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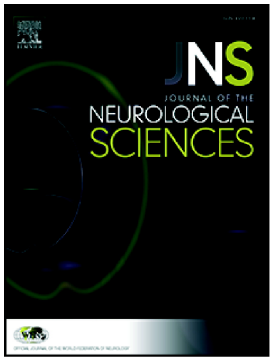

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Deep brain stimulation in Parkinson's disease: a multicentric, long-term, observational pilot study

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ABSTRACT

Background

The impact of deep brain stimulation (DBS) on cognitive and urinary disorders, falls, and eventually hospitalizations and mortality in Parkinson's disease (PD) is still debated.

Objective

We compared the rates of dementia, mild cognitive impairment (MCI), urinary incontinence, nocturia, falls, hospitalizations, and mortality in a cohort of PD patients undergoing DBS to a cohort of medically-treated patients chosen as controls.

Methods

We conducted a retrospective pilot study in six Italian DBS centers. 91 PD patients receiving DBS and 91 age- and gender-matched controls receiving the best medical treatment alone with a minimum follow-up of one year were enrolled. Clinical data were collected from baseline to the last follow-up visit using an ad-hoc developed web-based system.

Results

The risk of dementia was similar in the two groups while patients in the surgical cohort had lower rates of MCI, urinary incontinence, nocturia, and falls. In contrast, the risk of hospital admissions related to PD was higher in the surgical cohort. However, when excluding hospitalizations related to DBS surgery, the difference between the two cohorts was not significant. The surgical cohort had a lower number of hospitalizations not related to PD. The risk of death was similar in the two groups.

Conclusion

Despite a higher risk of hospitalization, patients receiving DBS had a lower rate of MCI, urinary incontinence, nocturia and falls, without evidence of an increased risk of dementia and mortality. Although these findings need to be confirmed in prospective studies, they seem to suggest that DBS may play a significant role in the management of non-motor symptoms and common complications of advanced PD.

Keywords: Dementia, Deep Brain Stimulation, Falls, Parkinson's disease, Urinary symptoms, Non-motor symptoms.

Abbreviations

adj. RR adjusted relative risks (adj. RR)

CI confidence intervals

DBS deep brain stmulation

IQR interquartile range

MC medical cohort

MCI mild cognitive impairment

PD Parkinson's disease

RR relative risk

SC surgical cohort

T time.

1. INTRODUCTION

Deep brain stimulation (DBS) is an effective treatment for advanced Parkinson's disease (PD). When evaluated at 10 years after surgery, control of motor functions and performances during daily life activities was still preserved.[1] However, long-term disability of PD not only depends on motor symptoms' progression and motor fluctuations but also on non-motor symptoms [2] and other common

complications such as falls and hospitalizations. Whether and how DBS affects these aspects of the disease is still debated.[3]

Cognitive impairment, ranging from mild frontal and executive dysfunctions to dementia, is a common feature of advanced PD.[4] Cognitive disorders may significantly affect patients' abilities and dementia seems to double the mortality risk in PD.[5] However, although certain aspects of cognitive performance [5–8] may decline after DBS, no long-term and controlled studies have been performed in large cohorts of patients.[8] Additionally, available data are still conflicting and usually refer to studies performed when DBS was considered only in the advanced stage of the disease.

Another common, bothersome non-motor symptom with a detrimental effect on patients' quality of life is represented by urinary symptoms.[10] The prevalence of nocturia, urgency, and urinary incontinence ranges from 38% to 71%.[10] Since urinary symptoms may improve or deteriorate in response to dopaminergic treatments, their responsiveness to DBS is hard to predict.[10] Early reports suggest that subthalamic stimulation increases bladder capacity, delays first desire to empty the bladder [3,11] and improves nocturia.[12] However, these preliminary data have never been confirmed in large samples.

Long-term disability depends also on patients' falls, experienced by almost 50% of patients over a three month-period.[13] Falls can cause injuries and fear of falling, and may lead to activity avoidance, physical deconditioning, and increased institutionalization. However, since some reports have shown gait and balance worsening after surgery [14–17] while others have found improvement of falls and fear of falling, [18,19] the effect of DBS remains unclear.

Patients' overall well-being depends also on preventing hospital admissions, usually more frequent and longer for PD patients than for controls.[20] Some authors found that DBS is a risk factor for hospital admissions and for recurrent encounters.[21] However, these findings have never been confirmed in controlled studies.

Lastly, life expectancy is shorter in PD.[22] Many studies have looked at the causes of death in patients with PD showing that most of them are PD-related disorders.[23] Several independent factors have been associated with an increased mortality in PD [5] but DBS-induced effect on long-term mortality remains unclear. Indeed, most studies lack a control group and include only small samples of patients.[9,24–27]

Hence, although a growing attention has been recently focused on non-motor symptoms pharmacological management, the role of DBS on cognitive and urinary disorders has never been systematically assessed. Likewise, DBS effect on falls, hospitalizations and mortality remains debated. In this multicenter pilot study, we recruited a cohort of PD patients undergoing DBS and medically-treated PD patients (chosen as controls) to investigate DBS impact on the development of the above long-term disease complications.

2. MATERIALS AND METHODS

Experimental design

The investigation was a retrospective cohort study and was performed between 2013 and 2016 in six Italian PD centers. The study was conducted according to the Declaration of Helsinki. Each patient gave his/her written informed consent to the study and the protocol was approved by the local ethical committee.

We enrolled all patients having idiopathic PD according to the British PD Society Brain Bank criteria [28] and treated with DBS or for whom this treatment was indicated according to the protocol “Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD”) (i.e. patients with motor fluctuations or tremor uncontrolled with the medical treatment) but not performed (i.e. patients who had no access to a DBS center, who refused surgery or were selected for alternative treatments). We required a minimum follow-up of one year. Enrolled patients were included in two

different cohorts. Patients with PD receiving DBS (either subthalamic nucleus or globus pallidus internus DBS) entered the surgical cohort (SC) while controls receiving medical treatment alone entered the medical cohort (MC). Controls for whom surgery was contraindicated owing to cognitive impairment at baseline or severe medical comorbidities that could reduce life expectancy were not accepted.

We decided to opt for a sample of at least 90 patients in the SC, with 90 matched controls in the MC (1:1 ratio). The choice was motivated by the limited number of medically treated PD patients in our centres that complies with the inclusion criteria of the study. Indeed, only a minority of those patients had no contraindications for surgery such as dementia or significant comorbidities that could affect life expectancy at baseline. The sample was compatible with a planned estimate of the number of controls available in all centres, that was not expected to be greater than 90. Since the selection of the MC patients was extremely difficult, the local investigators were invited to identify medical patients first and, for comparison, age- and sex-matched surgical patients.

We collected data referred to the baseline (time 0 (T0), within 1 month before surgery in SC or at time of indication for surgery in MC) and to the last available follow-up (T1) in both cohorts. Every effort was made to update each patient follow-up to the most recent date.

Data collection

Data were collected, firstly, from medical records and, secondly, through a direct interview to the patient or his/her relatives to collect unavailable information.

First, patients' demographic and clinical characteristics (date of birth, gender, relevant comorbidities) and information about PD history (date at onset of symptoms, disease duration at T0, pharmacological treatment) were collected. Next, in the SC we collected information about the surgical intervention for DBS (target, date at surgery, complications after surgery). Then, we collected at each time assessment

the following data: 1) general data about patients' clinical status: relevant comorbidities (recorded as presence or absence of at least one relevant comorbidities among the following categories: cardiovascular, infectious, endocrine, orthopedic/rheumatic, neurologic, hematologic, gastrointestinal, genitourinary, respiratory, metabolic, oncologic, psychiatric), pharmacological treatment, DBS parameters; 2) information about cognitive functions (presence of MCI/dementia according to the reported definitions,[29,30] urinary symptoms (presence of urinary incontinence/ use of incontinence pad and nocturia), falls (presence of falls and severe falls defined as those requiring medical intervention or causing even temporary disability), hospitalizations (date and causes of hospitalization), and death (date and causes). At T0 we assessed the outcomes over the last 12 months before the assessment and at T1 over the time interval between T0 and T1.

All collected data were recorded in a specifically developed web-based system for clinical and neurophysiological data collection and analysis, called WebBioBank.[31]

Primary and secondary outcomes

The primary outcome measures were the differences between SC and MC at T1 in the rate of patients with dementia, urinary incontinence or use of incontinence pad, falls, severe falls, the rate of hospitalization (divided into three categories according to the reason for hospitalization as follows: Related to PD; Not related to PD; Related to PD excluding hospitalizations related to DBS surgery (i.e. Battery replacement)), and mortality.

Secondary outcomes were the differences between SC and MC in the rate of patients with MCI and nocturia at T1.

Statistical analysis

Demographic and clinical characteristics at T0 were described and compared between SC and MC. Categorical variables were described by count and percentage, and numerical variables by median and interquartile range (IQR). Differences between the two cohorts were assessed using the Chi-square or the Fisher's exact test for categorical variables and the Wilcoxon-Mann-Whitney test for numerical variables.

The rate of patients experiencing each outcome in SC and MC at T1 was calculated using different univariable and multivariable Poisson models, specifying the logarithm of follow-up duration as an offset variable (in order to model rates instead of counts, to account for different follow-up durations between patients in SC and MC). The comparison between the two cohorts was expressed in terms of relative risks (RR) and adjusted relative risks (adj. RR), with 95% confidence intervals (95% CI). Relative risks were calculated as the ratio of the rates between SC and MC. All models were adjusted for disease duration (time from disease onset to T0, in years) and the presence of the outcome at T0; the model on severe falls was adjusted for the presence of any fall at baseline; models on the total number of hospitalizations and hospitalizations not related to PD were adjusted for the number of types of comorbidities (among cardiovascular, infectious, endocrine, orthopedic/rheumatic, neurologic, hematologic, gastrointestinal, genitourinary, respiratory, metabolic, oncologic, psychiatric). The significance level was set at 5% and all tests were two-tailed. Missing data were handled using the listwise deletion method. Data were analyzed using the SAS statistical package (version 9.2; SAS Institute, Cary, NC, USA).

3. RESULTS

The sample included 182 patients (91 in the SC and 91 in the MC). Patients in the SC underwent DBS between 1998 and 2015. For patients' demographic and clinical characteristics at T0 see Table 1.

Table 1. Clinical and demographic characteristics of the sample at baseline

	Surgical Cohort (N=91)			Medical Cohort (N=91)	
Gender					
Female	32	(35.2)		32	(35.2)
Male	59	(64.8)		59	(64.8)
Age (years)	60.3	(53.9-64.5)		61.9	(56.4-67.1)
Disease duration (years)	11.6	(8.3-14.5)		7.4	(4.9-11.8)
Number of types of comorbidities					
0	67	(74.4)		61	(67.0)
1-2	18	(20.0)		24	(26.4)
3-5	5	(5.6)		6	(6.6)
Levodopa equivalent daily dose	1065 (1)	(655-1450)		875.0	(621-1258)
Neuropsychiatric treatment	6 (1)	(6.7)		6	(6.6)
Mild cognitive impairment	10	(11.0)		18	(19.9)
Incontinence or use of incontinence pad	12	(13.2)		6 (1)	(6.7)
Nocturia	17 (13)	(21.8)		18 (8)	(21.7)
Falls	15 (4)	(17.2)		18 (3)	(20.5)
Severe falls*	10 (4)	(11.5)		4 (2)	(4.5)
Hospitalizations related to Parkinson's disease	8 (2)	(9.0)		14 (1)	(15.6)
Hospitalizations not related to Parkinson's disease	10 (2)	(11.2)		11 (1)	(12.2)

Data described by count (percentage), or by median (interquartile range). The neuropsychiatric treatment included: antidepressants, antipsychotics, mood stabilizers and anxiolytics and hypnotics. (n): number of missing data; *falls requiring medical intervention or causing even transitory disability.

In the SC, 87 patients (95.6%) had been implanted in the subthalamic nucleus and 4 (4.4 %) in the globus pallidum internus. Most patients had bilateral DBS (83 patients, 91.2%). One patient reported transient confusion after surgery and four patients complained about minimal and transient unspecific side effects such as insomnia. However, only two patients had severe short-term surgery related complications after surgery such as an intracerebral and a subclavian bleeding, respectively.
The SC was followed for a total of 367.5 person-years (median 3.4 years, IQR: 1.8 - 4.9) and the MC for 230.7 person-years (median 2.3 years, IQR: 1.3 - 3.3). At last follow-up, the median levodopa equivalent daily dose was 665.0 (IQR: 447.8-970.0) for the SC and 1000.0 (IQR: 710.0-1358.0) for MC.

Primary outcomes

No significant difference between SC and MC was found for the risk of dementia (Fig. 1).

Figure 1. Primary and secondary outcomes. All models were adjusted for disease duration and presence of the outcome at baseline. “Total hospitalizations” and “Hospitalization not related to Parkinson’s disease” were adjusted for number of types of comorbidities. * falls requiring medical intervention or causing even transitory disability.

The risk of incontinence or use of incontinence pad was significantly lower in the SC than in the MC (Fig. 1). A reduced risk of incontinence was observed in the SC in patients without incontinence at T0 but not in patients already symptomatic at T0 (Fig. 2).

Figure 2. Primary and secondary outcomes stratified analysis by presence/absence of the outcome at baseline. All models were adjusted for disease duration. "Total hospitalizations" and "Hospitalization not related to Parkinson's disease" were adjusted for number of types of comorbidities. * falls requiring medical intervention or causing even temporary disability. ** strata were defined according to the presence/absence of any fall at baseline.
T0= Time 0

The risk of falls was significantly lower in the SC than in the MC (Fig. 1) while the risk of severe falls was similar in the two cohorts (Fig. 1). No differences in the effect of DBS on falls were found between patients reducing medication and patients not reducing medication (data not shown). No significant differences were found for the SC compared to MC according to the presence of falls or severe falls at T0 (Fig. 2).

The total number of hospitalizations in the SC was similar to that reported in the MC (Fig. 1). However, we observed a significantly increased risk of hospitalizations related to PD in the SC. In patients without hospitalizations related to PD at T0, the SC had a significantly higher risk of hospitalizations related to PD during follow-up than the MC (Fig. 2). When we excluded hospitalizations related to DBS surgery (i.e. battery replacement, etc.), the difference between the two cohorts was no longer significant (Fig. 1). Among the causes of hospitalizations related to surgery, we found DBS complications in three patients (dislocation of the right electrode, suboptimal electrode placement, and implantable pulse generator malfunctioning, respectively). Additionally, the SC showed a significantly reduced risk of hospitalizations not related to PD (Fig. 1). Hospitalizations occurred in the sample with causes are summarized in Supplementary Table 1.

Patients who died during follow-up were 1 in the SC (1.1%) and 2 in the MC (2.1%). Causes of death were a car accident, an advanced stomach cancer and a cerebrovascular event, respectively.

Secondary outcomes

The risk of MCI was lower in the SC than in the MC (Fig. 1). Stratified analysis confirmed a reduced risk of MCI in SC compared to MC in patients asymptomatic at T0 (Fig. 2).

As compared to the MC, the SC showed a significant reduction of the risk of nocturia. In patients without nocturia at T0, a significant risk reduction was found for the SC compared to the MC (Fig. 2).

4. DISCUSSION

This is the first study to compare surgical and pharmacological treatment impact on long-term disabling PD complications in a large cohort of patients. DBS did not seem to affect the risk of dementia but the rate of MCI, urinary incontinence, nocturia and falls was lower in our SC cohort compared to the MC. Lastly, surgical treatment increased hospitalizations related to PD and did not influence mortality.

Dementia is one of the most disabling complications of advanced PD. In our study, only a minority of patients developed dementia in both cohorts and the risk of MCI was lower in the SC. The hypothesis that cognitive decline reported years after surgery depends on the natural history of the disease has been largely accepted. However, this hypothesis has been supported by a few controlled studies and several small cohorts of patients [6,7, 9, 27, 32,33, 34, 35, 36, 37, 38]. The present study is in line with this hypothesis since it suggests that DBS does not represent per se a risk factor for dementia. Since most studies on the incidence of dementia after surgery had a short follow-up, our results allow to expand previous findings over time. Indeed, the only available study with a long follow-up included 16 patients and the control group was an historical reference population not paired for age to the SC.[27]

Ultimately, although the retrospective nature of our study design did not allow to exclude the subtle

changes in frontal functions reported in previous studies (37, 39), it gives us important information on patients and caregivers' perception of cognition after surgery. Although our data suggest a lower risk of MCI in the SC, the difference between the two cohorts could also be partly influenced by the strict selection criteria for cognition in candidates for surgery.

Our findings also support a role of DBS in improving urinary incontinence and in reducing the risk of incontinence in patients asymptomatic before surgery. Additionally, DBS decreased the risk of nocturia especially in patients asymptomatic before surgery. Our study is in line with the available reports.[11,12,40-41] As previously suggested, the improvement of urinary symptoms is thought to rely on an inhibitory effect of DBS on the micturition reflex.[11, 40] However, it is again difficult to compare our findings with the others since none has previously assessed the presence of incontinence in everyday life and most previous studies have used tests evaluating a short time interval, have been performed few months after surgery and lack a control group.[11,40-41] To our knowledge, only one study compared the prevalence of urinary disorders in patients treated by DBS to controls.[12] The authors reported an isolated improvement of nocturia in the SC with no differences in other symptoms.[12] However, patients were not paired for age and disease duration and were assessed only for a period of two weeks.[12]

Our study also found a reduction of falls in the SC compared to the MC. Although our study design did not allow to assess in detail the causes of falls, this finding is essential for patients' management. In fact, falls are a common complication in PD.[22] Although the effect of DBS on falls has been assessed by implanting different targets (i.e. pedunculopontine nucleus, etc.), we compared our findings only with those obtained from STN or GPi DBS studies. [18,19] Two studies found an improvement in the fear of falls [18,19] but no significant changes in the falls' rate.[19] However, the first study included only 10 patients and was performed by assessing acute DBS's effect while the second included only 20 patients and assessed only a 3-month follow-up period.[18,19] Moreover, both studies lack a control

group. DBS effects on motor fluctuations, dyskinesias, and levodopa-responsive gait disorders and the reduction of dopaminergic treatments that can cause itself orthostatic hypotension and confusion, in turn responsible of falls, may have contributed to falls' improvement in our cohort. However, previous studies reported gait deterioration as a possible adverse effect after surgery.[14,15, 42] Nevertheless, the complexity of gait disorders and the multifactorial mechanisms of falls in PD may explain the conflicting findings reported so far.

Although the total number of hospitalizations remained similar in the two cohorts, DBS patients had a higher rate of hospitalizations related to PD. However, differences were not significant when hospitalizations related to DBS surgery were excluded. Moreover, hospitalizations unrelated to PD had a lower rate in the SC. A higher risk of hospitalizations after surgery has already been reported by Hassan and colleagues.[21] However, the study did not compare hospitalization rates in the SC with a MC having same disease severity. The most common reason for hospitalizations in both cohorts was PD symptoms' management as it has already been reported in previous studies (43). By contrast, our study found a decrease of non- PD related hospitalizations in the SC. These results are difficult to explain. Although our analysis was adjusted for number of types of comorbidities, we cannot exclude that the severity of comorbidities was higher in the MC thus requiring a higher number of hospitalizations. On the other hand, we can speculate that the improvement of motor fluctuations, urinary disorders and falls induced by DBS could at least partially contribute to these results. However, these findings need to be assessed by prospective studies.

Furthermore, in our study, the mortality rate did not differ between SC and MC. Various mortality rates have been reported in DBS patients, [24,25,27,44,45] according to patients' age at surgery, and disease and follow-up duration. To our knowledge, only three studies have a control group.[25, 44, 45] Our study is in contrast with the first two studies that found a reduced mortality in the SC[25; 44] while is in line with the third, where no significant differences in mortality had been reported.[45] Despite the

high number of patients enrolled in the study from Weaver et al (2011), MC and SC patients were not matched for disease duration nor for disease severity and no information was available about comorbidities or contraindications to surgery in the MC. As a result, the modest survival advantage found in the SC may reflect unmeasured differences between groups rather than the effect of DBS. However, the low mortality rate found in our study and the shorter follow-up compared to the study from the group of Ngoga [25] and Weaver (45) may have had an impact on our results.

Our study has also critical aspects. Firstly, the retrospective nature of the study did not allow us to describe in detail some outcomes [i.e. neuropsychological assessment and gait analysis or scores of scales such as the UPDRS, the Hoehn and Yahr scale or executive functions' tests were not available for all patients]. Moreover, we tried to collect unavailable data by interviewing patients and surrogates. Although this procedure provided the best available knowledge and was applied in both cohorts thus allowing a uniform data collection, it carried the limitations of retrospective information [i.e. since OFF/ON medication assessments were not available, we could not assess whether gait/balance disorders related to falls were levodopa responsive, etc.]. Secondly, our sample, although one of the largest available in controlled studies, is small compared to the high prevalence of the disease. Anyway, our study included patients from the main PD Italian centers thus allowing us to suppose that it could be representative of patients affected by the disease. The limited number of patients developing dementia and experiencing severe falls leads to a lack of power for detecting clinically important differences for these two outcomes, particularly in the case of dementia, and even if our data did not suggest differences between the two cohorts, no definite conclusions could be drawn. Additionally, disease duration and follow-up were different in the two cohorts. We tried to limit a possible bias by adjusting the analysis for disease and follow-up duration. Since both were shorter in the MC, PD complications would be expected to be more frequent and severe in the SC, but this was not the case in our study.

5. CONCLUSIONS

Even though further research is required to prospectively confirm and extend our findings, our pilot study supports a role of DBS in improving MCI, urinary incontinence, nocturia and falls with no evidence of an increased risk of dementia nor of mortality compared to the best medical treatment. Finally, a higher risk of hospitalizations has to be considered in the SC.

The following are the supplementary data related to this article.

Supplementary Table 1. Number and causes of hospitalizations.

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Summary declaration of interest statement

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HIGHLIGHTS

- The impact of DBS on advanced Parkinson's disease complications is still debated.
- The rate of MCI, urinary symptoms and falls is lower in the surgical cohort.
- DBS does not increase the risk of dementia and mortality.
- DBS may improve the management of non-motor symptoms of Parkinson's disease.
- DBS increases the risk of hospitalizations compared to the best medical treatment.

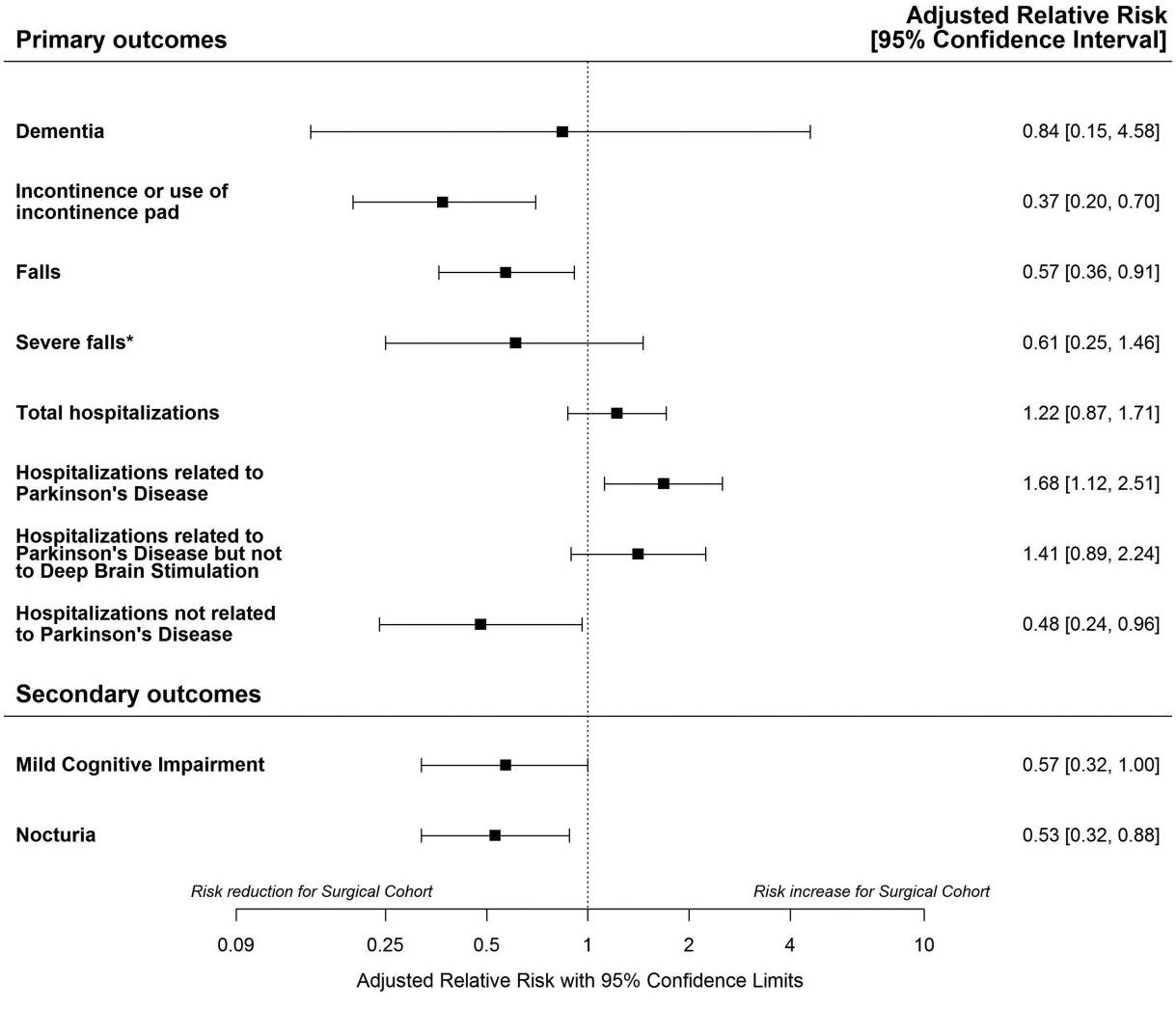
Primary outcomes
Adjusted Relative Risk [95% Confidence Interval]
Dementia
0.84 [0.15, 4.58]
Incontinence or use of incontinence pad
0.37 [0.20, 0.70]
Falls
0.57 [0.36, 0.91]
Severe falls*
0.61 [0.25, 1.46]
Total hospitalizations
1.22 [0.87, 1.71]
Hospitalizations related to Parkinson's Disease
1.68 [1.12, 2.51]
Hospitalizations related to Parkinson's Disease but not to Deep Brain Stimulation
1.41 [0.89, 2.24]
Hospitalizations not related to Parkinson's Disease
0.48 [0.24, 0.96]
Secondary outcomes
Mild Cognitive Impairment
0.57 [0.32, 1.00]
Nocturia
0.53 [0.32, 0.88]
Risk reduction for Surgical Cohort
Risk increase for Surgical Cohort
0.09
0.25
0.5
1
2
4
10
Adjusted Relative Risk with 95% Confidence Limits

Figure 1

Primary and secondary outcomes stratified analysis

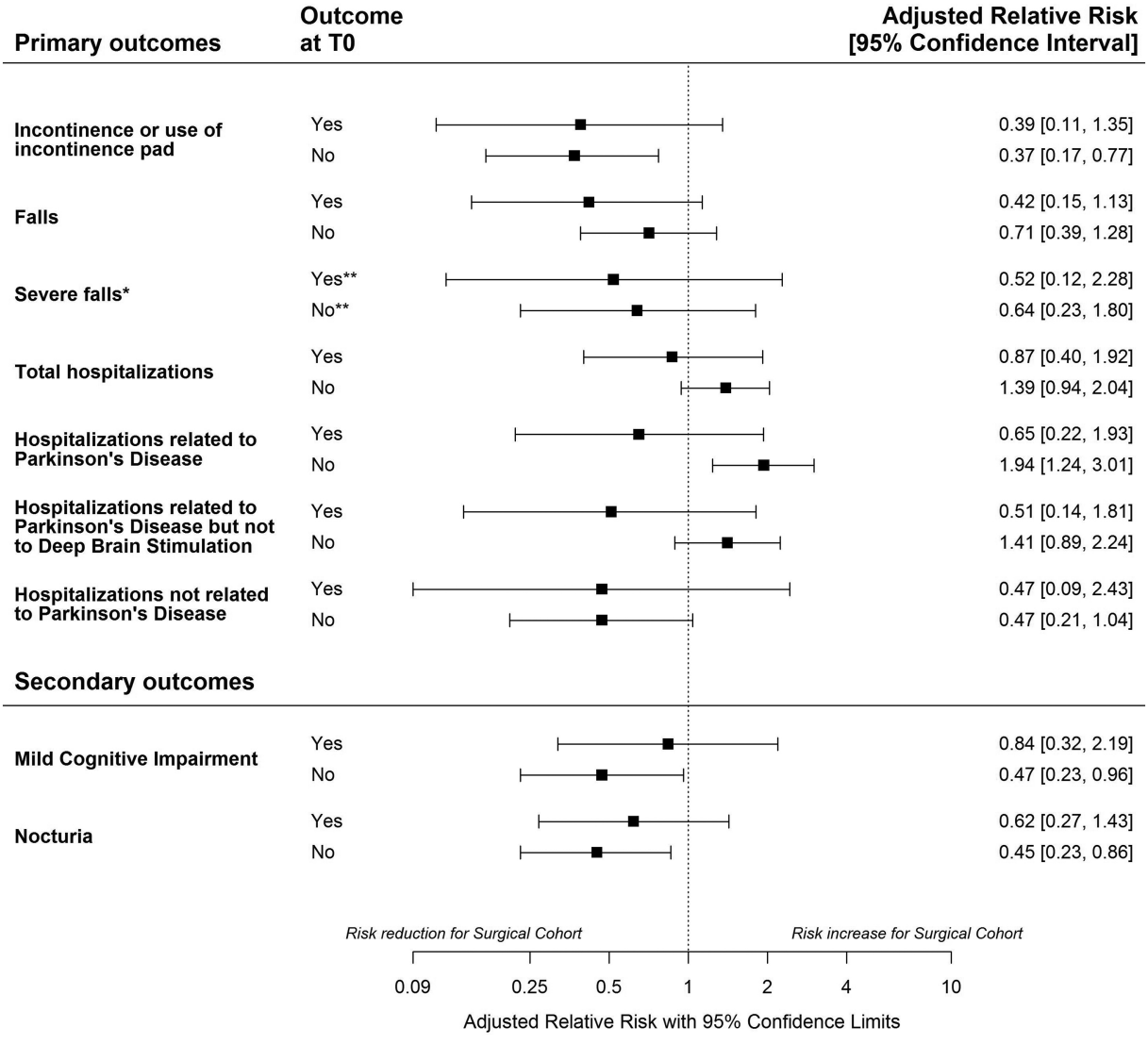

Figure 2