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# The Mediating Effect of Perceived Injustice and Pain Catastrophizing in the Relationship of Pain on Fatigue and Sleep in Breast Cancer Survivors: A Cross-Sectional Study

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# Abstract

**Objective:** Multidimensional aspects of pain have raised awareness about cognitive appraisals, such as perceived injustice (PI) and pain catastrophizing (PC). It has been demonstrated that they play an important role in patients' pain experience. However, the mediating effect of these appraisals has not been investigated in breast cancer survivors (BCS), nor have they been related to fatigue and sleep. **Methods:** Cross-sectional data from 128 BCS were analysed by structural path analysis with the aim to examine the mediating effect of PI and PC in the relationship of pain on fatigue and sleep. **Results:** The indirect mediating effects of PI on fatigue (CSI*PI=0.21; P<0.01 and VAS*PI=1.19; P<0.01) and sleep (CSI*PI=0.31; P<0.01 and VAS*PI=1.74; P<0.01) were found significant for both pain measures (Central Sensitization Inventory (CSI) and Visual Analogue Scale (VAS)). PC, on the other hand, only mediated the relationship between pain measured by VAS and fatigue (VAS*PC=0.80; P=0.03). Positive associations were found, indicating that higher pain levels are positively correlated with PI and PC, which go hand in hand with higher levels of fatigue and

sleep problems. **Conclusion:** PI is an important mediator in the relationship of pain on fatigue and sleep, while PC is a mediator on fatigue after cancer treatment. These findings highlight that both appraisals are understudied and open new perspectives regarding treatment strategies in BCS.

**Keywords:** Cancer; Fatigue; Mediation Analysis; Pain; Pain Catastrophizing, Perceived Injustice and Sleep Disorders

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# Introduction

Nowadays, breast cancer remains by far the most prevalent malignancy among women worldwide, affecting one in eight women during their lifetime.[1,2] Fortunately, improved detection and treatment techniques have ensured a 10-year survival in 80% of the breast cancer population.[3] However, disease-free does not mean symptom-free as a significant subgroup of the breast cancer survivors' (BCS) population experiences troublesome and debilitating sequelae during and following curative treatment. Persistent pain is one of the most common sequelae, occurring in about 1 out of 3 BCS.[4,5]

Recent insights and multidimensional aspects of pain have raised the awareness regarding psychological factors (e.g. cognitive appraisals and expectations), which have been shown to be important determinants in pain experience.[6-9] It is presumed that maladaptive cognitions such as perceived injustice (PI) and pain catastrophizing (PC) form key cornerstones in the development and maintenance of chronic pain.[10]

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In the context of chronic pain, PI has been operationalised as a multidimensional appraisal process of pain-related losses in terms of severity and irreparability, an experience of unfairness and attribution to blame others for someone's suffering.[11,12] Patients deflecting beliefs of injustice are more likely to exhibit high pain intensity and to display heightened pain behaviours.[12-14] Not only do these misleading pain representations form a stumbling block for recovery,[12,13] they also result in increased opioid prescription,[13] and prospectively predict opioid use at 1-year follow-up.[11] Individuals who perceive their pain symptoms in terms of injustice may display more pain behaviour as a means of communicating the magnitude of their suffering and losses, which inadvertently increases the likelihood that clinicians will prescribe opioids.[13]

Another possible feature in the maintenance of chronic pain is the so-called phenomenon "pain catastrophizing", which is defined as the tendency to magnify or exaggerate the mental set during actual or anticipated painful experiences.[15] The anticipated pain narrows one's ability to assimilate threat-related cues and increases pain intensity, resulting in both activity intolerance and emotional distress.[16,17] In breast cancer surgery, regardless of the possible presence of persistent post-

surgical pain, no differences in treatment- or disease-related variables have been observed.[18,19] However, differences in PC are identified as one of the key-mechanisms of the fear-avoidance model contributing to the development of persistent pain complaints.[17,20,21]

Nevertheless, pain is not the only persistent side-effect BCS are often confronted with. Commonly BCS experience multiple other debilitating symptoms such as fatigue, sleep disturbance, depression, anxiety, etc.[22,23] Up to now, most of these symptoms have been targeted independently, even though they rarely occur alone.[22] Therefore, recent studies clustered concomitant and related symptoms[23] to better understand their shared etiology and influence, which in turn might lead to the development of innovative and effective treatments.[22-24] Throughout the current literature, pain, fatigue and sleep disturbance have been frequently highlighted as fundamental components in different clusters for BCS.[22,25,26] However, their underlying interferences in relation to maladaptive cognitions are understudied.

So far, no consensus is available on the definition of cancer-related fatigue and it remains poorly established in BCS.[27,28] This could be caused by the high variety in degree of perceived fatigue.[27] Additionally, it is complicated to distinguish cancer-

related fatigue from fatigue related to age or other comorbidities.[27,29] The prevalence of cancer-related fatigue is extremely heterogeneous and not only determined by the exact time point after treatment ends but also by various predisposing treatment factors, such as higher disease stage, chemotherapy and some combinations of cancer treatment modalities.[23] Nowadays, guidelines recommend assessing treatable contributing factors of fatigue.[30] Pain, for instance, can be one of these factors. However, according to our knowledge, only two studies have identified pain as a predictor for fatigue in BCS.[31,32]

Sleep disturbances in BCS have repeatedly come to light as a self-reported difficulty to initiate or maintain sleep or nonrestorative sleep, occurring at least 3 times a week for at least 3 months.[33-36] The prevalence of sleep disturbances amongst BCS varies widely, ranging from 14% to 93%.[37] Several risk factors for developing sleep disturbances in BCS have been identified: pain, depressive symptoms, fatigue, hot flashes, non-Caucasian race and menopausal status.[37] In particular, BCS with pain and fatigue were respectively 2.31 and 2.82 times more likely to develop sleep disturbances compared to pain-free and non-fatigued BCS.[37] The adverse effect of sleep disturbance on pain sensitivity has been thoroughly investigated.[38-41]

Nevertheless, it has also been demonstrated that pain has an adverse effect on sleep disturbance, illustrating the bidirectional relationship between these two cardinal features of BCS.[5,42,43]

Fresh perspectives have emphasised the importance of cognitive appraisals (PI and PC) on pain and fatigue, but these have not been studied on sleep disturbance.[23,44,45] There is no doubt about the existing association of pain, fatigue, sleep and psychological distress in BCS since these symptoms are generally clustered in studies.[23,46] However, according to our knowledge, the mediating effects of PI and PC between the different pain groups in relationship to fatigue and sleep disturbances have not been previously studied in BCS. Identifying the potential mediating effect of appraisals is an important milestone to provide an appropriate and tailored treatment for BCS.[47]

The purpose of this cross-sectional study was to determine whether the relationship of pain on fatigue and on sleep disturbances in BCS can partially be explained by the cognitive appraisals PI and PC. It is hypothesised that PI and PC have a mediating role in the relationship of pain on fatigue and on sleep disturbances.

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# Methods

## *1. Study design*

To investigate whether the effect of pain on fatigue and sleep in BCS is mediated by PI and PC, an observational cross-sectional study was performed. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline for cross-sectional studies was used as a reference for reporting the study.[48] The medical ethics committee of the University Hospital of Brussels authorized the protocol of this study B.U.N. 143201524229. Written and signed consents were procured from all study subjects before their inclusion.

## *2. Participants*

### 2.1. Inclusion criteria

To be included, all subjects had to meet the cancer survivor's definition of The European Organisation of Research and Treatment of Cancer (EORTC) Survivorship Task Force: 'any person who has been diagnosed with breast cancer, has completed

their primary treatment (except for maintenance therapy), and has no evidence of active disease'.[49] Furthermore, BCS had to be in complete remission and at least 3 months past the ending of their curative treatment. BCS receiving hormone therapy or targeted immunotherapy formed the exceptions and were also included since these are long-term therapies that can go on years after primary treatment ends. Additionally, patients had to be able to speak and read Dutch to provide written informed consent and complete the questionnaires.

2.2. Exclusion criteria

Patients who were afflicted with other cancers besides breast cancer or showed signs of metastases or recurrences were excluded. Additionally, patients were excluded when suffering from a chronic disease, or a severe psychological and/or a psychiatric disease that goes along with dementia or cognitive impairments that prevented them from understanding the test instructions.

2.3. Recruitment and setting

All BCS in this cross-sectional study were recruited through convenience sampling. All subjects with an appointment in the Oncologic Center of the University Hospital of Brussels were screened for the predefined in- and exclusion criteria between

September 2017 and April 2020. Eligible BCS received a phone call requesting them to participate in this study. For BCS that agreed to enrol in the study an envelope with all questionnaires, study explanation and informed consent was provided the day of their next appointment at the hospital. In addition, researchers approached eligible acquaintances, support- and rehabilitation groups for BCS with the same envelope, accompanied with a stamped and pre-addressed envelope for its return.

## *3. Variables*

### 3.1. Demographic and medical data

A self-report questionnaire and medical reports were used to summarize demographic and medical data such as the presence of pain, the use of pain medication, the breast cancer treatment plan, and the presence of lymphedema.

### 3.2. Visual Analogue Scale (VAS)

The VAS is a subjective and widely used measurement tool for the assessment of pain intensity.[50] It consists of a 100 mm horizontal line, of which the minimal and maximal extremes of pain perception are defined as ‘no pain’ for 0 mm and ‘the worst possible pain’ for 100 mm.[50,51] Subjects were asked to place a vertical mark on

the line at the point that illustrates their overall pain severity for the past week. The VAS-scale has proven its validity and reliability in subjects with chronic pain.[52,53]

3.3. Douleur Neuropathique 4 questionnaire (DN-4)

The French Neuropathic Pain Group designed a simple 10-item diagnostic tool, grouped in 4 sections, to make a distinction between neuropathic and nociceptive pain.[54] The first 7 items relate to the quality of pain (burning, painful cold, electric shock) and its correlation to abnormal sensation within the painful region (tingling, pins and needles, numbness, itching).[54-56] The last 3 items are related to the neurological examination and consist of sensorial hypoesthesia (touch & pinprick) and evoked allodynia (brushing).[55,56] Each present item is braced with a score of 1 ('yes') or 0 ('no') when the item is absent. The Dutch version of the DN-4 is a valid,[57] and reliable tool.[58,59]

3.4. Central Sensitization Inventory (CSI)

The CSI is a screening tool designed to identify symptoms in patients indicative for the presence of central sensitization.[60] It helps clinicians in syndrome categorization, severity identification, sensitivity and treatment planning.[61] The total score of the CSI ranges from 0 to 100.[61] The psychometric strength, clinical utility, and initial construct

validity of the CSI was demonstrated in patients with chronic pain and central sensitization-related symptoms.[62] The Dutch CSI showed good clinical properties in patients with chronic pain.[63]

### 3.5. European Organisation for Research and Treatment of Cancer Fatigue and Sleep Subscale

The EORTC Fatigue and Sleep are subscales of the 'The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire' (EORTC QLQ-C30), which is a 30-item self-report questionnaire that covers the general health-related quality of life in cancer survivors.[64] The EORTC QLQ-C30 consists out of nine multi-item subscales: five functional scales (physical, role, emotional, cognitive and social), three symptom subscales (pain, fatigue, and nausea/vomiting), and a global health (quality of life) subscale. In addition, the tool incorporates six single-items (dyspnea, anorexia, diarrhoea, constipation, financial difficulties and sleep disturbance).[64]

#### 3.5.1. EORTC subscale fatigue

The EORTC Fatigue is composed out of three items (1: Did you need to rest?; 2: Have you felt weak?; 3: Were you tired?). For each of these items, the degree of

fatigue, experienced during the past week, is reported on a 4 point-Likert scale. The total score of fatigue perceptions is converted to a 0-100 scale, of which 0 is indicative for 'no fatigue' and 100 as 'maximum fatigue'. The validity of the EORTC QLQ-C30 Fatigue scale was found to be acceptable to measure the physical fatigue in BCS.[65,66]

3.5.2. EORTC subscale sleep

The EORTC Sleep is a single item scale, assessing sleep disturbances during the past week by the following question (1: Have you had trouble sleeping?).[64,67] The question is reported on a 4 point-Likert scale and total score ranges from 0 to 100.[64] A higher score indicates a greater level of sleep disturbances.[64] According to a systematic review, this tool is widely used to assess sleep disturbances.[37,67] The EORTC QLQ-C30 Sleep scale was found to be reliable.[66,67]

3.6. Pain Catastrophizing Scale (PCS)

The PCS is a 13-item self-report questionnaire assessing the different perspectives on catastrophizing (magnification, rumination and helplessness) in patients with chronic pain.[68] Each item represents a 5-point Likert scale of which the extreme limits go from 0 ('not at all') to 4 ('all the time'). The total score ranges from 0 to 52.

The PCS reliability and validity was found adequate in different chronic pain subgroup populations.[69,70]

3.7. Injustice Experience Questionnaire (IEQ)

The IEQ is used to assess perceptions of injustice associated with the experience of debilitating mental and health conditions. Two appraisals can be distinguished: "Self-blame" and "severity/irreparability of loss".[71] The respondents have to indicate the degree of their experience on each of the 12 different thoughts and feelings described in the questionnaire. The items are scored on a 5-point scale, with 0 representing "not at all" and 4 representing "all the time". The overall score ranges from 0-48, with higher scores indicative of increased PI levels.[71,72] The IEQ has proven to be reliable and valid in acute and chronic pain populations.[11,71,73,74]

*4. Statistical Analysis*

In preparation for the mediation analysis, several assumptions were verified: linearity of the relationship, normal distribution of residuals, homoscedasticity and absence of influential outliers. Note that missing values were imputed with chained equations.

Fatigue and sleep scores were then each regressed on each of the pain measurements (CSI, VAS and DN-4) separately, signalling with explained variance which pain scores are most informative. The resulting residuals were then regressed on the alternative pain measurements to establish whether they have additional informative value on top of the pain measurement already in the model. Based on these two steps, both CSI and VAS were retained for the final analyses.

For the path analysis, the Lavaan package in R was used. Lavaan is an open-source package developed for latent variable modelling.[75] This analysis addresses the mediating effects and displays the estimation of the direct effect between independent (VAS and CSI) and dependent variables (sleep and fatigue), as well as the estimation of the indirect effects through the mediators (cognitive appraisals that were correlated). The *p* values and confidence intervals were obtained with 5,000 bootstrap samples. Note that all incorporated variables in the path analysis are observed variables. Age was included as a control variable in the analysis and did not come out as a relevant variable for understanding fatigue and sleep.

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# Results

*1. Sample size*

A total of 152 subjects were found eligible for study participation. Twenty-three out of 152 subjects did not return completed questionnaires. However, a high response rate of 85% was attained.[76] In-depth screening of questionnaires resulted in supplementary exclusion of one BCS who did not provide sufficient data for further analysis.

*2. Patient characteristics*

A total of 128 women were included, with an average age of 59.8 ± 11.3 years (range 33-90 years). Breast surgery was performed in all participants, with 72 (58.6%) patients requiring a segmentectomy. The remaining 56 (43.8%) patients underwent a total mastectomy. Additional axillary surgery was carried out in the majority of the patients (n= 111; 86.7%), encompassing a sentinel lymph node removal (SLNB) (n= 66; 54.1%) or a full axillary lymph node removal (ALND) (n= 44;

36.1%). Regarding the adjuvant treatment modalities, a larger proportion of subjects had received radiotherapy (n= 108; 85.7%), followed by hormone therapy (n=81; 64.8%) and chemotherapy (n=56; 44.8%). Pain medication usage was registered in 39 survivors (30.7%), and lymphedema was present in 34 subjects (26.8%). Overall, eighty-three subjects (64.8%) reported experiencing any form of pain at the time of the survey. From the dataset, 3 variables (VAS (n=1), CSI (n=1) and IEQ (n=1)) were missing and simply imputed. A detailed overview of the patient characteristics and questionnaire outcomes can be found in ***Table 1.***

*3. Observed associations*

The correlation coefficients of the variables of interest are listed in ***Table 2,*** with absolute scores ranging from 0.41 to 0.69, making the correlation of acceptable importance to be included on the hypothesised path analyses (all pairwise correlations are significant, $p < .00001$). Interpretations of the correlation coefficients were categorised as follows: “very high” for 0.90-1.00, “high” for 0.70-0.90, “moderate” for 0.50-0.70, “low” for 0.30-0.50 and values of 0.00-0.30 were considered as “negligible”.[77]

### *4. Pain measurements*

Simple regression analyses (i.e., regression of an outcome on one single predictor variable) performed to explain the predictable impact of each pain variable on fatigue, wherein significant scores for VAS (b= 6.57, p < 0.001), DN-4 (b= 6.38, p < 0.001) and CSI (b= 1.40, p < 0.001) were obtained. For sleep, simple regression analyses resulted in significant scores for VAS (b= 7.01, p<0.001), DN-4 (b= 8.52, p < 0.001) and CSI (b= 1.41, p < 0.001). The linearity, normality and homoscedasticity assumptions of the regressions were acceptable. Some potential outliers have been observed but they had only a minor impact on the estimates.

For fatigue, simple regression analysis demonstrated that CSI explained the highest proportion of variance (41%), followed by VAS (33.4 %) and DN-4 (19.1%). Taking into consideration the importance of CSI and bringing in VAS and DN-4, additional variance was explained by VAS (9.4%) and DN-4 (0.8%). Since DN-4 did not provide any supplementary value in explaining what was not yet clarified by CSI, it brought us to the decision to remove DN-4 from further analysis. Considering the moderate correlation between CSI and VAS (r=0.54), bringing together both pain

measurements into a general model, 48.8% of the total variance for fatigue was explained.

The same phenomenon was observed for sleep in which simple regression analysis revealed that CSI explained the highest proportion of variance (28.6%), followed by VAS (26%) and DN-4 (23.4%). By bringing in VAS and DN-4, additional variance was explained by VAS (7%) and DN-4 (4.8%). Again, the DN-4 was removed from further analysis since it did not explain something additional what was not yet clarified by CSI. Taking together both pain measurements into a general model, 35.7% of the total variance for sleep was explained.

Consequently, the path analysis was performed and slight changes in the estimates of the simple regression analyses were observed ***(Table 3)***. All the linear associations between pain (CSI, VAS) and fatigue or sleep were significant ***(Figures 1a, 2a)***. To explain the nature of these associations, mediators (PI, PC) were incorporated in the model.[78]

*5. Path Analyses for VAS and CSI*

The final path analytical model, with the mediators incorporated ***(Figures 1b, 2b)***, displays direct relations between pain measurements (VAS, CSI), cognitive appraisals (PI, PC), fatigue or sleep. For fatigue, significant direct effects were found for PI (PI ~ fatigue = 0.80; P<0.05), PC (PC ~ fatigue = 0.38; P<0.05), CSI (CSI ~ fatigue = 0.71; P<0.05) and VAS (VAS ~ fatigue = 1.76; P<0.05) in BCS. For sleep, on the other hand, only significant direct effects for PI (PI ~ sleep = 1.18; P<0.05) and CSI (CSI ~ sleep = 0.58; P<0.05) could be retrieved. Given the fact that all these significant variables were positively related to fatigue or sleep, higher levels of pain (CSI or VAS), PI or PC contributed to an increased degree of fatigue or sleep disturbances.

Finally, the mediating role of PI and PC in the relationship of pain on fatigue and sleep were analysed ***(Figures 1c, 2c)***. The indirect path between pain (VAS) and fatigue through PI (VAS*PI-fatigue = 1.19; P<0.05) and PC (VAS*PC-fatigue = 0.80; P<0.05) was significant in both settings. The same trend was observed for the indirect path between pain (CSI) through PI (CSI*PI-fatigue = 0.21; P<0.05), but not for PC (CSI*PC-fatigue = 0.09; P=0.07). Looking at the sleep model, the indirect pathways were significant for both pain measures (VAS*PI-sleep = 1.74; P<0.05;

CSI*PI-sleep = 0.31; P<0.05) through PI. For PC, on the other hand, no significant results could be observed for both pain measures (VAS*PC-sleep = 0.69; P=0.14; CSI*PC-sleep = 0.08; P=0.18). A detailed overview of these direct and indirect relations is presented in *Table 3*. Note that a correlation between the mediators is implied for every model.

# Discussion

The aim of this study was to examine the mediating role of PI and PC in the relationship of pain on fatigue and on sleep disturbances in BCS. Our findings demonstrated that PI significantly mediated both pain measures (CSI and VAS) on fatigue and sleep. For PC, only pain measured by VAS demonstrated a significant relation on fatigue. Positive associations were found for all significant mediations, indicating that higher pain levels are positively correlated with PI and PC, which go hand in hand with higher levels of fatigue and sleep disturbances in BCS.

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The results of this study complement previous findings by showing that cognitive appraisals such as PI and PC play a cardinal role in the fatigue experience of BCS.[79] Our study demonstrated a significant direct effect of pain (VAS and CSI) on fatigue in BCS. This finding is in concordance with prior research that demonstrated that overall pain and fatigue are strongly associated with each other in BCS,[23] and with a recent study from Druce et al. in which, regardless of the presence of musculoskeletal pain, greater fatigue was particularly predicted by central sensitization in non-cancer population.[80] Nevertheless, one must take into account that fatigue was mainly explained by central sensitization (CSI) and pain intensity (VAS) rather than neuropathic pain (DN-4) in BCS. This finding might be explained by the fact that pain intensity in neuropathic patients significantly reduced after administration of Gabapentin, which in turn reduces their sleep interference and improves their fatigue experience, this regardless of adverse effects (dizziness, somnolence, gait disturbance, and peripheral oedema) that Gabapentin might cause.[81]

On top of that, a significant relationship was found between PC and fatigue, which adds to the evidence that PC is an important predictor for increased fatigue after

breast cancer treatment.[79,82,83] Moreover, our study was the first to provide evidence for the mediating role of PC in the relationship of pain (VAS) on fatigue in BCS. A possible explanation for this finding might be that less-educated patients have a tendency to report higher levels of pain to receive more opioid analgesic medication.[84] These patients tend to catastrophize more, and in turn report poorer sleep quality.[84]

PI was found significant in all our direct and indirect relationships with fatigue and sleep disturbances. Even though the relations between PI and fatigue or sleep disturbances have never been considered in BCS, previous research demonstrated that experiencing PI at work might lead to sleep disturbances in healthy employees.[85] Furthermore, a recent study examined the association between opioids prescription and PI and showed that chronic pain patients with increased PI might display abnormal pain behaviour to magnify their suffering, leading to more aggressive opioid treatment.[86] It is known from numerous studies that the use of opioids tends to reduce the sleep quality in some cancer survivors, which might amplify their daytime fatigue, somnolence and napping, and in turn generates

disturbed night rest.[87-89] The importance of understanding PI in BCS needs to be recognized and further research is warranted.

*1. Clinical implications*

Despite these recent insights on cognitive appraisals, one must come to the conclusion that, until now, pharmacological therapy sadly remains the treatment of choice by physicians for pain after breast cancer.[90,91] In fact, opioids are often prescribed in BCS to target their pain severity, which in turn should lead to an increase of their sleep-quality and daily physical activities.[89] However, as mentioned above, the use of sedatives rather tends to reduce the sleep quality in some cancer survivors,[87-89] which contributes to abnormal sleep patterns and daytime fatigue.[89,92] This calls for urgent non-pharmacological and biopsychosocial treatment options that consider maladaptive appraisals such as PI and PC in BCS.[92-94] A possible treatment option is mindfulness based-behavioural therapy, which demonstrated to have a favourable effect on cognitive appraisals.[20,47,86] The main goal of this approach is to increase patients' self-efficacy and to shift their symptom-focuses to the background.[47,95,96] Mindfulness-based stress reduction diminished cognitive

appraisals and fatigue,[97] but revealed no significant effects on pain in BCS.[98] Furthermore, cognitive behavioural therapy has shown promising evidence on dysfunctional cognitions, fatigue and sleep variables in cancer survivors.[99-102] However, further high-quality randomized clinical trials are needed before the use of cognitive behavioural therapy, with a primary focus set on those maladaptive cognitions, can be proclaimed as best-evidence treatment strategy for fatigue in BCS. Likewise, acceptance and commitment therapy has demonstrated encouraging results on pain and insomnia, although understudied in this population.[103]

*2. Study strengths and limitations*

This study should be considered in light of its strengths and limitations. To the best of our knowledge, this study was the first to examine the cognitive appraisals (PC and PI) as mediators for the relationship between pain, fatigue and sleep in BCS. Strengths of our study include a large sample of BCS and an exhaustive analysis of mediation between the variables. Despite the innovative aspect of the current study, a few limitations should be acknowledged as well. First, subjects were chosen by convenience sampling. This might have caused a sample bias since our recruitment

was centralised in Brussels and its surroundings. Second, this study is based on 'Patient-Reported Outcome Measures' (PROM's), that were obtained on subjective and cross-sectional bases, making the accuracy of our assumptions possibly questionable.[104-107] It is postulated that fatigue-perception and severity show a tendency to change or fluctuate over time and mask significant outcomes.[108,109] On top of that, we should also take in consideration that BCS have a tendency to minimalize their side-effects because they have conquered such a horrible disease.[110] This phenomenon has been previously described as a 'response shift'.[111] Unfortunately, the phenomenon is challenging to measure and simultaneously responsible for measurement biases.[112] Therefore, future research with a wider geographical distribution and longitudinally focused data is needed before generalising the current results.[105] Third, the entire EORTC QLQ-C30 was assessed in our sample, but according to the purpose of our study, only fatigue and sleep subscales were used. However, these subscales are not satisfying measurement tools to make conclusions. The boundaries of our study need to be expanded with the use of more valid and reliable measurement tools to assess fatigue and sleep disturbances in BCS. Also, a solid consensus on the definition and

measurement tools for fatigue and sleep disturbance in BCS is currently missing.[23,37] Last, most of the used measurement tools were only validated in non-cancer populations.

# Conclusions

This study revealed the mediating role of cognitive appraisals relative to pain, fatigue and sleep in BCS. The indirect mediating effect of PI was found significant for both pain measures (CSI and VAS) on fatigue and sleep. For PC, on the contrary, only pain measured by VAS demonstrated a significant relation on fatigue. Unfortunately, the wide spectrum of definitions and invalid measurement tools in BCS makes it tough to picture some of the relations. Moreover, further longitudinal research is needed with implementation of other potential mediators to unravel the exact relationships between pain, fatigue, sleep, PI and PC in BCS. Bearing in mind the importance of PI and PC, new treatment strategies should be developed to target

fatigue and sleep disturbances in BCS with a primary focus set on those maladaptive cognitions.

**Author Contributions:** Conceptualization, L.L.; methodology, A.L., S.I., J.N., D.B. and L.L.; software, W.C.; validation, E.R.; formal analysis, W.C.; investigation, A.L., S.I., E.R. and L.L.; resources, J.N., D.B. and L.L; data curation, A.L. and L.L.; writing—original draft preparation, A.L. and S.I., ; writing—review and editing, A.L., J.N., D.B., C.F. and L.L.; visualization, A.L.; supervision, J.N., D.B., C.F. and L.L.; project administration, A.L.; funding acquisition, A.L., J.N., D.B., C.F. and L.L. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of University Hospital of Brussels (protocol B.U.N. 143201524229 and approved on 23 April 2015).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author, A.L., upon reasonable request.

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# Tables:

**Table 1. Patient characteristics and questionnaire outcomes of 128 breast cancer survivors. Abbreviations:** ALND, Axillary Lymph Node Dissection; CSI, Central Sensitization inventory; DN-4, Douleur Neuropathique 4 Questionnaire; EORTC fatigue and sleep, European Organisation for Research and Treatment of Cancer Fatigue and Sleep Subscale; IEQ, Injustice Experience Questionnaire; n, sample size; PCS, Pain Catastrophizing Scale; SD, Standard Deviation; SLNB, Sentinel Lymph Node Biopsy; VAS, Visual Analogue Scale.

**Table 2. Observed associations between the main variables in breast cancer survivors (n=128). Abbreviations:** CSI, Central Sensitization Inventory; DN-4, Douleur Neuropathique 4 questions; EORTC fatigue, European Organisation for Research and Treatment of Cancer Fatigue and Sleep Subscale; IEQ, Injustice Experience Questionnaire; PCS, Pain Catastrophizing Scale; VAS, Visual Analogue Scale.

**Table 3. Parametric estimations of the path analysis. Abbreviations:** CSI, Central Sensitization Inventory; HRQoL, Health-related Quality of Life; PC, Pain Catastrophizing; PI, Perceived Injustice; SE, Standard Error; VAS, Visual Analogue Scale; **Bold** = $p < 0.05$; Significant as per 95% bias-corrected confidence intervals estimated through 5000 bootstrapped resamples.

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# Figures:

**Figure 1. Path Analysis Models for fatigue,** e.g. The total estimate between pain (CSI) and fatigue is significant and amounts to 1.01 (figure 1a). The direct effect stays significant after incorporating the mediators PI and PC, which amounts to 0.71 (figure 1b). The direct effects from pain (CSI) to PI (0.26) and PI to fatigue (0.80) are both significant. This means that the association between pain (CSI) and fatigue is partially explained by the mediator PI since both the indirect effect and direct effect are significant. The indirect effect is interpreted as: A 1-unit increase in central sensitization on the CSI-scale will result through PI in a 0.21-unit increase in fatigue (figure 1c). PI explained 21% (that is 0.21/1.01) of the whole relationship between pain (CSI) and fatigue. **Abbreviations**: * = $p < 0.05$; CSI, Central Sensitization Inventory; PC, Pain Catastrophizing; PI, Perceived Injustice; VAS, Visual Analogue Scale.

**Figure 2. Path Analysis Models for sleep,** e.g. The total estimate between pain (VAS) and sleep is significant and amounts to 4.31 (figure 2a). Incorporating the mediators PI and PC in the model makes the direct effect insignificant and amounts to 1.88 (figure 2b). The direct effects from pain (VAS) to PI (1.48) and PI to sleep (1.18) are both significant. This means that the association between pain (VAS) and sleep is completely explained by the mediator PI since the indirect effect is significant and the direct effect is not. The indirect effect is interpreted as: A 1-unit increase in pain intensity on the VAS-scale will result through PI in a 1.74-unit increase in sleep disturbances (figure 2c). PI explained 40% (that is 1.74/4.31) of the whole relationship between pain (VAS) and sleep. **Abbreviations:** * = $p < 0.05$; CSI, Central Sensitization Inventory; PC, Pain Catastrophizing; PI, Perceived Injustice; VAS, Visual Analogue Scale.

| | | |
|---|---|---|
| Age (years) (mean ± SD) | | 59.8 ± 11.3 |
| Type of treatment n (%) | | |
| Breast surgery | | |
| | Breast conserving therapy | 72 (58.6%) |
| | Mastectomy | 56 (43.8%) |
| Axillary surgery | | |
| | SLNB | 66 (54.1%) |
| | ALND | 44 (36.1%) |
| | Missing | 6 |
| Chemotherapy | | |
| | No | 69 (55.2%) |
| | Yes | 56 (44.8%) |
| | Missing | 3 |
| Radiotherapy | | |
| | No | 18 (14.3%) |
| | Yes | 108 (85.7%) |
| | Missing | 2 |
| Hormone therapy | | |
| | No | 44 (35.2%) |
| | Yes | 81 (64.8%) |
| | Missing | 3 |
| Pain medication | | |
| | No | 88 (69.3%) |
| | Yes | 39 (30.7%) |
| | Missing | 1 |
| Questionnaire outcome values (mean ± SD) | | |
| VAS-score | | 23.7 ± 26.4 |
| DN-4 score | | 1.9 ± 2.1 |
| CSI score | | 35.2 ± 13.9 |
| EORTC fatigue | | 41.6 ± 30.3 |
| EORTC sleep | | 43.5 ± 36.6 |
| PCS | | 16.9 ± 14.9 |
| IEQ | | 16.1 ± 11.4 |

| | VAS | DN-4 | CSI | EORTC sleep | EORTC fatigue | PCS | IEQ |
|---|---|---|---|---|---|---|---|
| **VAS** | 1.000 | 0.625 | 0.535 | 0.510 | 0.578 | 0.493 | 0.507 |
| **DN-4** | 0.625 | 1.000 | 0.576 | 0.483 | 0.438 | 0.410 | 0.449 |
| **CSI** | 0.535 | 0.576 | 1.000 | 0.535 | 0.641 | 0.426 | 0.494 |
| **EORTC sleep** | 0.510 | 0.483 | 0.535 | 1.000 | 0.692 | 0.534 | 0.638 |
| **EORTC fatigue** | 0.578 | 0.438 | 0.641 | 0.692 | 1.000 | 0.601 | 0.668 |
| **PCS** | 0.493 | 0.410 | 0.426 | 0.534 | 0.601 | 1.000 | 0.639 |
| **IEQ** | 0.507 | 0.449 | 0.494 | 0.638 | 0.668 | 0.639 | 1.000 |

| | Estimate [95%CI] | SE | t-value | p-value |
|---|---|---|---|---|
| **Total effects** | | | | |
| VAS ~ HRQoL fatigue | 3.75 [2.06, 5.44] | 0.86 | 4.35 | **0.00** |
| CSI ~ HRQoL fatigue | 1.01 [0.67, 1.34] | 0.17 | 6.12 | **0.00** |
| VAS ~ HRQoL sleep | 4.31 [2.02, 6.60] | 1.17 | 3.69 | **0.00** |
| CSI ~ HRQoL sleep | 0.97 [0.54, 1.40] | 0.22 | 4.32 | **0.00** |
| | **Estimate [95%CI]** | **SE** | **z-value** | **p-value** |
| **Direct effects** | | | | |
| VAS ~ PC | 2.08 [1.10, 3.05] | 0.50 | 4.19 | **0.00** |
| VAS ~ PI | 1.48 [0.74, 2.21] | 0.37 | 3.95 | **0.00** |
| CSI ~ PC | 0.24 [0.06, 0.43] | 0.10 | 2.55 | **0.01** |
| CSI ~ PI | 0.26 [0.12, 0.40] | 0.07 | 3.64 | **0.00** |
| VAS ~ HRQoL fatigue | 1.76 [0.20, 3.33] | 0.80 | 2.21 | **0.03** |
| CSI ~ HRQoL fatigue | 0.71 [0.42, 1.00] | 0.15 | 4.76 | **0.00** |
| PC ~ HRQol fatigue | 0.38 [0.09, 0.68] | 0.15 | 2.56 | **0.01** |
| PI ~ HRQol fatigue | 0.80 [0.41, 1.20] | 0.20 | 4.04 | **0.00** |

| | | | | |
|---|---|---|---|---|
| VAS ~ HRQoL sleep | 1.88 [-0.29, 4.04] | 1.10 | 1.70 | 0.09 |
| CSI ~ HRQoL sleep | 0.58 [0.18, 0.98] | 0.21 | 2.82 | **0.00** |
| PC ~ HRQol sleep | 0.33 [-0.08, 0.74] | 0.21 | 1.59 | 0.11 |
| PI ~ HRQol sleep | 1.18 [0.64, 1.72] | 0.28 | 4.27 | **0.00** |
| **Indirect effects** | | | | |
| VAS * PI - fatigue | 1.19 [0.36, 2.01] | 0.42 | 2.82 | **0.00** |
| VAS * PC - fatigue | 0.80 [0.08, 1.51] | 0.37 | 2.18 | **0.03** |
| CSI * PI - fatigue | 0.21 [0.06, 0.36] | 0.08 | 2.70 | **0.01** |
| CSI * PC - fatigue | 0.09 [-0.01, 0.19] | 0.05 | 1.81 | 0.07 |
| VAS * PI - sleep | 1.74 [0.56, 2.92] | 0.60 | 2.90 | **0.00** |
| VAS * PC - sleep | 0.69 [-0.22, 1.59] | 0.46 | 1.49 | 0.14 |
| CSI * PI - sleep | 0.31 [0.09, 0.53] | 0.11 | 2.77 | **0.01** |
| CSI * PC - sleep | 0.08 [-0.04, 0.20] | 0.06 | 1.35 | 0.18 |

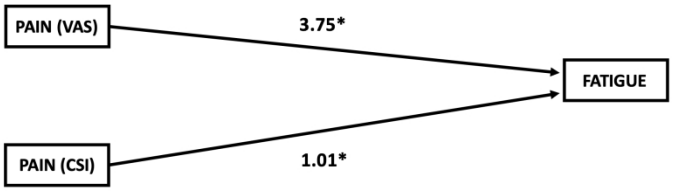


**Figure 1a Total effect model for fatigue.**

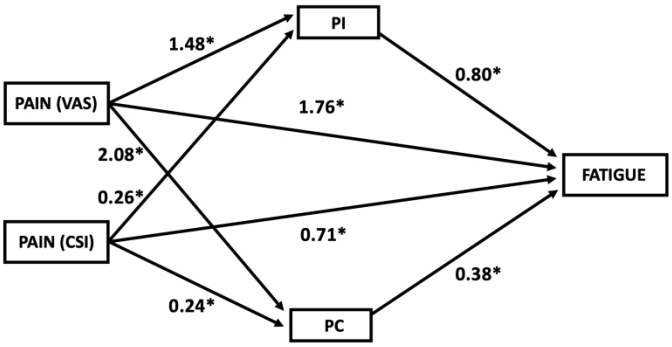


**Figure 1b Mediator model (PI, PC) for fatigue (direct effects).**

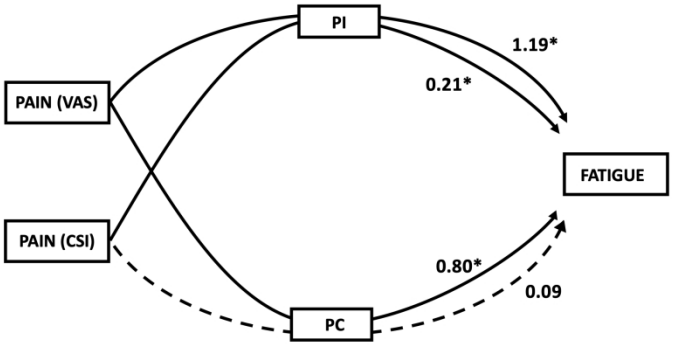


**Figure 1c Mediator model (PI, PC) for fatigue (indirect effects).**

Figure 1. Path Analysis Models for fatigue, e.g. The total estimate between pain (CSI) and fatigue is significant and amounts to 1.01 (figure 1a). The direct effect stays significant after incorporating the mediators PI and PC, which amounts to 0.71 (figure 1b). The direct effects from pain (CSI) to PI (0.26) and PI to fatigue (0.80) are both significant. This means that the association between pain (CSI) and fatigue is partially explained by the mediator PI since both the indirect effect and direct effect are significant. The indirect effect is interpreted as: A 1-unit increase in central sensitization on the CSI-scale will result through PI in a 0.21-unit increase in fatigue (figure 1c). PI explained 21% (that is 0.21/1.01) of the whole relationship between pain (CSI) and fatigue. Abbreviations: * = $p < 0.05$; CSI, Central Sensitization Inventory; PC, Pain Catastrophizing; PI, Perceived Injustice; VAS, Visual Analogue Scale.

874x1237mm (72 x 72 DPI)

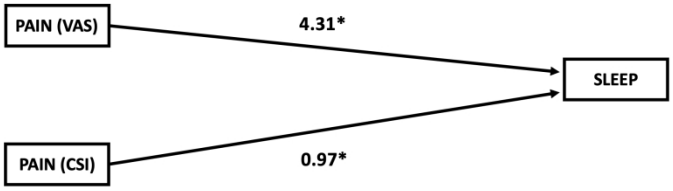


**Figure 2a Total effect model for sleep.**

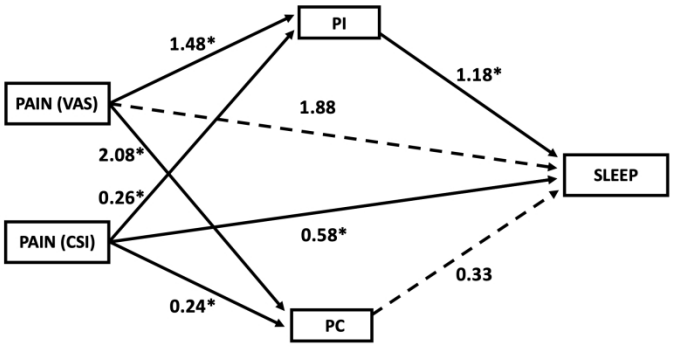


**Figure 2b Mediator model (PI, PC) for sleep (direct effects).**

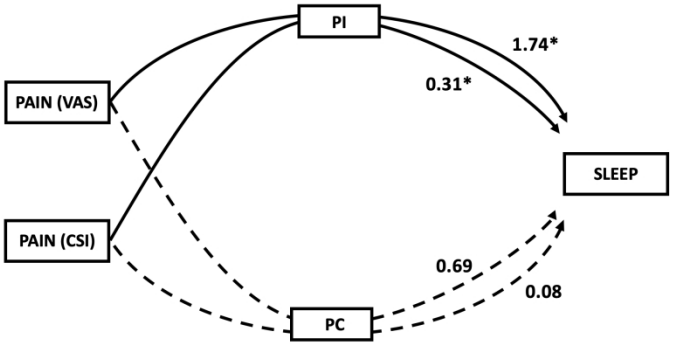


**Figure 2c Mediator model (PI, PC) for sleep (indirect effects).**

Figure 2. Path Analysis Models for sleep, e.g. The total estimate between pain (VAS) and sleep is significant and amounts to 4.31 (figure 2a). Incorporating the mediators PI and PC in the model makes the direct effect insignificant and amounts to 1.88 (figure 2b). The direct effects from pain (VAS) to PI (1.48) and PI to sleep (1.18) are both significant. This means that the association between pain (VAS) and sleep is completely explained by the mediator PI since the indirect effect is significant and the direct effect is not. The indirect effect is interpreted as: A 1-unit increase in pain intensity on the VAS-scale will result through PI in a 1.74-unit increase in sleep disturbances (figure 2c). PI explained 40% (that is 1.74/4.31) of the whole relationship between pain (VAS) and sleep. Abbreviations: * = $p < 0.05$; CSI, Central Sensitization Inventory; PC, Pain Catastrophizing; PI, Perceived Injustice; VAS, Visual Analogue Scale.

874x1237mm (72 x 72 DPI)