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Gait and balance worsening after bilateral deep brain stimulation of the subthalamic nucleus (STN-DBS) for Parkinson's disease: a systematic review

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ABSTRACT

Background Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a widely applied therapy in Parkinson's disease (PD). Occasionally, postoperative worsening of gait or balance occurs, even in the face of a persistently gratifying appendicular symptom improvement. The characteristics vary considerably, and the risk factors for this postoperative gait or balance worsening are largely unknown. We systematically investigated the literature for all cases of gait or balance worsening after STN-DBS in PD and explored its characteristics and determinants. In consecutive populations with best medical treatment as the control group, we also explored its incidence.

Methods We searched PubMed, Embase and Cochrane. We considered all cases occurring between 1 month after surgery (to exclude immediate postoperative complications as most likely cause) and 12 months after surgery (to exclude disease progression).

Results From 2719 entries, we included 20 studies (n=1010 operated patients). Freezing of gait and falls were the most commonly reported symptoms. The first worsening of symptoms occurred between 3 and 6 months after surgery. Modulation of pedunculopontine afferents was more likely associated with worsening of gait and balance. In controlled trials with consecutive patients, 24 cases (15.9%) were reported, compared with 5.8% with best medical treatment (p=0.0013).

Conclusions Gait or balance worsening after STN-DBS is a complex phenomenon that cannot readily be explained by mere disease progression. The multifactorial nature warrants further study in gait labs and through advanced imaging techniques. Future studies should also estimate the actual incidence, which we could not establish as we excluded cohorts without any reported cases.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Deep brain stimulation of the subthalamic nucleus (STN-DBS) significantly improves various appendicular symptoms, but occasionally results in worsening of gait or balance.

WHAT THIS STUDY ADDS

⇒ (Worsening of) freezing of gait and falls are commonly reported symptoms of postoperative symptomatic worsening and occur between 3 and 6 months after surgery. Worsening may be caused by inadvertent stimulation of gait tracts near the STN and is unlikely explained by disease progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These insights advance our understanding of symptomatic worsening after DBS and aid in preoperative patient counselling.

INTRODUCTION

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a widely accepted therapy in advanced Parkinson's disease (PD). STN-DBS often leads to an improvement in motor symptoms and quality of life and reductions in levodopa equivalent dose (LED).[1–5] While gait and balance often improve after DBS,[6] worsening of gait or balance worsening (GBW) after STN-DBS is a known adverse event,[7 8] with significant negative impact on quality of life.[9 10] In studies that report GBW, incidence varies considerably from 4 up to 20%.[1 11–13] Freezing of gait (FOG), festination, decreased balance and falls can be manifestations, unresponsive to medication or stimulation settings.[14 15] Risk factors and pathophysiological mechanisms of GBW are not yet elucidated. GBW after STN-DBS has previously been associated with final electrode position, stimulation-related factors and medication adjustments.[12 16–18] Some studies suggest a higher GBW risk in persons with a shorter disease duration,[12 19] and higher age at surgery and higher disease stage have also been associated with GBW.[20] Various studies have investigated GBW after STN-DBS, but a systematic investigation is lacking.

In the current review, we aimed to give insight into the characteristics and risk factors of persistent GBW after STN-DBS, with specific emphasis on consecutive cohorts reporting such cases. With this review, we hope to contribute to solving the complex puzzle of GBW and ultimately improve gait and balance outcomes after STN-DBS.

METHODS

Standard protocol approvals

Data were reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This protocol does not report original data of any human experiments, and therefore, no institutional approval or informed consent by participants was necessary. There was no patient or public involvement.

Eligibility criteria

All articles describing any adverse event or motor scale- or lab-based measure of worsening of gait or balance after STN-DBS were considered eligible. GBW was defined as novel and persistent onset or worsening of FOG, gait slowness, shuffling, propulsion, festination, or other gait abnormalities or cases with balance problems or falls after STN-DBS. Cases were excluded if worsening occurred within 1 month after surgery, in order to exclude complications directly linked to surgery, and if they were not refractory within the period of interest. To reduce the risk of gait or balance worsening due to disease progression, only GBW up to 12 months postsurgery was included to make disease progression as the main contributing factor less likely.[12 21 22] For studies with a longer follow-up than 1 year, follow-up data up to 1 year were considered. Some landmark DBS studies with no interim outcome up to 1 year therefore had to be excluded, including the EARLY-STIM study.[4] For two or more studies with overlapping data, the one with the largest number of included patients was selected. GBW that was clinically significantly improved by adjusting stimulation settings, that was reported as transient[23] or that was caused by obvious electrode misplacement (as noted in the manuscript or apparent from the data, eg, as relative to the target zone) was excluded, as we aimed to identify persistent (and therefore the most clinically relevant) cases of GBW. Furthermore, postoperative gait or balance problems that were not clearly worsened compared with the pre-operative status were excluded. Only studies that reported the onset of GBW on the individual patient level were included. Therefore, group-level reports demonstrating mean worsening on gait or balance test items were not included.

Information sources and search strategy

A multidatabase search strategy was designed with the support of a certified medical librarian (online supplemental material). PubMed, Embase and the Cochrane Library were searched for eligible studies until December 2023. All original study types in English were considered for inclusion. Reference lists of the included articles were screened for additional eligible studies.

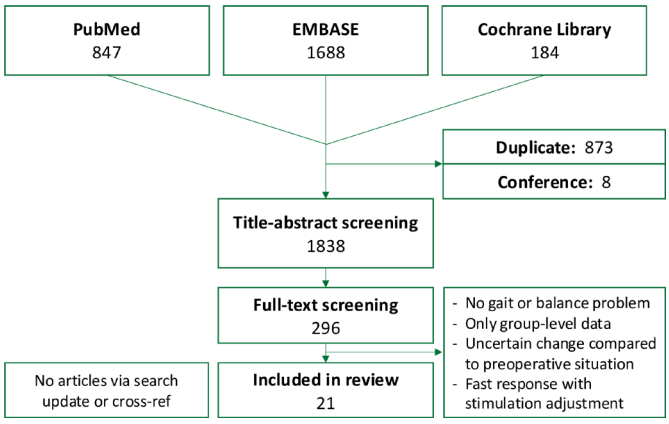

Figure 1 Flowchart for literature search and article selection.

Selection process

The selection procedure was independently performed by two authors (JMJ and AS). First, title and abstract were screened for DBS outcome studies, and studies were included after full-text scanning if they reported one or multiple cases of GBW as our aim was to evaluate all reported GBW cases in the literature and to avoid underestimation of GBW incidence. Therefore, studies that do not report any case of GBW were excluded from this analysis. A flowchart of the selection process is outlined in figure 1. During a consensus meeting, inter-rater differences were resolved by discussion with a third reviewer (RSV).

Data extraction, quality assessment and risk of bias

In a standardised extraction form, the following study characteristics were collected: first author name, year of publication, study design, participant selection criteria, consecutive or non-consecutive design and follow-up duration. To assess phenomenology, all available details regarding the onset, phenomenology and related clinical features and symptoms of GBW were extracted. To better understand the pathophysiology of GBW, we extracted age, disease duration, interval between surgery and GBW, gender, Movement Disorders Society Unified Parkinson's disease rating scale (MDS-UPDRS), preoperative levodopa response, preoperative cognitive function and preoperative gait or balance impairment, electrode position, stimulation parameters and other parameters that might give insight into risk factors, such as imaging findings. Finally, to estimate the incidence of GBW, we extracted the number of patients at risk and the numbers of patients with GBW from all articles using the previously described eligibility criteria.

Quality assessment of cohort studies and case series was performed for each study using the eight-item Newcastle–Ottawa scale,[24] with a maximum of 1 point per item. For quality assessment of randomised clinical trials, the Jadad scale was applied.[25]

Summary measures for characteristics, risk factors and incidence

Different studies were used for exploring characteristics, risk factors and incidence. First, from all studies, details regarding the moment of onset and phenomenology were summarised. Second, disease characteristics and assessed risk factors were summarised from all studies to evaluate potential risk factors of GBW. Lastly, the percentage of patients with GBW was calculated for only the consecutive cohorts in controlled studies to estimate the incidence of GBW. At-risk person-years were calculated from the number of individuals at risk and the follow-up duration. Using a $\chi 2$ test, the percentages and incidence rates (per person-year) of GBW in the STN-DBS group were compared with the best medical treatment (BMT) control group. In this way, we took into account GBW due to disease progression. $p<0.05$ was considered statistically significant.

Because most included studies were too heterogeneous with regard to the description of GBW and putative risk factors, other quantitative analyses such as meta-analysis or meta-regression of risk factors and predictors were considered invalid.

RESULTS

Study selection

The search strategy in PubMed, EMBASE and Cochrane yielded a total of 2719 publications. 297 articles remained for full-text analysis after duplicate removal (881 entries) and title-abstract screening. After a consensus meeting, this led to a total inclusion of 20 articles. Reference screening and the search update did not result in additional inclusions. An overview of the selection process is depicted in the online supplemental material.

Characteristics and quality of included studies

Studies consisted of three randomised controlled trials (RCTs), three non-randomised trials, nine cohort studies with consecutive patients, two cohorts with non-consecutive inclusion, two case reports and two case series (table 1). A total of 1010 patients were included and 187 cases of GBW after bilateral STN-DBS were identified. In total, five studies included a BMT control group (n=232), with over 90% originating from two studies with short follow-up (6 months).[1 13 15 26 27] Two studies specifically compared baseline and imaging parameters of individuals with and without GBW.[12 16] Median total study follow-up was 1 year (range 6 months to 4 years). Characteristics of the included studies are presented in table 1. An expanded version can be found in online supplemental table 3.

The average study quality score of cohort studies and case series (using the Newcastle-Ottawa scale) was 5.1 (online supplemental table 1). Two studies scored the maximum of 8, while three studies scored a 2 or 3. A clearly described method of assessing gait and balance was only present in 59% of studies, and ascertainment that the GBW was not pre-existent was only met in 53% of studies. Therefore, the severity of preoperative gait problems in patients who had new-onset gait problems or significant postoperative gait worsening is unclear for the other half of the studies. Only one RCT scored maximum quality scores on the Jadad scale (online supplemental table 2), while the other two RCTs scored 3 out of 5 points on the scale due to a lack of outcome assessor blinding.[1 26]

Characteristics of gait or balance worsening (GBW)

The noted onset of GBW postsurgery varied from 2.5 months,[28] 3 months,[11 16 17] 6 months,[18 13–15 21 26 29–33] to 12 months,[12 27 34 35] although the exact time of onset was usually not noted. Most studies were larger DBS efficacy trials that reported gait problems as adverse effects without analysing phenomenology or risk factors. Studies describing GBW reported (increased) falls,[12 13 15 17 23 29] FOG,[11 12 14 17 26–28 31 32 36] balance problems (eg, backward falling, impaired postural control in stance and during step initiation, stopping or walking)[13 17 19 33 35] and festination.[36] Additionally, objectively measured decreased gait velocity was reported (0.1–0.2 m/s worsening with 0.5–1.0 m/s as OFF gait speed).[29 30] One study reported improvement in postoperative gait scores, but worsening of falls.[23] Nine studies (n=349)[13 15 17 19 21 27 33–35] reported the occurrence of gait and balance problems separately. In these studies, worsening of gait (9.2%) and balance (12.2%) occurred in similar frequencies (p=0.38), although most studies did not make explicit whether gait and balance co-occurred in the same case.[13 17 33 34] A homogeneous estimation of the severity of worsening was not possible due to insufficient quantitative data. However, several case series and observational studies report worsening on gait and balance scales including MDS-UPDRS III subitems, self-reported mobility in the MDS-UPDRS II and Timed Up and Go Test.[12 14 16 17 21 29 30]

Risk factors

Several studies have investigated the relation between GBW and patient characteristics. Eight studies[12 16 17 19 26 29 30 34] evaluated the association between GBW and age. The largest cohorts do not report differences in age at surgery[12 16 26] (mean population age 55, 57, 53 years), although three smaller studies with older mean population ages (59, 64, 78 years)[17 19 34] suggest increased GBW with older age at surgery. One large consecutive cohort study (n=331) reported shorter preoperative disease duration in people with worsened FOG versus improved FOG (12.0 vs 13.8 years of disease duration, 11.7 for unchanged FOG, p=0.004).[12] This was also the case for increased falls (11.3 vs 14.1 years, 12.2 for unchanged falls, p=0.007). However, smaller studies report no significant association.[8 16 17 29] There were no differences in gender,[8 12 16] preoperative MDS-UPDRS part III OFF scores,[12 16] preoperative levodopa response[19 26] or preoperative cognitive function[12 16 26] between patients with and without postoperative GBW. Evidence for the association between GBW and severity of preoperative

Table 1 Overview of all included GBW cases in the literature

			STN-DBS			Best medical treatment		
First author	**Study type (lead type)**	**Nature of cohort**	**n=**	**GBW**	**% GBW**	**n=**	**GBW**	**% GBW**
Ahrweiller[16]	Prospective cohort (N/A)	Consecutive	56	10	*17.9%*			
Barbe[32]	Non-randomised trial (Directional, Vercise, Boston Scientific)	Selected	11	1	*9.1%*			
Barbe[26]	Randomised controlled trial (circular, Medtronic)	Consecutive	16	9	*56.3%*	15	6	*40%*
Buhmann[8]	Retrospective cohort (N/A)	Consecutive	78	9	*11.5%*			
Deuschl[1]	Randomised-pairs trial (circular, Medtronic)	Consecutive	71	3	*4.2%*	73	1	*1.4%*
Ferraye[11]	Retrospective cohort (N/A)	Consecutive	50	10	*20.0%*			
González-Herrero[28]	Retrospective cohort (N/A)	Consecutive	48	3	*6.3%*			
Guehl[17]	Retrospective cohort (circular, Medtronic)	Consecutive	44	8	*18.2%*			
Jia[31]	Case report (N/A)	Selected	1	1	*N/A*			
Karachi[12]	Prospective cohort (circular, Medtronic)	Selected	331	93	*28.1%*			
Kelly[29,30]	Case series (circular, Medtronic)	Selected	8	3	*37.5%*			
Mei[14]	Case report (circular, Medtronic)	Selected	1	1	*N/A*			
Russmann[19]	Retrospective cohort (circular, Medtronic)	Consecutive	52	5	*9.6%*			
Sharma[34]	Retrospective cohort (N/A)	Consecutive	30	4	*13.3%*			
St George[15]	Prospective cohort (circular, Medtronic)	Selected	11	5	*45.5%*	8	0	0%
Tassorelli[35]	Non-randomised trial (N/A)	Selected	75	5	6.7%			
Thobois[33]	Retrospective cohort (circular, Medtronic)	Consecutive	18	1	5.6%			
Van Nuenen[21]	Retrospective cohort (N/A)	Consecutive	55	9	*16.4%*			
Vercruysse[27]	Non-randomised controlled trial (circular, Medtronic)	Consecutive	4	2	50%	2	1	*50%*
Weaver[13]	Randomised controlled trial (circular, Medtronic)	Consecutive	60	10	*16.7%*	134	5	*3.7%*
Weighted average	All studies*		1010	187		232	13	
Weighted average	Consecutive controlled trials†		151	24	**15.9%‡**	224	13	**5.8%‡**

n=number of study participants at risk of GBW.
Only cases from consecutive cohorts with best-medical treatment control group are used to estimate GBW incidence. A more detailed table also containing available determinants per study is available in the online supplemental material.
*Excluding case reports and case series.
†Additionally excluding enriched cohorts, potential selection bias, missing data.
‡p<0.01 for between-group difference.
GBW, gait or balance worsening.

gait parameters was conflicting.[12 16 17 28] Postoperative mean MDS-UPDRS scores (in OFF and ON conditions, including OFF-stimulation) did not differ between DBS patients in the GBW and non-GBW groups, apart from specific gait items.[12 16 26] Worse postoperative cognitive performance was associated with increased falls severity in one study.[12]

Several studies have associated electrode position and stimulation parameters with GBW. One cohort study evaluating the effect of stimulation of ventral versus dorsal STN did not show any differences in gait and balance outcomes.[37] Furthermore, the largest cohort studying GBW[12] could not identify differences in electrode position within the STN to be associated with GBW. High-frequency stimulation (≥130 Hz) has been associated with GBW onset.[30 31 36] However, this large cohort could also not identify differences in stimulation settings; most of these patients were treated with high-frequency stimulation and statistical power for frequency comparisons was lacking.[12] Occasional improvement is reported after lowering stimulation frequency to 60–80 Hz[31,36] although we strived to exclude stimulation-responsive cases from this review. A fluorodeoxyglucose PET imaging study demonstrates that GBW patients have increased infratentorial activity compared with patients without GBW.[16] Infratentorial regions that were implicated included the mesencephalic locomotor region (MLR) and pedunculopontine nucleus (PPN) in connection with cerebellar motor regions.[16 38] This association with regional cerebellar (over)activity was also found in a case report.[14] Finally, two studies report that gait-specific rehabilitation as treatment for GBW after STN-DBS is largely ineffective.[17 35]

Incidence of gait or balance worsening (GBW)

Across all included consecutive cohorts, GBW occurred in 14.3% of cases (range 4.2–56.3%). Among these were four trials that also had a BMT control group (n=151 STN-DBS, n=224 BMT),[1 13 26 27] although over 80% of cases originated from two studies.[1 13] Incidence of GBW in these four studies was 15.8% in the STN-DBS group, compared with 5.8% in the BMT group (p=0.0013). Corrected for the number of person-years per treatment arm in these studies, incidence rates also differed significantly (0.28 vs 0.11, p=0.004).

DISCUSSION

In this study, we have included all studies reporting GBW cases after STN-DBS. FOG and increased falls were the most reported characteristics of GBW, usually occurring between 3 and 6 months after surgery. Evidence for associations between GBW and disease duration and preoperative gait parameters were conflicting, but older age at surgery, especially in older study populations, was associated with more GBW. Large cohort studies did not report significant trends or associations between GBW and gender or between GBW and preoperative scores on MDS-UPDRS part III, levodopa response or cognitive function. Electrode position (within the STN) was not associated with GBW. Some studies suggest high-frequency (≥130 Hz) stimulation as a potential risk factor for GBW. A potential mechanism of GBW is concomitant anti-dromic modulation of brainstem nuclei of the MLR, specifically the PPN. Finally, in consecutive studies, new-onset GBW is a relatively common side effect after bilateral STN-DBS compared with BMT.

Phenomenology

Most studies do not report the phenomenology of GBW in detail. GBW was frequently accompanied by other axial symptoms such as dysarthria and cognitive dysfunction, but the exact percentage of co-occurrence could not be established because of limitations in reporting. Some studies investigated GBW by conducting gait lab measurements, which mostly show decreased gait velocity and stride length. The phenotypic overlap between GBW and gait problems in advanced PD without STN-DBS suggests overlap in pathways that are involved in the pathophysiology of GBW and PD, which will be discussed later.

Risk factors

We could not identify any patient characteristics or surgical parameters as evident risk factors for GBW. However, studies including older individuals more often reported an association between GBW and age. Evidence for a predictive role of preoperative gait impairment, disease duration, baseline LED, levodopa response, baseline cognitive function and electrode position (within the STN) was conflicting. More complex causal mechanisms might be at play. For example, slight worsening of cognitive dysfunction is a common side effect of STN-DBS[8] and might influence gait and falls in the long term, possibly together with older age.[7 39] Additionally, fast disease progression (shorter disease duration with comparable UPDRS scores) might make individuals more prone to GBW.[20] Speculatively, this might be due to less (motor) reserve in these individuals,[40] especially if less motor reserve incapacitates one to compensate for STN-DBS-induced gait asymmetry and dyscoordination that is observed in gait labs.[41]

Several studies investigated the association between GBW and stimulation parameters. First, some studies found an association between stimulating at high frequency (~130 Hz) and GBW onset, possibly through maladaptive modulation of gait-related networks. Although we strive to exclude all GBW cases that were reversible on stimulation reprogramming, evidence exists of worsening of axial symptoms that improved on lowering frequency[20 36 38 42–45] or asymmetric programming,[46] often worsening appendicular symptoms.[36 38 42 43 47–49] A recent report suggests post-DBS axial symptoms improved with reducing left-sided stimulation amplitude by 50%, suggesting a causal role of overstimulation.[50] However, transient gait improvement after reprogramming followed by deterioration is no

exception.[51 52] Hypothetically, this symptom trade-off could be caused by a reduction in the co-stimulation of the pallido-PPN pathway and at the same time a reduction of stimulation of the pallidothalamocortical pathway by stimulating the pallidothalamic tract.[53 54] Speculatively, considering the low (40–60 Hz) stimulation frequency of PPN-DBS, higher-frequency stimulation may inadvertently inactivate subpopulations of the PPN by a depolarisation block, causing gait or balance problems.[55] Lastly, increased (ON-phase) gait freezing might also be caused by an increase in ON time, a phenomenon observed in a minority of patients.[56] Conversely, we cannot exclude the possibility that shuffling and gait slowness might be partly due to increased OFF time, although we strived to exclude cases with transient symptoms or improvement by altering stimulation or medication parameters.

Functional and structural imaging studies have shed light onto the mechanisms of GBW. One study that assessed fluordeoxyglucose PET activity in GBW cases[16] observed increased brain activity similar to that in PD patients with gait disorders, namely in the MLR.[57] This possibly clarifies both the phenomenological overlap as well as earlier reports that hold disease progression accountable. This MLR activity could be consistent with potential inadvertent co-stimulation of gait-related white matter tracts within the volume of tissue activation (VTA), determined by the stimulation amplitude, pulse width and electrode location. Examples of pathways that may be involved include the zona incerta and the fields of Forel (H2), where the pallidothalamic tract and pedunculopontine efferents to the STN are located. These tracts are involved in gait and PD-related gait disorders and are part of the MLR.[14 19 53 58 59] This costimulation might gradually modulate these networks and thereby disturb their functioning in the long term, explaining the multiple-month delay of GBW onset. Alternatively, this delay could be explained by the stimulation protocol that is used. Usually, the stimulation amplitude is gradually increased until the maximum clinical benefit is reached with the least adverse effects. This gradually increases VTA, which at one point may include the aforementioned adjacent gait networks, subsequently causing gait problems. However, the fact that modifying stimulation settings did not resolve GBW in patients with persistent GBW indicates long-term functional changes in this network caused by neuromodulation. Studies that investigate novel techniques such as image-guided programming and current steering might give more accurate insight into the role of MLR co-stimulation as a contributor to GBW after STN-DBS. Finally, whether medication and stimulation have differential effects on GBW,[14 60] or whether medication and stimulation modify each other's effect on gait,[54 60] is unknown. Insufficient data were available to study the role of medication reductions after stimulation initiation in GBW onset.

INCIDENCE

Finally, we have summarised all reported cases of GBW after STN-DBS. Although we only included consecutive cohorts that mentioned at least one case of GBW, the incidence of GBW varied between studies (between 4% and ~20%). Because we only included studies that reported GBW, we had to exclude several landmark DBS studies that did not report any GBW,[3 4 61] likely overestimating its incidence. Estimation of the true incidence across the literature is hampered by variations in reporting of gait problems. Various studies only report gait outcomes on the population level instead of the individual, some do not report gait specifically,[1 61] and some show no or only a temporary effect with worsening on the long term, especially compared with appendicular symptoms and compared with internal globus pallidus (GPi) DBS.[8 15 62–71] The lack of available details in individual cases prohibited a more precise incidence estimation stratified by phenotype (such as freezing vs balance or falls). Importantly, various studies show improvement on gait scales[5 27 72 73] or gait lab measures.[74–78]

Some studies have argued that GBW is not related to DBS and is caused by natural progression of age or disease, which induces gradual structural and eventually functional degeneration of gait networks.[12 21 22] Indeed, we may have inadvertently included gait or balance worsening within 12 months postsurgery that might have been due to disease progression. However, the significant axial symptom deterioration within 1 year (and usually within 6 months) after STN-DBS as identified in this study seems faster than expected from normal disease progression.[79] Furthermore, it should be noted that gait worsening occurs in the context of significantly improving appendicular symptoms. Finally, in consecutive cohorts with a BMT control group,[1 13 26 27] GBW was more prevalent in the DBS group compared with the control group, further corroborating claims of GBW being a DBS-induced phenomenon.

LIMITATIONS

This study has several limitations. First, details on postoperative gait or balance deterioration were sparse and variably reported, reported only on group level. This hampered a quantitative analysis of risk factors as well as the incidence estimation. We also had to exclude some landmark DBS studies as no GBW cases were reported, or data on GBW at 12 months were lacking.[2 4 61] Notably, one of these RCTs also reports a higher GBW incidence at 2 years post-surgery compared with BMT.[4] Some studies included the MDS-UPDRS III gait sub-item as the sole gait-related outcome, and various trials included no specific gait or balance outcomes. As most MDS-UPDRS III items tend to improve significantly after DBS, this may also lead to sum scores potentially overshadowing postoperative gait deterioration.[30 80] Furthermore, many potential risk factors are largely non-controlled, including

surgical practice heterogeneity, lesion effects, identifying optimal stimulation parameters, medication adjustments and heterogeneity in gait-related outcome measures, all in the context of a progressive and variable disease. To mitigate underestimation due to potential underreporting, we only included studies that reported any signs of GBW, which does not allow for accurate incidence estimation. Still, over 95% of control group patients were from randomised studies, therefore limiting the risk of confounding by indication. Finally, at project initiation, we envisioned to exclude GBW onset within 1 month postsurgery to exclude postoperative complications, although we did not identify any cohorts that reported GBW within this period. To definitively answer the question of the causative relation and incidence between STN-DBS and GBW, one should compare a large, randomised cohort consisting of STN-DBS and BMT groups with prospective follow-up and detailed pre- and postoperative assessment of gait and balance, including stimulation settings and medication adjustments. This would also allow for better insight into predictors of GBW.

GBW is a well-known adverse event after STN-DBS that can have a large impact on quality of life. The incidence of GBW between studies varies largely, and included studies are heterogeneous in methodology and reporting, which hampers quantitative analysis on risk factors and causes of GBW. Future studies are needed that conduct a clear assessment of gait and balance pre- and postsurgery, detailed assessment of patient characteristics, imaging techniques, electrode position, stimulation parameters and medication changes over time. If such studies report these measures stratified by gait or balance outcomes, identification of risk factors and mechanisms of GBW will be accelerated. This will eventually make for better patient counselling and ultimately improved outcomes of STN-DBS in the long term.

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