Effect of pain neuroscience education after breast cancer surgery on pain, physical, and emotional functioning : a double-blinded randomized controlled trial (EduCan trial)

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000002838

Effect of pain neuroscience education after breast cancer surgery on pain-, physical-, and emotional functioning: a double-blinded randomized controlled trial (EduCan trial)

Lore Dams, PhD[1,2,3,*], Elien Van der Gucht, PhD[1,2,3,*], Nele Devoogdt, PhD[2,4], Ann Smeets, PhD[5], Koen Bernar, Msc[6], Bart Morlion, PhD[6,7], Lode Godderis, PhD[8,9], Vincent Haenen, MSc[1,2,3], Tessa De Vrieze, PhD[2], Steffen Fieuws, PhD[10], Niamh Moloney, PhD[11,12], Paul Van Wilgen, PhD[3, 13,14], Mira Meeus, PhD[1,3,15*], An De Groef, PhD[1,2,3,*]

[*]These authors contributed equally to this manuscript

[1]University of Antwerp, Faculty of Medicine and Health Sciences, Department of Rehabilitation Sciences and Physiotherapy, MOVANT, Antwerp, Belgium

[2]KU Leuven - University of Leuven, Department of Rehabilitation Sciences, Leuven, Belgium

[3]Pain In Motion International research group, www.paininmotion.be

[4]Department of Vascular Surgery and Department of Physical Medicine and Rehabilitation, Center for Lymphedema, UZ Leuven - University Hospitals Leuven, Leuven, Belgium.

[5]Department of Surgical Oncology, University Hospitals Leuven, Leuven, Belgium

[6]The Leuven Centre for Algology and Pain Management, University Hospitals Leuven, Leuven, Belgium

[7]Department of Cardiovascular Sciences, Section Anaesthesiology and Algology, KU Leuven - University of Leuven, Leuven, Belgium

[8]Centre for Environment and Health, University of Leuven, Leuven, Belgium

[9]IDEWE, External Service for Prevention and Protection at Work, Leuven, Belgium

[10]Interuniversity Center for Biostatistics and Statistical Bioinformatics, University of Leuven and University of Hasselt, Leuven, Belgium.

[11]Department of Health Professions, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW, Australia

[12]Department of Exercise Sciences, Faculty of Science, University of Auckland, New Zealand

[13]Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium.

[14]Transcare, Transdisciplinary Pain Management Centre, Groningen, The Netherlands

[15]Ghent University, Faculty of Medicine and Health Sciences, Department of Rehabilitation Sciences and Physiotherapy, Ghent, Belgium

Corresponding author: Lore Dams Department of Rehabilitation Sciences and Physiotherapy University of Antwerp Campus Drie Eiken – Universiteitsplein 1, R.315 2610 Wilrijk, Belgium 0032 16 376 680 lore.dams@uantwerpen.be

https://www.uantwerpen.be/nl/personeel/lore-dams/

ABSTRACT

Pain is one of the most common and long-lasting side effects reported by women surgically treated for breast cancer. Educational interventions may optimize the current physical therapy modalities for pain prevention or relief in this population. Pain neuroscience education (PNE) is an educational intervention that explains the pain experience not only from a biomedical perspective, but also the psychological and social factors that contribute to it. Through a double-blinded randomized controlled trial (EduCan trial) it was investigated if PNE, in addition to the standard physiotherapy program immediately following breast cancer surgery,

was more effective over the course of 18 months postoperatively than providing a biomedical explanation for pain. Primary outcome was the change in pain-related disability (Pain Disability Index, 0-70) over 12 months. Secondary outcomes included change in pain intensity, upper limb function, physical activity level and emotional functioning over 4, 6, 8, 12 and 18 months postoperatively. Multivariate linear models for repeated (longitudinal) measures were used to compare changes. Pre- and postoperative moderators of the change in pain-related disability were also explored. Of 184 participants randomized, the mean (SD) age in the PNE and biomedical education group was 55.4 (11.5) and 55.2 (11.4) respectively. The change in pain-related disability from baseline to 12 months postoperatively did not differ between the two groups (PNE 4.22 (95%CI: 1.40-7.03), biomedical 5.53 (95%CI: 2.74-8.32), difference in change -1.31 (95%CI: -5.28-2.65), P=0.516). Similar results were observed for all secondary outcomes. Future research should explore whether a more patient-tailored intervention would yield better results.

Keywords: breast cancer, randomized controlled trial, pain neuroscience education, biopsychosocial, pain-related disability

INTRODUCTION

One of the most common side effects of breast cancer (treatment) is pain [30]. The literature reports average pain prevalence ~~rates~~ of 31% one to two years after breast cancer surgery [64,15]. Of particular concern is the potential impact of pain, as pain can cause limitations in daily activities, participation, and interaction with the environment, with consequences for physical and emotional functioning [16]. Adequate pain management in the early stage of breast cancer treatment is essential for resolving and preventing these problems, both in the

short and long term [19]. Educational interventions may optimize pain management by improving patient knowledge, perceived control, and attitudes toward pain [46,44].

However, clinically relevant effects of educational interventions for the management of pain in cancer populations are currently lacking [3,51,45]. Perhaps because those interventions often describe pain from a biomedical perspective (e.g., explanations of structures that can cause pain and analgesic advice) and hence fail to explain other reasons why pain can persist beyond the healing process. Increased understanding of pain (neuro)physiology has resulted in a neuroscience-based educational intervention aimed to reconceptualize pain beyond the biomedical model and toward a biopsychosocial understanding [17]. Pain neuroscience education (PNE) explains that pain is not always a true representation of tissue damage, but rather the nervous system's interpretation of the threat of injury, which is influenced by a variety of psychosocial factors [4,43,44]. As a result of this pain reconceptualization, people may perceive pain as less threatening, and barriers to participating in (previously avoided) activities due to pain may be removed, potentially resulting in less pain-related disability and better physical and mental functioning [47,40].

To our knowledge, only two studies compared the effect of perioperative PNE to biomedical education in women undergoing breast cancer surgery [10,35]. The first was a pilot randomized controlled trial that examined two educational interventions given before breast cancer surgery [10]. The intervention group watched a 90-minute pain psychoeducational video (n=36), while controls received digital health and nutrition education (n=32). No significant effect for pain-related disability, pain intensity, physical or emotional functioning was found up to 12 weeks after surgery. The second study was a retrospective non-randomized case-control trial that compared perioperative PNE (n=51) to biomedical

education (n=51) in patients with persistent postoperative pain one year after breast cancer surgery, excluding pain from other cancer treatments [35]. They found that PNE was more effective than biomedical education for pain-related disability, pain intensity, central sensitization related symptoms, and pain-related catastrophizing, although effect sizes were small.

Given the inconclusive results and limitations of previous studies in terms of design (non-randomized controlled trial), short follow-up, small sample size, and study population (no generalization to the general breast cancer population), we conducted a double-blinded randomized controlled trial with 18-month follow-up to determine whether breast cancer patients who received postoperative PNE reported more favorable changes in functioning than controls who received biomedical education, both in addition to standard physiotherapy. The primary outcome was the change in pain-related disability over 12 months. Secondary outcomes included changes in pain intensity, physical and emotional functioning 4, 6, 8, 12 and 18 months postoperatively.

METHODS

Study Design

The EduCan trial was a parallel, two-arm randomized controlled trial approved by the Ethical Committee of the University Hospitals Leuven (s60702) and registered at ClinicalTrials.gov (NCT03351075). A detailed description of the protocol has been published [12].

Participants

Recruitment took place at the Multidisciplinary Breast Center of the University Hospitals Leuven campus Gasthuisberg (Belgium) between November 2017 and March 2020. Potential participants signed informed consent prior to inclusion. Inclusion criteria were: being

diagnosed with histologically confirmed invasive or non-invasive primary breast cancer; scheduled for one of the following surgeries: mastectomy with sentinel node biopsy or axillary lymph node dissection (with or without breast reconstruction) or breast conserving surgery with axillary lymph node dissection; no distant metastasis; female; aged 18 years or older; could comply with the study protocol; comprehension of the Dutch language (reading, listening, writing and speaking).

Randomization

After enrollment, participants were randomly assigned (1:1) to the intervention (PNE) or control group (biomedical education). This computer-generated randomization was performed by an independent coworker (T.D.V.) using permuted blocks (size=4).

Blinding

Participants, assessors and physical therapists performing the standard physical therapy program were all blinded to group allocation. Before consenting to participate in the study, participants were informed that they would be randomized to either "traditional biomedical education" or a "modern educational intervention". The difference between these interventions was neither explained during recruitment, nor in the written consent document. To prevent contamination between the two groups, both the educational sessions and physiotherapy were one-on-one, minimizing possible interaction between participants. An informative session on prevention and treatment of lymphedema did take place in a group of approximately 10 participants. A communication sheet was drawn up to ensure that standardized answers were given to patient's questions during the standard physical therapy program. If the participants asked pain-related questions, they were referred to the physiotherapist delivering the educational interventions. An independent statistician (S.F.) of

the Leuven Biostatistics and statistical Bioinformatics Center analyzed the data to ensure additional blinding of the research team.

Interventions

Standard physical therapy program

All participants attended a one-on-one 30-minute standard physical therapy program once or twice weekly (intensive phase) starting the first week post-surgery, independent of group allocation. These sessions took place at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven campus Gasthuisberg (Belgium) and were delivered by four physiotherapists (L.D., F.P., V.H. and E.V.d.G.) with a master's degree in Rehabilitation Sciences and Physiotherapy. The program included three modalities, tailored to the individual needs of the participant: (1) manual techniques (passive mobilizations to restore shoulder range of motion, myofascial techniques to improve muscle flexibility and scar tissue massage to improve flexibility of the scar(s)), (2) specific exercises to improve shoulder range of motion and upper limb strength and (3) advice on general exercises to increase physical activity level.

After 4 months, this intensive program was replaced by three individual follow-up sessions (maintenance phase), at 6, 8 and 12 months after surgery. At these time points, participants received a physiotherapy session (by L.D. or E.V.d.G.) and were referred to a physiotherapy practice in primary care for further intensive follow-up if needed.

Additionally, participants were asked to attend one informative group session regarding prevention and treatment of lymphedema, given by a physical therapist with a master's degree in Rehabilitation Sciences and Physiotherapy and specialized in treatment of breast cancer-related lymphedema (T.D.V. or L.V.). If the participants reported symptoms of lymphedema,

they were referred for thorough evaluation and treatment at the Center for Lymphedema of the University Hospitals Leuven.

Educational sessions

Throughout the whole study period, participants attended six one-on-one, 30-minute educational sessions on pain after breast cancer treatment. These sessions took place at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven campus Gasthuisberg (Belgium) and were delivered by a physical therapist proficient in pain management (A.D.G. or K.B.). Three sessions were scheduled in the intensive phase (starting 1-3 weeks after surgery) and three sessions in the maintenance phase at 6, 8 and 12 months after surgery. In case a face-to-face session in the hospital was not possible, a digital session with live therapist interaction covering the same content was provided. During the educational sessions, information was presented both verbally and with a PowerPoint presentation. Additionally, participants received a booklet and a web-link to an online summarizing presentation to read at home. Knowledge regarding the principles that were covered during the educational sessions was tested before the first and after the third session (intensive phase) and before the start of the fourth session (maintenance phase) by means of a questionnaire based on the Neurophysiology of Pain Test [36], adapted to the educational content of both groups.

Women who did not experience pain at the time of the educational sessions were taught how to cope with possible future pain. During the three maintenance sessions, the physiotherapist went through the information provided in the intensive phase and discussed the implementation in future stages of the recovery process. For these sessions, the participants received a second booklet with specific information for this phase.

Participants in the control group and intervention group had the same schedule and format of educational sessions, only the content of the education differed between the groups.

Control group: biomedical education

The learning goal consisted of gaining biomedically oriented knowledge about pain after breast cancer treatment. The participants were explained that pain is related to tissue injury caused by the different treatment procedures for breast cancer. The physical therapist providing the education talked about the side effects of these different treatment modalities, the role of different structures and injured versus healthy tissue in acute and persistent pain. Additionally, patients received guidance on activity management based on the load – loadability principle (physical activity – rest). The physical therapist advised them to listen to their body and adjust their physical activity level accordingly. He/she also went over the current recommendations for general exercises after cancer treatment, based on the American Cancer Society Guidelines for Physical Activity: at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week (or a combination of these), preferably spread throughout the week [32]. Finally, advice on work resumption in the context of the different (persistent) side effects of the treatments was provided, with a focus on ergonomic factors. The different factors influencing return to work were discussed and patients were informed on whom to contact to address those factors (this information was the same in both groups).

Intervention group: pain neuroscience education

The learning goal consisted of gaining biopsychosocial oriented knowledge about pain after breast cancer treatment. Participants were explained the physiological and psychological processes involved in the pain experience to help reconceptualizing pain. The authors did so

by adapting the content and images from the books 'Explain Pain' [4], 'Pijneducatie een praktische handleiding voor (para)medici' [63], and 'The Pain Toolkit' [41] for use in a breast cancer population. The sessions included the following topics: characteristics of acute versus persistent pain, specific side effects of breast cancer treatment modalities in relation to pain, how pain is a product of the brain, how pain becomes persistent (plasticity of the nervous system, modulation, modification, central sensitization) and potential sustaining factors of pain (such as emotions, stress, pain cognitions and pain behavior). Additionally, the experimental intervention included advice on activity management while experiencing pain and other symptoms, considering the intertwinement of influencing biopsychosocial factors. Participants learned about increasing general exercises and activities according to the principles of graded activity and pacing reported by the International Association for the Study of Pain [37]. This includes general exercise activities according to pacing strategies for 'persisters' (i.e. restructuring the activity pattern to avoid peaks of overactivity and exacerbations of their pain) and graded activity for 'avoiders' (i.e. time-contingent increase of physical activity). Finally, it was explained that work resumption could break the vicious cycle of biopsychosocial components and persistent pain. In addition, the principles described above for activity management were applied to the working situation. The different factors influencing return to work were discussed and patients were informed on whom to contact to address those factors (this information was the same in both groups).

Outcomes

All participants were evaluated pre- and postoperatively (within one week before and after surgery) and at 4, 6, 8 ,12 and 18 months postoperatively.

Primary outcome measure

The primary outcome was the change in pain-related disability from before surgery to 12 months after surgery. Pain-related disability was evaluated using the Dutch language version of the Pain Disability Index (PDI-DLV) [50,62]. The primary endpoint of the study was set at 12 months postoperatively because the majority of recovery from breast cancer surgery occurs within 12 months of surgery and the studied intervention was designed to operate primarily within this time frame. The PDI assesses the degree of pain interference with normal role functioning in seven different life domains (family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care and life-support activity) on a ten-point Likert scale ranging from 0 (no disability) to 10 (total disability) (total score range 0-70) [50,62]. One of two researchers (L.D. or E.V.d.G.) administered the PDI-DLV during the evaluation consultations at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven campus Gasthuisberg (Belgium). In addition to written instructions, the researchers provided a standard verbal instruction, stating that mean pain-related disability from any cause should be indicated.

Secondary outcome measures

Secondary outcomes were threefold: 1) pain symptoms and characteristics 2) physical functioning and 3) emotional functioning. Assessments of secondary outcomes were completed by the participants at home, either electronically via the digital patient record or on paper within one week before or after the evaluation consultation.

1) Pain symptoms and characteristics

Pain intensity

The Visual Analog Scale (VAS) is a horizontal 100-mm line with two endpoints representing the extreme states, “no pain” and “worst pain possible” [29]. Participants were asked to rate

the global mean pain intensity experienced in the past week. In addition to written instructions, the researchers provided a standard verbal instruction, stating that mean pain-related disability from any cause should be indicated. The VAS was found to have good psychometric properties to evaluate pain in women diagnosed with breast cancer [20].

2) Physical functioning

Physical activity level

A waist worn tri-axial accelerometer (ActiGraph® wGT3X-BT+) was used to evaluate physical activity level. More precisely, the parameters derived from this device were physical activity energy expenditure (kcals/day), sedentary time (min/day), moderate-to-vigorous physical activity (min/day), (very) vigorous physical activity (min/day) and step counts (steps/day). Physical activity outcomes were only evaluated postoperatively and at 4 and 12 months postoperatively. Participants were instructed to wear the device on the right hip during seven consecutive days for at least 12 hours during waking hours (except for showering or swimming) [38]. Data collection was considered valid when at least four days with a recording period of ≥600 minutes were available [38]. ActiLife software (version 6.13.4 Full Edition) was used to process the data. A sample rate of 90Hz, 60-second epoch setting and modified version of the Choi algorithm (60-0-1 using vector magnitude) was applied. The Freedson VM3 combination cut points were used to evaluate categories of activity intensity (moderate: 2691-6166, vigorous: 6167-9642 and very vigorous physical activity: 9643-∞ counts per minute) [56,38]. A minimum bout length of 10 minutes, with maximum 150 counts per minute using the vertical axis from hip accelerations was used to categorize sedentary time [31,38]. The Freedson VM3 combination algorithm was used to measure physical activity energy expenditure [1]. The ActiGraph GT3X+ has demonstrated excellent relative

reliability (two-week interval) for sedentary behavior and good relative reliability for moderate-to-vigorous physical activity in patients 12 months after breast cancer surgery [49].

Upper limb function

The Disabilities of the Arm, Shoulder and Hand questionnaire (DASH) is a 30-item questionnaire that assesses symptoms and functional status, with a focus on physical function, in populations with upper extremity musculoskeletal conditions [24,48]. The items cover upper extremity-related symptoms and measure functional status at the level of disability. Patients score each item on a 5-point Likert scale (1-5), with higher scores reflecting higher disability/worse symptoms. The total score of the DASH ranges between zero and 100. Because of its consistently large effect sizes for construct validity and responsiveness, the DASH is recommended for assessing upper extremity function in breast cancer survivors [21].

3) Emotional functioning

Pain-related catastrophizing

The Pain Catastrophizing Scale (PCS) is a 13-item questionnaire that reflects on previous painful experiences and asks to indicate the degree to which each of the 13 described thoughts or feelings were experienced while in pain. Each question is scored on a five-point Likert scale from 0 (not at all) to 4 (all the time). Total PCS scores can be evaluated (ranging from 0 to 52), with higher scores corresponding to more pain-related catastrophizing, as well as three subscales scores assessing rumination about pain (rumination, score range 0 to 16), magnification of negative consequences in the context of pain (magnification, score range 0 to 12) and experienced helplessness in the context of pain (helplessness, score range 0 to 24) [60,61,8].

Depression, anxiety, stress

The Depression, Anxiety and Stress Scale (DASS-21) evaluates the presence of negative emotional states of severity of depression, anxiety, and stress over the past week. Each subscale consists of 7 questions with each question scored on four-point Likert scale from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time) [34,11].

Psychological symptoms, existential well-being and support

The McGill Quality of Life Questionnaire (MQOL) is multidimensional tool that evaluates the overall quality of life over the past two days. The following MQOL subscales are related to psychosocial functioning and included in the present study: psychological symptoms (4 items), existential well-being (6 items) and support (2 items). Each item is scored on an 11-point Likert scale from 0 to 10 with opposite anchors at the end with higher scores reflecting a better psychosocial functioning [7,13].

Sample size

The sample size was based on a comparison of the changes for the primary outcome measure (PDI-DLV) at 12 months after surgery. Since no information was available on the standard deviation (SD) of the changes, the calculation was based on a comparison of the values at 12 months (note this corresponds to assuming a correlation between baseline and 12 months equal to 0.5, in which case the SD of the change equals the SD at 12 months). Assuming a coefficient of variation (CV) equal to 0.5, 87 participants per group were needed based on a two-sample pooled t-test of a mean ratio with lognormal data and α=0.05 to detect with 80% power a difference of 20% in PDI [6,58]. To anticipate a drop-out rate of 5%, a total of 184 subjects were needed to be recruited.

Statistical methods

Descriptive statistics for continuous values are presented as mean (SD) and median (interquartile range (IQR)). Categorical variables are presented as frequency and proportion (%).

A multivariate linear model for longitudinal measures with an unstructured covariance matrix (fitted on the measurements pre-op, 4, 6, 8, 12 and 18 months) was applied for each continuous (primary and secondary) outcome, correcting for the postoperative assessment (allowing the relation between the postoperative value and the value at the other timepoints to be timepoint specific). From this model, changes versus the preoperative value were reported (with 95%CI) and compared between both groups. Using likelihood-based estimation, subjects with a missing value at one or more timepoints were still included in the analyses. For the outcomes with missing postoperative values, the model was fitted applying a multiple imputation approach (MCMC method within each group and using 20 imputed datasets). For the physical activity outcomes that were measured post-op, at 4 months and at 12 months, changes versus the postoperative value were evaluated.

If model residuals showed a right-skewed distribution and zero values were present, an inverse hyperbolic transformation was applied. Since this transformation is a log-transform, a change refers to a ratio after back-transformation.

Furthermore, moderator analyses were performed for the effect on PDI-DLV at 12 months. First, a multiple imputation was performed (MCMC method). To ensure that imputed values were in the 0-70 range, the imputation was performed on logit transformed values (PDI-DLV values equal to 0 were replaced by value 0.5 before applying the transformation). Second, Spearman correlations were reported between pre- and postoperative variables and the change in PDI-DLV after 12 months, as well as the slopes from a linear regression model. In the

latter model, the interaction was verified, referring to a difference in slope between both groups. Rubin's rule was used to combine the results from the imputed datasets. Following pre- and postoperative variables were explored as potential moderators: pain-related disability, pain intensity, upper limb function, pain-related catastrophizing, depression, anxiety, stress, psychological symptoms, existential well-being and support.

Data were analyzed using SAS software, version 9.4. P<.05 was considered significant. No corrections for multiple testing were performed.

RESULTS

In total, 493 women were eligible, of which 184 were included in the study (Figure 1). Both intervention and control groups had similar demographic and clinical characteristics at baseline (Table 1). Attendance at educational interventions was 98% in the intervention group and 99% in the control group during the intensive phase. During the maintenance phase, 97% of participants in the intervention group and 98% of participants in the control group attended the educational interventions.

The primary analysis (Table 2) revealed no significant difference in pain-related disability change from baseline to 12-months after surgery between the intervention and control groups (intervention 4.2; 95%CI: 1.4-7.0, control 5.5; 95%CI: 2.7-8.3, difference in change -1.31; 95%CI: -5.3-2.7, P=0.516). Similar results were found at 4, 6, 8, and 18 months after surgery. Figures 2 and 3 show graphically the scores and changes over time for pain-related disability, respectively.

Analysis of secondary outcomes showed that there were no statistically significant differences in change between the intervention and control groups (Table 2-4). Over the 18-month follow-up, both groups experienced increases in pain intensity (intervention 3.91, 95%CI: -1.70-9.52, control 8.71; 95%CI: 3.17-14.24) (Table 2) and a decline in upper limb function (intervention 6.56; 95%CI: 3.15-9.97, control 9.72; 95%CI: 3.17-14.24) (Table 3) relative to the preoperative level. Regarding emotional functioning (Table 4), both groups experienced decreases in psychological symptoms (intervention 2.07; 95%CI: 1.57-2.57, control 2.09; 95%CI: 1.60-2.57) and social support (intervention -0.54; 95%CI: -0.96- -0.11, control -0.83; 95%CI: -1.24- -0.42) and an increase in existential well-being (intervention 1.07; 95%CI: 0.64-1.49, control 0.61; 95%CI: 0.20-1.03) compared to the preoperative level, over the 18-month follow-up.

Considering the results of the moderator analysis, there was no evidence of a relation with the effect of the intervention on pain-related disability one year after surgery for any of the pre- or postoperative variables (pain-related disability, pain intensity, upper limb function, pain-related catastrophizing, depression, anxiety, stress, psychological symptoms, existential well-being and support) (Supplement 1, available at http://links.lww.com/PAIN/B759).

DISCUSSION

This study shows that women who received PNE in addition to standard physiotherapy immediately after breast cancer surgery had no different change in pain-related disability from before surgery to 12 months postoperatively when compared to a group that received biomedical pain education. Similar results were observed for secondary outcomes pain intensity, physical and emotional functioning up to 18 months after surgery.

Two previous studies investigated the effectiveness of perioperative PNE in women undergoing breast cancer surgery [10,35]. The first was a pilot randomized controlled trial that examined two different educational interventions given before breast cancer surgery [10]. The intervention group watched a 90-minute pain psychoeducational video that included information on cognitions, emotions and physiologic hyperarousal related to pain (n=36), while controls received digital education about health and nutrition (n=32). Our study differed in that our educational interventions were provided postoperatively, and we had more and face-to-face educational sessions, additional physiotherapy, and a longer follow-up period. Similar to our findings, they found no significant effect for pain-related disability, pain intensity, physical or emotional functioning up to 12 weeks after surgery. One possible explanation is that those with low pain scores were unable to recognize the pain information at the time provided, potentially impeding the learning process, which is important to the success of pain psychoeducation/PNE. This may also have influenced our findings, given that 54% of participants in our study rated their pain intensity lower than 30/100 at their first postoperative PNE session. In a study that found significant effects of perioperative PNE in a musculoskeletal pain population, perioperative pain scores were indeed higher [33].

The second study was a retrospective non-randomized case-control trial that compared perioperative PNE (n=51) to biomedical education (n=51) in patients with persistent postoperative pain one year after breast cancer surgery [35]. Similar to our study, educational interventions were face-to-face, delivered by a physiotherapist with use of a pamphlet and combined with physiotherapy. In contrast to our findings, they found that PNE was more effective than biomedical education in reducing pain-related disability, pain intensity, symptoms related to altered central somatosensory functioning, and pain-related catastrophizing [35]. The effect sizes were all small (r=0.20-0.29), with the exception of the

effect size for pain intensity, which was found to be moderate (r=0.31). One explanation for the discrepancy in findings could be the difference in study population. While they excluded participants whose main pain was cancer treatment-related other than persistent post-surgical pain (e.g., chemotherapy-induced peripheral neuropathy, aromatase inhibitor-induced arthralgia), these patients were included in our study. This is because many breast cancer patients receive (neo)adjuvant therapies, and one-fifth of those who receive taxanes-based chemotherapy will develop peripheral neuropathy [59,55], and about half of women treated with aromatase inhibitors will experience hormonal therapy-induced joint pain [2]. If we excluded these patients, we would be limiting our ability to apply our study results to the general population following breast cancer. Aside from the study population, there was also a difference in the way educational interventions were integrated into the perioperative rehabilitation process. The other study provided an educational session before surgery as well as at each physiotherapy session (i.e., once every 1-2 weeks for 3 months), whereas in our study, a fixed number of six educational sessions were provided alongside the physiotherapy sessions at predetermined timepoints after breast cancer surgery. The fact that educational sessions were not integrated into the physiotherapy sessions in our study (to specifically assess the effect of the educational interventions) may have also contributed to the difference in the additional effect of PNE.

Aside from the low prevalence of clinically relevant postoperative pain and the implementation of PNE alongside physiotherapy, a number of other factors could have influenced our study results. First, increased psychological distress in the early postoperative stage may have hampered the process of conceptual change [22,52,25]. The first three educational sessions were given within the first month after surgery. Increased psychological distress is common at this stage, which is known to negatively impact cognitive functions

(e.g., attention, memory) [22,52,25]. Consequently, participants may have been less receptive/engaged in the educational sessions, or not ready to reconceptualize pain. Second, conceptual change learning is shaped around challenging existing knowledge rather than simply learning new information [54,42]. Given that existing knowledge is often limited to a biomedical understanding of pain and the biomedical point of view is more widely accepted, it is possible that the intensity of PNE was insufficient to allow a paradigm shift to a biopsychosocial explanation of pain [9,5]. Third, the attention given to the project participants as a result of their participation may have influenced the results. Because both groups engaged with the same rigorous physiotherapy program at a specialized institution, the possibility of obtaining an additional effect from PNE may have been diminished (ceiling effect). A strong therapeutic alliance has been shown to increase satisfaction and outcomes in pain patients [18,28]. Despite a comprehensive physical therapy program at a specialized institution and a potentially strong therapeutic alliance, we were unable to completely prevent an increase in pain-related impairment compared to preoperative levels in either group at any follow-up. The objective of the current study was to achieve a greater change toward pre-operative level in the PNE group than in the biomedical education group. We cannot, however, conclude that educational interventions are ineffective in breast cancer patients because we did not include a control group that received physiotherapy without any type of education.

Some limitations of the current study need to be acknowledged. First, sample size was calculated based on PDI-scores in non-breast cancer populations, which could have led to an approximation that differed if PDI-scores from a population with breast cancer were used instead. Second, both educational interventions were given by the same physiotherapist convinced of the importance of a biopsychosocial approach to pain, which might have

influenced treatment fidelity. Treatment fidelity was not assessed in the study (e.g., by recording educational sessions and inspecting recordings for forbidden elements). On the other hand, having the same therapist teach both educational interventions, may have minimized the impact of nonspecific therapy factors. Third, no validated outcome measures assessing pain knowledge, attitudes, and beliefs were included. We also had to limit ourselves to a small number of moderators for the moderator analysis. We concentrated on pre- and postoperative moderators that could be used in clinical practice to identify patients before or immediately after surgery who might benefit more or less from PNE after surgery. Fourth, the study design of a randomized controlled trial does not mimic a real-life situation and might have undermined the external validity. However, in addition to being a limitation, the research design could be viewed as a strength. Randomized controlled trials ensure internal validity and provide a rigorous tool for investigating cause-effect relationships between intervention and outcome. Other strengths of this study were its large sample size, long follow-up, double blinding, consistent assessment of the primary outcome parameter and incorporation of maintenance sessions of education at 6, 8 and 12 months after surgery.

Minimizing symptom burden after treatment is paramount in order to restore quality of life after breast cancer. PNE is a convenient technique for improving pain-related functioning in persistent pain populations [65]. Despite the fact that we found no additional effect of PNE in patients immediately following breast cancer surgery, our findings add to the body of knowledge about PNE in this population and provide a basis for future research to fine-tune the optimal delivery format. Perhaps PNE should be integrated, administered only to patients experiencing postoperative pain or at risk of persistent pain, and only when patients are willing to receive information. If patients and healthcare professionals agree on treatment decisions, applying PNE would be an inherent choice based on the patient's individual needs

and readiness, instead of a one-size-fits-all imposed formula [23,66,14]. This (more pragmatic) approach has the potential to enhance the process of conceptual change learning that PNE aims to accomplish [27,53,26].

CONCLUSION

Adding six sessions of PNE to physiotherapy after breast cancer surgery did not result in a better course of pain-related disability, pain intensity, physical or emotional functioning up to 18 months postoperatively as compared to biomedical pain education. Future research on PNE should look into the effects of a more patient-tailored approach, depending on a patient's specific needs and readiness.

ACKNOWLEDGEMENTS – CONFLICT OF INTEREST

The study is funded by Research Foundations – Flanders (FWO) (T005117N). Dr. Morlion reports personal fees from Pfizer, from Gruenenthal, from Kyowa-Kirin, from GSK, from Reckit and Benckiser, from Shionogi, outside the submitted work. The other authors have no conflicts of interest to declare.

REFERENCES

1. ActiGraph. What's the difference among the Cut Points available in ActiLife? ActiGraph website2019 [updated 3/1/2019. Available from: https://actigraphcorp.force.com/support/s/article/What-s-the-difference-among-the-Cut-Points-available-in-ActiLife.
2. Beckwée D, Leysen L, Meuwis K, Adriaenssens N. Prevalence of aromatase inhibitor-induced arthralgia in breast cancer: a systematic review and meta-analysis. Support Care Cancer. 2017;25(5):1673-86.
3. Bennett MI, Bagnall AM, Jose Closs S. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. Pain. 2009;143(3):192-9.
4. Butler DS, Moseley GL. Explain Pain. South Australia: Noigroup Publications; 2003.
5. Caneiro JP, Bunzli S, O'Sullivan P. Beliefs about the body and pain: the critical role in musculoskeletal pain management. Braz J Phys Ther. 2021;25(1):17-29.
6. Chibnall JT, Tait RC. The Pain Disability Index: factor structure and normative data. Arch Phys Med Rehabil. 1994;75(10):1082-6.

7. Cohen SR, Mount BM. Living with cancer: "good" days and "bad" days--what produces them? Can the McGill quality of life questionnaire distinguish between them? Cancer. 2000;89(8):1854-65.
8. Crombez G, De Paepe AL, Veirman E, Eccleston C, Verleysen G, Van Ryckeghem DML. Let's talk about pain catastrophizing measures: an item content analysis. PeerJ. 2020;8:e8643.
9. Darlow B, Dowell A, Baxter GD, Mathieson F, Perry M, Dean S. The enduring impact of what clinicians say to people with low back pain. Ann Fam Med. 2013;11(6):527-34.
10. Darnall BD, Ziadni MS, Krishnamurthy P, Flood P, Heathcote LC, Mackey IG, Taub CJ, Weber A. "My Surgical Success": Effect of a Digital Behavioral Pain Medicine Intervention on Time to Opioid Cessation After Breast Cancer Surgery-A Pilot Randomized Controlled Clinical Trial. Pain Med. 2019;20(11):2228-37.
11. de Beurs E, Van Dyck R, Marquenie LA, Lange A, Blonk RWB. De DASS: Een vragenlijst voor het meten van depressie, angst en stress. [The DASS: A questionnaire for the measurement of depression, anxiety, and stress.]. Gedragstherapie. 2001;34(1):35-53.
12. De Groef A, Devoogdt N, Van der Gucht E, Dams L, Bernar K, Godderis L, Morlion B, Moloney N, Smeets A, Van Wilgen P, Meeus M. EduCan trial: study protocol for a randomised controlled trial on the effectiveness of pain neuroscience education after breast cancer surgery on pain, physical, emotional and work-related functioning. BMJ Open. 2019;9(1):e025742.
13. De Vrieze T, Coeck D, Verbelen H, Devoogdt N, Tjalma W, Gebruers N. Cross-cultural Psychometric Evaluation of the Dutch McGill-QoL Questionnaire for Breast Cancer Patients. Facts Views Vis Obgyn. 2016;8(4):205-9.
14. Eisen T, Kooijstra EM, Groeneweg R, Verseveld M, Hidding J. The Needs and Experiences of Patients on Pain Education and the Clinical Reasoning of Physical

Therapists Regarding Cancer-Related Pain. A Qualitative Study. Front Pain Res (Lausanne). 2021;2:675302.

15. Evenepoel M, Haenen V, De Baerdemaecker T, Meeus M, Devoogdt N, Dams L, Van Dijck S, Van der Gucht E, De Groef A. Pain prevalence during cancer treatment: a systematic review and meta-analysis. J Pain Symptom Manage. 2021.

16. Ferreira VT, Dibai-Filho AV, Kelly de Oliveira A, Gomes CA, Melo ES, Maria de Almeida A. Assessing the impact of pain on the life of breast cancer survivors using the Brief Pain Inventory. J Phys Ther Sci. 2015;27(5):1361-3.

17. Moseley GL. Reconceptualising pain according to modern pain science. Physical Therapy Reviews. 2007;12(3):169-78.

18. Hall AM, Ferreira PH, Maher CG, Latimer J, Ferreira ML. The influence of the therapist-patient relationship on treatment outcome in physical rehabilitation: a systematic review. Phys Ther. 2010;90(8):1099-110.

19. Hamood R, Hamood H, Merhasin I, Keinan-Boker L. Chronic pain and other symptoms among breast cancer survivors: prevalence, predictors, and effects on quality of life. Breast Cancer Res Treat. 2018;167(1):157-69.

20. Harrington S, Gilchrist L, Sander A. Breast Cancer EDGE Task Force Outcomes: Clinical Measures of Pain. Rehabil Oncol. 2014;32(1):13-21.

21. Harrington S, Michener LA, Kendig T, Miale S, George SZ. Patient-reported upper extremity outcome measures used in breast cancer survivors: a systematic review. Archives of physical medicine and rehabilitation. 2014;95(1):153-62.

22. Hedayati E, Schedin A, Nyman H, Alinaghizadeh H, Albertsson M. The effects of breast cancer diagnosis and surgery on cognitive functions. Acta Oncol. 2011;50(7):1027-36.

23. Hoffmann TC, Del Mar CB. Shared decision making: what do clinicians need to know and why should they bother? Med J Aust. 2014;201(9):513-4.

24. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med. 1996;29(6):602-8.

25. Kaiser J, Dietrich J, Amiri M, Rüschel I, Akbaba H, Hantke N, Fliessbach K, Senf B, Solbach C, Bledowski C. Cognitive Performance and Psychological Distress in Breast Cancer Patients at Disease Onset. Front Psychol. 2019;10:2584.

26. King R, Robinson V, Elliott-Button HL, Watson JA, Ryan CG, Martin DJ. Pain Reconceptualisation after Pain Neurophysiology Education in Adults with Chronic Low Back Pain: A Qualitative Study. Pain Res Manag. 2018;2018:3745651.

27. King R, Robinson V, Ryan CG, Martin DJ. An exploration of the extent and nature of reconceptualisation of pain following pain neurophysiology education: A qualitative study of experiences of people with chronic musculoskeletal pain. Patient Educ Couns. 2016;99(8):1389-93.

28. Kinney M, Seider J, Beaty AF, Coughlin K, Dyal M, Clewley D. The impact of therapeutic alliance in physical therapy for chronic musculoskeletal pain: A systematic review of the literature. Physiother Theory Pract. 2020;36(8):886-98.

29. Kjeldsen HB, Klausen TW, Rosenberg J. Preferred Presentation of the Visual Analog Scale for Measurement of Postoperative Pain. Pain Pract. 2016;16(8):980-4.

30. Kline-Quiroz C, Nori P, Stubblefield MD. Cancer Rehabilitation: Acute and Chronic Issues, Nerve Injury, Radiation Sequelae, Surgical and Chemo-Related, Part 1. Med Clin North Am. 2020;104(2):239-50.

31. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing sedentary behavior. Med Sci Sports Exerc. 2011;43(8):1561-7.

32. Kushi LH, Doyle C, McCullough M, Rock CL, Demark-Wahnefried W, Bandera EV, Gapstur S, Patel AV, Andrews K, Gansler T, The American Cancer Society 2010 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. CA Cancer J Clin. 2012;62(1):30-67.

33. Lluch E, Dueñas L, Falla D, Baert I, Meeus M, Sánchez-Frutos J, Nijs J. Preoperative Pain Neuroscience Education Combined With Knee Joint Mobilization for Knee Osteoarthritis: A Randomized Controlled Trial. Clin J Pain. 2018;34(1):44-52.

34. Lovibond SH, Lovibond PF. Manual for the depression anxiety stress scales. Psychology Foundation [Internet]. 1995; 2nd. Ed. Available from: http://www2.psy.unsw.edu.au/dass//.

35. Manfuku M, Nishigami T, Mibu A, Yamashita H, Imai R, Tanaka K, Kitagaki K, Hiroe K, Sumiyoshi K. Effect of perioperative pain neuroscience education in patients with post-mastectomy persistent pain: a retrospective, propensity score-matched study. Support Care Cancer. 2021.

36. Meeus M NJ, Elsemans KS, Truijen S, De Meirleir K. Development and properties of the Dutch neurophysiology of pain test in patients with chronic fatigue syndrome. Journal of Musculoskeletal Pain. 2010;18(1):58-65.

37. Meeus M NJ, Van Wilgen P, Noten S, Goubert D, Huijnen I. Moving on to movement in patients with chronic joint pain. PAIN: CLINICAL UPDATES. 2016;24(1):1-8.

38. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nyström C, Mora-Gonzalez J, Löf M, Labayen I, Ruiz JR, Ortega FB. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. Sports Med. 2017;47(9):1821-45.

39. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55.

40. Mokhatri-Hesari P, Montazeri A. Health-related quality of life in breast cancer patients: review of reviews from 2008 to 2018. Health Qual Life Outcomes. 2020;18(1):338.

41. Moore P, Cole F. Pain Toolkit. 2002. Available from: www. paintoolkit. org.

42. Moseley GL, Butler DS. Explain Pain Supercharged. South Australia: Noigroup Publications; 2017.

43. Moseley GL, Butler DS. Fifteen Years of Explaining Pain: The Past, Present, and Future. J Pain. 2015;16(9):807-13.

44. Nijs J, Wijma AJ, Leysen L, Pas R, Willaert W, Hoelen W, Ickmans K, van WIlgen CP. Explaining pain following cancer: a practical guide for clinicians. Braz J Phys Ther. 2019;23(5):367-77.

45. Oldenmenger WH, Geerling JI, Mostovaya I, Vissers KCP, de Graeff A, Reyners AKL, van der Linden YM. A systematic review of the effectiveness of patient-based educational interventions to improve cancer-related pain. Cancer Treat Rev. 2018;63:96-103.

46. Oldenmenger WH, Sillevis Smitt PA, van Dooren S, Stoter G, van der Rijt CC. A systematic review on barriers hindering adequate cancer pain management and interventions to reduce them: a critical appraisal. Eur J Cancer. 2009;45(8):1370-80.

47. Olsson Möller U, Beck I, Rydén L, Malmström M. A comprehensive approach to rehabilitation interventions following breast cancer treatment - a systematic review of systematic reviews. BMC Cancer. 2019;19(1):472.

48. Palmen CM, van der Meijden E, Nelissen Y, Köke AJA. De betrouwbaarheid en validiteit van de Nederlandse vertaling van de Disability of the Arm, Shoulder, and Hand questionnaire (DASH). Nederlands tijdschrift voor fysiotherapie. 2004;114(2):30-5.

49. Pfister T, Matthews CE, Wang Q, Kopciuk KA, Courneya K, Friedenreich C. Comparison of two accelerometers for measuring physical activity and sedentary behaviour. BMJ Open Sport Exerc Med. 2017;3(1):e000227.

50. Pollard CA. Preliminary validity study of the pain disability index. Percept Mot Skills. 1984;59(3):974.

51. Prevost V, Delorme C, Grach MC, Chvetzoff G, Hureau M. Therapeutic Education in Improving Cancer Pain Management: A Synthesis of Available Studies. Am J Hosp Palliat Care. 2016;33(6):599-612.

52. Reid-Arndt SA, Cox CR. Stress, coping and cognitive deficits in women after surgery for breast cancer. J Clin Psychol Med Settings. 2012;19(2):127-37.

53. Robinson V, King R, Ryan CG, Martin DJ. A qualitative exploration of people's experiences of pain neurophysiological education for chronic pain: The importance of relevance for the individual. Man Ther. 2016;22:56-61.

54. Vosniadou S. Conceptual Change in Naïve Biology. New York: Routledge; 2008.

55. Salehifar E, Janbabaei G, Alipour A, Tabrizi N, Avan R. Taxane-induced peripheral neuropathy and quality of life in breast cancer patients. J Oncol Pharm Pract. 2020;26(6):1421-8.

56. Sasaki JE, John D, Freedson PS. Validation and comparison of ActiGraph activity monitors. J Sci Med Sport. 2011;14(5):411-6.

57. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-32.

58. Soer R, Reneman MF, Vroomen PC, Stegeman P, Coppes MH. Responsiveness and minimal clinically important change of the Pain Disability Index in patients with chronic back pain. Spine (Phila Pa 1976). 2012;37(8):711-5.

59. Song SJ, Min J, Suh SY, Jung SH, Hahn HJ, Im SA, Lee JY. Incidence of taxane-induced peripheral neuropathy receiving treatment and prescription patterns in patients with breast cancer. Support Care Cancer. 2017;25(7):2241-8.

60. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess. 1995;7:524–32.

61. Van Damme S, Crombez G, Vlaeyen JWS, Goubert L, Van den Broeck A, Van Houdenhove B. De Pain catastrophizing Scale: Psychometrische karakteristieken en normering. Gedragstherapie. 2000;33:209-20.

62. Van der Gucht E, Dams L, Bernar K, De Vrieze T, Haenen V, De Groef A, Godderis L, Morlion B, Meeus M, Devoogdt N. The Dutch Version of the Pain Disability Index (PDI-DLV): Psychometric Properties in Breast Cancer Patients Physiotherapy Theory and Practice. 2022.

63. van Wilgen CP, Nijs J. Pijneucatie: een praktische handleiding voor (para)medici. Houten: Bohn Stafleu van Loghum; 2010.

64. Wang L, Cohen JC, Devasenapathy N, Hong BY, Kheyson S, Lu D, Oparin Y, Kennedy SA, Romerosa B, Arora N, Kwon HY, Jackson K, Prasad M, Jayasekera D, Li A, Guarna G, Natalwalla S, Couban RJ, Reis S, Khan JS, McGillion M, Busse JW. Prevalence and intensity of persistent post-surgical pain following breast cancer surgery: a systematic review and meta-analysis of observational studies. Br J Anaesth. 2020;125(3):346-57.

65. Watson JA, Ryan CG, Cooper L, Ellington D, Whittle R, Lavender M, Dixon J, Atkinson G, Cooper K, Martin DJ. Pain Neuroscience Education for Adults With Chronic Musculoskeletal Pain: A Mixed-Methods Systematic Review and Meta-Analysis. J Pain. 2019;20(10):1140.e1-.e22.

66. Wijma AJ, Bletterman AN, Clark JR, Vervoort S, Beetsma A, Keizer D, Nijs J, Van WIlgen P. Patient-centeredness in physiotherapy: What does it entail? A systematic review of qualitative studies. Physiother Theory Pract. 2017;33(11):825-40.

LEGENDS OF FIGURES

Figure 1. *Flowchart of the EduCan trial according to the Consort 2010 flow diagram [57,39]*

A0: baseline assessment, A1: postoperative assessment, A4: 4 months post-surgery assessment (= end of intensive phase), A6: 6 months post-surgery assessment, A8: 8 months post-surgery assessment, A12: 12 months post-surgery assessment, A18: 18 months post-surgery assessment (end of maintenance phase). Missing data and reason are shown for the primary outcome measure (pain-related disability evaluated with Pain Disability Index).

Figure 2. *Pain Disability Index (PDI, total score) over time*

pre: baseline assessment before surgery, post: postoperative assessment, 4m: 4 months post-surgery assessment (= end of intensive phase), 6m: 6 months post-surgery assessment, 8m: 8 months post-surgery assessment, 12m: 12 months post-surgery assessment, 18m: 18 months post-surgery assessment (end of maintenance phase).

Figure 3. *Change in Pain Disability Index (PDI, total score) vs preoperative assessment*

pre: baseline assessment before surgery, 4m: 4 months post-surgery assessment (= end of intensive phase), 6m: 6 months post-surgery assessment, 8m: 8 months post-surgery assessment, 12m: 12 months post-surgery assessment, 18m: 18 months post-surgery assessment (end of maintenance phase).

Table 1. *Characteristics of participants according to treatment allocation. Numbers (%) are given unless specified otherwise.*

	Intervention group n=92	**Control group n=92**
Age (years), mean (SD) median (IQR)	55.4 (11.5) 54.0 (14.1)	55.2 (11.4) 54.0 (15.4)
BMI (kg/m²), mean (SD) median (IQR)	25.4 (4.3) 24.2 (6.4)	25.9 (5.9) 24.7 (6.8)
Educational level*		
Primary education or no diploma	3 (3.5%)	3 (3.5%)
Lower secondary education	5 (6%)	5 (6%)
Upper secondary education	23 (26%)	28 (33%)
Higher education: professional bachelor	30 (34.5%)	32 (37%)
Higher education: academic bachelor or master	25 (29%)	19 (22%)
Surgery at dominant side	44 (48%)	41 (45%)
Type of surgery		
BCS + ALND	4 (4%)	9 (10%)
ME + SLNB	41 (45%)	43 (47%)
ME + ALND	47 (51%)	40 (43%)
Tumor size		
pTis	5 (5%)	8 (9%)
pT0	8 (9%)	9 (10%)
pT1	30 (33%)	26 (28%)
pT2	30 (33%)	38 (41%)
pT3	17 (18%)	11 (12%)
pT4	2 (2%)	0 (0%)
Lymph node stage		
pNx	1 (1%)	0 (0%)
pN0	43 (47%)	50 (54%)
pN1	36 (39%)	29 (31.5%)
pN2	9 (10%)	7 (8%)
pN3	3 (3%)	6 (6.5%)
Radiotherapy	74 (80%)	66 (72%)
Breast	3 (3%)	9 (10%)
Thorax	63 (69%, N=91)	53 (58%)
MSP	68 (75%, N=91)	59 (64%)
Axilla	5 (5%, N=91)	7 (8%)
Hormone therapy (ongoing)	69 (75%)	68 (74%)
Tamoxifen	18 (20%)	11 (12%)
Aromatase inhibitors	51 (55%)	57 (62%)
Chemotherapy	63 (68.5%)	55 (60%)
Neo-adjuvant	25 (27%)	25 (27%)
Adjuvant	38 (41%)	30 (33%)
Anthracyclines	39 (42%)	38 (41%)
Taxane-based	63 (68.5%)	38 (41%)
Xeloda	2 (2%)	5 (5%)
Target therapy (ongoing)	23 (25%)	20 (22%)
Number of physical therapy sessions, mean (SD) median (IQR)	20.1 (6.6) 19.5 (8.0)	20.3 (7.7) 20.0 (10)

*Assessed retrospectively at 4 months after surgery, so only calculated from data available at 4 months postoperatively
ALND: axillary lymph node dissection, BCS: breast conserving surgery, BMI: body mass index, ME: mastectomy, MSP: median subclavian and parasternal lymph node areas, SLNB: sentinel lymph node biopsy.

Table 2. *Observed results and estimates for within and between group changes in primary outcome pain-related disability and secondary outcome pain intensity at different time points after surgery versus before surgery from a multivariate linear model for longitudinal measures*

	Observed information						**Change WITHIN groups**		**Difference in change BETWEEN groups**	
	Intervention group			Control group			Intervention group	Control group		
	Mean	Median (IQR)	n	Mean	Median (IQR)	n	Estimate (CI)	Estimate (CI)	Estimate (CI)	p value
Pain-related disability (PDI-DLV 0-70) (primary outcome)										
Preoperatively	4.9	0.0 (4.0)	91	4.6	0.0 (8.0)	92				
1 week postoperatively	20.5	17.5 (27.0)	92	21.6	22.0 (27.0)	89				
At 4 months	8.5	3.25 (11.9)	88	9.3	5.0 (12.0)	89	3.70 (1.37;6.04)	4.67 (2.35; 6.99)	-0.97 (-4.26;2.33)	0.5655
At 6 months	8.8	3.5 (14.0)	86	9.7	5.0 (13.5)	88	4.06 (1.71;6.42)	5.07 (2.74; 7.40)	-1.01 (-4.32;2.31)	0.5521
At 8 months	7.9	2 (10.0)	86	10.0	4.0 (15.0)	87	3.22 (0.67;5.77)	5.48 (2.94; 8.01)	-2.26 (-5.86;1.34)	0.2180
At 12 months (primary endpoint)	9.3	4.0 (12.0)	82	9.9	3.5 (15.5)	84	4.22 (1.40;7.03)	5.53 (2.74; 8.32)	-1.31 (-5.28;2.65)	0.5163
At 18 months	7.9	3.0 (11.0)	83	8.7	5.0 (14.0)	86	3.13 (0.59;5.67)	4.19 (1.68; 6.70)	-1.07 (-4.64;2.51)	0.5592
Pain intensity (VAS 0-100)										
Preoperatively	15.5	10.0 (21.0)	91	15.1	7.0 (23.0)	92				
1 week postoperatively	31.8	28.0 (31.0)	92	28.9	25.0 (32.5)	92				
At 4 months	22.7	16.0 (34.5)	88	24.6	20.0 (46.0)	89	7.26 (1.87;12.65)	9.49 (4.14;14.85)	-2.23 (-9.84;5.37)	0.5630
At 6 months	24.1	19.0 (34.0)	85	25.7	20.5 (39.0)	88	8.72 (2.80;14.63)	10.42 (4.58;16.27)	-1.70 (-10.03;6.62)	0.6869
At 8 months	21.2	14.5 (36.0)	86	23.4	18.0 (30.0)	87	5.95 (0.41;11.49)	8.67 (3.17;14.17)	-2.72 (-10.54;5.09)	0.4928
At 12 months	21.6	16.0 (25.0)	81	25.5	24.5 (41.0)	84	6.31 (1.06;11.57)	10.61 (5.43;15.79)	-4.30 (-11.68;3.09)	0.2524
At 18 months	19.0	15.0 (28.0)	83	23.7	14.5 (45.0)	86	3.91 (-1.70;9.52)	8.71 (3.17;14.24)	-4.80 (-12.69;3.09)	0.2315

Within-group changes versus preoperatively moment and comparison of these changes between both groups are derived from the multivariate linear model for longitudinal measures.

Table 3. *Observed results and estimates for within and between group changes in physical functioning at different time points after surgery versus before surgery from a multivariate linear model for longitudinal measures*

	Observed information						Change WITHIN groups		Difference in change BETWEEN groups	
	Intervention group			Control group			Intervention group	Control group		
	Mean	Median (IQR)	n	Mean	Median (IQR)	n	Estimate (CI)	Estimate (CI)	Estimate (CI)	p value
Sedentary time (accelerometry, min/day)										
1 week postoperatively	400.4	396.2 (97.9)	64	398.5	418.3 (110.5)	66				
At 4 months	372.3	380.8 (138.7)	72	377.3	391.7 (109.7)	71	-19.9 (-39.4; -0.3)	-20.8 (-40.6; -1.0)	0.9 (-26.9;28.7)	0.9479
At 12 months	356.5	371.1 (113.3)	48	372.2	364.3 (113.6)	48	-34.9 (-59.6; -10.1)	-23.9 (-48.6;0.8)	-10.9 (-45.9;24.0)	0.5376
Time in moderate-to-vigorous physical activity (accelerometry, min/day)										
1 week postoperatively	29.5	30.2 (29.01)	64	31.4	22.4 (34.3)	66				
At 4 months	33.6	28.5 (37.5)	72	32.8	26.3 (29.0)	71	3.45 (-1.43;8.33)	2.54 (-2.41;7.50)	0.90 (-6.05;7.86)	0.7980
At 12 months	45.4	44.2 (38.4)	48	38.1	35.1 (25.5)	48	13.41 (6.55;20.26)	6.75 (-0.11;13.61)	6.66 (-3.04;16.35)	0.1770
Time in (very) vigorous activity (accelerometry, min/day)										
1 week postoperatively	0.47	0.0 (0.14)	66	0.48	0.0 (0.17)	66				
At 4 months	1.31	0.0 (0.29)	72	0.67	0.0 (0.25)	71	0.18 (-0.01;0.36)	0.12 (-0.07;0.31)	0.06 (-0.21;0.32)	0.6620
At 12 months	1.91	0.14 (0.95)	48	1.24	0.14 (0.54)	48	0.39 (0.12;0.66)	0.22 (-0.05;0.49)	0.17 (-0.21;0.55)	0.3731
Step count average (accelerometry, steps/day)										
1 week postoperatively	6499	5909 (4232)	64	6201	5909 (3798)	66				
At 4 months	6673	7241 (4560)	72	6609	5943 (3079)	71	50 (-600;700)	342 (-316;1000)	-293 (-1218;632)	0.5332
At 12 months	7905	8221 (3593)	48	6642	6390 (3365)	48	1100 (349;1850)	261 (-489;1010)	839 (-221;1900)	0.1201
Upper limb function (DASH 0-100)										
Preoperatively	13.2	7.1 (20.8)	86	12.0	7.5 (17.7)	88				
1 week postoperatively	41.8	41.4 (24.2)	85	39.2	40.0 (22.5)	85	28.39 (24.76;32.03)	27.10 (23.47;30.73)	1.29 (-3.84;6.43)	0.6197
At 4 months	22.0	17.5 (27.5)	79	20.5	17.5 (24.4)	86	10.05 (7.05;13.05)	7.81 (4.89;10.72)	2.24 (-1.94;6.43)	0.2915
At 6 months	23.1	20.0 (21.3)	83	22.5	19.6 (24.2)	82	10.02 (7.01;13.02)	10.40 (7.44;13.37)	-0.39 (-4.60;3.83)	0.8563
At 8 months	22.1	14.6 (24.4)	84	23.3	20.3 (26.7)	86	9.16 (5.73;12.58)	10.60 (7.22;13.97)	-1.44 (-6.25;3.37)	0.5558
At 12 months	21.6	15.8 (20.0)	81	22.8	19.2 (26.7)	83	8.51 (5.39;11.64)	10.15 (7.07;13.22)	-1.63 (-6.02;2.75)	0.4632
At 18 months	19.1	12.5 (21.7)	79	22.1	19.2 (27.1)	82	6.56 (3.15;9.97)	9.72 (6.37;13.07)	-3.16 (-7.94;1.63)	0.1944

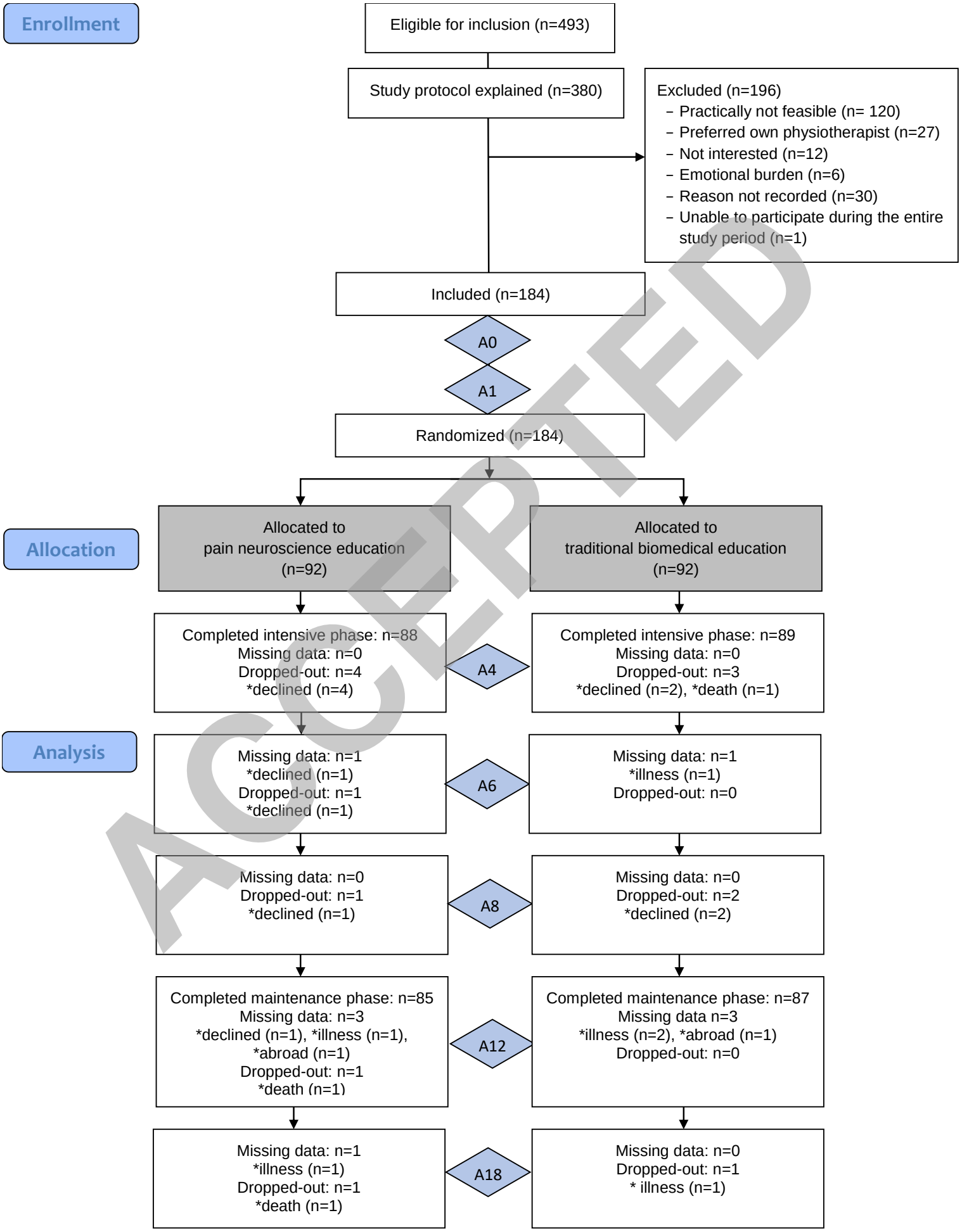
Within-group changes versus preoperatively moment and comparison of these changes between both groups are derived from the multivariate linear model for longitudinal measures.

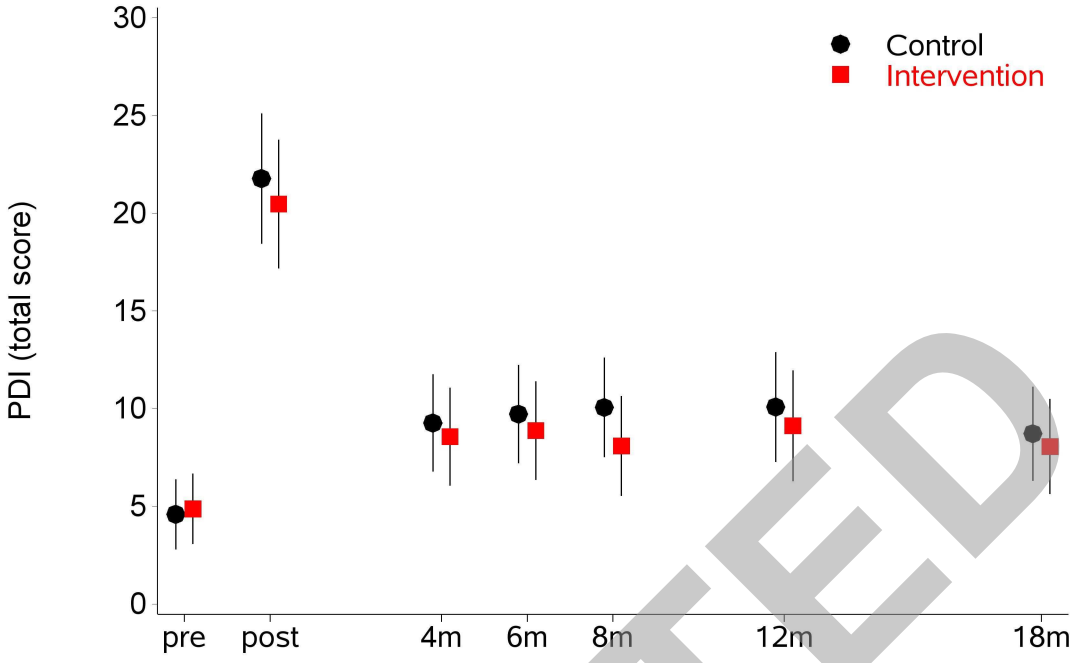
Table 4. *Observed results and estimates for within and between group changes in emotional functioning at different time points after surgery versus before surgery from a multivariate linear model for longitudinal measures*

	Observed information						**Change WITHIN groups**		**Difference in change BETWEEN groups**	
	Intervention group			Control group			Intervention group	Control group		
	Mean	Median (IQR)	n	Mean	Median (IQR)	n	Estimate (CI)	Estimate (CI)	Estimate (CI)	p value
Pain-related catastrophizing (PCS 0-52) *										
Preoperatively	10.3	8.5 (13.0)	90	8.6	7.0 (11.0)	89				
1 week postoperatively	9.2	8.0 (11.0)	90	8.5	6.5 (9.0)	90				
At 4 months	9.6	7.0 (15.0)	79	9.2	7.0 (12.0)	86	0.896 (0.676;1.188)	1.077 (0.818;1.419)	0.831 (0.561;1.233)	0.3590
At 6 months	9.6	9.0 (12.0)	84	8.8	6.5 (13.0)	82	0.870 (0.661;1.145)	0.958 (0.727;1.261)	0.908 (0.615;1.340)	0.6277
At 8 months	9.9	8.0 (12.5)	84	8.9	7.0 (13.0)	87	0.877 (0.662;1.162)	1.005 (0.761;1.328)	0.873 (0.587;1.297)	0.5001
At 12 months	9.1	7.0 (11.0)	81	9.5	8.0 (14.0)	83	0.894 (0.679;1.176)	1.065 (0.811;1.399)	0.839 (0.570;1.236)	0.3744
At 18 months	8.3	5.0 (9.5)	80	9.4	6.0 (12.0)	81	0.762 (0.562;1.033)	0.898 (0.663;1.216)	0.848 (0.552;1.304)	0.4533
Depression (DASS-21 0-42) *										
Preoperatively	7.5	4.0 (8.0)	90	6.3	6.0 (8.0)	91				
1 week postoperatively	6.8	4.0 (8.0)	90	5.6	4.0 (6.0)	91				
At 4 months	6.3	4.0 (10.0)	79	5.9	4.0 (6.0)	84	0.802 (0.588;1.092)	0.930 (0.686;1.261)	0.862 (0.558;1.330)	0.5018
At 6 months	7.1	4.0 (11.0)	84	6.2	4.0 (8.0)	83	0.819 (0.611;1.100)	0.956 (0.713;1.282)	0.857 (0.565;1.299)	0.4674
At 8 months	6.7	2.0 (8.0)	85	5.7	3.0 (8.0)	86	0.822 (0.608;1.112)	0.748 (0.554;1.010)	1.099 (0.717;1.683)	0.6653
At 12 months	5.3	2.0 (8.0)	82	5.3	4.0 (8.0)	83	0.625 (0.459;0.851)	0.774 (0.570;1.052)	0.808 (0.522;1.248)	0.3362
At 18 months	6.2	4.0 (8.0)	80	5.5	2.0 (8.0)	82	0.718 (0.535;0.963)	0.749 (0.560;1.003)	0.958 (0.633;1.449)	0.8375
Anxiety (DASS-21 0-42) *										
Preoperatively	5.4	4.0 (6.0)	90	5.1	4.0 (6.0)	91				
1 week postoperatively	4.9	4.0 (6.0)	90	4.8	2.0 (8.0)	91				
At 4 months	5.5	4.0 (6.0)	79	5.7	4.0 (8.0)	84	1.045 (0.772;1.415)	0.987 (0.733;1.328)	1.059 (0.693;1.620)	0.7902
At 6 months	5.2	4.0 (5.0)	84	6.1	4.0 (6.0)	84	0.963 (0.731;1.269)	1.213 (0.922;1.596)	0.794 (0.538;1.171)	0.2445
At 8 months	4.1	2.0 (6.0)	85	5.5	4.0 (8.0)	86	0.746 (0.562;0.992)	0.924 (0.697;1.224)	0.808 (0.541;1.206)	0.2973
At 12 months	4.6	2.0 (6.0)	82	4.9	4.0 (8.0)	83	0.783 (0.575;1.067)	0.839 (0.617;1.139)	0.934 (0.604;1.443)	0.7578
At 18 months	4.7	3.0 (8.0)	80	5.0	4.0 (8.0)	82	0.829 (0.625;1.100)	0.821 (0.621;1.085)	1.010 (0.679;1.504)	0.9600
Stress (DASS-21 0-42) *										
Preoperatively	10.6	10.0 (12.0)	90	9.6	8.0 (10.0)	91				
1 week postoperatively	7.5	7.0 (10.0)	90	7.5	6.0 (12.0)	91				
At 4 months	8.5	8.0 (10.0)	80	8.3	8.0 (11.0)	84	0.812 (0.598;1.101)	0.760 (0.563;1.026)	1.068 (0.696;1.639)	0.7619
At 6 months	9.4	10.0 (12.0)	84	9.1	7.0 (12.0)	84	0.909 (0.675;1.225)	0.866 (0.644;1.165)	1.049 (0.689;1.597)	0.8225

At 8 months	9.8	8.0 (8.0)	85	9.5	10.0 (12.0)	86	0.984 (0.736;1.314)		0.920 (0.690;1.226)	1.069 (0.711;1.608)	0.7482
At 12 months	9.0	8.0 (12.0)	82	8.0	6.0 (11.0)	84	0.782 (0.574;1.064)		0.721 (0.532;0.979)	1.084 (0.702;1.673)	0.7169
At 18 months	9.1	10.0 (12.0)	80	8.8	8.0 (10.0)	82	0.857 (0.629;1.167)		0.868 (0.639;1.178)	0.987 (0.639;1.525)	0.9535
Psychological symptoms (MQOL 0-10)											
Preoperatively	5.4	5.5 (3.7)	89	5.5	5.7 (4.0)	92					
1 week postoperatively	7.0	7.2 (3.2)	90	7.0	7.6 (4.2)	90					
At 4 months	7.4	7.7 (2.7)	78	7.2	7.7 (3.5)	86	1.93 (1.37;2.48)		1.68 (1.13;2.22)	0.25 (-0.53;1.03)	0.5306
At 6 months	7.3	8.0 (3.5)	84	7.0	7.5 (3.7)	83	1.88 (1.35;2.40)		1.41 (0.89;1.93)	0.47 (-0.27;1.21)	0.2118
At 8 months	7.0	8.0 (4.5)	83	7.4	7.7 (3.2)	87	1.57 (0.97;2.16)		1.92 (1.33;2.50)	-0.35 (-1.19;0.49)	0.4118
At 12 months	7.6	8.1 (3.0)	82	7.3	8.1 (3.5)	84	2.07 (1.49;2.65)		1.82 (1.25;2.39)	0.25 (-0.56;1.06)	0.5441
At 18 months	7.6	8.5 (3.7)	79	7.6	8.0 (2.5)	83	2.07 (1.57;2.57)		2.09 (1.60;2.57)	-0.02 (-0.71;0.68)	0.9646
Existential well-being (MQOL 0-10)											
Preoperatively	6.5	6.5 (1.8)	89	6.5	6.8 (2.7)	90					
1 week postoperatively	6.5	6.5 (2.5)	90	6.6	6.7 (2.2)	90					
At 4 months	6.7	7.0 (2.5)	80	7.0	7.2 (2.2)	86	0.19 (-0.14;0.52)		0.51 (0.19;0.84)	-0.32 (-0.78;0.14)	0.1745
At 6 months	7.0	7.0 (2.7)	84	7.2	7.7 (2.6)	83	0.48 (0.11;0.85)		0.66 (0.29;1.03)	-0.18 (-0.70;0.34)	0.5014
At 8 months	7.1	7.5 (2.7)	83	7.0	7.3 (2.3)	87	0.61 (0.22;1.00)		0.58 (0.20;0.96)	0.03 (-0.52;0.58)	0.9192
At 12 months	7.4	7.5 (2.3)	82	7.2	7.3 (1.9)	84	0.90 (0.52;1.27)		0.71 (0.34;1.09)	0.18 (-0.35;0.71)	0.5025
At 18 months	7.5	7.7 (2.2)	79	7.1	7.7 (3.3)	83	1.07 (0.64;1.49)		0.61 (0.20;1.03)	0.45 (-0.14;1.05)	0.1363
Support (MQOL 0-10)											
Preoperatively	8.3	8.5 (2.0)	88	8.3	8.5 (2.0)	91					
1 week postoperatively	8.2	8.5 (2.0)	89	8.2	8.5 (2.0)	90					
At 4 months	7.6	8.0 (2.0)	80	7.7	8.0 (2.0)	86	-0.59 (-0.97; -0.22)		-0.58 (-0.94; -0.22)	-0.02 (-0.54;0.50)	0.9479
At 6 months	7.6	8.0 (2.0)	84	7.8	8.0 (2.0)	81	-0.60 (-0.95; -0.25)		-0.48 (-0.83; -0.13)	-0.12 (-0.61;0.38)	0.6482
At 8 months	7.5	8.0 (2.0)	83	7.6	8.0 (2.0)	87	-0.75 (-1.14; -0.36)		-0.67 (-1.05; -0.28)	-0.09 (-0.64;0.46)	0.7552
At 12 months	7.9	8.0 (2.0)	82	7.8	8.0 (2.2)	84	-0.34 (-0.70;0.01)		-0.45 (-0.80; -0.10)	0.11 (-0.39;0.61)	0.6705
At 18 months	7.7	8.0 (2.0)	79	7.4	8.0 (2.5)	83	-0.54 (-0.96; -0.11)		-0.83 (-1.24; -0.42)	0.29 (-0.30;0.89)	0.3289

Within-group changes versus preoperatively moment and comparison of these changes between both groups are derived from the multivariate linear model for longitudinal measures.
* Since the analysis has been performed on transformed values (inverse hyperbolic sign), the estimates for the within-group changes and between-group differences in these changes are back transformed and thus refer to ratios.





Control (N)	92	89	89	88	87	84	86
Intervention (N)	91	92	88	86	86	82	83