



Life expectancy of parkinsonism patients in the general population

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ABSTRACT

Introduction: Detailed data on the life expectancy of patients with parkinsonism from the general population are largely lacking. This study aimed to determine the absolute life expectancy of patients newly-diagnosed with parkinsonism.

Methods: This study was part of the Rotterdam Study, an ongoing, population-based cohort study in the Netherlands. We included 12,789 participants of 50 years and older, free of parkinsonism. Patients diagnosed with parkinsonism were matched to controls on sex, birth year, dementia status, cancer status, and coronary heart disease status. We used Gompertz regression and lifetables to estimate the remaining life expectancy per year of age.

Results: The mean age of our study population was 65.0 (SD 9.7) years and 57.6% were women. During an average follow-up of 12 years, 297 participants were diagnosed with parkinsonism. The mean age at parkinsonism diagnosis was 78.6 (SD 8.1) years. Once diagnosed with parkinsonism, the life expectancy was lower than matched controls across a wide age range. At 65 years, the life expectancy of patients with parkinsonism was reduced with 6.7 [95% CI: 2.4;10.7] years compared to controls. At 85, the difference in life expectancy was 1.2 [95% CI: -2.2;4.5] years compared to controls.

Conclusion: Patients diagnosed with parkinsonism have a reduced life expectancy compared to their peers in the general population. The absolute life expectancy is mainly reduced if parkinsonism is diagnosed before the age of 70.

1. Introduction

Parkinson's disease (PD) has a considerable impact on the life of patients and their caregivers [1,2]. PD does not only decrease quality of life, previous studies have also shown that it reduces survival [3]. Most survival estimates of PD originate from clinical settings [3,4], which might differ considerably from the survival of patients with PD in the general population.

The mortality in patients with PD is estimated to be increased approximately 1.5 times [3] and the mortality risk in patients with atypical parkinsonism is even greater [4]. Studies presenting mortality ratios are important to uncover risk factors of early death in parkinsonism, but they can be difficult to interpret in terms of prognosis. Absolute life expectancy estimates are easier to share with patients and could help care-planning. However, these estimates are underreported in the literature [5,6].

In this study, we aimed to establish the life expectancy of

individuals diagnosed with incident parkinsonism in the general population. Hereto, we studied the life expectancy of patients with parkinsonism across different ages and compared the life expectancy between men and women and PD and atypical parkinsonism. In addition, we aimed to determine the burden of parkinsonism, expressed in the number of years a person in the general population lives with parkinsonism.

2. Methods

2.1. Study population

This study was embedded within the Rotterdam Study, an ongoing, population-based cohort study in the Netherlands. The design of the Rotterdam study has been described previously [7]. The first cohort started in 1990. All inhabitants of Ommoord, a district in Rotterdam, who were 55 years and older were invited to participate and 7,983

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agreed. In 2000, the cohort was extended with 3,011 inhabitants who had become 55 years and older or who moved into Ommoord. The cohort was further enlarged with 3,932 participants aged 45 years and older in 2006. The response rate over the three cohorts was 72%. At baseline and at each four-year follow-up visit, participants underwent a home interview and examinations at the research center.

2.2. Parkinsonism ascertainment

We used a two-phase design to identify participants with parkinsonism at study entry [8–10]. Participants were asked about a previous diagnosis of parkinsonism, medication use was determined, and signs of parkinsonism were assessed at the research center. Positively screened participants were evaluated further for the presence of parkinsonian symptoms by a research physician with expertise in neurological disorders.

During follow-up, multiple modalities were used to evaluate parkinsonism. Sources of information were in-person screenings at the research center, interviews with participants, anti-Parkinson medication use, and continuous monitoring of clinical records for terms related to parkinsonism [8–10]. Clinical records of participants that appeared in any of the screening modalities were assessed and case reports were evaluated by a panel led by an experienced neurologist. Records of possible parkinsonism cases were continuously monitored till January 1, 2015 and any changes in diagnoses over time were routinely updated in the data.

Parkinsonism was defined as the presence of hypo- or bradykinesia and at least one of the following cardinal signs: resting tremor, rigidity, or postural imbalance, as observed by any physician; or a clinical diagnosis of parkinsonism by a neurologist or geriatrician. Parkinsonism was subdivided into the following causes: PD, drug-induced parkinsonism, vascular parkinsonism, multiple system atrophy, progressive supranuclear palsy, Lewy body dementia, parkinsonism with dementia, corticobasal degeneration, tumor-induced parkinsonism, and unspecified parkinsonism. PD entailed the criteria of parkinsonism, a clinical history suggestive for PD, and at least one of the following: (a) a clinical PD diagnosis by a neurologist or geriatrician; (b) a positive response to dopaminergic treatment; (c) or dopamine transporter scan findings consistent with PD. Atypical parkinsonism was defined as all parkinsonism subtypes apart from PD.

Participants with prevalent parkinsonism, not screened for parkinsonism at the research center at baseline, or not providing informed consent for follow-up were excluded from the analyses. The time at risk for parkinsonism ended at the first of the following: diagnosis of incident parkinsonism, death, loss to follow-up, or January 1, 2015. Participants with prevalent dementia were at risk for all parkinsonism subtypes except for PD. The time at risk for PD ended at the first of the following: diagnosis of incident parkinsonism, incident dementia, loss to follow-up, death, or January 1, 2015.

2.3. Mortality ascertainment

Records of the municipal administration of Rotterdam, general practitioner files and nursing home files were continuously evaluated to obtain information on the participants' vital status. Follow-up for mortality was complete until May 2018. To determine the cause of death, participants' medical records were reviewed by trained research assistants. The cause of death was coded by two independent research physicians and reviewed by a medical expert in the field [7]. Cause of death was coded according to the International Classification of Diseases, 10th edition (ICD-10) [11]. Follow-up for cause-specific mortality was complete until January 2015.

2.4. Covariates ascertainment

Marital status, education level, and smoking status were determined

during home-interviews. Marital status was defined as living with or without a partner. Education was divided into four different levels: primary education; lower or intermediate general education or lower vocational education; intermediate vocational education or higher general education; and higher vocational education or university. Participants were categorized as never, former, or current smokers. Height and weight were measured at the research center and body mass index (BMI) was calculated as weight divided by height squared. Diagnoses of dementia, cancer and coronary heart disease (CHD) were ascertained with repeated screening and review of medical records [7].

2.5. Statistical analysis

Missing values of the covariates marital status (missing in 7.7%), educational attainment (missing in 2.8%), smoking status (missing in 2.8%), and BMI (missing in 11.8%) were imputed based on age, sex, the other covariates, and the outcomes, using the mean of five imputations.

To compare the survival and life expectancy of parkinsonism patients with control subjects, we matched patients with incident parkinsonism and controls on sex, birth year (maximum 2 year difference), dementia status, cancer status, and CHD status in a one to two ratio. The follow-up start date of the cases was set to the date of parkinsonism diagnosis and this date was also used as the start date of the corresponding controls. Kaplan Meier curves were made to estimate the median survival in both groups. Causes of death were determined in parkinsonism patients and controls, and proportions were calculated in both groups. In addition, we calculated the absolute life expectancy of patients newly diagnosed with parkinsonism and compared this to individuals without parkinsonism using life tables starting at age 55 and ending at age 100. In this analysis, participants could undergo two transitions: from no diagnosed parkinsonism to death and from diagnosed parkinsonism to death. We calculated overall age-specific incidence rates for both transitions with Gompertz regression. Gompertz regression is a parametric proportional hazard regression with a Gompertz distribution, which is suitable for mortality data [12,13]. Subsequently, we multiplied the overall incidence rates with a weighing factor to obtain sex-specific incidence rates. This weighing factor consisted of sex-specific hazard ratios for death, obtained using Gompertz regression, and the men to women ratio per 10-year age category. We adjusted the hazard ratios for marital status, educational attainment, smoking status, and BMI. Confidence intervals were calculated using Monte Carlo simulation (parametric bootstrapping) with 10,000 runs. The analyses were repeated for PD and atypical parkinsonism separately.

To estimate the number of years lived with parkinsonism, we created a multistate life table. A multistate life table is a demographic tool that combines multiple health states to estimate the number of years lived in different health states [14,15]. The multistate life table started at age 55 and ended at age 100. We formulated three states: no diagnosed parkinsonism, diagnosed parkinsonism, and death. Transitions between these states were possible from no parkinsonism to parkinsonism, from no parkinsonism to death, and from parkinsonism to death. We calculated age-specific incidence rates for each of the three transitions with Gompertz regression and calculated confidence intervals again with Monte Carlo simulation.

Incidence rates and hazard ratios were calculated using Stata 15.1 and matching was performed in R 3.5.2. Life tables and the corresponding confidence intervals were calculated in Excel version 2010, using @Risk (Palisade Corporation, New York, USA) to perform Monte Carlo simulations.

3. Results

The study population comprised 12,789 participants at risk for parkinsonism, including 12,413 participants at risk for PD. Fig. 1 shows the flow diagram of the study participants. The mean age of our study

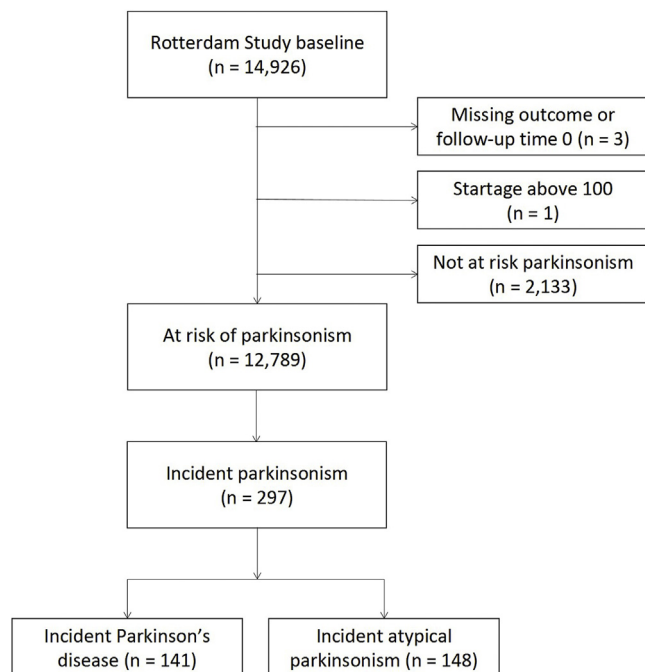


Fig. 1. Flowdiagram of study participants. The number of Parkinson's disease patients and atypical parkinsonism patients do not add up to the total number of parkinsonism patients (297) because Parkinson's disease patients with dementia prior to diagnosis were excluded in both subgroups, but included in the all-cause parkinsonism group. The life expectancy analyses included 273 parkinsonism patients, 138 Parkinson's disease patients, and 134 atypical parkinsonism patients because not all patients could be matched to two controls.

Table 1
Baseline characteristics.

| Characteristic | Total (n = 12,789) |
|----------------------------------|--------------------|
| Women, No. (%) | 7,368 (57.6) |
| Age, mean (SD) years | 65.0 (9.7) |
| Birth year, mean (SD) year | 1933 (15) |
| Lives with partner, No. (%) | 9,399 (73.5) |
| Education, No. (%) | |
| Primary | 2,224 (17.4) |
| Lower | 5,166 (40.4) |
| Intermediate | 3,479 (27.2) |
| Higher | 1,920 (15.0) |
| Smoking, No. (%) | |
| Never | 4,514 (35.3) |
| Former | 5,575 (43.6) |
| Current | 2,700 (21.1) |
| BMI, mean (SD) kg/m ² | 26.9 (4.1) |
| Dementia, No. (%) | 291 (2.3) |
| Cancer, No. (%) | 467 (3.7) |
| CHD, No. (%) | 809 (6.3) |

Education was categorized as follows: Primary, primary education; Lower, lower or intermediate general education or lower vocational education; Intermediate, intermediate vocational education or higher general education; Higher, higher vocational education or university.

population was 65.0 (SD 9.7) years. More than half of the study participants (57.6%) were women. At baseline, 291 participants (2.3%) were diagnosed with dementia, 467 (3.7%) with cancer, and 809 (6.3%) with CHD (Table 1).

During an average follow-up of 12 years, 297 participants were diagnosed with parkinsonism, including 141 participants who were diagnosed with PD and 148 who were diagnosed with atypical parkinsonism (Table 2). The mean age at parkinsonism diagnosis was 78.6 (SD 8.1) years and 54.5% of incident parkinsonism patients were women. In total, 273 parkinsonism patients, 138 PD patients, and 134

Table 2
Incident parkinsonism during follow-up.

| | No. (%) ^a | Age diagnosis, mean (SD) | Women, No. (%) |
|-----------------------|----------------------|--------------------------|-------------------------|
| Parkinsonism | 297 (2.3) | 78.6 (8.1) | 162 (54.5) ^b |
| Parkinson's disease | 141 (1.1) | 77.3 (7.9) | 67 (47.5) ^c |
| Atypical parkinsonism | 148 (1.2) | 78.4 (7.7) | 91 (61.5) ^d |

^a Total number at risk for parkinsonism was 12,789. Total number at risk for Parkinson's disease was 12,413.

^b Percentage of total parkinsonism.

^c Percentage of total Parkinson's disease.

^d Percentage of total atypical parkinsonism. Total number of parkinsonism cases includes patients with dementia before Parkinson's disease, which were excluded in both Parkinson's disease and atypical parkinsonism group.

atypical parkinsonism could be matched with controls in a one to two ratio. Of the 273 parkinsonism patients, 54 (19.8%) had prevalent dementia. During follow-up, 60 parkinsonism patients (27.4% of those without dementia at baseline) were diagnosed with dementia, compared to 66 (15.1%) controls. PD patients with prevalent dementia were excluded. During follow-up, 38 (27.5%) PD patients were diagnosed with dementia compared to 47 (17.0%) controls. In atypical parkinsonism patients, 53 (39.6%) had a dementia diagnosis at baseline and 22 (27.2%) patients were diagnosed with dementia during follow-up, compared to 27 (16.7%) controls.

The median survival in patients with parkinsonism was 4.3 [95% confidence interval: 3.6;5.0] years, compared to a median survival of 7.5 [6.5;8.5] years in matched controls. The median survival in patients with PD was 5.5 [4.7;7.2] years, compared to 9.4 [8.5;10.6] years in matched controls. In patients with atypical parkinsonism, the median survival was 3.3 [2.9;4.1] years, compared to 5.6 [4.8;6.7] years in controls. Supplemental Fig. 1 shows the Kaplan Meier curves of patients with parkinsonism versus matched controls, for all-cause parkinsonism, PD, and atypical parkinsonism separately. The causes of death of patients with parkinsonism and matched controls can be found in Supplemental Table 1.

Fig. 2 shows the estimated remaining life expectancy after parkinsonism diagnosis for men and women separately. The life expectancy of patients diagnosed with parkinsonism, both men and women combined, was reduced with 10.1 [5.6;14.3] years compared to participants without parkinsonism at diagnosis age of 55 years. This difference was 6.7 [2.4;10.7] years at 65 years, 3.5 [-0.4;7.2] years at 75 years, and 1.2 [-2.2;4.5] years at 85 years. The life expectancy of PD patients was 10.5 [6.2;14.5] years reduced compared to participants without parkinsonism at diagnosis age 55 years, 7.5 [3.4;11.3] years reduced at 65 years, 4.3 [0.5;7.9] years reduced at 75 years, and 1.7 [-1.6;4.8] years reduced at 85 years. Patients with atypical parkinsonism had a lower life expectancy than patients with PD at every diagnosis age. The life expectancy of patients with atypical parkinsonism was reduced with 8.7 [3.9;13.2] years compared to controls at 55 years, 5.3 [0.8;9.5] years at 65 years, 2.4 [-1.6;6.3] years at 75 years, and 0.5 [-2.9;3.9] years at 85 years. The life expectancy of parkinsonism patients was reduced more in men than in women.

Fig. 3 shows the proportion of the remaining life expectancy lived with parkinsonism in the entire study sample (n = 12,789). The average proportion of the remaining life expectancy lived with parkinsonism ranged from 1.4% [1.0%;2.0%], corresponding to 0.4 [0.3;0.6] years, at 55 years to 8.1% [2.1%;39.2%], corresponding to 0.07 [0.0;0.3] years, at 99 years.

4. Discussion

In this population-based study we found that after diagnosis of parkinsonism, the life expectancy of patients aged 55 years and over is decreased compared to age, sex, and comorbidity matched controls. The absolute life expectancy is lower in atypical parkinsonism than in

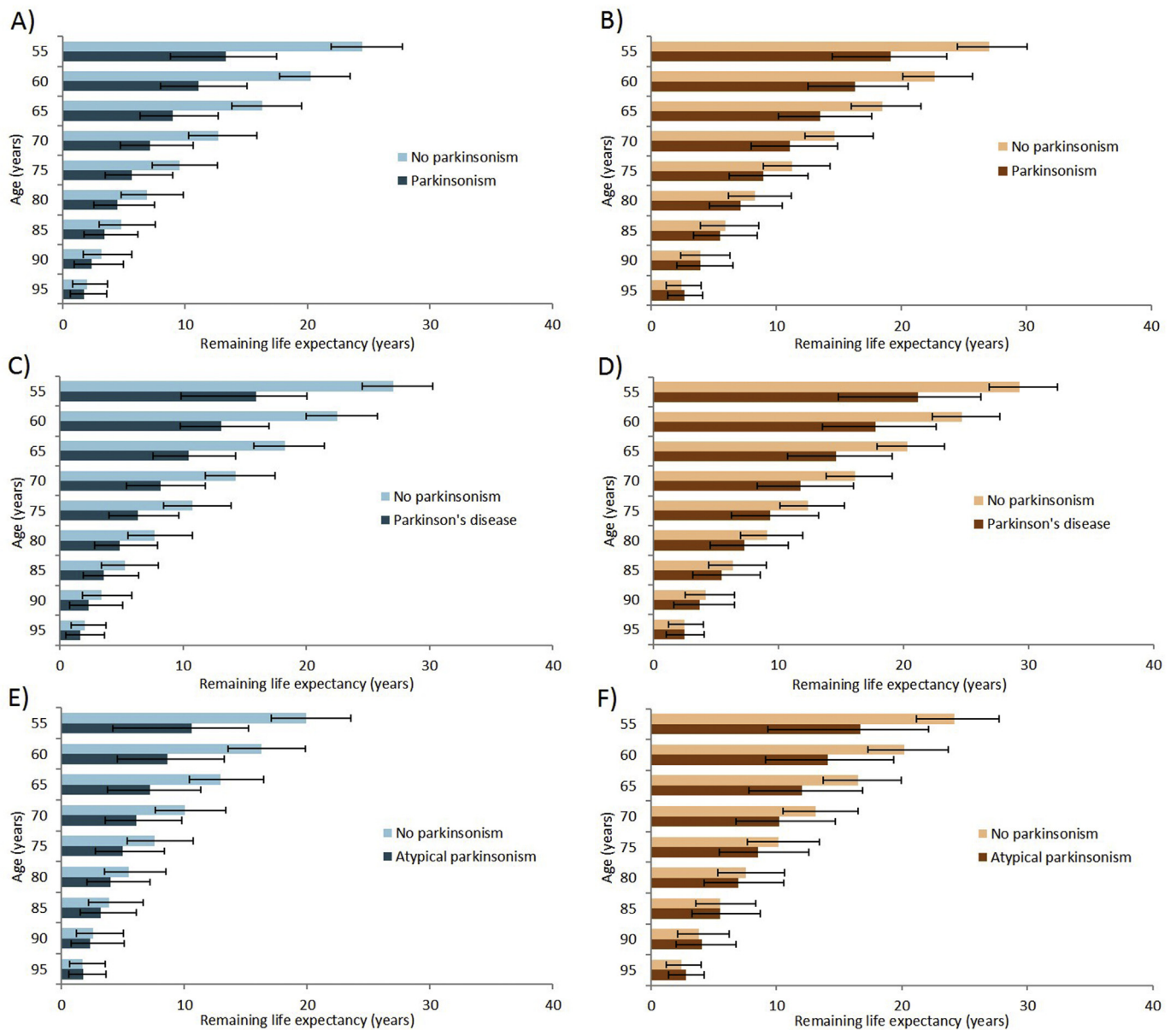


Fig. 2. Estimated remaining life expectancy for all-cause parkinsonism, Parkinson's disease and atypical parkinsonism after diagnosis. Panels A and B represent the remaining life expectancy of individuals with (n = 273) and without (n = 546) incident all-cause parkinsonism per five years for men (A) and women (B) separately. Panels C and D represent the remaining life expectancy of individuals with (n = 138) and without (n = 276) incident Parkinson's disease per five years for men (C) and women (D) separately. Panels E and F represent the remaining life expectancy of individuals with (n = 134) and without (n = 268) incident atypical parkinsonism per five years for men (E) and women (F) separately. The error bars show the 95% confidence intervals.

Parkinson's disease patients and the reduction in life expectancy is most prominent if the disease is diagnosed before the age of 70. In addition, we found that a relatively small proportion of the remaining life expectancy is lived with parkinsonism in the general population aged 55 years and over.

A limitation of our study is that death rates per year could only be obtained using a parametric approach because of a small number of parkinsonism patients diagnosed between the age of 50 and 60 years. Although parkinsonism diagnoses around the age of 50 are common in movement disorder clinics, it represents only a very small part of the patients in the general population [16]. In addition, the follow-up for parkinsonism was complete until January 2015, whereas the follow-up for all-cause mortality was complete until May 2018. This difference in follow-up time could have resulted in misclassification of patients as controls. However, this effect is expected to be small because of the low incidence of parkinsonism. A strength of our study is the continuous

case ascertainment with standardized criteria for parkinsonism. This approach diminished the possibility of time-trends in diagnoses and enabled us to study the life expectancy directly from the moment of parkinsonism diagnosis. Continuous follow-up of clinical records allowed us to update the diagnosis if this changed over time, which increases the accuracy of diagnosis, although the diagnosis is not as accurate as pathologic examination [17]. Our population-based design made it possible to study both patients seen by a medical specialist and those who presented only at the general practitioner, resulting in a good representation of all parkinsonism cases in the general population. Furthermore, we matched patients with controls not only on sex and birth year, but also on dementia, cancer, and CHD status. Finally, we showed robustness of our results by presenting both the commonly-described Kaplan Meier estimates and the absolute life expectancy estimates, which showed comparable results.

The burden of parkinsonism has been investigated previously in

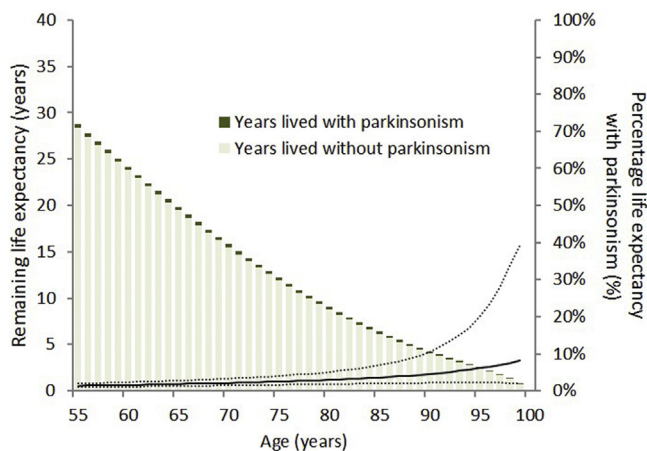


Fig. 3. Estimated remaining life expectancy with and without parkinsonism. The bars (left y-axis) represent the absolute remaining life expectancy and the line (right y-axis) reflects the percentage of the remaining life expectancy lived with diagnosed parkinsonism. The dotted lines show the 95% confidence intervals.

terms of disability-adjusted life-years and costs [18,19]. However, our study is novel in expressing the burden in the number of years a person in the general population lives with parkinsonism. Our results show that from 55 to 99 years of age 1.4%–8.1% of the remaining life expectancy is lived with parkinsonism. This estimate is important considering the impact parkinsonism has on quality of life [20–23]. Nevertheless, the described proportions are relatively small and correspond to a low number of absolute years lived with parkinsonism, which can be explained in three ways. First, the proportion of the remaining life expectancy lived with parkinsonism is influenced by the low incidence of parkinsonism in the general population [24]. Second, PD and several other parkinsonism subtypes have a prediagnostic phase that starts years before clinical diagnosis [25], which is not taken into account when looking at parkinsonism from the moment of diagnosis. Individuals in the general population might thus live more years with disease than reported in this study. Third, the proportion of the remaining life expectancy lived with parkinsonism is influenced by the survival after diagnosis, which is decreased.

The survival of parkinsonism patients has often been studied by the relative increase in mortality risk [3,26,27]. Previous studies have described an approximately 1.5 times increased mortality risk in patients with PD [3] and an even greater risk in other parkinsonism subtypes [4]. Although these risks give an indication on survival, these estimates are difficult to translate to patients. Absolute life expectancy estimates are easier to interpret and can help patients to better understand their prognosis.

Few previous studies have reported the absolute life expectancy of patients with parkinsonism [4–6,28], and even fewer have shown the course of the life expectancy compared to the general population [5,6]. Our results are consistent with the findings of Ishihara et al. who calculated the life expectancy of patients with PD from previously reported standardized mortality ratios and compared this to the life expectancy in the United Kingdom [5]. The study of Savica et al. found a one year difference in age at death for PD patients compared to controls at a diagnosis age around 75 [4]. This difference is smaller than the difference of 4.3 years that we found for PD compared to controls at age 75. However, our confidence interval around this difference was wide [95% confidence interval: 0.5;7.9] and overlaps with their estimate. In addition, the study of Savica et al. showed that the life expectancy was mainly reduced in MSA and DLB patients. We also found a lower life expectancy in atypical parkinsonism patients than in PD patients, but the difference with controls was smaller than in PD. This can be explained by the one-year higher mean age of patients with atypical

parkinsonism and the inclusion of patients with prevalent dementia in this group. Importantly, our group of atypical parkinsonism patients includes a wide variety of parkinsonism subtypes, including drug-induced and vascular parkinsonism, and might thus represent a different patient population than participants of the study of Savica et al.

In our study, PD patients were free of dementia at the time of PD diagnosis because the cases were ascertained according to the old criteria for diagnosing PD [29]. Still, we found a considerable negative effect of PD on the remaining life expectancy in both men and women. Our findings differ in this aspect from the results of several previous studies that did not describe an increased mortality risk in cognitively normal patients [6,27]. However, we did not rule out mild cognitive impairment in our study. The increased mortality risk could be partly attributed to the increased risk of developing dementia after PD, as suggested by a previous study within the Rotterdam Study [30] and also supported by our data showing that PD patients developed dementia more frequently than controls.

A meta-analysis by Macleod et al. indicated that most studies found increasing age at diagnosis to predict mortality risk in PD [3]. When looking at the absolute life expectancies, however, we find that the reduction in life expectancy is largest before the age of 70. This result is in accordance with previous studies presenting absolute life expectancies [5,6]. We found a larger difference in life expectancy between parkinsonism patients, both PD and atypical parkinsonism, and controls in men than in women. This different prognosis of PD in men and women was also found by some previous studies, but not confirmed by the meta-analysis of Macleod et al. [3]. The effect of sex on the remaining life expectancy of different parkinsonism subtypes has been limitedly studied so far. Therefore, future studies are warranted to provide further insight into the sex-differences in the life expectancy of parkinsonism subtypes.

5. Conclusions

In conclusion, our study showed that the absolute life expectancy of individuals diagnosed with parkinsonism is reduced compared to individuals without parkinsonism, especially if disease is diagnosed before the age of 70. Future studies are warranted to investigate sex-differences in the life expectancy of rarer causes of parkinsonism.

Author contributions

LJD contributed to the data acquisition, design and conceptualization of the study, the data analysis and interpretation, and drafting the manuscript. AH contributed to the data acquisition, design of the study, interpretation of findings, and revising the manuscript critically for important intellectual content. SKLD and PJK contributed to the data acquisition and revising the manuscript critically for important intellectual content. MAI contributed to the conceptualization of the study, interpretation of findings, and revising the manuscript critically for important intellectual content. MKI contributed to the data acquisition, design and conceptualization of the study, interpretation of findings, and revising the manuscript critically for important intellectual content.

Ethics approval

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictcp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and

to have their information obtained from treating physicians. The authors are grateful to the study participants, the staff from the Rotterdam Study, and the participating general practitioners and pharmacists.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2020.06.018>.

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