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Title: Associations between pain thresholds for heat, cold and pressure, and Pain Sensitivity Questionnaire (PSQ) scores in healthy women and in women with persistent pelvic pain

Running head: PSQ correlates with pain thresholds in PPP patients

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Conflicts of interest

None declared.

Significance

The PSQ reflects pain sensitivity in women with PPP and can be used as a non-invasive and painless way to assess this condition in clinical practice.

Abstract

Background: The Pain Sensitivity Questionnaire (PSQ) is a self-rating instrument developed as a time- and cost-saving alternative to quantitative sensory testing (QST). The aims of the study were to assess 1) the associations between PSQ scores and QST in women with persistent pelvic pain and in pain-free controls, and 2) to what extent demographic variables and psychological distress influenced PSQ scores.

Methods: Fifty-five healthy women and 37 women with persistent pelvic pain participated. All filled in the PSQ and Hospital Anxiety and Depression Scale and had QST (heat, cold, and pressure pain thresholds) performed on six locations on the body. Information on age, body mass index, smoking habits, and pain duration were collected. Principal component analysis and orthogonal partial least square regressions were used.

Results: The patients scored significantly higher on PSQ than the controls. Significant multivariate correlations between pain thresholds and PSQ scores were found only in the patient group. In the patient group, the heat and cold pain thresholds correlated more strongly with PSQ scores than the pressure pain threshold.

Conclusions: The PSQ score was significantly higher in pelvic pain patients, and correlations between QSTs and the PSQ were only found for patients.

1 Introduction

Chronic pain is a clinical challenge and the underlying mechanisms are not fully understood. Quantitative Sensory Testing (QST) for assessing pain sensitivity is widely used to explore the pain system under controlled settings. It is often done in advanced laboratory settings, and painful stimuli may not be accepted by the patient (Backonja et al., 2013; Rolke et al., 2006).

Assessment of pain sensitivity using a self-rating instrument may be an attractive alternative. The Pain Sensitivity Questionnaire (PSQ) is based on ratings of imagined painful everyday life situations (Ruscheweyh et al., 2012; Ruscheweyh, Marziniak, Stumpenhorst, Reinholz & Knecht, 2009). The PSQ has shown good reliability and can predict responses to experimental pain stimuli in healthy individuals (Ruscheweyh et al., 2009).

The PSQ was recently evaluated in a selected Swedish population to compare how pain sensitivity related to sociodemographic factors and pain characteristics such as the spread, intensity, frequency and duration of pain in patients with pain. A positive association between the spreading of pain on the body, pain intensity, age and female gender, and level of pain sensitivity as measured by PSQ was found (Larsson, Gerdle, Björk & Grimby-Ekman, 2017).

In women with persistent pelvic pain (PPP) symptoms usually originate from a combination of nociceptive, inflammatory, angiogenetic, neurovascular and neuropathic mechanisms, and sometimes manifest as dysmenorrhea or endometriosis (Kobayashi, Yamada, Morioka, Niiro & Shigemitsu, 2014). Pain hypersensitivity has been detected in women with PPP as assessed by QST (As-Sanie et al., 2013; Bajaj, Bajaj, Madsen, & Arendt-Nielsen, 2003; Grundström et al., 2019; He, Liu, Zhang, & Guo, 2010; Laursen, Bajaj, Olesen, Delmar, & Arendt-Nielsen, 2005; Stratton, Khachikyan, Sinaii, Ortiz & Shah., 2015). The hypersensitivity profile includes increased pain sensitivity (As-Saine et al., 2013; Bajaj et al., 2003) widespread generalized hyperalgesia (Grundström et al., 2019; He et al., 2010; Laursen et al., 2005), decreased pain thresholds (Grundström et al., 2019; He et al., 2010; Stratton et al., 2015), elevated sensory thresholds (He et al., 2010) and myofascial trigger points (Stratton et al., 2015).

In our previously published study concerning pain thresholds in women with PPP we found widespread alterations in pain thresholds in women with PPP that are indicative of central sensitization and a time-dependent correlation (Grundström et al., 2019). The present study represents a secondary analysis of the data from that study. The aims of this study were to assess 1) the associations between PSQ scores and QST in women with PPP and in pain-free controls, and 2) to what extent demographic variables and psychological distress influenced PSQ scores.

2 Methods

2.1 Study design and sample

This cross-sectional observational comparative study was conducted between December 2013 and June 2016 at the Department of Obstetrics and Gynecology at a central hospital and a university hospital in southeast Sweden. The study was approved by the Regional Ethics Board of Linköping University (Dnr 2013/19-3).

Women with symptoms that could indicate endometriosis and who had been referred for diagnostic laparoscopy were eligible for the study. Inclusion criteria were being 18-40 years of age, able to write, read and speak Swedish, and having had PPP, defined as self-reported pelvic pain for a period of four months or longer. Pregnant or breast-feeding women, or women who had a previously surgically verified diagnosis of endometriosis or any other diagnosed chronic pain syndrome, mental illness with anti-depressive medication or mental disability, or ongoing substance abuse were excluded.

During the study period, 46 women fulfilled the inclusion and exclusion criteria and were invited to participate by phone by the first author. They received detailed verbal and written information about the study and 40 agreed to participate. Three women did not come to the scheduled appointment, resulting in 37 participants with PPP. Before inclusion, all participants gave their written informed consent.

The control group consisted of 55 healthy women without PPP or other symptoms that might indicate endometriosis, or any other chronic pain syndrome or any medication that could have a known effect on pain thresholds. They were 18-40 years old and were enrolled through local announcements at the participating hospitals and the affiliated university. The experimental sessions were conducted between days 1-7 of the menstrual cycle in women who were not using hormonal contraceptives with the intention of minimizing the effect of menstrual cycle variability on the pain thresholds (Bajaj, Arendt-Nielsen, & Madsen, 2001; de Tommaso, 2011).

The experimental session was conducted within four weeks prior to planned surgery and included the measurements of pain thresholds for cold, heat and pressure. The result of the pain threshold measurement was not reported to the participant. After the pain threshold measurements, all participants completed the PSQ and the Hospital Anxiety and Depression

Scale (Zigmond & Snaith, 1983). Information on age, body mass index (BMI), smoking (dummy variable: coded smoking=1, non-smoking=0) and pain duration were also registered.

2.2 Measurements

Pain Sensitivity Questionnaire (PSQ)

The PSQ (Ruscheweyh et al., 2009) contains descriptions of 17 painful everyday situations, where the patients grade the imagined painfulness of each situation on a scale from 0 (not painful at all) to 10 (worst pain imaginable). Fourteen of the items relate to situations that are assessed as painful by a majority of healthy individuals. Three items are intended to serve as non-painful sensory reference as they describe situations that are usually not rated as painful (e.g. taking a warm shower) and are excluded when calculating the final score. The items cover a variety of pain types such as blunt, cold, hot and sharp, divided into different pain intensities at altered body sites (head, upper, and lower extremity)

The PSQ total score was calculated as the average rating of all but the three non-painful items. The PSQ minor score includes items referring to mildly painful situations and was calculated as the average rating of items 3, 6, 7, 10, 11, 12, and 14, while PSQ moderate score was calculated as the average rating of items 1, 2, 4, 8, 15, 16 and 17, and thereby consists of items referring to moderately painful situations. Thus, a higher PSQ score indicates higher pain sensitivity (Ruscheweyh et al., 2009).

The Swedish version of the PSQ has not yet been formally checked for reliability or validity. The questionnaire used in this study is the one used by Larsson et al. (2017), which was translated using an interactive forward-backward process.

Hospital anxiety and depression scale (HADS)

The HADS is a self-rating test assessing symptoms of anxiety and depression. The 14 items in the form are divided into two subscales (anxiety subscale and depression subscale), each one composed of seven questions. The range for each subscale is 0–21 points, with higher scores indicating more symptoms of anxiety and depression. The cut-off level of subclinical and clinically relevant levels of anxiety and depression is set at a score of eight. (Zigmond & Snaith, 1983). The instrument has been validated in a Swedish setting (Lisspers, Nygren, & Söderman, 1997).

Quantitative sensory testing (QST)

Pain thresholds were measured by QST (Mücke et al., 2016) according to the standardized protocol recommended by the German Research Network on Neuropathic Pain (Rolke et al., 2006) with the deviations that the ramped thermal stimuli were preset at 1.5°C/s and the pressure stimuli were applied with a rate of approximately 40 kPa/s. Pain thresholds for heat, cold and pressure were measured on six body sites; five sites commonly associated with the location of referred pain from the pelvic organs, and one control point. The locations were: a) the abdominal wall, seven cm lateral to the umbilicus on both sides, b) just above the symphysis pubis, five cm lateral to the midline on both sides, c) the medial plane of the low back just below the fifth lumbar vertebra, and d) on the dominant leg, four cm distally from the tuberositas tibiae (the control area).

The Medoc TSA II NeuroSensory Analyzer (Medoc Ltd. 1 Ha'dekel St. Ramat Yishai 30095 Israel) was used for determining heat and cold pain thresholds. The thermode with a surface area of 3x3 cm^2 was computer-controlled. The temperature increased from a baseline of 32°C to maximum 50°C or decreased to minimum 0°C with a preset rate of 1.5°C/s . The participants were instructed to press the stop button, which was connected to the computer, on detection of the first painful stimulus, to stop the stimulation. The computer registered the temperature of the thermode when stopped. Three measurements were performed on each location for each stimulus with an interval of 10 seconds and the arithmetic average of these three measurements presented the actual pain threshold. During the pause, the thermode returned to the baseline temperature of 32°C (Mücke et al., 2016).

A hand-held electronic algometer (Sometic AB, Hornby, Sweden) was used for pain pressure threshold measurements. The pressure surface area of the probe (1 cm^2) was applied to the body sites at a rate of approximately 40 kPa/s. When the women perceived the first sensation of pain, they said “stop”, upon which the examiner discontinued the stimulation. As for the thermo testing the pressure was applied three times on each location with a 10-second pause between the measurements. The pressure was registered in a protocol and the arithmetic average was calculated and used as the actual pressure pain threshold (Mücke et al., 2016). Since the differences in pain thresholds between the PPP and controls on all sites were almost similar and symmetric for bilateral sites (Grundström et al., 2019) and in order to minimize multiple testing, we choose to use a composite measure of pain threshold in the

analyses. The mean value for each modality (heat, cold and pressure) was calculated as the average of the pain thresholds on all locations and used in the analyses.

The testing order of the different body sites and the three stimuli were altered randomly in the participants. The majority of the QST measurements were performed by the first author, but three research nurses experienced in QST carried out the remaining measurements.

2.3 Statistical analysis

Basic statistical analyses were conducted with the software Statistica v 13.1 (Dell Software, 5 Polaris Way, Aliso Viejo, CA 92656, USA) and the SIMCA-P software version 13 (Umetrics, Sartorius Stedim Biotech, Umeå) was used to conduct the advanced multivariate data analysis (MVDA).

A between-group comparison of demographic, clinical characteristics, pain thresholds and questionnaire data was conducted by means of non-parametric tests; a Man-Whitney U-test was used for continuous data and Fisher's exact test for nominal data. The level of statistical significance was set at $p < 0.05$.

With classical statistical methods (e.g. regression), there is a risk of downplaying the interrelationships among different factors and thus reaching incorrect conclusions (Jansen et al., 2012). Classical methods also assume variable independence when interpreting results (Pohjanen et al., 2007) and it can be risky to consider one variable at a time (Eriksson, Byrne, Johansson, Trygg, & Vikström, 2013). If multicollinearity (i.e., high correlations) occurs among the X-variables, the regression coefficients become unstable and their interpretability breaks down. SIMCA-P+, in contrast to traditional statistical packages such as SPSS, uses the Nonlinear Iterative Partial Least Squares algorithm (NIPALS algorithm) when compensating for missing data – for variables/scales, max 60% missing data and for subjects, max 50% missing data. In the context of the obvious risks for multicollinearity problems (i.e. the pain thresholds were highly correlated, see results), we refrained from using multiple linear regression in the present study. Instead, we used advanced MVDA i.e., Principal Component Analysis (PCA) for the multivariate correlation analyses to detect outliers and Orthogonal Partial Least Square Regressions (OPLS) for the multivariate regressions using SIMCA-P+. MVDA does not require normal distribution (Wheelock & Wheelock, 2013). Variables were

unit variance (UV) scaled prior to the analyses. PCA was used to check for multivariate outliers; this was done since outliers can markedly bias regressions. R^2 describes the goodness of fit – the fraction of sum of squares of all the variables explained by a principal component. Q^2 describes the goodness of prediction – the fraction of the total variation of the variables that can be predicted by a principal component using cross validation methods (Eriksson, Johansson, Kettaneh-Wold & Trygg, 2006). Outliers were identified using two methods: 1) score plots in combination with Hotelling's T^2, and 2) distance to model in X-space (Eriksson et al., 2006). No extreme outliers were detected in the present study.

OPLS was used to explore the relative roles of the mean of pain thresholds for each stimulus together with background data (age, BMI, smoking and pain duration) to explain the variations in PSQ scores (Eriksson et al., 2006). The variable influence on projection (VIP) indicates the relative relevance of each X-variable. VIP ≥ 1.0 was considered significant if the VIP value had a 95% jack-knife uncertainty confidence interval non-equal to zero (Eriksson et al., 2006). P(corr) was used to note the direction of the relationship (positive or negative). P(corr) depicts the loading of each variable scaled as a correlation coefficient, thus standardizing the range from -1 to +1. P(corr) is stable during iterative variable selection and comparable between models. An absolute P(corr) > 0.4-0.5 is generally considered significant (Wheelock & Wheelock, 2013). For each regression, we report the R^2, Q^2, and the result (i.e., p-value) of a cross-validated analysis of variance (CV-ANOVA). In the present study we required significant CV-ANOVA for a regression to be significant. A certain variable was considered a significant variable when VIP > 1.0 and absolute p(corr) > 0.50.

3 Results

A total of 92 women completed the study; 37 women with PPP and 55 healthy controls. The median duration of pain among the women with PPP was 36 months (range 4-162 months). The demographics, clinical characteristics, heat pain thresholds (HPT), cold pain thresholds (CPT) and pressure pain thresholds (PPT) and the scores of the HADS and PSQ forms are presented in Table 1. Hence, the women in the PPP group were significantly younger, had a lower parity and were more often smokers than the women in the control group. The women with PPP had significantly lower mean pain thresholds (heat, cold and pressure) and scored higher on symptoms of anxiety and depression in HADS. The three PSQ variables (minor, moderate and total) were higher in the PPP group than in the control group.

Taking all subjects together, significant bivariate correlations existed between the PSQ variables and the three pain thresholds and the two psychological distress variables (Table 2).

In the next step the variables that in a multivariate context were most strongly correlated with the three PSQ variables were determined. The means of the three pain thresholds were highly intercorrelated (r:0.66-0.86) indicating a considerable risk for multicollinearity. Highly significant regressions of the three PSQ scores in all subjects taken together (n=92) were obtained (Table S1). The three regressions showed, as expected, important similarities. The two thermal pain thresholds were the most important regressors in the three regressions of the PSQ variables. HADS depression (HADS-D) was the third most important regressor followed by PPT. HADS anxiety (HADS-A) was the fifth most significant regressor of PSQ minor while age, BMI, and smoking were not significant regressors.

Regressions in each of the two groups were performed. In the patient group (n=37) highly significant regressions were obtained (Table 3). In fact, these explained variations (R^2) were higher (R^2: 0.52-0.57) than in all subjects taken together (R^2: 0.26-0.41). In this group, the two thermal pain thresholds were equally important in the three regressions. PPT was the third most important regressor for PSQ total and PSQ minor. BMI was a regressor of both PSQ total and PSQ moderate. Also, age and pain duration were significant regressors of PSQ moderate.

In contrast to the PPP group, no significant regressions of the PSQ variables were obtained for the control group (Table S2). The three non-significant regressions had in common that the two HADS variables tended to be especially important regressors.

4 Discussion

This study showed that the three PSQ variables were significantly higher in patients than in controls. In the patient group, significant multivariate correlations between pain thresholds and the three PSQ variables were found. These relationships were not found for the control group. In the PPP group, the thermal pain thresholds correlated more strongly with PSQ variables than PPT.

4.1 PSQ in persistent pain patients and in healthy controls

Recently it has been reported that women with PPP have significantly reduced thermal and pressure pain thresholds (Grundström et al., 2019). Tuna et al. (2018a) reported that chronic pain patients had significantly higher PSQ total and PSQ minor compared to healthy controls (Tuna, Van Obbergh, Van Cutsem, & Engelman, 2018a), and in lumbar disc herniation patients, significantly higher scores for PSQ total, moderate and minor compared to healthy controls were found (Azimi et al., 2016). Moreover, in a population study, PSQ total was significantly higher in individuals with pain than in pain-free individuals, and positive correlations were found between PSQ and pain intensity and the number of pain sites (i.e., higher in widespread pain) (Larsson et al., 2017). Positive correlations between PSQ variables and pain intensity have been found in patient groups (Ruscheweyh et al., 2009; Ruscheweyh et al., 2012). Pain intensity was not registered in the present study to explore this relationship.

The present study confirmed previous data (Ruscheweyh et al., 2009) where no significant correlations were found between PSQ scores and pain thresholds in healthy subjects. When analyzing the individual items of their composite pain threshold variable, a positive correlation ($r=0.34$, $p<0.05$) between PSQ minor and CPT in healthy subjects was found (Ruscheweyh et al., 2009). Moreover, they reported that PSQ ratings correlated positively with experimental pain intensity (Ruscheweyh et al., 2009).

In another study using the Norwegian version of PSQ, no significant correlations were found between pain threshold and any of the three PSQ variables in healthy subjects (Valeberg, Pedersen, Girotto, Christensen, & Stubhaug, 2017) confirming the present study. The authors suggested that PSQ did not reflect pain threshold but that it was associated with supra-threshold intensities (Valeberg et al., 2017). PSQ has been suggested as descriptor of "general pain sensitivity" representing healthy subjects (Ruscheweyh et al., 2009). Based on the literature PSQ seems to be lower in healthy subjects, but the lack of relationships between PSQ and pain thresholds in healthy subjects is a limitation of the instrument.

In patients with chronic pain the PSQ scores correlate with pain thresholds (Ruscheweyh et al., 2012). In patients with subacute shoulder pain, weak significant correlations were found with PPT outside the painful area but not with HPT (Coronado &

George, 2018). Our study using advanced multivariate techniques confirms correlations between PSQ scores and pain thresholds for three stimuli in female patients with PPP.

4.2 Regressors of PSQ variables

Significant regressions were obtained for all subjects taken together indicating that pain thresholds for thermal stimuli, HADS-D and PPT were significant regressors of the three PSQ variables; the explained variations (R^2) ranged from 26 to 41%. However, from the separate analyses of the patient group and the control group a more complicated picture emerged. In the patient group, significant regressions existed which explained the slight majorities of the variations in the three PSQ variables (52-57%), while none of the regressions in the control group were significant.

Both the analysis of all subjects pooled and in the patient group separately clearly showed that the two thermal thresholds were the most important regressors of the investigated PSQ variables, both in all subjects taken together and in the patient groups separately. PPT was also a significant regressor in all subjects and in two out of three regressions in the patient group. PPT was less strongly associated, as previously described (Ruscheweyh et al., 2012). Hence, based upon our results, PSQ appears to be more associated with thermal pain thresholds than mechanical stimuli (pressure) in patients with PPP. The reason for this is not clear and need to be confirmed in future studies; it may reflect properties of the PSQ instrument or a physiological result. Only a limited number of studies have compared different pain thresholds. Our results agree with Ruscheweyh et al 2012 but disagree with other studies (Valeberg et al., 2017; Coronado & George, 2018).

4.3 Influence of background variables and psychological distress on PSQ scores

It has been argued that PSQ scores are independent of age and gender both in healthy subjects and in patients with chronic pain (Bjørnnes et al., 2018; Ruscheweyh et al., 2009; Ruscheweyh et al., 2012). However, the results concerning gender have been challenged in a study of patients with lumbar spinal stenosis which reported significantly higher total PSQ and PSQ minor in women than in men when controlling for various relevant factors (Kim et al., 2013). Moreover, our large population-based study found that PSQ total correlated significantly with both age and sex (higher in women) (Larsson et al., 2017). In the present

study, neither the bivariate correlations nor the multivariate regressions in all subjects taken together showed age dependence for the PSQ variables investigated. A recent study reported conflicting results for age in patients scheduled for spine surgery (Tuna, Boz, Van Obbergh, Lubansu, & Engelman, 2018b). Hence, PSQ dependency on age and gender in patients and individuals with chronic pain needs further investigation.

The PSQ has shown that both in chronic pain patients and in healthy controls, anxiety and catastrophizing correlated significantly with PSQ minor while no significant correlations existed for depressive symptoms (Ruscheweyh et al., 2012). In major depression patients, higher PSQ minor scores have been found as well as lower PPT (Hermesdorf et al., 2016). In patients with subacute shoulder pain, significant correlations were found between PSQ (total and minor) and resilience, anxiety and negative affect but not with e.g. depressive symptoms (Coronado & George, 2018). In the bivariate correlations of all subjects we found that both HADS-D and HADS-A correlated significantly with the three PSQ variables. In a multivariate context, only HADS-D was a significant regressor - more important than PPT. However, in the patient group these two variables (HADS-D and HADS-A) were not significant regressors. The non-significant regressions in the control group indicated that psychological distress variables were more important than pain thresholds for the PSQ scores.

4.4 Limitations

There were some limitations of the study. Firstly, the answering of questionnaires followed QST, which might influence the PSQ scoring. However, the participants were not informed about the results of the QST. Secondly, **only experimental pain thresholds but no experimental pain** intensity ratings were used in the present study. Thirdly, our results need to be confirmed in larger cohorts even though the present sample size in relation to number of variables was sufficient for PCA and OPLS. The literature on the subject was scanty when the study started, so no sample size calculation could be done. We therefore relied on data from the very few papers that addressed the issue.

A strength of this study was the use of MVDA that utilizes the data set's properties optimally. Classical statistical methods such as multiple linear regression used in several of the studies referred to above can quantify the level of relations of individual factors but disregard interrelationships among different factors and thereby ignore system-wide aspects

(e.g., when a group of variables correlates with the investigated dependent outcome) (Jansen et al., 2012). Such classical methods also assume variable independence when interpreting results (Eriksson et al., 2013; Pohjanen et al., 2007). In the context of our aims, there is an obvious risk of multicollinearity problems. Therefore, we refrained from using multiple linear regression. Instead, we used statistical methods taking advantage of intercorrelated regressors. Moreover, it is not possible, as in multiple linear regression, to isolate the effects for a certain variable upon the dependent life impact variables regressed.

5 Conclusions

Pain sensitivity according to PSQ was significantly higher in the patients than in the controls. In the patient group, significant multivariate correlations were found between PSQ and QST (heat, cold and pressure pain thresholds). No correlations were seen in the control group. Hence, the validity of PSQ in the context of pain sensitivity in healthy subjects is unclear. In the PPP group, PSQ had a stronger association with the thermal pain threshold than with pressure pain thresholds. The fact that PSQ showed strong multivariate correlations with pain thresholds in PPP indicate that it can be used as a non-time-consuming way to indicate the level of pain sensitivity in clinical practice. .

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Author contributions

Preben Kjølhede and Hanna Grundström designed and conducted the study. Hanna Grundström led data collection. All authors contributed to writing the draft of the manuscript. Hanna Grundström and Preben Kjølhede wrote the introduction and methods, Björn Gerdle and Britt Larsson carried out the statistical analysis and wrote the results. All authors contributed to the interpretation and discussion of results. Comments on the manuscript and approval of the final version were given by all authors.

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Legends and footnotes for tables

Table 1

Legend:
Table 1. Demographic, clinical characteristics, pain thresholds for heat, cold and pressure, HADS and PSQ subscale scores of women with persistent pelvic pain and healthy controls.

Footnote:
Figures denote mean and ±SD; range, or number of women and (%). BMI – body mass index. HADS=Hospital Anxiety and Depression Scale. PSQ=Pain Sensitivity Questionnaire

Table 2

Legend:
Table 2. Bivariate correlations (r and p-value presented) between the three PSQ variables and the other variables investigated in all subjects taken together (n=92 except for the variable pain duration: n=37) and in the PPP and control group.

Footnote:

HPTm= mean value of heat pain thresholds; CPTm= mean value of cold pain thresholds, PPTm= mean value of pressure pain thresholds; HADS= Hospital anxiety and depression scale; HADS-D= depression scale of HADS; HADS-A= anxiety scale of HADS; BMI= body mass index; Smoking=currently smoking (i.e. dummy variable: smoking=1, non-smoking=0).

Table 3

Legend:
Table 3. OPLS analyses of PSQ total (left part, PSQ moderate (middle part) and PSQ minor (right part) in the patient group (n=37).

Footnote:
Variables with VIP > 1.0 and absolute p(corr)>0.50 are significant and shown in bold type. The sign of p(corr) indicates the direction of the correlation with the dependent variable (+ = positive correlation; - = negative correlation). The four bottom rows of each regression report number of patients included in the regression (n), R^2, Q^2, and p-value of the CV-ANOVA. HPTm= mean value of heat pain thresholds; CPTm= mean value of cold pain thresholds, PPTm= mean value of pressure pain thresholds; BMI= body mass index; Smoking=currently smoking (i.e. dummy variable: smoking=1, non-smoking=0); HADS= Hospital anxiety and depression scale; HADS-D= depression scale of HADS; HADS-A= anxiety scale of HADS.

Table S1

Legend:
Table S1. OPLS analyses of PSQ total (left part, PSQ moderate (middle part) and PSQ minor (right part) in all subjects taken together (n=92)). The variable pain duration was omitted since most subjects i.e. the controls had missing data for this variable.

Footnote:
Variables with VIP > 1.0 and absolute p(corr)>0.50 are significant and shown in bold type. The sign of p(corr) indicates the direction of the correlation with the dependent variable (+ = positive correlation; - = negative correlation). The four bottom rows of each regression report number of patients included in the regression (n), R^2, Q^2, and p-value of the CV-ANOVA. HPTm= mean value of heat pain thresholds; CPTm= mean value of cold pain thresholds, PPTm= mean value of pressure pain thresholds; BMI= body mass index; Smoking=currently smoking (i.e. dummy variable: smoking=1, non-smoking=0); HADS= Hospital anxiety and depression scale; HADS-D= depression scale of HADS; HADS-A= anxiety scale of HADS.

Table S2

Legend:
Table S2. OPLS analyses of PSQ total (left part, PSQ moderate (middle part) and PSQ minor (right part) in the control group (n=55).

Footnote:
Variables with VIP > 1.0 and absolute p(corr)>0.50 are significant and shown in bold type. The sign of p(corr) indicates the direction of the correlation with the dependent variable (+ = positive correlation; - = negative correlation). The four bottom rows of each regression report number of patients included in the regression (n), R^2, Q^2, and p-value of the CV-ANOVA. HPTm= mean value of heat pain thresholds; CPTm= mean value of cold pain thresholds, PPTm= mean value of pressure pain thresholds; BMI= body mass index; Smoking=currently

smoking (i.e. dummy variable: smoking=1, non-smoking=0); HADS= Hospital anxiety and depression scale; HADS-D= depression scale of HADS; HADS-A= anxiety scale of HADS.

Table 1. Demographic, clinical characteristics, pain thresholds for heat, cold and pressure, HADS and PSQ subscale scores of women with persistent pelvic pain and healthy controls.

Variable		Women with persistent pelvic pain (n=37)	Control group of healthy women (n=55)	*p*-value
Age (years)		26.4±5.9; 18-40	30.2±5.6;18-40	0.002
Parity (no. of deliveries)		0.4±0.9; 0-3	1.1±1.2; 0-5	0.003
BMI (kg/m^2)		24.6±4.8; 18-33	24.2±3.8; 18-35	0.796
Currently smoking (no. of women)		9 (24.3)	2 (3.6)	0.006
Hormonal birth control medication (no. of women)		20 (54.1)	34 (61.8)	0.520
Mean pain threshold	Heat (°C)	43.9±3.8; 36.9-49.7	47.5±2.0; 40.9-50.0	<0.001
	Cold (°C)	13.1±8.6; 0-28.1	3.9±5.5; 0-25.2	<0.001
	Pressure (kPa)	324 ±150; 95-732	548±174; 237-1119	<0.001
HADS	Anxiety score	9.9±4.4; 2-21	4.7±3.4; 0-14	<0.001
	Anxiety score < 8	12 (32%)	44 (80%)	
	Anxiety score 8-10	8 (22%)	7 (13%)	
	Anxiety score 11-14	11 (30%)	4 (7%)	
	Anxiety score >15	6 (16%)	0 (0%)	
	Depression score	7.9±4.3; 1-20	2.3±2.4; 0-9	<0.001
	Depression score < 8	17 (46%)	51 (93%)	
	Depression score 8-10	10 (27%)	4 (7%)	
	Depression score 11-14	8 (22%)	0 (0%)	
	Depression score >15	2 (5%)	0 (0%)	
PSQ score	Minor	3.2±1.5; 1-7	2.2±0.9; 0-4	<0.001
	Moderate	5.8±1.6; 3-9	4.7±1.4; 1-8	0.002
	Total	4.5±14; 2-8	3.4±1.0; 1-6	<0.001

Figures denote mean and ±SD; range, or number of women and (%). BMI – body mass index. HADS=Hospital Anxiety and Depression Scale. PSQ=Pain Sensitivity Questionnaire

Table 2. Bivariate correlations (r and p-value presented) between the three PSQ variables and the other variables investigated in all subjects taken together (n=92 except for the variable pain duration: n=37) and in the PPP and control group.

		PSQ total			**PSQ moderate**			**PSQ minor**		
Variables	**Correlations**	All (n=92)	PPP (n=37)	Controls (n=55)	All (n=92)	PPP (n=37)	Controls (n=55)	All (n=92)	PPP (n=37)	Controls (n=55)
HPTm	r	-0.55	-0.63	-0.09	-0.44	-0.53	-0.06	-0.59	-0.65	-0.12
	p-value	<0.001	<0.001	0.500	<0.001	0.001	0.638	<0.001	<0.001	0.403
CPTm	r	0.50	0.56	0.08	0.41	0.44	0.10	0.53	0.60	0.03
	p-value	<0.001	<0.001	0.548	<0.001	0.006	0.447	<0.001	<0.001	0.829
PPTm	r	-0.43	-0.43	-0.15	-0.36	-0.34	-0.12	-0.44	-0.46	-0.16
	p-value	<0.001	0.008	0.269	<0.001	0.037	0.366	<0.001	0.004	0.235
HADS-A	r	0.37	0.19	0.18	0.25	-0.03	0.16	0.45	0.38	0.18
	p-value	<0.001	0.260	0.180	0.016	0.877	0.251	<0.001	0.019	0.177
HADS-D	r	0.47	0.27	0.34	0.43	0.23	0.36	0.46	0.31	0.24
	p-value	<0.001	0.086	0.011	<0.001	0.177	0.007	<0.001	0.064	0.078
Pain duration	r		-0.27			-0.41			-0.09	
	p-value		0.109			0.011			0.613	
Smoking	r	-0.09	-0.25	-0.27	-0.13	-0.32	-0.24	-0.03	-0.16	-0.25
	p-value	0.372	0.129	0.050	0.209	0.057	0.078	0.746	0-353	0.065
Age	r	-0.11	0.30	-0.25	-0.07	0.35	-0.20	-0.13	0.21	-0.28
	p-value	0.319	0.067	0.062	0.500	0.032	0.140	0.216	0.202	0.038
BMI	r	0.21	0.46	0.01	0.21	0.45	0.03	0.19	0.40	-0.02
	p-value	0.043	0.005	0.940	0.052	0.005	0.843	0.070	0.014	0.882

HPTm= mean value of heat pain thresholds; CPTm= mean value of cold pain thresholds, PPTm= mean value of pressure pain thresholds; HADS= Hospital anxiety and depression scale; HADS-D= depression scale of HADS; HADS-A= anxiety scale of HADS; BMI= body mass index; Smoking=currently smoking (i.e. dummy variable: smoking=1, non-smoking=0).

Table 3. OPLS analyses of PSQ total (left part, PSQ moderate (middle part) and PSQ minor (right part) in the patient group (n=37).

PSQ total			**PSQ moderate**			**PSQ minor**		
X-Variables	VIP	p(corr)	X-Variables	VIP	p(corr)	X-Variables	VIP	p(corr)
CPTm	**1.60**	**0.91**	**HPTm**	**1.33**	**-0.66**	**CPTm**	**1.60**	**0.92**
HPTm	**1.59**	**-0.90**	**CPTm**	**1.32**	**0.65**	**HPTm**	**1.58**	**-0.91**
PPTm	**1.21**	**-0.69**	**BMI**	**1.23**	**0.61**	**PPTm**	**1.26**	**-0.72**
BMI	**1.10**	**0.62**	**Age**	**1.13**	**0.56**	BMI	0.99	0.57
HADS-D	0.79	0.45	**Pain duration**	**1.05**	**-0.52**	HADS-D	0.92	0.53
Age	0.58	0.33	Smoking	0.83	-0.41	HADS-A	0.56	0.32
Pain duration	0.36	-0.20	PPTm	0.83	-0.41	Age	0.41	0.24
HADS-A	0.33	0.19	HADS-D	0.42	0.21	Pain duration	0.14	-0.08
Smoking	0.20	-0.11	HADS-A	0.19	-0.10	Smoking	0.10	-0.05
n	37		n	37		n	37	
R^2	0.52		R^2	0.57		R^2	0.52	
Q^2	0.45		Q^2	0.44		Q^2	0.42	
CV ANOVA p-value	<0.001		CV ANOVA p-value	<0.001		CV ANOVA p-value	<0.001	

Variables with VIP > 1.0 and absolute p(corr)>0.50 are significant and shown in bold type. The sign of p(corr) indicates the direction of the correlation with the dependent variable (+ = positive correlation; - = negative correlation). The four bottom rows of each regression report number of patients included in the regression (n), R^2, Q^2, and p-value of the CV-ANOVA.

HPTm= mean value of heat pain thresholds; CPTm= mean value of cold pain thresholds, PPTm= mean value of pressure pain thresholds; BMI= body mass index; Smoking=currently smoking (i.e. dummy variable: smoking=1, non-smoking=0); HADS= Hospital anxiety and depression scale; HADS-D= depression scale of HADS; HADS-A= anxiety scale of HADS.