The increasing prevalence of Parkinson’s disease in Estonia

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INTRODUCTION

Prevalence of a disease depends on how quickly new cases of the disease arise and how long people with the disease survive.1 Demographic data suggest that European populations are aging, mainly due to low birth rates and higher life expectancy. As Parkinson’s disease (PD) is predominantly related to older age, a rise in its overall prevalence is expected and thus its burden on patients, caregivers, and society will increase.2

Objectives: A previous epidemiological study of Parkinson’s disease (PD) in the county of Tartu, Estonia, found an adjusted prevalence rate of 152/100 000 persons. We aimed to determine PD prevalence almost 20 years later, as well as evaluate any dynamic changes in disease frequency compared to the first study.

Methods: A cross-sectional, community-based study was conducted over 2010-2016 in the county of Tartu, Estonia. Multiple case-finding sources, including information from neurologists, family doctors, the local PD Society, nursing institutions, and the database of the Estonian Health Insurance Fund were used to identify patients with PD of all ages.

Results: Total crude PD prevalence was 283 and age-adjusted prevalence (standardized to the 2014 age structure of the Estonian population) 314/100 000. No significant differences in age-adjusted prevalence rates were found between men and women, nor people living in urban and rural areas. After adjustment to the same standard population used in the previous prevalence study, the overall age-adjusted prevalence rate was 197/100 000. Patients in the current study were older and often had a more severe form of PD and a longer disease duration, compared to those reported in the first epidemiological study 20 years ago.

Conclusions: The age-specific crude rates in oldest age-groups have risen substantially, and the age-adjusted prevalence has moderately increased compared to 20 years ago in Estonia. We hypothesize that the increased life expectancy of the Estonian population and improved diagnosis of PD contributed most to the increase in disease frequency.

KEYWORDS
community-based, environmental factors, Estonia, Parkinson’s disease, prevalence

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were screened. The existing body of research on PD epidemiology suggests that disease frequency peaks in the age-group 80–89 years old and then declines; other studies have found the highest age-specific prevalence rates among the oldest groups studied.

A much-debated question is whether gender is a risk factor of PD. Males have been related to higher age-adjusted prevalence rates in many studies; in only a few studies did females have higher rates. Several other studies did not observe a statistically significant difference between gender and adjusted PD prevalence rates. Results on the role of urban or rural living on prevalence of PD are controversial.

The heterogeneity in prevalence rates across studies has at least partially been attributed to differences in case ascertainment and diagnostic accuracy. Therefore, repeated studies of a population using the same case ascertainment methodology and diagnostic criteria are very valuable to evaluate epidemiological trends. There have only been a few repeated epidemiological studies of PD prevalence.

The first epidemiological study in Estonia was conducted in 1996 and reported an age-adjusted PD prevalence rate of 152/100 000 persons, which was similar to the rates of several other European community-based PD studies conducted during the 1990s, that is, 135-183/100 000. Current study enabled us to evaluate the dynamics of PD epidemiology using a similar case ascertainment methodology on the same population.

This study of Tartu City and County aimed to (i) determine the current frequency of PD among the population; (ii) evaluate prevalence trends by comparing the results to those of a survey conducted among the same population approximately 20 years ago; and (iii) describe the clinical profile of patients with PD.

2 METHODS

2.1 Area and population

Tartu County is located in South Estonia and had a population of 152 188 (71 395 men, 80 793 women) during the last census in January 2014. The county is administratively divided into 3 urban and 19 rural municipalities and covers a total of 2993 km². Tartu, the second largest city of Estonia, is the administrative center of Tartu County. The male-female proportion in the entire country was the same as in Tartu in 2014, that is, 43% 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.

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 1 local hospital that provides outpatient and inpatient services for neurological patients, and 10 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.

2.2 Study design and ethical issues

A community-based cross-sectional study was conducted in the county of Tartu during the period 2010-2016. Ethical approval was obtained from 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 2.2-7/13643).

2.3 Case ascertainment and diagnostic criteria

The following information from all available sources was regularly obtained during 2010-2016 for case-ascertainment. Inpatient and outpatient neurology visit data to Tartu University Hospital were processed and neurologists were asked to provide the list of their patients with PD. 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. The full case record review of each case was conducted by the first author to find evidence for the presence of confirmed PD (ie, description of cardinal parkinsonian symptoms, prescription of antiparkinsonian treatment, no indications to other conditions besides PD). Eligible patients were contacted; the residence of patients was verified with data of the Estonian Population Register.

All patients with PD living in the county of Tartu on the 1st of October 2013 were included in the study. This specific prevalence day was chosen because it was in the midpoint of our study period and the proportion of clinically examined study participants was highest on that time. Diagnosis was based on the Queen Square Brain Bank Diagnostic Criteria: clinical diagnosis of PD is confirmed by the presence of bradykinesia and at least one of the following symptoms: resting tremors, rigidity, or impaired postural reflexes. Subjects were classified as prevalent cases if their initial parkinsonian symptoms had occurred before the prevalence day. Those who refused to participate were unreachable or had died before their identification, but were alive on the prevalence day and were enrolled as prevalent cases if they had a confirmed diagnosis of PD based on medical records. Patients with other parkinsonian syndromes including secondary or atypical parkinsonism were excluded from the PD sample.

2.4 Data collection and clinical examination

Participants or their caregivers were informed about the study before signing an Informed Consent Form. Data were collected during patient interviews and from medical documentation and recorded on the Patient Case Report Forms. Patients’ neurological status was assessed using the Movement Disorders Society’s Parkinson’s Disease Unified Rating Scale (MDS-UPDRS), Hoehn and Yahr Rating Scale.
2.5 | Statistical analysis

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. Furthermore, using the European 2011 standard population as a reference, a corresponding age-adjusted prevalence rate was also calculated.

95% confidence intervals 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 2 time-points were statistically evaluated using the Z test. Familywise error rate was controlled with Bonferroni method. All statistical analyses were performed in R version 3.3.3.

3 | RESULTS

The overall study population from all sources with suspected PD in Tartu County comprised 1011 subjects (Figure 1). 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.

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) patients with PD 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 1. The total crude prevalence rate was higher for women than for men. There was no significant difference in age-adjusted prevalence rates between the groups and between 2 time-points were statistically evaluated using the Z test. Familywise error rate was controlled with Bonferroni method. All statistical analyses were performed in R version 3.3.3.

FIGURE 1 Flow diagram of the case ascertainment procedure. CBD, corticobasal degeneration; EPS, extrapyramidal syndrome; LBD, dementia with Lewy bodies; MSA, Multiple system atrophy; PD, Parkinson’s disease; PSP, progressive supranuclear palsy
between age-adjusted prevalence rates of men and women (rate ratio [RR] = 0.83, \(P = .07\); Table 1). In terms of living area, no significant difference in adjusted prevalence rates of PD was shown between urban and rural populations (RR = 1.02, \(P = .83\)). 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.

The age-specific and total crude rates of current study and the study conducted in Estonia in 1996 are shown in Table 2. Comparison of the adjusted prevalence rates of the 2 Estonian studies is shown in Table 3. We found that the overall age-adjusted prevalence rate was significantly higher in the current study (RR = 1.30, \(P = .004\)), and among men (RR = 1.44, \(P = .0018\); Table 3).

Of the 431 patients included in the prevalence analysis, 84% agreed to participate in the interview and clinical evaluation. Patients were examined in the Department of Neurology (n = 265), at home (n = 65), or in a nursing home or hospital (n = 33). Clinical and sociodemographic data of the 363 patients (139 men, 224 women) are shown in Table 4. Mean age at PD onset was 67.9 ± 9.9 years (range: 35-92) and the mean time from PD symptoms until diagnosis 2.0 ± 2.1 years (range: 0.1-13). 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. Of those on levodopa treatment, 63% were using controlled release levodopa, 14% standard release levodopa; and 9% combination with a catechol-O-methyl transferase 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).

**DISCUSSION**

The first aim 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, ranging from 109 to 183/100 000.3,4,6-8 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.5,7,8,10,13-15,18 Although 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.4,6,20 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, that is, 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. Results of an incidence study that is ongoing at this time in Tartu County should give more precise answers to the matter of risks related to gender and PD in Estonia.

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, but is supported by several other previous surveys. However, a trend of higher incidence rates of PD among the urban compared to the rural population of Tartu County was found in a previous PD incidence study. A nested case-control study by Tanner et al. supported the role of pesticides in PD pathophysiology; these environmental factors have long been linked with the disease's etiology. 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 lifetime, a rate that is lower than reported in one other study. 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 second 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 crude rates in the older age-groups have grown considerably. Considering the demographical situation in Tartu

| Age- groups | Study population, 1996 | Study population, 2013 |
|-------------|-----------------------|-----------------------|
|             | Cases | Population | Age-specific crude rate | Cases | Population | Age-specific crude rate |
| 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   | 15 324    | 546                     | 431   | 152 188   | 283 (257-310)           |
| Total crude rate per 100 000 | 176 (155-197) | 283 (257-310) |

| Study population in 1996 | Study population in 2013 | RR of adjusted prevalence | P-value\(^{\text{b}}\) |
|--------------------------|--------------------------|---------------------------|----------------------|
| All patients             | 270                      | 152 (128-176)             | 431                   | 197 (178-216)             | 1.30                      | .004                    |
| Males                    | 88                       | 154 (130-178)             | 160                   | 221 (187-256)             | 1.44                      | .0018                   |
| Females                  | 182                      | 153 (128-177)             | 271                   | 183 (160-206)             | 1.20                      | .08                     |
| Urban patients           | 183                      | 160 (135-185)             | 307                   | 198 (175-221)             | 1.24                      | .029                    |
| Males                    | 60                       | 171 (146-197)             | 116                   | 232 (189-275)             | 1.36                      | .017                    |
| Females                  | 123                      | 157 (133-182)             | 191                   | 178 (151-205)             | 1.13                      | .26                     |
| Rural patients           | 87                       | 139 (116-162)             | 124                   | 193 (158-228)             | 1.39                      | .011                    |
| Males                    | 28                       | 128 (106-150)             | 44                    | 204 (143-265)             | 1.59                      | .022                    |
| Females                  | 59                       | 145 (122-169)             | 80                    | 194 (149-239)             | 1.34                      | .058                    |

CI, confidence interval; RR, rate ratio.
For the additional comparison among the subgroups the significance threshold after Bonferroni correction was set to .0062. Statistically significant P-values are in bold.
\(^{a}\)Adjusted to 1989 Estonian population for age.
\(^{b}\)For overall comparison between the 2 studies a P-value below .05 was considered statistically significant.
TABLE 4  Characteristics of patients with PD, clinical evaluation conducted in period 2010-2016

| Variable                                | n  | Mean (SD) or n(%) | Range |
|-----------------------------------------|----|------------------|-------|
| Age at examination, years              | 363| 74.8 (8.9)       | 47-96 |
| Disease duration, years                | 360| 7.0 (5.5)        | 0.3-35|
| First PD symptom                       | 357|                 |       |
| Tremor                                  |    | 245 (68.6)       |       |
| Akinesia + rigidity                     |    | 55 (15.4)        |       |
| Handwriting                             |    | 13 (3.6)         |       |
| Postural stability                      |    | 37 (10.4)        |       |
| Other symptoms                          |    | 7 (2)            |       |
| Clinical phenotype                      |    |                 |       |
| Tremor                                  |    | 157 (43.3)       |       |
| PIGD                                    |    | 101 (27.8)       |       |
| Akinesia-rigidity                       |    | 105 (28.9)       |       |
| MDS-UPDRS score                         |    |                 |       |
| Part I                                  |    | 13.3 (7.8)       | 0-39  |
| Part II                                 |    | 17.2 (9.0)       | 1-52  |
| Part II                                 |    | 44.6 (18.5)      | 8-106 |
| Part IV                                 |    | 0.9 (2.9)        | 0-18  |
| HY                                      |    |                 |       |
| 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*                                 |    | 363 75 (4.5)     | 0-100 |
| MMSE*                                   |    | 348 28 (4.5)     | 0-30  |
| BDI                                     |    | 318 15.1 (8.9)   | 0-47  |
| Duration of levodopa treatment, years   |    | 298 4.5 (5.0)    | 0.1-22|
| LEDD, mg                                |    | 363 396 (328)    | 0-2518|
| Living status                           |    |                 |       |
| With a spouse                           |    | 167 (46)         |       |
| With children                           |    | 65 (17.9)        |       |
| Alone                                   |    | 103 (28.4)       |       |
| Nursing institution                     |    | 28 (7.7)         |       |
| Education                               |    |                 |       |
| Primary                                 |    | 132 (36.5)       |       |
| Secondary                               |    | 141 (38.9)       |       |
| Higher                                  |    | 89 (24.6)        |       |
| Exposure to toxins                      |    |                 |       |
| Pesticides                              |    | 13 (3.6)         |       |
| Heavy metals                            |    | 16 (4.4)         |       |
| Solvents and paints                     |    | 51 (14)          |       |
| Current smoking                         |    | 16 (4.4)         |       |
| Former smoking                          |    | 68 (18.7)        |       |

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

*Median.
profile of our study participants is generalizable to the Estonian PD population as a whole. Last, given that there are only a few repeated 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, that is, 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 were not used in the previous PD prevalence study, thus lowering the comparability of the 2 studies.

In summary, the current research extends our knowledge of increasing trends in PD epidemiology over time. Only a few repeated prevalence studies of the same population measured a change in PD frequency. In the view of continuously aging populations, we anticipate an ongoing increase in the burden PD has upon society in the future. The proportion of patients with more severe stages of the disease has increased. To manage an increasing disease burden, health planning should take into account, for example, the growing requests for nursing institutions and rehabilitation services. Taken together, the 2 prevalence studies in Estonia are valuable for suggesting clues as to the possible causes of PD, as well as providing future projections regarding the social burden of this chronic disease.

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CONFLICT OF INTERESTS

The authors declare that they have no financial or non-financial competing interests.

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