Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Has Deep Brain Stimulation Changed the Very Long-Term Outcome of Parkinson's Disease? A Controlled Longitudinal Study

Philipp Mahlknecht, MD, PhD,[1,] Marina Peball, MD,[1] Katherina Mair, MD,[1] Mario Werkmann, MD,[1] Michael Nocker, MD,[1] Elisabeth Wolf, MD,[1] Wilhelm Eisner, MD,[2] Sweta Bajaj, MD,[2] Sebastian Quirbach, MD,[2] Cecilia Peralta, MD,[3] Sabine Eschlböck, MD,[1] Gregor K. Wenning, MD, PhD,[1] Peter Willeit, MD, PhD,[1,4] Klaus Seppi, MD,[1] and Werner Poewe, MD[1,*]*

ABSTRACT: Background: The long-term impact of deep brain stimulation (DBS) on Parkinson's disease (PD) is difficult to assess and has not yet been rigorously evaluated in comparison to its natural history.
Objective: Comparison of key disability milestones (recurrent falls, psychosis, dementia, and institutionalization) and death in patients with PD with versus without DBS.
Methods: We collected retrospective information from clinical notes of patients with PD at our center that were implanted with subthalamic DBS >8 years ago (1999–2010) and a control group of PD patients without DBS similar in age at onset, age at baseline, sex distribution, and number of comorbidities at baseline (extracted from a registry study performed in 2004). Cox regression models were used to calculate hazard ratios, adjusted for potential baseline confounding variables (age, sex, disease duration, disease severity, and number of comorbidities).
Results: A total of 74 DBS-treated and 61 control patients with PD were included. For a median observational period of 14 years, patients treated with DBS were at lower risk of experiencing recurrent falls (hazard ratio = 0.57; 95% confidence interval, 0.37–0.90; $P = 0.015$) and psychosis (hazard ratio = 0.26; 95% confidence interval, 0.12–0.59; $P = 0.001$) compared with control patients. There was no significant difference in risk for dementia, institutionalization, or death. Disease progression as assessed by Hoehn and Yahr scores was not slower in DBS-treated patients.
Conclusions: Treatment with chronic subthalamic DBS was associated with lower risk for recurrent falls and psychotic symptoms, effects that may be mediated through improved motor symptom control and reduction in dopaminergic therapies, respectively. There was no evidence for DBS effects on underlying disease progression.

Parkinson's disease (PD) is a relentlessly progressive neurodegenerative disorder leading to increasingly disabling motor and nonmotor symptoms with a substantial risk for dependency and reduced life expectancy.[1] In the very advanced stages of the disease, a set of disability milestones including psychosis, falls, dementia, and institutionalization tend to cluster together before death.[2] Although levodopa and other dopaminergic therapies can effectively control motor symptoms, these treatments do not modify underlying disease progression or normalize life expectancy.[3,4] Deep brain stimulation (DBS) of the nucleus subthalamicus (STN) is dramatically effective in reducing levodopa-related motor complications and improving quality of life in patients with moderately advanced PD with benefits shown to persist for up to 5 to 10 years.[5] However, the effect of DBS on the eventual evolution

[1]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria;* [2]*Department of Neurosurgery, Innsbruck Medical University, Innsbruck, Austria;* [3]*Movement Disorder and Parkinson's Disease Program, CEMIC (Centro de Educación Médica e Investigaciones Clínicas) University Hospital, Buenos Aires, Argentina;* [4]*Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom*

***Correspondence to:** Dr. Philipp Mahlknecht, Department of Neurology, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria; E-mail: philipp.mahlknecht@i-med.ac.at; or Prof. Werner Poewe, Department of Neurology, Innsbruck Medical University, Anichstrasse 35, A-6020 Innsbruck, Austria; E-mail: werner.poewe@i-med.ac.at
Keywords: nucleus subthalamicus (STN), deep brain stimulation (DBS), nursing home placement, survival, mortality, hallucination.
Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 26 April 2020; accepted 23 May 2020.
Published online 21 September 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13039

of key disability milestones and on overall survival is largely unknown. In fact, there are only a few uncontrolled long-term studies reporting frequencies of key disability milestones in DBS patients,[6] and 4 controlled studies have assessed survival compared with medically managed patients[7–10] yielding conflicting findings.[11]

The aim of our study was to assess the impact of STN-DBS on emergence of psychosis, recurrent falls, dementia, institutionalization, and death as well as progression of disability in a longitudinal cohort of patients with PD under long-term subthalamic stimulation in comparison with a purely medically managed cohort.

Methods

Cohort

We searched our database for all patients with PD with subthalamic DBS implanted at our center more than 8 years before data collection (December 2018) and 77 patients with a surgery date between 1999 and 2010 were included. Standard (exclusion) criteria for surgery had been used at our center:[6,12] patients with PD younger than 70 to 75 years (biological age), a good motor response to levodopa, and severe motor fluctuations, disabling levodopa-induced dyskinesia, and/or severe rest tremor, despite optimization of medical therapy, were considered for surgery. Exclusion criteria were dementia, major active psychiatric disorders, major abnormalities on preoperative brain magnetic resonance imaging scans, and other major contraindications to surgery (e.g. coagulopathies, uncontrolled hypertension, malignancies). Patients were followed at least annually from surgery until December 2018 or until death. A control group of medically managed patients with PD was extracted from a registry study (EuroPa),[13] a random prospective outpatient sample of patients with PD entered in 2004 at our center, for whom data on corresponding long-term outcomes could be obtained. Baseline was defined as the last visit before surgery for the DBS group and the index date in the middle of the EuroPa study period for the control group. Of the 203 patients entered in the EuroPa registry at our site, we went ahead with complete data extraction as detailed below for all that were similar in age at onset (approximate range of DBS patients 30–65 years), age at baseline (approximate range of DBS patients 40–75 years), and would have met DBS eligibility criteria at baseline but did not undergo DBS (n = 64). Patients from the EuroPa study that had DBS (n = 23) were either included in the DBS group (if eligible) or excluded from the current analysis (if surgery was after 2010).

The study was approved by our local ethics committee and performed in accordance with the Declaration of Helsinki.

Data Extraction and Definition of End Points

Baseline data were retrospectively extracted from clinical records (hospital discharge letters and outpatient reports). They included age of onset, age at baseline, sex, and number of comorbidities according to the Charlson comorbidity index at baseline; and Hoehn and Yahr (H&Y) stage on medication, levodopa equivalent dose,[14] and total number of medications including non-PD-associated therapies at baseline and last follow-up visit. In addition, for the DBS group, H&Y stages on medication were extracted from the 3-month (range 2–4) visit after the DBS procedure. Source data from all included patients were systematically and independently screened by 2 authors (P.M. and M.P. or M.W.) for the following end points: (1) recurrent falls (i.e. more than 1 fall per year),[15] (2) psychosis defined as persistent hallucinations or delusions in 2 subsequent hospital letters/reports or hallucinations or delusions on 1 occasion with the need of reducing offending PD medication or the need of introducing antipsychotic medications (transient episodes of hallucinations/delusions attributed to precipitators such as infections or metabolic causes were not included), (3) diagnosis of dementia as per formal neuropsychological assessment[16] or cognitive decline in hospital letters/reports with the introduction of antidementive therapies, (4) institutionalization, and (5) death. Death was additionally ascertained by information obtained from the official Austrian

TABLE 1 *Baseline characteristics of groups*

Characteristics	STN-DBS, n = 74	Controls, n = 61	*P* Value
Female/male	24/50	20/41	0.56
Age at baseline	62.6 (56.7–68.8)	63.4 (55.4–70.0)	0.53
Age at onset	49.2 (41.0–55.0)	50.9 (46.1–57.1)	0.095
Disease duration	11.9 (9.3–15.8)	8.4 (5.3–15.1)	0.014
Number of comorbidities[a]	0 (0–0)	0 (0–0.5)	0.97
Number of medications	6.0 (4.0–8.0)	4.0 (2.0–7.0)	0.003
LED	1210 (930–1563)	900 (600–1325)	<0.001
LED post DBS[b]	532 (288–900)		<0.010
H&Y baseline	2.0 (2.0–2.5) 2.30 ± 0.43	2.0 (1.5–2.0) 2.00 ± 0.60	0.001
H&Y post DBS[b]	2.0 (2.0–2.5) 2.12 ± 0.55		0.21

Metric and ordinal variables are given in medians (25th–75th percentile) and Hoehn and Yahr scores are additionally given in means ± standard deviation to visualize the slight difference more accurately.
[a]According to the Charlson comorbidity index.
[b]Post DBS refers to a visit undertaken approximately 3 (range 2–4) months after DBS implantation.
DBS, deep brain stimulation; LED, levodopa equivalent dose; H&Y, Hoehn and Yahr stage; STN, subthalamic nucleus.

TABLE 2 *Follow-up characteristics of groups*

Characteristics	STN-DBS, n = 74	Controls, n = 61	*P* Value
Observational period until 12/2018, yrs	13.3 (10.6–16.7)	14.6 (14.6–14.6)	0.065
Time from baseline until last FU or death, yrs	8.9 (7.3–11.5)	9.3 (4.8–13.6)	0.94
n medications last FU	7 (5–9)	8 (4–11)	0.11
n medications difference from baseline	1 (−1 to 3)	3 (1–6)	<0.001
LED last FU	788 (500–900)	1100 (900–1500)	<0.001
LED difference from baseline	−508 (−753 to −100)	200 (−100 to 445)	<0.001
H&Y last FU	4.0 (2.5–4.0) 3.43 ± 0.97	4.0 (2.5–4.0) 3.52 ± 1.00	0.63
Increase H&Y baseline to last FU	1.0 (0.5–2.0) 1.14 ± 0.94	1.5 (1.0–2.0) 1.53 ± 0.91	0.025
Increase H&Y post DBS[a] to last FU	1.0 (0.5–2.0) 1.32 ± 0.88		0.22

Metric and ordinal variables are given in medians (25th–75th percentiles) and Hoehn and Yahr scores are additionally given in means ± standard deviation to visualize the slight difference more accurately.
[a]Post DBS refers to a visit undertaken approximately 3 (range 2–4) months after DBS implantation.
DBS, deep brain stimulation; FU, follow-up; LED, levodopa equivalent dose; H&Y, Hoehn and Yahr stage; STN, subthalamic nucleus.

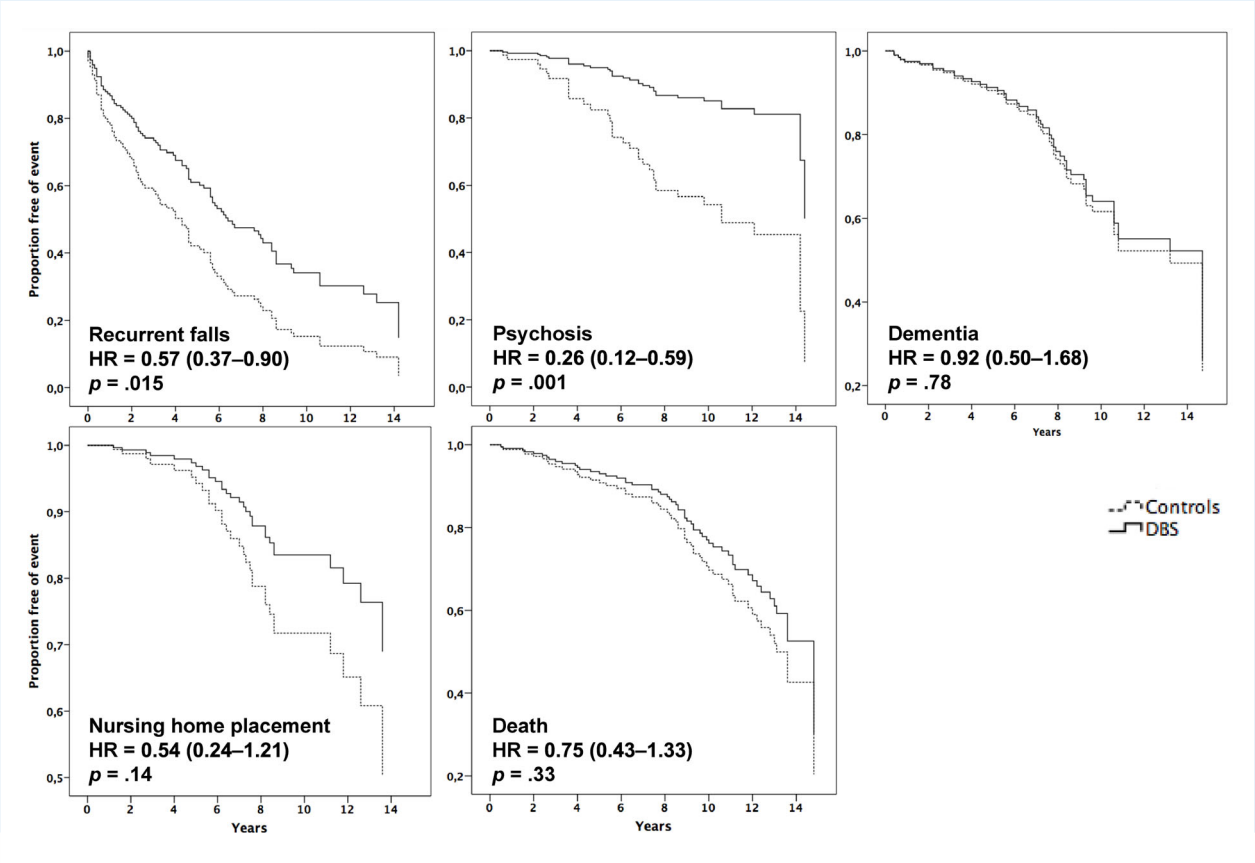

FIG. 1. Event-free survival in the DBS-treated group and in the control Parkinson's disease group. Cox regression models were used to calculate hazard ratios, adjusted for potential baseline confounders (age, sex, disease duration, disease severity according to Hoehn and Yahr scores, and number of comorbidities). DBS, deep brain stimulation; HR, hazard ratios.

Institute of Statistics *(Statistik Austria)*. For end points 1 to 3, the event was set at the time for which both investigators agreed that data unequivocally documented its presence.

Statistical Analysis

For comparisons between groups, the chi-square test for categorical variables and the Mann-Whitney *U* test for metric variables were used, as non-normal distributions were shown by the Kolmogorv-Smirnov test throughout. To compare risk for the predefined end points, Cox regression models were used to calculate hazard ratios (HR), adjusted for the potential baseline confounders age, sex, disease duration, disease severity according to H&Y scores, and number of comorbidities. As a crude measure of disease progression, differences in H&Y scores between baseline and last follow-up were calculated in each patient. In patients with DBS, this was done using

H&Y scores pre-DBS (thus including the period of immediate symptomatic effect of DBS) and post-DBS from the 3-month visit (thus excluding the period of immediate symptomatic effect of DBS). Odds ratios for 1-unit increments in H&Y scores were calculated with ordinal logistic regression analysis adjusted for the same baseline confounders as noted previously and for time from baseline to last follow-up. SPSS 22.0 (IBM Corp., Armonk, NY) was used for all statistical analyses. The significance level was set at a 2-sided P value of <0.05.

Results

Of the 77 patients who underwent a STN-DBS procedure between 1999 and 2010, 3 patients were excluded: in 2 DBS systems had to be explanted as a result of system infection, and both refused a second procedure. Because of the short period of stimulation (6 months), 1 of the 2 patients was included in the medically managed control group. A third patient was eventually diagnosed as having multiple system atrophy–parkinsonian type and was also excluded from analysis. Of the eligible 64 control patients, 4 were excluded because of diagnostic reclassification after baseline (2 multiple system atrophy–parkinsonian type, 2 functional parkinsonism). Thus, the present analysis included 74 patients in the DBS group and 61 patients in the control group (see Supplementary Fig. 1 for a flowchart of patients). Patients' baseline characteristics are summarized in Table 1. Apart from H&Y scores and disease duration, which were both slightly but significantly higher in the DBS cohort, groups were well balanced at baseline. As summary of stimulation parameters used can be found in the Supplementary Appendix.

The median observational period until the end of the study (December 2018) was approximately 14 years, and the median time from baseline until last follow-up or death was approximately 9 years (Table 2). The cumulative time spent free of the assessed end points are plotted in Figure 1 along with the respective HR (see Supplementary Table 1 for crude incidence rates). Patients in the DBS group were at significantly lower risk of recurrent falls (HR = 0.57; 95% confidence interval [CI], 0.37–0.90; P = 0.035) and psychosis (HR = 0.26; 95% CI, 0.12–0.59; P = 0.001) compared with medically managed patients, whereas there were no differences with regard to time to dementia, institutionalization, or death. Increment in H&Y scores from baseline to last follow-up was smaller in the DBS-treated patients (Table 2), but this was not statistically significant when difference was calculated from the first post-DBS visit to the last follow-up visit. Accordingly, the adjusted odds ratio for a 1-unit increment in H&Y for the DBS group in reference to the control group was 0.51 (95% CI, 0.27–0.96; P = 0.038) from baseline to last follow-up and 0.74 (95% CI, 0.39–1.41; P = 0.36) from the post-DBS visit to last follow-up.

Discussion

Data on the impact of various treatment strategies including DBS on the time to evolution of key disability milestones in PD are scarce. Findings from the long-term follow-up of the Sydney multicenter cohort suggest that, after 15 to 20 years of disease duration, >80% of patients will have developed recurrent falls, >50% will suffer from hallucinations and/or dementia, and >40% will have been placed in a nursing home.[17,18] By such time, levodopa-induced motor complications affect almost all patients but are usually not considered a leading cause of disability.[2] Our series of patients with PD operated with DBS more than 8 years prior to the current study is comparable with such long-term cohorts with median disease durations at baselines of 8 to 12 years and additional follow-up periods of about 9 years. We found reduced risks to develop recurrent falls and psychosis in DBS-treated patients when compared with a group of medically managed patients who were similar in age at onset, age at baseline, sex, and comorbidities. There were no significant risk differences with regard to dementia, institutionalization, or death.

There is only one long-term study reporting on the incidence of falls in patients treated with STN-DBS, where 9 of 19 patients (47%) had falls 5 years after DBS implantation and 30 years after disease onset.[19] In our study, in both groups the majority of patients developed recurrent falls. However, time to this end point was longer in stimulated patients, resulting in a significantly reduced relative risk for recurrent falls of 43% in the DBS group. It is likely that this reduction in risk is attributed to improved motor symptom control over extended periods of time rather than to a true disease-modifying effect.

There are a few long-term studies reporting rates of psychosis and dementia after STN-DBS in small patient numbers. They found variable proportions of 5% to 60% for dementia and 20% to 60% for psychosis after 8 to 12 years of chronic subthalamic stimulation.[20–22] In our cohort, a similar proportion of about one third of patients had developed dementia by the time of last follow-up with no risk difference between DBS and medically treated groups. On the other hand, among stimulated patients, the relative risk for persistent psychosis was significantly reduced by 74%. This difference is likely attributed to dose reductions of dopaminergic medication that are a key component of the clinical effects of subthalamic stimulation.[5]

Uncontrolled studies have reported rates of institutionalization of 40% to 50% after up to 10 to 12 years of chronic DBS,[20,22] which is comparable with the frequencies reported in medically managed patients.[17,18] A single controlled study, however, reported a markedly reduced risk of 90% of institutionalization in DBS-treated patients compared with a group of patients with PD from the same institution meeting eligibility criteria for DBS who had declined.[9] The latter fact could theoretically by itself have introduced bias, and other relevant information on comorbidity, baseline disease severity, and cognition was not available. Nonetheless, we observed a similar, but nonsignificant, trend for longer latency to institutionalization in our study as well. It has to be kept in mind that besides disease-related factors, the rates of institutionalization will also largely depend on the respective health care setting and sociocultural characteristics of the countries/regions studied.

Controlled studies assessing survival in DBS-treated compared with purely medically managed patients overall seem to suggest a marginal survival advantage in DBS-treated patients,[9,10] although findings are conflicting and methodological issues including the

insufficient controlling for confounders limit conclusions.[11] We did not observe significant differences in survival between the DBS and medically managed groups. Also, disease progression as assessed by H&Y scores was slower in the DBS-treated patients only when including the immediate drop in H&Y scores after commencement of stimulation, again arguing against a disease-modifying effect of DBS beyond its symptomatic impact. H&Y scores are a crude measure of disease severity and were already slightly higher in the DBS group at baseline. These results should therefore be interpreted very cautiously.

Our study has several limitations, including the retrospective data collection, relatively low number of patients leading to wide confidence intervals, and a lack of detailed data on motor status including medication *off* motor scores. However, our main goal was to focus on long-term outcome in terms of key disability milestones that are beyond traditional motor and other end points usually employed by clinical trials. Although not a prospectively planned study, DBS patients were compared with a carefully selected control cohort similar in age at onset, age at baseline, sex distribution, and comorbidities at baseline that was identified during the time period of DBS procedures. We furthermore adjusted statistical analyses for various potential confounders, including disease duration and disease severity. The latter 2 baseline characteristics were slightly but statistically significantly higher in the DBS group, and the beneficial effects of DBS on risk for recurrent falls and psychosis observed here are therefore very unlikely to be driven by these 2 potential confounders. It has to be kept in mind that assessing differences in long-term outcomes requires sufficiently long time periods over several years, which are unfeasible to study prospectively in a randomized design (it would be unethical to withhold DBS in medically managed patients who could eventually benefit from it). Multicenter registry studies could further help fill this knowledge gap and potentially also look into the effect of various stimulation modes (eg, low pulse width, low-frequency stimulation) on the occurrence of late-stage disease milestones.

Within the limitations imposed by the retrospective design, our study suggests that long-term treatment with subthalamic DBS is associated with lower risk to recurrent falls and onset of psychotic symptoms. These 2 effects may be mediated through improved motor symptom control over extended periods of time[5] and a reduction in dopaminergic therapies, respectively. They do not in themselves provide evidence for a true disease-modifying effect of DBS, and there was no evidence for beneficial effects of DBS on the long-term evolution of dementia, need for nursing home placement, or on overall survival.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

P.M.: 1A, 1B, 1C, 2A, 2B, 3A, 3B
M.P.: 1C, 3B
K.M.: 1C, 3B
M.W.: 1C, 3B
M.N.: 1C, 3B
E.W.: 1C, 3B
W.H.: 1C, 3B
S.B.: 1C, 3B
S.Q.: 1C, 3B
C.P.: 1C, 3B
S.E.: 1C, 3B
G.K.W.: 1C, 3B
P.W.: 1A, 2A, 2C, 3B
K.S.: 1A, 1B, 2C, 3B
W.P.: 1A, 1B, 2C, 3B

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. Informed patient consent was not necessary for this retrospective work.

Funding Sources and Conflicts of Interest: The authors report no conflict of interest related to this work. There was no specific funding for this study.

Financial Disclosures for the Previous 12's Months: W.E. reports consultancy and lecture fees from Medronic and Abbott outside the submitted work. K.S. reports personal fees from Teva, UCB, Lundbeck, AOP Orphan Pharmaceuticals AG, Roche, Grünenthal, and Abbvie; honoraria from the International Parkinson and Movement Disorders Society; and research grants from the FWF Austrian Science Fund, Michael J. Fox Foundation, and International Parkinson and Movement Disorder Society outside the submitted work. W.P. reports consultancy and lecture fees in relation to clinical drug programs for Parkinson's disease from AbbVie, Allergan, AstraZeneca, BIAL, Boehringer-Ingelheim, Boston Scientific, Britannia, Cynapsus, Grünenthal, Intec, Ipsen, Lundbeck, Medtronic, Denali, Novartis, Neuroderm, Orion Pharma, Takeda, Teva, UCB, and Zambon and royalties from Thieme, Wiley Blackwell, Oxford University Press, and Cambridge University Press outside of the submitted work. G.K.W. reports consultancy and lecture fees from AbbVie, Affiris, AstraZeneca, Biogen, Lundbeck, Merz, Novartis, Ono, Teva, and Theravance outside of the submitted work. All other authors have nothing to report.

References

1. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Prim* 2017;3:1–21.
2. Coelho M, Ferreira JJ. Late-stage Parkinson disease. *Nat Rev Neurol* 2012;8:435–442.
3. Macleod AD, Taylor KSM, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2014;29:1615–1622.
4. Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med* 2019;380:315–324.
5. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. *Lancet Neurol* 2013;12:1025–1034.

6. Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol* 2019;15:234–242.
7. Schüpbach MWM, Welter ML, Bonnet AM, et al. Mortality in patients with Parkinson's disease treated by stimulation of the subthalamic nucleus. *Mov Disord* 2007;22:257–261.
8. Lilleeng B, Brønnick K, Toft M, Dietrichs E, Larsen JP. Progression and survival in Parkinson's disease with subthalamic nucleus stimulation. *Acta Neurol Scand* 2014;130:292–298.
9. Ngoga D, Mitchell R, Kausar J, Hodson J, Harries A, Pall H. Deep brain stimulation improves survival in severe Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2014;85:17–22.
10. Weaver FM, Stroupe KT, Smith B, et al. Survival in patients with Parkinson's disease after deep brain stimulation or medical management. *Mov Disord* 2017;32:1756–1763.
11. Contarino MF, Marinus J, van Hilten JJ. Does deep brain stimulation of the subthalamic nucleus prolong survival in Parkinson's disease? *Mov Disord* 2018;33:947–949.
12. Defer GL, Widner H, Marié RM, Rémy P, Levivier M. Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD). *Mov Disord* 1999;14:572–584.
13. Peralta CM, Frauscher B, Seppi K, et al. Restless legs syndrome in Parkinson's disease. *Mov Disord* 2009;24:2076–2080.
14. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25:2649–2653.
15. Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwinderman AH. Prospective assessment of falls in Parkinson's disease. *J Neurol* 2001;248:950–958.
16. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 2007;22:1689–1707.
17. Hely MA, Morris JGL, Reid WGJ, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord* 2005;20:190–199.
18. Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord* 2008;23:837–844.
19. Merola A, Zibetti M, Angrisano S, et al. Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients. *Brain* 2011;134:2074–2084.
20. Bang Henriksen M, Johnsen EL, Sunde N, Vase A, Gjelstrup MC, Østergaard K. Surviving 10 years with deep brain stimulation for Parkinson's disease—a follow-up of 79 patients. *Eur J Neurol* 2016;23:53–61.
21. Fasano A, Romito LM, Daniele A, et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 2010;133:2664–2676.
22. Constantinescu R, Eriksson B, Jansson Y, et al. Key clinical milestones 15 years and onwards after DBS-STN surgery-a retrospective analysis of patients that underwent surgery between 1993 and 2001. *Clin Neurol Neurosurg* 2017;154:43–48.

Supporting Information

Supporting information may be found in the online version of this article.

Supplementary Table 1. Frequency and hazard ratios for major disease milestones

Supplementary Figure 1. Flow chart of participants