shorter disease duration and who had suffered from motor complications for up to three years (Schuepbach et al., 2013). The results showed favourable outcomes of DBS compared to medical treatment alone. In addition, Hacker and colleagues stated in a recently published study that early DBS treatment in PD provides long-term motor benefit and decreases the need for and complexity of PD medication (Hacker et al., 2020). The positive effects of DBS have been shown to last over 10 years (Constantinescu et al., 2017). However, the benefits of DBS alleviate over time because PD patients develop stimulation and L-dopa-resistant axial symptoms and NMSs (Constantinescu et al., 2017; Nagao & Patel, 2019).

The rigorous mechanisms of DBS action in the treatment of motor complications in PD remain still ambiguous. However, one hypothesis is that DBS modulates the pathological neuronal firing patterns within the cortico-basal ganglia networks and regulates the activity from persistent synchronised activity to more dynamic pattern mimicking non-PD activity (Marsili et al., 2020; Nagao & Patel, 2019). The STN

and globus pallidus interna (GPi) are the most common target nuclei of DBS in PD, but there is no consensus on the preferred target for stimulation (Moro et al., 2010; Nagao & Patel, 2019). STN-DBS allows the reduction of dopaminergic medications while using lower stimulation parameters, but nevertheless, STN-DBS is linked to increased risk of cognitive and psychiatric problems and to provoking dyskinesias in early phases of programming (Nagao & Patel, 2019). GPi-DBS is reported to have less impact on cognitive and psychiatric functions and greater reduction of dyskinesias (Nagao & Patel, 2019). However, the possibility of decreasing dopaminergic medication is rare with GPi-DBS, and it requires higher stimulation parameters compared to STN-DBS (Moro et al., 2010). Ventral intermediate nucleus (VIM) DBS improves tremor but no other parkinsonian symptoms and is therefore practically abandoned as a target nucleus in PD treatment (Krack et al., 2019).

The initial DBS leads have ring-shaped electrodes generating a spherical electrical field, but recently, new technology with directional (so-called segmental) leads were introduced. These new segmental leads allow the stimulation to be directed toward the area of interest and away from structures that might cause stimulation-induced adverse effects, possibly leading to a wider therapeutic window and better DBS outcome (Krack et al., 2019). At present, DBS treatment is conventional, indicating that stimulation is delivered continuously at a constant rate (Krack et al., 2019). The most recent effort is to modernise DBS treatment to so-called closed-loop DBS. This new technological innovation would account for the fluctuating nature of symptoms in PD; stimulation depends on a feedback signal from the brain or peripheral sensors (Krack et al., 2019).

2.5.2.2 Levodopa-carbidopa intestinal gel and Levodopa-entacapone-carbidopa intestinal gel infusions

Oral L-dopa bioavailability affects factors like unpredictable absorption and delayed gastric emptying (Urso et al., 2020). LCIG infusion enables the steady infusion of L-dopa from the external pump directly to the jejunum, bypassing the stomach via a percutaneous gastrojejunostomy tube (PEG-J) (Nagao & Patel, 2019). It allows the titration of L-dopa on a higher dose and provides more stable therapeutic plasma L-dopa concentrations compared to oral drug administration (Dijk et al., 2020). Infusion consists of a morning bolus dose and a continuous maintenance infusion which is usually administered only during the daytime. Infusion therapies are treatment options for advanced PD, which is associated with motor and non-motor fluctuations, dyskinesias, narrowed therapeutic window, worsening QoL and increased caregiver burden (Fox et al., 2018). However, statements on implementing device-aided therapies, including LCIG, have already been presented at the beginning of the advanced phase before established dyskinesias (Antonini & Nitu, 2018). Exclusion

criteria are looser for LCIG compared to DBS; it can also be a suitable treatment for older patients and patients with mood and cognitive problems (Dijk et al., 2020).

It has been reported previously in several studies that LCIG has a superior effect in adding on-time and reducing off-time as well as diminishing the time with troublesome dyskinesias compared to optimal medical treatment (Antonini et al., 2016b; Olanow et al., 2014). However, 15% of LCIG patients tend to develop diphasic dyskinesias which appear as ballistic choreiform movements dominantly in the legs (Marano et al., 2019). The enhancement of LCIG infusion or dopaminergic medication can alleviate this adverse effect (Dijk et al., 2020). LCIG is also quite commonly associated with device- and procedure-related complications, such as infection, tube dislocations, stoma complications and peritonitis (Nagao & Patel, 2019). In addition, patients with LCIG have increased risk of polyneuropathy, B12 deficiency and weight loss (Lang et al., 2016). Polyneuropathy is usually slowly progressive sensory axonal polyneuropathy, but it can sometimes clinically resemble acute inflammatory polyneuropathy (Lang et al., 2016).

The most recent advancement in pump therapies has been the addition of the COMT-inhibitor, entacapone, to the formulation of intestinal infusion. Entacapone decreases L-dopa conversion to 3-O-methyldopa along with increasing the plasma concentration of L-dopa (Nyholm et al., 2012). The first clinical trial with LECIG was published in 2017, and the results showed that the L-dopa dose can be reduced without lowering L-dopa exposure with LECIG infusion compared to LCIG infusion (Senek et al., 2017). A recent study proposed that the continuous maintenance dose of LECIG can be decreased by 35% to obtain corresponding drug exposure as with LCIG (Senek et al., 2020).

2.5.2.3 Continuous subcutaneous apomorphine infusion

Apomorphine is subcutaneously administered DAs with an affinity to all DA receptor subtypes (Dijk et al., 2020). Acute injections are shown to be effective in alleviating off-periods, but the injections are underutilised due to challenges in self-administration of drugs during severe off-periods (Antonini & Nitu, 2018). CSAI is intended for the treatment of severe motor fluctuations in advanced PD, and it provides continuous subcutaneous infusion of apomorphine via an external mini-pump system. CSAI is a less invasive treatment than other device-aided therapies and is also easily reversible.

Effects on the reduction of off-time, increase of on-time, and improved off-related disability is reported in multiple earlier studies (Antonini & Nitu, 2018; Katzenschlager et al., 2018). Instead, the effect on dyskinesias reportedly depends on the possibility of increasing the apomorphine infusion rate along with reducing the dose of L-dopa (Sesar et al., 2017). Besides the positive impact on motor

complications, improved NMSs and QoL have also been detected with CSAI (Martinez-Martin et al., 2015). The first randomised, double-blinded, placebo-controlled study of CSAI was published in 2018 (Katzenschlager et al., 2018). The TOLEDO study observed that CSAI provides significant reduction in off-time of approximately 2 hours more than placebo and equal addition of on-time without troublesome dyskinesias. Typical side effects associated with CSAI include skin nodules at infusion site, nausea, somnolence and skin erythema (Katzenschlager et al., 2018). More severe and uncommon adverse effects are severe hypotension, leukopenia, nonhemolytic anaemia, confusion and hallucinations (Katzenschlager et al., 2018). Consequently, some patients may be forced to discontinue the CSAI treatment, and as many as two-thirds of patients were reported to cease the therapy in a 10-year observational study published in 2017 (Kimber et al., 2017). Neuropsychiatric complications like hallucinations and ICDs were the most common reasons for interrupting the treatment (Kimber et al., 2017).

2.5.2.4 Magnetic resonance–guided focused ultrasound

Magnetic resonance–guided focused ultrasound (MRgFUS) is a novel and minimally invasive therapy for the symptomatic treatment of PD. The main principle of the treatment is to induce ultrasonic energy into a target tissue to produce localised tissue destruction (Quadri et al., 2018). The target nuclei of cerebral ablation include the VIM, STN and GPi (Moosa et al., 2019). MRgFUS aims at minimising the complications associated with more invasive neurosurgical procedures such as infections or brain haemorrhages linked to DBS operations (Moosa et al., 2019). However, MRgFUS procedures, especially when done bilaterally, are reported to have commonly reversible adverse effects like gait impairment, taste disturbances and hand ataxia (Quadri et al., 2018).

Bond and colleagues published a double-blinded, sham-controlled randomised controlled trial of MRgFUS ablation of the VIM in PD patients with the tremor-dominant phenotype (Bond et al., 2017). According to the results, 62% of treated patients obtained improvement in tremor scores from baseline to three months postoperatively, whereas 22% of control patients demonstrated improvement. One open-label trial of MRgFUS subthalamotomy for PD patients reported improvements of 71% for rigidity, 36% for akinesia, and 77% for tremor six months after treatment (Martínez-Fernández et al., 2018). Further, an open-label trial of MRgFUS pallidotomy for PD patients showed improvement of 52% of dyskinesias and overall motor scores at six months postoperatively (Jung et al., 2019). However, further studies are needed on the use of MRgFUS of the STN and GPi for treatment of the cardinal motor features of PD, the safety of performing bilateral lesions, and durability of MRgFUS lesions (Moosa et al., 2019).

3 Aims of the study

The principal aims for each substudy were as follows:

I: The primary aim was to systematically investigate the motor benefit of the DBS operation in monogenic PD compared to the general PD population. An additional aim was to evaluate the effects on NMSs, including possible cognitive and neuropsychiatric symptoms.

(Systematic review)

II: The primary aim was to investigate recent trends in mortality of a large hospital-based cohort of Finnish PD patients.

(Retrospective record-based study)

III: The primary aim was to investigate the risk of PD after a diagnosis of a schizophrenia spectrum disorder (SCD) from large regional (Part I) and national (Part II) cohorts of Finnish PD patients.

(Part I: Retrospective record-based case-control study; Part II: Nested case-control register study)

IV: The aim was to provide proof of concept for automated data mining and pattern recognition of electronic health records (EHRs) of PD patients. An additional specific aim was to study associations between prodromal markers and mortality in PD.

(Retrospective record-based study)

Note: The Roman numerals refer to the original publications.

4 Materials and Methods

4.1 Subjects

4.1.1 Study I

Study I is a systematic review. The initial PubMed search identified 220 articles, and 16 additional relevant studies were found in the manual search of reference lists. Of these 236 studies, 46 met all the selection criteria and were included in the systematic review. In total, 221 genetic PD patients who were treated with DBS were reported in these studies. However, one study reported long-term outcome of DBS in patients with GBA mutations (Lythe et al., 2017), but shorter follow-up of some of the same patients were reported previously in another study (Angeli et al., 2013). It was not possible to separate patients that were reported in both studies.

4.1.2 Studies II–IV

The Turku Clinical Research Center (TurkuCRC, http://www.turkucrc.fi/en) maintains the Turku University Hospital database, which stores all EHRs generated at the hospital for medical research. Health records have been in electronic format since 1 January, 2004, enabling annual longitudinal analyses. The database contains detailed clinical data of patients who have visited Turku University Hospital or regional hospitals. The data are pseudonymised, protecting the identity of the patients while making it possible to link data elements to individual patients.

The study population of study II consisted of PD patients diagnosed between 2006 and 2014 at Turku University Hospital in southwestern Finland (n=1521). In study III, the regional (Part I) study cohort included all PD patients who were treated between 1 January 2004, and 31 July 2019, throughout Turku University Hospital District (n=3045). The control population was identified from the same digital database, and controls were age- and sex-matched (1:1 ratio) with the PD population. The national (Part II) study cohort included people who received drug reimbursement for PD between 1996 and 2015 and were community-dwelling at the time of diagnosis (n=22,189). Controls without PD were identified from the register that included all Finnish residents. The matching criteria were age (1-year caliper),

sex and hospital district within the country on the PD diagnosis date of the referent case. After exclusion, 2–7 controls remained for each PD patient (n=148,009). Further, in study IV, the cohort population consisted of PD patients who were treated between 2006 and 2014 at Turku University Hospital District (n=2654).

The diagnostic criteria of PD are based on the Finnish Current Care Guidelines of PD in Finland (Parkinson's disease: Current Care Guidelines, 2019). To receive drug reimbursement for PD, the diagnosis must be made by a certified neurologist using either the UK Brain Bank criteria or the MDS clinical criteria (Postuma et al., 2015) based on clinical examination, and primary symptoms and possible imaging findings must be reported. Thus, all PD diagnoses in studies II–IV were based on these criteria.

4.2 Methods

4.2.1 Study I

Search terms and the PubMed search were designed by two authors. The search was executed from inception to June 26, 2018, with the following keywords: "deep brain stimulation or DBS", "Parkinson's or Parkinson or Parkinsonism" and "genetic or gene or GBA or PRKN or PARKIN or LRRK2 or SNCA or PINK1 or VPS35 or DJ-1 or UCHL1 or GIGYF2 or HTRA2 or TMEM230 or CHCHD2 or RIC3 or ATP13A2 or PLA2G6 or FBX07 or SYNJ1 or VPS13C or DNAJC6". Original English language articles concerning genetic PD patients treated with DBS were included. Animal studies and review articles were excluded.

An overview of study inclusion and exclusion is presented in **Figure 6**. At first, 184 studies were excluded after screening all abstracts of 236 studies (no monogenic PD patients or patients not treated with DBS n=64, review or commentary article n=92, animal study n=28). Six more studies were excluded after fully reviewing the other 52 studies (genetic test negative n=2, no genetic testing n=1, review or commentary article n=3). Finally, 46 studies met all selection criteria and were included in the systematic review. The data extracted from each study were study year, first author's family name, number of patients, mutated gene, specific mutation, patient age at disease onset and DBS implantation, target nucleus of DBS, lead positioning, preoperative L-dopa response, pre- and postoperative UPDRS III scores, follow-up time and outcome. An improvement of 30% or more in the UPDRS-III motor score was considered to indicate favourable outcome; 20–30% was considered moderate outcome and <20% poor/mild outcome.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed (Moher et al., 2016). The quality of the included studies was evaluated according to the Newcastle-Ottawa Scale (Wells et al., 2011).

The scale ranged from 0 to 12 stars, with the highest rating representing the greatest quality. A total score of 0–3 was considered to indicate to poor quality, 4–7 moderate quality, and 8–12 good quality.

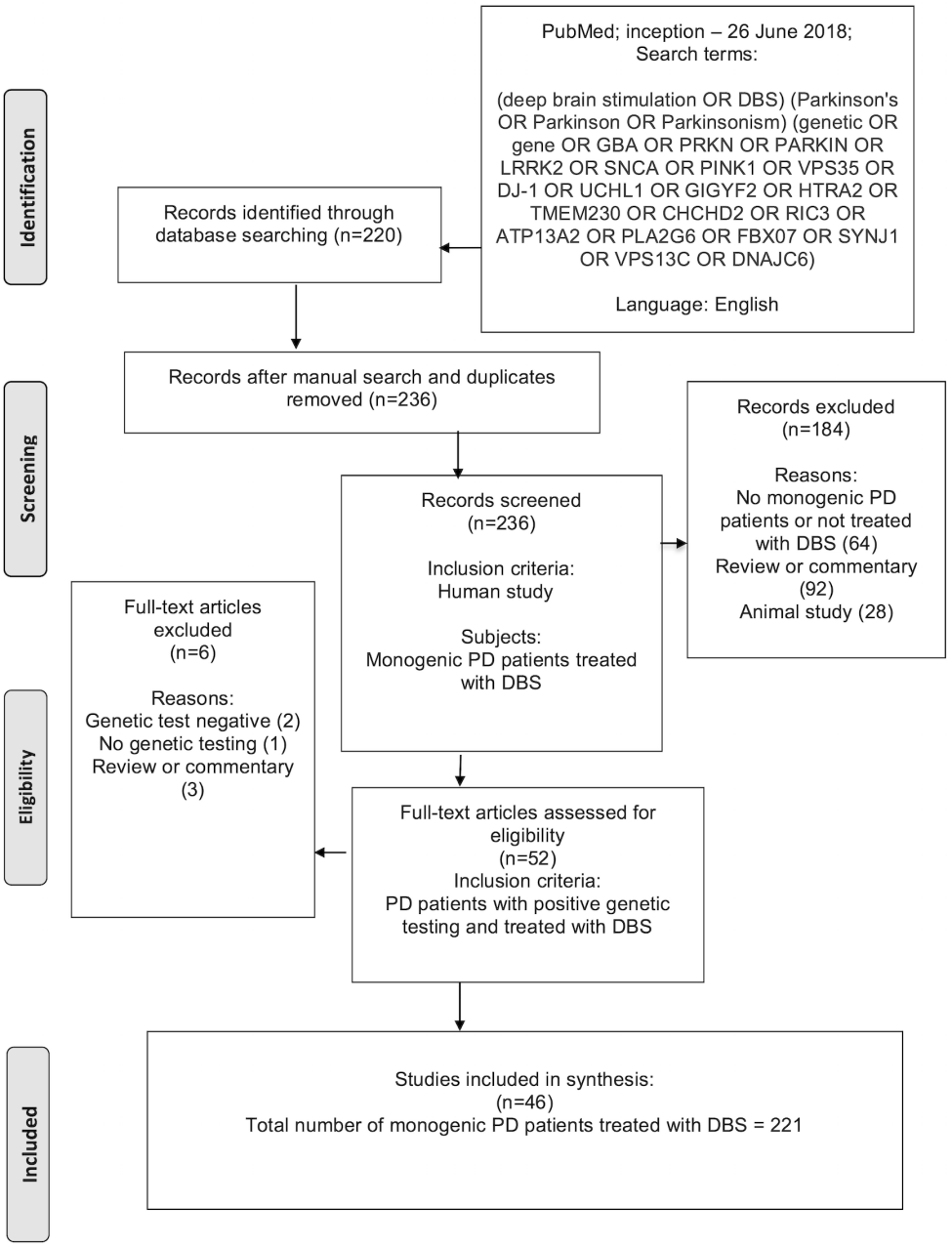

Figure 6. Study inclusion and exclusion in study I.

4.2.2 Study II

PD patients were identified from the digital database on the basis of ICD-10 code G20*. The date of diagnosis was defined as the first appearance of the diagnosis code in the patient records. After identifying patients and diagnosis dates, all individual clinical data were collected from the database. Dates and individual causes of death were obtained from the national authority, Statistics Finland (www.stat.fi). The beginning of the follow-up period was 1 January 2006, and the end of the follow-up period was set to 31 December 2016.

The cohort was divided into three groups based on the year of diagnosis (2006–2008, 2009–2011 and 2012–2014) to investigate longitudinal changes in survival. Overall survival was defined as the percentage of patients who were still alive at 1, 2 and 4 years after their diagnosis. Data analysis was separately performed for a sample in which patients with device-aided therapies were excluded. In addition, changed or removed diagnoses were investigated within a two-year timeline in 2011, which was the midpoint of the follow-up period, to investigate possible differences in the correctness of PD diagnoses between men and women. Potential changes in antiparkinsonian medication according to sex were also analysed.

4.2.3 Study III

4.2.3.1 Part I: Regional data

After identifying PD patients similarly from the digital database as in study II, PD patients with concurrent diagnosis of SCD (ICD-10 code F2*) and, separately, PD patients with a diagnosis of SCZ (ICD-10 code F20*) were identified. EHRs of patients with comorbidities were manually reviewed to confirm that the diagnoses were based on valid clinical criteria of PD and SCD. Controls were identified from the same digital database, and they were age- and sex-matched (1:1 ratio) with the PD cohort. Control patients with a diagnosis of SCD and SCZ were identified, and their EHRs were reviewed, respectively. The data collected from the EHRs included age at PD diagnosis, age at onset of psychotic symptoms, sex, primary motor symptoms of PD, primary symptoms of SCZ/SCD and last known neurological/psychiatric pharmacotherapy. Diagnostic brain imaging results, including DA transporter imaging ([123I]FP-CIT SPECT), were also evaluated and recorded if available for patients who carried both SCD and PD diagnoses.

Patients were excluded if the PD or SCD/SCZ diagnosis was considered incorrect or uncertain, if SCD/SCZ diagnosis was made after the age of 60 years or less than 6 years before the PD diagnosis. The age limit of 60 years was used to exclude patients with very late-onset SCD because psychotic symptoms among elder

people may be related to the prodromal phase of another neurodegenerative disease, such as DLB (Howard et al., 2000). Furthermore, to confirm results, an additional analysis was performed using the same exclusion criteria, but patients diagnosed with SCD/SCZ after the age of 45 years were excluded. The six-year lag was used to verify that the two diagnoses were distinctly separate and to reduce the likelihood of including PD patients with dominant psychiatric symptoms or SCD patients with dominant motor symptoms. The time lag was also used to exclude patients who were treated with antiparkinsonian drugs that could induce psychotic symptoms before the formal diagnosis of PD and to exclude Lewy body disease spectrum patients who could experience early hallucinations and are misdiagnosed with SCD.

The original search identified a total of 3045 PD patients, 78 of whom had concurrent SCD diagnoses and were treated between 1 January 2004, and 31 July 2019, at Turku University Hospital. After reviewing the EHRs of these 78 patients, 55 were excluded (DIP n=10; VP n=1; PD diagnosis uncertain n=5; DLB n=3; atypical parkinsonism n=1; PD diagnosis before psychotic symptoms, interval between diagnoses fewer than six years, or psychotic symptoms after the age of 60 years n=30; other psychiatric diagnosis n=3; psychiatric data not available n=1; EHR test patient n=1).

Twelve patients with SCD diagnoses were identified from the non-PD control population, and seven were excluded after reviewing patients' EHRs (psychotic symptoms after the age of 60 years n=3; psychiatric diagnosis not SCD n=1; DLB n=1; psychiatric data not available n=1; other neurodegenerative disease suspected n=1).

4.2.3.2 Part II: National data

The Special Reimbursement register was used to identify people who received drug reimbursement for PD during 1996–2015 and who were community-dwelling at the time of diagnosis (n=29,942). The flow chart of study exclusion is presented in **Figure 7**. People who had exclusion diagnoses indicating diagnoses other than PD (such as AD or secondary parkinsonism) within the two-year time window of the diagnosis date (before and/or after), as presented previously (Paakinaho et al., 2020), were excluded. Patients were also excluded if the age at the time of PD diagnosis was under 35 years or if the ICD-10 code for reimbursement was something other than G20*. In total, 25.9% of patients (n=7753) were excluded. For every PD patient, up to seven matched controls without PD were identified from the register that includes all Finnish residents. The matching criteria were age (1-year caliper), sex and hospital district within the country on the PD diagnosis date of the referent case (index date). Otherwise, the exclusion criteria were the same as those used for cases, but dementia due to PD (ICD-10 code F02.3), resulting in 2–7 controls for each PD patient (n=148,009).

Data on SCD/SCZ were obtained from the Care Register for Health Care from 1972 until the index date. SCZ was identified using ICD-10 codes F20* (excluding

F20.4), ICD-9 codes 2950–2953, 2956 and 2959, and ICD-8 codes 2950–2953, 2956, 2958 and 2959. SCD was identified with ICD-10 codes F2*, ICD-9 codes 295, 297, 298, 3010 and 3012, and ICD-8 codes 295, 297, 298, 29999, 3010 and 3012. As in Part I, patients with SCD/SCZ diagnoses after the age of 60 years or fewer than six years before the PD diagnosis were excluded from the analyses. A confirmatory analysis of patients diagnosed with SCD/SCZ under the age of 45 years was performed, respectively, to Part I.

In addition, data on the use of PD medications and antipsychotic medications were collected from the Special Reimbursement register at three time points (2 years before PD diagnosis, 2 years after PD diagnosis and 5 years after PD diagnosis) for patients with comorbidity of PD and SCD.

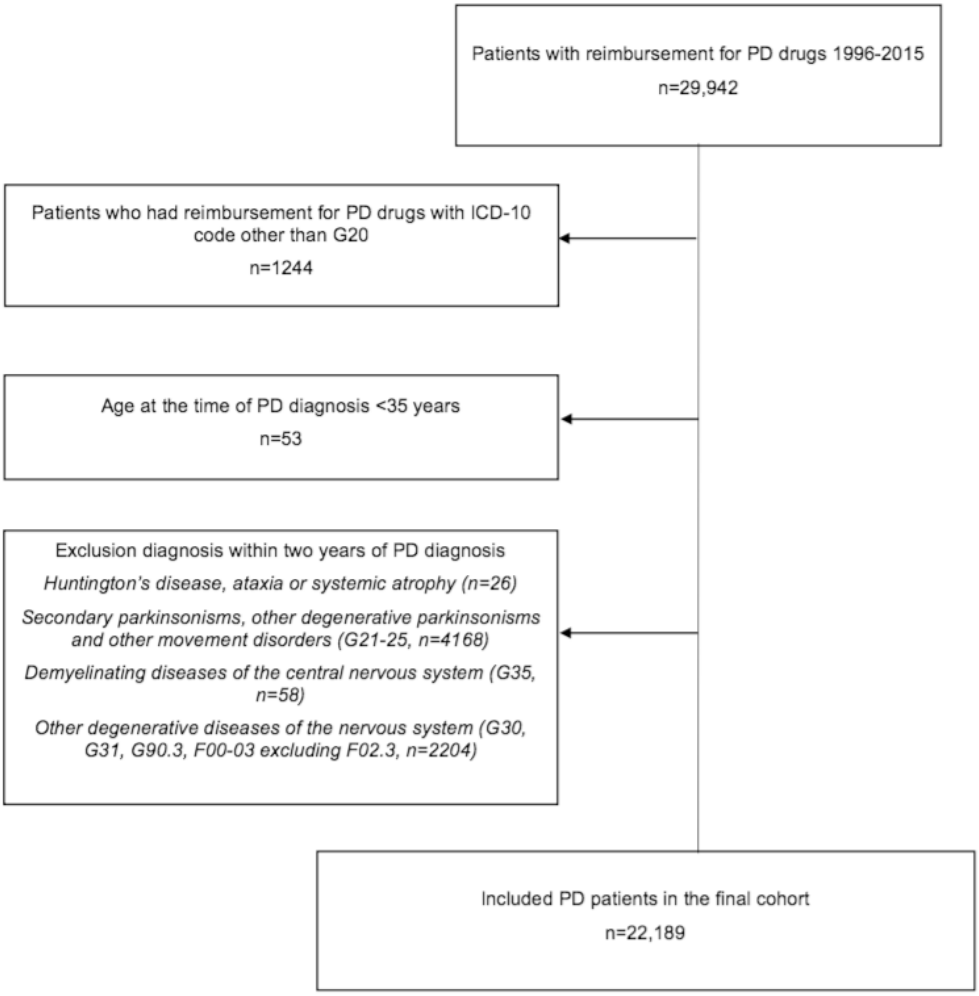

Figure 7. Flow chart of study exclusion in Part II of study III.

4.2.4 Study IV

After identifying PD patients and diagnosis dates correspondingly to study II, all individual clinical data were collected from the database. All diagnostic texts of PD patients from the EHRs were utilised. Finnish stop words were removed from the tokens, and the occurrence of all words was counted. The follow-up period was divided into three different time episodes with respect to the date of PD diagnosis (Time period I: 0–3 years before PD diagnosis; time period II: 0–3 years after PD diagnosis; time period III: 3–6 years after PD diagnosis). Consequently, we identified the 5000 most common words separately from each time period. A search allowed a specific word to occur only once in the same time period. All 15,000 words were reviewed manually by two investigators, and suitable words were categorised to 10 categories, which were determined in advance. Two word categories (hyposmia and sleep disorders) were excluded due to an insufficient number of words. The final eight categories were words related to parkinsonism, depression, psychosis/hallucinations, cognition, constipation, pain, cancer and circulation.

4.3 Statistical analyses

In all statistical analyses, P-values less than 0.05 were considered to be significant.

4.3.1 Study II

Continuous and categorical variables were compared between groups using ANOVA and chi-square tests. Kaplan–Meier analysis was used to analyse changes in overall survival. Log-rank tests were used to calculate the P-values between survival curves. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0, 2017 (IBM Corp, Armonk, NY, USA).

4.3.2 Study III

In Part I, logistic regression was used to compare the prevalence of SCD and SCZ diagnoses between the PD patient group and the control group. Associations between exposure and outcome in Part II were assessed with conditional logistic regression, which accounted for the matching of patients and controls. Statistical analyses were performed with SAS 9.4 for Windows (Cary, NC, USA) (Part I of the study) and Stata MP14.0 (Part II of the study).

4.3.3 Study IV

The relationship between words appearing within three years before PD diagnosis and five-year survival of PD patients was investigated with age- and sex-adjusted Cox regression analysis. The results were presented by HR with 95% confidence intervals. Logistic regression using generalised estimating equations to account for repeated measurements was utilised to analyse the differences in changes in word appearances compared to a control category (cancer). We chose the category of cancer for a control group because we assumed it would appear relatively constantly between different time episodes before and after PD diagnosis. Statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC).

4.4 Ethics

Because studies I–IV did not involve patient contacts, approvals from the Ethics Committee were not required.

The studies received registry study permits from Turku University Hospital (TT263/2017, T204/2019, diary number TK-53-652-18).

5 Results

5.1 The outcome of DBS in genetic PD (study I)

In study I, 46 included studies reported 221 monogenic DBS-treated PD patients, and mutations were documented in six different genes. A summary of key results is presented in **Table 4**.

5.1.1 LRRK2

Among *LRRK2* patients, 87 had DBS treatment (target: STN n=79, not reported n=8). The outcome data were available for 83.9% of patients (n=73). The motor outcome was mainly favourable in *LRRK2* patients. Five studies reported 10 patients with poor/mild/moderate outcomes. Two patients with the p.T2031S (c.6091A>T) mutation developed neuropsychiatric problems 5–7 years after implantation. The outcome appeared poor in patients with p.R1441G (c.4321C>G) mutations, whereas it appeared excellent in patients with p.G2019S (c.6055G>A) mutations.

5.1.2 PRKN

There were 67 *PRKN* patients (target: STN n=51, GPi n=5, zona incerta n=1, not reported n=10), and the outcome data were available for 85.1% (n=57). Of those patients, 76.1% (n=51) had favourable long-term motor outcomes, and 9.0% (n=6) were reported to have modest or poor outcomes.

5.1.3 GBA

Fifty *GBA* patients (target: STN n=33, GPi n=4, VIM n=1, not reported n=12) were reported, but two studies (Angeli et al., 2013; Lythe et al., 2017) reported some of the same patients. The outcome data were available for 60.0% of patients (n=30); 36.0% of patients (n=18) were reported to have favourable outcomes, 6.0% of patients (n=3) moderate and 18.0% of patients (n=9) poor long-term motor outcomes. One study reported better outcomes with STN-DBS and VIM-DBS than

with GPi-DBS (Angeli et al., 2013). GBA patients developed cognitive impairment faster compared to the general PD population.

5.1.4 SNCA

Five *SNCA* patients were reported (target: STN n=4, GPi n=1), and the motor outcome was favourable for all patients in the short-term. However, three of the five patients developed cognitive and/or neuropsychiatric problems a few years after DBS operation.

5.1.5 VPS35

Five *VPS35* patients (target: STN n=3, not reported n=2) were reported. The motor outcome was favourable in four patients, and one patient was reported to have minor motor benefit complicated by dysarthria.

5.1.6 PINK1

Five cases with *PINK1* mutation (target: STN n=4, GPi n=1) were reported. Favourable motor outcome was reported in three patients and moderate outcome in one case. One patient developed imbalance, gait impairment, dysarthria and behavioural changes after DBS implantation, and mental deterioration was documented a few years later.

Table 4. Summary of key findings of study I according to the mutated gene.

Gene	Studies (n)	Patients (n)	Target	Outcome
LRRK2	17	87[1]	STN: 90.8 % (n=79) NA: 9.2 % (n=8)	Mostly favourable motor outcome. Four studies with eight patients (9.2%) reported poor motor outcomes and one study reported moderate outcomes for two patients. Both patients with the LRRK2 p.T2031S (c.6091A>T) mutation (n=2) developed neuropsychiatric problems 5-7 years after implantation. The outcome appears poor in patients with LRRK2 p.R1441G (c.4321C>G) mutations (n=5) whereas it appears excellent in patients with LRRK2 p.G2019S (c.6055G>A) mutations.
PRKN	18	67[2]	STN: 76.1% (n=51) GPi: 7.5% (n=5) Zona incerta: 1.5% (n=1) NA: 14.9 % (n=10)	Fifty-one patients (76.1%) had favourable long-term motor outcomes. Four patients (6.0%) were reported to have modest outcome in two different studies and one study with two patients (3.0%) reported poor benefit.
GBA	5	50[3]	STN: 66.0 % (n=33) GPi: 8.0 % (n=4) VIM: 2.0 % (n=1) NA: 24.0 % (n=12)	Eighteen patients were reported to have favourable, three patients moderate and nine patients poor long-term motor outcomes. One study reported better outcomes with STN-DBS and VIM-DBS than with GPi-DBS. GBA mutation carriers developed cognitive impairment faster than patients without mutations.
SNCA	5	5	STN: 80.0 % (n=4) GPi: 20.0 %) (n=1)	Favourable motor outcome but three of five patients developed cognitive or neuropsychiatric problems a few years after implantation.
VPS35	4	5	STN: 60.0 % (n=3) NA: 40.0 % (n=2)	Favourable motor outcome in four cases and minor motor benefit complicated by dysarthria in one case.
PINK1	5	5[2]	STN: 80.0 % (n=4) GPi: 20.0 % (n=1)	Favourable motor outcome in three cases and moderate in one case.
22q11.2.Del. Syndrome	1	3	STN: 33.3 % (n=1) GPi: 66.6 % (n=2)	Favourable motor outcome.

* STN = Subthalamic nucleus, GPi = Globus pallidus interna, VIM = Ventral intermediate nucleus, NA = not available.

[1] One patient had also PRKN mutation and one had GBA mutation.

[2] One patient had both PRKN and PINK1 mutations.

[3] Two studies reported partially same patients, but it was not possible to separate individual patients that were reported twice. One patient had also LRRK2 mutation and one had PRKN mutation.

Some studies lacked important information such as DBS target, pre- and postoperative evaluation, adequate follow-up time or outcome information. Moreover, two studies mentioned above partially reported the same patients, and it was not possible to reliably identify patients that were included in both studies. After excluding the smaller study and poorer quality studies, the results remained essentially the same.

5.2 Prognosis of PD patients (study II)

5.2.1 Demographic and clinical characteristics

Demographic characteristics of the patients are presented in **Table 5**. In total, 1521 PD patients (54.2% men) were diagnosed between 2006 and 2014 at Turku University Hospital. Men were diagnosed at a younger age than women (71.6 years, SD 10.5 years vs 74.1 years, SD 10.4 years; $p<0.01$), but the age difference and mean age at diagnosis remained stable (men: $p=0.41$, women: $p=0.84$). The number of new PD diagnoses was stable over the study period (men: 261–292 diagnoses per three years, $p=0.14$; women: 216–256 diagnoses per three years, $p=0.14$). At the midpoint of the follow-up period in 2011, 55 men and 54 women were diagnosed with PD. Two years later, the diagnoses remained unaltered for 76.4% of men (n=42) and 77.8% of women (n=42). There were no significant differences in the diagnostic inaccuracy between men and women (men: 23.6%, women: 22.2%, $p=0.86$). The number of PD patients using L-dopa and DAs remained stable over the study period in both sexes (L-dopa: men: 55.2–60.6% per three years, $p=0.39$, women: 54.2–60.2% per three years, $p=0.41$; DAs: men: 40.6–43.8% per three years, $p=0.72$, women: 38.2–41.8% per three years, $p=0.24$).

During the study period, 685 patients died (47.1% of men and 42.6% of women). The most common immediate cause of death in all time periods in both genders was pneumonia (38.2% of deaths in men and 25.9% of deaths in women) followed by heart failure and myocardial infarction. There were no marked changes in the causes of death over the study period. PD was reported as a contributing factor to death in 36.3% of men and 38.4% of women, and the percentage did not change significantly during the follow-up period (men: 40.3% vs 33.6% vs. 30.7%, $p=0.25$, women: 41.6% vs 35.4% vs 34.0%, $p=0.50$).

5.2.2 Kaplan–Meier analysis and log-rank statistics

The overall survival of male PD patients increased during the follow-up period ($p=0.03$), but no change was observed in women ($p=0.42$) (**Figure 8**). The HR for men in the last follow-up period was 0.71 (95% CI: 0.53–0.95) ($p=0.02$) (**Table 5**), indicating better survival for men if the diagnosis was made later in the follow-up period. The results remained the same when patients receiving device-aided therapies (n=29) were excluded from the analysis.

Table 5. Demographic characteristics of the patients and changes in the overall survival according to the year of PD diagnosis.

Year of diagnosis	Diagnoses m/w n (%)	Age at diagnosis m/w (years)	Deaths m/w n	Overall survival m/w %			Hazard ratio (95% CI, p) m/w
				1 year after diagnosis	2 years after diagnosis	4 years after diagnosis	
2006–2008	271/256 (51.4/48.6)	72.2/74.3	191/154	86.0 / 89.8	79.0 / 82.8	62.0 / 69.1	-
2009–2011	261/225 (53.7/46.3)	71.7/74.2	122/96	90.4 / 94.2	82.8 / 88.4	67.8 / 74.7	0.80 (0.63-1.01, 0.057) / 0.92 (0.70-1.20, 0.534)
2012–2014	292/216 (57.5/42.5)	71.0/73.8	75/47	91.1 / 93.1	86.3 / 87.5	71.5 / 77.3	0.71 (0.53-0.95, 0.019) / 0.79 (0.56-1.12, 0.191)
Total	824/697 (54.2/45.8)	71.6/74.1	388/297	P-value for Kaplan-Meier analysis: m: p=0.03, w: p=0.42			

* CI = Confidence interval, m = Men, p = P-value, w = Women.

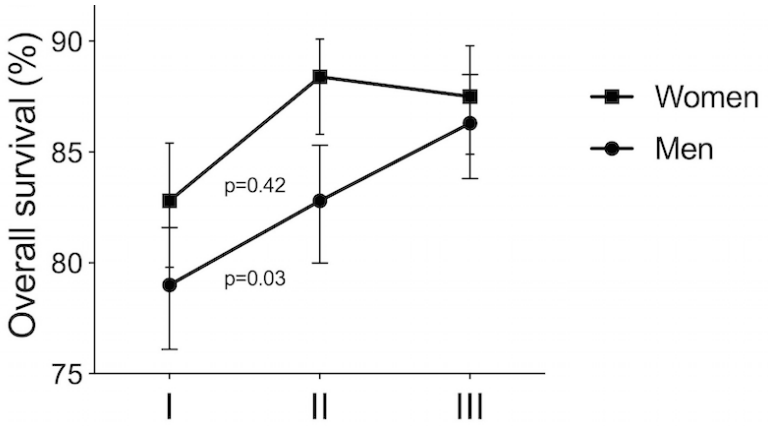

Figure 8. Overall survival two years after diagnosis according to follow-up period. I = Diagnosis years 2006–2008, II = Diagnosis years 2009–2011, III = Diagnosis years 2012–2014.

5.3 Comorbidity of PD and SCZ (study III)

5.3.1 Demographic and clinical characteristics

5.3.1.1 Part I: Regional data

In the regional PD cohort (n=3045), there were 0.76% of patients (n=23) with SCD who later developed PD, and 0.46% (n=14) of patients had specific diagnosis of SCZ

(**Table 6**). The mean age of patients at the time of PD diagnosis was 61.7 years (SD=10.7, median=61), and the mean age of patients at the onset of psychotic symptoms was 36.7 years (SD=13.9, median 38). In an age- and sex-matched control population (n=3045), there were 0.16% (n=5) of individuals with SCD, and 0.10% (n=3) of controls had specific diagnosis of SCZ. In non-PD controls, psychotic symptoms started under the age of 40 years in 3 patients, at the age of 41 in one patient, and data were not available for one patient.

Of the 23 PD patients, 11 underwent diagnostic DA transporter imaging ([123I]FP-CIT SPECT), and all of them had a striatal dopaminergic defect. Therefore, 47.8% of regional patients with SCD and PD were confirmed to have presynaptic dopaminergic dysfunction consistent with PD diagnosis. However, all 23 patients were diagnosed by a neurologist using PD diagnostic criteria, and all patients had a positive levodopa response for several years, increasing confidence in PD diagnoses.

5.3.1.2 Part II: National data

In the national PD cohort (n=22,189), 1.50% of patients (n=332) had previously diagnosed SCD, and 0.65% of patients (n=144) had specific diagnoses of SCZ (**Table 6**). In the control population (n=148,009), there were 1.31% of individuals (n=1943) with diagnosis of SCD and 0.61% of individuals (n=902) with diagnosis of SCZ. The mean age at the index date was 70.9 years (SD=9.7) for patients with PD and 70.5 years (SD=9.7) for individuals without PD. In the PD population, the mean ages at SCD diagnosis and SCZ diagnosis were 52.2 years (SD=16.3) and 46.5 years (SD=15.1), respectively. In the control population, the mean ages at SCD diagnosis and SCZ diagnosis were 49.1 years (SD=15.0) and 45.7 years (SD=14.0), respectively. A total of 54.8% of PD patients and 55.1% of controls were men.

The most commonly used antipsychotic drugs in patients with previously diagnosed SCD were quetiapine, olanzapine and risperidone. The percentage of antipsychotic users was relatively constant over time: 72.0% (n=239) of patients used antipsychotic drugs two years before PD diagnosis, 67.8% (n=225) two years after PD diagnosis and 74.1% (n=246) five years after PD diagnosis. Nevertheless, 97.9% (n=325) of all patients used antiparkinsonian drugs five years after PD diagnosis, and 88.9% used L-dopa-carbidopa or L-dopa-benserazide, and additionally, 17.5% used L-dopa-carbidopa-entacapone after five years.

5.3.2 Logistic regression analyses

5.3.2.1 Part I: Regional data

The odds ratios (ORs) for PD after SCZ diagnosis and PD after SCD diagnosis were 4.68 (1.35–16.31, p=0.02) and 4.63 (1.76–12.19, p<0.01) (**Table 6**). After excluding patients diagnosed with SCD/SCZ after the age of 45 years, the ORs for PD after SCZ diagnosis and PD after SCD diagnosis were 3.34 (0.92–12.15, p=0.07) and 2.81 (1.01–7.81, p=0.048), respectively. If no patients had been excluded from the analysis, the search would have identified 78 PD patients with SCD diagnoses and 12 non-PD patients with SCD diagnoses, and the primary result would have been essentially the same (OR=6.64, CI=3.61–12.23, p<0.01).

5.3.2.2 Part II: National data

The ORs for PD after SCZ diagnosis and PD after SCD diagnosis were 1.09 (0.91–1.30, p=0.34) and 1.17 (1.04–1.31, p<0.01) (**Table 6**). After including only patients who were diagnosed with SCD/SCZ before the age of 45 years, the ORs for PD after SCZ and PD after SCD were 1.16 (0.94–1.44, p=0.18) and 1.23 (1.06-1.44, p<0.01), respectively.

Table 6. Sample sizes and odds ratios of PD risk in regional and national data.

Diagnosis	**Regional data**			**National data**		
	PD patients n=3045 (n/%)	**Non-PD patients** n=3045 (n/%)	**OR (95% CI, p)**	**PD patients** n=22,189 (n/%)	**Non-PD patients** n=148,009 (n/%)	**OR (95% CI, p)**
SCZ	14/0.46	3/0.10	4.68 (1.35–16.31, 0.02)	144/0.65	902/0.61	1.09 (0.91–1.30, 0.34)
SCD	23/0.76	5/0.16	4.63 (1.76–12.19, <0.01)	332/1.50	1943/1.31	1.17 (1.04–1.31, <0.01)

* CI = Confidence interval, OR = Odds ratio, p = P-value, SCD = Schizophrenia spectrum disorder, SCZ = Schizophrenia.

5.4 Prediagnostic expressions predicting mortality of PD patients (study IV)

EHR data were available for 2522 PD patients in the three-year time period before PD diagnosis; 33.3% (n=839) of these died during a five-year period after the diagnosis. The appearance of psychosis/hallucination-related words within three years before PD

diagnosis was associated with worse survival for PD patients (HR 1.71, 95% CI 1.46–1.99, p<0.0001). Appearances of words related to pain (HR 1.34, 95% CI 1.12–1.60, p=0.0011), constipation (HR 1.34, 95% CI 1.15–1.56, p=0.0002), and cognition (HR 1.23, 95% CI 1.05-1.43, p=0.0087) over the prediagnostic period were associated with decreased survival according to age- and sex-adjusted Cox regression analysis. However, parkinsonism-, depression-, circulation- and cancer-related words were not significantly associated with survival of PD patients (**Table 7**).

Table 7. Associations between prediagnostic word categories and 5-year survival of PD patients.

Word category	Deaths/Patients (%)	Age and sex adjusted HR (95% CI)	P-value
Circulation			
Suitable word -	67 / 249 (26.9)		
Suitable word +	772 / 2273 (34.0)	1.01 (0.78–1.30)	0.9509
Cancer			
Suitable word -	537 / 1676 (32.0)		
Suitable word +	302 / 846 (35.7)	1.07 (0.93–1.24)	0.3396
Parkinsonism			
Suitable word -	31 / 71 (43.7)		
Suitable word +	808 / 2451 (33.0)	0.82 (0.57–1.18)	0.2849
Depression			
Suitable word -	647 / 1915 (33.8)		
Suitable word +	192 / 607 (31.6)	1.10 (0.93–1.29)	0.2583
Cognition			
Suitable word -	244 / 899 (27.4)		
Suitable word +	595 / 1633 (36.4)	1.23 (1.05–1.43)	0.0087
Constipation			
Suitable word -	613 / 1956 (31.3)		
Suitable word +	226 / 566 (39.9)	1.34 (1.15–1.56)	0.0002
Pain			
Suitable word -	154 / 601 (25.6)		
Suitable word +	685 / 1921 (35.7)	1.34 (1.12–1.60)	0.0011
Psychosis/hallucinations			
Suitable word -	624 / 2083 (30.0)		
Suitable word +	215 / 439 (49.0)	1.71 (1.46–1.99)	<0.0001

* CI = Confidence interval, HR = Hazard ratio, Suitable word +/- = Suitable word appeared/not appeared in prediagnostic time period.

The search identified 27,671,364 words from EHRs of PD patients, 765,633 of which were unique. The relative increase in the appearance of words between the prediagnostic time episode I and the postdiagnostic time episode II was the largest in

the psychosis/hallucinations category followed by words related to constipation, depression, cognition, cancer, pain, circulation and parkinsonism. There were significant changes in the appearance of all word categories over time except for pain-related words, which remained unaltered compared to the control category (cancer). Examples of common words in different word categories are presented in **Figure 9**.

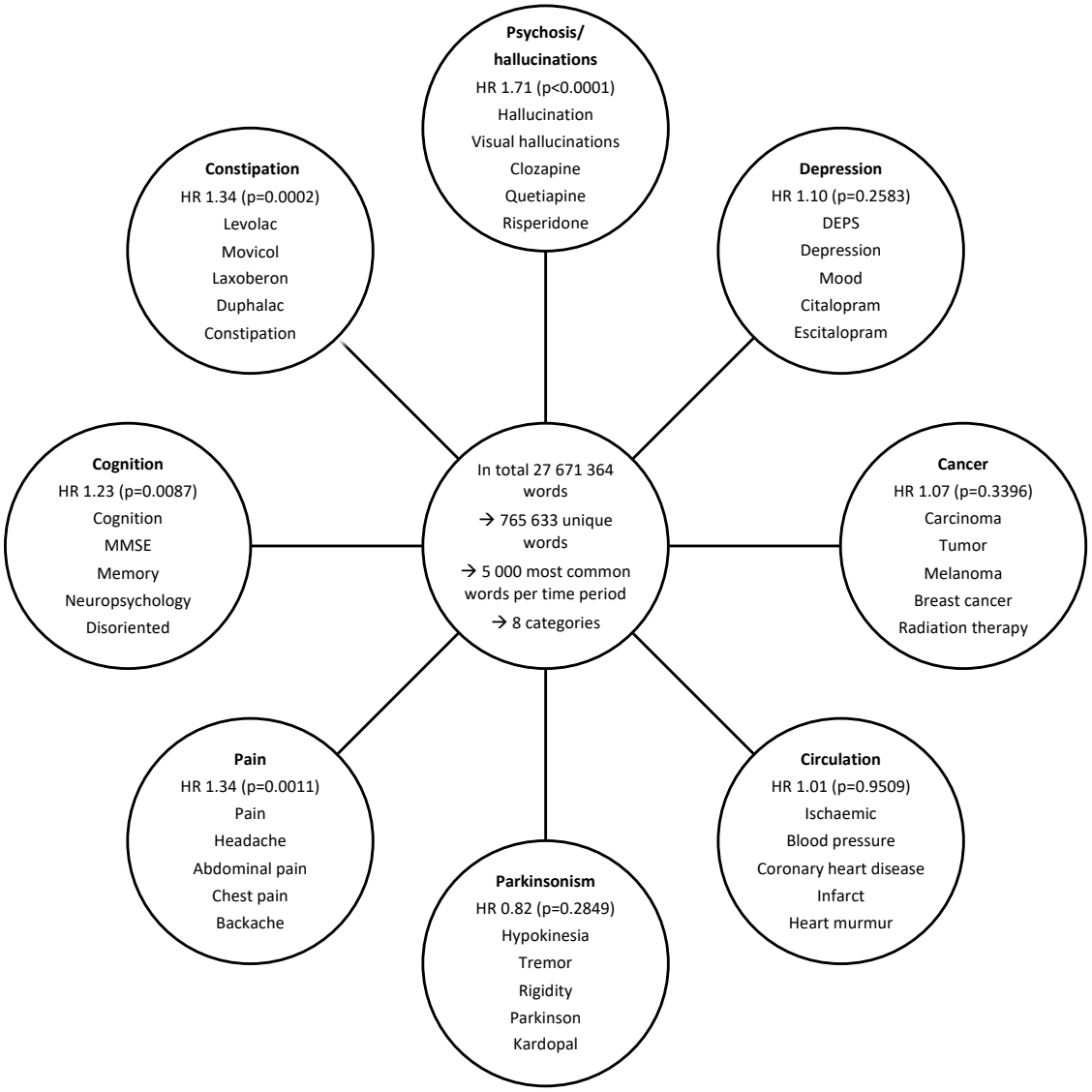

Figure 9. Examples of common words in different categories and hazard ratios for 5-year survival. DEPS = Depression Scale, Duphalac = trade name for lactulose, HR = Hazard ratio Kardopal = trade name for carbidopa/levodopa, Laxoberon = trade name for sodium picosulfate, Levolac = trade name for lactulose, MMSE = Mini-Mental State Examination, Movicol = trade name for macrogol, p = P-value.

6 Discussion

6.1 The outcome of DBS in genetic PD compared to the general PD population

The results of study I showed that the outcome of DBS is excellent in patients with *LRRK2* p.G2019S (c.6055G>A) mutations, very good in patients with *PRKN* mutations and poor in patients with *LRRK2* p.R1441G (c.4321C>G) mutations. The benefit of DBS in patients with *SNCA*, *GBA* and *LRRK2* p.T2031S (c.6091A>T) mutations may deteriorate due to the rapid progression of cognitive and neuropsychiatric symptoms. In DBS-treated PD patients with other mutations, the outcome seems to be typically comparable to that of DBS-treated idiopathic PD patients.

The understanding of the genetics of PD has deepened in recent decades as more PD-causing genes and genetic risk factors have been identified (Deng et al., 2018). It is well known that genetic factors affect the clinical phenotype of PD patients, which may also influence treatment responsiveness to DBS (Kasten et al., 2017). Moreover, PD patients with genetic mutations appear to be overrepresented in the PD population who undergo DBS operation (Angeli et al., 2013). Consequently, there has been growing interest in how genetic factors influence the outcome of DBS in PD patients, and recently, three other reviews have published observations comparative to the results of our study I (Artusi et al., 2019; de Oliveira et al., 2019; Rizzone et al., 2019).

The most extensive data were available for DBS-treated PD patients with *LRRK2* and *PRKN* mutations. Patients with *LRRK2* mutations seem to have good DBS responsiveness. Furthermore, patients with the most common *LRRK2* mutation, the p.G2019S mutation (Deng et al., 2018), may have even better outcomes than those without mutations. *LRRK2* cases of p.R114G, p.T2031S and p.N1437H mutation carriers appears to have less favourable outcomes, although the interpretation is limited by the small number of reported patients with DBS. For the *PRKN* mutation carriers, the outcome of DBS seems to be favourable, and these patients may be optimal candidates for DBS as PD patients with *PRKN* mutations are characterised as having a young or very young age at onset and early development of L-dopa motor fluctuations (Puschmann, 2013).

Some studies have reported that STN-DBS is associated with potentially higher risks of neuropsychiatric symptoms compared to GPi-DBS (Rodriguez-Oroz et al., 2005). Consequently, further studies are needed to evaluate the difference in outcomes between GPi-DBS and STN-DBS in patients who have genetic PD associated with more pronounced cognitive or neuropsychiatric problems. The localisation of DBS electrodes is an important predictor of the postoperative outcome of DBS (Okun et al., 2008). In addition, stimulation parameters may influence to manifestation of side effects; high intensity stimulation may spread to brain areas near the target and may provoke cognitive side effects in patients who are already at risk for cognitive impairment (Rizzone et al., 2019). Unfortunately, most studies lacked information about lead positioning and stimulation parameters, and in the future, the effect of lead positioning and parameter settings should be investigated in more detail. Moreover, it should be noted that if it is possible to avoid these stimulation-induced cognitive side effects with loop DBS if it becomes clinically available.

The limitation of the study is that apart from *LRRK2* and *PRKN* mutations, the published literature concerning DBS is scarce, which complicates the interpretation. The data are limited with respect to both number of patients and duration of follow-up. In these patients with rarer mutations, the need for DBS should be evaluated considering the accumulating evidence from the literature and individual clinical factors. It is also important to note that genotype may have a positive as well as a negative influence on the outcome of DBS operation and, this issue should be taken into consideration in the interpretation of DBS studies. For example, the EARLYSTIM trial was performed with young-onset PD patients (Schuepbach et al., 2013), and there could have been an overrepresentation of *PRKN* patients in the sample. Although DBS has been available since 1995 in Finland, there are only a few published studies on DBS outcomes in Finland (Koivu et al., 2018). More larger-scale studies are needed to make further conclusions about DBS outcome in genetic Finnish PD patients.

6.2 Sex-dependent improvement in survival of Finnish PD patients

In study II, the results showed that the mortality of male Finnish PD patients has decreased over a period of 11 years, but corresponding decline was not observed in the mortality of female PD patients. In Finland, the diagnostic criteria and treatment lines of PD are regionally homogeneous and are based on national current care guidelines. In addition, treatment-related changes in survival would likely affect both sexes to the same degree. Therefore, the result could reflect greater improvements in male survival compared to female survival at the population level, and the same sex

differences can likely be seen in other regions with ageing PD populations and comparable healthcare systems.

PD is associated with increased mortality according to several studies (Macleod et al., 2014). Reported mortality ratios have varied from 0.9 to 3.8, and the survival in PD patients has been estimated to decrease approximately 5% every year when cohorts are followed (Macleod et al., 2014) . Although antiparkinsonian medications – particularly L-dopa – provide benefits for QoL via symptom control, there is no evidence of an effect on longevity (Lees et al., 2009; Rascol et al., 2011). We do not think that sex differences in pharmacotherapy were a major contributing factor in the results, as the pharmacotherapy for PD remained essentially the same in Finland during the study period, as did the proportion of male and female PD patients using L-dopa and DAs in our cohort. Although there is a lack of neuroprotective therapies and L-dopa has remained the gold standard for motor control for 40 years, there have been relevant changes in the treatment of PD. Especially along DBS, CSAI, LCIG infusion and LECIG infusion, there is a new domain to manage motor complications in advanced PD. Importantly, these device-aided therapies have achieved a firmer state in the treatment of PD within the last two decades, and they particularly influence the performance of patients that previously drifted towards complete, often fatal immobility. Indeed, DBS and device-aided pump therapies have shown a fundamental effect on QoL in patients with advanced PD, but there is no evidence for an effect on longevity, either (Antonini et al., 2018b; Antonini & Nitu, 2018; Obeso et al., 2001). The results of study II remained the same when the patients treated with device-aided therapies were excluded from the analysis, and therefore, advances in device-aided therapies did not explain the results. To impact longevity in PD, one would need measures to prevent the degeneration of dopaminergic neurons, but neuroprotective therapies, although intensively investigated, remain elusive.

It should be noted that there are potentially highly relevant changes in treatment options other than pharmacological and device-aided therapies which could affect mortality, namely improved rehabilitation, fall prevention, and changes in end-of-life care for PD patients (Monticone et al., 2015; Veronese et al., 2017). Non-pharmacological therapies, including physiotherapy, speech therapy and occupational therapy, are given mainly in local healthcare centres in Finland. These data were not available for us, and this can be considered a limitation of our study because the convention and intensity of these therapies might have changed during the follow-up period.

We postulate that the most important reason for the change in the life expectancy of male PD patients is likely caused by population-level changes in morbidity and mortality. Mortality has declined, and life expectancy has lengthened remarkably in the whole population in Finland during the last 40 years; the changes can be seen in

both males and females, and the improvement extends to elderly populations as well (Salomaa et al., 2016). However, according to Statistics Finland, life expectancy has increased, especially in Finnish men; in 73-year-old individuals in the general population (mean age of the PD population in study II), the life expectancy increased almost twice as much in men as in women (1.1 vs 0.6 years) during our study period, 2006–2016. In addition, Statistics Finland has reported that age-standardised mortality from diseases of the circulatory system, which are the most important cause of death in Finland, has declined more for men than for women. Therefore, it is apparent that our result is at least partially related to the societal general gender-differences in survival and that a substantial part of the improved life expectancy is likely to be due to the decline in cardiovascular mortality. However, the reason for the prominently increased male life expectancy in Finland is not entirely clear, but it is probably related to successful actions taken for the prevention and control of noncommunicable diseases – mainly cardiovascular diseases, cancers, chronic respiratory diseases and diabetes – that are the most important causes of death worldwide and have affected men more than women according to the World Health Organization. The North Karelia project has probably had a notable influence on the decline of mortality and growth of LE during the last 40 years in Finland (Salomaa et al., 2016).

There was a slight difference in the ages at diagnosis between men and women in the PD cohort of study II (mean difference of 2.5 years, men diagnosed earlier). It has been proposed that the phenotype of PD in women may be more benign, and symptoms may begin later than in men, which could explain this difference (Picillo et al., 2017).

6.3 Increased risk of Parkinson's disease in patients with schizophrenia spectrum disorders

The results of study III showed that SCD increases the risk of PD later in life; the association was seen in both regional case-control data and in a nationwide nested case-control study with community-dwelling Finnish individuals as a source population. Despite the opposite dopaminergic disease mechanisms, it seems that SCD does not decrease the risk of PD but paradoxically increases the risk. The results were seen despite that fact that the increased mortality of severe SCZ patients dilutes the effect. The results of study III could be explained by the increased vulnerability of the DA system in the residual phases of SCD induced by an illness phase-dependent mechanism including DA dysregulation.

DIP typically emerges as a diverse effect of antipsychotic drugs, which block the postsynaptic dopaminergic receptors (Erro et al., 2015; Yang et al., 2007). However, it has been hypothesised that the use of neuroleptic drugs can also cause degenerative

PD, causing a long-term hypodopaminergic state that predisposes to nigral cell degeneration (Erro et al., 2015). In addition, SCZ patients have lower tonic DA release throughout the disease, with phases combined with oversensitive phasic DA release during the psychotic episodes (A. A. Grace, 1991; A. A. Grace, 2016). Thereby, as negative and cognitive symptoms typically dominate over the psychotic episodes in later and residual phases of the disease, SCZ patients likely suffer from a chronic hypodopaminergic state (Schennach et al., 2015). There is another hypothesis that neuroleptic drugs could predispose to the development of degenerative PD because of the neurotoxic effects on dopaminergic neurons through the inhibition of the mitochondrial respiratory chain, increased DA turnover and enhanced production of neurotoxic free radicals (Erro et al., 2015). A previously published prospective population-based study supports increased long-term risk of developing incident PD after neuroleptic exposure (Huang et al., 2019). Thus, the increased PD risk in patients with SCD could be related to neuroleptic exposure, but neurobiological mechanisms in SCZ may be the primary risk-altering factors.

There were no previous case-control studies of PD risk in patients with SCZ or SCD. However, in addition to case reports of SCD and PD comorbidity, there are two published register-based studies that have extensively investigated comorbid diseases and symptoms of SCZ patients, not specifically PD. According to the results of the first study, patients with SCZ were more likely to have PD compared to the control population (Smith et al., 2013). The results of a more recent published study with SCZ patients from Spain reported the OR for PD to be as high as 47.89 (95% CI 44.49–51.55, $p<0.001$) (Gabilondo et al., 2017). It is important to note that neither of the two studies excluded patients with DIP, which likely increases estimates of comorbidity because secondary parkinsonism is a well-known side effect of antipsychotic medications used in SCD patients. In study III, we employed a methodological approach that reduced the possibility of aberrating the results, as we excluded patients with secondary parkinsonism from both the regional and national data. In addition, time limits in diagnoses/ages were used as exclusion criteria to avoid misclassifications due to partially overlapping clinical phenotypes of PD and SCD. Although there are sources of error in a register-based analysis, the data can be considered to be free from diagnostic inaccuracy. The study results showed that there is a similar risk for PD in regional individual data and in national data with more than 20,000 analysed PD patients. The specific risk of increased PD in SCZ patients was detected in the regional data but not in the national data, which could be due to diagnostic classification. Especially at the early stage of the doctor–patient relationship, it is more plausible to set a diagnosis of SCD than a specific diagnosis of SCZ. Thus, in large patient cohorts like in our national data, it is likely that some of the SCZ patients have an SCD diagnosis in the registries.

Patients with SCZ have been reported to have 2.5 times the risk of dying compared to the general population (Saha et al., 2007). The greater mortality is associated with increased risk of cardiovascular diseases, autoimmune diseases, infections, chronic obstructive pulmonary disease and cancers in patients with SCZ (Olfson et al., 2015). Moreover, the rates of smoking and suicides are also reported to be high among SCZ patients (De Leon & Diaz, 2005; Palmer et al., 2005). For the results of study III, this means that there were likely patients with severe SCD who were not included in the analysis because of premature death before the typical age of PD onset. However, regardless of the diluting effect of increased mortality, the effect of increased PD risk was clearly seen in the study population. It is possible that the greater subcortical release of DA and D2 receptor augmentation (Brisch et al., 2014) in the most severe cases of SCZ leads to a particularly increased PD risk over time, a risk that is neutralised by the increased mortality in the most severe cases. This theory should be tested by classifying and studying SCD patients according to symptom severity in the future studies.

Study III has strengths and weaknesses. One of the limitations in registry-based evaluations is diagnostic accuracy, which can be suboptimal for PD. This was also seen in our regional data as 25.6% of PD patients (n=20) were excluded due to incorrect or uncertain PD diagnosis (DIP n=10, vascular parkinsonism n=1, PD diagnosis uncertain n=5, LBD n=3, atypical parkinsonism n=1). However, if we presume that a similar level of diagnostic inaccuracy is also the case for the main sample of 3045 patients, the effect would in fact increase, not decrease. We can assume that the effect is at least a fivefold increase, and with the PD diagnostic inaccuracy, the true difference is probably larger. In addition, the possibility of DIP in some patients was a limitation of study III. Many of the PD patients were still medicated with antipsychotic drugs, although mostly with atypical quetiapine, olanzapine or risperidone, at the time of PD diagnosis. However, 97.9% of PD patients with earlier SCD remained on L-dopa or other PD medications five years after PD diagnosis, which indicates a long-term positive response to dopaminergic medications in these patients and supports diagnoses of idiopathic PD. Further, all diagnoses of PD in both regional and national data were based on individual clinical examinations by neurologists using diagnostic criteria, reducing the possibility of DIP. It is possible that the regional data do not represent the general population as well as national data because our regional cohort included only patients from the university hospital database without patients treated by general practitioners or in the private sector. This probably explains why the prevalence of SCD and SCZ in control groups was lower in regional than in national data. The estimates of median lifetime prevalence of SCZ varies between studies and is reported to be 0.4–1.3% (Chang et al., 2017), which correlates with the prevalence observed in our national data. However, although the patients treated outside special health care were missing from

our regional data, the impact is same for both PD and SCD patients. Thus, this does not influence our final conclusions. The same intrinsic differences in the data sets probably explain the difference in the mean ages of PD populations between regional and national data, as older patients treated outside the university hospital increase the mean age of the PD population of national data compared with regional data. The difference in ORs for PD following the diagnoses of SCZ and SCD between the regional data and the national data is probably due to the large difference in sample sizes between regional and national data, which can induce analytical bias in logistic regression (Nemes et al., 2009). However, the primary result of increased PD risk was also clearly seen in our considerably larger national data.

6.4 Prediagnostic expressions predicting mortality of PD patients

Study IV presented a methodological approach allowing analyses of massive data sets of large PD cohorts. Moreover, the results of the study pointed out that prediagnostic screening of medical terms in PD patients' EHRs can discover indicators of PD patient survival. Based on our results, prediagnostic psychosis/hallucination-, cognition-, constipation- and pain-related word categories were associated with increased mortality for PD patients. On the other hand, no associations with parkinsonism-, depression-, circulation-, or cancer-related words were detected.

NMSs have a remarkable influence on PD patients QoL (Schapira et al., 2017), and some NMSs have also been identified as risk factors for PD mortality (Santos-García et al., 2018). Previous studies have observed that psychotic symptoms (Wetmore et al., 2019) and cognitive impairment/dementia (De Lau et al., 2005; Levy et al., 2002) are associated with decreased survival in PD patients. Nevertheless, these associations have been demonstrated in diagnosed patients often years after the onset of the first symptoms, whereas the results of study IV focused specifically on the prediagnostic period. De Pablo-Fernandez and colleagues have also published that the early development of autonomic dysfunction or individual autonomic abnormalities (including constipation, orthostatic hypotension, urinary symptoms, upper gastrointestinal tract symptoms, sweating abnormalities, and erectile dysfunction in males) are independent determinants of more rapid disease progression and shorter survival in already diagnosed PD (De Pablo-Fernandez et al., 2017). However, there were no previous publications on the direct association between pain and survival in PD. PD-related pain has been reported to increase the risk of falls, which could secondarily affect occurrence of acute complications and deaths in PD patients (Xu et al., 2014).

The clinical importance of pain in PD is distinct. Previous studies have shown that PD patients suffer from pain more than age-matched controls (Antonini et al., 2018a), and as much as 61.8% of PD patients have reportedly experienced at least one form of chronic pain, according to the DoPaMiP study (Nègre-Pagès et al., 2008). Although pain is a significant NMS of PD, it still remains an underdiagnosed and undertreated symptom negatively influencing the QoL of PD patients (Antonini et al., 2018a; Nègre-Pagès et al., 2008). The results of study IV observed a possible link between pain in the prediagnostic period of PD and mortality within the first five years after diagnosis. The poor survival may be related to early balance problems or comorbidity, but future studies with other methods are needed to investigate this in detail.

It is also important to note that although our study focused on the prediagnostic period, it was not the same as the premotor stage. The PD diagnosis date was set as the first appearance of the diagnosis code in the EHRs, and the diagnostic latency from motor symptom occurrence to clinical diagnosis of PD typically varies from months to a few years (Breen et al., 2013; Wan et al., 2019). Therefore, the results should be interpreted to indicate that psychosis/hallucination-, cognition-, constipation- and pain-related expressions are associated with worse survival in the early motor phase of PD, albeit belonging to the prediagnostic period.

Parkinsonism-, depression-, circulation-, and cancer-related expressions within three years before PD diagnosis were not associated with increased mortality. As expected, the appearance of parkinsonism-related words was high in PD patients in all three time periods (97.2% vs 98.3% vs 93.9%), and the very high prevalence of parkinsonism-related expressions in all time periods made longitudinal analyses less meaningful. Moreover, it is important to note that the search allowed specific words to occur only once in the same time period. Therefore, the appearance of an expression indicates merely that a patient had a certain symptom or health-related problem without information about its severity. This, together with the duration of follow-up (max 8 years), may explain why depression-, circulation- or cancer-related expression was not associated with PD mortality. Reported results about the association of depression with PD mortality are somewhat mixed; for instance, De Lau and colleagues have reported that depression is a predictor of decreased survival in PD (De Lau et al., 2014), while Starkstein and colleagues did not observe a significant relationship between depression and PD mortality (Starkstein et al., 1990).

As EHRs are becoming more prevalent in medical care worldwide, a similar automated analysis of PD medical texts is possible in many regions. EHRs may be used to assess study feasibility, facilitate patient recruitment, and streamline data collection at baseline and follow-up (Cowie et al., 2017). Although the method used in study IV provides advantages by enabling investigations of massive sample sizes,

there are limitations that should be considered when the results are interpreted, such as less reliable documentation, possibility of missing data, and difficulty verifying documented information. Furthermore, variability in the quality of documentation among healthcare professionals affects data quality. Considering these limitations, this method is best at generating research hypotheses to be tested using other methods.

6.5 Summary

In summary, this thesis is based on four studies. Study I was a systematic review of 46 studies that reported DBS outcomes in 221 genetic PD patients. Study II was a retrospective record-based study that included PD patients who were diagnosed between 2006 and 2014 at Turku University Hospital in southwestern Finland. Study III was divided into two parts: part I was a retrospective record-based case-control study that included PD patients treated between 2004 and 2019 throughout Turku University Hospital District, and part II of the study was a nested case-control register study that included Finnish PD patients who received drug reimbursement for PD between 1996 and 2015. Study IV was a retrospective record-based study, and the study cohort consisted of PD patients treated during 2004–2016 throughout Turku University Hospital District.

Study I showed that monogenic PD patients have variable DBS outcomes depending on the mutated gene. The best outcomes of DBS seem to be in PD patients with *LRRK2* p.G2019S mutation or *PRKN* mutation. However, although most patients benefit from the operation, the current evidence is questionable for DBS implantation for patients with T2031S or R114G mutations in the *LRRK2* gene or mutations in the *SNCA* or the *GBA* genes. The NMSs of genetic PD may be a limiting factor in the overall benefit of DBS in some mutations, and while the motor benefit from DBS may initially be clear, the rapid non-motor progression may lessen the sum value for the QoL.

Study II demonstrated that the survival of male Finnish PD patients has improved over a period of more than a decade, while it has remained unchanged in female PD patients. We suggest that the results reflect a decreasing sex gap in life expectancy because treatment lines of PD are the same for both sexes, and treatment-related changes would likely affect both sexes to the same degree. Thus, the results showed a difference in mortality between male and female PD patients, which has led and will probably continue to lead to an increasing male-to-female ratio in PD prevalence.

Study III showed an increased risk of hypodopaminergic PD after being diagnosed with hyperdopaminergic SCD. The result was observed in both individual regional and nationwide data. This increase could be associated with risk-altering

DA receptor antagonists or disease-related neurobiological effects that increase vulnerability. However, further studies are needed to investigate whether the severity of psychotic symptoms or the type or dosing of antipsychotic drugs impact the risk of PD. According to current knowledge, different environment-, hereditary-, and patient-related factors influence the risk of developing PD, and the results of study III demonstrated that a previously diagnosed psychotic disorder or SCZ may be one factor that increases the risk of PD later in life.

Study IV demonstrated a methodological approach for PD research that can be used to mine massive clinical samples of patients. The method can be used to bring previously undetected clinically relevant factors to the surface. The validity of the method can be seen in text mining of EHRs in early stages of PD, which shows that psychosis/hallucination-, cognition- and constipation-related words are related to worse survival, as previously reported using other methods of investigation. In addition, the results showed a possible link between pain in the prediagnostic period of PD and mortality within the first five years after diagnosis. Further studies with other methods are needed to investigate this in detail.

7 Conclusions

I Clinical outcome of DBS treatment in monogenic PD patients seems to depend on the mutated gene. The outcome appears excellent in patients with *LRRK2* p.G2019S mutations and good in patients with *PRKN* mutations, whereas it seems less favourable in patients with *LRRK2* p.R1441G mutations. The overall benefit of DBS in *SNCA*, *GBA* and *LRRK2* p.T2031S mutations may be decreased due to rapid progression of cognitive and neuropsychiatric symptoms.

II The survival of Finnish male PD patients has improved over a period of 11 years without a similar change in female PD patients. Since improvements in the treatment of PD likely affect both sexes similarly, our results probably stem from the higher increase of general life expectancy in Finnish males compared to Finnish females in recent years. This will probably lead to an even higher male-to-female ratio in PD prevalence.

III Despite the opposite dopaminergic disease mechanisms of PD and SCZ, the diagnosis of SCD seems to increase the risk of PD in later life. This association may be related to risk-altering DA receptor antagonists or disease-related neurobiological effects.

IV Automated data mining and pattern recognition of the EHRs of PD patients can be used to detect clinically relevant factors from massive data sets. In line with previously reported results, we observed that psychosis/hallucination-, cognition- and constipation-related words in the early stages of PD are related to worse PD survival. Further studies are needed to verify the relationship between prediagnostic pain and worse survival in PD.

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