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Department of Neurology and Neurosurgery, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia.

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CONTENTS

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ABBREVATIONS

CI	confidence interval
COMT	catechol-O-methyltransferase
GBA	glucocerebrosidase
EHIF	Estonian Health Insurance Fund
EQ5D	Euro Qol 5D
HY	Hoehn and Yahr staging
HRQoL	health-related quality of life
ICDs	impulse control disorders
LEDD	levodopa equivalent daily dose
LRRK2	gene encoding leucine-rich repeat kinase 2
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society Revision of the Unified Parkinson Disease Rating Scale
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NHP	Nottingham Health Profile
NMSS	Non-Motor Symptoms Scale
NMSQ	Non-Motor Symptoms Questionnaire
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Quality of Life Questionnaire
PIGD	postural instability and gait disorder
QSBB	Queen Square Brain Bank
RR	rate ratio
SE-ADL	Schwab and England Activities of Daily Living Scale
SF-36	Medical Outcome Study Short-Form Health Survey
SI	summary index
SNCA	gene encoding α-synuclein
UPDRS	Unified Parkinson Disease Rating Scale
VPS35	gene encoding vacuolar protein sorting 35
WHO	World Health Organization

1. INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder of still largely unknown etiology (Poewe et al., 2017), and it is estimated that the number of patients will reach minimally 8.7 million by 2030, leading to the increasing disease-related burden on the society (Dorsey et al., 2007). Aging is known to be the greatest risk factor for the development of idiopathic PD, illustrated by the worldwide prevalence and incidence rates increasing steadily with age (Hirsch, Jette, Frolkis, Steeves, & Pringsheim, 2016; Pringsheim, Jette, Frolkis, & Steeves, 2014). It is estimated that 0.3% of all the population and up to 4% of the people in the highest age groups are suffering from this chronic and progressive neurodegenerative disease (de Lau & Breteler, 2006).

Men and women are affected both, however, males have frequently reported to be at higher risk for the disease development than women (Moisan et al., 2016). Incidence and prevalence rates of PD vary across different studies to a large extent and this has been proposed to result from environmental and genetic factors as well as due to methodological discrepancies across the studies (Abbas, Xu, & Tan, 2018). There are only few studies that have investigated PD epidemiology in the same geographical area using the same study design and diagnostic criteria, showing an increasing prevalence of PD, however, the results on the dynamics of incidence have been more inconclusive (Evans et al., 2016; Kuopio, Marttila, Helenius, & Rinne, 1999a; Yamawaki, Kusumi, Kowa, & Nakashima, 2009). It has been shown that PD patients have an average of 1.5 times higher risk of dying compared to the general population (Macleod, Taylor, & Counsell, 2014). The risk of mortality has been found to be related to the duration of disease (de Lau, Verbaan, Marinus, & van Hilten, 2014; Hobson & Meara, 2018; Pinter et al., 2015). It has been shown that PD diagnosis is frequently underreported on death certificates (Benito-León, Louis, Villarejo-Galende, Romero, & Bermejo-Pareja, 2014; Hobson & Meara, 2018).

Neuropathologically, PD is characterized by nerve cell loss in the *Substantia nigra* in the midbrain and the presence of Lewy bodies and Lewy neurites (Gibb & Lees, 1988), i.e α-synuclein-containing inclusion bodies, that are indicative pathological hallmarks of sporadic PD, and not only found in the basal ganglia, but also in other brain regions (Spillantini 1997; Braak et al. 2003). The general idea of the Braak staging is that α-synuclein pathology has a caudal-to-rostral progression, spreading from medulla oblongata or the olfactory bulb (stages 1 and 2) up to the the neocortex (stages 5 and 6) (Braak et al., 2003). Lewy-type pathology in PD patients can also be found in tissues outside the central nervous system, in particular in the sympathetic ganglia, gastrointestinal tract, heart, adrenal and salivary glands and skin (Adler et al., 2016; Gelpi et al., 2014; Gibbons, Garcia, Wang, Shih, & Freeman, 2016).

Clinical cardinal manifestations of PD include tremor, bradykinesia, rigidity and postural instability (Lees, Hardy, & Revesz, 2009; Poewe et al., 2017). In

addition to the alterations in dopaminergic nigrostrial pathways in the brainstem that are related to the emergence of motor features, degeneration also occurs in other brain structures and neurotransmitter systems. Involvement of non-dopaminergic patterns of neurodegenerations is associated with most of the non-motor symptoms of PD that are classified into sensory features, neuro-psychiatric symptoms, sleep and autonomic disorders (Jellinger, 2015; Schapira, Chaudhuri, & Jenner, 2017). Among other factors, higher burden of non-motor symptoms has been linked with longer duration and greater severity of the disease, as well as with postural instability and gait disorder (PIGD)- dominant subtype (Barone et al., 2009; Hely, Morris, Reid, & Trafficante, 2005; Müller, Larsen, Wentzel-Larsen, Skeie, & Tysnes, 2011).

PD is an uncurable neurological condition and currently available pharmaco-therapy is only symptomatic (Charvin et al. 2018). Levodopa is the most frequently used antiparkinsonian medication, however, as the disease progresses, levodopa becomes less effective, higher doses are needed to manage the motor symptoms, and eventually, levodopa treatment-related motor and non-motor complications occur in majority of patients (Chaudhuri, Poewe, & Brooks, 2018). Most commonly, cumulative dose and longer treatment duration of levodopa and longer disease duration are reported as risk factors associated with the occurrence of motor complications (Hashim et al., 2014; Hauser, McDermott, & Messing, 2006; Kum et al., 2009; Olanow et al., 2013; Schrag & Quinn, 2000a).

Non-motor symptoms dominate in the clinical profile of moderate and advanced PD patients and predict an impaired quality of life, disability and mortality (Chaudhuri, Healy, & Schapira, 2006). Numerous studies have demonstrated that non-motor symptoms may be more detrimental for reduced health-related quality of life (HRQoL) than motor symptoms (Erro et al., 2016; Müller, Assmus, Herlofson, Larsen, & Tysnes, 2013; Ophey, Eggers, Dano, Timmermann, & Kalbe, 2018; Prakash, Nadkarni, Lye, Yong, & Tan, 2016). Besides the non-motor and motor symptoms of PD, literature on the determinants of HRQoL has highlighted several other predictors including disease duration and severity, presence of motor complications and several socio-demographic factors (Soh, Morris, & McGinley, 2011).

The primary aim of this study was to investigate the prevalence, incidence and mortality rates of PD in a defined population in Estonia. As it was the second population-based study using the identical diagnostic criteria and substantially overlapping case-ascertainment methods in the same geographical region, we also aimed at investigating dynamic changes in prevalence and incidence rates over 20 years. Mortality of PD in Estonia has not been studied before. The second main objective of this study was to assess the clinical characteristics of the disease, particularly the frequency of non-motor symptoms and their association with various clinical and socio-demographic factors. The third aim was to investigate the frequency of levodopa-induced motor complications and factors associated with them. Finally, the fourth aim was to investigate the HRQoL and its determinants in people with PD.

2. REVIEW OF THE LITERATURE

2.1. Epidemiology of PD

2.1.1. General aspects

Point prevalence is defined as the number of affected persons present in the population at a specific date divided by the number of persons in the population at that point in time (Gordis, 2014). The prevalence of PD is generally estimated to be 0.3% of the entire population, about 1% in people over 60 years of age, and up to up to 4% in the highest age groups (de Lau & Breteler, 2006). The incidence rate of a disease is defined as the number of new cases of a disease that occurs during a specified period of time in a population at risk for developing the disease (Gordis, 2014). The incidence of PD disease ranges from 8–18 per 100,000 person-years (de Lau & Breteler, 2006). Both prevalence and incidence vary widely across different studies, that could most likely be attributed to methodological differences such as distinct study designs, case-finding strategies and diagnostic criteria. Differences in the exposure of environmental and genetic risk factors could also affect the variability of PD epidemiological estimates across populations worldwide (Abbas et al., 2018).

Mortality of PD is less studied compared to the prevalence and incidence. A frequently used estimate to evaluate the mortality is a standardized mortality ratio, i.e the ratio of the total number of deaths actually observed to the total number of deaths expected in the general study population without the disease (Gordis, 2014). Majority of prospective cohort studies have found that PD patients have a nearly 2-folded higher mortality risk than persons without PD, and the risk is related to the duration of disease (de Lau et al., 2014; Hobson & Meara, 2018; Pinter et al., 2015).

2.1.2. Diagnostic accuracy and diagnostic criteria

No single disease-specific *ante mortem* diagnosing method is yet available and the diagnosis of PD is clinical, therefore the diagnostic accuracy presents a challenging issue in PD related research studies. In a recent metaanalysis of 11 autopsy-verified studies, a pooled diagnostic accuracy of 81% was reported (Rizzo et al., 2016). Schrag et al. (2002) showed that a diagnosis of probable PD was confirmed in 83% of patients with a prior diagnosis. Diagnostic accuracy improves over time, because new aspects in the clinical picture of the condition may give suspicion to alternative neurological disorders. A prospective cohort study on PD incidence by Duncan et al. (2014a) showed that 86% of those who were initially suspected to have PD retained the clinical diagnosis of probable PD 18 months later. In the metaanalysis by Rizzo et al. (2016), the most frequent misdiagnoses among hospital-based studies were multiple system

atrophy, Lewy body dementia, vascular encephalopathy, and progresssive supranuclear palsy.

The most widely used criteria for PD in clinical practice and research have been the UK Parkinson's Disease Society Queen Square Brain Bank (QSBB) criteria that use a three-step process for establishing PD diagnosis (Gibb & Lees, 1988; Lees et al., 2009). First, for the diagnosis of parkinsonian syndrome, bradykinesia in combination with either muscular rigidity, rest tremor or postural instability must be present. Second step is to define whether parkinsonism is actually caused by PD, i.e no exclusion criteria should be present. Finally, for establishing the definite diagnosis of PD, at least three supportive criteria should be met (Table 1).

Table 1. QSBB clinical diagnostic criteria for the diagnosis of PD (Gibb & Lees, 1988; Lees et al., 2009).

Step 1 Diagnosis of parkinsonian syndrome
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions)
And at least one of the following:
• 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
• History of repeated strokes with stepwise progression of parkinsonian features
• History of repeated head injury
• History of definite encephalitis
• Oculogyric crises
• Neuroleptic treatment at onset of symptoms
• More than one affected relative
• Sustained remission
• Strictly unilateral features after 3 years
• Supranuclear gaze palsy
• Cerebellar signs
• Early severe autonomic involvement
• Early severe dementia with disturbances of memory, language, and praxis
• Babinski signs
• Presence of a cerebral tumour or communicating hydrocephalus on CT scan
• Negative response to large doses of levodopa
• MPTP exposure

Table 1. Continuation

Step 3 Supportive prospective positive criteria of PD
Three or more required for diagnosis of definite PD:
• Unilateral onset
• Rest tremor present
• Progressive disorder
• Persistent asymmetry affecting the side onset most
• Excellent response (70–100%) to levodopa
• Severe levodopa-induced chorea
• Levodopa response for 5 years or more
• Clinical course of 10 years or more
• Hyposmia
• Visual hallucination

Abbrevations: PD, Parkinson's disease; QSBB, Queen Square Brain Bank; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

In the light of numerous advances in genetics and pathology, the new clinical diagnostic criteria for PD created by the International Parkinson and Movement Disorder Society (MDS) were published in 2015 (Postuma et al., 2015). In these criteria, core parkinsonian features are bradykinesia, rigidity and rest tremor. Postural instability is not a part of MDS-PD criteria (because when present early, it is suggestable to an alternative diagnosis) (Postuma et al., 2015). Similarly to the QSBB criteria, the second step of the MDS-PD criteria is to define whether parkinsonism is attributable to PD. Finally, for the clinically established diagnosis of PD, absolute exclusion criteria must be absent, at least two supportive criteria met and no red flags present. The non-motor symptoms have been incorporated into these criteria and particularly into the separate criteria for prodromal PD (Berg et al., 2015; Postuma et al., 2015).

2.1.3. Prevalence and incidence

2.1.3.1. Age-adjusted rates

Most population-based studies that combined multiple available sources to identify cases in all ages and examined participants in-person, found the age-adjusted prevalence rates of PD to range from 105 to 218 per 100,000 persons (Hobson, Gallacher, & Meara, 2005; Osaki, Morita, Kuwahara, Miyano, & Doi, 2011; Walker, Hand, Jones, Wood, & Gray, 2010; Wermuth et al., 2008). Age-adjusted prevalence rates obtained from door-to-door type of surveys that screened patients at all ages range from 53 to 202 per 100,000 (Das et al., 2010; Durmus, Gokalp, & Hanagasi, 2015). Studies with an approach to case-ascertainment based on the drug prescription archive or healthcare insurance

databases without in-person examination of participants have yielded to age-adjusted prevalence rates varying from 130 to 511 per 100,000 in surveys where all ages were screened (Blin et al., 2015; Heinzel et al., 2018; Newman, Grosset, & Grosset, 2009). Table 2 and 3 show the reported prevalence rates of PD from worldwide epidemiological studies with different study designs.

Reported age-adjusted incidence rates of PD range mostly from 6 to 36 new cases per 100,000 person-years in various study designs used and all ages accounted (Blin et al., 2015; Caslake et al., 2013; Das et al., 2010; Savica, Grossardt, Bower, Ahlskog, & Rocca, 2016; Van Den Eeden et al., 2003). Studies with case-ascertainment based on healthcare insurance databases or drug prescription archives have yielded to more variable age-adjusted incidence rates when all ages accounted compared to prospective studies with multiple case-finding sources and in-person examination of cases, ranging from 10.5 to 84 (Blin et al., 2015; Heinzel et al., 2018; Morioka et al., 2002; Van Den Eeden et al., 2003) and, 9 to 22.5, respectively (Alves et al., 2009; Duncan et al., 2014a; Linder, Stenlund, & Forsgren, 2010; Winter et al., 2010a). Table 4 and 5 show the reported incidence rates of PD from worldwide epidemiological studies with different study designs.

Table 2. Overview of the selected worldwide PD prevalence studies that used available medical information sources for case-ascertainment (i.e registers and/or records) with or without in-person examination of the cases.

Study reference	Region	Ages (years)	Number of PD cases/ Study population	Crude prevalence rate/ 100,000	Adjusted prevalence rate/ 100,000
*Schrag et al. 2000b**	UK, London	All	156 / 121,608	128	168[a]
*Taba & Asser 2002**	Estonia, Tartu	All	270 / 153,240	176	152[a]
*Hobson et al. 2005**	UK, North Wales	All	112 / 77,388	144	105[a]
*Porter et al. 2006**	UK, North Tyneside	All	161 / 108,597	148	139[a]
*Wermuth et al. 2008**	Denmark, The Faroe Islands	All	100 / 48,371	206.7	218[a]
*Morgante et al. 2008**	Italy, Sicily	≥40	14 / 6494	215.6	151.7[a]
*Alrefai et al. 2009**	Jordan, Irbid Governorate	≥30	102/ 173,450	59	–
Newman et al. 2009	UK, West Scotland	All	610 / 511,927	119.2	129.5[a]
*Walker et al. 2010**	UK, North Northumberland	All	106 / 59,613	178	142[a]
*Yamawaki et al. 2009**	Japan, Yonago	All	254 / 140,911	180.3	166.8[a]
*Osaki et al. 2011**	Japan, Koban district	All	116 / 66,465	175	109[a]
Chillag-Talmor et al. 2011	Israel	20–84	7134 / 1,8 mil	170.8–260.6	334[a]
Bauso et al. 2012	Argentina, Buenos-Aires	All	–	219	–
Blin et al. 2015	France	All	200,273 / 65 mil	–	308[a]
Gordon et al. 2015	USA, Navajo Nation	All	316 / 217,158	146	261[b]
Riedel et al. 2016	Germany	≥65	10,596 / 815,573	1331	1680[a]
Liu et al. 2016	Taiwan	All	41,606 / 23 mil	179.1	147.7[a]
Moisan et al. 2016	France	All	149,672 / 64 mil	230.4	–
Nerius et al. 2017	Germany	≥50	4736–5751 / 491,038	–	797–961[a]
Myall et al. 2017	New Zealand	All	9340 / 4 mil	–	210[a]
Heinzel et al. 2018	Germany	All	27,714 / 82 mil	587.7	511.4[a]

Age-adjustments to: a – corresponding national census; b – US 2000 population;
*Case confirmation in these studies was based on in-person examination of majority of PD cases;
Abbrevations: PD, Parkinson's disease; mil, million.

Table 3. Overview of the selected worldwide door-to-door PD prevalence studies.

Study reference	Region	Ages (years)	Number of PD cases/ Study population	Crude prevalence rate/100,000	Adjusted prevalence rate/ 100,000
Clavería et al. 2002	Spain, Cantalejo	≥40	20 / 1,653	1267	901[a]
Nicoletti et al. 2003	Bolivia, Cordillera Province	≥40	5 / 1780	286	304[b]
Benito-Leon et al. 2003	Spain, Margaritas, Lista, Arévalo	≥65	81 / 5278	1500	–
Bergareche et al. 2004	Spain, Bidasoa	≥65	18 / 1790	1500	–
Chan et al. 2005	Australia, Sidney	≥55	17 / 501	776	–
Racette et al. 2009	USA, Amish community	≥60	15 / 262	5,703	–
Yamawaki et al. 2009	Japan, Daisen	All	21 / 6,849	306.6	192.6[c]
Das et al. 2010	India, Kolkata	All	41 / 100,802	40.7	52.9[b]
El-Tallawy et al. 2013	Egypt, Al Kharga district	≥40	33 / 15,482	213.2	–
Durmus et al. 2015	Turkey, Baskale	All	19 / 26,191	72	202[c]
Khan et al. 2016	Pakistan, Khyber Pakhtunkhwa	≥50	11 / 3715	430	660[d]
Ferreira et al. 2017	Portugal	≥50	12 / 5048	237.7	240[a]

Age-adjustments to: a – European Standard Population; b – World Standard population; c – corresponding national census; d – US 2000 population; Abbrevations: PD, Parkinson's disease.

Table 4. Overview of the selected worldwide longitudinal PD incidence studies with varying duration of follow-up.

Study reference	Region (name of the study)	Case ascertainment	Incidence period	Ages (years)	Number of PD cases/ Person-years at risk or study population	Crude incidence rate/ 100,000 person-years	Adjusted incidence rate/ 100,000 person-years
Chen et al. 2001	Taiwan, Yilan	door-to-door	1993–1997	≥40	15 / 49,830	30.1	10.4[a]
De Lau et al. 2004	The Netherlands, Rotterdam	door-to-door	1990–1999	≥55	67 / 38,422	174.4	–
Foltynie et al. 2004	UK, Cambridgeshire (CamPaIGN)	register and records	2000–2002	All	201 / 708 725	13.6	10.8[b]
Benito-Leon et al. 2004	Spain, Margaritas, Lista, Arévalo (NEDICES)	door-to-door	1994–1998	≥65	30 / 12,710	235.9	186.8[b]
Tan et al. 2007	Singapore (SPEEDS)	register and records	2001–2003	≥50	12 / 31,426	33	32[c]
Alves et al. 2009	Norway (ParkWest)	register and records	2004–2006	All	265 / 1 mil	13.7	12.6[b]
Perez et al. 2010	France, Gironde (PAQUID)	door-to-door	1988–2003	≥65	68 / 25,820	263.0	–
Winter et al., 2010a	Russia, Moscow	register and records	2006–2008	All	308 / 3 mil	10	9[d]
Linder et al. 2010	Sweden, Umeå	register and records	2004–2007	All	112 / 567,800	19.7	22.5[d]
Das et al. 2010	India, Kolkata	door-to-door	2003–2007	All	23 / 100,802	4.6	5.7[e]
Caslake et al. 2013	UK, North East Scotland (PINE)	register and records	2002–2009	All	363 / 1,1 mil	17.9	17.5[d]
Duncan et al. 2014	UK, Newcastle and Gateshead (ICICLE-PD)	register and records	2009–2011	All	155 / 488,576	15.9	12[b]
Darweesh et al. 2016	The Netherlands, Rotterdam	door-to-door	2000–2011	≥55	10 / 22,224	45	–
Evans et al. 2016	UK, Cambridgeshire (PICNICS)	register and records	2008–2010	All	173 / –	13	15.8[d]

Age-adjustments to: a – US 1970 census; b – European Standard population; c – US 1990 census; d – national census of the corresponding country;
In-person examination for the verification of diagnosis was used in all studies, except in the study by Tan et al. (2007);
Comparative studies in the same geographical area using similar case-ascertainment methods were conducted in Rotterdam and Cambridgeshire;
Abbrevations: PD, Parkinson's disease; mil, million.

Table 5. Overview of the selected worldwide record and/or register-based PD incidence studies with or without in-person examination.

Study reference	Country	Incidence period	Ages (years)	Number of PD cases/ Person-years at risk or study population	Crude incidence rate/ 100,000 person-years	Adjusted incidence rate/100,000 person-years
Morioka et al. 2000	Japan, Wakayama	1997	All	229 / 1 mil	16.9	10.5[a]
Van Den Eeden et al. 2003	USA, Northern California	1994–1995	All	588 / 4,7 mil	12.3	13.4[b]
Leentjens et al. 2003	The Netherlands	1990–2000	All	139 / –	22.4	–
Taba & Asser 2003	Estonia, Tartu	1990–1998	All	264 / 156,417	18.8	16.8[a]
Yamawaki et al. 2009	Japan, Yonago	2000–2004	All	34 / 140,911	18.4	10.3[a]
Hristova et al. 2010	Bulgaria, Plovdiv	2002–2004	≥40	244 / 2 mil	11.4	11.7[a]
Chillag-Talmor et al. 2011	Israel	2000–2007	20–84	5288 / 1.8 mil	33	45[a]
Jones et al. 2012	Canada, British Colombia	1992–2001	≥65	10,910 / 6 mil	252	–
Bauso et al. 2012	Argentina, Buenos-Aires	2003–2008	All	239 / 754,082	31.2	13.7[a]
Horsfall et al. 2013	UK	1999–2009	≥50	9051 / 10,8 mil	84	–
Blin et al. 2015	France	2005–2010	All	138 174 / 384 mil	–	36[a]
Gordon et al. 2015	USA, Navajo Nation	2001–2011	All	524 / 2,3 mil	22.5	35.9[c]
Liu et al. 2016	Taiwan	2011	All	8031 / –	34.7	28.8[a]
Moisan et al. 2016	France	2010	All	25,438 / 64 mil	39.3	–
Savica et al. 2016	USA, Minnesota	1976–2005	All	464 / 3,3 mil	14	17.2[b]
Nerius et al. 2017	Germany	2004–2010	≥50	3994 / 1,4 mil	270.2	222.8[a]
Myall et al. 2017	New Zealand	2006–2013	All	10,095 / 24 mil	–	31[a]
Heinzel et al. 2018	Germany	2015	All	3541 / 3,7 mil	95.8	84.1[a]
Valent et al. 2018	Italy, Friuli Venezia Giulia	2016	All	341 / 1,2 mil	28	–

Age-adjustments to: a – national census of the corresponding country; b – US 1990 census; c – US 2000 census;
Sources to identify incident cases were based both on medical records and registries and confirmed by in-person examination in studies by Taba & Asser (2003), Hristova et al. (2010) and Yamawaki et al. (2009), other studies were conducted without in-person examination.
Abbrevations: PD, Parkinson's disease; mil, million.

2.1.3.2. Age-specific rates

A recent meta-analysis of the worldwide data revealed a sharply rising prevalence of PD with the increasing age: 41 per 100,000 in individuals 40 to 49 years old, reaching as high as 1903 per 100,000 in individuals over age 80 (Pringsheim et al., 2014). There are inconclusive findings whether the frequency of PD increases along with the advancing age till the very end of life or not. Some population-based prevalence studies have found that the highest age-specific prevalence rates are among the oldest groups studied, i.e over 85 or 95 years old (Newman et al. 2009; Blin et al. 2014), others suggest that the disease frequency peaks in the age-group of 80–84 years old and declines thereafter (Walker et al., 2010; Wermuth et al., 2008). It has been suggested that the decline in the age-specific prevalence rates in the oldest old is likely an artifact caused by decreased diagnostic uncertainty due to comorbid disorders, diagnostic denial, and selective loss to follow-up (de Rijk et al., 2000).

Similarly to the meta-analysis of the prevalence, the worldwide data on the PD incidence revealed a sharply rising occurence of PD with the increasing age with the peak in those older than 80 years for both men and women (Hirsch et al. 2016). Recent meta-analysis on the age-specific incidence rates found that these peaked in age-group of 70–79 (Macleod et al., 2018). Several population-based studies have reported that incidence of PD declines sharply after the age of 80 years or over (Duncan et al., 2014a; Hristova et al., 2010; Linder et al., 2010). On the contrary, many other studies have demonstrated that incidence rates continued to rise in the oldest old people (Bauso et al., 2012; Caslake et al., 2013; Savica et al., 2016; Van Den Eeden et al., 2003). It has been proposed that mostly diagnostic uncertainty and difficulties with case-finding in the elderly people may be responsible for the underestimation of rates of the oldest old people in epidemiological and research studies of PD (Macleod et al., 2018).

2.1.3.3. Repeat incidence studies and timetrends

There have only been a few repeated epidemiological studies of PD prevalence in the same geographical area over different time periods showing a modestly increasing frequency of the disease (Kuopio et al. 1999a; Wermuth et al. 2008; Yamawaki et al. 2009). Prevalence estimates based on studies that report the dynamics for several consecutive years have mostly shown an upward trend of the disease frequency (Chillag-Talmor et al., 2011; Liu et al., 2016; Myall et al., 2017). This observation of an increasing frequency of PD is most likely related to the shifts in the demographical situation, i.e aging of populations and lengthened survival.

Few studies on the time trends in incidence of PD have found no change or reduced incidence rate of overall PD (Chillag-Talmor et al., 2011; Darweesh et al., 2016; Horsfall et al., 2013; Liu et al., 2016; Myall et al., 2017). Some researchers have shown the trend of increasing incidence of PD particularly among men but not in women (Savica et al. 2016; Kuopio et al. 1999a). Three

record-based epidemiological studies using the same case-finding methodology and diagnostic criteria in Yonago, Japan in 1980, in 1992, an in 2004, have shown quite a large increase in overall crude incidence rates (rising from 10.2 to 18.2 per 100,000), but no changes in adjusted incidence rates (10.3 per 100,000 in 2004 and similar rates for two earlier studies) (Harada et al. 1983; Kusumi et al. 1996; Yamawaki et al. 2009). Another repeat incidence study in Cambridgehire, UK, conducted in years 2000–2002 and 2008–2010, found no significant differences in age-adjusted incidence rates, being around 13 per 100,000 person-years (Evans et al., 2016; Foltynie et al., 2004).

2.1.3.4. Influence of gender

In a meta-analysis on PD prevalence conducted by Pringsheim et al. (2014) that included 47 door-to-door or population-based studies, a significant difference in age-specific prevalence rates dominating in men was found only for individuals 50 to 59 years old. Males have been related to higher age-adjusted prevalence rates in majority of studies (Kuopio et al. 1999a; Ferreira et al. 2017; Blin et al. 2014; Newman et al. 2009; Nerius et al. 2017; Riedel et al. 2016). Other studies have not observed a statistically significant difference between gender and adjusted PD prevalence rates or have reported higher rates for women (Das et al. 2010; Osaki et al. 2011; Taba & Asser 2002; Walker et al. 2010; de Rijk et al. 1997; Yamawaki et al. 2009).

Higher age-adjusted incidence of PD in men than in women has been found in numerous surveys (Hristova et al. 2010; Alves et al. 2009; Caslake et al. 2013; Moisan et al. 2016; Savica et al. 2016). Meta-analysis of PD incidence studies conducted worldwide from 2001 to 2014 reported an annual crude incidence rate of PD in females 40 years and older, 38 per 100,000 person-years, and 61 in males 40 years and older (Hirsch et al., 2016). One recent meta-analysis of 22 incident studies found the overall pooled male-to-female incidence ratio to be 1.57 (Moisan et al., 2016). However, no significant gender differences in PD incidence have been observed in several other studies (Chen et al., 2001; Das et al., 2010; Linder et al., 2010; Morioka et al., 2000; Taba & Asser, 2003; Tan et al., 2007). Taken together, the effect of gender on PD remains an unresolved issue, however, many possible gender-related risk factors that shift males to be more predisposed to PD have been proposed (Gillies, Pienaar, Vohra, & Qamhawi, 2014).

2.1.3.5. Influence of geographical region and race/ethnicity

With regard to the geographical distribution, notable continental differences in the frequency and occurrence of PD arise. Door-to-door studies from 1985 to 2010 in the Republic of China that enrolled subjects aged 55 years or more, found the age-adjusted prevalence rate to range from 17−177 per 100,000 (Zou, Liu, Tian, Lu, & Zhou, 2015). African studies conducted in the mid-1980s and mid-1990s that used different study designs and screened subjects in variable

ages, found the crude prevalence in range of 10 to 43 per 100,000 (Okubadejo, Bower, Rocca, & Maraganore, 2006). Crude prevalence rate estimates in Europe based on studies of various designs and age-groups enrolled ranged from 65.6 per 100,000 to 12,500 per 100,000 (von Campenhausen et al. 2005). More recent systemic review on the prevalence of PD reported that the crude prevalence rate of PD in Europe, North-America and Australia range from 113/100,000 in persons aged 50 to 59 up to 2953 per 100,000 in persons aged 80 years and more. For comparison, the same rates for South America and Asia were 228 up to 6096 and 88 up to 1418, respectively (Pringsheim et al., 2014).

Age-adjusted incidence estimates in Europe varied from 9 to 84 new cases per 100 000 person-years when all ages accounted and different study types used (Alves et al., 2009; Blin et al., 2015; Caslake et al., 2013; Heinzel et al., 2018; Hristova et al., 2010; Linder et al., 2010; Moisan et al., 2016; Myall et al., 2017; Winter et al., 2010a). In North-America, age-adjusted incidence rates ranged from 238 to 446 per 100,000 person-years among people aged 65 or more (Gordon et al., 2015; Jones et al., 2012; Willis, Evanoff, Lian, Criswell, & Racette, 2010). In Asian countries, the age-adjusted incidence rate for people at all ages ranged from 5.7 to 17 per 100,000 person-years (Das et al. 2010; Morioka et al. 2000). Taken together, prevalence and incidence of PD appear to be higher in western than in eastern countries referring to possible role of environmental exposures and genetic predisposition, however, different methodological approaches may hamper the comparison of studies (Abbas et al., 2018; Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011).

In terms of race and ethnicity, a significant ethnic diversity in the prevalence and incidence of PD was found in an epidemiologic study of PD among people aged 65 years and more living in USA. When compared to the Whites, the ratios of crude prevalence and incidence rates were 0.58 and 0.69 for Asians and 0.62 and 0.74 for Blacks, respectively (Willis et al., 2010). Another population-based study screening PD incident cases at all ages in USA found that the age- and gender-adjusted incidence rates were highest among Hispanics, followed by non-Hispanic Whites, Asians, and Blacks (Van Den Eeden et al., 2003). Across the major ethnic groups within the New Zealand, Europeans were found to have the highest age-adjusted incidence rate of 33 per 100,000 person-years, followed by Asian, 28, Pasifika, 27, and Māori groups, 20, respectively (Pitcher et al., 2018). High frequency of PD has been found to be in Israel with the adjusted prevalence and incidence rates of 334 per 100,000 and 45 per 100,000, respectively, a phenomenon that is likely to be related to the specific genetic backround (Chillag-Talmor et al., 2011). One of the highest frequences of PD has been found in an Amish community in USA where the crude prevalence rate was reported to be 5,703 per 100,000 in persons aged 60 years or more (Racette et al., 2009).

2.1.4. Mortality and comorbidity

Majority of studies with varying methodological approaches and disease duration have found that PD patients have a significantly higher overall mortality risk than persons without PD, with standardized mortality ratio ranging from 0.5 to 3.8 (Hely, Reid, Adena, Halliday, & Morris, 2008; Pinter et al. 2015; Hobson & Meara 2018; de Lau et al. 2014; Morgan et al. 2014; Das et al., 2010). One recent meta-analysis reported the overall pooled standardized mortality ratio to be 1.52 (Macleod et al., 2014). Several reports have shown that there is no excess of mortality in the first ten years of the disease (Williams-Gray et al. 2013; Zhang et al. 2018). PD patients with dementia have shown to have a particularly higher risk of mortality (Herlofson et al. 2004; Lau et al. 2014; Posada et al. 2011; Pinter et al. 2015). Other risk factors of mortality have been found to be higher age, male sex, PIGD, and the presence of psychotic symptoms (de Lau et al., 2014; Williams-Gray et al., 2013; Zhang et al., 2018). No significant gender differences in standardized mortality ratios of PD males and PD females have been found by two of the longest follow-up cohort studies (Hely et al., 2008; Pinter et al., 2015). Some studies have reported that female PD patients had a greater reduction in lifespan compared to male PD patients (Morgan et al., 2014) and that survival rates of men were closer to that of women in patients with PD than in persons without PD (Chen et al., 2001).

Most of the information on causes of death comes from death certificates. It has been identified by many studies that PD is often underrepresented on death certificates, mentioned as a primary or underlying cause of death in 15 to 60% among those who had the clinical diagnosis while alive (Benito-León et al., 2014; Goldacre, Duncan, Griffith, & Turner, 2010; Hobson & Meara, 2018; Moscovich et al., 2017; Williams-Gray et al., 2013). The leading underlying causes of death among PD patients are pneumonia, cerebrovascular and cardiovascular diseases (Williams-Gray et al. 2013; Allyson Jones et al. 2012; Moscovich et al. 2017; Pinter et al. 2015; Hely et al. 2005; Das et al. 2010). There is evidence from cohort studies that cancer in PD patients is less commonly represented on death certificates than in persons without PD (Benito-León et al. 2014; Hobson & Meara 2018; Allyson-Jones et al. 2012), although not shown by some other studies (Pinter et al. 2015). Some tumours, particularly melanoma, are found to be more common in patients with PD compared to the general population (Ferreira et al., 2010).

Studies investigating the burden of comorbidities among PD patients compared to the general population have yielded to inconsistent results. Several longitudinal cohort studies have found that PD patients have a higher frequency of comorbidities and total load of polypharmacy compared to healthy controls (García et al., 2017; McLean, Hindle, Guthrie, & Mercer, 2017). On the contrary, no differences between the overall load of comorbidities was evidenced in a cohort study of incident PD patients (Macleod, Goddard, & Counsell, 2016). Recent record-based cohort study in Germany found that PD patients

have a significantly higher prevalence of diabetes and hypertension compared to controls (Heinzel et al., 2018).

2.1.5. Risk factors

No exact molecular mechanism of the neurodegeneration has yet been identified but oxidation of dopamine, mitochondrial dysfunction, endoplasmic reticulum stress, impaired autophagy, and dysregulation of immunity are widely accepted as the main contributive factors involved in the death of dopaminergic neurons in the *Substantia nigra* (Blennow, Biscetti, Eusebi, & Parnetti, 2016; Zeng, Geng, Jia, Chen, & Zhang, 2018). Although majority of PD cases are sporadic, monogenetic forms with a high penetrance account for approximately 5–10% of all cases and these have contributed to our understanding of the pathogenesis of the disease (Poewe et al. 2017; Mullin & Schapira 2015). Several single genes have been identified that are confirmed to cause PD of classic Mendelian inheritance. Genes encoding α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2) and vacuolar protein sorting 35 (VPS35) are linked with the autosomal dominant hereditary PD (Mullin & Schapira, 2015). LRRK2 is the most commonly mutated gene in PD that is associated with less severe disease, slower rate of progression and less frequent presence of cognitive decline and anosmia than idiopathic PD (Healy et al. 2008). The highest frequency of LRRK2 mutations (both hereditary and sporadic cases) has been found in north African Arabs and Ashkenazi Jews (Healy et al., 2008). Other genes, particularly Parkin-gene, PINK-1-gene, DJ-1 and ATP13A2-gene are associated with the autosomal recessive hereditary pattern of the disease (Mullin & Schapira, 2015).

Beyond the monogenic PD cases, whole-genome association studies have identified a growing number of disease-predisposing genes (Lill et al., 2012). So far, at least 24 loci with polymorphisms within certain genes that may influence the risk for the disease occurrence have been identified (Redenšek, Trošt, & Dolžan, 2017). These are relatively common mutations with lower or variable penetrance compared to monogenic PD forms accounting for up to 30% of PD cases (Mullin & Schapira, 2015). There is some overlap between genes associated with familial and sporadic disease; in particular, SNCA and LRRK2 are involved in both forms (Borrageiro et al. 2018; Redenšek et al. 2017). One of the greatest genetic risk factors for the development of PD are heterozygous mutations in gene encoding the lysosomal enzyme glucocerebrosidase (GBA). Single GBA mutation increases the risk for the development of PD by approximately 5-fold (Sidransky et al. 2009). GBA-associated PD is linked to the higher likelihood of earlier disease onset, higher incidence of cognitive decline, more rapid progression and reduced survival (Brockmann et al., 2015; Sidransky et al., 2009). GBA mutations are particularly high among the Ashkenazi Jewish, being present in 15% of PD patients of this ethnoreligious nation (Sidransky et al., 2009). Mendelian and identified high-risk loci

explain altogether between approximately 10% and 40% of PD risk in most populations assessed (Hardy, 2010).

Beyond the inherited forms of PD, risk of developing sporadic PD is with great probability multifactorial, resulting from complicated interaction between environmental, genetic and epigenetic factors affecting numerous fundamental cellular processes (Kalia & Lang, 2015; Lees et al., 2009). One of the strongest risk factors for the development of PD is increasing age (Poewe et al., 2017). Disease onset is relatively infrequent under the age of 55, only approximately in 4–10% of all cases in the population-based studies conducted in the Eastern Europe (Hristova et al., 2010; Taba & Asser, 2003; Winter et al., 2010a).

No environmental risk factor with a convincing pathogenic role in the disease has yet been described (Hardy, 2010). However, epidemiological studies have provided evidence that the incidence of PD is significantly greater in individuals exposed to certain environmental factors. Living in rural area has been found to be a risk factor for PD in some studies (Kuopio et al. 1999a; Kab et al. 2017), but not supported by other surveys (Hristova et al., 2010; Taba & Asser, 2003). A nested case-control study by Tanner et al. (2011) supported the role of pesticides in PD pathophysiology; these environmental factors have long been linked with the disease's etiology. Exposure to pesticides, consumption of dairy products, history of melanoma, and traumatic brain injury were found to be associated with the increased PD risk in a recent review (Ascherio & Schwarzschild, 2016). Numerous potential protective factors of PD have been proposed, among them, cigarette smoking and coffee drinking most frequently shown to be inversely related to PD (Ascherio & Schwarzschild, 2016; Martino et al., 2017; Noyce et al., 2012). Rossi et al. (2018) have suggested that there will be an increase of additional 10% of PD cases by the year 2040, when the prevalence of non-smoking is accounted. Also higher serum urate concentrations, physical activity, and use of ibuprofen have been linked with the reduced risk of PD (Ascherio & Schwarzschild, 2016).

2.2. Clinical presentation of the disease

PD is a progressive neurodegenerative disorder characterized by the presence of motor and non-motor features. There are four cardinal parkinsonian features including bradykinesia, rest tremor and rigidity, as well as postural instability that is more characteristic to the later course of the disease (Jankovic, 2008; Lees et al., 2009). The wide range of non-motor problems encompass sensory features (i.e olfactory deficits, visual disturbances, pain and somatosensory disturbances), neuropsychiatric symptoms (i.e anxiety, depression, apathy and fatigue, cognitive deficits, dementia and psychoses), sleep disorders and autonomic dysfunction (i.e bladder and gastrointestinal dysfunction and cardiovascular features) (Schapira et al., 2017).

Population-based incidence studies indicate that the mean age of onset of motor symptoms is most commonly in the range of 65 to 77 years (Kuopio et al. 1999a; Hristova et al. 2010; Caslake et al. 2013; Nerius et al. 2017). Early motor features can be subtle, worsen gradually and patients may first come to medical attention some time after the occurrence of first symptoms (Lees et al., 2009). Mean time from onset of motor symptoms to the diagnosis of PD has been reported to vary from 1.4 to 2.2 years (Hristova et al., 2010; Linder et al., 2010; Taba & Asser, 2003). The most frequent initial classical symptom of PD appears to be tremor, reported in 55 to 72% of all incident cases (Caslake et al., 2013; Linder et al., 2010; Taba & Asser, 2003; Winter et al., 2010a).

It is currently well accepted that pathological changes of PD begin earlier than classical motor signs appear, giving rise to a number of non-motor symptoms (Gaig & Tolosa, 2009). The so-called prodromal phase of PD, is characterized by the presence of specific non-motor symptoms, particularly olfactory deficit, REM sleep behaviour disorder, constipation, depression and excessive daytime sleepiness, that may manifest years or even decades before the onset of classical motor symptoms (Claassen et al., 2010; Gaenslen et al., 2014; Ross, Abbott, Petrovitch, Tanner, & White, 2012).

Cross-sectional data on PD patients using different instruments to measure individual non-motor symptoms suggest that at least one non-motor symptom is present in almost all PD patients, with the mean number of 8–11 features in each patient (Kovács et al. 2016; Gallagher et al. 2010; Martinez-Martin, Rodriguez-Blazquez, Kurtis & Chaudhuri 2011a). The most common non-motor symptoms assessed with the Non-Motor Symptoms Questionnaire (NMSQuest) among patients with the mean duration of disese about 8 years have been reported to be nocturia (65%), urgency (60%), memory difficulties (51%), low mood (49%), constipation (48%), taste/olfactory deficit (43%) and dribbling saliva (42%) (Chaudhuri et al. 2010). Female PD patients may experience more severe depressive and anxiety symptoms, pain, and orthostatic problems compared to men (Kovács et al., 2016). On the contrary, men have been found to experience more frequently sexual problems, sialorrhoea and excessive daytime sleepiness (Martinez-Martin et al. 2012).

2.2.1. Clinical subtypes

Clinical picture and rate of progression of PD are highly heterogenous indicating to the underlying biological or pathophysiological differences between individuals (Marras & Lang, 2013). Several different subtype classification systems have been introduced with an attempt to classify patients according to age-at-onset categories, major motor phenotypes, patterns of cognitive impairment, and other non-motor symptoms (Marras & Chaudhuri, 2016). Among the PD clinical subtypes based on the most prominent motor feature, common categorizations divide the phenotype into tremor-dominant versus PIGD or tremor-dominant and akinetic-rigid/PIGD and mixed phenotypes (Alves,

Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Jankovic et al., 1990; Stebbins et al., 2013; Thenganatt & Jankovic, 2014). In general, patients with the PIGD type of PD tend to have higher risk for dementia and mortality; while patients with tremor-dominant phenotype have a more benign course and slower rate of cognitive decline (Reijnders et al. 2009; Alves et al. 2006; Anang et al. 2014). It has been proposed that different motor subtypes of PD may not represent different biological entities, but rather different stages of disease (Nutt 2016). Alves et al. (2006) found that 44% of patients with tremor-dominant phenotype at baseline had converted to PIGD after a follow-up of 8 years. With regard to the classification by age of onset, patients with younger age at onset may have a slower disease progression, an increased rate of dystonia at onset or during treatment, lower rate of dementia, and an increased rate of dyskinesias in response to levodopa treatment (Wickremaratchi, Ben-Shlomo, & Morris, 2009).

2.2.2. Progression of the disease

Progression of PD is characterized by worsening disability due to an increase in severity of motor symptoms and with the occurrence of levodopa-induced motor complications, as well as due to an increase in the burden of non-motor symptoms (Coelho & Ferreira, 2012). As regards motor symptoms, the progression of PD appears to have a faster rate of motor deterioration in the earlier stage and the decreasing rate of progression in more advanced stage of disease, whereas the disability continues to deteriorate along with the entire duration of disease (Schrag et al., 2007). Prognostic factors for faster motor impairment have been found to be male gender, and cognitive dysfunction present at newly diagnosed patients (Velseboer et al., 2013). The median increase of the Unified Parkinson Disease Rating Scale (UPDRS) part III (Fahn, Elton, & UPDRS Program Members, 1987) over the follow-up of 2 years has been reported to be 4 points in patients with the mean disease duration of 5.8 years at baseline PD (Prakash et al., 2016). One of the largest, multi-center, international, cross-sectional study of the 3206 PD patients (the Quality of Life in Parkinson's disease [QUALPD] study cohort) showed that all the subcores of Parts I–IV of the Movement Disorder Society (MDS)-revision of the UPDRS (MDS-UPDRS) (Goetz et al., 2008) increased significantly with 5-year increments of duration only in the first 15 years of disease (Skorvanek et al., 2017). The same study also revealed that all the subscores of MDS-UPDRS Parts I–IV increase along with the progression of Hoehn and Yahr (HY) stages (Hoehn & Yahr, 1967) through I to V.

Longitudinal data suggests that the overall burden of non-motor symptoms increases significantly over time (Antonini et al., 2012; Erro et al., 2016; Müller et al., 2013). In contrary, another prospective study enrolling newly diagnosed PD patients (n=227) found the total burden of non-motor symptoms to be slightly decreased over the follow-up of 2 years (Prakash et al., 2016). By

individual symptoms, sleep and autonomic problems, cognitive impairment and skin disturbances became more prevalent along with the duration of disease in another prospective study with 707 prevalent cases followed for 2 years (Antonini et al., 2012). Erro and co-workers (2016) found that swallowing difficulties, nausea/vomiting, nocturia, hallucinations, sex drive, dizziness, daytime sleepiness and restless leg syndrome were the non-motor symptoms that had the highest increase after 4 years since diagnosis.

Surveys such as that conducted by Williams-Gray et al. (2013) and Hely et al. (2008) have shown that dementia is present in about 50% of patients after 10 years, and in 83% of patients after 20 years from disease onset, respectively. Motor and non-motor fluctuations, mild dementia, hallucinations, repeated falls, and difficulty with activities of daily living are indicators to the stage of advanced PD (Antonini, Moro, Godeiro, & Reichmann, 2018). Late-stage PD is defined as a phase of the disease where patients are highly dependent on caregivers for activities of daily living, owing to motor symptoms or non-motor symptoms that are resistant to levodopa (Coelho & Ferreira, 2012). In a clinico-pathological study, visual hallucinations preceded death by about 5 years, regular falls by 4.1 years, dementia by 3.3 years, and need for residential care by 3.3 years stage (Kempster, O'Sullivan, Holton, Revesz, & Lees, 2010).

2.3. Treatment

Currently available PD pharmacotherapy is only symptomatic, it does not prevent, delay, halt neither slow the progression of the disease (Charvin et al., 2018; Lang & Espay, 2018). Although there is no general consensus when to initiate the therapy, the widespread recommended strategy is to start PD treatment as early as possible because this is likely to relief motor features, improve the quality of life and maintain the productivity of affected patients (Löhle, Ramberg, Reichmann, & Schapira, 2014). One earlier longitudinal study over 18 months showed that the HRQoL was lower in those patients who were left untreated (n=114) compared to those (n=74) who had started antiparkinsonian treatment soon after the diagnosis was established (Grosset et al., 2007).

The Movement Disorder Society Evidence-Based Medicine Committe recommends oral levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors, amantadine and anticholinergics as a monotherapy or as an adjunct therapy to levodopa for reducing motor symptoms in early or stable PD patients (Fox et al., 2018). Specific drug choice class for the initial treatment depends on characteristics of patients (age, mental status, occupation, comorbidities), disease severity and efficacy, safety and side-effects of each drug (Stocchi, Vacca, & Radicati, 2015).

2.3.1. Levodopa induced complications

Levodopa, the first drug introduced specifically for PD in the 1960s (Lees, Tolosa, & Olanow, 2015), is the most effective and most frequently prescribed antiparkinsonian medication. As the disease progresses, levodopa becomes less effective, higher doses are needed to manage the motor symptoms, and eventually, levodopa treatment-related motor and non-motor complications (i.e. motor and non-motor fluctuations and dyskinesias) emerge in majority of patients (Chaudhuri et al., 2018).

In the early phases of PD, oral dopaminergic therapies are usually effective, but when the disease progresses these conventional oral treatments no longer ameliorate the symptoms, including levodopa induced fluctuations and dyskinesias (Odin et al., 2015). Advanced PD is also characterized by an increasing burden of non-motor (e.g. cognitive impairment, orthostatic hypotension) and axial symptoms (e.g. freezing, postural instability, falls, dysarthria, dysphagia), features that are known to respond poorly to dopaminergic drugs, therefore complicating even more the management of those patients (Antonini et al., 2018).

To postpone the onset of motor complications, a levodopa-sparing initial therapy is justified for young patients (<60 years), as well as for those with mild symptoms or when tremor is the most prominent symptom (Connolly & Lang, 2014). A longitudinal study by Lopez et al. (2010) reported that all PD patients needed levodopa within 5 years since diagnosis and the frequency of motor complications by the 10^{th} year since diagnosis was similar among those whose initial treatment was levodopa compared to those who received another drug. Furthermore, no long-term benefit of a levodopa sparing initial therapy was evidenced in controlled trials comparing levodopa and bromocriptine (Katzenschlager et al., 2008) and dopamine agonists or MAO-B inhibitors and levodopa alone (PD MED Collaborative Group, 2014). An earlier guideline for therapeutic management of PD concluded that controlled-release levodopa does not delay motor complications compared with standard levodopa (Ferreira et al., 2013).

The main risk factors for the development of motor complications are higher cumulative dose and longer treatment duration of levodopa and longer disease duration (Hauser et al., 2006; Olanow et al., 2013; Scott, Macleod, & Counsell, 2016). It is recommended to use low doses of levodopa that provides satisfactory clinical control but postpones levodopa-induced complications (Olanow et al., 2013). Female gender (Bjornestad et al., 2016; García-Ruiz, del Val, Fernández, & Herranz, 2012; Olanow et al., 2013; Scott et al., 2016), and younger age at onset (Bjornestad et al., 2016; García-Ruiz et al., 2012; Hashim et al., 2014; Olanow et al., 2013) are among other variables that potentially increase the risk for earlier occurrence of motor complications.

2.3.1.1. Motor fluctuations

Motor fluctuations are alterations of clinical state with a good motor response to medication ("on") and clinical state with no response to medication and worsening of motor symptoms ("off") (Aquino & Fox, 2015). Classification of motor fluctuations by clinical pattern includes wearing-off, delayed on, dose-failures and random on-off (Chaudhuri et al., 2018). Most common subtype of motor fluctuation is a wearing-off phenomenon being present in about 80% of those with motor fluctuations (Chapuis, Ouchchane, Metz, Gerbaud, & Durif, 2005; Hely et al., 2005).

Cross-sectional studies involving PD patients with variable duration of disease have found the frequency of motor fluctuations in a range of 22% to 75% (Chapuis et al., 2005; Hechtner et al., 2014; Kum et al., 2009; Larsen, Karlsen, & Tandberg, 2000; Perez-Lloret et al., 2017). Prospective studies have reported the prevalence of motor fluctuations to range from 21% to 50% after 5 years (Bjornestad et al., 2016; Kumar, Van Gerpen, Bower, & Ahlskog, 2005; López et al., 2010; Scott et al., 2016), 95% after 10 years (López et al., 2010), and 100% of patients after 20 years from diagnosis (Hely et al., 2008). The prevalence of motor fluctuations across different studies is illustrated in Table 6.

For advanced PD patients with motor fluctuations, the evidence-based review recommends to use dopamine agonists including apomorphine, levodopa, catechol-O-methyltransferase (COMT) inhibitors, and MAO-B inhibitors (Fox et al., 2018). If motor complications are not satisfactorily controlled by orally delivered agents, device-aided therapies (levodopa/carbidopa intestinal gel infusion, apomorphine infusion, and deep brain stimulation) are recommended (Antonini et al., 2018).

2.3.1.2. Dyskinesias

Dyskinesias are abnormal hyperkinetic movements, usually affecting head, neck, trunk, and limbs, most typically presenting as peak-dose or biphasic. Off-period dystonia is another type of dyskinesia that frequently involves the foot and leg; it is often painful and usually starts at night or early in the morning (Aquino & Fox, 2015; Vijayakumar & Jankovic, 2016).

Based on cross-sectional studies, the frequency of dyskinesias ranges from 10% to 77% (Chen et al., 2014; Kum et al., 2009; Perez-Lloret et al., 2017; Schrag & Quinn, 2000a). Similar to motor fluctuations, prospective studies have consistently shown an association between dyskinesias and disease duration, occurring in 13% to 28% of patients by the 5th year (Bjornestad et al., 2016; Scott et al., 2016), in 71% by the 10th year (López et al., 2010), in 94% by the 15th year (Hely et al., 2005), and in 100% by the 20th year (Hely et al., 2008). The prevalence of dyskinesias across different studies is illustrated in Table 6.

When dyskinesias are severe, antidyskinetic agents such as amantadine or clozapine as oral forms of medications are recommended to be used. Among surgical interventions used to treat dyskinesias, intestinal infusion of levodopa

and deep brain stimulation and pallidotomy have also proven to be clinically useful and to have acceptable safety properties (Fox et al., 2018).

2.3.1.3. Non-motor fluctuations

Long-term dopaminergic therapy may complicate not only with the fluctuations of motor symptoms but also with a range of non-motor symptoms classified into neuropsychiatric, autonomic and sensory features (Chaudhuri et al. 2018). Cross-sectional studies using different assessment methods have reported the prevalence of non-motor fluctuations to range from 14% to 40% of patients, with higher rates in women (Altavista et al., 2015; Brun et al., 2014; Picillo et al., 2016). Anxiety, mood changes, pain and cloudy mind have been the most frequently reported non-motor features that fluctuate (Altavista et al., 2015; Picillo et al., 2016; Stocchi et al., 2014).

Presence of motor fluctuations has been found to be the predictor for the development of non-motor fluctuations and they may develop on average of 10 years after disease onset (Brun et al., 2014). Other factors reported to be associated with the risk of emergence of non-motor fluctuations include female gender, younger age at disease onset, longer duration of levodopa and severity of the disease (Altavista et al., 2015; Picillo et al., 2016). Management is similar to the treatment of motor-fluctuations including device-aided continuous dopaminergic treatments (Martinez-Fernandez et al., 2016).

Table 6. Overview of the selected worldwide non-interventional PD studies showing the prevalence of motor complications.

Study reference	Region	Study design	PD sample (n)	Disease duration (years)	Levodopa treatment duration (years)	Daily dose of levodopa (mg)	Motor fluctuations (%)	Dyskinesias (%)
Larsen et al. 2000	Norway	community-based, cross-sectional	240	8.1–12.3	5.3–9.7	449–668	22	–
Schrag & Quinn 2000a	UK	community-based, cross-sectional	87	6.8	5.2	423	40	28
Chapuis et al. 2005	France	hospital-based, single centre, cross-sectional	143	9.1	7.7	771	66	57
Kumar et al. 2005	USA, Minnesota	population-based retrospective cohort	91	–	5	–	–	29
Benbir et al. 2006	Turkey	hospital-based, single centre, cross-sectional	555	4.8–9.7	3.0–8.0	330–511	46 (wearing off)	30
Müller et al. 2007	International	hospital-based, multi-centre, cross-sectional	1900	8.9	–	531–634	–	34
Hely et al. 2008	Australia	hospital-based, multi-centre, prospective cohort	30	20	20	729	100	100
Kum et al. 2009	Hong Kong	register-based, single centre, cross-sectional	98	7.4	5.2	454	75	78
López et al. 2010	Spain	hospital-based, single centre, prospective cohort	38	10	–	550	95	71
Yoritaka et al. 2013	Japan	hospital-based, single centre, cross-sectional	1453	9.7	–	548	45 (wearing off)	27

Table 6. Continuation

Study reference	Region	Study design	PD sample (n)	Disease duration (years)	Levodopa treatment duration (years)	Daily dose of levodopa (mg)	Motor fluctuations (%)	Dyskinesias (%)
Hechtner et al. 2014	5 European countries	hospital-based, multi-centre, cross-sectional	817	3.3	–	–	25	6–15
Hashim et al. 2014	Malaysia	hospital-based, single centre, cross-sectional	95	6.0	3.0	500	50	44
Stocchi et al. 2014	Italy (DEEP)	hospital-based, multi-centre, cross-sectional	617	8.0	3.6	420	57–67 (wearing off)	–
Cilia et al. 2014	Ghana	hospital-based, multi-centre, cross-sectional	91	5.0	1.0	365	56	14
Chen et al. 2014	China	hospital-based, multi-centre, cross-sectional	1558	5.4	4.1	413	47 (wearing off)	10
Scott et al. 2016	UK (PINE)	community-based, prospective cohort	183	5.0	–	–	21	28
Altavista et al. 2015	Italy (WORK-PD)	hospital-based, multi-centre, cross-sectional	532	7.0	4.0	–	69 (wearing off)	–
Bjornestad et al. 2016	Norway (PARKWEST)	population-based, prospective cohort	158	5	–	587*	31	13
Nicoletti et al. 2016	Italy (FRAGAMP)	hospital-based, multi-centre, cross-sectional	485	6.6–8.1	4.4–5.7	475–570*	–	26
Perez-Lloret et al. 2017	France (COPARK)	hospital-based, multi-centre, cross-sectional	681	4.2−10.5	–	327–841	35	27

* here presented levodopa equivalent daily dose instead of levodopa daily dose;
Abbrevations: PD, Parkinson's disease; n, number; mg, milligram.

2.4. Health-related quality of life

World Health Organization **(**WHO) defines quality of life as an individual's pereception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (Whoqol Group, 1995). HRQoL is a more narrower concept characterized by domains related to physical, mental, emotional, and social functioning, and focuses on the impact health status has on quality of life (Martinez-Martin, 1998). It has been well documented that PD patients have a significantly reduced quality of life compared to the general population based on using generic instruments such as Short-Form Health Survey (SF-36) and Euro Qol (EQ5D) (Schrag, Jahanshahi, & Quinn 2000c; Reuther et al. 2007). Furthermore, a multicenter cohort study on multimorbidity among elderly persons in Germany found that out of all chronic diseases PD has the most negative impact on the HRQoL, and „self-care" and „usual activities" of the EQ5D were the dimensions affected the most (Brettschneider et al., 2013).

Among the disease-specific instruments that measure HRQol in PD patients, the most thoroughly tested and used is the Parkinson's disease Questionnaire (PDQ-39) (Martinez-Martin et al., 2011b). PDQ-39 is composed of 39 items grouped in 8 domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort (Jenkinson, Fitzpatrick, Norquist, Findley, & Hughes, 2003; Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995). The highest scores (showing worse quality of life) in PD patients have been reported to be in the domains of mobility, activities of daily living, emotional well-being and bodily discomfort, while the lowest scores (i.e least affected) in the domain of social support (Barone et al., 2009; Rodríguez-Violante et al., 2013; Sławek, Derejko, & Lass, 2005). Assessment of HRQoL of PD patient helps to understand his or her condition, identify the main factors causing HRQoL impairment, and establish priorities of management according to them (Martinez-Martin, 2017). The PDQ-39 and its short form PDQ-8 are common outcome measures used in many trials to assess the therapeutic effect (Martinez-Martin, Rodriguez-Blazquez, Forjaz, & Kurtis, 2015).

Persons with PD are particularly vulnerable to deterioration of HRQoL due to the progressive nature of motor disability and the increasing burden of non-motor symptoms (Chaudhuri et al., 2006). While some clinically relevant factors have been almost conclusively found to be negative independent strong predictors of HRQol (eg. depression) (Müller et al., 2013; Skorvanek et al., 2018; van Uem et al., 2018), results on other determinants (e.g. dyskinesias) have been more inconclusively reported by various authors (Hechtner et al., 2014; Rahman, Griffin, Quinn, & Jahanshahi, 2008; Winter et al., 2011). Impact of certain socio-demographic factors may also contribute to the reduced HRQoL. A summary of cross-sectional studies on HRQoL determinants using multiple regression analysis is demonstrated in Table 7. Determinants of HRQol are reported in more detail in the text below.

2.4.1. Impact of gender, age and age at onset

There are inconclusive results about the influence of gender on HRQoL. Some studies have identified female gender to be an independent negative predictor of lower HRQol (Balzer-Geldsetzer et al., 2018; Behari, Srivastava, & Pandey, 2005; Kovács et al., 2016; Morimoto et al., 2003), but others have not found such an association (Hinnell, Hurt, Landau, Brown, & Samuel, 2012; Klepac et al., 2007; Marras et al., 2008; Ophey et al., 2018; Prakash et al., 2016; Schrag, Jahanshahi, & Quinn, 2000d; Skorvanek et al., 2015). Women have demonstrated significantly more negative assessment of their HRQoL than men in domains of mobility, emotional-well-being and bodily discomfort (Balzer-Geldsetzer et al., 2018; Kovács et al., 2016). Several studies have found that women seem to have a higher total burden of non-motor symptoms, particularly regarding depression, anxiety, fatigue and pain (Guo et al. 2013a; Kovács et al. 2016; Solla et al. 2012). Women have also known to be at higher risk of developing dyskinesias (Bjornestad et al., 2016; García-Ruiz et al., 2012; Olanow et al., 2013; Scott et al., 2016), and non-motor fluctuations (Picillo et al., 2016). Some authors have reported that female PD patients have worse postural stability (Kovács et al., 2016; Solla et al., 2012). In light of the abovementioned gender differences, there might be several reasons why quality of life of female PD patients could be more affected than that of men.

A number of prospective and cross-sectional studies have postulated no convergence between age and the overall HRQoL (Balzer-Geldsetzer et al., 2018; Carod-Artal, Vargas, & Martinez-Martin, 2007; Marras et al., 2008; Prakash et al., 2016; Skorvanek et al., 2015). However, authors of one earlier prospective cohort study in Norway using the generic health questionnaire Nottingham Health Profile (NHP) reported that higher age at baseline of prevalent PD cases was associated with poorer overall quality of life in a follow-up of 8 years. Aspects of energy, social isolation and physical mobility were affected the most (Forsaa, Larsen, Wentzel-Larsen, Herlofson, & Alves, 2008). One other prospective study (DATATOP trial) that used the SF-36 as an outcome measure of HRQoL found that advancing age predicts impairment in mental domain (Marras et al., 2008). Also Winter et al. (2010b) found in their cross-sectional study conducted in Russia that increasing age was an independent determinant for reduced HRQoL assessed by the EuroQol instruments. On the other hand, Schrag et al. (2000c) described that particularly younger PD patients were more prone to reduced quality of life in aspects of physical and social functioning, physical role limitations and general health perceptions when compared to the norms retrieved from the general population. Younger age predicted poorer HRQoL also in a few other studies (Hinnell et al. 2012; Rodríguez-Violante et al. 2013).

The impact of PD on HRQoL may differ depending on age at onset. Higher age at onset was found to be a prognostic factor for a steeper decline of the HRQoL in a prospective CARPA study in the Netherlands (Velseboer et al., 2013). One earlier cross-sectional study in Poland did not identify any

differences in the overall HRQoL between PD patients of young-onset or old-onset (young-onset defined as below 47 years of age, old-onset defined as above 66 years of age) (Zach, Friedman, Sławek, & Derejko, 2004). Nonetheless, differences in several aspects of quality of life stratified by onset age were found, i.e. young-onset patients reported to have poorer HRQoL in domains of activities of daily living, emotional well-being, stigma and communication, while social support was assessed higher compared to patients with older onset age (Zach et al., 2004). Younger age at onset also predicted a lower quality of life in aspects of mental health and vitality assessed by the SF-36 (Kuopio, Marttila, Helenius, Toivonen, & Rinne, 2000). In a case-control study by Knipe and colleagues (2011) early-onset PD patients (defined as below 45 years of age) were found to have poorer overall HRQoL assessed by the PDQ-39, however the effect was weakened after the adjustment for depression as an intermediary factor. In the same study, younger onset age was also a predictor for poor emotional well-being independent of depression status (Knipe, Wickremaratchi, Wyatt-Haines, Morris, & Ben-Shlomo, 2011).

2.4.2. Impact of other socio-demographic variables

Lower education has been revealed to be an independent determinant of HRQol by some authors (Carod-Artal et al., 2007; Cubo et al., 2002; Knipe et al., 2011) but not by others (Prakash et al., 2016; Rodríguez-Violante et al., 2013; Skorvanek et al., 2018; Sławek et al., 2005). In terms of living area, some studies have found no difference between the quality of life between PD patients living in urban or rural area (Kuopio et al., 2000), while others have reported that rural living is an independent negative predictor of reduced HRQoL (Klepac et al., 2007; Soh, McGinley, Watts, Iansek, & Morris, 2012). Higher number of persons in household was found to be an independent positive predictor of better HRQoL (Winter er al. 2010b), but living together with children or grandchildren did not emerge as a significant determinant of quality of life in other studies (Behari et al., 2005; Sławek et al., 2005). Comorbidities were found to be independently related to the reduced quality of life in several studies (Carod-Artal, Ziomkowski, Mourão Mesquita, & Martínez-Martin, 2008; Hinnell et al., 2012; Post, Muslimovic, van Geloven, & Speelman, 2011), but no such association was found in other studies (Sławek et al., 2005).

2.4.3. Impact of disease duration

A number of cross-sectional studies have found that increasing disease duration is related to the reduced HRQoL (Benge et al., 2016; Morimoto et al., 2003; Zach et al., 2004). Change might not be uniform across all components of HRQol. A prospective study on *de novo* PD patients followed over 4 years in Italy showed an improvement of the domain of stigma, whereas the domain of

the bodily discomfort significantly got worse (Erro et al., 2016). On the contrary, cross-sectional studies have demonstrated that disease duration contributes most to the activities of daily living, stigma and communication, but it does not affect social support nor bodily discomfort (Benge et al., 2016; Zach et al., 2004). With the progression of neurodegeneration and advancing disease severity, several non-motor problems such as cognitive impairment, autonomic dysfunction and sleep disorders become to dominate the clinical picture and are the main determinants of quality of life and institutionalization (Chaudhuri et al., 2006).

2.4.4. Impact of motor and non-motor symptoms

Among the motor symptoms, the most related to the impaired HRQoL are problems with activities of daily living (Skorvanek et al., 2018; Müller et al. 2013; Rahman et al. 2008; Muslimović et al. 2008; Schrag et al. 2000d; Cubo et al. 2002; Martínez-Martín, Rodríguez-Blázquez et al. 2014; Carod-Artal et al. 2007; Behari et al. 2005). Dependency in activities of daily living is most commonly assessed using the Schwab and England Activities of Daily Living Scale (S&E) (Schwab & England, 1969) and Part II of UPDRS in earlier studies or of the MDS-UPDRS in more recent studies, that evaluate the performance of motor daily living experiences. One of the main results of the QUALPD study was that activities of daily living (assessed by the MDS-UPDRS Part II), followed by the non-motor symptoms (MDS-UPDRS Part I) contribute most to the reduced HRQol (Skorvanek et al., 2018). Shuffling, difficulty turning, falls, and difficulty in dressing have been found to be significant predictors of poor HRQoL (Rahman et al., 2008). The author concluded that interventions to facilitate everyday life activities should be interrogated to the multidisplinary management approach of PD patients (Rahman et al., 2008).

Axial impairment has also found to be a risk factor for reduced HRQoL (Marras et al., 2008; Müller et al., 2013; Muslimović et al., 2008; Rahman et al., 2008; Schrag et al., 2000d). There is an interrelation between axial impairment and reduced functionality, i.e patients with PIGD as the dominant feature are also more disabled in everyday activities (Muslimović et al., 2008). A prospective cohort study (n=188) in Germany that investigated HRQoL in early PD patients with the use of SF-36, found that gait dysfunction and activities of daily living assessed by the UPDRS Part II, were the most important motor symptoms predicting risk for reduced HRQoL at the time of diagnosis and 3 years later (Müller et al., 2013). Studies that have compared the HRQoL between tremor-dominant and non-tremor dominant patients have yielded to inconclusive results (Rodríguez-Violante et al., 2013; Schrag et al., 2000d).

Disease severity as measured by the HY staging also has been found to be a predictive factor for reduced HRQoL (GPDS Steering Committee, 2002; Morimoto et al., 2003; Schrag et al., 2000d; Sławek et al., 2005). The scale is based on the concept that the severity of overall parkinsonian dysfunction

relates to the bilateral motor involvement and worsening balance and gait (Hoehn & Yahr, 1967). Rahman et al. (2008) indicated that patients with advanced stage of PD (HY≥3) compared to those with HY ≤2.5 have worse HRQoL in all aspects except in the domain of bodily discomfort.

Another frequently used outcome for evaluating the severity of motor symptoms is the motor section of the MDS-UPDRS (Part III) that includes 18 items covering the nearly full range of motor features (Goetz et al., 2008). Inconclusive findings have emerged from the literature in terms of the assoction between HRQoL and Part III of the UPDRS or the more recent MDS-UPDRS. Higher score of UPDRS Part III has been found to be an independent determinant of HRQoL in some studies (Klepac et al., 2007; Rodríguez-Violante et al., 2013; Winter et al., 2011), but not in many others (Cubo et al., 2002; Martínez-Martín et al., 2014; Müller et al., 2013; Schrag et al., 2000d; Skorvanek et al., 2018). Gait was the only motor symptom from the MDS-UPDRS Part III that correlated with the PDQ-8 in the QUALPD study cohort (Skorvanek et al., 2018). It has been proposed that HY scale might be more sensitive tool than the motor section of UPDRS to assess the impact of illness's severity on patients' lives (Schrag et al., 2000d). However, limitations of HY scale include the fact that it is weighted toward postural instability assessments, progressive disability and impairments due to other features of PD, are not captured by the HY scale (Goetz et al., 2004).

There is an evidence from both cross-sectional and longitudinal studies that non-motor symptoms may be more detrimental for reduced HRQoL than motor symptoms (Erro et al., 2016; Müller et al., 2013; Ophey et al., 2018; Prakash et al., 2016; Rodríguez-Violante et al., 2013). Non-motor symptoms dominate in the clinical profile of moderate and advanced PD patients and predict an impaired quality of life, disability and mortality (Chaudhuri et al., 2006). The main non-motor symptoms negatively associated with the HRQol are depression, anxiety, apathy, memory impairment, fatigue, autonomic disturbances and sleep problems (D'Iorio et al., 2017; Gallagher et al., 2010; Martinez-Martin et al., 2011a; Rodríguez-Violante et al., 2013; Skorvanek et al., 2018), a more detailed insight into each of these non-motor symptoms is described below.

2.4.4.1. Depression

There is a number of surveys in different cultural regions of the world with the use of heterogenous study methods and study participants which suggest that depression has the strongest association with reduced HRQol (Carod-Artal et al., 2007; Gallagher et al., 2010; Ophey et al., 2018). The prevalence of clinically significant depression is as high as about 35% (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008) and some studies suggest that it is more common and more severe in female than in male PD patients (Kovács et al., 2016; Solla et al., 2012). In the longitudinal analysis on PROPARK cohort (n=411) over 5 years of follow-up, female gender, more severe disability, more cognitive impairment, motor fluctuations, nighttime sleep problems, increased daytime

sleepiness, more autonomic dysfunction (urinary and cardiovascular domains) and the use of antidepressants were independently associated with higher BDI scores over the time (Zhu, van Hilten, & Marinus, 2016). Interestingly, depression was found to be a less strong contributor to HRQoL in one longitudinal study of early PD patients after a follow-up of 3 years compared to the baseline (Müller et al., 2013).

2.4.4.2. Anxiety

Among several neuropsychiatric symptoms, anxiety with its wide spectrum has a prevalence of 31% (Broen, Narayen, Kuijf, Dissanayaka, & Leentjens, 2016) and has an important negative impact on HRQoL (Carod-Artal et al., 2008; D'Iorio et al., 2017; Skorvanek et al., 2015). In a study by Duncan et al (2014b) on the quality of life of 158 PD patients in early stage of disease (mean disease duration of 6.3 years), anxiety was found to be among the most common non-motor symptoms (42%) and also among the significant determinants that reduced the HRQoL. Anxiety has been identified to affect negatively certain aspects of the HRQoL, such as emotional well-being and cognition (assessed by PDQ-39) (Skorvanek et al., 2015). Anxiety has been demonstrated to be more frequent in female PD patients compared to men (Kovács et al., 2016; Solla et al., 2012). One recent prospective study on the course and predictors of depression and anxiety in Singapore in mild PD patients (n=89) revealed that unlike depression that remained relatively stable over 18 months, anxiety symptoms reduced over the study period. In the same study, the strongest predictors for anxiety were mainly demographic variables such as younger age at diagnosis, older age, higher education, and with smaller contribution, also concomitant depression and excessive daytime sleepiness (Wee et al., 2016).

2.4.4.3. Apathy

Apathy which has a prevalence of about 40% (den Brok et al., 2015), has found to be among the main determinants of reduced HRQoL in some studies (D'Iorio et al., 2017; Skorvanek et al., 2018). Risk factors that are associated with apathy include higher age, lower cognitive ability, co-morbidity of depression, higher severity of motor symptoms and disability of PD (den Brok et al., 2015). Out of all the valuated 12 types of non-motor symtoms, presence of apathy was associated with the worst quality of life in the PRIAMO study (Barone et al., 2009). Apathy has been reported to be more common in male than in female PD patients (Kovács et al., 2016). Certain non-motor symptoms, including apathy, depressive mood, features of dopamine dysregulation syndrome and urinary problems were found to be independent negative determinants of the PDQ39 domain stigma (Skorvanek et al., 2015).

2.4.4.4. Memory impairment

A recent case-control study (ONSET PD) revealed that memory complaints were significantly more common in early PD patients compared to the general population in the same age, reported by 32% of patients with a mean disease duration of 11 months and by 20% of the age-matched healthy controls (Pont-Sunyer et al., 2014). Cognitive decline is a typical feature of the advanced or late-stage PD with a prevalence of 84% in patients of 15 years of disease duration (Hely et al., 2005). One cross-sectional study (n=302) identified that the mean scores of the PDQ-39 domain cognition were similar across PD patients with 0–5 and 6–10 years of disease, but the outcome was significantly worse in those with longer (11+ years) than in those with shorter disease duration (Benge et al., 2016).

Overall HRQoL, and domains of mobility and activities of daily living have been found to be significantly lower in PD patients with dementia compared to non-demented PD patients (van Uem et al., 2018). Lower Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score was identified as one of the significant predictors of the PDQ-39 domain of activities of daily living but not in case when demented patients were excluded from the analysis (van Uem et al., 2018). Cognitive impairment has been identified to be among the main contributors of the reduced HRQoL in few studies that have included this clinical characteristic as a potential determinant into the multiple regression models (Rodríguez-Violante et al., 2013; Schrag et al., 2000d; Winter et al., 2011). On the contrary, the CARPA study on newly diagnosed PD patient followed up for 5 years showed that cognitive impairment at baseline was the most important predictor for increased progression of disability and motor impairment, but it did not predict the deterioration of HRQoL (Velseboer et al., 2013). Supportive to the previous finding, no contribution of cognitive impairment to the HRQoL was found in another large, multi-center, cross-sectional study (Skorvanek et al., 2018).

2.4.4.5. Impulse control disorders

Impulse control disorders (ICDs), mainly caused by dopaminergic treatment, have a prevalence of 18% to 30% across all PD patients (Antonini et al., 2017; Hurt et al., 2014) and up to 55% among patients with dyskinesias (Biundo et al., 2017). No significant relationship between HRQoL and impulse control disorders were found in some cross-sectional studies (D'Iorio et al., 2017), however other studies have reported the negative impact of those on disability and HRQoL (Leroi et al., 2011; Skorvanek et al., 2015).

2.4.4.6. Fatigue

Among other non-motor symptoms besides the neuropsychiatric disturbances, fatigue with a prevalence of about 50% of cases (Del Sorbo & Albanese, 2012)

has been found to be one of the main predictors of HRQol in several studies (Dogan et al., 2015; Gallagher et al., 2010; Skorvanek et al., 2018). It has been revealed that fatigue impacts negatively most of the aspects of HRQoL, particularly mobility, activities of daily living and cognition (Skorvanek et al., 2015). Female PD patients have been found to have more frequent and more severe complaints of fatigue compared to men (Martinez-Martin et al., 2012; Solla et al., 2012). Some cross-sectional studies have established an association between fatigue and longer disease duration (Barone et al. 2009; Guo et al. 2013b) while others have not found such an association (Solla et al., 2014). However, the contribution of fatigue to the HRQoL increased markedly over a follow-up of 3 years in a longitudinal study enrolling incidence PD patients (n=188) by Müller et al. (2013). The higher overall burden of non-motor symptoms has been reported to predict the higher occurrence and severity of fatigue (Solla et al., 2014).

2.4.4.7. Autonomic disturbances

In the study by Martinez-Martin et al. (2013) with 434 PD patients enrolled, the common autonomic non-motor symptoms assessed by the MDS-UPDRS Part I were constipation (70%), urinary problems (64%), and lightheadedness (36%). Reduced olfaction, urinary problems, hypersalivation and constipation have been found to be the most frequent autonomic symptoms already in the early stage of PD (Müller et al., 2011). With the duration of the disease, most of the autonomic symptoms have shown to become more common and severe (Guo et al. 2013b; Erro et al. 2016). Several studies have demonstrated the evidence that autonomic disturbances, particularly urinary incontinence, constipation and orthostatic hypotension, have a significant negative impact on the quality of life of PD patients (Gallagher et al., 2010; Rahman et al., 2008).

2.4.4.8. Sleep problems

In PD, sleep disorders have been found in over 60% of patients and their frequency correlates with the duration of disease (Barone et al. 2009; Guo et al. 2013b). In some surveys, sleep disturbances were found to be independent strong determinants of HRQoL (Qin et al. 2009; Visser et al. 2009; Kovács et al. 2016; Duncan et al. 2014b; Gallagher et al. 2010), other studies have shown only low or no association between HRQoL and sleep problems (Müller et al., 2013; Skorvanek et al., 2015, 2018). It has been reported that sleep problems affect particularly some HRQoL aspects such as emotional well-being and cognition (Rodríguez-Violante et al., 2013; Skorvanek et al., 2015). Daytime sleepiness has been found to be more frequent and severe in men than in women (Kovács et al., 2016; Martinez-Martin et al., 2012).

2.4.5. Impact of levodopa dose and levodopa induced complications

It has inconclusively been shown that a higher intake of levodopa is associated with lower HRQoL (Behari et al., 2005; Hinnell et al., 2012; Ophey et al., 2018; Prakash et al., 2016; Skorvanek et al., 2018), but no such a finding has been reported by few other studies (Qin et al., 2009). One recent prospective cohort study with the follow-up of 6 months in Finland evaluated the changes of HRQoL in patients whose medication dose was increased for clinical reasons (n=82) and in patients whose medication remained unchanged (n=137). No differences in the baseline or in the change of HRQoL (assessed by the generic instruments EQ-5D and 15D) between the treatment groups were seen (Järvelä & Kaasinen, 2016).

Several studies have reported that motor fluctuations significantly worsen the HRQoL (Chapuis et al. 2005; Hechtner et al. 2014; Rahman et al. 2008; Kerr et al. 2016; Sławek et al. 2005). Usual daily activities frequently identified by PD patients as the most bothersome during "off"- time' compared to "on"-time include dressing, washing and keeping clean, communicating effectively, getting around the house and walking short distances (Kerr et al., 2016). On the contary, mixed findings concerning the impact of dyskinesias on the quality of life have been demonstrated (Chapuis et al., 2005; Hechtner et al., 2014; Rahman et al., 2008; Rodríguez-Violante et al., 2013; Winter et al., 2011). For example, one study in Germany involving 817 PD patients did not identify the presence of dyskinesias to be a predictor for the reduced overall quality of life, although abnormal movements did affect the activities of daily living, cognition, stigma, and bodily discomfort (Hechtner et al., 2014). It has been proposed that dyskinesias may not always be a major concern for PD patients because nowadays they are frequently mild and not disabling (Kerr et al., 2016). Recent cross-sectional study in France reported that the severity but not the duration of dyskinesias is an independent determinant of HRQoL (Perez-Lloret et al., 2017).

Table 7. Overview of cross-sectional studies assessing HRQoL and its determinants in patients with PD.

Reference	PD sample (n)	Disease duration (years)	Variables associated with reduced HRQoL
GPDS Steering Committee 2002	1020	7.4	Depression, disease severity, medication, satisfaction with the explanation of the condition at diagnosis, current feeling of optimism
*Schrag et al. 2000d**	124	5.3	Depression, disability, postural instability, cognitive impairment,
*Kuopio et al. 2000**	228	8.4	Depression, disease severity, duration of PD, age at onset
Cubo et al. 2002	158	8.1	Depression, disability, psychotic symptoms, education
Morimoto et al. 2003	762	9.4	Female gender, duration of PD, disease severity
Zach et al. 2004	141	11.9	Depression, duration of PD, expenses related to treatment
Sławek et al. 2005	100	6.7	Depression, motor fluctuations, disease severity
Behari et al. 2005	278	4.7	Female gender, depression, disability, higher levodopa dose
Chapuis et al. 2005	143	9.1	Number of levodopa doses per day, motor severity of disease, abnormal movements' intensity
Klepac et al. 2007	111	5	Rural living, disease severity
Muslimović et al. 2008	190	3.3	Mood symptoms, axial impairment
Rahman et al. 2008	126	12.1	Depression, anxiety, shuffling, difficulty turning, difficulty in dressing, fatigue, confusion, urinary incontinence, unpredictable on/off fluctuations, pain
Carod-Artal et al. 2008	144	6.6	Depression, anxiety, disability, comorbidities
Qin et al. 2009	391	3.0	Depression, sleep disorders, fatigue, disease severity, rigidity
Winter et al. 2010b	100	6.7	Age, disease severity, dystonia, depression, number of persons in household
Gallagher et al. 2010	94	7.8	Depression, fatigue, thermoregulatory, gastrointestinal, and cardiovascular autonomic function, daytime somnolence, urinary problems

Reference	PD sample (n)	Disease duration (years)	Variables associated with reduced HRQoL
Winter et al. 2011	70	–	Disease severity, motor fluctuations, dyskinesias, depression, dementia
Martinez-Martin et al. 2011a	411	8.1	Total load of non-motor symptoms, motor symptoms
Rodríguez-Violante et al. 2013	177	6.4	Motor impairment, total load of non-motor symptoms, non-motor domains of depression/anxiety, cardiovascular, miscellaneous, age
Martínez-Martín et al. 2014	435	8.5	Motor and non-motor experiences of daily living
Hechtner et al. 2014	817	3.3	Motor fluctuations
Skorvanek et al. 2016	291	8.3	Total load of non-motor and motor experiences of daily living, motor complications, pain, fatigue, dopamine dysregulation syndrome
Kerr et al. 2016	305	7.9	Shorter "on-time", unpredictability of "off-time"
Kovács et al. 2016	621	7.6	Female gender, motor experiences of daily living, motor symptoms, disability, sleep problems, depression, anxiety, cognitive impairment, dyskinesias, ICDs
D'Iorio et al. 2017	84	–	Anxiety, executive apathy, reduced functional autonomy
Perez-Lloret et al. 2017	681	–	Severity of dyskinesias and duration of motor fluctuations
van Uem et al. 2018	47	–	Depression, total daily energy expenditure
Ophey et al. 2018	245	5.9	Depression, disease severity, LEDD
Skorvanek et al. 2018	3206	7.6	Total load of non-motor and motor experiences of daily living, depressed mood, dressing, apathy, pain, fatigue
Balzer-Geldsetzer et al. 2018	75	7.0	Female gender, depression, motor complications

*Case ascertainment in all studies was hospital-based, except in studies by Schrag et al. (2000d) and Kuopio et al. (2000) that were population-based surveys and used multiple sources for case identification;
Abbrevations: HRQoL, health-related quality of life; n, number; PD, Parkinson's disease; n, number; ICDs, impulse control disorders, LEDD, levodopa equivalent daily dose.

3. AIMS OF THE STUDY

The primary objective of the current study was to describe the epidemiologic characteristics of PD in a defined population in Tartu, Estonia. Additional goals of this study were to evaluate the clinical characteristics, the treatment-related complications and the HRQoL of patients with PD.

1. To evaluate the prevalence of PD in the city and county of Tartu and detect the dynamic changes in the disease frequency compared to the similar epidemiologic study conducted in the same geographical area 20 years ago (Study I).

2. To evaluate the incidence of PD in the city and county of Tartu and detect the dynamic changes in the disease occurrence compared to the similar epidemiologic study conducted in the same geographical area 20 years ago (Study II).

3. To describe the characteristics of mortality and causes of death of PD patients (Study II).

4. To describe the frequency of motor complications among patients with PD who receive levodopa treatment and to assess the effect of various demographic and clinical factors on the occurrence of motor complications (Study III).

5. To investigate the frequency and severity of non-motor PD symptoms and to identify differences in the prevalence of non-motor symptoms among subgroups of PD patients (Study IV).

6. To evaluate the impact of a wide range of socio-demographic and clinical factors upon the HRQoL of PD patients (Study V).

4. PATIENTS AND METHODS

4.1. Study design

All the studies included in this thesis were observational studies for which a large PD sample derived from the whole source population of city and county of Tartu was used.

Study I was a descriptive, cross-sectional, epidemiologic study that included prevalent and incident PD patients with a goal to determine the prevalence of PD on the prevalence day of 1st of October, 2013, in the city and county of Tartu.

Study II was a descriptive epidemiologic study investigating incidence and mortality of PD in the city and county of Tartu. For the incidence study, both a retrospective and prospective approach for finding new PD cases over a defined period (2002–2012) was used. For the mortality study, a prospective observation of a cohort of PD patients (stratified into inception and non-inception subcohorts) over a defined follow-up period (2010–2016) was used. The mortality rates of the PD patient cohort with those expected from the general population data were compared.

Study III was a cross-sectional multi-centre analytical study on motor complications of levodopa treatment based on a PD cohort derived from the earlier years (2010–2013) of the epidemiological study of the city and county of Tartu, but also included hospital-based samples of PD patients from two other regions of Estonia (i.e Pärnu and Tallinn).

Study IV on non-motor features, and Study V on HRQoL were cross-sectional analytical studies based on a PD cohort derived from the earlier years (2010–2013) of the epidemiological study of city and county of Tartu.

4.2. Ethical issues

All the studies have been approved by the Research Ethics Committee of the University of Tartu (Certificate No 216/M-29). Permission from the Estonian Data Protection Inspectorate was obtained to process personal data without the subject's consent (Certificate No 2.2-7/13/643r). Subjects gave their written informed consent.

4.3. Diagnostic criteria

Diagnosis was based on the QSBB clinical diagnostic criteria, i.e the diagnosis of PD was confirmed by the presence of bradykinesia and at least one of the following symptoms: resting tremor, rigidity, or impaired postural reflexes (Table 1; Gibb & Lees, 1988; Lees et al., 2009). Since this was primarily an

epidemiological study, all patients with a confirmed PD diagnosis were enrolled, and no other specific exclusion criteria (except those from the QSBB) were set. Two criteria of the QSBB were not taken into account, firstly, patients with Babinski sign were not excluded if they presented with typical PD and no other exclusion criteria were evidenced. Also patients were not excluded from the study if they had more than one relative with PD. Patients with drug-induced, vascular, atypical or unspecified parkinsonism were excluded from the PD sample.

4.4. Study area and population

Tartu County is located in South Estonia and had a population of 152,188 (71,395 men, 80,793 women) according to the census on 1st of January in 2014 (Statistics Estonia website, 2018). The county is administratively divided into 3 urban and 19 rural municipalities, and covers a total of 2,993 square kilometres. Tartu, the second largest city of Estonia, is the administrative centre of Tartu County. The male-female proportion in the entire country was the same as in Tartu in 2014, i.e 47% men and 53% women. 12.4% of individuals were over 70 years old, there were twice as many women than men in that age (16% of women vs. 8% of men) in Tartu in 2014 (Statistics Estonia website, 2018).

Tartu University Hospital is the regional hospital of South Estonia, with a well-developed digital patient record system that is connected to the national e-Health system, a platform that holds all the medical information of Estonian inhabitants. In addition to Tartu University Hospital, there is one local hospital that provides out- and in-patient services for neurological patients, and ten nursing homes and hospitals. In 2013, there were 61 family doctor's offices in Tartu County. In Estonia, patients with a possible PD are referred to a neurologist who confirms the diagnosis and starts the initial treatment that will be followed by a family doctor. The Tartu PD society was created in the end of 1995 and has an average of 70 members.

4.5. Case-ascertainment

The following information from all available sources was regularly obtained during 2010–2016 for case-ascertainment of patients with PD (irrespective of age). In- and out-patient neurology visit data of the Department of Neurology and Neurosurgery of Tartu University Hospital were processed and neurologists were asked to provide the list of their PD patients. The member list of the PD Society was reviewed, and family doctors and neurologists were contacted by e-mail to identify eligible patients. All nursing institutions in the region were visited. Data from the Estonian Health Insurance Fund (EHIF) on all patients with the diagnosis of PD (coded as G20 by the International Statistical Classification of Diseases ICD-10) received during 2010–2015 were processed in 2016.

4.6. Subjects and data collection of the studies

Although the case-finding methodology, diagnostic criteria and instruments used for the data collection were the same over the whole study period (2010–2016), study samples of PD patients varied depending on the aims of the studies.

4.6.1. Prevalence of PD

The overall study population with possible diagnosis of PD from all sources in Tartu County over a study period (2010–2016) comprised 1011 subjects. From medical records 455 patients were found, and a PD diagnosis confirmed in 88% of cases. From the additional search of the EHIF, 556 cases were found, but only 32% had a confirmed diagnosis of PD and were enrolled in our study. The flow diagram of the subjects included to, and excluded from the study is shown in Figure 1.

All patients with PD (n=431) living in the county of Tartu on the 1st of October 2013 were included into the final PD sample. This specific prevalence day was chosen at the midpoint of our study period and the proportion of clinically examined study participants was highest at that time. Subjects were classified as prevalent cases if their initial parkinsonian symptoms had occurred before the prevalence day. Eligible patients were contacted; the residence of patients was verified with data of the Estonian Population Register. Of the 431 patients included in the prevalence analysis, 84.2% agreed to participate in the interview and clinical evaluation (more detailed information of clinical assessment is given below in the section of Clinical Examination, 4.7). Patients were examined in the Department of Neurology (n=265), at home (n=65), or in a nursing home or hospital (n=33). Those who refused to participate (7.4%), were unreachable (1%), or had died before their identification (7.4%), but were alive on the prevalence day, were enrolled as prevalent cases if they had a confirmed diagnosis of PD based on medical records. For these subjects, the full case record review of each case was conducted to find evidence for the presence of confirmed PD (i.e description of cardinal parkinsonian symptoms, prescription of antiparkinsonian treatment, no indications to other conditions besides PD).

4.6.2. Incidence and mortality of PD

All PD patients (n= 608) resident in Tartu county between 2010–2016 were included in the study. Retrospective PD onset data (i.e. the date of a subject's first PD symptoms) was based either on recall (by the patient or caregiver), or on information obtained from medical records. All subjects were tracked annually by the online Electronic Health (e-Health) Record until either the end

of the study period, or their death. E-Health is a digital platform which holds the medical information of Estonian residents. During the seven-year period of survey, 19 subjects were excluded from the PD sample when a condition other than PD was suspected on the basis of data retrieved directly from the neurologists or from the e-Health Record. Out of the excluded patients from the initial cohort, alternative diagnosis suspected to have instead of PD were as follows: 5 with essential tremor; 5 with Lewy body dementia; 3 with vascular parkinsonism; 3 with other tremors; 1 with multisystem atrophy; 1 with progressive supranuclear palsy; and 1 with drug-induced parkinsonism.

The final PD sample for the incidence analysis was based on those subjects (n=388) whose clinical onset of PD occurred between January, 2002 and December, 2012. The majority of incident subjects (76.3%) were seen once, in person, during the study period. A detailed information of clinical assessment is given below in the section of Clinical Examination, 4.7. Data for those patients who did not agree to participate in additional examination (7%), were unable to be contacted (0.5%), or who had died by the time of their identification (16.2%), was limited to the information obtainable from the electronic medical records.

Mortality analysis calculations were based on all patients with PD identified between January, 2010 and December, 2016 (n=589). Based on the onset year of the disease, subjects included to the mortality analysis were stratified into two subcohorts; i.e. inception cohort (disease onset since the year 2008, n=293) and non-inception cohort (disease onset was before the year 2008, n=296). Data on subjects' date of, and age at death was collected from the e-Health Record (and verified with data from the Estonian Population Registry). Data on causes of death was obtained from subjects' death certificates, which were provided by the Estonian Causes of Death Registry (coded in accordance with the International Classification of Diseases 10th Revision (ICD-10)).

4.6.3. Prevalence and factors associated with motor complications in PD

This study was conducted by three medical centres in different regions of Estonia (Tartu, Pärnu, and Tallinn) between October 2010 and September 2013. From the initial cohort of 486 parkinsonian patients, 16 were excluded due to correction of diagnoses including other tremors, secondary or atypical parkinsonism, or Lewy body dementia, and 15 more were excluded due to refusal or incomplete testing. All the participants had to be seen in-personally once and data relevant for the measurement of motor complications (i.e. fulfilled scale of MDS-UPDRS and patient card) had to be provided. A total of 455 patients were included in the final analysis. Majority of the study participants were derived from the PD cohort of epidemiological study in Tartu (n=353), other patients were enrolled and examined in Pärnu Hospital (n=96) and North Estonia Medical Centre (n=6). A majority of the study participants

were outpatients (n=390). A few were inpatients (n=14), in nursing homes (n=23) or visited at their own homes (n=28).

4.6.4. HRQoL and non-motor symptoms in patients with PD

These studies were conducted in the city and county of Tartu between October 2010 and May 2013. Study participants (n=268) in those two studies were identical and were derived from a population-based PD cohort of the epidemiological study including PD patients living in the city and county of Tartu. All the participants were seen in-personally once and data relevant for the measurement of HRQoL and non-motor symptoms (i.e. fulfilled scale of PDQ-39 and MDS-UPDRS) had to be provided.

4.7. Clinical examination

Clinical assessment included a semi-structured interview based on a special Patient Case Report Forms, neurological examination and use of validated clinometric scales and questionnaires. Demographic and social data (age, gender, urban/rural living, marital status, living alone/with others, level of education) and data regarding PD (age at disease onset, disease duration, initial PD symptom, prevalent motor phenotype) and antiparkinsonian treatment-related factors (levodopa daily dose, levodopa equivalent daily dose [LEDD], duration of levodopa treatment, time from symptom onset until the initiation of levodopa, presence of motor complications), and other factors (comorbidities, toxins) were recorded. Data on Case Report Forms regarding motor complications included binary questions assessing motor fluctuations, dyskinesias, and off-dystonia that had occurred at any time during the disease. LEDD was calculated using the standardized conversion formula (Tomlinson et al., 2010). During the neurological examination, a motor phenotype was determined based upon the most prevalent symptom: the dominance of tremor with other motor symptoms of only a mild level; non-tremor-dominant PD which includes syndromes with akinesia and rigidity; or PIGD.

For assessing the frequency and severity of a wide range of symptoms related to PD, all the parts of MDS-UPDRS were performed. In 2008 the MDS adopted a new, validated version of the MDS-UPDRS, which included several significant updates in comparison with the previous version, including new non-motor symptoms of PD (Goetz et al., 2008)

The Estonian version of the MDS-UPDRS was translated, validated and officially approved in 2011 by the MDS Translation Program for non-English official versions. The MDS-UPDRS Part IA contains questions regarding a number of neuropsychiatric symptoms and is completed by the interviewer; Part IB consists of questions other non-motor symptoms and is answered by the patient or caregiver. Part II regards the motor experiences of daily living and is

assessed by the patient or caregiver; Part III assesses motor symptoms based on an objective neurological examination by the investigator. Part IV regards motor complications and is completed by the interviewer. All items in MDS-UPDRS were scored by a scale of 0 to 4 (normal/slight/mild/moderate/severe), and the total score for each part was obtained from the sum of the corresponding item scores. The data on the prevalence of motor complications was obtained from two sources: Patient Case Report Forms and part IV of the MDS-UPDRS.

The clinical stage of PD was assessed using the HY scale and their level of disability by the SE-ADL scale. The HY scale ranges from 1 (unilateral involvement of the body) to 5 (wheelchair bound or bedridden). The SE-ADL scale ranges from 0% (completely dependent and bedridden) to 100% (completely independent). For assessment of depressive symptoms, the Beck Depression Inventory (BDI) was used (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), whereby a score of ≥14 was indicative of depression (Leentjens, Verhey, Luijckx, & Troost, 2000). Cognitive impairment was measured using the MMSE, whereby a score of ≤24 was evidence of cognitive impairment.

To evaluate HRQoL, PDQ-39 – a validated, disease-specific quality of life instrument – was used. The higher the PDQ-39 summary index (SI) score, the lower the perception by patients of their quality of life. An Estonian version of the PDQ-39 has been shown as a reliable instrument (Krikmann, Taba, Lai, & Asser, 2008)

4.8. Statistical analysis

4.8.1. Prevalence of PD

Total crude and age-, gender-, and living area-specific crude prevalence rates were calculated based on the number of PD cases on prevalence day and the number of inhabitants of the county of Tartu according to the population census on January 1st, 2014. Crude rates were adjusted for age-structure of Estonian population on January 1st, 2014, using the direct method of standardization. To compare our prevalence figures to the previous epidemiological study in Estonia, an additional age-adjustment was made according to the age-structure of Estonia in 1989, which was the reference population used in the study by Taba and Asser (Taba & Asser, 2002). Furthermore, using the European 2011 standard population as a reference (EuroStat website, 2018), a corresponding age-adjusted prevalence rate was also calculated. Descriptive statistics (percentages, means with standard deviation, medians with ranges) were used for the socio-demographic and clinical characteristics of the whole sample of the prevalent cases.

95% confidence intervals (CIs) for the prevalence rates were calculated assuming the Poisson distribution of observed cases. The differences in crude prevalence rates between the groups were statistically evaluated using Poisson

regression analysis. The differences in age-adjusted prevalence rates between the groups and between two time-points were statistically evaluated using the Z-test. Familywise error rate was controlled with Bonferroni method. All statistical analysis was performed in R version 3.3.3.

4.8.2. Incidence and mortality of PD

To measure the frequency of occurrence of new PD cases, the number of incident cases was divided by the total number of person-years at risk. The age-specific incidence rates for men and women, as well as for rural and urban patients, were estimated in 5-year age groups. Data on the age and gender of the study population were obtained from Statistics Estonia (Statistics Estonia website, 2018). Using the Europe 2011 Standard population as a reference, the age-adjusted incidence of PD was calculated by the use of direct method. Based on the age structure of Estonia in 1989, an additional age-adjustment was made, in order to compare the incidence rates of the two epidemiological studies (Taba & Asser, 2003). In order to assess the eligibility of the findings and conclusions based on the primary analysis of the incidence data, a sensitivity analysis was performed, for which incident PD cases were limited to the period of 2010–2012, and the results were compared to the more retrospective period of disease onset (2002–2012).

For the purpose of the mortality analysis, subjects were tracked prospectively on the e-Health system between January, 2010 and December, 2016, or until their death. The standardized mortality ratios (SMR) for inception and non-inception cohorts, as well as for men and women separately, were calculated based on the ratio of observed to expected deaths. The latter was calculated using the person-years at risk in each group based on 5-year age category, gender and calendar year. These person-years were multiplied by the corresponding group-specific mortality rates in the general Estonian population (EuroStat website, 2018). Additional SMR analysis for the estimation of cause-specific mortality in two disease categories (cancer and vascular diseases) was performed.

The 95% confidence intervals (CI) for the incidence and mortality rates were calculated assuming Poisson distribution of observed cases. Differences in socio-demographic or clinical characteristics for men and women were statistically evaluated using the Chi-square or Fisher's exact test (for categorical data) and the t-test or Wilcoxon test (for numerical data). Rate ratios (RRs) were calculated to compare incidence rates between urban and rural patients, and between males and females. Differences were considered statistically significant at a p-value of <0.05. All statistical analyses were conducted using R version 3.4.3.

4.8.3. Prevalence and factors associated with motor complications in PD

Primary analysis involved the evaluation of the frequency of motor complications in our sample of PD patients who received levodopa therapy. Out of the total cohort of 455 PD cases included to the study, 374 patients received levodopa therapy at the time of examination. Out of those 374 PD cases, 28 had started with levodopa the same day or a few days before the examination; therefore, they were excluded from the analysis. Another 18 levodopa users were excluded from the frequency analysis of motor complications due to missing the variable indicating the duration of their levodopa therapy.

Secondary analysis comprised descriptive statistics for the total study sample (n=328), for the patients on levodopa who did not have motor complications (n=243), and for the patients on levodopa who had motor complications (n=85). Group comparisons were performed using the two-sample t-test, chi-squared test, Fischer's exact test and Mann-Whitney U test. Multiple comparisons were corrected with the Bonferroni method.

Tertiary analysis incorporated logistic regression models to examine the effects of multiple predefined variables on the binary outcome variable (whether motor complications were present). Based on the literature and clinical experience, the following variables were entered into the main model: age, gender, age at onset of PD, time from initial symptoms until starting levodopa, LEDD, MDS-UPDRS Parts II and III scores, BDI, PDQ-39 SI score, and akinetic-rigid dominant, tremor-dominant and PIGD-dominant motor phenotype of the disease. Odds ratios (OR) with 95% CIs were calculated for all above-mentioned variables. The results were considered statistically significant at the $p<0.05$ level. Statistical analysis was performed in R version 3.3.1.

4.8.4. Prevalence and factors associated with non-motor symptoms in PD

Descriptive statistics (percentages, means with standard deviation, medians with interquartile ranges) were used for the variables of interest. The frequency of each non-motor symptom was expressed as the percentage of patients scoring 1 or more points for each item of the MDS-UPDRS Part I. The mean total scores of MDS-UPDRS Part I among the patient subgroups were compared using the Mann-Whitney U or Kruskal-Wallis test. For the group comparisons, patients were divided into subgroups in terms of gender (male; female), age (≤64 years; ≥65 years), disease onset age (≤50 years; ≥65 years), disease duration (≤5 years; 6–10 years; ≥10 years), HY(≤2.5; ≥3), SE-ADL (≥80; ≤75), MMSE (≥25; ≤24), clinical subtype (tremor; akinesia-rigidity; PIGD), motor complications in general (present; absent), and motor fluctuations (present; absent), dyskinesias (present; absent) and off-period dystonia (present; absent). The severity of each

non-motor symptom was expressed as the mean score of each item, including all the possible scores (0–4).

Statistical analysis of any differences in the frequency of individual non-motor symptoms among patient subgroups was performed using the chi-squared test or Fisher exact test (as appropriate), and multiple comparisons were corrected with the Bonferroni method. Spearman's rank correlation coefficients (ρ) were used to test the significance of correlations (1) between total MDS-UPDRS Part I scores and different characteristics of interest; and (2) between total MDS-UPDRS Part I scores and individual non-motor symptoms. Correlation coefficients were interpreted as very weak (r = 0–0.19), weak (r = 0.20–0.39), moderate (r = 0.40–0.59), strong (r = 0.60–0.79) or very strong (r = 0.80–1.00). A p-value below 0.05 was considered significant. Statistical analysis was performed using SPSS version 20 software (IBM, Armonk, NY, USA).

4.8.5. HRQoL of patients with PD

PDQ-39 SI measures of HRQoL were calculated according to its scoring algorithm (Jenkinson, Fitzpatrick, Peto, & Greenhall, 1997; Peto et al., 1995). Prevalence of non-motor symptoms was based on scores ≥1, which denoted the presence of a symptom. Student's t-test and z-test were applied for comparing socio-demographic and clinical outcomes between men and women. The non-parametric Mann-Whitney U and Kruskal-Wallis tests were used to compare PDQ-39 SI scores between the groups. Spearman's rank correlation coefficients (ρ) were calculated to assess associations between variables.

A multiple linear regression analysis – based on a backward elimination approach – was conducted to determine the factors that contribute to HRQoL in persons with PD. PDQ-39 SI was used as a dependent variable. The R^2 statistic was used to determine the proportion of variance explained by the predictors. The level of statistical significance was set at $p<0.05$. Statistical analysis was performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA) and SPSS version 20.0 (IBM Corporation, Armonk, NY, USA).

5. RESULTS

5.1. Prevalence of PD

The flow diagram of the case-ascertainment procedure is shown in Figure 1. A total of 431 patients (160 men, 271 women) fulfilled the study criteria and were included into the prevalence analysis. Of them, 71% lived in urban areas and 29% in rural areas. Without the use of the EHIF data, a total number of 321 (120 men, 201 women) PD patients were identified. On prevalence day, the mean age of participants was 77.4 ± 9 years and the mean duration of the disease was 7.0 ± 5.9 years. The crude and age-adjusted PD prevalence rates are shown in Table 8. The total crude prevalence rate was higher for women than for men. There was no significant difference between age-adjusted prevalence rates of men and women (RR=0.83, p=0.07; Table 8). In terms of living area, no significant difference in adjusted prevalence rates of PD was shown between urban and rural populations (RR=1.02, p=0.83). We found a trend of increasing age-specific prevalence with age for both genders, peaking in the age-group 80–84 years old per women and 85+ years old per men, followed by a significant decline among the most elderly women but not the men (Figure 2). After age-adjustment to the European 2011 standard population, the overall prevalence rate was 324/100,000 people.

Table 8. Crude and age-adjusted prevalence rates of PD according to gender and living area.

	Cases	**Study popu-lation**	**Crude prevalence rates/100,000 (95%CI)**	**Adjusted prevalence rates/100,000 (95%CI)[a]**	**RR of adjusted preva-lence**	**p-value**
All patients	431	152,188	283 (257–310)	314 (285–344)		
Males	160	71,395	224 (189–259)	355 (299–412)	0.83	0.07
Females	271	80,793	335 (296–375)	294 (259–330)		
Urban patients	307	104,952	293 (260–325)	316 (281–352)		
Males	116	47,956	242 (198–286)	369 (302–437)	0.78	0.04
Females	191	56,996	335 (288–383)	287 (246–329)		
Rural patients	124	47,236	263 (216–309)	309 (255–364)		
Males	44	23,439	188 (132–243)	333 (229–437)	0.93	0.70
Females	80	23,797	336 (262–410)	309 (240–377)		

[a] Adjusted to 2014 Estonian population for age;
Adjusted prevalence rate ratios show the relative difference of the prevalence rates between men and women;
p-value below 0.0125 (after Bonferroni correction) was considered significant;
Abbrevations: PD, Parkinson's disease; CI, confidence intervals; RR, rate ratio.

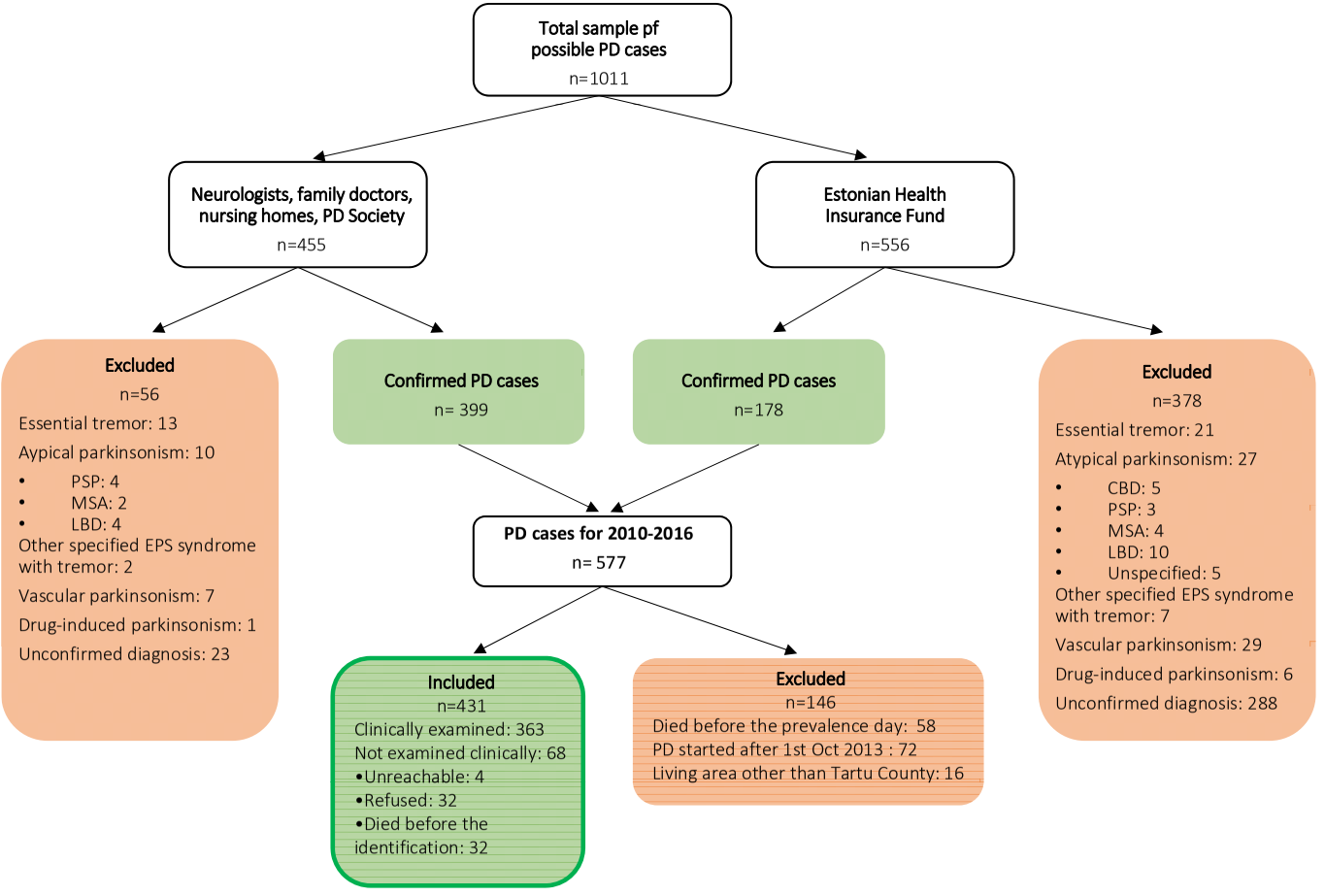

Figure 1. Flow diagram of the case-ascertainment procedure.

Abbrevations: PD, Parkinson's disease; PSP, progressive supranuclear palsy; MSA, Multiple system atrophy; LBD, dementia with Lewy bodies; CBD, corticobasal degeneration; EPS, extrapyramidal syndrome.

The age-specific, total crude and age-adjusted prevalence rates of current study and the study conducted in Estonia in 1996 are shown in Table 9. We found that the overall age-adjusted prevalence rate was significantly higher in the current study (RR=1.30, p=0.004), and among men (RR=1.44, p=0.0018; Table 9).

Clinical and socio-demographic data of the 363 patients (139 men, 224 women) involved in the full clinical examination are shown in Table 10. A total of 82.1% were using levodopa at the time of examination; 27% dopamine agonists; 17% MAO-B inhibitors; 16% amantadine; and 3% anticholinergics. Out of those on levodopa treatment, 63% were using controlled-release levodopa, 14% standard release levodopa; and 9% combination with a COMT-inhibitor carbidopa/levodopa/entacapon. The mean daily levodopa dose was 398 ± 219 mg (range: 100–1700). The proportion of patients with cognitive impairment was 23% (MMSE score ≤24), and with depressive symptoms 48% (BDI score ≥14).

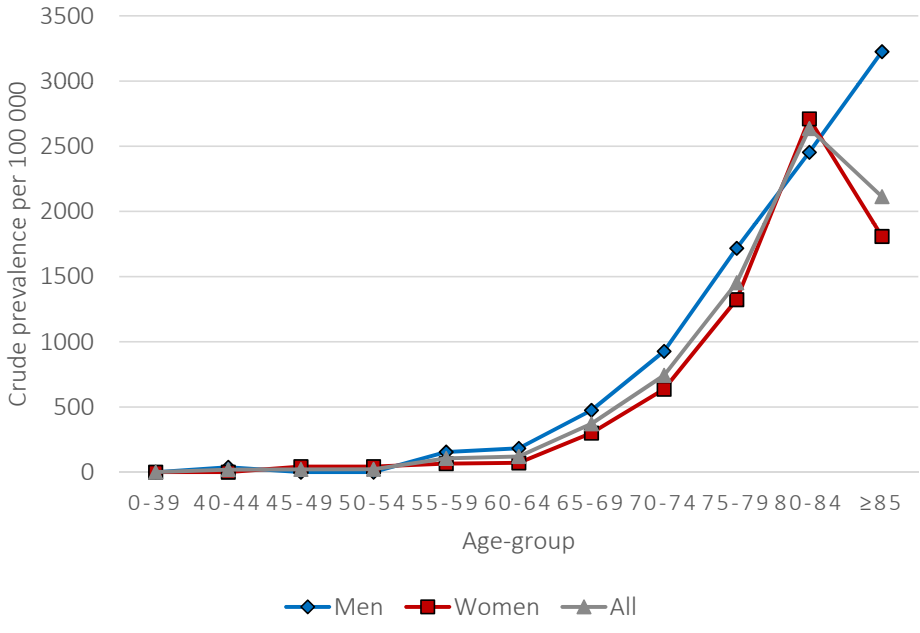

Figure 2. Age-specific prevalence rates of PD for all patients and according to gender on the prevalence day of 1st October, 2013.

Abbrevations: PD, Parkinson's disease.

Table 9. Age-specific, total crude for all, and age-adjusted prevalence rates for all and subgroups in two epidemiological studies of PD in Tartu, Estonia.

	Study population, 1996			Study population, 2013		
Age groups	Cases	Population	Age-specific rate/100,000	Cases	Population	Age-specific rate/100,000
0–39	0	87745	0	0	82322	0
40–44	3	9597	31	2	10580	19
45–49	1	8882	11	2	9302	22
50–54	7	8517	82	9	8958	22
55–59	15	8828	170	9	8472	106
60–64	24	8070	297	23	7486	120
65–69	53	7564	701	48	6195	371
70–74	76	5951	1277	77	6460	743
75–79	37	3218	1150	90	5298	1453
80–84	43	2855	1506	104	3945	2636
85+	11	2013	546	67	3170	2114
Total	270	153,240		431	152,188	
Total crude rates/ 100,000 (95%CI)		176 (155–197)				283 (257–310)

Adjusted rates/ 100,000 (95%CI)[a]	Study population, 1996	Study population, 2013	RR	p-value
All	152 (128–176)	197 (178–216)	1.30	0.004[b]
Males	154 (130–178)	221 (187–256)	1.44	0.0018[c]
Females	153 (128–177)	183 (160–206)	1.20	0.08[c]
Urban	160 (135–185)	198 (175–221)	1.24	0.029[c]
Males	171 (146–197)	232 (189–275)	1.36	0.017[c]
Females	157 (133–182)	178 (151–205)	1.13	0.26[c]
Rural	139 (116–162)	193 (158–228)	1.39	0.011[c]
Males	128 (106–150)	204 (143–265)	1.59	0.022[c]
Females	145 (122–169)	194 (149–239)	1.34	0.058[c]

[a] Adjusted to 1989 Estonian population for age;
[b] For overall comparison between the two studies a p-value below 0.05 was considered statistically significant;
[c] For the additional comparison among the subgroups the significance threshold after Bonferroni correction was set to 0.0062.
Abbrevations: PD, Parkinson's disease; CI, confidence interval; RR, rate ratio.

Table 10. Characteristics of prevalent patients with PD, clinical evaluation conducted in period 2010–2016.

Variable	Mean (SD) or n (%)	Range
Age at examination, years (n=363)	74.8 (8.9)	47–96
Disease duration, years (n=360)	7.0 (5.5)	0.3–35
Clinical phenotype (n=363)		
Tremor	157 (43.3%)	
PIGD	101 (27.8%)	
Akinesia-rigidity	105 (28.9%)	
MDS-UPDRS score (n=363)		
Part I	13.3 (7.8)	0–39
Part II	17.2 (9.0)	1–52
Part III	44.6 (18.5)	8–106
Part IV	0.9 (2.9)	0–18
HY (n=363)		
1–1.5	41 (11.3%)	
2–2.5	110 (30.3%)	
3	108 (29.8%)	
4	85 (23.4%)	
5	19 (5.2%)	
SE-ADL* (n=363)	75*	0–100
MMSE* (n=348)	28*	0–30
BDI (n=318)	15.1 (8.9)	0–47
Duration of levodopa treatment, years (n=298)	4.5 (5.0)	0.1–22
LEDD, mg (n=363)	396 (328)	0–2518
Living status (n=363)		
With a spouse	167 (46%)	
With children	65 (17.9%)	
Alone	103 (28.4%)	
Nursing institution	28 (7.7%)	
Education (n=362)		
Primary	132 (36.5%)	
Secondary	141 (38.9%)	
Higher	89 (24.6%)	
Exposure to toxins (n=363)		
Pesticides	13 (3.6%)	
Heavy metals	16 (4.4%)	
Solvents and paints	51 (14%)	
Current smoking	16 (4.4%)	
Former smoking	68 (18.7%)	

* median

Abbrevations: PD, Parkinson's disease; SD, standard deviation; n, number of patients; PIGD, postural instability and gait disorder; MDS-UPDRS, Movement Disorders Society Unified Parkinson´s Disease Rating Scale; HY, Hoehn and Yahr stage; SE-ADL, Schwab and England Activities of Daily Living Scale; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory; LEDD, levodopa equivalent daily dose.

5.2. Incidence and mortality of PD

5.2.1. Incidence of PD

388 cases of PD incidence were found over the course of 1,699,709 person-years. The clinical and socio-demographic data together with information on exposure to toxins are illustrated in Table 11. Age-specific incidence rates for both males and females rose exponentially until the 75–79 and 80–84 years age-groups, after which they sharply declined. The age-distribution of subjects by onset age, as well as age-specific rates for the total cohort, are illustrated in Figure 3. Males had a slightly higher age-adjusted incidence rate than did females; this difference was statistically significant (RR=1.25; p=0.04). Incidence rates among people living in rural vs. urban were identical (RR=1.0; p=0.97). Comparison of the age-specific, total crude and age-adjusted incidence rates in two epidemiological PD studies are provided in Table 12. Statistically significant differences between the current and previous study were found only for males (Table 12).

Sensitivity analysis confirmed that the age-adjusted incidence rates for all the subgroups (men, women, urban and rural patients) in the primary analysis (data extracted from the period of 2002–2012) were relatively comparable to the corresponding rates obtained for the period of 2010–2012. However, the total age-adjusted incidence rate (18.5/100,000) obtained from our primary incidence analysis was slightly below the confidence interval from the corresponding estimate retrieved from the analysis limited to the 2010–2012 period. Details of the sensitivity analysis are depicted in Table 13.

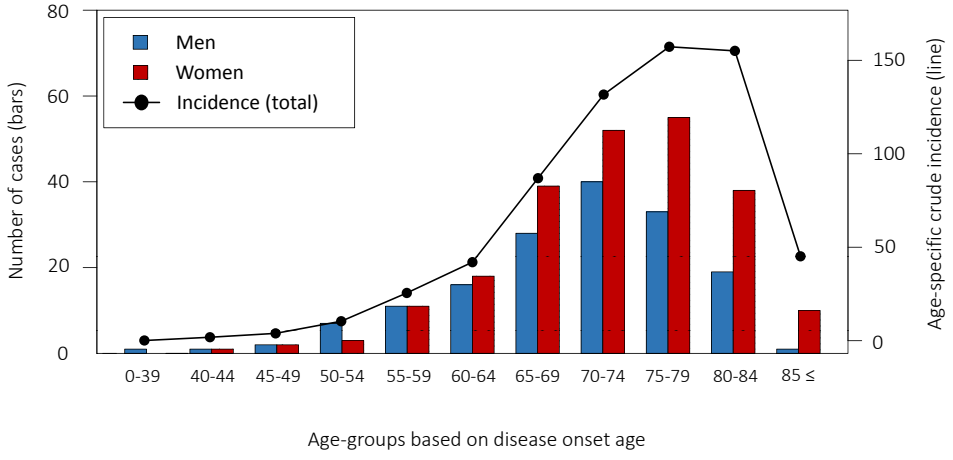

Figure 3. The overall age-specific incidence rates per 100,00 person-years, and age-distribution of PD cases stratified by gender in Tartu, Estonia, 2002–2012.

Abbrevations: PD, Parkinson's disease.

Table 11. Clinical and socio-demographic data of the incident patients with PD (disease onset between 2002–2012, clinical evaluation conducted in period 2010–2016), stratified by gender.

Characteristic	Mean (±SD) or n (%)			p-value
	Overall	Men	Women	
Age at onset of PD symptoms, years (n=388)	71.4 (8.7)	69.7 (9.0)	72.6 (8.4)	0.001[a]
Age at diagnosis, years (n=388)	73.1 (8.8)	71.3 (9.0)	74.4 (8.4)	0.0007[a]
Time from onset of PD symptoms to the diagnosis, years (n=388)	1.8 (1.8)	1.7 (1.7)	1.9 (2.0)	0.5[b]
First PD symptom (n=357)				
Tremor	232 (65.0)	85 (59.0)	147 (69.0)	
Bradykinesia-rigidity	65 (18.2)	33 (22.9)	32 (15.0)	
Handwriting problems	12 (3.4)	7 (4.9)	5 (2.4)	0.13[c]
Gait problems	39 (10.9)	14 (9.7)	25 (11.7)	
Other	9 (2.5)	5 (3.5)	4 (1.9)	
Nationality (n=386)				
Estonian	333 (86.3)	138 (87.3)	195 (85.5)	
Russian	47 (12.2)	18 (11.4)	29 (12.7)	0.92[c]
Other	6 (1.5)	2 (1.3)	4 (1.8)	
Living area (n=388)				
Urban	248 (63.9)	101 (63.5)	147 (64.2)	
Rural	140 (36.1)	58 (36.5)	82 (35.8)	0.98[d]
Exposure to toxins (n=309)				
Pesticides	13 (4.2)			
Fertilizers	11 (3.6)			
Heavy metals	12 (3.9)			
Solvents and paints	40 (12.9)	15 (12)	25 (13.6)	0.81[d]
Current smoking	18 (5.8)	9 (7.2)	9 (4.9)	0.55[d]
Former smoking	56 (18.1)	20 (16.0)	36 (19.6)	0.52[d]
PD family history (n=303)				
1st degree relative	23 (7.6)	11 (8.7)	12 (6.7)	
2nd degree relative	7 (2.3)	3 (2.3)	4 (2.3)	0.77[c]

Statistical tests used for gender comparisons:
[a] Student´s t-test;
[b] Wilcoxon test;
[c] Fischer exact test;
[d] Chi-squared test.
Exposure to certain toxins (i.e. pesticides, fertilizers, heavy metals) were very infrequent, therefore their prevalence is not displayed separately for men and women.
Abbrevations: PD, Parkinson´s disease; SD, standard deviation; n, number.

Table 12. Age-specific, total crude and age-adjusted incidence rates in two epidemiological PD studies in Tartu, Estonia.

Age group	Study population, 1990–1998			Study population, 2002–2012		
	Cases	Person-years at risk	Age-specific crude rate/100,000 person-years	Cases	Person-years at risk	Age-specific crude rate/100,000 person-years
All						
<39	1	814 674	0.1	1	961 481	0.1
40–44	2	87 085	2.3	2	108 521	1.8
45–49	5	79 848	6.3	4	102 467	3.9
50–54	14	80 178	17.5	10	96 075	10.4
55–59	11	79 783	3.8	22	86 167	25.5
60–64	35	75 148	46.6	34	80 966	42.0
65–69	69	66 479	103.8	67	77 067	86.9
70–74	60	47 909	125.2	92	69 871	131.7
75–79	36	33 976	106.0	88	55 965	157.2
80–84	24	24 233	99.0	57	36 762	155.1
85+	7	18 443	38.0	11	24 371	45.1
All ages	264	1 407 756	18.8 (10.3–27.2)	388	1 699 709	22.8 (20.6–25.1)
Men						
<39	0	410 227	0	1	483 845	0.2
40–44	2	41 606	4.8	1	53 546	1.9
45–49	4	37 069	10.8	2	49 211	4.1
50–54	5	36 212	13.8	7	44 811	15.6
55–59	3	34 921	8.6	11	38 553	28.5
60–64	13	31 163	41.7	16	34 492	46.4
65–69	25	24 682	101.3	28	30 419	92.0
70–74	15	15 490	96.8	40	25 389	157.5
75–79	13	9931	130.9	33	17 694	186.5
80–84	8	6538	122.4	19	9731	195.3
85+	2	4470	44.7	1	5261	19.0
All ages	90	652 309	13.8 (6.5–21.1)	159	792 950	20.1 (16.9–23.2)

Table 12. Continuation

Age group	Study population, 1990–1998			Study population, 2002–2012		
	Cases	Person-years at risk	Age-specific crude rate/100,000 person-years	Cases	Person-years at risk	Age-specific crude rate/100,000 person-years
Women						
<39	1	404 445	2.1	0	477 636	0
40–44	0	45 479	0	1	54 975	1.8
45–49	1	42 779	2.3	2	53 256	3.8
50–54	9	43 967	20.5	3	51 264	5.9
55–59	8	44 862	17.8	11	47 615	23.1
60–64	22	43 985	50.0	18	46 474	38.7
65–69	44	41 798	105.3	39	46 649	83.6
70–74	45	32 419	138.8	52	44 481	116.9
75–79	23	24 045	95.7	55	38 271	143.7
80–84	16	17 695	90.4	38	27 031	140.6
85+	5	13 973	35.8	10	19 111	52.3
All ages	174	755 477	23.0 (13.6–32.4)	229	906 759	25.3(22.0–28.5)

Age-adjusted incidence rates/ 100,000 person-years[a]			RR	p-values
All	16.8 (14.7–19.0)	18.5 (16.6–20.4)	1.11	0.19
Men	16.6 (13.5–19.8)	21.3 (18.0–24.7)	1.29	0.04
Women	17.1 (14.2–20.1)	16.8 (14.5–19.0)	1.0	0.99

[a] Adjusted to 1989 Estonian standard population for age;
For the comparison between the two studies a p-value below 0.05 was considered statistically significant;
Abbrevations: PD, Parkinson's disease; CI, confidence interval; RR, rate ratio.

Table 13. Sensitivity analysis – crude and age-adjusted incidence rates obtained from two periods based on the onset year of the disease (2002–2012, n=137; and 2010–2012, n=388).

	Disease onset in period 2010–2012		Disease onset in period 2002–2012	
	Crude incidence rate (95% CI)	Age-adjusted incidence rates/ 100,000 person-years[a] (95% CI)	Crude incidence rate (95% CI)	Age-adjusted incidence rates/ 100,000 person-years[a] (95% CI)
All	29.5 (24.6–34.5)	23.0 (19.1–27.0)	22.8 (20.6–25.1)	18.5 (16.6–20.4)
Men	25.9 (19.1–32.7)	27.6 (20.3–34.9)	20.1 (16.9–23.2)	21.3 (18.0–24.7)
Women	32.7 (25.6–39.9)	19.7 (15.3–24.2)	25.3 (22.0–28.5)	16.8 (14.5–19.0)
Urban	28.3 (22.4–34.3)	22.7 (17.9–27.6)	22.0 (19.3–24.8)	18.4 (16.1–20.8)
Rural	32.0 (23.1–40.8)	23.3 (16.7–29.8)	24.4 (20.4–28.5)	18.5 (15.3–21.6)

[a] Adjusted to 1989 Estonian standard population for age;
Abbrevations: PD, Parkinson's disease; CI, confidence interval.

5.2.2. Mortality and causes of death

The SMRs of the inception cohort were as follows: 1.12 for all (95% CI 0.88–1.36; p=0.3), 1.06 for the women (95% CI 0.77–1.37; p=0.7, and 1.11 for the men (95% CI 0.76–1.45; p=0.5) in our study. The SMRs of the non-inception cohort were as follows: 1.42 for all (95% CI 1.19–1.65; p=0.00001), 1.44 for the women (95% CI 1.13–1.74; p=0.0007), and 1.32 for the men (95% CI 0.99–1.65; p=0.03). The SMR of cancer was 0.86 (95% CI 0.56–1.15; p=0.4), and the SMR for vascular diseases was 1.3 (95% CI 1.1–1.51; p=0.001). Descriptive statistics on comorbidities and mortality are illustrated in Table 14.

Table 14. Morbidity and mortality data of PD patients who died during 2010–2016, Tartu, Estonia.

Characteristic	**Mean (±SD) or n (%)**			**p-value**
	Overall	Men	Women	
Number of patients	235 (100)	103 (43.8)	132 (56.2)	0.06[a]
Mean age at death, yrs	81.3 (6.7)	79.2 (6.8)	82.9 (6.2)	<0.00001[b]
PD duration until death, yrs	9.5 (6.4)	9.1 (6.3)	9.8 (6.4)	0.4[c]
Comorbidities during lifetime*				
Cerebrovascular	46 (19.7)	24 (23.3)	22 (16.8)	0.28[a]
Diabetes	31 (14.1)	15 (14.6)	18 (13.7)	1.0 [a]
Cardiovascular	182 (77.8)	75 (72.8)	107 (81.7)	0.14[a]
Tumors	44 (18.8)	22 (21.3)	22 (16.8)	0.47[a]
Rheumatological	72 (30.8)	22 (21.4)	50 (38.2)	0.01[a]
Peptic ulcer/gastritis	21 (9.0)	11(10.7)	10 (7.6)	0.56[a]
Psychiatric	20 (8.5)	5 (4.9)	15 (11.5)	0.12[a]
Immediate causes of death				
Cardiovascular	138 (58.7)	60 (58.3)	78 (59.1)	
Cerebrovascular	29 (12.3)	11 (10.7)	18 (13.6)	
Cancer	25 (10.6)	13 (12.6)	12 (9.1)	
PD	14 (6.0)	7 (6.8)	7 (5.3)	
Respiratory	14 (6.0)	6 (5.8)	8 (6.1)	
Sepsis	5 (2.1)	2 (1.9)	3 (2.3)	
Gastrointestinal	2 (0.9)	0 (0)	2 (1.5)	
Genitourinary	2 (0.9)	1 (1.0)	1 (0.8)	
Trauma	3 (1.3)	2 (1.9)	1 (0.8)	
Other	3 (1.3)	1 (1.0)	2 (1.5)	

* Data missing for one patient;
Statistical tests used for gender comparisons: [a] chi-squared test; [b] Student´s t-test; [c] Wilcoxon test;
Abbrevations: PD, Parkinson's disease; SD, standard deviation; n, number.

Of the deceased subjects with clinically-diagnosed PD (n=235), 46.8% had PD noted on their death certificates. Immediate causes of death are illustrated in Table 14. The most frequent underlying causes of death were cardiovascular diseases (58.3%), cancer (14.0%), PD (13.6%) and cerebrovascular diseases (6.4%). PD was cited as a contributory cause of death on 32.8% of the death certificates.

5.3. Prevalence and factors associated with motor complications in PD

Out of 328 patients on levodopa (130 men and 198 women), some type of motor complication was present in 85 patients (25.9%). Dyskinesias were present in 21% of patients and motor fluctuations in 20.1%, while 61% of all of those with motor complications experienced both fluctuations and dyskinesias. The sources for the case-identification of 69 patients with dyskinesias were distributed as follows: 61% were recorded on both patient cards and MDS-UPDRS Part IV, 29% on patient cards, and 10% on MDS-UPDRS Part IV. Presence of motor fluctuations among 66 patients was indicated as follows: 68% from both patient cards and MDS-UPDRS Part IV, 20% from MDS-UPDRS Part IV, and 12% from patient cards. The functional impact of dyskinesias was reported to be at least moderate (MDS-UPDRS item 4.2≥3) by 17.4% of patients. Just over one third of those patients with motor fluctuations indicated that the functional impact of off-state was at least moderate (MDS-UPDRS item 4.4≥3). As Table 15 shows, prevalence of motor complications was relatively low earlier in the course of PD but increased with the duration of levodopa treatment.

Table 15. Motor complications in levodopa users according to the duration of levodopa treatment.

Patients on levodopa therapy	Motor fluctuations	Dyskinesias	Motor fluctuations and/or dyskinesias
All patients (n=328)	66 (20.1%)	69 (21%)	85 (25.9%)
≤2.5 years (n=147)	7 (4.8%)	5 (3.4%)	9 (6.1%)
2.6–5 years (n=66)	14 (21.2%)	11 (16.7%)	19 (28.8%)
5.1–10 years (n=62)	19 (30.6%)	24 (38.7%)	27 (43.5%)
10.1–15 years (n=38)	15 (39.5%)	19 (50%)	19 (50%)
≥15.1 years (n=15)	11 (73.3%)	10 (66.7%)	11 (73.3%)
p-value*	<0.0001	<0.0001	<0.0001

* Fisher's exact test was used to examine the significance of the association (contingency) between the two kinds of classification;
Statistically significant p-values were set at 0.017.

The clinical profile of the entire study sample, as well as the group comparisons of those with and without motor complications, is depicted in Table 16. The ratio of females to males was similar in patients with and without motor complications (approximately 60% of females and 40% of males in both groups). Patients with motor complications were younger than patients without motor complications (71.7±8.9 vs. 75.2±8.2 years; t-test, p=0.002). The differences were most evident when regarding age at PD onset and duration of the disease. The outcomes of most of the clinometric scales differed more or less between patients with and without motor complications. No differences were seen in the severity of PD assessed by HY, with a median value of 3 in both groups. No statistically significant differences were found in the MMSE scores, with the median value of 27 among those without and 28 among those with motor complications (Mann-Whitney U test, p=0.08). Duration of levodopa treatment was higher among patients with motor complications compared to those without (8.8±5.3 vs. 3.7±4.1 years; Mann-Whitney U test, p<0.0001). Other antiparkinsonian treatment-related characteristics are shown in Table 17.

The results of the logistic regression can be found in Table 18. An increase of LEDD by one unit (keeping all other variables fixed) increased the odds of having motor complications by 0.3% (p=0.0005). As a hypothetical example, if there were two patients who differed in that one of them had a LEDD of 1000 mg and the other 1500 mg, and they were identical in all other variables entered into the model, then based on our model, the second patient would have 1.002561^500=3.69 times higher odds than the first of having motor complications.

Keeping all other variables fixed, each year of earlier initiation of levodopa from PD onset increased the odds of having motor complications by 34% (p=0.0006); each year younger of onset age increased the odds by 19.5% (p=0.000045); each year older of age at the time of examination increased the odds by 11% (p=0.018); and having akinesia-rigid phenotype of the disease (as opposed to the dominance of tremor) increased the odds by 156% (p=0.033). No statistically significant associations were found between motor complications and gender (p=0.3), PIGD-dominant phenotype of disease as opposed to tremor-dominant phenotype (p=0.9), BDI (p=0.8), MDS-UPDRS Part II and III scores (p=0.2, p=0.9, respectively), or PDQ-39 scores (p=0.5).

To confirm that the effect of clinical phenotype and LEDD is not due to possible confounders (duration of PD and duration of levodopa treatment), we conducted an analysis using the second model, in which we adjusted for these two possible confounders. LEDD (OR=0.003; 95% CI 1.001–1.004, p=0.0004) and akinesia-rigid phenotype as opposed to tremor-dominant phenotype (OR=2.549; 95% CI 1.1–6.2, p=0.04) still emerged as significant independent variables associated with the occurrence of motor complications with almost the same OR coefficients as in the first model. As a *post hoc* analysis we examined the LEDD of patients stratified by age and found that younger patients tended to be on a higher LEDD than older patients.

Table 16. Disease-related characteristics of PD patients with and without motor complications.

Variable	All patients n=328	Motor complications		p-value
		without n=243	with n=85	
Age at onset, years				
Mean (SD)	66.4 (10.4)	68.6 (9.7)	60 (9.6)	<0.0001[a]
Median (ranges)	67 (35–91)	70 (35–91)	61 (35–83)	
Missing	9	6	3	
Disease duration, years				
Mean (SD)	7.8 (6.2)	6.5 (5.8)	11.5 (5.7)	<0.0001[b]
Median (ranges)	6 (0–43)	5 (0.3–43)	10.6 (2.8–35)	
Missing	9	9	3	
Time from PD onset until diagnosis, years				
Mean (SD)	1.8 (3.0)	1.9 (3.4)	1.4 (1.7)	0.484[b]
Median (ranges)	1 (0–10)	1 (0–10)	1 (0–10)	
Missing	12	9	3	
Clinical phenotype of PD, n (%)				
Tremor	122 (37.2)	103 (42.4)	19 (22.4)	0.002[c]
Akinetic-rigid	120 (36.6)	77 (31.7)	43 (50.6)	
PIGD	86 (26.2)	63 (25.9)	23 (27.1)	
BDI				
Mean (SD)	15.7 (9.0)	15.1 (8.5)	17.4 (10.2)	0.126[b]
Median (ranges)	14 (0–48)	13 (0–45)	15 (2–48)	
Missing	44	32	12	
PDQ-39 SI				
Mean (SD)	31.9 (15.9)	30.5 (16.1)	35.9 (14.8)	0.011[a]
Median (ranges)	29.9 (1.6–71.1)	27.4 (1.6–71.1)	35.1 (6.6–68.6)	
Missing	43	31	12	
MDS-UPDRS Part I				
Mean (SD)	12.8 (6.8)	12.0 (6.5)	14.8 (7.1)	0.002[a]
Median (ranges)	12 (0–38)	12 (0–35)	14 (1–38)	
MDS-UPDRS Part II				
Mean (SD)	17.8 (8.9)	16.4 (8.1)	21.8 (10.0)	<0.0001[a]
Median (ranges)	17 (0–45)	15 (1–45)	20 (3–42)	
MDS-UPDRS Part III				
Mean (SD)	44.1 (18.0)	42.3 (16.6)	49.1 (20.7)	0.007[a]
Median (ranges)	41.5 (9–106)	40 (9–83)	48 (11–106)	

Statistical tests used for group comparisons:
[a] t-test; [b] Mann Whitney U test; [c] chi-squared test;
Statistically significant p-values after Bonferroni's correction were set at 0.0045;
Abbrevations: PD, Parkinson's disease; SD, standard deviation; n, number; PIGD, postural instability and gait disorder; BDI, the Beck Depression Inventory; PDQ-39 SI, the Parkinson's Disease Questionnaire Summary Index; MDS-UPDRS, the Movement Disorders Society's Unified Parkinson's Disease Rating Scale.

Table 17. Antiparkinsonian treatment of PD patients with and without motor complications.

Variable	All patients n=328	Motor complications		p-value
		without n=243	with n=85	
Current antiparkinsonian treatment, n (%)				
Levodopa summarily	328 (100%)	243 (100%)	85 (100%)	
Regular levodopa	62 (18.9%)	50 (20.6%)	12 (14.1%)	0.251[a]
CR levodopa	220 (67.1%)	181 (74.5%)	39 (45.9%)	<0.0001[a]
Soluble levodopa	6 (1.8%)	2 (0.8%)	4 (4.7%)	0.041[b]
Levodopa + COMT inhibitors	63 (19.2%)	19 (7.8%)	44 (51.8%)	<0.0001[a]
Dopamine agonists	103 (31.4%)	55 (22.6%)	48 (56.5%)	<0.0001[a]
MAO-B inhibitors	64 (19.5%)	46 (18.9%)	18 (21.2%)	0.771[a]
Amantadine	67 (20.4%)	32 (13.2%)	35 (41.2%)	<0.0001[a]
Anticholinergics	9 (27%)	8 (3.3%)	1 (1.2%)	0.456[b]
Time from PD onset until levodopa treatment, years				
Mean (SD)	2.6 (3.6)	2.6 (3.9)	2.5 (2.7)	
Median (ranges)	2 (0–10)	2 (0–38)	2 (0–13)	0.629[c]
Missing	9	6	3	
Levodopa daily dose, mg				
Mean (SD)	433.5 (221.9)	390.8 (184.0)	555.3 (271.8)	<0.0001[c]
Median (ranges)	400 (100–1300)	400 (100–1000)	500 (100–1300)	
LEDD, mg				
Mean (SD)	537.1 (362.7)	421.7 (222.9)	865.8 (469.3)	<0.0001[c]
Median (ranges)	450 (75–2518)	399 (75–1120)	808.5 (100–2518)	
Missing	1	1	0	

Statistical tests used for group comparisons:
[a] chi-squared test;
[b] Fischer's exact test;
[c] Mann Whitney U test;
Statistically significant p-values after Bonferroni's correction were set at 0.0041;
Abbrevations: PD, Parkinson's disease; n, number; SD, standard deviation; CR, controlled release; LEDD, levodopa equivalent daily dose.

In order to assess a possible association between levodopa daily dose and the presence of motor complications, we conducted an analysis based on another logistic model in which we entered all the same variables as in the first model but included levodopa daily dose instead of LEDD. No evidence was found for associations between motor complications and levodopa daily dose (OR=1.002; 95% CI–1.0 to 1.003, p=0.07).

Table 18. Factors associated with motor complications in PD: the logistic regression model.

Variable	Odds ratio	95% CI
Gender	1.616	0.721–3.727
Age	1.106*	1.018–1.203
Age at onset of PD	0.837***	0.766–0.910
Time from onset to initiation with levodopa	0.746***	0.624–0.870
Akinetic-rigid phenotype	2.559*	1.087–6.199
PIGD phenotype	1.024	0.379–3.188
LEDD	1.003***	1.001–1.004
MDS-UPDRS II	1.058	0.979–1.145
MDS-UPDRS III	0.998	0.969–1.027
BDI	1.008	0.956–1.063
PDQ-39 SI	0.987	0.956–1.019

***p<0.001, **p <0.01, *p<0.05;
Abbrevations: PD, Parkinson's disease; CI, confidence interval; PIGD, postural instability and gait disorder; LEDD, levodopa equivalent daily dose; MDS-UPDRS, the Movement Disorders Society's Unified Parkinson's Disease Rating Scale; BDI, the Beck Depression Inventory; PDQ-39 SI, the Parkinson's Disease Questionnaire Summary Index.

5.4. Prevalence and factors associated with non-motor symptoms in PD

The basic characteristics of the sample of 268 PD patients included: mean age equalled 74.2±8.8 years (range: 47–96 years), duration of the disease was 7.6±5.9 years (range: 0.1–35 years), and age at onset amounted to 66.8±10.1 years (range: 35–88 years). Of the total sample, 94.8% were on antiparkinsonian treatment. A total of 81.3% were using levodopa therapy (41% on monotherapy); 31.3% dopamine agonists; 19% amantadine; 17.5% MAO-B inhibitors; 3% anticholinergics, and 35.8% were undergoing a combination of therapies. The mean duration of levodopa therapy at enrolment was 5.03±5.2 years (range: 0.1–23) and the mean daily dose of levodopa 430±232 mg (range: 100–1200 mg).

Among the patients screened, 99.6% complained of at least one non-motor symptom. There were a mean number of 6.7± 2.5 non-motor symptoms per patient of the 13 symptoms included in the MDS-UPDRS Part I. The most

frequent non-motor symptoms were cognitive impairment, night time sleep disorders, bladder disorders, fatigue, pain, daytime sleepiness and depression. Hallucinations and ICDs were the most infrequently reported non-motor symptoms. We did not find a statistically significant difference between mean BDI scores for persons with PD and with ICDs, and persons with PD and without ICDs (mean score 19.1 and 15.1, respectively, p= 0.254). Prevalence of non-motor symptoms is given in Table 19.

Table 19. Prevalence of non-motor symptoms (n=268).

Non-motor symptoms	**N**	**%**
Cognitive impairment	199	74.3%
Nighttime sleep problems	192	71.6%
Urinary problems	192	71.6%
Fatigue	184	68.7%
Pain	172	64.2%
Daytime sleepiness	166	61.9%
Depressed mood	163	60.8%
Constipation problems	156	58.2%
Anxious mood	151	56.3%
Lightheadedness on standing	140	52.2%
Apathy	122	45.7%
Hallucinations and psychosis	37	13.8%
ICDs	21	7.8%

Abbrevations: ICDs, impulse control disorders.

The frequency of non-motor symptoms was high, but the severity was assessed as low by the patients. The distribution of scores according to the severity range 0–4 and the mean scores for each item are provided in Figure 4. Most frequently, in cases of the presence of a non-motor symptom, patients reported the problem to be slight or mild (scores 1–2), night-time sleep disorders had the highest and ICDs the lowest mean score.

Statistically significant differences in the mean scores of MDS-UPDRS Part I among patient subgroups are shown in Figure 5: higher scores were seen in patients with a longer duration and advanced stages of the disease, the PIGD-dominant motor phenotype and the presence of motor complications, depression, and impaired cognitive status. There were no statistically significant differences between the mean MDS-UPDRS Part I scores in terms of gender, age, and age at onset of the disease. As regards motor complications in their variations, significantly higher MDS-UPDRS Part I scores were reported in patients with motor fluctuations, compared to non-fluctuating patients ($p<0.026$), but no difference was seen comparing patients with or without dyskinesias ($p<0.046$), nor with or without off-period dystonia ($p<0.065$).

A significantly increased frequency of some non-motor symptoms in several specific subgroups of PD patients is shown in Table 20a and 20b. The different profile of specific non-motor symptoms was found in all group comparisons, including a higher rate of ICDs and fatigue in patients with onset age ≤50 years compared to patients with onset age ≥65 years. In patients of a more severe disease stage, most of the non-motor symptoms were more frequently complained of when compared to patients of less severe disease stage or disability. Additionally, several specific non-motor symptoms including hallucinations and psychoses, depressed mood, sleep problems, and fatigue occurred more frequently in patients with motor complications compared to patients without those disabling problems (Table 20b).

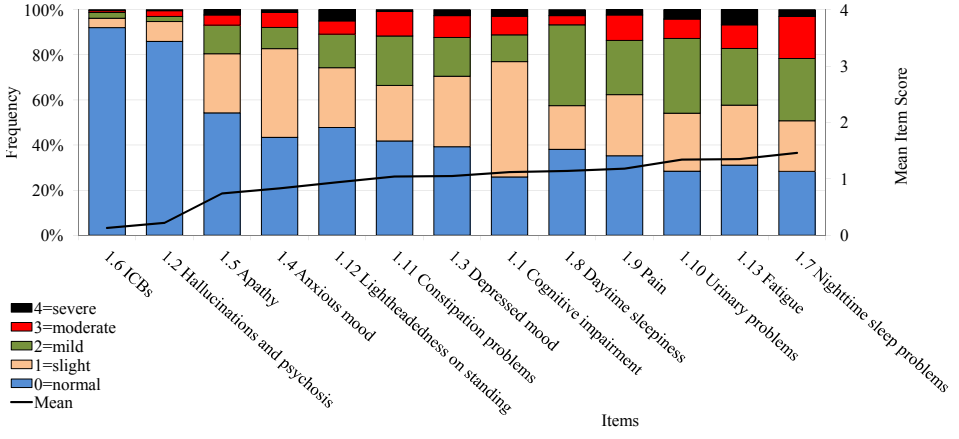

Figure 4. Bar diagram showing the two aspects of the severity of each non-motor symptom. Firstly, the proportional distribution of responses of MDS-UPDRS Part I for each item is shown in bars. Severity scores range from 0 (symptom is absent) to 4 (symptom is severe). Secondly, the mean scores of each item of MDS-UPDRS Part I are shown by the continuous line, ICDs being with the lowest and nighttime sleep problems with the highest value.

Abbrevations: MDS-UPDRS, the Movement Disorders Society's Unified Parkinson's Disease Rating Scale ICDs, impulse control disorders.

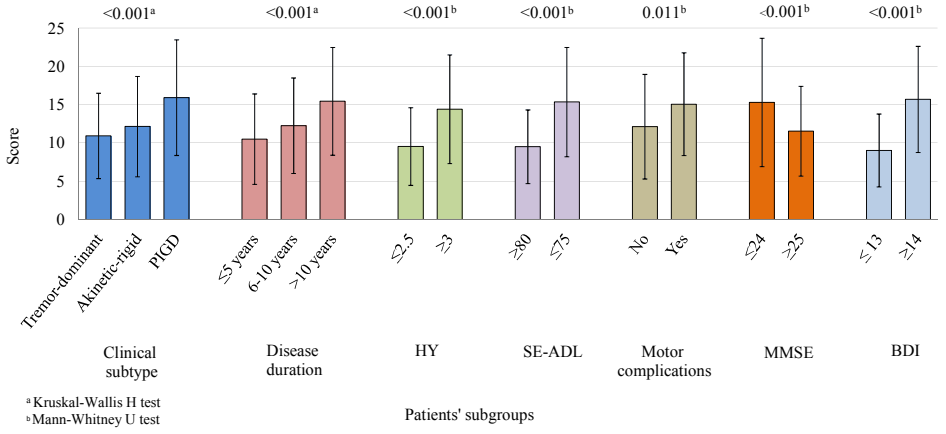

Figure 5. Bar diagram showing significant differences in mean scores of MDS-UPDRS Part I among subgroups of patients.

Abbrevations: PIGD, postural instability and gait disorder; HY, Hoehn and Yahr stage; SE-ADL, Schwab and England Activities of Daily Living Scale; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory.

Table 21 illustrates the correlation analysis between the MDS-UPDRS Part I scores and different variables. The strongest correlations were found between BDI and MDS-UPDRS Part I (ρ=0.621, $p<0.001$) and between PDQ-39 and MDS-UPDRS Part I (ρ=0.617, $p<0.001$), indicating that the presence of higher load of non-motor symptoms was associated with more severe depression or reduced quality of life. When assessing correlations between individual non-motor symptoms, we found a statistically significant association between a depressed mood and anxiety (ρ=0.492, $p<0.001$) and between a depressed mood and apathy (ρ=0.451, $p<0.001$), indicating that more depressed patients have more frequently also other psychiatric symptoms. For the correlations between individual non-motor symptoms and total MDS-UPDRS Part I scores, we found that cognitive impairment (ρ=0.623, $p<0.001$) and fatigue (ρ=0.66, $p<0.001$) were strongly related to the higher overall burden of non-motor symptoms.

Table 20a. Frequency of each non-motor symptom among patients´ subgroups (n=268).

	Gender		**Age**		**Disease onset age**		**Disease duration**			**Clinical phenotype**		
	Male (n=105)	Female (n=163)	≤64 (n=35)	≥65 ((n=233)	≤50 (n=20)	≥65 (n=165)	≤5 (n=120)	6–10 (n=68)	>10 (n=72)	Tremor (n=110)	Akinesia-rigidity (n=77)	PIGD (n=73)
1.1 Cognitive impairment	75.2%	73.6%	51.4%	77.7%**	60.0%	78.7%	70.8%	72.1%	81.3%	69.1%	74.0%	82.2%
1.2. Hallucinations and psychosis	14.3%	13.5%	11.4%	77.7%	20.0%	10.9%	7.5%	16.2%	21.3%*	10.0%	13.0%	20.5%
1.3. Depressed mood	49.5%	68.1%	62.9%	60.5%	75.0%	60.6%	60.0%	48.5%	72.5%*	57.3%	59.7%	68.5%
1.4. Apathy	45.7%	63.2%**	69.7%	55.2%	55.0%	52.7%	52.9%	55.9%	62.5%	53.6%	54.5%	65.8%
1.5. Anxious mood	38.1%	50.3%**	48.6%	45.3%	45.0%	43.9%	39.5%	44.1%	56.3%	43.1%	41.6%	56.2%
1.6. ICDs	9.5%	6.7%	14.3%	6.9%	20%*	4.9%	4.2%	10.3%*	11.3%*	6.4%	10.4%	8.2%
1.7. Nighttime sleep problems	69.5%	73.0%	74.3%	71.2%	85%	67.3%	63.3%	73.5%	82.5%*	69.1%	74.0%	78.1%
1.8 Daytime sleepiness	70.5%*	56.4%	45.7%	63.4%*	50%	61.8%	52.5%	66.2%	72.5%*	55.5%	62.3%	74.0%*
1.9. Pain	51.4%	72.4%***	54.3%	65.7%	65.0%	64.6%	61.3%	61.8%	72.2%	63.3%	67.1%	69.9%
1.10. Urinary problems	77.1%	68.1%	60.0%	74.0%	65.0%	70.3%	66.7%	70.6%	80.0%	64.5%	74.0%	79.5%
1.11. Constipation	60.0%	57.1%	37.1%	61.4%**	30.0%	61.6%**	55.0%	55.9%	65.0%	53.6%	58.4%	67.1%
1.12. Lightheadedness on standing	42.9%	58.3%*	48.6%	52.8%	40.0%	55.2%	50.8%	51.5%	55.0%	50.9%	48.1%	61.6%
1.13. Fatigue	67.7%**	46.0%	70.6%	68.7%	89.5%*	63.6%	59.2%	71.6%	81.3%**	59.6%	70.1%	80.8%*

*p<.05; **p<.01;***p<0.001;
Chi-squared test for all the differences in the frequency of individual non-motor symptoms, except Fischer exact test in the frequency of (1) 1.2, 1.3, 1.5, 1.7, 1.13 among age onset groups; (2) 1.2 among age groups; and (3) 1.6 among age, disease onset age and disease duration groups.
Abbrevations: ICDs, impulse control disorders; PIGD, postural instability and gait disorder.

Table 20b. Frequency of each non-motor symptom among patients with and without motor complications (n=237).

	Dyskinesias		**Motor fluctuations**		**Off-state dystonias**	
	No (n=236)	Yes (n=31)	No (n=237)	Yes (n=30)	No (n=251)	Yes (n=16)
1.1 Cognitive impairment	73.4%	80.6%	73.8%	80.0%	74.1%	81.2%
1.2 Hallucinations and psychoses	12.2%	25.8%*	12.2%	26.7%*	13.1%	25.0%
1.3 Depressed mood	57.4%	87.1%*	57.4%	90.0%*	58.6%	100.0%***
1.4 Apathy	55.3%	64.5%	55.3%	63.3%	55.8%	62.5%
1.5 Anxious mood	46.6%	38.7%	45.8%	43.3%	45.2%	50.0%
1.6 ICDs	6.8%	16.1%	6.3%	16.7%	6.8%	18.8%
1.7 Nighttime sleep problems	70.0%	83.9%	68.8%	93.3%*	70.1%	93.8%*
1.8 Daytime sleepiness	59.5%	80.6%*	58.6%	86.7%*	60.6%	81.2%
1.9 Pain	64.4%	66.7%	65.7%	58.6%	64.7%	68.8%
1.10 Urinary problems	70.9%	77.4%	70.9%	76.7%	72.1%	62.5%
1.11 Constipation problems	58.2%	58.1%	57.4%	63.3%	58.2%	56.2%
1.12 Lightheadedness on standing	52.7%	48.4%	52.7%	50.0%	53.8%	31.2%
1.13 Fatigue	66.9%	83.9%	66.9%	83.3%	67.2%	93.8%*

*p<.05; **p<.01;***p<0.001;
Chi-squared test for all the differences in the frequency of individual non-motor symptoms.
Abbrevations: ICDs, impulse control disorders.

Table 21. Spearman's correlation analysis between the total score of non-motor symptoms assessed by the MDS-UPDRS Part I, and variables.

Variable	Correlation coefficient ρ[a]	p-value
Age	0.192	0.002
Disease onset age	0.005	0.940
Duration of disease	0.278	<0.001
HY	0.457	<0.001
SE-ADL	–0.524	<0.001
BDI	0.621	<0.001
MMSE	–0.243	<0.001
PDQ-39 SI	0.617	<0.001
MDS-UPDRS II	0.579	<0.001
MDS-UPDRS III	0.364	<0.001
MDS-UPDRS IV	0.160	0.009
Duration of levodopa therapy	0.285	<0.001
Daily dose of levodopa	0.300	<0.001

[a] Spearman rank coefficient;
Abbrevations: MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; HY, Hoehn and Yahr stage; SE-ADL, Schwab and England Activities of Daily Living Scale; BDI, Beck Depression Inventory; MMSE, Mini Mental State Examination; PDQ-39 SI, Parkinson´s Disease Questionnaire Summary Index.

5.5. HRQoL of patients with PD

Demographic and clinical characteristics of the study population are given in Table 22. Men were slightly younger than women (72.1 and 75.6 years respectively, p=0.0014), which reflects the shorter life expectancy of men in Estonia. No significant differences in terms of PD onset age, disease duration, HY stage, SE-ADL stage or MMSE performance were found between men and women. The mean BDI depression score was significantly higher in women compared to men (17.1 and 12.3 respectively, p=0.0001). A significantly higher rate of men compared to women were: a family status as married (71.4% and 32.5 % respectively, p<0.0001), and living together with their spouse and or children (89.5% and 60.1% respectively, p<0.0001). There were more widows among female than male patients (48.5% and 17.1% respectively, p=0.02). Women had a higher mean number of comorbidities compared to men (2.2 and 1.9, respectively, p=0.0124), including a significantly higher rate of cardio-vascular diseases (99.4% and 89.6% respectively, p<0.0001). Mean scores of PDQ-39 domains are presented in Figure 6. In persons with PD, mobility was the most negative HRQoL domain and social support the least negative domain.

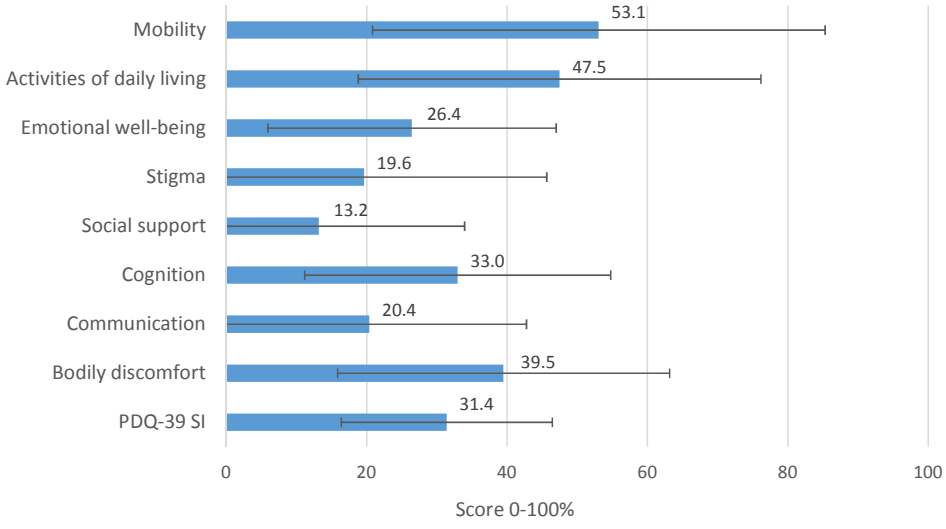

Figure 6. Mean values of PDQ-39 domains. HRQoL was assessed by using the PDQ-39. PDQ-39 is composed of 39 items grouped in 8 subscales: (1) mobility, (2) activities of daily living, (3) emotional well-being, (4) stigma, (5) social support, (6) cognition, (7) communication, and (8) bodily discomfort. The PDQ-39 SI is an overall score calculated from these domains, with 0 indicating the best HRQoL and 100 the worst.

Abbrevations: HRQoL, health-related quality of life; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; SI, Summary Index score.

Table 22. Characteristics of the PD patients included to the study on HRQoL (n=268).

Variable	Value	Range
Age, years [a]	74.2±8.8	47–96
Disease onset age, years [a]	66.8±10.1	35–88
Duration of disease [a]	7.6±5.9	1–35
HY ≥3, n (%)	164 (62.6%)	
SE-ADL ≤75%, n (%)	139 (53.3%)	
MMSE ≥25, n (%)	197 (76.7%)	
BDI ≥14, n (%)	134 (52.1%)	
MDS-UPDRS		
MDS-UPDRS Part I	12.52 (6.79)	0–38
MDS-UPDRS Part II	18.2 (8.4)	1–48
MDS-UPDRS Part III	46.3 (18.3)	10–106
MDS-UPDRS Part IV	1.3 (3.4)	0–18
Clinical subtype		
Tremor dominant	118 (44%)	
Akinetic-rigid dominant	77 (28.7%)	
PIGD	73 (27.3%)	
LEDD, mg[a]	427.5±231.6	100–1200
Duration of levodopa treatment, years [a]	3.9±5.03	0.1–23
Marital status, n (%)		
Single	20 (7.4%)	
Married	128 (47.8%)	
Divorced	23 (8.6%)	
Widowed	97 (36.2%)	
Living status, n (%)		
With a spouse	137 (51.1%)	
With children	55 (20.5%)	
Alone	66 (24.6%)	
Nursery home	10 (3.8%)	
Education, n (%)		
Primary	104 (38.8%)	
Secondary	95 (35.5%)	
Higher	69 (25.7%)	

[a] Mean±standard deviation;
Abbreviations: HRQoL, health related quality of life; HY, Hoehn and Yahr stage; mg, milligrams; SE-ADL, Schwab and England Activities of Daily Living Scale; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait disorder; LEDD, levodopa equivalent daily dose.

The results of univariate analysis of socio-demographic and clinical parameters and mean scores of PDQ-39 SI in persons with PD are shown in Table 23. Emotional well-being and bodily discomfort affected women significantly more than men (mean scores for the corresponding subdomains: 20.2 for men, 30.4 for women, p=0.0001; and 34.4 for men and 42.7 for women, p= 0.0048, respectively). Being over 65 years old was associated with lower mobility (mean scores 35.7 for ≤64 years old and 55.7 for ≥65 years old, p=0.0007); being younger was associated with higher stigmatisation (mean scores 31.3 for ≤64 years old and 17.9 for ≥65 years old, p=0.0012). Marital status was not significantly associated with PDQ-39 scores. Emotional well-being was significantly related to living status, i.e. patients living alone had lower emotional well-being compared to patients living with their spouse (mean scores 31.3 and 23.5, respectively, p=0.012). Education did not significantly influence overall HRQoL. People who had undergone no more than the primary level of education were significantly more affected in the domain of mobility (mean scores of 61.8 for patients with primary education, 49.9 for patients with secondary education, 44.3 for patients with higher education, p= 0.001).

Overall HRQoL was significantly lower in patients with depression, which had an impact on all the PDQ-39 domains. Longer disease duration, a HY stage ≥3 and SE-ADL ≤75% were associated significantly with lower overall HRQoL and affected most of the PDQ-39 domains. Patients with cognitive impairment had lower overall HRQoL and were significantly more adversely affected in the domains of mobility, activities of daily living and communication. By clinical PD subtype, the group with PIGD had the lowest overall HRQoL (compared to the tremor and akinetic-rigid clinical subtypes).

PDQ-39 SI correlated significantly with higher MDS-UPDRS Part II, BDI and MDS-UPDRS Part IB scores. All non-motor symptoms – except ICDs – correlated significantly with PDQ-39 SI. All correlations between PDQ-39 and the other characteristics of PD are shown in Table 24.

Table 23. PDQ-39 associations with demographic and clinical features.

Variable	PDQ-39 SI[a]	p value
Gender		0.066
Male	29.8 (15.5)	
Female	32.7 (15.1)	
Living area		0.192
Urban	32.5 (15.3)	
Rural	29.6 (15.1)	
Marital status		0.770
Single	32.7 (17.4)	
Married	30.8 (15.3)	
Divorced	34.2 (13.1)	
Widowed	31.7 (15.4)	
Living status		0.638
With a spouse	30.6 (15.4)	
With children	31.5 (17.1)	
Alone	33.5 (13.5)	
Nursery home	32.7 (15.3)	
Education		0.339
Primary	33.6 (13.6)	
Secondary	30.4 (15.1)	
Higher	30.1 (17.6)	
Clinical subtypes		0.0017; 1vs. 3
Tremor	28.6 (14.9)	
Akinetic-rigid	30.5 (14.4)	
Postural instability and gait disturbance	37.3 (15.3)	
Disease duration		0.00010; 1 vs. 3
≤5 yr	26.5 (13.0)	
6–10 yr	32.1 (16.1)	
>10 yr	38.8 (14.8)	
HY		<0.0001
≤2.5	24.2 (13.9)	
≥3	35.7 (14.6)	
SE-ADL		<0.0001
≥80	25.0 (14.4)	
≤75	37.0 (14.0)	
MMSE		0.0037
≥25	29.9 (14.9)	
≤24	35.9 (14.6)	
BDI		<0.0001
<14	23.0 (11.9)	
≥14	39.2 (14.1)	

[a] Mean (standard deviation);
The Mann–Whitney U and Kruskal-Wallis tests were used to compare PDQ-39 SI scores between the groups;
Abbrevations: HY, Hoehn and Yahr stage; SE-ADL, Schwab and England Activities of Daily Living Scale; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory.

Table 24. Spearman's correlation analysis of clinical variables and PDQ-39 SI scores.

Variable	Coefficient	p value
Disease duration	0.30	<0.0001
HY	0.51	<0.0001
SE-ADL	–0.51	<0.0001
MMSE	–0.25	0.0001
BDI	0.63	<0.0001
Daily dose of levodopa	0.32	<0.0001
Duration of levodopa treatment	0.23	0.0001
Number of comorbidities	0.07	0.5041
MDS-UPDRS Part I – Non-motor experiences of daily living	0.62	<0.0001
MDS-UPDRS Part IA	0.51	<0.0001
MDS-UPDRS Part IB	0.61	<0.0001
Cognitive impairment	0.38	<0.0001
Hallucinacions and psychosis	0.24	0.0001
Depressed mood	0.35	<0.0001
Anxious mood	0.29	<0.0001
Apathy	0.33	<0.0001
ICDs	0.07	0.2490
Nighttime sleep problems	0.29	<0.0001
Daytime sleepiness	0.35	<0.0001
Pain and other sensations	0.38	<0.0001
Urinary problems	0.30	<0.0001
Constipation problems	0.13	0.0281
Lightheadedness on standing	0.34	<0.0001
Fatigue	0.44	<0.0001
MDS-UPDRS Part II – Motor experiences of daily living	0.65	<0.0001
MDS-UPDRS Part III – Motor examination	0.46	<0.0001
MDS-UPDRS Part IV – Motor complications	0.22	0.0003

Abbrevations*:* PDQ-39, the Parkinson's Disease Questionnaire; SI, summary index score; PIGD, postural instability and gait disturbance; HY, Hoehn and Yahr stage; SE-ADL, Schwab and England Activities of Daily Living Scale; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory; MDS-UPDRS, Movement Disorders Society Unified Parkinson´s Disease Rating Scale; ICDs, impulse control disorders.

Potential predictors were determined based on the previous correlation analysis. Duration of disease, HY, SE-ADL, MMSE, BDI, MDS-UPDRS Parts IA, IB, II–IV, duration of levodopa treatment, daily dose of levodopa, were identified as independent variables using univariate regression analysis. Multiple linear regression analysis was then performed on all the independent variables found during the previous univariate regression analysis and common epidemiological variables, i.e. age and gender. The final model (Table 25) explained 59.9% (adjusted R^2, $p<0.0001$) of the variance of PDQ-39 SI, with BDI, MDS-UPDRS II, MDS-UPDRS Part IB significant predictors and depression the most significant predictor of HRQoL.

Tabel 25. Predictors of HRQoL in stepwise multiple regression analysis.

Model	**Unstandardized coefficients**		**p value**
	B	SE	
BDI	0.734	0.089	0.0001
MDS-UPDRS Part IB	0.603	0.201	0.003
MDS-UPDRS Part II	0.546	0.127	0.0001
MDS-UPDRS Part III	0.067	0.050	0.182
Age	–0.124	0.077	0.108
Duration of the disease	0.251	0.184	0.175
Duration of levodopa treatment	–0.339	0.211	0.109
	Multiple	R^2=0.611	
	Adjusted	R^2=0.599	

Abbrevations: HRQoL, health-related quality of life; SE, standard error; BDI, Beck depression Inventory; MDS-UPDRS, Movement Disorder Society Unified Parkinson´s Disease Rating Scale.

6. DISCUSSION

6.1. Prevalence of PD

The first goal of this study was to determine the current frequency of PD in Estonia. Age-adjusted prevalence rates of PD in several other community-based studies as well as in our previous study that used the same diagnostic criteria, have reported remarkably lower rates than the current study (197/100,000), ranging from 109–183/100,000 (Kuopio et al., 1999a; Osaki et al., 2011; Schrag et al., 2000b; Taba & Asser, 2002; Walker et al., 2010). However, the use of different case-ascertainment methods and standard populations sets limits to the comparability of prevalence estimates reported by various studies.

In line with the literature, PD prevalence increased continuously with age among both men and women (Blin et al., 2015; Kuopio et al., 1999a; Liu et al., 2016; Newman et al., 2009; Riedel et al., 2016). Though the crude prevalence rate was significantly higher for women, no difference of the age-adjusted prevalence rates was evidenced between men and women, the latter finding being in line with a few earlier studies (de Rijk et al., 1997; Taba & Asser, 2002; Walker et al., 2010). The discrepancy of the crude and adjusted prevalence rates in our study might result from the predominance of women in the oldest age groups in Estonia, i.e, in 2014, there were 3.8 times more women than men aged 85 years and more. The highest age-specific crude rate for women in the subgroup of 80–84 year old people had big influence on the crude measure, while the standardization removed the difference coming from the population structure.

Our study did not demonstrate a statistically significant difference between the prevalence rates of PD among urban and rural populations, a finding that contrasts with the results of some Scandinavian studies where higher PD prevalence rates were found in rural compared to urban areas (Kuopio et al., 1999a; Tandberg et al., 1995), but is supported by several other previous surveys (Benito-León et al., 2003; de Rijk et al., 1997; Walker et al., 2010). There is substantial evidence that exposure to pesticides is associated with an increased risk of PD although specific compounds remain unclear (Ascherio & Schwarzschild, 2016). A nested case-control study by Tanner et al. (2011) found that rotetone impairs mitochondrial function and paraquat increases oxidative stress. The use of pesticides has not been extensive in Estonia, supported by only a minority (3.6%) of patients in our study indicating that they had been exposed to these chemicals over their life-time, a rate that is lower than reported in one other study (Kuopio et al., 1999b). Exposure to chemical solvents or paints was reported by a higher number of patients (14%), but these environmental factors are less linked with living area than occupation.

With respect to the research question regarding PD prevalence over time, we found that the overall disease prevalence in Estonia has risen from 152/100,000 in 1996 to 197/100,000 in 2013. Age-specific rates in the older age-groups have

grown considerably. Considering the demographical situation in the entire country in 1996 and 2014, the changes have been substantial. An increase in the population proportion of older age groups and a decrease in younger groups are notable. A total of 4.8% of people in Estonia were aged 75 years or more in 1996, the same proportion was as high as 8.9% in 2014. We believe that longer life expectancy nowadays compared to 20 years ago has an important contribution to the higher frequency of PD. Life expectancy of men was 64 years in 1996 and 72 years in 2014; and for women 75 years in 1996 and 81 years in 2014 (Statistics Estonia website, 2018). The most striking aspect to emerge from the results is that the prevalence of PD has increased mainly among men. Men's life expectancy is longer now due to better health behaviours and improved medical care.

Another reason for the higher prevalence of PD could be related to awareness. First, knowledge of the management of PD has improved remarkably among family doctors and neurologists due to continuous research on the disease, and new insights into the clinical heterogeneity and therapeutic approaches to PD have been adopted into clinical practice. Second, resulting from the improved general awareness of the disease in society, patients themselves are more attentive to the physical signs and seek specialist consultation. The internet might have a major role in spreading information on PD among the society; this source was almost unavailable 20 years ago (Lubi, Vihalemm, & Taba, 2013). Men's health receives more attention than decades ago, resulting in improved medical care. It could be possible that 20 years ago, an undetermined number of actual cases of PD were missed, because people were less likely to seek help from the medical system.

In the current study, we used the same diagnostic criteria and a similar case-ascertainment methodology as the previous epidemiological study by Taba and Asser (2002) except that the EHIF database was used as an additional source in the current study, with a high number of persons with suspected PD (coded as G20 in ICD-10). However, quite a large proportion of them were removed from the study, as their initial family doctor's diagnosis was not confirmed by a specialist (Figure 1).

Another objective of this research was to describe the natural history of PD. The proportion of patients moderately or severely affected by the disease compared to mild disease was higher in the current study than in the previous study in Estonia (Taba & Asser, 2002) as well as in prevalence surveys with in-person examination conducted elsewhere (Benito-León et al., 2003; Wermuth et al., 2008). First, this could be associated with the relatively high proportion of patients who were visited at their homes or in nursing institutions, indicating that they were bed-ridden or had otherwise serious problems with walking or general health. Second, patients in our cohort were older and had a longer disease duration compared to the earlier study in Estonia (Taba & Asser, 2002). As prevalence is associated with the duration of the disease, an increased frequency of PD could at least partially be attributed to this trend. Approxi-mately half of our patients presented depressive symptoms and a quarter were

cognitively impaired, which makes the management of this chronic disorder even more challenging.

The main strength of our study was the nearly complete identification of PD cases, based on all available sources over a long time frame, including the database of the EHIF that includes all recorded cases in the country. Second, the evaluation of the participants was thorough, including the collection of socio-demographic and disease-related data from quite a large sample of study subjects. Furthermore, wide-ranging clinical aspects were assessed based on validated clinometric scales and questionnaires. We think that the profile of our study participants is generalizable to the Estonian PD population as a whole. Last, given that there are only a few repeat epidemiological PD studies conducted on the same population at different time periods, our study provides valuable information about temporal trends of PD prevalence.

Some limitations of this study need to be taken into account when interpreting the findings. The first limitation concerns the small but existing proportion of patients whose diagnosis was only obtained through a review of medical records, i.e. they were not personally examined during the study. Another limitation is the extra source list used in our repeat study, as data from the EHIF was not used in the previous PD prevalence study, thus affecting the comparability of the two studies.

6.2. Incidence and mortality of PD

The main result of interest in this study was that the overall incidence of PD has remained comparatively unchanged since the previous epidemiological study in Estonia (incidence rate of 18.5/100,000 in the current study compared to 16.8/100,000 approximately twenty years ago) (Taba & Asser, 2003). The age-adjusted incidence in males has increased slightly (a 1.3-fold increase compared to the first Estonian study). These findings, of comparable overall incidence, and an increase in incidence for males, align with those of a study in Turku, Finland, in which PD incidence was reinvestigated after an interval of approximately thirty years (Kuopio et al., 1999a). However, retrospective studies in Taiwan (Liu et al., 2016) and the UK (Horsfall et al., 2013), and a prospective study in the Netherlands (Darweesh et al., 2016) each showed a decline in incidence over time. Three record-based studies in Japan, Yonago (1980, 1992, 2004), found no change in adjusted incidence rates (Harada et al., 1983; Kusumi et al., 1996; Yamawaki et al., 2009). Prospective comparative incidence studies in Cambridgeshire, UK, conducted in years 2000–2002 and 2008–2010, also did not find a change in incidence rates over time (Evans et al., 2016; Foltynie et al., 2004). However, a record-based retrospective study in Minnesota, USA, showed an increased incidence of PD over a thirty-year period, particularly for males over 70 years of age (Savica et al., 2016). The slight increase in PD prevalence in Estonia reported in our previous study (Kadastik-Eerme, Taba, Asser, & Taba, 2018) may be attributable to the aging population, the higher

absolute number of elderly people at risk, and the longer duration of disease, rather than to increased incidence.

This study's observation of the slightly higher occurrence of PD for males adds to the already extensive body of epidemiological evidence for this finding. However, in the current study, the risk of PD for males was not as high as that reported in most other studies. For example, the male to female incidence ratio was 1.25:1, whereas a nearly two-fold increase in risk for males was reported in several other studies (Alves et al., 2009; Caslake et al., 2013; Hristova et al., 2010; Jones et al., 2012; Moisan et al., 2016; Myall et al., 2017). On the other hand, other studies have reported no gender difference in the adjusted incidence rates (Das et al., 2010; Linder et al., 2010; Winter et al., 2010a). Furthermore, a recent meta-analysis reported the pooled total crude incidence rate for males as 44.2/100,000 and for females as 37.2/100,000 (Hirsch et al., 2016). In the current study, crude estimates were much lower (i.e. 20/100,000 for males, and 25/100,000 for females).

A recent meta-analysis by Macleod et al. (2018) reported the pooled estimate of mean age at symptom onset to be 68.1 years (95% CI 65.8–70.4). The current study's mean onset age of 71.4 years was slightly higher, but was more similar to the pooled estimate of 71.6 (95% CI 70.6–72.6) years reported by the same meta-analysis including specifically those studies that showed the mean age at diagnosis. No significant differences in age-specific incidence rates for males and females were observed. However, the small sample size of subjects in each of the different age groups may have limited the power of the subgroup analysis to reveal gender differences. In contrast, Moisan et al. (2016) reported that, in France, male-female incidence ratios increased with age. In line with the results of other studies, males in this current study were observed to develop PD approximately two years earlier than females (Alves et al., 2009; Heinzel et al., 2018; Winter et al., 2010a). Possible factors which may contribute to the male preponderance include a neuroprotective effect of female sex hormones, a sex-associated genetic mechanism, or differences in levels of exposure to environmental risk factors (Gillies et al., 2014).

This study's observation of a comparative increase in PD incidence for males since the previous Estonian study may be partly attributable to the fact that life expectancy, particularly for males, has risen substantially over the intervening time period. As onset of the disease is typically in the late sixties, less number of males might historically have developed the disease because of their shorter life expectancy. In other words, the increased incidence rate of PD for males over time may be attributable to demographical changes, and to the higher representation of males in the healthcare system. However, there may also be other explanations for the observed change in incidence rates for males. For example, some studies have suggested that smoking has a protective effect on the development of PD (Martino et al., 2017). Smoking rates in Estonia have significantly decreased since 1990, particularly for males. In 1996, 45.4% of males were everyday smokers, whereas this figure was 31.4% in 2014 (for women, the rates were 20.8% and 15.8%, respectively) (National Institute for

Health Development website. 2018). The observed increase in PD incidence rates in Estonia may be partially attributable to this change. In addition, a previous meta-analysis identified exposure to pesticides, previous head injury, rural living, beta-blocker use, farming/agricultural occupation and well-water drinking as significant risk factors for PD (Noyce et al., 2012). However, in the current study, exposure to different environmental factors was not seen to differ between males and females (Table 11). In addition, the current results did not show PD to be associated with either rural (Kab et al., 2017; Kuopio et al., 1999a) or urban living (Horsfall et al., 2013; Hristova et al., 2010), as had been found in previous studies.

For both men and women, the age-specific incidence rates peaked in the 75–84 years age-group, after which a sharp decline in incidence rates was observed. This decline in older age-groups aligns with the results of multiple other studies; indicating that PD may be an age-dependent rather than an aging-dependent disease (Alves et al., 2009; Linder et al., 2010; Myall et al., 2017; Winter et al., 2010a). Other studies have found the incidence of PD to increase up until the ninth decade (Blin et al., 2015; Caslake et al., 2013; Jones et al., 2012). Methodological issues related particularly to studies on elderly people (such as smaller sample size and under-reporting) may contribute to the observed heterogeneity of these results (Hirsch et al., 2016).

The majority of longitudinal cohort studies have found PD patients to have an approximately two-fold higher mortality risk than persons without PD. This risk correlates with the duration of disease (de Lau et al., 2014; Heinzel et al., 2018; Hobson & Meara, 2018; Pinter et al., 2015). Several reports have observed no higher mortality rates than in the general population in the first ten years of the disease (Williams-Gray et al., 2013; Zhang et al., 2018). In the current study, mortality risk for the inception cohort was similar to the general Estonian population. The phenomenon of the lower standardized mortality ratio in the inception cohorts and higher estimate in the non-inception cohorts is supportive to Macleod et al. (2014) who suggested that non-inception cohorts tend to capture those with longer disease duration and biasing towards shorter survival. The ratio of observed to expected deaths was insignificant in our inception cohort, whereas a 1.5-folded increased risk of mortality among PD patients was reported in the abovementioned meta-analysis. We believe that this difference could at least partially be attributed to the relatively short follow up duration in the current study (i.e. median of 5 years) compared to the follow-up time of 9 years in the meta-analysis by Macleod et al. (2014).

A comparison of the results for causes of death with those of other studies confirms that PD is underrepresented on death certificates. A PD diagnosis was noted on 46.8% of death certificates in this study. This result was slightly lower than that of some previous studies (Hobson & Meara, 2018; Williams-Gray et al., 2013), but higher than that of others (Benito-León et al., 2014; Moscovich et al., 2017). The inconsistent reporting of PD on death certificates indicates the suboptimal quality of these documents (Hobson & Meara, 2018). Other studies have shown that, compared with the general population, PD patients have an

increased risk of dying of pneumonia (Hobson & Meara, 2018; Moscovich et al., 2017; Pinter et al., 2015; Zhang et al., 2018). However, the current study did not find respiratory diseases to be amongst the most common causes of death. Underdiagnosis of pneumonia in our study cannot be excluded. For example, an accuracy of the death causes of those who died at homes or nursing homes might not be as high as in those cases who died in the hospital. Different documentation practices across distinct geographical areas could also at least partially be related to the much lower prevalence of pneumonia as an immediate or underlying death cause in the current study.

PD patients and the general population had a comparable risk of dying from cancer, the finding also shown in the study by Pinter et al. (2015). Several other studies have found that cancer as a death cause is less common in PD population compared to controls (Hobson & Meara 2018; Hely et al. 2005). Our finding of an increased risk of dying from vascular diseases among PD patients is supportive to one study showing that PD patients had a higher risk of having cardiovascular and cerebrovascular diseases recorded as death causes (Pinter et al., 2015), but another longitudinal study did not show such a difference compared to the general population (Hely et al. 2005).

The most important limitation of the current study was that the incidence data was based largely on retrospective information. Case-ascertainment in the current study was more thorough than in the previous Estonian incidence study, since the current study sourced data from the Estonian Health Insurance Fund (a source which was not previously available). The higher number of identified cases in the current study may therefore partially be attributable to this change in methodology. According to the sensitivity analysis limited to the incidence data for the period 2010–2012, a slight underestimation of the real burden of the disease cannot be excluded, and therefore this should be taken into account when interpreting the findings. The short-term duration of the follow-up of patients for the estimation of SMRs allows us only to draw conclusions in regards of the death risk in the early years of the disease duration.

One of the strengths of the current study was that subjects were identified from multiple sources and over a long period of time. An almost complete sample of PD patients from the geographical area of interest was therefore obtained. Another strength of the current study was that a clinical examination was conducted and a detailed history (including information about possible risk factors) was collected from the majority of subjects. The current study was conducted across the same geographical area and used the same diagnostic criteria and substantially overlapping case-ascertainment methods (Taba & Asser, 2003).

6.3. Prevalence and factors associated with motor complications in PD

This study aimed to address two main questions. Our first goal was to assess the prevalence of motor complications among a representative sample of PD patients in Estonia. Our second goal was to examine the association between multiple factors and the development of the disabling side effects of levodopa.

With respect to the first research question of this study, we found a slightly lower frequency of motor complications in our patients than several other studies (approximately 20% of our study participants with either of the motor complications vs. more than 22% of motor fluctuations and more than 26% of dyskinesias in other cross-sectional studies) (Hashim et al., 2014; Larsen et al., 2000; Nicoletti et al., 2016; Schrag & Quinn, 2000a; Yoritaka et al., 2013). It is possible that the somewhat lower frequency of motor complications was partly due to the profile of the study participants. Regarding the usage of levodopa, the mean daily levodopa dose of 434 mg in our study was lower than that reported in other studies (500 mg in the study by Hashim et al. (2014); and 548 mg in the study by Yoritaka et al. (2013). As this study was part of an epidemiologic survey of PD, all patients in the region were enrolled, included early cases. Among patients with early stages of PD who have been on levodopa therapy for a short time, motor complications are rather unexpected, a phenomenon demonstrated in Table 15. This finding contrasts with the results of Stocchi et al. (2014), in which more than half of patients under levodopa therapy for one to two years were diagnosed as having wearing-off symptoms, whereas only a minority of patients under levodopa ≤2.5 years had motor fluctuations in our study. Discrepancies in results could be caused by the variability in cohorts or by differing methodology of assessment. MDS-UPDRS Part IV was used in our study, whereas Stocchi et al. (2014) used a patient-assessed 19-item Wearing-off Questionnaire with the aim to detect wearing-off symptoms in early stages of PD.

With respect to the second research question, our findings confirm the results by others showing that motor complications are perhaps the greatest concern for PD patients who receive high cumulative doses of dopaminergic medications (Larsen et al., 2000; Nicoletti et al., 2016; Olanow et al., 2013; Schrag & Quinn, 2000a; Scott et al., 2016). Instead of levodopa daily dose, we chose LEDD as a total daily dose of medication expressing dose intensity of different antiparkinsonian drug regimens. Levodopa equivalent dose of a drug is defined as that which produces the same level of symptomatic control as 100 mg of immediate release levodopa (Tomlinson et al., 2010). Advanced PD patients are often treated with a combination of antiparkinsonian medications to handle their PD symptoms and levodopa-induced side effects. Therefore, especially in Estonia, where levodopa doses seem to be somewhat lower than in other countries, levodopa daily dose may underestimate the total dopaminergic load. Furthermore, approximately half of patients (57%) with motor complications were on dopamine agonists, which were used more than twice as than

they were by patients without motor complications (Mann-Whitney U, $p<0.0001$). Our findings on LEDD emerged from the multivariate regression analysis as a significant predictor of motor complications that was not found for the levodopa daily dose. It may support our observation that the levodopa dose alone may underestimate the cumulative dopaminergic burden. Although motor complications are traditionally considered to result from long-term use of levodopa (Aquino & Fox, 2015), the total burden of antiparkinsonian treatment may play a significant role in the emergence of motor complications.

One of the key findings of this study is that a shorter duration of disease until the initiation of levodopa appears to increase the odds of motor complications. This finding is supportive of a few studies indicating that earlier initiation of levodopa might be associated with earlier emergence of motor complications (Denny & Behari, 1999; Schrag & Quinn, 2000a) but contrary to some other surveys suggesting that delaying the start of levodopa therapy is not associated with a smaller risk of motor complications in the long term (Cilia et al., 2014; Scott et al., 2016). Our results support the opinion that younger age at onset of PD seems to be a risk factor for motor complications *per se* (Bjornestad et al., 2016; García-Ruiz et al., 2012; Hashim et al., 2014; Olanow et al., 2013). *Post hoc* analysis revealed that younger patients tended to be on a higher LEDD than older patients. They might be more prone to the higher usage of dopaminergic treatment in order to reduce their parkinsonian symptoms than older patients as a result of having more commitments concerning their employment status and families than older patients. Levodopa may be postponed in patients who are not troubled by their PD-related motor symptoms and in patients with young-onset PD who are at the highest risk for developing levodopa-related complications (Jankovic & Poewe, 2012). At the same time, the possibility of the different effects of dyskinesias and motor fluctuations on quality of life should be taken into account. Some studies have found that PD patients with fluctuations have lower quality of life than patients without fluctuations (Skorvanek et al., 2015; Stocchi et al., 2014), but no such association was found between quality of life and dyskinesias in another study (Hechtner et al., 2014). In our survey, a majority of patients with dyskinesias reported that drug-induced complications impair their functional ability only mildly, and severe dyskinesias were rarely described. This finding may provide some support for the possibility that patients themselves might not be particularly troubled by their dyskinesias, at least when those features are mild. In summary, we conclude that the traditional clinical approach of balancing efficacy and risk of motor complications is needed for each patient, using the lowest dose of levodopa that will provide satisfactory clinical control (Olanow et al., 2013). Still, improved quality of life should be the ultimate goal of our treatments.

In controversion with the data of recent studies, we did not find female gender to be associated with higher occurrence of motor complications (Bjornestad et al., 2016; García-Ruiz et al., 2012; Olanow et al., 2013; Scott et al., 2016; Stocchi et al., 2014; Yoritaka et al., 2013). It has also been suggested that the severity of motor PD symptoms predicts a higher risk of developing

motor complications (Bjornestad et al., 2016). However, this does not appear to be the case in our study, supporting the results of another study based on a cohort of incident PD patients (Scott et al., 2016). Although we found more severe MDS-UPDRS Part II scores for those experiencing motor complications, according to logistic regression analysis, everyday activities were not significantly associated with the presence of levodopa-induced side effects, which does not support the observation by one other study based on a cohort of early PD patients (Olanow et al., 2013).

One rather important finding was that the akinetic-rigid phenotype of PD emerged as a significant independent associated factor in the higher occurrence of motor complications. This association remained significant even after including possible confounders, such as duration of PD and levodopa therapy, to the second model. Patients with non-tremor dominant types of PD are characterized as being more often depressed and having a more severe clinical picture, higher LEDD, and longer disease duration than patients with tremor-dominant subtype (Burn et al., 2012). In a recent case-control study in Italy investigating the relationship between clinical phenotype and the risk of developing dyskinesias, a significant negative association between tremor-dominant phenotype as an initial PD manifestation and levodopa-induced dyskinesia was established (Nicoletti et al., 2016). Another case-control study conducted in Finland investigated differences in the binding of striatal dopamine transporter and the extent of caudate dopamine terminal loss, and the consequent dopamine function was relatively more preserved in PD patients with tremor compared to akinetic-rigid patients (Kaasinen, Kinos, Joutsa, Seppänen, & Noponen, 2014). Our study allows us to confirm information about the clinical heterogeneity of distinct PD phenotypes. Due to the higher risk for motor complications, achieving effective treatment results in patients whose dominant symptoms are akinesia and rigidity might be more challenging than in patients with the tremor-dominant disease.

Our study has several strengths. First, the case identification in our study was based on all available sources in the area, and we accordingly enrolled a relatively large sample of patients with PD, including early cases as well as both moderately and severely ill patients. Thus, the results may be extrapolated to the Estonian PD population as a whole. Secondly, the evaluation of the participants was thorough, and wide-ranging aspects (motor, non-motor, functional, cognitive, and emotional) were assessed based on validated clinometric scales and questionnaires. Therefore, we believe that the measurements are accurate and reflect the profile of study participants correctly.

Some limitations of this study need to be taken account when interpreting the findings. The main weakness of the study is a relatively small sample size of patients with motor complications, which can be a source of low power for the logistic regression analysis. The second limitation might be a potential underestimation of motor complications with subtle presentations, especially among patients with impaired cognitive ability. Finally, due to the cross-sectional design of our study, each patient was assessed once, so no pattern of

progression of the disease could be estimated, and causes and effects could not be determined.

6.4. Non-motor symptoms in PD

We assessed non-motor symptoms in Estonian PD patients and found that the frequency of the total load of non-motor symptoms and specific items showed considerable differences with respect to their association with some demographic and clinical variables. The data analysis revealed that age, PD progression, presence of depressive symptoms, cognitive impairment, lower quality of life, and higher dose or longer duration of levodopa treatment correlated significantly with the total burden of non-motor symptoms.

An association between the increasing burden of non-motor symptoms with disease duration has been shown in several previous studies (Barone et al., 2009; Guo et al., 2013a; Krishnan, Sarma, Sarma, & Kishore, 2011; Špica, Pekmezović, Svetel, & Kostić, 2013), but a relationship with increasing age and non-motor symptoms was not found (Krishnan et al., 2011) or was weak (Guo et al. 2013a; Špica et al. 2013) as in the present study. However, some particular non-motor symptoms appear to become more frequent in older PD patients, such as urinary and gastrointestinal disturbances including constipation, or cognitive impairment (Kim et al., 2013; Krishnan et al., 2011; Müller et al., 2011), that were complained more frequently by patients older than 65 years also in our study, additionally to daytime sleepiness. While several of these non-motor symptoms occur quite commonly in normal elderly populations, their presence is significantly higher in PD patients (Duncan et al., 2014b; Kim et al., 2013; Krishnan et al., 2011; Müller et al., 2011). Krishnan et al. (2011) found that 68% of controls reported non-motor features associated with aging, but presented less severe levels than in PD patients, and that cardiovascular disorders, mood and cognition impairment, and perceptual problems and hallucinations were more related to PD than normal aging. A South Korean group found that the domains of perceptual problems and hallucinations, and sexual function, were more related to PD than the age *per se* (Kim et al., 2013).

Cognitive impairment was the most frequently reported non-motor symptom among our study participants (74.3%), which was higher than in several previously published studies (44.7–54%) (Barone et al., 2009; Gallagher et al., 2010; Martinez-Martin et al., 2011a; Špica et al., 2013). However, 63% of our patients admitted having cognitive problems only at slight or mild level. Though the use of different scales may play a role, a study by Martinez-Martin et al. demonstrated a convergent validity for the MDS-UPDRS and NMSS (Martinez-Martin et al., 2013). Although both studies included patients at any age and disease stage, in comparison with our study, the mean age and disease severity of the participants differed significantly in the study by Martinez-Martin et al. (2013). The higher rate of cognitive impairment among our patients might at least partly be explained by the older mean age and more advanced

disease severity, i.e. the mean age of 74.2 years vs. 66.7 years and the percentage of patients with HY stage ≥3 62.7% in our study participants and only 26.7% in the study of Martinez-Martin et al. (2013).

In this study, ICDs were the most uncommon non-motor symptoms complained by our patients, with the higher rate in patients with longer duration of PD and younger age at disease onset, the latter has been also demonstrated in the study by Voon et al. (Voon et al., 2007). Among other factors, dopamine agonist treatment, younger age, a pre-PD history of ICDs, a personal or family history of substance abuse, bipolar disorder, and gambling problems have been found to be possible risk factors for ICDs (Weintraub, David, Evans, Grant, & Stacy, 2015). As the initial treatment with a dopamine agonist is recommended in younger patients according to the PD treatment recommendations (Ferreira et al., 2013), ICDs may cumulate with risks related to use of agonists: therefore, challenging issues in treatment in young patients may arise (Weintraub et al., 2015).

Some studies have demonstrated that sexual dysfunction (Guo et al. 2013a), restless legs (Špica et al., 2013), excessive sweating (Špica et al., 2013), and loss of taste or smell (Kägi et al., 2010) are more common in patients with younger onset age of the disease. However other studies have demonstrated opposite results with higher prevalence of loss of taste or smell (Guo et al. 2013a; Špica et al. 2013) and restless legs (Kägi et al., 2010) in patients with older onset age of disease. In addition to ICDs, our study found that fatigue was more prevalent in patients with younger onset age of PD, and constipation was more frequent in patients with older onset age of the disease. Defining tresholds for the classification of early versus late onset subtypes vary in different studies, ranging from 45–55 years (Guo et al. 2013a; Špica et al. 2013; Kägi et al. 2010). Distinct profile of specific non-motor symptoms among younger vs. older onset age groups may partly be explained by different questionnaires (e.g. NMSQuest by Kägi et al. and Spica et al., and NMSS by Guo et al.), and different border-lines for defining the age groups. Younger onset age has been also shown to be associated with lower prevalence and severity of the total load of non-motor symptoms (Guo et al. 2013a; Špica et al. 2013), but this difference was not revealed in our study nor in one previous study (Kägi et al., 2010). In addition, the same study by Kägi et al., found that patients with genetic forms of PD reported significantly less non-motor symptoms compared to patients without proven genetic aetiology of PD.

The present study did not demonstrate gender differences regarding the total load of non-motor symptoms, supporting the same observation in some other studies (Guo et al. 2013a; Picillo et al. 2013), however other studies have shown more non-motor symptoms among female patients (Krishnan et al., 2011; Solla et al., 2012). We found a different profile of specific non-motor symptoms, with a depressed mood, anxiety, pain, and light-headedness more frequently in women, and daytime sleepiness and fatigue more often reported by men (Table 20a). Similar gender differences were found in a study by Solla et al. (Solla et al., 2012), except that fatigue was more common in women, as it was in a study by Barone et al. (Barone et al., 2009).

Our analysis revealed an association between the presence of cognitive impairment and a higher burden of all other non-motor symptoms that is consistent with the study by Barone et al. (Barone et al., 2009). Also fatigue – one of the most common complaints in our study – was strongly related to the higher overall burden of non-motor symptoms in our and a previous study (Solla et al., 2014). In addition to gender differences, we found that fatigue appears to be more frequent in patients with younger age at PD onset, longer disease duration, advanced disease severity, and the PIGD clinical phenotype. Generally, participants with the PIGD as the leading symptom experienced a higher burden of non-motor features compared to patients with tremor or akinetic-rigid predominant symptoms, which is in concordance with some other studies (Duncan et al., 2014b; Müller et al., 2011).

There was an overall trend towards the more frequent occurrence of non-motor symptoms in patients with the PIGD phenotype that may be associated with a more complex pathophysiology, involving other neurotransmitters in addition to the dopaminergic system. This is supported by observations that the symptoms of axial impairment are typically less responsive to dopaminergic therapy for PIGD than other subtypes of PD, indicating differences in the mechanisms between distinct clinical subtypes of PD (Lees et al., 2009). However, by individual symptoms some differences have been described in other studies suggesting that patients of PIGD phenotype are more likely to experience a higher frequency of depression, anxiety, cognitive impairment, constipation and hypersalivation (Anang et al., 2014; Burn et al., 2012; Duncan et al., 2014b; Müller et al., 2011), but in our study, daytime sleepiness and fatigue were significantly more frequently experienced.

Longer disease duration, advanced disease, longer levodopa use and higher daily dose of levodopa in early PD are the known risk factors for motor complications (Aquino & Fox, 2015) but majority of the abovementioned factors are also associated with the higher occurrence of non-motor symptoms of PD (Barone et al. 2009; Krishnan et al. 2011; Špica et al. 2013; Guo et al. 2013a). In our study, a higher burden of non-motor symptoms was demonstrated only in patients with motor fluctuations but not in patients with dyskinesias or off-period dystonia that could be associated with a phenomen that the concomitant non-motor symptoms also fluctuate: pathogenesis of non-motor fluctuations has also been explained with pulsatile dopaminergic stimulation, similarly to motor fluctuations (Chaudhuri, Odin, Antonini, & Martinez-Martin, 2011). Seki et al. (2013) reported that 53% of patients with motor fluctuations, also suffer from non-motor fluctuations, and patients with both motor and non-motor complications exhibited more severe motor symptoms, more non-motor symptoms, and higher levodopa daily doses.

The strengths of this study included a relatively large sample of PD patients, including the most elderly, severely ill, disabled and institutionalised patients, which represented a whole PD population. Patients were evaluated with a wide range of rating scales that covered motor, non-motor, functional, cognitive, and emotional aspects.

This study had some methodological limitations. First, we did not cover all the non-motor symptoms of PD, e.g. sexual function, olfaction, or restless legs as these are not included into the MDS-UPDRS. Another limitation was the collection of clinical data at a single point in time that did not reflect the progression of the disease. Also, there were no controls to assess differences in the prevalence of non-motor symptoms in an ageing general population compared to those with PD.

6.5. HRQoL of patients with PD

The purpose of this study was to investigate factors that may contribute to low HRQoL in persons with PD. We found that the main clinical determinants of low HRQoL in persons with PD were depressive symptoms and the high burdens of motor and non-motor aspects of daily living. None of the investigated socio-demographic variables were significantly associated with HRQoL.

Clinically significant depression has an average prevalence of about 35% among persons with PD (Reijnders et al., 2008) and is a recognized predictor of low HRQoL. As previous studies (Carod-Artal et al., 2007; Gallagher et al., 2010), we found depression to be one of the most significant determinant of HRQoL. A study by Leentjens et al. (2002) demonstrated that the risk factors in the general population for depression – such as older age, female gender, somatic comorbidities, and personal and family history of depression – also predict depression in persons with PD. In our sample the prevalence of depression in female patients was significantly higher than in male patients (58% and 43% respectively, $p=0.0189$). In addition to BDI, depressed mood was more often reported by women according to the item 1.3 of the MDS-UPDRS Part IA. Studies examining gender differences regarding prevalence of depression have yielded inconsistent results. While van der Hoek et al. (2011) found no difference in the prevalence of depression in male and female persons with PD, Solla et al. (2012) found prevalence of depression significantly higher in female persons with PD. The reason why women are more disposed to depression might partly be explained by the greater exposure of competing risk factors, as suggested by Sonnenberg et al. (2000) who demonstrated this association in a study on gender differences for depression in the elderly of a general population: controlling for age, comorbid somatic disease, and a number of other risk factors reduced the relative risk of depression in women by more than a half. The female patients in our study were slightly older than the male patients, were more often widowed and had a higher mean number of comorbidities. Men in our cohort were significantly more often married and lived together with their wife and or children. Based on the studies by Sonnenberg et al., it could be assumed that controlling for several factors associated with social and health status might reduce the relative risk of depression in female persons with PD.

In recent years there has been increasing evidence suggesting that the impact of non-motor symptoms on HRQoL is more important than the impact of motor features (Gallagher et al., 2010; Martinez-Martin et al., 2011a). Similar to previous studies, our study revealed that HRQoL was significantly lower with higher loads of non-motor symptoms. All non-motor symptoms correlated significantly with PDQ-39 SI, except the features of ICDs: a heterogeneous group of pathological behaviours associated with dopamine replacement treatment that include pathological gambling, compulsive sexual behaviour, compulsive shopping, and binge eating, together with pounding and the addiction-like compulsive use of dopamine replacement therapy (Djamshidian, Averbeck, Lees, & Sullivan, 2011). A case-control study by Voon et al. (2011) indicated that patients with ICDs have more depressive symptoms than patients without ICDs. We did not find a statistically significant difference between mean BDI scores for persons with PD and with ICDs (based on positive item 1.6 in MDS-UPDRS Part IA), and persons with PD and without ICDs. Reducing the dosage or discontinuing the administration of dopaminergic agonists or substituting another drug from this group is a frequently effective therapeutic measure (Djamshidian et al., 2011). Only a few studies on the impact of ICDs on HRQoL have been published and some found controversial results, i.e. ICDs as a predictor of lower HRQoL (Leroi et al., 2011; Phu et al., 2013), but in other studies ICDs did not affect HRQoL (D'Iorio et al., 2017). The current study did not reveal a negative impact of ICDs on quality of life. Our finding is supported by a study by Ondo and Lai (2008), where only 18% of patients with increased impulsivity felt that the change was deleterious. Our daily clinical practice suggests that ICDs cause considerable distress to patients' families or caregivers, but the patients themselves are not that annoyed by these behaviours. Out of the 268 patients screened in our study, 7.8% (n=21) complained of ICDs. It could be assumed that at least one reason why ICDs did not correlate significantly with HRQoL is that the pathological behaviours were relatively mild. About half (52%) of these patients reported only slight problems with behavioural disturbances and it could be that the problems did not yet affect their social and occupational functioning.

Dependency in activities of daily living as assessed using the SE-ADL scale and disability in the performance of daily living experiences as measured by the previous version of the UPDRS Part II, have been found to be significant contributors to HRQoL (Carod-Artal et al., 2007). A study by Rodriguez-Blazquez et al. (2013) showed that there was a significant negative association between the more advanced disability (assessed by the MDS-UPDRS Part II) and HRQoL. The current study demonstrated that disability evaluated by SE-ADL and MDS-UPDRS Part II significantly contributed to lower HRQoL. However, motor symptoms (MDS-UPDRS Part III) were not an independent predictor of HRQoL. Even though for antiparkinsonian treatment Part III with motor assessments is of high importance, it can be seen that for HRQoL, the self-assessment of non-motor symptoms and ability to perform daily activities have more impact.

An axial impairment has been shown to be associated with reduced HRQoL in persons with PD (Muslimović et al., 2008). We found that patients with PIGD had significantly lower overall HRQoL compared to patients with tremor dominance or akinetic-rigid dominance of motor phenotype. Persons with PD in general, but particularly patients with the PIGD, are likely to become less able to move around inside their homes and out in the community. They also become more prone to falls as the disease progresses. Regular physical exercise is associated with higher HRQoL, mobility, physical function, slowing the progression of the disease, lower caregiver burden, and less cognitive decline (Oguh, Eisenstein, Kwasny, & Simuni, 2014). In view of this, patients with the PIGD may benefit most from education on using rehabilitation activities (e.g. physical exercise, physiotherapy) and assistive devices (e.g. reaching aids). Therefore, in addition to pharmacological treatment, the management of PD should include rehabilitative care, which helps to maintain patients' ability to participate in daily living activities and avoid the decline of HRQoL.

In our study, socio-demographic characteristics including age, gender, urban/ rural living, level of education, marital status and living alone/with others, did not significantly affect overall HRQoL. However, we found several associations between these factors and domains of PDQ-39. Women received lower scores for emotional well-being and bodily discomfort, which is in accordance with the study by Carod-Artal et al. (2007). As regards to patients' living status, those who lived alone received lower scores for emotional well-being compared with patients who lived with others. Another study by Winter et al. (2010b) showed that patients living alone had worse HRQoL than patients living with somebody. Our results did not reveal any statistically significant difference in HRQoL among patients with different educational backgrounds, whereas greater number of years in education was found to be associated with higher HRQoL in some other studies (Carod-Artal et al., 2007). Klepac et al. (2007) found that rural patients had lower overall HRQoL, with most of the domains of PDQ-39 affected. In contrast, the results of our study suggest that living area is not associated with overall HRQoL. Moreover, our results showed that patients living in rural areas had significantly less stigmatization and better social support than patients living in urban areas.

The strength of the study was the relatively large sample of persons with PD, which included institutionalised and severely ill patients, and thus was representative of the PD population as a whole. The study participants were also evaluated with a wide range of clinimetric properties that covered motor, non-motor, functional, cognitive and emotional aspects.

The study has some methodological limitations that ought to be recognized and taken into account when interpreting the findings. The analysis was based on clinical data collected at a single point in time; therefore, any pattern of progression of the disease could not be estimated. Also, we cannot exclude the possibility that some of the variables, such as gender (female patients outnumbered male patients) or stage of disease (62.6 % of patients had HY $\geq$3) could have influenced the results found.

7. CONCLUSIONS

1. As there are only a few studies of repeat prevalence and incidence of PD in the same geographical area, the main contribution of our epidemiologic surveys in the County of Tartu has been to evaluate the dynamic changes in the frequency and occurrence of this neurodegenerative disease. Over the last twenty years, the overall incidence of PD in Estonia has remained comparatively stable. Increased incidence among males may be related to demographic changes and improved diagnosis; however environmental causes cannot be ruled out. In the contrary, the overall prevalence of PD has risen significantly. A stable incidence accompanied with an increased prevalence may be explained by a lengthened disease duration and aging of the general population. To manage an increasing disease burden, health planning should take into account, for example, the growing requests for nursing institutions and rehabilitation services.
2. Mortality rates of PD in Estonia have never before been studied. No significant differences in the mortality risk among PD patients in the first 5 years of the disease and general population were found. PD patients and the non-recruited controls had a comparable risk of dying from cancer, but PD patients were at higher risk of dying from vascular diseases. The latter finding attenuates the need to control more efficiently the cardiovascular risk factors of the patients with PD. Data obtained from the death certificates revealed that approximately only half of all the deceased subjects with clinically-diagnosed PD had the disease noted on their death certificates. This finding reflects that death certificates may not provide enough validity for their use in the surveillance of this neurodegenerative disease.
3. A total of approximately 25% of patients on levodopa therapy had some type of motor complication, indicating to the relatively low frequency of those antiparkinsonian medication-related side-effects in our PD population compared to other studies. Patients receiving a higher LEDD and having akinetic-rigid dominant phenotype as opposed to tremor-dominant phenotype of the disease are at greater risk of having motor complications. The results of the research do not support the idea that levodopa should be initiated as early as possible; instead, postponing the start of levodopa, together with prescribing optimal daily doses, might reduce the odds of motor complications.
4. Though the severity of individual non-motor symptoms assessed with the MDS-UPDRS Part I was generally rated by PD patients as “mild” or less, these symptoms were highly prevalent in patients. A higher frequency of the total burden of non-motor symptoms in patients with the PIGD as the leading motor symptom and in patients with more advanced stage and longer duration of the disease, also in those with depression, cognitive disorder or motor complications. This highlights the need to pay a special attention to the screening for non-motor symptoms in these groups.

5. Approximately 60% of the variation in the PDQ-39 SI score reflecting the HRQoL of PD patients was explained by the predictive variables identified in this study, i.e. depression, non-motor and motor aspects of daily living. Our results are consistent with other studies that have suggested depression to be the strongest predictor of HRQoL in persons with PD, and therefore should be recognized early and treated appropriately.

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SUMMARY IN ESTONIAN

Parkinsoni tõbi Eestis: epidemioloogia, elukvaliteet, kliinilised karakteristikud ja farmakoteraapia

Parkinsoni tõve vanusele kohandatud levimus-ja haigestumuskordajad varieeruvad uuringutes ulatuslikult, jäädas vastavalt vahemikesse 53–511/100 000 inimese kohta ning 6–36/100 000 inimaasta kohta (Blin et al., 2015; Das et al., 2010; Heinzel et al., 2018; Myall et al., 2017). Epidemioloogiliste uuringute võrreldavust kahandavad erinevused uuringu disainis, uuritavate värbamismeetodites, diagnoosikriteeriumites ja populatsiooni iseärasustes. Väga vähe on tehtud korduvaid Parkinsoni tõve epidemioloogilisi uuringuid samas geograafilises regioonis haigestumus- ja levimusnäitajate dünaamika hindamiseks. Tartumaal on Parkinsoni tõve epidemioloogilisi näitajaid uuritud ligikaudu 20 aastat tagasi, mil leiti, et vanusele kohandatud levimus- ja haigestumuskordajad olid vastavalt 152/100 000 kohta ja 16,8/100 000 inimaasta kohta (Taba & Asser, 2002, 2003). Hiljutise metaanalüüsi järgi on Parkinsoni tõvega patsientidel ligi 1,5 korda suurem suremisrisk võrreldes üldpopulatsiooniga (Macleod et al., 2014). Suremust pole Eesti Parkinsoni tõvega haigete seas varem uuritud.

Levinuimad mittemotoorsed sümptomid Parkinsoni tõvega haigetel on urineerimishäired, mäluprobleemid, alanenud meeleolu, kõhukinnisus, valu ja unehäired (Chaudhuri et al., 2010). Mõned uuringud on näidanud, et mittemotoorsetel sümptomitel võib Parkinsoni tõvega patsiendi elukvaliteedile olla suurem kumulatiivne negatiivne mõju kui motoorsetel sümptomitel (Erro et al., 2016; Gallagher et al., 2010; Ophey et al., 2018).

Parkinsoni tõve ravi on sümptomaatiline. Kliinilises praktikas kasutatavaimaks ja efektiivseimaks ravimiks on suukaudselt manustatav levodopa, mille kõrvaltoimena võivad kasutajal tekkida motoorsed komplikatsioonid (on-off fluktuatsioonid ja düskineesiad) (Chaudhuri et al., 2018). Motoorsete komplikatsioonide peamisteks riskiteguriteks peetakse levodopa suuremaid annused ja pikaaegset ravimi tarvitamist (Olanow et al., 2013; Scott et al., 2016).

Uurimistöö eesmärgid

1. Kirjeldada Parkinsoni tõve levimus-ja haigestumusnäitajaid Tartu linnas ja maakonnas ning hinnata esinemisnätajate dünaamilisi muutusi võrreldes eelmise epidemioloogilise uuringuga samas regioonis (Uuring I, II).
2. Kirjeldada Parkinsoni tõve kohordi suremusnäitajaid, surmatunnistusele märgitud Parkinsoni tõve diagnoosi esinemissagedust ja teisi surmapõhjuseid (Uuring II).
3. Hinnata motoorsete komplikatsioonide esinemissagedust levodopa ravi saavatel Parkinsoni tõvega patsientidel, ja analüüsida valitud demograafiliste ja kliiniliste tegurite seost nimetatud ravimist tingitud kõrvaltoimete tekkega (Uuring III).

4. Hinnata Parkinsoni tõve korral esinevate mittemotoorsete sümptomite levimust ja raskusastet, ning analüüsida nende sümptomite esinemissageduse varieeruvust Parkinsoni tõvega patsientide alagruppide vahel (Uuring IV).
5. Iseloomustada Parkinsoni tõvega patsientide tervisega seotud elukvaliteeti ning analüüsida viimast mõjutavaid sotsiodemograafilisi ja kliinilisi tegureid (Uuring V).

Uuritavad ja meetodid

Tegemist oli Parkinsoni tõve epidemioloogilise ja kliinilise uuringuga, mille jaoks andmete kogumine vältas perioodil 2010–2016. Uuringu lõplik valim koosnes 589 Parkinsoni tõve diagnoosiga uuritavast (neist mehi, 236; naisi, 353), kellest 65% elas Tartu linnas ja 35% Tartu maakonnas. Lisaks Tartu Ülikooli Kliinikumi Närvikliinikule, osalesid uuringus ka Pärnu Haigla ja Põhja-Eesti Regionaalhaigla, nende keskuste poolt värvatud patsiendid (n=102) olid kaasatud ainult motoorsete komplikatsioonide uuringusse. Parkinsoni tõve diagnoos lähtus Suurbritannia PT Ühingu Ajupanga tunnustatud diagnoosikriteeriumitest – Parkinsoni tõbe kinnitab, kui kliiniliselt esineb bradükineesia ja lisaks üks järgnevatest sümptomitest: rahutreemor, rigiidsus või posturaalsete reflekside häire (Gibb & Lees, 1988; Lees et al., 2009).

Uuritavate värbamiseks olid kasutusel järgmised allikad – Tartu Ülikooli Närvikliinik, erakliinikute neuroloogid, Tartu Parkinsoni Haiguse Selts, linna ja maakonna perearstid, hooldusasutused ja Eesti Haigekassalt saadud nimekiri kõikide isikute kohta regioonis, kellele perioodil 2010–2015 olid elektroonsesse meditsiinisüsteemi märgitud G20 diagnoosikood. Need isikud, kes keeldusid kliinilisest testimisest, polnud kättesaadavad või olid identifitseerimise hetkeks surnud, kaasati siiski epidemioloogilisse uuringusse, kui meditsiinilises dokumentatsioonis olid fikseeritud kindlad viited Parkinsoni tõvele. Iga uuritavat jälgiti prospektiivselt üleriigilise elektroonilise terviselugude süsteemi kaudu kuni uuringuperioodi lõpuni või uuritava surmani.

Uuritavate põhjalik hindamine hõlmas ühekordsel kokkusaamisel sotsiodemograafiliste ja kliiniliste andmete kogumist, mille aluseks oli poolavatud intervjuu spetsiifiliselt selle uurimistöö jaoks välja töötatud patsiendi kaardi baasil ja neuroloogiline läbivaatus. Lisaks hindasime patsiendi haiguse raskusastet, mõju funktsionaalsele võimekusele, meeleolu, kognitiivset seisundit ja elukvaliteeti, kasutades erinevaid valideeritud kliinilisi skaalasid ja küsimustikke.

Haiguse levimuse väljendamiseks kasutati levimuskordajaid 100 000 elaniku kohta, milleks leiti Parkinsoni tõve haigusjuhtude esinemise osakaal Tartu linna ja maakonna populatsioonis levimuspäeval 01.10.2013. Haiguse avaldumise väljenduseks kasutati haigestumuskordajaid 100 000 inimaasta kohta, milleks leiti valdavalt retrospektiivselt Parkinsoni tõve esmased haigusjuhud ajaperioodil 2002–2012 summaarse riskiaja kohta Tartu linna ja maakonna populatsioonis. Parkinsoni tõve suremusuuringusse kaasati kõik haigusjuhud regioonist perioodil 2010–2016. Suremust väljendati standardiseeritud suremuskordajatega,

referentspopulatsiooniks kasutati Eesti soo- ja vanusspetsiifilisi suremuskordajaid vastaval kalendriaastal. Surma põhjuste registrist saadud andmete alusel leiti vaadeldud perioodil surnud uuritavate (n=235) surmapõhjused.

Doktoritöö teised osad baseerusid läbilõikelistel kliinilistel uuringutel, mida kajastavad Uuringud III–V (motoorsete komplikatsioonide esinemissagedus ja prognostilised faktorid; mittemotoorsete sümptomitega seonduvad tegurid; elukvaliteedi determinandid). Neis uuringutes kasutati vastavaid statistilisi meetodeid nagu logistilist regressioonanalüüsi, korrelatsioonanalüüsi, mitmest regressioonanalüüsi, ja gruppide võrdlusteste. Statistilise olulisuse nivooks oli üldjuhul võetud $p<0,05$.

Tulemused ja arutelu

Levimus, haigestumus ja suremus (Uuring I, II)

Levimuspäeval 01.10.2013 tuvastati Tartu linnas ja maakonnas 431 Parkinsoni tõvega patsienti. Vanusele kohandatud levimuskordaja oli 314/100 000. Võrreldes Parkinsoni tõve varasema epidemioloogilise uuringuga, oli vanusele kohandatud levimuskordaja oluliselt tõusnud (152/100 000 vs 197/100 000 kohta; RR=1,3; p=0,004).

Perioodil 2002–2012 tuvastati 1 699 709 inimaasta jooksul 388 uut Parkinsoni tõve juhtu. Vanusespetsiifilised haigestumuskordajad kasvasid nii meestel kui ka naistel eksponentsiaalselt kuni 75–84 aastasete vanusgrupini, millele järgnes haigestumuse langus. Vanusele kohandatud haigestumuskordaja kogukohordile oli 28/100 000 inimaasta kohta, mis on võrreldav teiste viimaste aastate uuringute vastavate näitajatega. Vanusele kohandatud haigestumuskordaja meestel oli veidi kõrgem kui naistel (32,0 vs 25,6/100 000 inimaasta kohta; RR=1,25; p=0,04). Mitmed teised uuringud on näidanud pigem veelgi ülekaalukamat meeste riski haigestuda võrreldes naistega. Võrreldes Parkinsoni tõve varasema haigestumusuuringuga, püsis vanusele kohandatud haigestumuskordaja oluliselt muutumatuna (16,8 ja 18,5/100 000 inimaasta kohta; RR=1,1; p=0,19), mida on näidanud ka teised samalaadsed korduvad epidemioloogilised uuringud. Stabiilne haigestumus kasvava levimuse foonil toetab arvamust, et haiguse esinemissageduse tõus on seotud eeskätt vananeva ühiskonnaga. Meeste seas oli täheldatav mõningane haigusavaldumuse tõus (16,6 ja 21,3/100,000 inimaasta kohta; RR=1,3; p=0,04). Nimetatud nähtust saab vähemalt osaliselt seletada meeste pikenenud elueaga, kuid välistada ei saa ka seost teatud keskkonnateguritega. Parkinsoni tõvega patsiendid praeguses uuringus olid pikema haiguse kestusega ning suurem osakaal oli nendel isikutel, kelle haigusstaadium oli kaugelearenenud.

589 Parkinsoni tõvega patsienti Tartu linnas ja maakonnas, keda jälgiti 3145 inimaasta jooksul, lisati suremusanalüüsi. Standardiseeritud suremuskordajad Parkinsoni tõvega patientide kohordile, kelle esmashaigestumine oli 2008. aastal või hiljem, olid järgmised: 1,1 kõikidele (95% CI 0,–1,3), 1,0 naistele (95% CI 0,7–1,3), ja 1,1 meestele (95% CI 0,8–1,4). Parkinsoni tõve diagnoos

oli veidi alla pooltel surnud uuritavate surmatunnistustel, mis on kooskõlas teiste uuringutega, ning viitab viletsale surmapõhjuste dokumenteerimisele. Kõige sagedasemad surma algpõhjused olid järgmised: kardiovaskulaarsed haigused (58%), vähk (14%), Parkinsoni tõbi (14%) ja tserebrovaskulaarsed haigused (6%). Kaasuva haigusena oli Parkinsoni tõbi märgitud 33% surmatunnistustest.

Motoorsed komplikatsioonid (Uuring III)

Läbilõikelisse uuringusse kaasati 328 Parkinsoni tõvega patsienti, kes kõik kasutasid levodopat (levodopa päevase annuse mediaan oli 450 mg). Düskineesiaid esinesid 21% ja motoorseid fluktuatsioone (on-off perioode) 20% patsientidest. Kuivõrd muu maailmaga võrreldes on Eestis motoorsete komplikatsioonide esinemissagedus pigem madalamapoolne, siis nimetatud nähtus võibki olla seotud arstide poolt määratud antiparkinsonistlike ravimite optimaalsete annustega. Motoorsete komplikatsioonide sagedus kasvas koos levodopa kasutusajaga, kõrgeim esinemissagedus (73,3%) oli neil, kelle levodopa kasutusaeg oli vähemalt 15 aastat. Logistilisel regressioonanalüüsil selgus, et motoorsete komplikatsioonide esinemise šanssi suurendavad LEDD (OR=1,003; 95% CI 1,001–1,004), akineetilis-rigiidne motoorne fenotüüp (OR=2,559; 95% CI 1,087–6,199), lühem aeg haigestumisest levodopa kasutuselevõtuni (OR=0,746; 95% CI 0,624–0,870), noorem iga haigestumisel (OR=0,837; 95% CI 0,766–0,910) ja kõrgem vanus uurimise ajal (OR=1,106; 95% CI 1,018–1,203).

Mittemotoorsed sümptomid ja elukvaliteet (Uuring IV, V)

268-st läbilõikelisse uuringusse kaasatud isikust (keskmine vanus 74,2±8,8 aastat, keskmine haiguse kestus 7,6±5,9 aastat) esines 99,6% vähemalt üks ning keskmiselt 6,7±2,5 mittemotoorset sümptomi ühe patsiendi kohta. Kuigi mittemotoorsed sümptomid olid sagedased, siis üldiselt oli nende kaebuste raskusaste kerge. Kõige sagedasemad mittemotoorsed sümptomid olid kognitsioonihäire (74,3%), öised unehäired (71,6%), põiehäired (71,6%), väsimus (68,7%), valu (64,2%), päevane liigne unisus (61,9%) ja alanenud meeleolu (60,8%). Hallutsinatsioonid (13,8%) ja impulsi kontrolli häired (7,8%) olid kõige harvemini esitatud mittemotoorsed sümptomid. Mitmesel regressioonanalüüsil, kus küsimustiku PDQ-39 summaarne indeks oli sõltuvaks tunnuseks, ilmnes, et elukvaliteedile avaldavad tugevaimat mõju depressioon, mittemotoorsed ja motoorsed igapäevaeluga seotud aspektid. Need sõltumatud tunnused seletasid ära 59,9 (R^2=0,599) elukvaliteedi küsimustiku summarse indeksi hajuvusest. Ükski sotsiodemograafiline tegur ei mõjutanud elukvaliteeti.

Töö tulemused lubavad väita, et suur mõju patsientide elukvaliteedile on depressioonil ning sellel, kuidas nad tulevad toime enda igapäevaelu toimin-

gutega (riietumine, hügieen jne.). Neuroloogi poolt objektiivselt hinnatud parkinsonistlike sümptomite raskusaste ei pruugi peegeldada seda, kuidas haige tegelikult enda elukvaliteeti tunnetab.

Kokkuvõte

Käesolev korduv epidemioloogiline uurimistöö samas baaspopulatsioonis, kasutades samu diagnoosikriteeriume ja suuresti kattuvaid värbamismeetodeid, näitas Parkinsoni tõve diagnoosiga patsiente arvu olulist kasvu Eestis 20 aasta jooksul. Samas Parkinsoni tõve haigestumus pole võrreldes 1990-ndate aastatega oluliselt muutunud, mistõttu saab järeldada, et haiguse levimuse kasvu võib eelkõige seostada vananeva rahvastiku, pikenenud haiguskestuse, paranenud haigusteadlikkusega ühiskonnas ning diagnostika arengutega. Pikema haiguse kestuse ning enamväljendunud raskusastmega Parkinsoni tõvega patsiente oli nüüdses uuringus rohkem kui varasemas uuringus. Nimetatud tulemused võivad osutada sellele, et ühiskonnas tekib kasvav vajadus Parkinsoni tõvega patsientidele rehabilitatsiooniteenuste ja hooldusasutuste kättesaadavuse tagamiseks.

Motoorsete komplikatsioonide edasilükkamiseks võib kasu olla sellest, kui ei kiirustata levodopa alustamisega (seda eeskätt just nooremate patsientide puhul) ning hoitakse päevase dopaminergilise ravimite koguannused optimaalsel tasemel. Oluline on siinjuures see, et motoorsete komplikatsioonide edasilükkamine ei tuleks langenud elukvaliteedi arvelt – antiparkinsonistlike ravimite doosid peaksid olema siiski piisavalt suured, et vähendada patsientide motoorseid vaevuseid ja kasvaks haige subjektiivne rahulolu enda eluga. Mittemotoorsed sümptomid kuuluvad selle kliiniliselt heterogeense haiguse sümptomatoloogia hulka ning nende skriinimine kuulub iga Parkinsoni tõvega haige käsitluse hulka. Depressioonil on Parkinsoni tõvega patsientide elukvaliteedi mõjutajana kandev roll, mistõttu tuleb meeleoluhäireid nendel haigetel rohkem uurida ja vajadusel ravivõimalusi pakkuda.

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Publikatsioonid:

1. Kadastik-Eerme, L., Taba, N., Asser, T., & Taba, P. Incidence and mortality of Parkinson's disease in Estonia. *Neuroepidemiology* (avaldamiseks sisestatud).
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