Psychological factors predict an unfavorable pain trajectory after hysterectomy: a prospective cohort study on chronic postsurgical pain

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Abstract
Chronic postsurgical pain (CPSP) is a well-recognized potential complication with negative personal, social, and health care consequences. However, limited data exist on CPSP and on the course of pain over time after hysterectomy. Using data from a prospective cohort study on a consecutive sample assessed at 4 time points, presurgery (T1), 48 hours (T2), 4 months (T3), and 5 years postsurgery (T4), we sought to examine women’s PSP trajectories using assessments of pain at T3 and T4. In addition, this study aimed to investigate presurgical and postsurgical risk factors associated with an unfavourable pain trajectory (PT). Based on pain data collected at T3 and T4, 3 distinct trajectories of PSP emerged: no CPSP (PT1; n = 88), prolonged PSP (PT2; n = 53), and CPSP (PT3; n = 29). Moreover, reported CPSP prevalence at 5 years was 17.1%. Multinomial logistic regression models controlling for age, presurgical pain, and type of hysterectomy tested for baseline and acute postsurgical predictive variables. Membership in PT2 and PT3 was predicted by presurgical anxiety (odds ratio [OR] = 1.131, P = 0.015; OR = 1.175, P = 0.009, respectively), emotional representation of the surgical disease (OR = 1.155, P = 0.034; OR = 1.213, P = 0.020, respectively), and pain catastrophizing (OR = 1.079, P = 0.043; OR = 1.143, P = 0.001, respectively). Furthermore, acute PSP intensity and frequency determined membership of women in PT3 (OR = 1.211, P = 0.033; OR = 3.000, P = 0.029, respectively), and postsurgical anxiety (OR = 1.182, P = 0.026) also played a key predictive role. This study identified factors that can be easily screened before and after surgery and are amenable to change through carefully designed timely and tailored interventions for women at risk of an unfavorable PSP trajectory posthysterectomy.

Keywords: Hysterectomy, Postsurgical pain trajectory, Chronic postsurgical pain, Prospective cohort study, Psychological factors, Acute postsurgical pain

1. Introduction
Chronic pain after surgery is a well-recognized potential complication, being acknowledged as a major clinical problem with significant individual, social, and health care costs.¹,²,³ It is a serious public health issue because surgeries are widely performed, increasing the numbers of those at risk.²,³,⁴ Indeed, the current version of the International Classification of Diseases (ICD-11) for chronic pain categorization already proposes chronic postsurgical pain (CPSP) as a new distinct entity among 7 groups of chronic pain disorders.⁵

Chronic PSP was first mentioned in 1998,⁶ being highlighted that 22.5% of patients attending 10 pain clinics pointed surgery as the cause of chronic pain. Despite improvements in knowledge regarding epidemiology and CPSP burden, its underlying mechanisms are not fully understood.⁷,⁸ However, evidence suggests that CPSP development is multifactorial, rooted in a dynamic and complex interplay among biological, psychosocial, and environmental factors.⁹,¹⁰ To increase knowledge, research has focused increasingly on understanding risk factors, in hopes of finding new ways to treat and ultimately prevent CPSP from occurring.

Risk factors are often conceptualized into presurgical, intrasurgical, and postsurgical, embracing variables such as age, surgery type, previous pain, and acute PSP.¹,²,³,⁵,⁶,⁷,¹² Psychological factors are well-documented predictors for CPSP across different surgeries,²,¹³,¹⁴,¹⁶,¹⁷ including anxiety,¹⁸,¹⁹ depression,¹⁸,⁵⁰,⁵⁶,⁵⁸,⁹⁹ pain catastrophizing,²⁸,⁵⁰,⁵⁶,⁵⁸,⁹⁹ and optimism.⁴⁰,⁸² In an attempt to systematize information, VanDenKerkhof et al.¹⁰,¹⁴ proposed a framework wherein risk factors are organized into 5 domains: demographic, pain, clinical, surgery related, and psychological. Hysterectomy is the most common gynecologic surgery performed in women in Western countries.⁸⁵,⁹⁸ In a review including 11 hysterectomy studies, with follow-up times up to 2 years, CPSP was reported by 5% to 32% of women.²

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Subsequent studies kept diverging on prevalence rates. These differences were likely due to distinct CPSP definitions, heterogeneity of measurement, and differences in follow-up times; some were 3, 4, 6, 7, 9, 10 months, or 2 years.\(^7\) Simultaneously, risk factors that have been most highlighted were age,\(^7\) 9 sleep,\(^7\) presurgical pain,\(^7\) other pain problems,\(^6,7,9\) and psychological factors.\(^7\) Within the latter, there was some heterogeneity because of different measures used. Furthermore, acute CPSP intensity was more strongly related with CPSP in some hysterectomy studies\(^6,10,11\) than in others,\(^6,7\) with one of the studies proposing CPSP frequency as a better predictor than intensity.\(^7\)

Although the incidence and risk factors for CPSP have been widely explored, knowledge on the course of PSP over time is limited. Identifying patients who are at risk of an unfavorable pain trajectory (PT), culminating in CPSP, provides a unique opportunity to investigate the transition from acute to chronic pain and is critical to developing a more comprehensive understanding of CPSP and establishing potential targets for psychosocial and clinical interventions.

Therefore, the aims of this study were: (1) to examine PSP trajectory up to 5 years after hysterectomy; (2) to investigate baseline predictors of different pain trajectories; and (3) to further explore the added predictive value of acute postsurgical factors in pain chronification.

## 2. Methods

### 2.1. Participants and procedure

This study was conducted in a central hospital in northern Portugal and approval was granted by the Hospital Ethics Committee. This was a prospective cohort study with longitudinal assessments at 4 time points: 24 hours before surgery (T1), 48 hours (T2), 4 months (T3), and 5 years (T4) after surgery. Assessments were performed between March 2009 and January 2015. A consecutive sample of 203 women, undergoing hysterecortomy due to benign causes, was invited to participate in the study and all provided written informed consent. Inclusion criteria were age between 18 and 80 years, and the ability to understand consent procedures and questionnaire materials. Exclusion criteria were the presence of psychiatric or neurologic pathology (eg, dementia) and undergoing hysterectomy due to malignant conditions or in emergency setting. Time 1 and T2 assessments took place in hospital, T3 and T4 follow-up assessments were conducted by telephone interview. Inclusion in each assessment point and the reasons for loss to T2, T3, and T4 are shown in a flowchart (Fig. 1). The final sample is comprised of 170 women (retention rate: 83.7%; age: M = 50.8; SD = 9.03; minimum = 35; maximum = 76) with assessments performed at T1, T2, T3, and T4. The 33 women lost to follow-up, from T1 to T4, did not differ significantly from the women evaluated over 5 years in terms of baseline demographic, psychological, and clinical characteristics, namely on surgical, anesthetic, and analgesic issues.

Data related to this sample have been described in 4 previous publications reporting predictors of acute PSP,\(^6,7,9\) predictors of rescue analgesia administration,\(^9\) and predictors of persistent PSP 4 months after hysterectomy.\(^7\) The present work is the first to report the long-term outcomes in this sample, 5 years posthysterectomy, including the 4 assessment points.

### 2.2. Data collection

#### 2.2.1. Presurgical assessment—24 hours before surgery (T1)

At hospital admission, and to get a baseline evaluation of women, the Portuguese versions of the following questionnaires were administered, in a face-to-face interview, by a trained health psychologist.

#### 2.2.1.1. Sociodemographic Questionnaire

Included questions on age, height, weight, education, residence, marital status, professional status, household, and parity.

#### 2.2.1.2. Clinical Questionnaire

Enquired about previous pain, either related to the cause of surgery or due to other causes, previous surgeries, menopause status, diagnosis/indication for hysterectomy and disease onset, uterus height and weight, as well as the use of psychotropic drugs (anxiolytics and antidepressants).

#### 2.2.1.3. The Brief Pain Inventory—short form

Used among women reporting presurgical pain (related with the disease underlying the surgery).\(^24\) It measured pain location in the body; pain intensity on an 11-point numerical rating scale (NRS; 0 represents “no pain” and 10 the “worst pain imaginable”); analgesic intake; perception of analgesic relief; and pain interference with daily life on an 11-point NRS (0 = “does not interfere” and 10 = “completely interferes”) in distinct dimensions (general activity, mood, walking, work, relations with others, sleep, and enjoyment of life). Higher scores represent higher levels of pain interference. In this study, the internal consistency reliability\(^27\) for the pain interference subscale scores was high (α = 0.90).

#### 2.2.1.4. The Hospital Anxiety and Depression Scale

Comprised by 2 subscales used to measure anxiety and depression through 7 items each.\(^110\) Subscale scores range from 0 to 21 and result from the sum of each item (Likert scale ranging from 0 to 3). Higher scores correspond to higher levels of anxiety and depression. In the current sample, internal consistency reliability was adequate for both anxiety (T1: α = 0.77; T2: α = 0.84) and depression (T1: α = 0.81).

#### 2.2.1.5. The Surgical Fear Questionnaire

Used to evaluate specific surgical fears through 8 items aggregated in 2 subscales, “fear of immediate consequences of surgery” (α = 0.77; 4 items) and “fear of long-term consequences of surgery” (α = 0.75; 4 items).\(^107\) Each item score ranges from 0 to 10; item scores are summed to calculate each total subscale score. Subscale scores range between 0 and 40, with higher values indicating higher levels of fear.

#### 2.2.1.6. The Revised Illness Perception Questionnaire

Used to assess patient beliefs about the underlying disease that lead to surgery, is comprised by 7 dimensions.\(^68\) In the current study, and with the aim of diminishing participant burden, a psychometrically shortened version\(^77,79\) was used, with 3 items composing each one of the 7 subscales: “timeline acute/chronic” (α = 0.79; eg, “My illness will last for a long time”); “timeline cyclical” (α = 0.74; eg, “My symptoms come and go in cycles”); “consequences” (α = 0.56; eg, “The disease underlying surgery has major consequences on my life”); “personal control” (α = 0.53; eg, “I have the power to
influence my illness”); “treatment control” (α = 0.76; eg, “Surgery can control my illness”); “illness coherence” (α = 0.78; eg, “My illness is a mystery for me”); and “emotional representation” (α = 0.88; eg, “When I think about my illness I get upset”). “Consequences” and “personal control” were not included because of their low score reliability in this sample (α = 0.56 and α = 0.53, respectively). Each item is rated on a scale of 1 to 5, and to calculate each total subscale score, items are summed. Each subscale varies between 5 and 15, with high scores revealing less adaptive illness perceptions, with the exception of personal and treatment control subscales, which score inversely.

2.2.1.7. The Coping Strategies Questionnaire—revised form

Used to evaluate 6 pain coping strategies: “pain catastrophizing” (5 items; α = 0.88); “praying and hoping” (3 items; α = 0.88); “ignoring pain” (5 items; α = 0.92); “distraction/diverting attention” (5 items; α = 0.77); “reinterpreting pain” (4 items; α = 0.74); and “pain coping self-statements” (4 items; α = 0.70). During pilot testing, subjects were often confused by the usual 7-point Likert-type scale. Therefore, a 5-point rating scale was used (1 = never, 2 = almost never, 3 = sometimes, 4 = almost always, and 5 = always), which was shown to be more easily understood. The total subscale score was obtained by the sum of the item scores, with higher scores indicating greater use of the specific coping strategy.

2.2.1.8. Life Orientation Test—revised

Evaluated the personality trait optimism using 8 items. The total score ranges from 0 to 12 (α = 0.95), with high values associated with more optimism.

2.2.2. Postsurgical assessment—48 hours after surgery (T2)

Forty-eight hours after surgery, women were again assessed in a face-to-face interview by the same psychologist who performed the baseline assessment in T1.

2.2.2.1. Acute postsurgical pain measurement

Worst and average levels of acute pain intensity, within the first 48 hours after surgery, were assessed using an 11-point NRS (from the BPI-SF described above). Pain could be defined either as constant (continuous and steady), intermittent (periodic and rhythmic), or brief (momentary and transient).

2.2.2.2. Postsurgical anxiety

Post-surgical anxiety was evaluated again at this time point using the Hospital Anxiety and Depression Scale anxiety subscale already described.
2.2.3. Postsurgical assessment—4 months (T3) and 5 years after surgery (T4)

Four months and 5 years after surgery, telephone calls were made to every participant to check for the presence of pain. The question was: “Do you still have any pain that you could link to surgery or that you could relate to the surgical procedure?” This is an adaptation of the BPI-SF first question on pain prospection. If women answered no, those women were classified as cases without pain. Contrarily, if women answered yes, they were considered pain cases. For those women reporting pain, additional measures were used, which focused on pain assessment.

2.2.3.1. The Brief Pain Inventory—short form

As described above.24

2.2.3.2. Pain frequency description

Pain frequency could be described as constant, daily, several times a week but not daily, several times a month but not weekly, during sexual intercourse, by touch or lifting weight.

2.2.3.3. Neuropathic Pain Questionnaire (DN-4)

Previous research described CPSP as a potential neuropathic pain.4,48,51 This instrument assesses pain characteristics/quality using 10 items. Seven of them refer to specific pain sensory descriptors, such as burning, pinpricking or numbness, and patients answer if their pain has those characteristics using a dichotomous response format (yes or no). The last 3 items result from the sensory examination of patients performed by a clinician. For the purpose of this study, only the first 7 items were included.5 Besides the information regarding pain quality, this questionnaire also provides information concerning the potential likelihood of neuropathic pain, corresponding to a cutoff of 3 (DN4 ≥ 3).

2.3. Surgical procedures, anesthetic, and analgesic techniques

Clinical data related to the surgery, anesthesia and analgesia were collected from medical records.

Regarding surgical procedure, among the 170 women who underwent surgery, 122 (71.8%) were submitted to total abdominal hysterectomy, 31 (18.2%) to vaginal hysterectomy, 11 (6.5%) to total laparoscopic hysterectomy, and 6 (3.5%) to laparoscopically assisted vaginal hysterectomy. In abdominal hysterectomy (n = 122), a Pfannenstiel incision was performed in 102 women (83.6%), being established as the first choice, with a vertical infraumbilical incision being performed in 20 women (16.4%), corresponding to cases wherein a previous vertical surgical scar was present.

Concomitant procedures, such as oophorectomy, ovarian cystectomy, salpingectomy, cystoscopy, or vaginal repair, were also performed in a few patients. Moreover, uterus weight and height were also recorded.

Concerning the type of anesthesia, 51 (30.0%) patients had general anesthesia, 22 (12.9%) had locoregional, and 97 (57.1%) were submitted to combined anesthesia (general + locoregional). ASA score (physical status classification of the American Society of Anesthesiologists) was recorded, including cases of ASA grade I (49, 28.8%), II (107, 62.9%), and III (14, 8.2%).

In what regards analgesic procedures, a postsurgical 48 hours standardized analgesia protocol was assigned to all patients. This protocol was established and supervised by the Acute Pain Service, before the transferring of patients to the infirmary.

Delivery of the analgesic protocol was either epidural or intravenous. The standardized epidural protocols could be: (1) a continuous epidural infusion delivered infusion balloon with ropivacaine (0.1%) and fentanyl (3 μg/mL), administrated to 105 (61.8%) women; or (2) administration of an epidural morphine bolus (2-3 mg, 12/12 h), assigned to 14 (8.2%) women. The intravenous protocol consisted in a continuous intravenous infusion delivered infusion balloon of tramadol (600 mg), metamizol (6 g), and metoclopramide (60 mg) and was used with 51 (30.0%) patients.

Paracetamol (1 g 6/6 h) and nonsteroidal anti-inflammatory drugs (ketorolac 30 mg 12/12 h or parecoxib 40 mg 12/12 h) were always included as coadjuvant analgesics. In addition, all analgesic regimens included prokinetic treatment that was standardized to metoclopramide (10 mg intravenously 8/8 h). In cases of moderate or severe acute PSP levels (NRS ≥ 3), rescue analgesia was prescribed beyond the standardized analgesic protocol. Because of the great variability in analgesics’ protocol and dosages, no attempt was made to determine total equianalgesic medication dosages. Instead, it was recorded whether rescue analgesics were given to patients or not.

The use of psychotropic drugs (anxiolytics and antidepres-
sants) during hospital stay was detailed from hospital records.

2.4. Statistical analyses

The primary outcome variable under study is PSP trajectory, corresponding to 3 possible PT groups: (1) No CPSP or pain trajectory 1 (PT1), comprised by women who did not report pain neither at 4 months nor at 5 years after surgery; (2) prolonged PSP or pain trajectory 2 (PT2), including women who complained of pain 4 months after surgery, but not 5 years after; and (3) CPSP or pain trajectory 3 (PT3), comprising those women who reported pain both at 4 months and 5 years after hysterectomy. These groups were defined taking into account pain report (yes [presence] or no [absence]) 4 months and 5 years after hysterectomy (T3 and T4).

To compare the 3 groups on the variables under analysis, chi-square or Fisher tests and one-way analysis of variance statistical tests were computed. For the latter, in the case of significant results (P < 0.05), Bonferroni post hoc tests were performed to further investigate between-group differences. These preliminary analyses were exploratory and were performed to determine the predictor variables to include in the subsequent regression analyses.

Finally, a set of predictive multinomial logistic regression models were conducted to investigate risk factors associated with PT group membership. The sociodemographic, clinical, and psychological variables selected for the regression analyses were those that distinguished PT groups in univariate analyses. Two structural models were developed: model 1 (M1), investigating the role of baseline presurgical variables (T1), allowing for the establishment of a presurgical risk profile; and model 2 (M2), aiming at further understanding the role of acute postsurgical factors, 48 hours after hysterectomy (T2). These basic structural models, include demographic (age) and clinical (pain-related [presurgical pain] and surgery-related [type of hysterectomy]) variables that significantly distinguished the groups in univariate analyses, to control these effects in group comparisons.

Considering the role of presurgical baseline predictors, and due to shared variance among the 5 psychological predictors (and consequent multicollinearity), which emerged as significant in the distinction of the 3 groups, 3 different submodels were considered. The first model (M1A) focused on emotional variables
(presurgical anxiety and fear), the second (M1B) centered on illness perceptions (emotional representation of the disease underlying surgery), and the third model (M1C) tested the role of pain coping strategies (pain catastrophizing).

Regarding acute postsurgical factors, 2 models were computed, both controlling for the same abovementioned demographic and clinical variables that were controlled for in presurgical models. Beyond these covariates, the first model (M2A) tested for the specific predictive role of acute PSP intensity and frequency. The second postsurgical model (M2B) was akin to the first, although it had the addition of postsurgical anxiety.

Data were analyzed using the IBM SPSS Statistics version 24.0. Internal consistency of responses to the questionnaires was assessed using Cronbach alpha. Results were considered significant for $P$ values $< 0.05$. Effect size (ES) measures were interpreted considering the Cohen rule of thumb for eta squared ($\eta^2$): small $ES = 0.02$; medium $ES = 0.13$; large $ES = 0.26$; and Rea and Parker rules for Cramer phi ($\phi$) or Cramer V for nominal data: negligible association: 0 and under 0.10; weak association: 0.10 and under 0.20; moderate association: 0.20 and under 0.40; relatively strong association: 0.40 and under 0.60; strong association: 0.60 and under 0.80; and very strong association: 0.80 and under 1.00.

### 3. Results

#### 3.1. Pain trajectory according to pain report 4 months (T3) and 5 years (T4) after hysterectomy

Table 1 presents the number of women within each PT group, according to the course of pain up to 5 years after surgery.

<table>
<thead>
<tr>
<th>Pain trajectory</th>
<th>Chronic pain report 4 months (T3)</th>
<th>Chronic pain report 5 years (T4)</th>
<th>Group designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain trajectory 1</td>
<td>No</td>
<td>No</td>
<td>Pain trajectory 1 (no chronic postsurgical pain)</td>
</tr>
<tr>
<td>Pain trajectory 2</td>
<td>Yes</td>
<td>No</td>
<td>Pain trajectory 2 (prolonged postsurgical pain)</td>
</tr>
<tr>
<td>Pain trajectory 3</td>
<td>Yes</td>
<td>Yes</td>
<td>Pain trajectory 3 (chronic postsurgical pain)</td>
</tr>
</tbody>
</table>

#### 3.2. Differences among pain trajectory groups on sociodemographic, clinical, and psychological variables

Table 2 shows that before surgery, PT groups differed in age ($P = 0.013$; $\eta^2 = 0.051$, small ES), with PT1 being older than PT2 ($P = 0.003$). Concerning clinical measures, the groups were similar in terms of surgical disease onset, body mass index, previous surgical procedures, or presurgical psychotropic use. Regarding presurgical pain, the 3 groups of women differed significantly on presurgical pain related to the condition underlying surgery ($P = 0.032$; $\phi = 0.201$, moderate association), but not on previous chronic pain because of other causes (Table 2). Among the 3 empirically derived PT groups, and regarding psychological variables measured before surgery, there were significant differences in anxiety ($P < 0.001$; $\eta^2 = 0.094$, small ES), surgical fear related to long-term consequences of surgery ($P = 0.022$; $\eta^2 = 0.045$, small ES), emotional representation of surgical disease ($P = 0.001$; $\eta^2 = 0.081$, small ES), and pain catastrophizing ($P < 0.001$; $\eta^2 = 0.090$, small ES). For all these variables, higher values were associated with chronic pain group membership in PT2 or PT3.

In terms of surgery, the PT groups could be distinguished based on the type of surgical approach ($P = 0.007$; $\phi = 0.242$, moderate association) and among those undergoing abdominal hysterectomy, there were also differences across groups on the type of abdominal incision ($P = 0.003$; $\phi = 0.260$, moderate association). The PT2 and PT3 groups had more women undergoing abdominal hysterectomy and a Pfannenstiel incision.

In the acute postsurgical period, 48 hours after surgery, the 3 PT groups of women showed differences in acute pain report, regarding worst ($P < 0.001$; $\eta^2 = 0.096$, small ES) and average ($P = 0.001$; $\eta^2 = 0.086$, small ES) pain intensity, pain frequency ($P = 0.001$; $\phi = 0.286$, moderate association), and postsurgical anxiety ($P < 0.001$; $\eta^2 = 0.109$, small ES). These differences showed that the PT2 and PT3 groups scored more negatively on these variables.

### 3.3. Pain incidence, characteristics, and perceived impact 5 years after hysterectomy

Among the 170 women who completed the 4 assessments, 29 (17.1%) revealed an unfavorable PT after hysterectomy, reporting pain both at 4 months and 5 years after surgery, therefore being considered CPSP cases (Table 3). From these 29 cases of CPSP, Table 3 highlights that in terms of pain frequency, most women (44.8%) reported pain several times a week, with 24.2% of women perceiving pain on a daily basis and 20.7% complaining of pain only during sexual intercourse or by touch. In addition, the mean of worst pain intensity was 3.17 (SD = 1.61) and the mean average level of pain intensity was 1.89 (SD = 0.88), on the 0 to 10 NRS. It was also shown that 34.5% of CPSP women rated their worst pain intensity above 3 (NRS > 3), indicating moderate and/or severe pain levels. Table 3 also reveals that the pain sensory characteristics more often described by patients with CPSP were feeling of pins and needles (51.7%) and numbness (31.0%).

#### Table 1

<table>
<thead>
<tr>
<th>Pain trajectories</th>
<th>Chronic pain report 4 months (T3)</th>
<th>Chronic pain report 5 years (T4)</th>
<th>Group designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain trajectory 1</td>
<td>No</td>
<td>No</td>
<td>Pain trajectory 1 (no chronic postsurgical pain)</td>
</tr>
<tr>
<td>Pain trajectory 2</td>
<td>Yes</td>
<td>No</td>
<td>Pain trajectory 2 (prolonged postsurgical pain)</td>
</tr>
<tr>
<td>Pain trajectory 3</td>
<td>Yes</td>
<td>Yes</td>
<td>Pain trajectory 3 (chronic postsurgical pain)</td>
</tr>
</tbody>
</table>
was reported in all domains, the most common being mood (57.1%), enjoyment of life (50.0%), general activity (42.9%), normal work (42.9%), and walking ability (28.6%). Nevertheless, mean values of pain interference were in the low-to-medium range.

### 3.4. Predictors of postsurgical pain trajectory

To identify the presurgical predictors of an unfavorable PT, 3 multinomial regression models were computed (Table 4), controlling for the demographic and clinical variables that distinguished the 3 groups: age, previous surgical pain, and type of hysterectomy. The first model (M1A) further tested for the influence of psychological factors related to emotional distress, namely presurgical anxiety and surgical fear related to the long-term consequences of surgery. Table 4 shows that presurgical anxiety is a predictor of PT, being a determinant of group membership, with higher anxiety scores being associated with both the “Prolonged PSP group” (PT2; odds ratio [OR] = 1.131, $P = 0.009$; for each unit increased in presurgical anxiety, the odds of being in the PT2 group is 1.131 times higher than those of being in the PT1 group) and the “CPSP group” (PT3; OR = 1.175, $P = 0.009$), when compared with the “No CPSP group” (PT1). All other variables were not significant. Table 4 also reveals results on the influence of psychological factors associated with illness perceptions (M1B) and pain coping strategies (M1C). Within

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### Table 2

Differences between pain trajectory groups on sociodemographic, clinical, and psychological variables measured 24 hours before (T1) and 48 hours after hysterectomy (T2).

<table>
<thead>
<tr>
<th>Measures</th>
<th>PT1 (n = 88)</th>
<th>PT2 (n = 53)</th>
<th>PT3 (n = 29)</th>
<th>$F/r^2$</th>
<th>$P$</th>
<th>$\eta^2/c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic: Age (y [SD])</td>
<td>52.8 (10.2)$^a$</td>
<td>48.7 (6.43)$^b$</td>
<td>48.7 (8.19)$^{ab}$</td>
<td>4.446</td>
<td>0.013</td>
<td>0.051</td>
</tr>
<tr>
<td>Presurgical clinical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease onset (mo)</td>
<td>39.2 (48.6)</td>
<td>36.3 (46.0)</td>
<td>44.9 (71.4)</td>
<td>0.250</td>
<td>0.779</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28.8 (4.26)</td>
<td>29.0 (4.78)</td>
<td>27.9 (4.15)</td>
<td>0.585</td>
<td>0.558</td>
<td>0.007</td>
</tr>
<tr>
<td>Previous surgeries (yes)</td>
<td>62 (70.5%)</td>
<td>37 (69.8%)</td>
<td>21 (72.4%)</td>
<td>0.063</td>
<td>0.969</td>
<td>0.019</td>
</tr>
<tr>
<td>Psychotropic use* (yes)</td>
<td>28 (33.7%)</td>
<td>19 (37.3%)</td>
<td>14 (48.3%)</td>
<td>1.941</td>
<td>0.379</td>
<td>0.109</td>
</tr>
<tr>
<td>Presurgical pain (yes)</td>
<td>44 (50.0%)</td>
<td>36 (67.9%)</td>
<td>21 (72.4%)</td>
<td>6.858</td>
<td>0.032</td>
<td>0.201</td>
</tr>
<tr>
<td>Previous pain due to other causes† (yes)</td>
<td>49 (55.7%)</td>
<td>37 (69.8%)</td>
<td>21 (72.4%)</td>
<td>4.176</td>
<td>0.124</td>
<td>0.157</td>
</tr>
<tr>
<td>Psychological variables (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS: anxiety (0-21)</td>
<td>6.02 (3.84)$^a$</td>
<td>7.87 (3.96)$^a$</td>
<td>9.38 (4.81)$^a$</td>
<td>8.015</td>
<td>&lt;0.001</td>
<td>0.094</td>
</tr>
<tr>
<td>SFQ: Immediate consequences (0-40)</td>
<td>9.02 (8.55)</td>
<td>10.8 (7.26)</td>
<td>13.3 (10.1)</td>
<td>2.892</td>
<td>0.058</td>
<td>0.033</td>
</tr>
<tr>
<td>SFQ: Long-term consequences (0-40)</td>
<td>4.61 (6.78)$^a$</td>
<td>4.66 (5.33)$^a$</td>
<td>8.41 (8.12)$^a$</td>
<td>3.929</td>
<td>0.022</td>
<td>0.045</td>
</tr>
<tr>
<td>IPQ-R: Timeline acute/chronic (3-15)</td>
<td>6.11 (1.39)</td>
<td>5.98 (1.01)</td>
<td>6.52 (1.53)</td>
<td>1.607</td>
<td>0.204</td>
<td>0.019</td>
</tr>
<tr>
<td>IPQ-R: Treatment control (3-15)</td>
<td>12.2 (0.98)</td>
<td>12.2 (0.77)</td>
<td>12.1 (0.75)</td>
<td>0.231</td>
<td>0.794</td>
<td>0.003</td>
</tr>
<tr>
<td>IPQ-R: Interference (3-15)</td>
<td>9.27 (2.76)</td>
<td>9.36 (2.60)</td>
<td>9.90 (2.58)</td>
<td>0.604</td>
<td>0.548</td>
<td>0.007</td>
</tr>
<tr>
<td>CSQ-R: Pain catastrophizing (4-20)</td>
<td>9.57 (4.22)$^a$</td>
<td>10.0 (4.04)</td>
<td>10.5 (3.67)</td>
<td>0.560</td>
<td>0.573</td>
<td>0.007</td>
</tr>
<tr>
<td>LOT-R: Optimism (0-12)</td>
<td>12.4 (5.81)</td>
<td>11.9 (6.18)</td>
<td>11.0 (6.12)</td>
<td>0.568</td>
<td>0.568</td>
<td>0.007</td>
</tr>
<tr>
<td>LOT-R: Negative affect (0-12)</td>
<td>10.6 (5.74)</td>
<td>11.9 (6.18)</td>
<td>11.0 (6.12)</td>
<td>0.568</td>
<td>0.568</td>
<td>0.007</td>
</tr>
<tr>
<td>LOT-R: Pain coping self-stat (4-20)</td>
<td>15.0 (4.12)</td>
<td>16.3 (4.04)</td>
<td>16.0 (4.04)</td>
<td>0.568</td>
<td>0.568</td>
<td>0.007</td>
</tr>
<tr>
<td>LOT-R: Distraction (0-20)</td>
<td>9.40 (4.26)</td>
<td>9.56 (3.88)</td>
<td>9.36 (3.88)</td>
<td>0.133</td>
<td>0.876</td>
<td>0.002</td>
</tr>
<tr>
<td>LOT-R: Pain distraction (4-20)</td>
<td>12.6 (3.21)</td>
<td>13.2 (3.21)</td>
<td>12.9 (3.21)</td>
<td>0.231</td>
<td>0.794</td>
<td>0.003</td>
</tr>
<tr>
<td>LOT-R: Pain ignoring (4-20)</td>
<td>10.6 (4.26)</td>
<td>11.6 (4.26)</td>
<td>11.4 (4.26)</td>
<td>0.231</td>
<td>0.794</td>
<td>0.003</td>
</tr>
<tr>
<td>LOT-R: Pain catastrophizing (6-30)</td>
<td>9.25 (4.28)$^a$</td>
<td>11.3 (5.81)$^a$</td>
<td>13.6 (6.50)$^a$</td>
<td>8.232</td>
<td>&lt;0.001</td>
<td>0.090</td>
</tr>
<tr>
<td>LOT-R: Pain ignoring (0-12)</td>
<td>7.30 (3.48)</td>
<td>6.63 (3.01)</td>
<td>7.14 (3.29)</td>
<td>0.663</td>
<td>0.517</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean (SD); categorical variables are presented as n (%). Different letters represent $P$-values < 0.05 in analysis of variance post hoc tests; for example, in age groups comparisons, PT1 (represented with $a$) is significantly different from PT2 (represented with $b$) and PT3 does not significantly differ from PT1 and PT2 (represented with $ab$).

$*$ Psychotropic use: consumption/intake of anxiolytics and antidepressants.

† Other previous chronic pain states not related to the cause of surgery.

‡ Type of hysterectomy: n (%) of Pfannenstiel incisions vs infraumbilical vertical incision and laparoscopies.

§ Abdominal incision: n (%) of Pfannenstiel incisions vs infraumbilical vertical incision and laparoscopies.

¶ BMI, body mass index; CSQ-R, Coping Strategies Questionnaire-Revised; HADS, Hospital Anxiety and Depression Scale; IPQ-R, Illness Perception Questionnaire-Revised; LOT-R, Life Orientation Test-revised; PT, pain trajectory; SFQ, Surgical Fear Questionnaire.
Table 3
Incidence, characteristics, and impact of pain 5 years after hysterectomy (N = 29).

<table>
<thead>
<tr>
<th>Pain 5 y after hysterectomy—T4</th>
<th>N (%)</th>
<th>M (SD)</th>
<th>Min-max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain report—CPSP*</td>
<td>29 (17.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>7 (24.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Several times a week but not daily</td>
<td>13 (44.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Several times a month but not weekly</td>
<td>3 (10.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During sexual intercourse/by touch</td>
<td>6 (20.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity† (NRS 0-10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst level</td>
<td>3.17 (1.61)</td>
<td>1-7</td>
<td></td>
</tr>
<tr>
<td>NRS &gt; 3</td>
<td>10 (34.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average level</td>
<td>1.89 (0.88)</td>
<td>1-4</td>
<td></td>
</tr>
<tr>
<td>NRS &gt; 3</td>
<td>1 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DN-4‡ (could report 1 or more)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pins and needles</td>
<td>15 (51.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td>9 (31.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td>6 (20.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tingling</td>
<td>3 (10.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>2 (6.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful cold</td>
<td>1 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electric shocks</td>
<td>1 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DN4 &lt; 3</td>
<td>23 (82.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DN4 ≥ 3</td>
<td>5 (17.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain interference§ (NRS 0-10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General activity</td>
<td>12 (42.9)</td>
<td>1.07 (1.41)</td>
<td>0-4</td>
</tr>
<tr>
<td>Mood</td>
<td>16 (57.1)</td>
<td>1.64 (1.83)</td>
<td>0-5</td>
</tr>
<tr>
<td>Walking ability</td>
<td>8 (28.6)</td>
<td>0.57 (1.03)</td>
<td>0-3</td>
</tr>
<tr>
<td>Normal work</td>
<td>12 (42.9)</td>
<td>1.14 (1.56)</td>
<td>0-5</td>
</tr>
<tr>
<td>Relations with other people</td>
<td>5 (17.8)</td>
<td>0.32 (0.77)</td>
<td>0-3</td>
</tr>
<tr>
<td>Sleep</td>
<td>2 (7.2)</td>
<td>1.79 (0.67)</td>
<td>0-3</td>
</tr>
<tr>
<td>Enjoyment of life</td>
<td>14 (50)</td>
<td>1.32 (1.68)</td>
<td>0-5</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean (SD); categorical variables are presented as n (%).
* Women reporting CPSP—chronic postsurgical pain 5 years after hysterectomy.
† NRS: numerical rating scale (0-10).
‡ DN-4: Neuropathic Pain Questionnaire.
§ Items from BPI-SF: Brief Pain Inventory—short form.

M1B, emotional representation of the condition underlying surgery emerged as the only factor significantly associated with group membership, with high scores predicting PT2 (OR = 1.165, P = 0.018) and PT3 (OR = 1.246, P = 0.005) membership. Within M1C, pain catastrophizing was the only variable yielding a significant association with either membership in PT2 (OR = 1.079, P = 0.043) or PT3 (OR = 1.143, P = 0.001) groups. Concerning factors that could distinguish PT2 from PT3 membership, Table 4 indicates that the psychological construct fear of long-term consequences of surgery was the only significant predictor (OR = 1.078, P = 0.049).

To further explore the role of acute postsurgical variables in the development of an unfavorable PT, over and above demographic and clinical factors, 2 subsequent models were tested (Table 5). The first model (M2A) revealed that acute PSP intensity and frequency determined inclusion of women in PT3 (OR = 1.211, P = 0.033 and OR = 3.000, P = 0.029, respectively). The second postsurgical model (model 2B) added postsurgical anxiety to the variables of the previous model to test its predictive role. Subsequently, both acute PSP intensity and frequency ceased to be significant and postsurgical anxiety became the only variable predicting PT3 (CPSP) (OR = 1.182, P = 0.026). Age, previous pain, and type of hysterectomy did not contribute to the prediction of an unfavorable PT in any of the models (Tables 4 and 5).

4. Discussion
This prospective cohort study followed women up to 5 years after hysterectomy and found that presurgical anxiety, emotional illness representations, and pain catastrophizing were risk factors for PSP. Higher postsurgical anxiety, acute pain intensity, and frequency increased the likelihood of a worst PT. These results are novel because there are no prospective studies on CPSP after hysterectomy with such a long follow-up and that consider the trajectory of pain over 2 long-term follow-up times (4 months and 5 years posthysterectomy). This study also adds to previous findings regarding pain at 48 hours75,76 and 4 months79 postsurgery.

4.1. Chronic postsurgical pain prevalence after hysterectomy
Almost half of women (48.2%) reported pain 4 months after hysterectomy. Five years later, 17.1% still complained of pain. Within hysterectomy studies, the longest follow-up period that we are aware of (2 years) revealed a CPSP prevalence of 24.1% and 16% in abdominal and vaginal hysterectomy, respectively.67 With a 1-year follow-up, Theunissen et al.100 reported a prevalence of 9%, although the criteria underlying CPSP definition was a cutoff level of 3 (NRS > 3), indicative of moderate or severe pain intensity. A retrospective study72 reported 31.5% prevalence and in a prospective study,5 4 months postsurgery and using a different CPSP definition (pain with impact on daily living), the prevalence rate was 16.7%. Two other studies described a prevalence of 14%103 and 26%,80 6 months posthysterectomy.

These figures clearly reveal large discrepancies in CPSP report, most likely due to the diverse range of follow-up times and CPSP definitions.69,80 The relatively higher prevalence of CPSP found in our study may be due to not having included only those women reporting moderate to severe pain (NRS > 3). On the other hand, our findings show that pain only interfered with the lives of some women and that interference was in the low-to-medium range.

4.2. Predictors of chronic postsurgical pain after hysterectomy
4.2.1. Demographic and clinical factors
In contrast to earlier findings,6,7,67,79,97,100,103 age and presurgical pain did not predict CPSP. Studies that found such relationships had shorter follow-ups, from 4 months to 2 years. Consistent with previous results,3,6,7,97,100,103 hysterectomy type did not predict CPSP albeit this does not support our earlier findings,79 nor Montes et al.67 conclusions. These results were unexpected and suggest that the strength of association of demographic and clinical factors probably diminishes with time, as psychological factors play an increasingly greater role. A similar conclusion was drawn previously in a postmastectomy study with a 3-year follow-up.6

Acute PSP intensity is a well-established key predictive factor,13,14,52,55,61,62 including in hysterectomy CPSP studies.6,80,97,100,103 Present results support this and further add PSP frequency, as previously found in this sample.76 To the best of our knowledge, only Fletcher et al.35 found pain frequency to be a CPSP predictor. These results highlight pain frequency as a new potential target in CPSP prevention. When adding postsurgical anxiety to the equation, both acute pain predictors ceased to be significant, which indicates both their shared variance and the unique contribution of postsurgical anxiety in the prediction of CPSP.
It is noteworthy that the acute postsurgical variables only predicted pain 5 years later. This suggests that to prevent long-term posthysterectomy pain, women should be screened and targeted throughout the perioperative period, and not only before surgery. Baseline assessments are useful for medium- and long-term pain prediction, whereas acute postsurgical variables seem to better predict long-term chronic pain.

### 4.2.2. The key role of psychological predictors

Presurgical anxiety and pain catastrophizing were predictive of an unfavorable PSP trajectory and CPSP, which corroborates previous findings. Presurgical anxiety, already shown to be a predictor of CPSP 4 and 6 months posthysterectomy, is also predictive of CPSP 5 years later. Furthermore, pain catastrophizing, a well-established CPSP psychological risk factor, emerges as a predictor for the first time in our hysterectomy studies.

Our results also confirm the important role of emotional representation of the surgical disease and of postsurgical anxiety. Other studies have demonstrated the impact of cognitive and affective responses triggered by illness on health outcomes, although the investigation of their predictive role on PSP has been scarce. Posturgical anxiety is such a response, present findings highlighting the need to address anxiety throughout the perioperative period, and not only before surgery.
Augmented activation of pain pathways may involve endogenous opioids, serotonin, and noradrenaline, presenting both excitatory and inhibitory actions on spinal cordafferent projection neurons and could be activated by psychological factors.11 Catastrophizing, anxiety, and other negative emotions are associated with reduced effectiveness in descendingpain-inhibitory systems, facilitating spinal nociception, and pain, whereas positive affect and self-regulatory skills inhibit spinal nociception and pain.28,39,88-90 The primary role of catastrophizing in pain modulation has been highlighted16,18,34,50,94 and suggested to be associated with diminished endogenous inhibition of pain coupled with central sensitization.63 Moreover, an association was shown between adaptive pain coping strategies and activation of descendingendogenous opioid systems1 and between depressed mood and impaired endogenous inhibition of pain.30

### 4.3. Practical and clinical implications

Because chronic pain is very difficult to treat, the importance of secondary prevention is highlighted.38,93 Besides, and despite the enthusiastic and promising findings of some trials focusing on preventive analgesic approaches,10,12,21,29,74,96 there is not yet any robust evidence to support the unequivocal efficacy of systemic drugs for CPSP prevention.9,17,19,43,53,60,63,86
Moreover, notwithstanding the advances in knowledge about pain genetics, it is not, until now, sustained influencing management, precisely through psychological interventions. Targeting them might yield adaptive and functional changes in brain pain processing, thus being an effective way to prevent CPSP development. 

The effectiveness of psychological interventions in pain is well established, although in the surgical field it is overdue. 

As substantial advances are being made in identifying risk factors for CPSP, the design and testing of preventive pain management strategies stemming from this evidence is warranted as well as the analysis of their cost-effectiveness. An enthusiastic and promising novelty in this field is the development and implementation of a Transitional Pain Service, a multidisciplinary program aimed at preventing and managing CPSP, which offers simultaneous psychological and pharmacological interventions. 

Psychological interventions have the power to impact supraspinal mechanisms involving higher pain centers, influencing endogenous modulation of pain, thereby improving endogenous analgesia, similarly to mechanisms underlying pharmacological analgesia. For example, cognitive-behavioral therapy has been related to changes in brain limbic activity, which has been implicated in improvement of anxiety and potentiation of descending modulatory inhibition of pain. Increased gray matter in prefrontal and parietal brain regions linked with chronic pain, was also observed after cognitive-behavioral therapy, being associated with a decrease in pain catastrophizing.

4.4. Limitations and strengths

This is a single-site and single-country study, which compromises its external validity, thus limiting the generalization of results. Sample attrition is a potential limitation, stemming from the longitudinal design, although our study showed high retention over time. Other potential limitation is the absence of a physical examination at T3 and T4, screening for inflammation or nerve injury. The breath of presurgical measures, embracing demographic, clinical, and a thorough range of psychological variables was a strength, along with the long-term follow-up of 5 years.

4.5. Conclusions

This study identified risk factors that can be easily screened before and after surgery, and are amenable to intervention. The design of timely and tailored interventions for women at risk of an unfavorable PSP trajectory after hysterectomy is a key priority. Incorporating risk-targeted multidisciplinary and feasible interventions focused on CPSP prevention into surgical routine practice is an important challenge that is likely to contribute to the improvement of pain management and patient care throughout the process of surgery.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Supplemental video content

Video content associated with this article can be found at http://links.lww.com/PAIN/A540.

Reference


