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DOCTORAL SCHOOL
BIOMEDICAL SCIENCES



PAIN SCIENCE EDUCATION AFTER BREAST CANCER SURGERY

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“It can be argued that pain cannot and should not be prevented, as it is essential for survival, but what has to change is what a person does when he experiences pain.”

A. Louw

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ABBREVIATIONS

A0	assessment within one week before surgery
A1	assessment within one week after surgery
A4/6/8/12	assessment at six, eight or 12 months after surgery
AUC	area under the curve
BMI	body mass index
BPE	biomedical pain education
CG	control group
CONSORT	consolidated standards of reporting trials
COPE	committee on publication ethics
COVID-19	coronavirus disease 2019
DASH	disabilities of the arm, shoulder and hand questionnaire
EDGE	evaluation database to guide effectiveness
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
IASP	International Association for the Study of Pain
IG	intervention group
ICC	intraclass correlation coefficient
ICF	international classification of functioning, disability and health
IMMPACT	initiative on methods, measurement and pain assessment in clinical trials
IQR	interquartile range
MDC	minimal detectable change
PDI	pain disability index
PDI-DLV	Dutch language version of the pain disability index
PR	progesterone receptor
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROMIS	patient-reported outcomes measurement information system

PROSPERO	international prospective register of systematic reviews
PSE	pain science education
RoB 2	revised Cochrane risk-of-bias tool for randomized trials
ROBINS-I	risk of bias in non-randomized studies – of interventions
ROC	receiver operating characteristics
SAS	statistical analysis system
SD	standard deviation
SEM	standard error of measurement
SPSS	statistical package for the social sciences
TNM	tumor node metastasis
WHO	world health organization
WSCV	within-subjects coefficient of variation

SUMMARY

ENGLISH SUMMARY

The Belgian Cancer Registry reported 10,905 new female breast cancer patients in 2018. Despite the fact that successful screening, early intervention and enhanced treatment options have improved breast cancer survival, 90% of survivors suffer lifelong sequelae. These long-term complications are a major issue since they substantially impair daily life functioning and quality of life. One of the most frequently reported side effects of breast cancer treatments is pain, possibly affecting all aspects of functioning, including physical activity, upper limb use and return to work. As a result, adequate pain management during the early stages of breast cancer treatment is essential for resolving and preventing these issues, both in the short and long term.

Over the last few decades, there has been a greater understanding of the important role of educational interventions in the management of pain. However, they mainly focus on tissue injury as the source of pain and are often restricted to **biomedical** pain management instructions. Only recently, increased knowledge on pain mechanisms has resulted in a more modern educational approach, also known as *pain science education* (PSE). During the sessions, the patient is explained that pain is not always a true representation of the actual state of the tissues, but that it is the brain's interpretation of the threat of the injury, which is influenced by a variety of psychosocial factors. By zooming out of the purely biomedical vision on pain, PSE aims for a reconceptualization from a biomedical or structural model to an actual **biopsychosocial** one. Patients who understand that tissue damage is not the only cause of pain, but that stress, sleep, social interactions, previous pain experiences and physical activity, among other things, can all influence the pain experience (meaning that pain can occur without tissue damage), may be more likely to engage in activities they previously avoided due to pain. This, in turn, may lead to improved functioning.

The existing evidence for the potential benefits of PSE in non-cancer pain populations, along with the lack in methodologically strong studies in breast cancer patients, led us to the main research objective of this PhD research project, which was to investigate the **effectiveness of PSE in improving functioning after breast cancer surgery**. More specifically, the research aims of this PhD project were formulated as follows:

1. To conduct a systematic review on the effectiveness of perioperative PSE in improving pain, psychological factors and physical functioning in adults who underwent surgery

2. To examine the psychometric properties (including validity and reliability) of the Dutch language version of the Pain Disability Index one year after surgery for breast cancer

3. To conduct a randomized controlled trial to evaluate the effectiveness of postoperative PSE compared to biomedical pain education in improving pain-related disability, physical activity and upper limb functioning after breast cancer surgery

4. To investigate the effect of postoperative PSE in breast cancer patients on return to work by means of a randomized controlled trial

As an introduction, a comprehensive review of the literature on PSE provided during the perioperative period (of different types of general surgeries) was conducted (**Chapter I**). Based on the findings of this systematic review, we concluded that perioperative PSE did not significantly improve postoperative pain, psychological factors nor physical functioning compared to control interventions. However, because the specific context for the pain experience after breast cancer surgery likely differs from that of patients undergoing surgery for non-oncological problems, it is possible that the parameters for PSE will differ. In that case, it would not be appropriate to combine the findings of all these studies into a conclusion that would also apply to breast cancer patients.

Next, the psychometric properties (including validity and reliability) of the Dutch language version of the Pain Disability Index (PDI-DLV), which was used as the primary outcome measure in the subsequent chapter, were investigated (**Chapter II**). The findings showed that the PDI-DLV is a valid questionnaire to assess pain-related disability one year after breast cancer surgery. Since the absolute reliability is questionable, using it to evaluate changes within individual patients may not be as meaningful. Therefore, we do not recommend using the PDI-DLV to measure pain-related disability in individuals during follow-up after breast cancer surgery. However, the more observations are included, the more reliable the outcome. Because PDI-DLV scores in Chapter III were processed as group averages (n=184), the PDI-DLV's questionable absolute reliability did not rule it out as an adequate outcome measure.

The final two chapters discussed the findings of a randomized controlled trial on the effectiveness of PSE in improving functioning one year after breast cancer surgery (EduCan trial). First, the effects on pain-related disability (primary outcome), physical activity level and upper limb function (secondary outcomes) were reported (**Chapter III**). One hundred eighty-four participants received five postoperative educational sessions (either PSE or biomedical pain education) in addition to a standard physiotherapy program starting immediately after surgery. The change in pain-related disability from pre-surgery to 12 months after surgery did not differ between the two groups. Similar results were observed for physical activity level and upper limb function.

The last chapter on the randomized controlled trial described the effects of PSE compared to biomedical pain education on return to work (**Chapter IV**). For this, we selected all participants from the EduCan trial who were working at time of diagnosis (n=111) and compared the proportion working one year after surgery, time until work resumption and return to work expectations. Although the outcomes were in favor of the group receiving PSE, the differences were not statistically significant.

In conclusion, this work provides deeper insights into the follow-up of pain-related disability after breast cancer surgery, as well as the clinical application of PSE in this population and recommendations for further research. At first glance, our findings suggest that PSE does not ensure more favorable outcomes compared to biomedical pain education. However, several concerns were raised about the PSE intervention's cookie-cutter approach, leading to the conclusion that the question should not be whether educational interventions are necessary, but rather how the delivery method, timing and other factors could be refined to achieve a change in behavior and, as a result, improved functioning after breast cancer surgery. The complexity of educational interventions combined with a health care system that is entirely biomedical in nature will require years of efforts to optimize these interventions through a variety of mechanisms. Therefore, further research should explore how the effectiveness of PSE in the breast cancer population could be increased.

NEDERLANDSE SAMENVATTING

De Belgische Stichting Kankerregistratie rapporteerde 10.905 nieuwe vrouwelijke borstkankerpatiënten in 2018. Ondanks het feit dat succesvolle screening, vroegtijdige interventie en verbeterde behandelingsopties de overlevingskansen na borstkanker hebben verhoogd, kampt 90% met levenslange complicaties. Deze vormen een groot probleem omdat ze het dagelijks functioneren en de levenskwaliteit aanzienlijk belemmeren. Pijn is een van de meest gerapporteerde bijwerkingen als gevolg van borstkankerbehandelingen en heeft negatieve gevolgen op alle aspecten van het functioneren, waaronder lichamelijke activiteit, gebruik van de bovenste ledematen en werkhervatting. Bijgevolg is een adequate pijnbehandeling in de vroege stadia van de borstkankerbehandeling van cruciaal belang om deze problemen te verhelpen en te voorkomen, zowel op korte als op lange termijn.

De laatste decennia heeft men meer inzicht gekregen in de belangrijke rol van educatieve interventies bij de behandeling van pijn. Deze richting zich echter voornamelijk op weefselschade als oorzaak van pijn en beperken zich vaak tot **biomedische** instructies. De groeiende kennis over pijnmechanismen heeft pas recentelijk geleid tot een modernere educatieve aanpak, ook wel gekend als *pain science education* (PSE). Tijdens PSE legt een therapeut uit dat pijn niet altijd een correcte weergave is van de werkelijke toestand van de weefsels, maar dat het de interpretatie is van de hersenen van de dreigende weefselschade, dewelke op zijn beurt wordt beïnvloed door allerlei psychosociale factoren. Door uit te zoomen van de louter biomedische visie op pijn, beoogt PSE een reconceptualisering van een biomedisch of structureel model naar een echt **biopsychosociaal** model. Patiënten die begrijpen dat weefselschade niet de enige factor is die pijn veroorzaakt, maar dat onder andere ook stress, slaap, sociale interacties, eerdere pijnervaringen en lichamelijke activiteit de pijnervaring kunnen beïnvloeden (wat betekent dat pijn ook zonder weefselschade zou kunnen worden ervaren), zullen wellicht meer geneigd zijn om deel te nemen aan activiteiten die zij voordien vermeden omwille van de pijn. Dit zou de doeltreffendheid van de algemeen gebruikte kinesitherapeutische modaliteiten voor de behandeling en preventie van pijn-gerelateerde beperkingen na de behandeling van borstkanker kunnen verbeteren.

De combinatie van het wetenschappelijk bewijs voor de mogelijke voordelen van PSE in pijnpatiënten die geen kanker hebben en het gebrek aan methodologisch sterke studies bij borstkankerpatiënten bracht ons tot de belangrijkste onderzoeksdoelstelling van dit PhD project, namelijk het onderzoeken van de **effectiviteit van PSE in verbetering van het functioneren na de operatie voor borstkanker**. Concreter werden de onderzoeksdoelen van dit PhD-project als volgt geformuleerd:

1. Het uitvoeren van een systematische review over de effectiviteit van perioperatieve PSE ter verbetering van pijn, psychologische factoren en fysiek functioneren bij volwassenen die een operatie hebben ondergaan

2. Het onderzoeken van de psychometrische eigenschappen (inclusief validiteit en betrouwbaarheid) van de Nederlandstalige versie van de Pain Disability Index één jaar na de operatie voor borstkanker

3. Het uitvoeren van een gerandomiseerde gecontroleerde studie om de effectiviteit te evalueren van postoperatieve PSE in vergelijking met biomedische pijn educatie ter verbetering van pijn-gerelateerde beperkingen, fysieke activiteit en functioneren van de bovenste ledematen na de operatie voor borstkanker

4. Onderzoeken van het effect van postoperatieve PSE bij borstkankerpatiënten op werkhervatting door middel van een gerandomiseerde gecontroleerde studie

Ter inleiding werd een uitgebreide review van de literatuur uitgevoerd over PSE tijdens de perioperatieve periode (van verschillende soorten algemene operaties) (**Hoofdstuk I**). Gebaseerd op de bevindingen van deze systematische review concludeerden wij dat perioperatieve PSE geen significante verbetering gaf van postoperatieve pijn, psychologische factoren noch fysiek functioneren in vergelijking met controle interventies. Echter, omdat de specifieke context voor de pijnervaring na borstkankeroperaties wellicht verschilt van die van patiënten die voor niet-oncologische problemen worden geopereerd, is het mogelijk dat de parameters voor PSE zullen verschillen. In dat geval zou het niet juist zijn om de bevindingen van al deze studies te combineren tot een conclusie die ook zou gelden voor borstkankerpatiënten.

Vervolgens werden de psychometrische eigenschappen (waaronder validiteit en betrouwbaarheid) van de Nederlandstalige versie van de Pain Disability Index (PDI-DLV), die in het volgende hoofdstuk als primaire uitkomstmaat werd gebruikt, onderzocht (**Hoodstuk II**) De bevindingen toonden aan dat de PDI-DLV een valide vragenlijst is om pijngerelateerde beperking te evalueren één jaar na een borstkankeroperatie. Omdat de absolute betrouwbaarheid twijfelachtig is, is het minder zinvol om via deze vragenlijst veranderingen binnen individuele patiënten te evalueren. Daarom wordt het gebruik van de PDI-DLV voor het meten van pijngerelateerde beperking bij individuen tijdens de follow-up na een borstkankeroperatie niet aanbevolen. Echter, hoe meer metingen worden opgenomen, hoe betrouwbaarder de uitkomst. Omdat de PDI-DLV scores in Hoofdstuk III werden gebruikt als groepsgemiddeldes (n=184), sluit de twijfelachtige absolute betrouwbaarheid de PDI-DLV niet uit als een adequate uitkomstmaat van Hoofdstuk III.

De laatste twee hoofdstukken bespraken de bevindingen van een gerandomiseerde gecontroleerde trial naar de effectiviteit van PSE in het verbeteren van het functioneren één jaar na een borstkankeroperatie (EduCan trial). Eerst werden de effecten op pijn gerelateerde beperking (primaire uitkomstmaat), fysiek activiteitenniveau en functie van de bovenste ledematen (secundaire uitkomstmaten) gerapporteerd (**Hoodstuk III**). Honderdvierentachtig deelnemers kregen vijf postoperatieve educatieve sessies (PSE of biomedische pijneducatie) in aanvulling op een standaard kinesitherapeutisch programma dat direct na de operatie van start ging. De verandering in pijngerelateerde beperking van voor de operatie tot 12 maanden na de operatie verschilde niet tussen de twee groepen. Vergelijkbare resultaten werden waargenomen voor het fysieke activiteitenniveau en de functie van de bovenste ledematen.

Het laatste hoofdstuk over de gerandomiseerde gecontroleerde trial beschreef de effecten van PSE in vergelijking met biomedische pijneducatie op terugkeer naar het werk (**Hoofdstuk IV**). Hiervoor selecteerden we alle deelnemers uit de EduCan trial die aan het werk waren op het moment van de diagnose (n=111) en vergeleken de proportie die een jaar na de operatie aan het werk was, de tijd tot werkhervatting en de verwachtingen ten aanzien van terugkeer naar het werk. Hoewel de uitkomsten in het voordeel waren van de groep die PSE kreeg, waren de verschillen niet statistisch significant.

Concluderend kan worden gesteld dat dit werk diepere inzichten verschaft over de opvolging van pijngerelateerde beperking na een borstkankeroperatie, evenals de klinische toepassing van PSE in deze populatie en aanbevelingen voor verder onderzoek. Op het eerste gezicht suggereren onze bevindingen dat PSE niet zorgt voor gunstigere uitkomsten in vergelijking met biomedische pijneducatie. Er werden echter verschillende bedenkingen geformuleerd over de "one-size-fits-all" opzet van de PSE interventie, wat leidde tot de conclusie dat de vraag niet zou moeten zijn of educatieve interventies noodzakelijk zijn, maar eerder hoe de aanbiedingsvorm, timing en andere factoren zouden kunnen worden verfijnd om een gedragsverandering te bereiken en, als gevolg daarvan, een verbeterd functioneren na borstkankerchirurgie. De complexiteit van educatieve interventies gecombineerd met een gezondheidszorgsysteem dat volledig biomedisch van aard is zal jarenlange inspanningen vereisen om deze interventies via verschillende mechanismen te optimaliseren. Daarom moet verder onderzoek uitwijzen hoe de effectiviteit van PSE in de borstkankerpopulatie kan worden geoptimaliseerd.

GENERAL INTRODUCTION

The general introduction to this PhD dissertation covers four specific topics. At first, information on *breast cancer* is provided, including epidemiology, diagnosis, classification and treatment. Secondly, *consequences of breast cancer treatment*, such as *pain-related disability* and *return to work*, are discussed. The third section goes into more detail about *pain science education*, including the rationale for and current knowledge on pain science education in the breast cancer population. Finally, the *outline and specific aims* of this doctoral thesis are presented.

1. Breast cancer

1.1. Epidemiology

Breast cancer is the most frequent malignancy among women worldwide and the main cause of cancer death.[2] It is estimated that in 2020, 2.1 million women were diagnosed with breast cancer, accounting for 1 in 4 of all new female cancer diagnoses.[2] In Europe, one out of seven women will be diagnosed over the course of her lifetime.[3] Belgium has the world's highest incidence, which increases with age, from 22.9 cases per 10,000 in women years 15-39 of age to a peak of 437.4 cases per 10,000 in women aged 70 years or older.[4] The median age of Belgian women at the time of breast cancer diagnosis is 63.[4] Despite this high incidence, the average 5-year survival rate has risen up to 91% due to the ongoing improvement of detection method accuracy, early diagnosis and breast cancer treatment itself.[5-7] [4] Males contribute to 1% of breast cancer cases.[8]

Less than 10% of breast cancers results from hereditary or genetic factors.[9] Non-hereditary causes, such as those linked to menstruation (early age at menarche, later age at menopause), fertility (nulliparity, late age at first birth and fewer children), exogenous hormone consumption (oral contraceptive use and hormone replacement therapy), diet (alcohol intake) and anthropometry (higher weight, weight gain during adulthood and body fat distribution), are most commonly responsible for breast cancer.[9, 10] Breastfeeding and physical activity are two factors that have been linked to a reduced risk of breast cancer.[9]

1.2. Diagnosis and classification

Breast cancer is **diagnosed** based on a triple assessment using physical examination, imaging and pathological assessment. Physical examination includes bimanual palpation of the breasts and locoregional lymph nodes.[8] Imaging involves bilateral mammography and ultrasound of the breast and regional lymph nodes.[8] Mammography can be less efficient in locating minor breast lesions, detecting breast cancer in women with breast implants and in younger women who tend to have dense breast tissue. Magnetic resonance imaging of the breast is sometimes recommended for diagnosis in these cases, as well as in women with a genetic mutation or

multifocal disease, or in cases with ambiguous mammogram or ultrasound findings.[8, 11] In clinical practice, pathological evaluation is often based on fine-needle aspiration or core needle biopsy from the primary tumor and axillary nodes (if involvement is suspected).[11]

In addition to diagnosis, a corresponding **classification** is determined to select the best treatment. This classification is made according to different criteria.

Histopathological type: Each breast is composed of 15 to 20 *lobes* of glandular tissue (formed by smaller functional units, the *lobules*). These lobes are arranged radially around the *nipple*, with each lobe having its own excretory *duct*, separated and supported by connective and *adipose tissue* (**Figure 1**). Because the outer upper quadrant of the breast has plenty of glandular tissue, the majority of cancers (61%) develop closest to the armpit.[12] Breast cancer can originate in various areas of the breast: the ducts, the lobules, or occasionally, the tissue in between. The most common type is *invasive ductal carcinoma* (IDC) (50-70% of invasive breast cancers), which starts growing in a milk duct and invades the nearby breast tissue outside. The second most common type of breast cancer (10%) is *invasive lobular carcinoma* (ILC), which originates in the lobules. Invasive breast cancers can spread to other tissues and organs by entering the bloodstream or lymphatic system (metastatic breast cancer). Less common are the non-invasive neoplasms of the breast, which stay within the milk ducts or lobules and are broadly divided into two major types, *lobular carcinoma in situ* (LCIS) and *ductal carcinoma in situ* (DCIS). Although these are not life threatening, having DCIS can increase the risk of developing an invasive breast cancer later on.[13]

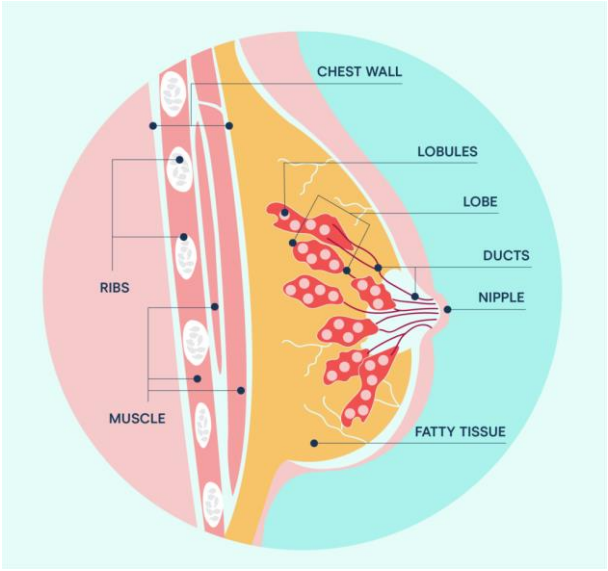

Figure 1 Healthy breast tissue.
Illustration reproduced with permission from the National Breast Cancer Foundation

Grading: It is recommended to use the Nottingham system[14] to assess the *grade of the tumor.* Grading entails matching the shape of cancer cells to that of normal breast cells. Healthy breast cells take on a specific shape that reflects their function (i.e. differentiate), whereas cancer cells

do not. In people with breast cancer, uncontrolled cell division occurs and the cells that usually shape the milk ducts in an ordered manner become disorganized. As the cells lose the features seen in healthy breast cells, they are classified as "well differentiated" (*grade I*), "moderately differentiated" (*grade II*), and "poorly differentiated" (*grade III*).

Receptor status/expression of proteins and genes: The majority of breast cancers cells (70%) contain an over-expression of hormone receptors to which estrogen and/or progesterone can bind to boost their growth.[15] Hormone sensitive or hormone receptor-positive (*ER+/PR+*) cancers are far more likely to respond to hormone therapy than hormone receptor-negative tumors. HER2 is another receptor that is over-expressed in about 20% of breast cancers. These cancer cells (*HER2+*), which divide and grow at a much faster rate than HER2- cells, benefit from HER2-taregted therapy.[15] Triple-negative tumors (*ER-/PR-/HER2-*), which account for 15% of all breast cancer diagnosis, are characterized by the absence of expression of all three receptors (estrogen, progesterone and HER2).[15] This means that neither the hormones estrogen and progesterone, nor the HER2 protein, are fueling the cancer's development. As a result, triple-negative breast cancer does not respond to hormone treatment or medicines that target the HER2 protein receptor. Among all the breast cancer subtypes, triple-negative breast cancer is associated with worse prognosis.[16] When compared to other types of breast cancer, it is considered more aggressive, is more likely to have spread at the time of diagnosis and returns more often after treatment.[17]

Staging: Final pathological diagnosis should be made according to the World Health Organization (WHO) classification[18] (**Figure 2**) and the eighth edition of the American Joint Committee on Cancer[19] tumor, node, metastasis (TNM) staging system.[8] Apart from anatomical information (quantitative classification categories for the primary tumor, regional lymph nodes and distant metastases, which are combined to determine an overall *TNM-stage*), this staging system includes prognostic information related to tumor biology (tumor grade, estrogen receptor, progesterone receptor, HER2 and gene expression data if available).[19] Staging can be done either before (*clinical staging:* cTNM) or after surgery (*pathological staging:* pTNM).[8] In general, pathological staging provides the most information to determine a patient's prognosis.

TUMOR SIZE	T0	T1	T2	T3	T4
T		0-20 mm	21-50 mm	>51 mm	Extension to chest wall, skin or ulceration
NODES	N0	N1	N2	N3	
N	No lymph node metastases	1-3	4-9	<10	
METASTASIS	M0	M1			
M	No evidence of cancer metastasis	Evidence of metastasis			

Figure 2 Simplified version of the Tumor, Node, Metastasis classification system.
From: https://epos.myesr.org/posterimage/esr/ecr2018/143735/mediagallery/755628

1.3. Treatment

Treatment modalities will depend on both diagnostic findings (and the resulting classification), as well as age, menopausal status, general health and preference of the patient.[8] For non-metastatic breast cancer, the goal of therapy is twofold – one, tumor removal from the breast and (if positive) regional lymph nodes, and two, preventing metastases. *Local therapy* consists of surgical resection of the tumor and removal of axillary lymph nodes (if positive), with consideration of postoperative radiotherapy. *Systemic therapy* may be preoperative (neo-adjuvant), postoperative (adjuvant) or both. Since the scope of this doctoral thesis is limited to non-metastasized breast cancer, we will only elaborate on the treatment modalities for this group.

Local therapy

Depending on the size and location of the tumor, standard surgical approaches for the breast include either total *mastectomy* (removal of the entire breast) or *breast-conserving surgery* (also known as lumpectomy, partial mastectomy or wide local excision), in which the cancer is removed alongside a rim of intact breast tissue. Surgical management of axillary lymph nodes is considered separately from surgical therapy of the breast. An *axillary lymph node dissection* is performed if the sentinel node is positive or if a positive axillary node is found during "clinical staging" (cfr. cTNM, described above under “Staging”). A *sentinel lymph node biopsy* (**Figure 3**)

is used to stage the axilla in patients with clinically negative nodes by palpation, with either invasive ductal carcinoma or a highly suspicious diagnosis of invasive carcinoma.[20] The sentinel lymph node is the first lymph node to which cancer cells from the primary tumor are most likely to spread. As tumor cells usually follow an orderly progression, the histology of the first lymph node would be representative of all the other axillary nodes.[20] A negative sentinel node biopsy means that the cancer has not spread and there is no need to remove the remaining nodes.

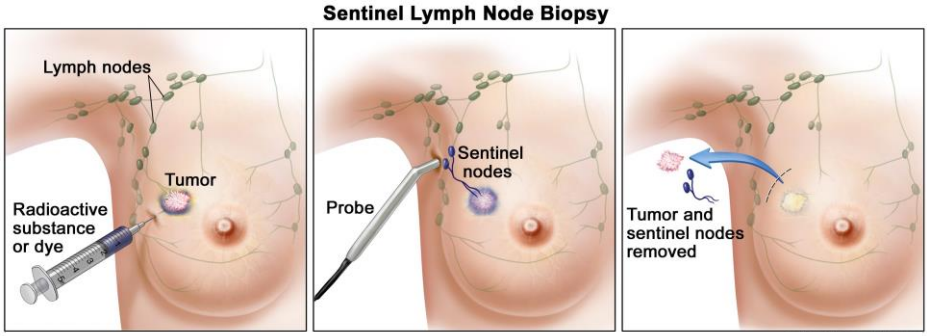

Figure 3 Sentinel lymph node biopsy.
For the National Cancer Institute © 2010 Terese Winslow LLC, U.S. Govt. has certain rights (illustration reproduced with permission)

Additionally, radiotherapy may be used to destroy any individual cancer cells that could have remained in the breast region after surgical excision of the tumor. This involves the use of high-energy X-rays, protons or other particles which can be administered externally (external beam radiotherapy), internally (brachytherapy) or as a combination of both. Depending on the involved tissues, radiation may target the whole breast or part of the breast (after breast-conserving therapy), the chest wall (after mastectomy) and/or the regional lymph nodes.

Systemic therapy

While surgery and radiotherapy aim to reduce the risk of local recurrence, systemic therapy addresses the risk of metastatic spread of cancer cells throughout the body through the bloodstream. Systemic therapy may be *neo-adjuvant* (to shrink the tumor before surgery), *adjuvant* (to reduce cancer recurrence by destroying any microscopic cancer cells that may have remained after surgery) or both.

Systemic therapy is guided by breast cancer subtype. Hormone therapy (e.g. tamoxifen) slows or stops the growth of hormone receptor-positive tumors (ER+/PR+) by preventing estrogen/progesterone from binding to these receptors. Additional chemotherapy may be needed for certain patients with hormone receptor-positive tumors. In patients with HER2-positive tumors, HER2-targeted antibodies (e.g. trastuzumab and pertruzumab) attach to the

HER2 receptor to slow or stop tumor growth. This treatment is often used in conjunction with chemotherapy (with additional hormone therapy if concurrent hormone receptor-positive). Patients diagnosed with triple-negative breast cancer are typically treated exclusively with chemotherapy (in addition to systemic therapy).[15]

2. Increased survival with functional challenges

Although improved treatment options have caused an increase in survival, 90% of breast cancer survivors experience long-term complications[5-7, 21], which in turn can negatively influence all aspects their functioning.[21-25] In the International Classification of Functioning, Disability and Health (ICF), which is the WHO's framework for measuring health and disability[26], *functioning* refers to all body functions, activities and participations, while *disability* is similarly an umbrella term for the negative aspects of functioning (i.e. impairments, activity limitations and participation restrictions).[27, 28] The biopsychosocial model of functioning and disability, embodied in the ICF, perceives functioning and disability as a dynamic interaction between health conditions and contextual factors, both personal and environmental.[26] An example of the ICF-model applied to breast cancer is portrayed in **Figure 4**.

Along with axillary web syndrome and lymphedema, breast cancer patients may experience decreased aerobic capacity and physical activity levels, as well as upper limb dysfunctions, including restrictions of arm and shoulder movements and decreased strength.[21, 27, 29] In addition, also intangible side effects are often reported, including (but not limited to) pain, fatigue, depression, anxiety, psychological distress and cognitive dysfunction.[21, 30-32] Altogether, these complications can result in, among others, fear of cancer recurrence, sleep disturbances, concerns about body image, reduced social contacts and sexual problems, all of which can have a significant impact on patients' quality of life.

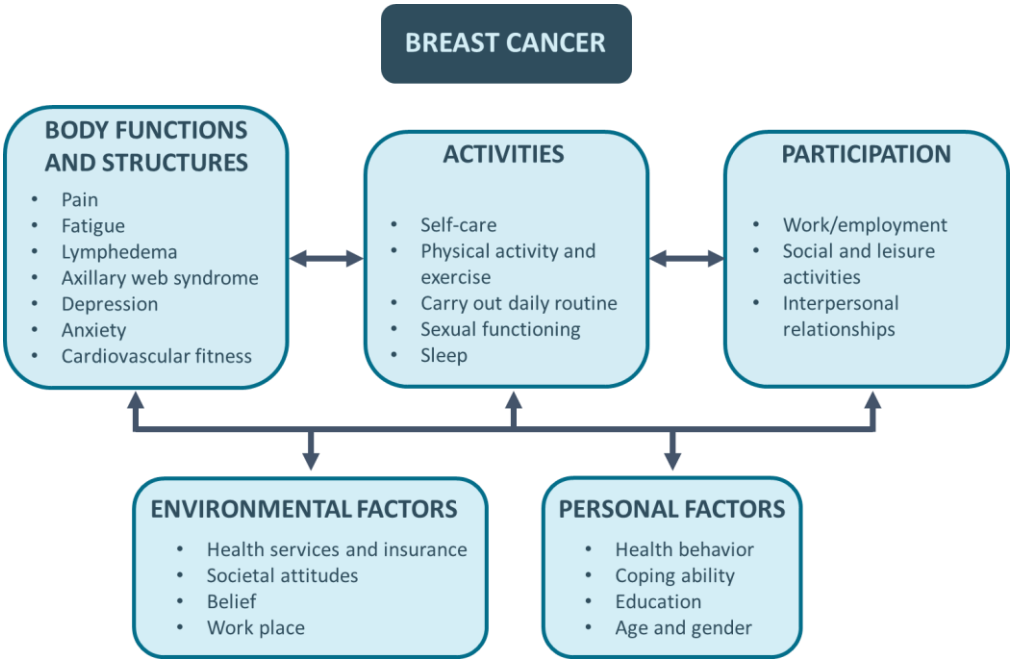

Figure 4 Breast cancer portrayed according to the ICF-model.

2.1. Pain and pain-related disability

One of the most common consequences of breast cancer therapies is pain (**Table 1**).[33, 34] Initially, pain serves as our own protection mechanism by promoting careful treatment of the injured area. While one would expect pain to decrease after treatments, as healing occurs, it can remain

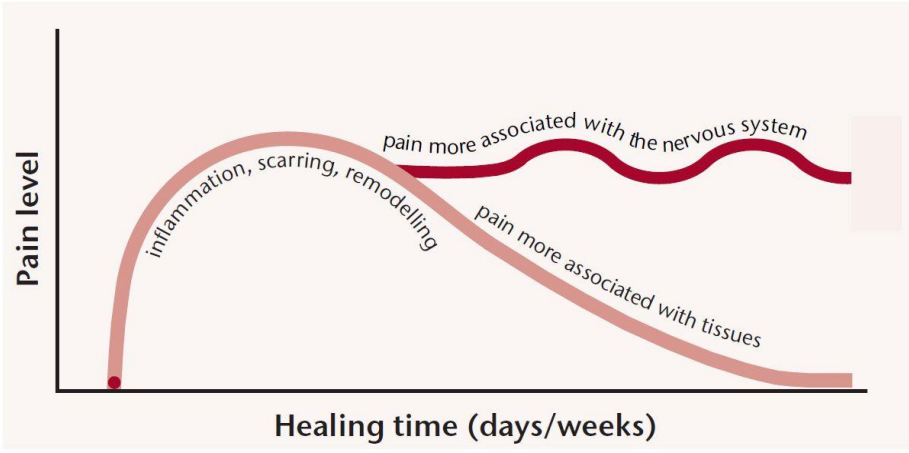

Figure 5 Simplified representation of the phases of soft-tissue healing
From: https://www.nhsaaa.net/media/1985/20170713pain.pdf

after tissues have healed and may then develop into a persistent state (**Figure 5**). This can be seen within the definition of pain and the additional remarks in **Table 1**, stating that pain does not equal tissue damage and is a personal and subjective experience. Persistent pain is experienced by almost half of all women undergoing breast cancer surgery and about one in four describe this pain as moderate-to-severe.[35] Up to 10 years after the end of treatment, about 30% of breast cancer survivors experience above-average pain (compared to age-specific population norms) without significant improvement in either prevalence or intensity.[35, 36]

What is pain?

Pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[1]. In addition:

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological and social factors
- Pain and nociception are different phenomena and pain cannot be inferred solely from activity in sensory neurons
- Through their life experiences, individuals learn the concept of pain
- A person's report of an experience as pain should be respected
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain

Table 1 The International Association for the Study of Pain (IASP) definition of pain.

According to the International Classification of Diseases 11th Revision, persistent pain may be conceived as a disease in its own right (*chronic primary pain*) or secondary to an underlying disease (*chronic secondary pain*).[37] Persistent cancer-related pain is a subgroup of the latter and is defined as persistent pain caused by the primary cancer itself or metastases (*chronic cancer pain*) or its treatment (*chronic postcancer treatment pain*). If the cause of persistent pain is known, or only one treatment was given, the following specific subdiagnoses can be used: (1) *chronic postcancer medicine pain* (caused by any disease-modifying anticancer medicine, including systemic chemotherapy and hormonal treatment), for example chronic painful chemotherapy-induced polyneuropathy and chronic arthralgia (which is associated with hormone therapy); (2) *chronic postradiotherapy pain* (caused by delayed local damage to the nervous system, bones, or other soft tissues in the field of radiotherapy given to treat the primary tumor or metastases), including chronic painful

radiation-induced neuropathy; (3) *chronic postcancer surgery pain*.[38] However, most patients receive an extensive combination of treatment modalities, making it nearly impossible to pinpoint the precise cause of persistent postcancer treatment pain. In this context, the IASP states that the general diagnosis of *chronic postcancer treatment pain* will be appropriate.[38]

Possible risk factors for persistent postcancer treatment pain are, among others, younger age, higher BMI, preoperative pain, mastectomy (compared to breast conserving surgery), axillary lymph node dissection (compared to sentinel node biopsy), damage to the intercostobrachial nerve, acute postoperative pain, radiotherapy, chemotherapy, hormone therapy and lymphedema.[34, 39]

As previously mentioned, the side effects of breast cancer treatments, including pain, can have a debilitating impact on all aspects of functioning. Aside from the knowledge that pain does not always imply tissue damage, several studies have demonstrated that the relationship between pain and disability is not straightforward and suggest looking at the pain experience as a biopsychosocial phenomenon for a better understanding of how it can become a persistent problem.[40-42] The *biopsychosocial model* (originally introduced by George Engel) suggests that not only the biological factors should be considered to understand a person's medical condition, but also the psychological and social ones.[43] The main assumption is that pain and pain-related disability are not only influenced by tissue injury (if present), but also by psychological and social factors. This is supported by the aforementioned definition of pain by the IASP (**Table 1**), implying that pain is a subjective and multidimensional experience, resulting from a variety of both physical and non-physical factors (**Figure 6**). On a side note, it should be mentioned that the (negative) factors displayed in **Figure 6** are only a selection of the many, intertwined, influences on the pain experience. In addition, also neutral (e.g. attention, interpretation) and positive (e.g. self-efficacy) psychological factors, as well as social factors (e.g. marital status, social support) can affect how pain is perceived.[44, 45] This means that a painful experience not only results *in* physical and non-physical factors, but also results *from* physical and non-physical factors.[46] The analogy can be made between the biopsychosocial model of pain and the above-mentioned ICF-model portraying disease-related disability.

To fully capture the enigmatic concept of pain, we therefore cannot reduce it to a mere structural impairment, but should instead consider the entire pain experience, including all biopsychosocial contributing factors and consequences. We do this by targeting the more general term *pain-related functioning/disability*. Using this outcome, we acknowledge the fact that pain is a subjective and multidimensional experience, fundamentally unobservable by those

who are not experiencing it. Pain-related disability defines pain as its consequences and impact on an individual's life (a personal experience), which is a valuable guideline during rehabilitation.

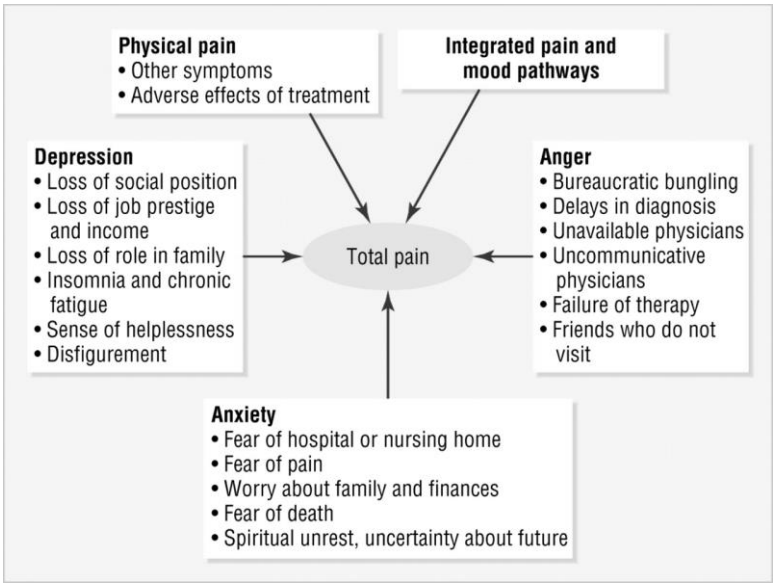

Figure 6 Factors affecting patient's perceptions of pain.
From: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1450053/

2.2. Work disability and return to work

Another aspect of functioning that is often affected by the consequences of breast cancer treatment (such as pain) is return to work. In fact, pain is one of the strongest predictors for long-term absenteeism.[47] *Average time to work resumption* in breast cancer survivors differs among countries, ranging between three months in Sweden and 11 months in the Netherlands.[48] According to a large-scale study conducted by the Christelijke Mutualiteit (a Belgian health insurance fund) in 7,600 women with breast cancer (all stages combined) who were working at the time of diagnosis, average time to work resumption varied between 7.6 and 12.4 months (median 6.2-11.9 months).[49] Chances of work resumption decrease enormously in patients on sick leave for more than six months.[50-52] The *prevalence of return to work within one year of diagnosis* varies from 43% (the Netherlands) to 93% (USA).[48] In Belgium, the likelihood of returning to work within one year after diagnosis is 35%, increasing to 67% two years after diagnosis.[49] At the latter time point, 23% remains incapacitated for work.[49] Differences between countries are, among others, due to differences in health insurance systems. Belgium has national health insurance, which is found to delay or reduce work resumption. In the USA, where

a universal healthcare program is lacking, most people rely on private healthcare. Fear of losing insurance can significantly influence return to work after cancer treatment.[53]

In conclusion, these treatment-related consequences are not only experienced on the level of body functions, but may also affect activities, participation and interaction with the world around, which corresponds to de definition of disability as described above.[26-28]

3. Pain science education

Currently, evidence-based pain management in breast cancer patients consists of multimodal pharmacotherapy, physical rehabilitation and psychosocial interventions.[54, 55] In addition, as many breast cancer survivors still experience pain and pain-related disability, recent years have witnessed a growing academic interest in adding educational interventions to the existing approach.[56-58] Educational interventions that explain the pain experience from a biomedical perspective (in terms of tissue damage) have little effect on reducing pain and disability and may even increase fear and anxiety[59-62], which are known to be strong predictors for pain and disability.[63, 64] This might not be surprising, as tissue damage falls short in explaining persistent pain following cancer.

Recent discoveries have resulted in a biopsychosocial educational intervention that broadens the scope on the pain experience. In addition to a biological explanation for pain, it considers an array of many psychosocial contributing factors, such as previous pain experiences, beliefs and fears about pain[65-69], which is consistent with the reasoning behind the biopsychosocial model as stated earlier. This intervention is known by several different names, including pain education, explain pain, pain neuroscience education, pain physiology education, pain biology education and pain science education. From here on, we will refer to the biopsychosocial educational intervention for pain as *pain science education* (PSE).



Figure 7 Pain is an output of the brain, not an input of the body.

PSE explains the neurobiology and neurophysiological concepts of pain (processing) within the nervous system, so patients understand *how* their pain is produced. They learn that pain is not always a true representation of the actual state of the tissues, but that it is *the nervous system's*

interpretation of the threat of their injury (**Figure 7**), which in turn is subject to various psychological factors (e.g. fear avoidance, catastrophizing, expectations, cognitions and beliefs).[70] PSE, which aims to improve people's pain-related cognitions as well as their perceptions of the biochemical mechanisms believed to constitute pain, reconceptualizes pain as a true biopsychosocial phenomenon. Since any proof of danger to body tissue can increase pain and any proof of protection will decrease pain, PSE does not question the presence of pain in the absence of tissue injury, but rather explains how pain can be perceived even though tissues are not endangered (**Figure 8**).[70-72]

By explaining the scientific concepts that are central to the development and persistence of pain, PSE aims to create lasting changes in the patient's beliefs about pain, which they can integrate into their wider pain and function-related beliefs, attitudes, behaviors, treatment and lifestyle choices.[71] This in turn, can increase their engagement in the biopsychosocial recommendations made for pain management and reduction.

As perceptions guide behavior, people may be more likely to engage in activities previously avoided because of pain once they change their pain-related beliefs and perceive pain as less threatening. Knowing that participating in an exercise is safe is often enough to motivate patients to increase their activity levels. They may start to engage in exercise, return to work and other activities of daily living, not letting pain get in the way of regaining their functional activities and life roles.[71]

3.1. State of the art

Literature indicates that PSE is successful in enhancing pain levels, pain knowledge, disability, pain catastrophizing, kinesiophobia, attitudes regarding pain, physical movement and work status in persistent non-cancer pain populations.[70, 73-75] However, PSE as a standalone treatment does not seem to be sufficient for clinically important improvements in pain and disability and should be combined with physical interventions (e.g. physiotherapy).[70, 71, 74] Wood and Hendrick (2019) identified moderate evidence for PSE in addition to usual physiotherapy in the



Figure 8 Pain science education explains how pain can be perceived even though tissues are not endangered.
Illustration reproduced with permission from: https://dynamicdiscdesigns.com/community-approach-pain-education/pain-education/

short-term improvement of disability and pain scores.[75] In the short to medium term, clinically meaningful improvements were seen in pain catastrophizing and kinesiophobia (i.e. fear of movement).[76] Barbari et al. (2020) found that PSE, graded exposure and cognitive behavioral therapy were the most effective interventions for behavior modification and compliance with exercise, with benefits also in the long-term.[77]

Research on the effectiveness of PSE in non-persistent pain populations is limited. A systematic review of existing studies has been performed and its results are described in Chapter I.

3.2. Pain science education and (breast) cancer

Despite the fact that pain being a frequently reported side effect of cancer treatments with disabling impact on daily-life activities, research on the effectiveness of PSE in general cancer populations is limited. One observational, uncontrolled study showed decreased pain, catastrophizing and improved pain-related quality of life (medium effect sizes) following a single session of PSE in 30 patients suffering from persistent pain following cancer.[78] However, this was pilot study without a control group and a physical intervention. While in persistent non-cancer pain populations this is known to increase the effectiveness of PSE, up to our knowledge, no research has been conducted on the combination of physiotherapy and PSE in general cancer populations.

Research on the effectiveness of PSE in breast cancer patients seems particularly important because psychosocial risk factors for pain are prevalent and/or exacerbated during and after treatments. As far as we know, only two studies have looked at the effect of PSE in a breast cancer only population.[79, 80] PSE

The first study, a pilot randomized controlled trial by Darnall et al. (2019), looked at the effects of a 90-minute preoperative video on pain psychoeducation compared to a digital text education about health and nutrition (framed in terms of their importance in enhancing recovery after surgery).[79] Because the authors had not found evidence of an interaction effect on either one of the follow-up time-points (two-, four-, eight- and 12-week follow-up), they created a composite postsurgical measure for each of the outcomes (average pain intensity, physical function, pain interference, pain catastrophizing, anxiety and depression) over all the postsurgical follow-up assessments. Doing so, the intervention group showed a significant increase in average postsurgical pain from baseline compared to controls. There were no interaction effects for average physical function, pain interference, pain catastrophizing, anxiety and depression. Several downsides of this study should be addressed. Firstly, the intervention did not allow for any interaction seen its digital format. In addition, it was offered once and before surgery for

breast cancer, when most people are not (yet) in pain. This could have made application of the newly learned knowledge more difficult. Moreover, the primary outcome was to look at the feasibility and acceptability of the digital behavioral pain medicine intervention and the outcomes we are interested in were only secondary and tertiary. Lastly, the study did not have a long enough follow-up period to assess possible effects on pain chronification.

In the second study, a retrospective propensity score-matched study by Manfuku et al. (2021), the effects of PSE were compared to those of biomedical pain education (BPE).[80] Starting one week after surgery, both the intervention and control group attended a similar individual standard physiotherapy program (40 minutes once every 1–2 weeks during three months) at the clinic under the supervision and treatment of a physical therapist. Both groups received their education at the same time-points (one week before surgery and at every postoperative physiotherapy session). One year after surgery, the group receiving PSE reported significantly lower pain intensity (moderate effect size), pain catastrophizing and pain interference compared to controls (all small effect sizes). The limitations of this study were that that it was a retrospective study with non-randomized group allocation and the two groups were separated over time.

4. Outline and specific aims

Pain is one of the many complications of breast cancer treatments that can negatively impact resumption of functional activities and life roles, as well as dramatically alter quality of life. Although physiotherapy, as part of non-pharmacological pain therapy, can help to alleviate pain and its consequences (including upper limb dysfunction)[81, 82], many breast cancer survivors are still disabled by pain on many aspects of their daily-life functioning. The combination of evidence for the potential benefits of PSE in non-cancer pain populations and the lack in methodologically strong studies on this topic in breast cancer patients leads us to the main research objective of this PhD research project, which was to investigate the effectiveness of PSE after breast cancer surgery. For this purpose, my colleague Lore Dams and I collaborated on the set up and implementation of a double-blinded randomized controlled trial (EduCan trial). In this study, we evaluated several outcomes between a group of breast cancer patients who had received PSE education and controls who had received a biomedically focused education (BPE) up to one year after surgery. While this thesis focused on the effect of PSE on pain-related disability and other aspects of daily-life functioning, Lore Dams' dissertation elaborated on the impact on pain mechanisms and psychosocial factors (including pain catastrophizing, depression, anxiety and

stress). In addition to the EduCan trial, two other studies were conducted for the purpose of this doctoral thesis.

As the EduCan trial was set up to study the effectiveness of PSE after breast cancer surgery (starting shortly after surgery), we were curious about the existing literature on perioperative (preoperatively and early postoperatively) PSE after common surgical procedures in general. These results could help us with interpreting our own future findings. Therefore, we conducted a systematic review (2020) to examine the postoperative impact of PSE on pain, psychosocial factors and physical functioning in adults who underwent surgery (**Chapter I**).

Given that pain during and after breast cancer treatments is prevalent and it exerts a disabling impact on all aspects of functioning, pain-related disability was selected as the primary outcome to assess the effectiveness of PSE in the EduCan trial. Pain-related disability was measured with the Dutch language version of the Pain Disability Index (PDI-DLV), for which literature on the psychometric properties in breast cancer patents was non-existent. As psychometric properties are not an inherent trait of a questionnaire (but are situation-dependent), exploring them within a Dutch-speaking breast cancer population would strengthen the results of the primary outcome of the EduCan trial. For this, we looked at the reliability and validity of the PDI-DLV one year after surgery for breast cancer (**Chapter II**).

Furthermore, the effectiveness of PSE in improving pain-related disability was researched using a randomized controlled trial. The intervention group receiving PSE was compared to a control group receiving BPE (each group received five educational sessions over an eight-month period). In addition to the educational sessions, both groups attended the same standard physical therapy program. The outcomes of this research aim were subdivided into two chapters. **Chapter III** reports on the effects on pain-related disability, physical activity level and upper limb function. In addition, as breast cancer survivors have higher unemployment (which is partially influenced by pain), we were interested to explore the possible effects of PSE on return to work in this population **(Chapter IV)**. It should be noted that the results of the EduCan trial (Chapters III and IV) are preliminary, since the follow-up period of the EduCan trial has not yet been completed. In this thesis, we discussed the results up to one year after surgery, while the last assessment time point of the EduCan trial is 18 months postoperatively.

The specific aims of this doctoral project were:

1. To conduct a systematic review on the effectiveness of perioperative pain science education in improving pain, psychological factors and physical functioning in adults who underwent surgery
2. To examine the psychometric properties of the PDI-DLV one year after surgery for breast cancer
3. To study the effectiveness of pain science education after breast cancer surgery in improving pain-related disability, physical activity and upper limb functioning by means of a randomized controlled trial
4. To investigate the effect of pain science education after breast cancer surgery on return to work by means of a randomized controlled trial



EFFECTIVENESS OF PERIOPERATIVE PAIN SCIENCE EDUCATION ON PAIN, PSYCHOLOGICAL FACTORS AND PHYSICAL FUNCTIONING: A SYSTEMATIC REVIEW

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ABSTRACT

Objective To synthesize the evidence on the effectiveness of pain science education on pain, psychological factors and physical functioning in adults who underwent surgery.

Data sources A systematic literature search of English articles using PubMed/Medline, Embase, Web of Science Core Collection and Cochrane Library.

Review methods The search strategy was constructed as follows: *[((pain) AND (education)) OR (pain education)] AND (surgery).* Only controlled quantitative studies in adults reporting outcome(s) on pain, psychological factors and/or physical functioning were included. Risk of bias was assessed using the Cochrane risk of bias tools. P-values and corresponding effect sizes for interaction-effect (time x group) portrayed the difference in change over time between groups were of interest. The last search was conducted on February 28, 2021.

Results Nine papers (n=1,078) were deemed eligible for this review. Two randomized controlled trials showed significant interaction effects. Breast cancer patients who had received one preoperative pain science education session showed a significant increase in postoperative *pain* compared to controls (P-value=0.0394). Furthermore, p*sychological factors* (pain catastrophizing and kinesiophobia) decreased in participants who had received pain science education before total knee arthroplasty, while this was not the case in the control group (P-value<0.001, ɳ2p:0.11).

Conclusions Overall, pain science education did not result in any significant postoperative effects on pain, psychological factors and/or physical functioning compared to controls. There is currently no strong evidence for the implementation of pain science education in the perioperative period.

Registration number PROSPERO: ID 161267, registration number CRD42020161267

INTRODUCTION

Pain is a frequent problem after surgery, with serious consequences on both an individual as a societal level if insufficiently controlled. Between 58-86% of patients experience pain immediately after surgery.[83, 84] At that point in time, pain is normal and serves as a protection mechanism to promote tissue healing. However, in 10-50% of patients, pain persists after tissues have healed and develops into a chronic state.[85-89]

There are several risk factors for chronic postsurgical pain, including **pain** (preoperative pain, higher intensity of acute postsurgical pain, acute postsurgical pain lasting more than five days), **psychological factors** (fear or anxiety, depression, pain catastrophizing) and **physical functioning** (worse pain interference).[85, 86] Although these factors inform us about patients at risk for chronic postsurgical pain, they could present potential cues for preventive and curative therapies.

Apart from improvements in surgical techniques, multimodal pharmacotherapy and physical rehabilitation, recent years have witnessed a growing academic interest in educational interventions in the management of pain.[56-58] New insights have led to a biopsychosocial educational intervention that broadens the scope on the pain experience, not only explaining it from a biomedical or structural perspective, but also considering possible psychosocial contributing factors.[65-69] *Pain science education* explains *how* pain is produced. The patient is educated that pain is not always a true representation of the actual state of the tissues, but it is *the nervous system's interpretation of the threat of their injury*, which in turn is subject to various psychological factors, including fear avoidance, catastrophizing, expectations, cognitions and beliefs.[71]

Several systematic reviews and meta-analyses on pain science education in chronic musculoskeletal pain populations have reported evidence for, among other things, improving pain ratings, pain knowledge, disability, pain catastrophizing, kinesiophobia, attitudes regarding pain and physical movement.[70, 74, 75] However, to achieve clinically important improvements, education should be combined with physical interventions.[70, 71, 74, 76]

Considering the aforementioned risk factors for chronic postsurgical pain and their overlap with factors targeted in pain science education, it could be beneficial to look at the possible attenuating effect of perioperative pain science education (preoperative and early postoperative) at different time points post-surgery. If patients understand at an early stage that pain may not only result from tissue damage, but also from increased nerve sensitivity (and could thus be overprotective), they can adjust their beliefs, attitudes, behaviors, treatment and

lifestyle choices, which in turn might positively influence their current and future pain experience.

For this purpose, the aim of this systematic review was to look at the effect of perioperative pain science education in adults on pain, psychological factors and physical functioning compared to controls.

METHODS

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[90] Before the start of the review, a detailed protocol had been registered at the International Prospective Register of Systematic Reviews (PROSPERO: ID 161267, registration number CRD42020161267). We followed the Committee on Publication Ethics (COPE) international standards for authors to ensure integrity of this manuscript.[91]

Table 2 presents the pre-specified criteria for inclusion and exclusion of articles.

Table 2 Eligibility criteria for inclusion and exclusion of studies, based on the PICOS-format (Patients, Intervention, Comparison, Outcome, Study design).

Patients	Adults (mean age ≥18 years) who will undergo or underwent surgery
Intervention	Pain science education - Consistent with the definition of pain science education as described by Louw and colleagues[70]: "(An) educational session(s) describing the neurobiology and neurophysiology of pain (processing) by the nervous system. Patients are educated that the nervous system's processing of their injury, in conjunction with various psychosocial aspects, determines their pain experience and that pain is not always a true representation of the status of the tissues." For the full definition, see *Appendix I*. - Delivered orally or written, individually or in group, isolated or in combination with other forms of treatment. - At least one session took place in the perioperative period (between one month prior to surgery and one month after surgery).
Comparison	The interventional group was compared to either: a) *a non-exposed control group* A group that did not receive an educational intervention (apart from the lack of education, the comparison group had to be treated the same way as the interventional group, so the effect of pain science education could be isolated) or b) *another intervention* A group that had received an alternative educational intervention (apart from the educational intervention, the comparison group had to be treated the same way as the interventional group, so the effect of pain science education could be isolated). This control intervention might have been a routine educational intervention that is accepted in the hospital and that patients would have received anyway (usual care), or an additional educational intervention rather focusing on pain as a reflection of tissue damage or injury (a biomedical focus instead of the broader biopsychosocial focus of pain science education).
Outcome	Studies that reported on at least one of the following outcome parameters: - Pain - Psychological factors (pain catastrophizing, kinesiophobia, self-efficacy, depression, anxiety and stress) - Physical functioning No limitations were set on the measurement tool used to examine the effect of pain science education on the outcomes.
Study design	Original studies: controlled quantitative study designs Full-text availability in Dutch or English

A comprehensive literature search was conducted with the help of a biomedical information specialist (T.V.). Electronic searches were performed in the databases PubMed (including MEDLINE; 1946 – 2021) Embase (1974 – 2021), Web of Science Core Collection (1955 – 2021) and the Cochrane Library (Cochrane Database of Systematic Reviews (1995 – 2021) and Cochrane Central Register of Controlled Trials (no inception date)) to identify relevant studies.

The search strategy *[((pain) AND (education)) OR (pain education)] AND (surgery)* was adapted for each database. For PubMed, Embase and the Cochrane Library, indexterms (MeSH –terms and Emtree-terms) were included and combined with free textwords to search in title, abstract and keywords. The full search strategy for PubMed is set out in *Appendix II*. The search was performed on February 28, 2021.

After deduplication in Endnote, two independent raters (E.V.d.G. and L.D.) first screened the included titles and abstracts for eligibility in Rayyan,[92] using the above-mentioned eligibility criteria. Disagreements regarding the selection of studies were resolved through discussion until the raters reached consensus. Full texts were obtained for all citations that could potentially fit the eligibility criteria. During the second screening performed by the same raters, full text papers of studies that did not to meet the eligibility criteria were rejected and the reasons for exclusion reported (**Figure 9**).

The following information was extracted from the included studies: 1) study characteristics (author, year of publication, country in which the study was conducted, study design), 2) sample characteristics (type of surgery, sample size, eligibility criteria), 3) patient characteristics (age, gender ratio, baseline pain), 4) treatment characteristics (timing, delivery mode), 5) outcomes on pain, psychological factors and physical functioning (time points, outcome measures), 6) results (statistical analysis, statistical significance).

Data extraction was performed by E.V.d.G. and L.D. Any disagreement was resolved by either consensus or consultation of an independent third reviewer (M.M.). Authors of studies of which important data was missing were contacted by email.

E.V.d.G. and L.D. independently verified the risk of bias (outcome level) of all included papers, after which any disagreements were discussed until they reached consensus. Risk of bias in randomized trials was assessed using the second version of the revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[93] The resulting overall risk of bias represents the following five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. We used the Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) assessment tool (version

for cohort studies) to assess risk of bias in the results of non-randomized studies.[94] The final overall risk of bias represents the following seven domains: confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result.

P-values for interaction effect (time x group) portrayed the difference in change over time between groups. The common effects for both intervention groups (unless otherwise specified) over time were presented with p-values for time-effect, as this value could clarify on the result of a possible interaction effect. We chose not to depict p-values for group-effect, since they would not have contributed to the scope of this review (i.e. p-values for group-effect would inform us on whether two groups differ in general, not taking into account the course over time of this difference). Effect sizes were reported if available from the original study.

RESULTS

Following deduplication, the search yielded 9,001 publications (**Figure 9**). After screening the titles/abstracts and full texts against the eligibility criteria, nine publications reporting eight studies were included (one publication reported on long-term follow-up of a study that had already been included).[95, 96]

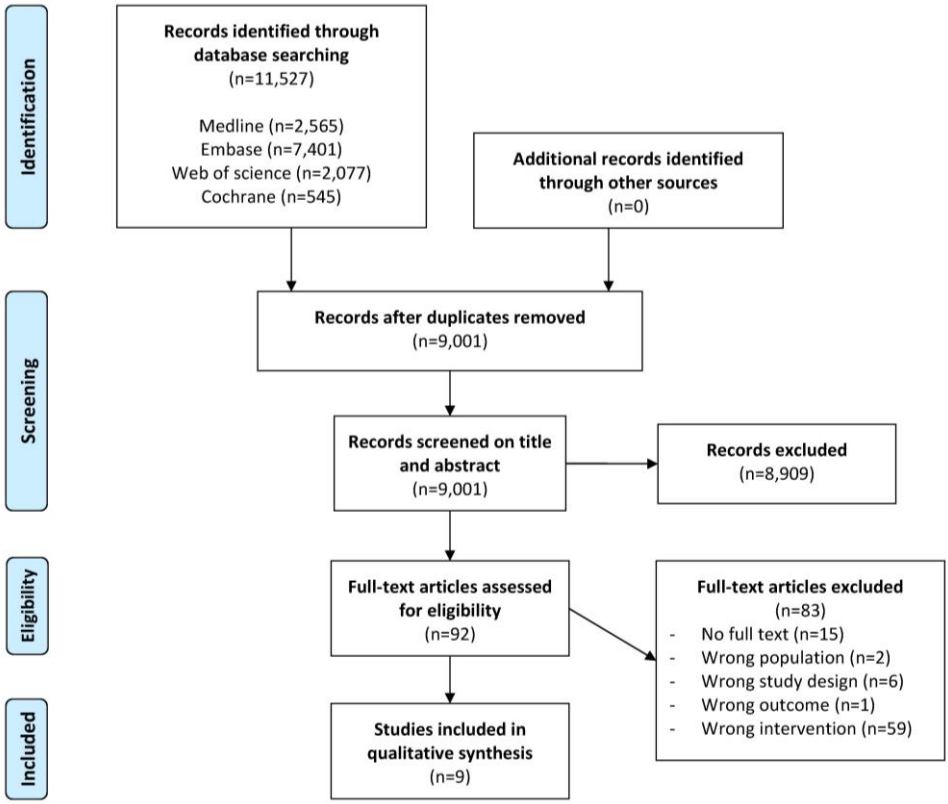

Figure 9 PRISMA flow diagram of study identification, screening and inclusion.

Seven randomized controlled trials and one controlled clinical trial were included. Study characteristics are summarized in **Table 3**. Sample sizes ranged from 31 to 402 with a total of 1,078 unique participants, 468 of whom received pain science education. Eight studies included patients with moderate to severe pain at baseline (Visual Analogue Scale ≥ 35mm or Numeric Rating Scale ≥ 4[97, 98])[95, 96, 99-104], among which five[95, 96, 99, 101, 103, 104] reported duration of preoperative pain (mean = 4.36 years).

Table 3 Study characteristics.

STUDY **Author; year; country; design**	**SAMPLE** **Type of surgery** **Sample size** (IG/CG) **Eligibility criteria**	**PATIENT CHARACTERISTICS** **Age (years)** *mean (SD)* **Gender ratio (♀/♂)** **Baseline pain** *mean (SD)*		**OUTCOMES** **Time points** **Outcome measures**	**RESULTS** **Statistical analysis** **Statistical significance** *p-value* (unless specified otherwise)
		IG	**CG**		
Lluch et al.[103]; 2018; Spain; RCT	Total knee arthroplasty N=54 (27/27) Inclusion - Knee osteoarthritis pain >3m Exclusion - Previous total knee arthroplasty/other lower limb surgery of the affected knee <6m - Inflammatory, metabolic or neurological comorbidities - Chronic widespread pain	67.7 (7.8) 59/41 Numeric Rating Scale (0-10) 6.2 (1.5)	72.8 (5.6) 68/32 5.4 (1.6)	- T0: preop - T1: after treatment (preop) - T2: 1m follow-up (preop) - T3: 3m postop **Pain and disability** - Western Ontario and McMaster Universities Arthritis Index **Psychological factors** - Pain Catastrophizing Scale - Tampa Scale for Kinesiophobia-11	PPA (22/22) **Pain and disability** - P int=0.35 - P time<0.0001*:↘ **Psychological factors** - P int<0.001* - P time CG(T0-T3) =/ns - P time EG(T0-T3) <0.001*:↘ - P int<0.001* - P time CG(T0-T3) =/ns - P time EG(T0-T3) <0.001*:↘
Núñez-Cortés et al.[104]; 2019; Chile; RCT	Carpal tunnel surgery N=31 (16/15)	56.8 (8.4) 100/0	50.8 (17.7) 100/0	- T0: preop - T1: 4w postop - T2: 12w postop	PPA (15/15) Composite measure: mean value T1 and T2

	Inclusion - ≥18y Exclusion - Prior pain education - Prior surgery on the extremity requiring carpal tunnel surgery	Visual Analogue Scale (0-100) 72.6 (22.1)	61.7 (21.6)	**Pain** - Visual Analogue Scale **Psychological factors** - Pain Catastrophizing Scale - Tampa Scale for Kinesiophobia-11 **Physical functioning** - Quick Disabilities of Arm, Shoulder and Hand questionnaire	**Pain** - P int=0.816 - P time=0.040*:↘ **Psychological factors** - P int=0.510 - P time=0.510 - P int=0.717 - P time=0.278 **Physical functioning** - P int=0.506 - P time=0.024*:↗
Louw et al.[99]; 2019; USA; Controlled clinical trial	Total knee arthroplasty N=103 (49/54) Exclusion - Previous total knee arthroplasty - Scheduled for bilateral total knee arthroplasty	74.1 (9.5) 65/44 Numeric Rating Scale (0-10) 4.7 (2.2)	69.6 (10.6) 55/45 4.7 (2.2)	- T0: before education - T1: 1m postop - T2: 3m postop - T3: 6m postop **Pain** - Numeric Rating Scale **Psychological factors** - Pain Catastrophizing Scale - Tampa Scale for Kinesiophobia-11	PPA (31/36) ITTA (only reported if different from PPA) **Pain** - P int=0.386 - P time(T0- T3) <0.001*:↘ **Psychological factors** - P int=0.819 - P time(T0-T3) <0.001*:↘ - P int=0.245 - P time(T0-T3) <0.001*:↘

				Physical functioning - Western Ontario and McMaster Universities Arthritis Index	**Physical functioning** - P int=0.222 - P time(T0-T3) <0.001*:↗
Louw et al.[95]; 2014; USA; RCT	Lumbar surgery for radiculopathy N=67 (35/32) Exclusion - <18y or >65y - Instrumented lumbar surgery - Participation in formal back school or multidisciplinary pain management program - Chronic pain-related conditions - Symptoms of cord compression	49.59 (53/47) Numeric Rating Scale: low back (0-10) 4.57 Numeric Rating Scale: leg (0-10) 5.25	49.65 (54/46) 5.12 6.06	- T0: preop - T1: 1m postop - T2: 3m postop - T3: 6m postop - T4: 12m postop **Pain** - Numeric Rating Scale: low back - Numeric Rating Scale: leg **Physical functioning** - Oswestry Disability Index	PPA (28/33) and ITTA (only reported if different from PPA) **Pain** - P int>0.167 - P time(T0-T4) <0.002*: ↘ - P int>0.167 - P time(T0-T4) <0.002*:↘ **Physical functioning** - P int>0.167 - P time(T0-T4) <0.002*:↘
Louw et al.[96]; 2016; USA; RCT	See Louw et al. 2014	See Louw et al. 2014	See Louw et al. 2014	- T0: preop - T1: 1m postop - T2: 3m postop - T3: 6m postop - T4: 12m postop - **T5: 3y postop**	See Louw et al. 2014

					Pain - Numeric Rating Scale: low back - Numeric Rating Scale: leg **Physical functioning** - Oswestry Disability Index	**Pain** - P int=0.405 - P time(T0-T5) <0.001*:↘ - P int=0.665 - P time(T0-T5) <0.001*:↘ **Physical functioning** - P int=0.520 - P time(T0-T5) <0.001*:↘
Riddle et al.[101]; 2019; USA; RCT	Total knee arthroplasty N=402 (130/135/137) (72/28) Inclusion - ≥45y - Diagnosed with osteoarthritis - Pain Catastrophizing Scale ≥16 Exclusion - Scheduled for revision surgery - Hip or knee arthroplasty 6m prior to or after surgery - Self-reported diagnosis of inflammatory arthritis - Bilateral knee arthroplasty	62.6 (7.9) (63/37) Numeric Rating Scale: knee (0-10) 6.0 (1.8)	64.2 (8.5) 6.0 (2.0)	62.7 (7.7) (64/36) 6.2 (1.9)	- T0: 1w preop - T1: 2m postop - T2: 6m postop - T3: 12m postop **Pain** - Western Ontario and McMaster Universities Arthritis Index: pain scale - Numeric Rating Scale **Psychological factors** - Pain Catastrophizing Scale **Physical functioning** - Western Ontario and McMaster Universities Arthritis Index:	ITTA **Pain** - P int=0.73 - P time<0.001*:↘ - P int>0.05 - P time<2e-16*:↘ **Psychological factors** - P int>0.05 - P time(T0-T3) =<2e-16*:↘ **Physical functioning** - P int>0.05 - P time(T0-T3)=/*:↗

					physical function scale	
				-	Short Physical Performance Battery	- P int>0.05 - P time=2.619e-10*:↗
				-	6 Minute Walk Test	- P int=0.96 - P time<2e-16*:↗
Darnall et al.[105]; 2019; USA; Pilot RCT	Breast cancer surgery N=127 (77/50) Inclusion - >18y - Scheduled for lumpectomy or mastectomy Exclusion - Pregnancy - Ongoing pain- or disability-related legal claim	51.27 (100/0) Numeric Rating Scale (0-5) 1.47 (0.12)	51.16 (100/0) 1.74 (0.13)	-	T0 - T1: 2w postop - T2: 4w postop - T3: 8w postop - T4: 12w postop	PPA (36/32) No evidence of postop interaction effect (T1, T2, T3, T4). Measures were averaged to create a <u>composite postsurgical measure</u>. For each of the covariates, they specified a mixed-design ANOVA with treatment, time and treatment x time as predictors.
				Pain		**Pain**
				-	Numeric Rating Scale	- P int=0.0394* - P time=0.0016*:↗ - P time IG=0.0002* - P time CG=0.4191
				-	Patient-Reported Outcome Measurement Information System: pain interference	- P int>0.008 - P time>0.008

				Psychological factors - Pain Catastrophizing Scale - Patient-Reported Outcome Measurement Information System: anxiety and depression **Physical functioning** - Patient-Reported Outcome Measurement Information System	**Psychological factors** - P int=0.34 - P time=0.03*:↘ - P int>0.008 - P time>0.008 **Physical functioning** - P int>0.008 - P time>0.008
Glindvad and Jorgensen[102]; 2007; Denmark; RCT	Surgery for inguinal hernia N=234 (103/131) Inclusion - >18y Exclusion - Scheduled for laparoscopic and bilateral surgery	54.2 (17.7) (8/92) Visual Analogue Scale: rest (0-100) 3.0 Visual Analogue Scale: while moving (0-100) 11.0	54.0 (15.0) (6/94) 2.0 7.0	- T0: preop - T1: 1st day postop - T2: 3rd day postop - T3: 7th day postop **Pain** - Visual Analogue Scale: rest - Visual Analogue Scale: while moving	PPA **Pain** - P int=/ - P time(T0-T3)=/ - P int=ns - P time(T0-T3)=/

Birch et al.[100]; 2020; Denmark; RCT	Total knee arthroplasty N=60 (31/29) Inclusion - Primary knee osteoarthritis - ≥18y - Pain Catastrophizing Scale>22 Exclusion - Severe depression - Contralateral total knee arthroplasty within 1y after surgery of interest	66 (9) (69/31) Visual Analogue Scale: during activity (0-100) 48 (18) Visual Analogue Scale: rest (0-100) 19 (14)	66 (10) (62/38) 49 (21) 25 (17)	- T0: preop - T1: 3m postop - T2: 12m postop **Pain** - Visual Analogue Scale: during activity - Visual Analogue Scale: rest **Pain and physical functioning** - Oxford Knee Score **Psychological variables** - Pain Catastrophizing Scale - Pain Self-Efficacy Scale **Physical functioning** - 6 Minute Walk Test - 30 Seconds Sit To Stand Test	ITTA **Pain** - P int=/ns - P time(T0-T2)=/*:↘ - P int=/ns - P time(T0-T2)=/*:↘ **Pain and physical functioning** - P int=/ns - P time=/*:↗ **Psychological variables** - P int=/ns - P time=/*:↘ - P int=/ns - P time=/ns **Physical functioning** - P int=/ns - P time=/ns - P int=/ns - P time=/ns

**= significance in original study; /=p-values not shown in original manuscript; CG=control group; IG=intervention group; ITTA=intention-to-treat analysis; m=month(s); N=study sample (randomized); ns=non-significant; P int=P value interaction effect; PPA=per-protocol analysis; P time=P value for time effect; RCT=randomized controlled trial; SD=standard deviation; T0=baseline assessment; T1/2/3/…=assessment 1/2/3/…; w=week(s); y=year(s)*

Table 4 presents details on the timing and delivery mode of treatment in both groups (intervention and control). The following names were given to the interventions by the authors of the original studies: pain neuroscience education (n=5)[95, 96, 99, 103, 104], education (n=1)[102], behavioral pain medicine (n=1)[105], patient education based on cognitive behavioral therapy (n=1)[100] and pain coping skills (n=1)[100]. Six papers implemented a preoperative pain science education intervention,[95, 96, 99, 103-105] two an intervention containing both preoperative and postoperative sessions[100, 101] and one paper investigated the effect of a postoperatively delivered pain science education.[102]

Table 5 provides a brief description of the content categories that were included as part of pain science education interventions. A more elaborated description of treatment content in both groups (as provided by the authors of the original publications) can be found in *Appendix III*.

Pain, psychological factors and physical functioning were evaluated with a wide range of self-reported outcome measures, for which both disease-specific and general questionnaires were used (**Table 3**). Two randomized controlled trials showed a significant interaction effect (i.e. a significant difference in outcomes between groups over time) on pain and psychological factors.[103, 105] No statistically significant interaction effects were reported for outcomes on physical functioning.

In the first randomized controlled trial with a significant interaction effect, breast cancer patients who had received a digital behavioral pain medicine intervention reported an increase in average postoperative **pain**, which was not observed in the control group whom had been informed on general health via text.[105] The authors did not calculate effect sizes to measure the strength of this significant interaction effect.

In the second randomized controlled trial with a significant interaction effect on **psychological factors**, pain catastrophizing and kinesiophobia decreased in participants who had received four pain science education sessions combined with knee mobilization before undergoing total knee arthroplasty.[103] Over the same period of time (i.e. three months after surgery), the values in the control group remained unchanged. A medium effect size, calculated as the partial eta squared (η2p:0.11), was reported for both the interaction effects of pain catastrophizing and kinesiophobia.

An overview of the risk of bias can be found in **Table 6**. The vast majority of included studies (n=6) were at high risk of bias.[96, 100-103, 105]

Table 4 Treatment timing and delivery mode.

Study	Both groups	Intervention group	Control group
Lluch et al. (2018)[103]	**Knee mobilization sessions** - Preop - After each educational session **Delivery mode** - PT - Intervention group: pain-guided - Control group: not pain-guided and non-threatening word choice	**Pain neuroscience education** - 2m-1m preop - 4 x (1/w) - 1st session 50-60', 2nd-4th session 20-30' **Delivery mode** - One-on-one - PT - Verbally and visually with the aid of a computer	**Biomedical education** - 2m-1m preop - 4 x (1/w) - 1st session 50-60', 2nd-4th session 20-30' **Delivery mode** - One-on-one - PT - Verbally and visually with the aid of a computer
Núñez-Cortés et al. (2019)[104]	**Hand therapy** - 1w postop **Delivery mode** - Verbal and written instructions - Home exercise program	**Pain neuroscience education** - 1 x 30' - 1w preop **Delivery mode** - One-on-one - PT - Audio visual approach - Pictures, examples, metaphors, stories	**Usual care** - 1 x 30' - 1w preop **Delivery mode** - One-on-one - Audiovisual approach
Louw et al. (2019)[99]	**Traditional hospital education** - Preop **Delivery mode** - Group - Booklet	**Pain neuroscience education** - 1 x 30' - Preop - Prior to traditional hospital education **Delivery mode** - Group - PT	

	100% (n=103) of the patients received postop PT	- PowerPoint presentation - Booklet		
Louw et al. (2014 and 2016)[95, 96]	**Usual care** - Preop **Delivery mode** - Surgeons and staff	**Pain neuroscience education** - 1 x 30' - Preop **Delivery mode** - One-on-one - PT - Verbal - Pictures, examples, metaphors and drawings - Booklet		
Riddle et al. (2019)[101]	Patients were routinely prescribed medications for pain control and are referred for physical therapy following total knee arthroplasty.	**Pain coping skills training** - 8 x 50' - 2w preop-6w postop **Delivery mode** - One-on-one - PT - 1st session in-person, other sessions via telephone - Written maintenance plan	**Arthritis education** - 8 x 50' - 2w preop-6w postop **Delivery mode** - One-on-one - Nurse - Presentation and discussion format - 1st session in-person, other sessions via telephone	**Usual care**
Darnall et al. (2019)[105]		**Behavioral pain medicine intervention** - 1 x 90' - Preop	**General health education** - Preop	

		Delivery mode - Website - Video on pain psychoeducation (including PowerPoint presentation)	**Delivery mode** - Digital text education
Glindvad and Jorgensen (2007)[102]	**Routine information** - 1 x 5-10' - Preop	**Education** - 1 x 30-60' - Postop - Follow-up telephone call 2d postop	**Discharge information** - Postop
	Delivery mode - Oral - Ward nurse - 5 pamphlets	**Delivery mode** - One-on-one - Project nurse - Communication guide	**Delivery mode** - Oral
Birch et al. (2020)[100]	**Usual care** - 1w preop - 1w postop - 2, 4, 12w postop	**Patient education based on cognitive behavioral therapy** - 7/6 x 45' - 2w preop-3m postop - 3 x preop - 4 x postop	
	Delivery mode - Multidisciplinary information meeting - Phone call - Control visits	**Delivery mode** - One-on-one - 2 PT's - PowerPoint - Handbook - Mp3 player	

'=minutes; m=month; PT=physiotherapist; w=week(s); y=year(s)

Table 5 Educational content included as part of pain science education interventions.

Basic neurophysiology and pain physiology[95, 96, 99-105]
Chronic pain physiology and central sensitization[95, 96, 99, 100, 103, 104]
Pain neuromatrix[100, 103-105]
Influencing/sustaining factors[95, 96, 99-105]
Multifactorial experience of pain[95, 96, 99-105]
Activity pacing[100-102]
Transfer knowledge about pain to an adaptive behavioral change[100-104]
Reconceptualization of pain[95, 96, 99-104]
Mindfulness/relaxation/breathing exercise[100-102, 105]

Table 6 Risk of bias assessment according to the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) and the Risk Of Bias In Non-Randomized Studies – of Interventions (ROBINS-I) assessment tool.

RoB 2	**1**	**2**	**3**	**4**	**5**	**=**		
Birch 2020	-	+	+	-	+	-		
Darnall 2019	+	-	?	+	-	-		
Glindvad 2007	+	+	-	+	+	-		
Lluch 2018	+	-	+	+	+	-		
Louw 2014	+	+	+	+	+	+		
Louw 2016	+	-	?	+	?	-		
Núñez-Cortes 2019	+	?	+	+	+	?		
Riddle 2019	+	+	+	-	+	-		
ROBINS-I	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**=**
Louw 2019	+	+	+	+	+	?	+	+

RoB 2: *risk of bias (1) arising from the randomization process, (2) due to deviations from the intended interventions, (3) due to missing outcome data, (4) in measurement of the outcome, (5) in selection of the reported result, (=) overall risk of bias*
ROBINS-I: *bias (1) due to confounding, (2) in selection of participants into the study, (3) in classification of interventions, (4) due to deviations from intended interventions, (5) due to missing data, (6) in measurement of outcomes, (7) in selection of the reported result, (=) overall risk of bias*
(-) High risk
(+) Low risk
(?) Some concerns

DISCUSSION

The purpose of this systematic review was to synthesize the literature on the effect of perioperative pain science education. Although significant interaction effects were present in two studies, there was no conclusive evidence for an overall effect on pain, psychological factors nor physical functioning.

In the first study with a significant interaction effect, breast cancer patients who had received one preoperative pain science education session showed a significant increase in postoperative **pain** compared to controls.[105] This is an interesting finding as this result was the opposite of the effect we had anticipated. It should be pointed out why we have to be careful drawing conclusions from this study to answer our research question. First of all, it was only a pilot randomized controlled trial on feasibility and acceptability of the educational program, with pain intensity as a secondary outcome. The authors also created a composite postsurgical measure for pain intensity (averaging pain intensity over all the postsurgical follow-up assessments) because they had not found evidence of an interaction effect on either one of the follow-up time-points (two-, four-, eight- and 12-week after surgery) and only p-values without effect sizes were reported. Lastly, the distinction between this study and the others was twofold. First, breast cancer surgery is not a surgery for a painful condition, so this was the only study including participants without preoperative pain. This raises the additional research question whether pain science education can serve a preventive role, compared to a curative role in the other studies. Second, breast cancer patients were the only oncological population included (compared to musculoskeletal surgeries). It might be feasible that pain science education results in different effects in oncological populations, as the specific contexts of their pain experiences differs.

Regarding the impact on **psychological factors**, only the study by Lluch et al. showed a significant interaction effect of pain science education on both pain catastrophizing and kinesiophobia after total knee arthroplasty.[103] In the intervention group that had received four one-on-one sessions, pain catastrophizing and kinesiophobia decreased compared to baseline, while values for the control group remained the same. This beneficial effect was in line with previous research in chronic pain populations, showing that pain science education by itself has minor effects and should be combined with physical exercises.[74, 106-109] The study by Lluch et al. was among the two included studies that had indeed implemented an additional controlled physical intervention (knee mobilization physiotherapy sessions), similar for both the intervention and control group.[103, 104] Three other studies described whether or not patients in both groups were

referred for postoperative physical therapy, though this could have been unevenly distributed among intervention and control groups.[99-101]

There are several **possible explanations** to why no overall beneficial effects of perioperative pain science education were found.

The first one is that most studies were conducted in subjects who underwent surgery for a painful condition, which was reflected in moderate to severe pain at baseline.[95, 96, 99-104] Therefore, we cannot rule out a general pain-reducing effect of surgery and postoperative use of pain medication, irrespective of group allocation. Indeed, all studies in populations with preoperative pain showed a decrease in postoperative pain over time up to three months post-surgery in both the control and intervention group, which did not depend on group allocation.[95, 96, 99-104]

An alternative explanation for the lack of significant differences in post-surgical pain levels is that the post-surgical healing process is painful because of tissue injury (to promote healing) rather than (bio)psychological factors addressed in the pain science education. In this particular population, short-term pain relieving effects can be expected to be less but it may be more valuable to look at long-term effects for prevention of chronification.

Furthermore, it might not be surprising that we did not find an effect on pain, as pain science education targets a reconceptualization of pain through knowledge.[71] Although patients see their pain in a different light, they can still experience pain. However, through pain science education, the knowledge per se that pain can be overprotective could encourage patients to change their behavior and result in a better well-being and quality of life. In future research, this might be a reason to select studies based on outcomes other than pain, e.g. pain-related functioning.

In addition, it is possible that positive findings for pain science education in chronic pain populations cannot directly be translated to patients undergoing surgery. In previous research[70, 74, 75, 77], chronic pain patients receiving pain science education without surgery were guided through the stages of behavioral change, resulting in active self-management of their problem without the "time pressure" of a scheduled surgery or notion that surgery is their only valid option for a pain-free life. Behavioral change is typically nonlinear and people continuously change through a cyclical process, which can result in a long process.[110-112] In contrast, most participants included for this review (who were likely experiencing chronic pain, as their preoperative pain duration averaged four years[95, 99-104]), were taught about the importance of biopsychosocial factors as possible contributors to their pain *after* their decision to undergo

surgery. According to the transtheoretical model of behavioral change, it is harder to trigger inherent motivation to change behavior once people have set their mind on a surgical remedy.[112] Apart from that, the postoperative circumstances and condition of the tissues create a new context for the patient's interpretation of educational content. However, this reasoning should be interpreted with caution, as none of the authors reported evidence about behavioral change as a result of the interventions. It is possible that participants did, in fact, change behaviors and still experienced pain.

Furthermore, the format of the intervention should be discussed as an explanation for the results. Currently, there are no clear guidelines on intensity or amount of sessions, which may not be surprising as pain is characterized by strong inter-individual variability. Nonetheless, it may well be argued that a more elaborate educational approach is required to substantially change beliefs/cognitions and induce behavioral change in people who have been in pain for a while.[113] Changes in participants' pain knowledge before and after education could help us further unravel the optimal educational format for this population. However, none of the included studies evaluated whether participants comprehended the education provided.

Lastly, another question is whether we observed limited effects because most participants did not experience a significant effect (group level) or because most of them did not experience any benefits (non-responders), while others experienced a very pronounced effect (responders). In line with this train of thought, a possible explanation could be that we did not stratify on group level (e.g. diagnosis, dominant pain mechanism, level of anxiety, catastrophizing, kinesiophobia…).[85, 86] Future studies need to investigate whether the effect of pain science education might be more pronounced after stratification, by defining responders to perioperative pain science education. This can be done based on the known risk factors for development of chronic pain as described in the introduction.

To summarize, pain science education was not effective for reducing post-surgical pain, psychosocial factors and physical functioning, regardless of whether or not study participants reported pre-surgical pain. However, several more nuanced **clinical recommendations** can be made based on interpretation of the results of the individual studies.

For the above-mentioned reasons, it could be beneficial to educate patients in pain *before* the decision for surgery. This way, they could make an informed decision about whether or not, and why, they would want surgery or rather explore other possibilities, possibly resulting in less pain and disability without the side-effects of surgery. Perhaps, after being in pain for a long time, they might have expected surgery as the final magic bullet. Health care providers, in this case

mostly surgeons and anesthesiologists, still often ignore the biopsychosocial paradigm of chronic pain, leading to informed consent for surgery based on incomplete information.

In patients without preoperative pain, pain science education does not seem the best option. It is plausible that pain science education triggers anxious behavior in this subgroup, for they do not experience any relatable pain when being educated on the matter. The question then rises whether people who are not in pain can be ready to change, as they cannot (yet) link any behavior to pain. Therefore, a possible recommendation could be to plan the educational session(s) whenever patients experience acute postoperative pain. Nevertheless, it is premature to draw such conclusions based on our results, as there was only one study included regarding preoperative pain science education in patients without pain.[105] Besides, this study in breast cancer patients was the only one using a none face-to-face educational format (90-minute video).

The generalizability of the results is subject to certain **limitations**. Firstly, the included studies were quite heterogeneous in terms of population (eligibility criteria, type of surgery, preoperative pain, exclusion of patients with low catastrophizing), intervention (amount of sessions, timing and mode of delivery, stand-alone treatment or in combination with others), outcome measures and comparators. Hence, it was not possible to conduct a meta-analysis. Secondly, the overall quality of the included studies was rather low, which compromises confidence that the results represent a true treatment effect. A possible explanation for this is that one of the questions in the risk of bias assessment tool was whether the assessors were blinded to intervention assignment. Because participants are considered assessors in case of patient-reported outcome measures, blinding for type of educational intervention is rather challenging. The assessment tool states that once one item is graded as high risk of bias, the whole paper is considered high risk of bias. Lastly, for the scope of this review, we wanted to look at the possible attenuating effect of perioperative pain science education on postoperative pain and other possible risk factors for chronic postsurgical pain. However, our eligibility criteria did not filter out patients with preoperative pain and there was no specification on minimal follow-up period. For these reasons, it was very difficult to look at a possible effect of pain science education on pain chronification on the long-term.

In general, perioperative pain science education in adults does not result in significant effects on pain, psychological factors or physical functioning compared to controls. Only one study indicated that subjects receiving pain science education after total knee arthroplasty (in combination with a physical therapy program) showed greater statistically significant improvements in pain catastrophizing and kinesiophobia. Further work needs to be done to

determine the optimal timing of pain science education (before the decision to undergo surgery, before surgery or afterwards) in both people with and without existing pain, as well as to define responders to pain science education so the effect of population-specific pain science education can be studied in the future. In addition, research on the effectiveness of pain science education should include a checklist to verify whether participants comprehended the educational content and follow-up periods should be long enough to study the effect on pain chronification.

APPENDICES

Appendix I: Definition of pain science education as defined by Adrian Louw et al. (they used the term "neuroscience education")

Neuroscience education can be best described as an educational session or sessions describing the neurobiology and neurophysiology of pain, and pain processing by the nervous system. Instead of a traditional model of connecting tissue injury or nociception and pain, neuroscience education aims to describe how the nervous system, through peripheral nerve sensitization, central sensitization, synaptic activity, and brain processing, interprets information from the tissues and that neural activation, as either upregulation or downregulation, has the ability to modulate the pain experience. Patients are thus educated that the nervous system's processing of their injury, in conjunction with various psychosocial aspects, determines their pain experience and that pain is not always a true representation of the status of the tissues. By reconceptualizing their pain as the nervous system's interpretation of the threat of the injury, rather than an accurate measure of the degree of injury in their tissues, patients may be more inclined to move, exercise, and push into some discomfort. Depending on the timing of its administration, neuroscience education may be viewed as a preventive measure in acute pain situations and as a treatment/rehabilitation intervention in chronic pain situations.

Appendix II: search strategy for PubMed/Medline

((("Pain"[Mesh] OR pain*[tiab]) AND ("Health Education"[Mesh] OR “psychoeducation”[tiab] OR “Medical information”[tiab] OR "Education"[Mesh:NoExp] OR patient-education*[tiab] OR education-of-patient*[tiab] OR "Health Communication"[Mesh] OR “Health communication”[tiab] OR “patient communication”[tiab] OR communication-patient*[tiab] OR “Health literacy”[tiab] OR “Preoperative education”[tiab] OR ((informati*[tiab] OR educati*[tiab]) AND (brochure*[tiab] OR leaflet*[tiab] OR booklet*[tiab] OR pamphlet*[tiab])))) OR (“Pain education”[tiab] OR “Neuroscience education”[tiab] OR “Explain pain”[tiab] OR “Pain science education”[tiab] OR “Pain communication”[tiab] OR “Pain neuroscience approach”[tiab] OR “Pain physiology education”[tiab] OR “Pain neurophysiology education”[tiab] OR “Pain biology education”[tiab])) AND ("Specialties, Surgical"[Mesh] OR "Surgical Procedures, Operative"[Mesh] OR "surgery" [Subheading] OR operative-procedure*[tiab] OR operative-intervention*[tiab] OR operative-repair*[tiab] OR operative-restoration*[tiab] OR operative-treatment*[tiab] OR resection*[tiab] OR operation*[tiab] OR surger*[tiab] OR surgic*[tiab] OR "Postoperative Complications"[Mesh:NoExp] OR postop*[tiab] OR post-op*[tiab] OR preop*[tiab] OR pre-op*[tiab] OR periop*[tiab] OR peri-op*[tiab] OR mastectom*[tiab] OR mammectom*[tiab] OR lumpectom*[tiab] OR tylectom*[tiab] OR arthroplast*[tiab] OR bone-tunnel-enlargement*[tiab] OR bone-tunnel-widening*[tiab] OR alloarthroplast*[tiab] OR joint-reconstruction*[tiab] OR arthroscop*[tiab] OR arthroendoscop*[tiab] OR discectom*[tiab] OR diskectom*[tiab] OR laminectom*[tiab] OR laminoplast*[tiab] OR laminotom*[tiab] OR amputation*[tiab] OR arthrodes*[tiab] OR articular-process-fusion*[tiab] OR joint-fusion*[tiab] OR skeletal-fixation*[tiab] OR fracture-fixation*[tiab] OR fracture-reduction*[tiab] OR bone-fixation*[tiab] OR osteotom*[tiab] OR bone-section[tiab] OR debridement[tiab] OR appendectom*[tiab] OR appendicectom*[tiab] OR cholecystectom*[tiab] OR hemorrhoidectom*[tiab] OR haemorrhoidectom*[tiab] OR hemorrhoid-excision*[tiab] OR hemorrhoidopex*[tiab] OR tonsillectom*[tiab] OR laparoscop*[tiab] OR celioscop*[tiab] OR peritoneoscop*[tiab] OR pelvic-endoscop*[tiab] OR videolaparoscop*[tiab] OR thoracotom*[tiab] OR pleura-incision*[tiab] OR pleural-incision*[tiab] OR pleuracotom*[tiab] OR pleurotom*[tiab] OR rethoracotom*[tiab] OR hysterectom*[tiab] OR colpohysterectom*[tiab] OR hysterocolpectom*[tiab] OR panhysterectom*[tiab] OR uterus-extirpation*[tiab] OR herniorrhaph*[tiab] OR hernia-repair*[tiab] OR hernioplast*[tiab] OR herniaplast*[tiab] OR saphenectom*[tiab] OR sternotom*[tiab] OR sternum-osteotom*[tiab] OR hip-replacement*[tiab] OR hip-joint-replacement*[tiab] OR knee-replacement*[tiab] OR knee-joint-replacement*[tiab] OR cesarean-section*[tiab] OR abdominal-deliver*[tiab] OR caesarean-section*[tiab] OR c-section*[tiab] OR postcesarean-section*[tiab] OR caesarean-

birth[tiab] OR cesarean-deliver*[tiab] OR fetectom*[tiab] OR repeated-cesarotom*[tiab] OR section-caesarea[tiab] OR "Radiculopathy"[Mesh] OR radiculopath*[tiab] OR radiculiti*[tiab] OR neuroradiculitis[tiab] OR polyneuroradiculitis[tiab] OR polyradiculoneuropath*[tiab] OR radiculoneuropath*[tiab] OR nerve-root-disorder*[tiab] OR nerve-root-inflammation*[tiab] OR nerve-root-avulsion*[tiab] OR nerve-root-disease*[tiab] OR polyradiculopath*[tiab] OR radicular-neuropath*[tiab]) NOT (“animals”[Mesh] NOT “humans”[Mesh])

Appendix III: Study characteristics: detailed content of interventions

1. Lluch et al. (2018)

Knee joint mobilization

Knee joint mobilization was applied using Mulligan's mobilization with movement following the protocol from Takasaki. Mobilization with movement during active knee flexion and/or extension, depending on which was the limited/painful movements for each patient, was applied progressing from non-weight-bearing to weight-bearing positions. All the mobilizations were performed for three sets of 10 repetitions and patients were asked to perform self-applied mobilizations at home involving four series of 20 movement repetitions per day. Home treatment adherence was recorded by means of a diary. The mobilization with movement techniques used in this study are described elsewhere.

Biomedical education

The information was provided by the same physiotherapist performing pain neuroscience education (PNE) in the other group through visualization of several videos that were presented on a computer.

- No reference to PNE or pain biology
- Anatomy, physiology and biomechanics of the knee
- Disease knowledge: normal course, etiology and clinical presentation of knee osteoarthritis
- Principles of conservative management of knee osteoarthritis: exercise, physical activity, weight loss and drugs
- Surgical treatment for knee osteoarthritis and expected course of postoperative knee pain

Pain neuroscience education

Topics addressed included the physiology of the nervous system with special interest in the pain system, characteristics of acute versus chronic pain; how pain becomes chronic (plasticity of the nervous system, central sensitization, etc.); potential sustaining factors of central sensitization like emotions, stress, pain behavior and cognitions; surgical experiences and environmental aspects affecting nerve sensitivity; and reconceptualization of postoperative pain after knee joint replacement.

- No reference to pathoanatomical models
- Acute pain versus chronic pain, transition from acute to chronic pain Neurons, synapsis and action potentials Peripheral and central sensitization
- Descending inhibition and facilitation of pain

- Sustaining factors of central sensitization (i.e. emotions, stress, pain behavior, cognitions)
- The pain matrix in the brain
- Reconceptualization of pain as a normal brain response to perceived threat
- Surgical experiences and environmental aspects affecting nerve sensitivity
- (Re)conceptualization of postoperative pain
- Transfer knowledge about pain to an adaptive behavioral change

2. Núñez-Cortés et al. (2019)

Hand therapy

Instructions for a home exercise program that included active digital flexor tendon gliding; active thumb opposition; and active wrist range of motion (flexion and extension).

Usual care education

Information about the medical, anatomical, and pathological aspects of carpal tunnel surgery.

- Basic aspect of the anatomy of the wrist in general and of the carpal tunnel in particular.
- Surgery procedures was explained and illustrated with pictures.
- The objective of the education was to teach people about the surgery of carpal tunnel release.
- There was up to 10 minutes extra time for questions for each participant.

Pain neuroscience education

The key contents of the session included the neurophysiological and biopsychosocial aspects of pain and the concept of peripheral and central sensitization.

- Basic physiology of the nervous system in general and of the pain system in particular.
- The theoretic information was illustrated with pictures and examples. Metaphors and stories to help understand the biology of pain.
- The objective of the education was to teach people about the multifactorial experience of pain.
- There was up to 10 minutes extra time for questions for each participant.

3. Louw et al. (2019)

The **traditional hospital preoperative program** was consistent with current preoperative total knee arthroplasty protocols. Participants in both intervention groups received education covering anatomy of the knee joint, information about the joint replacement surgery, what to expect when they were admitted for surgery, what to expect immediately after surgery, pain medications, postoperative rehabilitation/physical therapy, and so on. All patients received a hospital-based booklet with this information.

The **pain neuroscience education (PNE)** session was presented in the form of a PowerPoint presentation, prior to receiving the usual preoperative education program from the hospital. The PNE program used in this study was an adaptation of the PNE program developed for lumbar surgery (for content see Louw 2014). The educational material and content used in the spine surgery study were altered to reflect knee pain, knee osteoarthritis, and total knee arthroplasty. Patients also received a patient booklet specific to PNE containing the same information provided during the live lecture program.

4. Louw et al. (2014)

Usual care: preoperative education from the surgeons and staff. To ensure all surgeons involved in this study provided relatively similar usual care, each surgeon was asked to complete the Spine Surgery Education Questionnaire (SSEQ) to determine if their treatment followed the usual care established in SSEQ study. Two investigators independently reviewed the surgeons' responses to the SSEQ to ensure their preoperative education was in line with the findings of the SSEQ. All participating surgeons used usual care per the SSEQ.

Content SSEQ

- Surgical procedure
- Complications
- Outcomes/expectations
- Anatomy
- Amount of postoperative pain expected
- Hospital stay
- How surgery will affect pain
- Precautions after surgery
- Infection
- Smoking

The content of **the neuroscience education** sessions as found in the systematic review on neuroscience education (Louw et al., 2011) was used to develop appropriate messages for patients considering surgery for lumbar radiculopathy (**Table 7**).

Table 7 Content of neuroscience education used in the development of the preoperative neuroscience educational program.
Neurophysiology of pain
No reference to anatomical or patho-anatomical models
No discussion of emotional or behavioral aspects to pain
Nociception and nociceptive pathways
Neurons
Synapses
Action potential
Spinal inhibition and facilitation
Peripheral sensitization
Central sensitization
Plasticity of the nervous system

Preoperative **pain neuroscience education (PNE)** covered the sensitivity of the nervous system metaphorically described as an alarm system accompanied with drawings of action potentials was used to describe peripheral sensitization, central sensitization and plasticity of the nervous system. Material covered in the PNE included all of the following: (1) the decision to have lumbar surgery (LS); (2) the nervous system's physiology and pathways; (3) peripheral nerve sensitization; (4) surgical experiences and environmental issues effects on nerve sensitivity; (5) calming the nervous system; (6) recovery after lumbar surgery; (7) scientific evidence for the PNE booklet content; and (8) an opportunity to reflect and write questions to ask the surgeon prior to surgery. Patients in the experimental group received usual care in addition to the preoperative PNE program. PNE was provided by participating physical therapists in a one-on-one verbal format, with the use of pictures, examples, metaphors, and drawings as needed. This was done in a conversational and personal approach rather than a lecture format. To ensure a standardized PNE program, a systematic checklist was developed. The educational sessions averaged 30 minutes. Patients were additionally provided with a preoperative PNE booklet summarizing the educational content of the preoperative PNE session, including pictures, examples, and metaphors. Patients were asked to read the PNE booklet at least once before and once after their surgery.

5. Darnall et al. (2019)

Health education

Before surgery, patients received digital text education about health and nutrition that was framed in terms of their importance in enhancing recovery after surgery (this group received no 90-minute video).

Digital behavioral pain medicine intervention

Video content included information and skills to regulate cognition, emotion, and physiologic hyperarousal related to pain, including relaxation, thought reframing and behaviors that modulate attention and counteract helplessness about pain. During the video, learners were guided to self-tailor and apply the information by completing their Personalized Plan for Surgical Success.

Link to the video where the author explains part of the intervention:

https://www.youtube.com/watch?v=-_xRM4fxoig

6. Riddle et al. 2019

Usual care

Patients in the usual care group only received care that they would have routinely received had they not been entered in the study. Patients were routinely prescribed medications for pain control and referred for physical therapy following total knee arthroplasty.

Arthritis education

Patients randomly assigned to the arthritis education arm received detailed information from a registered or licensed practical nurse educator about osteoarthritis and its treatment. The arthritis education intervention controlled for participation in a trial, time and clinician attention. The arthritis education sessions used a presentation and discussion format similar to that originally described by Lorig for arthritis education (complete manuals of arthritis education and pain coping skills training intervention can be found on the Journal of Bone and Joint Surgery website: https://www.jbjs.org/). Figures and discussion sessions presented information on the nature of arthritis, the post-operative course of knee arthroplasty, treatment of osteoarthritis, the role of exercise, joint protection and making future treatment decisions.

Pain coping skills training (CST)

The (CST) protocol: (1) provided a rationale for the coping skills intervention; (2) trained patients in cognitive restructuring as well as a variety of skills that provide patients with opportunities to observe the impact of coping skills on changes in negative pain-related cognitions typical of pain catastrophizing (i.e. thoughts related to pain rumination, pain magnification, and helplessness in the face of pain); and (3) provided training in strategies for enhancing maintenance of gain following treatment.

Melzack and Wall's gate control model of pain was used to help patients reconceptualize their pain and emphasize their own abilities to control pain. The gate control model highlights the role that thoughts, feelings, and behaviors can play in influencing the transmission of noxious signals from the periphery to the brain. Training in pain coping skills was described as a way of changing thoughts, feelings, and behaviors that contribute to pain. Using techniques drawn from cognitive therapy, patients were taught how to identify irrational, maladaptive, and catastrophic pain-related thoughts and to replace these with alternative, rational, reassuring and adaptive thoughts. Self-instructional training was used to teach patients how to use calming self-statements as a way of coping with pain flares. Activity-rest cycling and pleasant activity scheduling was used to help patients increase their activity level and observe the resultant impact on their pain-related cognitions. Activity-rest cycling teaches patients to target activities they tend to overdo (e.g. prolonged standing or walking while shopping) and learn to break these activities into periods of moderate activity (e.g. 30 minutes of shopping) followed by a limited rest break (e.g. 5 minutes of rest). Over time, the goal was to help patients raise their activity level by increasing the length of their activity and decreasing the length of their rest periods. In pleasant activity scheduling, patients learn how to identify activities they enjoy doing (e.g. reading, doing hobbies, and visiting friends) or that give them a sense of mastery (learning how to do something new such as typing or a new language) and then set and record weekly activity goals. Patients were also trained in three attention diversion methods that could be used to alter negative pain related cognitions: relaxation, imagery, and distraction. Progressive relaxation training helped patients learn to concentrate on muscle tension signals and use them as cues to relax. Patients were taught how to use pleasant imagery as a way to alter their pain-related thought patterns and foster relaxation. Distraction training involved training in how to focus on physical stimuli (e.g. a photograph or picture of a nature scene) or auditory stimuli (e.g. listening to music) when experiencing increased pain. Using pain science education prevention methods, each patient developed a written maintenance plan that included the list of pain coping skills learned during the study, potential high-risk situations, early warning signs of setbacks, and plans

about how the patient might apply these skills in dealing with future setbacks and challenges. **Table 8** highlights the key elements of the CST protocol.

Table 8 Components of the pain coping skills intervention.

Training objective	Coping skill training methods
Altering Cognitions to Change Pain Catastrophizing	Cognitive Restructuring, Self-Instructional Training
Altering Activity Patterns To Change Pain Catastrophizing	Activity-Rest Cycling, Goal Setting
Using Attention Diversion to Change Pain Catastrophizing	Relaxation Training, Imagery, Distraction
Enhancing Maintenance	Relapse Prevention Training

7. Glindvad and Jorgensen (2005)

Routine information took approximately 5-10 minutes to deliver. The *preoperative oral information* covered postoperative pain, postoperative stomach and bowel function and recommendations about lifting and sick leave. The *discharge oral information* covered prospective pain, administration of analgesics, lifting to the pain tolerance limit, postponing showers until 24 hours after the operation, avoiding baths and swimming baths until removal of sutures, removal of sutures and use of laxatives. Finally, *five pamphlets containing* information about anesthesia, the hospital stay and pre- and postoperative care were issued.

The intervention group received *routine preoperative oral information and the same five pamphlets*. The discharge oral information was replaced by 30-60 minutes of individual **education** and a follow-up telephone call on the second postoperative day. The starting point of the education was the patient's earlier experiences with pain and knowledge of treatment of pain. A communication guide with 78 points was used, partly to aid the project nurse and partly to be used after discharge as a checklist for patients to remind them of the main points of the conversation. Patients could check whether all points had been discussed and could use the checklist in the telephone call on the second postoperative day.

Content of the education:

- Pain: patients' experiences of pain to date, information about the risk and frequency of pain, its character and localization and the course of the pain. The project nurse included patients' earlier experiences of pain relating to illnesses, operations and accidents and also their own strategies in treating or controlling pain.
- Effect/side effects of analgesics.

- Administration of analgesics: it was stressed to patients that they should not delay treating pain, but should treat it as soon as it began.
- Physiology of pain, including which factors can increase or decrease pain.
- Instruction in change in posture, motion, lifting technique and when to resume sports.
- Wound care instructions.
- Complications: showing photographs of haematomas and cyanosis around the wound and scrotum and infection in the wound in order to give patients an idea of what to accept as expected reactions. Information on when to contact the hospital in the case of bleeding, seeping of fluid from the wound, haematoma or infection.
- Relaxation: patients' methods of relaxation were discussed. Yoga and meditation were included. Cassette tapes with relaxing music were offered.
- Advice on diet and prevention of constipation was given.
- Recommendations about resuming work were discussed (1–2 days of convalescence for light and sedentary work and 1–2 weeks for hard physical work). It was stressed that the degree of pain should be the only decisive factor in when to resume work.

8. Birch et al. (2020)

Patients in the control group received **usual care**. Preoperatively this consisted of a multidisciplinary information meeting for patients and their relatives, approximately 1 week before the operation. Postoperative patients in the usual care group were offered a phone call after 1 week and 3 control visits after 2, 4, and 12 weeks with the nurse, physiotherapist and operating surgeon respectively. Further, some of the patients will receive physical rehabilitation in their local community.

In addition to usual care the intervention group participated in **patient education based on cognitive behavioral therapy**, covering 3 main components: (1) education in pain and the interaction between cognition and pain perception; (2) training in cognitive and behavioral pain coping skills; and (3) training in how to apply the learned coping skills in real-life situations. The goal of the patient education was to teach the patients about pain to gain a better understanding of how cognitions and behavior affect the pain experience. We wanted them to understand the link between thoughts, feelings, bodily reactions and behavior and to realize their own role in controlling their pain experience. The patients learned to use appropriate coping strategies such as activity pacing and pleasant activity scheduling to increase their activity level and observe the resultant impact on their pain related cognitions. Additionally, the patients were trained in cognitive restructuring. Using techniques drawn from cognitive therapy the patients were taught how to identify irrational, maladaptive and catastrophic related thoughts that contribute to pain

and how to replace them with alternative rational and more positive thoughts. Each patient learned about their own early warning signs of setbacks and potential high risk situations and how to use the coping skills learned in the seven sessions to deal with future challenges. The content of each of the seven sessions is described in **Table 9**.

In the first session, the patient were handed out a patient hand-book containing all the key points from the sessions and material for the homework. Further, they received an mp3 player with different relaxation and mindfulness exercises and a pain diary.

Table 9 An overview of the content of each of the seven sessions in the cognitive-behavioral intervention.

Session/time	Focus and skills
1. Session *2 weeks preoperative*	Introduction to the patient education. Causes and consequences of pain. Different types of pain. Introduction to the cognitive triangle – The link between thoughts, feelings, bodily reactions and behavior. *Homework*: Identify and write down thoughts in relation to painful or stressful situations.
2. Session *1 week preoperative - relatives are invited to participate*	Active and passive coping strategies. How to cope with pain and distress in relation to family, relatives and work. The consequences of fear avoidance and the link between activity and pain. Relaxation and mindfulness exercise. *Homework*: Identify and write down your own coping strategies when in pain or distress. Relaxation and mindfulness exercise.
3. Session *3–5 days preoperative*	Appropriate activity management – activity pacing. Pleasant activity scheduling. Goal setting. Introduction to pain diary. *Homework*: Identify five activities you used to enjoy and would like to do again.
4. Session *During hospitalization* *1-2 days postoperative*	Summary of learned skills from previous sessions. Goal setting for the next 14 days. Appropriate rest and activity. *Homework*: Use the pain diary the next 14 days.
5. Session *14 days postoperative*	The cognitive triangle – The link between thoughts, feelings, bodily reactions and behavior. Learning how to change negative automatic thoughts and catastrophic pain-related thoughts into more realistic thoughts by using cognitive restructuring techniques Pleasant activity scheduling and activity pacing. *Homework*: Use pacing techniques and pleasant activity scheduling to restart daily activities and hobbies. Write down how it affects your mood and pain level. Identify and write down troubled thoughts and how they affect your feelings, bodily reactions and behavior. Consider alternative realistic thoughts.
6. Session *4 weeks postoperative*	Restructuring of inappropriate thoughts. Working with the patient's individual problems. Goal setting for the next 2 months.

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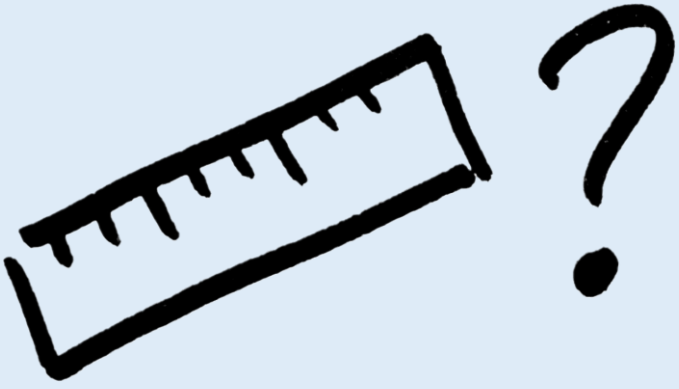
	Homework: Identify catastrophic and negative thoughts and try to change them to alternative more realistic thoughts.
7. Session *3 months postoperative*	Brush up from the 6 previous sessions and a reflection of which coping techniques and cognitive techniques the patient can and will use in the future How to manage and control flare-ups Plan for the future
All sessions begins with questions and a talk about the homework from the previous session	



THE DUTCH LANGUAGE VERSION OF THE PAIN DISABILITY INDEX: PSYCHOMETRIC PROPERTIES IN WOMEN TREATED FOR BREAST CANCER

Elien Van der Gucht, Lore Dams, Koen Bernar, Tessa De Vrieze, Vincent Haenen, An De Groef, Lode Godderis, Bart Morlion, Mira Meeus and Nele Devoogdt

ABSTRACT

Background To assess the psychometric properties, including reliability and validity, of the Pain Disability Index-Dutch language version (PDI-DLV) in women one year after breast cancer surgery.

Methods With a test-retest interval of one week, *relative reliability* was portrayed by calculating the intraclass correlation coefficient and *absolute reliability* by the standard error of measurement, minimal detectable change, within-subjects coefficient of variation and Bland and Altman's 95% limits of agreement. *Internal consistency* was measured with Cronbach's α. For validity, *face validity*, *convergent validity* and *known-group/discriminative validity* were examined.

Results One hundred twenty-three subjects were included for this study. *Relative reliability* was good (intraclass correlation coefficient=0.80). Standard error of measurement and minimal detectable change of the 95% confidence interval (*absolute reliability*) were 5.57 and 15.45 points, respectively. The mean difference between the two measurements was -1.98 points, with 95% limits of agreement equal to 13.19 and -17.15 points. The within-subjects coefficient of variation was 59%. *Internal consistency* was confirmed (Cronbach's α=0.87). *Face validity* was established, as the majority of the subjects scored the PDI-DLV as understandable and complete. Ninety-three % of pre-specified hypotheses regarding *convergent validity* were met and the PDI-DLV was able to distinguish between people with and without pain, which confirmed *known-group validity*.

Conclusions The PDI-DLV is a valid questionnaire to assess pain-related disability one year after breast cancer surgery. Although its *absolute reliability* is disputable, the PDI-DLV can be used to evaluate changes between subjects, as *its relative reliability* is moderate to good.

Keywords Pain-related disability; Pain Disability Index; Breast cancer; Reliability; Validity

INTRODUCTION

Pain is a common and persistent side effect of breast cancer treatments.[34] Because of the increasing survival rate and life expectancy after diagnosis, emphasis on rehabilitation and reintegration into daily life is growing. Pain is not only experienced on the level of body function and structure, but also during activities, participation and interaction with the world around us, which corresponds to the definition of *disability* according to the World Health Organization.[26, 28] Therefore, rehabilitation should not focus on change in pain per se, but rather on the disability that comes with pain, potentially affecting all aspects of someone's life.

In order to correctly measure pain-related disability, it is important to consider the psychometric properties of the questionnaire of interest.[114] This includes looking at the degree of both its measurement consistency and to which it is free from error (**reliability**), as well as whether it measures what it is intended to measure (**validity**).[115]

A commonly used instrument to evaluate pain-related disability is the **Pain Disability Index** (PDI).[116] The PDI has the advantage that it does not only focus on pain-interference on the level of body function and structure, but also captures activity limitations and participation restrictions due to pain. By addressing this broader concept of disability, the PDI allows a better understanding of all functional dimensions of breast cancer patients with pain.[117, 118] This brief questionnaire can be used in all populations with pain as a limiting factor (which simplifies comparison with other pain populations), for different types of pain and pain in all body regions. This is especially interesting for the evaluation of breast cancer patients, as they can experience different types of pain in various locations.[35, 119] In 1984, Pollard and colleagues developed the original English version of the PDI, which has since been translated into several other languages and tested in various musculoskeletal populations.[120] In 1999, a Dutch language version of the PDI was developed (PDI-DLV).[121] Up to now, only two authors have reported the reliability and validity of the PDI-DLV in non-cancer populations, which were comparable to those of the PDI in other languages.[122, 123]

In terms of **reliability**, test-retest reliability coefficients of the PDI, indicating the *relative reliability* (i.e. the degree to which individuals maintain their position in a sample over repeated measures)[124], vary between 0.44 and 0.91.[117, 120, 123, 125-128] The *absolute reliability* (i.e. the degree to which repeated measurements vary for individuals)[124], typically expressed by the standard error of measurement (SEM), was 6.5 points in the study by Soer et al. and 1.2 in the study by Beemster et al. and the minimal detectable change 17.9 and 3.4 points, respectively.[122, 123] Cronbach's α values for *internal consistency* (homogeneity, i.e. the extent to which the items succeed in measuring the various aspects of the same characteristic and nothing else) range

between 0.83 and 0.87.[117, 120, 125-128] Measurement **validity** is supported in musculoskeletal populations with persistent pain by *criterion-related validity*[128] and *construct validity* (convergent[117, 118, 120, 123, 126, 128] and discriminant[116, 127]).

However, because psychometric properties are not an inherent trait of a questionnaire, they will not always be the same in all situations. That is why these properties should be evaluated within the context of the PDI's targeted use, including language, population and setting to which it will be applied.[115] As, to the best of our knowledge, properties of the PDI-DLV have never been studied in a breast cancer population, the aim of the present study was to assess the psychometric properties, including reliability and validity, of the PDI-DLV after breast cancer surgery.

METHODS

Participants and procedures

Participants were included between November 2017 and November 2020 at the University Hospitals Leuven, campus Gasthuisberg (Belgium). All women were recruited from a randomized controlled trial investigating the effectiveness of pain science education in breast cancer patients (EduCan trial, ClinicalTrials.gov NCT03351075)[129], for which they had given written informed consent. As a consequence, the eligibility criteria of the EduCan trial also applied to this study, demanding that the participants: (1) had been diagnosed with histologically confirmed invasive or non-invasive primary breast cancer, (2) had undergone one of the following unilateral surgeries: mastectomy including either a sentinel node biopsy or axillary lymph node dissection (with or without breast reconstruction) or breast conserving surgery including axillary lymph node dissection, (3) were female, (4) aged 18 years or older, (5) could comply with the study protocol, (6) comprehended the Dutch language (reading, listening, writing and speaking). Breast cancer patients with active metastasis were excluded because of potentially deviant pain experiences and higher risk of mortality.

The follow-up timepoints in the EduCan trial were: before surgery, one week after surgery, four-, six-, eight- and twelve months after surgery. As patients finish most of their treatments within one year after surgery, the constructs of pain and its related disability should be more stable than during the treatments. For this reason, we selected the assessment timepoint of 12 months after surgery to assess the psychometric properties of the PDI-DLV.

This study was designed in accordance with the Consensus-based Standards for the selection of health Measurement INstruments study design (COSMIN) checklist for patient-reported outcome measurement instruments.[130]

Three different subgroups were created for the various outcomes of the aims of the present study. The same patient may have been included in different groups.

- **Reliability (group A)**

At 12 months after surgery, all EduCan trial-participants filled out the PDI-DLV. The participants were consecutively asked if they wanted to complete the PDI-DLV a second time at the hospital with a one-week interval, which required an extra visit. Thirty-six patients consented and filled out the PDI-DLV twice in the presence of an assessor (either L.D. or E.V.d.G.). One week between the two administrations should be long enough to prevent recall and short enough to ensure no clinical change has occurred.

- **Content validity (group B1)**

Participants were consecutively asked whether they would be willing to fill out an additional questionnaire regarding *face validity* of the PDI-DLV (developed by the research team). Fifty-one women agreed to this and were subsequently recruited for this aim.

- **Construct validity (group B2)**

Forty consequent participants with pain and 40 without pain were selected for *known-group/discriminative validity*. Data of those 80 participants were available from the standard assessments of the EduCan trial. The same group was used to assess *convergent validity*.

No 'gold standard' exists to investigate construct validity of patient-reported outcome measures. A frequent method to investigate construct validity is to test a priori hypotheses concerning:

> (1) Logical relationships that should exist with other reliable and valid outcomes measures or characteristics of patients[131] (i.e. *convergent validity*): McGill Quality of Life questionnaire, Disabilities of the Arm, Shoulder and Hand questionnaire, Brief Pain Inventory – Short Form, Depression, Anxiety and Stress Scale – 21 items, Pain Catastrophizing Scale and the Visual Analogue Scale for pain.
>
> (2) Expected differences between relevant groups[130] (i.e. *known group/discriminant validity*). For this, we explored whether the PDI-DLV could discriminate between

individuals with and without (clinically relevant) pain, based on a score of ≥ 30mm or < 30mm on the Visual Analogue Scale for average pain over the past week.[132]

All outcomes were patient-reported. Participants completed the questionnaires at home with the exception of the PDI-DLV.

Outcome measurement instruments

- **Reliability (group A)**

Pain Disability Index – Dutch Language Version [116]

The PDI measures the degree of interference of pain with normal role functioning on seven different life domains (family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care and life-support activity) (**Table 10**).[116] A score of zero (no disability) to 10 (total disability) is indicated for each domain, generating a total score ranging from 0–70, with higher scores reflecting higher self-perceived pain-related disability.

In line with previous research, participants were allowed to miss one item.[122, 123] If so, the missing value was replaced by the mean of the other six items. If more than one item was missed, the subject was excluded for analyses.

The assessors provided both oral and written instructions before the participants completed the PDI-DLV.

Table 10 Original items of the Pain Disability Index.

Items	Content description
1. Family or home responsibilities	Activities related to the home or family. It includes chores or duties performed around the house (e.g., yard work) and errands or favors for other family members (e.g., driving the children to school).
2. Recreation	Hobbies, sports and other leisure time activities.
3. Social activity	Activities that involve participation with friends and acquaintances other than family members. This includes parties, theatre, concerts, dining out and other social functions.
4. Occupation	Activities that are part of or directly related to one's job. This includes nonpaying jobs such as that of a housewife or volunteer work.
5. Sexual behavior	The frequency and quality of one's sex life.
6. Self-care	Activities that involve personal maintenance and independent daily living (e.g., taking a shower, getting dressed, etc.).
7.Life support activity	Basic life-supporting behaviors such as eating, sleeping and breathing.

- **Content validity (group B1)**

The included questions covered the following topics: (i) Understandability of the PDI-DLV (including the general instructions, general purpose and the seven separate questions of the PDI-DLV (yes/no)). In addition, participants had to rate how difficult it was to relate their disability to pain on a Numeric Rating Scale (zero=no difficulty and 10=extreme difficulty) in order to verify the understandability of the general construct of the PDI-DLV (pain-related disability). (ii) Clarity of the scoring system of the PDI-DLV (yes/no) and (iii) completeness of the PDI-DLV (i.e. whether the participant considered every component of 'pain-related disability in daily life activities' included) (yes/no). If a participant answered "no" to one of the questions, they were asked to elaborate.

- **Construct validity (group B2)**

Description of the patient-reported outcome measures for construct validity are portrayed in **Table 11**.

Table 11 Patient-reported outcome measures for construct validity.

McGill Quality of Life questionnaire[133, 134]	This 17-item multidimensional tool comprises five domains: physical well-being, physical symptoms, psychological symptoms, existential well-being and support, as well as overall quality of life (i.e. a single-item scale). It was originally developed for patients receiving palliative care and relevant to all phases of the disease trajectory for people with a life-threatening illness.[133] Answers are rated based on an 11-point Likert scale (0-10), with higher scores reflecting higher quality of life. Internal consistency is good for the global scale as well as the subscales [135] and the questionnaire has been found to be reliable.[136] Fair construct validity has been reported for the subscales and moderate to good construct validity for the total score.
Disabilities of the Arm, Shoulder and Hand questionnaire[137, 138]	This 30-item questionnaire assesses symptoms and functional status, with a focus on physical function, in populations with upper extremity musculoskeletal conditions. The items cover upper extremity-related symptoms and measure functional status at the level of disability. Each item is scored on a 5-point Likert scale (1-5), with higher scores reflecting higher disability/worse symptoms and a total score between zero and 100. Reliability is excellent and construct validity is moderate to good.[139, 140] Harrington et al. recommended this questionnaire to assess upper extremity function in breast cancer survivors because it had the most consistently large effect sizes for construct validity and responsiveness.[141]

Brief Pain Inventory – Short Form[142]	The Brief Pain Inventory measures pain intensity and interference in oncological patients. In the original questionnaire, pain interference is rated on a Likert scale from 0-10, but for this study, we used a Visual Analogue Scale to mark the point of pain interference. Reliability and validity in both cancer and chronic pain patients is excellent.[143-148] Validity in chronic pain populations is moderate[146] and discriminant validity in cancer patients is mixed.[147] Abahussin et al. concluded that the Brief Pain Inventory – Short Form had the strongest evidence to support its selection for the measurement of cancer pain.[149]
Depression, Anxiety and Stress Scale – 21 items[150-153]	Each of these domains (depression, anxiety and stress) contains seven items, scored on a 4-point Likert scale ranging from zero ('did not apply at all') to three ('applied most/all of the time'). Total scores for the subscales (0-42) are calculated by multiplying the item-scores by two, with higher scores indicating worse symptoms. The questionnaire demonstrates sufficient high-quality evidence for reliability and validity.[154] In cancer patients, internal consistency is acceptable and construct validity is supported.[155, 156]
Pain Catastrophizing Scale[157, 158]	This 13-item questionnaire examines the rumination, magnification and helplessness patients have about their perceived ability to manage their pain. Items are scored on a 5-point Likert scale (0-4), with a total score ranging between zero and 52. Higher scores indicate higher levels of pain catastrophizing. Reliability and validity is sufficient.[157, 159-161]
Visual Analogue Scale	Global pain intensity over the past week was measured with the Visual Analogue Scale. This scale consists of a 10 cm horizontal line anchored by two extremes of pain ('no pain' and 'worst possible pain') on which patients mark the point that represents the level of perceived pain intensity. The score is obtained by measuring the distance in mm from 'no pain' to the point marked by the patient. The Visual Analogue Scale is a reliable and valid method to measure pain intensity.[162]

Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences software (SPSS for Windows, version 27.0). **Table 12** summarizes the statistical approach for the analyses of the psychometric properties of the PDI-DLV.

Table 12 Methods and analyses of the psychometric properties of the PDI-DLV.

		Inclusion criteria	Psychometric properties	Analyses
Reliability		Participants who filled out PDI-DLV twice with a one-week interval.	1. *Relative reliability*	– Intraclass correlation coefficient (agreement)[1, 2]
			2. *Absolute reliability*	– Standard error of measurement[1, 2] – Minimal detectable change[1, 2] – Within-subjects coefficient of variation[1] – Bland and Altman's 95% limits of agreement[1]
			3. *Internal consistency*	– Cronbach's α[1]
Validity				
	Content	Participants who filled out a questionnaire on *face validity* of the PDI-DLV	4. *Face validity*	– Qualitative description
	Construct	Participants who filled out questionnaires to assess *convergent* and *known group validity* of the PDI-DLV. Two groups were created based on whether their score on the visual analogue scale was either lower than 30mm or higher than/equal to 30mm (no pain vs pain).	5. *Convergent validity* 6. *Known-group validity*	– Correlations (Spearman's rho) with other outcome measures – Compare differences in PDI-DLV scores between people with and without pain (Mann-Whitney *U* test) – Area under the ROC-curve

PDI-DLV=pain disability index-Dutch language version; ROC-curve=receiver operating characteristic curve

[1]Calculated for the PDI-DLV total score

[2]Calculated for the separate item scores of the PDI-DLV

- **Reliability (group A)**

Relative reliability was quantified by the intraclass correlation coefficient ($ICC_{agreement}$) based on a two-way random effects model. Possible values range from 0.00 to 1.00, with higher values indicating greater relative reliability.[115] Excellent relative reliability implies an ICC above 0.90, with good reliability above 0.75 and moderate reliability between 0.50 and 0.75.[115]

Absolute reliability was assessed through the standard error of measurement (SEM) using ICC and pooled standard deviations (S_p) of test-retest trials ($SEM=S_p\sqrt{(1-ICC)}$), providing the standard deviation of the true score of the PDI-DLV. To be confident in a measured score, the relative reliability coefficient should be high and the absolute reliability reflect a limited range.[115] The minimal detectable change based on a 95% confidence interval (MDC_{95}), defined as the 95% range of likely differences ($MDC=z*SEM*\sqrt{2}*1.96$), was calculated to verify whether real improvement/decline had occurred. This means that based on measurement error, 5% of differences between two values are expected to exceed the MDC_{95} value. Less reliable instruments will have larger MDC's, indicating that even greater change scores are required before it can be distinguished from measurement error.[115] As more than one measure of reliability should be provided in reliability studies[163, 164], a Bland-Altman plot was created by plotting the difference between test and retest PDI-DLV total scores (vertical axis) against the mean of those scores for each subject (horizontal axis). This type of plot helps to evaluate the magnitude of disagreement (both error and bias), spot outliers (which can influence the calculation of the ICC) and look for trends.[165] The 95% limits of agreement represent the interval between which 95% of the differences between the test and retest scores lie (although this interval does not tell us whether those limits are acceptable). Furthermore, the plot helps us to evaluate whether the SEM (and ICC) are not oversimplified, as it is possible for the SEM to fluctuate as a function of the PDI-DLV total score. If so, it could be more useful to portray the SEM relative to the mean PDI in the sample (i.e. the within-subjects coefficient of variation (WSCV) calculated as the SEM/mean).

To check for *internal consistency*, Cronbach's α was calculated as a function of the correlation among the seven items of the PDI-DLV.[115] A value between 0.70 and 0.90 is considered strong.[115]

Given that the total PDI-DLV score was rightly skewed, the ICC was additionally reported after applying a (natural) log transformation (after adding a constant 1 to deal with zero values). The results for the SEM, MDC_{95} and Bland-Altman plot were reported using the non-transformed data, because these result in meaningful (clinically applicable) values.

- **Content validity (group B1)**

Face validity was described in both a qualitative and a quantitative way.

- **Construct validity (group B2)**

Correlations were calculated using Spearman's rho. *Convergent validity* was established if at least 75% of the pre-specified hypotheses (see **Table 17**) was met.[114] The Mann-Whitney *U* test was used to compare the differences in PDI-DLV scores between people with and without pain (*known-group validity*). This was further quantified with the area under the ROC-curve (AUC), with values 0.5 and 1 referring to random prediction and a perfect discrimination, respectively. The AUC can be interpreted as the probability that a subject with pain has a higher PDI-DLV total score than a subject without pain. Areas under the ROC curve of 0.70 to 0.80 are 'acceptable', 0.80 to 0.90 'excellent' and 0.9 or above 'outstanding'. The higher the AUC value, the better the discriminative ability.[166]

RESULTS

A total of 123 different female breast cancer patients participated in this study. Patient characteristics and baseline measures of pain and pain-related disability are portrayed in **Table 13**.

Table 13 Baseline patient characteristics.

	Group A	Group B	
	Reliability (n=36)	**B1.Content validity** (n=51)	**B2.Construct validity** (n=80)
Age (years)	56.8 (9.2) / 57.1 (13.4)	56.2 (12.5)	56.9 (14.1)
Body mass index (kg/m^2)	23.8 (6.9)	24.6 (7.0)	24.4 (7.2)
Work status			
Retired*	13 (36)	18 (35)	28 (35)
Employed**	23 (64)	33 (65)	52 (65)
Returned to work***	9 (39)	16 (48)	23 (44)
Time since surgery (months)	11.90 (0.4)	11.93 (0.4)	11.98 (0.4)
Surgery on dominant arm	12 (33)	18 (35)	44 (55)
Type of breast surgery			
Mastectomy	34 (94)	47 (92)	72 (90)
Lumpectomy	2 (6)	4 (8)	8 (10)
Type of axillary surgery			
Axillary lymph node dissection	18 (50)	30 (59)	47 (59)
Sentinel node biopsy	18 (50)	21 (41)	33 (41)
(Neo)adjuvant therapy			
Radiotherapy	28 (78)	41 (80)	64 (80)
Chemotherapy	21 (58)	33 (65)	53 (66)
Hormone therapy	28 (78)	38 (75)	71 (89)
Immunotherapy	6 (17)	12 (24)	18 (23)
Mean pain intensity (Visual Analogue Scale) 0-100	19.19 (17.7)	19.1 (19.3)	31.5 (24.4)
Mean pain-related disability (Pain Disability Index) 0-70	8.5 (11.6)	8.2 (11.6)	12.4 (14.9)

n=sample size

Data are mean (standard deviation) / median (interquartile range), or numbers (percentages)

**Proportion of women who had retired at time of breast cancer diagnosis of the total sample*

*** Proportion of women who were employed at time of breast cancer diagnosis of the total sample*

****Proportion of women who have returned to work of the sample of women who were working at time of breast cancer diagnosis*

- **Reliability (Group A)**

Relative reliability of PDI-DLV total score was good (ICC=0.80) and declined (ICC=0.73) after transformation of the data. ICC's for the individual items are presented in **Table 14**.

Absolute reliability portrayed by the SEM was 5.57 points for the PDI-DLV total score. The MDC_{95} for the PDI-DLV total score implied that an individual would have to change with at least 15.45 points for the observed change to be considered true change in pain-related disability and not a result of measurement error. The Bland-Altman plot (**Figure 10**) showed a mean difference PDI-DLV total score between the two measurements of -1.98 points (red line), with 95% limits of agreement equal to 13.19 and -17.15 points (green lines). The WSCV was 59%. However, the Bland-Altman plot showed one excessive outlier with a difference in PDI-DLV total score of 37 points between the two measurements.

Recalculation after exclusion of this subject resulted in improved values for *relative* and *absolute reliability*; ICC=0.92, SEM=3.45 and MDC_{95}=9.56 (**Table 15**). After transformation of the data without the outlier, the ICC was 0.83. The Bland-Altman plot (**Figure 11**) now depicted a mean value of -0.98 points (red line) and the 95% limits of agreement were 8.73 and -10.69 (green lines). Several larger difference scores were found in some patients with high mean PDI-DLV scores. The WSCV decreased to 38%, meaning that a subject with for instance a total score of five on the PDI-DLV would have a SEM of two points and someone scoring 10 points a SEM of 3.8 points.

Internal consistency was confirmed (Cronbach's α=0.87).

Table 14 Reliability outcomes of the Pain Disability Index – Dutch language version (n=36).

	Relative reliability						Absolute reliability	
	T0		T1					
PDI-DLV item (0-10)	**Mean (SD)**	**95%CI**	**Mean (SD)**	**95%CI**	**ICC**	**95%CI**	**SEM**	**MDC_{95}**
1. *Family or home responsibilities*	1.35 (2.22)	0.60-2.10	1.81 (2.32)	1.02-2.59	0.68	0.46-0.82	1.28	3.55
2. *Recreation*	1.67 (2.69)	0.76-2.58	2.14 (2.63)	1.25-3.03	0.64	0.40-0.80	1.60	4.43
3. *Social activity*	0.83 (1.87)	0.20-1.47	0.92 (2.08)	0.21-1.62	0.76	0.58-0.87	0.97	2.68
4. *Occupation*	1.25 (2.36)	0.45-2.05	1.69 (2.29)	0.92-2.47	0.62	0.37-0.78	1.46	3.98
5. *Sexual behavior*	1.22 (2.52)	0.37-2.07	1.75 (3.04)	0.72-2.78	0.81	0.66-0.90	1.44	3.34
6. *Self-care*	0.86 (1.78)	0.26-1.46	0.83 (1.78)	0.23-1.44	0.78	0.60-0.88	0.84	2.34
7. *Life-support activity*	1.28 (1.70)	0.70-1.85	1.31 (2.29)	0.53-2.08	0.57	0.30-0.76	1.18	3.28
PD-DLVI total (0-70)	8.46 (11.57)	4.55-12.38	10.44 (13.36)	5.92-14.96	0.80	0.65-0.89	5.57	15.45

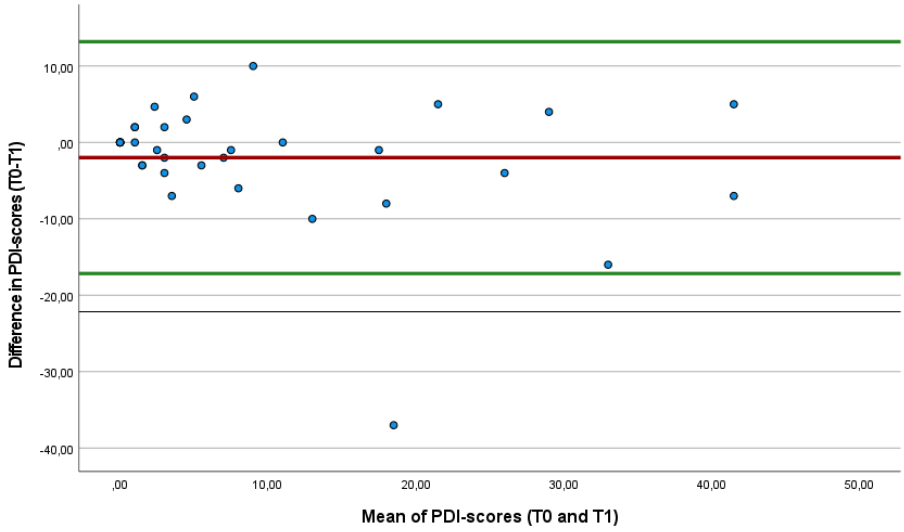
95%CI=95%confidence interval; ICC=intraclass correlation coefficient; MDC_{95}=minimal detectable change based on the 95% confidence interval; N=sample size; PDI-DLV=Dutch language version of the Pain Disability Index; SEM=standard error of measurement; SD=standard deviation; T0=1st measurement of the PDI at 12 months postsurgery; T1=2nd measurement of the PDI at 12 months + 1 week after surgery

Table 15 Reliability outcomes of the PDI-DLV after exclusion of outlier (n=35).

	Relative reliability						Absolute reliability	
	T0		T1					
PDI-DLV item (0-10)	**Mean (SD)**	**95%CI**	**Mean (SD)**	**95%CI**	**ICC**	**95%CI**	**SEM**	**MDC_{95}**
1. *Family or home responsibilities*	1.39 (2.24)	0.62-2.16	1.71 (2.28)	0.93-2.50	0.74	0.54-0.86	1.15	3.19
2. *Recreation*	1.71 (2.72)	0.78-2.65	1.97 (2.47)	1.12-2.82	0.74	0.55-0.86	1.32	3.67
3. *Social activity*	0.86 (1.90)	0.21-1.51	0.74 (1.82)	0.12-1.37	0.93	0.86-0.96	0.49	1.36
4. *Occupation*	1.29 (2.38)	0.47-2.10	1.54 (2.13)	0.81-2.28	0.72	0.51-0.85	1.19	3.30
5. *Sexual behavior*	1.26 (2.55)	0.38-2.13	1.57 (2.88)	0.58-2.56	0.92	0.84-0.96	0.77	2.13
6. *Self-care*	0.89 (1.79)	0.27-1.50	0.83 (1.81)	0.21-1.45	0.78	0.60-0.88	0.84	2.34
7. *Life-support activity*	1.31 (1.71)	0.73-1.90	1.31 (2.32)	0.52-2.11	0.57	0.29-0.76	1.32	3.66
PDI-DLV total (0-70)	8.70 (11.65)	4.70-12.71	9.69 (12.74)	5.31-14.06	0.92	0.84-0.96	3.45	9.56

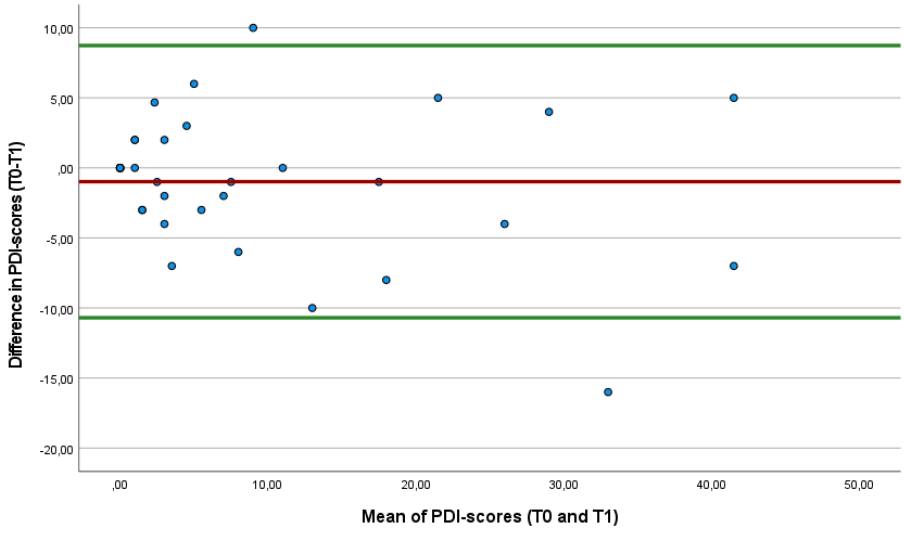
95%CI=95%confidence interval; ICC=intraclass correlation coefficient; MDC_{95}=minimal detectable change based on the 95% confidence interval; N=sample size; PDI-DLV=Dutch language version of the Pain Disability Index; SEM=standard error of measurement; SD=standard deviation; T0=1st measurement of the PDI at 12 months postsurgery; T1=2nd measurement of the PDI at 12 months + 1 week after surgery

Figure 10 Bland-Altman plot for PDI total scores (outlier included).



PDI=Pain Disability Index; T0=1st measurement of the PDI at 12 months postsurgery; T1=2nd measurement of the PDI at 12 months + 1 week after surgery

Figure 11 Bland-Altman plot for PDI total scores (outlier excluded).



PDI=Pain Disability Index; T0=1st measurement of the PDI at 12 months postsurgery; T1=2nd measurement of the PDI at 12 months + 1 week after surgery

- **Content validity (Group B1)**

Fifty-one participants filled out the questionnaire on *face validity*. Fifty participants (89%) indicated that both the general instructions and general purpose of the PDI were understandable and between 96% and 100% rated the seven separate life domains as understandable. Reasons for considering items as incomprehensible are portrayed in **Table 16**. When asked to rate the difficulty relating disability in activities to pain on a Numeric Rating Scale (zero=no difficulty and 10=extremely difficult), the most circled option (24%) was the median score of two (interquartile range=2). Ninety-eight percent rated the scoring system as clear and one person suggested adding the option "does not apply" to each domain of the PDI. Lastly, 11% of the participants marked that they did not think the PDI was complete. Someone suggested adding a category "miscellaneous", because she could not classify certain pains under the current domains (e.g. a painful, stiff feeling in hands, pelvis and feet that fades 30 minutes after getting out of bed). Four people recommended adding a category that entails the impact of pain on mental health (for example on the ability to focus, stress and mood). One person also suggested providing a blank space after each question to write personal examples for pain-related disability on that life-domain.

Table 16 Reported reasons for incomprehensibility of the separate items of the pain disability index.

Items of the pain disability index	Participants considering item incomprehensible (n)	Reasons for incomprehensibility
1. *Family or home responsibilities*	2	− Difficult to understand − The examples of yard work and driving children to school are very dissimilar
2. *Recreation*	1	− Reading and sports are two recreational activities, but totally different
3. *Social activity*	0	
4. *Occupation*	1	− Jobs can be very different, for example cleaning or paperwork
5. *Sexual behavior*	0	
6. *Self-care*	1	− Driving a car does not require large movements and is totally different
7. *Life support activity*	1	− People also move in their sleep, while eating requires less movement (only the mouth)

- **Construct validity (Groups B2)**

The results of correlations of the PDI-DLV with other scales *(convergent validity)* are presented in **Table 17**. Ninety-three percent (14/15) of the hypotheses was met. The PDI-DLV scores in the group with pain (mean rank=26.60) differed significantly (p<0.00) from those without pain (mean rank=54.40) (*known-group validity*). The area under the ROC-curve for *known-group validity* was 0.85 (95%CI=0.76-0.94), indicating excellent discrimination

Table 17 Hypotheses testing for construct validity of the pain disability index (PDI-DLV).

Pain Disability Index	Hypothesized correlations	Result	Hypothesis met
Convergent validity (comparison with other outcome measurement instruments)			
1. Family or home responsibilities	1. At least a *moderate* correlation is expected with the items of the DASH representing family or home responsibilities (items 1, 3-12 and 20)	0.599**	yes
2. Recreation	2. At least a *moderate* correlation is expected with the items of the DASH representing recreational activities (items 17-20)	0.566**	yes
3. Social activity	3. At least a *moderate* correlations is expected with the item of the BPI that evaluates the interference of pain (during the last 24 hours) with relationships with other people	0.510**	yes
	4. At least a *fair* correlation is expected with item 22 of the DASH assessing the extent to which the arm, shoulder or hand problem interfered with normal social activities with family, friends, neighbors or groups over the past week	0.409**	yes
4. Occupation	5. At least a *moderate* correlation is expected with the item of the BPI that measures the interference of pain (during the last 24 hours) with normal work (including both work outside the home and housework).	0.618**	yes
5. Sexual behavior	6. At least a *fair* correlation is expected with item 21 of the DASH assessing the ability to do sexual activities in the last week	0.408**	yes
6. Self-care	7. At least a *fair* correlation is expected with the items of the DASH representing self-care (items 13-15)	0.342**	yes
7. Life support activity	8. At least a *fair* correlation is expected with the items of the DASH representing life-support activities (items 16 and 29)	0.379**	yes
Total score	9. At least a *fair* correlation is expected with the global VAS for pain intensity over the past week	0.672**	yes
	10. At least a *fair* correlation is expected with the single item scale of the MQOL, assessing self-perceived quality of life	-0.522*	yes
	11. At least a *moderate* correlation is expected with the BPI total score	0.623**	yes
	12. At least a *moderate* correlation is expected with the total score of the PCS	0.356**	no
	13. At least a *fair* correlation is expected with the domain score depression of the DASS-21	0.381**	yes
	14. At least a *moderate* correlation is expected with the DASH total score	0.602**	yes

	15. At least a *fair* correlation is expected with the items of the DASH representing global daily-life disabilities and feelings of usefulness due to arm, shoulder or hand problems (items 23 and 30)	0.530**	yes
Known-group validity (comparison between subgroups)			
	16. The total score of the PDI will be higher in the group with pain (VAS≥30mm) compared to the group without pain (VAS<30mm)	<0.001*	yes

Little or no association: 0.00 to 0.25; fair association: 0.26 to 0.50; moderate association: 0.51 to 0.75; good association: > 0.75[167]

DASH=disabilities of arm, shoulder and hand questionnaire; BPI=brief pain inventory; VAS=visual analogue scale; MQOL=McGill quality of life questionnaire; PCS=pain catastrophizing scale; DASS-21=depression, anxiety and stress scale-21 items

***Correlation is significant at the 0.01 level (2-tailed)*

**Correlation is significant at the 0.05 level (2-tailed)*

DISCUSSION

The present study was the first to investigate the psychometric properties of the PDI-DLV in women after breast cancer surgery.

In terms of the PDI-DLV's **reliability**, the results suggested good *relative reliability*. This was in line with those previously established, indicating that subjects maintained their position in the sample over both measurements. Similarly to our study, Grönblad et al. used a one-week time interval to evaluate relative reliability, which resulted in an ICC of 0.91.[117] Other researchers have used different time intervals (two weeks, one month and two months), resulting in ICC's of 0.76, 0.74 and 0.44, respectively.[120, 123, 128]

The magnitude of the *absolute reliability* statistics suggested significant within-subject variability on repeated measurements, which makes the PDI-DLV less suitable to assess pain-related disability in individuals at one-year after breast cancer surgery. The SEM and MDC were situated between the remarkably wide range of values established by Soer et al. and Beemster et al.[122, 123] It might be worth noting that Beemster used the ICC from Soer et al. (who had a more heterogeneous study sample) to calculate the SEM (and consequentially the MDC). As stated by Beckers, *"(…) applying a previously reported ICC to a more homogeneous population will lead to SEM's which are too small and therefore misleading."*, the small values obtained by Beemster might be deceiving, with an underestimation of *absolute reliability* of the PDI-DLV.[122] The SEM and MDC_{95} values in our study were smaller than those calculated by Soer et al., indicating better absolute reliability. However (for all we know), the author did neither further explore this by means of the WSCV nor inspection of a Bland-Altman plot.

In addition, it should be noted that there was one excessive outlier with zero points on the first assessment and 37 points one week later (item scores: 5, 8, 7, 7, 8, 1, 1). Before participants completed the PDI-DLV, they were instructed that it investigates the overall impact of pain on one's life and not just when the pain is at its worst. As there are no guidelines on the time period that should be kept in mind while filling out the PDI, the participants were asked to fill out the PDI-DLV over a timespan of the previous two weeks. It might have been possible that the outlier had interpreted the instructions differently the second time, the recall period of two weeks was too long or she had a painful experience between the time-interval of one week (however, she had scored minimal, maximal and mean pain intensity over the previous week all as zero on a Visual Analogue Scale (0-100)). Another possibility could be the effect of current pain when filling out the PDI-DLV the second time, as present pain has a biasing influence on the reporting of past pain, but this was also scored as zero.[168] The relative and absolute reliability were recalculated without this outlier, after which the results slightly improved. Nevertheless, the resulting WSCV

of 38% still indicated a measurement error of factor 0.38. With the range of PDI-DLV total scores of this sample in mind (0-45), someone scoring 45 points would have a SEM of 17 points, which is larger than the MDC_{95}. The SEM of people scoring higher than 26 on the PDI-DLV exceeds the MDC_{95}, indicating that it would not be possible to tell real change from random error. However, as stated by Portney: *"Reliability cannot be interpreted as an all-or-none condition. It is a measurement property that is attained to varying degrees. (…) The amount of tolerable error depends on how a measured value will be used in decision-making."*[115] Therefore, although the absolute reliability statistics suggested that the PDI-DLV was less useful for interpreting clinical measurements obtained from an individual subject (changes within a patient), it does not discard its use as the primary outcome measure of the randomized controlled trial (Chapter III) as measurement error on group level can be calculated by dividing the SEM by √n.

As a side note, it is possible that pain-related disability is not a stable construct 12 months after breast cancer surgery (as in general, treatments have just finished and therefore pain resulting from these treatments might still be acute). If so, we cannot conclude the PDI-DLV would not be reliable based on its high SEM, as pain-related disability would fluctuate throughout the days. The preceding discussion implied that pain-related disability was a stable construct between two measurements.

Although multiple studies have assessed **validity** of the PDI, literature regarding *face validity* is non-existent. In general, the PDI-DLV was considered a questionnaire with understandable instructions, purpose, questions and scoring system. However, someone commented that she tended to link her pain only to breast cancer treatments and had forgotten about other, lighter, pains. Several subjects recommended adding a category regarding the impact of pain on psychological factors, which suggests a broader experience of pain than the mere tangible experiences (such as hobbies and self-care).

More than 75% of the hypotheses to assess *convergent validity* were met. Several of these relationships had been previously established with the PDI in other languages, which our results mimicked for the associations with pain intensity[117, 118, 120, 123, 126, 169], quality of life[123], depression[118, 126] and upper limb disability[169]. Only the correlation with pain catastrophizing was lower than expected based on existing literature.[126] This might be because the participants in that study by Gauthier et al. suffered from (probably treatment-resistant) persistent pain due to a musculoskeletal condition, for which they were receiving treatment in a pain clinic. Therefore, all their participants were in pain, compared to 50% of participants in the validity group of our study. This was reflected in their baseline characteristics (mean total PDI score of 36.1 (±14.7) and mean baseline Pain Catastrophizing Scale score of 26.2 (±12.2)), which were considerably

higher than the scores of our sample (12.95 (±14.95) and 10.72 (±8.94), respectively). Seventy percent of patients with persistent pain scoring more than 30 points on the Pain Catastrophizing Scale remained unemployed one year post injury and described themselves as totally disabled for occupationally-related activities.[170] This might be a reason why the correlation between the PDI and the Pain Catastrophizing Scale the study by Gauthier et al. was higher than the one in this study.

Several **limitations** of this study should be discussed, followed by the resulting **recommendations for future research**. *Firstly*, it is recommended that a sample size of at least 50 participants be used to define (high quality) measurement properties of a health status questionnaire.[114] Although both groups for validity met this criterion, the smaller sample size in the reliability group may have resulted in less accurate results, as well as being more influenced by potential outliers.[114] The *second* limitation relates to the fact that psychometric properties are population- and situation-specific. In contrast to the use of the PDI-DLV as an outcome measure in research, it can be argued that its application in clinical practice will be limited to patients with pain and at different time points after surgery. As only 22% of the subjects in the reliability group rated their average pain as 30 mm or more on the Visual Analogue Scale for pain (0-100) (which can be considered mild) and we only looked at the psychometric properties at one year after surgery, our results warrant caution for clinical use in breast cancer patients with pain at different time points. In addition, the low pain- and pain-related disability scores in our sample could have possibly resulted in a floor effect. Future research should therefore assess the psychometric properties of the PDI-DLV in a sample of at least 50 participants with at higher pain and pain-related disability scores and at different timepoints after surgery. Furthermore, it would be valuable to investigate the PDI-DLV's ability to detect clinically relevant changes in pain-related disability by looking at its responsiveness and minimal clinically important change. A floor effect, on the other hand, may provide a challenge when addressing responsiveness because improvements cannot be evaluated in those patients already presenting with low pain-related disability. *Thirdly*, selection bias may have occurred in the reliability group since participants had to make an effort for an additional hospital visit. However, there were no remarkable differences when comparing the characteristics of our study sample with the entire EduCan-sample. A *fourth* limitation of this study could be the way in which the hypotheses for convergent validity were stated. The use of the term "at least" could have increased the likelihood of finding significant correlations. *Additionally*, the choice to select patients with and without pain to evaluate discriminative ability of the PDI-DLV could be questioned, as pain and pain-related disability are different constructs. Future research should select a group with disability and one without (for example using the Brief Pain Inventory[142]) from a cohort of

patients experiencing pain. *Sixth*, the PDI-DLV was translated from English to Dutch in 1999 after which backward translation was performed in 2013 by Soer et al. (both translators were from the Netherlands). The participants in our study were from Flanders, Belgium, where Dutch is also the first language. Although there are some differences in vocabulary, none of the subjects in the face validity group reported this to be a problem. A *last* limitation was the lack of normality in our data, which was addressed by transforming the data in order to better fit the normal distribution.

Notwithstanding, out an extensive evaluation of psychometric properties of the PDI-DLV was carried out in accordance with the COSMIN study design.[130]

Assuming that pain-related disability is a stable construct, the PDI-DLV is less effective for interpreting individual follow-up during treatment of breast cancer patients. As a result, it is not recommended to adjust treatment based on a specific score on the PDI-DLV, as the range within which the true score lies is quite wide. However, the PDI-DLV can be used to estimate the relative position of an individual within a group. When using the PDI-DLV as a measure of pain-related disability in breast cancer patients, a SEM of 38-59% of the PDI-DLV total score is expected and a change in PDI-DLV total score of 9.56-15.45 points is considered a true change in pain-related disability.

In conclusion, the PDI-DLV is a valid questionnaire to assess pain-related disability in breast cancer patients one year after surgery. Although *absolute reliability* of the PDI-DLV is questionable, the questionnaire can be used to evaluate changes between subjects as its *relative reliability* is good.

Implications for the EduCan trial

By evaluating how much of our measurement (observed score) is attributable to error, reliability reflects how well observed scores represent true scores. The difference between the true and observed values is referred to as measurement error (variability). The assumption is made that if enough measurements were taken, random errors would eventually cancel each other out, making the average score a good estimate of the true score[115] (i.e. reliability increases with sample size). As we will be comparing group averages in the EduCan trial, we may therefore conclude that incorporating the PDI-DLV as an outcome measure in the analyses of Chapter III is a reliable and valid method to assess pain-related disability.



PAIN SCIENCE EDUCATION AFTER BREAST CANCER SURGERY: RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background Pain during and after breast cancer treatment is a frequent and increasing problem with disabling consequences on all levels of functioning. New insights have led to an educational intervention that elaborates the pain experience, not only explaining pain from a biomedical perspective, but also highlighting its many biopsychosocial contributing factors. Pain science education explains that pain is not always a true representation of the actual status of the tissues, but that it is the nervous system's interpretation of the threat of their injury, which in turn is subject to various psychosocial factors (including social support, pain catastrophizing, psychological distress and fear avoidance). When pain is perceived as less threatening, people may be more inclined to participate in activities previously avoided because of pain, thus limiting its disabling impact.

Aim To investigate (through a randomized controlled trial with a 12-month follow-up period) whether the postoperative change in pain-related disability would be more beneficial for breast cancer patients receiving pain science education compared to those receiving biomedical pain education (primary outcome). As secondary aims, we looked at the effect on physical activity level and upper limb function.

Methods In addition to a standard postoperative physiotherapy program, patients were randomly assigned to either pain science education or biomedical pain education. Throughout the intensive phase (the first four months following surgery), physiotherapy sessions were scheduled once or twice weekly and participants attended three educational sessions. During the maintenance phase (six to 12 months after surgery), two educational sessions and two physiotherapy sessions were held at the same time at six and eight months postoperatively. Pain-related disability (Pain Disability Index) and upper limb function (Disabilities of the Arm, Shoulder and Hand questionnaire) were assessed preoperatively, immediately after surgery, and at four, six, eight and 12 months postoperatively. Physical activity level (hip-worn tri-axial accelerometer) was measured after surgery, at four and 12 months following surgery.

Results The change in pain-related disability from baseline to 12 months after surgery did not differ between the two groups ($p=0.525$). Similar results were observed for the secondary outcomes.

Conclusion Adding five sessions of pain science education to physiotherapy after breast cancer surgery did not result in a better course of pain-related disability up to 12

months postoperatively as compared to biomedical pain education. Future research should be carried out to see whether a patient-tailored intervention would yield better results.

Key words Pain science education; breast cancer; pain-related disability; physical activity; upper limb function; randomized controlled trial

INTRODUCTION

Breast cancer is the most common disease among women all over the world.[171] Treatment modalities go hand in hand with debilitating side effects, which can have a significant influence on quality of life.[22, 25] As survival and life expectancy are increasing, more attention is given to those side effects, which can persist for months or even years following diagnosis.[5, 6, 33]

Pain is one of the most prevalent side effects of breast cancer treatment.[33] During and right after treatment, it serves as our own defense mechanism by encouraging careful handling of the injured area. Although one would expect pain to decrease as healing progresses, it can remain after tissues have recovered and may then develop into a persistent state.[172] Approximately 30% of breast cancer survivors experience above-average pain (1/2 standard deviation worse than age-specific population norms) up to 10 years after treatment.[35, 36] Of particular concern is the potential impact of pain, as the pain experience is not only limited to the body or mind, but also impacts activities, participation and interaction with the environment, which corresponds to de definition of *disability* according to the World Health Organization.[26, 28, 173] Apart from the impact of breast cancer treatments on pain-related functioning, physical functioning (including physical activity levels and upper limb function) significantly reduces as well.[174, 175] Adequate pain management in the early stages of breast cancer treatment is essential for resolving and preventing these problems, both in the short and long term.

Besides improvements in surgical techniques, multimodal pharmacotherapy and physical rehabilitation, considerable literature has grown up around the theme of pain management educational interventions.[56-58] Currently, there is no evidence that patient education improves quality of life or reduces the amount that pain interferes with daily living in cancer patients.[57, 176] It might be due to the fact that those interventions often describe pain from a **biomedical** point of view (in terms of tissue damage) and therefore fail to explain pain persisting beyond the healing process. New insights have led to an educational intervention that elaborates the pain experience, not just explaining pain from a structural perspective, but also emphasizing its many **biopsychosocial** contributing factors.[65-69] *Pain science education* (PSE) shows that pain is not necessarily a true representation of the actual condition of the tissues, but that it is the nervous system's interpretation of the threat of their injury, which in turn is subject to various psychosocial factors (including social support, pain catastrophizing, psychological distress and fear avoidance).[45, 177] Through the reconceptualization of pain (from a marker of tissue damage to that of a marker of the need for protection), people may perceive pain as less threatening. Consequentially, barriers are removed to participate in activities previously avoided because of pain with improved physical functioning and eventually, on a global level, less pain-related

disability and better quality of life as a result.[25, 178] This can be seen within Leventhal's Common-Sense Model of Self-Regulation, which provides a framework for the dynamic interaction between perceptions generated in response to a threat (e.g. pain) and the behavior to manage that threat.[179]

Several systematic reviews indicate that PSE is effective in populations with persistent non-cancer pain at, among others, improving pain ratings, pain knowledge, disability, pain catastrophizing, kinesiophobia, attitudes regarding pain and physical movement.[70, 74, 180] However, the positive results should be viewed in light of the heterogeneous nature of the studies included in these reviews (e.g. education-only approaches versus PSE combined with movement-based therapy, type of control intervention, follow-up period, diagnosis…). A systematic review on the effectiveness of PSE in the perioperative period (preoperative and early postoperative) in people who will undergo or underwent surgery did not show evidence for significant effects on pain, psychological factors or physical functioning throughout the postoperative period.[181] Among the eight included studies, one study (with a 12 week follow-up period) was conducted in a breast cancer only population.[79] To our knowledge, only one other research group (which was not included in the systematic review on perioperative PSE) has looked at the effects of perioperative PSE in a breast cancer population up until 12 months after surgery for breast cancer.[79, 80] Taken together, the results of both studies were inconclusive regarding pain(-related disability) and physical function.

We therefore conducted a double-blinded randomized controlled trial with a 12-month follow-up period to determine whether breast cancer patients who received postoperatively delivered PSE would report more favorable changes in pain-related disability than controls who received biomedical pain education (BPE), both in addition to a standard physiotherapy program. As secondary aims, we looked at the effect of the same interventions on physical activity level and upper limb function.

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.[182] Findings were

reported in accordance with the CONsolidated Standards of Reporting Trials (CONSORT) guidelines.[183, 184]

Participants

Recruitment took place at the Multidisciplinary Breast Center of the University Hospitals Leuven campus Gasthuisberg (Belgium). Potential participants signed informed consent prior to inclusion. The following inclusion criteria were applied: (1) diagnosed with histologically confirmed invasive or non-invasive primary breast cancer, (2) scheduled for one of the following surgeries: mastectomy including either a sentinel node biopsy or axillary lymph node dissection (with or without breast reconstruction) or breast conserving surgery including axillary lymph node dissection, (3) female, (4) aged 18 years or older, (5) could comply with the study protocol and (6) comprehended the Dutch language (reading, listening, writing and speaking). Patients with active metastasis were excluded because of the higher risk of other comorbidities and mortality.

Randomization and masking

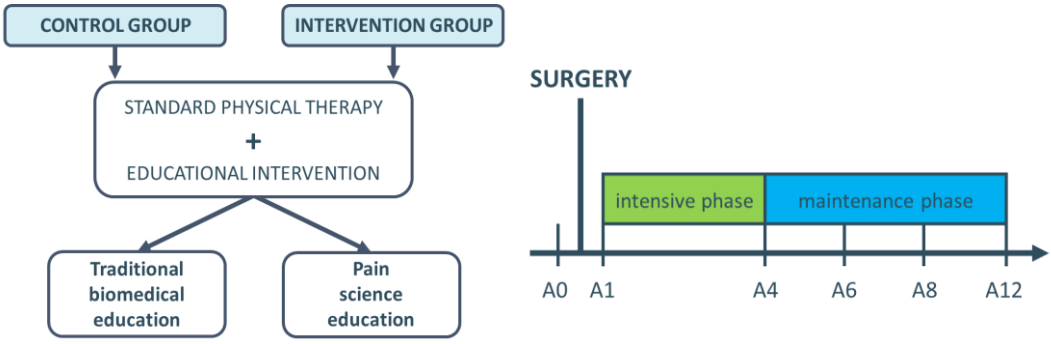
After enrollment (by L.D. and E.V.d.G.), participants were randomly assigned (1:1) to the intervention (PSE) or control group (BPE). This computer generated randomization was performed by an independent coworker (T.D.V.) using permuted blocks (size=4). The randomization sequence was determined by participant identification numbers, which they had received after signing informed consent to de-identify personal information.

Participants, assessors, physical therapists and those who interpreted the data were blind to group allocation. Before consenting to participate in the study, participants were informed that (in addition to following a standard physiotherapy program) they would be randomized to either “traditional biomedical education” (BPE) or to receive a “modern educational intervention” (PSE). The difference between these two interventions was neither explained during recruitment, nor in the written consent document. To prevent contamination between the two intervention groups, both the educational sessions and physiotherapy were one-on-one, minimizing possible interaction between participants. Only the informative session on prevention and treatment of lymphedema was given in groups of approximately 10 people. The physiotherapists drew up a communication sheet to ensure that their answers to patient questions during physiotherapy sessions were standardized. If participants asked pain-related questions, they were referred to the physiotherapist delivering the educational interventions. An independent statistician (S.F.) of the Center for Biostatistics of KU Leuven analyzed the data to ensure additional blinding of the research team.

Interventions

All interventions took place at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven campus Gasthuisberg (Belgium). A visual representation of the interventions and timeline of the assessments and intervention phases is portrayed in **Figure 12**.

Figure 12 Interventions (left) and timeline of the assessments and intervention phase (right).



A0=assessment within one week before surgery; A1=assessment within one week after surgery; A4/6/8/12=assessment at 4/6/8/12 months after surgery

Standard physical therapy program

Independent of group allocation, all participants attended a one-on-one, individually tailored physical therapy program of 30 minutes (once or twice weekly during the **intensive phase** (A1-A4) starting the first week post-surgery, followed by two follow-up sessions during the **maintenance phase** (A6 and A8)). These sessions were delivered by one of four physiotherapists (L.D., F.P., V.H. or 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 patients: (1) manual techniques (passive mobilizations to restore shoulder range of motion, myofascial techniques to improve upper limb 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 four months, this intensive program was replaced by two individual follow-up sessions (maintenance phase), at six and eight months after surgery. At these time points, participants received a physiotherapy session and were referred to a physiotherapy practice in primary care for further intensive

follow-up if needed. Additionally, patients 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 participants reported symptoms of lymphedema, they were referred for thorough evaluation and diagnosis at the Centre for Lymphedema of the University Hospitals Leuven.

Educational sessions

Throughout the whole study period, participants attended five one-on-one 30-minute educational sessions on pain after breast cancer treatment. These were delivered face-to-face 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 two sessions in the **maintenance phase** at six and eight months after surgery (A6 and A8). In case a face-to-face session in the hospital was not possible, a digital session covering the same content was scheduled. During the 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 Questionnaire[185, 186], 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 two maintenance sessions, the physiotherapist went through the information provided in the intensive phase and discussed implementation in future stages of the recovery process. For these sessions, participants received a second booklet with specific information for this phase.

The information delivered during the educational sessions varied depending on which group the patient was randomized to.

Control group: biomedical pain education

The learning goal consisted of gaining biomedically oriented knowledge about pain after breast cancer treatment. Pain was connected to the biomechanics and pathoanatomy of structures involved in various breast cancer treatment modalities. 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).[187] Finally, advice on work resumption against the background of different (persistent) treatment-related side effects was provided. This was based on the load – loadability principle (physical activity – rest) with a focus on ergonomic factors. In addition, other 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 science 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 their pain. 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, taking into account 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.[188] 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 and measurements

Primary outcome

Pain-related disability was evaluated with the Dutch language version of the Pain Disability Index (PDI-DLV).[116] Assessment time points were within one week before surgery (A0), one week after surgery (A1), four (A4), six (A6), eight (A8) and 12 (A12) months after surgery. The PDI measures the degree of interference of pain with normal role functioning on seven different life domains (family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care and life-support activity).[116] A score of zero (no disability) to 10 (total disability) is indicated for each domain, generating a total score ranging from 0–70, with higher scores reflecting higher self-perceived pain-related disability. The assessors provided both oral and written instructions before the participants completed the PDI-DLV at the hospital. This took place before the educational session of that time point to ensure that the score on the PDI-DLV represented the effect of the previous educational sessions. In line with Beemster et al. and Soer et al., participants were allowed to miss no more than one item on the PDI.[122, 123] If so, the missing value was replaced by the mean of the other six items. If more than one item was missed, the participant was excluded for analyses.

Psychometric properties of the PDI-DLV in a breast cancer population have been studied in Chapter II. The results indicated that the PDI-DLV is a valid questionnaire to assess pain-related disability in female breast cancer patients one year after surgery. Although absolute reliability of the PDI-DLV is questionable, it can be used to evaluate changes between subjects, as its relative reliability is moderate to good.

Secondary outcomes

Physical activity level

A waist worn tri-axial accelerometer (ActiGraph® wGT3X-BT+ ((ActiGraph, LLC)) was used to evaluate physical activity level at A1, A4 and A12 (in contrast to the other outcomes, physical activity level was not evaluated at A0 for feasibility reasons). 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). Accelerometer use was explained face-to-face by the physical therapist or assessor (L.D. or E.V.d.G.) after which the participants received identical written instructions for them to re-read at home if desired. They were instructed to wear the

accelerometer on the right hip during seven consecutive days for at least 12 hours during waking hours (except for showering or swimming).[189]

As recommended by the systematic review of Migueles et al., which provides age-specific practical considerations based on validation/calibration studies, sampling frequency (i.e. the rate at which raw data is sampled) was set at 90Hz. Raw accelerometer data were downloaded in ActiLife (version 6.13.4 Full Edition) and filtered and accumulated into 60-second epoch files. In consonance with the work of Bergman et al. and verified with the ActiGraph support team, we categorized and removed non-wear time according to the recommendations by Migueles et al. following a modified version of the Choi algorithm (60-0-1 using vector magnitude).[189-191] Non-wear periods were deleted and the remaining accelerometer data was classified according to different categories of activity intensity using the Freedson VM3 combination (2011) cut points (activity cut points to categorize light: 0-2690, *moderate*: 2691-6166, *vigorous*: 6167-9642 and *very vigorous physical* activity: 9643-∞ counts per minute).[189, 192] 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*.[189, 193] The Freedson VM3 combination (2011) algorithm was used to measure *physical activity energy expenditure.*[194] Only data of participants whom had worn the accelerometer for four days with at least 600 minutes of wear time per day were included for analyses.[189]

The ActiGraph GT3X+ has demonstrated excellent relative reliability (two-week interval) for sedentary behavior (ICC=0.93) and good relative reliability for moderate-to-vigorous physical activity (ICC=0.88) in patients 12 months after breast cancer surgery.[195]

Upper limb function

The Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)[137, 138] was filled out to measure upper limb function at A0, A1, A4, A6, A8 and A12. This 30-item questionnaire assesses symptoms and functional status, with a focus on physical function, in populations with upper extremity musculoskeletal conditions. 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. Participants completed the questionnaires at home, either electronically or paper-based, according to their preference. Participants filled out the questionnaire either written or digitally within a timeframe of two weeks before or after filling out the PDI-DLV.

In musculoskeletal populations, relative reliability has been shown to be excellent (ICC=0.82-0.98).[140] In terms of absolute reliability, standard error of measurement varied from 2.84 to 5.22 and minimal detectable change from 5.5 to 12.2 points.[140] Construct validity (convergent and known group) and responsiveness are good.[139, 140] In post-treatment breast cancer patients, the DASH has shown excellent relative reliability (one-week interval) (ICC=0.997).[196] Internal consistency was excellent (Cronbach's $\alpha = 0.97$).[141] Known-group validity (as part of construct validity) was established.[141] Harrington et al. recommended this questionnaire to assess upper extremity function in breast cancer survivors because it had the most consistently large effect sizes for construct validity and responsiveness.[141]

Statistical analysis

Sample size calculation was performed by the Leuven Biostatistics and Statistical Bioinformatics Center of KU Leuven for the primary outcome measure (PDI-DLV) at A12.[182] This calculation was based on data available in the literature for the PDI[125, 197] and calculated to detect a difference of 20% in PDI after one year with 80% power. Assuming a coefficient of variation (CV) equal to 0.5, 87 participants per group are needed based on a two-sample pooled t-test of a mean ratio with lognormal data and setting alpha equal to 0.05. The assumed CV is a conservative estimate, derived from the observed CV of 0.30 in a sample of normative data for women with chronic pain. To anticipate a dropout rate of approximately 5%, 184 participants in total had to be included.

To assess the difference between the two groups over time, a multivariate linear model for repeated (longitudinal) measurements with an unstructured covariance matrix was applied for each continuous outcome. Missingness of outcomes at more than one timepoint was addressed using a direct likelihood approach and inferences remained valid under the missing at random assumption. The main focus was the comparison of changes versus the preoperative value at A12.

As specified in the published protocol[182], a model was fitted correcting for the post-operative assessment (A1), allowing the relation between the postoperative value and the value at the other timepoints to be timepoint specific (except for the outcomes on physical activity level). From this model, changes versus the A0 value were reported (with 95% confidence intervals (CI)) and compared between both groups. For the outcomes with missing A1, the model was fitted applying a multiple imputation approach (20 imputed datasets). The imputation for the A1 value was performed within each group separately, using the Markov chain Monte Carlo (MCMC) method. Rubin's rule was used to combine the results from the imputed datasets.

Physical activity outcomes were measured at A1, A4 and A12. For these outcomes, changes versus the A1 were evaluated (based on a linear model for repeated measures). For some percentage in time variables a logit transform was used such that predictions stay within the 0-100 range.

Significance level alpha was set to 0.05. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows.

RESULTS

Of the 493 women eligible for participation between November 16, 2017 and February 28, 2020, 380 had been informed about the study protocol and invited for participation. Finally, 184 subjects signed an informed consent prior to randomization, of whom the characteristics can be found in **Table 18**. Throughout the entire study, 12 participants dropped out, among which seven during the intensive phase (intervention group (IG=4); control group (CG=3) and five during the maintenance phase (IG=3; CG=2). Comparing the variables portrayed in **Table 18** between those who dropped out during the course of the study and those who did not (results portrayed in *Appendix I*), the only two variables that were significantly different were preoperative pain ($p=0.002$) and number of physiotherapy sessions ($p<0.001$). In addition, neither the PDI scores from A0 and A1 differed between the dropouts and inclusions. A CONSORT flow diagram of the two groups (enrollment, allocation and data analysis) is portrayed in **Figure 13**.

Of the 166 (90.22%) participants who were handed the accelerometers at A1, 130 (70.65%) had a minimum of four valid days (IG=64; CG=66). At A4, 157 (85.33%) participants wore the accelerometers, 144 (78.26%) of whom met the conditions of valid wear periods (IG=72; CG=72). Lastly, among the 112 (64.37%) participants wearing the accelerometers at A12, 97 (52.72%) wore them adequately (IG=49; CG=48).

Table 18 Patient characteristics (according to treatment allocation).

	Intervention group n=92	**Control group** n=92
Age (years)	55.4 (11.5) / 54.0 (13.9)	55.2 (11.4) / 54.0 (15.1)
Body mass index (kg/m²)	25.4 (4.3) / 24.2 (6.2)	25.9 (6.0) / 24.71 (6.7)
*Working at time of diagnosis**	58 (67)	57 (63)
*Educational level**		
Primary education or no diploma	3 (3.5)	3 (3.5)
Lower secondary education	5 (5.8)	5 (5.8)
Upper secondary education	23 (26.4)	28 (32.6)
Higher education: professional bachelor	30 (34.5)	32 (37.2)
Higher education: academic bachelor or master	25 (28.7)	19 (22.1)
Pain (Visual Analogue Scale) 0-10		
Preoperatively	15.5 (19.3) / 10 (21)	15.1 (20.3) / 7 (23)
One week postoperatively	31.8 (21.4) / 28 (30.5)	28.9 (21.9) / 25 (31.8)
12 months postoperatively	21.6 (12.0) / 16 (25)	25.6 (23.0) / 24.5 (40.5)
Type of surgery		
Mastectomy		
Sentinel node biopsy	34 (37.0)	39 (42.4)
Axillary lymph node dissection	46 (50.0)	40 (43.5)
Tissue expander	2 (2.2)	1 (1.1)
Immediate reconstruction	6 (6.5)	3 (3.3)
Breast conserving		
Axillary lymph node dissection	4 (4.4)	9 (9.8)
Surgery at dominant side	44 (47.8)	41 (44.6)
Tumor size		
pT0	8 (8.7)	9 (9.8)
pTis	5 (5.4)	8 (8.7)
pT1	30 (32.6)	26 (28.3)
pT2	30 (32.6)	38 (41.3)
pT3	17 (18.5)	11 (12.0)
pT4	2 (2.2)	0 (0.0)
Lymph node stage		
pNX	1 (1.1)	0 (0.0)
pN0	43 (46.7)	50 (54.4)
pN1	36 (39.1)	29 (31.5)
pN2	9 (9.8)	7 (7.6)
pN3	3 (3.3)	6 (6.5)
Treatments		
Neo-adjuvant chemotherapy	26 (28.3)	25 (27.2)

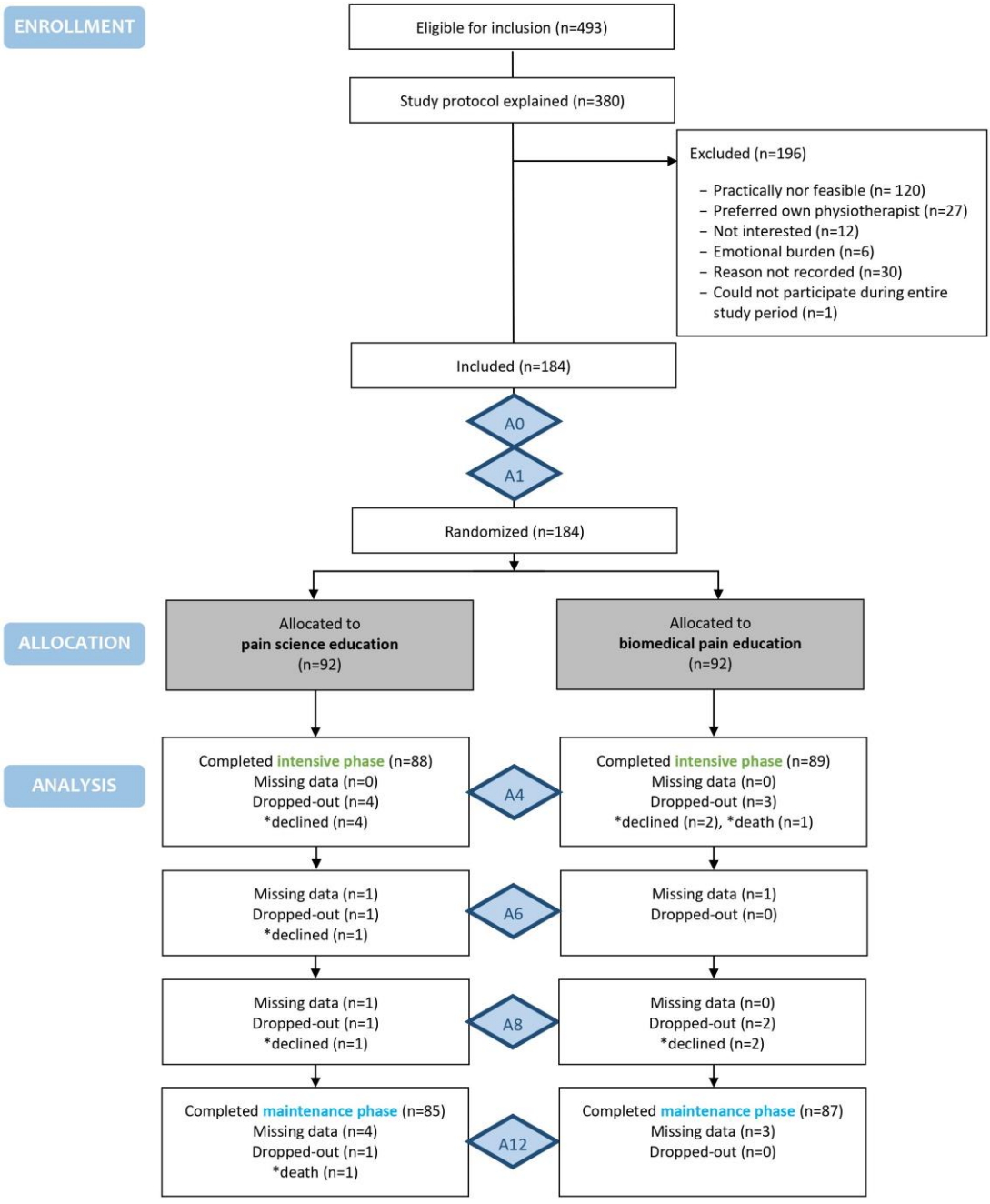
Radiotherapy	75 (81.5)	66 (71.8)
Chemotherapy	62 (67.4)	55 (59.8)
Endocrine therapy	69 (75.0)	68 (73.9)
Target therapy/immunotherapy	23 (25.0)	20 (21.7)
Physiotherapy sessions	20.2 (6.6) / 19.5 (8)	20.3 (7.7) / 20 (10)

n=sample size

Data are mean (standard deviation) / median (interquartile range), or numbers (percentages)

**Assessed retrospectively at 4 months after surgery, so only calculated from data available at 4 postoperatively*

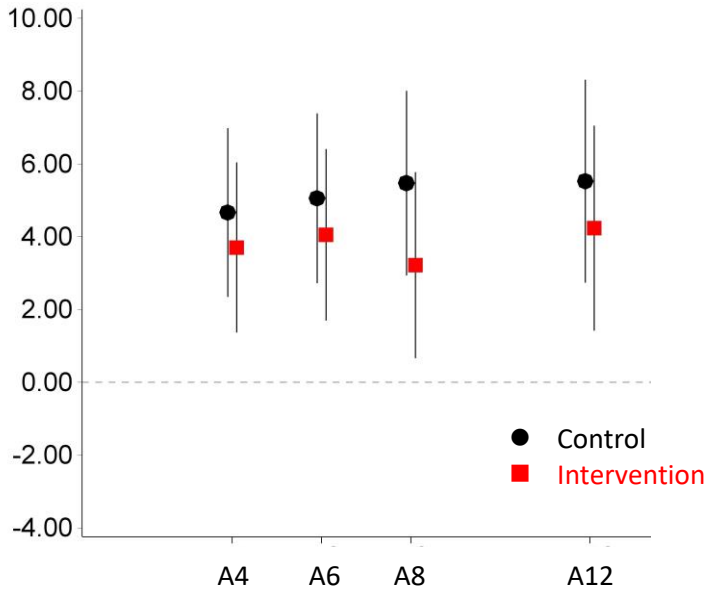
Figure 13 CONSORT Flow diagram.



**reason for drop-out*
A0=assessment within one week before surgery; A1=assessment within one week after surgery; A4/6/8/12=assessment at 4/6/8/12 months after surgery

After an initial significant increase from A0 to A1, the PDI-scores in both groups remained steady throughout the entire postoperative period and did not return to preoperative levels at A12 (**Table 19**). Both groups showed a significant increase in PDI score from baseline to A12 (IG=4.24 points (p=0.0031), CG=5.53 points (p=0.0001)), indicating increased pain-related disability. However, the difference in change between the groups did not significantly differ (p=0.525) (primary analysis) (**Table 19**). Changes in *pain-related disability* from baseline to A12 are graphically portrayed in **Figure 15**.

Figure 15 Change in Pain Disability Index (total score) vs baseline.



A4/6/8/12=assessment at 4/6/8/12 months after surgery

Energy expenditure increased significantly in both groups throughout the entire postoperative study period (**Table 19**). Although there was no difference between the groups, this suggests that all of the women in our study became more active at one year after surgery than they were immediately after surgery. Both groups showed a significant decline in *sedentary time* from the early postoperative period to 12 months after surgery (from roughly 6.5 to 6 hours/day) but this did not depend on group allocation (**Table 19**). During the postoperative period, time spent in *moderate-to-vigorous physical activity* and *(very) vigorous physical activity* increased

significantly for the intervention group, although this change was not statistically different from controls (**Table 19**). Twelve months after surgery, women in the intervention group significantly improved their *daily step count* by 1100 steps, compared to an increase of 265 steps in the control group (not significant). The difference in change between the two groups was not significant (**Table 19**). Overall, none of the changes in physical activity outcomes differed between the group who received PSE and those who received BPE.

Compared to baseline, both groups showed a significant decrease in upper limb function at A12 (**Table 19**). The difference between this functional decrease in the intervention and control group was not statistically significant.

Table 19 Estimates for between group differences from a multivariate linear model for longitudinal measures for pain-related disability primary outcome, physical activity and upper limb function at different time points.

	Intervention group		**Control group**		**Difference in change** from baseline between both groups		
	Mean	CI	Mean	CI	Estimate	CI	P-value
Primary outcome							
Pain-related disability (PDI-DLV) 0-70							
A0	4.9	3.1;6.7	4.6	2.8;6.4			
A1	20.5	17.19;23.76	21.77	18.44;25.10			
A4	8.6*	6.07;11.06	9.26*	6.78;11.75	-0.96	-4.25;2.33	0.567
A6	8.9*	6.35;11.40	9.70*	7.20;12.20	-1.00	-4.32;2.31	0.554
A8	8.1	5.54;10.64	10.06*	7.52;12.60	-2.25	-5.85;1.34	0.220
A12	9.1*	6.32;11.96	10.09*	7.29;12.89	-1.29	-5.25;2.68	0.525
Secondary outcomes							
Physical activity							
Energy expenditure average kcals/day							
A1	294.7	256.9;332.4	327.7	290.6;364.8			
A4	331.6**	289.3;373.9	341.6	299.7;383.5	23.1	-20.3;66.5	0.295
A12	411.9**	343.8;479.9	403.0**	335.1;470.8	42.0	-47.6;131.5	0.356
Sedentary time min/day							
A1	396.2	376.3;416.0	396.5	376.9;416.0			
A4	376.3**	355.4;397.2	375.7**	354.8;396.5	0.9	-26.9;28.7	0.948
A12	361.3**	338.2;384.5	372.5	349.4;395.7	-10.9	-45.9;24.0	0.538
Time in moderate-to-vigorous physical activity min/day							
A1	29.5	24.18;34.78	31.14	25.93;36.36			
A4	32.93	27.26;38.60	33.69	28.04;39.34	0.90	-6.05;7.86	0.798
A12	42.89**	35.96;49.82	37.89	30.98;44.81	6.66	-3.04;16.35	0.177
Time in (very) vigorous activity min/day							
A1	0.24	0.09;0.40	0.24	0.09;0.39			

A4	0.42	0.23;0.63	0.36	0.17;0.56	1.060	0.814;1.382	0.662
A12	0.67**	0.38;1.00	0.47	0.20;0.77	1.189	0.811;1.741	0.373
Step count average steps/day							
A1	6485	5804;7167	6319	5648;6989			
A4	6535	5848;7221	6661	5976;7346	-293	-1218;632	0.533
A12	7585**	6902;8268	6579	5898;7260	839	-221;1900	0.120
Upper limb function (DASH) 0-100							
A0	13.24	10.36;16.12	12.40	9.54;15.25			
A1	41.62	37.88;45.35	39.50	35.77;43.22	2.32	-1.87;6.50	0.276
A4	23.34*	19.68;27.01	20.18*	16.58;23.78	-0.40	-4.61;3.82	0.853
A6	23.25*	19.48;27.02	22.80*	19.06;26.55	-1.45	-6.25;3.36	0.553
A8	22.39*	18.42;26.36	23.00*	19.07;26.92	-1.57	-5.94;2.80	0.479
A12	21.77*	18.01;25.53	22.50*	18.77;26.23	2.32	-1.87;6.50	0.276

A0=assessment within one week before surgery; A1=assessment within one week after surgery; A4/6/8/12=assessment at 4/6/8/12 months after surgery; CI=95% confidence interval; DASH=Disabilities the Arm, Shoulder and Hand questionnaire; PDI-DLV=Pain Disability Index Dutch language version

**Significant within-group change from baseline (A0 corrected for A1)*

***Significant within-group change from baseline (A1)*

Results are obtained after applying multiple imputation 20 datasets for the post value

Changes are calculated after correction for postoperative assessment (so not necessarily the same if calculated from the values on the left side of the table)

DISCUSSION

In this randomized controlled trial, we investigated the effectiveness of PSE after breast cancer surgery and additional to a standard physical therapy program. When compared to BPE, the most important findings were that changes in pain-related disability (primary outcome), physical activity and upper limb function (secondary outcomes) did not differ significantly between the two groups from baseline to 12 months following surgery.

To date, the clinical benefits of PSE in breast cancer patients have not been generally supported by the literature. Of the two published studies, one pilot randomized controlled clinical trial compared a group watching a 90-minute pain psychoeducational video (n=36) to controls receiving digital general health care education (n=32), both before undergoing breast cancer surgery (Darnall et al., 2019).[105] The authors did not find evidence of an interaction effect on either pain interference or physical function up to 12 weeks after surgery. However, it should be noted that the women in their study did report rather low pain intensity while receiving the preoperative educational session. Therefore, a possible explanation for the fact that patients without pain did not benefit from the additional information on psychosocial aspects of pain, might be that they could not relate to it at that time, which questions the potential preventive role of PSE in this subgroup. In a similar way, the average pain intensity reported by the patients in our study at time of their first PSE session was considered mild (not clinically relevant) based on a cutoff point of 30 mm on the Visual Analogue Scale for pain. Moreover, in comparison to the existing literature on the effectiveness of PSE in musculoskeletal pain populations with persistent pain, the postoperative pain scores in our sample were relatively low, so not reflecting those of a population that would normally receive PSE. As pain interference in their study was evaluated with a different outcome measure (PROMIS Pain Interference and Physical Function) and they only portrayed baseline scores, we could not compare our results (PDI-DLV) to theirs. In contrast to the study by Darnall et al, we administered an additional physiotherapy intervention in both groups. The reason for this was that in order to achieve clinically relevant effects (i.e., limiting the disabling impact of pain through application of knowledge regarding the reconceptualization of pain); PSE must be delivered in conjunction with physical interventions and not as a stand-alone intervention.[74, 198] Despite attempts to address the shortcomings of the study by Darnall et al. (short follow-up period, no physical intervention, not the primary outcome (they did however correct for multiple testing)), our results were non-significant.

In contrast to the breast cancer patients without pain in the study by Darnall et al., the second study by Manfuku et al. (2021) retrospectively compared perioperative PSE (n=51) to BPE (n=51)

in patients *with* persistent post-mastectomy pain one year after surgery for breast cancer.[80] Similar to our study, both interventions had the same duration, were face-to-face, delivered by a physiotherapist with use of a pamphlet (pictures and illustrations) and combined with physical therapy. Although they concluded that PSE was more effective than BPE in reducing pain interference (small effect size), this should be interpreted with caution. As the difference between the two groups was only one point on a scale of 0-10, we must be careful in concluding whether these significant effects were clinically relevant. Then again, the difference in pain-related disability between the two groups in our study was only one point on a scale of 0-70 at the same time point (one year after surgery). In addition, Manfuku et al. had excluded subjects whose main pain at one year after surgery was cancer treatment-related pain other than persistent post-mastectomy pain (e.g. chemotherapy-induced peripheral neuropathy or arthralgia induced by aromatase inhibitors), which might have resulted in a sample that was not representative of the general breast cancer population. Consequently, their findings might have been the result of a sample similar to persistent musculoskeletal pain populations, in which previous studies have found significant effects of PSE. Another difference is that they had implemented more educational sessions (i.e. one week before surgery) and at every postoperative physiotherapy session (i.e. once every one to two weeks for three months, starting one week after surgery), which might have contributed to a better learning effect. Lastly, their study was non-randomized (retrospective case-control study with propensity score matching) and the two interventions did not take place during the same period in time.

Our results might be explained by several factors. *Firstly*, even though our sample consisted of people with and without pain, all participants still received an educational intervention. Therefore, we do not know whether there was a lack of effect in the entire sample or whether patients with pain might have benefited from PSE and those without pain did not, resulting in overall insignificant result. As mentioned earlier, the effectiveness of PSE in patients without pain might be questionable, as the information on pain might have been unrelatable to them (impeding the learning process, as the course did not apply to them) or that the information had induced pain catastrophizing and anxiety, which are known to be strong predictors for pain and disability.[63, 64] However, referring to the transtheoretical model of behavior change[112], which suggests that it is unrealistic to expect patients to make a change if they are not motivated, the effect could increase in a situation of shared decision-making. If patients and healthcare professionals contribute to this process and agree on treatment decisions, receiving PSE (and its timing of delivery) would be an inherent choice based on a patient's individual needs and readiness instead of a one-size-fits-all imposed formula. This (more pragmatic) approach could

motivate and enhance the process of behavior change that PSE aims to accomplish and improve pain outcomes.[199] *Secondly*, as the biomedical point of view is widely accepted and more people have internalized its concepts (including the social network of the patient, but more importantly also healthcare professionals), PSE might have created a rehabilitation context lacking interdisciplinarity, possibly confusing the patient with conflicting messages. As a result, the group receiving PSE might needed a more intensive intervention to stimulate behavioral changes. *Thirdly*, considering the predominantly biomedical environment, patients might had accepted their pain as a normal side effect during and right after treatment. This feeling might have been reinforced by the possibility that the content of PSE was less applicable compared to that of BPE, as treatment-related scars and burns are a visual reminder of tissue damage. It is true that pain has a protective role in this phase and explaining all those additional factors might not have provided additional benefits. Altogether, this might have caused a lack of effect. *Fourthly*, the possible influence of fatigue could not be eliminated, as we did not evaluate this outcome. This common side effect of breast cancer treatments might have affected the level of physical activity and upper limb functioning, since in these outcomes the influence of fatigue could not be excluded. This differed from the evaluation of pain-related disability, where patients were explicitly asked to relate their disability to pain. *Lastly*, it might have been possible that the overall positive effect of both interventions and lack of difference in change between them was due to the attention the participants received by participating in the project. As pain is usually underrecognized in breast cancer patients, the project follow-up was more intense than they would normally had received. This could have been reflected in lower PDI-scores throughout the entire study period compared to those established earlier in mixed breast cancer populations after surgery.[200, 201] A deduction might be that we therefore cannot conclude that educational interventions are not meaningful in breast cancer patients, as we did not add a control group receiving physiotherapy without any type of educational sessions.

A number of **limitations** need to be noted regarding the present study. *First*, the sample size was calculated based on existing PDI-scores in non-breast cancer populations, which might have resulted in an approximation that could have been different in case PDI-scores of a comparable breast cancer population would have been used. Ideally, we should have conducted a pilot study so did not have to depend on data in non-cancer pain populations to calculate the sample size. A *second* issue was that only one physiotherapist provided the educational sessions in both groups, which could have influenced the outcome if this person (subconsciously) was a believer of one of the two types of education and acted accordingly. Although we did include a group-specific checklist to assure that the relevant themes were covered, this information could not

tell us for example whether certain topics that belonged to the PSE were addressed in the BPE and vice versa. However, one could argue that these digressions would have been evenly balanced as this was a randomized controlled trial. In future research, this issue could be addressed by having an external person attend and observe the educational sessions at random. A *third* limitation was that the timing of assessment of secondary outcomes was not necessarily the same as the primary outcome. We ensured that de PDI was administered before the educational intervention, so the score would capture the knowledge (implementation) of the previous session(s). In contrast, physical activity levels and upper limb function were measured within a two-week time frame before/after the educational sessions, so it was possible that these secondary outcomes reflected the effect of an additional educational intervention compared to the PDI score at that time. A *last* limitation is the study design, given that a randomized controlled trial does not mimic a real-life situation. In normal circumstances, therapy is patient-tailored and offered through shared-decision making and interdisciplinary collaboration. This might have undermined the external validity.

In addition to being a limitation, the research design could be considered as a **strength**. Randomized controlled trials ensure internal validity and provide a rigorous tool for investigating cause-effect relationships between intervention and outcome. Other key strengths of this study were its large sample size, long follow-up, the fact that is was double blinded (which minimizes bias arising from measurement of the outcome), that mainly one physiotherapist delivered the educational sessions in both groups (which minimizes the effect of the person delivering the education) and the consistent assessment of our primary outcome parameter.

Minimizing symptom burden after treatment is paramount in order to resume life after breast cancer. PSE is a convenient technique to improve pain-related functioning in persistent pain populations. Our findings add to the understanding of PSE in breast cancer patients in several ways and they provide a basis for future research to fine-tune the optimal delivery format in this population. This study showed that adding five postoperative PSE sessions to physiotherapy in a mixed breast cancer population (with and without pain) did not improve pain-related functioning, physical activity and upper limb function when compared to adding the same amount of postoperative BPE sessions one year after surgery for breast cancer. Perhaps, PSE should be provided to patients experiencing postoperative pain, or at least at their request. Furthermore, it might be important to assess the stage of behavior change in order to establish the extent to which patients applied their new knowledge and whether this resulted in behavior change. PSE may had led to a progression earlier in the process rather than a change in behavior.

In this way, sessions could be tailored to the patient's specific progress. An important insight for future research is indeed to study the effect of a PSE program that is more patient-tailored, while monitoring the patient's stage of behavior change. In retrospect, another interesting exploration could be the post hoc analysis of influence of personal factors (including catastrophizing, depression, anxiety and stress) with a responder- or moderator (although the limitation would be that these post hoc analyses would not have been powered).

In conclusion, adding five sessions of PSE to physiotherapy after breast cancer surgery did not result in a better course of pain-related disability, physical activity level and upper limb function up to 12 months postoperatively as compared to BPE. However, these results raised several questions regarding the cookie-cutter approach of the PSE intervention. Future research on PSE (content, intensity, timing of delivery, presence or absence of pain) should look into the effects of a more patient-tailored approach, depending on a patient's specific needs and readiness instead of imposing a one-size-fits-all formula. This (more pragmatic) approach could have the potential to stimulate and improve the process of behavior change that PSE aims to achieve.

APPENDICES

Appendix I: Patient characteristics of dropouts versus inclusions

	Lost to follow-up n=12	Not lost to follow-up n=172	T or X^2	P-value
Age (years)	52.5 (12.9)	55.5 (11.4)	-0.884	0.378
Body mass index (kg/m²)	26.0 (4.5)	25.6 (5.2)	0.277	0.782
*Working at time of diagnosis***	3 (0.3)	112 (0.7)	2.546	0.111
*Educational level***			5.726	0.334
Primary education or no diploma	0 (0.0)	7 (4.07)		
Lower secondary education	0 (0.0)	9 (5.2)		
Upper secondary education	2 (16.7)	47 (27.3)		
Higher education: professional bachelor	5 (41.7)	51 (29.6)		
Higher education: academic bachelor or master	2 (16.7)	43 (25.0)		
Pain (Visual Analogue Scale) 0-10				
Preoperatively	31.8 (23.7)	14.1 (19.0)	3.061	0.003*
One week postoperatively	27.2 (24.0)	30.6 (21.5)	-0.522	0.602
Pain-related disability (Pain Disability Index) 0-70				
Preoperatively	7.3 (10.5)	4.6 (8.6)	1.035	0.302
One week postoperatively	14.7 (16.6)	21.5 (15.9)	-1.361	0.175
Type of surgery			3.721	0.445
Mastectomy				
Sentinel node biopsy	6 (50.0)	67 (39.0)		
Axillary lymph node dissection	6 (50.0)	80 (46.5)		
Tissue expander	0 (0.0)	3 (1.7)		
Immediate reconstruction	0 (0.0)	9 (5.2)		
Breast conserving				
Axillary lymph node dissection	0 (0.0)	13 (7.6)		
Surgery at dominant side	4 (33.3)	81 (47.1)		0.389
Tumor size			5.757	0.331
pT0	2 (16.7)	15 (8.7)		
pTis	0 (0.0)	13 (7.6)		

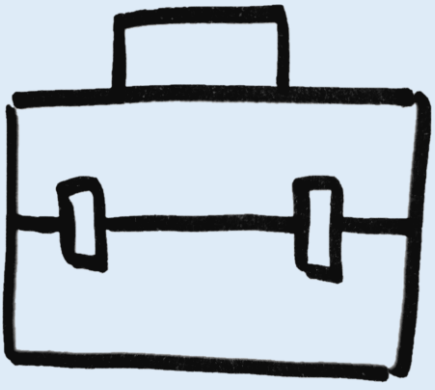
pT1	2 (16.7)	54 (31.4)		
pT2	4 (33.3)	64 (37.2)		
pT3	4 (33.3)	24 (14.0)		
pT4	0 (0.0)	2 (1.2)		
Lymph node stage				0.466
pNX	0 (0.0)	1 (0.6)		
pN0	7 (58.3)	86 (50.0)		
pN1	5 (41.7)	60 (34.9)		
pN2	0 (0.0)	16 (9.3)		
pN3	0 (0.0)	9 (5.2)		
Treatments				
Neo-adjuvant chemotherapy	4 (33.3)	47 (27.3)		0.740
Radiotherapy	9 (75.0)	132 (76.7)		1.000
Chemotherapy	8 (66.7)	109 (63.4)		1.000
Hormone therapy	9 (75.0)	128 (74.4)		1.000
Target therapy/immunotherapy	3 (25.0)	40 (23.3)		1.000
Physiotherapy sessions	12.3 (7.8)	20.79 (6.8)	-4.174	<0.001*

n=sample size

Data are mean (standard deviation), or numbers (percentages)

**significance at the level 0.05, if significant = different*

***Assessed retrospectively at 4 months after surgery, so only calculated from data available at 4 months postoperatively*



RETURNING TO WORK AFTER BREAST CANCER SURGERY: AN IMPORTANT ROLE FOR PAIN SCIENCE EDUCATION?

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ABSTRACT

Background Pain is a common and long-lasting side effect of breast cancer treatment that can have a significant impact on all aspects of daily-life functioning, including return to work. Erroneous pain-related beliefs (such as viewing pain as a sign of tissue damage and the body should therefore rest) might unnecessarily limit people from resuming their daily-life activities. *Pain science education* teaches patients that pain is the brain's perception of the threat of tissue injury (and thus not necessarily reflects true tissue damage), which is influenced by a variety of psychosocial variables. Correcting these perceptions may result in improved return to work outcomes.

Aim To investigate the effect of pain science education compared to biomedical pain education after breast cancer surgery (both in addition to a standard physiotherapy program) by means of a randomized controlled trial. More specifically, we evaluated (1) work status at 12 months postoperatively, (2) time until work resumption and (3) change in return to work expectations up until 12 months after surgery for breast cancer.

Methods Participants were randomly assigned to either pain science education or biomedical pain education in addition to a standard physical therapy program after surgery for breast cancer. Throughout the intensive phase (the first four months following surgery), physiotherapy sessions were scheduled once/twice weekly and participants attended three educational sessions. During the maintenance phase (six to 12 months after surgery), two educational sessions and two physiotherapy sessions were held simultaneously at six and eight months postoperatively. All outcomes were assessed at four, six, eight and 12 months postoperatively.

Results One hundred eleven patients were included. In the group that had received pain science education, 20% more women were working at 12 months after surgery compared to controls (not statistically significant (p=0.07)). In addition, neither time until work resumption (p=0.28) nor change in estimation of own ability to return to work up to 12 months postoperatively (p=0.27) significantly differed between both groups.

Conclusion While none of differences between both groups were statistically significant, the proportion of women working one year postoperatively was 20% higher for those who had received pain science education. Although further research is warranted to confirm this finding as being clinically relevant, this study could be a first step toward the potential

application of pain science education in return to work interventions following breast cancer surgery.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women worldwide and its incidence is increasing.[202] Although improved treatment options have resulted in an increase in survival, 90% of survivors experience persistent sequelae[5-7, 21], which in turn can negatively impact resumption of functional activities and life roles and impair quality of life.[21-25] Fatigue, pain and upper limb impairments are frequently reported side effects of breast cancer (treatments).[21, 27] In addition, psychosocial side effects (including reduced social contacts[30], depression[31] and psychological distress[32]) are often described.

As a result, breast cancer survivors have higher unemployment and diminished work ability compared to healthy controls.[24, 203] This puts an economic burden on both patients and society, since almost half of the survivors are younger than 65 years.[203] At the individual level, long-term work disability is related to financial difficulties, future unemployment, psychological problems and social exclusion.[204] On the other hand, employment (being a sign of recovery[205]) contributes to a sense of normality[206], provides financial security[207-209] and is associated with improved quality of life[210, 211]. Therefore, it is important to prevent long-term absenteeism and encourage return to work.

Various factors influencing work resumption have been identified, both modifiable and non-modifiable.[48] The former group is of primary interest, as these can potentially guide interventions aimed at facilitating return to work. One of these modifiable factors is *pain*, a common and long-lasting reported side effect of breast cancer treatment.[33] Despite improvements in surgical techniques, multimodal pharmacotherapy and physical rehabilitation, up to 72% of breast cancer survivors still report pain persisting at one year after surgery.[212] Pain is a complex biopsychosocial experience, not only influenced by structural damage, but also by various psychosocial factors.[1] In addition, it can negatively influence all aspects of functioning, including activities of daily living and participation in society (such as work resumption).[48] More specifically, pain is a strong predictor for long-term absenteeism.[47] An important way in which pain influences return to work is through pain-related beliefs/perceptions, including kinesiophobia (i.e. fear of movement) and pain catastrophizing.[213] In addition, return to work expectations have been shown to predict return to work outcomes and successful work functioning.[213, 214] Work resumption may in turn improve kinesiophobia and pain catastrophizing, which are known predictors of persistent pain[215], possibly breaking the vicious circle of pain perceptions and activity restrictions.[216] For the above reasons, it might be an interesting approach to explore the effect of biopsychosocial pain interventions on work resumption after breast cancer.

Pain science education (PSE) is one of those applications of the **biopsychosocial** model of pain, which considers an array of many psychosocial contributing factors in addition to explaining pain from a strict biomedical or structural perspective.[65-69] The **biomedical** vision on pain indirectly hampers functioning, viewing pain as a sign of tissue damage. This view might be true in the acute phase, as pain then serves a protective role, but the contributing role of psychosocial factors increases with pain persistence. In that case, biomedical pain education (BPE) falls short in explaining how pain can exist in the absence of objective injury. If persistent pain is viewed in the same light as acute pain, patients will disable themselves by needless protection (resulting in decrease in daily life activities). PSE explains the neurobiology and neurophysiological concepts of pain within the nervous system, so patients understand how their pain is produced. They learn that pain is not always a true representation of the actual state of the tissues, but that it is the nervous system's interpretation of the threat of their injury, which in turn is subject to various psychological factors (e.g. fear avoidance, pain catastrophizing, expectations, cognitions and beliefs).[70] Once people correct their erroneous pain-related beliefs/perceptions (e.g. fear avoidance and pain catastrophizing) and perceive pain as less threatening, they may be more likely to engage in activities previously avoided because of pain, including work-related activities. Instead of first building their resilience to the point where they can handle the workload again, they may see work resumption as a way out and a step toward normality that could be taken regardless of pain. This way, PSE could impact the factors responsible for how pain influences return to work.

This can be seen within Leventhal's Common-Sense Model of Self-Regulation, which provides a framework for the dynamic interaction between perceptions generated in response to a threat (e.g. pain) and the behavior to manage that threat.[179] The model shows that beliefs and expectations about an illness or somatic symptom (in this case pain) have an important influence on people's coping mechanisms, which in turn affect illness outcomes. In other conditions, such as multiple sclerosis, rheumatoid arthritis and kidney disease, it has been shown that functional outcomes can be worse or better regardless of diagnosis.[217-219] This could imply that pain perceptions of the disabilities that may arise as a result of breast cancer diagnosis and treatment will either promote or hinder work resumption.

Several systematic reviews indicate that PSE is effective in populations with persistent non-cancer pain at, among others, improving pain ratings, pain knowledge, disability, pain catastrophizing, kinesiophobia, attitudes regarding pain, physical movement and work status.[70, 73-75] However, the positive results should be viewed in light of the heterogeneous nature of the studies included in these reviews (e.g. education-only approaches versus PSE combined with movement-based therapy, type of control intervention, follow-up period, different outcome

measures, diagnosis…). To our knowledge, only two studies have looked at the effect of PSE compared to biomedical pain education (BPE) in a breast cancer only population.[79, 80] Both found inconclusive results regarding pain and did not report on the effect on work resumption.

Consequently, the key research question of this study was whether PSE would result in improved return to work compared with biomedical pain education (BPE) (both in addition to a standard physiotherapy program). More specifically, as return to work can be considered a measurable and final result, but also a process[220], we evaluated (1) *work status at 12 months postoperatively,* (2) *time until work resumption* and (3) *return to work expectations*.

METHODS

Study design

The present manuscript reports on secondary analyses of the EduCan Trial.[129] 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.[129] Findings were reported in accordance with the CONsolidated Standards of Reporting Trials (CONSORT) guidelines.[183, 184]

Participants

Subjects were recruited from a cohort of breast cancer patients participating in a clinical trial on the effectiveness of postoperatively delivered PSE (EduCan trial) at the Multidisciplinary Breast Center of the University Hospitals Leuven campus Gasthuisberg (Belgium). Potential participants for the EduCan trial signed informed consent prior to inclusion. The following inclusion criteria were applied: (1) diagnosed with histologically confirmed invasive or non-invasive primary breast cancer, (2) scheduled for one of the following surgeries: mastectomy including either a sentinel node biopsy or axillary lymph node dissection (with or without breast reconstruction) or breast conserving surgery including axillary lymph node dissection, (3) female, (4) aged 18 years or older, (5) could comply with the study protocol and (6) comprehended the Dutch language (reading, listening, writing and speaking). Patients with active metastasis were excluded because of the higher risk of other comorbidities and mortality. Additionally for this secondary analysis, (7) only participants working at time of diagnosis and those who were not retiring in the near future were included.

Randomization and masking

After enrollment (by L.D. and E.V.d.G.), participants were randomly assigned (1:1) to the intervention (PSE) or control group (BPE). This computer generated randomization was performed by an independent coworker (T.D.V.) using permuted blocks (size=4). The randomization sequence was determined by participant identification numbers, which they had received after signing informed consent to de-identify personal information.

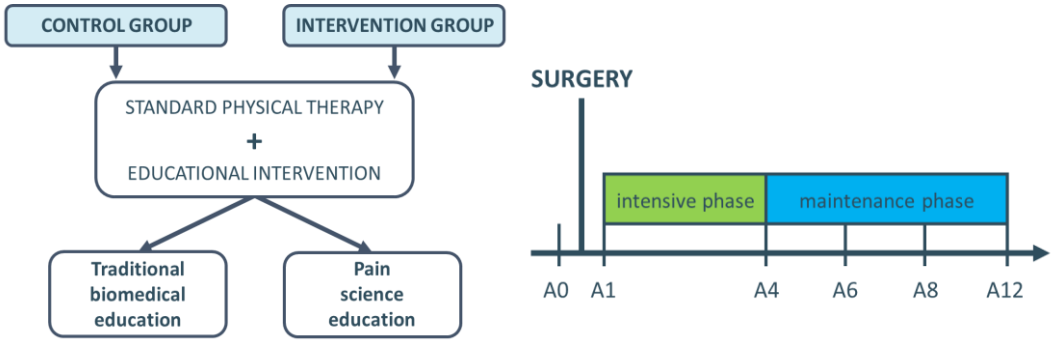
Participants, assessors, physical therapists and those who interpreted the data were blind to group allocation. Before consenting to participate in the study, participants were informed that (in addition to following a standard physiotherapy program) they would be randomized to either "traditional biomedical education" (BPE) or to receive a "modern educational intervention" (PSE). The difference between these two interventions was neither explained during recruitment, nor in the written consent document. To prevent contamination between the two intervention groups, both the educational sessions and physiotherapy were one-on-one, minimizing possible interaction between participants. Only the informative session on prevention and treatment of lymphedema was given in groups of approximately 10 people. The physiotherapists drew up a communication sheet to ensure that their answers to patient questions during physiotherapy sessions were standardized. If participants asked pain-related questions, they were referred to the physiotherapist delivering the educational interventions.

An independent statistician (S.F.) of the Center for Biostatistics of KU Leuven analyzed the data to ensure additional blinding of the research team.

Interventions

All interventions took place at the Department of Physical Medicine and Rehabilitation of the University Hospitals Leuven campus Gasthuisberg (Belgium). A visual representation of the interventions and timeline of the assessments and intervention phases is portrayed in **Figure 16**.

Figure 16 Interventions (left) and timeline of the assessments and intervention phase (right).



A0=assessment within one week before surgery; A1=assessment within one week after surgery; A4/6/8/12=assessment at 4/6/8/12 months after surgery

Standard physical therapy program

Independent of group allocation, all participants attended a one-on-one, individually tailored physical therapy program of 30 minutes (once or twice weekly during the **intensive phase** (A1-A4) starting the first week post-surgery, followed by two follow-up sessions during the **maintenance phase** (A6 and A8)). These sessions were delivered by one of four physiotherapists (L.D., F.P., V.H. or 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 patients: (1) manual techniques (passive mobilizations to restore shoulder range of motion, myofascial techniques to improve upper limb 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 four months, this intensive program was replaced by two individual follow-up sessions (maintenance phase), at six and eight months after surgery. At these time points, participants received a physiotherapy session and were referred to a physiotherapy practice in primary care for further intensive follow-up if needed. Additionally, patients 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 participants reported symptoms of lymphedema, they were referred for thorough evaluation and diagnosis at the Centre for Lymphedema of the University Hospitals Leuven.

Educational sessions

Throughout the whole study period, participants attended five one-on-one 30-minute educational sessions on pain after breast cancer treatment. These were delivered face-to-face 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 two sessions in the **maintenance phase** at six and eight months after surgery (A6 and A8). In case a face-to-face session in the hospital was not possible, a digital session covering the same content was scheduled. During the 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 Questionnaire[185, 186], 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 two maintenance sessions, the physiotherapist went through the information provided in the intensive phase and discussed implementation in future stages of the recovery process. For these sessions, participants received a second booklet with specific information for this phase.

The information delivered during the educational sessions varied depending on which group the patient was randomized to.

Control group: biomedical pain education

The learning goal consisted of gaining biomedically oriented knowledge about pain after breast cancer treatment. Pain was connected to the biomechanics and pathoanatomy of structures involved in various breast cancer treatment modalities. 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).[187] Finally, advice on work resumption against the background of different (persistent) treatment-related side effects was provided. This was based on the load – loadability principle (physical

activity – rest) with a focus on ergonomic factors. In addition, other 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 science 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 their pain. 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, taking into account 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.[188] 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 and measurements

The outcomes of interest for this secondary analysis were threefold:

1. *Work status at 12 months postoperatively* (proportion of women working at 12 months after surgery)
2. *Time until work resumption* (time between surgery and return to work)

The information for the first two outcomes was obtained by a questionnaire developed by the research team. This included questions regarding the moment when participants had stopped working because of breast cancer diagnosis, whether or not they had returned to work (yes/no, independent of whether this was full- or part-time) and in case of the latter the date of work

resumption. In addition, they had to indicate whether they were working according to a part-time or full-time work schedule. The participants filled out this questionnaire at four (A4), six (A6), eight (A8) and 12 (A12) months after surgery.

3. *Return to work expectations* (estimation of own ability to return to work)

The third outcome was evaluated with one item on the Quickscan questionnaire (a questionnaire assessing return to work needs and predicts risks of long-term sick leave).[221] The item on return to work expectations was used for this outcome and covered the following question: "Do you think you can restart your normal work within a period of four weeks, without limitations due to your illness?" which was rated on a 6-point Likert-scale (0='certainly not' to 5='most certainly'). At four (A4), six (A6), eight (A8) and 12 (A12) months after surgery, participants completed the questions at home, either written or electronically.

Statistical analysis

Sample size calculation was based on the primary outcome of the EduCan trial (i.e. pain-related disability measured with the Pain Disability Index).[129] Results of the primary analysis have been previously described in this thesis manuscript (Chapter III).

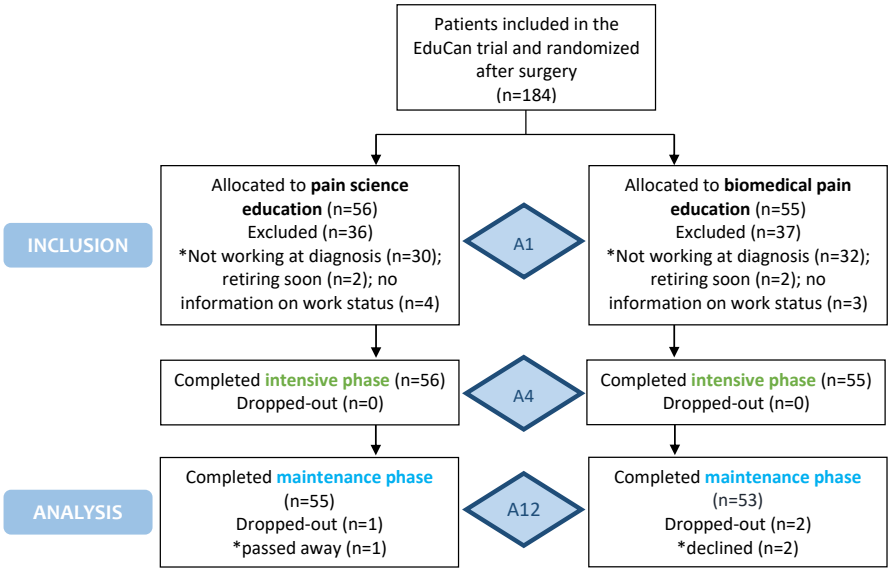
Statistical analyses were according to the intention-to-treat principle. *Work status at 12 months postoperatively* was compared using a Fisher exact test. In addition, the complement of Kaplan-Meier estimates were used to visualize the univariate relationship between the educational interventions and *time until work resumption*. Differences were tested using the log-rank test. Only the time between surgery and the first moment of return to work was evaluated. Whether or not a subject kept working after work resumption was irrelevant for this analysis and subjects who never stopped working were not included in this analysis. For subjects who never stopped working, the interval between the date of stop working and the surgery was not defined and they were not included in the analysis of this outcome. *The mean return to work expectation* (based on the Quickscan) was compared per time point and averaged over all time points using a linear model for longitudinal measures with an unstructured covariance matrix.

All analyses were performed using SAS software, version 9.4 of the SAS System for Windows.

RESULTS

Between November 16, 2017 and February 28, 2020, 184 participants were included in the EduCan trial. One hundred fifteen (62.5%) were working at time of diagnosis (IG=58; CG=57),

Figure 17 Flowchart of the participants in the intervention and control group.



A1=postoperative assessment; A4/12=assessment at four and 12 months after

among which four planned to retire in the near future. From the resulting 111 participants (IG=56; CG=55) included in this study, five never stopped working throughout the entire treatment period (IG=2; CG=3). Throughout the entire study, three (2.70%) participants were lost to follow-up. A participant flowchart is shown in **Figure 17.** Patient characteristics are portrayed in **Table 20**.

Table 20 Patient characteristics (according to treatment allocation) (N=111).

	Intervention group n=56	**Control group** n=55
Age (years)	49.6 (7.6) / 50.5 (10.5)	48.8 (7.3) / 50.2 (9.0)
Body mass index (kg/m²)	24.8 (4.2) / 24.0 (5.0)	25.5 (5.6) / 24.7 (6.0)
Employment status		
Student	0 (0.0)	1 (1.8)
Employee	47 (83.9)	44 (80.0)
Self-employed	6 (10.7)	12 (21.8)
Unemployed	2 (3.6)	0 (0.0)
Looking for a job	0 (0.0)	0 (0.0)
Educational level		

Primary education or no diploma	1 (1.8)	3 (5.6)
Lower secondary education	1 (1.8)	0 (0.0)
Upper secondary education	14 (25.0)	12 (22.2)
Higher education: professional bachelor	20 (35.7)	23 (42.6)
Higher education: academic bachelor or master	20 (35.7)	16 (29.6)
Pain (Visual Analogue Scale) 0-10		
Preoperatively	12.7 (15.8) / 9.5 (19.0)	15.9 (21.8) / 8 (24.0)
One week postoperatively	32.4 (21.8) / 28.5 (29.0)	34.8 (21.0) / 33.0 (27.0)
Four months postoperatively	23.2 (22.2) / 16.0 (32.0)	24.7 (20.9) / 24.0 (43.5)
12 months postoperatively	20.5 (19.4) / 15.0 (24.0)	27.2 (23.6) / 25.5 (36.8)
Type of breast surgery		
Mastectomy		
Sentinel node biopsy	21 (37.5)	24 (43.6)
Axillary lymph node dissection	27 (48.2)	22 (40.0)
Tissue expander	1 (1.8)	1 (1.8)
Immediate reconstruction	5 (8.9)	3 (5.5)
Breast conserving		
Axillary lymph node dissection	2 (3.6)	5 (9.1)
Surgery at dominant side	29 (51.8)	28 (50.9)
Tumor size		
pT0	6 (10.7)	6 (10.9)
pTis	5 (8.9)	5 (9.1)
pT1	19 (33.9)	16 (29.1)
pT2	18 (32.1)	21 (38.2)
pT3	6 (10.7)	7 (12.7)
pT4	2 (3.6)	0 (0.0)
Lymph node stage		
pNX	0 (0.0)	0 (0.0)
pN0	29 (51.8)	31 (56.4)
pN1	21 (37.5)	16 (29.1)
pN2	5 (8.9)	5 (9.1)
pN3	1 (1.8)	3 (5.5)
Treatments		
Neo-adjuvant chemotherapy	3 (5.4)	0 (0.0)
Radiotherapy	43 (76.8)	40 (72.7)
Chemotherapy	37 (66.1)	36 (65.5)
Hormone therapy	39 (69.6)	38 (69.1)
Target therapy/immunotherapy	17 (30.4)	13 (23.6)
Physiotherapy sessions	21.6 (6.02) / 20 (8.5)	21.6 (8.3) / 21 (10.0)

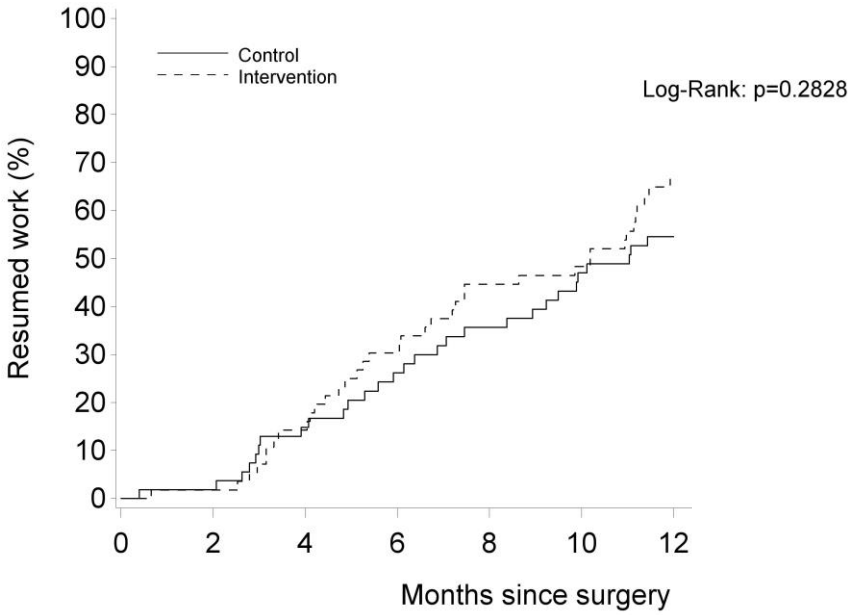
n=sample size

Data are mean (standard deviation) / median (interquartile range), or numbers (percentages)

The proportion of women working at 12 months postoperatively was 0.71 (95% CI 0.57;0.82) in the group receiving PSE and 0.53 (95% CI 0.39-0.67) in the BPE group. Difference in proportion was -0.18 (95% CI -0.36;0.01) (p=0.07).

Time until work resumption is portrayed in **Figure 18**. Among those that had returned to work within 12 months after surgery, median time between surgery and return to work did not differ significantly between the two groups (IG=10.2 months; CG=11.0 months) (p=0.28). Hazard ratio was 1.30 (95% CI 0.80;2.12).

Figure 18 Complement of Kaplan-Meier curve describing time between surgery and work resumption.



Estimation of own ability to return to work (return to work expectations) did neither differ significantly between the two groups at the individual time points, nor after comparing the overall difference (irrespective of time point) (p=0.27). Average mean scores for IG and CG were 2.32 (95% CI 1.91-2.74) and 1.99 (95% CI 1.56-2.41), respectively.

DISCUSSION

Because pain is a frequently reported side effect of breast cancer treatments and is known to impact return to work, it was hypothesized that work resumption would be more successful among breast cancer patients who received PSE versus those assigned to BPE. Despite the outcomes being in favor of the PSE group, none of the results were statistically significant.

To our knowledge, no data have shown the effectiveness of PSE on work resumption after breast cancer surgery. A study in chronic low back pain patients showed that the PSE group was twice as likely as the control group to have a greater improvement in work status 12 months post intervention (OR=2.4; 95%CI 0.9-6.6).[73] Apart from the population, a difference with our study was that they had only included patients with persistent pain, whereas our sample was a mix of people with and without (persistent) pain.

Despite the lack of statistically significant differences between the PSE and BPE group, one notable observation was that when both groups were combined, the proportion of women working at one year after surgery exceeded the reported prevalence one year after breast cancer diagnosis reported in a large-scale study by the Christelijke Mutualiteit (a Belgian health insurance fund).[49] They reported that 35% of female breast cancer patients had resumed their work one year and 67% two years after diagnosis.[49] The latter more closely matches the percentage found in our study already one year after surgery. An important side note however, is that time until work resumption in the study by the Christelijke Mutualiteit was calculated using the time between *diagnosis* and work resumption, whereas we had used the time between *surgery* and work resumption for this calculation. As a result, their one-year window does not exactly correspond to ours, as neo-adjuvant chemotherapy (after diagnosis and before surgery) may have led to an underestimation on our part. To allow comparison of our results, we therefore looked at the percentage of work resumption in their study at 13-14 months after diagnosis (40-45%), since the mean/median time between diagnosis and surgery in our study was 2.11-2.32/0.69-0.82 months. However, even after this correction, more women in our study were found to be working at that time, suggesting a better work resumption rate compared to that of Belgian women after breast cancer in general. This finding could provide an argument for further investigation of the effectiveness of combining physical therapy with PSE after surgery for breast cancer.

A *first* possible **explanation of the lack of statistically significant findings** is that 65% in both groups received adjuvant chemotherapy treatment and 73-78% radiotherapy. Adjuvant chemotherapy starts within four to six weeks after surgery and has a duration between 12 and 24 weeks depending on the type of chemotherapy. After a three-week break, this is often

followed by radiotherapy. In general, patients do not return to work while undergoing any of these treatments and in the immediate period thereafter. Therefore, our follow-up period may not have been long enough to determine the significant difference in time to work resumption between the two groups. *Secondly*, our sample consisted of people with and without pain. It is questionable whether extensively educating people without pain on pain is meaningful. The low average pain scores at group level made us wonder how many patients could be categorized with at least moderate pain (using a cutoff score of 30mm on the Visual Analogue Scale). After inspection, it appeared that at A0, 16 patients (14%) were experiencing at least moderate pain (IG=7 (13%); CG=9 (16%)), which increased at A1 to 58 (52%) (IG=27 (48%); CG=31 (56%)). At A4, this number decreased to 44 (40%) (IG=20 (36%); CG=24 (44%)) with a further decline at A12 of 31 (28%) (IG=13 (23%); CG=18 (33%)). To make matters even more complicated, people who were not in pain may have returned to work despite being in pain, and other who were not in pain may have decided not to for other reasons. Apart from pain (and arm morbidity, which was dealt with during the physiotherapy sessions), one's decision to return to work can depend on various other modifiable and non-modifiable factors. For example, life satisfaction, better role-functioning, self- and environment-motivation and social support positively influence return to work.[222, 223] Other comorbidities and symptoms (such as fatigue and depression) and barriers at the workplace (including manual work, stressful job and lack of support from colleagues) can hinder work ability and resumption.[48, 222, 224, 225] The importance of these factors (including pain) in work resumption may vary from one individual to another, as no two persons, nor two jobs, are identical. Therefore, a more extensive, individually tailored intervention may be needed, focusing on both personal factors and those related to the work environment. A *third* reason for the overall lack of difference in results between both groups could be the fact that the PSE intervention was not powerful enough to create lasting changes. Living in a biomedically focused world, the group receiving PSE might have needed a more intensive approach in order to shift their vision on pain and result in measurable changes, while the BPE group was being taught on widely accepted concepts. We do not know to which extent people had implemented the educational knowledge, which makes it difficult to make assumptions about the actual effect of PSE. It could have been possible that PSE had induced a progress through the stages of behavior change, but not yet to the extent that this progression had influenced return to work outcomes.

This research was **limited** in several ways. *First*, our study may have been underpowered to address the research questions due to a lack of sample size calculation. A *second* limitation was the study design. Randomized controlled trials may not be the optimal way to evaluate complicated interventions like PSE, since they tend to interact with individual factors for which cannot be controlled. *Furthermore*, sampling bias may have comprised external validity, since

patients' willingness to participate may have been related to characteristics affecting the study, resulting in a non-representative sample.

A *first* key **strength** of the present study was that the study participants, physiotherapists and people interpreting the results were blinded to group allocation, which minimized detection and performance bias. *Secondly*, an intention-to-treat analysis was carried out, which lowered the risk of bias induced by comparing groups that differed in prognostic variables caused by dropouts. *Thirdly*, the study design, being both a limitation and a strength, allowed for establishment of causal relationships and ensured excellent internal validity.

Being the first study to provide an insight into the effects of PSE on work resumption after breast cancer, many questions were raised in need of **further investigation**. As stated in the introduction, we hypothesized that once people correct their pain-related beliefs and perceive pain as less threatening, they will be more likely to engage in activities they had previously avoided because of pain, including work-related activities. However, we did not include an outcome measure to evaluate the patient's pain-related perceptions, so we were unable to determine the interaction between these perceptions and the overt behavioral response (return to work parameters). Therefore, future research on the effect of PSE on work resumption after breast cancer should include outcome measures to assess possible change in factors preceding behavior change. Moreover, further studies could be undertaken to compare the characteristics (including their level of pain-related disability) of the patients in the PSE group that had returned to work to the ones who had not. By investigating the factors correlated with work resumption, responders and non-responders to PSE can be defined. Subsequently, while it is important to establish the interaction between certain perceptions and predictors with a behavioral response (as stated in Leventhal's Common-Sense Model of Self-Regulation), Hale et al. (2007) emphasized the value of *understanding* the factors that might influence a person's disease interpretation and their response to it, as those (co-)determine treatment-effectiveness.[179, 226] Therefore, future research should focus not only on identifying patients who respond to PSE (in terms of work resumption), but also on the dynamic mechanisms underlying these predictive relationships (by examining what they did, how they did it, which factors prevented non-responders to return to work etc.).[179] As stated by Leventhal et al. (2016): *"Having both types of data allows us to identify specific targets for intervention at the individual, family or community level, and to generate the conditions for addressing the processes underlying action, a necessary step for improving health behaviors and health indicators."*[179]

This study was the first to compare the effects of two approaches to pain (PSE versus BPE) on return to work after surgery for breast cancer. While none of differences between the groups

were statistically significant, the proportion of women working one year postoperatively was 20% higher for those who had received PSE. Although further research is warranted to confirm this finding as being clinically relevant, this study could be a first step toward the potential application of pain science education in return to work interventions following breast cancer surgery.

GENERAL DISCUSSION

In 2018, breast cancer was diagnosed in 10,905 Belgian women at a mean age of 63 years.[4] Because of improved detection accuracy, early diagnosis and treatment modalities, the average 5-year survival rate has risen up to 91%.[4] The rising incidence, along with a decrease in mortality, results in an increasing number of breast cancer survivors. As a result, debilitating treatment-related side effects have become an even more pressing concern because they substantially impair daily life functioning and quality of life. Pain is one of the most frequently reported sequalae during and after breast cancer treatment[33], which can have disabling consequences on the level of body function and structure, as well as on activities and participation in everyday life.

While current pain management techniques are primarily based on the biomedical or structural components of pain, recent studies have focused on an educational approach that looks beyond this restricted view by also targeting psychosocial aspects of the pain experience. This biopsychosocial educational intervention (also known as *pain science education* (PSE)) corrects erroneous perceptions of pain that can lead to pain-sustaining behaviors. PSE teaches patients the mechanisms of pain as an output of the brain and that pain is not always a consequence of structural damage, but can be influenced by various biopsychosocial factors. Literature shows that PSE has the ability to reduce pain intensity and disability in non-cancer persistent pain populations[70, 74, 75], raising the important question of whether the same results would be obtained if it were offered to breast cancer patients. Particularly since psychosocial risk factors for pain seem to be prevalent and/or exacerbated during and after breast cancer treatments (e.g. stress, depression, sleep disturbances and decreased physical activity).[27, 174]

With this background, the main objective of this PhD project was to investigate the **effectiveness of PSE on decreasing pain-related disability** after breast cancer surgery. Results on the effectiveness of PSE on biopsychosocial risk factors have been analyzed by my dear colleague Lore Dams and are presented in her doctoral thesis.

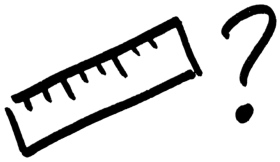
As an introduction, we conducted a comprehensive review of the literature on PSE implemented during the perioperative period (preoperative and early postoperative) (**Chapter I**). Next, the properties of the Dutch language version of the Pain Disability Index (PDI-DLV) were investigated (**Chapter II**), which was used as the primary outcome measure in the subsequent chapter. The final two chapters discussed the findings of the randomized controlled trial on the effectiveness of PSE in breast cancer patients (EduCan trial, trial register number NCT03351075). First, the effects on pain-related disability were described (**Chapter III**), followed by the effects on return to work (**Chapter IV**).

This general discussion will reflect on the *main findings* of the chapters, *interpretation of these findings and critical reflection* on the intervention and outcome measures, *methodological considerations* of the project, *clinical implications* of the results and *future perspectives*. Finally, an *overall conclusion* is formulated to highlight the key messages that this project has taught us.

1. Main findings



As the potential effectiveness of perioperative PSE in improving pain and functioning after common surgical procedures is largely unknown, we decided to conduct a systematic search of the current literature (**Chapter I**). Based on the findings of this systematic review, we concluded that PSE did not significantly improve postoperative *pain*, *psychological factors* nor *physical functioning* compared to control interventions. In line with this conclusion, the only included study in breast cancer patients (Darnall et al., 2019) did neither show any significantly better postoperative evolutions in the abovementioned outcomes for the group that received PSE compared to controls receiving standard care up to 12 weeks after surgery.[79] Even more, the PSE group showed a significant increase in pain compared to controls when the postoperative assessments were averaged to create a composite postsurgical measure. The combination of this result and the fact that the patients were not experiencing pain when receiving PSE provided us with food for thought. It is possible that the (at that moment) non-relatable educational content could have induced distress in anticipation of future pain, which may have increased the actual risk of developing persistent pain. In addition, frequent pain assessments and pain talk may actually worsen pain, which was introduced as a phenomenon of 'explain pain pain' by Louw et al.[227, 228] However, being part of a systematic review (which is at the highest level on the evidence pyramid), this one study does not permit a general conclusion about PSE after breast cancer surgery. The purpose of this review was to examine the effect of PSE in different types of surgery (so broader than breast cancer) and there was only one study included in a breast cancer population. Moreover, the specific context for the pain experience after breast cancer surgery likely differs from that of patients undergoing surgery for non-oncological problems, so it is feasible that effectiveness of PSE has different requirements. In that case, the parameters for PSE after breast cancer surgery may vary and it would not be appropriate to combine the findings of all these studies into a robust conclusion that would also apply to breast cancer patients.



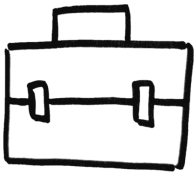
Chapter II described our quest for the psychometric properties of the PDI-DLV[121] one year after surgery for breast cancer. The original English version of the PDI[116], a questionnaire that evaluates pain-related disability (0-70), is proven to be valid and reliable in various musculoskeletal pain populations.[116-118, 120, 122, 123, 125-128] However, as psychometric properties are not an inherent feature of a questionnaire (but are situation-dependent), examining them within a Dutch-speaking breast cancer population would strengthen the results of the primary outcome of the EduCan trial (i.e. pain-related disability at 12 months after surgery for breast cancer). The results showed that *relative reliability* (i.e. the degree to which individuals maintain their position in a sample over the two measures with a one-week interval)[124] was good ($ICC_{agreement}$=0.80). *Absolute reliability* (i.e. the degree to which repeated measurements vary for individuals)[124] was evaluated by calculating the standard error of measurement (SEM), which was 5.57 points. We used this value to calculate the minimal detectable change (linked to the 95% confidence interval) of 15.45 points. This implies that 95% of stable patients (those who have not changed) in this population demonstrated random variation of less than 16 points in repeated measurements with the PDI-DLV and a change of at least 16 points would be needed to conclude that a real change in pain-related disability had occurred. After inspection of the Bland-Altman plot, the SEM appeared to fluctuate as a function of the PDI-DLV total score, suggesting that measurement consistency would depend on whether a patient had high or low pain-related disability. Therefore, we portrayed the SEM relative to the mean PDI-DLV score (i.e. the within-subjects coefficient of variation), resulting in a measurement error factor of 0.59. This means that someone who scores five points on the PDI-DLV will have a SEM of three points, but someone scoring 10 points will have a SEM of six points. *Internal consistency* was confirmed (Cronbach's α=0.87), indicating that the seven items on the PDI-DLV succeeded in measuring the various aspects of the same characteristic and nothing else. *Face validity* was established, as the majority of the subjects scored the PDI-DLV as understandable and complete. Ninety-three percent of pre-specified hypotheses regarding *convergent validity* were met and the PDI-DLV was able to distinguish between people with and without pain, which confirmed *known-group validity*. Based on these results, we concluded that the PDI-DLV is a valid questionnaire to assess pain-related disability one year after breast cancer surgery. Since the absolute reliability of the PDI-DLV is questionable, using it to evaluate changes within individual patients may not be as meaningful. Therefore, we do not recommend using the PDI-DLV to measure pain-related disability in individuals during follow-up after breast cancer surgery. However, measurement error at group-level is smaller than at the individual level (SEM divided by the square root of the sample size of the group).[115] Hence, the more measurements are included, the better the absolute reliability. Because we compared group averages in the EduCan

trial, the questionable absolute reliability of the PDI-DLV does not rule it out as an adequate outcome measure in our analysis. However, it is essential to not lose sight of the questionable absolute reliability as it provides a framework for how we may or may not interpret individual data or profiles correctly. This might be important if we would define responders to PSE based on labels attached to individual changes in PDI-DLV scores, as these might as well be fluctuations and therefore be wrongly labeled as a (non-)responder to PSE.



The effect of PSE on pain-related disability, physical activity levels and upper limb function after breast cancer surgery was described in **Chapter III**. Through a randomized controlled trial with a 12-month follow-up period (EduCan trial), we investigated whether the postoperative *change in pain-related disability* (PDI-DLV) (primary outcome) was more favorable for breast cancer patients receiving PSE compared to those receiving biomedical pain education (BPE). As secondary aims, we looked at the effect on *physical activity level* (hip-worn tri-axial accelerometer) and self-reported *upper limb function* (Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)). The change in pain-related disability from pre-surgery to 12 months after surgery did not differ between the two groups (p=0.525). Similar results were observed for physical activity level and upper limb function. As none of the interaction effects were significant, we concluded that five sessions of PSE did not significantly improve any of the pain-related disability and functioning outcomes compared to five sessions of BPE up to 12 months after surgery for breast cancer. These findings raised some concerns regarding the PSE intervention's cookie-cutter approach. Consequentially, we hypothesized that all health care providers should participate in the care pathway and deliver the same message. Shared decision-making and shared responsibilities make part of effective pain management, but can be challenged by opposing attitudes and goals. Furthermore, health care practitioners should optimize communication in order to bridge the gap between them and the patient. In order to induce a reconceptualization of pain (challenging the often biomedically oriented existing knowledge), delivering PSE should be patient-tailored rather than a one-size-fits-all applied formula to ensure that the patient understands the concepts and can apply them to his/her individual situation. Through successful reconceptualization, this (more pragmatic) approach has the potential to initiate the behavior change process that PSE seeks to achieve, which in turn can improve daily-life functioning (e.g. pain-related disability). Following the fact that all participants received educational interventions (regardless of their pain), a second speculation was whether teaching patients without pain on pain can even be effective. Deducted from the scores on the Visual Analogue Scale (0-100 mm) immediately after surgery, 46% of the patients in the PSE group rated their average pain as 30 mm or more. Motivation for behavior change in the context

of PSE necessitates dissatisfaction with current pain perceptions in order to retain the new concepts and integrate them with attitudes and beliefs.[229, 230] In addition to the hypotheses mentioned earlier, this could be a reason for the lack of effect in the aforementioned study in breast cancer patients by Darnall et al. (Chapter I), as they had implemented the educational interventions before surgery (so in people without pain).



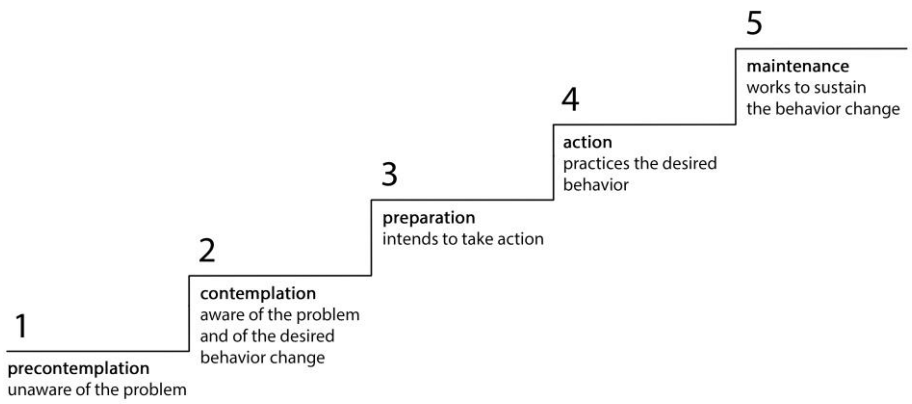
Sequelae of breast cancer treatment can impact all aspects of one's functioning, including return to work. In addition to the disabling impact of pain, it is known that breast cancer survivors have higher unemployment and diminished work ability compared to cancer-free controls.[24, 203] As pain is both prevalent in breast cancer patients[35] and known to influence return to work[48], we were interested in the possible effect of PSE on return to work after breast cancer surgery (**Chapter IV**). In addition, work resumption has a positive influence on pain-related outcomes. For this purpose, all participants from the EduCan trial who were working at time of diagnosis were selected (n=111). The *proportion of women working* one year after surgery was about 20% higher in the group receiving PSE (71% vs 53%). Despite the lack of statistical significance (p=0.07), this difference may support the hypothesis that learning about the biopsychosocial nature of pain after breast cancer could contribute to enhanced work resumption. However, future research is warranted to further investigate this matter. An additional noteworthy observation was that in both groups, the proportion of women working at one year after surgery exceeded the reported prevalence one year after breast cancer diagnosis reported in a large-scale study by the Christelijke Mutualiteit.[49] Their paper reported that 35% of female breast cancer patients had resumed their work one year and 67% two years after diagnosis. The latter more closely matches the percentage found in our study one year after surgery. Moreover, PSE did neither result in *earlier work resumption* (p=0.283) (time between surgery and return to work), nor in improved *return to work expectations* (p=0.285) (estimation of own ability to return to work) at 12 months after surgery compared to controls. This may not come as a surprise since neither pain intensity (results portrayed in Lore Dams' doctoral thesis), nor pain-related disability (Chapter III) showed significantly better improvement in the PSE group compared to controls. The findings of this study (which was the first to assess the impact of PSE after breast cancer surgery on return to work) may provide a context for future research on the application of PSE in addition to physiotherapy as part of return to work interventions after breast cancer surgery. Further research should focus on potential explanations of why PSE might be beneficial in this population, for example, by looking into the role of psychosocial patient-characteristics as well as work-related factors through mediator and moderator analyses. In addition, qualitative research (e.g. interviewing both those who did

return to work and those who did not after the PSE intervention and compare these result to subjects in the BPE group) could provide insights into the dynamic mechanisms behind the relationships.

2. Interpretation and critical reflection

Studying the effectiveness of educational interventions is challenging, mainly because the complexity of both the individual history, thoughts, opinions, surroundings etc. of the patient and the health care provider is intertwined in this process. These parameters further complicate matters as PSE aims at behavior change by creating lasting changes in the patient's beliefs about pain (reconceptualization of pain as a marker of tissue damage to that of a marker of the perceived need to protect body tissue).[71] The **Transtheoretical Model of Health Behavior Change** by Prochaska and DiClemente (1982)[231] explains how people can successfully change their behavior through different stages, with the patient progressing from being uninterested, unaware or unwilling to make a change (*precontemplation*), to being aware that a problem exists and considering a change (*contemplation*). Following the decision and preparations to make a change (*preparation*), patients take determined *action* to overcome the problem and eventually attempt to sustain their success throughout the *maintenance* stage (**Figure 19**). Their framework illustrates that it makes no sense to aim for a reconceptualization of pain and a change in behavior in someone in the precontemplation stage (convinced of own theories and not open to new ideas), as there is no intrinsic motivator to drive behavior change and long-term changes. A patient must be prompted to consider that this transition is necessary, resulting in a shift where the benefits of changing behavior outweigh the disadvantages; this is where the desire to take

Figure 19 The Stages of Change model.



action kicks in. This whole process takes time and the therapeutic techniques depend on the stage of behavior change of the patient.

2.1.1. The pain science education program

In contrast to the patient-tailored approach necessary to induce a change in health behavior as described above, the EduCan trial was conducted in a highly regulated setting and therefore did not accurately reflect real-life conditions. In this section, we will discuss several **aspects of the PSE intervention that could be improved for better outcomes**. The resulting suggestions for application in clinical practice are outlined later (4. Clinical applications).

A *first* potential obstacle is the **timing** of the intervention. Many patients are overwhelmed by all that comes with a breast cancer diagnosis. While in survival mode, they undergo surgery and have to decide on adjuvant treatment modalities. As the first three educational sessions took place within one month after surgery, pain might have seemed insignificant in comparison to all the other things they were dealing with. In addition, this turbulent period is often accompanied by impaired cognitive performance.[232-234] Overall, the information may not have gotten across as patients might not have been receptive to the educational content. Another issue concerning the timing of the intervention was the phase of tissue healing in the early postoperative period. At this stage, undeniable tissue injury sends danger messages to the brain, which in turn calls for action by producing pain (and thus protecting the painful area to avoid further damage so it can heal). As patients can see damage (biological factors) and feel pain, their experience may not have been consistent with the additional psychosocial content of PSE. From this follows a *second* issue. The extensive **content** of PSE (learning about the underlying mechanisms of how the brain produces pain and the influence of psychosocial factors) may have induced distress in anticipation of potentially persistent pain in the future. Moreover, frequent pain assessments and pain talk (PSE) could have actually worsened pain (‘explain pain pain’). Furthermore, health literacy (defined as "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions")[235] may have influenced the efficacy of PSE. As it depends on intelligence (cognitive abilities)[236], low health literacy has been associated with poorer ability to interpret medical information and a reduction in the use of preventive health services.[237] Knowledge of a patient’s health literacy and/or cognitive abilities could help selecting a more patient-tailored format, which could contribute to conceptual change and thus effectiveness of the PSE. Moreover, the general population may have been more receptive to BPE, as a biomedical model could be considered “common sense” since our entire health care system is biomedically oriented. Apart

from the content of the education, the **implementation method** may also have influenced the outcome. The educational sessions in both groups used a similar format; they were scheduled at the same time points, with the same frequency, educational materials etc. Learning is not only intentional (i.e. explicit learning), but also involves acquiring skills and knowledge without conscious awareness (i.e. implicit learning).[238] As a result, the pervasive biomedical ideologies (which were omnipresent in their daily lives in contrast to the PSE content) may have necessitated a more intensive intervention in the group that received PSE. They truly had to make a mind switch, while the information received by the biomedical group probably confirmed what they already knew.

The following topics are discussed in the context of the abovementioned Transtheoretical Model of Health Behavior Change. People in the first stage (precontemplation) are not ready to change, as they are unaware of the possible consequences of their behavior. The patient must understand the information delivered during the educational sessions in order to induce ambivalence (i.e. proceed to the contemplation stage) and further preparation (which is the most important as skipping this stage will cause relapse to earlier stages). The fact that the educational interventions were implemented at fixed defined time points, regardless of the **presence or absence of pain**, could have been a reason for the lack of progression into further stages of behavioral change. Patients *without pain* often did not consider the information relevant, as they were not experiencing any pain. On the other hand, people without pain may also exhibit characteristics that are linked to an increased risk of developing persistent pain (e.g. stress, anxiety, depression and decreased physical activity levels). In this group, a failed information transfer could result in a missed opportunity to anticipate a possible future problem and thus on the course of persistent pain. If a patient is unaware of their problems, they cannot be motivated to change. However, perhaps also patients *with pain* did not always relate to the educational content and therefore could not progress into further stages of behavior change. Linked to the previously mentioned predominant biomedical ideology, patients might had assumed that their pain would disappear once their tissues had healed, reluctant about the biopsychosocial information received during the educational sessions. This **lack of shared-decision making**, which is defined as "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences"[239] could have undermined motivation, a prerequisite for intentional behavioral change. Lastly, in context of this shared-decision making, the **lack of interdisciplinarity** has to be pointed out as well. A systematic review on healthcare professionals' knowledge and attitudes on cancer-related pain management found that they did not understand the nature, origin and transmission of pain, the effects of

anxiety and depression on pain and differences and links between acute and persistent pain.[240] As a consequence, the message the patients in the PSE group received from their physicians may not have been consistent with the information offered during the PSE sessions, potentially leaving the patient confused. This was partially due to the fact that our study took place in a research setting at the hospital and was not part of the usual postoperative follow up trajectory mostly in a primary care setting. In clinical practice, more pragmatic and interprofessional dialogues ensure that all health care providers are on the same page.

Altogether, the above-mentioned shortcomings of the PSE intervention could have contributed to its lack of effectiveness in behavior change. On the other hand, it is possible that this absence of effect was not due to the intervention, but to the choice of constructs and outcome measures we had selected to quantify those constructs.

2.2. Outcome measures

To verify the effectiveness of the educational sessions, it is important that both the constructs (which express the unobservable concepts that we aimed to change with PSE) and the instruments to measure them were chosen wisely. The latter implies that the psychometric properties of the outcome measures must be acceptable. If not, it is possible that the selected outcome measures contributed to the lack of observed effect.

2.2.1. Primary outcome

To fully capture the impact of pain in the context of daily-life functioning, we chose **pain-related disability** as the primary outcome measure of the EduCan trial. This construct was measured with the PDI-DLV, which yields a total score between 0-70, with higher scores indicating higher pain-related disability. The PDI[116] is a widely used instrument for the evaluation of pain-related disability in non-cancer patients, but can be administered in all populations with pain, for different types of pain and pain in all body regions. In addition, the Oncology Section Breast Cancer EDGE Task Force highly recommends the PDI to measure pain-related disability in breast cancer patients.[241] Since participant recruitment for the EduCan took place in Flanders (the Dutch-speaking part of Belgium), we used the PDI-DLV[121] to assess pain-related disability. It is worth noting that the PDI measures the impact of pain in general, not the specific pain caused by breast cancer treatments.

We expected the change in pain-related disability to be more positive in the group that received PSE than in the control group, because by explaining that pain does not equal damage, PSE aimed to enable people to resume their daily life activities without fear of damaging their bodies and

increasing pain. Consequently, being more active could even result in less pain. After an initial increase in pain-related disability from before surgery (five points) to immediately after surgery (21 points), PDI-DLV scores decreased in both groups and remained stable throughout the entire postoperative period (around nine/ten points) without returning to preoperative levels (which highlights the persisting problem of pain-related disability after breast cancer surgery). As a result, pain-related disability increased significantly in both groups from baseline (preoperative PDI-DLV scores corrected for the postoperative scores) to one year after surgery and this increase did not depend on the type of education the participants had received. When comparing to the available literature, PDI-DLV scores in both groups at each assessment were similar to those in breast cancer patients on average 33 months after axillary lymph node dissection (mean PDI=7.1 (±9.9)) and 20 months after mastectomy (mean PDI=9.4 (±12.8)).[200, 242] Results of a different study on average 54 months after breast cancer surgery showed a mean PDI score of 16 (±14), but the participants were recruited as they consulted their physical therapist for complaints of either pain, fatigue or lymphedema, which could have resulted in a sample with higher pain scores.[243]

According to the findings of the study in Chapter II, the PDI-DLV is a valid questionnaire for assessing pain-related disability one year after breast cancer surgery. The results confirmed that the PDI-DLV does, in fact, measure pain-related disability. In terms of reliability (calculated from two measurements with a one-week interval), the absolute reliability (within subject variability) was questionable and the relative reliability (between subject variability) was good. As previously mentioned, the dubious individual relative reliability had little impact on the interpretation of the primary outcome of the EduCan trial because the standard error of the mean decreases as the sample size increases. However, interpretation of individual data or profiles from this sample would impose a problem (such as defining responders and non-responders to PSE). This would require interpretation of fluctuations on an individual level, while these might not be a reliable representation of the construct being measured (i.e. pain-related disability).

Reliability indicates how well *observed* scores reflect *true* scores. The difference between the true value and the observed value is called *measurement error*, which is a function of many different variables, including the stability of the construct being measured.[115] Reliability is an estimate of how much of a measurement can be attributed to error and how much of it reflects the accuracy of the measurement.[115] Therefore, assessing the reliability of an instrument implies that the true score remains constant, meaning that there would be no real change in the construct being measured between the two measurements (stable construct).[115] By controlling for as many anticipated sources of error as possible, higher measurement error most likely

indicated poorer reliability of the PDI-DLV. However, what if the construct was not stable throughout the interval and genuine changes in pain-related disability had occurred? In that case, measurement error is inevitable and it would be practically impossible to assess reliability of the instrument used to measure the construct, which could mean that we might have underestimated our reliability. Based on our data, we could not determine whether the resulting measurement error reflected the absolute reliability of the PDI-DLV or the instability of the construct pain-related disability. In the latter case, it would be pointless to use a different outcome measure to evaluate the same construct, since the poor reliability is then attributed to the construct and not to the outcome measure (and these cannot be distinguished). If pain-related disability were a stable construct over a one-week interval, we could make several suggestions for a different time interval or a more reliable outcome measure. However, there is no way to know whether pain-related disability is a stable construct or not.

Responsiveness is an important quality when using a test to assess effectiveness of an intervention. However, responsiveness of the PDI-DLV has not yet been researched in breast cancer patients, which is its ability to detect clinically important changes in pain-related disability over time.

2.2.2. Secondary outcomes

As stated in the IMMPACT (Initiative on Methods, Measurement and Pain Assessment in clinical Trials) recommendations, it is important to include measures of physical functioning in chronic pain clinical trials.[244] During treatment, but also years later, breast cancer patients are less physically active compared to the general population.[174] Yet, an increase in physical activity may actually improve health related outcomes (including quality of life and pain(-related disability)).[25, 178] Therefore, one of the secondary outcomes was **physical activity level**, measured with a waist worn tri-axial accelerometer (ActiGraph® wGT3X-BT+). Because patients in the PSE group were taught that pain does not equal tissue damage, we hypothesized that they would be less restricted by their pain and that this would be reflected in, among other things, an increase in physical activity levels (behavior change). However, none of the physical activity parameters changed more favorably over time in the group that received PSE compared to controls. Participants were instructed to wear the accelerometer during seven consecutive days for at least 12 hours during waking hours.[189] As recommended, only data of participants whom had worn the accelerometer for four days with at least 600 minutes of wear time per day were included for analyses.[189] Although these strict requirements for a valid day and week provided data with high reliability, they also resulted in greater sample loss. One option would be to request participants to wear the accelerometer 24 hours a day, as 24-hour protocols have better

wear-time compliance than waking-hour protocols. This would increase the likelihood of data meeting the requirements for valid wear time. Moreover, we used cut-points to classify accelerometer counts per minute into different physical activity intensities (light, moderate, vigorous and (very) vigorous) derived from the general population.[189, 192] Several studies have argued that those are not appropriate to quantify time spent in different intensities for breast cancer patients, since chemotherapy severely impairs VO_2max.[245, 246] The authors concluded that categorizing physical activity intensities based on general-population cut-points may underestimate physical activity intensities for women treated for breast cancer and thus recommend using (lower) breast cancer-specific cut-points to assess physical activity intensity.[245, 246] Since this is an emerging area of research and only two studies have defined specific cut-off values in breast cancer patients (which were also inconsistent), we decided to use the well-known cut-points of the general population. Lastly, physical activity level is the result of a dynamic interplay of several different factors, of which pain is just one. It might be possible that other factors played a bigger role in whether or not patients increased their physical activity level (e.g. anxiety, fear avoidance, kinesiophobia).

Another frequently documented issue after breast cancer surgery that is part of physical function is impaired **upper limb function**. As pain at the upper limb region can interfere with daily life activities, we hypothesized that patients receiving PSE would be less impaired in their activities than those receiving BPE. The Oncology Section Breast Cancer EDGE Task Force on breast cancer outcomes recommends the DASH[137, 138] as a clinical measure of upper limb function.[247] This 30-item questionnaire assesses own perception of symptoms and functional status, with a focus on physical function, in populations with upper extremity musculoskeletal conditions.[248] Total scores range between 0-100, with higher scores reflecting higher disability/worse symptoms and a total score greater than 15 points indicates impaired upper limb function. In post-treatment breast cancer patients, the DASH has shown excellent *relative reliability* (one-week interval) (ICC=0.997) and *internal consistency* (Cronbach's α = 0.97).[141, 249] Known-group validity as part of *construct validity* indicated that the DASH could distinguish between breast cancer survivors without pain and a normative ultrasound of the shoulder and those with pain and an abnormal ultrasound and lastly, between survivors with pain and a normative ultrasound and those with pain and an abnormal ultrasound.[141] Harrington et al. recommended this questionnaire to assess upper extremity function in breast cancer survivors because it had the most consistently large effect sizes for construct validity and *responsiveness*.[141]

In the EduCan trial, mean scores on the DASH increased after surgery to about 40 points, after which they decreased (and stagnated) at four months after surgery to scores between 20 and 23. The progression did not significantly differ between the two groups. Using the cutoff point

of 15 as an indicator of upper limb disability, 86-94% of patients were impaired in the immediate postoperative period. Four months later, this proportion dropped to about 57% and stabilized around this percentage during the remaining postoperative period. This suggests that impaired upper limb function was indeed a problem after breast cancer surgery. However, it has to be noted that the DASH does not specifically evaluate the upper limb function at the operated side, but instead asks to rate the difficulty to perform the activity in general, regardless of which hand or arm is used. Lastly, similar to physical activity, upper limb function might have been impaired by a variety of other factors in addition to pain (e.g. range of motion, fatigue).

The last group of secondary outcomes were **work status** at 12 months postoperatively, **time until work resumption** and **return to work expectations**. Work status was assessed by asking the patient whether they had returned to work at one year after surgery (yes/no) and time until work resumption by calculating the time between the diagnosis and the first day of going back to work. In addition, as own expectation to return to work has been significantly linked to the length of sick leave in sick-listed insured Belgian citizens[214], return to work expectations (estimation of own ability to return to work) was evaluated with one item on the Quickscan[221] questionnaire. Even more than the previously mentioned outcomes, return to work may be influenced by many other factors besides pain. Work resumption also depends on the patient's family, employer, type of work, sympathy from colleagues, in relation the patient's own physical, cognitive and emotional functioning. Thus, it could have been possible that people became more empowered by the education and possibly had made progression through the stages of behavior change, but had regressed before we measured them due to the many other factors. On that account, it might be interesting to additionally record the reason why patients had not yet returned to work.

2.2.3. Possible additional outcomes

The success of PSE is established through effective reconceptualization of pain, which has the potential to initiate behavior change and in turn improve daily-life functioning (e.g. pain-related disability). A disadvantage of focusing on pain-related disability as the main outcome to evaluate the effectiveness of PSE is that it limits the interpretation of possible changes earlier in the process.

A first step in the process (and a prerequisite to measure the effectiveness of PSE) is the **reconceptualization of pain**. Although we used the Neurophysiology of Pain Questionnaire[186] to assess patients' knowledge regarding the principles of PSE, we did not use it as an outcome measure as its' primarily use was to guide the educational sessions and there were too many methodological constraints to draw conclusions from these data. In addition, we had only

administered it on two occasions (before the first educational session and after the third), potentially missing reconceptualization taking place after the fourth and fifth session. Lastly, only the psychometric properties of its revised version have been studied in a breast cancer population[250], while we used a self-modified version of the original 19-item questionnaire in Dutch[185]. Therefore, we either recommend using the 19-item questionnaire in Dutch or the revised version after translation and validation. Regarding the timing, we would recommend to let participants fill out the Neurophysiology of Pain Questionnaire before every PSE session.

Secondly, **progression through the stages of behavior change** in itself would have also have been an important effect of PSE. It could be interesting to further refine the outcome by additionally assessing the various stages of behavior change according to the earlier mentioned Transtheoretical Model of Health Behavior Change (for example with the Pain Stages of Change Questionnaire[251]). This will allow us to verify whether patients might be progressing without an overall effect on pain-related disability.

Lastly, in addition to refining the outcome measures of the steps that occur before a possible change in pain-related disability, it would be interesting to add a broader questionnaire to describe the possible impact of PSE on a patient's **self-rated health** (such as the EuroQol five-dimension scale[252]). This questionnaire measures five dimensions of health: mobility, self-care, usual activates, pain/discomfort and anxiety/depression. Moreover, this questionnaire could help us to measure the health benefits of PSE and use it in cost-utility analyses. Lastly, the combination of the EuroQol five-dimension scale with the abovementioned recommendations for additional outcome measures could offer valuable insights for both the patient ("What is the influence on my quality of life and functioning?") and the therapist/researcher ("Which factors are responsible for health-improvement?").

3. Methodological considerations of the project: strengths and limitations

A major **strength** of the EduCan trial was that the design allowed controlling for bias arising from the randomization process. The resulting lack of baseline differences between the intervention and control group was achieved by random allocation sequence and the fact that it was adequately concealed (the person generating the random allocation sequence was separated from the ones recruiting the participants). *Secondly*, participants and physiotherapists delivering the standard physiotherapy sessions were blind to group assignment and intention-to-treat analyses were performed. In addition, the same physiotherapist delivered educational sessions in both groups, which limits the effect of the person delivering the education. *Thirdly*, bias due

to missing outcome data was low (for the primary outcome), as data for more than 95% of subjects was available. *Fourthly*, the risk of bias in measurement of the outcome was low, since the PDI-DLV was suitable to evaluate pain-related disability, data collection did not differ between the two groups and the outcome assessors were not aware of the intervention received by the participants. A *final* strength of the randomized controlled EduCan trial was the a priori publication of the study protocol.[182]

Furthermore, the present study was subject to a number of potential methodological **weaknesses**, which make an overall conclusion about PSE in female breast cancer patients rather difficult. *Firstly*, generalizability of our results to non-trial settings (external validity) was limited by the fact that our intervention was well controlled in contrast to real-life situations where therapy is (or should be) patient-tailored and educational interventions are integrated with other treatment modalities (e.g. application during exercises). In addition, the quality of care possibly differed from non-trial settings, as breast cancer patient's standard hospital trajectory does not include physiotherapy nor pain education. Therefore, the study participants received more attention and a more intensive follow-up and we were very flexible regarding scheduling appointments etc. *Secondly*, as the physiotherapist delivering the educational sessions could not be blinded, we were unable to reassure that there were no deviations from the intended intervention that arose because of the trial context, which could have led to bias in estimated intervention effects. Based on these conditions reported in the revised Cochrane risk-of-bias tool for randomized trials (RoB 2)[93], we can therefore not state that the risk of bias due to deviations from the intended interventions was minimized. *Thirdly*, the outcome measures we chose might have not been responsive enough to detect significant changes. To the extent possible, we selected outcome measures that had been validated in breast cancer patients, but this was not always possible. A first step in studying the effectiveness of PSE could be to check whether patients understood the educational content and if so, to what extent they had converted this to consistent behavior change. As mentioned earlier, there are many small steps between being informed and behavior change. This whole process takes time and the techniques you use as a therapist depend on the stage of behavior change of the patient. By assessing those stages, we would know whether perhaps the patients made progression without an overt effect, which would also be an important effect. This way, we can link the changes in the outcomes to the educational intervention. Another possibility would have been to ask the patients in retrospect whether they experienced an effect, by using a global perceived effect scale. *A fourth* limitation was that the sample size calculation was based on data available in literature for the PDI in patients with persistent non-cancer pain.[125, 253] The PDI-values in the study by Chibnall et al. (1994) belonged to participants with persistent pain originating from a work accident (44.2%),

unknown origin (18.5%), non-work accident (18.2%), illness/surgery (9.5%), other (4.8%) and missing (4.8%).[125] The second study where we based our sample calculation on was the research by Soer et al. (2012) in patients with persistent back pain.[253] Furthermore, we did not power the study for the secondary outcome measures. A *fourth* possible limitation, stemming from having the educational sessions in both groups delivered by the same physiotherapist, was that he might have (subconsciously) made an effort if this person was a believer of one of the two types of education. In addition, we did not include a process evaluation to verify whether the educational sessions went as planned. A possible solution would have been to record the educational sessions and then verify with a checklist whether certain topics actually belonged to the other educational intervention (forbidden elements) or that two different therapists were hired for each type of intervention. However, this too could have been considered a limitation.

4. Clinical implications for pain science education after breast cancer surgery

The findings of the EduCan trial contribute to the premise that pain is an extremely complex problem, as does the refinement of the optimal parameters of an educational intervention that addresses it. Our results show no additional effect of five PSE sessions compared to five BPE sessions (both in combination with a standard physiotherapy program). While this means that the search for excellence continues, it does not mean that we cannot deduct valuable recommendations for clinical practice from our results. However, it should be noted that these guidelines are a combination of what is known in literature and our personal experience with the patients as physiotherapists in the EduCan trial.

As the first key process that underpins the effectiveness of PSE is the reconceptualization of pain, the solution to the above-mentioned issue of **timing** of the educational intervention is dependent on the receptiveness of the patient to PSE. The fact that pain intensity is generally low to non-existent prior to surgery, along with the turmoil that comes with a breast cancer diagnosis, makes the entire perioperative time one of poor receptivity to learning. Also, the post-surgical healing process is painful due to tissue injury, rather than a product of the psychosocial factors addressed in PSE, which could result in patients being unable to relate to the educational content of PSE and thus being unreceptive for it. As a result, we do not recommend scheduling PSE (in the format used in the EduCan trial) immediately before or after surgery. However, it is important to keep an eye on patients presenting with risk factors for persistent pain and disability (including pain catastrophizing, depression, worrying and anxiety), and even more importantly, those with a lack of social support (as appears from the results of the research of my colleague Lore Dams). This can be accomplished by assessing risk factors for persistent pain

and disability in the perioperative period. In addition, as physiotherapy should start within the first weeks after surgery for all patients, regardless of pain intensity, those at risk could be closely monitored so that PSE can be offered if necessary and its delivery mode tailored to the patient's individual needs rather than a one-size-fits-all formula. For this group, we would suggest to consider how to communicate the information rather than to withhold it. This strategy would also address the lack of a patient-tailored approach of the PSE intervention in the EduCan trial in terms of timing, absence or presence of pain etc. This could take the form of scheduling more frequent physiotherapy sessions (with a physiotherapist who is familiar with PSE), who could provide rather basic PSE during the physiotherapy sessions if needed and give the patient a sense of support. Providing in-depth pain education in the early postoperative period (as offered during PSE) might leave patients overwhelmed or pressure them into feeling they should immediately implement the things they learned. Therefore, it would be better to stick to the basics, only briefly touching the more extensive subjects and point out where they can find more information when they are ready. As part of paving the way for future PSE, this will also strengthen the therapeutic alliance, which will be essential throughout this process and facilitate shared-decision making. Whenever patients are receptive to PSE (which can range in timing, depending on the individual person), it is important to evaluate of the stage of behavior change to know how to tailor the future treatments.

As a possible reason for the lack of effect between the two groups was their similar **delivery mode** (such as frequency, duration and used educational material) in the context of our generally biomedically oriented health care system, we advise a more intensive approach for PSE in clinical practice. Since patients' basic knowledge is often limited to a biomedical understanding of pain, switching to a biopsychosocial explanation of pain may need more (mental) effort and time than simply reaffirming their pre-existing biomedical knowledge. However, considering the previously mentioned issue of timing of PSE, intensity should only be increased when patients are ready, often after the initial hectic period around diagnosis and onset of treatments. To prevent patients from only reviewing the information occasionally and to increase the likelihood that they will understand and apply the information in their daily activities (reconceptualization and behavior change), educational sessions could be scheduled more frequently and the techniques adapted to the patient's stage of behavior change.

As previously suggested by the literature, we recommend combining educational interventions with **physical interventions** (such as physiotherapy). This allows patients to experience the effects of putting their acquired knowledge into action. People with persistent pain often believe that increasing physical activity would make their pain worse (as pain is traditionally seen as a manifestation of tissue damage and the painful area should thus be protected).[216] These

cognitions may be the results of information patients have received (e.g. from the media, a health care provider or neighbor) or from personal experience (for example, anticipating future pain by avoiding situations or actions that elicit pain based on their beliefs and/or prior experiences). By avoiding the confrontation with these factors, one's fear of pain will only increase.[216] This could lead to a downward spiral of inactivity and pain, with greater pain-related disability as a result. Therefore, the sooner people realize that increasing physical activity without increasing pain is possible, the better.

The subsequent recommendation is consistent with the importance of addressing **both personal and work-related factors** in interventions to promote work resumption. Apart from the individual patient (cognitions, body, personality…), his/her context (e.g. work) and context-specific goals (e.g. work performance) may play a role in their pain experience.[254] If performing at work is an important motivator for the patient, work resumption may lead to less avoidance of pain-related behaviors.

The earlier described ICF framework provides a common language for functioning and disability. Functioning is defined as "a dynamic interaction between a person's health condition, environmental factors and personal factors".[173] Functioning and disability are understood as umbrella terms denoting the positive and negative aspects of functioning from a biological, individual and social perspective. The ICF therefore provides a multi-perspective, biopsychosocial approach, which is reflected in the multidimensional model. From this model, it is clear that all domains are intertwined and can influence each other. As a physiotherapist, who is often considered to be only concerned about the physical aspects, it is essential to remember that psychosocial factors may have a significant impact on a person's functioning and that it therefore makes no sense to reduce a patient to a mere physical entity. Therefore, physical rehabilitation should not only target physical impairments, but also evaluate possible influencing psychological and environmental factors, as those may improve or hinder treatment outcomes. However, since there is only so much you can do or falls within your skill level, it is of great importance to involve all disciplines with their complementary knowledge and skills in the treatment of a patient. In this regard, we emphasize the importance of working together as a team and **improving interdisciplinary collaboration**. It is important that patients receive a clear, unambiguous message from all their health care providers. One person (especially a physician) expressing anything contradictory may be enough for patients to begin to develop doubts, undermining treatment's effectiveness.

5. Future perspectives

Contributing to the ongoing search for optimizing pain therapies after breast cancer surgery, we make several suggestions for further research based on our findings.

At first, future research should explore **how the effectiveness of PSE can be increased**. Subgroup analysis can be used to investigate if patients with specific characteristics (e.g. pain, low physical activity level, manual jobs, certain psychosocial risk factors, intelligence and personality types) have different outcomes regarding the clinical effect of PSE than those without these risk factors. On the current dataset, this could be done by comparing pain-related disability between patients with and without pain on a certain point in time. Another option would be to conduct a responder analysis to define the characteristics of responders and non-responders to the intervention (predictive factors). However, defining responders based on PDI-DLV scores is not recommended due to its' poor absolute reliability on the individual level, which could result in fluctuations and thus incorrectly labelling patients as (non-)responders to PSE. In future research, it could be interesting to add outcomes on personality types and look at whether the influence of PSE varies, for example, between people who differ on traits such as receptiveness, intelligence, perceived injustice, critical thinking or the way people adapt to new experiences or information (assimilation vs accommodation). Moreover, a more patient-tailored approach should be studied where the intensity and delivery method are adapted to the needs of the patient (which would better mimic real-life situations). In case of the latter, we would suggest assessing the different stages of behavior change, in order to closely monitor the educational parameters.

For the *second* suggestion, we would like to refer to Leventhal's Common-Sense Model of Self-Regulation.[179] In addition to identifying the factors or patient characteristics that predict less pain-related disability or a positive behavioral outcome, they emphasize the value of knowing the **dynamic mechanisms** behind these relationships. By examining individuals who have these characteristics that predict a positive outcome, how they succeed and how they sustain their behavior, we can become much more specific and patient-tailored. Exploring these underlying mechanisms to understand the relationship between PSE and pain-related disability could be done through qualitative analyses (focus groups and interviews), as well as quantitative analyses (mediation and moderation).

Thirdly, pain-related disability was evaluated with the PDI-DLV. In addition to evaluating its validity and reliability, it is important to know the amount of change in pain-related disability that is clinically important for a specific patient population and whether the PDI-DLV would be responsive to detect this change. Therefore, a natural progression of this work would be to

assess the **responsiveness** and **minimal clinically important change** of the PDI-DLV in a breast cancer population.

Lastly, we would like to emphasize the importance of **evaluating biopsychosocial outcomes**, considering the growing body of knowledge and research on the implementation of the biopsychosocial model. This will allow this complex yet fascinating research area to be further unraveled.

6. COVID-19 pandemic

Even this project was not immune to the boundless and rampant coronavirus. When Belgium went into a strict lockdown to prevent a wave of COVID-19 cases (during the same week we had included the final participant for the EduCan trial), we had to be flexible and consequently come up with creative alternatives for therapies and assessment of outcome measures. Postoperative *physical therapy sessions* were allowed to continue (following strict safety measures) for those patients in the initial phase of the study in whom intensive physical therapy was deemed necessary (i.e., patients who would otherwise have been at high risk of long-term limited range of motion, etc.). In the group of patients who were in the same phase, but for whom the physiotherapy sessions were not considered essential, we offered the possibility of reviewing the exercises via video consultation, while the physiotherapists checked for correct execution, implying that manual therapy was not achievable. Since not all patients could or wished to receive remote physiotherapy sessions, the corona pandemic resulted in more patients receiving fewer physical therapy appointments. During the lockdown, *educational sessions* were offered via phone or video consultation instead of in "real life" at the hospital, so there was no effect on the number of attended educational sessions. In addition, we essentially had no additional missing data due to the pandemic because we had digitized the questionnaires and thus the *outcome measures* could still be surveyed at the pre-determined time points. Only the data collection with the accelerometers encountered some difficulties, as we physically handed them to the patients in the hospital. On the other hand, there were no additional dropouts during this period. On a final note, the lockdown measures (e.g. telecommuting as the norm) might have had a positive effect on work resumption, as the threshold to return to work might have been lower, which might have been more feasible for some participants.

In the end, the consequences were not catastrophic and we may even have learned some valuable lessons from this (hopefully) once-in-a-lifetime experience. For example, remote

interventions (eHealth) are becoming more relevant in this period and it is up to us to figure out how we can integrate these booming virtual resources in the future.

7. Conclusion

Pain remains an under-treated side effect of breast cancer treatments, partially because of its mysterious intertwinement with both tangible and intangible factors. By bringing these factors together, PSE aims to induce behavior change that limits, or ideally, even reduces the impact of pain on all aspects of human functioning. At the same time, educational interventions are one of the most difficult ways to induce behavior change and their outcome depends on numerous different aspects.

With this work, we hope to provide deeper insights into the follow-up of pain-related disability after breast cancer surgery, as well as the clinical application of PSE in this population and recommendations for further research on this topic. At first glance, our findings suggested that PSE after breast cancer surgery does not ensure more favorable outcomes compared to biomedical pain education. However, several concerns were raised about the PSE intervention's cookie-cutter approach, leading to the conclusion that the question should not be whether educational interventions are necessary, but rather how the delivery method, timing and other factors could be refined to achieve a change in behavior and, as a result, improved functioning after breast cancer surgery. The complexity of educational interventions, combined with a health care system that is entirely biomedical in nature, will require years of efforts to optimize these interventions through a variety of mechanisms. Therefore, further research should explore how the effectiveness of PSE in the breast cancer population could be increased.

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APPENDICES

According to the tradition at the Faculty of Movement and Rehabilitation Sciences, I hereby present three appositions (in Dutch):

1. Hoewel de huidige zorg enorm onder druk staat, is het van primair belang om het menselijke te blijven respecteren (en tonen) tijdens de dagelijkse zorgactiviteiten.

2. Een regelmatige opvolging van het geestelijke welzijn moet minstens even vanzelfsprekend zijn als een lichamelijke check-up.

3. Het van jongs af aan stimuleren van creativiteit en 'thinking outside the box' moeten we zien als een kans om de gevolgen van het aan onze tijd/cultuur typerende perfectionisme minder zwaar te laten doorwegen.

ABOUT THE AUTHOR

Elien Van der Gucht was born in Mortsel (Antwerp), Belgium on August 23, 1992. She graduated from high school (Sint-Gabriëlcollege in Boechout) in 2010 after which she had the opportunity to attend high school (Boonville High School) in Boonville, Indiana (U.S.A.) during one year. Elien received the degree of Master of Rehabilitation Sciences and Physiotherapy (MSc) cum laude (with specialization in neurological disorders) at the KU Leuven in 2017. In October of the same year, she started as a doctoral researcher at the Department of Rehabilitation Sciences in the Research Group for Rehabilitation in Internal Disorders (GRID) at the KU Leuven and at the Department of Rehabilitation Sciences and Physiotherapy in the Research Group MOVANT at the University of Antwerp. The doctoral project, which was under supervision of prof. dr. Nele Devoogdt, prof. dr Mira Meeus, prof. dr. An De Groef, prof. dr. Bart Morlion and prof. dr. Lode Godderis, focused on pain science education after breast cancer surgery. Throughout her PhD career, Elien was a member of the Pain in Motion research group (international research group on pain and physical activity). Besides the research within her PhD project, she was involved in teaching activities within the Bachelor program of Rehabilitation Sciences and Physiotherapy at the KU Leuven, as well as mentored students during the process of their Master thesis' research. In 2019, she received the Louis Gifford Prize for the highest scoring participant in the European Diploma in Pain Physiotherapy (Valencia, Spain).

PUBLICATIONS

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Oral presentations at international congresses

1. Van der Gucht, E., Dams, L., Penen, F., De Groef, A., Devoogdt, N., Bernar, K., Godderis, L., Morlion, B., Smeets, A., Meeus, M. (2019) Reliability, Validity, Responsiveness and Minimal Clinically Important Change of the Dutch Version of the Pain Disability Index (DV-PDI) in Female Breast Cancer Patients. Oral presentation at the Pain Science in Motion, Savona, Italy.

Oral presentations at national congresses and symposia

1. Van der Gucht, E., Dams, L., Bernar, K., Devoogdt, N., Meeus, M., Godderis, L., Morlion, B., De Groef, A. (2021) Pain Science Education Does Not Result in Better Pain-Related Functioning Compared to Biomedical Pain Education in Breast Cancer Patients: Results of a Randomized Controlled Trial. Oral presented at the FIRRI Webinar Series: Recent advances in Rehabilitation of Cardiorespiratory and Internal Diseases (Oncologic Rehabilitation: the importance of Quality that comes with Life), Online.

Poster presentations at national and international congresses and symposia

1. Van der Gucht, E., Dams, L., Bernar, K., De Vrieze, T., Haenen, V., De Groef, A., Godderis, L., Morlion, B., Meeus, M., Devoogdt, N., (2021). The Dutch Language Version of the Pain Disability Index (PDI-DLV): Psychometric Properties in Breast Cancer Patients. Poster presentation at the IASP world congress on pain, Online.
2. Van der Gucht, E., Dams, L., Bernar, K., Devoogdt, N., Meeus, M., Godderis, L., Morlion, B., De Groef, A. (2021) Pain Science Education Does Not Result in Better Pain-Related Functioning Compared to Biomedical Pain Education in Breast Cancer Patients: Results of a Randomized Controlled Trial. Poster presented at the FIRRI Webinar Series: Recent advances in Rehabilitation of Cardiorespiratory and Internal Diseases (Oncologic Rehabilitation: the importance of Quality that comes with Life), Online.
3. Dams, L., De Groef, A., Penen, F., Van der Gucht, E., Haenen, V., De Baerdemacker, T., Devoogdt, N., Meeus, M. (2020). Quantitative sensory testing in women treated for breast cancer: a systematic review and meta-analysis. Poster presentation at the IASP world congress on pain, Online.
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7. Van der Gucht, E., Dams, L., Meeus, M., Devoogdt, N., Beintema, A., Penen, F., Hoelen, W., De Vrieze, T., De Groef, A. (2019). Kinesiophobia Contributes to Pain-Related Disability in Breast Cancer Survivors. Poster presentation at the EFIC Congress, Valencia, Spain.
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10. Dams, L., Van der Gucht, E., Meeus, M., Devoogdt, N., Morlion, B., Godderis, L., De Groef, A. (2019). The effectiveness of Pain Neuroscience Education (PNE) for pain-related disability after breast cancer surgery (EduCan Trial): study protocol for a randomized controlled trial. Presented at the Pain Science in Motion, Savona, Italy.
11. De Groef, A., Devoogdt, N., Dams, L., Van der Gucht, E., Debeer, P. (2018). The effectiveness of botulinum toxin A for persistent pain at the pectoral region after breast cancer treatment: randomized controlled trial. Presented at the International Society of Physical and Rehabilitation Medicine (ISPRM), Paris.
12. Van der Gucht, E., Dams, L., Devoogdt, N., Meeus, M., De Groef, A. (2018). The effectiveness of Pain Neuroscience Education (PNE) for pain-related disability after breast cancer surgery. Poster presentation at the 1st International Conference on Physical Therapy in Oncology, Amsterdam, the Netherlands.
13. Morlion, B., De Groef, A., Devoogdt, L., Van der Gucht, E., Bernar, K., Godderis, L., Smeets, A., Moloney, N., Van Wilgen, P., Meeus, M. (2018). Effectiveness of postoperative Pain Neuroscience Education on pain-related functioning in breast cancer patients: RCT. Presented at the Belgian Pain Society, Bluepoint Brussels.

Master thesis supervision

1. The validity and reliability of the Dutch version of the Pain Disability Index in breast cancer patients by Liese Aerts and Jolien Van den Bosch, KU Leuven, 2019 (co-supervisor for two years).
2. Relation between change of self-reported pain and change of upper limb function, physical activity and sedentary time between 1 and 4 months after surgery for breast cancer by Jani Van Roy and Valérie Michiels, KU Leuven, 2020 (co-supervisor for two years).
3. Influence of time on predictive factors for return-to-work after breast cancer treatment by Fleur Brebels and Ellen Alaert, KU Leuven, 2021 (co-supervisor for two years).
4. Physical functioning (physical activity and upper limb use) after breast cancer surgery by Tine Janssens and Aurélie Sevenants, KU Leuven, 2021 (co-supervisor for one year).

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Prof. dr. Nele Devoogdt, prof. dr. Mira Meeus, prof. dr. An De Groef, prof. dr. Bart Morlion, prof. dr. Lode Godderis (all (co-)supervisors of the PhD researcher) and prof. dr. Ann Smeets wrote out the **research proposal** (FWO-TBM) for the EduCan trial (conception and design), as well as **supervised the PhD project**, provided support in interpreting the data and revised all manuscripts.

In addition to the abovementioned (co-)supervisors, the **supervisory committee** of the PhD researcher consisted of three experts in the research field (**internal jury members**): prof. dr. Daniel Langer (KU Leuven), prof. dr. Jeroen Luyten (KU Leuven) and prof dr. Filip Struyf (University of Antwerp). The Supervisory Committee's role was to monitor the progress of the doctoral research in an annual meeting **chair**ed by prof. dr. Thierry Troosters (delegate from the Doctoral Committee). For the final **examining committee**, prof. dr. Rob Smeets was invited as an external expert in the field (**external jury member**) to provide feedback on the final version of the doctoral manuscript together with the internal jury.

The following representatives were appointed as members of the **advisory board** for the project: Nicole Timmerman (professional association for physical therapists in Belgium (AXXON)), Chris Heremans (Kom Op Tegen Kanker), dr. Saskia Decuman (National Institute of Health and Disability Insurance (NIHDI)) and dr. Huget Désiron (Arbeids Consulting Team Désiron, specialized in re-integration and work participation).

Prof. dr. An De Groef, prof. dr. Nele Devoogdt, prof. dr. Mira Meeus, prof. dr. Lode Godderis, prof. dr. Bart Morlion, prof. dr. Ann Smeets, prof. dr. Paul Van Wilgen, dr. Niamph Moloney, Koen Bernar, Lore Dams and the author of this manuscript decided on the **content of the educational sessions** as well as contributed to the design of the booklets. The content and material of the **physiotherapy sessions** were prepared by prof. dr. An De Groef, Lore Dams and the author of this manuscript.

Lore Dams and the author of this manuscript **recruited** all the participants (with help from the medical staff of the Multidisciplinary Breast Center of the University Hospitals Leuven campus Gasthuisberg (Belgium)) and **evaluated** them (quantitative sensory testing and questionnaires) at all follow-up timepoints. Following inclusion, dr. Tessa De Vrieze was responsible for **randomization** of the participants.

Koen Bernar was the physiotherapist who delivered the majority of the **educational sessions** to the participants. Lore Dams, Vincent Haenen, Frauke Penen and the author of this manuscript were the project physiotherapists delivering the standard **physiotherapy sessions** during the follow-up of the EduCan trial. Dr. Tessa De Vrieze en Lore Vos organized the monthly informative group **sessions on prevention and treatment of lymphedema**. Dr. Steffen Fieuws from the Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat) performed the **statistical analyses** and created the figures for Chapters III and IV. In addition, he provided advice on statistical analyses and interpretation of the data of Chapter II. Dr. Thomas Vandendriessche guided the process of designing the **search strategy for the systematic review** described in Chapter I. **Data entry** was achieved by An-Kathleen Heroes, Lore Dams, the author of this manuscript and students who wrote their master's thesis based on this project.

PERSONAL CONTRIBUTION

The author of this manuscript was responsible for recruitment and postoperative physiotherapy guidance of the participants. Additionally, she also performed the follow-up assessments, including material preparation and data collection, as well as contributed to the conception, execution, analyses, interpretation and reporting of all included studies and chapters in this doctoral thesis manuscript. She was assisted by her colleague Lore Dams and by her (co-)supervisors prof. dr. Nele Devoogdt, prof. dr. Mira Meeus, prof. dr. An De Groef, prof. dr. Lode Godderis and prof. dr. Bart Morlion. All co-authors of the different chapters critically revised the papers for important intellectual content and approved the final manuscripts before submission.

CONFLICT OF INTEREST STATEMENT

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"People rarely succeed unless they have fun in what they are doing." – Dale Carnegie

Zonder collega's geen fun en zonder fun kan je niet functioneren, of zou dit functioneren toch maar zeer beperkt zijn.

El Damz, allesbehalve een Damzel in distress. Compatibele collega én vriendin. Blind Getrouwd editie 2017 had dan toch al één succes voortgebracht. Ik herinner me nog (alsof het gisteren was) hoe we zorgvuldig onze eerste meting hadden voorbereid. 21 November 2017, we waren er helemaal klaar voor. De haren netjes geordend op een handdoekje, van lage mN naar hoge mN, de TSA-vloeistof correct aangevuld zoals "nauwkeurig" gedemonstreerd door TSA Tony, de kinetafel op de juiste hoogte ingesteld… Het zag er beeldig uit en kon niet misgaan, maar dat deed het wel. En dat gingen we 184 x 7 keer mogen doen (dat is 1288 keer, maar dat durfden we toen niet uitrekenen). In het totaal goed voor zo een 1932 uren PDI's afnemen, haren prikken, thermodes bevestigen, accelerometers ontsmetten en nuanceren tussen tintelen en kriebelen. BUT WE DID IT! Ik kan me geen betere partner inbeelden om samen onze rammelkar voor de vijfhondervierenzeventigste keer (zo voelde het) de lift in te hijsen naar E631, dezelfde onmacht te ervaren op het moment haar nummer 5 nóg eens uit onze handen glipt en dan tevergeefs de grond afspeuren zodat den Herms nog is uit den hottub kon komen om zijn lijmkunsten te demonstreren, brainless latenight data in te geven op O&N IV gefueled door Donki en zoute toasten en al helemaal om onze patiënten in de watten te leggen. Merci voor de strijdplannen, de make "that the cat wise"-momentjes, het bijvullen van den TSA, de ondersteuning én de vriendschap. Merci Lore, om er niet alleen op professioneel-, maar ook op persoonlijk vlak voor mij te zijn. Onze scheiding is blijkbaar aangevraagd, but I'll keep you in the holes. It goes you well, Damzel.

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