**Universidade do Minho**
Escola de Psicologia

Patrícia de jesus Ribeiro Pinto

# Psychological Predictors of Acute and Persistent Postsurgical Pain in patients submitted to Hysterectomy and to Total Knee and Hip Arthroplasty

Abril de 2012

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# Psychological Predictors of Acute and Persistent Postsurgical Pain in patients submitted to Hysterectomy and to Total Knee and Hip Arthroplasty

Tese de Doutoramento em Psicologia
Especialização em Psicologia da Saúde

Trabalho realizado sob a orientação da
**Professora Doutora Teresa McIntyre**
e do
**Professor Doutor Armando Almeida**
e da
**Professora Doutora Vera Araújo-Soares**

Abril de 2012

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**Orientadores: Professora Doutora Teresa McIntyre, Professor Doutor Armando Almeida e Professora Doutora Vera Araújo-Soares**

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***“Belief becomes biology”***

Cousins, 1989

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**Abstract**

Pain is a complex human subjective and idiosyncratic experience. After surgery, acute pain is the most common and expected problem. The development of persistent post-surgical pain (PPSP) is an undesirable but common adverse outcome after surgery. Surgery provides a unique opportunity to examine the influence and predictive nature of a variety of demographic, clinical and psychological factors on subsequent pain persistence. Psychological factors have emerged as consistent predictors of acute and persistent post-surgical pain. Factors identified to date include negative emotions, coping strategies and surgery-specific beliefs or expectations, suggesting that perceptual/cognitive, emotional, and behavioral factors play key roles in influencing post-surgical pain experience.

The aim of this thesis was to explore and examine, prospectively, the joint role of demographic, clinical and psychological variables as predictors of the following outcomes: a) acute post-surgical pain; b) PPSP; c) post-surgical rescue analgesia provision; and, d) post-surgical anxiety. A consecutive sample of 203 women (age: 51.0 ± 9.22) undergoing hysterectomy for benign disorders and of 130 patients (age: 65.2 ± 7.97) scheduled for total knee and hip arthroplasty (TKA and THA), were evaluated in a single site prospective study with assessments 24h prior to surgery (T1), 48h (T2), and 4/6 months (T3) after surgery. In the five studies conducted, several demographic and clinical variables were evaluated. Psychological variables assessed were anxiety, depression, pain coping skills (e.g. pain catastrophizing), surgical fears, optimism and illness representations.

Acute post-surgical pain, in the hysterectomy sample (study 1), was better predicted by an integrative model which included younger age, pre-surgical pain severity, pain due to other causes, pre-surgical anxiety and pain catastrophizing. The results indicated the full mediation role of pre-surgical pain catastrophizing between pre-surgical anxiety and post-surgical pain intensity, which is a novel finding. As pre-surgical anxiety increases, women tend to catastrophize more about pain and this seems to predict increased acute post-surgical pain intensity. Study 2 examined post-surgical rescue analgesia (RA) provision in an effort to understand the variables that influence clinical decisions on RA provision. The results indicated that RA provision may be influenced not only by clinical variables (e.g. post-surgical pain intensity) but also by patient pre-surgical fear, pain catastrophizing and post-surgical anxiety. These psychological factors are likely

to influence patient-provider interactions. Study 3 investigated the predictors of PPSP among women submitted to hysterectomy, with age, pain due to other causes and type of hysterectomy emerging as predictors. Pre-surgical psychological factors, such as anxiety, emotional illness representations and pain catastrophizing, were found to be additional risk factors for PPSP. Post-surgical anxiety added to the prediction of PPSP.

In arthroplasties (study 4), the model which predicted acute pain in hysterectomy could not be replicated and optimism was the only significant predictor of pain intensity 48 hours after surgery. In this sample, there was also a strong association between post-surgical anxiety and acute pain after surgery. Moreover, post-surgical anxiety was predicted by a similar model to the one found for the prediction of acute post-surgical pain. Pre-surgical optimism, emotional representations and pre-surgical anxiety were significant predictors of post-surgical anxiety (T2). After total knee and hip arthroplasty (Study 5), PPSP seems to be better predicted by pre-surgical (T1) and post-surgical anxiety, as well as by acute post-surgical pain intensity (T2).

In conclusion, the five studies conducted highlight the role of psychological factors in crucial aspects of the surgical experience: a) acute and persistent post-surgical pain; b) rescue analgesia administration; and, c) post-surgical anxiety. These results have important implications for patient care at pre-surgery and during the post-surgery follow up. The data points to the need to assess psychological factors at different stages of the surgery process, and the important role of Health Psychologists within acute pain team services. These professionals can contribute to a multidisciplinary and systemic approach in acute pain management and control, which aims at preventing the development of persistent post-surgical pain.

**Resumo**

A dor é uma experiência humana complexa e idiossincrática. A dor aguda é o problema mais comum e esperado após uma cirurgia. Por sua vez, o desenvolvimento de dor persistente pós-cirúrgica (DPPC) é uma ocorrência adversa indesejável mas comum. A cirurgia é um excelente modelo para examinar a influência e a natureza preditiva de uma variedade de factores no desenvolvimento subsequente de dor persistente. No contexto da investigação sobre dor cirúrgica, os factores psicológicos têm emergido como preditores consistentes de dor pós-cirúrgica aguda e persistente. Os factores identificados até agora incluem emoções negativas, estratégias de *coping* e crenças ou expectativas específicas à cirurgia, sugerindo que os factores perceptuais/cognitivos, emocionais e comportamentais desempenham um papel chave na influência da experiência de dor pós-cirúrgica.

O objectivo desta tese foi de explorar e examinar prospectivamente a influência de um conjunto de variáveis demográficas, clinicas e psicológicas como predictores dos seguintes resultados: a) dor aguda pós-cirúrgica; b) DPPC; c) administração pós-cirúrgica de analgésicos de resgate; e d) ansiedade pós-cirúrgica. Uma amostra consecutiva de 203 mulheres (idade: 51.0 ± 9.22) com histerectomia programada devido a causas benignas e uma amostra consecutiva de 130 pacientes (idade: 65.2 ± 7.97) agendados para a realização de artroplastia de joelho ou anca, foram avaliados num estudo prospectivo 24 horas antes da cirurgia (T1), 48 horas (T2) e 4/6 meses (T3) depois da cirurgia. Nos cinco estudos descritos, diversas variáveis demográficas e clínicas foram analisadas. As variáveis psicológicas avaliadas foram a ansiedade, a depressão, estratégias de confronto da dor (ex: catastrofização), os medos cirúrgicos, o optimismo e as representações da doença subjacente à realização da cirurgia.

Na amostra de mulheres submetidas a histerectomia (estudo 1) foi identificado um modelo integrativo preditor da dor aguda pós-cirúrgica que incluía a idade (mais jovem), a intensidade da dor pré-cirúrgica, a dor devido a outras causas, a ansiedade pré-cirúrgica e a catastrofização da dor. Os resultados identificaram ainda o papel mediador da catastrofização da dor entre a ansiedade pré-cirúrgica e a intensidade da dor pós-cirúrgica, achado inovador na literatura deste dominio. À medida que aumenta a ansiedade pré-cirúrgica, as mulheres tendem a catastrofizar mais acerca da dor e isso parece associar-se a um aumento da intensidade da dor aguda pós-cirúrgica. O estudo 2 debruçou-se sobre o consumo pós-cirúrgico de analgesia de resgate, no

sentido de compreender as variáveis que influenciam as decisões clínicas subjacentes à provisão de analgesia de resgate. Os resultados indicaram que a provisão de analgesia de resgate pode ser influenciada não só por factores clínicos (intensidade da dor pós-cirúrgica), mas também pelos medos pré-cirúrgicos, catastrofização da dor e ansiedade pré-cirúrgica. Estes factores psicológicos têm o potencial de influenciar as interacções entre os pacientes e os prestadores de cuidados. O estudo 3 investigou os preditores de DPPC nas pacientes submetidas a histerectomia, evidenciando-se a idade, a dor devido a outras causas e o tipo de histerectomia como preditores. Os factores psicológicos pré-cirúrgicos como a ansiedade, as representações emocionais da doença subjacente à cirurgia e a catastrofização da dor, surgiram como factores de risco adicionais para o desenvolvimento de DPPC. A ansiedade pós-cirúrgica revelou-se como um factor adicional para a predicção da DPPC.

Nas artroplastias (estudo 4), o modelo predictor da dor aguda após a histerectomia não se confirmou e o optimismo foi o único predictor significativo da intensidade da dor 48 horas após a cirurgia. Nesta amostra, observou-se também uma forte associação entre a ansiedade pós-cirúrgica e a dor aguda pós-cirúrgica. A ansiedade pós-cirúrgica também foi predicta a partir dum modelo semelhante ao utilizado para a previsão da dor aguda pós-cirúrgica. O optimismo pré-cirúrgico, a representação emocional da doença e a ansiedade pré-cirúrgica, revelaram-se como preditores significativos dos níveis de ansiedade após estas cirurgias. Por sua vez, os níveis de ansiedade pré e pós-cirúrgica, bem como a intensidade da dor pós-cirúrgica, foram preditores de DPPC após artroplastia total do joelho e da anca (estudo 5).

Em conclusão, os cinco estudos apresentados evidenciam o papel dos factores psicológicos nos seguintes aspectos da experiência cirúrgica: a) dor aguda e dor persistente pós-cirúrgica; b) administração de analgesia de resgate; e, c) ansiedade pós-cirúrgica. Estes resultados têm implicações clinicas importantes no acompanhamento dos pacientes no momento pré-cirúrgico e no seguimento pós-cirúrgico. Os dados salientam a necessidade de avaliação dos factores psicológicos ao longo dos varios momentos do processo cirúrgico, assim como a importância da colaboração de Psicólogos da Saúde nos serviços de dor aguda. Estes profissionais podem contribuir para uma abordagem multidisciplinar e sistémica na gestão e controlo da dor, de forma a prevenir o desenvolvimento de dor persistente pos-cirúrgica.

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Chapter 1

# Introduction

# 1. INTRODUCTION

*"The aim of the wise is not to secure pleasure, but to avoid pain."*

Aristotle

## 1.1. Pain – a multidimensional experience

Pain is a complex human experience (Chapman & Okifuji, 2004). The symptom of pain is common to almost any illness and is the most usual reason for seeking medical care (Schug, 2011). It is a totally subjective phenomenon being better defined as "... whatever the experiencing person says it is and exists whenever he/she says it does" (McCaffery, 1989).
Acute pain and reversible inflammatory pain have a biological protective function, usually supposed to work as an early warning aimed to protect the body from tissue damage and to promote organism protection from additional insult by initiating withdrawal or recuperative behavior, fostering body healing (McNally, 1999; Almeida, Leite-Almeida, & Tavares, 2006; Basbaum, Bautista, Scherrer, & Julius, 2009). Thus, it works like an alarm system or a warning device, activated in face of the occurrence of potential damage (Scholz & Woolf, 2002).

### 1.1.1. Pain Theories and Conceptualization of Pain: a brief review

Early pain theories described pain as an unidimensional phenomenon, resulting directly from a physical injury or pathology and being proportional to its nature and extent. This perspective did not acknowledged other potential influences on pain perception. Factors such as emotions or cognitions were kept aside, and best considered as mere reactions or consequences of pain (Melzack & Wall, 1996). If pain was reported and the concomitant physical injury or disease could not be objectively found, then those individuals were rather conceived as psychiatric patients and treated like that (Melzack, 1999b). Pain was conceived as a result of nociception. Nociception refers to the objective evidence of body damage, caused by a lesion, injury or pathology and the subsequently triggered neurobiological reactions (Rainville, 2002). Nociception is conceived as a non-conscious process (Chapman, 2004), that consists of the physiological detection of tissue damage through the activation of specialized sensory receptors, called nociceptors, attached to A delta (Aδ) and C fibres (Melzack, 1999b). But pain, a conscious phenomenon, is not only a primitive sensory message of tissue trauma, but a complex psychological experience (Chapman, 2004). Indeed, the role of psychosocial factors within the pain experience is important in acute and chronic pain settings as well as in the transition from acute to chronic pain (Linton, 2000; Pincus et al., 2002).

Nowadays there is an absolute consensus in recognizing pain as a multidimensional subjective experience consisting of complex interactions between sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions. This is in accordance with the gate control theory (Melzack & Casey, 1968), as well as the neuromatrix theory (Melzack, 1999a) of pain, also falling under the cognitive–behavioral model and the biopsychosocial approach to pain (Asmundson & Wright, 2004).

Overall, the gate control theory states that pain is influenced by higher brain centers responsible for psychological processes, such as cognitions (thoughts, beliefs and expectations) and emotions (such as anxiety and depression). In addition, this theory advocates the existence of mechanism acting within the dorsal horn of the spinal cord, which would act as a gate, thus opening and closing according to the type of stimuli arriving. Hence, the gate is supposed to further open by activation of fibers that convey noxious stimuli whereas it would be closed by activation of non-nociceptive fibers. Activation of these latter fibers, for instance by rubbing the skin, has the potential of inhibiting pain that arises from the stimulation of nociceptive fibers. The influence of such a gate is not only at the peripheral afferent nerve activity level, but also at the central pathways levels. In fact, central pathways, descending from the brain, may also open or close the gate, modulating the transmission of nociceptive information at spinal cord level (Almeida et al., 2006; Ossipov, Dussor, & Porreca, 2009). Moreover, psychological factors would exert an influence on pain perception at this level, via descending pathways that modulate spinal nociceptive transmission to the brain. In sum, gate control theory emphasizes the modulation of inputs at the spinal dorsal horns level by the dynamic role of the brain in pain process (Melzack, 1999a).

The neuromatrix theory of pain, in turn, considers pain as the result of synthesis and processing of inputs from a widely distributed network of brain neurons, called the body–self neuromatrix, which integrates the same cognitive-evaluative, sensory-discriminative, and motivational-affective components proposed by Melzack and Casey (1968) within the gate control theory. Therefore this theory conceptualizes pain as the consequence of the output of the widely distributed brain neural network rather than a direct response to sensory input following tissue injury, inflammation, and other pathologies (Melzack, Coderre, Katz, & Vaccarino 2001). It also underlines that pain is a major psychological stressor that alters homeostasis and triggers stress regulatory processes (namely the HPA axis and release of cortisol amongst other hormones) that, in turn, can further influence pain experience (Gatchel, Peng, Peters, Fuchs, & Turk, 2007).

The cognitive–behavioral model of pain recognizes the importance of underlying tissue pathology as a source of pain, further highlighting the importance of cognitive factors (such as beliefs about pain control and feelings of helplessness), emotional factors (such as anxiety and depression), and behavioral factors (such as pain related social interactions and social support) on pain reporting and adjustment (Keefe & Sommers, 2010).

Finally, the biopsychosocial approach to pain (Asmundson & Wright, 2004) complements the formers by adding and emphasizing the role of social and cultural contexts in shaping the behavioral responses of individuals to the perceptions of their physical injuries (Turk & Flor, 1999). Thus, the biopsychosocial model views pain as the final result of the dynamic interaction amongst physiologic, psychological and social factors, with the latter ones yielding the potential of perpetuating and even worsen the various clinical presentations of pain (Gatchel et al., 2007).

The above mentioned and briefly summarized current multidimensional pain theories embrace one of the key messages coming from the Australian and New Zealand College of Anesthetists - ANZCA (Macintyre, Schug, Scott, Visser, & Walker, 2010) that states, in their latter report, that "pain is an individual, multifactorial experience influenced by culture, previous pain events, beliefs, mood and ability to cope".

### 1.2. Surgery and Pain

Acute pain is the most common, anticipated and expected problem after surgery (Apfelbaum, Chen, Mehta, & Gan, 2003; Strassels, McNicol, & Suleman, 2005), and it is currently defined as a predicted physiological response to a noxious chemical, thermal or mechanical stimulus associated with surgery, trauma or acute illness (Carr & Goudas, 1999). Acute pain is a situation all medical professionals have to face regularly in their daily clinical practice and are asked to resolve (Schug, 2011). This is especially true for Anaesthesiologists, who have to deal daily with the most common manifestation of acute pain, post-surgical pain (Schug, 2011).

Therefore, surgery provides an opportunity to examine the influence and predictive nature of a variety of demographic, clinical and psychological factors on the subsequent occurrence of pain. Post-surgical studies examine a group wherein all subjects have had an injury and thus the occurrence of pain is completely predictable, allowing for a good planning of timetable assessments and permitting longitudinal and prospective analyses. Indeed, Kehlet, Jensen, & Woolf (2006) argue that surgical pain seems to provide an appealing and relevant "human pain model", which may be used in clinical studies for understanding either acute or chronic pain development.

Within surgical pain research, and in the realm of predictive studies seeking for potential risk factors of pain experience, psychological factors have emerged as consistent predictors of acute and chronic post-surgical pain, exerting at least moderate effects on these outcomes. Factors identified up to now involve negative emotions, coping strategies and specific beliefs or expectations, suggesting that perceptual/cognitive, emotional, and behavioral factors play key roles in influencing post-surgical pain experience (Burn & Moric, 2011).

### 1.2.1. Acute Post-surgical Pain

*"Strictly speaking, there is but one real evil: I mean acute pain. All other complaints are so considerably diminished by time that it is plain the grief is owing to our passion, since the sensation of it vanishes when that is over."*

Lady Mary Wortley Montagu

Within a surgical setting, acute pain can be conceptualized as "pain that is present in a surgical patient because of preexisting disease, the surgical procedure (with associated drains, chest or nasogastric tubes, or complications), or a combination of disease related and procedure-related sources." (ASA Task Force on Acute Pain Management, 2004).

Acute pain is common, occurring in around 80% of patients after surgery (Apfelbaum et al., 2003; Schug, 2011) with various surveys showing patients reporting moderate to severe levels of acute post-surgical pain after a variety of inpatient and outpatient surgical procedures (Warfield &

Kahn, 1995; Chung, Ritchie, & Su, 1997; Lynch et al., 1997; Beauregard, Pomp, & Choiniere, 1998; Svensson, Sjöström, & Haljamäe, 2000; Apfelbaum et al., 2003; McNeill, Sherwood, & Starck, 2004; Janssen et al., 2008).

#### 1.2.1.1. Mechanisms and pathways

Depending on the type of surgery, acute pain might be caused by damage to a variety of tissues. It could involve skin, muscle, bone, tendons, ligaments, and visceral organs. At a first level, symptoms are likely to vary depending upon the type and extent of tissue injured (IASP, 2011a).

Within surgical procedures, the surgical injury itself and respective tissue damage initiates a local inflammatory response (Carr & Goudas, 1999) sustained by the local release of algogenic substances and inflammatory neurotransmitters such as prostaglandins, serotonin, $H^+$, $K^+$, histamine, glutamate, aspartate, substance P, leukotrienes and bradykinin, amongst others (Spacek, 2006). This joint release directly stimulates and sensitizes nociceptors, which transduce the various noxious stimuli into nerve impulses that are conveyed to the dorsal horn of the spinal cord by A-delta (Aδ) and C-fibres (Spacek, 2006). Within this process, the site of injury becomes hyperalgesic and allodynic, which means that a process of peripheral sensitization takes place. This process means that (Chapman & Okifuji, 2004): a) nociceptors respond more to noxious stimuli and a stimulus that was already noxious becomes more painful (hyperalgesia); b) nociceptors thresholds lower, making them fire in face of stimuli that did not make them fire before, the surrounding uninjured tissue also becomes increasingly sensitive to any stimuli, as a result of central nervous system changes (allodynia). Peripheral sensitization of primary afferents (innocuous and nociceptive sensory fibers) is an outstanding factor in several pain states once it amplifies the intensity of noxious signals arriving from damaged tissue. In addition, peripheral sensitization leads to the activation of nociceptors that used to be silent (*silent nociceptors)*, thus resulting in an increased number of nociceptors that are available to transmit signals of noxious stimuli to the CNS. Moreover, sensory endings of A-Beta fibers (Aβ), which have not a nociceptive function may also be 'recruited' and start functioning like nociceptors, responding also to noxious events (Costigan, Scholz, & Woolf, 2009).

The central integration of these impulses occurs within the dorsal horn of spinal cord, fostered by a variety of molecules and their receptors like opioids, *N*-methyl-Daspartate (NMDA)-receptors, sodium- and calcium-channels, $\alpha 2$-adrenergic-receptors, $\gamma$-aminobutyric acid and substance P receptors. Afterwards, the integrated nociceptive impulses are transmitted by spinal nociceptive neurons with axons projecting to the thalamus, limbic system, and cerebral cortex, where the sensory responses are integrated with affective and cognitive neural elements (Strassels et al., 2005).

At higher brain centers nociceptive signals are integrated with psychological processes like emotions, expectations, beliefs, perceived environmental requirements or past pain memories. Acute pain perception arises from a complex process that integrates and weights all these issues and each individual pain report is the final product of this (Williams, 1999).

A mechanism by which sensory information conveyed from periphery to the spinal cord is modulated occurs from higher levels of the central nervous system (CNS), through descending inhibitory or facilitatory systems. Modulation of pain implies that the transmission of pain from peripheral tissues through the spinal cord to the higher centers of the brain is not merely a simple passive process using exclusive pathways. In fact, circuitry within the spinal cord has the potential to change the relation and the balance between the stimulus and the response to pain in an individual. The descending control from the brain is triggered by higher centers (cortex and subcortical areas) that modulate brainstem nuclei (the periaqueductal grey, raphe nuclei and locus coeruleus-subcoeruleus complex), which project to the spinal dorsal horn and block (antinociception) or facilitate (pronociception) spinal nociceptive transmission to the brain. The main neurotransmitters implicated in descending pain control are serotonin, noradrenaline and the endogenous opioids, although others also play a role. In addition, dorsal horn nociceptive neurons may be sensitized by peripheral trauma, becoming excessively responsive to normal inputs and leading to the phenomenon of central sensitization, which in turn can cause persistent pain (Costigan et al., 2009). Thus, sensitization of peripheral and central neuronal structures can amplify and sustain post-surgical pain (IASP, 2011a).

In the postsurgical period, clinically significant pain is generally associated with tissue injury and varying degrees of inflammation. However, it is noteworthy to underline that sometimes pain may be a consequence of damages or dysfunctions in peripheral or central nervous system, thus not resulting from directly activation of nociceptors (Basbaum et al., 2009; von Henn, Baron, & Woolf, 2012). This pain is called neuropathic. Neuropathic pain may be a consequence of certain types of surgeries, mainly in certain invasive procedures that present a higher risk of nerve damage, such as thoracotomy or breast surgery (Poobalan et al., 2001; Bruce et al., 2003; Jung, Gretchen, Oaklander, & Dworkin, 2003). In other cases, no nerve lesion nor peripheral noxious stimuli are detected, but general pain is present as with case of fibromyalgia (dysfunctional pain) (Costigan et al., 2009).

The surgery can also be described and perceived by the organism as a stressor that will initiate a stress response. Both during and after surgical injury, the body reacts with deep changes in neural, endocrine and metabolic systems along with changes in organ functions. These alterations are characterized by augmented secretion of catabolic hormones, decreased secretion or effects of anabolic hormones, hypermetabolism and increased cardiac work caused by autonomic system activation. Other impacts that can be observed are impaired pulmonary function, gastrointestinal side effects with nausea and ileus, changes in the coagulatory-fibrinolityc systems favouring coagulation and thrombosis, loss of muscle tissue and immunosuppression (Kehlet, 1997).

It is noteworthy to highlight that nociception triggers important physiological responses even in unconscious anesthetized patients (Carr & Goudas, 1999).

#### 1.2.1.2. Demographic, clinical and psychological predictors

Patients submitted to the same surgical procedures report different levels of pain and show different analgesic needs (Munafo & Stevensson, 2001; Rasmussen, 2007), as pain is not only a primitive sensory message of tissue trauma, but a complex psychological experience (Nielsen, Rudin, & Werner, 2007), as previously established. Psychological states can either exacerbate or inhibit nociception and the experience of pain through descending modulatory pathways (Rhudy & Meagher, 2000; Tracey & Mantyh, 2007). Although initially conceptualized as mere reactions to pain, psychological factors are now acknowledged as an intrinsic component of the pain process, opening new perspectives on both pain research and treatment, and eliciting new intervention targets (Melzack, 1999a,b). Therefore, it is now widely acknowledged that there are other factors, beyond surgical factors (type of surgery, anaesthesia and analgesia, as well as other clinical issues), influencing surgical pain experience (Figure 1).

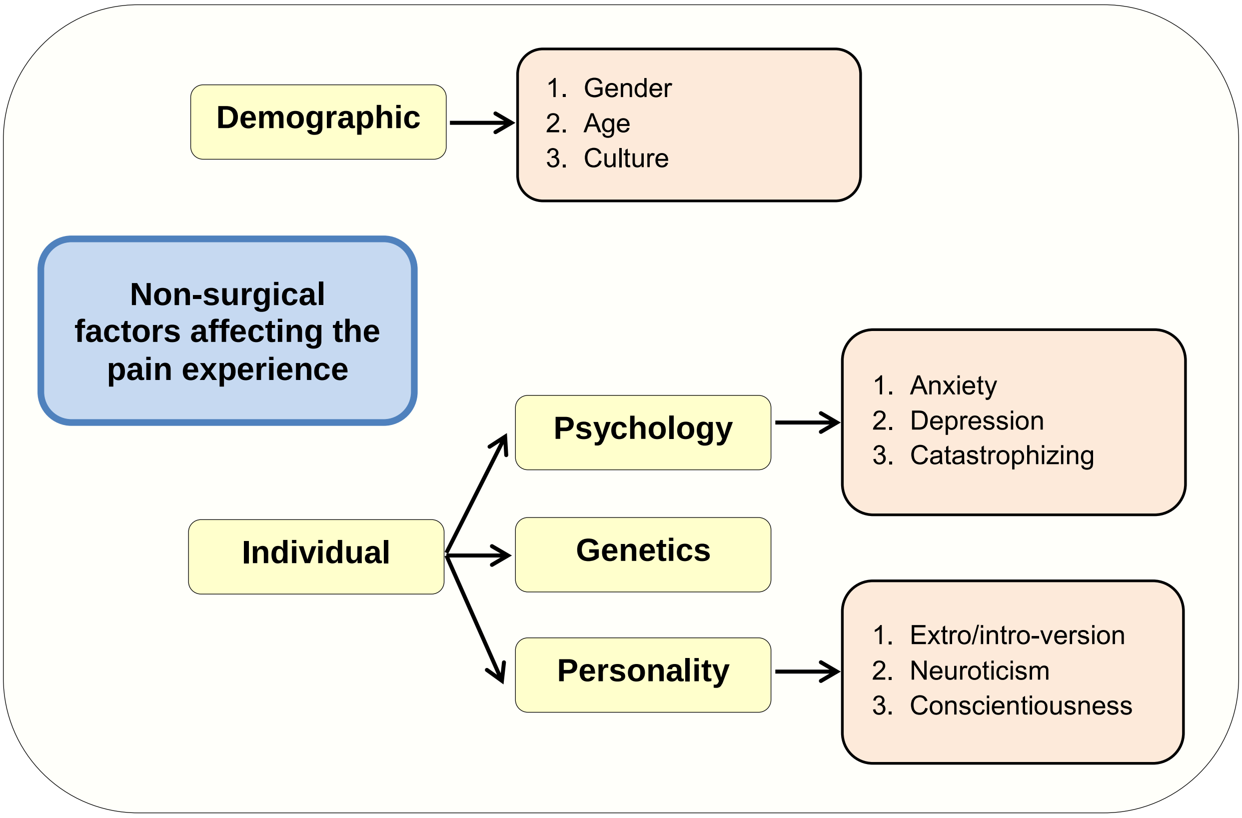


***Figure 1.*** A summary of the individual and demographic factors affecting pain experience (adapted from Khan et al., 2011).

The main demographic variables that are predictors of acute post-surgical pain are age (Katz et al., 2005; De Cosmo et al., 2008; Ene, Nordberg, Sjöström, & Bergh, 2008) and sex (Thomas, Robinson, Champion, McKell, & Pell, 1998; Papaioannou et al., 2009; Sommer et al., 2009). However, while several studies found that pain levels decrease with advancing age (Bisgaard, Klarskov, Rosenberg, & Kehlet, 2001; Kalkman et al., 2003; Katz et al., 2005; Ene et al., 2008) others have found no differences (Ozalp, Sarioglu, Tuncel, Aslan, & Kadiogullari, 2003; De Cosmo et al., 2008; Papaioannou et al., 2009). Sex differences also have been inconsistent in terms of their association with acute pain experience after surgeries, with the majority of studies revealing women as reporting more pain (Thomas et al., 1998; Uchiyama et al., 2006; De Cosmo et al., 2008; Papaioannou et al., 2009). Pre-surgical pain experience has also been widely studied but again results were not uniform across the studies, with some suggesting a predictive role of this variable (Brander et al., 2003; Hanz-Fritz et al., 2009; Sommer et al.,

2010) and others not (Wickstrom, Nordberg, & Johansson, 2005; Pan et al., 2006; Gerbershagen et al., 2009).

Amongst the acknowledged psychological factors, anxiety, depression, pain catastrophizing and, to a lesser extent fear, have been those most intensively investigated (Granot & Ferber, 2005; Pavlin Sullivan, Freund, & Roesen, 2005; DeCosmo et al., 2008; Hanz-Fritz et al*., 2009;* Papaioannou et al., 2009; Sommer et al., 2010), although with conflicting results.

In attempt to systematize the available information from several studies, a recent systematic review (Ip, Abrishami, Peng, Wong, & Chung, 2009) suggested that preexisting pre-surgical pain, anxiety, age, and type of surgery were the four most significant predictive factors for post-surgical pain intensity. Pain catastrophizing and preexisting chronic pain were also indicated as significant predictors for post-surgical pain. More recently, the Australian and New Zealand College of Anesthetists - ANZCA (Macintyre et al., 2010) recognized that pre-surgical anxiety, catastrophizing, neuroticism and depression were associated with higher post-surgical pain intensity.

Nonetheless, despite these abovementioned studies, little is known yet about the joint contribution of demographic, psychological, and surgical factors (Ip et al., 2009) as predictors of pain after surgery. Therefore, as it is important to augment knowledge on predictors and potentially modifiable determinants of acute post-surgical pain, in order to facilitate early identification of and intervention in patients at risk, predictive studies should focus simultaneously in all these type of factors and not uniquely in some of them.

#### 1.2.1.3. Physiological, psychological and social consequences

Unless properly treated, acute post-surgical pain creates needless suffering; delays healing process, puts patients at risk of increased postoperative morbidity and mortality and increases hospital stay and costs of care (McNeill et al., 2004; IASP, 2011a; Shug, 2011). Overall, it may have detrimental effects in both physiological and psychological domains (Charlton, 2005, Spacek, 2006; Goncalves et al., 2008). Physiologically, it can impact the metabolic (Kehlet, 1997; Barratt, Smith, Kee, Mather, & Cousins, 2002), immune (Cousins, Power, & Smith, 2000; Macintyre et al., 2010), cardiovascular (Cousins et al., 2000), gastrointestinal (due to pain medication, especially opioids) (Kehlet, 1997) and other systems (Cousins et al., 2000; Rigg et al., 2002; Gagliese, Gauthier, Macpherson, Jovellanos, & Chan, 2008; IASP, 2011b), with higher rates of complications and associated costs (Devine et al., 1999; IASP, 2011c). Psychologically, it is associated with higher levels of distress with increasing anxiety, inability to sleep, a feeling of helplessness, loss of control, inability to think and interact with others (Cousins, Brennan, & Carr, 2004). These effects may alter pain perception (Macntyre et al., 2010) and initiate a vicious cycle that might result in chronic pain development (Perkins & Kehlet, 2000; Schug et al., 2005; Macintyre et al., 2010; Schug & Pogatzki-Zahn, 2011). In fact, several studies (Kalkman et al.,2003; Granot & Ferber, 2005; Ozalp et al.,2003; Hsu et al., 2005; De Cosmo et al.,2008; Gagliese et al., 2008; Papaioannou et al.,2009; Strulov et al., 2007) have demonstrated the added value of assessing acute pain until 48 hours after surgery (some studies focus on the first hour, others on the 24 hours after surgery and others go until the 48 hours) in order to foster early surgical recovery and prevent the later development of  chronic pain. In sum, acute post-surgical pain can be considered a major clinical, economic, human and social problem (Filos & Lehmann, 1999; Strassels *et al.*, 2005). Therefore, understanding how to prevent acute post-surgical pain early on in the recovery process, can support better and more efficient recovery from surgery (Kehlet & Holte, 2001; Bonnet & Marrett, 2005).

#### 1.2.1.4. Important issues in pain management

The International Association for the Study of Pain (IASP) is the leading professional forum for science, practice and education in the field of pain (Schug, 2011) and in October 2010 has launched the Global Year Against Acute Pain, with the motto being "*Anticipate, Assess, Alleviate*". *Anticipation* of a potential situation inductive of acute pain (e.g. surgical procedure) should lead to an adequate plan of pain relieving and to the implementation of appropriate techniques. In turn, *assessment* of acute pain in a regular basis will lead to improvements in pain management and should be based in self-reporting, as pain is by its definition an individual, personalized and subjective experience. In fact, patients self-report is the single most reliable indicator of pain (Devine et al., 1999) and should also include monitoring of pain related outcomes (ASA Task Force on Acute Pain Management. 2004). Moreover, as underlined by ANZCA latter pain report (Macintyre et al., 2010), in acute pain management assessment must be undertaken at proper frequent intervals, with focus on its intensity, but also on its functional impact and treatment side effects. This pain assessment will potentially lead to changes in management, whenever necessary, as well as in the re-evaluation of the patient in order to ensure improvements in the quality of care (Gordon et al., 2005). Finally, *alleviating* acute pain should always be the ultimate goal as pain relief is a fundamental human right (Brennan, Carr, & Cousins, 2007). Overall, these statements imply the formulation of a pain control plan, as recommended by the *Practice Guidelines for Acute Pain Management in the Perioperative* Setting, a report by the American Society of Anesthesiologists Task Force on Acute Pain Management (2004). In addition, the importance of these three key approaches has been validated by the campaign promoting pain as the fifth vital sign. This campaign began in 2000 with pain assessment becoming a mandatory pre-requisite for the accreditation of American hospitals with the Joint Commission. In fact, nowadays, pain is documented as a fifth vital sign in most hospitals (Schug, 2011).

### 1.2.2. Analgesic Consumption and Rescue Analgesia

As stated above, acute post-surgical pain constitutes the most common, anticipated and expected problem after surgery (Apfelbaum et al., 2003; Strassels et al., 2005). However, if not managed properly, it may have detrimental systemic effects (Macintyre *et al.*, 2010). Pain relief after surgery is a key condition for early postsurgical recovery (Kehlet & Holte, 2001; Bonnet & Marret, 2005). Adequate control of post-surgical pain prevents potential negative consequences associated with its inadequate management. Acute Pain Services address this problem through standardized analgesia protocols focused on pain management. These protocols are determined according to expected pain severity given the type of surgery (minor, moderate, major) and individual characteristics (age, health status, body mass index). Despite these efforts, patients respond differently, showing distinct analgesic needs and reporting varying levels of pain even when submitted to the same surgical and analgesic procedures/protocols (Munafo & Stevensson, 2001; Rasmussen, 2007). Accordingly, all analgesia protocols include the possibility of administering extra doses of analgesics, called rescue analgesia (RA). Post-surgical pain guidelines state that a pain numerical rating scale (NRS) above 3, on a scale of 0-10, is the necessary indication for RA provision (Bodian, Freedman, Hossain, Eisenkraft, & Beilin, 2001; Hartrick, Kovan, & Shapiro, 2003; Dihle, Helseth, Paul, & Miaskowski, 2006). Thus, complaints, reports or assessments of high post-surgical pain intensity may lead to RA administration.

Nevertheless, there is a generalized consensus concerning the undermanagement of acute pain, which has been stated as being sometimes less than optimal (Dolin, Cashman, & Bland, 2002; Apfelbaum et al., 2003). Moreover, Schug (2011) argues that acute pain in 2011 continues to be poorly managed, stating that there is still a general lack of appropriate assessment and treatment of acute pain in relevant settings both in the developing and in the developed countries. Given the available knowledge on the efficacy of many of the medications widely used, on the best modes to deliver those, and on the value given to the importance of individualized care, as well as the important factors to consider in the clinical setting of the individual practitioner, the lack of a consistent implementation of this type of care is surprising (Schug, 2011). In addition, authors seem to agree that despite the improvements observed in patient and health professional education around issues related to the assessment of pain, more needs to be done on education for both parties around pain and pain management (Devine et al., 1999).

Analgesic administration should be tailored to pain intensity (Soler-Company, Banos, Faus-Soler, Morales-Olivas, & Montaner-Abasolo, 2002) and not influenced by other issues. However, "the relation between pain and analgesic consumption is still puzzling" (Strulov et al., 2007). In fact, as Soler-Company et al. (2002) states, analgesic interventions frequently depends more on "customary habits" of the care providers than on patient reported pain levels. It is likely that analgesic consumption is influenced by various factors that not only pain intensity, but also the attitudes of health providers, the specific type of analgesia, fear of side effects, among others. In order to better understand this issue, several studies have focused on the factors that could influence the consumption of analgesics following surgery (De Cosmo et al., 2008).

Regarding demographic factors as potential predictors, age and sex have been widely investigated, although revealing disparity results. While in some studies outcomes showed younger age as a risk factor for higher analgesic consumption (Perry, Parker, White, & Clifford, 1994; Joels et al., 2003), in others there was an opposite tendency, with older patients reporting more analgesic needs (Macintyre & Jarvis, 1996), or no association has been found between age and analgesic use (Chia et al., 2002; De Cosmo et al., 2008). Concerning sex, the same tendency has been showed: some studies revealed men as consuming more analgesics (De Kock & Scholtes, 1991; Chia et al., 2002; Joels et al., 2003), others found women to requiring more (Cepeda & Carr, 2003) and others did not find differences between genders (De Cosmo et al., 2008).

With respect to clinical factors, pre-surgical pain has been studied as a potential pre-surgical predictor of analgesic consumption, revealing its significant influence on analgesic consumption in some studies (Thomas et al., 1998; Slappendel, Weber, Bugter, & Dirksen, 1999), while in others this association was not confirmed (Jamison et al., 1997; Manias et al., 2002).

The specific role of psychological factors on pain relief and in patients using patient-controlled analgesia (PCA) in the post-surgical period has been approached by several studies (De Cosmo et al., 2008; Katz, Buis, & Cohen, 2008). Concerning the use of PCA, anxiety emerged as the most important psychological predictor (Perry et al., 1994; Ozalp et al., 2003; Hsu et al., 2005; De Cosmo et al., 2008; Katz et al., 2008, Papaioannou et al., 2009). Pre-surgical depression was also associated with higher opioid requirements and PCA demands (Ozalp et al., 2003; De Cosmo et al., 2008). Maladaptive coping strategies were most strongly positively associated with morphine consumption and predicted increased use of analgesics, regardless of the patients' level of pain while in the hospital (Cohen, Fouladi, & Katz, 2005). A specific pain coping strategy, pain catastrophizing, also predicted analgesic use in some studies (Papaioannou et al., 2009), whereas in others it did not yield significant results (Granot & Ferber, 2005).

A recent systematic review has identified type of surgery, age, and psychological distress as predictors of higher analgesic consumption after surgery (Ip et al., 2009). However, there is a general lack of studies focusing on the factors involved in decision-making regarding RA provision by the health care professional (when PCA is not available). Are those decisions strictly dependent on the standardized analgesic protocol guidelines? Or, are they also dependent on patient-related factors that influence patient healthcare provider interaction? Overall, one may wonder whether the decision to administer extra RA will rely on clinical behaviors, namely pain assessment procedures or on the healthcare-patient interaction.

### 1.2.3. Post-surgical Anxiety

Undergoing a surgery is an extremely stressful event (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998). Anxiety is associated with increased pain perception, increased risk to health as well as extension of pain experience (Williams, 1999). In a sample of women submitted to major abdominal gynaecological surgery (Carr, Thomas, & Wilson-Barnet, 2005), anxiety and pain were so interrelated that during the post-surgical period changes in anxiety were significantly related with changes in pain. Several studies showed this significant relationship in diverse chronic pain conditions, even after adjusting for a wide range of potential confounding variables including age, gender, educational level, ethnicity, and the presence of other pain conditions (McWilliams, Goodwin, & Cox, 2004). After surgery, whether pain causes anxiety or whether anxiety leads to pain remains difficult to establish (McWilliams et al., 2004). Nevertheless, both are usually associated and therefore, taking into account their strong co-variation, both should be addressed in terms of surgical research (Kiecolt-Glaser et al., 1998).

In addition, anxiety also has negative consequences on the process of recovery from surgery (Kiecolt-Glaser et al., 1998), as anxiety associated with acute pain can further complicate clinical outcomes (Bonica, 1990). It can cause a very high increase in the neuroendocrine secretion of catecholamines and cortisol with potential consequences for instance on cardiac output, intestinal ischemia and risk of thromboembolism. Anxiety may also cause increases in ventilation with the potential consequence of respiratory troubles. Negative emotions, like anxiety, are also powerful determinants of pain experience, including sensitization (Janssen, 2002). It lowers pain threshold (Rhudy & Meagher, 2000), leading patients to over interpret a vast array of sensations as painful (Williams, 1999). This seems to occur because anxiety is believed to have an intensifying effect on the experience of pain by influencing the cognitive processing of nociceptive information (Nisbett & Schachter, 1996). Furthermore, some studies provide evidence supporting a relationship between psychological factors (e.g. anxiety, as measured by the HADS - Hospital Anxiety and Depression scale) and delayed wound healing, which could be mediated by several mechanisms, including a neuroimmunologic pathway (Kiecolt-Glaser et al., 1998; Cole-King & Harding, 2001). A potential mechanism for this interaction is the influence of anxiety in the secretion of proinflammatory cytokines at wound site, a possible mechanism by which stress may delay wound healing (Cole-king & Harding, 2001). Despite all of these considerations, post-surgical anxiety has been scarcely aimed in surgical studies. As post-surgical pain and post-surgical anxiety seem to influence reciprocally (McWilliams et al., 2004; Carr et al., 2005), it seems worthwhile that studies should seek to identify more accurately the independent and joint contribution of demographic, clinical and psychological variables as predictors of post-surgical anxiety, after different surgical procedures.

### 1.2.4. Persistent or Chronic Post-surgical Pain

*"Pain is inevitable. Suffering is optional."*

Although acute pain is an anticipated and expected outcome after surgery (Apfelbaum et al., 2003; Strassels et al., 2005), the development of chronic or persistent post-surgical pain (PPSP) is an undesirable but common adverse outcome (Perkins & Kehlet, 2000). PPSP refers to pain that is developed after a surgery, persisting at least for two months following surgery, as a direct consequence of the surgical procedure. Other causes for such pain, i.e. malignancy, chronic infection, pre-existing pain, recurring disease, must be excluded (Macrae & Davies, 1999; Macrae, 2001). PPSP is a major clinical problem with significant individual, social and health care costs (Perkins & Gopal, 2003; Shipton & Tait, 2005; Kehlet et al., 2006). This often under reported problem is sometimes considered as a "silent epidemy" (Visser, 2006), and has recently been recognized as a possible and common consequence of several surgeries (Crombie, Davies, & Macrae, 1998; Perkins & Kehlet, 2000; Macrae, 2008), which leads to an increasing amount of interest and research on this subject (Schug & Pogatzki-Zahn, 2011). The incidence of PPSP differs with surgery and frequency ranges from 10% to 60% (Aasvang & Kehlet, 2005); figures also vary within the same surgery. This might be due to different study designs and methodologies, surgical techniques, selected samples and PPSP definitions used.

Several predictors for the development of PPSP have been identified and can be systematically grouped into three type of factors: pre-surgical (pre-existing pain, psychological factors, work related compensation issues, some demographic factors and genetic predisposition), intra-surgical (nerve injury, repeated surgery, type of anesthesia) and post-surgical factors (acute post-surgical pain, psychological factors, type of analgesia, adjuvant chemotherapy or/and radiotherapy) (Perkins & Kehlet, 2000; Visser, 2006; Kehlet & Rathmell, 2010; MacIntyre et al., 2010; Wu & Raja, 2011). Figure 2 summarizes these factors.

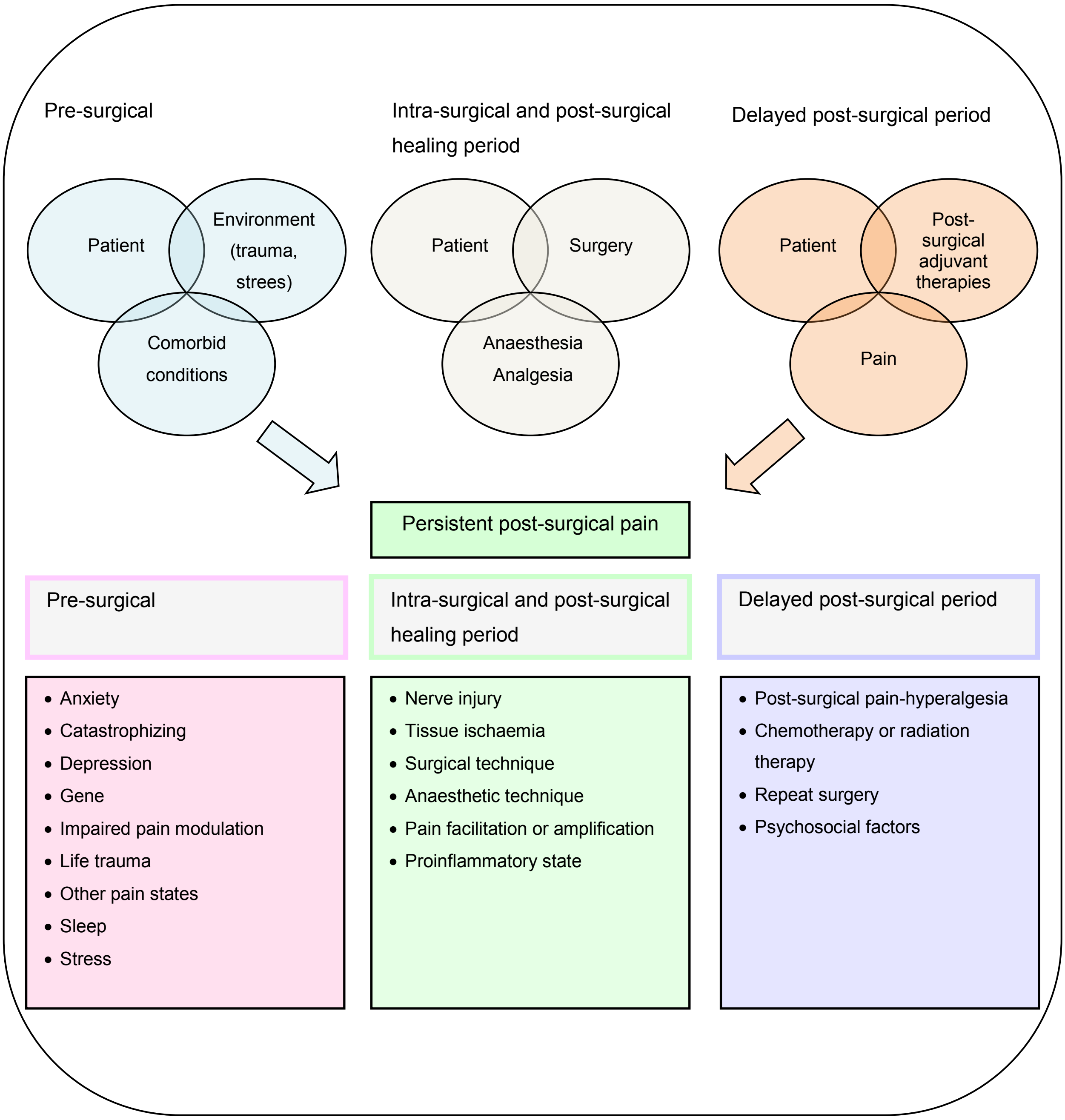


***Figure 2.*** Potential risk determinants of persistent postsurgical pain (Adapted from Wu & Raja, 2011

Several studies demonstrate age, type of surgery, previous pain (related and not related to surgery) and acute post-surgical pain as relevant predictors of PPSP (Wolters, Wolf, Stutzer, & Schroder, 1996; Perkins & Kehlet, 2000; Kehlet & Rathmell, 2010; Macintyre et al., 2010).

A recent systematic review (Hinrichs-Rocker et al., 2009), focusing on psychosocial predictors and correlates of PPSP, identified the following risk factors: depression, psychological vulnerability, stress, and duration of disability (measured by the time taken to return to work).

Anxiety and depression have emerged as predictors of chronic pain after surgery (Gergershagen et al., 2009; Brander et al., 2003), although other studies were not able to confirm this role (Taillefer et al., 2006; Peters et al., 2007). Several pain coping strategies have also been examined as potential predictors, with the most studied and effective predictor being pain catastrophizing (Forsythe, Dunbar, Hennigar, Sullivan, & Gross, 2008; Riddle, Wade, Jiranek, & Kong, 2010; Sullivan et al., 2011). Nevertheless, these studies are scarce. Within the area of surgery the vast majority of studies have focused on the influence of demographic and clinical factors rather than on psychological factors.

Other important set of psychological predictors are patients' illness perceptions. The Common-Sense Self-Regulation Model (CS-SRM) (Leventhal, Nerenz, & Steele, 1984; Leventhal & Diefenbach, 1991) demonstrates that over time, and particularly in face of an illness, people tend to develop schematic representations of illness, both cognitive and emotional (Leventhal et al., 1997; Petrie & Weinman, 2006; Hermele, Olivo, Namerow, & Oz, 2007). These representations have been shown to explain significant variation in outcomes in a wide range of medical conditions and in response to different treatments (Hagger & Orbell, 2003; Petrie & Weinman, 2006; Moss-Morris, Humphrey, Johnson, & Petrie, 2007). However, to date, no study has focused on the relationship between illness representations and post-surgical pain, either acute or chronic. Past studies using this theoretical perspective focused on the associations between illness representations and functional activity, post-surgical adjustment or surgical recovery, rather than on their relationship with pain outcomes (Orbell, Johnston, Rowley, Espley, & Davey, 1998; Mccarthy, Lyons, Weinman, Talbot, & Purnell, 2003; Llewellyn, McGurk, & Weinman, 2007)

Hinrichs-Rocker et al. (2009) suggest that several methodological improvements should be included in PPSP studies, namely: (i) the performance of prospective studies with sufficient power (sample numbers) and good completion rates at follow-up; (ii) the use of standardized measures; and (iii) follow-up periods of at least three months. Therefore, in order to develop a more comprehensive understanding of possible causes of PPSP and potential targets for preventive interventions, studies aimed at circumventing these abovementioned limitations are needed. Moreover, in the prediction of PPSP, studies should focus on the examination of the joint role of a various set of predictors, such as socio-demographic, clinical and psychological risk factors.

## 1.3. Surgical Procedures

Although being the subject of only a few studies (Kalkman et al., 2003; Peters et al., 2007), type of surgery has been mentioned as a strong predictor for both post-surgical pain and analgesic consumption (Meissner et al. 2008; Ip et al., 2009). Despite the widely recognized individual variability in pain perception, one must acknowledge that different types of surgery may imply varying degrees of tissue damage. A recent qualitative systematic review concluded that open abdominal surgery and orthopedic surgery of major joints were amongst the most painful operations (Ip et al., 2009). Moreover, these findings are in accordance with other study outcomes like QUIPS project (Meissner et al, 2008), which was focused on quality improvement in post-surgical pain management, with a sample of 12879 from 30 departments in 6 hospitals in Germany. Concerning post-surgical analgesic consumption, major and abdominal surgeries were found to be the type of surgical procedures with higher analgesic consumption (Ip et al., 2009).

### 1.3.1. Hysterectomy

Hysterectomy is the most common gynecologic surgery performed in women in Western countries (Thakar, Ayers, Clarkson, Stanton, & Manyonda, 2002; Recker & Perry, 2011). In Portugal, 10496 hysterectomies were performed in 2010 [source: national database of HDG (Homogeneous Diagnostic Groups)] while in United States figures are around 600000 hysterectomies yearly (Wu, Wechter, Geller, Nguyen, & Visco, 2007).

Hysterectomy refers to the surgical removal of the uterus and might be performed along with other concomitant procedures, such as oophorectomy, ovarian cystectomy, salpingectomy, cystoscopy or vaginal repair. It is indicated for women with benign disorders such as dysfunctional uterine bleeding, uterine fibroids, prolapse, endometriosis and adenomyosis, or pelvic pain; it is also indicated for malign disease like premalignant changes in cervix and endometrium and cancer (Schwartz & Williams, 2002). The procedure is a major surgical operation that is indicated only when appropriate drugs or simpler procedures are ineffective or inappropriate (Garry et al., 2004). Several studies provide strong evidence that hysterectomy significantly improves symptoms associated with gynecologic disorders such as leiomyomas, abnormal uterine bleeding, and endometriosis (Lefebvre, Allaire, Jeffrey, Vilos, 2002). Nevertheless, studies also reveal that some women do not have their symptoms relieved or may develop new symptoms and other problems after surgery (Carlson, Miller, & Fowler, 1994; Kjerulff et al., 2000).

According to Brandsborg, Nikolajsen, Kehlet, & Jensen (2008) hysterectomy represents an ideal model for studying post-surgical pain, because of the existence of different surgical approaches with different risks of nerve injury. Common surgical approaches are: abdominal hysterectomy (the most frequent approach), vaginal hysterectomy, laparoscopic hysterectomy and laparoscopic assisted vaginal hysterectomy.

Concerning surgical pain, relatively few studies have sought to find predictors of acute post-surgical pain experience after hysterectomy (Kain, Sevarino, Alexander, Pincus, & Mayes, 2000; Hsu et al., 2005; Brandsborg, Dueholm, Nikolajsen, Kehlet, & Jensen, 2009). Most studies in this area focused on the emotional and sexual impact of undergoing this surgery (Schwartz & Williams, 2002; Ayoubi et al., 2003; Dragisic & Milad, 2004; Ewalds-Kvist, Hirvonen, Kvist, Lertola, & Niemela, 2005; Flory, Bissonnette, & Binik, 2005) and others have addressed the development of chronic or persistent pain after hysterectomy (PPSP) (Stovall, Ling, & Crawford, 1990; Brandsborg, Nikolajsen, Hansen, Kehlet, & Jensen, 2007; Sperber et al., 2008). Nevertheless, the vast majority of hysterectomy studies have focused on the influence of demographic and clinical factors rather than on the influence of psychological factors, in the prediction of both acute and persistent pain. Additionally, to the best of our knowledge, no studies have evaluated the joint role of socio-demographic, clinical and psychological risk factors in the prediction of both acute and persistent post-surgical pain after hysterectomy.

### 1.3.2. Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA)

Arthroplasties, specifically Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA) are amongst the most commonly performed surgeries worldwide (Kurtz, Ong, Lau, Mowat, & Halpern, 2007; Learmonth, Young, & Rorabeck, 2007; Losina et al., 2009; Vilardo & Shah, 2011). In Portugal, 5691 TKA and 8200 THA were performed in 2010 [source: national database of HDG (Homogeneous Diagnostic Groups)] while in United States of America figures are around 523000 TKA and 285000 THA yearly (Swansson, Schmalzried, & Dorey, 2010). With the aging population, it is expected a significant rise in the prevalence of knee and hip osteoarthritis and consequently an increase on the number of surgical interventions such as TKA and THA, aimed at reducing pain and disability, improving functional status/outcomes and thus fostering quality of life (Bachmeier et al., 2001; Lingard, Katz, Wright, Sledge, & Kinemax Outcomes Group, 2004; Hamel, Toth, Legedza, & Rosen, 2008; Wylde, Hewlett, Learmonth, & Dieppe 2011).

Joint arthroplasties often improve functional status and yields significant pain relief for the majority of patients who undergo these procedures. However, some patients may carry experiencing significant pain following surgery, as well as scarce improvements in functional outcomes (Brander et al., 2003). Importantly, in several cases where patients report less surgical success, claiming that pre-surgical problems were not resolved or did not improve as expected, radiographic data show objective indicators of surgical success (Brander et al., 2003). These results seem to point to the potential influence of non-clinical factors on the short and long term outcomes of these kind of surgeries.

Arthroplasties are categorized as major surgeries (Peters et al., 2007) and therefore, it is expected in some degree, the occurrence of pain after surgery. However, to date, few studies (Roth, Tripp, Harrison, Sullivan, & Carson, 2007) have examined the impact of psychological factors on acute post-surgical pain after specific procedures such as TKR and THR. They rather tend to focus on demographic and clinical data (Nilsdotter, Aurell, Siösteen, Lohmander, & Roos, 2001; Nikolajsen, Sørensen, Jensen, & Kehlet, 2004; Ebrahimpour, Do, Bornstein, & Westrich, 2011) and on long-term outcomes, like chronic pain or functional status (Brander, Gondek, Martin, & Stulberg, 2007; Lingard & Riddle, 2007; Sullivan et al., 2011). But even in the latter studies the focus has been mainly on demographic and clinical features. Thus, there is a lack of studies aiming to understand the contribution of psychological variables to the experience of both acute and chronic pain after TKA and THA.

### 1.4. Aims

The overall aim of the present thesis was to explore and examine the joint role of demographic, clinical and psychological variables as predictors of acute and persistent post-surgical pain (PPSP) following surgery, as well as for related issues – analgesic consumption and anxiety – in order to identify and target vulnerable patients and at the same time contribute to the improvement of post-surgical pain management and control.

1. The first study (**Study 1**) of the present thesis recognizes the importance of augmenting knowledge on predictors and potentially modifiable determinants of acute post-surgical pain, in order to facilitate early identification of and intervention in patients at risk. It aims to examine the independent and joint contribution of demographic, clinical and psychological variables as predictors of acute post-surgical pain in women undergoing hysterectomy due to benign causes. In addition, potential direct and mediation effects of psychological predictors were explored. Understanding how to prevent acute post-surgical pain early on in the recovery process, can contribute to a better recovery processes (Kehlet & Holte, 2001; Bonnet & Marrett 2005).

2. The second study (**Study 2**) aimed to evaluate which pre and post-surgical clinical and patient-related factors may influence healthcare professional decisions on Rescue Analgesia (RA) administration, among women submitted to hysterectomy for benign disorders. Are they strictly dependent on the standardized analgesic protocol? Or, are they also dependent on patient-related factors that influence patient healthcare provider interaction? Adequate control of post-surgical pain prevents potential negative consequences associated with its inadequate management. Therefore, this work examines the role of clinical variables, other than post-surgical pain, in RA provision (e.g. type of anesthesia), as well as key psychological factors (e.g. pain coping strategies), pre and post-surgery, that may impact clinical decision-making regarding RA. Understanding the variables that influence clinical decisions on RA provision should support better acute post-surgical pain control and management for women submitted to hysterectomy for benign disorders.

3. The third study (**Study 3**) takes into account what was already studied within persistent post-surgical pain (PPSP) field, seeking to circumvent the limitations (Hinrichs-Rocker et al., 2009) showed by past studies, and aiming to gain further knowledge on the predictive role of psychological factors. Thus, it explores additional potential psychological predictive factors that were not addressed to date and that could help in a more throughout and

comprehensive understanding and prediction of PPSP development. In addition, it focuses on PPSP after hysterectomy, which is a very common surgical procedure but yet hardly addressed. Therefore, the main aim of this study was to examine the joint role of socio-demographic, clinical and psychological risk factors for the development of PPSP 4 months after hysterectomy for benign causes.

4. The fourth study (**Study 4**) presented here aims to bridge the lack of orthopedic studies focused on immediate acute post-surgical pain. Effectively, to date few studies (Roth et al., 2007) have examined the impact of psychological factors on acute postsurgical pain after specific orthopedic procedures such as joint arthroplasties, namely total knee arthroplasty (TKA) and total hip arthroplasty (THA). Past studies rather tend to focus on demographic and clinical data (Nilsdotter et al., 2001; Nikolajsen et al., 2009; Ebrahimpour et al., 2011) and on long-term outcomes, like chronic pain or functional status (Brander et al., 2007; Lingard & Riddle, 2007; Sullivan et al., 2011). In addition, post-surgical anxiety after joint arthroplasties has not been studied yet. As post-surgical pain and post-surgical anxiety seem to be highly correlated (McWilliams et al., 2004), the aims of this study were to examine the independent and joint contribution of demographic, clinical and psychological variables as predictors of acute post-surgical pain intensity and of post-surgical anxiety, in patients submitted to TKA and THA.

5. Finally, the fifth study (**Study 5**) of the present thesis intends to focus on the prediction of persistent post-surgical pain after TKA and THA. As stated above, despite the existence of several studies regarding long-term outcomes following these surgeries, like chronic pain development or functional status (Brander et al., 2007; Lingard & Riddle, 2007; Sullivan et al., 2011), they rather tend to direct their attention mainly to demographic and clinical data (Nilsdotter et al., 2001; Nikolajsen et al., 2009; Ebrahimpour et al., 2011), leaving a gap on the understanding of the contribution of psychological factors. Therefore, the aim within this last study was to explore the potential role of psychological factors on PPSP, 4-6 months after primary TKA and THA, but also taking into account the influence of demographic and clinical variables.

## 1.5. Methodology

### 1.5.1. Participants and Procedure

This study was conducted in a central hospital in northern Portugal (Alto Ave Hospital Center). This hospital serves a population of 400 thousand people distributed around 6 cities. Ethical approval was granted by the Hospital Research Ethics Committee and all participants were informed about the study and then read and signed the written informed consent sheet.

This was a single site prospective cohort study with assessments 24 h prior to surgery (T1), 48 h (T2), and 4/6 months (T3) after surgery.

#### 1.5.1.1. Hysterectomy for benign disorders

A consecutive sample of 203 women undergoing hysterectomy was invited to take part in the study. Inclusion criteria were age between 18 and 75 years, and the ability to understand consent procedures and questionnaire materials. Exclusion criteria were existing diagnoses of psychiatric or neurologic pathology (e.g. dementia) and undergoing hysterectomy due to malign conditions. Emergency hysterectomies were also excluded due to procedural reasons.

Twenty four hours before (T1) and 48 hours (T2) after surgery, women were assessed at the Hospital. Follow-up assessment was performed by telephone, 4 months later. From T1 to T2, 8 women were withdrawn due to: canceled surgery (n=3), early discharge from hospital (n=2), unavailability during post-surgical assessment (n=1), or review of surgical procedure during surgery (bilateral oophorectomy, n=1; miomectomy, n=1). From T2 to T3, 9 women were excluded due to reoperation (n=4), malignancy outcomes (n=1) and unavailability (n=4). This left 186 women with T1, T2 and T3 assessments for data analyses.

#### 1.5.1.2. Total knee Arthroplasty (TKA) & Total Hip Arthroplasty (THA)

A consecutive sample of 130 patients with osteoarthritis was enrolled (all invited participants accepted). Inclusion criteria were 18 to 80 years old, being able to understand written information (informed consent), no psychiatric or neurologic pathology (e.g. psychosis, dementia) and undergoing THA and TKA for diagnosis of coxarthrosis and gonarthrosis only (osteoarthrosis). Arthroplasties that were performed due to fractures were excluded, as well as hemiarthroplasties, revision and emergency arthroplasties.

Patients were initially assessed at the Hospital setting 24 hours before (T1) and 48 hours after (T2) surgery. Follow-up assessments were performed 4-6 months (T3) later in the follow-up orthopedic outpatient consultations. From T1 to T2 measurement points, 6 patients were withdrawn due to: canceled surgery (n=3), repeated surgery/reoperation (n=2), and ASA status IV along with occurrence of post-surgical delirium (n=1). This left 124 patients with both T1 and T2 assessments who underwent primary TKA (n=60) and primary THA (n=64). In turn, from T2 to T3, 22 patients were lost to follow-up, leaving a sample of 92 patients for analyses. This was due to cases such as: post-surgical complications (like infections) or accidents (prosthesis displacement) that required the performance of a revision arthroplasty in the operated joint (n=5), undergoing an arthroplasty in another joint (n=5) or not attendance at the follow-up orthopedic outpatient consultation (n=12).

### 1.5.2. Measures

The Portuguese versions of the following questionnaires were used along the study to collect information about selected studied variables (predictors and outcomes).

(1*) Socio-Demographic and Clinical Data Questionnaire*. It included questions on age, education, residence, marital status, professional status, household and parity, previous pre-surgical pain, pain due to other causes, previous surgeries, height, weight, menopause, diagnosis/indication for surgery and disease onset, comorbidities as well as the use of psychotropic drugs. Clinical data related to surgical procedure, type of anaesthesia and analgesia was retrieved from medical files.

(2) *Brief Pain Inventory – short form* (BPI-SF) (Cleeland & Ryan, 1994). It was only used with those patients presenting pre-surgical pain. The BPI-SF measured pain intensity, on an 11-point numerical rating scale (NRS - from 0 or "no pain" to 10 or "worst pain imaginable"), pain analgesics, perception of analgesics relief (0-100%), pain interference in daily activities [general

activity, mood, walking, work, relations with others, sleep and enjoyment of life (0-10 scale)] and pain location.

(3) Neuropathic Pain Questionnaire (DN-4) (Bouhassira et al., 2005). Previous research described PPSP as a potential neuropathic pain (Poobalan et al., 2001; Bruce et al., 2003; Jung et al., 2003), hence the need to control for it. This instrument evaluates pain characteristics or quality through 10 items. Seven of them refer to specific pain sensory descriptors, like burning, pinpricking or numbness and patients answered if their pain had those characteristics through a dichotomic format (yes or no). The last 3 items result from the sensory examination of patients performed by a clinician. For the purposes of this study only the first 7 items were included ($\alpha$ = 0.61).

(4) *Hospital Anxiety and Depression Scale* (HADS) (Zigmond & Snaith, 1983). The HADS consists of two 7-item sub-scales that measure anxiety (HADS-A) and depression (HADS-B) levels among patients in non-psychiatric hospital settings. Item response format is a Likert scale ranging from 0 to 3. Sub-scale scores vary between 0 and 21. Higher scores represent higher levels of anxiety and depression.

(5) *Revised Illness Perception Questionnaire* (IPQ-R) (Moss-Morris et al., 2002). It was used to assess patient beliefs about the underlying condition that lead to surgery, analyzing distinct dimensions of illness perceptions: “timeline acute/chronic” (e.g. “My illness will last for a long time”), “timeline cyclical” (e.g., “My symptoms come and go in cycles”), “consequences” (e.g., “The disease underlying surgery has major consequences on my life”), “personal control” (e.g., “I have the power to influence my illness”), “treatment control” (e.g., “Surgery can control my illness”), “illness coherence” (e.g., “My illness is a mystery for me”), and “emotional representation” (e.g., “When I think about my illness I get upset”). With the aim of reducing participant burden, a psychometrically shortened version (Sniehotta, Gorski, & Araujo-Soares, 2009) was used with each of the 7 subscales composed by 3 items each. To generate each total subscale score, the sum of the item scores was divided by the number of items. Hence, each subscale is rated on a scale of 1-5, in which high scores reveal worst results, with the exception of personal and treatment control subscales, which score inversely.

(6) *Life Orientation Test – revised* (LOT-R) (Scheier, Carver, & Bridges, 1994). It evaluates the personality trait optimism through 8 items. In this study just 3 items were used, corresponding to a subscale of optimism which ranges from 0 to 12, with high values associated with more optimism.

(7) *Surgical Fear Questionnaire* (Peters et al., 2007). Assesses specific surgical fears using 10 items in 2 subscales, "Fear of immediate consequences of surgery" (e.g. "I am afraid of the anaesthesia.") and "Fear of long-term consequences of surgery" (e.g. "I am afraid that I won't recover completely from the operation."). Scores range between 0 (no fear) and 10 (most extreme fear), with higher values reflecting higher levels of fear.

(8) *Coping Strategies Questionnaire – Revised Form* (CSQ-R) (Riley & Robinson, 1997). Includes 27 items that assess 6 pain coping strategies: "Distraction/diverting attention" (e.g. "I do something I enjoy, such as watching TV or listening to music."), "Praying and hoping" (e.g. "I pray for the pain to stop."), "Ignoring pain sensations" (e.g. "I don't think about the pain."), "Reinterpreting pain sensations" (e.g. "I imagine that the pain is outside of my body."), "Pain coping self-statements" (e.g. "I tell myself that I can overcome the pain.") and "Pain catastrophizing" (e.g. "It's awful and I feel that it overwhelms me."). Items were rated on a 5-point adjective rating scale (1=never, 2=almost never, 3=sometimes, 4=almost always, and 5=always) rather than the 7-point scale used in the original instrument, due to difficulties expressed by pilot study patients in discriminating the 7 points. To generate the total scale score, the sum of the item scores was divided by the number of items. Scale scores vary between 1 and 5, with higher scores indicating greater use of each specific coping strategy.

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Chapter 2

# Results

Chapter 2.1

# Hysterectomy

Chapter 2.1.1

**STUDY 1**

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Pinto, P.R., McIntyre, T., Almeida, A., & Araújo-Soares, V.

**The mediating role of pain catastrophizing in the relationship between presurgical anxiety and acute postsurgical pain after hysterectomy**

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# The mediating role of pain catastrophizing in the relationship between presurgical anxiety and acute postsurgical pain after hysterectomy

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ABSTRACT

The aim of this study was to examine the joint role of demographic, clinical, and psychological variables as predictors of acute postsurgical pain in women undergoing hysterectomy due to benign disorders. A consecutive sample of 203 women was assessed 24 hours before (T1) and 48 hours after (T2) surgery. Baseline pain and predictors were assessed at T1 and postsurgical pain and analgesic consumption at T2. Several factors distinguished women who had no or mild pain after surgery from those who had moderate to severe pain, with the latter being younger, having more presurgical pain, and showing a less favorable psychological profile. Younger age (odds ratio [OR] = 0.90, $P < .001$), presurgical pain (OR = 2.50, $P < .05$), pain due to other causes (OR = 4.39, $P = .001$), and pain catastrophizing (OR = 3.37, $P = .001$) emerged as the main predictors of pain severity at T2 in multivariate logistic regression. This was confirmed in hierarchical linear regression ($\beta = -0.187$, $P < .05$; $\beta = 0.146$, $P < .05$; $\beta = 0.136$, $P < .05$; $\beta = 0.245$, $P < .01$, respectively). Presurgical anxiety also predicted pain intensity at T2. Findings revealed an integrative heuristic model that accounts for the joint influence of demographic, clinical, and psychological factors on postsurgical pain intensity and severity. In further mediation analysis, pain catastrophizing emerged as a full mediator between presurgical anxiety and postsurgical pain intensity. The potential clinical implications for understanding, evaluating, and intervening in postsurgical pain are discussed.

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## 1. Introduction

Hysterectomy is one of the most common surgeries in women. In Portugal, approximately 11,000 hysterectomies are performed annually; in the United States, around 600,000 hysterectomies are performed yearly [50]. Acute pain is the most common, anticipated and expected problem after surgery [1,84], and it is a predicted physiological response to a noxious chemical, thermal, or mechanical stimulus associated with surgery, trauma, and acute illness [11]. Patients submitted to the same surgical procedures report different levels of pain and show different analgesic needs [59,71], because pain is not only a primitive sensory message of tissue trauma, but also a complex psychological experience [14,61]. Psychological states can either exacerbate or inhibit nociception and the experience of pain through descending modulatory pathways [72,89]. The gate control theory [58], as well as the neuromatrix theory [57] of pain, recognized that pain is a multidimensional subjective experience consisting of complex interactions between sensory-discriminative, motivational-affective and cognitive-evaluative dimensions.

A recent systematic review [42] suggested that preexisting presurgical pain, anxiety, age, and type of surgery were the 4 most significant predictive factors for postsurgical pain intensity. Pain catastrophizing and preexisting chronic pain were also indicated as significant predictors for postsurgical pain. More recently, the Australian and New Zealand College of Anesthetists [53] recognized that presurgical anxiety, catastrophizing, neuroticism, and depression were associated with higher postsurgical pain intensity.

Acute postsurgical pain creates needless suffering, puts patients at risk of increased postoperative morbidity and mortality, and increases hospital stay and costs of care [39,78]. Overall, it may have

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detrimental effects in both physiological and psychological domains [15,33]. Physiologically, it can impact the metabolic [3,49], immune [18,53], cardiovascular [18], gastrointestinal (due to pain medication, especially opioids) [49], and other systems [18,32,40,74], with higher rates of complications and associated costs [22,41]. Psychologically, it is associated with higher levels of distress, with increasing anxiety, inability to sleep, a feeling of helplessness, loss of control, and inability to think and interact with others [19]. These effects may alter pain perception [53] and initiate a vicious cycle that might result in chronic pain development [53,65,77,79]. In sum, acute postsurgical pain can be considered a major clinical, economic, human, and social problem [30,84]. Thus, it is important to augment knowledge on predictors and potentially modifiable determinants of acute postsurgical pain to facilitate early identification of and intervention in patients at risk.

Little is known about the joint contribution of demographic, psychological and surgical factors [42] as predictors of pain after surgery. Moreover, relatively few studies have sought to find predictors of acute postsurgical pain experience after hysterectomy [8,38,45]. Most studies in this area focused on the emotional and sexual impact of undergoing this surgery [2,24,28,31,80], and others have addressed the development of chronic pain after hysterectomy [7,82,83].

The aim of this study was to examine the independent and joint contribution of demographic, clinical and psychological variables as predictors of acute postsurgical pain in women undergoing hysterectomy due to benign causes. Potential direct and mediation effects of psychological predictors were explored.

## 2. Methods

### 2.1. Participants and procedure

This study was conducted in a central hospital in northern Portugal. Procedures were approved by the Hospital Ethic Committee. This was a prospective cohort study, with 2 assessments (T1 and T2) performed between March 2009 and September 2010. After written informed consent was obtained from all participants, a consecutive sample of 203 women undergoing hysterectomy was enrolled in the study (all invited participants accepted). Inclusion criteria were age between 18 and 75 years and the ability to understand consent and questionnaire materials. Exclusion criteria were existing diagnoses of psychiatric or neurologic pathology (e.g., dementia) and undergoing hysterectomy due to malignant conditions. Emergency hysterectomies were also excluded due to procedural reasons.

Women were initially assessed 24 hours before (T1) and 48 hours after (T2) surgery, at the hospital. Follow-up assessments were performed by telephone, 4 months and 12 months later; these data, reporting pain chronification, will be presented elsewhere. From T1 to T2, 8 women were lost to follow-up (3.94%) due to canceled surgery (n = 3), early discharge from hospital (n = 2), unavailability during postsurgical assessment (n = 1), or review of surgical procedure during surgery (oophorectomy, n = 1; myomectomy, n = 1). The remaining 195 women constituted the data analyses sample. The sociodemographic and clinical characteristics of the sample are presented in Table 1. Mean age was 51.0 years (SD = 9.22), 124 (63.6%) women had 4 years or less of formal education, and 60 (30.8%) lived in a rural setting.

### 2.2. Measures

Before the study, all instruments and study procedures were piloted in a sample of 20 women for evaluation of their feasibility. Those women underwent hysterectomy at the same hospital in which the present study was conducted, and presented similar sociodemographic and clinical characteristics as the study sample.

#### 2.2.1. Presurgical assessment—predictive measures

Upon hospital admission, 24 hours before surgery (T1), the following baseline questionnaires were administered, in a face-to-face interview by a trained psychologist.

*2.2.1.1. Sociodemographic and clinical data questionnaire.* This questionnaire included questions on age, education, residence, marital status, professional status, household and parity, previous pain, pain due to other causes, previous surgeries, height, weight, menopause, diagnosis/indication for hysterectomy and disease onset, as well as the use of psychotropic drugs.

*2.2.1.2. Brief Pain Inventory—Short Form.* Used with those patients presenting presurgical pain, the Brief Pain Inventory—Short Form (BPI-SF) [17] measured pain intensity on an 11-point numerical rating scale (Numerical Rating Scale (NRS) – from 0 or "no pain" to 10 or "worst pain imaginable"), pain analgesics, perception of analgesics relief (0 to 100%), pain interference in daily activities (general activity, mood, walking, work, relations with others, sleep and enjoyment of life, 0 to 10 scale), and pain location. In this study, the internal consistency reliability [20] (see later) for the pain interference subscale scores was very high ($\alpha = 0.93$).

*2.2.1.3. Hospital Anxiety and Depression Scale.* The Hospital Anxiety and Depression Scale (HADS) [91] consists of two 7-item subscales that measure anxiety (HADS-A) and depression (HADS-B) levels among patients in nonpsychiatric hospital settings. Item response format is a Likert scale ranging from 0 to 3. Subscale scores vary between 0 and 21. Higher scores represent higher levels of anxiety and depression. In the current sample, internal consistency reliability [20] was adequate for both anxiety (T1: $\alpha = 0.79$) and depression (T1: $\alpha = 0.79$).

*2.2.1.4. Pain Catastrophizing Scale of the Coping Strategies Questionnaire—Revised Form.* The Pain Catastrophizing Scale of the Coping Strategies Questionnaire—Revised Form (CSQ-R) [75] subscale has 6 items that assess pain catastrophizing. Items were rated on a 5-point adjective rating scale (1 = never, 2 = almost never, 3 = sometimes, 4 = almost always, and 5 = always) rather than the 7-point scale used in the original instrument, due to difficulties expressed by pilot study patients in discriminating the 7 points. To generate the total scale score, the sum of the item scores was divided by the number of items. Scale scores vary between 1 and 5, with higher scores indicating greater use of the specific coping strategy. In the current sample, the Cronbach alpha internal consistency reliability coefficient [20] was 0.87, indicating good reliability.

#### 2.2.2. Surgical procedure and anesthetic technique

Clinical data related to surgery and to anesthesia were retrieved from medical records. From the 195 women who underwent surgery, 142 (72.8%) were submitted to total abdominal hysterectomy, 34 (17.4%) to vaginal hysterectomy, 13 (6.7%) to total abdominal laparoscopic hysterectomy, and 6 (3.1%) had laparoscopically assisted vaginal hysterectomy. Concomitant procedures, such as oophorectomy, ovarian cystectomy, salpingectomy, cystoscopy, or vaginal repair, were also performed in some patients; however, this refined distinction was not considered for the purpose of our study analyses. In abdominal hysterectomies (n = 142), abdominal incision was indicated as being Pfannenstiel (n = 119) or vertical (n = 23), with the former being the first usual choice and the latter being performed just in cases of existence of a previous vertical surgical scar and in exploratory laparotomy. For

**Table 1**
Differences between acute pain severity groups (T2) on sociodemographic and clinical characteristics and psychological measures (T1).

| Patient characteristics | Total sample (N = 195) | Absence of pain or mild pain (n = 65) | Moderate to severe pain (n = 130) | P |
|---|---|---|---|---|
| Sociodemographic | | | | |
| Age (y) | 51.0 (9.22) | 55.4 (10.6) | 48.7 (7.5) | <.001 |
| Marital status (married) | 167 (85.6%) | 55 (84.6%) | 112 (86.2%) | NS |
| Parity | 2.04 (1.20) | 2.12 (1.23) | 2.00 (1.18) | NS |
| Education (⩽4 y education) | 124 (63.6%) | 43 (67.2%) | 81 (62.3%) | NS |
| Residence (urban setting) | 60 (30.8%) | 21 (32.3%) | 39 (30.2%) | NS |
| Professional status (employed) | 96 (49.2%) | 30 (46.2%) | 66 (50.8%) | NS |
| Clinical—general indicators | | | | |
| Premenopausal | 129 (66.2%) | 30 (46.2%) | 99 (76.2%) | <.001 |
| Disease onset (mo) | 38.8 (52.5) | 38.5 (55.4) | 39.0 (51.1) | NS |
| BMI (kg/m$^2$) | 28.6 (4.50) | 28.6 (4.44) | 28.6 (4.55) | NS |
| Previous surgeries | 137 (70.3%) | 42 (64.6%) | 95 (73.1%) | NS |
| Psychotropic use | 64 (32.8%) | 23 (36.5%) | 41 (34.9%) | NS |
| Clinical—presurgical pain indicators | | | | |
| Presurgical pain (yes) | 118 (60.5%) | 28 (43.1%) | 90 (69.2%) | <.001 |
| Intensity (worst level) | 3.12 (3.20) | 2.41 (2.58) | 4.49 (3.19) | <.001 |
| Intensity (average level) | 2.11 (2.13) | 1.17 (1.64) | 2.58 (2.20) | <.001 |
| Presurgical analgesic use | 58 (29.7%) | 9 (13.8%) | 49 (37.7%) | .001 |
| Pain total interference (0–10) | 1.29 (1.85) | 0.80 (1.62) | 1.45 (1.90) | NS |
| Pain due to other causes | 125 (64.1%) | 33 (50.8%) | 92 (70.8%) | .001 |
| Psychological measures | | | | |
| HADS: anxiety | 7.29 (4.42) | 5.65 (3.48) | 8.12 (4.62) | <.001 |
| HADS: depression | 2.35 (3.04) | 1.68 (2.22) | 2.69 (3.33) | <.05 |
| CSQ-R: pain catastrophizing | 1.80 (0.90) | 1.43 (0.61) | 1.99 (1.00) | <.001 |

Continuous variables are presented as mean (SD); categorical variables are presented as n (%).
BMI = body mass index, CSQ-R = Coping Strategies Questionnaire, Revised, HADS = Hospital Anxiety and Depression Scale, T1 = 24 hours before surgery, T2 = 48 hours after surgery.

all women, uterus weight and height were also recorded. The type of anesthesia was classified as general (n = 57, 29.2%), locoregional (n = 24, 12.3%) or combined (general plus locoregional; n = 114, 58.4%), and the American Society of Anesthesiologists score (physical status classification of the American Society of Anesthesiologists) was recorded, including cases of American Society of Anesthesiologists grade I (58, 29.7%), II (123, 63.1%) and III (14, 7.2%).

*2.2.3. Postsurgical assessment*

*2.2.3.1. Primary outcome measure: acute postsurgical pain.* Women were asked to rate their worst and average pain level within the first 48 hours after surgery, on an 11-point numerical rating scale (NRS from the BPI-SF), already described.

*2.2.3.2. Clinical measures.* Clinical data related to surgery, anesthesia and analgesia were obtained from medical records. Information about type of hysterectomy and uterus weight and height was registered. Concerning anesthesia, the type of anesthesia and American Society of Anesthesiologists score were also gathered. Furthermore, information about the use of psychotropic drugs during hospital stay as well as the duration of hospital length were collected. In addition to the 11-point pain numerical rating scale (NRS), women were assessed on analgesic relief using the scale from 0 to 100%, from the BPI-SF [17].

All patients were assigned to an individualized standardized 48-hour analgesia protocol that was determined and supervised by the Acute Pain Service and established before transferring the patient 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); or (2) administration of an epidural morphine bolus (2 to 3 mg, 12/12 hours). The intravenous protocol was composed by a continuous intravenous infusion (delivered infusion balloon) of tramadol (600 mg), metamizol (6 g), and metoclopramide (60 mg). Paracetamol (1 g 6/6 hours) and nonsteroidal anti-inflammatory drugs (ketorolac 30 mg 12/12 hours or parecoxib 40 mg 12/12 hours) were always included as coadjuvant analgesics. All analgesic regimens included prokinetic treatment that was standardized to metoclopramide (10 mg intravenously 8/8 hours). All protocols had indications for the prescription of rescue analgesics beyond the standardized analgesic protocol given moderate to severe acute postsurgical pain levels (NRS ⩾ 4). Because of the great variability in analgesics' medications and dosages, no attempt was made to determine total equianalgesic medication dosages. It was rather recorded whether rescue analgesics were given to patients.

*2.3. Statistical analyses*

The software G Power, version 3.1.2 [27], was used to investigate the sample size required to test the proposed effects. With 147 participants, there would be 95% power to detect an effect size of 0.15 (medium effect size), assuming a type I error of 5% and 6 predictors included in the linear regression analysis. Based on previous studies conducted by the team with a similar sample [67], we expected a 15% attrition rate from T1 to T2. Therefore, collecting 169 patients would be sufficient to assure statistical power. Given that this is part of a larger prospective cohort study (4 time points), a total of 203 patients were included in the study.

Data were analyzed using the Statistical Package for the Social Sciences, version 18.0 (SPSS, Inc., Chicago, Illinois, USA). Internal consistency of responses to the questionnaires was assessed using Cronbach alpha [20]. The outcome variable in this study is "worst level of acute postsurgical pain" either assessed as a dichotomous variable (pain severity) or as a continuous variable (pain intensity; NRS 0 to 10). For the dichotomous outcome, patients were classified into 2 groups, absence of pain or mild pain (NRS ⩽ 3 for "worst pain level") and moderate to severe pain (NRS ⩾ 4 for "worst pain level"). The selected cut-point was based on: (1) the specific analgesic procedures of the hospital, which state that an NRS value of ⩾4 determines further administration of rescue analgesics; (2) recommendations from other studies suggesting that this threshold determines distinct acute pain consequences with higher levels of functional limitation when a patient states pain of level 4 or more [5,23,26,36].

Both *t* tests (for continuous variables) and $\chi^2$ tests (for nominal variables) were performed to compare demographic, clinical and psychological measures between patients with and without moderate or severe pain 48 hours after surgery. Furthermore, Pearson correlation coefficients were also calculated among study variables to determine the predictor variables to include in the regression analyses.

Logistic regression analyses were conducted to determine risk factors for the presence of moderate to severe pain, using pain severity as outcome. Multiple linear regression analyses were performed to identify significant predictors for worst postsurgical pain intensity as outcome. The variables included in both regression analyses were either the ones that were found to distinguish between the 2 pain groups ($P \leqslant .001$) or those that showed a strong association with worst pain intensity ($P < .001$). Additionally, univariate regression analyses, along with findings of previous studies [13,35,42,47,48] assisted in the final selection for multiple and logistic hierarchical regression models. To control for the influence of multicollinearity, we calculated the variance inflation factor value for every independent variable. The variable was included if variance inflation factor was <3. The option to use both logistic and linear regression to investigate the predictors of acute postsurgical pain is related to an interest in both pain severity (cut-point with clinical implications) and intensity as outcomes variables. A replication of findings via these 2 procedures will reinforce their robustness.

For mediation analysis, and to circumvent recognized issues with the Baron and Kenny method and the Sobel test for testing mediation [55], the Preacher and Hayes (2008) bootstrapping methods [69] were used for testing indirect effects. To test for mediation, a distinction between the various effects and their corresponding weights was performed (Fig. 1). The total effect of presurgical anxiety on postsurgical pain intensity (weight *c*) consists of both a direct effect of presurgical anxiety on postsurgical pain intensity (weight *c*′), and also an indirect effect of presurgical anxiety on postsurgical pain intensity through a mediator, that is, pain catastrophizing (weight *ab*). The effect of presurgical anxiety on pain catastrophizing is represented by weight *a*, whereas weight *b* is the effect of pain catastrophizing on postsurgical pain intensity. To assess this indirect effect, a bootstrapping method was used following the procedure described by Preacher and Hayes [37,69]. Specifically, point estimates and 95% bias-corrected and accelerated bootstrapped confidence intervals were estimated with 5000 bootstrap resamples.

## 3. Results

### 3.1. Sociodemographic, clinical and psychological characteristics

Sixty-five women reported absence of pain or mild pain (NRS ⩽ 3) after surgery, whereas 130 reported moderate to severe pain (NRS ⩾ 4). Table 1 shows sociodemographic and clinical characteristics of both the total patient sample and those of each postsurgical pain severity group (NRS ⩽ 3 and NRS ⩾ 4). Apart from age, the groups did not differ significantly on any of the sociodemographic measures. Aside from being younger ($t = 4.55$, $P < .001$), women with moderate to severe postsurgical pain were also more likely to be premenopausal ($\chi^2 = 17.42$, $P < .001$) and to present more presurgical pain either related to the illness underlying surgery ($\chi^2 = 12.41$, $P < .001$) or to other causes ($\chi^2 = 7.56$, $P = .001$) (Table 1). Furthermore, these women showed a worse psychological profile (Table 1), revealing more anxiety ($t = -4.17$, $P < .001$), depression ($t = -2.53$, $P < .05$), and pain catastrophizing ($t = -4.90$, $P < .001$) (Table 1).

Regarding the impact of surgery, abdominal hysterectomy was more significantly associated with moderate to severe pain than vaginal hysterectomy ($\chi^2 = 10.63$, $P = .001$) (Table 2). The groups did not show any difference on other clinical parameters such as uterus weight and height, type of anesthesia, or type of analgesia (Table 2). Additionally, 48 hours after surgery (T2), women with moderate to severe pain were given more rescue analgesics ($\chi^2 = 32.19$, $P < .001$) than women with no or mild postsurgical pain (Table 2).

### 3.2. Risk factors for postsurgical pain severity

To determine the risk factors associated with postsurgical pain severity, a logistic regression was conducted (Table 3), with the dichotomous pain severity scores as outcome (2 pain groups: absence of pain or mild pain, NRS ⩽ 3; versus moderate to severe pain, NRS ⩾ 4). Age was included in the first step, and the type of hysterectomy was entered in the second step due to its significance in previous analyses. Presurgical pain (absent, present) was entered along with pain due to other causes (absent, present) in the third step. In the fourth and fifth steps, anxiety and pain catastrophizing were added, respectively, as the psychological variables expected to have the largest impact on postsurgical pain, taking into account either previous univariate analyses or results from other studies [13,35,42,47,48]. As shown in Table 3, the variables that emerged as predictors of pain severity in the final model were age (OR = 0.90, 95% confidence interval [CI] 0.86 to 0.95, $P < .001$), presurgical pain (OR = 2.50, 95% CI 1.12 to 5.60, $P < .05$), pain due to other causes (OR = 4.39, 95% CI 1.83 to 10.5, $P = .001$), and pain catastrophizing (OR = 3.37, 95% CI 1.63 to 6.95, $P = .001$), with younger women and those presenting increased level of the other 3 characteristics having a higher probability of being in the moderate to severe pain group. The type of hysterectomy and presurgical anxiety were not significant predictors in the final model. However, presurgical anxiety was a significant predictor in step 4, before being corrected for pain catastrophizing (OR = 1.09, 95% CI 1.00 to 1.19, $P < .05$). After pain catastrophizing was entered on step 5, presurgical anxiety was no longer significant (OR = 0.96, 95% CI 0.86 to 1.08, not significant).

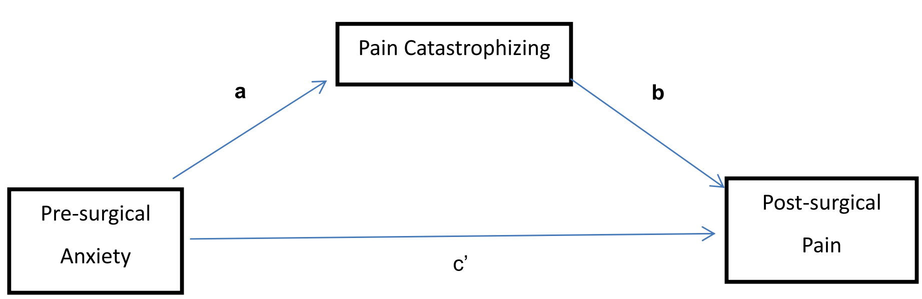


**Fig. 1.** Graphic representation of the mediation model. Note that the total effect (weight c) consists of a direct effect (weight c′) and the indirect effect (ab weight).

**Table 2**
Differences between acute pain severity groups on postsurgical, anesthetic, and surgical variables (T2).

| Postsurgical data | Total sample (N = 195) | Absence of pain or mild pain (n = 65) | Moderate to severe pain (n = 130) | *P* |
|---|---|---|---|---|
| Clinical—general indicators | | | | |
| Type of hysterectomy: abdominal | 155 (79.5%) | 43 (66.2%) | 112 (86.2%) | .001 |
| Uterine weight (g) | 208 (204) | 177 (216) | 223 (196) | NS |
| Uterine height (cm) | 9.48 (2.56) | 9.13 (2.43) | 9.66 (2.62) | NS |
| Type of anesthesia: combined | 114 (58.5%) | 35 (53.8%) | 79 (60.8%) | NS |
| Epidural analgesia | 136 (69.7%) | 44 (67.7%) | 92 (70.8%) | NS |
| Length of hospital stay (d) | 3.12 (1.22) | 2.98 (0.75) | 3.19 (1.34) | NS |
| Psychotropic use | 73 (37.4%) | 26 (40.0%) | 47 (36.4%) | NS |
| Clinical pain and analgesic indicators | | | | |
| Rescue analgesics | 95 (48.7%) | 13 (20.0%) | 82 (63.1%) | <.001 |
| Percent relief from analgesics (0–100) | 92.0 (19.04) | 100 (0.0) | 88.0 (22.8) | NS |

Continuous variables are presented as mean (SD); categorical variables are presented as n (%). Type of hysterectomy: open abdominal and abdominal laparoscopic versus vaginal and vaginal assisted laparoscopic; combined anesthesia (general + loco-regional) versus general anesthesia alone or loco-regional anesthesia alone; epidural analgesia versus intravenous analgesia.
T2 = 48 hours after surgery.

**Table 3**
Hierarchical logistic regression for risk factors (T1) predicting pain severity, 48 hours (T2) after hysterectomy (n = 188[a]).

| Variables | Odds ratio (CI) | *P* |
|---|---|---|
| Step 1 | | |
| Age[b] | 0.92 (0.89–0.96) | <.001 |
| Step 2 | | |
| Type of hysterectomy[c] | 1.88 (0.85–4.14) | NS |
| Step 3 | | |
| Presurgical pain[d] | 1.68 (0.83–3.39) | NS |
| Pain due to other causes[e] | 3.21 (1.58–6.54) | .001 |
| Step 4 | | |
| Presurgical anxiety[f] | 1.09 (1.00–1.19) | <.05 |
| Step 5 (final model) | | |
| Age[b] | 0.90 (0.86–0.95) | <.001 |
| Type of hysterectomy[c] | 1.82 (0.72–4.66) | NS |
| Presurgical pain[d] | 2.50 (1.12–5.60) | <.05 |
| Pain due to other causes[e] | 4.39 (1.83–10.5) | .001 |
| Presurgical anxiety[f] | 0.96 (0.86–1.08) | NS |
| Pain catastrophizing[g] | 3.37 (1.63–6.95) | .001 |

T1 = 24 hours before surgery; T2 = 48 hours after surgery.
[a] After removing 7 outliers, the final model correctly predicted 76% of all patients.
[b] Continuous variable, in years.
[c] Dichotomous variable: 0 = vaginal, 1 = abdominal.
[d] Dichotomous variable: 0 = no, 1 = yes.
[e] Dichotomous variable: 0 = no, 1 = yes.
[f] Continuous variable: Hospital Anxiety and Depression Scale, anxiety subscale.
[g] Continuous variable: Coping Strategies Questionnaire, Revised (pain catastrophizing subscale).

### 3.3. Predicting postsurgical pain intensity

Table 4 presents Pearson correlation coefficients between worst postsurgical pain intensity and other study variables. Worst postsurgical pain intensity was significantly correlated with age ($r = -0.29$, $P < .001$) and previous pain intensity ($r = 0.33$, $P < .001$). Worst postsurgical pain was also significantly correlated with psychological measures such as presurgical anxiety ($r = 0.28$, $P < .001$) and pain catastrophizing ($r = 0.35$, $P < .001$). These results were used to determine the set of predictors to include in the regression model.

To determine the predictors of postsurgical pain intensity, a hierarchical linear regression analysis was performed (Table 5). The regression model was the same as previously described for pain severity as outcome (Table 3). Furthermore, we sought to understand and clarify the specific relationship between presurgical anxiety and pain catastrophizing, and postsurgical pain intensity. The results of the hierarchical linear regression analysis, presented in Table 5, showed an initial model that replicates the results obtained for the first 3 steps of the logistic regression (Table 3). On step 4, presurgical anxiety was included and proved to be a significant predictor ($\beta = 0.184$ $P = .009$), explaining an additional 3% of the variance in pain intensity. On the final step, pain catastrophizing was entered, also emerging as a significant predictor ($\beta = 0.245$, $P = .002$), adding 3.9% to the explained variance. However, whereas the other variables were still significant predictors, the contribution of presurgical anxiety was no longer significant ($\beta = 0.048$, $P = .554$). The variance explained by the initial model (first 4 steps) was 20.2%, whereas the variance explained by the final model increased to 24.0%. The inclusion of pain catastrophizing in the model improved the variance explained and seemed to reveal a full mediation effect between anxiety and postsurgical pain. The next analysis explores this potential mediation.

### 3.4. Mediation analysis

We investigated the mediation hypothesis further using Preacher and Hayes' [69] bootstrapping methods to test for indirect effects. Hence, we tested whether the effect of presurgical anxiety on postsurgical pain was mediated by pain catastrophizing (Fig. 1). Presurgical anxiety was positively and significantly associated with postsurgical pain intensity ($c = 0.19$, SE = 0.05, $P = .0001$) and with pain catastrophizing ($a = 0.12$, SE = 0.01, $P < .0001$). Additionally, pain catastrophizing was positively and significantly related to postsurgical pain intensity ($b = 0.89$, SE = 0.27, $P = .001$).

When pain catastrophizing was tested as a mediator, the direct effect of presurgical anxiety on postsurgical pain intensity became nonsignificant ($c' = 0.09$, SE = 0.06; Fig. 1) and the indirect effect of presurgical anxiety on postsurgical pain (i.e., simple mediation) was significant ($ab = 0.11$, SE = 0.03), as the bootstrapped confidence interval (bias-corrected and accelerated 95% CI: 0.04 to 0.17 with 5000 resamples) excluded zero. These results support the mediation effect of pain catastrophizing between presurgical anxiety and postsurgical pain intensity.

## 4. Discussion

The present study is, to our knowledge, the first aiming to identify the joint and independent contribution of demographic, clinical and psychological risk factors for acute postsurgical pain intensity after hysterectomy due to benign disorders. This is also the first study showing the mediating role of pain catastrophizing between presurgical anxiety and postsurgical pain intensity, indicating that it is not presurgical anxiety per se that predicts postsurgical pain intensity, but rather anxiety mediated through pain catastrophizing.

**Table 4**
Intercorrelations of age, psychological measures, and pain at T1 and T2.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1. Age | – | .11 | −.25*** | −.01 | −.11 | −.36*** | −.27*** | −.29*** | −.27*** |
| 2. Pain due to other causes | | – | .18* | .009 | .24** | .16* | .10 | .19** | .21** |
| 3. HADS: anxiety T1 | | | – | .55*** | .57*** | .15* | .13 | .28*** | .25*** |
| 4. HADS: depression T1 | | | | – | .45*** | .07 | .08 | .19** | .22** |
| 5. CSQ-R: pain catastrophizing T1 | | | | | – | .17* | .12 | .35*** | .39*** |
| 6. Worst pain T1 | | | | | | – | .92*** | .33*** | .37*** |
| 7. Average pain T1 | | | | | | | – | .31*** | .34*** |
| 8. Worst pain T2 | | | | | | | | – | .73*** |
| 9. Average pain T2 | | | | | | | | | – |

CSQ-R = Coping Strategies Questionnaire, Revised, HADS = Hospital Anxiety and Depression Scale, T1 = 24 hours before surgery, T2 = 48 hours after surgery.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

**Table 5**
Hierarchical linear regression analysis for predictors of postsurgical pain intensity, 48 hours after hysterectomy (N = 195).

| Variables | t | β | $R^2$ | $\Delta R^2$ | ΔF |
|---|---|---|---|---|---|
| Step 1 | | | 0.085 | 0.085 | 17.670*** |
| Age[a] | −4.204*** | −0.291 | | | |
| Step 2 | | | 0.100 | 0.016 | 3.301 |
| Type of hysterectomy[b] | 1.817 | 0.134 | | | |
| Step 3 | | | 0.172 | 0.071 | 8.085*** |
| Presurgical pain[c] | 2.131* | 0.155 | | | |
| Pain, other causes[d] | 3.047** | 0.206 | | | |
| Step 4 | | | 0.202 | 0.030 | 7.040** |
| Presurgical anxiety[e] | 2.653** | 0.184 | | | |
| Step 5 (final model) | | | 0.240 | 0.039 | 9.484** |
| Age[a] | −2.526* | −0.187 | | | |
| Type of hysterectomy[b] | 1.183 | 0.083 | | | |
| Presurgical pain[c] | 2.079* | 0.146 | | | |
| Pain, other causes[d] | 2.030* | 0.136 | | | |
| Presurgical anxiety[e] | 0.593 | 0.048 | | | |
| Pain catastrophizing[f] | 3.080** | 0.245 | | | |

T1 = 24 hours before surgery; T2 = 48 hours after surgery.
* $P < .05$.
** $P < .01$.
*** $P < .001$.
[a] Continuous variable in years.
[b] Dichotomous variable: 0 = vaginal and vaginal assisted laparoscopic, 1 = open abdominal and abdominal laparoscopic.
[c] Dichotomous variable: 0 = no, 1 = yes.
[d] Dichotomous variable: 0 = no, 1 = yes.
[e] Continuous variable, Hospital Anxiety and Depression Scale, anxiety subscale.
[f] Continuous variable, Coping Strategies Questionnaire, Revised (pain catastrophizing subscale).

### *4.1. Predictors of moderate/severe postsurgical pain after hysterectomy*

Several presurgical factors distinguished women who had absence of or mild postsurgical pain from those who had moderate to severe pain, with the latter being younger, having higher level of presurgical pain and showing a worse psychological profile in cognitive and emotional evaluations.

Regarding sociodemographic predictors, in both regression analyses (logistic and linear), younger women showed an increased risk for higher postsurgical pain severity and intensity. This replicates results from other studies in which age emerged as a significant predictor, with younger patients reporting more postsurgical pain in cases of breast surgery [43,48], cholecystectomy [4], abdominal surgeries [13], prostatectomy [26] and inguinal hernioplasty [52]. The protective effect of increased age has been related to a reduction in peripheral nociceptive function [66,88]. However, considering the type of surgery (hysterectomy), other factors may contribute to higher pain perception, namely the fear of losing the uterus at a young age and its impact on fertility, body image and sexuality [2,24,28,29,31,80].

In terms of clinical predictors, abdominal hysterectomies have been associated with higher postsurgical pain than vaginal hysterectomies [44]. Open abdominal surgeries are among the most painful surgical procedures [16,47]. However, in the present study, the surgical route was not a significant predictor of postsurgical pain. This reinforces the relevance of psychological factors when experiencing and dealing with postsurgical symptoms.

The existence of either presurgical pain (related to the causes that required a hysterectomy) or pain due to other causes was shown to be a significant predictor of postsurgical pain, which replicates findings from other studies on breast surgery [48,62], cholecystectomy [87], abdominal surgery [13,47,85], or inguinal hernioplasty [10]. Prolonged pain stimulation has been shown to exacerbate the nociceptive system through mechanisms of peripheral and central sensitization of nociceptors and central nervous system neurons, respectively [51]. It is possible that plastic changes in the nociceptive system and supraspinal pain control system [33,60,68] may contribute to this association between the presence of presurgical and postsurgical pain. For patients who come for surgery and are screened with presurgical pain or other chronic pain states, it is important to offer special care in terms of presurgical intervention focused on pain management and promoting effective pain coping strategies.

Concerning psychological factors, several studies demonstrated that presurgical anxiety is one of the most important predictors of postsurgical pain in a variety of surgical procedures [21,42,45,48,53]. Pain catastrophizing has also been identified as a major predictor of acute pain experience [35,63,64,73,81,86] in a wide range of surgeries, although no study to date has reported its influence on hysterectomy. Additionally, few studies have included and explored both anxiety and pain catastrophizing as predictors of postsurgical pain. Granot and Ferber [35] focused on the specific relationship between presurgical anxiety, pain catastrophizing, and postsurgical pain in patients undergoing hernioplasty (n = 34) and cholecystectomy (n = 4). Their results indicated that pain catastrophizing predicted postsurgical pain intensity after controlling for anxiety. The study explored a potential mediation between these variables, but only a partial mediation was found. To test for mediation, Granot and Ferber [35] used the Baron and Kenny method. This method presents recognized limitations such as low statistical power and the absence of a measure for the strength of the mediated effect [37,54]. Furthermore, this study had a small (n = 38) and heterogeneous sample (34 hernioplasties and 4 cholecystectomies). In a study by Sommer et al. [81] with 217 ear, nose and throat surgery patients, the investigators concluded that anxiety is not a significant predictor of acute postsurgical pain, whereas pain catastrophizing is. These results seem to contradict previous reports on the determinant role of anxiety on acute pain.

To the best of our knowledge, the present study is the first to explore this mediation in a sample of benign hysterectomy patients. In accordance with the literature [21,42,45,48,53], we found that presurgical anxiety was a significant predictor of postsurgical pain severity and intensity. However, when the effect of presurgical anxiety was corrected for pain catastrophizing, this effect was no longer significant. In the absence of collinearity problems, which might have accounted for the suppression of the effect of presurgical anxiety, the data indicate a mediation effect via pain catastrophizing. The mediation analysis conducted using state-of-the-art bootstrapping methodology supported the mediation hypothesis. We found that the relationship between anxiety and postsurgical pain is fully mediated by pain catastrophizing. Thus, presurgical anxiety seems to be associated with negative cognitions about pain that predict increased postsurgery pain reports. Pain catastrophizing involves magnification of the threat value of pain and generalization of its negative impact, as well as feelings of helplessness and pessimism in the ability to deal with pain [70,86]. This has clinical implications: as presurgical anxiety increases, women will tend to catastrophize more about pain and this will predict increased acute postsurgical pain intensity.

These mediation results might contribute to clarify apparently incongruent data in the relationship between anxiety and pain [6,26,88,90] and answer some of the questions raised by Sommer et al. [81] as well as by Granot and Ferber [35]. The association found between anxiety and pain catastrophizing and the role of the latter in predicting acute postsurgical pain suggest that both emotional and cognitive factors need to be considered in the prevention and management of acute pain, and that intervening in cognitive factors may have a direct impact on pain experience after surgery. These results may also help to clarify why presurgical pharmacological interventions, through the administration of anxiolytic drugs such as benzodiazepines, have not yet proven to be effective in the reduction of postsurgical pain intensity [12,46]. Prescribing large-spectrum anxiolytic drugs seems to miss a key cognitive factor associated with presurgical anxiety, which is pain catastrophizing.

### 4.2. Limitations of the study

There are some methodological limitations that need to be considered. Postsurgical pain was assessed both in terms of average pain and in terms of worst pain experienced. Only the latter was analyzed here as outcome. Average pain presented a bimodal distribution, which raises issues regarding its accuracy and statistical reliability, and thus we decided not to use it as an outcome variable. Furthermore, sometimes women were not able to understand the concept of average pain, which is more an integrative measure. This could also have affected the accuracy of the measure and might have influenced its final statistical properties and distribution.

The outcome variable, worst level of postsurgical pain, was assessed only 48 hours after surgery. This assessment at 48 hours after surgery was not focused on the pain at that exact assessment time but rather on the worst level of pain perception during the past 48 hours. We might question whether a more regular assessment of pain intensity, such as at 12, 24 and 48 hours after surgery, could describe more accurately the acute postsurgical pain experience.

Finally, this is a single-site and single-country study, and thus the generalization of the conclusions to populations in other countries should be considered with caution. Future studies need to be conducted to analyze whether this effect can be replicated.

### 4.3. Clinical practice implications

The integrative model presented here reveals the simultaneous influence that demographic, clinical and psychological factors may have on postsurgical pain. This is a heuristic parsimonious model that may have clinical implications in understanding and evaluating postsurgical pain, and can be applied directly and easily in the presurgical period to women scheduled for hysterectomy. A clinician can quickly assess these variables without the need of a long and complex protocol that would require highly specialized training. By knowing patient age, presurgical pain, presence or absence of pain due to other causes, levels of pain catastrophizing, and presurgical anxiety, clinical practitioners can quickly and pragmatically assess the risk of women undergoing hysterectomy to develop moderate to severe postsurgical pain. In sum, with this practical model, women at risk for increased acute postsurgical pain can easily be identified and targeted with appropriate intervention strategies.

Our study identified 2 factors amenable to change or to active management through psychological presurgical interventions, namely presurgical anxiety and pain catastrophizing. To deal with anxiety, brief cognitive behavior therapy intervention techniques (such as brief relaxation) have been widely used [9,34,76]. Our results shift the focus to the role of cognitive factors in acute postsurgical pain, suggesting that presurgery interventions should address pain catastrophizing cognitions. These interventions delivered before surgery should aim at challenging and substituting the negative cognitive contents associated with pain catastrophizing with positive pain coping self-statements [9,25,34,56,76]. Such an intervention would be easy to implement within the 24-hour period preceding surgery, when women are already in the hospital setting.

## Conflict of interest statement

None declared.

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Chapter 2.1.2

**STUDY 2**

Pinto, P.R., McIntyre, T., Fonseca, C., Almeida, A., & Araújo-Soares, V.

**Pre and post-surgical factors that predict the provision of rescue analgesia following hysterectomy**

(*Manuscript under review*)

**Pre and post-surgical factors that predict the provision of rescue analgesia following hysterectomy**

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**ABSTRACT**

**Background**: To better manage post-surgical pain, standardized analgesic protocols allow for rescue analgesia (RA). This study seeks to determine which pre and post-surgical clinical and patient-related factors, in addition to post-surgical pain, may influence healthcare professional decisions on RA administration.

**Methods**: A consecutive sample of 185 women, submitted to hysterectomy for benign disorders, was assessed 24 hours before (Time 1; T1) and 48 hours after (Time 2; T2) surgery. At Time 1, baseline demographic, clinical and psychological predictors were assessed and at Time 2, post-surgical pain, anxiety and RA administration were recorded.

**Results**: Logistic regressions revealed several pre-surgical (T1) factors associated with post-surgical RA: being anesthetized with only general or locoregional anaesthesia (Model 1: OR = 2.008, $p = 0.023$; Model 2: OR = 2.003, $p = 0.024$), having other previous pain states (Model 1: OR = 2.678, $p = 0.002$; Model 2: OR = 2.788, $p = 0.024$), pre-surgical fear (OR = 1.191, $p = 0.044$) and pain catastrophizing (OR = 1.654, $p = 0.010$). Concerning post-surgical variables, higher pain intensity (OR, 1.591; 95% CI, 1.353-1.871, $p < 0.001$) and post-surgical anxiety (OR, 1.245; 95% CI, 1.084-1.430, $p = 0.002$) were significantly associated with RA provision.

**Conclusions**: Healthcare decision-making to administer RA might be influenced not only by post-surgical pain intensity but also by pre-surgical clinical factors, such as previous pain and type of anaesthesia. Patient-related psychological characteristics, such as pre-surgical fear, pre-surgical pain catastrophizing and post-surgical anxiety, may also play a role in decision-making on RA provision. Implications for practice are discussed.

## 1. Introduction

Acute post-surgical pain constitutes the most common, anticipated and expected problem after surgery (Apfelbaum et al., 2003; Strassels et al., 2005). However, if not managed properly, it may have detrimental systemic effects (Macintyre et al., 2010). Acute Pain Services address this problem through standardized analgesia protocols focused on pain management. These protocols are determined according to expected pain severity given the type of surgery and individual characteristics. Despite these efforts, patients respond differently, showing distinct analgesic needs and reporting varying levels of pain even when submitted to the same surgical and analgesic procedures (Rasmussen, 2007). All analgesia protocols include the possibility of administering extra doses of analgesics, called rescue analgesia (RA). Post-surgical pain guidelines state that a pain numerical rating scale (NRS) above 3, on a scale of 0-10, is the necessary indication for RA provision (Hartrick et al., 2003; Dihle et al., 2006). Thus, complaints, reports or assessments of high post-surgical pain intensity may lead to RA administration. Previous studies have identified surgery type, age, and psychological distress as predictors for higher analgesic consumption after surgery (Ip et al., 2009). However, there is a general lack of studies focusing on decision-making regarding RA provision.

We evaluated which pre and post-surgery clinical and patient-related factors may influence healthcare professional decisions on RA administration, among women submitted to hysterectomy for benign disorders. It examines the role of clinical variables, other than post-surgical pain, in RA provision, as well as key psychological factors, pre and post-surgery, that may impact clinical decision-making regarding RA. Understanding the variables that influence clinical decisions on RA provision should support better acute post-surgical pain control and management for women submitted to hysterectomy for benign disorders.

## 2. Materials and Methods

### 2.1. Participants and General Procedures

The study was conducted in a central hospital in northern Portugal. Ethical approval was granted by the Hospital's Ethic Committee. Patient informed consent was obtained.

All patients received routine care and no research-related change was introduced in the standard clinical protocol. Healthcare professionals were blind to their patient's participation in the study.

The study was a prospective cohort study with Time 1 and Time 2 measures (see below) performed between March 2009 and September 2010. After informed consent, a consecutive sample of 203 women undergoing hysterectomy was enrolled (all invited participants accepted). Inclusion criteria were age between 18 and 75 years, and the ability to understand the patient information sheet, consent form and questionnaire materials. Exclusion criteria were existing diagnoses of psychiatric (e.g. schizophrenia) or neurologic (e.g. dementia) pathology and undergoing hysterectomy due to malign disease. Emergency hysterectomies were also excluded due to procedural reasons.

Women were initially assessed 24 hours before (Time 1; T1) and 48 hours after (Time 2; T2) surgery, at the Hospital. From Time 1 to Time 2, eight women were withdrawn due to canceled surgery (n=3), early discharge from hospital (n=2), unavailability during post-surgical assessment (n=1), or review of surgical procedure during surgery (oophorectomy, n=1; and miomectomy, n=1).

Furthermore, as certain analgesic protocols were applied to very few patients, 10 women were excluded (see below) and did not differ significantly from the remaining 185 women in terms of baseline characteristics (demographic, clinical and psychological). These excluded were protocols that: (i) were based on PCA (patient-controlled analgesia) devices (*n*=2); (ii) included solely the coadjuvant analgesics, which were paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs: ketorolac or parecoxib) (*n*=5); (iii) excluded the administration of NSAIDs (*n*=3) due to patients' health issues, such as allergies or diseases that prevented them from being prescribed NSAIDs (e.g. gastrointestinal disease). This left 185 women with Time 1 and Time 2 measures who underwent hysterectomy due to benign causes.

### 2.2. Pre-surgical assessment

Upon hospital admission, 24 hours before surgery (T1), the following baseline questionnaires were administered by a trained psychologist:

(1) Socio-Demographic and Clinical Data Questionnaire: collects information on age, education, residence, marital and professional status, household and parity, previous pre-surgical pain (related with the disease underlying surgery ), analgesic consumption, other previous pain states (acute or chronic, but not related to surgery), previous surgeries, height, weight, menopause

status, diagnosis/indication for hysterectomy and disease onset, as well as the use of psychotropic drugs (anxiolytics and anti-depressants).

(2) Numerical Rating scale (NRS) (Hartrick et al., 2003): assesses worst intensity of pre-surgical and post-surgical pain on an 11 point numerical rating scale where "0" represents "no pain" and "10" the "worst pain imaginable".

(3) Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983): includes two sub-scales that measure anxiety (HADS-A; $\alpha$ = 0.80) and depression (HADS-D; $\alpha$ = 0.78). Each subscale includes 7 items, with scores ranging from 0 to 21, resulting from the addition of the 7 items (each one ranging from 0 to 3). Higher scores represent higher levels of anxiety and depression.

(4) Surgical Fear Questionnaire (Peters et al., 2007): assesses specific surgical fears using 10 items in two subscales, "Fear of immediate consequences of surgery" ($\alpha$ = 0.77; e.g. "I am afraid of the anaesthesia.") and "Fear of long-term consequences of surgery" ($\alpha$ = 0.62; e.g. "I am afraid that I won't recover completely from the operation."). To generate each total subscale score, the sum of the item scores was divided by the number of items. Thus, scores range between 0 (no fear) and 10 (most extreme fear), with higher values reflecting higher levels of fear.

(5) Coping Strategies Questionnaire – Revised Form (CSQ-R) (Riley and Robinson, 1997): includes 27 items that assess 6 pain coping strategies: "Distraction/diverting attention" ($\alpha$ = 0.77; e.g. "I do something I enjoy, such as watching TV or listening to music."), "Praying and hoping" ($\alpha$ = 0.87; e.g. "I pray for the pain to stop."), "Ignoring pain sensations" ($\alpha$ = 0.92; e.g. "I don't think about the pain."), "Reinterpreting pain sensations" ($\alpha$ = 0.74; e.g. "I imagine that the pain is outside of my body."), "Pain coping self-statements" ($\alpha$ = 0.70; e.g. "I tell myself that I can overcome the pain.") and "Pain catastrophizing" ($\alpha$ = 0.87; e.g. "It's awful and I feel that it overwhelms me."). Instead of the usual 7-point Likert-type scale, items were rated on a 5-point scale (1=never, 2=almost never, 3=sometimes, 4=almost always, and 5=always) due to difficulties with the 7-point format encountered in our previous research (Pinto et al., 2012). To generate each total subscale score, the sum of the item scores was divided by the number of items. Hence, sub-scale scores vary between 1 and 5, with higher scores indicating greater use of the specific coping strategy.

## 2.3. Surgical Procedure and Anesthetic Technique

Clinical data related to surgery and to anaesthesia were retrieved from medical records. From the selected sample of 185 women who underwent surgery, 139 (75.1%) were submitted to total abdominal hysterectomy (TAH), 30 (16.2%) to vaginal hysterectomy (VH), 11 (5.9%) to total laparoscopic hysterectomy (TALH) and 5 (2.7%) had laparoscopically assisted vaginal hysterectomy (LAVH). Concomitant procedures, such as oophorectomy, ovarian cystectomy, salpingectomy, cystoscopy or vaginal repair, were also performed in some patients; however, this refined distinction was not considered for the purpose of this study. Among abdominal hysterectomies (n=139), incision was indicated as being Pfannenstiel (n=116) or vertical (n=23), with the former being the first choice and the latter being performed just in cases of a previous median surgical scar and in exploratory laparotomy. For all women uterus weight and height were also recorded. The type of anaesthesia was classified as general (n=50/27.0%), locoregional (n=22/11.9%) or combined (general + locoregional; n=113/61.1%) and ASA score (physical status classification of the American Society of Anesthesiologists) was recorded, including cases of ASA grade I (53/28.6%), II (120/64.9%) and III (12/6.5%).

## 2.4. Post-surgical assessment

### 2.4.1. Primary outcome measure: rescue analgesic consumption

All patients were assigned to a standardized analgesia protocol, established prior to patient transfer to the infirmary, which was determined and supervised by the Acute Pain Unit, led by an Anesthesiologist. RA provision by the health care team was based on pain behavior observations (e.g. verbal and non-verbal expression of pain by patient) and the guidelines of the the Acute Pain Unit for RA administration. These guidelines state that patients experiencing a limiting pain (above 3 in the NRS scale), should be given additional analgesics (Hartrick *et al.,* 2003; Dihle *et al.,* 2006).

RA provision is referent to the fact that the person actually received rescue analgesia and was recorded (yes or no) from medical records. Depending on the assigned standard analgesic protocol, RA drugs could be either epidural local anesthetic [ropivacaine 0,2% (5 ml)] or intravenous petidine (20 mg). All standard analgesic protocols were designed to last for 48 h after surgery and RA drugs were available during that 48 hours period. The standard epidural protocols could be either: a) a continuous epidural infusion (DIB - delivered infusion baloon) with ropivacaine (0.1%) and fentanyl (3μg/ml) or; b) administration of an epidural morphine bolus (2-3 mg, administered from 12 to 12 hours) and ropivacaine [0,2% (5 ml)] was the RA drug correspondent to both epidural protocols. The intravenous protocol consisted of a continuous intravenous infusion (DIB) of tramadol (600 mg), metamizol (6 grams) and metoclopramide (60 mg), with intravenous petidine (20 mg) being the RA drug administered to those who were attributed these protocol. Paracetamol (1 gram administered from 6 to 6 hours) and NSAIDs (ketorolac 30 mg or parecoxib 40 mg, both administered from 12 to 12 hours) were always included as coadjuvant analgesics in all protocols. All analgesic regimens included prokinetic treatment that was standardized to metoclopramide (10 mg i.v. administered from 8 to 8 hours).

#### 2.4.2. Acute post-surgical pain

Women were asked to rate their worst pain level within the first 48 hours after surgery, using the 11-point NRS.

#### 2.4.3. Analgesics' secondary effects: postoperative nausea and vomiting (PONV) and pruritus

In the first 48 hours, either the occurrence of PONV or the occurrence of pruritus was recorded. In cases of moderate or severe PONV, ondansetron (4 mg i.v. 8 hourly) was administered. In order to prevent PONV, all patients were prophylactically medicated with dexamethasone (10 mg) during surgery. The occurrence of pruritus was categorized in the same manner, with moderate and severe levels requiring antipruritus treatment that consisted on hydroxyzine administration (25 mg i.m. 8 hourly). In order to control for potential side effects, that can be more pronounced if RA is administered, information on the prescription of ondansetron or hydroxizine was retrieved from medical records.

#### 2.4.4. Post-surgical anxiety

Post-surgical anxiety was assessed using the anxiety subscale of the HADS ($\alpha$ = 0.85). The use of psychotropic drugs (anxiolytics and anti-depressants) during hospital stay was also recorded.

## 2.5. Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 19.0). Internal consistency of scale scores was assessed using Cronbach's alpha internal consistency reliability coefficients (Cronbach, 1951) [see $\alpha$ (Cronbach's alpha) values above].

The outcome variable in this study is RA consumption, a dichotomous variable (no *vs* yes). Normality for continuous variables was assessed with the Kolmogorov-Smirnov Test and variable distribution was not normal for both the total sample and subgroups (with or without RA administration). Mann-Whitney U and Chi-square tests were performed to compare RA subgroups on demographic, clinical, and psychological measures prior to surgery. The results of these analyses were used to guide the choice of predictors to enter in the logistic regressions. Descriptive statistics for continuous variables are presented as medians and range, and categorical data are presented as numbers and percentages. Spearman correlations were calculated amongst the psychological variables that distinguished between RA groups in order to further investigate the strength of association between psychological constructs. In all comparisons, two-sided tests were performed with $p < 0.05$ used to indicate statistical significance.

Three different logistic regression models were used to analyze the factors associated with RA administration. Two of the models aimed to determine pre-surgical (T1) and surgical predictors whereas the third one sought to find post-surgical (T2) predictors. The variables included in the logistic binomial hierarchical regression models were the ones which were found to distinguish between the two RA groups (with and without RA administration). Due to shared common variance among psychological factors (see **Table S1**), two separate regression models were conducted: Model 1 with clinical factors and pre-surgical emotional factors (anxiety and fear) and Model 2 with clinical factors and negative coping. For Models 1 and 2, "Type of anaesthesia" was entered on step 1 and "Other previous pain states" on step 2. In Model 1, "pre-surgical anxiety" and "pre-surgical fear of immediate consequences of surgery" were entered jointly in step 3. For Model 2, pre-surgical pain catastrophizing was entered in step 3. Another model was tested which included the same variables as Models 1 and 2, in the first two steps, and positive coping strategies in step 3 ("pre-surgical coping self-statements" and "pre-surgical reinterpreting pain sensations"). This model was not significant for coping factors and is not reported. In respect to the regression model focused on post-surgical (T2) predictors of RA provision, "acute post-surgical pain" was entered in step 1 and "post-surgical anxiety" was entered in step 2. In all regression models, to exclude the influence of multicollinearity, we calculated the variance inflation factor value (VIF) for the independent variables in the equation and the variable was included in that model if VIF < 2.

Additional statistical analyses were performed to address possible confounding factors regarding the variability of the different regimes for both standard analgesia protocols. Mann-Whitney U and Chi-square tests were performed to determine if there were any differences amongst the protocols regarding either the administration of RA or the intensity of post-surgical pain.

## 3. Results

### 3.1. Socio-demographic, clinical and psychological characteristics of RA groups

From a total sample of 185 women, 91 were administered RA after surgery whereas 94 were not. **Table 1** presents descriptive statistics on the pre-surgical socio-demographic, clinical and psychological characteristics of the total sample and RA subgroups, as well as the results of non-parametric tests (Mann-Whitney U and Chi Square tests) which compare RA subgroups. RA subgroups did not differ on any of the socio-demographic measures. On clinical variables, a higher percentage of women who were given RA presented previous pain states ($\chi 2$=9.28, $p$=0.002). Furthermore, women provided with RA showed a worst psychological profile, with more "pre-surgical anxiety" (Z=-2.17, $p$=0.03), more "fear of immediate consequences of surgery" (Z=-2.45, $p$=0.014), and fewer adaptive pain coping strategies (more pain catastrophizing and less positive coping).

Results of post-surgical variables are presented in **Table 2**. Type of anaesthesia seems to be related with RA provision: Women with combined anaesthesia (general + locoregional) were less likely to receive RA ($\chi 2$=5.232, $p$=0.022). In addition, 48 hours after surgery, RA was more frequently delivered to women who reported higher level of post-surgical pain (Z=-6.80, $p$<0.001) and more anxiety (Z=-5.24, $p$<0.001). No association was found between RA provision and the occurrence of side effects (like PONV or pruritus) as evidenced by the administration of ondansetron ($\chi 2$=1.33, $p$=*0.249*) or hydroxizine ($\chi 2$=1.94, $p$=*0.164)*.

### 3.2. Comparison amongst standardized analgesic protocols

Results of the Mann-Whitney U and Chi-square tests, respectively, revealed that there were no differences between analgesic protocols both in terms of post-surgical pain intensity ($z=-0.383$, $p=0.701$) and in RA provision ($\chi2=1.687$, $p=0.194$) (**Table S2**). Therefore, the variability of the standard analgesic protocols did not seem to be influencing the results of these two post-surgical variables.

### 3.3. Factors associated with RA provision

To analyze the factors associated with RA provision, three logistic hierarchical regression analyses were conducted.

The first two regressions tried to predict RA provision, from baseline measures. The variables entered at each step, have been previously noted and are presented in **Table 3**. In Models 1 and 2 (pre-surgical factors), "type of anaesthesia" emerged as a significant predictor of RA provision as did "other previous pain states" (Model 1: OR = 2.008, 95% CI 1.101-3.661, $p = 0.023$ and OR = 2.678, 95% CI 1.421-5.050, $p = 0.002$; Model 2: OR = 2.003, 95% CI 1.095-3.664, $p = 0.024$ and OR = 2.788, 95% CI 1.467-5.298, $p = 0.002$). "Pre-surgical anxiety", was entered in step 3, along with "pre-surgical fear of the immediate consequences of surgery" (see Model1). The former was not a significant predictor of RA provision whereas the latter emerged as a significant factor (OR = 1.191; 95% CI 1.004-1.413, $p = 0.044$). When "pain catastrophizing" was included in the third step (Model 2), the results were also significant for the prediction of RA delivery (OR = 1.654, 95% CI 1.129-2.424, $p = 0.010$).

A third logistic regression analysis was performed to examine post-surgical predictors. More specifically, it aimed at determining whether RA provision is simply influenced by post-surgical pain intensity (NRS>3 = RA) or if psychological factors that may affect doctor-patient communication, such as post-surgical anxiety and its manifestation (in overt and covert behaviors), is also a contributing factor. This hierarchical logistic regression model (**Table 4)** included two steps: "worst level of post-surgical pain intensity" (step 1) and "post-surgical anxiety" (step 2). In the final model, both "worst level of post-surgical pain intensity" (OR = 1.591, 95% CI 1.353-1.871, $p < 0.001$) and "post-surgical anxiety" (OR = 1.245, 95% CI 1.084-1.430, $p = 0.002$) were significantly associated with RA administration 48 hours after surgery. As can be shown on **Table 4**, after controlling for “worst level of post-surgical pain”, “post-surgical anxiety” remained as a significant risk factor for RA delivery.

## 4. Discussion

This study sought to determine which factors may influence clinical decisions on rescue analgesia (RA) provision after hysterectomy. The results indicate that RA provision may be influenced not only by clinical issues, such as post-surgical pain intensity, but also by patient-related psychological characteristics, such as pre-surgical fear, pain catastrophizing and post-surgical anxiety. These factors are likely to influence patient-provider interactions.

### 4.1. Predictors of rescue analgesia provision

#### 4.1.1. Baseline clinical predictors

Concerning clinical factors, type of anaesthesia (general or locoregional, in isolation versus combined) was a significant predictor of RA provision. Providers tended to administer RA more often to women without a combined protocol. In fact, a higher incidence of post-surgical pain has been reported for patients submitted to a non-combined protocol (Aubrun et al., 2008). Accordingly, we could hypothesize that women without a combined protocol actually did experience less pain, being that the reason for not being so often administered with RA. However and interestingly in present sample there were no significant differences between the two anaesthesia groups in terms of post-surgical pain intensity. Therefore, this finding may be related to a tendency of professionals to associate combined anaesthesia with less pain experience, regardless of patients actual pain experience.

The report of “other previous frequent pain states” (acute or chronic, but not related to surgery) emerged as a predictor of RA delivery, although pre-surgical pain (related to surgery) did not distinguish between RA groups. Within this sample, pre-surgical pain was not a strong determinant of the decision to perform surgery, as 40% of women did not present pain symptoms related to the scheduled surgery (60% did). However, having previous pain that hysterectomy does not resolve, may have had detrimental impact. Prolonged pain stimulation can exacerbate the nociceptive system through mechanisms of peripheral and central sensitization of nociceptors and central nervous system neurons, respectively (Latremoliere and Woolf, 2009). In our sample, we found an association between previous pain, and acute post-surgical pain intensity and pain catastrophizing (Z=-2.79, *p*=0.005; Z=-3.29, *p*=0.001). This suggests that psychological factors may mediate this relationship, in addition to peripheral and central nervous system changes. These specific relationships, to the best of our knowledge, have not been explored.

In terms of how previous pain might affect RA provision, two mechanisms may be considered: (1) *The American Society of Anesthesiologists Task Force on Acute Pain Management* recommends a detailed pre-anesthetic assessment that takes into account patients' previous pain history (ASA Task Force on Acute Pain Management, 2004); this information may influence clinical decision-making regarding RA. (2) One may also speculate that these patients would experience higher pain intensity post-surgery and express more pain complaints, which could also influence decisions regarding RA administration.

#### 4.1.2. Baseline psychological predictors

A key contribution of this study is the investigation of psychological factors, pre and post-surgery, that might impact RA provision. The results confirmed that emotional and cognitive-behavioural patient characteristics predict RA provision. Women with higher pre-surgical fear of immediate consequences of surgery, more pain catastrophizing, and higher post-surgical anxiety, received RA more often.

##### 4.1.2.1. Pre-surgical fear

Pre-surgical anxiety has been considered as one of the most important psychological predictors of analgesic consumption (Ip et al., 2009; Macintyre et al., 2010). However, in this study, pre-surgical anxiety was not a significant predictor whereas pre-surgical fear was. One possible reason for this finding is that the surgical fear questionnaire embraces more closely the concerns of women undergoing surgery (e.g. fear of surgery, anaesthesia, pain and pain side-effects) than the Hospital Anxiety and Depression Scale (HADS). Pre-surgical fear maybe expressed both verbally and non-verbally, thus exerting influence on provider decisions to administer RA. Few studies have addressed pre-surgical fears (e.g. Kindler et al.; 2002; Peters et al., 2007; Sommers et al., 2010). Studies using the same scale in patients undergoing a variety of surgical procedures (Peters et al., 2007; Sommers et al., 2009, 2010), found that pre-surgical fear is an important predictor of acute post-surgical pain. As far as we know, the current study is the first one focusing on the relation between pre-surgical fears and RA and it is also the first one employing the Surgical Fear Questionnaire (Peters et al., 2007) to the study of RA.

#### 4.1.2.2. Pain catastrophizing

The current study found that patients with higher pain catastrophizing were given more RA by healthcare providers. Some studies have evaluated the role of pain catastrophizing as predictor of analgesic consumption (Pavlin et al., 2005;). However, to the best of our knowledge, no studies to date have focused on RA provision and in particular, RA provision after hysterectomy. In a variety of surgeries (Granot and Ferber, 2005; Pavlin et al., 2005;; Riddle et al., 2010; Pinto et al., 2012), pain catastrophizing correlated with higher post-surgical pain intensity, a finding replicated in our study (r=.33, $p$<.01). Pain catastrophizing involves magnification of the threat value of pain as well as feelings of helplessness and pessimism in the ability to deal with it (Sullivan et al., 2001; Quartana et al., 2009). Therefore, pain catastrophizing may influence the way women manifest their pain, verbally and non-verbally, thus influencing clinical decisions regarding RA provision. Strulov et al. (2007) reported that pre-surgical pain catastrophizing correlated with the patient's request for analgesia after caesarean section, albeit just in the recovery room and not in the ward, but was not investigated or explored as a potential predictor. Similarly, Granot and Feber (2005) and Pavlin *et al.* (2005), found that pre-surgical pain catastrophizing did not predict post-surgical analgesic use. Distinct assessment methods may be one reason for the differing results. These studies used a specific assessment tool tailoring only pain catastrophizing - PCS (Pain Catastrophizing scale) (Sullivan et al., 1995), whereas in our study we used a generic pain coping scale that included a Pain Catastrophizing subscale (Riley and Robinson, 1997) (see methods section).

Overall, the data on pre-surgical predictors of RA provision indicate that clinical factors weigh heavily in terms of RA provision. The results show that psychological factors carry slightly lower weight as predictors but are significant factors in RA administration. Pre-surgical fear and pain catastrophizing may act jointly to impact clinical decision-making regarding RA.

### 4.2. Post-Surgical Factors Associated with Rescue Analgesia Consumption

Another important goal of this study was to understand if the provision of RA is simply determined by post-surgical pain intensity (NRS> 3 = provision of RA) or if psychological factors, such as post-surgical anxiety, could impact RA provision. The results confirmed previous findings that having more pain after surgery was associated with more RA provision (Dahmani et al., 2001; Katz et al., 2008). However, post-surgical anxiety was also significantly associated with RA delivery, regardless of pain report. These two variables were found to be correlated (r = 39, $p$<.01; Table S1), which suggests a dynamic relationship between pain experience and emotional state during the post-surgical period. The data suggests that this duo will most likely affect RA provision.

### 4.3. Limitations of the study

The type of anesthetic procedures and RA protocols used was controlled in all analyses but not empirically standardized. Staff within the Anesthesiology unit was not fully informed of the study goals in order to assure that normal procedures would be enacted; protocols were tailored to the needs and specificities of each patient. Therefore, anesthetic procedures were recorded a posteriori. Additional analyses, already reported, do not support the existence of potential confounding effects of type of anaesthetic protocol both in terms of post-surgical pain intensity and RA administration.

This study only measured post-surgical pain intensity and anxiety, although other psychological variables are likely to influence RA provision, such as coping style, a variable that was assessed prior to surgery. This option was due to a concern not to burden patients with too many questionnaires to fill out 48 hours after surgery.

Finally, this is a single site and single country study, which limits generalization of the results to other countries. The study population is also confined to hysterectomy patients and thus studies with other surgeries are needed. Further research is also warranted to replicate these results elsewhere.

### 4.4. Clinical implications

Findings from this study support further reflection on post-surgical pain management by healthcare professionals. Pain relief after surgery is a key condition for early post-surgical recovery (Kehlet and Holte, 2001).

The results suggest that post-hysterectomy pain management benefits from a collaborative process where pre and post-surgical psychological variables are considered to assure appropriate clinical care, given that the present study seems to reveal their influence on the decision of clinicians to administer extra analgesics - RA. Raising clinicians' awareness on the potential influence of those factors would help in a more accurate assessment of patients in need for extra analgesia.

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**Table 1**

***Descriptive statistics and group differences on pre-surgical socio-demographic, clinical and psychological variables for the total sample and the two RA subgroups (no rescue analgesia vs. rescue analgesia)***

| **Pre-surgical Characteristics** | **Total sample (*N* = 185)** | **No Rescue Analgesia (*n* = 94)** | **Rescue Analgesia (*n* = 91)** | ***p*** |
|---|---|---|---|---|
| ***Socio-demographic*** | | | | |
| Age (years) | 49 (39) | 50 (38) | 48 (36) | *0.088* |
| Marital status (married) | 158 (85.4%) | 78 (83%) | 80 (87.9%) | *0.342* |
| Parity | 2 (8) | 2 (6) | 2 (8) | *0.513* |
| Education (≤ 4 yrs) | 119 (64.7%) | 60 (64.5%) | 59 (64.8%) | *0.964* |
| Residence (urban) | 55 (29.9%) | 27 (28.7%) | 28 (31.1%) | *0.724* |
| Professional status (employed) | 91 (49.2%) | 46 (48.9%) | 45 (49.5%) | *0.944* |
| ***Clinical – general indicators*** | | | | |
| Disease onset (months) | 19.0 (358) | 18 (356) | 22 (238) | *0.133* |
| BMI (Kg/m2) | 28.6 (21.1) | 28.9 (20.4) | 28 (21.1) | *0.118* |
| Previous surgeries (yes) | 131 (70.8%) | 64 (68.1%) | 67 (73.6%) | *0.407* |
| Psychotropic use[a] | 62 (36%) | 33 (37.1%) | 29 (34.9%) | *0.770* |
| **Clinical - pre-surgical pain** | | | | |
| Pre-surgical pain (yes) | 112 (60.5 %) | 51 (54.3%) | 61 (67.0%) | *0.075* |
| Intensity (worst level) | 2 (10) | 2 (10) | 3 (10) | *0.482* |
| Pre-surgical analgesic use | 56 (30.3%) | 28 (29.8%) | 28 (30.8%) | *0.884* |
| Other previous pain states (yes)[b] | 118 (63.8%) | 50 (53.2%) | 68 (74.7%) | 0.002 |
| **Psychological measures** | | | | |
| **HADS**[c] | | | | |
| Anxiety | 7 (19) | 6 (15) | 8 (19) | 0.030 |
| Depression | 1.00 (14) | 1 (14) | 1 (11) | *0.958* |
| **Surgical Fear Questionnaire**[d] | | | | |
| Immediate consequences | 2.5 (9) | 2 (7.5) | 2.75 (9) | *0.014* |
| Long-term consequences | 2.83 (9) | 2.33 (7.5) | 3.17 (9) | *0.058* |

| | | | | |
|---|---|---|---|---|
| **CSQ-R**[e] | | | | |
| Pain Catastrophizing | 1.5 (4) | 1.33 (2.5) | 1.67 (4) | *0.005* |
| Ignoring Pain | 2.4 (4) | 2.6 (4.) | 2.2 (4) | *0.091* |
| Pain Coping Self-statements | 4 (3.5) | 4.25 (3.5) | 3.75 (3.5) | *0.012* |
| Reinterpreting Pain Sensations | 1.5 (4) | 1.5 (4) | 1.5 (2.75) | *0.053* |
| Praying and Hoping | 3.33 (4) | 3.33 (4) | 3.67 (4) | *0.504* |
| Distraction / Diverting Attention | 1.8 (4) | 1.8 (4) | 1.6 (3.4) | *0.118* |

*Note*. Continuous variables are medians (range), categorical variables are n (%).

[a] Consumption / Intake of anxiolytics and anti-depressants; [b] Other previous pain states (either acute or chronic, not related to the cause of surgery, but nonetheless frequent); [c] Hospital Anxiety and Depression Scale, with scores ranging from 0 to 21; higher scores indicate higher levels of either anxiety or depression; [d] Surgical Fear Questionnaire, with scores ranging from 0 to 10; higher scores indicating higher levels of fear; [e] Coping Strategies Questionnaire Revised, with scores ranging from 1 to 5; higher scores indicating higher levels of each coping strategy used.

**Table 2**

***Descriptive statistics and group differences on anesthetic, surgical and analgesic variables for the total sample and the two RA subgroups (no rescue analgesia vs. rescue analgesia), 48 hours after hysterectomy***

| **Post-surgical Characteristics** | **Total sample ($N$ = 185)** | **No Rescue Analgesia ($n$ = 94)** | **Rescue Analgesia ($n$ = 91)** | ***p*** |
|---|---|---|---|---|
| ***Clinical – general indicators*** | | | | |
| Hysterectomy type: abdominal | 139 (75.1%) | 65 (69.1%) | 74 (81.3%) | *0.056* |
| Uterine weight (grams) | 140 (1060) | 160 (1060) | 136 (875) | *0.877* |
| Uterine height (cm) | 9 (17) | 9 (17) | 9 (14.5) | *0.894* |
| Anaesthesia: combined | 113 (61.1%) | 65 (69.1%) | 48 (52.7%) | *0.022* |
| Epidural Analgesia | 136 (73.5%) | 73 (77.7%) | 63 (69.2%) | *0.194* |
| Length of stay | 3 (15) | 3 (6) | 3(14) | *0.438* |
| Psychotropic use [a] | 71 (38.6%) | 33 (35.5%) | 38 (41.8%) | *0.382* |
| ***Clinical - pain & analgesic indicators*** | | | | |
| Worst level surgical pain[b] | 5 (10) | 3(10) | 7(8) | < 0.001 |
| Ondansetron SOS | 31 (16.9%) | 13 (13.8%) | 18 (20.2%) | *0.249* |
| Hydroxizine SOS | 17 (9.3%) | 6 (6.4%) | 11 (12.4%) | *0.164* |
| ***HADS*** [c] | | | | |
| Anxiety | 2 (19) | 0.5(13) | 4(19) | < 0.001 |

Note: Continuous variables are medians (range), categorical variables are n (%).

[a]Consumption / Intake of anxiolytics and anti-depressants; [b]NRS: Numerical Rating Scale (0 - 10); [c] Anxiety subscale of Hospital Anxiety and Depression Scale, with scores ranging from 0 to 21; higher scores indicate higher levels of anxiety.

**Table 3**

***Hierarchical binomial logistic regression results for pre-surgical and surgical predictors of rescue analgesia provision after hysterectomy* (*N* = 185)**

| **MODEL 1** | Odds Ratio (CI) | *p* |
|---|---|---|
| **Step 1** | | |
| Type of anaesthesia[a] | 2.008 (1.101 – 3.661) | *0.023* |
| **Step 2** | | |
| Other previous pain states [b] | 2.678 (1.421 - 5.050) | *0.002* |
| **Step 3 (final model)** | | |
| Type of anaesthesia[a] | 2.180 (1.150 - 4.132) | *0.017* |
| Other previous pain states [b] | 2.808 (1.433 - 5.503) | *0.003* |
| Pre-surgical anxiety[c] | 1.017 (0.933 - 1.109) | *ns* |
| Pre-surgical fear of immediate consequences of surgery[d] | 1.191 (1.004 - 1.413) | *0.044* |
| **MODEL 2** | | |
| **Step 1** | | |
| Type of anaesthesia[a] | 2.003 (1.095 – 3.664) | *0.024* |
| **Step 2** | | |
| Other previous pain states [b] | 2.788 (1.467 - 5.298) | *0.002* |
| **Step 3 (final model)** | | |
| Type of anaesthesia[a] | 2.155 (1.138 - 4.079) | *0.018* |
| Other previous pain states [b] | 2.353 (1.214 - 4.559) | *0.011* |
| Pre-surgical pain catastrophizing[e] | 1.654 (1.129 - 2.424) | *0.010* |

Note: Model 1 correctly predicted 65.4% of all patients; Model 2 correctly predicted 69.9% of all patients; CI= Confidence Interval.

[a] Dichotomous variable: 0= Combined: general + loco-regional; 1= Just general or just loco-regional; [b] Dichotomous variable: 0= Absent; 1= Present; [c] Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - Anxiety subscale; [d] Continuous variable, Surgical Fear Questionnaire - Fear of immediate consequences of surgery subscale; [e] Continuous variable, CSQ-R: Coping Strategies Questionnaire Revised - Pain catastrophizing subscale.

**Table 4**

***Hierarchical binomial logistic regression for post-surgical predictors of rescue analgesia provision after hysterectomy* (*N* = 180)**

| PREDICTORS | Odds Ratio (CI) | *p* |
|---|---|---|
| **Step 1** | | |
| Post-surgical pain intensity (worst level)[a] | 1.701 (1.452 – 1.994) | *<0.001* |
| **Step 2 (final model)** | | |
| Post-surgical pain intensity (worst level)[a] | 1.591 (1.353 – 1.871) | *<0.001* |
| Post-surgical anxiety[b] | 1.245 (1.084 – 1.430) | *0.002* |

Note. After removing 5 outliers, the final model correctly predicted 75.0% of all patients; CI = Confidence Interval.

[a] Continuous variable, NRS: Numerical Rating Scale (0 - 10); [b] Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale.

**Table S1**

***Spearman correlation coefficients among psychological variables and with post-surgical pain***

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1. ANX T1 | - | .57*** | .54*** | -.35*** | -.10 | .43*** | .25** |
| 2. Fear | | - | .38*** | -.35*** | -.19* | .29*** | .19** |
| 3. Pain CAT | | | - | -.49*** | -.26*** | .35*** | .33** |
| 4. Pain SS | | | | - | .42*** | -.38*** | -.22** |
| 5. RE Pain | | | | | - | -.08 | -.12 |
| 6. ANX T2 | | | | | | - | .39*** |
| 7. PS Pain | | | | | | | - |

**p*<.05. ***p*<.01. ****p*<.001.

ANX T1= Pre-surgical anxiety at T1 (HADS: Hospital Anxiety and Depression scale); Fear= Fear of immediate consequences of surgery (Surgical Fear Questionnaire subscale); Pain CAT= Pain catastrophizing (CSQ-R: Coping Strategies Questionnaire - revised); Pain SS= Pain coping self-statements (CSQ-R: Coping Strategies Questionnaire - revised); RE Pain= Reinterpreting pain sensations (CSQ-R: Coping Strategies Questionnaire - revised); ANX T2= Post-surgical anxiety at T2 (HADS: Hospital Anxiety and Depression scale); PS Pain=Worst level of acute post-surgical pain intensity.

**Table S2**

***Results of the Chi-Square and Mann-Whitney U tests for the comparison between standardized analgesic protocols, in terms of RA provision and post-surgical pain intensity 48 hours after hysterectomy* (*N*=185)**

| | **ANALGESIC PROTOCOLS** | | |
|---|---|---|---|
| | **Intravenous (*n* =49) (Petidine 20 mg)** | **Epidural (*n* =136) (Ropivacaine 0.2%)** | ***p*** |
| RA provision (yes) | 28 (57.1%) | 63 (46.3%) | *0.194* |
| Post-surgical pain intensity[a] | 5 (10) | 5 (10) | *0.701* |

Note: Continuous variable *post-surgical pain intensity* is median (range), categorical variable *RA provision* is n (%).

[a]NRS: Numerical Rating Scale (0 - 10)

Chapter 2.1.3

**STUDY 3**

Pinto, P.R., McIntyre, T., Nogueira-Silva, C., Almeida, A., & Araújo-Soares, V.

**Risk factors for persistent post-surgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study**

(*Manuscript under review*)

**Risk Factors for Persistent Post-surgical Pain in Women undergoing Hysterectomy due to Benign Causes: a Prospective predictive Study**

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**Abstract**

Persistent post-surgical pain (PPSP) is a major clinical problem with significant individual, social and health care costs. The aim of this study was to examine the role of demographic, clinical and psychological risk factors in the development of persistent post-surgical pain (PPSP) after hysterectomy due to benign disorders. In a prospective study, a consecutive sample of 186 women was assessed 24 hours before (T1), 48 hours (T2) and 4 months (T3) after surgery. Regression analyses were performed to identify predictors of PPSP. Four months after hysterectomy, 93 (50%) participants reported experiencing pain (NRS>0). Age, pain due to other causes and type of hysterectomy emerged as significant predictive factors. Baseline pre-surgical psychological predictors identified were anxiety, emotional representation of the condition leading to surgery and pain catastrophizing. Acute post-surgical pain frequency and post-surgical anxiety also revealed a predictive role in PPSP development. These results increase the knowledge on PPSP predictors and point healthcare professionals towards specific intervention targets such as anxiety (pre and post-surgical), pain catastrophizing, emotional representations and acute pain control after surgery.

Keywords: hysterectomy; persistent post-surgical pain; anxiety; emotional illness representation; pain catastrophizing.

## 1. INTRODUCTION

Hysterectomy is the most common gynecologic surgery performed in women in Western countries.[4,69] Although acute pain is an anticipated and expected outcome after surgery,[2,78] the development of chronic or persistent post-surgical pain (PPSP) is a common adverse unforeseen outcome.[62] PPSP refers to pain that is developed after surgery, persisting at least for two months following surgery. Other causes for such pain, i.e., malignancy, chronic infection, pre-existing pain, recurring disease, must be excluded.[48,50] PPSP is a major clinical problem with significant individual, social and health care costs.[36,61,74] This often under-reported problem is sometimes considered a "silent epidemy" (*p*.74)[82] and has recently been recognized as a possible and common consequence of several types of surgeries[16,48-50] leading to increasing research in this area.[49,73] Incidence rates of PPSP depend on the type of surgery and range from 10% to 60%[1]. The variability in incidence rates might be due to different study designs and methodologies, surgical techniques, selected samples and PPSP definitions used.

Several individual, pre-surgical, intra-surgical and post-surgical factors such as age, type of surgery, previous pain (related and not related to surgery) and acute post-surgical pain[37,47,62,83] have been identified as predictors for the development of PPSP. Moreover, a recent systematic review[29] focusing on psychosocial predictors of PPSP, identified pre-and post-surgical psychological distress and negative emotional states as risk factors for PPSP. Anxiety and depression have emerged as predictors of persistent pain after surgery in some studies,[6,22] but not in others.[80] Strategies of functional or dysfunctional coping with pain, such as pain catastrophizing, have also been examined as potential predictors but evidence to date is inconclusive.[21,70] A recent systematic review concluded that more high quality studies are needed, with standardized measures, appropriate follow-up periods and sufficient power.[29]

Other potentially important but understudied determinant of PPSP are patients' illness perceptions. The Common-Sense Self-Regulation Model (CS-SRM)[43,44] suggests that in the context of an illness, people tend to develop individual cognitive and emotional representations of their illness.[20,28,42,64] These presentations have been shown to explain significant variation in outcomes in a wide range of medical conditions and in response to different treatments.[27,56,64] Past studies using this theoretical perspective focused on the associations between illness representations and functional activity, post-surgical adjustment or surgical recovery, rather than on their relationship with pain outcomes.[45,53,60] However, to date, no study has focused on the relationship between illness representations and PPSP.

The present study aims to examine the joint role of socio-demographic, clinical and psychological risk factors for the development of PPSP 4 months after hysterectomy for benign causes in order to develop a more comprehensive understanding of possible causes of PPSP and potential targets for psychosocial interventions.

## 2. MATERIALS AND METHODS

### 2.1. Participants and Procedure

This study was conducted in a central hospital in northern Portugal (Alto Ave Hospital Center). Ethical approval was granted by the Hospital Ethics Committee. This was a prospective study with assessments 24 hours prior to surgery (T1) and 48 hours (T2) and 4 months after surgery (T3). Assessments were performed between March 2009 and January 2011. A consecutive sample of 203 women undergoing hysterectomy was invited to take part in the study and all provided written informed consent. Inclusion criteria were age between 18 and 75 years, and the ability to understand consent procedures and questionnaire materials. Exclusion criteria were existing diagnoses of psychiatric or neurologic pathology (e.g. dementia) and undergoing hysterectomy due to malign conditions. Emergency hysterectomies were also excluded due to procedural reasons. Time 1 and T2 assessments took place in hospital, T3 follow-up assessment was conducted by telephone. From T1 to T2, 8 women were withdrawn due to: cancelled surgery (n = 3), early discharge from hospital (n = 2), unavailability during post-surgical assessment (n = 1), or review of surgical procedure during surgery (bilateral oophorectomy, n = 1; miomectomy, n = 1). From T2 to T3, 9 women were excluded due to reoperation (n=4), malignancy outcomes (n=1) and unavailability (n=4). Thus, data for 186 women at T1, T2 and T3 were available for analysis.

### 2.2. Measures

All instruments and study procedures were piloted at an initial stage with a sample of 20 women for evaluation of their acceptability, feasibility and comprehensibility. Those women were not included in the final sample. During the study all questionnaires and interviews were conducted by a trained postgraduate psychologist.

### 2.2.1. Pre-surgical assessment – 24 hours before surgery.

Upon hospital admission, 24 hours before surgery (T1), the following baseline questionnaires were administered, in a face to face interview.

**(1) Socio-Demographic & Clinical factors**

- Socio-Demographic and Clinical Data Questionnaire: included questions on age, height, weight, education, residence, marital status, professional status, household and parity, previous pain (related to the cause of surgery) and its duration and frequency, pain due to other causes (either acute or chronic, not related to the cause of surgery, but nonetheless frequent), previous surgeries, menopause, diagnosis/indication for hysterectomy and disease onset, as well as the use of psychotropic drugs (anxiolytics and anti-depressants).
- The Brief Pain Inventory – short form (BPI-SF)[15] used with patients presenting pre-surgical pain. It measured: pain intensity on an 11 point numerical rating scale (0 represents "no pain" and 10 the "worst pain imaginable"); analgesic intake; perception of analgesic relief; pain interference with daily life (general activity, mood, walking, work, relations with others, sleep and enjoyment of life) and pain location in the body. Higher scores represent higher levels of pain interference. In this study, the internal consistency reliability[17] for the pain interference subscale scores was very high (T1: $\alpha$ = 0.92; T3: $\alpha$ = 0.90).

**(2) Psychological factors**

- The Hospital Anxiety and Depression Scale (HADS)[85] was used to measure anxiety (HADS-A) and depression (HADS-B). Each subscale is comprised of 7 items, with a subscale score ranging from 0 to 21, resulting from the sum of each item on a Likert scale ranging from 0 to 3. Higher scores represent higher levels of anxiety and depression. In the current sample, internal consistency reliability[17] was adequate for both anxiety T1: α = 0.78; T2: α = 0.81; T3: α = 0.88) and depression (T1: α = 0.80; T3: α = 0.85).

- The Revised Illness Perception Questionnaire (IPQ-R)[57] was used to assess patient beliefs about the underlying condition that lead to surgery, analyzing distinct dimensions of illness perceptions: "timeline acute/chronic" (e.g. "My illness will last for a long time"; α=0.78); "timeline cyclical" (e.g., "My symptoms come and go in cycles"; α=0.75); "consequences" (e.g., "The disease underlying surgery has major consequences on my life"; α=0.55); "personal control" (e.g., "I have the power to influence my illness"; α=0.54); "treatment control" (e.g., "Surgery can control my illness"; α=0.76); "illness coherence" (e.g., "My illness is a mystery for me"; α=0.78); "emotional representation" (e.g., "When I think about my illness I get upset"; α=0.87). With the exception of "consequences" and "personal control" subscales, with low internal consistency (0.55 and 0.54, respectively), the remaining sub-scales presented adequate properties. In this study, and with the aim of reducing participant burden, a psychometrically shortened version[77] was used with each of the 7 subscales composed by 3 items each. To generate each total subscale score, the mean response was computed. Hence, each subscale is rated on a scale of 1-5, in which high scores reveal less adaptive illness perceptions results, with the exception of personal and treatment control subscales, which score inversely.
- The Surgical Fear Questionnaire[63] was used to assess specific surgical fears through 10 items aggregated in 2 subscales, "fear of immediate consequences of surgery" (6 items) and "fear of long-term consequences of surgery" (4 items). Each item score ranges from 0 to 10; to calculate each total subscale score, the sum of the item scores was divided by the number of items. Thus, each subscale is rated on a scale of 0-10, with higher values reflecting higher levels of fear. In the present study, internal consistency[17] was 0.77 (fear of immediate consequences of surgery) and 0.62 (fear of long-term consequences of surgery).
- The Coping Strategies Questionnaire – Revised Form (CSQ-R)[71] was used to assess 6 coping strategies with pain: "distraction/diverting attention" (α=0.77); "praying and hoping" (α=0.87); "ignoring pain sensations" (α=0.92); "reinterpreting pain sensations" (α=0.74); "pain coping self-statements" (α=0.71) and "pain catastrophizing" (α=0.87).

During pilot testing several subjects were confused by the usual seven-point Likert-type scale, therefore, items were presented on a five-point adjective rating scale (1=never, 2=almost never, 3=sometimes, 4=almost always, and 5=always). To generate the total subscale score, the sum of the item scores was divided by the number of items. Subscale scores vary between 1 and 5, with higher scores indicating greater use of the specific coping strategy (either adaptive or non-adaptive).

### 2.2.2. Post-surgical assessment – 48 hours after surgery

Forty-eight hours after surgery (T2), women were assessed in a face to face interview.

#### (1) Acute post-surgical pain measurement

Women were asked to rate the intensity of their worst and average pain level within the first 48 hours after surgery, as well as to identify pain location and perception of analgesics relief (through the BPI-SF questionnaire described above).

Post-surgical pain frequency assessment was performed using the frequency scale of the McGill Pain Questionnaire.[55] Women could define their pain either as constant (continuous, steady), intermittent (periodic, rhythmic) or brief (momentary, transient). This specific subscale was used at T2 given that the characterization of a pain that is confined to a period of 48 hours cannot be described in terms of days, weeks or months, as was done for the assessment of pre-surgical pain at T1 and PPSP at T3.

#### (2) Clinical and psychological post-surgical measures

The use of psychotropic drugs (anxiolytics and anti-depressants) during hospital stay was detailed from hospital records. All patients were assigned to a standardized analgesia protocol for 48 hours. This protocol was determined and supervised by the Acute Pain Service and established prior to transferring the patient to the infirmary. Delivery of the analgesic protocol was either epidural or intravenous. The standardized epidural protocols were: a) a continuous epidural infusion (DIB - delivered infusion balloon) with ropivacaine (0.1%) and fentanyl (3ug/ml); or b) administration of an epidural morphine bolus (2-3 mg, 12/12h). The intravenous protocol was composed by a continuous intravenous infusion (DIB) of tramadol (600 mg), metamizol (6 gr) and metoclopramide (60 mg). Paracetamol (1 gr 6/6h) and non-steroidal anti-inflammatory drugs (NSAIDs - ketorolac 30 mg 12/12h or parecoxib 40 mg 12/12h) were always included as coadjuvant analgesics. All analgesic regimens included prokinetic treatment that was standardized to metoclopramide (10 mg i.v. 8/8h). In cases of high acute post-surgical pain levels (numerical rating scale, NRS>3) rescue analgesics were prescribed beyond the standardized analgesic protocol. Due to the great variability in analgesics' protocol and dosages, no attempt was made to determine total equianalgesic medication dosages. It was rather recorded whether rescue analgesics were given to patients or not.[66] Clinical data were obtained from patient medical records. Furthermore, women were assessed on post-surgical anxiety symptoms through the HADS anxiety subscale.

### 2.2.3. Post-surgical assessment – 4 months after surgery

Four months after surgery (T3) the following measures were assessed in a standardized telephone interview.

- Clinical variables: use of psychotropic drugs (anxiolytics and anti-depressants); menopause status (induced by surgery due to simultaneous performance of oophorectomy) and hormonal replacement therapy (HRT).
- Hospital Anxiety and Depression Scale (HADS)[85]

The following measures were administered only with patients who reported having pain 4 months post surgery.

- Brief Pain Inventory – short form (BPI-SF)[15], as described above.
- Pain description: pain frequency was described, similarly to T1, as: constant, daily, several times a week, several times a month, during sexual intercourse, by touch or lifting weight.
- Neuropathic Pain Questionnaire (DN-4):[5] previous research described PPSP as a potential neuropathic pain.[10,33,68] This instrument evaluates pain characteristics/quality through 10 items. Seven of them refer to specific pain sensory descriptors, like burning, pinpricking or numbness and patients answered if their pain had those characteristics through a dichotomous format (yes or no). The last three items result from the sensory examination of patients performed by a clinician. For the purposes of this study only the first seven items were included ($\alpha = 0.61$).

## 2.3. Surgical procedures and anesthetic techniques

Clinical data related to the surgery and anesthesia was retrieved from medical records. From the 186 women who underwent surgery, 135 (72.6%) have been submitted to total abdominal hysterectomy (TAH), 34 (18.3%) to vaginal hysterectomy (VH), 11 (5.9%) to total laparoscopic hysterectomy (TLH) and 6 (3.2%) to laparoscopically assisted vaginal hysterectomy (LAVH). In abdominal hysterectomies a Pfannenstiel incision (n=114) was usually the first choice, with a vertical infra-umbilical incision (n=21) being performed just in cases of existence of a previous vertical surgical scar. Concomitant procedures, such as oophorectomy, ovarian cystectomy, salpingectomy, cystoscopy or vaginal repair, were also performed in a few patients. We have controlled in all predictive statistical analyses for oophorectomies because of its consequences in terms of the immediate occurrence of early menopause and the eventual intake of HRT (hormonal replacement therapy). Therefore, we have distinguished women who have entered menopause because of surgery (simultaneous performance of oophorectomy) from the ones who did not and kept their previous menopause status. Likewise, HRT consumption was already registered. For all women uterus weight and height were also recorded. The type of anesthesia was classified as general (n=53/28.5%), locoregional (n=24/12.9%) or combined (general + locoregional; n=109/58.6%) and ASA score (physical status classification of the American Society of Anesthesiologists) was recorded, including cases of ASA grade I (54/29%), II (118/63.4%) and III (14/7.5%). Grade I is related to healthy patients, grade II describes mild systemic disease with no functional limitation and grade III means that severe systemic disease is present with definite functional limitation.[83]

## 2.4. Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 18.0). Internal consistency of responses to the questionnaires was assessed using Cronbach's alpha.[17] Distribution of predictive data differed significantly from normality assumptions. Thus, continuous variables are presented as median and range, and categorical data are presented as numbers and percentages. The primary outcome variable in this study is the report of PPSP, defined as pain at the 4-month follow-up [yes (presence) or no (absence)]. Mann-Whitney Test or Chi-square tests ($\chi 2$) were performed to compare socio-demographic, clinical and psychological measures in patients with and without pain 4 months after surgery. Sequential logistic regression analyses were conducted to determine risk factors for PPSP. The socio-demographic and clinical variables selected for the regression analysis were the ones that were found to distinguish between the groups of women with and without pain 4 months after hysterectomy ($p<0.05$). Additionally, univariate regression analyses, along with findings of previous studies on acute and persistent (or chronic) pain after different surgical procedures,[25,29,65,67] assisted in the final selection for the logistic sequential regression models. A basic model, embracing socio-demographic and clinical factors is presented, either alone or as the first step of the subsequent models (4 models). The first model tested the predictive role of 4 variables that distinguished the groups in univariate analysis: age, previous surgical pain, pain due to other causes and type of hysterectomy (Table 2). The remaining 4 models focused on the role of pre-surgical predictors (3 models), and on the role of acute post-surgical risk factors (1 model) for PPSP development. To control for the influence of multicollinearity, the variance inflation factor value (VIF) for every independent variable was calculated, only being included if VIF < 2.

## 3. RESULTS

### 3.1. Incidence, characteristics and perceived impact of pain 4 months after hysterectomy

Of the 186 assessed women, 78 (41.9%) reported no pain (NRS=0) at follow-up, of whom 15 (8.1%) complained about discomfort, like numbness or itch but stating this was not perceived as pain. From the remaining 93 women who reported some level of pain the most common locations were the pelvic region (52.7%) and the abdominal scar (**Table 1**). Some women had pain in more than one location. Table 1 demonstrated that of the 93 patients reporting pain 4 months after surgery, 48 (51.6%) perceived it on a daily basis and 18 (19.4%) several times a week. Ten (10.8%) women reported pain during sexual intercourse and 6 (6.5%) felt pain only when touching the surgical scar. Worst pain intensity was 4 (range, 0.5-10) and average pain intensity was 3 (range, 0.5-6) on the 0-10 NRS. The pain sensory characteristics were described by 57% as a feeling of pins and needles, by 53.8% as numbness on the surgical location, by 49.6% as an itching sensation and by 22.6% as tingling. Sensations of burning, electrical shock and painful cold were described by a minority (15.1%) (**Table 1**).

Although 93 women reported PPSP at follow-up, only 16 (17.2%) took analgesics regularly to cope with pain perception, namely paracetamol (16.2%), NSAIDs (13.2%) and antispasmodic (4.4%). Percentage relief obtained from those analgesics was around 60% (ranging from 0% to 100%). Almost half of those feeling pain (44%) reported pain interference in a variety of domains, the most common being: mood (73.2%); enjoyment of life (65.9%); general activity (63.4%); normal work (61.0%) and; walking ability (53.7%). In addition, **Table 2** shows that 54 (29%) women entered early menopause due to surgery as a result of oophorectomy procedures conducted at the same time as the hysterectomy. There were significant differences between women who developed PPSP and those who did not, with the former entering menopause more often due to concomitant oophorectomy procedures. Amongst those 54 women who entered early menopause, only 24 (44.4%) were taking hormonal replacing therapy (HRT), although this factor did not show any significant difference between the distinct pain groups. Furthermore, 4 months after hysterectomy, women with PPSP presented more anxiety ($p<0.001$) and depression ($p=0.001$) related symptoms, although with no differences in psychotropic use.

### 3.2. Pre-surgical (T1) risk factors for PPSP 4 months following hysterectomy

Before surgery, women presenting PPSP were younger ($p=0.014$) and, more likely to be pre-menopausal ($p=0.009$) (**Table 2**). Groups did not differ in any further socio-demographic measures. Moreover, both groups were similar concerning clinical issues like surgical disease onset, BMI (body mass index), previous surgical procedures or pre-surgical psychotropic use. Women with PPSP reported more often pre-surgical pain ($p=0.003$), presenting higher levels of pre-surgical pain either related to the condition underlying surgery ($p<0.001$) or to other causes ($p=0.021$), and they were also more likely to report higher total pain interference ($p=0.036$) (see **Table 2**). Furthermore, women with PPSP presented, before surgery, higher anxiety ($p<0.001$) and fears associated with the "immediate consequences of surgery" ($p=0.007$), worst cognitions associated with the surgical illness ("Cyclical duration": $p=0.040$; "Consequences": $p=0.008$; "Emotional representation": $p<0.001$) and higher levels of pain catastrophizing ($p<0.001$) (**Table 2**).

In order to identify the pre-surgical predictors of PPSP development 4 months after hysterectomy, a set of sequential logistic regression models were conducted (**Table 3**). The first, most basic model (Model 1) contains 4 variables which have been consistently found to predict PPSP in previous research and which were associated with PPSP in univariate analysis: age, previous surgical pain, pain due to other causes and type of hysterectomy (see **Table 2**). Pre-surgical menopause status (collinearity with age), type of surgical incision (collinearity with type of hysterectomy) and pre-surgical pain interference (collinearity with previous surgical pain) as further candidate variables showed considerable overlap to other predictors and where excluded from this Model 1 due to multicollinearity (Variance Inflation Factors>2). Model 1 showed that younger women (OR, 0.945; 95% CI, 0.907-0.985), those who had more pain due to other causes aside surgical illness (OR, 3.035; 95% CI, 1.499-6.146) and those who underwent open abdominal hysterectomy (OR, 3.233; 95% CI, 1.454-7.187), had a higher risk of developing PPSP; previous surgical pain did not contribute to the prediction of PPSP (see **Table 3**).

In order to further explore the role of pre-surgical psychological factors in PPSP development, over and above established demographic and clinical predictors, 3 alternative models were tested adding blocks of variables measuring emotional distress (Model 2a), illness perceptions (Model 2b) and coping strategies (Model 2c) to the demographic and clinical variables in Model 1 (see **Table 3**). When adding *emotional distress* variables (Model 2a), pre-surgical anxiety emerged as the significant predictor of PPSP development (OR, 1.116; 95% CI, 1.014-1.228), whereas fear of surgery did not and age no longer added to the prediction. Symptoms of depression as assessed by the HADS were withdrawn from this model because of lack of significance in previous differences analysis, along with collinearity problems (VIF>2). In the *illness perceptions model* (Model 2b; Table3), illness perception variables were added to the second step and the pre-surgical emotional representation of surgical disease (emotions in response to the illness underlying hysterectomy) emerged as a significant PPSP predictor (OR, 1.751; 95% CI, 1.174-2.611). Finally, Model 2c adding *coping strategies shows* that pre-surgical pain catastrophizing contributes to the prediction of PPSP over and above Model 1 variables (OR, 3.112; 95% CI, 1.664-5.821).

The three psychological variables found to be predictive of PPSP in models 2a-c were substantially correlated; anxiety correlated with pain catastrophizing (rho=.56) and with emotional representations (rho=.49). Emotional representations and pain catastrophizing correlated (rho=.46) suggesting that the underlying processes might be interrelated.

### 3.3. Post-surgical (T2) risk factors for PPSP 4 months following hysterectomy

Forty-eight hours after surgery, abdominal hysterectomy (*p*=0.001) and pfannenstiel incision (p<0.001) were more significantly associated with the occurrence of PPSP (**Table 2**). The groups did not show any difference on other clinical parameters such as uterus weight and height, type of anesthesia, type of analgesia, length of stay or consumption of psychotropic. Women who presented PPSP at T3 revealed a heightened acute pain experience 48 hours after surgery (p<0.001), having pain more frequently (*p*<0.001). Moreover, after surgery these women were also more anxious (*p*<0.001) than those without pain 4 months after hysterectomy (Table 2).

**Table 4** shows a similar sequential logistic regression model to the one on **Table 3** testing the additional predictive utility of post-surgical variables (T2) for PPSP over and above the same demographic and clinical variables used for model 1 in **Table 3**. At step 2, acute post-surgical pain intensity and frequency were included. Interestingly, only pain frequency yielded significant results, with constant acute post-surgical pain emerging as a predictor (OR, 2.251; 95% CI, 1.043-4.861) of later development of persistent pain. Furthermore, post-surgical anxiety was added to the model in step 3, emerging as a significant predictor (OR, 1.155; 95% CI, 1.015-1.315). However, after this addition, in the final model, pain frequency ceased to be significant, although predictors of first step remained significant. Correlation between post and pre-surgical anxiety was lower (rho=.43) than the correlations observed between different psychological distress variables assessed at T1.

## 4. DISCUSSION

The present study is the first to identify the joint role of demographic, clinical and psychological risk factors for persistent pain experience 4 months after hysterectomy due to benign disorders. Amongst the assessed risk factors, age, pain due to other causes and type of hysterectomy were the key demographic and clinical predictors of PPSP development. Regarding baseline pre-surgical psychological factors, anxiety, emotional illness representations and dysfunctional pain coping through catastrophizing were found to be additional risk factors for PPSP. Furthermore, post-surgical anxiety added to the prediction on PPSP. The results of this study improve knowledge on persistent post-surgical pain (PPSP) and increase potential intervention targets for healthcare professionals.

## 4.1. Pain 4 months after hysterectomy

Half of women reported pain 4 months after hysterectomy, and half of these complained of daily pain. Furthermore, those with pain presented more anxious and depressive symptomatology. Other hysterectomy study found lower prevalence rates (e.g. 16.7%) 4 months after surgery.[7] The key distinction between the present and that study is the way we opted to define persistent pain: any kind of pain linked to the surgical procedure, regardless of its location, intensity, interference or concomitant analgesic consumption.[67] As it is not well understood why some patients are totally pain-free shortly after surgery and others suffer from ongoing post-surgical pain,[40] and given that a mild pain problem can also impact daily life, we opted to use the criteria proposed and adopted by Poleshuck and col. (2006)[67] to further understanding within this area.

## 4.2. Predictors of pain 4 months after hysterectomy

### 4.2.1. Demographic and clinical baseline predictors

In line with previous evidence, type of hysterectomy and pain due to other causes were consistently found to be significant PPSP predictors. Abdominal hysterectomies have been associated with higher acute post-surgical pain than vaginal hysterectomies,[31] as open abdominal surgeries are amongst the most painful surgical procedures.[14,34] Vaginal route[41,75] or laparoscopic[13,23,51] approaches to hysterectomy should be considered when possible, due to low incisions and lower impact on pain outcomes.

The existence of pain due to other causes emerged as a predictor of PPSP, although pre-surgical pain (related to surgery) did not yield significant results. Within this sample, pre-surgical pain was not the only reason to perform surgery: 40% of women did not present pain symptoms related to the scheduled surgery. However, having other previous frequent pain states can have a detrimental impact. These results are consistent with those of other studies[7,8,59,84] and suggest that prolonged pain stimulation can exacerbate the nociceptive system through mechanisms of peripheral and central sensitization of nociceptors and central nervous system neurons, respectively[38]. It is possible that this may contribute to an association between the existence of pain due to other causes and later development of PPSP.

Moreover, even though not so consistently, age was also found to be a risk factor for PPSP, with younger women being more likely to report persistent pain. These results are in accordance with other studies indicating that younger patients tend to develop PPSP more often in different types of surgery. [3,10,12,20,30,35,39,68]

### 4.2.2. The Role of Psychological Predictors

The finding that psychological measures related to negative affect were predictive of PPSP over and above age and clinical variables adds to our understanding of PPSP.

While previous research has identified pre- surgical anxiety as risk factor for acute post-surgical pain, few studies to date have provided evidence for the its role in PPSP developmen.[6,22,26] Forty-eight hours after surgery, anxiety was, again, predictive of PPSP. Surprisingly, anxiety after surgery was never studied as a potential predictor for PPSP before. It can therefore be assumed that it is not only before surgery that anxiety seems to affect PPSP, but also anxiety levels after surgery.

Contrary to expectations, the present study did not find acute post-surgical pain intensity as a significant predictor,[58,62] but rather acute post-surgical pain frequency. This is the first time this effect has been shown. While we found that post-surgical pain frequency, rather than intensity, as suggested by previous research,[58,61] added to the prediction over age and clinical variables, this relationship was attenuated to insignificance when post-surgical anxiety was entered (see **Table 4**).

To our knowledge, this was the first study to test illness perceptions as potential risk factors for post-surgical pain. We found that emotional representations, e.g., the affective response to the condition addressed by the hysterectomy, predicted PPSP. In the current study the emotional representation of the health threat emerged as a significant predictor, which means that the specific emotional response to the illness, like feeling depressed, angry or upset, appears to influence pain outcomes.This scale does not constitute a simple indicator of patients' general mood, but it provides an evaluation of the emotional responses triggered by illness, regardless of its actual severity.[57] In patients with osteoarthritis, participants who reported more negative emotional illness representations experienced more limitation in activities of daily living than explained by the objective limitations diagnosed by radiographs.[4]

Pain catastrophizing has been found to be a reliable predictor of acute post-surgical pain[25,65] and there is some emerging evidence for its role as risk factor for PPSP.[21,70,79]

The predictive models as well as the correlations between the emotional and coping variables seem to demonstrate that negative emotions as well as maladaptive coping skills (pain catastrophizing) form a cluster of psychological circumstances that influence the development of persistent post-surgical pain.

### 4.3. Limitations of the study

A potential limitation of the present study is the absence of a physical examination of women reporting pain at T3. This study focused on pain as experienced by women after hysterectomy. Future research could also test for inflammatory or neuropathic elements and analyze nerve injury to provide a more comprehensive model of factors contributing to pain. It would also have been important to measure the length of incision in women who had an open abdominal hysterectomy, in order to further clarify and understand this issue as a potential risk factor.[46,54,66,76,81]

Psychological measures, with the exception of anxiety and depression, were assessed prospectively only before the scheduled hysterectomy. We might argue that they should be reassessed after surgery, during T2, given the likely impact of surgery on these variables; with arguments for and against. However, at T2 the goal was to reduce questionnaire burden and at T3 the aim was to collect data on our outcome variable (PPSP) using T1 and T2 variables as predictors. Moreover, T3 measures were obtained through a telephone interview.

Another possible limitation of this study is related to the clarification of PPSP etiology. Understanding to what extent chronic or persistent pain after hysterectomy results from a new pain or merely reflects a continuation of the previous pain that led to surgery [9,49] seems to be a fundamental issue. In the predictive analysis conducted in this study pre-surgical pain did not emerge as a significant predictor whilst post-surgical pain frequency did, which may reflect a major role of new pain.

### 4.4. Clinical implications

In terms of pre-surgical interventions, younger women that come for surgery and are screened with other previous chronic pain states could be offered special care in terms of pre-surgical intervention. Our results suggest that women should be screened in terms of emotional distress, illness perceptions and pain coping strategies. For those with high levels of anxiety, pain catastrophizing and worst emotional representation of the condition leading to surgery, brief psychological pre-surgical interventions could be delivered. To deal with anxiety, cognitive behavior therapy interventions techniques (such as brief relaxation)[11,24,72] could be provided before surgery. Nevertheless, addressing emotional illness representations might be a more promising strategy as specific beliefs can be easier modified in brief interventions than broader emotional states such as anxiety. Pain catastrophizing can be targeted before surgery through cognitive pain coping interventions, such as distraction techniques, pain ignoring strategies and positive coping self-statements.[11,19,24,52,72] After assessment patients could be assisted by health professionals in learning and applying more effective coping skills and to manage the emotional representations that they have developed in face of their illness.[28]

The surgical procedures should be carefully selected pondering all individual characteristics. Future research should evaluate the potential risk of abdominal hysterectomies, making sure that a more accurate and detailed physical assessment of the patient and of the incision *per se* is conducted.

After surgery, data from this study indicates that anxiety levels should be monitored and managed. Moreover, special care should be directed to those surgical patients who frequently report pain and are unable to get efficient relief from analgesics.

Psychological interventions, either before surgery or immediately after surgery, could focus on acute post-surgical pain control and management[18,32] in order to further support patients to prevent the development of PPSP.

In sum, by identifying patients at risk of developing PPSP following hysterectomy, more accurate surgical and analgesic individual approaches can be implemented along with more appropriate short term psychological interventions and better post-surgical surveillance.

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**Conflict of Interest statement**

We declare that none of the authors have any financial or other relationships that might lead to conflict of interest.

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**Table 1**
***Characteristics and impact of pain 4 months after hysterectomy (N=93)***

| **Pain 4 Months after Hysterectomy – T3** | ***N* (%)** | ***Median*** | ***Range*** |
|---|---|---|---|
| **Pain Report - PPSP[1]** | **Yes: 93 (50.0%)** | | |
| Location[2] (can report one or more) | | | |
| Pelvic region | 49 (52.7%) | | |
| Abdominal scar | 46 (49.5%) | | |
| Vagina | 22 (23.7%) | | |
| Lower back | 5 (0.05%) | | |
| Frequency | | | |
| Daily | 48 (51.6%) | | |
| Several times week | 18 (19.4%) | | |
| Several times month | 11 (11.9%) | | |
| During sexual intercourse | 10 (10.8%) | | |
| By touch | 6 (6.5%) | | |
| Intensity[3] (NRS 0-10**)** | | | |
| Worst level | | 4 | 0.5 – 10 |
| Average level | | 3 | 0.5 - 6 |
| DN-4[4] (can report one or more) | | | |
| Pins and Needles | 53 (57.0%) | | |
| Numbness | 50 (53.8%) | | |
| Itching | 38 (40.9%) | | |
| Tingling | 21 (22.6%) | | |
| Other (burning, painful cold, electric shocks) | 14 (15.1%) | | |
| Analgesic Consumption[5] | 16 (17.2%) | | |
| Paracetamol | 11 (16.2%) | | |
| NSAIDs* | 9 (13.2%) | | |
| Antispasmodic | 3 (4.4%) | | |

Note: Continuous variables are presented as median (range); categorical variables are presented as *n* (%); T3 – 4 months after surgery; [1]Women reporting PPSP - persistent post-surgical pain; [3]NRS: Numerical Rating Scale (0 - 10); [4]DN-4: Neuropathic Pain Questionnaire; [2,3,5] Itens from BPI-SF: Brief Pain Inventory – short form; *NSAIDs: non-steroidal anti-inflammatory drugs.

**Table 2**
***Differences between women with and without pain (T3) on socio-demographic, clinical and psychological measures determined at T1, T2 and T3***

| MEASURES | Total (*N* = 186) | No PPSP (*n* = 93) | PPSP (*n*= 93) | *p* |
|---|---|---|---|---|
| **Women baseline characteristics – T1** | | | | |
| *Socio-demographic:* Age (years) | 49 (35 - 76) | 50 (37 - 76) | 48 (35 - 68) | *0.014* |
| **Clinical - pre-surgical pain indicators** | | | | |
| Pre-surgical pain (yes) | 112 (60.2%) | 46 (49.5%) | 66 (71.0%) | *0.003* |
| Intensity[1] (worst level) | 2.5 (0 - 10) | 1 (0 - 10) | 5 (0 - 10) | *< 0.001* |
| Pain Total Interference[2] (0-10) | 0 (0 -7.6) | 0 (0 - 4.7) | 0.7 (0 - 7.6) | *0.036* |
| Pain due to other causes (yes)[3] | 121 (65.1%) | 53 (57.0%) | 68 (73.1%) | *0.021* |
| **Psychological variables** | | | | |
| **HADS[a]:** Anxiety | 7 (0 - 19) | 6 (0 - 15) | 8 (0 - 19) | *< 0.001* |
| **HADS[a]:** Depression | 1 (0 - 14) | 1 (0 - 12) | 1 (0 - 14) | *ns* |
| **SFQ[b]:** Immediate consequences | 2.83 (0 - 9) | 2.33 (0 - 9) | 3.08 (0 – 7.7) | *0.007* |
| **SFQ[b]**: Long-term consequences | 0.75 (0 – 8.8) | 0.50 (0 – 8.8) | 1.0 (0 - 6.5) | *ns* |
| **IPQ - R[c]:** Timeline acute/chronic | 2 (1 - 4) | 2 (1 - 4) | 2 (1 - 3.7) | *ns* |
| **IPQ - R[c]:** Timeline cyclical | 2.3 (1 - 4.7) | 2 (1 - 4.3) | 2.7 (1 - 4.7) | *0.04* |
| **IPQ - R[c]:** Consequences | 2 (1 - 4.3) | 1.67 (1 - 4.3) | 2 (1 - 4.3) | *0.008* |
| **IPQ - R[c]:** Personal control | 2 (1 - 4.3) | 2 (1 - 4.3) | 2 (1.3 - 4) | *ns* |
| **IPQ - R[c]:** Treatment control | 4 (3 - 5) | 4 (3 - 5) | 4 (3.3 - 5) | *ns* |
| **IPQ - R[c]:** Illness coherence | 3.3 (1 - 4.7) | 3.3 (1 - 4.7) | 3.3 (1.3 – 4.7) | *ns* |
| **IPQ - R[c]:** Emotional representation | 2.67 (1 - 5) | 2 (1 - 5) | 3.3 (1 - 5) | *< 0.001* |
| **CSQ-R[d]:** Pain catastrophizing | 1.5 (1 - 5) | 1.3 (1 - 4.3) | 1.7 (1 - 5) | *< 0.001* |
| **CSQ-R[d]:** Ignoring pain | 2.4 (1 - 5) | 2.6 (1 - 5) | 2.2 (1 - 5) | *ns* |
| **CSQ-R[d]:** Self statements with pain | 4 (1.5 - 5) | 4.3 (1.5 - 5) | 4 (1.8 - 5) | *ns* |
| **CSQ-R[d]:** Reinterpret. pain sensations | 1.5 (1 - 5) | 1.5 (1 - 4.8) | 1.5 (1 - 5) | *ns* |
| **CSQ-R[d]:** Praying and hoping | 3.7 (1 - 5) | 3.3 (1 - 5) | 3.7 (1 - 5) | *ns* |
| **CSQ-R[d]:** Distraction/diverting attention | 1.8 (1 - 5) | 1.6 (1 - 4.4) | 1.8 (1 - 5) | *ns* |
| **Postsurgical data 48H after surgery-T2** | | | | |
| Type hyst[4]: open abdominal | 135 (72.6%) | 57 (61.3%) | 78 (83.9%) | *0.001* |
| Abdom. Incis.[5]: Pfannenstiel | 114 (61.3%) | 44 (47.3%) | 70 (75.3%) | *< 0.001* |
| Acute post-surgical pain intensity[1] | 5 (0 - 10) | 4 (0 - 10) | 5 (1 - 10) | <0.001 |
| Pain Frequency[6]: constant | 58 (31.9%) | 20 (19.8%) | 38 (46.9%) | <0.001 |
| HADS[a]: Anxiety | 2 (0 - 19) | 1 (0 - 13) | 3 (0 - 19) | <0.001 |
| **Postsurgical data 4M after surgery-T3** | | | | |
| Menopause due to surgery | 54 (29.0%) | 19 (20.4%) | 35 (37.6%) | 0.01 |
| **HRT [7] (yes)** | 24 (44.4%) | 6 (31.6%) | 18 (51.4%) | *ns* |
| **HADS[a]:** Anxiety | 4 (0 - 20) | 2 (0 - 12) | 6 (0 - 20) | < 0.001 |
| **HADS[a]:** Depression | 0 (0 - 16) | 0 (0 - 9) | 1 (0 - 16) | 0.001 |

Note. Continuous variables are presented as median (range); categorical variables are presented as *n* (%); T1 – 24 hours before surgery; T3 – 4 months after surgery; [1]NRS: Numerical Rating Scale (0 - 10); [1,2]Itens from BPI-SF: Brief Pain Inventory – short form; [3]Other previous pain states (either acute or chronic, not related to the cause of surgery, but nonetheless frequent); [4]Type of hysterectomy: n(%) of open abdominal hysterectomies vs abdominal laparoscopic, vaginal and vaginal assisted laparoscopic; [5]Abdominal incision: n(%) of pfannenstiel incisions vs infraumbilical vertical incision and laparoscopies; [6]Pain Frequency: constant pain vs intermittent or brief pain, assessed via frequency subscale of McGill Pain Questionnaire. [7]HRT: Hormonal Replacement Therapy due to menopause occurrence because of surgery (hysterectomy + bilateral oophorectomy); [a]HADS: Hospital Anxiety and Depression Scale; [b]Surgical Fear Questionnaire; [c]IPQ-R: Illness Perception Questionnaire-Revised; [d]CSQ-R: Coping Strategies Questionnaire-Revised; [e]SIP: Sickness Impact Profile.

**Table 3**

***Sequential logistic regression analysis of Persistent Post-surgical Pain four months following hysterectomy on demographic, clinical and psychological measures at baseline***

| **MODELS** | Wald | Odds Ratio (CI) | *p* |
|---|---|---|---|
| **MODEL 1 - Demographic and clinical predictors** | | | |
| Age[1] | 7.253 | 0.945 (0.907 – 0.985) | *0.007* |
| Type of Hysterectomy[2] | 8.286 | 3.233 (1.454 – 7.187) | *0.004* |
| Pre-surgical pain[3] | 0.930 | 1.416 (0.699 – 2.869) | *ns* |
| Pain due to other causes[4] | 9.514 | 3.035 (1.499 – 6.146) | *0.002* |
| **MODEL 2a - Emotional distress (Final Model)** | | | |
| Age[1] | 2.672 | 0.966 (0.928 - 1.007) | *ns* |
| Type of Hysterectomy[2] | 6.489 | 2.774 (1.265 - 6.081) | *0.011* |
| Previous pre-surgical pain[3] | 1.722 | 1.629 (0.786 - 3.377) | *ns* |
| Pain due to other causes (yes)[4] | 5.314 | 2.302 (1.133 - 4.679) | *0.021* |
| Pre-surgical anxiety[a] | 5.033 | 1.116 (1.014 - 1.228) | *0.025* |
| Pre-surgical fear[b] | 0.434 | 1.064 (0.885 - 1.279) | *ns* |
| **MODEL 2b - Illness perceptions (Final Model)** | | | |
| Age[1] | 5.312 | 0.947 (0.903 - 0.992) | *0.021* |
| Type of Hysterectomy[2] | 9.744 | 3.769 (1.638 - 8.670) | *0.002* |
| Previous pre-surgical pain[3] | 2.273 | 1.906 (0.824 - 4.409) | *ns* |
| Pain due to other causes (yes)[4] | 7.291 | 2.806 (1.327 - 5.936) | *0.007* |
| Timeline acute/chronic[c] | 0.176 | 0.823 (0.331 - 2.045) | *ns* |
| Timeline cyclical[c] | 2.452 | 0.709 (0.461 - 1.090) | *ns* |
| Consequences[c] | 0.900 | 1.283 (0.766 - 2.149) | *ns* |
| Personal control[c] | 2.189 | 1.506 (0.876 - 2.590) | *ns* |
| Treatment control[c] | 0.000 | 1.005 (0.274 - 3.688) | *ns* |
| Illness coherence[c] | 0.009 | 0.980 (0.658 - 1.461) | *ns* |
| Emotional representation[c] | 7.553 | 1.751 (1.174 - 2.611) | *0.006* |
| **MODEL 2c - Coping strategies (Final Model)** | | | |
| Age[1] | 4.497 | 0.947 (0.900 - 0.996) | *0.034* |
| Type of Hysterectomy[2] | 7.210 | 3.485 (1.401 - 8.670) | *0.007* |
| Previous pre-surgical pain[3] | 0.592 | 1.377 (0.610 - 3.111) | *ns* |
| Pain due to other causes (yes)[4] | 5.586 | 2.583 (1.176 - 5.672) | *0.018* |
| Distraction/diverting attention[d] | 0.056 | 0.949 (0.616 - 1.463) | *ns* |
| Praying and hoping[d] | 0.027 | 1.024 (0.776 - 1.350) | *ns* |
| Ignoring pain sensations[d] | 0.926 | 1.219 (0.814 - 1.824) | *ns* |
| Reinterpreting pain sensations[d] | 2.622 | 1.515 (0.916 - 2.504) | *ns* |
| Pain coping self-statements[d] | 2.142 | 1.467 (0.878 - 2.452) | *ns* |
| Pain catastrophizing[d] | 12.627 | 3.112 (1.664 - 5.821) | *< 0.001* |

Model1: after removing 3 outliers, this model correctly predicted 66.7% of all patients; Model2a: after removing 1 outlier, this model correctly predicted 66.8% of all patients; Model2b: after removing 3 outliers, this model correctly predicted 73.2% of all patients; Model2c: after removing 5 outliers, this model correctly predicted 70.0% of all patients.

Note: [1]Continuous variable, in years; [2]Dichotomous variable: 0= abdominal laparoscopic, vaginal and vaginal assisted laparoscopic; 1= open abdominal hysterectomies; [3]Dichotomic variable: 0= No, 1= Yes; [4] Dichotomic variable: 0= No, 1= Yes; [a]Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale; [b]Continuous variable, Surgical Fear Questionnaire – fear of immediate consequences of surgery subscale; [c]Continuous variable, IPQ-R: Illness Perception Questionnaire Revised – all subscales; [d]CSQ-R: Coping Strategies Questionnaire Revised – all subscales;

**Table 4**

***Sequential logistic regression analysis of Persistent Post-surgical Pain four months following hysterectomy on demographic, clinical at baseline and post surgical pain perceptions and anxiety 24h after surgery***

| **MODEL 3 – Post-surgical variables (T2)** | Wald | Odds Ratio (CI) | *p* |
|---|---|---|---|
| **Step 1** | | | |
| Age[1] | 6.732 | 0.948 (0.911 - 0.987) | *0.009* |
| Type of Hysterectomy[2] | 7.447 | 2.974 (1.360 - 6.507) | *0.006* |
| Previous pre-surgical pain[3] | 1.831 | 1.620 (0.805 - 3.259) | *ns* |
| Pain due to other causes (yes)[4] | 9.135 | 2.948 (1.462 - 5.942) | *0.003* |
| **Step 2** | | | |
| Post-surgical pain intensity[5] | 1.815 | 1.090 (0.962 – 1.236) | *ns* |
| Post-surgical pain frequency[6] | 4.273 | 2.251 (1.043 – 4.861) | 0.039 |
| **Step 3 (Final Model)** | | | |
| Age[1] | 3.974 | 0.957 (0.917 - 0.999) | *0.046* |
| Type of Hysterectomy[2] | 5.571 | 2.670 (1.181 - 6.037) | *0.018* |
| Previous pre-surgical pain[3] | 1.663 | 1.633 (0.775 - 3.439) | *ns* |
| Pain due to other causes (yes)[4] | 4.090 | 2.147 (1.024 - 4.503) | *0.043* |
| Post-surgical pain intensity[5] | 0.162 | 1.029 (0.897 – 1.179) | *ns* |
| Post-surgical pain frequency[6] | 2.024 | 1.793 (0.802 – 4.010) | *ns* |
| Post-surgical anxiety[a] | 4.789 | 1.155 (1.015 - 1.315) | *0.029* |

After removing 4 outliers, this model correctly predicted 65.9% of all patients.

Note: [1]Continuous variable, in years; [2]Dichotomous variable: 0= abdominal laparoscopic, vaginal and vaginal assisted laparoscopic; 1= open abdominal hysterectomies; [3]Dichotomic variable: 0= No, 1= Yes; [4] Dichotomic variable: 0= No, 1= Yes; [5]Continuous variable, NRS 0-10 from BPI-SF: Brief Pain Inventory-Short Form; [6]Dichotomic variable: 0= intermittent or brief pain, 1=constant pain, frequency subscale of McGill Pain Questionnaire; [a]Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale

Chapter 2.2

# Total Knee Arthroplasty & Total Hip Arthroplasty

Chapter 2.2.1

**STUDY 4**

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Pinto, P.R., McIntyre, T., Ferrero, R., Almeida, A., & Araújo-Soares, V.

## Predictors of acute postsurgical pain and anxiety following primary total hip and knee arthroplasty

*(Manuscript under preparation)*

**Predictors of acute post-surgical pain and anxiety following primary total hip and knee arthroplasty**

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**Abstract**

The aim of this study was to examine the joint role of demographic, clinical and psychological variables as predictors of acute post-surgical pain and anxiety in patients undergoing total knee arthroplasty (TKA) and total hip arthroplasty (THA). A consecutive sample of 124 patients was assessed 24 hours before (T1) and 48 hours after (T2) surgery. Baseline pain and predictors were assessed at T1 and several post-surgical pain issues, anxiety and analgesic consumption were evaluated at T2. Sequential logistic regression analyses were performed to identify predictors of acute pain and anxiety levels following surgery. In the final multivariate models, pre-surgical optimism ($\beta$=-0.237, $p$=0.008) emerged as the main significant predictor of post-surgical pain intensity. Pre-surgical optimism revealed also a significant role in the prediction of post-surgical anxiety ($\beta$=-0.211, $p$=0.011), along with pre-surgical anxiety level ($\beta$=0.358, $p$<0.001) and emotional representation of the condition leading to surgery (osteoarthritis) ($\beta$=0.238, $p$=0.009). Moreover, it was also confirmed the strong association between post-surgical anxiety and acute pain after surgery (r=.51). The present study increase the knowledge on acute pain predictors following TKA and THA by showing that some psychological factors emerge over and above a set of potential predictors, that includes surgical, anesthetic and analgesic factors. These results could prove useful for the design of interventions aimed at acute post-surgical pain and anxiety management following major joint arthroplasties.

**Keywords**: total knee arthroplasty (TKA); total hip arthroplasty (THA); acute post-surgical pain; post-surgical anxiety; psychological predictors

## 1. Introduction

Arthroplasties, specifically Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA) are amongst the most commonly performed surgeries worldwide (Kurtz, Ong, Lau, Mowat, & Halpern, 2007; Learmonth, Young, & Rorabeck, 2007; Losina et al., 2009; Vilardo & Shah, 2011). With the aging population, it is expected a significant rise in the prevalence of knee and hip osteoarthritis and consequently an increase on the number of surgical interventions such as TKA and THA, aimed at reducing pain and disability, improving functional status and thus fostering quality of life (Bachmeier et al., 2001; Lingard, Katz, Wright, Sledge, & Kinemax Outcomes Group, 2004; Hamel, Toth, Legedza, & Rosen, 2008; Wylde, Hewlett, Learmonth, & Dieppe 2011).

Arthroplasties are categorized as major surgeries and thus it is expected, in some degree, the occurrence of pain after surgery. Indeed, acute pain is the most common, anticipated and predicted problem after surgery (Apfelbaum, Chen, Mehta, & Gan, 2003; Strassels, McNicol, & Suleman, 2005), being defined as an expected physiological response to a noxious chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness (Carr & Goudas, 1999). Despite its predictability, it is important to implement ways of improving post-surgical pain control and management. High levels of pain after surgery may have deleterious effects on individuals, both at physiological and psychological domains (Charlton, 2005; Cousins, Brennan, & Carr, 2004), hindering short and long-term recovery, increasing length of stay, delaying ambulation and functional restoration (Brander et al., 2003; Morrison et al., 2003), and being also a key risk factor for the development of chronic post-surgical pain (Macintyre, Schug, Scott, Visser, & Walker, 2010; Perkins & Kehlet, 2000; Schug et al., 2005; Schug and Pogatzki-Zahn, 2011]. Nevertheless, even with the most recent advances in research and the establishment of new guidelines and standards for treatment, post-surgical pain continues to be undermanaged (Wu & Raja, 2011).

Several studies have shown that emotional distress, like pre-surgical anxiety, and cognitive factors, such as pain catastrophizing, are associated with increased post-surgical pain (Carr, Thomas, & Wilson-Barnet, 2005; Katz et al, 2005; Nielsen, Rudin, & Werner, 2007; Pinto, McIntyre, Almeida, & Araújo-Soares, 2012). A systematic review of predictors of post-surgical pain (Ip, Abrishami, Peng, Wong, & Chung, 2009) suggested that preexisting pre-surgical pain, anxiety, age, and type of surgery are the four most significant predictive factors for post-surgical pain intensity. Other potentially important but understudied determinant of acute post-surgical pain are patients' illness perceptions. The Common-Sense Self-Regulation Model (CS-SRM) (Leventhal, Nerenz, & Steele, 1984; Leventhal & Diefenbach,1991) suggests that in the context of an illness, people tend to develop cognitive and emotional representations of their illness (Leventhal et al., 1997; Petrie & Weinman, 2006; Hermele, Olivo, Namerow, & Oz, 2007), which have been shown to explain outcomes in a wide range of medical conditions and in response to different treatments (Hagger& Orbell, 2003; Petrie & Weinman, 2006; Moss-Morris, Humphrey, Johnson, & Petrie, 2007). Past studies using this theoretical perspective focused on functional activity, post-surgical adjustment or surgical recovery, rather than on their relationship with pain outcomes (Orbell, Johnston, Rowley, Espley, & Davey, 1998; Mccarthy, Lyons, Weinman, & Purnell, 2003; Llewellyn, McGurk, & Weinman, 2007).

Another potential predictor, dispositional optimism, a generalized expectation that good things will happen (Rasmussen, Scheier, & Greenhouse, 2009), has been identified as a significant predictor of positive outcomes in a variety of health and disease related conditions (Scheier & Carver, 1993; Scheier et al., 1999; Kubzansky, Martin, & Buka, 2009; Rasmussen et al., 2009). However, the role of optimism in post-surgical acute and chronic pain has received less attention (Peters, 2009), although there are some indications concerning the association between optimism and surgical pain during the early recovery period (Mahler & Kulic, 2000).

After surgery, pain and anxiety have been reported as being inter-woven (McWilliams, Goodwin, & Cox, 2004). Anxiety is thought to have an intensifying effect on pain experience, although whether pain causes anxiety or whether anxiety leads to pain remains difficult to establish. Moreover, anxiety also has negative consequences on recovery from surgery, with some studies supporting a relationship between anxiety and wound healing (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998; Cole King & Harding, 2001; Janssen, 2002).

Few studies (Roth, Tripp, Harrison, Sullivan, & Carson, 2007) have examined the impact of psychological factors on acute post-surgical pain after specific procedures such as TKR and THR. They rather tended to focus on demographic and clinical data (Nilsdotter, Aurell, Siösteen, Lohmander, & Roos, 2001; Nikolajsen, Sørensen, Jensen, & Kehlet, 2004; Ebrahimpour, Do, Bornstein, & Westrich, 2011) and on long-term outcomes, like chronic pain or functional status (Brander, Gondek, Martin, & Stulberg, 2007; Lingard & Riddle, 2007; Sullivan et al., 2011). In addition, post-surgical anxiety after major joint arthroplasties has not been targeted in surgical studies. As post-surgical pain and post-surgical anxiety seem to interrelate and influence recovery (McWilliams et al., 2004; Carr et al., 2005), the aims of this study were twofold: to examine the independent and joint contribution of demographic, clinical and psychological variables as predictors of acute post-surgical pain intensity and post-surgical anxiety, in patients submitted to TKA and THA.

## 2. Methods

This study was conducted in a central hospital in northern Portugal. Ethical approval was granted by the Hospital Research Ethics Committee and all participants were informed about the study and then read and signed the written informed consent.

### 2.1. Participants and Procedures

This was a prospective cohort study with time 1 (T1) and time 2 (T2) assessments performed between March 2009 and December 2010. A consecutive sample of 130 patients with osteoarthritis was enrolled (all invited participants accepted). Inclusion criteria were 18 to 80 years old (although none had less than 40), being able to understand written information (informed consent), without psychiatric or neurologic pathology (e.g. psychosis, dementia) and undergoing THA and TKA for diagnosis of coxarthrosis and gonarthrosis only (osteoarthrosis). Arthroplasties that were performed because of fall fractures were excluded, as well as hemiarthroplasties, revision and emergency arthroplasties.

Patients were initially assessed 24 hours before (T1) and 48 hours after (T2) surgery, at the Hospital. Follow-up assessments were performed 4-6 months in the follow-up consultations. From T1 to T2 measurement points, 6 patients were withdrawn due to: canceled surgery (n = 3), repeated surgery / reoperation (n = 2), and ASA status IV along with occurrence of post-surgical delirium (n = 1). This left 124 patients (experimental mortality from T1 to T2 was 4.62%). From these, 60 underwent primary TKA and 64 primary THA.

### 2.2. Measures

#### 2.2.1. Pre-surgical assessment – predictive measures

Upon hospital admission, 24 hours before surgery (T1), the following baseline questionnaires were administered, in a face to face interview by a trained psychologist.

(1*) Socio-Demographic Questionnaire*. It included questions on age, education, residence, marital status, professional status, household and parity.

(2*) Clinical Data Questionnaire*. It included questions about previous pre-surgical pain, its onset, duration and frequency, pain due to other causes, pain in other joints (specifically in knees and hips), back pain, disease onset, previous surgeries, height, weight, comorbidities, as well as the use of psychotropic drugs.

(2.1) Co-morbidities: the existence of pre-surgical co-morbid conditions that could affect TKA and THA surgical outcomes were asked to the patient or extracted from the medical chart. For that purpose, Deyo–Charlson index (Charlson, Pompei, Ales, & MacKenzie, 1987) was used, given that it is the most commonly used comorbidity measure, consisting of a weighted scale of 17 comorbidities, such as: hypertension, cardiac, pulmonary, renal and hepatic disease, diabetes mellitus, cancer, etc. The total number of co-morbid health conditions was summed in order to yield a total score. The weighting of severity was not used in our study, but only the summative score related to the total number of comorbid conditions, as already performed elsewhere (Jones, Voaklander, & Suarez-Almazor, 2003).

(3) *Brief Pain Inventory – short form* (BPI-SF) (Cleeland & Ryan, 1994). The BPI-SF measured pain intensity on an 11-point numerical rating scale (from 0 or "no pain" to 10 or "worst pain imaginable"), pain analgesics, perception of analgesics relief, pain interference in daily activities (general activity, mood, walking, work, relations with others, sleep and enjoyment of life) and pain location. In this study, the internal consistency reliability (Cronbach, 1951) (see point 2.2.) for the pain interference subscale scores was very high ($\alpha$=0.87).

(4) *Hospital Anxiety and Depression Scale* (HADS) (Zigmond & Snaith, 1983). The HADS is comprised of two 7-item sub-scales measuring anxiety (HADS-A) and depression (HADS-B) symptomatology amongst patients in non-psychiatric hospital settings. Item response format is a Likert type scale ranging from 0 to 3. Sub-scale scores vary between 0 and 21. Higher scores represent higher levels of anxiety and depression. In the current sample, internal consistency

reliability (Cronbach, 1951) was adequate for both anxiety (T1: $\alpha$ = 0.79, and T2: $\alpha$ = 0.83) and depression (T1: $\alpha$ = 0.73).

(5) Revised Illness Perception Questionnaire (IPQ-R) (Moss-Morris et al., 2002). It assesses patient beliefs about the underlying condition that lead to surgery. A psychometrically short version (Sniehotta, Gorski and Araujo-Soares, 2009) was used with 7 subscales composed by 3 items each and analyzing distinct dimensions of illness perceptions: "timeline acute/chronic" ($\alpha$ = 0.97; e.g. "My illness will last for a long time"); "timeline cyclical" ($\alpha$ = 0.56; e.g. "My symptoms come and go in cycles"); "consequences" ($\alpha$ = 0.46; e.g. "The disease underlying surgery has major consequences on my life"); "personal control" ($\alpha$ = 0.80; e.g. "I have the power to influence my illness"); "treatment control" ($\alpha$ = 0.87; e.g. "Surgery can control my illness"); "illness coherence" ($\alpha$ = 0.87; e.g. "My illness is a mystery for me"); "emotional representation" ($\alpha$ = 0.90; e.g. "When I think about my illness I get upset"). To generate the total scale score, the sum of the item scores was divided by the number of items. Each subscale is rated on a scale of 1-5, high scores reveal worst results, with the exception of personal and treatment control subscales. With the exception of "timeline cyclical" and "consequences" subscales, which revealed low internal consistency (0.56 and 0.46), the remaining sub-scales presented adequate properties.

(6) Life Orientation Test – revised (LOT-R) (Scheier, Carver, & Bridges, 1994). It evaluates the personality trait optimism through 8 items. In this study just 3 items were used, corresponding to a subscale of optimism which ranges from 0 to 12, with high values associated with more optimism. In the current sample, internal consistency (Cronbach, 1951) was excellent ($\alpha$ = 0.96).

(7) "Pain Catastrophizing scale" of the *Coping Strategies Questionnaire – Revised Form* (CSQ-R) [34]. This sub-scale has 6 items that assess pain catastrophizing. Items were rated on a 5-point adjective rating scale (1=never, 2=almost never, 3=sometimes, 4=almost always, and 5=always) rather than the 7-point scale used in the original instrument, due to difficulties expressed by pilot study patients in discriminating the 7 points. To generate the total scale score, the sum of the item scores was divided by the number of items. Scale scores vary between 1 and 5, with higher scores indicating greater use of the specific coping strategy. In the current sample, the Cronbach alpha internal consistency reliability coefficient [20] was 0.94, indicating good reliability.

**2.2.2. Post-surgical assessment:** acute pain and anxiety

(1) Acute pain - patients were asked to rate their worst and average pain level within the first 48 hours after surgery, on an 11-point numerical rating scale (from the *BPI-SF*), already described. A composite measure was calculated, resulting from the sum and mean of worst pain level and average pain level.

(2) Anxiety - was measured through the anxiety subscale of HADS, already described. The use of psychotropic drugs, namely the consumption of anxiolytic drugs, during the 48 hours post-surgical period was also recorded.

**2.2.3. Post-surgical assessment:** additional measures

(1) Post-surgical relief from analgesics - patients were assessed on analgesic relief trough a scale from *Brief Pain Inventory – short form* (BPI-SF) (Cleeland & Ryan, 1994) which evaluates the perception of analgesic relief from 0 to 100%.

(2) Post-surgical pain frequency - this assessment was performed using the frequency subscale of the McGill Pain Questionnaire (Melzack, 1975). Patients could define their pain either as constant (continuous, steady), intermittent (periodic, rhythmic) or brief (momentary, transient). This specific subscale was used at T2 given that the characterization of a pain that is confined to a period of 48 hours cannot be described in terms of days, weeks or months, like it was done for the assessment of pre-surgical pain at T1.

(3) Rescue analgesia - all protocols had indications for the prescription of rescue analgesics beyond the standardized analgesic protocol given moderate to severe acute post-surgical pain levels (NRS>4). Due to the great variability in analgesics' medications and dosages, no attempt was made to determine total equianalgesic medication dosages. It was rather recorded whether rescue analgesics were given to patients.

**2.3. Clinical variables**

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

After surgery, standardized postoperative nursing and physical therapy protocols were used for all patients. Patients were mobilized out of bed on the second postoperative day, and all patients had a postoperative anticoagulation protocol using LMWH (low-molecular-weight heparin). Postoperatively patients were given systemic prophylactic antibiotics and prophylactic anticoagulant to decrease deep venous thrombosis risk.

Moreover, no research-related change was introduced in the standard clinical protocol. Healthcare professionals were blind to their patient's participation in the study.

### 2.3.1. Surgical Procedure

From the sample of 130 patients, 60 (48%) were submitted to Total Knee Arthroplasty and 64 (52%) to Total Hip Arthroplasty. Surgeries were performed by the team of Orthopedic Surgeons of the Orthopedic Public Service of the above mentioned hospital.

A) Total Knee Arthroplasty (TKA)

In this TKA surgical group 37 patients had surgery in the right knee and 23 in the left one.

For the knee, a cruciate-sacrifice prosthesis with a cobalt chromium bearing surface on an ultrahigh-molecular-weight polyethylene insert surface was placed in all cases. The surgical technique in all patients was an anterior midline approach with a medial parapatellar arthrotomy. These patients all had cruciate-sacrifice TKAs with all three components (tibial, femoral and patellar) cemented with a meticulous cement preparation technique. Resurfacing of the patellae was at the discretion of the surgeon. The most commonly technique for bone resection uses a 5° to 7° (depending on body habitus) valgus femoral cut and neutral tibial cut. Additionally, a correct ligament balancing was performed and tested to achieve equal and symmetric fixation and extension gaps. Intramedullary alignment guides were used for femoral and tibial cuts. The posterior cruciate ligament was resected. Bicondylar femoral and tibial components were implanted and cemented. A polyethylene liner was inserted between the metallic femoral and tibial prostheses. When already at the infirmary, continued passive range of motion was applied to these patients, who were also instructed to weight bear as tolerated.

B) Total Hip Arthroplasty (THA)

Within this type of surgery 34 patients had surgery in the right hip and 30 in the left hip.

For hip patients, a press-fit technique was used for both components: femoral and acetabular. Supplemental screws were used to fix the cup, when necessary. Cobalt chromium on ultrahigh-molecular-weight polyethylene was the bearing surface in all cases. The surgical technique was quite similar in every case. All procedures were done through a direct antero-lateral approach (Watson-Jones). The choice of surgical approach was based upon surgeon preference given the clinical scenario (ie, body habitus, severity of disease, etc). In all cases a cementless technique was performed and tapered stem design (to interlock in the metaphysis with no diaphyseal fixation). Moreover, proximal porous coating was used to impart stability and allow for bone ingrowth. The implant was always collarless, allowing the prosthesis to be wedged into the bony metaphysis, providing for optimal fit and bone ingrowth. In addition, the tapered design allows subsidence into a tight fit and optimizes proximal load sharing of the implant, thereby optimizing bone ingrowth and minimizing stress shielding.

For both types of surgeries, anterior–posterior (AP) and lateral knee radiographs were taken and reviewed before patient was transferred to the infirmary for continued care. The radiographs were reviewed to ensure that the prosthesis was inserted properly and that alignment was correct. Compression dressings were removed the day after surgery.

### 2.3.2. Anaesthetic Technique

In all patients, the mode of anaesthesia was determined by the health care team according to the usual standard anaesthetic protocols at the hospital, with no research-related change being introduced.

The type of anesthesia in use was classified as: 1) loco-regional alone (n=82/66.1%), BSA (block spinal anaesthesia) or epidural, or as: 2) loco-regional (BSA or epidural) plus peripheral nerve blocks (n=42/33.9%). Amongst these latter, 23 (54.8%) had a femoral nerve block, 10 (23.8%) had a lumbar nerve block, 7 (16.7%) a sciatic–femoral nerve block and 2 (4.8%) had a sciatic-lumbar nerve block. ASA score (physical status classification of the American Society of Anesthesiologists) was recorded, including cases of ASA grade I (9/7.3%), II (91/73.4%) and III (24/19.4%).

### 2.3.3. Analgesic Protocols

All patients were assigned to a standardized analgesia protocol according to the usual standard of care at the Hospital, established prior to patient transfer to the infirmary, which was determined and supervised by the Acute Pain Unit, led by an Anesthesiologist.

Delivery of the analgesic protocol could be intravenous, epidural or peri-neural, followed by oral analgesics on subsequent days.

The standardized intravenous protocol was composed by a continuous intravenous infusion (DIB) of tramadol (600 mg), metamizol (6 gr) and metoclopramide (60 mg). The standardized epidural protocol was a continuous epidural infusion (DIB - delivered infusion baloon) with ropivacaine (0.1%) and fentanyl (3ug/ml). Finally, the standardized peri-neural protocol included a continuous peri-neural infusion (DIB - delivered infusion baloon) with ropivacaine (0.1%). For the 3 types of protocols, Paracetamol (1 gr 6/6h) and Non steroidal anti-inflammatory drugs (NSAIDS - ketorolac 30 mg 12/12h or parecoxib 40 mg 12/12h) were always included as coadjuvant analgesics. All analgesic regimens included prokinetic treatment that was standardized to metoclopramide (10 mg i.v. 8/8h). All protocols had indications for the prescription of rescue analgesics beyond the standardized analgesic protocol given moderate to severe acute post-surgical pain levels (NRS>3) (Hartrick, Kovan, & Shapiro, 2003; Dihle, Helseth, Paul, & Miaskowski, 2006).

### 2.4. Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 18.0 software). Internal consistency of responses to the questionnaires was assessed using Cronbach's alpha (Cronbach, 1951). The outcome variables in this study are "acute post-surgical pain" and "post-surgical anxiety", both assessed as continuous variable (pain intensity, NRS 0-10; anxiety levels, HADS 0-21). For "acute post-surgical pain" a composite measure was calculated, resulting from the sum and mean of worst pain level and average pain level.

Descriptive statistics were computed on sample characteristics. Furthermore, *t*-tests (for continuous variables) and Chi-square tests ($\chi 2$, for nominal variables) were performed to compare demographic, clinical and psychological measures between men and women. In addition, to determine the predictor variables to include in the regression analyses and to assess concurrent and prospective relations amongst study variables, Pearson correlation coefficients were calculated among continuous variables and point-biserial correlation coefficients between dichotomous and continuous variables. Multiple hierarchical regression analyses were performed to identify significant predictors either of acute post-surgical pain intensity or of post-surgical anxiety. The variables included in the model were the ones that showed a strong association with each of the dependent variables in previous bivariate associations. To control for the influence of multicollinearity the variance inflation factor value (VIF) and the tolerance coefficients for each variable were established as being above 2 and greater than .70, respectively.

## 3. Results

### 3.1. Socio-demographic, clinical and psychological sample characteristics at T1

The study sample included 41 (33.1%) men and 83 (66.9%) women. **Table 1** displays the sample characteristics for the whole group but also for each sex group, showing eventual differences between men and women in the assessed characteristics. In the whole sample, mean age was 65.2 years (*SD*=7.97), almost all patients (96.8%) had 4 years or less of formal education and 54 (43.5%) lived in a rural setting. In terms of socio-demographic differences men and women differed on marital and professional status, with men being more often married ($p$ =0.003) and less often retired ($p$=0.026). Concerning general clinical indicators (**Table 1**) the average time of disease onset was 110.7 months (SD=113.5), mean BMI was 33.7 (SD=44.3), and the total number of comorbidities was 2.16 (SD=1.22). Men and women differed on the use of psychotropics, with women revealing a higher use ($p<0.001$). With respect to clinical indicators related to pain issues, all patients complained of pre-surgical pain with moderate intensity (NRS: M=5.73; SD=1.48) and of interference on performance of daily activities (**Table 1**). Almost half of the sample (49.2%) complained of back pain, 38.5% reported pain in other joints and 66.4% had other previous pain states. These pain issues were significantly different between men and women, with the latter complaining more of both pre-surgical pain and other types of pain. On psychological measures data from Table 1 shows that generally patients had low levels of anxiety and depression like symptoms, with women presenting higher scores when compared to men on both ($p$=0.009; $p$=0.035). On beliefs about the illness underlying surgery, patients revealed a tendency to view their disease as chronic (M=2.80; SD=0.94) and cyclical (M=2.97; SD=0.79), exhibiting a negative emotional representation of it (M=3.19; SD=1.10), albeit showing good expectancies of surgery control (M=3.98; SD=0.38). Moreover, patients revealed high levels of optimism (M=7.93; SD=3.11) and low levels of pain catastrophizing (M=1.81; SD=1.01), with men showing better levels in both factors ($p$=0.022; $p<0.001$).

### 3.2. Surgical, anesthetic and post-surgical sample characteristics at T2

**Table 2** presents data on surgical, anesthetic and post-surgical issues, also comparing them in terms of sex. Within the 124 arthroplasties, 60 (48.4%) were Total Knee Replacement (TKR) and 64 (51.6%) were Total Hip Replacement (THR) surgeries, with no differences between men and women. Men and women did not present distinction in anesthetic, analgesic or clinical parameters, although revealing differences in psychotropic use (p=0.004), following the trend presented before surgery. The mean score for acute post-surgical pain was 5.26 (SD=1.75), with women reporting substantially more pain (p=0.001) and being provided more often with rescue analgesia (p=0.003). In fact, almost half of the sample (40.3%) had to be administrated with additional analgesia beyond the standardized analgesia protocol. In terms of frequency, half of the sample (50%) complained about constant, continuous and steady pain, with the other half reporting brief or intermittent pain, a tendency without significant differences between the groups. Regarding anxiety levels following surgery, mean score was 3.73 (SD=3.64) on a scale from 0 to 21, with no differences between sex.

### 3.3. Inter-correlations of acute post-surgical pain (T2) and socio-demographic, clinical and psychological variables (T1, T2)

**Table 3** and **4** present Pearson and Point-biserial correlation coefficients between acute post-surgical pain intensity and post-surgical anxiety and this potential predictive socio-demographic, clinical and psychological variables. As shown in both tables, acute post-surgical pain intensity and post-surgical anxiety are highly correlated (r=0.51, $p$<0.001). Analyzing **Table 3**, which indicates the associations between the 2 outcome variables and potential pre-surgical socio-demographic and clinical predictors, sex was significantly correlated with post-surgical pain intensity ($r_{pb}$ = 0.33, $p$ < 0.001), although not with post-surgical anxiety. In terms of clinical factors, pain related variables such as pre-surgical pain interference ($r$ = 0.37, $p$ < 0.001), pain due to other causes ($r_{pb}$ = 0.34, $p$ < 0.001) and pre-surgical pain intensity ($r$ = 0.26, $p$ < 0.01) were strongly associated with acute post-surgical pain intensity. The remaining clinical variables only achieved a significance around p<0.05. Regarding post-surgical anxiety, it is strongly associated with pre-surgical pain interference ($r$ = 0.37, $p$ < 0.001), presenting also significant associations with pain due to other causes ($r_{pb}$ = 0.22, $p$ < 0.05), back pain ($r_{pb}$ = 0.28, $p$ < 0.01) and total number of comorbidities ($r$ = 0.19, $p$ < 0.05). None of the other factors revealed significant relationship with this outcome measures, neither age nor sex.

In what concerns to the correlations between psychological measures and our outcome variables (**Table 4**), post-surgical pain was significantly inversely correlated with optimism ($r$=-0.37, $p$<0.001), pain catastrophizing ($r$=0.35, $p$<0.001) and emotional representation of the condition that leads to surgery, which is osteoarthritis ($r$=0.34, $p$<0.001). Other psychological variables, like pre-surgical anxiety and depression, also reached significant values (p<0.05 and p<0.01, respectively). Post-surgical anxiety presented a high correlation with pre-surgical anxiety ($r$=0.54, $p$<0.001) and pre-surgical depression ($r$=0.40, $p$<0.001). Similarly to acute post-surgical pain correlations, post-surgical anxiety also correlated strongly with optimism ($r$=-0.39, $p$<0.001), pain catastrophizing ($r$=0.33, $p$<0.001) and emotional representation of the condition leading to surgery ($r$=0.52, $p$<0.001). These results were used to assist in the selection of the set of socio-demographic, clinical and psychological predictors to include in the regression models.

### 3.4. Predicting post-surgical pain intensity and anxiety levels after hip and knee arthroplasties

To determine the predictors of post-surgical pain intensity and anxiety, separate multiple hierarchical regressions analyses were conducted (**Tables 5** and **6**). Yet it was a priority of this study to seek for a unique model that could predict both outcomes.

In each regression, sex was included in the first step due to its significance in bivariate associations and in previous studies (Kalkman et al., 2003; Gagliese, Gauthier, Macpherson, Jovellanos, & Chan, 2008; Papaioannou et al., 2009). On the next step, the pre-surgical score on the dependent variable (pre-surgical pain intensity or pre-surgical anxiety) was added, along with pain due to other causes. For post-surgical anxiety prediction, pain due to other causes and pre-surgical anxiety were split and put in an individual step each, given their different nature. Concerning the post-surgical pain model, initially pre-surgical pain intensity and interference was entered along with pain due to other causes (absent, present) in the second step. However, due to problems of multicollinearity (VIF>2, Tolerance <0.70), pre-surgical pain interference was excluded from this step. Other previous pain variables could also have been entered, like pain in other joints or back pain, however both were highly correlated with pain due to other causes. Therefore, pain due to other causes was chosen and kept in the model instead of the other two pain variables, once it seems to fully incorporate the other two measures. In terms of psychological variables expected to have the largest impact on post-surgical pain and anxiety, the selected ones were those with highest correlations with the variable to predict (**Table 4**). Therefore, optimism and emotional representation of the condition leading to surgery (osteoarthritis) were entered together in the last step. Pain catastrophizing had to be excluded due to collinearity issues with these two psychological predictors.

**Table 5** shows that, on the first step, sex appeared as a significant predictor ($\beta$=0.337, *p*<0.001) and explained 11.4% of the variance in post-surgical pain. When adding pre-surgical pain intensity and pain due to other causes in the second step, only the latter emerged as a significant predictor ($\beta$=0.238, *p*=0.01), accounting for an additional 7.1% of the variance. Psychological variables were entered in the final step and explained an additional 9.3% of the variance in post-surgical pain intensity, augmenting the variance explained by the final model to 27.8%. Optimism emerged as the main predictor and in the final model it was the only variable explaining post-surgical pain intensity ($\beta$=-0.237, *p*=0.008). In the final model, sex and pain due to other causes ceased to be significant, although sex presented a trend toward significance ($\beta$=0.171, *p*=0.061), as well as emotional representation ($\beta$=0.166, *p*=0.069).

On **Table 6** the results of the hierarchical regression for the prediction of post-surgical anxiety are presented. It followed the same steps described above, with the exception of pre-surgical pain intensity that was replaced by the appropriate pre-surgical variable of the outcome measure: pre-surgical anxiety. In this model both sex and pain due to other causes, entered in first and second steps, never reached statistical significance, together accounting for 4.1% of the variance in post-surgical anxiety. In the third step pre-surgical anxiety proved to be a significant predictor ($\beta$=0.558, *p*<0.001), explaining an additional 27.7% of the variance in post-surgical anxiety. On the final step, optimism and emotional representation were added, both emerging as significant predictors ($\beta$=-0.211, *p*=0.011; $\beta$=0.238, *p*=0.009) and adding 8.2% to the explained variance. In the final model pre-surgical anxiety remained significant ($\beta$=0.358, *p*<0.001) and this final model explained 40.1% of the total variance in post-surgical anxiety. Although pre-surgical anxiety level before surgery (M=6.52; SD=4.11) have dropped significantly (t=5.349; p<0.001) after surgery (M=3.73; SD=3.64), pre-surgical level of anxiety still influence significantly anxiety after surgery, revealing it as the best predictor.

## 4. Discussion

This study reveals the significant influence of psychological factors on both acute pain and post-surgical anxiety following primary total hip and knee arthroplasty. Pre-surgical optimism emerged as the most significant predictor of acute post-surgical pain intensity. For post-surgical anxiety, pre-surgical optimism also revealed a significant influence, along with pre-surgical emotional representation and pre-surgical anxiety level. The present study showed that psychological factors emerged over and above several potential predictors of acute pain intensity after TKA and THA, including surgical, anesthetic and analgesic factors. This work also confirms the strong association between post-surgical anxiety and acute pain after surgery (r=.51). These results could prove useful for the design of interventions aimed at acute post-surgical pain and anxiety management.

### 4.1. Prevalence of acute post-surgical pain and anxiety following TKA and THA

The high values of acute post-surgical pain intensity 48 hours after TKA and THA (mean=5.26 in 10) are in accordance with other study outcomes like QUIPS project (Meissner et al, 2008), in which orthopedic surgery was amongst the most painful surgical procedures. Moreover, a qualitative systematic review (Ip et al, 2009) identified major joint orthopedic surgeries as one of the most painful operations. Accordingly, 40.3% of our sample had to be administrated with rescue analgesics. Another fundamental issue is the strong association between acute post-surgical pain and post-surgical anxiety, drawing attention to the complex psychological and biological interplay of these two alarm systems (Symreng & Fishman, 2004). Carr et al. (2005) found that anxiety and pain were so inter-connected that, during the post-surgical period, changes in anxiety were significantly related with changes in pain. Several studies showed this significant relationship also in diverse chronic pain conditions, even after adjusting for a wide range of potential confounding variables (McWilliams et al., 2004). Psychological interventions focused on anxiety management could be delivered after surgery, during hospital stay. Managing anxiety can potentially be a target both before and after surgery, but this will need to be tested in future research. Feasibility, acceptability and effectiveness studies of such interventions should be the focus of future research.

## 4.2. Predicting acute post-surgical pain and anxiety following TKA and THA

Regarding acute post-surgical pain prediction, sex and pain due to other causes were, initially, significant predictors, in line with other studies in a range of surgeries (Caumo et al., 2002; Kalkman et al., 2003; Gagliese et al., 2008; Papaioannou et al., 2009; Pinto et al., 2012). However, after the addition of psychological variables, both ceased to be significant, indicating the primacy of psychological factors on pain experience.

Overall, dispositional optimism, a generalized expectation that good things will happen (Rasmussen et al., 2009), has been identified as a significant predictor of positive outcomes in a variety of health and disease related conditions (Scheier & Carver, 1993; Scheier et al., 1999; Kubzansky et al., 2001; Rasmussen et al., 2009). However, the role of optimism in pain conditions, either acute or chronic pain has received less attention (Peters, 2009).

The association between optimism and low levels of pain was shown in samples of adult patients with osteoarthritis (Ferreira & Sherman, 2007), facial pain (Sipila, Ylöstalo, Ek, Zitting, & Knuuttila, 2006) head, neck (Allison, Guichard, & Gilain, 2000) and lung cancer (Wong & Fielding, 2007). Additionally, regarding experimental pain conditions, previous studies revealed that dispositional optimism is associated with augmented pain tolerance and diminished pain sensitivity (Costello et al., 2002; Geers, Wellman, Helfer, Fowler, & France, 2008), being a significant predictor of placebo analgesia (Morton, Watson, El-Deredy, & Jones, 2009; Geers, Wellman, Fowler, Helfer, & France, 2010).

Optimistic patients seem to recover quicker and present less post-surgical complications than pessimistic patients (Scheier et al.,1999; Bowley, Butler, Shaw, & Kingsnorth, 2003; Peters et al., 2007). The advantages of higher optimism in its relation to surgical pain were found only during the early recovery period (Mahler & Kulic, 2000). A study by Peters et al. (2007) concluded that optimism did not predict pain 6 months after a variety of surgical procedures, although influenced quality of life, in line with other studies (Chamberlain, Petrie, & Azariah 1992; Rasmussen et al. 2009).

There are possible explanations for the influence of optimism on short-term surgical pain. It may be hypothesized that optimists might experience less pain because they are less attentive to pain stimuli, meaning that they could cope with pain through a process of mental disengagement from the pain stimuli (Affleck, Tennen, & Apter, 2001). Still regarding coping skills, optimists could also use more adaptive coping strategies, such as positive reinterpretation, acceptance, and reliance on problem-focused coping (Scheier, Weintraub, & Carver, 1986; Scheier & Carver, 1992). Accordingly, in our sample optimism revealed a negative significant correlation with pain catastrophizing, a negative pain coping strategy.

Finally, optimism could influence acute post-surgical pain experience through its impact on the immune system. Cytokine IL-6 has a central role in inflammation and immunity, showing increased systemic levels during physical and psychological stress (Mitchell et al., 1993; Hager et al., 1994). Optimistic appraisals have shown to influence the biological response to stress, namely through the decrease in levels of IL-6 (Costello et al., 2002; Byron, Walker, Wawrzyniak, Chart, & Steptoe, 2009), by counter-acting acute increases in IL-6 responses that could trigger inflammation and consequently pain. On the contrary, an association between low optimism, high pain sensitivity and exaggerated inflammatory response to stress with high levels of IL-6, has also been demonstrated (Costello et al., 2002). The circulating levels of this cytokine are augmented in a variety of inflammatory-type diseases, usually known to be aggravated by stress, such as arthritis, multiple sclerosis, fibromyalgia, rheumatoid arthritis, and also pain (Kotake et al., 1996; Clauw and Chrousos, 1997; Papanicolaou, Wilder, Manolagas, & Chrousos, 1998; Costello et al., 2002; Kemeny & Schedlowski, 2007; Naugler & Karin, 2008).

It is interesting to note that pre-surgical optimism also predicted post-surgical anxiety, with the current study being the first examining this specific relationship using the sub-scale optimism from the LOT-R (Life Orientation Test-Revised). Although using a different measure - The Future Self-Perception Questionnaire – that evaluates hopelessness and optimistic view of the future, Caumo et al. (2001) also found that a negative pre-surgical perception of the future was an independent risk factor for postoperative anxiety. Indeed, it has been shown in numerous studies that high dispositional optimism is associated with an adaptive response to health-related stress (Geers et al., 2008). Actually, in a former meta-analytic review (Andersson, 1986) using the LOT-R, the most reliable conclusion concerned the inverse association between optimism and negative affect, confirming dispositional optimism as an important determinant of psychological well-being (Chang, 1998; Schou, Ekeberg, Ruland, Sandvik, & Karesene, 2004). Dispositional optimism may buffer the impact of stress on psychological states and on biological processes too (Cohen et al., 1999), which might explain why after surgery optimistic patients experience less levels of anxiety. One interesting finding of this study indicates that in face of the prospect of undergoing an arthroplasty, the more patients are affected by their underlying disease (osteoarthritis), the more likely they are to present heightened pain levels and to be more anxious in the 48 h period after surgery. This means that the specific emotional response to the illness, like feeling depressed, angry or upset, appears to influence immediate surgical outcomes. As Moss-Morris et al., (2002) stated, this scale – emotional representation - does not constitute a simple indicator of patients' general mood, instead it provides an evaluation of the emotional responses triggered by illness, regardless of its actual severity. There are studies in other fields demonstrating how this variable relates with other health outcomes. Amongst patients with osteoarthritis, those with more negative emotional illness representations experienced more limitation in activities of daily living than explained by the objective limitations diagnosed by radiographs (Botha-Scheepers et al., 2006).

To the best of our knowledge, this was the first study focused on post-surgical pain and anxiety, using a psychometrically shorten version of the IPQ-R (Illness Perceptions Questionnaire-Revised; Sniehotta, Gorsky, Araújo-Soares, 2009) as a potential predictive measure. Previous studies tended to focus on more general emotional predictors like pre-surgical levels of anxiety or depression.

Empirical and revision studies have widely demonstrated that pre-surgical anxiety is associated with higher levels of post-surgical anxiety (Johnston, 1986; Taenzer, Melzack & Jeans, 1986; DeGroot et al., 1997; Caumo et al., 2001; Munafo & Stevensson, 2001; Carr, Brockbank, Allen, & Strike, 2006). Research using similar measures to the one used in this study (Carr et al., 2005) revealed that after controlling for sex, age, and medical variables, pre-surgical anxiety was positively associated with post-surgical anxiety. Our study, using HADS, corroborated the abovementioned study. Similar results were found on other studies (DeGroot, Boeke, Duivenvoorden, Bonke, & Passchier, 1996; DeGroot et al., 1997), regardless of the different anxiety measures used, which underlines the crucial influence of pre-surgical anxiety on post-surgical anxiety.

### 4.3. Limitations of the Study

As the choice of coping strategies appears to be the mediation mechanism through which optimism is related to less distress in the face of adversity and to better health outcomes (Scheier et al., 1986; Scheier et al., 1994), future investigations should focus on the further assessment of the relation amongst optimism, coping strategies (adaptive and maladaptive), post-surgical anxiety and pain.

Another potential limitation could be associated with the researcher gender (female). Previous studies reported socio-cultural influences on pain perception, which might be influenced by gender "norms" and gender roles (Pool, Schwegler, Theodore, & Fuchs, 2007). Males seem to report less pain and higher thresholds when tested by a female examiner (Gijshers & Nicholson, 2005). Thus one might wonder about the reliability of the sex outcomes found in this study.

Finally, this is a single site and single country study, and thus the generalization of the conclusions to populations in other countries should be considered with caution. Future studies need to be conducted in order to analyze if these results can be replicated, especially in what concerns the role of optimism on the prediction of acute pain.

### 4.4. Clinical practice implications

The results presented here reveal the influence that psychological factors may have on post-surgical pain and anxiety, even after controlling the effect of socio-demographic and clinical variables.

Our study identified three psychological factors, two of them proven to be amenable to change or to active management through psychological pre and post-surgical interventions: pre-surgical anxiety and emotional representation. This knowledge has the potential to guide treatment and prevention strategies. Results of present study also emphasize the strong relationship between acute pain and anxiety in patients undergoing joint arthroplasties. Those underline the potential appropriateness of developing broader psychological treatments that could target both conditions, either before surgery or in the short term hospital stay. Indeed, interventions that diminish anxiety levels may consequently reduce pain in persons whose pain is amplified by anxiety (Symreng & Fishman, 2004). To deal with anxiety, brief cognitive-behavior therapy intervention techniques (such as brief relaxation, imagery, positive coping self-statements), reassurance and information provision have been widely used (Good, 1999; Sjoling, Nordahl, Olofsson, & Asplund, 2003; Bruehl & Chung, 2004; Roykulcharoen & Good, 2004; Stoddard, White, Covino, & Strauss, 2005).

Concerning optimism, Peters (2009) concluded that pain patients could benefit from interventions to increase optimism, albeit temporarily, through a short visualization intervention.

Seligman (2006) also suggested that through cognitive therapy, it would be possible to increase optimism levels. Present findings suggest that pre-surgical arthroplasty patients could benefit from such preventive interventions in order to reduce levels of pain and anxiety following surgery, as long as a brief cost effective intervention could be offered.

The present study also suggest that restructuring pre-surgical negative emotions generated by the illness may support patients to cope more adequately with surgery, diminishing post-surgical anxiety levels. As this factor is amenable to change it seems important to assess individuals that present such negative emotions before surgery (Juergen et al., 2010). Interventions based on understanding and modifying illness representations have been useful in reducing disability and improving functioning in other conditions (Chan et al., 2009; Groarke *et al.*, 2005; Petrie & Weinman, 2006). Patients should be assisted by health professionals in learning and applying more effective coping skills, namely through cognitive-behavioral techniques, to manage the emotional representations that they have developed in face of their illness (Hermele et al., 2007). In sum, by identifying patients at risk, more appropriate psychological interventions and better post-surgical surveillance can be implemented.

Data from the present study, focusing on the short-term post-surgical period, confirms the determinant influence of psychological factors on acute pain and anxiety following joint arthroplasties, namely TKA and THA.

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**Table 1**

***Descriptive statistics and group differences on pre-surgical socio-demographic, clinical and psychological variables for the total sample and by sex***

| Patient characteristics | Total sample (*N*= 124) | Women (*n* = 83) | Men (*n*= 41) | *p* |
|---|---|---|---|---|
| ***Socio-demographic*** | | | | |
| Age (years(SD)) | 65.2 (7.97) | 66.0 (7.48) | 63.5 (8.76) | *ns* |
| Marital status (married) | 91 (73.4%) | 54 (65.1%) | 37 (90.2%) | *0.003* |
| Number of children | 3.20 (2.09) | 3.26 (2.30) | 3.07 (1.62) | *ns* |
| Education (≤ 4 yrs) | 120 (96.8%) | 81 (97.6%) | 39 (95.1%) | *ns* |
| Residence (rural setting) | 54 (43.5%) | 37 (44.6%) | 17 (41.5%) | *ns* |
| Professional status (retired) | 93 (75.6%) | 67 (81.7%) | 26 (63.4%) | *0.026* |
| ***Clinical – general indicators*** | | | | |
| Disease onset (months) | 110.7 (113.5) | 119.2 (119.1) | 94.3 (101.2) | *ns* |
| BMI[1] (Kg/m2) | 33.7 (44.3) | 36.0 (53.8) | 29.1 (4.39) | *ns* |
| Previous surgeries (yes) | 105 (85.4%) | 72 (87.8%) | 33 (80.5%) | *ns* |
| Psychotropic use[2] (yes) | 48 (38.7%) | 43 (51.8%) | 5 (12.2%) | *<0.001* |
| Comorbidities total[3] | 2.16 (1.22) | 2.26 (1.17) | 1.95 (1.30) | *ns* |
| **Clinical-pre-surgical pain indicators** | | | | |
| NRS[4] (BPI): Intensity | 5.73 (1.48) | 6.11 (1.42) | 4.98 (1.32) | <0.001 |
| BPI: [5]Pain Total Interference | 28.0 (12.3) | 31.8 (11.5) | 20.4 (10.2) | <0.001 |
| Pain Duration >3 yrs | 89 (73%) | 58 (70.7%) | 31 (77.5%) | *ns* |
| Other prev. pain states[6] (yes) | 81 (66.4%) | 65 (79.3%) | 16 (40.0%) | <0.001 |
| Pain in other joints (yes) | 47 (38.5%) | 38 (46.3%) | 9 (22.5%) | *0.011* |
| Back pain (yes) | 60 (49.2%) | 48 (58.5%) | 12 (30.0%) | *0.003* |
| ***Psychological measures*** | | | | |
| HADS[7]: Anxiety | 6.52 (4.11) | 6.19 (4.16) | 4.15 (3.68) | *0.009* |
| HADS[7]: Depression | 2.38 (3.13) | 2.80 (3.29) | 1.54 (2.64) | *0.035* |
| IPQ-R[8]: Timeline acut/chroni | 2.80 (0.94) | 2.88 (0.98) | 2.65 (0.85) | *ns* |
| IPQ-R[8]: Timeline cyclical | 2.97 (0.79) | 2.88 (0.83) | 3.15 (0.68) | *ns* |
| IPQ-R[8]: Treatment control | 3.98 (0.38) | 3.96 (0.38) | 4.02 (0.38) | *ns* |
| IPQ-R[8]: Illness coherence | 2.48 (1.01) | 2.52 (1.01) | 2.41 (1.02) | *ns* |
| IPQ-R[8]: Emotional represent | 3.19 (1.10) | 3.30 (1.07) | 2.96 (1.14) | *ns* |
| LOT-R[9]: Optimism | 7.93 (3.11) | 7.52 (3.31) | 8.76 (2.49) | *0.022* |
| CSQ-R[10]: Pain catastrophizing | 1.81 (1.01) | 2.02 (1.09) | 1.39 (0.70) | *<0.001* |

*Note: N=124.* Continuous variables are presented as Mean (Standard deviation); Categorical variables are presented as *n* (%); T1= 24 hours before surgery; [1]BMI = body mass index; [2]Psychotropic use: Consumption / Intake of anxiolytics and anti-depressants; [3]Comorbidities total = number of comorbid health conditions; [4]NRS(BPI) =Numerical Rating Scale 0-10 from Brief Pain Inventory; [5]Pain Total Interference Scale 0-70 from Brief Pain Inventory (BPI); [6]Other previous pain states = either acute or chronic, not related to the cause of surgery, but nonetheless frequent; [7]HADS = Hospital Anxiety and Depression Scale; [8]IPQ-R= Illness Perception Questionnaire-Revised; [9]LOT-R = Life Orientation Test – revised; [10]CSQ-R=Coping Strategies Questionnaire-Revised.

**Table 2**

***Descriptive statistics and group differences on anesthetic, surgical and analgesic variables at T2 for the total sample and by sex***

| **Post-surgical data** | **Total sample (*N* = 124)** | **Women (*n* = 83)** | **Men (*n* = 41)** | ***p*** |
|---|---|---|---|---|
| Type of arthroplasty[1] (TKR) | 60 (48.4%) | 45 (75%) | 38 (59.4%) | *ns* |
| Type of anesthesia[2]: loco-regional + peripheral nerve blocks | 42 (33.9%) | 32 (38.6%) | 10 (24.4%) | *ns* |
| Analgesia perineural[3] (yes) | 37 (30.1%) | 28 (34.1%) | 9 (22.0%) | *ns* |
| Length of hospital stay (days) | 7.16 (2.88) | 7.14 (2.15) | 7.22 (3.98) | *ns* |
| Psychotropic use[4] (yes) | 53 (42.7%) | 43 (51.8%) | 10 (24.4%) | *0.004* |
| HADS[5]: Anxiety | 3.73 (3.64) | 4.07 (3.66) | 3.02 (3.55) | ns |
| ***Clinical pain & analgesic indicators*** | | | | |
| NRS[6] (BPI): Intensity | 5.26 (1.75) | 5.67 (1.47) | 4.44 (1.98) | *0.001* |
| Frequency[7]: Constant | 62 (50%) | 45 (54.2%) | 17 (41.5%) | *ns* |
| Rescue analgesics (yes) | 50 (40.3%) | 41 (49.4%) | 9 (22.0%) | *0.003* |
| % Relief from analgesics (0-100%) | 90.5 (20.0) | 91.9 (16.8) | 87.50 (25.4) | *ns* |

Note. Continuous variables are presented as Mean (Standard deviation); Categorical variables are presented as *n* (%); T2 – 48 hours after surgery; [1]Type of arthroplasty: Total knee replacement (TKR) vs Total hip replacement (THR); [2]Type of anesthesia: Anesthesia loco-regional alone: BSA or epidural vs Anesthesia loco-regional (BSA or epidural) + peripheral nerve blocks; [3]Analgesia perineural vs intravenous and epidural analgesia; [4]Psychotropic use: Consumption / Intake of anxiolytics and anti-depressants; [5]HADS = Hospital Anxiety and Depression Scale; [6]NRS(BPI) =Numerical Rating Scale 0-10 from Brief Pain Inventory; [7]Pain Frequency: constant pain vs intermittent or brief pain, assessed via frequency subscale of McGill Pain Questionnaire.

**Table 3**

***Pearson and Point-biserial correlation coefficients between demographic and clinical variables (T1) and acute post-surgical pain and post-surgical anxiety (T2)***

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Acute Pain T2 | - | | | | | | | | | | | | |
| 2. HADS: Anxiety T2 | .51*** | - | | | | | | | | | | | |
| 3. Age | .13 | .01 | - | | | | | | | | | | |
| 4. Sex | .33*** | .14 | .15 | - | | | | | | | | | |
| 5. Pre-surgical pain intensity | .26** | .16 | .02 | .36*** | - | | | | | | | | |
| 6. Pre-surgical pain interferen | .37*** | .37*** | .02 | .44*** | .55*** | - | | | | | | | |
| 7. Other previous pain states | .34*** | .22* | .05 | .39*** | .20* | .38*** | - | | | | | | |
| 8. Pain in other joints | .23* | .13 | .17 | .23* | .11 | .24** | .56*** | - | | | | | |
| 9. Back pain | .20* | .28** | .06 | .27** | .16 | .29** | .63*** | .30** | - | | | | |
| 10. BMI | -.04 | -.02 | .00 | .07 | .09 | .05 | .09 | .14 | .11 | - | | | |
| 11. Comorbidities total | .19* | .19* | .21* | .12 | .10 | .17 | .52*** | .62*** | .58*** | .17 | - | | |
| 12. Previous surgeries | .16 | -.00 | -.07 | .10 | .15 | .11 | .24** | .14 | .17 | .04 | .13 | - | |
| 13. Type of anesthesia | -.23* | -.11 | .09 | -.14 | -.02 | -.08 | -.26** | -.31*** | -.08 | .05 | -.18 | -.15 | - |

*$p$<0.05 **. $p$<0.01 ***. $p$<0.001.

Note. T1 – 24 hours before surgery; T2 – 48 hours after surgery. SEX – 0=men & 1=women; Acute Pain and Pre-surgical pain T1- NRS score from BPI-SF: Brief Pain Inventory – Short Form; Pre-surgical pain interference from BPI-SF: Brief Pain Inventory; BMI = body mass index; Type of anesthesia: 0=Anesthesia loco-regional (BSA or epidural) & peripheral nerve blocks & Anesthesia loco-regional alone: BSA or epidural.

**Table 4**

***Pearson correlation coefficients between baseline psychological variables (T1) and acute post-surgical pain and post-surgical anxiety (T2)***

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Acute Pain T2 | - | | | | | | | | | | |
| 2. HADS: Anxiety T1 | .22* | - | | | | | | | | | |
| 3. HADS: Depression | .27** | .51*** | - | | | | | | | | |
| 4. IPQ-R: Timeli acut/chro | .08 | .23* | .32*** | - | | | | | | | |
| 5. IPQ-R: Personal control | -.04 | .15 | -.03 | .23** | - | | | | | | |
| 6. IPQ-R: Treatm control | -.15 | -.28** | -.37*** | -.27** | -.07 | - | | | | | |
| 7. IPQ-R: Illness coherenc | .05 | -.05 | .18* | .02 | -.07 | -.10 | - | | | | |
| 8. IPQ-R: Emotio represent | .34*** | .58*** | .40*** | .17 | .01 | -.16 | .03 | - | | | |
| 9. LOT-R: Optimism | -.37*** | -.40*** | -.50*** | -.26** | .02 | .33*** | -.05 | -.31*** | - | | |
| 10. CSQ-R: Pain catastrop | .35*** | .54*** | .51*** | .15 | -.07 | -.22* | -.00 | .55*** | -.42*** | - | |
| 11. HADS: Anxiety T2 | .51*** | .54*** | .40*** | .23** | -.08 | -.21 | -.02 | .52*** | -.39*** | .33*** | - |

*$p$<0.05 **. $p$<0.01 ***. $p$<0.001.

Note. T1 – 24 hours before surgery; T2 – 48 hours after surgery. Acute Pain - NRS score from BPI-SF: Brief Pain Inventory – Short Form; HADS: Hospital Anxiety and Depression Scale; IPQ-R: Illness Perception Questionnaire-Revised; LOT-R: Life Orientation Test-Revised; CSQ-R: Coping Strategies Questionnaire-Revised

**Table 5**

***Hierarchical multiple regression results for pre-surgical predictors of post-surgical pain intensity 48 hours after hip and knee arthroplasties (N=124)***

| Variables | $t$ | β | $R^2$ | Δ $R^2$ | Δ$F$ |
|---|---|---|---|---|---|
| ***Step 1*** | | | 0.114 | 0.114 | 15.376*** |
| Sex[1] | 3.921*** | 0.337 | | | |
| ***Step 2*** | | | 0.185 | 0.071 | 5.173** |
| Sex[1] | 2.057* | 0.194 | | | |
| Pre-surgical pain intensity[2] | 1.653 | 0.147 | | | |
| Other previous pain states[3] | 2,624** | 0.238 | | | |
| **Step 3 (final model)** | | | 0.278 | 0.093 | 7.487*** |
| Sex[1] | 1.895 | 0.171 | | | |
| Pre-surgical pain intensity[2] | 1.187 | 0.107 | | | |
| Other previous pain states[3] | 1.572 | 0.141 | | | |
| Optimism[4] | -2.716** | -0.237 | | | |
| Emotional representation[5] | 1.837 | 0.166 | | | |

*$p$≤0.05 **. $p$≤0.01 ***. $p$≤0.001.

Note. T1 – 24 hours before surgery; T2 – 48 hours after surgery; [1]Dichotomous variable: 0= Men; 1=Women; [2]Continuous variable, NRS 0-10 from BPI-SF: Brief Pain Inventory-Short Form; [3]Dichotomous variable: 0= No; 1= yes; [4]Continuous variable, LOT-R: Life Orientation Test - Revised; [5]Continuous variable, IPQ-R: Illness Perceptions Questionnaire - Revised (Emotional Representation subscale).

**Table 6**

***Hierarchical multiple regression results for pre-surgical predictors of post-surgical anxiety 48 hours after hip and knee arthroplasties*** **(*N*=124)**

| Variables | $t$ | β | $R^2$ | Δ $R^2$ | Δ$F$ |
|---|---|---|---|---|---|
| ***Step 1*** | | | 0.013 | 0.013 | 1.546 |
| Sex[1] | 1.243 | 0.114 | | | |
| ***Step 2*** | | | 0.041 | 0.028 | 3.472 |
| Sex[1] | 0.442 | 0.043 | | | |
| Other previous pain states[2] | 1,863 | 0.183 | | | |
| ***Step 3*** | | | 0,319 | 0,277 | 47,172*** |
| Sex[1] | -0,606 | -0.051 | | | |
| Other previous pain states[2] | 0,667 | 0.057 | | | |
| Pre-surgical anxiety[3] | 6,868*** | 0,558 | | | |
| **Step 4 (final model)** | | | 0.401 | 0.082 | 7.801*** |
| Sex[1] | -0.716 | -0.057 | | | |
| Other previous pain states[2] | -0.050 | -0.004 | | | |
| Pre-surgical pain anxiety[3] | 3.833*** | 0.358 | | | |
| Optimism[4] | -2.579* | -0.211 | | | |
| Emotional representation[5] | 2.671** | 0.238 | | | |

*$p$≤0.05 **. $p$≤0.01 ***. $p$≤0.001.

Note. T1 – 24 hours before surgery; T2 – 48 hours after surgery; [1]Dichotomous variable: 0= Men; 1=Women; [2]Dichotomous variable: 0= No; 1= yes; [3]Continuous variable, HADS: Hospital Anxiety and Depression Scale (Anxiety subscale); [4]Continuous variable, LOT-R: Life Orientation Test - Revised; [5]Continuous variable, IPQ-R: Illness Perceptions Questionnaire - Revised (Emotional Representation subscale).

Chapter 2.2.2

**STUDY 5**

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Pinto, P.R., McIntyre, T., Ferrero, R., Almeida, A., & Araújo-Soares, V.

**Predictors of persistent post-surgical pain after total knee and hip arthroplasty**

(*Manuscript under preparation*)

**Predictors of Persistent Post-Surgical Pain after Total Knee and Hip Arthroplasty**

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**Abstract**

Persistent post-surgical pain (PPSP) is a major clinical problem with significant individual, social and health care costs. The aim of this study was to examine the joint role of demographic, clinical and psychological risk factors in the development of persistent post-surgical pain (PPSP) after Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA). In a prospective study, a consecutive sample of 92 patients was assessed 24 hours before (T1), 48 hours (T2) and 4-6 months (T3) after surgery. Regression analyses were performed to identify predictors of PPSP. Four-six months after TKA and THA, 63 (68.5%) participants reported experiencing pain. In the 2 final multivariate models obtained through sequential logistic regression analysis, baseline pre-surgical anxiety (OR=1.409, p=0.021), post-surgical anxiety (OR=1.335, p=0.045) and acute post-surgical pain intensity (OR=1.387, p=0.026) revealed a predictive role in PPSP development. These results increase the knowledge on PPSP predictors and point healthcare professionals towards specific intervention targets such as anxiety (pre and post-surgical) and the need for fine acute pain control after surgery.

Keywords: total knee arthroplasty (TKA); total hip arthroplasty (THA); persistent post-surgical pain; pre-surgical anxiety; post-surgical anxiety; acute post-surgical pain intensity.

## 1. Introduction

With the aging population, it is expected a significant rise in the prevalence of knee and hip osteoarthritis and consequently an increase on the number of surgical interventions such as total knee arthroplasty (TKA) and total hip arthroplasty (THA), aiming at reducing pain and disability, improving functional status and thus restoring quality of life (Bachmeier et al., 2001; Lingard, Katz, Wright, Sledge, & Kinemax Outcomes Group, 2004; Hamel, Toth, Legedza, & Rosen, 2008; Wylde, Hewlett, Learmonth, & Dieppe 2011). Joint arthroplasties often improve functional status and yield significant pain relief for the majority of patients who undergo these procedures (MacWilliams, Yood, Verner, McCarthy, & Ward, 1996). However, some patients may carry on experiencing significant pain following surgery as well as scarce improvements in functional outcomes (Brander et al., 2003). Indeed, many patients experience persistent post-surgical pain (PPSP) over the following months after arthroplasty, despite an absence of clinical or radiographic evidence of abnormalities (Brander et al., 2003). This points to a potential influence of non-clinical factors on the short and long term outcomes of these types of surgeries. PPSP is a major clinical problem with significant individual, social and health care costs (Perkins & Gopal, 2003; Shipton & Tait, 2005; Kehlet, Jensen, & Woolf, 2006). Within arthroplasties studies aiming at long-term outcomes, attention has been mainly directed to potential predictors within demographic and clinical data (Nilsdotter, Aurell, Y., Siösteen, A., Lohmander, L., & Roos, 2001; Nikolajsen, Sørensen, Jensen, & Kehlet, 2004; Ebrahimpour, Do, Bornstein, & Westrich, 2011).

Amongst the few studies that sought to explore psychological factors, anxiety, depression and pain catastrophizing arose as the most important (Brander et al., 2003; Faller, Kirschner, & Konig,, 2003; Forsythe, Dunbar, Hennigar, Sullivan, & Gross 2008; Sullivan et al., 2011). Nevertheless, studies aiming to understand the added contribution of psychological variables on PPSP have missed the potential simultaneous influence of a multifactorial set of variables. Therefore, the aim of the present study is to explore simultaneously the joint contribution of demographic, psychological, and surgical factors as predictors of PPSP after knee and hip arthroplasties. A predictive model is explored in order to assist health care practitioners and patients in estimating the likelihood of success of major joint arthroplasties, providing clinicians with information that may be used to determine whether or not a patient should be submitted to the surgical procedure.

## 2. Methods

### 2.1. Participants and Procedures

This was a prospective study wherein a consecutive sample of 130 patients with osteoarthritis was enrolled. Inclusion criteria were 18 to 80 years old, being able to understand written information (informed consent), without psychiatric or neurologic pathology (e.g. psychosis, dementia) and undergoing THA and TKA for diagnosis of coxarthrosis and gonarthrosis only (osteoarthrosis). Arthroplasties that were performed because of fractures were excluded, as well as hemiarthroplasties, revision and emergency arthroplasties.

Patients were initially assessed 24 hours before (T1) and 48 hours after (T2) surgery, at the Hospital. Follow-up assessment was performed in the follow-up consultations 4 to 6 months later, accordingly to the specific schedule of each outpatient consultation. From T1 to T2 measurement points, 6 patients were withdrawn due to: canceled surgery (n = 3), repeated surgery / reoperation (n = 2), and ASA status IV along with occurrence of post-surgical delirium (n = 1). Of those 124 patients with knee and hip arthroplasties who were assessed both before and after surgery, 22 were lost to the 4-6 months follow-up assessment, leaving a sample of 92 patients for analyses. These exclusions were due to cases such as: post-surgical complications (like infections) or accidents (prosthesis displacement) that required the performance of a revision arthroplasty in the operated joint (n = 5), undergoing an arthroplasty in another joint (n = 5) or not attendance at the follow-up orthopedic consultation (n = 12). Thus the results for 92 patients (61 women), with a mean age at surgery of 64.0 ± 7.9 years were included in analyses.

### 2.2. Measures

The following questionnaires were administered in a face to face interview by a trained psychologist (for a rapid overview see **Table 1**).

(1*) Socio-Demographic Questionnaire*. It included questions on age, education, residence, marital status, professional status, household and parity.

(2*) Clinical Data Questionnaire*. It included questions about previous pre-surgical pain, its onset, duration and frequency, pain due to other causes, pain in other joints (specifically in knees and hips), back pain, disease onset, previous surgeries, height, weight, comorbidities, as well as the use of psychotropic drugs.

(2.1) Co-morbidities: the existence of pre-surgical co-morbid conditions that could affect TKA and THA surgical outcomes were asked to the patient or extracted from the medical chart. For that purpose, Deyo–Charlson index (Charlson, Pompei, Ales, & MacKenzie, 1987) was used, given that it is the most commonly used comorbidity measure, consisting of a weighted scale of 17 comorbidities, such as: hypertension, cardiac, pulmonary, renal and hepatic disease, diabetes mellitus, cancer, etc. The total number of co-morbid health conditions was summed in order to yield a total score. However, the weighting of severity used with this index was not used in our study, but only the summative score related to the total number of comorbid conditions, as already performed elsewhere (Jones, Voaklander, & Suarez-Almazor, 2003).

(3) Brief Pain Inventory – short form (BPI-SF) (Cleeland & Ryan, 1994). The BPI-SF measured pain intensity on an 11-point numerical rating scale (from 0 or "no pain" to 10 or "worst pain imaginable"), pain analgesics, perception of analgesics relief, pain interference in daily activities (general activity, mood, walking, work, relations with others, sleep and enjoyment of life) and pain location. In this study, the internal consistency reliability (Cronbach, 1951) for the pain interference subscale scores, was very high (T1: $\alpha$=0.88; T3: $\alpha$=0.92).

(4) "Frequency scale" of the McGill Pain Questionnaire (Melzack, 1975). Women could define their pain either as constant (continuous, steady), intermittent (periodic, rhythmic) or brief (momentary, transient). This specific subscale was used at T2 given that the characterization of a pain that is confined to a period of 48 hours cannot be described in terms of days, weeks or months, as was done for the assessment of pre-surgical pain at T1 and PPSP at T3.

(5) Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS consists of two 7-item sub-scales which measure anxiety (HADS-A) and depression (HADS-B) levels among patients in non-psychiatric hospital settings. Item response format is a Likert scale ranging from 0 to 3. Sub-scale scores vary between 0 and 21. Higher scores represent higher levels of anxiety and depression. In the current sample, internal consistency reliability (Cronbach, 1951) was adequate for both anxiety (T1: $\alpha$=0.76; T2: $\alpha$=0.83; T3: $\alpha$=0.84) and depression (T1: $\alpha$=0.72; T3: $\alpha$=0.97).

(6) Revised Illness Perception Questionnaire (IPQ-R) (Moss-Morris et al., 2002). It assesses patient beliefs about the underlying condition that lead to surgery. A psychometrically short

version (Sniehotta, Gorski and Araujo-Soares, 2009) was used with 7 subscales composed by 3 items each and analyzing distinct dimensions of illness perceptions: "timeline acute/chronic" (α=0.97; e.g. "My illness will last for a long time"); "timeline cyclical" (α=0.57; e.g. "My symptoms come and go in cycles"); "consequences" (α=0.48; e.g. "The disease underlying surgery has major consequences on my life"); "personal control" (α=0.79; e.g. "I have the power to influence my illness"); "treatment control" (α=0.85; e.g. "Surgery can control my illness"); "illness coherence" (α=0.87; e.g. "My illness is a mystery for me"); "emotional representation" (α=0.89; e.g. "When I think about my illness I get upset"). To generate the total scale score, the sum of the item scores was divided by the number of items. Each subscale is rated on a scale of 1-5, high scores reveal worst results, with the exception of personal and treatment control subscales. With the exception of "timeline cyclical" and "consequences" subscales, which revealed low internal consistency (0.57 and 0.48), the remaining sub-scales presented adequate properties.

(7) Life Orientation Test – revised (LOT-R) (Scheier, Carver, & Bridges 1994). It evaluates the personality trait optimism through 8 items. In this study just 3 items were used, corresponding to a subscale of optimism which ranges from 0 to 12, with high values associated with more optimism. In the current sample, internal consistency (Cronbach, 1951) was excellent (α = 0.95).

(8) "Pain Catastrophizing scale" of the *Coping Strategies Questionnaire – Revised Form* (CSQ-R) (Riley & Robinson, 1997). This sub-scale has 6 items that assess pain catastrophizing. Items were rated on a 5-point adjective rating scale (1=never, 2=almost never, 3=sometimes, 4=almost always, and 5=always) rather than the 7-point scale used in the original instrument, due to difficulties expressed by pilot study patients in discriminating the 7 points (Pinto, McIntyre, Almeida, & Araújo-Soares, 2012). To generate the total scale score, the sum of the item scores was divided by the number of items. Scale scores vary between 1 and 5, with higher scores indicating greater use of the specific coping strategy. In the current sample, the Cronbach alpha internal consistency reliability coefficient (Cronbach, 1951) was 0.94, indicating good reliability.

## 2.3. Statistical Analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS version 18.0). Internal consistency of responses to the questionnaires was assessed using Cronbach's alpha (Cronbach, 1951) (see above). Distribution of data differed significantly from normality assumptions. Thus, continuous variables are presented as median and range, and categorical data are presented as numbers and percentages. The primary outcome variable in this study is the report of pain at the 4 to 6 month follow-up. When asked about the presence of pain some patients considered "an impression" only reported during certain movements or if pressing that part of the body, defining it as a maximum pain level of 1 in the 0-10 NRS and stating that pain was not relevant and not significant. Accordingly, 2 groups were considered: a group with none or insignificant pain (NRS: 0–1) and a group with significant pain (NRS≥ 2). Mann-Whitney or Chi-square tests ($\chi 2$) were performed to compare socio-demographic, clinical and psychological measures between these 2 groups. Sequential logistic regression analyses were conducted to determine risk factors for PPSP. The potential predictors selected for the regression analysis were the ones that were found to distinguish between the 2 pain groups ($p<0.05$). The selected specific risk factors chosen for these analyses were divided into three categories: demographic, clinical and psychological risk factors. Two models were built, the first one centered on pre-surgical factors (T1) and the second one addressing the immediate post-surgical period (T2). Both models share the first two steps, which are comprised by the demographic and clinical variables that distinguished the groups in univariate analysis: sex in first step and pre-surgical pain interference and pain due to other causes in the second step. Psychological factors found to distinguish the 2 groups in T1 and T2 assessments were included in the subsequent steps. Therefore, the first model tested the predictive role of baseline psychological factors while the second one tested the influence of acute post-surgical pain and post-surgical anxiety for PPSP development, after controlling for sex and baseline pain issues. To control for the influence of multicollinearity, the variance inflation factor value (VIF) for every independent variable was calculated, only being included if VIF < 2.

## 3. Results

### 3.1. Pain 4 to 6 months after TKA and THA

Of the 92 assessed patients, 29 (31.5%) reported no pain or almost no pain (NRS≤1) at follow-up, whereas 63 (68.5%) patients reported a significant level of pain (NRS≥2) (**Table 2**). Four to six months after total joint arthroplasty there were significant differences between patients with and without PPSP, with the latter presenting more anxiety ($p<0.001$) and depression ($p=0.002$) related symptoms.

### 3.2. Socio-demographic, clinical and psychological characteristics by group (PPSP vs. no pain)

At T1 groups did not differ on any socio-demographic measure, apart from sex, with women presenting more often PPSP ($p=0.045$). Both groups were also similar concerning clinical measures like surgical disease onset, BMI (body mass index), previous surgical procedures and existence of medical comorbidities. Although the groups did not differ in terms of pre-surgical pain intensity, those with PPSP reported higher total pre-surgical pain interference on daily life activities ($p=0.037$), and more often pain due to other causes ($p=0.01$) as well as pain in other joints ($p=0.011$) (see **Table 2**). Furthermore, patients with PPSP presented higher anxiety levels ($p=0.013$), more chronic perception of illness ("Timeline acute / chronic": $p=0.034$) and higher levels of pain catastrophizing ($p=0.007$) (**Table 2**). At T2, 48 hours after surgery, patients presenting PPSP at T3 also showed higher anxiety ($p=0.003$) and heightened acute post-surgical pain intensity, both in terms of average (<0.001) and worst ($p=0.001$) pain. No other distinction on clinical parameters was found between groups 48 hours after surgery (e.g. type of anesthesia and analgesia, length of stay, rescue analgesia or pain frequency).

### 3.3. Pre-surgical (T1) risk factors for PPSP 4 to 6 months after TKA and THA

In order to identify the pre-surgical predictors of PPSP after TKA and THA, 2 sequential logistic regression models were conducted (Model 1; **Table 3**). In both models, the first and second steps included the 3 variables that distinguished those with and without PPSP: sex, pre-surgical pain interference and pain due to other causes (see **Table 2**). As a further candidate variable, pre-surgical pain in other joints (collinearity with age) showed considerable overlap to the predictor pain due to other causes and was excluded from Model 1 due to multicollinearity (VIF > 2). It was shown in the first step that women presented a higher likelihood of PPSP (OR, 5.056; 95% CI, 1.755-14.566). In the second step, those who had more pre-surgical pain interference had a higher risk of developing PPSP (OR, 1.075; 95% CI, 1.015-1.137), whereas pain due to other causes (not related to the condition leading to surgery) did not contribute to the prediction of PPSP (see Model 1; **Table 3**).

In order to further explore the role of pre-surgical psychological factors in PPSP development, over and above established demographic and clinical predictors, a block of psychological variables measuring emotional distress (anxiety), illness perceptions (timeline acute/chronic) and coping strategies (pain catastrophizing) was added to the demographic and clinical variables in the third step (see Model 1; **Table 3**). In this multivariate model, pre-surgical anxiety emerged as the psychological baseline significant predictor of PPSP development (OR, 1.409; 95% CI, 1.053-1.885), whereas the other variables remained non-significant and sex and pre-surgical pain interference ceased to be significant.

### 3.4. Post-surgical (T2) risk factors for PPSP 4 to 6 months after TKA and THA

**Table 4** shows a sequential logistic regression model predictive of post-surgical variables (T2) for PPSP over and above the same demographic and clinical variables used for model 1 in **Table 4**. At step 3, acute post-surgical pain intensity was included, yielding significant results (OR, 1.516; 95% CI, 1.161-1.980). Furthermore, post-surgical anxiety was added to the model in step 4, emerging as a significant predictor (OR, 1.335; 95% CI, 1.007-1.772). After this addition, in the final model, pain intensity remained significant (OR, 1.387; 95% CI, 1.040-1.849), although sex, which was a significant predictor at step one (OR, 4.025; 95% CI, 1.494-10.843) ceased to be significant.

## 4. Discussion

The present study is the first to identify the joint role of demographic, clinical and psychological risk factors for persistent pain experience 4 to 6 months after total knee (TKA) and hip arthroplasty (THA). Amongst the baseline demographic and clinical risk factors, sex and pre-surgical pain interference were the key predictors of PPSP development, nevertheless these variables ceased to be significant after the addition of psychological factors. At baseline pre-surgical anxiety was found to be a risk factor for the development of PPSP at T3. At T2, post-surgical anxiety added to the prediction of PPSP, along with acute post-surgical pain intensity. The results of this study improve knowledge on persistent post-surgical pain (PPSP) and point to potential intervention targets for healthcare professionals.

### 4.1. Predictors of pain 4 to 6 months after TKA and THA

In line with previous evidence, sex was found to be a significant PPSP predictor. In fact, previous research has already pointed that women revealed a higher trend to develop PPSP, either in major joint surgeries (McGuigan, Hozack, Moriarty, Eng, & Rothman, 1995; Valdes et al., 2001; Singh, Gabriel, & Lewallen, 2008) or in other various surgical procedures (Gotoda et al., 2001,Peolsson, Hedlund, Vavruch, & Oberg, 2003; Bruce & Krukowski, 2006). Moreover, even though not so consistently, pre-surgical pain interference and not intensity also appeared as a predictor, confirming other results (MacWilliams, et al. 1996). However, after the addition of psychological factors, both demographic and clinical factors ceased to be significant, highlighting the importance of psychological factors on PPSP development.The finding that both pre-surgical and post-surgical anxiety were predictive of PPSP over and above sex and clinical variables adds to our understanding of PPSP. While previous research has identified pre-surgical anxiety as a risk factor for acute post-surgical pain, few studies to date have provided evidence for its role on the development of PPSP (Brander et al., 2003). Forty-eight hours after surgery, anxiety was, again, predictive of PPSP. Surprisingly, anxiety after surgery was never studied as a potential predictor for PPSP before. It can therefore be assumed that it is not only before surgery that anxiety seems to affect PPSP, but also anxiety levels after surgery.

Accordingly to expectations and corroborating the findings of previous studies (Perkins and Kehlet, 2000; Kalkman *et al.*, 2003; Bisgaard, Rosenberg, & Kehlet, 2005; Poleshuck et al., 2006; Eisenach et al., 2008; Nikolajsen & Minella, 2009), the present work did find acute post-surgical pain intensity as a significant predictor of PPSP.

Pain catastrophizing has been found to be a reliable predictor of acute post-surgical pain (Papaioannou et al., 2009; Pinto et al., 2012) and there is some emerging evidence for its role as risk factor for PPSP (Riddle, Wade, Jiranek, & Kong,, 2010; Sullivan et al., 2011) either after major joint arthroplasties or following other surgical procedures. However, in this study it did not yield significant results, with anxiety emerging as the most important predictor of PPSP.

### 4.2. Clinical implications

In terms of pre-surgical interventions, the present results suggest that patients should be screened in terms of pre-surgical anxiety levels. Those with high levels of anxiety could be offered brief psychological pre-surgical interventions. To deal with anxiety, brief cognitive-behavior therapy intervention techniques (such as brief relaxation, imagery, and positive coping self-statements), reassurance and information provision have been widely used (Good, 1999; Sjoling, Nordahl, Olofsson, & Asplund, 2003; Bruehl & Chung, 2004; Roykulcharoen & Good, 2004; Stoddard, White, Covino, & Strauss, 2005) and should continue to be implemented. Reassurance could enhance the patient's ability to tolerate the uncertainties associated with surgery as well as with the recovery process and thus can reduce the negative effects of the surgical experience (Doering *et al.,* 2000; Johnston & Vogele, 1993). The provision of information should, in turn, focus on sensory and procedural information, in order to reduce unrealistic anxiety-provoking expectations and cognitions that increase pain (Powell & Johnson, 2007). Data from this study also seem to indicate that after surgery anxiety should be regularly monitored and managed. Moreover, special care should be directed to those surgical patients with heightened levels of acute post-surgical pain intensity. Recker and Perry (2011) suggested that preventing severe acute post-surgical pain may decrease the risk for persistent postsurgical pain. Therefore, patients should be supported with further training on pain management skills as well as on appropriate pain coping strategies, such as relaxation, distraction, imagery or hypnosis, which patients could then use during the acute post-surgical period. The main purpose of such a psychological intervention should be to elaborate a post-surgical pain management plan beginning before surgery and extending until discharge.

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**Table 1**

**Socio-demographic, clinical and psychological measures used in each assessment point T1, T2 and T3**

| **MEASURES** | **T1<br>Before Surgery** | **T2<br>48 H after surgery** | **T3<br>4 – 6 months after surgery** |
|---|---|---|---|
| Socio-Demographic Questionnaire | **X** | | **X** |
| Clinical Data | **X** | **X** | **X** |
| **BPI-SF:** Brief Pain Inventory – short form | **X** | **X** | **X** |
| **McGill Pain Questionnaire** (Frequency scale) | | **X** | |
| **DN-4:** Neuropathic Pain Questionnaire | | | **X** |
| **HADS:** Hospital Anxiety and Depression Scale | **X** | **X**<br>(only anxiety) | **X** |
| **IPQ-R:** Revised Illness Perception Questionnaire (psychometrically shortened version) | **X** | | |
| **LOT-R:** Revised Life Orientation Test (optimism) | **X** | | |
| **CSQ-R:** Revised Coping Strategies Questionnaire (Pain catastrophizing subscale) | **X** | | |

**Table 2**

***Differences between patients with and without pain (T3) on socio-demographic, clinical and psychological measures determined at T1, T2 and T3***

| MEASURES | Total (*N* = 92) | No PPSP (*n* = 29) | PPSP (*n*= 63) | *p* |
|---|---|---|---|---|
| **Patient baseline characteristics – T1** | | | | |
| *Socio-demographic:* Age (years) | 64 (43 - 78) | 64 (43 - 75) | 64 (48 - 78) | *ns* |
| *Socio-demographic:* Sex (women) | 61 (66.3%) | 15 (51.7%) | 46 (73.0%) | *0.045* |
| ***Clinical – general indicators*** | | | | |
| Disease onset (months) | 72 (6 - 600) | 54 (6 - 600) | 108 (7 - 552) | *ns* |
| BMI[1] (Kg/m2) | 29 (20 - 512) | 28 (21 - 37) | 30 (20 - 512) | *ns* |
| Previous surgeries (yes) | 80 (87%) | 25 (86.2%) | 55 (87.3%) | *ns* |
| Comorbidities total[2] | 2 (0 - 5) | 2 (0 - 4) | 2 (0 - 5) | *ns* |
| **Clinical - pre-surgical pain indicators** | | | | |
| Intensity[3] (worst level) | 7 (3 - 10) | 5 (0 - 10) | 7 (3 - 10) | *ns* |
| Intensity[3] (average level) | 4 (2 - 8) | 3 (0 - 6) | 5 (2 - 8) | *ns* |
| Pain Total Interference[4] (0-70) | 28 (3 - 50) | 16 (6 - 49) | 30 (3 - 50) | *0.037* |
| Pain due to other causes (yes) | 58 (63.7%) | 13 (44.8%) | 45 (71.4%) | *0.010* |
| Pain in other joints (yes) | 33 (35.9%) | 5 (17.2%) | 28 (44.4%) | *0.011* |
| Back pain (yes) | 45 (48.9%) | 12 (41.4%) | 33 (52.4%) | *ns* |
| **Psychological variables** | | | | |
| **HADS[a]:** Anxiety | 4.5 (0 - 17) | 3 (0 - 16) | 6 (0 - 17) | *0.013* |
| **HADS[a]:** Depression | 1 (0 - 17) | 0 (0 - 17) | 2 (0 - 11) | *ns* |
| **IPQ – R[b]:** Timeline acute/chronic | 2.3 (1.3 - 5) | 2 (1.3 - 5) | 3 (2 - 5) | *0.034* |
| **IPQ – R[b]:** Timeline cyclical | 3 (1.3 - 5) | 3 (1.3 – 4.3) | 3 (1.3 - 5) | *ns* |
| **IPQ – R[b]:** Consequences | 3.7 (1.7 - 5) | 3.3 (1.7 – 4.7) | 3.7 (1.7 - 5) | *ns* |
| **IPQ – R[b]:** Personal control | 2 (1.3 - 4) | 2 (1.3 – 3.7) | 2 (1.3 - 4) | *ns* |
| **IPQ – R[b]:** Treatment control | 4 (3 - 5) | 4 (3 - 5) | 4 (3 - 5) | *ns* |
| **IPQ – R[b]:** Illness coherence | 2 (1 – 4.7) | 2 (1 – 4.7) | 2 (1 – 4.3) | *ns* |
| **IPQ – R[b]:** Emotional representation | 3.3 (1 - 5) | 2.7 (1 – 4.7) | 3.3 (1 - 5) | *ns* |
| **LOT-R[c]:** Optimism | 9 (0 - 12) | 9 (0 - 12) | 9 (0 - 12) | *ns* |
| **CSQ-R[d]:** Pain catastrophizing | 1.2 (1 – 4.8) | 1 (1 – 4.5) | 1.7 (1 – 4.8) | *0.007* |
| **Postsurgical data 48H after surgery-T2** | | | | |
| Acute post-surgical pain intensity[3] – worst | 6,5 (0 - 10) | 5 (0 - 10) | 8 (3 - 10) | 0.001 |
| Acute post-surgical pain intensity[3]- average | 4 (0 - 6) | 3 (0 - 6) | 4 (0 - 6) | <0.001 |
| Pain Frequency[5]: constant | 49 (53.3%) | 12 (41.4%) | 37 (58.7%) | *ns* |
| HADS[a]: Anxiety | 3 (0 - 16) | 2 (0 - 9) | 4 (0 - 16) | 0.003 |
| **Postsurgical data 4M after surgery-T3** | | | | |
| **HADS[a]:** Anxiety | 3 (0 - 17) | 0 (0 - 8) | 5 (0 - 17) | < 0.001 |
| **HADS[a]:** Depression | 0 (0 - 13) | 0 (0 - 5) | 1 (0 - 13) | 0.002 |

Note. Continuous variables are presented as median (range); categorical variables are presented as *n* (%); T1 – 24 hours before surgery; T2 – 48 hours after surgery; T3 – 4-6 months after surgery; [1]BMI = body mass index; [2]Comorbidities total = number of comorbid health conditions; [3]NRS(BPI) =Numerical Rating Scale 0-10 from Brief Pain Inventory; [4]Pain Total Interference Scale 0-70 from Brief Pain Inventory (BPI); [5]Pain Frequency: constant pain vs intermittent or brief pain, assessed via frequency subscale of McGill Pain Questionnaire; [a]HADS = Hospital Anxiety and Depression Scale; [b]IPQ-R= Illness Perception Questionnaire-Revised; [c]LOT-R = Life Orientation Test – revised; [d]CSQ-R=Coping Strategies Questionnaire-Revised.

**Table 3**

***Model1 - Sequential logistic regression analysis of Persistent Post-surgical Pain 4-6 months following TKA and THA on demographic, clinical and psychological measures at baseline***

| **MODEL 1** | Wald | Odds Ratio (CI) | *p* |
|---|---|---|---|
| **Step 1** | | | |
| Sex[1] | 9.008 | 5.056 (1.755 - 14.566) | *0.003* |
| **Step 2** | | | |
| Pre-surgical pain interference[2] | 6.120 | 1.075 (1.015 - 1.137) | *0.013* |
| Pain due to other causes (yes)[3] | 0.641 | 1.696 (0.466 - 6.174) | *0.423* |
| **Step 3 (Final Model)** | | | |
| Sex[1] | 0.502 | 1.758 (0.369 - 8.361) | *0.479* |
| Pre-surgical pain interference[2] | 0.800 | 1.032 (0.964 - 1.104) | *0.371* |
| Pain due to other causes (yes)[3] | 0.001 | 1.024 (0.217 - 4.837) | *0.976* |
| Pre-surgical anxiety[a] | 5.325 | 1.409 (1.053 - 1.885) | *0.021* |
| Pre-surgical timeline acute/chronic[b] | 3.447 | 2.320 (0.954 - 5.639) | *0.063* |
| Pre-surgical catastrophizing[c] | 2.696 | 5.118 (0.729 - 35.928) | *0.101* |

After removing 5 outliers, this model correctly predicted 83.8% of all patients.

Note: [1]Dichotomous variable: 0= men; 1= women; [2]Continuous variable, 0-70 from BPI-SF: Brief Pain Inventory-Short Form; [3]Dichotomic variable: 0= No, 1= Yes; [a]Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale; [b]Continuous variable, IPQ-R: Illness Perception Questionnaire Revised - timeline acute/chronic subscale; [d]CSQ-R: Coping Strategies Questionnaire Revised - catastrophizing subscale.

**Table 4**

***Model 2 - Sequential logistic regression analysis of Persistent Post-surgical Pain 4-6 months following TKA and THA on demographic and clinical baseline measures and post-surgical pain and anxiety 48h after surgery***

| **MODEL 2** | Wald | Odds Ratio (CI) | *p* |
|---|---|---|---|
| **Step 1** | | | |
| Sex[1] | 7.585 | 4.025 (1.494 - 10.843) | *0.006* |
| **Step 2** | | | |
| Pre-surgical pain interference[2] | 3.477 | 1.048 (0.998 - 1.102) | *0.062* |
| Pain due to other causes (yes)[3] | 3.424 | 2.999 (0.937 - 9.596) | *0.064* |
| **Step 3** | | | |
| Post-surgical pain intensity[4] | 9.367 | 1.516 (1.161 – 1.980) | *0.002* |
| **Step 4 (Final Model)** | | | |
| Sex[1] | 0.332 | 1.494 (0.381 - 5.862) | *0.565* |
| Pre-surgical pain interference[2] | 0.710 | 1.024 (0.970 - 1.081) | *0.400* |
| Pain due to other causes (yes)[3] | 1.924 | 2.578 (0.676 - 9.828) | *0.165* |
| Post-surgical pain intensity[4] | 4.960 | 1.387 (1.040 - 1.849) | *0.026* |
| Post-surgical anxiety[a] | 4.023 | 1.335 (1.007 - 1.772) | *0.045* |

After removing 6 outliers, this model correctly predicted 76.7% of all patients.

Note: [1]Dichotomous variable: 0= men; 1= women; [2]Continuous variable, 0-70 from BPI-SF: Brief Pain Inventory-Short Form; [3]Dichotomic variable: 0= No, 1= Yes; [4]Continuous variable, NRS 0-10 from BPI-SF: Brief Pain Inventory-Short Form; [a]Continuous variable, HADS-A: Hospital Anxiety and Depression Scale - anxiety subscale

Chapter 3

# Discussion

## 3. DISCUSSION

*"... The mind-body connection is supported by the very best of modern-day research... It is very clear that what one thinks and believes affects one's health, one's well-being, and even one's chances of dying."*

Oakley Ray, 2004

In this work, through a prospective design, we sought to explore and examine the joint role of demographic, clinical and psychological variables as predictors of acute and persistent post-surgical pain (PPSP) following surgery. Moreover, to broaden our understanding about the experience of surgical pain, we investigated the influence of those potential predictive factors either on rescue analgesia provision or on post-surgical anxiety. The selected surgeries were hysterectomies and joint arthroplasties, namely total knee arthroplasty (TKA) and total hip arthroplasty (THA). Overall, the findings of the present work demonstrate the important role of psychological factors on post-surgical experience, such as on acute post-surgical pain, analgesic consumption, post-surgical anxiety and PPSP.

### 3.1. Acute post-surgical pain, rescue analgesia and post-surgical anxiety (Studies 1, 2 & 4)

The first aim of this work was to reach a better understanding of the experience of acute post-surgical pain. Therefore, two studies were set out to examine the independent and joint contribution of demographic, clinical and psychological variables as predictors of acute post-surgical pain experience either in women undergoing hysterectomy due to benign disorders (**Study 1**) or in patients submitted to total knee arthroplasty (TKA) and to total hip arthroplasty (THA) (**Study 4**). Furthermore, we set to determine the influence of those variables on rescue analgesia provision in the same sample of hysterectomy patients (**Study 2**). In addition, given that after surgery pain and anxiety have been reported as being inter-related (McWilliams, Goodwin, & Cox, 2004) and only a few studies have focused on post-surgical anxiety, we also sought to examine if post-surgical anxiety could be explained by a similar model to the one used to predict post-surgical pain, testing this hypothesis in the sample submitted to TKA and THA (**Study 4**).

With respect to acute post-surgical pain prediction, while in hysterectomies we found an integrative predictive model revealing the simultaneous role of younger age, pre-surgical pain severity, pain due to other causes, pre-surgical anxiety and pain catastrophizing, in arthroplasties this model could not be reproduced and optimism was the only predictor of pain intensity 48 hours after surgery. Moreover, within the hysterectomy sample (**Study 1**), results showed the mediating role of pre-surgical pain catastrophizing between pre-surgical anxiety and post-surgical pain intensity. This indicated that it is not pre-surgical anxiety *per se* that predicts post-surgical pain intensity in hysterectomy women, but rather anxiety mediated through pain catastrophizing. Thus, at least in women submitted to hysterectomy, pre-surgical anxiety seems to be associated with negative cognitions about pain that predict increased post-surgical pain report. Pain catastrophizing involves magnification of the threat value of pain and generalization of its negative impact, as well as feelings of helplessness and pessimism in the ability to deal with pain (Sullivan et al., 2001; Quartana, Campbell, & Edwards, 2009). This implies that as pre-surgical anxiety increases, women will tend to catastrophize more about pain and this will predict increased acute post-surgical pain intensity. With this finding we were able to confirm, for the first time, the full mediating role of pre-surgical pain catastrophizing between pre-surgical anxiety and post-surgical pain intensity. This mediation result might contribute to clarify apparently incongruent data reported about the relation between anxiety and pain (Boeke, Duivenvoorden, Verhage, & Zwaveling, 1991; Thomas, Robinson, Champion, McKell, & Pell, 1998; Wickstrom, Nordberg, & Johansson, 2005; Ene, Nordberg, Sjöström, & Bergh, 2008) and answer some of the questions raised by previous studies (Granot & Ferber, 2005; Sommer et al., 2009). The association found between anxiety and pain catastrophizing, and the role of the latter in predicting acute post-surgical pain, suggest that both emotional and cognitive factors need to be considered in the prevention and management of acute pain, and that intervening in cognitive factors may have a direct impact on pain experience after surgery. These results may also help to clarify why pre-surgical pharmacological interventions, through the administration of anxiolytic drugs like benzodiazepines, have not yet proven to be effective in the reduction of post-surgical pain intensity (Kain et al., 2001; Caumo et al., 2002). At least in hysterectomies, prescribing large spectrum anxiolytic drugs seems to miss a key cognitive factor associated with pre-surgical anxiety: pain catastrophizing.

In the study performed with arthroplasty patients (**Study 4**), this model could not be reproduced. Surprisingly, despite the fact that gender and pain due to other causes initially emerged as significant predictors of acute pain intensity, in the final model, after adding psychological variables, only pre-surgical optimism turned out to be significant. These findings suggest that in patients undergoing TKA or THA, pre-surgical optimism, a personality trait, will be the best indicator of the likelihood of patients reporting heightened acute pain levels 48 hours after surgery, irrespective of the patient's gender or prior experience of pain due to other causes. Despite these differences between the two studies, the evidence from both suggests unequivocally the determinant role of psychological factors on the experience of acute pain after surgery. The discrepancy found between the distinct psychological factors that emerged as predictors in each surgery seems to support the idea that each type of surgery carries different threats and specific personal questions to deal with (Johnston, 1987; Kalkman et al, 2003). In a qualitative systematic review (Ip, Abrishami, Peng, Wong, & Chung, 2009) aiming at identifying the risk factors for acute post-surgical pain, it was observed that despite the existence of some common factors (pre-surgical pain, anxiety and age), different type of surgeries carried different associate predictive factors.

In order to better understand the different results obtained for hysterectomies and arthroplasties, their distinct surgical procedures should be examined. Hysterectomy refers to the surgical removal of the uterus and is indicated for women with benign disorders, such as dysfunctional uterine bleeding, uterine fibroids, uterine prolapse, endometriosis, adenomyosis or pelvic pain. Although it is also indicated for malign disease, in the current work only hysterectomies for benign disorders were included, to avoid dealing with the potential negative impact of the strong emotional cancer-related issues. In turn, TKA and THA are mostly performed amongst individuals who present chronic long-term diseases such as: osteoarthritis, rheumatoid arthritis, and similar inflammatory and degenerative chronic diseases. Such chronic diseases have stronger impact on the individual's life than the benign diseases subjacent to benign hysterectomies, leading to potential severe limitations in physical function. Another fundamental difference between the two samples is pre-existence of pain symptoms. Within the sample of hysterectomy patients (**Study 1**), pre-surgical pain was not a strong determinant of the decision to perform surgery, as 40% of women did not present pain symptoms related to the scheduled surgery; however, in major joint arthroplasty sample (**Study 4**), all patients had pain before surgery, and this emerged as one of the main reasons to decide to perform surgery. Joint arthroplasties often lead to significant pain relief for the majority of patients, improve functional status significantly, reduce disability and foster quality of life (Bachmeier et al., 2001; Lingard, Katz, Wright, Sledge, & Kinemax Outcomes Group, 2004; Hamel, Toth, Legedza, & Rosen, 2008; Wylde, Hewlett, Learmonth, & Dieppe, 2011).

The diseases underlying the surgeries targeted in this thesis are distinct and consequently perceived differently by patients, probably depending on the perceived utility of the surgical procedure and on the balance between perceived advantages and disadvantages. The disease underlying arthroplasties is usually perceived by patients as being chronic, entailing several limitations and having a strong impact on quality of life, which might explain why optimism arose as the main predictor. Overall, dispositional optimism, a generalized expectation that good things will happen (Rasmussen, Scheier, & Greenhouse, 2009), has been identified as a significant predictor of positive outcomes in a variety of health and disease related conditions (Scheier & Carver, 1993; Scheier et al., 1999; Kubzansky, Martin, & Buka, 2009; Rasmussen et al., 2009). Given that arthroplasties arise as the last and only solution for certain impairments, it is plausible that those patients who are optimistic will face the surgery and the acute post-surgical period in a more positive framing. This could affect their acute pain perception, probably because they would be less attentive to pain stimuli (Affleck, Tennen, & Apter, 2001; Geer, Wellman, Helfer, Fowler, & France, 2008), focusing on their hopeful medium-term life improvements rather than on temporary but necessary present difficulties, and consequently more keen to bare pain and other negative outcomes in the short-term period after surgery. This perspective could also lead optimistic patients to engage in more adaptive coping strategies, such as positive reinterpretation, acceptance, and reliance on problem-focused coping (Scheier, Weintraub, & Carver, 1986; Scheier and Carver, 1992).

In the hysterectomy sample (**Study 1**), given that malign cases were not included, the aim of undergoing surgery was usually to improve symptoms associated with less severe gynecologic disorders, with pre-surgical pain being an issue for some (60% of sample) but not all of the patients, which was not the case of arthroplasties (100% had pre-surgical pain). Moreover, generally those women had a pre-surgical life without significant disease-associated functional impairments, likely perceiving surgery as something not as vital to improve their quality of life as osteoarthritis patients. For these women, other factors, such as the fear of losing one's uterus and the impact of surgery on fertility, body image and sexuality (Schwartz & Williams, 2002; Ayoubi et al., 2003; Dragisic & Milad, 2004; Ewalds-Kvist, Hirvonen, Kvist, Lertola, & Niemela, 2005; Flory, Bissonnette, & Binika, 2005; Farquhar, Harvey, Sadler, & Stewart, 2006) impact their perception of the surgical procedure as being a potential threat with negative consequences. Indeed, in the current study, younger women, for whom negative consequences would be more salient, were more likely to report higher levels of pain. Our results suggest that in this specific type of surgery, emotional and cognitive factors, rather than personality factors, such as optimism, are likely to be triggered, affecting pain perception. In fact, when comparing levels of pre-surgical anxiety, which vary between 0 and 21, hysterectomy women ($M$=7.29; $SD$=4.42) presented higher levels ($p$=0.001) in relation to either the total arthroplasty sample ($M$=5.52; $SD$=4.12) or the arthroplasty women ($M$=6.19; $SD$=4.16). Moreover, looking at the overall score of the Surgical Fear Questionnaire, which ranges between 0 and 10, women from the hysterectomy sample ($M$=2.24; $SD$=1.58) also presented higher levels of surgical fear ($p$=0.001) when compared to the total arthroplasty sample ($M$=1.58; $SD$=1.73) and to the subset of arthroplasty women ($M$=1.80; $SD$=1.79) ($p$=0.044).

Another important goal of our research was to increase knowledge on the factors associated with post-surgical rescue analgesia (RA) consumption in women submitted to hysterectomy (**Study 2**). Previous studies have identified surgery type, age, and psychological distress as predictors for higher analgesic consumption after surgery (Ip et al., 2009) but there is a general lack of studies addressing decision-making regarding RA provision. Our data indicated that RA provision may be influenced not only by clinical issues, such as post-surgical pain intensity, but also by patient-related psychological characteristics, such as pre-surgical fear, pain catastrophizing and post-surgical anxiety. These factors are likely to influence patient-provider interactions. Thus, patient-related psychological factors not only influence acute post-surgical pain intensity as reported by patients (**Studies 1** & **4**), but also the decision of health professionals to provide RA (**Study 2**). The data suggests that the psychological characteristics showed by women who undergo hysterectomy (fear, catastrophizing and anxiety) are likely to influence health professional decision-making regarding the administration of extra analgesia, above and beyond the single clinical factor which should influence that decision: post-surgical acute pain intensity levels above 3 in a scale of 0-10.

To reach a broader understanding of post-surgical pain and related issues, we aimed to further investigate post-surgical anxiety by examining its main predictors, more specifically, the role of pre-surgical anxiety, optimism and illness representations (**Study 4**). This interest arose because after surgery, pain and anxiety have been reported as being inter-related (McWilliams et al., 2004). Anxiety has been thought to have an intensifying effect on pain experience through its influence on the cognitive processing of nociceptive information (Nisbett & Schachter, 1996), leading to augmented somatic and environmental scanning that facilitate sensory receptivity and thus pain perception (Rhudy & Meagher, 2000). Biologically, anxiety and pain reveal overlapping areas of brain activation and anxiety could also be linked to pain via the activation of the sympathetic nervous system (SNS) (Symreng & Fishman, 2004). Nevertheless, the exact mechanisms by which anxiety and pain present a strong mutual influence are not yet fully elucidated, being difficult to discern which one is the determining factor (Symreng & Fishman, 2004). Furthermore, anxiety also has negative consequences on recovery from surgery (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998; Janssen, 2002), as some studies provide evidence supporting a relationship between anxiety and wound healing, through a neuroimmunologic pathway. More specifically, it is thought that anxiety influences the secretion of proinflammatory cytokines at wound site, and this is a possible mechanism by which stress may delay wound healing (Kiecolt-Glaser et al., 1998; Cole-king & Harding, 2001). Given this, both pain and anxiety should be addressed after surgery. Therefore, we sought to investigate whether post-surgical anxiety could be predicted from the same predictive model tested for the prediction of acute post-surgical pain, in the sample of patients submitted to arthroplasty (**Study 4**). As predicted, findings revealed that pre-surgical anxiety is the most important predictor of post-surgical anxiety experience, which is consistent with other studies (Johnston, 1986; Taenzer *et al.*, 1986; deGroot et al. 1997; Caumo et al., 2001; Munafo & Stevensson, 2001; Carr, Brockbank, Allen, & Strike, 2006). Those studies show that patients who are more anxious before surgery, are also more likely to be more anxious after surgery.

It was interesting to note that pre-surgical optimism, beyond predicting acute pain intensity, also predicted post-surgical anxiety in these patients. Indeed, it has been shown in numerous studies that high dispositional optimism is associated with an adaptive response to health-related stress

(Geers et al., 2008), being an important determinant of psychological well-being (Chang, 1998; Schou, Ekeberg, Ruland, Sandvik, & Karesene, 2004). Dispositional optimism may buffer the impact of stress on psychological states and on biological processes (Cohen, 1999; Brydon, Walker, Wawrzyniak, Chart, & Steptoe, 2009), which might explain why after arthroplasty, optimistic patients experience less anxiety. The ability of optimists to appraise a stressor in a more positive frame, would allow them to engage in more active problem-focused coping strategies (Scheier et al., 1986), which might protect them from the deleterious effects of acute stress on immune changes.

Another interesting finding of **study 4** indicates that in face of the prospect of undergoing an arthroplasty, patients that have a more negative emotional representation of their underlying disease (osteoarthritis), are also more likely to be anxious 48 hours after surgery. This means that the specific illness representations (such as those involving emotional responses to the illness) appear to influence immediate surgical outcomes. This is in accordance with studies in other pathologies, which have demonstrated that the emotional representation of a certain disease relates with other health outcomes (Scharloo et al., 2005; Botha-Scheepers et al., 2006; Llewellyn, McGurk, &, Weinman, 2007).

In summary, post-surgical anxiety after TKA and THA seems to be strongly predicted by pre-surgical anxiety level, optimism and emotional representation of the disease underlying these surgeries. Moreover, in **study 2,** which focused on rescue analgesia provision, post-surgical anxiety emerged as a crucial factor in the decision of health care providers to administer RA. As will be referred in the section below, in both studies that investigated the predictors of persistent post-surgical pain (**Studies 3** & **5**) post-surgical anxiety was shown to be a significant predictor of pain experience after surgery. Therefore, given the growing evidence of the importance of post-surgical anxiety either as an outcome (**Study 4**) or as a significant predictive factor for persistent pain experience (**Studies 3** & **5**), future studies should take this variable into account.

### 3.2. Predictors of persistent or chronic post-surgical pain (Studies 3 & 5)

The third and fifth studies included in this thesis aimed to extend the investigation of post-surgical pain into the medium-term period, namely 4-6 months after surgery. Therefore, 2 studies were conducted to examine the independent and joint contribution of demographic, clinical and psychological variables as predictors of chronic or persistent post-surgical pain (PPSP) experience either in women undergoing hysterectomy due to benign disorders (**Study 3**) or in patients submitted to total knee arthroplasty (TKA) and to total hip arthroplasty (THA) (**Study 5**).

Within hysterectomies, age, pain due to other causes and type of hysterectomy emerged as significant predictive factors for pain reported 4 months after hysterectomy. The baseline pre-surgical psychological predictors identified were anxiety, emotional representation of the condition leading to surgery and pain catastrophizing. Acute post-surgical pain frequency and post-surgical anxiety also showed a predictive role in the development of PPSP. These findings partially overlap the results found within the same sample but regarding acute pain (**Study 1**). In both studies (**Studies 1** & **3**), younger women and those with more pain due to other causes, were more likely to report higher levels of acute post-surgical pain and higher probability of presenting persistent pain 4 months after hysterectomy. Therefore, we can assume that at least for hysterectomy patients, these two factors exert an important influence along the post-surgical period, beginning in the short-term acute period and extending their influence at least to the 4 month period timeframe. These findings are in agreement with previous studies which showed that younger patients and patients with other causes of pain present a higher likelihood of experiencing both acute and chronic pain post-surgery (Smith, Bourne, Squair, Phillips, & Chambers, 1999; Katz et al., 2005; Nikolajsen, Sørensen, Jensen, & Kehlet, 2004; Kainu, Sarvela, Tiippana, Halmesmaki, & Korttila, 2010).

Among psychological predictors, pre-surgical anxiety and pain catastrophizing showed a crucial role in the prediction of both acute and persistent post-surgical pain after hysterectomy. However, the total mediation process found in the acute pain study, could not be replicated when focusing on persistent pain. Regarding the prediction of acute pain, pre-surgical anxiety was associated with higher levels of pain severity and intensity via pain catastrophizing. In the case of PPSP, those predictors seem to work independently to predict persistent pain, along with the emotional representation of the surgical disease. Post-surgical anxiety added to this cluster of psychological factors in the prediction of PPSP after hysterectomy. These differences between acute and persistent post-hysterectomy pain predictors can be explained in part by the specificities of each outcome. While acute pain is an expected and predictable outcome after surgery (Apfelbaum, Chen, Mehta, & Gan, 2003), persistent pain can be framed as an unexpected and unpredictable outcome (Perkins & Kehlet, 2000). PPSP seems to depend on more complex interactions of factors that are associated with both pre and post-surgical periods.

Among patients submitted to TKA and THA, optimism was the main predictor of acute pain perception in the first 48 hours after surgery (**Study 4**), whereas for persistent pain 4-6 months after surgery, anxiety levels, both pre and post-surgical, were the significant predictors (**Study 5**). Concerning optimism as a predictor, the findings are consistent with previous research which indicated that the benefit of higher optimism in terms of surgical pain was found only during the early recovery period whereas its impact on longer-term pain (6-12 months after surgery) remains more difficult to establish (Mahler & Kulic, 2000; Peters et al., 2007). An earlier study (Chamberlain, Petrie, & Azariah, 1992) that investigated recovery following joint arthroplasties, found that albeit optimism predicted improvement in positive aspects of recovery (acute post-surgical pain, positive well-being and self-rated health), it did not predict improvement in distress or pain in the long-term. Present findings are thus congruent with Rasmussen et al.'s (2009) statement, which posits that the association between optimism and health seems less evident for prospective studies of pain. However, it begs to answer the question on why optimism predicts short-term post-surgical pain and not PPSP. As stated above, optimists are likely to expect better surgical outcomes and acknowledge acute post-surgical pain as temporary and inevitable. This might explain why optimists would be willing to bare pain in the short-term period after surgery. Optimism could also affect acute pain perception due to less attention being paid to pain stimuli (Affleck et al., 2001; Geer et al., 2008). Nevertheless this trend would tend to fade in the face of persistent pain. Overall, our data indicates that PPSP may be less prone to be influenced by predisposing personality traits, such as optimism, but rather by pre and post-surgery-related factors, both clinical and psychological, such as acute post-surgical pain intensity and pre and post-surgical anxiety.

A major focus of our work was to identify the predictors of persistent pain post-surgery. Both emotional and cognitive factors emerged as important predictors of PPSP. The influence of pre-surgical anxiety on PPSP development is corroborated by previous research (Brander et al., 2003; Gerbershagen et al., 2009), whereas post-surgical anxiety has not been explored as a potential predictor. Within this thesis, post-surgical anxiety was approached both as an outcome (**Study 4**) and as a predictor of PPSP (**Studies 3** & **5**). As a predictor, it yielded significant results across the two types of surgery, further supporting the idea that it is not only pre-surgical anxiety that can contribute to persistent pain after surgery, but also post-surgical anxiety. It is somewhat surprising that post-surgical anxiety has not been studied as a PPSP predictor, as emotional factors seem to play a crucial role in the establishment of persistent post-surgical pain, regardless of the type of surgery. Furthermore, post-surgical anxiety is more proximal in time to persistent pain than pre-surgical anxiety. In fact, various studies on pain chronification, even in non-surgical populations, have already concluded about the primacy of emotional factors in the transition from acute to chronic pain (e.g. Boersma & Linton, 2005; Linton, 2005; Casey, Greenberg, Nicassio, Harpin, & Hubbard, 2008).

Regarding cognitive factors, such as pain catastrophizing, the literature also substantiated their important influence on PPSP (Riddle, Wade, Jiranek, & Kong, 2010; Sullivan et al., 2011). However, in the present work, this was just supported amongst hysterectomy women and not in arthroplasty patients. Differences in the psychological and clinical experience associated with these two types of surgery may account for this discrepancy in findings. Among cognitive factors, illness representations have been studied in relation to functional activity, post-surgical adjustment or surgical recovery (Orbell, Johnston, Rowley, Espley, & Davey, 1998; Mccarthy, Lyons, Weinman, Talbot, & Purnell, 2003; Llewellyn et al., 2007), but not in their relationship with PPSP. We hypothesized their potential important role in PPSP given that illness representations are believed to influence illness responses (Leventhal, Nerenz and Steele, 1984; Leventhal and Diefenbach, 1991) and have been shown to explain significant variation in coping and outcomes in a wide range of medical conditions and in response to different treatments (Hagger & Orbell, 2003; Moss-Morris, Humphrey, Johnson, & Petrie, 2007; Petrie & Weinman, 2006). In fact, in **study 3**, emotional representations of the condition leading to surgery emerged as a significant predictor of PPSP, but only amongst the hysterectomy group, although emotional representations had been a predictor of post-surgical anxiety for the arthroplasty patients.

Previous studies have noted the importance of acute post-surgical pain intensity as one of the crucial predictors of PPSP in a wide range of surgical procedures (Perkins & Kehlet, 2000; Kalkman et al., 2003; Bisgaard, Rosenberg, & Kehlet, 2005; Poleshuck et al., 2006; Eisenach et al., 2008; Nikolajsen & Minella, 2009). In our study, two distinct situations occurred. In the case of patients submitted to either TKA or THA (**Study 5**), acute post-surgical pain intensity emerged as a significant predictor of PPSP: higher levels of acute post-surgical pain intensity were associated with increased likelihood of pain reported 4-6 months after surgery, replicating the abovementioned previous findings. Nevertheless, amongst women submitted to hysterectomy, it was not acute post-surgical pain intensity which yielded significant results, but rather acute post-surgical pain frequency. This unanticipated finding indicates that frequent, reoccurring pain may play a more deleterious effect in the nociceptive system than intensity of pain *per se*, at least after hysterectomy. A recurrent experience of pain, especially if it is experienced "almost always" or "always", without appropriate management, might become a serious risk factor for chronic or persistent pain after surgery. Accordingly, in a prospective multisite study (Miaskowski, Crews, Ready, Paul, & Ginsberg, 1999), where pain duration was the assessed outcome and patients were asked to rate how often they were in moderate to severe pain after surgery, a significantly larger percentage of patients who were not cared for by an anesthesia-based pain service, reported to be "often", "almost always" and "always", in moderate to severe pain following surgery. These data support the crucial role of an organized anesthesia-based pain service, which addresses acute post-surgical pain control and management. There is a generalized lack of studies focused on post-surgical pain frequency. However, despite the novelty of our finding, the data must be interpreted with caution because after adding post-surgical anxiety to the prediction model, pain frequency ceased to be significant. In addition, this variable did not emerge as a significant predictor within the arthroplasties' study. Therefore, further work is required to establish the potential role of this variable in post-surgical outcomes. In cases of recurrent and frequent post-surgical pain, it could be hypothesized that the noxious input to the central nervous system is more frequent and may result in peripheral and central nervous system changes, which may lead to central sensitization and to PPSP (Visser, 2006; Searle & Simpson, 2010).

Overall, the results of **studies 3** and **5** increase knowledge on PPSP predictors and inform clinical intervention post-surgery. The predictors found, point healthcare professionals towards specific intervention targets in terms of clinical and psychological factors related to surgery. Anxiety (pre and post-surgical), pain catastrophizing and emotional representations emerge as important psychological factors. Among clinical factors, acute pain control after surgery, either in terms of its intensity or frequency, needs to be addressed. In addition, these findings besides increasing understanding of risk factors for acute and persistent pain following hysterectomy and major joint arthroplasties, also provide a basis for the development of preventive interventions. We will address these issues in the next section which includes a reflection on the clinical implications of our work and the role of Health Psychology within Hospital-based Acute Pain Services.

### 3.3. The role of Health Psychology in surgical pain management and control

The 5 studies presented in this thesis aimed to identify risk factors for both acute and persistent pain, as well as for related factors – analgesic consumption and post-surgical anxiety –, with the underlying goal of identifying and targeting at-risk patients and, at the same time, contributing to the improvement of post-surgical pain management and control. Overall, the findings from these studies, along with findings from other studies, raised important questions related to the role of Health Psychology and Health Psychologists in Acute and Chronic Pain Services.

Regarding pain management, Health Psychologists already have an important and recognized role in chronic pain settings, although their role in the acute pain management field is almost absent (Williams, 1996). Actually, Hawkins (1997) talked about the "infrequent involvement of psychologists in the treatment of acute pain" (pp. 565). This lack of involvement is certainly due to the nature of Acute Pain Services, which are more procedure-based than Chronic Pain Services. In addition, the interest in cost reductions along with the need to speed up patient flow, may explain why Health Psychologists have been typically kept away from this clinical field (Williams, 1996). Findings from the present thesis, however, highlight the crucial role of psychological factors in surgical pain perception both in acute post-surgical pain (**Studies 1** & **4**) and in persistent post-surgical pain development (**Studies 3** & **5**). Furthermore, data also indicates that besides psychological factors, acute post-surgical pain, both its intensity and frequency, also influence the likelihood of persistent post-surgical pain report (**Studies 3** & **5**). These factors stress the relevance of targeting appropriately acute post-surgical pain. Recker and Perry (2011) suggested that preventing severe acute post-surgical pain may decrease the risk for persistent post-surgical pain. Given the role of psychological factors in the prediction of post-surgical pain, the inclusion of Health Psychologists in Acute Pain Services, for assisting in acute pain management and control, is needed in order to address the emotional and cognitive factors that can prevent the development of persistent pain after surgery. The present findings suggest the need to develop a surgical pain management plan that would include psychological interventions, and that this intervention should begin before surgery and extend until the discharge of the patients.

Brander, Gondek, Martin, and Stulberg (2007) question whether the influence of psychosocial factors on clinical outcomes, such as post-surgical pain, is strong enough to warrant intervention. Recently, Burns and Moric (2011) raised this same question. These authors recognized that psychosocial factors are important predictors in acute and persistent post-surgical pain. However, they suggest the integration of studies regarding the predictive validity of psychosocial factors, in an attempt to make practical use of such information. As these authors state, "To the extent that anxiety, depression, stress, and coping poorly with pain are perceptual/ cognitive and emotional factors that actually lead to problematic post-surgical pain, changing one or more factors prior to surgery should also change the trajectory of acute and chronic pain risk." (pp. 92). The quasi experimental study of Riddle et al. (2011) illustrates this point. Within this study, patients undergoing total knee arthroplasty (TKA) were screened to determine their level of pre-surgical pain catastrophizing. Those with high scores on pain catastrophizing were recruited to a pre-surgical intervention. Consequently, 18 patients had coping skills training (within a cognitive-behavioral therapy framework) whereas 45 patients received standard care. The authors aimed to reduce the likelihood of patients experiencing high levels of post-surgical pain intensity by reducing the levels of a key perceptual/cognitive factor: pain catastrophizing. Results sustained the efficacy of the intervention, with targeted patients reporting significantly lower pain and disability levels at the 2-month follow-up, compared to the standard care group and to the lower pain catastrophizing group. Hence, targeting and intervening in a key psychological predictor of poor surgical pain outcomes proved to have positive effects on those outcomes.

Although more outcome research is needed, the findings from this and other studies suggest that identifying and treating potential dysfunctional thoughts or emotions before surgery, may be an important strategy to improve pain outcomes after surgery. The first step in this process should be an appropriate psychological assessment prior to surgery by which patients who reveal higher likelihood of presenting heightened acute post-surgical pain levels and higher risk of persistent post-surgical pain development could be preventively identified and then targeted with an appropriate intervention. Interventions should be implemented, whenever possible, on the basis of a patient-tailored approach in function of individual-based data gathered during the pre-surgical assessment. We will examine next the information gathered by the studies integrated in the present work, in terms of their potential clinical implications.

Overall, in terms of psychological factors, and concerning interventions targeting patients submitted to surgery, 4 of the studies (**Studies 1**, **3**, **4** & **5)** revealed important factors which are amenable to change via psychological surgical interventions. Pre and post-surgical anxiety, pain catastrophizing, optimism and emotional representation of the surgical condition, seem to be key factors.

### 3.3.1. Interventions before surgery

#### 3.3.1.1. Pre-surgical anxiety

Pre-surgical anxiety emerged as a key predictor in acute post-surgical pain (**Study 1**) and PPSP (**Study 3**) following hysterectomy, as well as a predictor of PPSP after arthroplasty (**Study 5**). To address pre-surgical anxiety, brief cognitive-behavior therapy intervention techniques (such as brief relaxation, imagery, and positive coping self-statements) seem to be the gold standard. One crucial feature of the treatments for pre-surgical anxiety is the use of strategies for reducing physiological arousal and lowering muscle tension, such as relaxation training (Good et al., 1999, 2001; McWilliams et al., 2004). The use of relaxation can regulate anxiety through a reduction on sympathetic activity, which has the potential of reducing the sensory and affective components of pain (Good et al., 1999). In addition, relaxation may also act on the higher pain perception centers, which modulate pain via descending control of the gate control mechanism (Melzack & Casey, 1968). Moreover, relaxation, by reducing muscular and mental tension, leads to a reduction in sympathetic stimulation of the hypothalamus (Benson, 1993), affecting the activation of endogenous opiates secretion in the central nervous system. These endocrine influences could moderate anxiety and pain processing in the central nervous. As a non-invasive anxiety-relieving modality, relaxation can be independently used by patients after appropriate training (Roykulcharoen & Good, 2004). Reassurance and information provision have also been widely used (Sjoling, Nordahl, Olofsson, & Asplund, 2003; Bruehl & Chung, 2004; Stoddard, White, Covino, & Strauss, 2005) and should continue to be implemented. Reassurance could enhance the patient's ability to tolerate the uncertainties associated with surgery and thus reduce the negative effects that can potentially be associated with the surgical experience (Doering et al., 2000; Johnston & Vogele, 1993). The provision of information should, in turn, focus on sensory and procedural information, in order to reduce unrealistic anxiety-provoking expectations and cognitions that affect pain perception (Powell & Johnston, 2007). However, interventions should be delivered taking into account the style of coping of each patient since previous studies (Gillies & Baldwin, 2001; Stoddard et al., 2005) have verified that not all patients show a reduction in anxiety levels after this specific type of intervention. On the contrary, some patients get more anxious when aware of such details. Again, interventions should be tailored and adjusted in function of patients' baseline profile, and some patients might not need an intervention at all.

#### 3.3.1.2. Pre-surgical catastrophizing

The association found between pre-surgical anxiety and pain catastrophizing (**Study 1**) and the specific role of the latter in predicting acute post-surgical pain, suggest that both emotional and cognitive factors need to be considered in the prevention and management of acute pain, and that intervening in cognitive factors may have a direct impact on pain experience after hysterectomy. Moreover, findings within this same sample, but concerning persistent pain (**Study 3**), also stress the importance of intervening in this area. The results from **Study 1** and **3** call attention to the role of cognitive factors in acute and persistent post-surgical pain, suggesting that pre-surgical interventions should address pain catastrophizing cognitions. These interventions, delivered before surgery, and within a cognitive-behavioral therapy framework, should aim at challenging and substituting the negative cognitive self-talk associated with pain catastrophizing, with positive pain coping self-statements (Eccleston, 2001; MacLellan, 2003; Bruehl & Chung, 2004; Roykulcharoen & Good, 2004). Such interventions could be easily implemented within the 24-hour period preceding surgery. However, the success of this brief intervention may be limited for those patients in which pain catastrophizing is part of a broader and more stable disposition to have a pessimistic view of their experience. For these patients, changing negative cognitions, such as pain catastrophizing, may require more lengthy interventions, which are not within the realm of acute pain services.

### 3.3.1.3. Pre-surgical optimism

Interventions pre and post-surgery can also address optimism, which is a stable characteristic with both emotional and cognitive components. Peters et al. (2007) concluded that pain patients could benefit from interventions to increase optimism, albeit temporarily, through a short visualization intervention, whereby patients are instructed to see themselves post-surgery, in a positive frame. The aim is to foster positive surgical expectations, for instance by imagining themselves recovering well from the surgery and managing post-surgical pain appropriately. They are also asked to imagine themselves in the medium and long-term period, doing things they were unable to do before surgery, specifically the things, tasks and activities they would like to do but are not yet able to accomplish. The intended focus would be on their desirable self, on the successful overcoming of present difficulties and on the positive feelings associated with that. Seligman (2006) also suggests that through cognitive therapy it would be possible to increase optimism levels, by changes in attributional/explanatory style. In order to implement such an intervention in pre-surgical brief sessions, the contents of that intervention would have to be specific and confined to the concrete occurrence of surgery and related issues. Therefore, it would be useful to apply cognitive techniques designed to train patients to recognize their negative thoughts, expectations and interpretations about surgery, as well as to its perceived associated benefits and disadvantages. Similarly to the visualization strategy, this would aid patients to reinterpret the surgical event and potential surgical benefits in a more positive light. The focus would be on fostering natural disposition to appreciate the surgical event in a more positive frame, promoting skills to change inner speech and develop more positive self-statements about the scheduled surgery. This could be applied to the surgical preparation by helping change patient's conscious thoughts about helplessness, hopelessness, failure and loss, and foster a more positive and hopeful view about surgery, pain and recovery. Present findings (**Study 4**) suggest that pre-surgical arthroplasty patients could benefit from such preventive interventions, targeting the promotion of optimism associated with surgery outcomes, in order to reduce pain and anxiety following surgery.

#### 3.3.1.4. Pre-surgical illness representations

The findings of **Studies 3** and **4** also suggest that interventions based on understanding and modifying illness representations may support arthroplasty patients in coping more adequately with surgery, diminishing post-surgical anxiety and post-surgical pain levels (**Study 4**), as well as preventing PPSP in hysterectomy women (**Study 3**). Other studies have found that challenging dysfunctional illness representations is effective in reducing disability and improving functioning (Petrie & Weinman, 2006; Chan et al., 2009). As these factors are amenable to change, it seems important to assess individuals's illness representations prior to surgery (Juergen, Seekatz, Moosdorf, Petrie, & Rief, 2010). These interventions are useful both pre and post-surgery, as the experience and cognitive representation of the surgery and pain associated with it may change at different moments of this process. For example, Petrie and Weinman (2006) have successfully implemented very brief cognitive-behavioral interventions which involve the identification of maladaptive illness representations and the promotion of adaptive cognitions regarding the illness (such as regarding illness duration, illness consequences and emotional responses). This specific intervention, aimed at restructuring illness cognitions, could be implemented along with interventions aimed at improving optimism, as detailed above. They share some common factors, such as the reframing of illness perceptions and the induction of a more positive view of the expectations concerning disease, pain and surgical recovery.

### 3.3.2. Interventions in the acute period following surgery

**Study 4** results revealed that acute post-surgical pain and post-surgical anxiety are inter-related, and are both significant predictors of persistent pain after either hysterectomy or arthroplasty (**Studies 3** & **5**). Therefore, one can argue for the development of broader psychological treatments that could target both pain and anxiety, before surgery, as already stated, but also during the short-term hospital stay, after surgery, for those patients in need of this. A more detailed reflection on potential intervention strategies is presented below.

#### 3.3.2.1. Post-surgical anxiety

The results of study 4 emphasized the strong relationship between acute pain and anxiety, post-surgery, in patients undergoing major joint arthroplasties. Thus, efforts should be made at detecting and resolving anxiety, not only before surgery, but also after surgery. Given that pre-surgical anxiety is a strong predictor of anxiety post-surgery, intervention on pre-surgical anxiety would benefit both pain and anxiety post-surgery. Indeed, in the acute post-surgical period, interventions that diminish anxiety levels may consequently reduce pain in people whose pain is amplified by anxiety (Symreng & Fishman, 2004). Hence, cognitive-behavioral interventions targeting pre-surgical anxiety, which were already described, also need to be implemented following surgery. As stated above, these techniques have been widely used and seem to be appropriate to deal both with acute post-surgical pain and post-surgical anxiety.

#### 3.3.2.2. Acute post-surgical pain

Preventing the development of persistent and chronic post-surgical pain is a key concern for health care providers. In accordance with previous studies, the present work (**Studies 3** & **5**) supports the significant influence that acute post-surgical pain may have on future persistent pain. This finding supports the importance of an organized Acute Pain Service, focused on acute post-surgical pain control and management. Given the key role of psychological factors, this service would benefit from the presence of a Health Psychologist, a professional trained on assessing and intervening to change pain-related cognitions, emotions and behaviors. Identifying patients at risk of heightened acute post-surgical pain and then intervening with them through the management of the abovementioned psychological variables, would be certainly a first step. Efforts should also be directed to the development of pain management techniques. Hence, patients should be supported with further training on pain management skills as well as on appropriate pain coping strategies, such as relaxation, distraction, imagery or hypnosis, which patients could then use during the acute post-surgical period (Bruehl & Chung, 2004; Stoddard et al., 2006).

In conclusion, the prevention of PPSP benefits from a multidisciplinary effort by which demographic, clinical and psychosocial factors can be addressed in an integrated manner. This implies good communication among surgeons, nurses, anesthesiologists, psychologists, and other professionals involved in surgery provision and recovery. This can be promoted by incorporating behavioral and psychosocial curricula in the training of health care professionals involved in pain management, which is starting to be implemented in Portuguese medical and nursing schools.

### 3.3.3. Interventions directed at health care professionals

The findings of **study 2** shed light on an important target for improving surgical outcomes: the processes involved in rescue analgesia provision. In fact, within the hysterectomy sample, findings from the rescue analgesia study (**Study 2**) support further reflection on post-surgical pain management by healthcare professionals. Patient-related psychological characteristics seem to influence not only pain experience, but also the decision of health professionals to provide rescue analgesia to women submitted to hysterectomy. Pain relief is a fundamental human right with various detrimental consequences when not effectively managed (Brennan, Carr, & Cousins 2007). Moreover, pain relief after surgery is a key condition for early post-surgical recovery (Kehlet & Holte, 2001; Bonnet & Marrett, 2005). The present results suggest that post-hysterectomy pain management benefits from a collaborative process where pre and post-surgical psychological variables are considered to assure appropriate clinical care. This study (**Study 2**) indicates that interventions aimed at a better control and management of acute post-surgical pain should target not only surgical patients but also health professionals. In fact, previous studies suggested that education and training for healthcare providers is associated with patients' decreased pain intensity (ASA Task Force, 2004). Raising clinicians' awareness about the potential influence of those patient-related psychological factors would support a more accurate assessment of patients in need for extra analgesia. Besides, health care professionals need to acknowledge that efforts to improve the quality of pain management must move beyond assessment and communication of pain (Gordon et al., 2005). Integrating this new knowledge into daily pain management practice is a challenging but essential process (Kehlet & Dahl, 2003).

Overall, the results of these five studies, revealed the joint impact of demographic, clinical and psychological factors in patient's experience of pain before and after surgery, offering a multifactorial model that can inform intervention in acute pain services. Major contributions of these studies for intervention development are the following: (a) the role of psychological factors in pain experience before and after surgery, (b) the need to attend to both emotional and cognitive dimensions of pain experience, and (c) the importance of intervening to manage both anxiety and pain during the acute post-surgical period, in order to prevent the development of persistent pain. In order to apply this multifactorial model in intervention development, multidisciplinary collaboration is a must.

### 3.4. Limitations and Strengths

There are several limitations to the present study notwithstanding its prospective design and the inclusion of two distinct surgical models. These limitations should be taken into consideration when designing future studies of post-surgical pain.

First of all, in terms of external validity of the study, this is a single site and single country study and thus the generalization of the conclusions to similar populations in other countries should be considered with caution. Therefore, future studies are warranted to replicate these results with other surgical populations and patients in other health systems.

In terms of internal validity issues, surgical, anesthetic and analgesic procedures were recorded a posteriori. The specificities of surgical, anesthetic and analgesic procedures delivered were controlled in all analyses but not systematically standardized. Staff within the Surgical and Anesthesiology unit was not fully informed of the study goals in order to assure that normal procedures would be enacted; protocols were tailored to the needs and specificities of each patient. Nevertheless, additional analyses, reported across the five studies conducted, do not support the existence of potential confounding effects of type of surgical, anesthetic or analgesic procedures in terms of outcome variables.

One of the major outcome variables of this work, acute post-surgical pain, also studied as a predictor for persistent post-surgical pain, was assessed only 48 hours after surgery and retrospectively. This assessment was not focused on the pain at that exact time (48h) but rather on the worst level of pain perception during the past 48 hours. We might question whether a more regular assessment of pain intensity, such as at 12, 24 and 48 hours after surgery, could describe more accurately acute post-surgical pain experience. Nevertheless, given the demands associated with the post-surgical period, we decided to keep patient burden to a minimum.

This study assesses a considerable number of psychological measures at baseline (T1). Psychological measures (e.g. fear of surgery, pain catastrophizing), with the exception of anxiety and depression, were assessed prospectively, only before the scheduled surgery. We might argue that they should be reassessed after surgery, during T2, given the likely impact of surgery on these variables. At T2, measures were not repeated due to a concern to reduce questionnaire burden 48 hours after surgery. At T3, the aim was to collect data on our outcome variable (PPSP) using T1 and T2 variables as predictors. Moreover, for women submitted to hysterectomy, T3 measures were obtained through a telephone interview, with clear implications on the number of questions to ask. Future study protocols can be developed to be able to assess these emotional and cognitive factors post-surgery.

Regarding T3 assessment, contrarily to hysterectomy patients who were evaluated via a telephone interview, arthroplasty patients were assessed in a face to face interview in a follow-up consultation. This methodological discrepancy is due to the fact that after a hysterectomy, the follow-up consultation occurs one month after surgery and usually coincides with discharge from hospital outpatient consultations. One month after surgery would be a very early time point assessment, given that our aim was to understand the predictors of the development of persistent post-surgical pain, an outcome that has to be assessed at least 2 months after surgery, considering the accepted criteria for PPSP definition (Macrae, 2001, 2008). Moreover, while hysterectomy patients lacked, as abovementioned, a clinical physical examination, the orthopedic patients were assessed by a specialized orthopedic doctor in terms of radiologic findings.

Another possible limitation of this study is related to the clarification of PPSP etiology. Understanding to what extent chronic or persistent pain after hysterectomy and arthroplasty results from a new pain or merely reflects a continuation of the previous pain that led to the surgery (Brandsborg, Nikolajsen, Kehlet, & Jensen, 2008; Macrae, 2008) seems to be a fundamental issue. In the predictive analysis conducted in studies 3 and 5, pre-surgical pain did not emerge as a significant predictor whereas post-surgical pain frequency or intensity did, which may reflect a major role of new pain in predicting PPSP. In the same line, a potential limitation of the hysterectomy study is the absence of a physical examination of women reporting pain at T3, which might point to other important clinical factors in post-surgical pain. Although this study focused on pain as experienced by women after hysterectomy, it would also have been important, for instance, to measure the length of incision in women who had an open abdominal hysterectomy, in order to further clarify and understand this issue as a potential risk factor (Piura, 1989; Tosun et al., 2006; Loos, Scheltinga, Mulders, & Roumen, 2008).

Although we are aware of the impossibility of evaluating "everything", given the burden of long assessment protocols, other psychological factors such as attitudinal factors (perceived control, expectations, self-efficacy), other emotional issues (anger, kinesiophobia), social variables (social support) and other personality-related variables were not evaluated in the current work.

Despite the abovementioned limitations, this group of studies has several strengths that are worth noting. The main strength of our study is the fact that patients were studied prospectively, at three time points and that we included two different types of surgeries: gynecologic (hysterectomy) and orthopedic (total knee and hip arthroplasty). Prospective studies have been warranted in detriment of retrospective ones (Hinrichs-Rocker et al., 2009; Kehlet & Rathmell, 2010). Furthermore, we tested a predictive model which reflected the joint contribution of demographic, clinical and psychological variables in the prediction of post-surgical pain. Indeed, in order to advance the understanding of the processes underlying risk factors for both acute and persistent post-surgical pain, several authors have called for the inclusion of baseline and post-surgical measures of relevant psychological, emotional, and physical variables (Katz & Cohen, 2004)

Chapter 4

# Conclusions and Future Perspectives

## 4. CONCLUSIONS & FUTURE PERSPECTIVES

Throughout this work we were able to identify several factors that contribute to a better understanding and prediction of acute and persistent surgical pain experience.

It stems from these studies that psychological factors are important determinants of the experience of acute and persistent post-surgical pain, as well as of rescue analgesia and post-surgical anxiety, over and above the influence of demographic and clinical variables. More specifically, we demonstrated the following:

1. **Acute post-surgical pain after hysterectomy** might be predicted by an integrative model which includes age, pre-surgical pain severity, pain due to other causes, pre-surgical anxiety and pain catastrophizing (**study 1**). Moreover, findings revealed the full mediating role of pre-surgical pain catastrophizing between pre-surgical anxiety and post-surgical pain intensity, indicating that it is not pre-surgical anxiety *per se* that predicts post-surgical pain intensity in women submitted to hysterectomy, but rather anxiety mediated through pain catastrophizing. This was the first study to reveal and test the full mediational role of this variable. This paper has been published in the renowned journal *Pain* (Pinto, McIntyre, Almeida, & Araújo-Soares, 2012).

2. **Persistent post-surgical pain after hysterectomy** seems to be predicted by a complex interaction of different pre and post-surgical factors (**study 3**). Age, pain due to other causes and type of hysterectomy emerged as the key demographic and clinical predictors of PPSP. Pre-surgical psychological factors such as anxiety, emotional illness representations and pain catastrophizing, were found to be additional risk factors for PPSP. Furthermore, post-surgical anxiety added to the prediction of PPSP, with post-surgical pain frequency also revealing a predictive role in the development of PPSP.

3. **Acute post-surgical pain after total knee and hip arthroplasty** was predicted by pre-surgical optimism (**study 4**). In this sample, there was also a strong association between post-surgical anxiety and acute pain after surgery. Moreover, post-surgical anxiety was

predicted using a similar predictive model to the one used for the prediction of acute post-surgical pain. Pre-surgical optimism, along with pre-surgical emotional representations and pre-surgical anxiety were significant predictors of anxiety after surgery. The influence of these psychological factors has emerged after controlling for a set of potential clinical predictors, including surgical, anesthetic and analgesic factors.

4. **Persistent post-surgical pain after total knee and hip arthroplasty** seems to be best predicted by baseline pre-surgical anxiety and post-surgical anxiety as well as from acute post-surgical pain intensity, regardless of clinical issues, such as surgical, anesthetic and analgesic factors (**study 5**).

5. **Rescue analgesia provision after hysterectomy** might be influenced not only by clinical issues, such as post-surgical pain intensity, but also by patient-related psychological characteristics, such as pre-surgical fear, pain catastrophizing and post-surgical anxiety. These factors are likely to influence patient-provider interactions. Thus, patient-related psychological factors not only influence acute post-surgical pain intensity, as reported by patients, but also the decision of health care professionals in providing rescue analgesia (**study 5**).

These findings cannot be extrapolated to all patients. Therefore, future studies should explore the potential utility of these predictive models in different pathologies and health care settings, as outlined below.

1. **Other surgical procedures.** Differences in type of surgery and underlying diagnosis could affect the degree of post-surgical pain experience. The present findings revealed different predictors for the different types of surgery targeted here. Therefore, it seems worthwhile to potentially identify suitable predictors for each type of surgery. However, the ability to identify a common set of psychological predictors across surgeries, is also an important goal for future research.

2. **In other hospitals / health settings or countries.** This is a single site and single country study and future studies are, therefore, warranted to replicate these results elsewhere.

A key novelty in this work is linked to the findings reported in the paper that was published in the journal *Pain* (Pinto et al., 2012) and that revealed, for the first time, the full mediational role of pain catastrophizing between pre-surgical anxiety and acute post-surgical pain intensity. This is an important target variable to intervention studies aimed at post-surgical pain. Thus, we suggest that future studies experimentally test the influence of **pre-surgical pain catastrophizing** by designing interventions that could target this variable, testing the impact of this intervention on acute pain or the development of persistent post-surgical pain after surgeries. Interventions focused on **restructuring emotional representations** of the condition leading to surgery can also be designed and tested in terms of their efficacy in reducing persistent pain after surgery. The specific focus on these two predictors is due to the fact that these are feasible targets for a short intervention to be implemented before surgery.

Another potential novelty in the present thesis is the role of **post-surgical anxiety** on persistent post-surgical pain experience, a question not yet explored in other studies. Thus, we suggest that future studies explore post-surgical anxiety and its predictive role in four ways : **i)** evaluate its relation to acute post-surgical pain; **ii)** unravel its most important predictors across various types of surgery; **iii)** investigate its potential role on PPSP development, amongst distinct surgical procedures; and **iv)** experimentally test the role of post-surgical anxiety by designing an intervention targeting this variable and the impact of this intervention on PPSP development .

Finally, the **utility of these predictive models should be tested** further by the following:

1. Design of **psychological surgical interventions** conceived to better manage and control surgical pain, wherein patients at risk for acute or persistent pain are identified on the basis of the predictive models tested, and targeted early on (preferably prior to surgery).
2. Effective implementation of those psychological interventions and subsequent **assessment of their efficacy and efficiency,** in the realm of surgical pain experience, both at acute

post-surgical pain levels and also in preventing the development of persistent post-surgical pain.

Overall, the results of these five studies call for a collaborative model of pain management and patient care during the process of surgery, which involves the **inclusion of Health Psychologists in Acute Pain Services.** Portuguese Acute Pain Services also need to adopt **a more evidence-based approach to patient care in surgery situations.** We hope that the present work has helped to advance knowledge in the science of surgical pain and the psychology of pain, thus contributing to evidence that can be used in **providing more effective patient care in Portuguese Acute Pain Units.**

"*...as we change our minds (our thoughts), we change our brains and therefore our bodies...* "

Oakley Ray, 2004

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