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REVIEW ARTICLE

Sacral neuromodulation and sexual function: a systematic review and meta-analysis of the literature

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Abstract

Introduction and hypothesis Sexual function is being increasingly recognized as an important patient-reported outcome. Sacral neuromodulation (SNM) is a treatment with an expanding list of indications. The effect of sacral neuromodulation on sexual function has been examined in a number of studies with variable results. In this review, we aim to systematically review the literature and pool the data if appropriate.

Methods The literature search was conducted primarily on the Healthcare Databases Advanced Search (HDAS) platform using the Medline, EMBASE and CINHAL search engines. Of 196 initial citations, 17 articles met our predefined inclusion criteria. Thirteen studies reported enough information to be included in our meta-analysis. RevMan5 software was used for analysis.

Results Eight of 17 studies reported a positive effect of SNM on sexual function. Pooled analysis of data from 11 studies involving 573 patients before SNM and 438 patients after SNM showed significant improvement in sexual function (SMD = −0.39; 95% CI: −0.58 to −0.19; $p = 0.0001$). The results remained significant in most subgroup analyses except in patients suffering from fecal incontinence.

Conclusions SNM in women with pelvic floor disorders, especially bladder dysfunction, seems to have a positive effect on sexual function. This needs to be verified in adequately powered primary research using sexual function as the primary outcome.

Keywords Sacral nerve stimulation · Sacral neuromodulation · Sex

Introduction

The World Health Organization defined sexual health as the physical, emotional, mental and social well-being of people in relation to sexuality [1]. Community studies estimate the prevalence of sexual dysfunction to be 25–63% [2]. This high prevalence was challenged in an epidemiological survey of 1489 women [3]. The authors employed clear previously published criteria for diagnosing sexual dysfunction, only allowing the diagnosis if the total symptoms score crossed a pre-defined threshold in a validated questionnaire, the Female Sexual Function Index (FSFI) [4], and caused distress beyond a predefined threshold according to a validated tool, the Female Sexual Distress Scale [5]. The prevalence of female sexual dysfunction (FSD) according to this strict definition was reported to be 5.8% (point prevalence: within the last 4 weeks) and 15.5% (life-time prevalence). FSD is common in women who have functional urinary or bowel problems such as incontinence or emptying disorders [6, 7]. An epidemiological survey in the USA found a significant association between the presence of urinary tract symptoms and arousal disorders and sexual pain, but not with low desire [2]. Another cross-sectional study of 2269 women found that 24% had fecal incontinence and that fecal incontinence was significantly associated with low sexual desire, difficulty with lubrication, difficulty with orgasm and pain/discomfort with intercourse. However, the frequency of sexual activity was not affected [8]. Advances in healthcare and changes in sexual attitudes have helped women remain sexually interested and active until late in life [9] when pelvic floor dysfunction is common. Traditionally sexual function did not receive academic attention similar to physical or psychological disorders [10], but as its impact on quality of life [3] and as its financial burden [11] became appreciated, attention turned to the effect

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of various treatments, including SNM, on sexual function. Indeed there are three published reviews on this topic. In 2010 a non-systematic review of SNM for Interstitial Cystitis/Painful Bladder Syndrome, chronic pelvic pain and sexual dysfunction found three studies that reported on the effect of SNM on female sexual function. The methodology of the review was not described. A brief summary of the studies was presented, and there was no conclusion [12]. In 2014 a systematic review of the literature regarding sacral neuromodulation and female sexuality was reported [13]. The methodology of the review followed the PRISMA statement [14]. It included ten studies in its qualitative synthesis, but did not perform a meta-analysis. It cited heterogeneity of the populations studied, the several types of pelvic floor dysfunction included and the numerous outcome measures used as reasons for not doing a meta-analysis. The review concluded that the data were insufficient to ascertain a positive effect of SNM on sexual function. In 2016, another review identified ten articles. The authors stated that a meta-analysis would be challenging because of heterogeneous populations, differences in technique and variability in reporting outcomes. Sexual function was not mentioned in its conclusion [15]. Some studies have not been included in these reviews, and others have been published since then. Heterogeneity in the types of pelvic floor dysfunction is a valid reason for not performing a meta-analysis, but if the association between various pelvic floor disorders and FSD is due to a common factor such as avoidance behavior or pelvic floor spasm, then the population becomes homogeneous from the sexual function viewpoint. Also, variability in measuring sexual function can be overcome by using standardized mean difference and subgroup meta-analysis. We therefore aimed to do an up-to-date systematic review of the effect of SNM on sexual function in female patients with functional pelvic floor disorders and to explore the possibility of performing a meta-analysis.

Materials and methods

This systematic review was carried out according to the PRISMA statement [14]. Ethical approval was not necessary. All the studies included were published in peer-reviewed journals or conference proceedings. A review protocol was designed a priori. The literature search was initially conducted in December 2016 and then finally updated in February 2018. The Healthcare Databases Advanced Search platform was used to conduct Medline, EMBASE and CINHAL searches. The following terms were used to conduct the searches: "sacral" and "sex*" and "neuro?modulation" or "nerve*stimulation." The only limitation used was "human." Case reports were excluded. References were hand-searched for potential additional articles. The academic publications section of Medtronic (Medtronic Minneapolis, MN, USA), the main company that manufactured a licensed device for SNM for bowel and bladder disorders at the time of the initial search, provided a list of publications, upon request, free of charge, but had no further input into the review (personal communications). Authors were contacted for further information where necessary. If there was no reply from the corresponding or senior author after two attempts, a decision was made to include or exclude the study based on the information available. Regarding studies reported in more than one conference abstract or publication by the same group, we used the most complete data set reported or supplied.

Selection criteria

We included in our systematic review the studies that met the following criteria:

1. Types of studies:

Prospective studies that examined female sexual function after sacral SNM treatment with a permanent device and compared it with what it was before treatment (before-after studies) or to a control group who did not undergo SNM (prospective controlled studies). The presence of two measurements of sexual function in each study was an essential criterion, whether these measurements were sequential (before-after studies) or parallel (controlled studies).

2. Types of participants:

Adult female patients who have undergone SNM treatment with a permanent implant for a functional bladder or bowel problem (problems with incontinence or emptying), but not exclusively or primarily for pain. Studies in which SNM was used predominantly to control pain were excluded.

3. Types of intervention:

The intervention studied is permanent SNM implant via an implantable programmable device rather than stimulation transcutaneously or percutaneously. Studies with variation of the neuromodulation technique of the nerve routes S2–4 were allowed if the majority of the patients had a lead implanted in the sacrum rather than peripherally, but a sensitivity analysis was done to explore the effect of excluding these studies.

4. Types of outcome:

Sexual function at least 3 months after treatment. This was measured by a sexual function tool or a questionnaire. The total score from the tool (where appropriate) was used to calculate our primary outcome (sexual function). For secondary

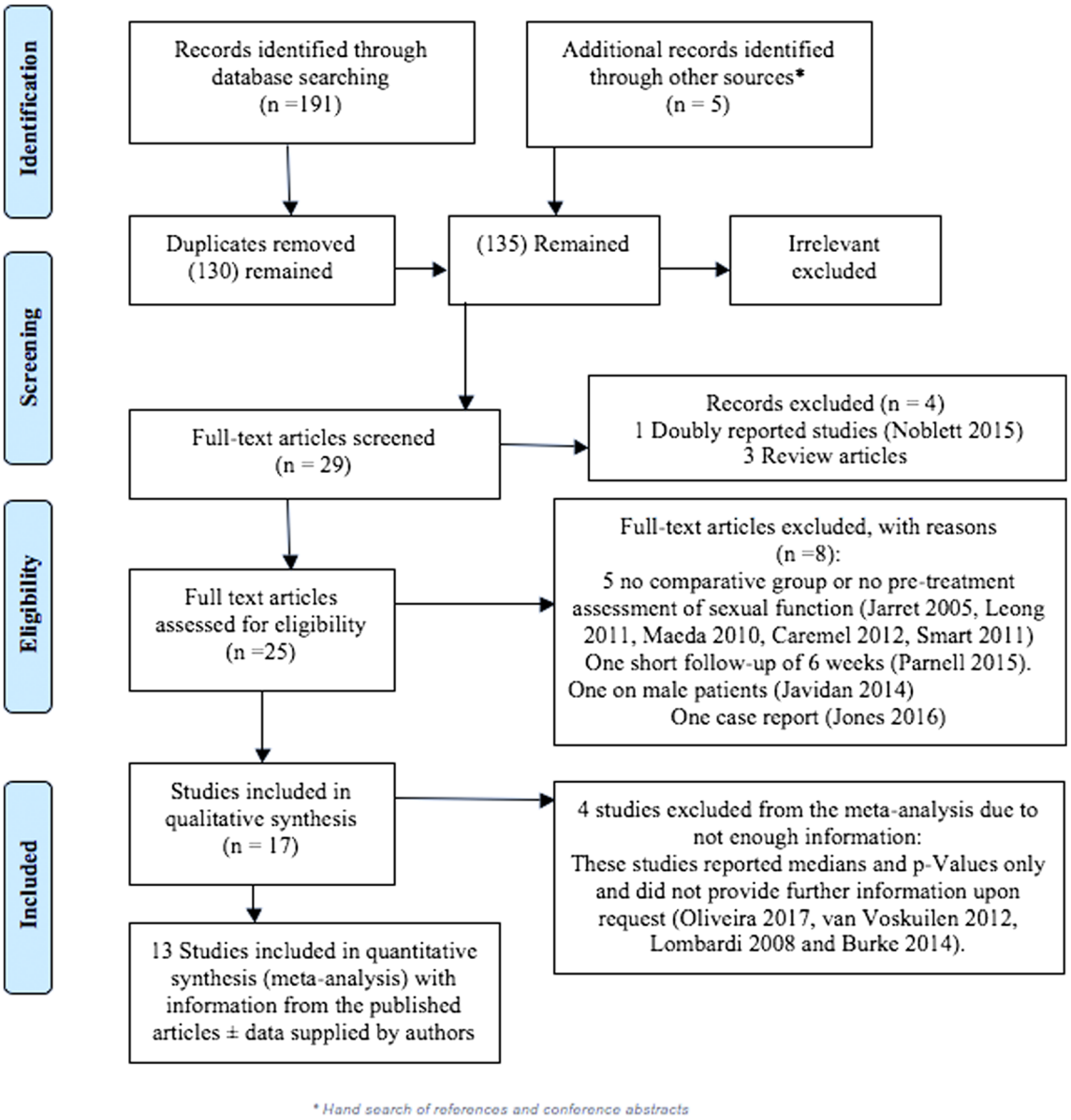

Fig. 1 PRISMA diagram

outcomes, a separate analysis is presented for specific components of sexual function. Studies that used tools with a score (continuous outcomes) were analyzed separately from studies that used a categorical outcome. Validated questionnaires were presented separately in subgroup analysis.

Data collection and quality assessment

Data collection was done using a tool based on the Cochrane consumers and communication review group's data extraction template. The tool was modified to suit the design of the majority of our selected studies (before-after design).

We used a tool on the National Heart, Lung and Blood Institute website (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after) with permission (personal communications) to assess the quality of the before-after studies, but we had to modify it to better suit the selected articles and designed a quality score based on the modified tool. The quality score tool was based on the following criteria:

1. Size of the cohort in the study with complete data (studies with ≥ 20 participants got a score of 1, while those with < 20 participants got a score of 0).
2. The tool used for sexual function assessment (studies that used a tool with a high level of validation got a score of 1, while studies that used a tool that did not have a high level of validation for measuring sexual function got a score of 0).

Table 1 Screened studies with reason of exclusion if applicable

Study	Included in the systematic review	Included in the meta-analysis	Reason for exclusion/ inclusion
Jarrett et al. 2005 [16]	No	No	Only retrospectively reported on change in sexual function. Did not compare measurements between two different time points or two different groups
Pauls et al. 2007 [17]	Yes	Yes	Raw data supplied by the author allowing fresh analysis
Zabihi et al. 2008 [18]	Yes	Yes	No reply from author to data enquiry, but RevMan calculator was used to estimate standard deviation from *p* value for difference in mean This study used a variation in the procedure technique (bilateral caudal epidural SNM) and therefore was excluded in the planned sensitivity analysis
Ferhi et al. 2008 [19]	Yes	Yes	Author replied to data query. No further data supplied; however study had enough information to be included in the data synthesis
Lombardi et al. 2008 [20]	Yes	No	No means reported, only medians. Only reported selectively on responders beyond 3 months. No reply from corresponding author to data query
Ingber et al. 2009 [21]	Yes	Yes	
Maeda et al. 2010 [22]	No	No	Only retrospectively reported on change in sexual function. Did not compare measurements between two different time points or two different groups
Signorello et al. 2011 [23]	Yes	Yes	
Gill et al. 2011 [24]	Yes	Yes	Raw data supplied by the author to allow analysis
Leong et al. 2011 [25]	No	No	Only retrospectively reported on change in sexual function. Did not compare measurements between two different time points or two different groups
Smart et al. 2011 [26]	No	No	No reply from first author. Reply from senior author, but no data provided. Appears to be an assessment at one time point
Caremel et al. 2012 [27]	No	No	No reply to data query. Did not report before and after scores, just reported percentage change in sexual function
Van Voskuilen et al. 2012 [28]	Yes	No	No means reported, only medians. No reply from the corresponding author to data query
Altaf et al. 2013 [29]	Yes	Yes	Further data supplied by senior author for fresh analysis
Jadav et al. 2013 [30]	Yes	Yes	
Yih et al. 2013 [31]	Yes This study was split into: Yih 1: 52 patients with FSFI score < 26 before intervention and Yih 2: 15 patients with FSFI ≥ 26 before intervention. The data were reported in this way for the preferred 6-month follow-up outcome		This study was included in the data synthesis although 36/152 in Yih 1 and 2/15 in Yih 2 had neuromodulation through a pudendal nerve lead*. It was excluded in the planned subgroup analysis
Banakhar et al. 2014. [32]	Yes	Yes	
Burke et al. 2014 [33]	Yes	No	No means reported, only medians. No reply from first author. Reply from senior author, but no data provided
Javidan et al. 2014 [34]	No	No	Excluded as it is a correspondence letter reporting on male patients
Gill-Sousa et al., 2014 [35]	Yes	Yes	
Parnell et al. 2015 [36]	No	No	Excluded as follow-up at 6 weeks only
Jones et al. 2016 [37]	No	No	Case report
Siegel et al. 2016 [38] same as [39]	Yes	Yes	Further data supplied by author upon query
Rydningen et al. 2017 [40]	Yes	Yes	Author supplied unpublished data upon query
Oliveira et al. 2017 [41]	Yes	No	No means reported, only medians. Only reported as an abstract so could not find contact details for corresponding author

3. Follow-up: We felt that the best time for follow-up would be 6–12 months after treatment as this would allow enough time for the effect of SNM on bladder or bowel function to stabilize in case re-programming was required to start with. Also, it is not too long to risk the introduction of other confounding factors in relation to sexual function, such as relationship matters. Therefore, studies that reported on follow-up within 6–12 months post SNM got a score of 1, while studies that reported on follow-up outside this time frame got a score of 0.
4. The presence of an independent control group in the study: studies that compared their cohort with a separate,

Table 2 Population characteristics for studies included in the systematic review

Population characteristics Study	Number of participants at the outset of the study	Participants with completed questionnaires before and after SNM	Age: mean (median)	Age range	Type of pelvic floor problem		
					Number with bladder problems (Neurogenic/ non- neurogenic)	Number with bowel problems	Number with pain
Pauls et al. [17]*	13	7	50	28–75	7	0	0
Ferhi et al. [19]*	41	37	53	?	37	0	0
Lombardi et al. [20]	33	31	37.6 for the 33 patients 38.45 for the 31 patients	23–48	31 (17/14)	0	0
Zabihi et al. [18]*	36	36	49.5	20–81	15	0	21
Ingber et al. [21]*	105	21	50	24–70	13 overactive bladder	?	12 pain plus frequency and urgency
Signorello et al. [23]*	30	12	62 (53) for the 30 patients	35–79	16 6/10	0	0
Gill et al. [24]*	33	8	(58.5) for 33 patients 53.5 (54) for 8 patients	48.3–66	8 3/5	0	0
Altaf et al. [29]*	22	6	51.6	37–77	2	4	0
van Vouskuilen et al. [28]	10	8	53.5	21–61	7	1	0
Yih et al. (a) [31]*	152	82	54	?	105	0	46
Yih et al. (b) [31]*	15	7	51	?	12	0	3
Jadav et al. [30]*	61	35	56.5 for 43 patients	?	All had bladder symptoms, but SNM was done for fecal incontinence	All	0
Banakhar et al. [32]*	33	23	51	21–71	23	0	0
Burke et al. [33]	22	8	55	34–74		All	
Gil-Sousa et al. [35]*	14 (both males and females)	12 (females)	54 (for the 14 patients)	39–82 (for the 14 patients)	12 3–5 with neurological disease	0	0
Siegel et al. [38]*	272 (91% females)	189 (all females) (57.4%)	57 for total 272 of both genders	?	All of them	0	0
Rydningen et al. [40]*	65	30 (in the SNM arm)	58.5	25–74 (for the original 65)	27/30 concomitant bladder symptoms	All 30	0
Oliveira et al. [41]	24 (both males and females)	15 (females)	41 (for the 24 patients)	26–72 (for the 24 patients)	23/24	1/24	

Studies included in the meta-analysis are marked with *

Table 3 Characteristics of studies included in the systematic review

Study	Study type	Numbers included	Tools used	Mean follow-up in months (median)	Mean before Mean after§ (Median before Median after) [Percentage before Percentage after in categorical data)	Standard deviation (or another spread measure)	*P* value	Further information obtained form author
Pauls et al. [17]*	Before-after	7	FSFI	5.7	20.742 30.228	4.283 3.244	0.002	Yes, authors provided data to allow fresh analysis
Ferhi et al. [19]*	Before-after	41	Questionnaire with yes/ no categorical answer to problem with sex	34 (?)	14/37 (37.8%) 5/37 (13.5%)			No
Lombardi et al. [20]	Before-after	31	FSFI	3 (3)	Neurogenic VD in 11 (22.7 26.02) Idiopathic VD in 8 (24.2 26.5)		0.018 0.024	No
Zabihi et al. [18]*	Before-after	36	FSFI	6 (6)	12 18.2	13.18 13.18	0.05	No
Ingber et al. [21]*	Before-after	21	FSFI	6 (6)	18.67 20.97	6.8 6	0.220	NA
Signorello et al. [23]*	Before-after	12	FSFI	(36.3)	18.4 22.7	4.8 4.5	0.012	NA
Gill et al. [24]*	Before-after	8	FSFI (+ FSHQ)	(3.2)	21.862 24.725 (Median = 22.6) (Median = 25.8)	5.119 5.388	0.018 (0.023)	Yes, authors supplied raw data allowing fresh analysis
Altaf et al. [29]*	Before-after	6	e-PAQ	19.8	40.33 38.83	37.89 37.99	0.9468	Yes, supplied raw data allowing fresh analysis
van Vouskuilen et al. [28]	Before-after	8	QSD (+ SCL-90 McGill-Mah Orgasm Q GRISS, MMQ)	?	(11.42) (13.65)	(Range 7.53 55.47)	0.959	No
Yih et al. (a). [31]*	Before-after	152	FSFI (+ICSI-PI GRA)	6 (6)	12 16	7.6 9	0.004@	No
Yih et al. (b) [31]*	Before-after	15	FSFI (+ICSI-PI GRA)	6 (6)	27 23	1 7.8	0.0584@	No
Jadav et al. [30]*	Before-after	35	e-PAQ	(6.8)	38.8	30.4	NS	NA

Table 3 (continued)

Study	Study type	Numbers included	Tools used	Mean follow-up in months (median)	Mean before Mean after§ (Median before Median after) [Percentage before Percentage after in categorical data)	Standard deviation (or another spread measure)	*P* value	Further information obtained form author
Banakhar et al. [32]*	Before-after	23	FSFI	4	32.8 15.49 18.33	34.2 9 10.96	0.011	NA
Burke et al. [33]	Before-after	8	FSFI FSDS	? (18)	(12.7) (8.6)		0.345	No
Gil-Sousa et al. [35]*	Before-after	12	FSFI	?	13.5 19.3	11.7 13.5	0.032	Yes
Siegel et al. [38]*	RCT, but sexual function is reported on in a before-after manner	242 before 189 after	FLUTSsex	36 (36)	6.3 4.8	4.1 2.9	< 0.00-01	Supplementary unpublished results supplied by authors
Rydningen et al. [40]*	RCT, but data used from one arm of the RCT and analyzed in a before-after manner in the meta-analysis	30	Questionnaire with yes/ no categorical answer to sexual complaints before and after intervention	6 (6)	Sexual complaints were present in the SNM arm of the RCT ion: Before 14/19 (73.6%) After: 5/16 (31.25%)		0.012	Supplementary unpublished data supplied
Oliveira et al. [41]	Before-after	15	FSFI		Median Before 24.1 After 26.3	IQR 20.3–30.2 23.5–30.4	?	Could not contact author as only published as abstract

Studies included in the meta-analysis are marked with *. RCT: randomized controlled trial, NA: not applicable. FSFI: female sexual function index, ePAQ: electronic pelvic floor assessment questionnaire. FSHQ: female sexual health questionnaire. QSD: questionnaire for screening for sexual dysfunction. GRISS: Golombok Rust Inventory of sexual satisfaction. SCL-90: symptom checklist 90. MMQ: Maudsley marital questionnaire. FSDS: female sexual distress scale. NS: not statistically significant. §: Total score for FSFI, FLUTSsex or general sex life for ePAQ (higher score in e-PAQ, FLUTSsex and QDS indicates worse sexual function, while a higher score in FSFI indicates better sexual function). @: Not provided in the article, but calculated from mean and standard deviation

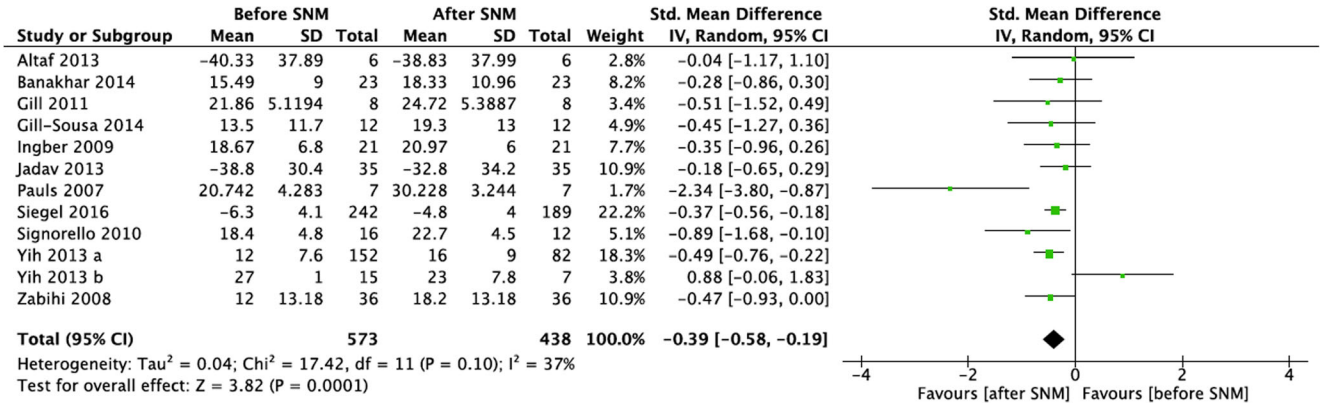

Fig. 2 Effect of sacral neuromodulation on sexual function in all studies with continuous outcome measures

independent, control group were allocated a score of 1, while studies that compared the sexual function of the cohort after SNM to before SNM (before-after studies) got a score of 0.

5. Lost to follow-up percentage (≥ 20% versus < 20%): studies in which ≥ 80% of participants with baseline data completed the follow-up questionnaire and had follow-up data got a score of 1, while those in which < 80% of the participants had follow-up data got a score of 0.

The first author extracted the data and the senior author doubled checked the extraction. Disagreements were resolved by discussion. Review Manager software (RevMan) version 5.3 (*Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014)* was used for the meta-analysis. When pooling figures from questionnaires that measure sexual function in opposite directions, figures from one questionnaire (the less frequently used one) were multiplied by −1 to allow pooling the data. Heterogeneity was tested for using the I^2 test. A value of ≥ 60 was considered indicative of significant heterogeneity. The random effect model was used throughout to accommodate the potential effect of other factors on sexual function. Results were expressed as standardized mean difference (SMD) and 95% confidence interval (CI) to allow pooling data from different questionnaires in studies that reported continuous outcomes. Results were expressed as odds ratios (ORs) and 95% CI when pooling data from studies that reported dichotomous outcomes. RevMan 5.3 was used to calculate the standard deviation value if it was not provided in the article. Stata statistical software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) was used to calculate any required output from primary research when raw data were provided by the authors.

Results

The PRISMA diagram (Fig. 1) summarizes the results of the literature search. Twenty-five studies were assessed for eligibility (Table 1) of which 17 met our inclusion criteria. Table 2 summarizes the population characteristics of the 17 studies, and Table 3 summarizes their results. Eight studies indicated a positive effect of SNM on sexual function. Four studies reported only medians rather than means; therefore, only 13 of the 17 studies were included in the meta-analysis. Eleven of the 13 studies used continuous outcome measures and therefore were pooled together; 10 of the 11 were before-after studies and 1 was a randomized controlled trial (RCT), but the RCT reported on sexual function in a before-after manner. Two of the 13 studies used categorical outcome measures; one was a before-after study and one was an RCT. The RCT reported enough data to allow before-after analysis for the SNM arm in the study, which was used for consistency and to allow pooling of the data with the other study.

Meta-analysis results for the primary outcome

The 11 studies in the meta-analysis that reported on continuous outcome measures included eight studies that reported on the total FSFI score, two studies that reported the score of

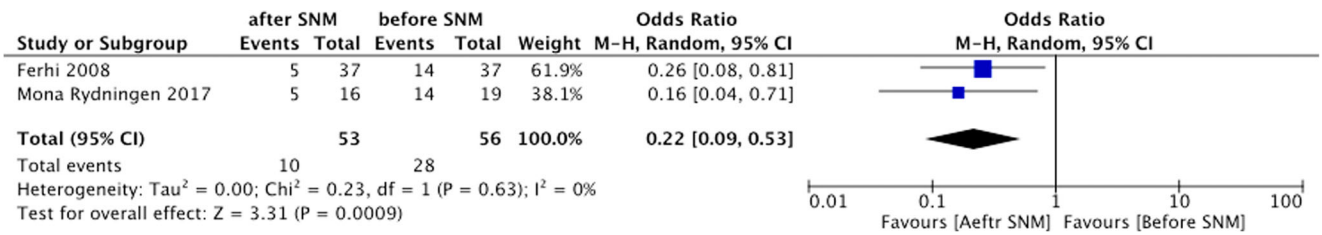

Fig. 3 Effect of sacral neuromodulation on sexual function in studies with dichotomous outcome measures

Table 4 Quality assessment tool for the studies included in the meta-analysis (score ≥ 3 out of 5 = high quality)

Quality indicator Study	Size of contribution to the meta analysis: ≥ 20 = 1 < 20 = 0	Comparison group: Concurrent control = 1 Historic = 0	Level of validation of measurement tool: High =1 Not high = 0	Questionnaire completion rate (100-lost to follow-up) ≥ 80% = 1 < 80% = 0	Length of follow-up: 6–12 months = 1 Outside 6–12 months = 0	Total score
Pauls et al. [17]	7 = 0	Historic = 0	1	7/7 = 100% = 1	5.7 months = 0	2
Zabihi et al. [18]	36 = 1	Historic = 0	1	36/36 = 100% = 1	6 = 1	4
Ingber et al. [21]	21 = 1	Historic = 0	1	21/27 = 77.7% = 0	6 months = 1	3
Signorello et al. [23]	12 = 0	Historic = 0	1	12/16 = 75% = 0	36.3 months = 0	1
Gill et al. [24]	8 = 0	Historic = 0	1	8/8 = 100% = 1	3.2 months = 0 (Median 3.7)	2
Altaf et al. [29]	6 = 0	Historic = 0	0	6/6 = 100% = 1	19.8 months = 0	1
Jadav et al. [30]	35 = 1	Historic = 0	0	35/35 = 100% =1	6.8 months = 1	3
Yih et al. (a) [31]	152 = 1	Historic = 0	1	82/152 = 53.9% = 0	6 months = 1	3
Yih et al. (b) [31]	15 = 0	Historic = 0	1	7/15 = 46.6% = 0	6 months = 1	2
Banakhar at al. [32]	23 = 1	Historic = 0	1	100% = 1	4 months = 0	3
Gil-Sousa et al. [35]	12 = 0	Historic = 0	1	1	? =0	2
Siegel et al. [38]	242 = 1	Historic = 0	1	189/242 = 78.09% = 0	36 months = 0	2

"general sex life" of the electronic Pelvic Assessment Questionnaire (ePAQ) and one study that reported the total score of the Female Lower Urinary Tract Symptoms-sex questionnaire (FLUTSsex). There were data from 573 female patients before SNM and from 438 patients after SNM. Meta-analysis showed that SNM resulted in a significant improvement in the sexual function standardized mean difference (SMD) of −0.39; 95% CI: −0.58 to −0.19; $p = 0.0001$ (Fig. 2). Heterogeneity was assessed using I^2, which was 37%. The other two studies reported on sexual function using categorical outcomes from 56 female patients before SNM and from 53 female patients after SNM. There was a significant reduction in sexual complaints with an odds ratio (OR) of 0.22 (0.09, 0.53); $p = 0.0009$; $I^2 = 0\%$ (Fig. 3). In subgroup analyses, the positive effect of SNM on sexual function remained significant when only the top five high-quality studies with a quality score ≥ 3 were included (Table 4): SMD = −0.40 (−0.59, −0.21); $p < 0.0001$; $I^2 = 0\%$. It also remained significant when the three studies with neuropathic patients [23, 24, 35] were excluded: SMD = −0.34 (−0.57, −0.11); $p = 0.004$; $I^2 = 49\%$, and it remained significant when the three studies with patients suffering from pain [18, 21, 31] were excluded: SMD = −0.42 (−0.68, −0.17); $p = 0.001$, $I^2 = 28\%$. The positive effect of SNM on sexual function remained significant when the two studies that used a modified technique for neuromodulation [18, 31] were excluded: SMD = −0.40 (−0.62, −0.19); $p = 0.0002$; $I^2 = 18\%$; and when the four studies that declared industry sponsorship or relations [18, 21, 31, 38] were excluded: SMD = −0.49 (−0.88, −0.11); $p = 0.01$; $I^2 = 38\%$. When the three studies in which mean patient age was < 51 years [17, 18, 21] were analyzed separately, there was a strong trend for improvement in sexual function: SMD = −0.75 (−1.49, 0.00); $p = 0.05$; $I^2 = 68\%$. The nine studies in which SNM was done primarily for urinary indications retained a positive effect on sexual function when analyzed separately: SMD = −0.42 (−0.65, −0.20); $p = 0.0003$; $I^2 = 44\%$ (Fig. 4), while the two studies in which SNM was done primarily for fecal incontinence [29, 30] did not: SMD =

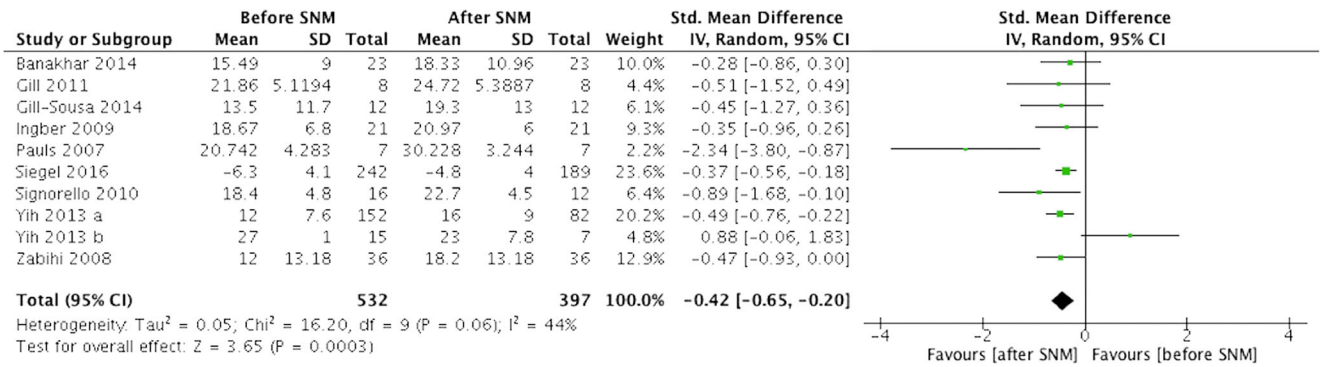

Fig. 4 Effect of sacral neuromodulation done for urinary indications on sexual function in all studies with continuous outcome measures

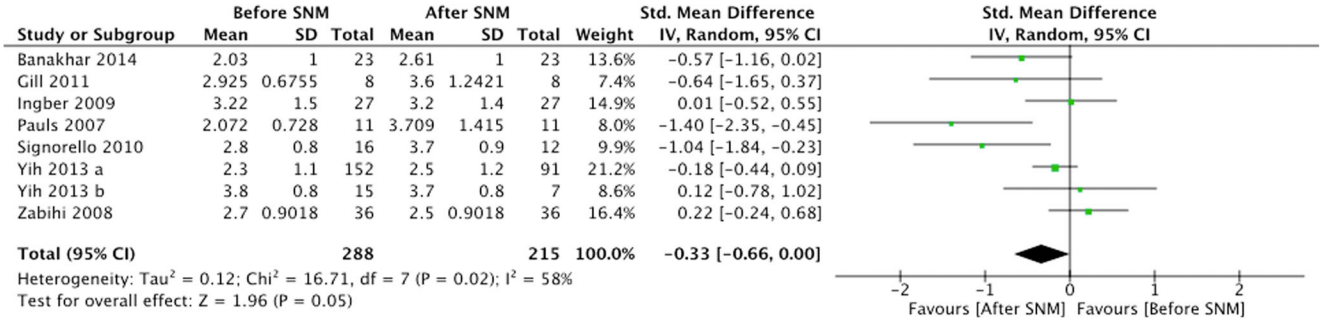

Fig. 5 Effect of sacral neuromodulation on desire as measured by the Female Sexual Function Index

−0.16 (−0.60, 0.27); $p = 0.46$; $I^2 = 0\%$. The latter two studies were the only ones that used the ePAQ tool. Eight studies used FSFI and retained a positive effect of SNM on sexual function when analyzed separately: SMD = −0.44 (−0.75, −0.14); $p = 0.004$; $I^2 = 49\%$. One study used FLUTSsex and showed a positive effect of SNM on sexual function when analyzed by itself: SMD = −0.37 (−0.56, −0.18); $p = 0.0002$ [38].

Meta-analysis for secondary outcomes

In our secondary outcomes analyses, we examined changes in components of sexual function as per the Female Sexual Function Index (FSFI): There was a strong trend toward improvement in desire after SNM (Fig. 5). There was a significant improvement in arousal (Fig. 6), satisfaction (Fig. 7) and pain (Fig. 8), but not in lubrication (Fig. 9) or orgasm (Fig. 10). We also examined individual components of the ePAQ tool; the effect of bladder symptoms on sexual function did not change after SNM (SMD = 0.04; −0.40 to 0.47; $p = 0.87$; $I^2 = 0\%$), the effect of bowel symptoms on sexual function did not change significantly after SNM (SMD = 0.38; −0.06 to 0.82; $p = 0.09$; $I^2 = 0\%$), the effect of vaginal symptoms on sexual function did not change significantly after SNM (SMD = 0.05; −0.80 to 0.91; $p = 0.90$; $I^2 = 53\%$), and the effect of dyspareunia on sexual function did not change significantly after SNM (SMD = 0.03; −0.41 to 0.46; p = 0.90; $I^2 = 0\%$).

Discussion

Our systematic review suggests that sexual function improves in patients undergoing SNM treatment for functional bladder disorders. These findings complement those from previous reviews [12, 13, 15], which recommended further research into this area. We agree that further high-quality research into this area with sexual function as the primary outcome is warranted, but as the number of studies in our review (17 studies) is larger than the number of studies in the other reviews (3, 10 and 10 studies, respectively), and as we were able to obtain raw data from a number of authors and to perform a meta-analysis, we feel that the finding of a positive effect of SNM on sexual function in patients with urinary disorders is a valid one.

The issue of whether the improvement in sexual function is entirely due to the resolution of a functional bladder disorder or due to a direct effect of SNM on sexual function needs further examination. We know from previous studies that other treatments of urinary incontinence do improve sexual function. A systematic review of 21 studies suggested that the improvement in sexual function following surgery for stress urinary incontinence was primarily due to a reduction in coital incontinence [42]. Regarding urge urinary incontinence, many studies showed an improvement in sexual function following medical treatment [43]. This improvement was associated with a reduction in coital incontinence as well [44]. Regarding SNM, four studies examined the correlation between improvement in bladder/bowel function with SNM

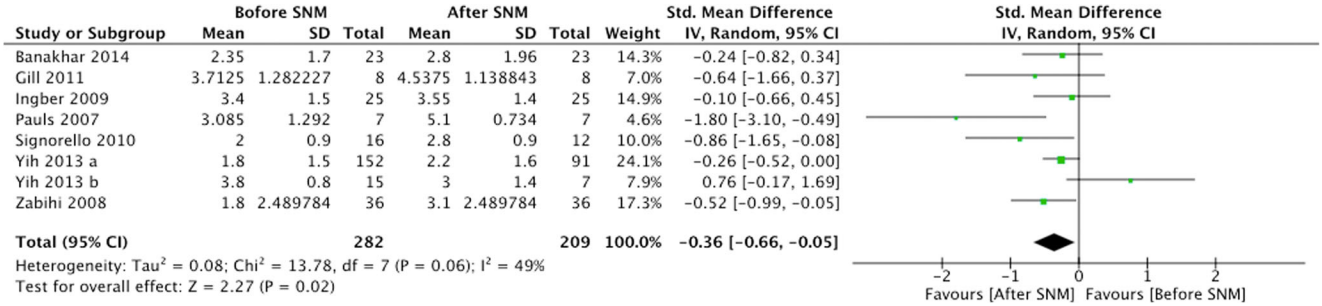

Fig. 6 Effect of sacral neuromodulation on arousal as measured by the Female Sexual Function Index

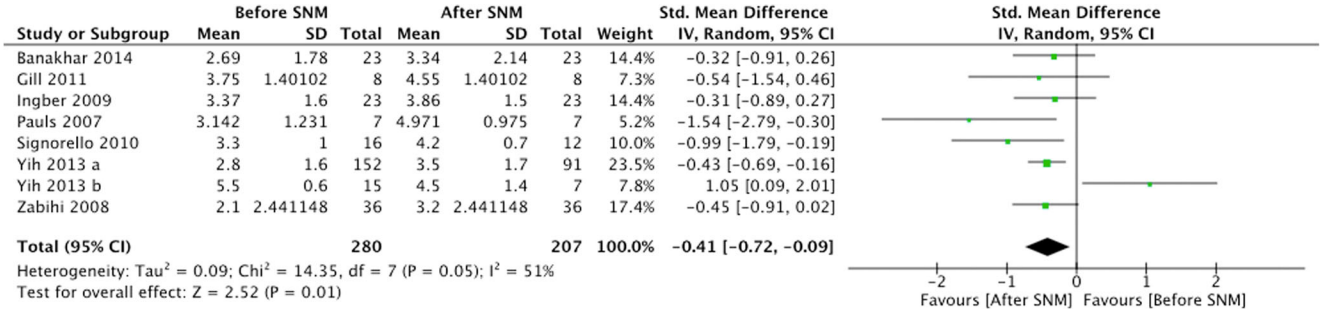

Fig. 7 Effect of sacral neuromodulation on satisfaction as measured by the Female Sexual Function Index

and improvement in sexual function. Banakhar et al. [32] reported on 23 patients who had SNM for bladder-related problems and found no significant correlation between improvements in bladder function and sexual function. Pauls et al. [17] also reported on 11 patients who had SNM treatment for bladder dysfunction and found no correlation between improvement in bladder function and sexual function. Similarly, Ingber et al. [21] found no correlation between changes in voiding diary parameters and changes in FSFI score in 21 patients; however, this study, contrary to the previous two, did not demonstrate an improvement in sexual function with SNM. The only study that suggested a significant correlation between changes in urinary frequency and voided volume and changes in FSFI was by Signorello et al. [23]. Only 12 patients in this study had complete follow-up data, of 16 eligible patients at its start, which undermines the strength of their findings. Therefore, the proposition that improvement in sexual function with SNM is, at least partly, independent from improvement in bladder function is plausible. Incontinence can lead to dryness in the lower vagina and vulva due to repeated cleansing and drying of the area. So, if the effect of SNM on sexual function was mediated entirely through its effect on continence, an associated improvement in lubrication would be expected. However, when the categories of the FSFI questionnaire were examined individually, lubrication and orgasm were not significantly affected by SNM. Furthermore, the ePAQ tool is designed with the ability to look for the impact of changes in bladder or bowel function on sexual function, and it did not find any in the two studies where it was used. It is important to point out though that ePAQ is not validated to a high level for assessment of sexual function and bowel function. Also, the number of patients in these two studies combined was only 41. It is, therefore, important to interpret the subgroup analysis of the two studies that used the ePAQ tool with caution. The potential explanation for a direct effect of SNM on sexual function could be through modulating neuronal activity at S3–4, which in turn affects the neuronal activity of the pudendal nerve. The latter plays a major role in the sexual experience.

It is important to note that our study has limitations. A meta-analysis is only as good as the studies included in it. As the majority of the studies were before-after studies with small numbers and high lost to follow-up rates, the results from these studies—and therefore from our meta-analysis—have to be treated cautiously. Another valid criticism is the way we designed our quality score. This rendered the largest study [38] ineligible for inclusion in the subgroup analysis of high-quality studies. However, we are reassured that our quality score is robust because the I^2 test for heterogeneity reported a value of 0% for the subgroup of five high-quality studies. Also, we are reassured that our finding of a positive effect of SNM on sexual function is a genuine one as it remained significant throughout most of the subgroup analyses we undertook. It could be argued that while using the standardized mean difference was appropriate when pooling data from different tools, it would have been more accurate to use the mean difference in the subgroup analysis when data from the same tool were pooled together. The reason we used the SMD all

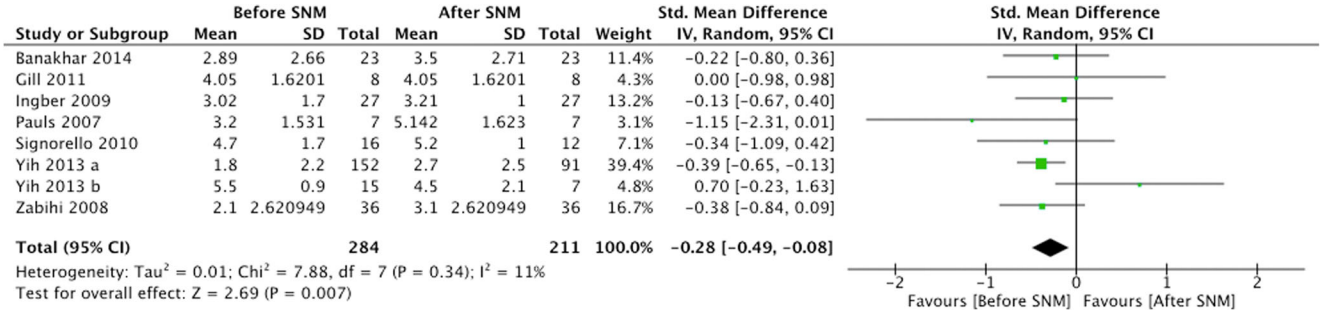

Fig. 8 Effect of sacral neuromodulation on pain as measured by the Female Sexual Function Index

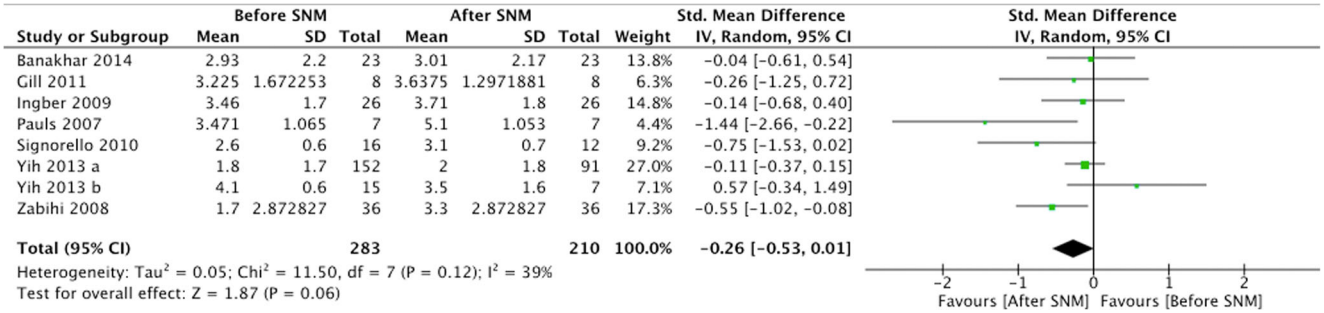

Fig. 9 Effect of sacral neuromodulation on lubrication as measured by the Female Sexual Function Index

the way through is to provide consistency with the primary outcome, as the effect size tends to be smaller with the SMD compared with the mean difference.

We do not believe including the four studies from which we did not have enough information to include in the meta-analysis would have changed the final results. One was a medium-size study (31 patients) with a positive effect of SNM on sexual function [20], and three were small studies [28, 33, 41]. We do not think publication bias is likely to have a significant effect on our results as many of the published studies are small in size with negative findings. We may be criticized for doing a meta-analysis in a potentially heterogeneous population, but the populations in our study, despite having variable pelvic floor disorders, may well have a universal cause for sexual dysfunction, whether this is avoidance behavior or imbalance in the neurological supply to the pelvis. The latter can lead to a spastic pelvic floor, manifesting as dyspareunia as well as functional bladder or bowel disorders. Ultimately, in many situations, as in our review, the decision to perform a meta-analysis is not exact science, but is subject to reasoning. For our primary outcome, the I^2 score was 37%, indicating low-to-moderate excess variance. This supports pooling the data on the one hand, but also justifies doing subgroup analysis on the other.

The mechanism of action of SNM is not fully understood, but the majority of the evidence supports the view that it works on the afferent pathway [45]. Evidence also suggests that SNM induces changes at higher cortical levels [46]. Therefore, the improvement in sexual function could arguably be taking place at the cortical level mediated by stimulation of the afferent pathways from the genital area by SNM. This hypothesis needs testing in primary studies by studying the effect of SNM treatment on women with sexual dysfunction without functional bladder or bowel problems. One advantage of using the random effect model is that the findings could potentially be generalizable more readily than in the fixed effect model. In other words, if SNM was found to improve sexual function in women with pelvic floor disorders, according to a random effect model, then it could be argued that a similar beneficial treatment effect could be expected in women with sexual dysfunction—such as vaginismus—but no pelvic floor dysfunction. If the latter were proven, the proposition that SNM may enhance sexual function in women without sexual dysfunction would become plausible, drawing a great deal of commercial interest and scientific and ethical controversy.

Conclusion

Sexual function seems to improve after SNM for functional bladder problems. This improvement is primarily seen in arousal, satisfaction and pain. Perhaps testing this theory in primary research by studying the effect of SNM on women with sexual dysfunction will help further our understanding of both sexual dysfunction and SNM.

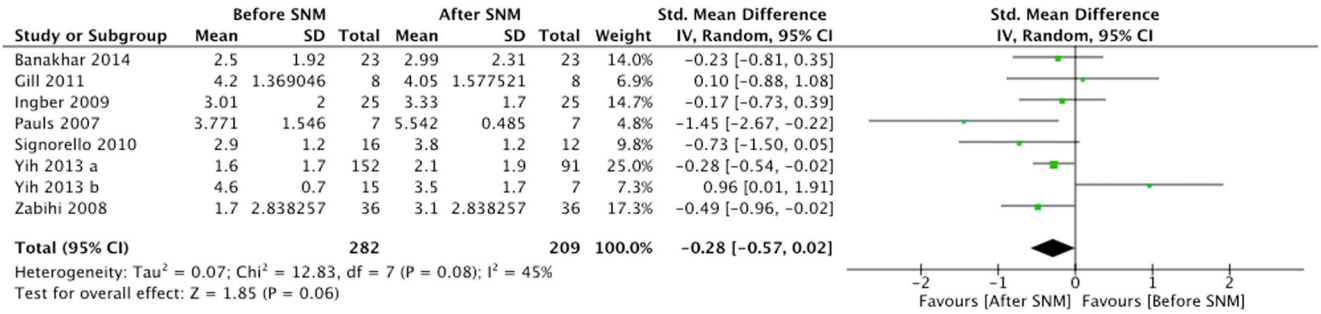

Fig. 10 Effect of sacral neuromodulation on orgasm as measured by the Female Sexual Function Index

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Compliance with ethical standards

Conflicts of interest Aethele Khunda received an educational travel grant from Medtronic plc.

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