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Sex differences in the short-term and long-term effects of subthalamic nucleus stimulation in Parkinson's disease

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ABSTRACT

Objective: To assess the influence of sex on the short-term and long-term effects of subthalamic nucleus stimulation (STN-DBS) in Parkinson's disease (PD)

Methods: We evaluated 48 male and 52 female PD patients enrolled in our prospective DBS registry who received bilateral STN-DBS between 2005 and 2013 and had 5-year follow-up data. Motor function, dyskinesia duration/disability, activities of daily living, health-related quality of life (HRQoL), cognitive function, and depression severity were investigated at baseline and at the 1- and 5-year follow-up visits. HRQoL was assessed using the 36-Item Short Form Health Survey (SF-36), which consists of physical-component summary (PCS) and mental-component summary scores.

Results: None of the changes from baseline to the 1- or 5-year follow-up in clinical outcomes differed between the men and women except for the SF-36 PCS scores. Compared with the baseline, there was an improvement in the PCS scores in both men ($p < 0.001$) and women ($p = 0.001$) at the 1-year follow-up; however, a trend toward greater improvement in men was observed ($p = 0.061$). At the 5-year follow-up, STN-DBS improved the PCS scores in men ($p < 0.001$) but not in women ($p = 0.409$) compared with the baseline, and there was a significant difference between the groups ($p = 0.002$).

Conclusions: Our data suggest that STN-DBS induce a similar degree of short-term and long-term effects on motor function, cognitive and depressive symptoms, and functional status between male and female PD patients. Nevertheless, physical HRQoL seemed to improve to a greater extent in men, and this sex difference was more prominent with long-term observation.

1. Introduction

Evidence is accumulating that sex-related differences exist in Parkinson's disease (PD). Epidemiological data have shown that men have a greater susceptibility to PD compared to women [1]. Female PD patients tend to have a milder phenotype at early stages, but they are at higher risk of developing levodopa-related motor complications such as motor fluctuations and dyskinesia [2–4]. There are also sex differences in relation to non-motor symptoms in PD patients [5,6]. Mechanisms underlying these differences in PD are poorly understood and may involve hormonal and reproductive factors, genetic influences, lifestyle exposures, and structural or functional differences in brain dopamine pathways [7,8].

Subthalamic nucleus deep brain stimulation (STN-DBS) improves motor function and levodopa-related motor complications and enables a reduction in the dosage of dopaminergic medications in patients with advanced PD [9]. There have been discussions on the influence of sex on the effect of STN-DBS in PD. Several short-term studies have suggested that overall improvements in motor and non-motor symptoms following STN-DBS are similar between male and female PD patients [10–12], whereas the short-term results on sex differences in postoperative health-related quality of life (HRQoL) are inconsistent [11,12]. Furthermore, the impact of sex on the long-term effects of STN-DBS remains unclear. Romito et al. [13] reported that STN-DBS induced similar long-term benefits in both sexes; however, these results are limited due to small sample

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sizes, and HRQoL outcomes were not considered in their study. To clarify these issues, we compared the short-term and long-term effects of STN-DBS on clinical outcomes including HRQoL between male and female PD patients over 5-years of follow-up.

2. Methods

2.1. Subjects

Since March 2005, patients who underwent STN-DBS at the Movement Disorder Center of Seoul National University Hospital (SNUH) have been assessed according to the prospective protocol reported previously [14]. Postoperative evaluations have been performed at 3, 6, 12 months and then yearly after STN-DBS. We reviewed the medical records of 193 PD patients (87 males and 106 females) who underwent bilateral STN-DBS at our center prior to October 2013. Of those, patients who had 5-year follow-up data were considered for this analysis. We excluded patients if they had undergone unilateral DBS implantation, DBS reoperation or associated major complications, or previous brain surgery. The study protocol was approved by the SNUH Institutional Review Board (1906-067-1041) and followed the principles of the Declaration of Helsinki.

2.2. Clinical assessment

The current study investigated the baseline (just before surgery) and the 1-, and 5-year postoperative follow-up data. We selected the 1-year follow-up data to assess sex differences in the short-term effects of STN-DBS. The baseline data were obtained from the off- and on-medication states, and the postoperative follow-up data were obtained from the off-medication/on-stimulation and on-medication/on-stimulation states [15]. Motor symptoms were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) part III. We measured the axial (the sum of items 18 and 22 [neck rigidity only] and 27–31), tremor (the sum of items 20–21), limb rigidity (the sum of item 22 [except for neck rigidity]), and limb bradykinesia (the sum of items 23–26) subscores from the UPDRS part III. The dyskinesia score (the sum of items 32–33) was obtained from the UPDRS part IV. Activities of daily living (ADLs) were evaluated with the UPDRS part II and Schwab and England (S&E) scale. HRQoL was evaluated with the Short-Form-36 Health Survey (SF-36), which consists of two main categories; physical health and mental health [16]. Physical health and mental health consist of four subcategories each; physical health includes physical functioning, role-physical, bodily pain and general health, and mental health includes vitality, social functioning, role-emotion, and mental health. The physical-component summary (PCS) and mental-component summary (MCS) scores were calculated according to the user's manual [17]. Higher scores indicate a better HRQoL. Overall cognitive function was evaluated with the Korean version of the Mini-Mental State Exam (K-MMSE). Depression was evaluated with the Beck Depression Inventory (BDI)-II. The levodopa equivalent daily dose (LEDD) was calculated according to the formula described by Tomlinson et al. [18].

2.3. Statistical analysis

All data are presented as the mean ± standard deviation. Data distribution and normality were evaluated with the Shapiro-Wilk test. Baseline demographic and clinical characteristics were compared with the chi-square test for categorical variables and Student's t-test for continuous variables. Changes from baseline for the measured variables were examined with the paired *t*-test to assess the effect within the group and with the analysis of covariance to compare the group effects adjusting for age at surgery, disease duration, change in LEDD (except for variables obtained from the off-medication state), and baseline value of each variable. Linear regression models were used to determine preoperative factors related to the postoperative change in HRQoL. In addition to sex, other potential baseline variables such as age at surgery, disease duration, UPDRS part III score during off-medication state (indicating disease severity), UPDRS part IV dyskinesia score, S&E score during off-medication state (indicating functional severity), K-MMSE score, BDI-II score, and LEDD were included in the linear regression models. All variables for which the p value was less than 0.2 in the simple linear regression models were included in a multiple linear regression model. Given the explorative nature of our study, the standard non-corrected significance α level of $p < 0.05$ was used to reduce the risk of a type II error. Calculations were performed with SPSS (IBM) version 25.

3. Results

3.1. Characteristics of the patients

A total of 48 male and 52 female PD patients were included in this study (Fig. 1). All patients but two had both 1-year and 5-year follow-up data. There were no significant differences in the baseline demographic and clinical variables between the men and women except for age at surgery and LEDD (Table 1). At baseline, the male patients were younger (57.3 ± 8.5 vs. 60.2 ± 6.7, $p = 0.042$) and had a higher LEDD (1461.7 ± 887.5 vs. 1158.8 ± 479.7, $p = 0.028$) compared to the female patients. Stimulation parameters at the 1-year and 5-year follow-ups did not differ between the two groups (Supplementary Table 1).

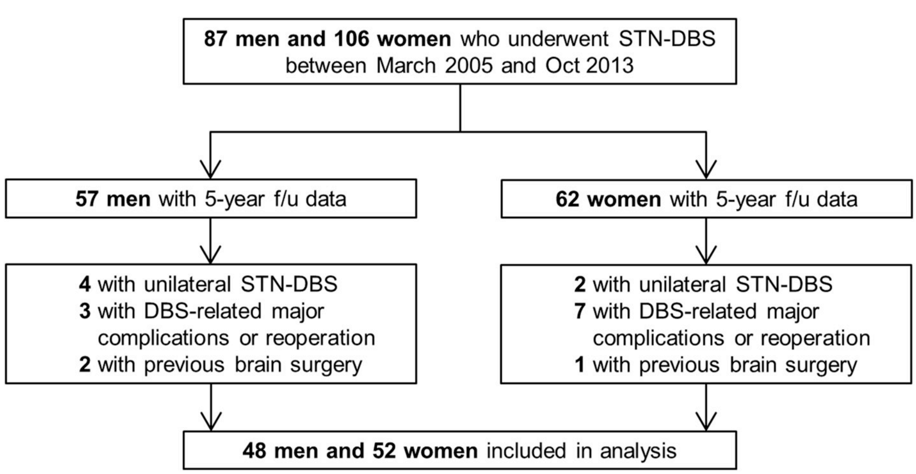

Fig. 1. Flow diagram of the patient selection
Abbreviation: STN-DBS = subthalamic nucleus deep brain stimulation.

Table 1
Baseline demographic and clinical characteristics.

Variables	Med	Men (n = 48)	Women (n = 52)	*p* value
Age at surgery, years		57.3 (8.5)	60.2 (6.7)	**0.042**
Age at onset, years		45.5 (9.9)	48.2 (6.5)	0.103
Disease duration, years		10.8 (4.0)	12.0 (4.7)	0.196
UPDRS part II score	On	9.9 (7.5)	9.0 (8.0)	0.560
	Off	24.0 (8.3)	22.1 (7.8)	0.240
UPDRS part III score	On	19.6 (11.9)	19.4 (11.3)	0.941
	Off	40.9 (14.6)	40.8 (13.5)	0.973
Tremor subscore	On	2.3 (4.1)	2.5 (3.9)	0.778
	Off	4.8 (5.1)	6.4 (5.5)	0.126
Rigidity subscore	On	3.5 (2.7)	2.6 (2.4)	0.086
	Off	7.0 (3.5)	6.5 (2.8)	0.406
Bradykinesia subscore	On	7.6 (4.8)	7.6 (4.7)	0.969
	Off	15.1 (6.1)	14.5 (5.6)	0.601
Axial subscore	On	5.1 (3.0)	5.7 (3.5)	0.305
	Off	11.9 (4.9)	11.5 (4.2)	0.651
UPDRS part IV dyskinesia score		4.0 (2.4)	4.5 (2.1)	0.222
Schwab and England Scale	On	82.1 (15.4)	82.1 (15.8)	0.992
	Off	49.6 (23.4)	53.3 (22.1)	0.420
LEDD, mg		1461.7 (887.5)	1158.8 (479.7)	**0.028**
BDI-II score		17.6 (9.4)	20.6 (9.7)	0.124
K-MMSE score		27.6 (2.3)	27.3 (2.4)	0.536
SF-36 score				
Physical-component summary		34.8 (9.1)	32.6 (8.1)	0.213
Physical functioning		42.2 (26.6)	39.6 (24.6)	0.613
Role-physical		20.7 (30.1)	17.2 (28.1)	0.543
Bodily pain		41.8 (28.5)	39.4 (24.5)	0.663
General health		48.7 (18.2)	46.5 (20.0)	0.563
Mental-component summary		38.2 (8.4)	39.4 (11.6)	0.550
Vitality		43.3 (22.6)	39.4 (20.2)	0.371
Social functioning		49.7 (25.7)	48.0 (29.1)	0.761
Role-emotional		17.0 (31.0)	30.7 (41.5)	0.069
Mental healthy		55.0 (17.8)	53.3 (21.3)	0.666

Data are presented as the mean (standard deviation).
Abbreviations: BDI = Beck depression inventory; K-MMSE = Korean version of the Mini-Mental State Examination; LEDD = levodopa equivalent daily dose; SF-36 = 36-Item Short Form Health Survey; UPDRS = Unified Parkinson's Disease Rating Scale.

3.2. 1-Year follow-up

Changes in clinical variables from baseline to the 1-year follow-up are summarized in Table 2. There were no significant differences in the changes between the men and women in the UPDRS part II during the on- and off-medication states, UPDRS part III total score and its subscores during the on- and off-medication states, UPDRS part IV dyskinesia score, S&E score during the on- and off-medication states, K-MMSE score, BDI-II score, and LEDD.

With respect to the SF-36 scores, there was an improvement in the PCS scores in both the men (mean difference, 7.6 points; 95% confidence interval [CI], 4.6 to 10.7 points; $p < 0.001$) and women (mean difference, 4.6 points; 95% CI, 2.1 to 7.1 points; $p = 0.001$). Although there was a trend toward greater improvement in the PCS scores of the men, the difference was not significant ($p = 0.061$) (Fig. 2A and Table 2). The scores for the MCS were not improved with STN-DBS in both the men and women with no difference between the groups ($p = 0.346$). Among the subdomains of physical and mental health, only improvement in physical functioning was greater in the men compared to the women ($p = 0.022$) (Fig. 2A and Table 2).

3.3. 5-Year follow-up

None of the changes in the clinical variables differed significantly between the men and women except for the SF-36 scores (Table 3). Compared to the baseline, the PCS scores at the 5-year follow-up were improved with STN-DBS in the men (mean difference, 6.1 points; 95% CI, 2.9 to 9.3 points; $p < 0.001$) but not in the women (mean difference, 0.9 points; 95% CI, −1.3 to 3.2 points; $p = 0.409$), and there was a significant difference between the groups ($p = 0.002$) (Fig. 2B and Table 3). Similar to the results of the 1-year follow-up data, STN-DBS did not improve the MCS scores in both the men and women with no difference between the groups ($p = 0.605$). Among the subdomains of physical and mental health, the degree of change toward improvement in physical functioning ($p = 0.016$), bodily pain ($p = 0.003$), and general health ($p = 0.008$) was greater in the men compared to the women (Fig. 2B and Table 3).

Based on these results showing potential correlations of sex with the long-term postoperative physical HRQoL, we further performed multiple linear regression analyses. Although simple linear regression models showed that sex, age at surgery, UPDRS part III score, and S&E score had a p value of less than 0.2, only two parameters, sex ($p = 0.026$) and age at surgery ($p = 0.018$), were independently associated with the postoperative change in the PCS scores from baseline to the 5-year follow-up in the subsequent multiple linear regression model (Table 4).

4. Discussion

In the current study, we assessed sex differences in the effects of bilateral STN-DBS in 48 male and 52 female PD patients over a 5-year follow-up through a retrospective analysis of prospectively collected data. Our results show that STN-DBS induced similar short-term and long-term effects in both sexes on motor, cognitive and depressive symptoms, and ADLs, which is roughly consistent with previous studies [10,12,13]. However, a sex difference was observed in the postoperative physical HRQoL changes. Short-term improvements in the physical HRQoL following STN-DBS seemed to be slightly greater in the men than in the women, and this difference was more prominent with the long-term observation. On the other hand, no sex difference was found in the short-term and long-term postoperative mental HRQoL.

Table 2
Changes in clinical outcomes from baseline to the 1-year follow-up.

Variables	Med	Men		Women		*p* value for sex difference
		Mean change (95% CI)	*p* value	Mean change (95% CI)	*p* value	
UPDRS part II score	On	−0.6 (−3.1 to 1.9)	0.616	0.0 (−2.6 to 2.6)	0.994	0.835
	Off	−8.4 (−10.9 to −6.0)	**< 0.001**	−6.7 (−9.5 to −4.2)	**< 0.001**	0.958
UPDRS part III score	On	−5.0 (−9.7 to −0.4)	**0.033**	−5.2 (−8.7 to −1.8)	**0.004**	0.782
	Off	−20.1 (−24.9 to −15.3)	**< 0.001**	−21.0 (−24.6 to −17.5)	**< 0.001**	0.177
Tremor subscore	On	−1.3 (−2.4 to −0.2)	**0.018**	−2.4 (−3.6 to −1.1)	**< 0.001**	0.058
	Off	−3.4 (−4.8 to −1.9)	**< 0.001**	−5.5 (−7.0 to −4.0)	**< 0.001**	0.071
Rigidity subscore	On	−2.0 (−3.0 to −0.9)	**0.001**	−0.8 (−1.5 to −0.1)	**0.020**	0.458
	Off	−4.0 (−5.2 to −2.7)	**< 0.001**	−4.1 (−4.8 to −3.3)	**< 0.001**	0.242
Bradykinesia subscore	On	−1.1 (−3.2 to 1.0)	0.279	−1.5 (−3.3 to 0.2)	0.085	0.957
	Off	−6.2 (−8.6 to −3.9)	**< 0.001**	−6.2 (−8.0 to −4.5)	**< 0.001**	0.262
Axial subscore	On	−0.4 (−1.8 to 0.9)	0.516	−0.6 (−1.6 to 0.5)	0.303	0.359
	Off	−5.7 (−7.2 to −4.2)	**< 0.001**	−4.7 (−5.8 to −3.5)	**< 0.001**	0.760
UPDRS part IV dyskinesia score		−3.2 (−4.0 to −2.4)	**< 0.001**	−3.7 (−4.4 to −2.9)	**< 0.001**	0.714
Schwab and England Scale	On	6.0 (−0.5 to 12.5)	0.070	2.1 (−3.9 to 8.1)	0.478	0.175
	Off	25.5 (17.5–33.6)	**< 0.001**	19.3 (12.4–26.2)	**< 0.001**	0.850
K-MMSE score		−0.5 (−1.3 to 0.3)	0.208	−0.4 (−0.9 to 0.2)	0.178	0.594
BDI-II score		−0.6 (−3.7 to 2.6)	0.715	−0.1 (−3.5 to 3.2)	0.932	0.335
LEDD, mg		−1006.4 (−1255.6 to −757.2)	**< 0.001**	−616.4 (−743.9 to −488.9)	**< 0.001**	0.133
SF-36 score						
Physical-component summary		7.6 (4.6–10.7)	**< 0.001**	4.6 (2.1–7.1)	**0.001**	0.061
Physical functioning		13.3 (4.9–21.7)	**0.003**	3.5 (−2.4 to 9.0)	0.234	**0.022**
Role-physical		6.8 (−5.4 to 19.0)	0.266	10.3 (0.0–20.5)	0.051	0.861
Bodily pain		31.5 (20.8–42.3)	**< 0.001**	22.2 (12.7–31.6)	**< 0.001**	0.094
General health		7.9 (0.8–15.0)	**0.031**	6.8 (1.3–12.3)	**0.017**	0.569
Mental-component summary		2.2 (−1.8 to 6.2)	0.370	2.7 (−0.9 to 6.4)	0.163	0.346
Vitality		7.2 (−2.3 to 16.6)	0.134	7.6 (1.0–14.3)	**0.025**	0.700
Social functioning		14.2 (2.8–25.6)	**0.016**	15.4 (7.7–23.2)	**< 0.001**	0.946
Role-emotional		6.1 (−8.6 to 20.8)	0.410	2.0 (−12.1 to 16.0)	0.781	0.310
Mental healthy		5.3 (−1.9 to 12.5)	0.147	4.5 (−2.4 to 11.5)	0.195	0.794

Abbreviations: BDI = Beck depression inventory; CI = confidence interval; K-MMSE = Korean version of the Mini-Mental State Examination; LEDD = levodopa equivalent daily dose; SF-36 = 36-Item Short Form Health Survey; UPDRS = Unified Parkinson's Disease Rating Scale.

Hariz et al. [11] compared the effects of STN-DBS between 31 male and 18 female PD patients over a mean duration of 19 months after surgery and found that a significant improvement of the HRQoL occurred only in females. Thus, in contrast to the current findings, they concluded that the HRQoL appears to improve to a greater extent in women. However, these results are limited by the lack of a direct comparison of the change in the HRQoL between the sexes and an absence of adjustment for confounding factors. On the other hand, another study has shown that the HRQoL improved equally in men and women at 12 months after STN-DBS [12]. Such conflicting results across studies could be attributed partly to the differences in scales for assessment of HRQoL. Unlike our study, the other studies used PD-specific HRQoL instruments, which could be more sensitive in measuring HRQoL in PD patients. The existence of a sex difference in the physical HRQoL in this study is supported by previous studies on PD patients with medical therapy alone, in which men tended to report

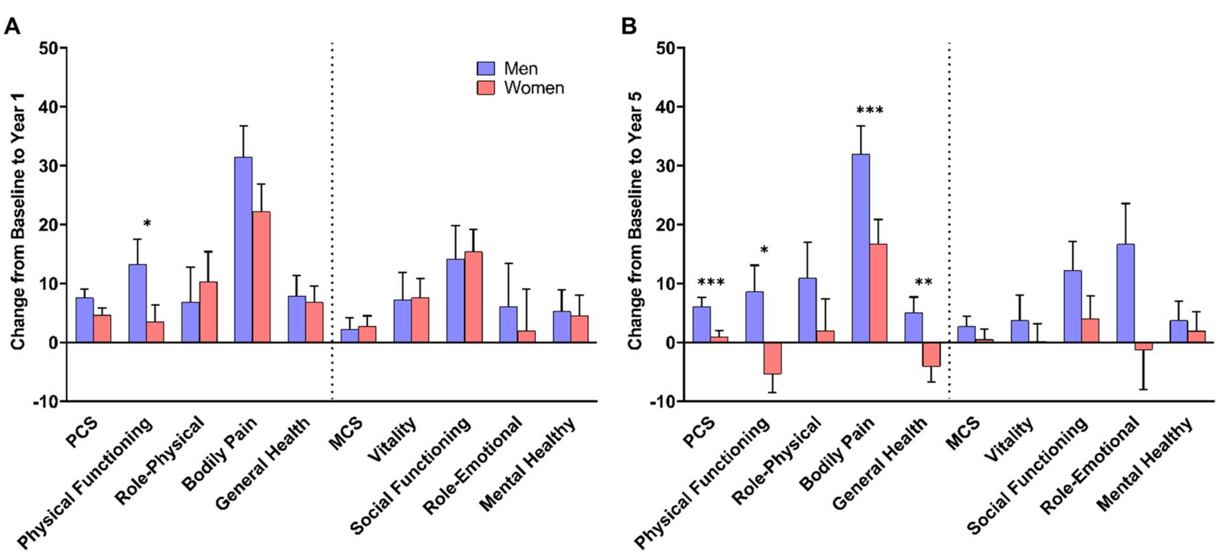

Fig. 2. Health-related quality of life as assessed by means of the 36-Item Short Form Health Survey (SF-36).
Panel A and B show the changes in the SF-36 physical health and mental health components from baseline to the 1-year and 5-year follow-up, respectively. Higher values indicate a better quality of life. *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$.
Abbreviations: MCS = mental-component summary; PCS = physical-component summary.

Table 3
Changes in clinical outcomes from baseline to the 5-year follow-up.

Variables	Med	Men		Women		*p* value for sex difference
		Mean change (95% CI)	*p* value	Mean change (95% CI)	*p* value	
UPDRS part II score	On	3.9 (0.4–7.4)	**0.032**	4.7 (2.1–7.2)	< **0.001**	0.902
	Off	−4.2 (−7.4 to −0.9)	**0.013**	−0.6 (−3.3 to 2.1)	0.654	0.292
UPDRS part III score	On	6.3 (1.2–11.3)	**0.016**	4.3 (0.5–8.1)	**0.026**	0.567
	Off	−12.6 (−18.7 to −6.6)	< **0.001**	−13.5 (−17.7 to −9.3)	< **0.001**	0.611
Tremor subscore	On	−0.7 (−1.7 to 0.2)	0.136	−1.6 (−2.8 to −0.4)	**0.012**	0.711
	Off	−3.4 (−5.0 to −1.9)	< **0.001**	−5.1 (−6.5 to −3.7)	< **0.001**	0.516
Rigidity subscore	On	−0.6 (−2.0 to 0.7)	0.353	0.0 (−0.9 to 0.9)	1.000	0.814
	Off	−3.3 (−4.7 to −1.9)	< **0.001**	−3.4 (−4.4 to −2.4)	< **0.001**	0.363
Bradykinesia subscore	On	3.6 (1.4–5.7)	**0.002**	2.5 (0.8–4.1)	**0.004**	0.541
	Off	−2.9 (−5.1 to −0.6)	**0.013**	−2.7 (−4.4 to −1.1)	**0.001**	0.655
Axial subscore	On	3.5 (1.6–5.3)	**0.001**	2.9 (1.6–4.1)	< **0.001**	0.509
	Off	−2.8 (−4.9 to −0.7)	**0.010**	−2.1 (−3.6 to −0.5)	**0.009**	0.851
UPDRS part IV dyskinesia score		−3.3 (−4.2 to −2.5)	< **0.001**	−3.4 (−4.1 to −2.6)	< **0.001**	0.459
Schwab and England Scale	On	−3.7 (−10.7 to 3.3)	0.295	−4.6 (−9.8 to 0.6)	0.080	0.640
	Off	16.5 (7.4–25.5)	< **0.001**	6.7 (−0.8 to 14.2)	0.077	0.272
K-MMSE score		−1.1 (−2.1 to 0.0)	**0.041**	−1.4 (−2.3 to −0.6)	< **0.001**	0.981
BDI-II score		0.9 (−2.5 to 4.3)	0.585	−1.7 (−4.1 to 0.7)	0.160	0.602
LEDD, mg		−755.5 (−1021.7 to −489.4)	< **0.001**	−451.1 (−593.2 to −309.0)	< **0.001**	0.710
SF-36 score						
Physical-component summary		6.1 (2.9–9.3)	< **0.001**	0.9 (−1.3 to 3.2)	0.409	**0.002**
Physical functioning		8.6 (−0.5 to 17.7)	0.065	−5.4 (−11.6 to 0.8)	0.085	**0.016**
Role-physical		10.9 (−1.3 to 23.1)	0.079	2.0 (−8.8 to 12.8)	0.712	0.151
Bodily pain		32.0 (22.4–41.6)	< **0.001**	16.7 (8.3–25.1)	< **0.001**	**0.003**
General health		5.0 (−0.4 to 10.5)	0.071	−4.1 (−9.4 to 1.1)	0.121	**0.008**
Mental-component summary		2.7 (−0.8 to 6.2)	0.148	0.5 (−3.0 to 4.0)	0.777	0.605
Vitality		3.7 (−5.0 to 12.3)	0.394	0.2 (−5.8 to 6.2)	0.946	0.217
Social functioning		12.2 (2.4–22.0)	**0.016**	4.0 (−3.8 to 11.8)	0.308	0.127
Role-emotional		16.7 (2.9–30.5)	**0.019**	−1.3 (−14.9 to 12.2)	0.844	0.321
Mental healthy		3.7 (−2.9 to 10.4)	0.261	1.9 (−4.6 to 8.5)	0.558	0.496

Abbreviations: BDI = Beck depression inventory; CI = confidence interval; K-MMSE = Korean version of the Mini-Mental State Examination; LEDD = levodopa equivalent daily dose; SF-36 = 36-Item Short Form Health Survey; UPDRS = Unified Parkinson's Disease Rating Scale.

higher levels of a HRQoL compared to women [19,20]. Interestingly, this tendency has also been observed in stroke patients. Ample evidence has shown that males have a better HRQoL after stroke than females do even after adjusting for age and other sociodemographic and functional status parameters [21].

We do not completely understand why a sex difference exists in postoperative physical HRQoL, even though DBS stimulation resulted in similar motor benefits in men and women. However, a number of hypotheses may be possible to explain this finding. Musculoskeletal problems occur frequently in PD patients and are associated with the female sex and a more severe disease status [22]. Musculoskeletal problems can still be distressing after STN-DBS 23, 24]. In our center, it was reported that musculoskeletal problems were the main cause of functional impairments at 3 years after STN-DBS [23]. Furthermore, pain due to these problems developed newly in approximately half of the PD patients with STN-DBS over 8 years of follow-up [24]. A previous study has shown that musculoskeletal problems in PD primarily have an influence on the HRQoL in relation to physical health, and this impact was more prominent in women [25]. Thus, these observations may explain why there was lesser improvement in the postoperative physical HRQoL in women, particularly during long-term follow-up. Alternatively, it is known that females are more vulnerable to emotional distress caused by disease development [26]. Considering that emotional distress also affects the physical HRQoL [27,28], we speculated that female PD patients could receive more severe emotional distress with disease progression, which may result in a greater detrimental influence on the physical HRQoL. However, this hypothesis cannot explain the finding that there was no sex difference in the mental HRQoL changes. It is also possible that younger age at the time of surgery in men could contribute to our finding, but this impact is

Table 4
Results of the linear regression analyses of the relationship between the change in the SF-36 PCS scores from baseline to the 5-year follow-up and preoperative variables.

Preoperative variables	Simple linear regression analysis			Multiple linear regression analysis		
	B	SE	*p* value	B	SE	*p* value
Sex	5.242	1.896	0.007	4.007	1.910	**0.026**
Age at surgery	−0.380	0.121	0.002	−0.298	0.124	**0.018**
Disease duration	−0.050	0.220	0.822	—	—	—
UPDRS part III score (off)	0.073	0.069	0.182	0.041	0.070	0.554
UPDRS part IV dyskinesia score	0.203	0.449	0.652	—	—	—
Schwab and England Scale (off)	−0.059	0.043	0.170	−0.027	0.044	0.532
K-MMSE score	0.081	0.431	0.852	—	—	—
BDI-II score	−0.085	0.104	0.417	—	—	—
LEDD	0.001	0.001	0.528	—	—	—

Abbreviations: B = unstandardized regression coefficient; BDI = Beck depression inventory; K-MMSE = Korean version of the Mini-Mental State Examination; LEDD = levodopa equivalent daily dose; PCS = physical-component summary; SE = standard error; SF-36 = 36-Item Short Form Health Survey; UPDRS = Unified Parkinson's Disease Rating Scale.

unlikely to be significant since we adjusted for age at the time of surgery in our analyses. On the other hand, we cannot exclude the possibility that the difference in socioeconomic status, lifestyle and comorbidities between the sexes might account for a part of the unexplained variance.

Our results show that the postoperative change in the mental HRQoL did not differ between the male and female PD patients. Growing evidence suggests a close relationship between non-motor symptoms and HRQoL in PD [29]. Müller et al. [30] reported that the variance of SF-36 MCS scores was much better explained by non-motor symptoms than by motor symptoms. Accordingly, similar effects of STN-DBS on non-motor symptoms between men and women may partly explain why there was no sex difference in the mental HRQoL.

This study has a number of strengths. The study sample was relatively large compared to previous studies investigating sex differences in the effects of STN-DBS [10–13]. Additionally, we compared both short-term and long-term effects of STN-DBS between men and women, which enabled us to assess how the effects change over time. However, there are several limitations. First, a large group of patients were excluded due to the lack of 5-year follow-up data, which might lead to selection bias. However, this is mainly because those patients did not conform to our STN-DBS protocol and not due to loss to follow-up. Furthermore, the exclusion rate due to the lack of 5-year follow-up data was roughly similar between the men and women, suggesting that this bias could have only minor effects on our results. Second, HRQoL was assessed using the SF-36 which is a tool to assess generic HRQoL. It is therefore necessary to validate our findings using HRQoL scales specific for PD. Third, among non-motor symptoms, we only included neuropsychiatric symptoms such as cognition and depression due to a lack of data. Moreover, the MMSE, which was used in the current study, may not be optimal for the assessment of cognitive function in PD patients. Future studies should be conducted using well-validated instruments covering various non-motor symptoms to clarify the impact of sex on non-motor symptoms following STN-DBS. Lastly, this study included a follow-up of the first 5 years after STN-DBS, which might limit the generalization of the results when assessed over longer periods.

In conclusion, we found that STN-DBS led to a similar degree of short-term and long-term effects on motor function, depressive and cognitive symptoms, and functional status between male and female PD patients. Nevertheless, the physical HRQoL appears to improve to a greater extent in men over a long-term observation. Further studies are warranted to reveal the precise mechanism underlying the sex-associated differences in postoperative HRQoL, and to design an effective strategy to improve HRQoL in women undergoing STN-DBS.

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Declaration of competing interest

No conflicting relationship exists for the authors.

Appendix A. Supplementary data

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