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Overall and area-specific tactile recovery following different methods of surgical reinnervation in post-mastectomy breast reconstruction – a systematic review and meta-analysis

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Summary

Background: Breast cancer is a term that encompasses malignancy of any tissue structurally forming the breast. Due to its high prevalence, breast cancer places a significant burden on both patients and the healthcare system. Treatments such as radiotherapy, chemotherapy, hormonal therapy, and mastectomy are developed. Mastectomy is a lifesaving procedure but can cause decreased aesthetic and functional factors. Recent advances in medical technology have thankfully allowed surgeons to use advanced modalities that enable microscopic reconstruction of tissues, vessels, and nerves, giving sensation to the newly reconstructed breast. Surgical reinnervation is a procedure that describes the restoration of neurological function – both sensory and recovery – towards a body part that is lost or damaged. Reinnervation can be achieved both spontaneously and via surgery, hence termed surgical reinnervation. In this study, we review three surgical reinnervation interventions. First, end-to-end reinnervation comes under the neurorrhaphy group. Neurorrhaphy involves anastomosis of residual nerves in the proximal (healthy) and distal (denervated) tissues. Second, nerve allografts come under nerve transplantation. Third, nerve conduits mimic auto-transplantation but with an artificial conductor instead of a nerve donor. This study aims to measure and compare the overall and area-specific tactile recovery following different methods of surgical reinnervation following post-mastectomy breast reconstruction. **Evaluation of the topic:** This study is a systematic review and meta-analysis written according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. Twelve studies used in this review, nine measured the difference between breasts receiving end-to-end nerve coaptation and those receiving no surgical reinnervation. Two studies used allogeneic nerve grafts, while one used polyglycolic acid (PGA) nerve conduit. Coincidentally, these three studies employ Pressure Specified Sensory Device (PSSD) instead of Semmes-Weinstein Monofilament Test to measure tactile recovery. The other nine studies measured tactile recovery using the earlier-found Semmes-Weinstein Monofilament Test (SWMT). Outcome of this study focused on tactile recovery to three interventions. The first group report from end-to-end coaptation, three studies report better outcome compared to flaps without surgical reinnervation. Pooled overall SWMT rod size in breasts with end-to-end nerve coaptation was found to be 3.96 (95% CI 2.96–4.96) with high heterogeneity (I^2 94%, $P < 0.01$). Pooled overall SWMT rod size in breasts without surgical reinnervation was found to be 5.27 (95% CI 4.93–5.60) with high heterogeneity (I^2 80%, $P < 0.01$). The second group report from nerve allograft, two studies report that nerve allograft has a significant effect to tactile recovery. The third group report from nerve conduit, one study report about nerve conduit reinnervation. The result of this study was lower that end-to-end nerve coaptation. We then performed an area-specific analysis and found that the largest SWMT rod sizes were generally in the flap nipple area. Pooled mean (95% CI) of SWMT rod size following end-to-end coaptation in the flap nipple area was 4.39 (95% CI 3.70–5.09), while in those not receiving surgical reinnervation 5.45 (95% CI 4.93–5.97). Pooled mean rod sizes were generally much lower in the non-flap areas than in the reconstructed breast. **Conclusion:** In conclusion, there is a significant difference in overall sensory recovery between breasts receiving and not receiving surgical reinnervation, particularly breasts receiving end-to-end coaptation. Area-specific analysis found this difference is specifically significant in the upper medial portion of the mastectomy skin. Further research is needed to investigate recovery by other surgical reinnervation methods, particularly end-to-side coaptation, side-to-side coaptation, neurotization, anastomosis using conduits, and nerve grafts.

Key words

reinnervation surgery – breast reconstruction – mastectomy – systematic review – meta-analysis

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Introduction

Breast cancer is the most prevalent type of cancer found in women. It is defined as an uncontrolled proliferation of any of the histologically heterogeneous tissues structurally forming the breast. Due to its high prevalence, breast cancer places a significant burden on both patients and the healthcare system. The American Cancer Society estimated that breast cancer accounts for up to 32% of newly diagnosed cancers in the US in 2024 [1]. This translates to around 310 thousand new cases every year, doubling colorectal cancer, which is second on the list [1]. Treatments such as single or combined anticancer modalities such as radiotherapy, chemotherapy, hormonal therapy, and mastectomy are developed to decrease morbidity and mortality [2]. Although cancer-related mastectomy is a life-saving procedure, this procedure risks the 'death' of women from a social standpoint. Enache (2011) described the effect of mastectomy on a woman as equivalent to the loss of femininity, shapes the sense of inferiority, and prompts the feeling of embarrassment [3]. While counselling does alleviate some of this burden, breast reconstruction has always been a definitive treatment to recover the lost breast's form and function [4–6]. This may be performed immediately or after a delay, not uncommonly years following initial mastectomy. Cosmetics may seem to be the most apparent concern during reconstruction; however, sensation recovery arguably carries a more critical role towards the increase in the patient's quality of life. Studies reported that there is a robust correlation between breast sensation and better physical, psychosocial, and sexual wellbeing [7–9].

Recent advances in medical technology have thankfully allowed surgeons to use advanced modalities that enable microscopic reconstruction of tissues, vessels, and nerves, giving sensation to the newly reconstructed breast. Various methods of surgical reinnervation have been described in previous studies [10]. However, to the best of our knowledge, there has never been any systematic review and meta-analysis which aims to compare sensory recovery using different methods of surgical reinnervation during post-mastectomy breast reconstruction.

This study aims to measure and compare the overall and area-specific tactile recovery following different methods of surgical reinnervation following post-mastectomy breast reconstruction. Results from this study can be used as a consideration when choosing from the various methods of surgical reinnervation during post-mastectomy breast reconstruction.

Evaluation of the topic

Methods of data collection and processing

This study is a systematic review and meta-analysis written according to PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [33]. We searched online databases, which include PubMed, ClinicalTrials.gov, Scopus, and Science Direct, on 1 June 2024 for interventional studies that report tactile recovery following post-mastectomy breast reconstruction with surgical reinnervation. We only included studies written in English and published before March 2024. We excluded articles based on reasons ranked as follows:

1. The study was not completed, and the results were not posted.
2. The study was duplicated or is a previous version of a follow-up study derived fully/partially from the same set of patients.
3. The study is not a peer-reviewed journal article.
4. The study was not written in English.
5. The study does not contain primary data.
6. The study contains less than five subjects.
7. The study does not report the population aimed to be observed in the study (post-mastectomy breasts).
8. The study does not report the intervention/comparison aimed to be observed in the study (breast reconstruction with surgical reinnervation).
9. The study does not report the outcome aimed to be observed in the study (tactile recovery).

We inserted search query results into Rayyan [11]. Two independent authors (RC and IGAMHP) manually excluded duplicated studies with the website's assistance. Following the exclusion of duplicates, two independent authors (RC and IGAMHP) manually screened each study's title and abstract for study eligibility. Following abstract exclusion, RC attempted to retrieve the full texts of studies eligible for full-text screening. Studies irretrievable were excluded. Two independent authors (RC and IGAMHP) manually screened each study's full text for eligibility.

Data extracted from studies eligible for reporting and synthesis were recorded by two independent authors (RC and IGAMHP) in separate standardized Microsoft Excel® sheets. Any disagreement and uncertainty were resolved through discussion. The authors will extract data from the longest duration of follow-up when presented with paired measurements in both one article or within multiple articles (a follow-up study).

Random-effect models were used to pool effect sizes due to the assumption of considerable heterogeneity. Effect sizes were drawn from overall innervated breasts, innervated breasts classified by surgical reinnervation procedure, and all non-innervated breasts. A forest plot with a 95% confidence interval (CI) will then be drawn on the random-effects model, with analysis done to pool the overall tactile and area-specific sensory recovery. The results will be visualized on a heat map based on the outlier-adjusted pooled results. All statistical analyses were conducted using R version 2023.6.2+561. The risk of bias assessment will be conducted based on

the ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) for non-randomized studies and RoB2 (Risk of Bias 2) for randomized controlled trials and visualized using the ROBVIS tool [34]. Two independent authors (RC dan IGAMHP) assessed each study's risk of bias.

Our literature search found 624 studies, of which 388 were from Science Direct, 109 were from PubMed, and 111 were from Scopus. Our search on ClinicalTrials.gov found 16 studies; however, 13 studies were yet to be completed. We then excluded 96 duplicate articles, 483 articles during the title and abstract screening, six articles being irretrievable, and 14 articles during full-text screening due to not meeting our eligibility criteria. During the full-text screening, three studies were excluded because they did not report the desired outcome, three were excluded because they did not perform or failed to specify intervention, two were excluded because of reporting less than five patients, two were excluded because of having a follow-up study, one was excluded because of not differentiating body part reconstructed, and one was excluded because of failing to differentiate the method of recon-

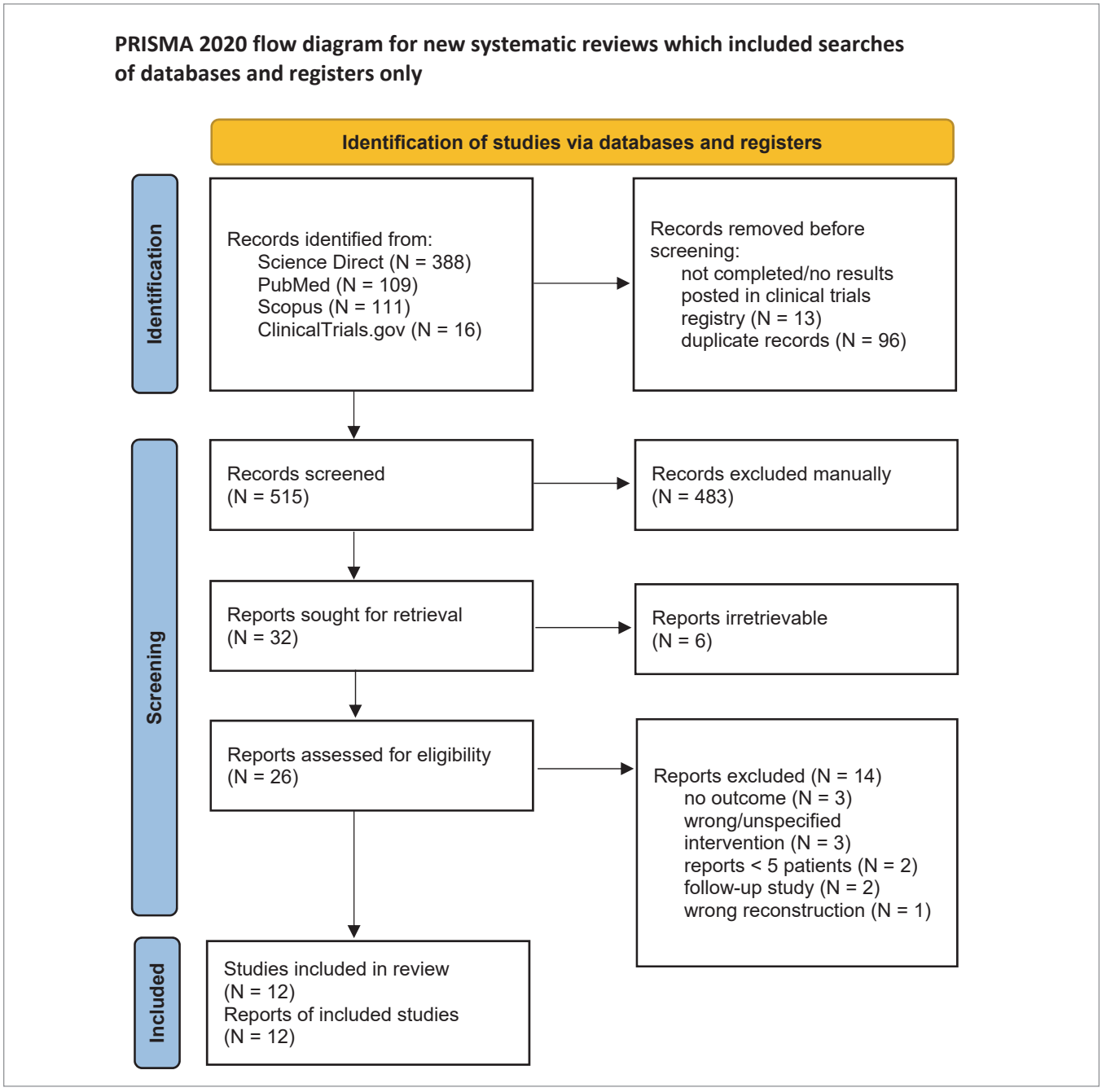

Fig. 1. PRISMA flowchart. A total of 624 studies across four databases were screened, resulting in the inclusion and synthesis of information from twelve studies [33]. For more information, see [36].

struction. We were then left with twelve studies for reporting and data synthesis. PRISMA flowchart can be seen in Fig. 1.

Five studies were done in the Netherlands, four in the United States, and one each in Belgium, Japan, and Finland. These twelve studies report a total of 481 innervated breasts alongside 295 controls. Six studies used DIEP flap, three used TRAM, two used LTP, one used VRAM, one used implant, and another one did not specify what was used for the reconstruction. Specified mastectomy procedure varies from conventional, skin-sparing, and nipple-sparing up to modified radical mastectomy. The complete study profile can be seen in Tab. 1.

Tab. 1. Complete study profile.

Study (year)	Country	Study design	Patients (breasts)	Age (years)	BMI	Immediate reconstruction	Oncologic	Mastectomy procedure	Other therapies
Beugels et al. [21]	Netherlands	prospective	36 (48)	50.3 ± 8.9	26.0 ± 3.2	58.3%	62.5%	immediate reconstruction by skin-sparing; delayed reconstruction unspecified	pre-reconstruction radiation therapy (35.4%); post-reconstruction radiation therapy (2.1%); history of chemotherapy (44.4%); neoadjuvant chemotherapy (19.4%); endocrine therapy (36.1%); immunotherapy (13.9%)
			45 (61)	50.0 ± 7.7	26.7 ± 2.9	34.4%	65.6%		pre-reconstruction radiation therapy (27.9%); post-reconstruction radiation therapy (1.6%); history of chemotherapy (55.6%); neoadjuvant chemotherapy (11.1%); endocrine therapy (40.0%); immunotherapy (11.1%)
Beugels et al. [22]	Netherlands	prospective	24 (37)	47.2 ± 10.0	24.0 ± 3.3	48.6%	45.9%	immediate reconstruction by skin-sparing; delayed reconstruction unspecified	pre-reconstruction radiation therapy (21.6%); neoadjuvant chemotherapy (8.3%); adjuvant chemotherapy (29.2%); endocrine therapy (33.3%); immunotherapy (8.3%)
			18 (26)	44.9 ± 8.7	23.3 ± 3.2	46.2%	50.0%		pre-reconstruction radiation therapy (30.8%); neoadjuvant chemotherapy (27.8%); adjuvant chemotherapy (44.4%); endocrine therapy (44.4%); immunotherapy (16.7%)
Rönkkö et al. [25]	Netherlands	prospective	67 (94)	52.0 ± 10.3	26.2 ± 3.9	55.3%	63.8%	unspecified	pre-reconstruction radiation therapy (22.3%); neoadjuvant chemotherapy (26.9%); adjuvant chemotherapy (3.8%); history of chemotherapy (54.8%); endocrine therapy (34.3%); immunotherapy (10.4%)
			58 (80)	55.2± 8.5	27.3 ± 4.2	48.8%	36.2%	unspecified	pre-reconstruction radiation therapy (23.8%); neoadjuvant chemotherapy (17.9%); adjuvant chemotherapy (7.7%); history of chemotherapy (53.7%); endocrine therapy (27.6%); immunotherapy (19.0%)
Bijkerk et al. [12]	Netherlands	retrospective and prospective	15 (15)[a]	49 ± 13	26.9 ± 3.3	46.7%	–	unspecified	–
			15 (15)[a]			53.3%	–	unspecified	–
Blondeel et al. [17]	Belgium	prospective	23 (24)	44.5 (30–68)	65.7 (52–92)	20.8%	–	modified radical (79.2%)	pre-reconstruction radiotherapy (39.1%); post-reconstruction radiotherapy (21.7%)
								skin-sparing (20.8%)	
			12 (13)	48.3 (34–73)	68.1 (54–92)	76.9%	–	modified radical (53.8%)	pre-reconstruction radiotherapy (25.0%); post-reconstruction radiotherapy (41.7%)
								skin-sparing (46.2%)	
			26 (28)	47.2 (30–63)	64.8 (49–90)	0.0%	–	modified radical (100.0%)	pre-reconstruction radiotherapy (69.2%)

[a] median (interquartile range)

BMI – body mass index, RCT – randomized control trial

Tab. 1 – continuing. Complete study profile.

Study (year)	Country	Study design	Patients (breasts)	Age (years)	BMI	Immediate reconstruction	Oncologic	Mastectomy procedure	Other therapies
Bubberman [14]	Netherlands	RCT	19 (29)	45.7 ± 8.6	28.1 ± 3.3	41.4%	44.8%	unspecified	radiation therapy (20.7%); adjuvant chemotherapy (36.8%); neoadjuvant chemotherapy (31.6%); endocrine therapy (42.1%); immunotherapy (10.5%)
			22 (38)	50.2 ± 11.1	27.2 ± 3.3	34.2%	60.5%	unspecified	radiation therapy (47.4%); adjuvant chemotherapy (31.8%); neoadjuvant chemotherapy (40.9%); endocrine therapy (40.9%); immunotherapy (9.1%)
Djohan et al. [19]	USA	retrospective	8 (15)	38.1 ± 7.5	23.7 ± 4.2	100.0%	73.3%	nipple-sparing (100.0%)	neoadjuvant chemotherapy (25.0%); adjuvant chemotherapy (25.0%)
Mori et al. [15]	Japan	retrospective	15 (15)	51.8 (47–61)	22.5 (19–24)	100.0%	100.0%	conventional (33.3%)	chemotherapy (33.3%)
				45.3 (31–52)	22.2 (20–28)			nipple-sparing (40.0%)	
				41.3 (31–49)	25.0 (23–28)			skin-sparing (26.7%)[a]	
			18 (18)	48.4 (40–58)	20.8 (19–24)	100.0%	100.0%	conventional (27.8%)	radiation therapy (5.6%); chemotherapy (22.2%)
				46.5 (42–53)	22.2 (20–28)			nipple-sparing (53.3%)	
				50.6 (38–60)	23.4 (20–34)			skin-sparing (27.8%)[a]	
Peled [20]	USA	prospective	47 (79)	46.3 (17–65)	23.04	100.0%	44.7%	nipple-sparing (100.0%)	adjuvant chemotherapy (4.3%); neoadjuvant chemotherapy (14.9%)
Puonti et al. [16]	Finland	retrospective and prospective	29 (29)	49.1 ± 8.2	–	14.6%	100.0%	unspecified	radiation therapy (48.8%); chemotherapy (63.4%)
			41 (41)	48.2 ± 7.0	–	27.6%	100.0%	unspecified	radiation therapy (48.3%); chemotherapy (48.3%)
Spiegel et al. [18]	USA	retrospective	35 (15)[a]	47.7 ± 7.1	–	25.0%	–	skin-sparing (75.4%); unspecified (24.6%)	–
			35 (33)[a]	49.1 ± 8.6	–	63.9%	–		–
			35 (9)[a]	49.4 ± 8.1	–	11.1%	–		–
Yap [36]	USA	prospective	7 (7)	51 (44–58)	–	57.1%	100.0%	unspecified	radiation therapy (57.1%); chemotherapy (28.6%)
			7 (7)	46 (44–51)	–	57.1%	100.0%	unspecified	radiation therapy (57.1%); chemotherapy (57.1%)

[a] median (interquartile range)

BMI – body mass index, RCT – randomized control trial

Of these twelve studies, nine measured the difference between breasts receiving end-to-end nerve coaptation and those receiving no surgical reinnervation. Two studies used allogeneic nerve grafts, while one used polyglycolic acid (PGA) nerve conduit. Coincidentally, these three studies employ Pressure Specified Sensory Device (PSSD) instead of Semmes-Weinstein Monofilament Test to measure tactile recovery. The other nine studies measured tactile recovery using the earlier-found Semmes-Weinstein monofilament test (SWMT). SWMT measures tactile recovery using a series of rods with a rod label size corresponding to the logarithmic value of ten times the force in milligrams required to buckle the monofilament rod [12]. Although interpolation towards pressure 'stress' values from point measurements described by Levin et al. can be done on the mean SWMT rod size, calculating rod size means before converting them will yield a statistically different value than converting them before calculating the means already in the pressure unit [13]. And since no study had reported individual patient data, direct comparison between studies using different measuring methods is not statistically correct and will not be done in this study. Tactile recovery results and follow-up can be seen in Tab. 2.

Tab. 2. Tactile recovery results and follow-up.

Study (year)	Flap	Surgical reinnervation	Follow-up (months)	Tactile Sensation (SWMT)
Beugels et al. [21]	DIEP	end-to-end	15 (11; 17)	4.17 ± 0.70
	DIEP	none	17 (12; 24)	5.52 ± 0.55***
Beugels et al. [22]	LTP	end-to-end	17 (10; 19)	4.04 ± 0.90
	LTP	none	15 (11; 25)	5.13 ± 0.70**
Beugels et al. [23]	DIEP	end-to-end	15 (12; 20)	4.53 ± 0.81
	DIEP	none	16 (11; 18)	5.15 ± 0.69***
Bijkerk [12]	DIEP/LTP	end-to-end	18.9 ± 5.2	4.42 (3.67; 5.13)
	DIEP/LTP	none		5.06 (4.60; 5.44)**
Blondeel et al. [17]	DIEP	end-to-end	21.4 (12.8–40.0)	2.72[a]
	DIEP	none	19.6 (12.0–37.8)	2.47[a]
	TRAM	none	19.9 (12.0–39.0)	1.62a**
Bubberman et al. [14]	DIEP	end-to-end	24	4.48[a]
	DIEP	none	24	5.20a**
Djohan et al. [19]	–	nerve graft	10.59 ± 3.57	58.55[a]
Mori et al. [15]	TRAM/VRAM	end-to-end	14.8 (12–19)	4.17 (3.22–6.45);
			13.0 (12–18)	5.88 (1.65 – > 6.65)
			13.8 (12–18)	6.10 (4.08 – > 6.65)
	TRAM/VRAM	none	31.6 (14–57)	5.07 (3.61 – > 6.65)
			13.8 (12–17)	6.10 (3.61 – > 6.65)
			14.2 (12–18)	4.93 (2.36 – > 6.65)
Peled et al. [20]	implant	nerve graft	> 12	0–20 g/mm^2 (75%)
				20–40 g/mm^2 (21%)
				> 40 g/mm^2 (4%)
Puonti et al. [16]	ms-TRAM	end-to-end (single)	25.66 ± 2.36	2.0 (1.3–3.0)
	ms-TRAM	end-to-end (dual)	29.93 ± 5.84	3.0 (2.3–3.9)**
Spiegel et al. [18]	DIEP	end-to-end	119.3 ± 57.5	69.78[a]
	DIEP	PGA conduit	88.1 ± 36.2	49.28[a]
	DIEP	none	182.3 ±115.5	72.94[a]
Yap et al. [36]	ms-TRAM	end-to-end	39 (35–46)	3.04 ± 0.52
	ms-TRAM	none	40 (31–46)	5.09 ± 1.09

* P < 0.05, ** P < 0.01. *** P < 0.001
DIEP – deep inferior epigastric artery perforator, LTP – lateral thigh perforator, PGA – polyglycolic acid, SWMT – Semmes-Weinstein monofilament test TRAM – traverse rectus abdominis muscle, VRAM – vertical rectus abdominis muscle

End-to-end coaptation

Pooled overall SWMT rod size in breasts with end-to-end nerve coaptation was found to be 3.96 (95% CI 2.96–4.96) with high heterogeneity (I^2 94%; P < 0.01). Pooled overall SWMT rod size in breasts without surgical reinnervation was found to be 5.27 (95% CI 4.93–5.60) with high heterogeneity (I^2 80%; P < 0.01). Three studies in the analysis reported a significant difference between flaps receiving end-to-end nerve coaptation compared to flaps without surgical reinnervation. Other studies which were not included in the analysis included Bijkerk et al., which reported that DIEP/LTP flaps receiving end-to-end nerve coaptation had a significantly lower (P < 0.01) median (interquartile range) SWMT rod size of 4.42 (3.67–5.13) compared to flaps not receiving surgical reinnervation at 5.06 (4.60–5.44) [12]. Bubberman et al. reported a significantly lower (P < 0.01) mean SWMT rod size of 4.48 in flaps re-

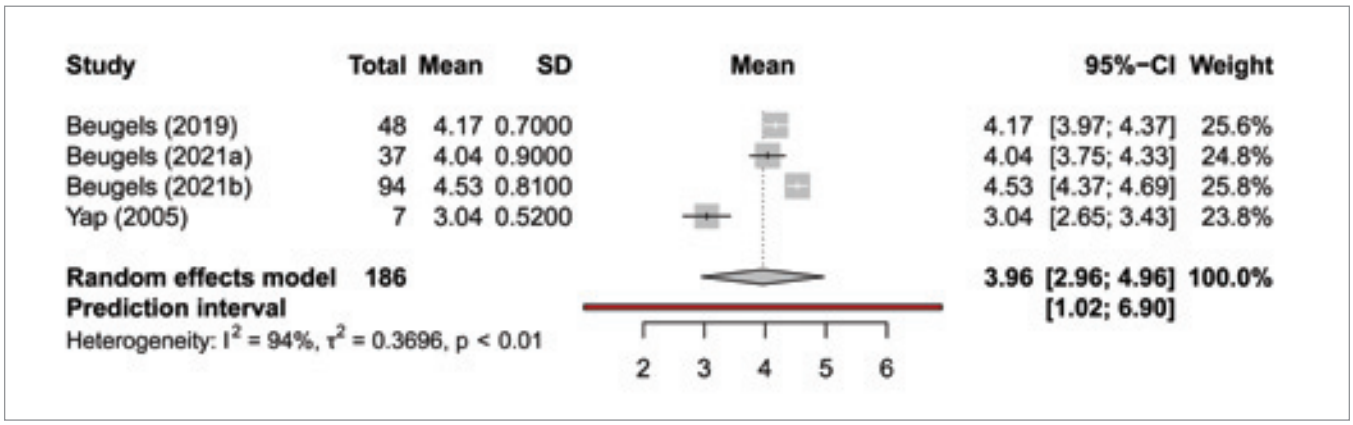

Fig. 2. Forest plot for SWMT rod size in breasts with end-to-end nerve coaptation. Pooled overall SWMT rod size in breasts with end-to-end nerve coaptation was found to be 3.96 (95% CI 2.96; 4.96) with high heterogeneity (I^2 94%, P < 0.01) in 186 patients across four studies.
SD – standard deviation, SWMT – Semmes-Weinstein monofilament test

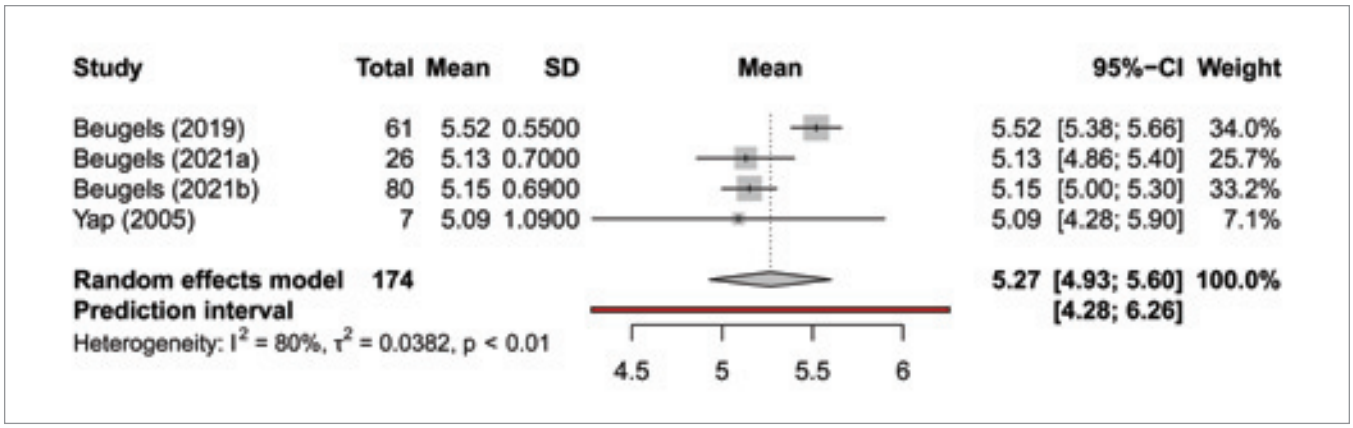

Fig. 3. Forest plot for SWMT rod size in breasts without surgical reinnervation. Pooled overall SWMT rod size in breasts without surgical reinnervation was found to be 5.27 (95% CI 4.93; 5.60) with high heterogeneity (I^2 80%, P < 0.01) in 174 patients across four studies.
SD – standard deviation, SWMT – Semmes-Weinstein monofilament test

ceiving end-to-end coaptation compared to flaps not receiving surgical reinnervation at 5.20 [14]. Similar results can also be seen in Puonti et al., Mori et al., and Blondeel et al., who reported these findings using methods specified in the respective studies [15–17]. Additionally, Puonti et al. reported that dual nerve coaptation resulted in better sensory recovery [16]. Different to other studies, Spiegel et al. measured tactile sensation in breasts receiving end-to-end coaptation using PSSD. They found a mean tactile threshold of 69.78 g/mm^2 [18]. Forest plot of SWMT rod size in breasts with end-to-end nerve coaptation, which can be seen in Fig. 2, while breasts without surgical reinnervation are seen in Fig. 3.

We found a pooled standardized mean difference (SMD) of −1.53 (95% CI −2.62–0.43) with high heterogeneity (I^2 87.2%; P < 0.05) between breasts receiving end-to-end coaptation and breasts not receiving innervation. The forest plot for the difference can be seen in Fig. 4.

Nerve allograft

Djohan et al. and Peled et al. reported sensory recovery following surgical reinnervation using an allogeneic nerve graft [19,20] Djohan et al. found a tactile threshold of 58.55 g/mm^2, while Peled et al. found that 75% of subjects included in the study had a threshold of 0–20 g/mm^2 and a few (21%) at 20–40 g/mm^2 [19,20] This recovery as described by Peled et al. is very notable because it brings the reconstructed breast's sensation to levels comparable to normal, healthy breasts as reported by Djohan et al. [19,20]. This difference can be attributed to the difference in follow-up duration, where breasts in Peled et al. had a follow-up of more than 12 months, while those in Djohan et al. had a mean follow-up time of around 11 months [19,20]. The results from these two studies were unable to be analyzed due to the difference in re-

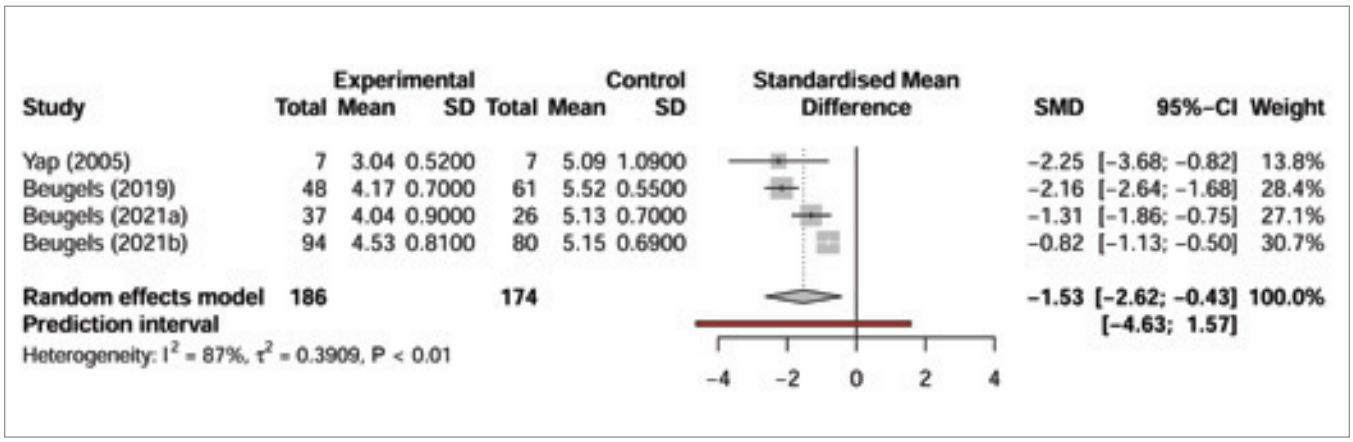

Fig. 4. Standardized mean difference for overall SMWT rod size in breasts with end-to-end nerve coaptation against no surgical reinnervation. Pooled overall SMWT rod size SMD between 186 patients with breasts receiving end-to-end coaptation and 174 patients with breasts not receiving innervation was found to be –1.53 (95% CI –2.62; –0.43) with high heterogeneity (I^2 87.2%, P < 0.05).

SD – standard deviation, SMD – standard mean difference, SWMT – Semmes-Weinstein monofilament test

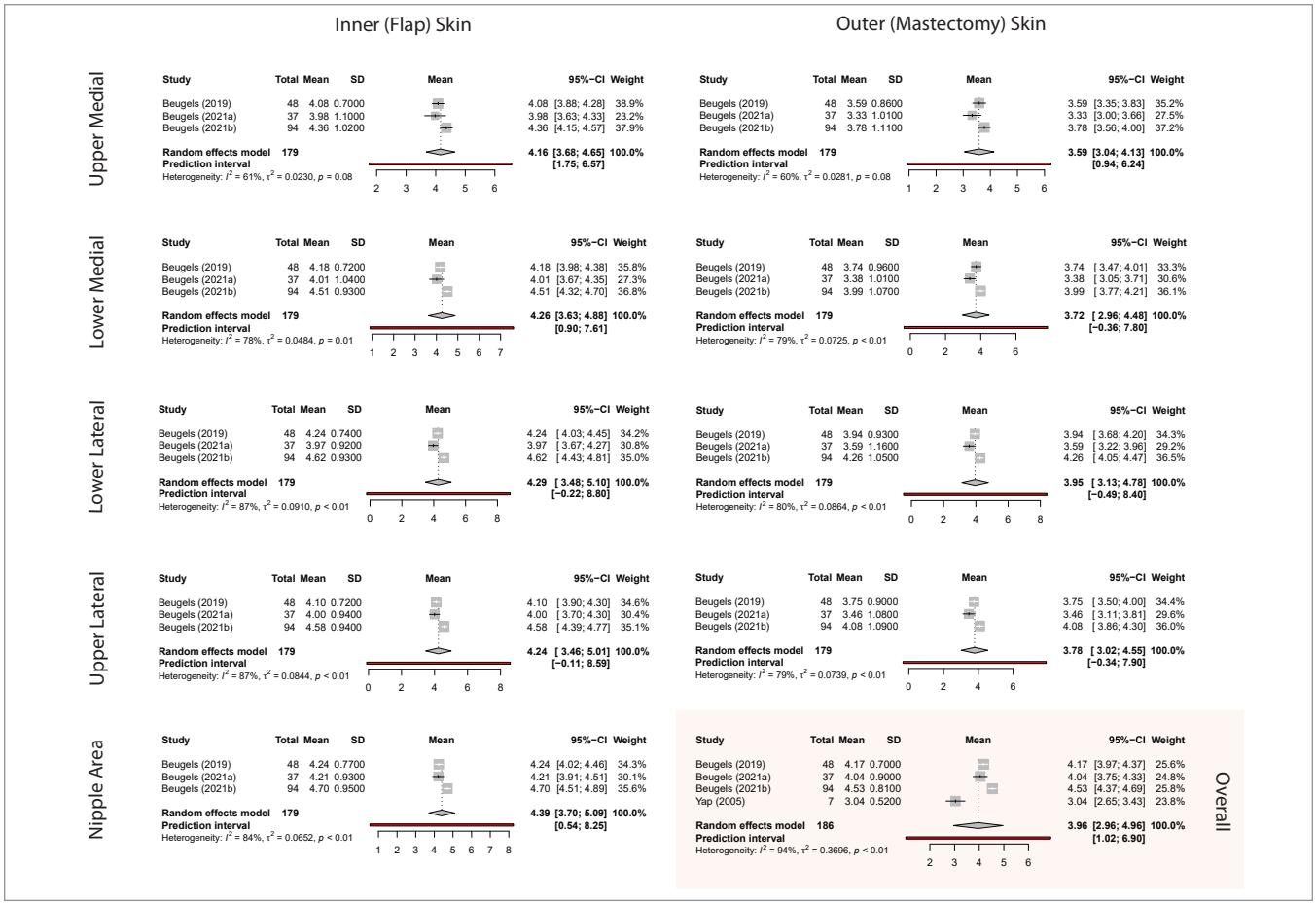

Fig. 5. Forest plot for area-specific SMWT rod size in breasts with end-to-end nerve coaptation in 179 patients across three studies. Pooled SMWT rod size was generally lower in outer (mastectomy) skin: 3.59 (95% CI 3.04; 4.13) for upper medial, 3.72 (95% CI 2.96; 4.48) for lower medial, 3.95 (95% CI 3.13; 4.78) for lower lateral, and 3.78 (95% CI 3.02; 4.55) for upper lateral sections. Pooled SMWT rod size for inner (flap) skin was found to be 4.16 (95% CI 3.68; 4.65) for upper medial, 4.26 (95% CI 3.63; 4.88) for lower medial, 4.29 (95% CI 3.48; 5.10) for lower lateral, 4.24 (95% CI 3.46; 5.01) for upper lateral, and 4.39 (95% CI 3.70; 5.09) for nipple sections.

SD – standard deviation, SWMT – Semmes-Weinstein monofilament test

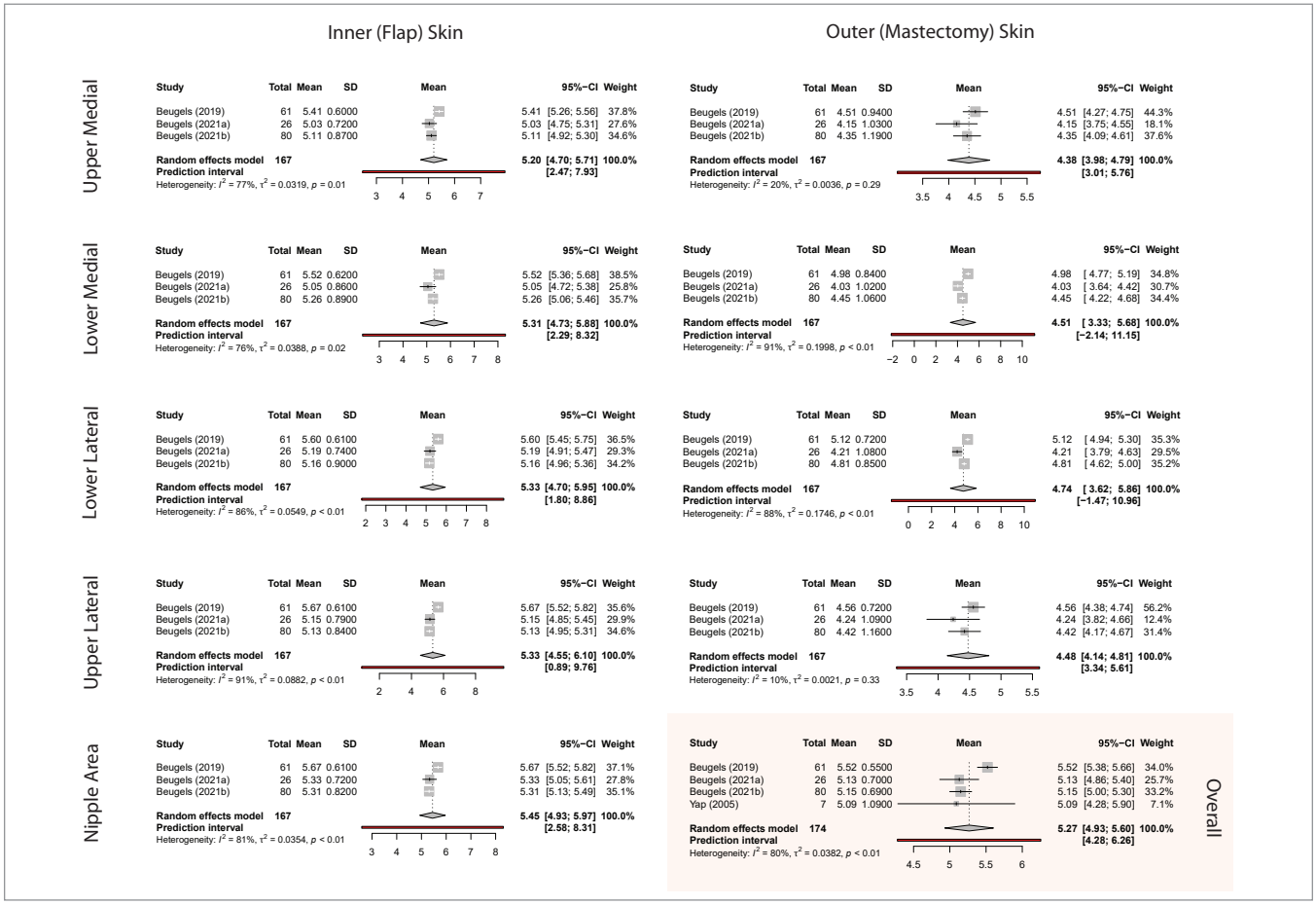

Fig. 6. Forest plot for area-specific SMWT rod size in breasts without surgical reinnervation in 167 patients across three studies. Pooled SMWT rod size was generally lower in outer (mastectomy) skin: 4.38 (95% CI 3.98; 4.79) for upper medial, 4.51 (95% CI 3.33; 5.68) for lower medial, 4.74 (95% CI 3.62; 5.86) for lower lateral, and 4.48 (95% CI 4.14; 4.81) for upper lateral sections. Pooled SMWT rod size for inner (flap) skin was found to be 5.20 (95% CI 4.70; 5.71) for upper medial, 5.31 (95% CI 4.73; 5.88) for lower medial, 5.33 (95% CI 4.70; 5.95) for lower lateral, 5.33 (95% CI 4.55; 6.10) for upper lateral, and 5.45 (95% CI 4.93; 5.97) for nipple sections.

SD – standard deviation, SWMT – Semmes-Weinstein monofilament test

porting methods, and these two studies also did not employ multiple treatment arms using different methods of surgical reinnervation.

Neither of these studies indeed compares sensory recovery in the same way. We have not made any statistical inference between the footage of this study; we only reported our findings without testing for statistical significance between the two groups. Additionally, we also remind the reader to interpret these findings with caution.

Nerve conduit

Spiegel et al. was the only study that performed surgical reinnervation with the polyglycolic acid (PGA) nerve conduit [18]. The sensory threshold was then found at 49.28 g/cm^2 [18]. This was notably lower than the same observation done on breasts receiving end-to-end nerve coaptation and no surgical reinnervation, albeit a much shorter follow-up time. In fact, the follow-up time for the nerve conduit was 25% less than the follow-up time for end-to-end nerve coaptation and more than 50% less than the follow-up time for breasts not receiving reinnervation.

Area specific analysis

We then performed an area-specific analysis and found that the largest SWMT rod sizes were generally in the flap nipple area. Pooled mean (95% CI) of SWMT rod size following end-to-end coaptation in the flap nipple area was 4.39 (95% CI 3.70–5.09), while in those not receiving surgical reinnervation 5.45 (95% CI 4.93–5.97). Pooled mean rod sizes were generally much lower in the non-flap areas than in the reconstructed breast. We only included Beugels et al., Beugels et al., and Beugels et al. because only these studies reported area-specific sensory recovery [21–23]. Forest plot for SWMT rod size in breasts receiving end-to-end nerve coaptation towards breast receiving no surgical innervation can be seen in Fig. 5, 6.

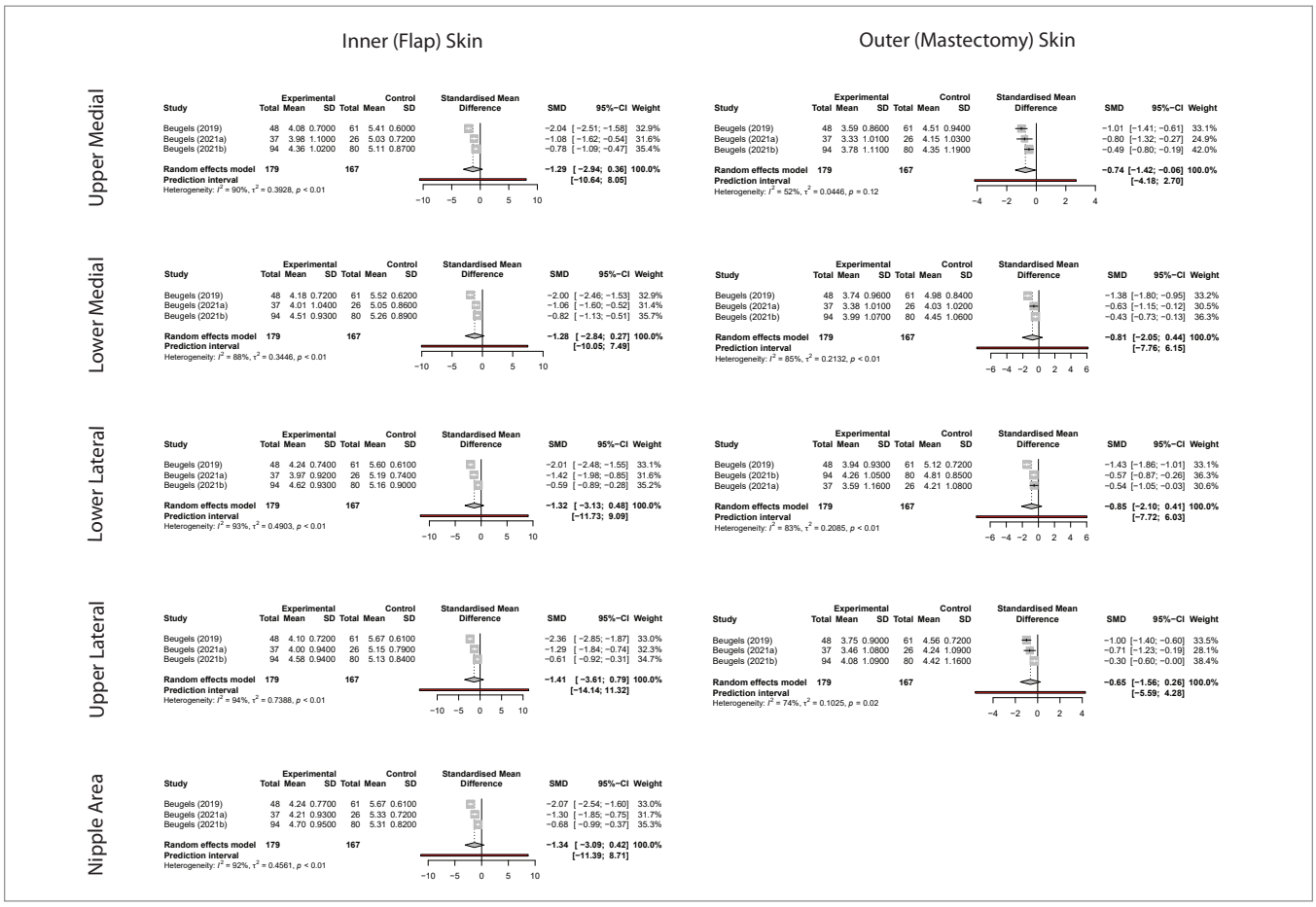

Fig. 7. Forest plot for pooled standardized mean difference (SMD) for overall SMWT rod size between breasts with end-to-end nerve coaptation against no surgical reinnervation. Significant difference was only seen in the upper medial section of outer (mastectomy) skin (SMD –0.74, 95% CI –1.42; –0.06). Pooled SMD in SMWT rod size was generally higher in outer (mastectomy) skin, albeit insignificant: –0.81 (95% CI –2.05; 0.44) for lower medial, –0.85 (95% CI –2.10; 0.41) for lower lateral, and –0.65 (95% CI –1.56; 0.26) for upper lateral sections. Pooled SMD in SMWT rod size for inner (flap) skin was found to be –1.29 (95% CI –2.94; 0.36) for upper medial, –1.28 (95% CI –2.84; 0.27) for lower medial, –1.32 (95% CI –3.13; 0.48) for lower lateral, –1.41 (95% CI –3.61; 0.79) for upper lateral, and –1.34 (95% CI –3.09; 0.42) for nipple section.

SD – standard deviation, SMD – standard mean difference, SWMT – Semmes-Weinstein monofilament test

Forest plot and details of standardized mean difference in SWMT rod size in breasts with end-to-end nerve coaptation towards breasts receiving no surgical innervation can be seen in Fig. 7 and Tab. 3.

Heat map for area-specific pooled SWMT rod size in breasts with end-to-end nerve coaptation towards breasts receiving no surgical innervation can be seen in Fig. 8.

Risk of bias

Eleven studies synthesized were analyzed using the ROBINS-I tool, while Bubberman et al. was analyzed using the RoB2 tool [14]. All non-RCT studies were deemed to have an overall moderate risk of bias, while Bubberman et al. had some concerns about its overall risk of bias [14]. Overall risk of bias can be seen in Table 4, and the risk of bias traffic light plot can be seen in Fig. 9.

Discussion

Mastectomy is a life-saving procedure, but this procedure risks the 'death' of women from a social standpoint. The loss of breasts implies a non-negligible psychological distress and reduction in quality of life. While counselling and psychotherapy may help in psychological recovery, reconstruction is the definitive treatment for lost breast form and function [4–6]. Studies have reported that reconstruction, especially those emphasizing sensory recovery, strongly correlates with better physical, psychosocial, and sexual well-being [7–9]. Women in these studies reported better quality of life following breast reconstruction [7–9].

Surgical reinnervation

Reinnervation is a term that describes the restoration of neurological function –

Tab. 3. Standardized mean differences in SWMT rod size.

	End–to–end coaptation pooled mean (95% CI)	No surgical reinnervation pooled mean (95% CI)	Standardized mean difference (95% CI)
upper-medial mastectomy skin	3.59 (3.04; 4.13)	4.38 (3.98; 4.79)	–0.74 (–1.42; –0.06)*
lower-medial mastectomy skin	3.72 (2.96; 4.48)	4.51 (3.33; 5.68)	–0.81 (–2.05; 0.44)
lower-lateral mastectomy skin	3.95 (3.13; 4.78)	4.74 (3.62; 5.86)	–0.85 (–2.10; 0.41)
upper-lateral mastectomy skin	3.78 (3.02; 4.55)	4.48 (4.14; 4.81)	–0.65 (–1.56; 0.26)
upper-medial flap skin	4.16 (3.68; 4.65)	5.20 (4.70; 5.71)	–1.29 (–2.94; 0.36)
lower-medial flap skin	4.26 (3.63; 4.88)	5.31 (4.73; 5.88)	–1.28 (–2.84; 0.27)
lower-lateral flap skin	4.29 (3.48; 5.10)	5.33 (4.70; 5.95)	–1.32 (–3.13; 0.48)
upper-lateral flap skin	4.24 (3.46; 5.01)	5.33 (4.55; 6.10)	–1.41 (–3.61; 0.79)
flap nipple area	4.39 (3.70; 5.09)	5.45 (4.93; 5.97)	–1.34 (–3.09; 0.42)
overalla	3.97 (2.96; 4.96)	5.27 (4.93; 5.60)	–1.50 (–2.59; –0.42)*

SWMT – Semmes-Weinstein monofilament test

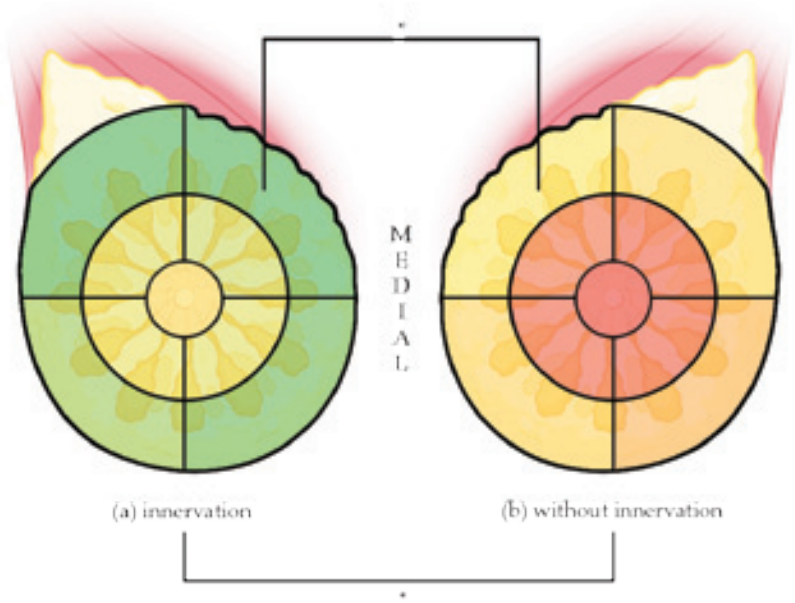

Fig. 8. Heat map for area-specific pooled SMWT rod size in breasts with surgical reinnervation (A) and without surgical reinnervation (B). There is a significant difference in sensory recovery in the overall and upper-medial mastectomy skin.
SD – standard deviation

Tab. 4. Overall risk of bias.

Study (year)	Risk of bias
Beugels et al. (2019) [21]	moderate
Beugels et al. (2021a) [22]	moderate
Beugels et al. (2021b) [23]	moderate
Bijkerk et al. (2020) [12]	moderate
Blondeel et al. (1999) [17]	moderate
Bubberman et al. (2024)* [14]	some concerns
Djohan et al. (2020) [19]	moderate
Mori et al. (2011) [15]	moderate
Peled et al. (2023) [20]	moderate
Puonti et al. (2016) [16]	moderate
Spiegel et al. (2013) [18]	moderate
Yap et al. (2005) [36]	moderate

both sensory and recovery – towards a body part that is lost or damaged. This can be achieved both spontaneously or via surgery, hence termed surgical reinnervation. Although chances of complete restoration of lost physiological functions following extensive diastasis between proximal and distal sites were still deemed slim to none, various surgical techniques in peripheral nerve surgery have been developed to accommodate various nerve lesions [10], Tuturov described four techniques available for tissue reinnervation, namely (i) neurorrhaphy, ii) autotransplantation, (iii) recovery using conduits, and (iv) neurotization [10]. Each set of methods was described to have its indications and contraindications.

Neurorrhaphy involves anastomosis of residual nerves in the proximal (healthy) and distal (denervated) tissues. Although nerve anastomosis may be done from end-to-end (ETE), end-to-side (ETS), and side-to-side (STS), the latter was less studied and performed [10,24]. Although anastomosis involving the sides and not the end of a nerve may

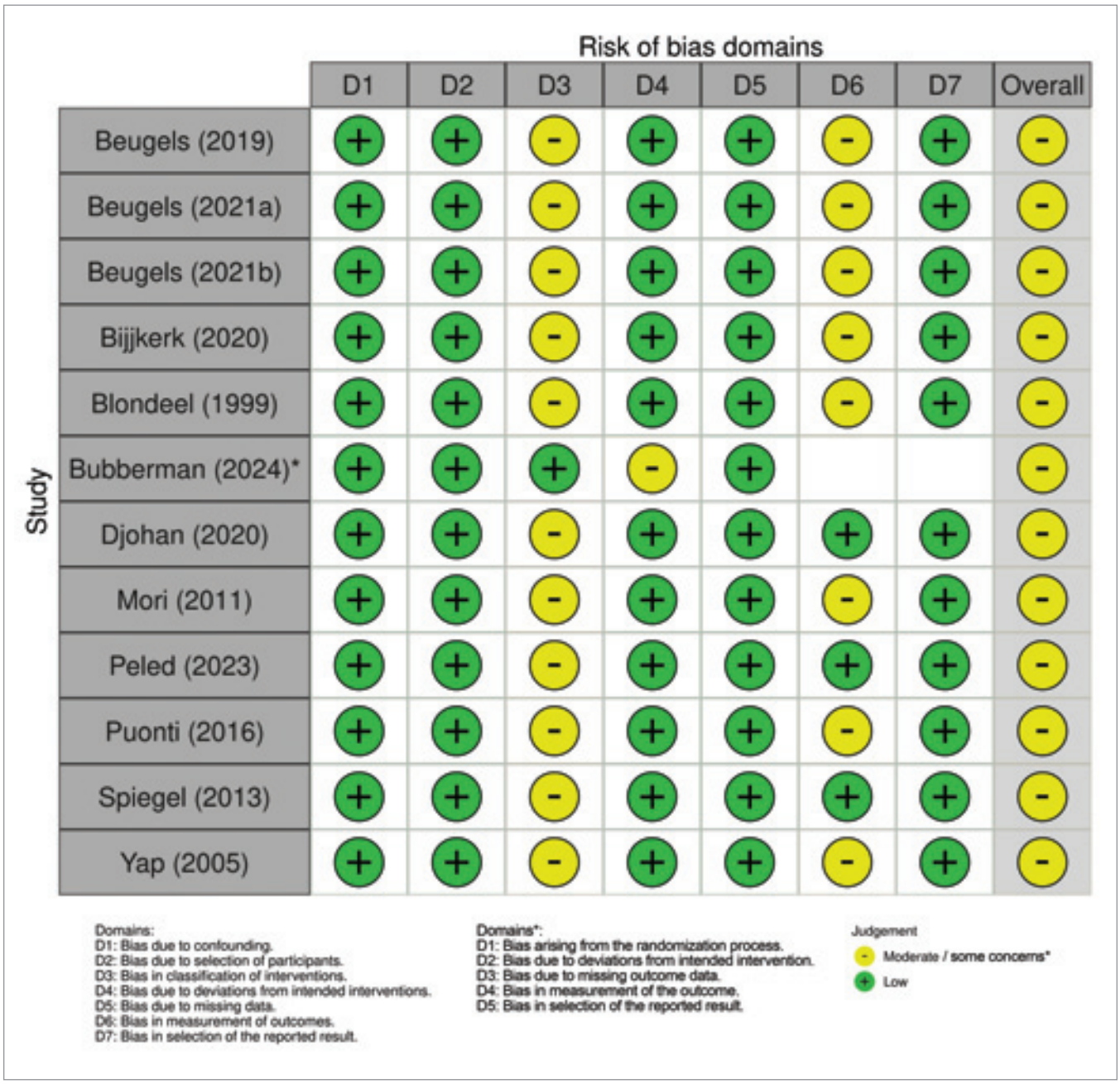

Fig. 9. Risk of bias traffic light plot. All studies had an overall moderate / some concern for bias.
SD – standard deviation

not be an obvious option, recent studies on termino-lateral regeneration and sprouting of collateral nerves alongside had opened the possibility of using ETS and STS [10,24]. However, studies such as those done by Rönkkö et al. and Viterbo et al. demonstrated conflicting results of whether ETE is superior to ETS and STS; although all agreed that ETS and STS is a viable option when conserving donor nerve function as a priority [24–26].

Autotransplantation involves an ETE of nerves in the proximal and distal tissues; however, it involves a nerve donor from another part of the body covering the diastatic segment [10]. However, reports by Bibbo et al. and Bhangra et al. reported that this method had long-term complications such as the formation of neuroma in anastomotic sites, varying degrees in loss of sensitivity, and rotation to kinking of bundles of nerve fibers [27,28]. Furthermore, donor site tissues innervated by the nerve graft are prone to neurologic morbidity. Even after considering all the risks, the donor nerve's diameters may as well not match the recipient nerve due to differences in anatomical features and function of

tissues innervated by the respective nerves [10,28]. The use of conduits mimics autotransplantation but with an artificial conductor instead of a nerve donor. This eliminates the shortcomings from autotransplantation, particularly those involving donor site morbidity [10].

Neurotization involves the direct attachment of proximal nerve endings into muscle tissue [10]. This technique is used if no distal nerve can be identified, or is deemed not viable for anastomosis [10]. However, forming new neuromuscular junctions (NMJs) involves a multi-step process of morphologically transforming muscle tissues serving as the attachment site into those resembling a normal NMJ. Results following this surgery were found to be conflicting, and it is the least used surgical technique compared to those previously mentioned [10].

Surgical reinnervation during breast reconstruction

Many studies have described the reconstruction outcome with reinnervation performed on other body parts, ranging from small, particular tongue tissues to the larger, more common breast tissues [29]. The consensus is that reconstruction, which includes reinnervation, provides better sensory recovery. Most studies reported in Table 1 found a significant difference in sensory recovery between breasts in the two groups. This is confirmed by our analysis, which found an overall significant standardized mean difference in sensory recovery between breasts in the two groups, albeit only including four studies.

Published studies done on different parts of the body generally validate our findings. For example, a study by Lee et al. reported that in patients with facial nerve palsy, dual innervation of the trigeminal nerve improves the dynamic movement of paralyzed facial muscles and shortens recovery [30]. Another study by Gil et al. reported that in patients with proximal ulnar nerve injury, patients receiving end-to-side nerve coaptation demonstrated superior strength and improved upper extremity function compared to those not receiving limb reinnervation [31]. Yuan et al. reported that patients receiving finger pulp reconstruction and nerve coaptation following reconstruction using reverse digital artery island flap yielded better static two-point discrimination and overall higher sensory function grades. A meta-analysis by Hardcastle et al. reported that in patients receiving surgical reinnervation via nerve graft and nerve transfer following brachial plexus injury, reanimation of shoulders showed better, although not statistically significant, functional recovery of shoulder function [32].

While there has been an increase in the number of studies reporting sensory outcomes following end-to-end nerve coaptation, non-preliminary studies done on other forms of reinnervation (STE and STS nerve coaptation, nerve conduits, and nerve grafts) were still scarce. Further investigation is needed to elucidate the specific impact of each surgical method on sensory recovery.

Limitations

This study does not include grey literature. There has been no adequate number of studies to statistically analyze the differences in sensory recovery outcomes based on the reinnervation surgical technique.

Conclusion

In conclusion, overall sensory recovery was significantly better in breasts receiving surgical reinnervation, particularly with end-to-end coaptation compared to not receiving surgical reinnervation. This shows a promising solution to sensory recovery following mastectomy. Area-specific analysis found this difference especially significant in the upper medial portion of the mastectomy skin. Further research is needed to investigate recovery by other surgical reinnervation methods, particularly end-to-side coaptation, side-to-side coaptation, neurotization, anastomosis using conduits, and nerve grafts.

Roles of the authors

Richard Christian Suteja – conceptualization, data curation, funding acquisition, methodology, resources, software, visualization, writing original and review editing; I Gusti Ayu Maha Hiranandini Prawista – conceptualization, investigation, methodology, project administration, resources, and software; Albert Salim – formal analysis, investigation, project administration, I Komang Hotra Adiputra – data curation, funding acquisition, and writing original draft; Giovanca Verentzia Purnama – resources, writing original and review editing, I Putu Divanaya Suryanov – conceptualization, formal analysis, funding acquisition, and investigation; Darren Junior – methodology, software and validation; I Gusti Ngurah Ariestha Satya Diksha – data curation, investigation, resources, and software; Steven Christian – data curation, project administration, writing original and review editing; Gede Wara Samsarga – supervision, validation, and writing review editing.

Conflict of interests

The author declared no conflict of interest.

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