Right on track: Towards improving DBS patient selection and care

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CHAPTER 3

What predicts Quality of Life after STN DBS in Parkinson's Disease? A systematic review

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Abstract

Background and purpose

Subthalamic deep brain stimulation (STN DBS) is an effective therapy against medication-refractory motor complications in patients with Parkinson's disease. However, it remains difficult to predict which baseline patient characteristics are associated with quality of life (QoL) after surgery. The objective was to identify preoperative factors associated with QoL after STN DBS by systematically reviewing publications of sufficient methodological quality.

Methods

Main databases were systematically searched up to March 2019 to identify studies that investigated factors associated with QoL after STN DBS in patients with idiopathic Parkinson's disease.

Results

In all, 869 studies were identified, of which 18 fulfilled the inclusion criteria. Higher QoL after DBS appears to be associated with a large preoperative difference between ON and OFF motor function in some studies, although there was no clear association of severity of motor function or motor complications with postoperative QoL. Four studies suggested that older age at surgery is associated with a lower improvement, although six other studies reported no association. No or limited evidence was found for cognitive impairment or psychiatric dysfunction.

Conclusion

Various relative contraindications for STN DBS such as cognitive impairment and psychiatric dysfunction appear to be unrelated to postoperative QoL. Lower severity of dyskinesias was associated with greater postoperative QoL improvement but has been insufficiently studied. Higher baseline QoL was suggestive of higher postoperative QoL. However, the lack of clear correlations with disease-related variables suggests that QoL may be individually influenced by other factors, indicating that an ideal preoperative patient profile with regard to QoL improvement cannot be readily provided.

Introduction

Parkinson's disease (PD) is a multisystem neurodegenerative disorder characterized by motor and non-motor symptoms that collectively contribute to decreased quality of life (QoL). Medication-related motor complications [1] occur in most patients within 10 years of medication use.[2] Subthalamic deep brain stimulation (STN DBS) is an effective therapy for patients with motor complications refractory to oral medication adjustments. STN DBS was demonstrated to be superior to best medical treatment in improving QoL.[3,4]

Traditionally, the primary outcome after STN DBS has been the improvement of motor symptoms.[5] However, motor improvement does not necessarily mirror improvement of QoL after DBS,[6,7] and some patients report dissatisfaction after surgery despite improvement of motor function.[8,9] This suggests that postoperative patient management should address other aspects that may influence individual well-being beyond motor improvement alone.[8] To date, it remains difficult to predict before surgery which patient characteristics are associated with benefit in terms of QoL improvement after STN DBS.

In order to further improve post-surgery satisfaction and QoL, and to tune the expectations of surgical candidates, more insight is needed into factors influencing postoperative QoL. Identification of such factors may help to improve patient management and provide additional information that could aid during the decision-making process for DBS eligibility.

In this systematic review, studies of sufficient methodological quality were analysed with the aim of identifying preoperative factors associated with QoL after STN DBS, and their potential utility in improving DBS screening is discussed.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Eight relevant databases were systematically searched for potentially eligible studies up to 1 March 2019.

Study selection

Studies were screened on title and abstract for the following inclusion criteria: (1) separate cohorts with idiopathic PD, (2) intervention STN DBS, (3) outcome QoL scale, (4) association between preoperative factors and postoperative QoL reported, (5) follow-up duration post-DBS ≥6 months, (6) original peer-reviewed article, (7) $n \geq 10$, (8) article in English. Studies

pooling the results of STN DBS and other targets were excluded. A minimum of 6 months was chosen as the follow-up duration to account for the time involved in achieving optimal stimulation parameter settings.[10,11] Both change in QoL from baseline and postoperative QoL scores if corrected for baseline QoL were accepted as outcomes. For clarity, results from different QoL scales were pooled together unless there was a discrepancy between separate QoL scales within the same study.

Data extraction

The initial screening (title and abstract) was performed by two independent reviewers (VJG and SF); full-text screening was decided upon after mutual agreement. Risk of bias was assessed using an in-house checklist (supplementary table 3.1; range 0–21, higher scores reflecting better quality). Items from a previous standard checklist [12] were adapted to fit the specific objectives of the present review. The quality threshold for inclusion was set at 11 points; low-quality studies were excluded. Included studies were classified as medium quality (quality index (QI) 11–13), high quality (QI 14–16) and very high quality (QI ≥ 17).

Results

The search performed on 1 March 2019 yielded 869 studies. After screening of title and abstract 150 studies remained for full-text screening; 18 studies were ultimately included (figure 3.1). Interrater agreement regarding eligibility (Cohen's κ) was 0.82. All included studies are detailed in table 3.1. Studies were subdivided by follow-up to account for differences in the time course of QoL following DBS: short-term follow-up (6 months), intermediate follow-up (6 months to 5 years) and long-term follow-up (>5 years). Most studies reported an improvement in QoL, although only on a subscale level in some studies.[13-21] One study reported no change in QoL.[22]

Sociodemographic variables

One study found that higher age was associated with lower Parkinson's Disease Questionnaire 39 (PDQ39) summary index (SI) improvement at 1-year follow-up,[19] and three other studies reported negative correlations of higher age and PDQ39 subscore stigma,[15] activities of daily living (ADL),[15,17,23] mobility,[15,17] cognition,[15,17] and communication [15] in the intermediate follow-up. Six different studies found no association between age and postoperative QoL, regardless of follow-up (0.5–6 years).[13,14,18,21,24,25]

Sex [18,19,21,24,26] and education [24] were not significantly associated with postoperative QoL (0.5–6 years' follow-up) (figure 3.2).

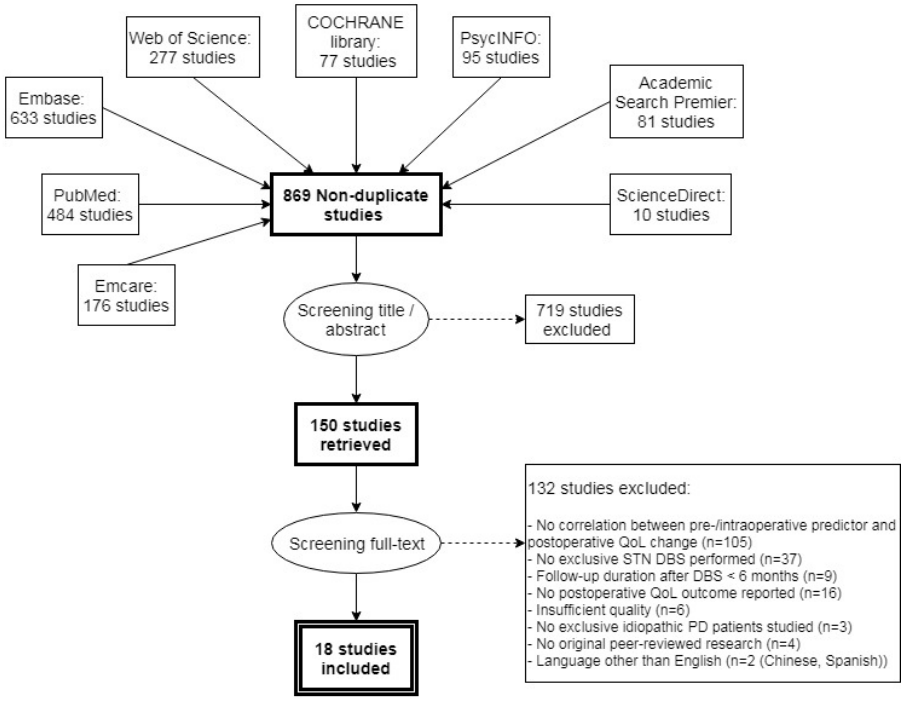

Figure 3.1. PRISMA flow diagram of selected studies
Several studies had multiple reasons for exclusion.

Clinical variables

The amount of Unified Parkinson's Disease Rating Scale Part III (UPDRS III) improvement after a dopamine challenge test correlated positively with the PD QoL scale (PDQL) improvement (1-year follow-up),[27] although this effect was not observed on the PDQ39 and Short Form 36 (SF36) scales in three different studies (0.5–2 years' follow-up).[14,24,25] A higher Hoehn and Yahr (HY) stage was associated with greater QoL improvement at 1-year follow-up,[24] whereas UPDRS III scores (either ON or OFF) were not associated with postoperative QoL change in four studies with 1–6 years' follow-up.[14,18,24,25]

Lower baseline dyskinesia scores (UPDRS IV) were associated with greater improvement in SF36 Physical Health (PH) scores at 0.5 years' follow-up but not with PDQ39 SI and SF36 Mental Health (MH) scores.[14] At 6 years' follow-up, lower baseline dyskinesia scores were associated with greater PDQ39 SI improvement.[18] In contrast, cumulative daily OFF time before surgery correlated positively with improvement in PDQ39 SI (but not with SF36 scores),[14] and severity of motor complications in general was not associated with QoL change at 2–6 years' follow-up.[18,25]

Table 3.1. Selected studies

Reference	N (PD)	Mean Age (years)	Follow-up (years)	Electrode placement	Outcome	Type of outcome	QoL improved?	QI	Comments
Bargiotas 2017 et al [30]	74	62.2	1	STN (unspecified)	PDQ39, SF36 MH / PH	Change from baseline	Yes	**	
Chandran 2014 et al [26]	51	55.3	1	Bilat. STN	PDQL[a]	Change from baseline	Yes	*	
Dafsari 2018 et al [13]	120	62.1	0.5	Bilat. STN	PDQ8	Change from baseline	Partly	***	Improvement of PDQ8 subscales depended on age
Daniels 2011 et al [14]	60	59.7	0.5	STN (unspecified)	PDQ39, SF36 MH / PH	Change from baseline	Partly	**	57% of patients reached the threshold for PDQ39-improvement (at least 10.9 points).
Derost 2007 et al [15]	57	61.9	0.5 / 1 / 2	Bilat. STN	PDQ39[a]	Change from baseline	Partly	**	QoL only improved in 'young' patients; stabilization or worsening of QoL in 'old' patients
Erola 2005 et al [23]	29	59.5	1	Bilat. STN	PDQ39[a]	Change from baseline	Yes	*	
Floden 2015 et al [29]	106	62.4	0.5	Uni- and bilat. STN	PDQ39	Change from baseline	Yes	*	
Frizon 2018 et al [21]	67	62.8	0.75	Uni- and bilat. STN	PDQ39	Change from baseline	Partly	**	Some, but not all, patients were classified as 'improvers' in terms of QoL
Hasegawa 2014 et al [28]	19	59.8	0.5	Bilat. STN	PDQ39	Change from baseline	Yes	**	
Katz 2015 et al [22]	108	?	2	Bilat. STN	PDQ39	Change from baseline	No	***	
Lezcano 2016 et al [16]	69	61.3	5	Bilat. STN	PDQ39	Absolute scores	Partly	***	Several, but not all, PDQ39 subscales improved.
Liu 2018 et al [24]	45	61.8	1	Bilat. STN	PDQ39	Change from baseline	Yes	**	
Ory-Magne 2007 et al [17]	45	60.1	1 / 2	Bilat. STN	PDQ39	Change from baseline	Partly	**	Several, but not all, PDQ39 subscales improved.
Schüpbach 2019 et al [25]	124	52.9	2	Bilat. STN	PDQ39	Change from baseline	Not reported	**	This article did not report whether QoL improved; however a different paper on the same cohort reported improved QoL after DBS STN.[4]
Siderowf 2006 et al [18]	18	57.3	0.5 / 6	Bilat. STN	PDQ39[a]	Change from baseline	Partly	**	Several, but not all, PDQ39 subscales improved.

Table 3.1. continued

Reference	N (PD)	Mean Age (years)	Follow-up (years)	Electrode placement	Outcome	Type of outcome	QoL improved?	QI	Comments
Smeding 2011 et al [27]	105	58.4	1	Bilat. STN	PDQL	Change from baseline	Yes	**	
Soulas 2011 et al [19]	41	62	0.5 / 1	STN (unspecified)	PDQ39, SF36 MH / PH	Absolute scores	Partly	**	Improvement of PDQ39 and SF36 PH, but not SF36 MH.
Witt 2011 et al [20]	60	60	0.5	STN (unspecified)	PDQ39[a]	Change from baseline	Partly	*	Improvement of QoL depended on cognition

[a] Including subdomains.
QI (quality index): *** ≥ 17; ** QI 14-16; * QI ≤ 11-13
PDQ39 / 8: Parkinson's Disease Questionnaire 39 / 8; PDQL: Parkinson's Disease Quality of Life questionnaire; SF36: Short Form 36 health form; MH: mental health component; PH: physical health component;
Bilat.: bilateral electrode placement; STN: Subthalamic Nucleus; QoL: Quality of Life; Unilat.: unilateral electrode placement.

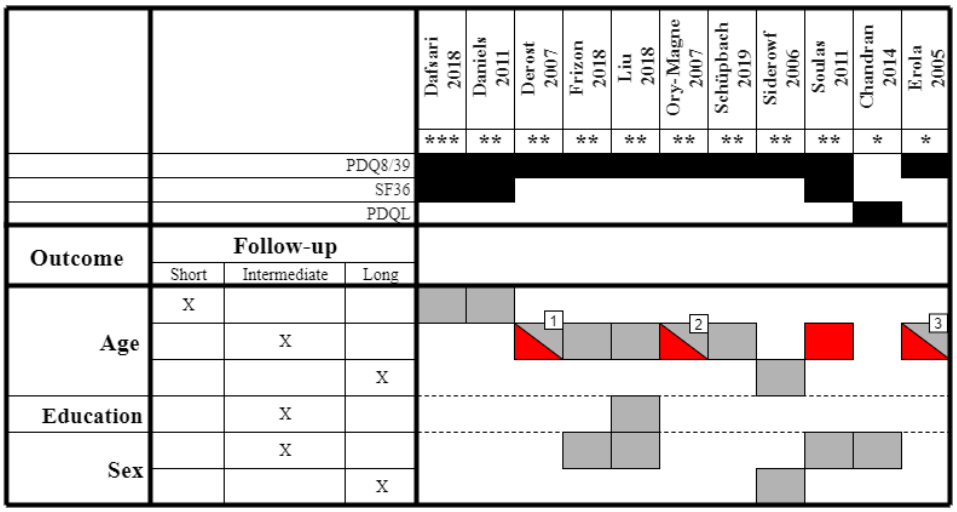

Figure 3.2. Demographic factors associated with QoL after DBS

Red box: significant negative association with QoL. Grey box: no significant association. Dual-shaded boxes indicate discrepancy between different (sub)scales used in the study.

[1] Significant negative association between age and subscales stigma, ADL, mobility, and cognition, but not with other PDQ39 subscales.

[2] Significant negative association between age and ADL, mobility, and cognition, but not with other PDQ39 subscales.

[3] Significant negative association between age and ADL, but not with other PDQ39 subscales.

Short-term follow-up (FU): 6 months; intermediate follow-up: 6 months – 5 years; long-term follow-up: > 5 years. Asterisks indicated quality index (QI): * medium quality (QI 11-13), ** high quality (QI 14-16), *** very high quality (QI ≥ 17). Studies are sorted based on their QI (highest quality on the left). Scales used to determine QoL are denoted below the studies. Factors are sorted in alphabetical order.

PDQ8/39: Parkinson's Disease Questionnaire 8/39; PDQL: Parkinson's Disease Quality of Life questionnaire; SF36: Short Form 36 health form.

Preoperative use of dopaminergic medication yielded contrasting results, with one study demonstrating that higher levodopa equivalent dosage (LED) was associated with a higher odds of being a 'responder' in terms of higher postoperative PDQ39 scores [21] contrasted by a different study with a similar follow-up duration (approximately 1 year) and similar LED that reported a negative association of LED with QoL improvement.[24] Two studies found no association of baseline medication use and QoL change, regardless of follow-up (0.5–6 years).[14,18] Other treatment variables and disease characteristics were not associated with QoL change (figure 3.3).

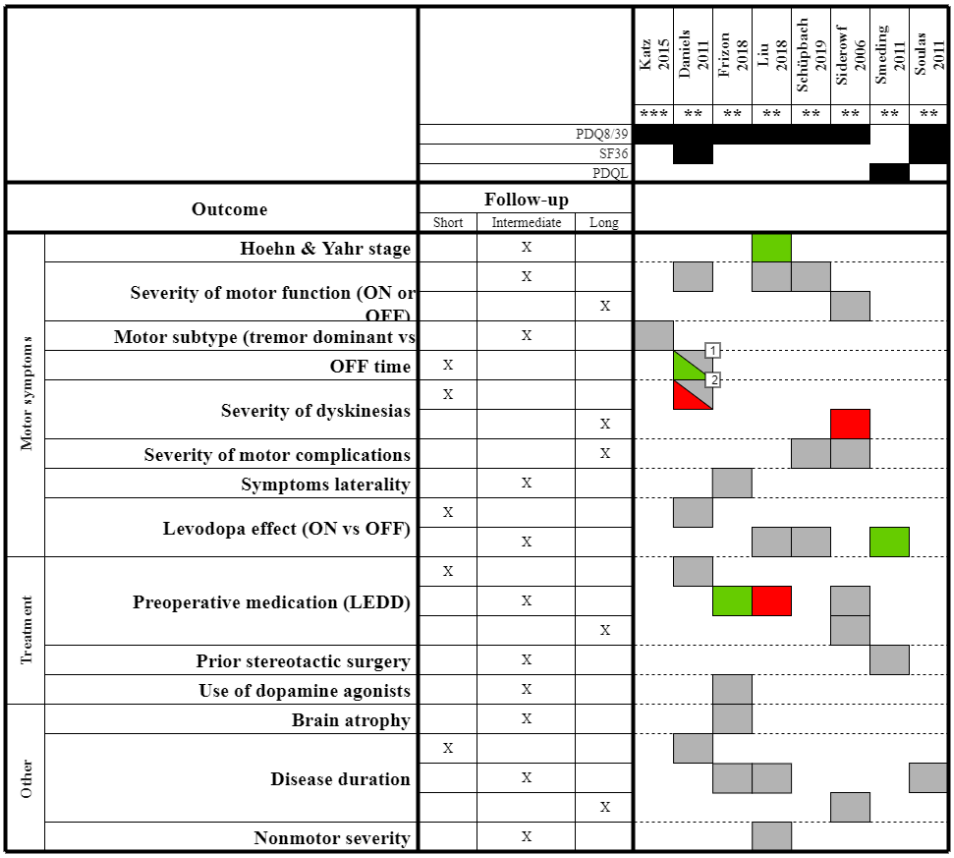

Figure 3.3. Preoperative clinical factors associated with QoL after DBS

Green box: significant positive association with Quality of Life (QoL) (either improvement of QoL or higher postoperative score). Red box: significant negative association with QoL. Grey box: no significant association. Dual-shaded boxes indicate discrepancy on between different (sub)scales used in the study.

[1] Significant positive association between cumulative daily OFF time and PDQ39, but not with SF36 mental health or physical health scores.

[2] Significant negative association between severity of dyskinesias and SF36 physical health, but not with PDQ39 or SF36 mental health.

Short-term follow-up (FU): 6 months; intermediate follow-up: 6 months – 5 years; long-term follow-up: > 5 years. Asterisks indicated quality index (QI): ** high quality (QI 14-16), *** very high quality (QI ≥ 17). Studies are sorted based on their QI (highest quality on the left). Scales used to determine QoL are denoted below the studies. Factors are sorted in alphabetical order.

LEDD: levodopa equivalent dose; PDQ8/39: Parkinson's Disease Questionnaire 8/39; PDQL: Parkinson's Disease Quality of Life questionnaire; PIGD: Postural-Instability-and-Gait-Difficulty; SF36: Short Form 36 health form

Psychosocial variables

Baseline QoL scores were positively correlated with PDQ39 improvement in three studies (1- to 5-year follow-up),[16,24,25] whereas one study with 1-year follow-up found that patients with worse baseline QoL had a higher odds of becoming a 'responder' in terms of PDQ39

improvement after STN DBS.[21] At 6 years' follow-up, baseline QoL was not significantly associated with postoperative PDQ39 SI change.[18] The preoperatively self-reported expected improvement in QoL (i.e. expected change in PDQ39 SI) correlated positively with actual improvement in PDQ39 SI at 0.5 years' follow-up.[28]

Cognition, usually assessed with the Mattis Dementia Rating Scale (MDRS) (one study used the Mini-Mental State Examination),[24] was only associated with QoL change at 0.5 years' follow-up in one study: the lowest quartile (MDRS 130–137, i.e. greater cognitive impairment) had significantly lower improvement of PDQ39 scores after 6 months compared to the three higher quartiles.[20] Six studies found no association of cognition and QoL change, regardless of follow-up duration (0.5–2 years).[14,19,24,25,27,29]

Psychiatric dysfunction, such as anxiety (Becks Anxiety Inventory or State-Trait Anxiety Inventory),[14,19] apathy (Starkstein Apathy Scale),[30] and depression (Becks Depression Inventory),[14,19,21,24,25] was not associated with QoL change in any study regardless of follow-up duration (0.5–2 years).

One study found that the extent to which a coping strategy focused on social support was used (Ways of Coping Checklist Revised) was negatively correlated with SF36 MH at 1 year (a focus on social support resulted in lower QoL) but not with PDQ39 SI or SF36 PH. No correlation was found for other coping strategies.[19] Various aspects of sleep metrics (Fatigue Severity Scale, Epworth Sleepiness Scale and sleep efficiency as part of the Multiple Sleep Latency Test) were not predictive of QoL outcomes at 1-year follow-up (figure 3.4).[30]

Discussion

The present systematic review included 18 studies of sufficient methodological quality that examined factors associated with QoL after STN DBS.

There is no evidence to support using sociodemographic factors to predict QoL after DBS. Four studies suggested that older age at surgery is associated with a lower improvement of QoL after intermediate follow-up, although six other studies reported no association. The inconsistency of the results points against the use of calendar age as a predictor of postoperative QoL.

A good preoperative response to levodopa is considered indicative of postoperative motor improvement,[31] and indeed a larger preoperative difference in motor scores between ON

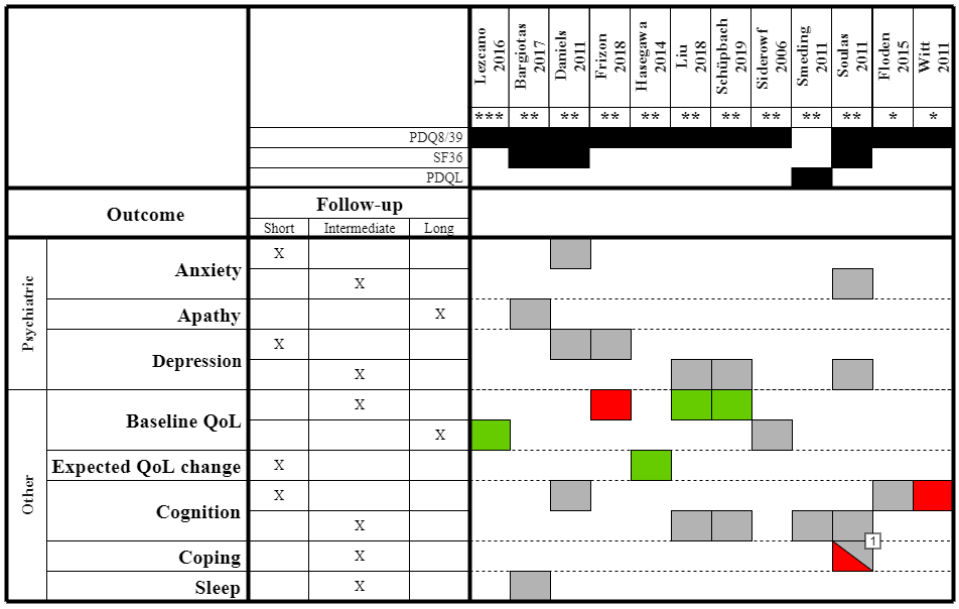

Figure 3.4. Preoperative psychosocial factors associated with QoL after DBS
Green box: significant positive association with Quality of Life (QoL) (either improvement of QoL or higher postoperative score). Red box: significant negative association with QoL. Grey box: no significant association. Dual-shaded boxes indicate discrepancy on between different (sub)scales used in the study.
[1] Significant negative association between a coping strategy focussed on social support and SF36 mental health, but not with PDQ39 or SF36 physical health.
Short-term follow-up (FU): 6 months; intermediate follow-up: 6 months – 5 years; long-term follow-up: > 5 years. Asterisks indicated quality index (QI): * medium quality (QI 11-13), ** high quality (QI 14-16), *** very high quality (QI ≥ 17). Studies are sorted based on their QI (highest quality on the left). Scales used to determine QoL are denoted below the studies. Factors are sorted in alphabetical order.
PDQ8/39: Parkinson's Disease Questionnaire 8/39; PDQL: Parkinson's Disease Quality of Life questionnaire; SF36: Short Form 36 health form.

and OFF states was significantly associated with better postoperative QoL in one large study ($n = 105$).[27] However, this finding was not confirmed in three other studies (of comparable size and quality). A possible explanation for this discrepancy is that Smeding *et al.*[27] used the PDQL scale to assess QoL, whereas the three studies that found no significant association used the PDQ39. The PDQL scale places greater emphasis on the motor aspects of QoL and is therefore more likely to pick up correlations with motor alterations following DBS, in contrast to the PDQ39 which focuses least on motor items. The actual level of motor severity was not associated with QoL, independent of follow-up.[14,18,22,24,25] The association of motor fluctuations with postoperative QoL remains unclear. More OFF time at baseline influenced several QoL subscales positively at short-term follow-up,[14] but severity of motor fluctuations in general was not associated with postoperative QoL at 6 years' follow-up.[18] This suggests that an initial

beneficial effect of improvements in motor fluctuations on QoL (i.e. a sudden gain in ON time increases short-term postoperative QoL) is lost in the long term, when other factors may be more relevant in determining QoL. Patients with greater severity of dyskinesias at baseline demonstrated smaller improvements on several QoL subscales at short-term follow-up [14] and with QoL after 6 years.[18] Whilst dyskinesias may be a source of stigma,[1] growing evidence shows that patients are less bothered by dyskinesias than by other symptoms as they are often unaware of the extent of their dyskinesias.[32] A potential limitation of all included studies is the use of the UPDRS to quantify dyskinesias, whereas the Unified Dyskinesia Rating Scale may be more appropriate. This might have led to an underestimation of the role of dyskinesias in determining QoL. Careful examination of the association between QoL and detailed assessments of dyskinesias is a potential target for future studies.

As preoperative dyskinesias may be associated with high LED, the positive psychotropic effects generated by LED may be substantially reduced following STN DBS resulting in lower responses on QoL scales. However, this effect can only explain the negative correlation in the short-term follow-up but not at 6 years' follow-up. Additionally, only one study showed a negative correlation between LED and change in QoL after surgery whereas three other studies found either no association or a positive correlation of change in LED and change in QoL after surgery.[14,18,24] Given that motor complications constitute an important reason to perform STN DBS,[34] the association of these factors with postoperative QoL needs to be further elucidated.

The only factors positively correlated with postoperative QoL improvement were preoperative expected QoL change and baseline QoL, although the latter was not consistent throughout all studies. Several hypotheses may underlie these observations, such as dispositional optimism (i.e. a higher baseline QoL may suggest better social functioning and a more active approach towards social reintegration) or an easier compliance to postoperative changes in ADL. One study reported an association between a greater likelihood of being a 'responder' in terms of postoperative QoL and lower baseline QoL,[21] which is possibly caused by a regression-to-the-mean phenomenon.

Although cognitive dysfunction and psychiatric disturbances are considered relative contraindications for DBS surgery,[31] the available literature demonstrates that these factors are not related to postoperative QoL. Only one study suggested a negative association of MDRS scores at group level with QoL improvement (i.e. the lowest quartile had less QoL improvement),[20] contrasted by results from a different study with a similar MDRS group composition that found no association, although the within-group composition of the lowest quartile in particular may have differed.[29] In the first study, there were significant differences

in other cognitive tests between the MDRS quartiles at baseline, whereas these differences were not observed in the latter study, indicating that other cognitive tests may have better potential for predicting postoperative QoL than MDRS. Moreover, no linear correlation was found between MDRS scores and either QoL scores or QoL improvement.[14,24,25] The limited variability in cognitive scores may explain the absence of a linear trend, suggesting that the MDRS may not be appropriate to predict QoL post-DBS. Likewise, preoperative psychiatric disturbances such as depression and anxiety were not associated with postoperative QoL.[14,19,21,24,25] As no results are available on more severe cognitive or psychiatric dysfunction, it is emphasized that these findings should not be extrapolated to patients with clinically significant cognitive deterioration or psychosocial disturbances.

Strengths include the use of the PRISMA guidelines, a systematic literature search and assessment of methodological quality. Due to the scarcity of relevant studies, differences in QoL instruments were disregarded, despite variations in content and responsiveness of individual instruments.[33] Furthermore, several studies were excluded due to a follow-up duration of less than 6 months or not exclusively examining QoL after STN DBS. A brief examination of the results of these studies revealed no new insights.

The association between preoperative predictors and QoL may differ per QoL subscale, which limits comparability between studies. Several included studies indeed suggested that outcomes were dependent on the type of QoL metric.[14,30] Both the PDQ39/8 and PDQL have been developed and validated specifically for PD patients, whereas the generic SF36 scale allows for comparability with other diseases. Given that the emphasis within the respective scales lies on different domains, caution is advised when comparing results between different scales, although most studies included in this review using SF36 also used PDQ39/8.

Most studies reported correlation coefficients whereas two studies addressed clinically relevant differences.[16,21] As the minimal clinically important difference for PDQ39 SI has been previously established,[34] it is recommended that future study designs incorporate this. Moreover, most studies applied univariate analyses. Although potentially useful for the identification of relevant variables, multivariate models are required to accurately model QoL improvements, particularly given the multidimensional nature of QoL assessments.

Should one or more factors consistently be related to postoperative QoL, it would be worth evaluating them in the screening stage for DBS and discussing them with DBS candidates. Unfortunately, none of the findings has been replicated in multiple studies with at least intermediate follow-up, and thus the available data are currently insufficient to suggest changes in clinical practice.

The lack of consensus between studies and the ambiguity of the mechanism behind the observations suggests that QoL may be influenced more by other (yet unstudied) factors. Although social adjustment is frequently associated with QoL in the general PD population and plays an important role during the pre- and post-surgical management of DBS patients,[8] this factor is not studied in depth so far and should be considered in terms of the prediction of postoperative QoL. Moreover, whether preoperative expectations of DBS surgery were met postoperatively [35] has never been studied with regard to QoL change. This review further demonstrates that QoL may be highly heterogeneous and individually determined, as well as scale dependent. An ideal preoperative patient profile with regard to postoperative QoL cannot be readily provided yet. Future studies may identify novel factors that contribute more to modelling the prediction of postoperative QoL.

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Supplementary material

Supplementary table 3.1 Risk of bias assessment

No.	Criteria	Requirements	Score
1	Study objectives	0. The objectives are not clearly stated. 1. The objectives are clearly stated.	
2	Study design	0. The study design is not clearly stated. 1. The study design is clearly stated.	
3	Characteristics of studied population	0. The studied population's characteristics are not clearly described. 1. Gender, age, disease duration, UPDRS (or equivalent CISI-PD) or H&Y are described. 2. Gender, age, disease duration UPDRS (or equivalent CISI-PD) and H&Y are described.	
4	Characteristics of the non-responders, excluded ones or responders with missing data	0. The characteristics of the non-responders or excluded ones are not described. 1. Gender and age of the non-responders or excluded ones are described. 2. Gender, age and disease duration of the non-responders or excluded ones are described.	
5	Sampling method for recruitment of study population	0. The sampling method for recruitment of the study population is not appropriately described. 1. The location(s) and the type of institution where study population is recruited are mentioned. 2. The location(s), type of institution, and amount of approached individuals are mentioned.	
6	Sample size	0. < 50 PD patients. 1. 50-100 PD patients. 2. > 100 PD patients.	
7	Choice of the instrument to assess the concerned domain is justified.	0. No justification of the choice of the instrument is given. 1. The choice of instrument is justified or the instrument is validated to assess the domain in PD. 2. The choice of instrument is justified and instrument is validated to assess the domain in PD.	
8	Selection of independent variables justified	0. The choice of < 50% of the independent variables is clearly justified. 1. The choice of 50- 70% of the independent variables is clearly justified. 2. The choice of 70-100% of the independent variables is clearly justified.	
9	Comprehensible statistical methods	0. The statistical methods applied are not comprehensible. 1. The statistical methods applied are comprehensible.	
10	Main factors associated with the concerned domain	0. Main factors associated with the concerned domain are not clearly stated. 1. The main factors associated with concerned domain are clearly stated. 2. The main factors associated with concerned domain are clearly stated and quantified, and described with a quantitative associated value (e.g. R^2).	
11	Agreement / disagreement with other studies	0. Agreements of findings from previous studies are not clearly described. 1. Agreements or discrepancies of findings from previous studies are clearly described. 2. Agreements and discrepancies of findings from previous studies are clearly described.	
12	Strengths / limitations	0. The limitations of the study are not clearly described. 1. The strengths or limitations of the study are clearly described. 2. The strengths and limitations of the study are clearly described.	
		Total quality score	

Modified from: Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. Lancet Neurol 2018;17:559-568.