PhD thesis submitted in fulfilment of the requirements for the joint degree of
Doctor of Medical Sciences (University of Antwerp) and Docteur en sciences de la motricité (UCLouvain)
to be defended by **Anthe Foubert**.

Supervisors: Prof. dr. Nathalie Roussel, Prof. dr. Mira Meeus, Prof. dr. Cédric Hermans
Counsellor: Dr. Sébastien Lobet

Faculty of Medicine and Health Sciences (University of Antwerp)
and Faculty of Motor Sciences (UCLouvain)
Department of Rehabilitation Sciences and Physiotherapy

Antwerp, 2023

Universiteit Antwerpen

UCLouvain

GAINING INSIGHT INTO THE COMPLEXITY OF PAIN IN PEOPLE WITH HAEMOPHILIA FROM A BIOPSYCHOSOCIAL PERSPECTIVE ANTHE FOUBERT

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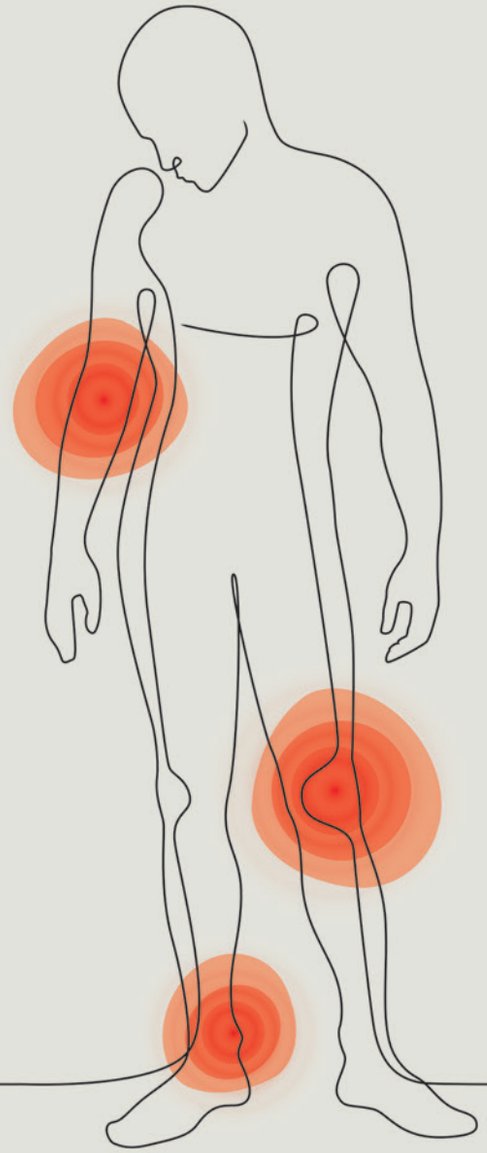

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GAINING INSIGHT INTO THE COMPLEXITY OF PAIN IN PEOPLE WITH HAEMOPHILIA FROM A BIOPSYCHOSOCIAL PERSPECTIVE

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Gaining insight into the complexity of pain in people with haemophilia from a biopsychosocial perspective.

Inzicht verwerven in de complexiteit van pijn bij mensen met hemofilie vanuit een biopsychosociaal perspectief.

PhD thesis submitted in fulfilment of the requirements for the joint degree of Doctor of Medical Sciences (University of Antwerp) and Docteur en sciences de la motricité (UCLouvain) to be defended by Anthe Foubert.

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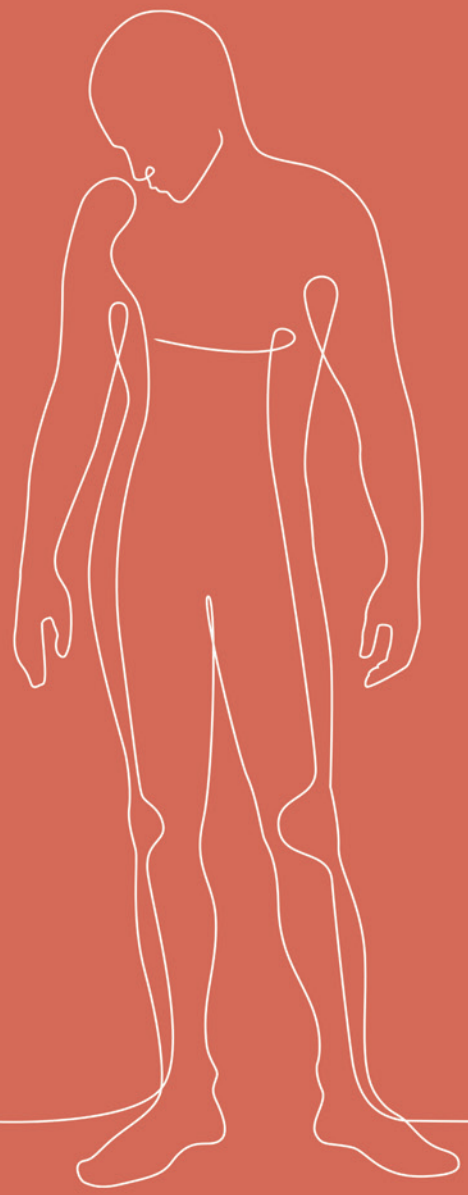
To all people with haemophilia, to their families and caregivers.

Table of contents

Index of abbreviations

PwH	People with Haemophilia
FVIII or FIX	Clotting factor VIII or IX
HR-QoL	Health-Related Quality of Life
IASP	International Association for the Study of Pain
HCPs	Health Care Professionals
MSK	Musculoskeletal
NRS	Numeric Rating Scale
VAS	Visual Analogue Scale
DN4	Douleur Neuropathique en 4 questions
BPI	Brief Pain Inventory
BPI-PS	Brief Pain Inventory-Pain Severity
BPI-PI	Brief Pain Inventory-Pain Interference
CSI	Central Sensitization Inventory
QBPDS	Quebec Back Pain Disability Scale
HADS	Hospital Anxiety and Depression Scale
PCS	Pain Catastrophizing Scale
IPQ-B	Illness Perceptions Questionnaire Brief Version
FABQ	Fear Avoidance Beliefs Questionnaire
EQ-5D-5L	EuroQol 5 Dimension 5 Levels Questionnaire
TSK	Tampa Scale for Kinesiophobia
QST	Quantitative Sensory Testing
DFNS	German Research Network on Neuropathic Pain
TS	Temporal Summation
CPM	Conditioned Pain Modulation
CDT	Cold Detection Threshold
WDT	Warmth Detection Threshold
HPT	Heat Pain Threshold
CPT	Cold Pain Threshold
PPT	Pressure Pain Threshold
(S)ALBP	(Sub)acute Low Back Pain
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance



GENERAL INTRODUCTION

This general introduction covers five sections. Section 1 defines what haemophilia is, while section 2 explains how bleeding events can lead to haemophilic arthropathy. Section 3 addresses the prevalence of pain in people with haemophilia (PwH). Section 4 covers the assessment of (joint) pain in haemophilia, whereas section 5 describes the impact of pain on the individual. To enhance the reader's understanding, additional background information is provided in text boxes throughout the sections. At the end of this general introduction, an overview of the objectives and outline of this doctoral thesis is presented.

1. Haemophilia

Haemophilia is a rare hereditary X-linked recessive (see Information Box 1) blood clotting disorder, resulting in a partial deficiency or complete absence of clotting factor VIII (FVIII, haemophilia A) or factor IX (FIX, haemophilia B). Haemophilia A and B are clinically similar and are currently classified according to the residual clotting factor level as severe (<1% FVIII/FIX), moderate (1-5% FVIII/FIX) and mild (6-24% FVIII/FIX). Bleeding tendency is inversely correlated with the level of FVIII/FIX. People with mild haemophilia only develop severe bleeding after major trauma or surgery, while people with severe haemophilia experience spontaneous and recurrent bleeding without adequate treatment (see Information Box 1). Nearly 70-80% of all bleeding occurs in synovial joints such as the ankles, knees, and elbows, while 10-20% occurs in muscles.[1]

2. Haemophilic arthropathy

Over time, repeated joint bleeds in the same joint initiate an irreversible pathological condition, called haemophilic arthropathy. This complex process involves both direct and indirect blood-induced mechanisms that destroy the synovium, cartilage and subchondral bone.[9] The function of the synovial tissue is to remove fluid and debris (including blood) from the synovial cavity. After a major bleed or repeated bleeding episodes in the same joint, the capacity of the synovium to reabsorb the amount of blood exceeds and iron collects in the form of haemosiderin (i.e. the breakdown product of haemoglobin).[10] This synovial inflammation leads to a vicious circle of synovial hypertrophy, hypervascularisation and impingement, increasing the bleeding risk (Figure 1).[11] In addition, the inflammatory process releases destructive enzymes leading to enzymatic degradation of the joint.[12] At the same time, the direct exposure of blood to the cartilage surface causes apoptosis of the chondrocytes, which will lead to a reduced matrix turnover and cartilage damage.

Information box 1.

Epidemiology of haemophilia

it is estimated that haemophilia A occurs in 1 in 5.000 male live births and haemophilia B in 1 in 30.000, with similar incidences in different ethnic populations.[2] Haemophilia is an X-linked recessive disease, usually inherited from a mother who carries the gene and passes it on to her son (see Figure A). Although most carriers are asymptomatic, some may experience increased bleeding tendency.[3]

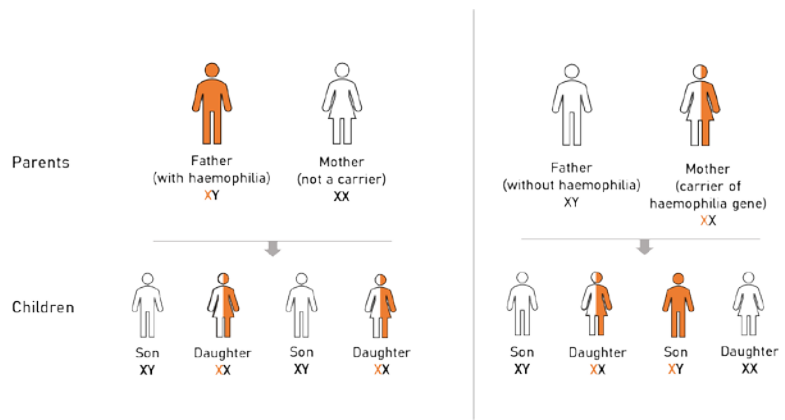


Figure A. Inheritance of haemophilia

Treatment of haemophilia

PwH are ideally followed up by a haemophilia treatment centre, which is equipped with a multidisciplinary team for the prevention and treatment of bleeding, musculoskeletal (MSK) complications and pain management.[1] By substitutive therapy, the missing clotting factors are administered to ensure adequate haemostasis. Prophylactic therapy initiated in early childhood is the preferred treatment for people with severe haemophilia.[4]

These long-term repeated (self)-injections of clotting factor concentrates or newly developed non-factor substitution therapy (i.e. emicizumab for people with haemophilia A with or without inhibitors) can prevent or reduce the frequency of bleeding and thus slow and ideally prevent the progression of joint damage.[5] On-demand therapy, on the other hand, is a more episodic treatment given at the time a bleeding is clinically suspected in order to stop it.[6]

In recent decades, tremendous scientific progress has been made in treatment modalities, reducing the development of haemophilic arthropathy and bringing the life expectancy of PwH close to that of the general population.[7] However, many MSK complications are observed, especially in the elderly population who did not benefit from prophylaxis during their childhood or in people living in developing countries who have limited access to clotting factor concentrates or non-factor substitution therapy.[8]

In summary, the pathophysiology of haemophilic arthropathy shows clinical similarities with rheumatoid arthritis due to the process of synovial inflammation and osteoarthritis due to progressive cartilage degeneration.[12] In line with these two chronic joint pain conditions, people with haemophilic arthropathy also suffer from restricted joint mobility, decreased health-related quality of life (HR-QoL) and functionality in activities of daily living, and chronic pain.[13-15]

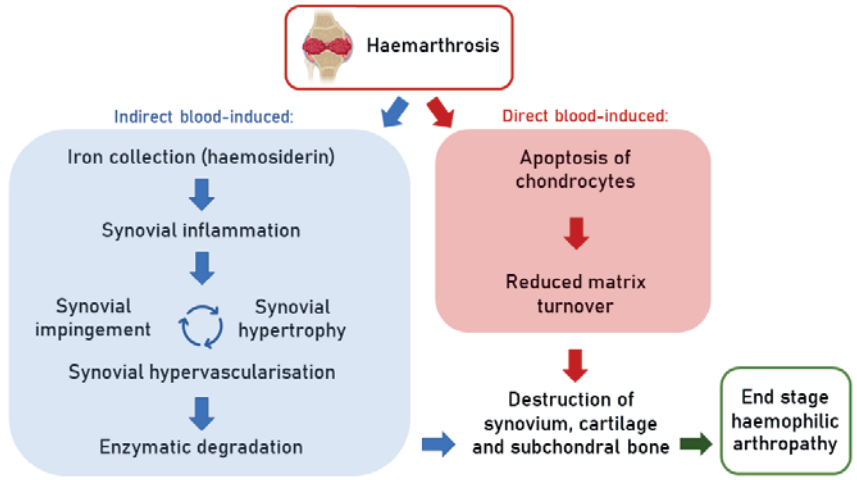


Figure 1. Pathophysiology of haemophilic arthropathy.

3. Prevalence of pain in haemophilia

Pain is recognised as a major issue in PwH that negatively affects their overall HR-QoL.[14, 16] According to a German survey, 86% of adults and 66% of children and adolescents reported suffering from episodes of pain.[17] Joint pain was the most common type of pain reported in 92% of adults and 80% of young patients.[17] When taking into account the pain locations, it was shown that 43% of adults with severe haemophilia experienced pain in 3-5 body regions, while 28% reported pain in at least 6 regions, indicating the widespread distribution of pain in haemophilia.[18] However, the current scientific literature shows a high variability of reported prevalence rates because of the following reasons:

- The lack of a uniformly applied **definition of pain** in PwH, since studies reporting pain within haemophilia include different definitions for pain. Following the International Association for the Study of Pain (IASP)[19] it is recommended for

researchers and health care professionals (HCPs) to use the following definition: Pain is defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”.[19]

- The additional challenge of **uncertainty about the origin of pain** in PwH. Specifically, any increase in pain intensity is often considered as acute pain and thus (falsely) linked to a haemarthrosis. Indeed, both patients and HCPs appear unable to reliably distinguish clinically between joint pain from an acute haemarthrosis or a flare-up of haemophilic arthropathy.[20]

- Furthermore, the lack of a **standardised approach** and the use of non-validated instruments to evaluate pain in haemophilia could be the reason why pain is often succinctly discussed or assessed during regular consultations.[21]

4. Biopsychosocial pain assessment

Currently, the assessment of pain in PwH in clinical settings remains excessively focused on biomedical aspects for the following reasons:

- The evaluation is often limited to the **momentary evaluation of pain intensity**, with the main goal being the detection of a haemarthrosis in order to urgently administer clotting factor concentrates.[22] However, when the presence of an acute haemarthrosis is ruled out, evaluating pain intensity as the only pain parameter shows limitations. Longitudinal studies in other chronic musculoskeletal (MSK) conditions have indeed shown that pain fluctuates over time. Consequently, assessing an individual’s pain intensity at a single point in time cannot provide sufficient information.[23]

- Moreover, many HCP’s and PwH hold the belief that there is a **direct relationship between pain intensity and the degree of tissue damage** on medical imaging. However, by analogy with MSK conditions such as osteoarthritis and low back pain, it became evident that this assumption was incorrect, as no one-to-one relationship exists.[20, 24]

These two arguments suggests that the pain experience of PwH is a **complex and multifactorial** phenomenon, determined not only by sensory input but also by other components.

A **biopsychosocial pain assessment** takes into account not only **biological/physical aspects** such as haemophilia severity, haemarthrosis, joint tissue inflammation/damage and (patho)physiology of pain (see Information box 2) but also pain-related **psychosocial factors** (i.e. beliefs, emotions and social support).[25] By analogy with previous findings in large cohorts of people suffering from chronic MSK conditions, we hypothesise that unhelpful psychosocial factors such as feelings of anxiety, stress and pain catastrophizing (i.e. an enhanced negative orientation towards pain) are related to an increased pain sensation[25, 26], disability and poorer treatment outcomes in PwH. [27]

Information box 2.

Pathophysiology of pain

This information box briefly describes the (patho)physiology of pain, namely how different parts of the peripheral and central nervous system detect and interpret pain.

From noxious stimulus to pain sensation

Nociceptors are located all over the body and can be activated by a potential noxious (or harmful) stimulus (this can be an intense thermal, chemical or mechanical stimulus).[28] In this initial phase the terminology ‘harmful’ is used, because no interpretation has yet been given to the message signal in the peripheral system. When the stimulus reaches the brain, it is analysed whether it can be perceived as painful or not.[29]

Figure B illustrates the pathways between the noxious stimulus and the brain. First, primary afferent nociceptive Aδ- and C-fibers send the nociceptive signal to the dorsal horn of the spinal cord. In the dorsal horn, the nociceptive signal is transduced through a synaptic contact between the primary and secondary afferent neuron fibres. From this moment, the signal is transmitted via the spinothalamic tract to the thalamus, which acts as a relay station to decode, process and afterwards transfer the information to different parts of the brain.[29] In the somatosensory cortex, sensory information (i.e. the body location and intensity of the stimulus) is processed, a cognitive meaning is given in the prefrontal cortex, and the limbic system adds an affective and emotional interpretation.[30] From the interaction between these different brain regions, we can conclude that pain is not only a sensory but also cognitive and emotional experience.

Pain modulation

In people with chronic pain, a prolonged neuronal activation may cause sensitization, i.e. an increased responsivity of the peripheral nerves (peripheral sensitization or primary hyperalgesia) and central nervous system (central sensitization or secondary hyperalgesia).[31, 32] While primary hyperalgesia presents itself as a local hypersensitivity to pain in order to protect further damage of injured tissue, secondary hyperalgesia is a more central mechanism in which also uninjured body regions become hypersensitive.[24, 25] The latter

can be due to alterations in the ascending pathway, but also in the descending system such as an impaired function of endogenous pain inhibition (i.e. our own pain control system that releases natural painkillers like endorphins, for example during exercise)[33] and cognitive emotional sensitization, in which cognitive-emotional factors change the sensitivity of the central nervous system.[25, 26]

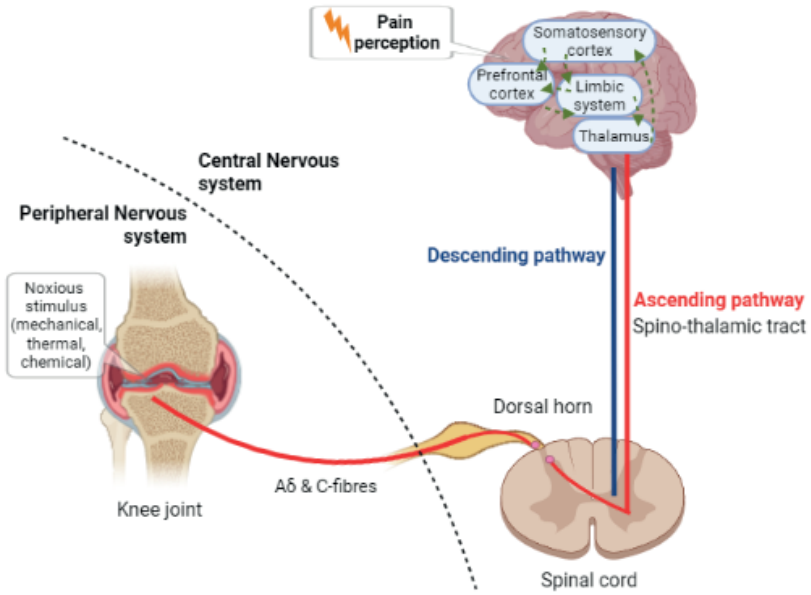


Figure B. Ascending and descending pain pathway.

As such, a biopsychosocial pain assessment also includes the assessment of the **underlying pain mechanisms** (i.e. nociceptive, neuropathic and nociplastic pain). It is assumed that pain in PwH is usually nociceptive in origin (i.e. due to activation of nociceptors by an acute haemarthrosis or haemophilic arthropathy in a normally functioning somatosensory system).[34] However, recent studies revealed that a certain proportion of PwH demonstrated signs of neuropathic pain (i.e. pain caused by injury or lesion of the somatosensory system).[20-22] By analogy with other chronic MSK conditions, it is suspected that at least a subgroup of PwH suffers from predominant nociplastic pain (i.e. pain due to altered somatosensory functioning without obvious activation of nociceptors or neuropathy). This is due to multiple indications such as: the more widespread distribution of pain in haemophilia[17], generalized hypersensitivity to painful stimuli (both at symptomatic and asymptomatic body locations)[35] and reduced efficacy of endogenous pain inhibition.[36]

Since the management plan is ideally tailored to the predominant pain mechanism, it is very important to identify which pain mechanism is involved and what impact it has on the person's daily life.[37] Therefore, the literature describes an extensive scale of different (self-reported) pain-related and psychosocial questionnaires to collect information about the individuals' pain experience (see Information Box 3).

Information box 3.

Table 1. Overview validated pain-related questionnaires included in doctoral thesis project

Outcome	Tool + application
Pain intensity	Numeric Rating Scale (NRS)[38]: • Asks participants to rate their current pain intensity • Scores range from 0 (no pain) to 10 (worst imaginable pain) Visual Analogue Scale (VAS)[39]: • Asks participants to rate their current pain intensity on a straight line • The left end represents 0 (no pain) and the right end represents 10 (worst imaginable pain)
Pain severity	Brief Pain Inventory – Pain severity subscale (BPI-PS)[40]: • Asks participants to rate their worst, least, average and current pain intensity within the last 24 hours • Scores range from 0 (no pain) to 10 (worst imaginable pain)
Pain distribution	Brief Pain Inventory – Body chart (BPI-Body chart) [40]: • Asks participants to indicate their painful body sites on the body chart
Pain interference with daily functioning	Brief Pain Inventory – Pain interference subscale (BPI-PI)[40]: • Measures how much pain has interfered with 7 daily activities: • General activity, walking, working, mood, enjoyment of life, relations with others, and sleep • Scores range from 0 (no interference) to 10 (interferes completely)
Symptoms and signs of neuropathic pain	Douleur Neuropathique en 4 questions (DN4)[41]: • Measures the presence of 10 symptoms or signs of neuropathic pain • A score of ≥4/10 indicates that the pain might be of neuropathic origin
Self-reported symptoms of central sensitization	Central Sensitization Inventory (CSI)[42]: • Part A: investigates the presence of 25 symptoms scored from 0 (never) to 4 (always) • A score of ≥40/100 indicates symptoms of central sensitization • Part B: questions previous diagnosis of central sensitization syndromes
Pain disability	Quebec Back Pain Disability Scale (QBPDS)[43]: • Asks participants to rate their level of disability • Scores range from 0 (no limitations) to 100 (totally limited)

Table 2. Overview validated psychosocial questionnaires included in doctoral thesis project

Outcome	Tool + application
Catastrophic thinking about pain	Pain Catastrophizing Scale (PCS)[44]: • Reflection on previous painful experiences • 13 items scored from 0 (not at all) to 4 (all the time) • Total score between 0-52, a higher score indicates higher levels of catastrophic thinking
Pain-related anxiety and depression	Hospital Anxiety and Depression Scale (HADS)[45]: • 14 items with two subscales each including 7 items scored from 0-3 • Total score between 0-21, a score of ≥8/21 serves as cut-off indicating anxiety and depression
Pain-related fear-avoidance beliefs	Fear-avoidance and Beliefs Questionnaire (FABQ)[46]: • 16 items questionnaire with a work and physical activity subscale scored from 0-6 • Total score between 0-96, a score of ≥15/ serves as cut-off indicating elevated fear-avoidance beliefs • Sub score work between 0-72 and physical activity between 0-24
Fear of movement	Tampa Scale for Kinesiophobia (TSK)[47]: • 17 items to assess kinesiophobia (i.e. fear of movement) • Total score between 17-68, a higher score indicates higher levels of kinesiophobia • A score ≥37 serves as cut-off indicating kinesiophobia
Illness perceptions related to pain	Illness Perceptions Questionnaire Brief-version (IPQ-B)[48]: • 10 items to assess the participants pain perceptions • 3 items to list the personal causes of the illness
Health-related quality of life	EuroQol 5 Dimension 5 Levels Questionnaire (EQ-5D-5L)[49]: • Measures HR-QoL across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by calculating a health utility index score between 0 (worst health state) 1 (best health state) • The EQ-VAS asks participants to rate their health state from 0 (worst imaginable) to 100 (best imaginable)

Additionally, clinical tests exist to help HCPs assess the individual's biopsychosocial context of pain. For example, several methods of **Quantitative Sensory Testing (QST)** have been described to investigate somatosensory functioning. The German Research Network on Neuropathic Pain (DFNS)[50] has developed a validated non-invasive QST examination battery including both 'static' and 'dynamic' tests.

Static tests determine the individual's thermal and mechanical detection and pain thresholds (i.e. the lowest magnitude to experience the stimulus and to experience the stimulus as painful/unpleasant). Dynamic tests investigate more complex mechanisms of pain processing with specific stimulation that explores central integration (see Information Box 4).

Information box 4.

Table 3. Overview Quantitative Sensory Testing measures included in doctoral thesis

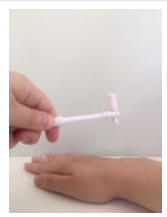
QST measure	Tool	Test procedure - Clinical sign	Fibre type
Static tests			
Cold & Warmth Detection Threshold (CDT & WDT)	 TSA-2	Detection of temperature where a cold/warm temperature stimulus is felt **Clinical sign:** Thermal (cold/ warm) hypo/hyper-aesthesia or hypo/hyper-algesia	Aδ, C
Cold & Heat Pain Threshold (CPT & HPT)		Detection of temperature where a cold/warm temperature stimulus is perceived as painful **Clinical sign:** Thermal (cold/ warm) hypo/hyper-algesia	Aδ, C
Pressure Pain Threshold (PPT)	 Algometer	Amount of pressure by which the pressure stimulus is perceived as unpleasant **Clinical sign:** Mechanical hypo/ hyper-algesia	Aδ, C
Dynamic tests			
Temporal summation (TS)	 Von Frey monofilament	Pain rating after first stimulus versus after a train of stimuli (increase = temporal summation or wind-up), pain rating 15s after final stimulus (aftersensation) **Clinical sign:** Temporal summation (wind-up or degree of pain facilitation)	Aδ, C

Table 3. Continued

QST measure	Tool	Test procedure - Clinical sign	Fibre type
Dynamic tests			
Conditioned Pain Modulation (CPM)	  Algometer + Occlusion cuff	Conditioned pain modulation (pain rating of single pressure stimulus and when this stimulus was applied in combination with an occlusion cuff on the upper arm, also known as the 'pain inhibits pain' paradigm) **Clinical sign:** efficacy of endogenous pain inhibition	/
Conditioned Pain Modulation (CPM)	 TSA-2	Conditioned pain modulation (pain rating of single thermal stimulus and when two thermal stimuli are applied simultaneously, also known as the 'pain inhibits pain' paradigm) **Clinical sign:** efficacy of endogenous pain inhibition	/

Unfortunately, there is an immense lack of studies using validated questionnaires and QST to comprehensively investigate both physiological and psychosocial components of pain in PwH. Since both components are investigated in this doctoral thesis, the term **psychophysiological pain assessment** is consistently used to name them.

5. Impact of pain in haemophilia

The results of a biopsychosocial pain assessment offer HCP's not only information on the interactions between physical and psychosocial factors, but also valuable insights into their influence on the individual's experience, impact and chronification of pain.[34]

Although pain experience and pain impact seem related concepts, an assessment of both dimensions is required. This was highlighted by an earlier longitudinal study in the adult population. [51] About a third of these adults reported chronic pain, but half of them reported that their pain did not impacted or interfered with their daily lives.[51] These findings suggest that pain interference is influenced by multiple components and not solely by pain intensity.

Accordingly, the impact of pain on PwH or how they deal with disease-related pain generally depends on their personal coping strategies and not just on their physical condition and medical treatment.[52] Coping strategies can be defined as cognitive-emotional and behavioural efforts an individual uses to deal with stressful situations, problems or pain.[53] In chronic MSK conditions it has been shown that maladaptive or unhelpful pain coping behaviour strategies (i.e. avoidance behaviour or excessive drug use)[54, 55] can increase the risk of poor health-related outcomes and decrease the individuals' HR-QoL. Based on the high rates of pain and discomfort[13], the question arises whether PwH are using helpful strategies to cope with their pain.

However, very little research has been done to examine pain coping behaviour strategies, the degree of pain severity, pain interference with daily functioning and their interrelationships within PwH. Based on longitudinal studies in chronic MSK conditions, we would expect unhelpful psychosocial factors[27, 56] and unhelpful pain coping behaviour strategies[57] to be associated with poor treatment outcome and pain chronification, but prospective studies in PwH are still lacking.

6. Outline and research objectives doctoral thesis

There is currently insufficient knowledge about the (patho)physiology, underlying pain mechanisms and biopsychosocial context of pain in PwH. Presumably, this explains the fact that, to date, only a limited number of haemophilia-specific pain management options exist and that PwH still report reduced HR-QoL and low satisfaction with their current pain treatment.[17, 58]

Therefore, the aim of this doctoral thesis was to gain insight into the complexity of pain in PwH from a biopsychosocial perspective. Part 1 and Part 2 are dedicated to an introduction regarding pain coping behaviour strategies used among PwH and a longitudinal pain study investigating the role of psychosocial and -physical factors in disability in another MSK condition, while Part 3 covers the analyses of the main study of this dissertation consisting of a large longitudinal study focussing on the biopsychosocial assessment of pain in PwH. Figure 2 provides an overview of the chapters and research questions included, which are divided into the following three main parts:

Part 1 describes one chapter conducted in preparation of the longitudinal study in PwH (**Part 3**). This preparation was used to delve deeper into the existing haemophilia literature regarding pain coping behaviour strategies.

Therefore, **Chapter 1** describes the results of a systematic review that aimed to gather the existing literature regarding the range of pain coping behaviour strategies used among PwH and the factors associated with their pain coping behaviour. This review was conducted as a preparatory step to gain insight into the biopsychosocial context of pain in PwH, in anticipation of the subsequent longitudinal observational study.

Part 2 contains study results of a longitudinal study in people with (sub)acute low back pain (S)ALBP, a related MSK condition. These results serve as a fundamental basis and provide guidance for **Part 3**, as they share the same methodology.

In **Chapter 2**, a dataset of people with (S)ALBP contained various elements: 1) a comprehensive psychophysical pain assessment to investigate pain sensitivity and -modulation by use of static and dynamic QST measures and psychological questionnaires and 2) the assessment of disability after a three-month follow-up period. The aim of **Chapter 2** was to investigate associations between baseline QST measures, psychological factors, and disability at three-months follow-up. Particularly for **Chapter 5**, this part is of great benefit as it serves as a solid foundation and provides valuable guidance. The methodology and research design of **Part 2** are directly applicable to the longitudinal study in PwH described in **Chapter 5**.

Part 3 aims to provide insight into the biopsychosocial context of pain in PwH by use of three chapters (**Chapter 3-5**) investigating the (patho)physiology of pain, underlying pain mechanisms and longitudinal investigation of pain in PwH:

Therefore, **Chapter 3** provides the results of a cross-sectional study conducting a comprehensive psychophysical pain assessment to identify differences in pain sensitivity, pain modulation and psychological factors between a large sample of PwH and age-matched healthy individuals. In addition, differences between subgroups of PwH based on their pain distribution and age-matched healthy individuals were examined. This approach was based on previous studies conducted in non-haemophilia populations, such as a chronic LBP study, which found that individuals with a widespread pain distribution showed greater activity limitations, more severe pain, symptoms of depression and lower HR-QoL compared to those without widespread pain.[59]

Chapter 4 reports the analysis in which the IASP grading system for nociplastic pain was applied to PwH. Through a secondary analysis of data obtained by the cross-sectional study described in **Chapter 3**, it was examined whether PwH with a suspected predominant nociplastic pain mechanism could be identified, based on the IASP grading system. Additionally, in order to gain insight into unique characteristics that may contribute to this suspected predominant nociplastic pain mechanisms, differences in participants characteristics (i.e. anthropometric, demographic and clinical features) and psychological factors were compared between PwH with suspected predominant nociplastic pain, PwH with unlikely nociplastic pain and healthy individuals.

Finally, The aim of **Chapter 5** was to investigate associations between pain characteristics and pain-related psychological factors assessed at baseline (**Chapter 3**) and pain interference with daily functioning at 12-months follow-up. The study design and methodology for this chapter were inspired by the approach used in people with (S) ALBP (**Chapter 2**).

Finally, a general discussion of this dissertation and a summary (in English, Dutch and French) are described at the end.

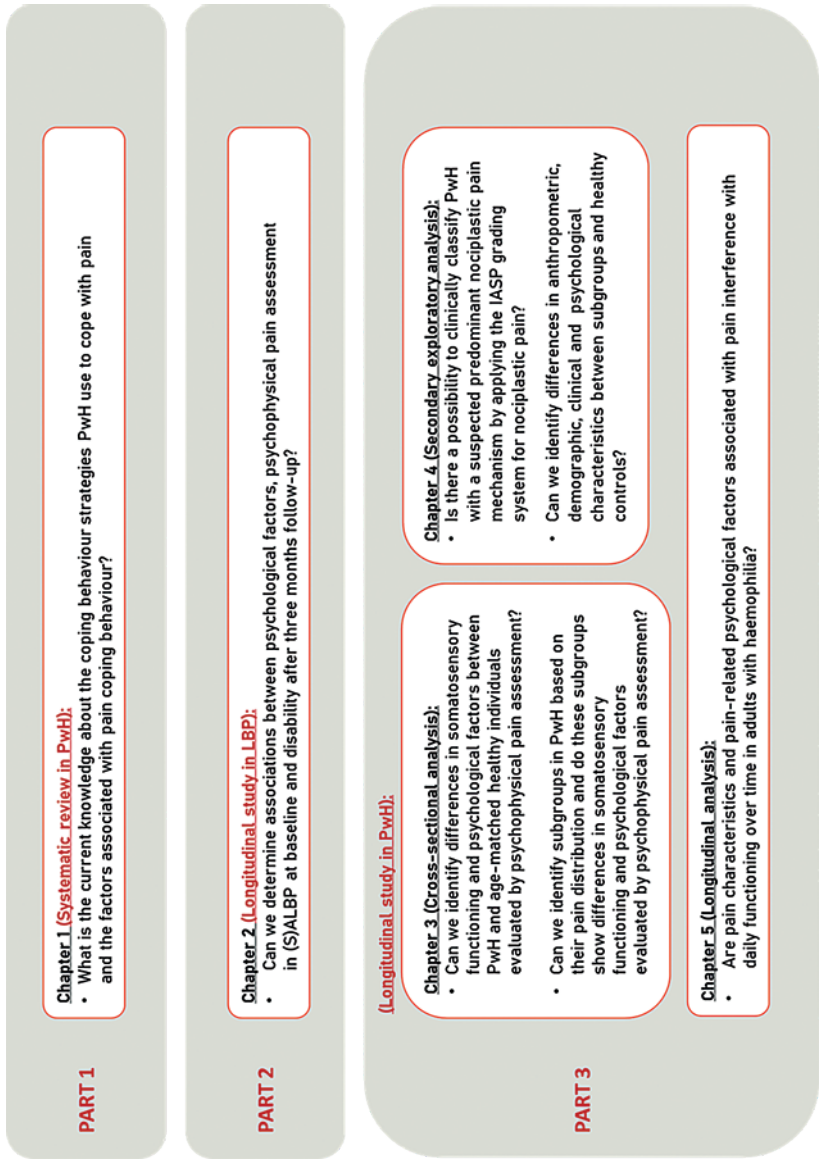


Figure 2. Overview PhD dissertation

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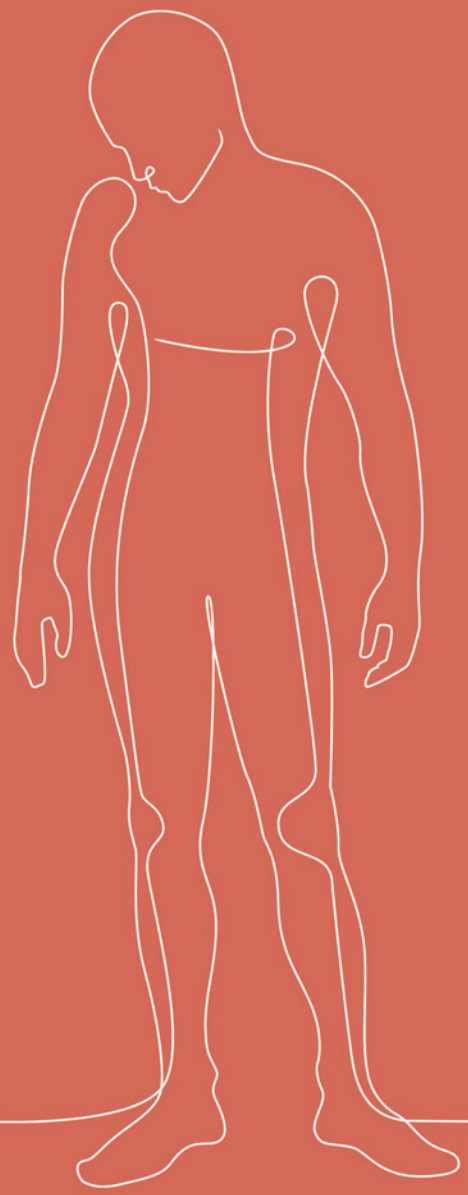
References figures, images and icons

Introduction

Figure 1. Pathophysiology of haemophilic arthropathy	Illustration developed by the author. Icons: BioRender.com
Figure 2. Outline PhD dissertation	Illustration created by the author in PowerPoint

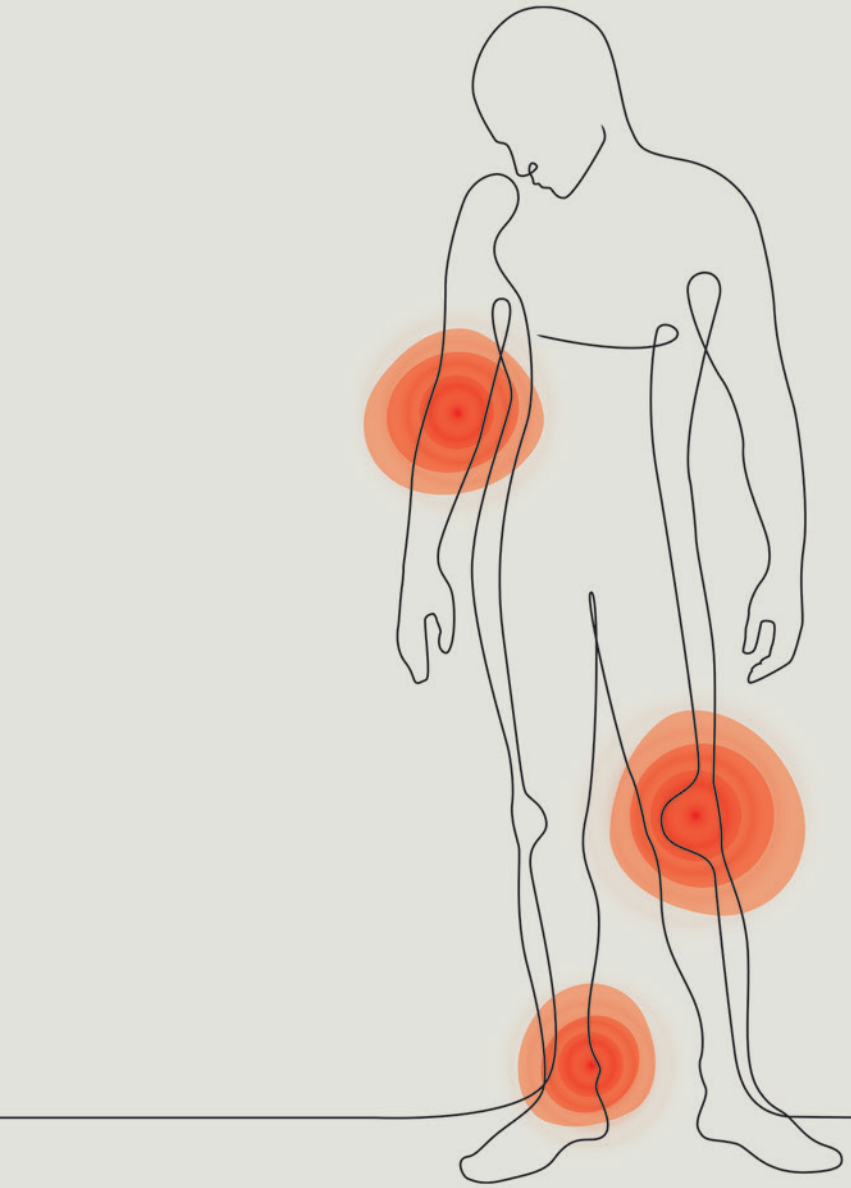
Information boxes

Figure A. Haemophilia inheritance	Illustration created by the author in PowerPoint Icons: PowerPoint
Figure B. Ascending and descending pain pathway	Illustration created by the author in BioRender.com
Image 1. TSA-2	Image provided by the author
Image 2. Algometer	Image provided by the author
Image 3. Von Frey monofilament	Image provided by the author
Image 4. Occlusion cuff	Image derived from Freepik.com



Part 1

EXPLORING PAIN IN HAEMOPHILIA LITERATURE



Chapter 1

Pain coping behaviour strategies in people with haemophilia: a systematic review

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Abstract

Introduction: Despite the fact that joint bleeds (hemarthrosis) frequently occur in people with haemophilia (PwH) with invalidating arthropathies as result, the clinical pain experience has received only limited attention. A sudden increase in pain intensity can be linked to a bleed, but in most cases, no acute bleed is confirmed. Nevertheless, a patient's perception of an acute bleed as cause of the pain might impact the patients' behavior in response to pain. It is therefore essential to gain more insight into pain coping strategies seen in PwH.

Aim: This systematic review aims to identify the range of pain coping behavior strategies used among PwH and the factors associated with pain coping behavior.

Methods: This review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines (PRISMA). PubMed and Web of Science were systematically screened for relevant literature using keyword combinations related to adult PwH, pain and pain coping behavior strategies. Risk of bias was assessed with the modified Newcastle-Ottowa Scale.

Results: Eleven full text articles (9 cross-sectional and 2 comparative studies) consisting of 1832 PwH met the inclusion criteria. Due to the heterogeneity of the study samples, quality of evaluation instruments and varying risk of bias, it was difficult to draw conclusions regarding the used pain coping behavior strategies and associated factors.

Conclusion: Literature on pain coping behavior strategies and associated factors in PwH is still scarce and describes heterogenous results. Validated haemophilia-specific instruments are warranted to inventory pain coping behavior in a standardized way.

Introduction

Haemophilia is a rare, X-linked inherited congenital disease, characterized by a deficiency of either coagulation factor VIII (haemophilia A) or factor IX (haemophilia B).[1] Recurrent spontaneous or trauma-related bleeding in muscles and joints is common in people with haemophilia (PwH), potentially resulting in very painful and irreversible haemophilic arthropathies.[1, 2] Especially patients with severe haemophilia or elderly who have not been able to benefit of prophylaxis during their childhood suffer from painful arthropathies. Therefore, better adherence to prophylactic treatment not only impacts the frequency of bleeding episodes but also the risk for pain and haemophilic arthropathies.[3] Besides the impact on joint level, comorbidities such as muscle and soft tissue fibrosis or co-infections with human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV) contribute to many complaints and pain.[4, 5] Consequently, the pain prevalence is very high in PwH.[6]

Knowledge about the underlying causes and optimal pain management in PwH is extremely limited.[7] Remarkably, scientific literature and clinical settings describe an unconditional association between "acute" pain relating to an acute bleed (hemarthrosis) and "chronic" pain originating from haemophilic arthropathy, although the terms acute and chronic refer to the timeline of pain and not the underlying cause.[8] Patients are even advised to consider every sudden increase in pain intensity as a possible bleed, and to take immediate actions to manage the bleed (such as the injection of additional clotting factor concentrates, conservative treatments such as rest, ice, compression and elevation (RICE method), etc.), leading to conditioned pain coping behavior. This is a concept based on "Classical conditioning", a theory of behavioral psychology were the coping reaction ("response") to pain ("stimulus") is a learned or conditioned behavior. However, using the increase in pain intensity as indication for a bleed was shown to be extremely inaccurate.[9] This is not surprising as distinguishing between the clinical symptoms of a bleed and a flare up of joint arthropathy is still a challenge for patients and clinicians.[8, 9] In this way, their conditioned pain coping behavior, mainly focusing on a pharmacological approach and RICE method, might be inefficient and have a huge impact on patients' clinical pain experience, intake of pain medication and health-related quality of life (HR-QoL).

However, how PwH deal with disease-related pain generally depends on their personal coping strategies and not only on their medical treatment.[4] Coping strategies can be defined as cognitive-emotional and behavioral efforts an individual uses to deal with stressful situations or problems.[10] Two broad categories of pain coping styles are differentiated: i.e. active and passive coping.[11] Active coping indicates strategies based on someone's own responsibility for managing pain, including efforts to retain normal function despite pain (e.g. seeking professional help or taking care of yourself).[11]

On the other hand, passive coping refers to depending on external sources of responsibility to manage pain (e.g. giving up social activities or pain catastrophizing).[11] Maladaptive coping strategies such as avoidance behavior, somatization, excessive drug use can be a risk factor for worse health outcome and psychopathology.[12, 13] Alternative conceptual models describe a slightly different division of coping strategies: e.g. coping efforts trying to control or change a stressful situation defined as problem-oriented (e.g. seeking help from a friend or professional) and coping strategies trying to manage the negative emotions related to the situation defined as emotion-oriented (e.g. positive thinking or meditation).[14] In stressful, acute situations emotion-oriented coping is considered as the most effective strategy, while problem-oriented coping seems the best approach in chronic diseases[14, 15], as evidenced in patients with chronic low back pain (CLBP)[16], chronic neck pain and headaches.[17] In chronic musculoskeletal conditions it has been shown that maladaptive pain coping can increase the risk of poor health related outcomes and decrease patients' HR-QoL[18] In contrast to these conditions, the clinical pain experience and pain coping behavior of PwH have received only limited attention.

The scarce number of studies investigating coping behavior mostly focus on how PwH cope with physical limitations or how family members cope with the disease but not how PwH cope with pain.[19- 21] As recurrent or chronic pain is extremely frequent in PwH, especially in the older population, it is necessary to evaluate pain coping behavior as well.[4] The objective of the present systematic literature search is to identify the range of pain coping behavior strategies used among PwH and the factors associated with pain coping behavior. This is in order to obtain an inventory of non-pharmacological strategies (i.e. cognitive-emotional and behavioral) and pharmacological strategies (i.e. intake of pain medication or additional clotting factors in response to pain and adherence to prophylactic treatment to prevent bleedings and control pain). Since the intake of additional clotting factors is mainly done in case pain is felt[22, 23], it should be considered as a pain coping strategy. The rationale for including adherence as a (preventive) pain coping strategy as well, relies on previous studies that demonstrated significant beneficial effects of better adherence to prophylaxis on pain.[3, 24, 25]

Methods

This systematic review is reported following the PRISMA-guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses).[26] The protocol of the systematic review was registered on PROSPERO (Registration number: CRD42020212438).

Eligibility criteria

Eligibility criteria were framed by the PICOS (Patient-Intervention-Comparison-Outcome-Study designs) methodology and presented in Table 1. For this systematic review, included articles had to report results of primary studies (S) evaluating pain coping behavior (O) in adult PwH aged 18 years and above (P).

Table 1. PICOS and eligibility criteria.

	Inclusion criteria	Exclusion criteria
Patients (P)	Adults aged 18 years and above diagnosed with congenital haemophilia of any severity: mild (>5%), moderate (1-5%) or severe (<1%) deficiency of FVIII (haemophilia A) or FIX (haemophilia B)	Non-human subjects (such as models of animals), subjects not diagnosed with haemophilia, other bleeding disorders or no separate data of people with haemophilia, children <18 years old
Intervention (I)	-	Studies investigating the effect of an intervention programme
Control (C)	-	-
Outcome (O)	Any kind of pain coping behavior	Pain coping behavior not included as outcome parameter
Study design (S)	Full text reports written in English, French or Dutch	Reviews, meta-analysis, expert opinions, congress proceedings, qualitative studies, abstracts or letters

Information sources and search strategy

To identify relevant articles, the online databases PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (https://login.webofknowledge.com) were searched in December 2021 by the first author (A.F.) and five students enrolled in academic Bachelor's and Master's program. Key words were derived from the PICOS-question and converted to possible MeSH-terms if available. The search strategy in PubMed is presented in Table 2. In addition, the reference lists of included articles were hand-searched by the first author (A.F.).

Table 2. Search strategy in PubMed.

(haemophilia A[MeSH Terms] OR haemophilia B[MeSH Terms] OR haemophilia OR hemophilia) AND (pain[MeSH Terms] OR pain) AND (Behavior[Mesh] OR pain behavior OR pain related behavior OR "health behavior"[MeSH Terms] OR health behavior OR "illness behavior"[MeSH Terms] OR illness behavior OR coping OR coping strategy OR coping strategies OR coping behavior OR avoid* OR persist* OR protect* OR somatization OR adaptive behavior OR maladaptive behavior OR "drug utilization"[MeSH Terms] OR drug use OR medication use OR help seeking OR medical shopping)

Study selection

In the first phase of screening, articles were selected based on title and abstract. If the citation was considered potentially eligible and relevant, the full text was retrieved. In the second phase, full text articles were evaluated again on meeting the eligibility criteria. The first and second phases of the screening were independently conducted by the first author (A.F.) and five academic students. In case of uncertainty, a decision was made in a separate consensus meeting.

Qualification of searchers/ raters

Literature was searched and screened by A.F., PhD candidate working on widespread pain in patients with haemophilia and five academic bachelor's and master's students from the department of Physiotherapy and Rehabilitation Sciences of the University of Antwerp. N.R. and M.M., both PhDs experienced in musculoskeletal and chronic pain research and conducting systematic reviews, supervised the literature search.

Data items and collection

In order to present the collected data, a subdivision was made into categories: validated and non-validated questionnaires. Under both headings two subcategories were made: 1. pain coping behavior in PwH and 2. factors associated with pain coping behavior in PwH. Extracted information was presented in an evidence table (Table 4) using three categories: 1. validated questionnaires, 2. validated and non-validated questionnaires and 3. non-validated questionnaires and selected on: 1. author and country, 2. study design, 3. sample size, 4. characteristics of study subjects, 5. applied questionnaires, 6. pain coping behavior strategies and associated factors.

Risk of Bias in individual studies

A risk of bias assessment was independently carried out by the first author and the five independent researchers (academic students) to determine internal validity. Afterwards,

results were discussed to reach consensus. Given the comparative study designs, the modified Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for case-control studies was used. The NOS is a reliable and valid tool for assessing the quality of non-randomized studies. For the cross-sectional studies, the NOS-adapted version for cross-sectional studies[27] was used. This version was developed to evaluate the quality of non-comparative observational designs and has been used for previous systematic reviews.[28] A star rating system was applied to determine the risk of bias in 3 dimensions including selection of cases, comparability and ascertainment of exposure.[27] Depending on the presence of 1 or 2 confounder(s), a star could be awarded. Detailed information is presented in Table 3.

Levels of conclusions per category were determined with the Evidence Based Richtlijn Ontwikkeling (EBRO) approach (www.cbo.nl). Level 1 of conclusion, indicating strong evidence, is represented by at least two independent A2 studies (prospective cohort studies with sufficient size, follow-up and adequate controlling for 'confounding', and selective follow-up has been ruled out). Level 2 conclusion is represented by one A2 or at least two independent B studies (prospective cohort studies without the features listed under A2, retrospective cohort studies, or patient-controlled studies). Level 3 conclusion is represented by one B or C study or conflicting results and level 4 conclusion by expert opinion only.

Results

Study selection

The search strategy resulted in 865 hits from both databases. After removing duplicates, 793 studies were screened for eligibility. Consecutively, after both screening phases, a hand search and one additional article retrieved via an expert in the field, eleven articles remained. A flowchart of the screening process is presented in Figure 1.

Risk of bias and level of evidence

The risk of bias and level of evidence of the studies are reported in Table 3. Initial agreement rate between the reviewers was 78.5%, reaching full agreement after a consensus meeting. Four studies were identified to have low[6, 29-31], four to have moderate[32-35] and three to have high risk of bias.[36-38] Bias was mostly due to the lack of a representative population or missing description of the response rate. A strength of most studies was the application of both validated and non-validated questionnaires and appropriate statistics. The level of evidence was at level C for non-comparative studies[6, 29-35, 38]and level B for comparative studies.[36, 37]

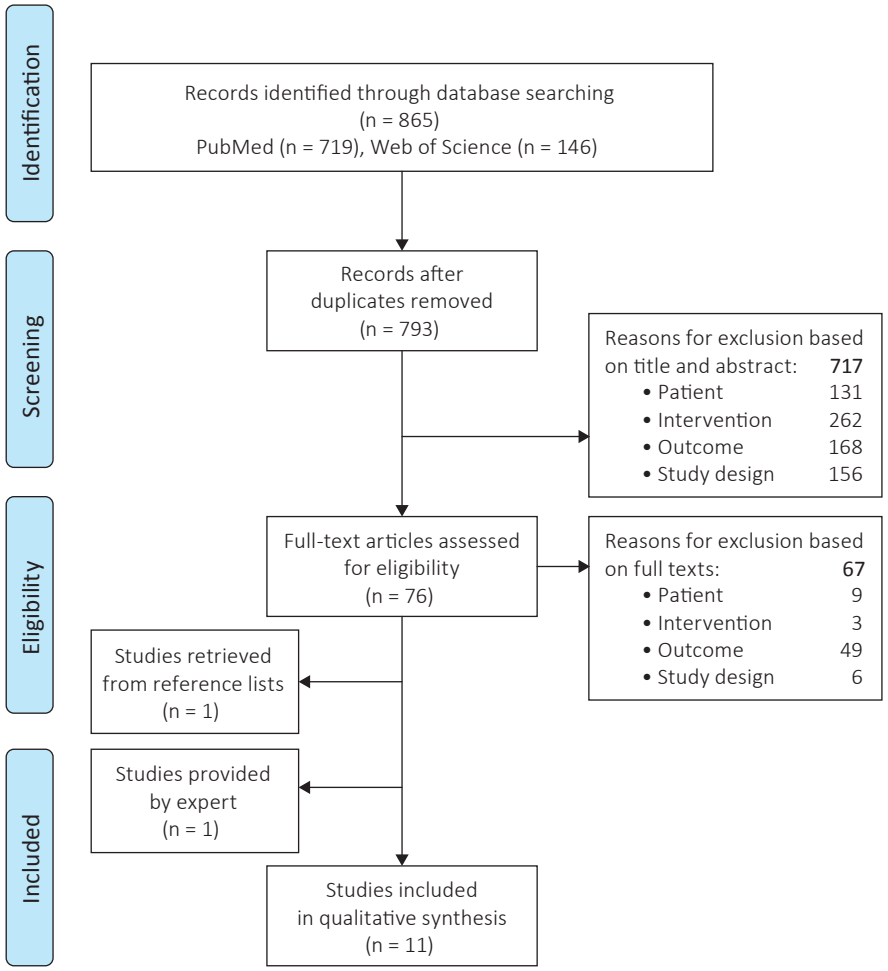

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flow diagram of the conducted research.

Study characteristics

The characteristics for which data were extracted are presented in Table 4. Studies were conducted in Europe[6, 29-33, 35-37] and the United States[34, 38]. The total number of PwH included across all studies was 1832. Most studies investigated men[6, 29-33, 35-38], only one study included 20 (1.6%) women.[34] The mean age varied between 38 and 49 years old (range between 18 and 84 years). All studies recruited people with haemophilia A and B, the majority had severe haemophilia.[29-38] Two studies compared PwH with study samples of healthy controls[36], severe PwH, CLBP and sickle cell disease.[37]

Table 3. Methodological quality assessment with the modified NOS and levels of evidence with EBRO.

		Selection				Comparability	Exposure[a] / Outcome[b]			Total score	Level of evidence
Study	Design	1	2	3	4	5	6	7	8		
Bago et al.[31]	cross-sectional	*	*	-	**	*	*	*	/	Low	C
Barry et al.[32]	cross-sectional	-	-	*	*	-	*	*	/	Moderate	C
Binnema et al.[36]	comparative study	-	-	-	*	*	-	*	-	High	B
Du Treil et al.[38]	cross-sectional	-	-	-	*	-	*	*	/	High	C
Elander et al.[35]	cross-sectional	-	-	-	*	*	*	*	/	Moderate	C
Elander et al.[30]	cross-sectional	*	*	-	**	*	*	*	/	Low	C
Elander et al.[37]	comparative study	-	-	-	-	*	-	*	-	High	B
Miesbach et al.[29]	cross-sectional	*	*	-	**	*	*	*	/	Low	C
Pinto et al.[6]	cross-sectional	*	*	*	**	*	*	*	/	Low	C
Torres et al.[33]	cross-sectional	*	-	-	**	-	*	*	/	Moderate	C
Witkop et al.[34]	cross-sectional	*	*	-	*	-	*	-	/	Moderate	C

[a]Comparative study design: 1. Adequate case definition, 2. Representativeness of cases, 3. Selection of controls, 4. Definition of controls, 5. Comparability of cases and controls, 6. Ascertainment of exposure, 7. Same method of ascertainment for cases and controls, 8. Non-response rate, maximum score is 10. **[b]Cross-sectional design:** 1. Representativeness of the sample, 2. Justified and satisfactory sample size, 3. Non-respondents, 4. Ascertainment of exposure, 5. Comparability of outcome groups, 6. Assessment of the outcome, 7. Appropriate statistical test, maximum score is 10.

Table 4. Evidence table.

Author and country	Study design	Sample size	Characteristics of participants	Applied questionnaires	Pain coping behavior strategies and associated factors	Remarks
Validated questionnaires						
Bago et al. (2021)[31] **Croatia**	Cross-sectional	82 male PwH (median age: 44.50, 18-73 years)	**Type of Haemophilia:** A (85%) and B (15%) **Severity:** Severe (94%) Moderate (6%) **Treatment:** Prophylaxis (100%)	**Adherence to prophylactic treatment:** VERITAS-Pro	**Adherence to prophylactic treatment:** 18-73y: 83% After controlling for demographic, socioeconomic and clinical variables, adherence to prophylactic treatment predicted better HR-QoL.	
Barry et al. (2002)[32] **United Kingdom**	Cross-sectional	61 male PwH (average age: 41, SD 13)	**Type of Haemophilia:** A and B **Severity:** Severe (100%) **Treatment:** Not described	**Non-pharmacological pain coping: (cognitive-emotional strategies):** Hemophilia-adapted CSQ	**Factors associated with pain coping behavior in PwH:** Negative thoughts~: Beliefs pain being controlled by chance happenings (r=0.29, p=0.03) Concerns about intake pain medication (r=0.26, p=0.06) Annual income (r=-0.28, p=0.04) Passive adherence~: Receiving benefits (r=0.35, p=0.01) Visits to health care professionals (r=0.43, p=0.001) Use of over-the-counter (r=0.22, p=0.12) and prescribed analgesics (r=0.29, p=0.04) Beliefs pain being controlled by doctors (r=0.32, p=0.02)	Secondary aim was to assess psychometric properties of the Hemophilia-adapted CSQ.
Binnema et al. (2014)[36] **The Netherlands**	Comparative study	86 male PwH (average age: 38, 18-68 years) 374 healthy male CG (average age: 41, SD 9.2)	**Type of Haemophilia:** A (85%) and B (15%) **Severity:** Severe (100%) **Treatment:** Prophylaxis (75%) On-demand (25%)	**Non-pharmacological pain coping: (cognitive-emotional strategies):** CISS-21	**Pain coping behavior in PwH:** Task-oriented coping: PwH = CG (p=0.13) Emotion-oriented coping: PwH < CG (p<0.05) Avoidance coping: PwH < CG (p<0.05) **Factors associated with pain coping behavior in PwH:** Emotion-oriented coping~: Poor psychological health (r=0.67, p<0.01) Less participation (r=0.32, p<0.01) Lack of social interaction (r=0.29, p<0.01)	Secondary analysis of data collected in 2003-2005.[37]
Elander et al. (2009)[37] **United Kingdom**	Comparative study	209 male PwH (average age: 49.5, SD 12.8)	**Type of Haemophilia:** A (78.9%), B (18.7%), not known (2.4%) **Severity:** Severe (63.2%) Moderate (11.5%) Mild (22%) Not known (3.3%)	**Non-pharmacological pain coping: (cognitive-emotional strategies):** HPCQ CPAQ	**Pain coping behavior in PwH:** Active coping: PwH > severe PwH Negative thoughts: PwH < severe PwH Passive adherence: PwH > severe PwH Praying and hoping: PwH < SCD and CLBP Pain acceptance: PwH > chronic pain (mostly CLBP)	Study compared results with previous study sample of severe PwH[35], SCD and CLBP[33].

Table 4. Continued.

Author and country	Study design	Sample size	Characteristics of participants	Applied questionnaires	Pain coping behavior strategies and associated factors	Remarks
Validated questionnaires						
			Treatment: Not described	**Intake of pain medication:** 2 items of the hemophilia-adapted CSQ	**Factors associated with pain coping behavior in PwH:** Haemophilia severity ~use of clotting factor (r=0.63, p<0.001) and pain intensity (r=0.35, p<0.001) Use of clotting factors ~pain intensity (r=0.16, p<0.05) Activity engagement ~active coping (r=0.34, p<0.001) Activity engagement & pain willingness ~negative thoughts (r=-0.38 & r=-0.49, p<0.001) & passive adherence (r=-0.29 & r=-0.26, p<0.001)	
Elander et al. (2013)[30] **United Kingdom**	Cross-sectional	101 male PwH (average age: 50.3, SD 12.2)	**Type of Haemophilia:** A (77.2%), B (19.8%), not known (3.0%) **Severity:** Severe (70.3%) Moderate (10.9%) Mild (18.8%) **Treatment:** Not described	**Non-pharmacological pain coping: (cognitive-emotional strategies):** HPCQ CPAQ	**Factors associated with pain coping behavior in PwH:** Negative thoughts~: Lower mental QoL (r=-0.50, p≤0.001) Lower pain acceptance (r=-0.57, p≤0.001) Lower activity engagement (r=-0.39, p≤0.001) Lower pain willingness (r=-0.56, p≤0.001) Passive adherence~: Pain acceptance (r=-0.34, p≤0.05) Activity engagement (r=-0.29, p≤0.05) Pain willingness (r=-0.26, p≤0.05)	
Miesbach et al. (2016)[29] **Germany**	Cross-sectional	192 male PwH (average age: 29, 20-85 years)	**Type of Haemophilia:** A (86.4%) and B (13.6%) **Severity:** Severe (92.7%) Moderate (7.1%) Not known (0.3%) **Treatment:** Prophylaxis (100%)	**Adherence to prophylactic treatment:** VERITAS-Pro	**Adherence to prophylactic treatment:** +60y (93.9%) > 20-59y (88.1%) +20y: better adherence to prophylactic treatment in PwH treated in haemophilia care center (p<0.001)	
Pinto et al. (2020)[6] **Portugal**	Cross-sectional	104 male PwH PwH with pain: (average age: 43.17, SD 13.0, 18-74) PwH without pain: (average age: 45.50, SD 17.3, 18-72)	**Type of Haemophilia:** A (84.6%) and B (15.4%) **Severity:** Severe (56.7%) Moderate (31.7%) Mild (11.6%) **Treatment:** Prophylaxis (32.7%)	**Non-pharmacological pain coping: (cognitive-emotional and behavioral strategies):** MHPQ **Intake of pain medication:** MHPQ	**Pain coping behavior and intake of pain medication in PwH:** Top 5 strategies used for pain coping: ice, rest, factor replacement, pain medication and elevation. The strategy providing the greatest perception of pain relief: factor replacement (77.81%), followed by pain medication (59.33%)	

Table 4. Continued.

Author and country	Study design	Sample size	Characteristics of participants	Applied questionnaires	Pain coping behavior strategies and associated factors	Remarks
Validated questionnaires						
Torres-Ortuna et al. (2019)[33] **Spain**	Cross-sectional	63 PwH (average age: 36.76, SD 15.20)	**Type of Haemophilia:** A (81%) and B (19%) **Severity:** Severe (51%) Moderate (17%) Mild (32%) **Treatment:** Prophylaxis (37%) On demand (63%)	**Non-pharmacological pain coping: (cognitive-emotional strategies):** CSI **(behavioral strategies):** IBQ	**Pain coping behavior in PwH:** Problem solving: better in married and working PwH ($p<0.05$) Problem-avoidance: more in moderate PwH ($p<0.01$) Self-criticism, social withdrawal, less wishful thinking: PwH using prophylaxis ($p<0.01$) **Factors associated with pain coping behavior in PwH:** Social withdrawal: general hypochondria ($r=0.27$, $p=0.031$) and irritability ($r=0.28$, $p=0.028$) Lower affective inhibition: emotional expression ($r=-0.38$, $p=0.002$) and social support ($r=-0.52$, $p=0.001$)	
Combination validated and non-validated questionnaires						
Elander et al. (2003)[35] **United Kingdom**	Cross-sectional	68 PwH (average age: 41, SD 14)	**Type of Haemophilia:** A (91%) and B (9%) **Severity:** Severe (100%) **Treatment:** Not described	**Non-pharmacological pain coping: (cognitive-emotional strategies):** Hemophilia-adapted CSQ **Intake of pain medication:** Open questions	**Intake of pain medication:** Over-the-counter analgesics (53%) > prescribed analgesics (34%) > illicit drugs (21%) > alcohol (13%) Concerns about drug use: 38% **Factors associated with pain coping behavior in PwH:** Negative thoughts~: lower income ($r=-0.32$, $p\leq0.05$) Passive adherence~: receiving income related benefits ($r=0.36$, $p\leq0.01$) and visits to health care professionals ($r=0.37$, $p\leq0.01$) Intake of prescribed analgesics~: not being employed ($r=-0.44$, $p\leq0.001$), lower income ($r=-0.34$, $p\leq0.01$), income related benefits ($r=0.39$, $p\leq0.001$), visits to health care professionals ($r=0.29$, $p\leq0.05$) Concerns about intake pain medication~: negative thoughts ($r=0.35$, $p\leq0.01$) and passive adherence ($r=0.36$, $p\leq0.01$) Bleeding pain frequency predicts intake of over-the-counter analgesics ($p<0.05$)	
Non-validated questionnaires						
Du Treil et al. (2007)[38] **USA**	Cross-sectional	28 male PwH (age: ≥18 years)	**Type of Haemophilia:** A and B **Severity:** Not described **Treatment:** Prophylaxis/ Immune tolerance (64%) On demand (36%)	**Adherence to prophylactic treatment:** Subject's infusion logs	**Adherence to prophylactic treatment:** PwH: 43% moderate > 39% high > 18% low On-demand/Immune tolerance > Prophylaxis ($p=0.018$)	

Table 4. Continued.

Author and country	Study design	Sample size	Characteristics of participants	Applied questionnaires	Pain coping behavior strategies and associated factors	Remarks
Non-validated questionnaires						
Witkop et al. (2012)[34] **USA**	Cross-sectional	764 PwH (3% female, average age: 42.15, 18-84 years)	**Type of Haemophilia:** A and B **Severity:** Severe (70%) Moderate – Mild- Not known (30%) **Treatment:** Not described	**Non-pharmacological pain coping: (cognitive-emotional and behavioral strategies):** Comprehensive list **Intake of pain medication:** Comprehensive list	**Pain coping behavior in PwH:** RICE method: preferred in both acute and persistent pain Alcohol: acute pain (13%) < persistent pain (15%) Additional clotting factors: acute pain (84%) > persistent pain (58%) Illicit drugs: acute pain (8%) = persistent pain (8%) **Intake of pain medication (% acute pain/persistent pain):** Short-acting opioids (55/48) > acetaminophen (53/46) > NSAIDs (36) > long-acting opioids (21/24) > non-opioid medications (7/1)	

Abbreviations: PwH: People with Haemophilia; SD: standard deviation; y: years; HR-QoL: Health-Related Quality of Life; SCD: Sickle Cell Disease; CLBP: Chronic Low Back Pain; CISS-21: Coping Inventory for Stressful Situations; CG: control group; r: Pearson correlation coefficient; CSQ: Coping Strategy Questionnaire; HPCQ: Hemophilia Pain Coping Questionnaire; CPAQ: Chronic Pain Acceptance Questionnaire; ~: associated with; MHPQ: Multidimensional Haemophilia Pain Questionnaire; CSI: Coping Strategy Index; IBQ: Illness Behavior Questionnaire; VERITAS-Pro: Validated Hemophilia Regiment Treatment Adherence Scale – Prophylaxis; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

PwH were evaluated by use of validated and non-validated questionnaires. Validated questionnaires were the Haemophilia Pain Coping questionnaire (HPCQ)[30, 37], the Coping Inventory for Stressful Situations (CISS-21)[36], the Chronic Pain Acceptance questionnaire (CPAQ)[30, 37], the Coping Strategy Index (CSI)[33], the Illness Behavior Questionnaire (IBQ)[33], the Multidimensional Haemophilia Pain Questionnaire (MHPQ)[6] and the Haemophilia-adapted Coping Strategy questionnaire (CSQ).[32, 35, 37] Non-validated questionnaires included open questions regarding pain coping behavior[35] and a comprehensive list of choices of treatment modalities.[34]

Intake of pain medication and adherence to prophylactic treatment was investigated by determining how subject's infusion logs matched with the doctor's recommendation[38], 2 items of the Haemophilia-adapted (CSQ)[37], 1 dimension of the MHPQ[6] and the Validated Hemophilia Regiment Treatment Adherence Scale - Prophylaxis (VERITAS-Pro).[29, 31] The included studies showed a wide heterogeneity in participants and applied questionnaires. An overview of all pain coping behavior strategies and their level of conclusion are summarized in Table 5. Overall, there is only preliminary conclusion.

Synthesis of results

Validated questionnaires

Pain coping behavior in PwH

The CSI and IBQ showed that PwH (n=63) tend to use both cognitive-emotional and behavioral coping strategies to change the situation, not neglecting their emotional state of environment.[33] Despite the fact that PwH suffered from pain, they perceived good control of their disease.[33] PwH on prophylactic treatment showed more maladaptive coping strategies such as self-criticism, social withdrawals and less wishful thinking, less perception of control and hypochondrial behavior.[33] Patients having moderate haemophilia showed more problem avoidance than PwH having the mild/severe form.[33] Pinto et al.[6](n=104) found that PwH preferred the use of ice, rest, factor replacement, pain medication and elevation as pain coping strategies. In which factor replacement had the greatest pain reduction effect, followed by pain medication.[6]

One study including subjects with mild, moderate and severe haemophilia (n=209) compared their results with a previous sample of only severe PwH and found that the sample of PwH of any disease severity showed more active coping and passive

Table 5. Overview of conclusion regarding pain coping behavior strategies, their related studies and Risk of bias.

Pain coping behavior strategies	Results for PwH	Level of evidence	Risk of bias	Level of conclusion	References
Validated questionnaires					
Non-pharmacological coping: (cognitive-emotional and behavioral strategies)	Task oriented coping: PwH = CG	B	High	Preliminary	(36)
	Emotion-oriented coping: PwH < CG	B	High		(36)
	- Pain acceptance: PwH > CLBP	B	High		(37)
	- Praying and hoping: PwH < SCD & CLBP	B	High		(37)
	Emotion-oriented coping~: Poor psychological health, less participation, less social interaction	B	High		(36)
	Avoidance coping: PwH < CG	B	High		(36)
	Negative thoughts about pain~: Beliefs pain being controlled by chance happenings, lower annual income, concerns about intake pain medication	C	Moderate		(32, 35)
	Lower mental QoL, pain acceptance, activity engagement & pain willingness	C	Low		(30)
	Passive adherence~: Pain being controlled by doctors, visits to health care professionals, use of pain medication, receiving income related benefits	C	Moderate		(32, 35)
	Less pain acceptance, activity engagement & pain willingness	C	Low		(30)
	Top 5 pain coping strategies: ice, rest, factor replacement, pain medication, elevation	C	Low		(6)
Intake of pain medication	~Disease severity, pain intensity	C	Low	Preliminary	(29)
	Strategy providing greatest pain relief: factor replacement > pain medication	C	Low		(6)
Adherence to prophylactic treatment	+60y > 20-59y	C	Low		(29)
	+20y: better in PwH treated in haemophilia care centre	C	Low		(29)
	18-73y: predicted better HR-QoL	C	Low		(31)
Non-validated questionnaires:					
Non-pharmacological coping: (cognitive-emotional and behavioral strategies)	Problem solving: better in married and working PwH	C	Moderate	Preliminary	(33)
	Problem avoidance: more in moderate PwH	C	Moderate		(33)
	Self-criticism, social withdrawal, wishful thinking: PwH using prophylaxis	C	Moderate		(33)
	Alcohol < illicit drugs	C	Moderate		(35)
	Alcohol > illicit drugs	C	Moderate		(34)
	RICE method: PwH with acute and persistent pain	C	Moderate		(34)
Intake of pain medication	Intake of pain medication~: Lower employment, lower income, income-related benefits, visits to health care professionals	C	Moderate	Preliminary	(35)
	Use of additional clotting factors: Acute pain > Persistent pain	C	Moderate		(34)
	Intake of pain medication: mostly short-acting opiods, acetaminophen and NSAIDs: acute and persistent pain	C	Moderate		(34)
Adherence to prophylactic treatment	Over-the-counter > Prescribed analgesics	C	Moderate		(35)
	On-demand > Prophylaxis	C	High		(38)

Abbreviations: PwH: People with Haemophilia; CG: control group; y: years; ~: associated with; HR-QoL: Health-Related Quality of Life; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; SCD: Sickle Cell Disease; CLBP: Chronic Low Back Pain.

adherence, but less negative thoughts about pain.[37] Two studies with high[36, 37] risk of bias compared PwH's pain coping behavior with other populations by use of the CISS-21[36], HPCQ and CPAQ[37]. Binnema et al.[36] (n=86) found PwH to use task-oriented coping as frequently as healthy controls, but significantly less emotion-oriented and avoidance coping. The CPAQ[37] showed better pain acceptance and less praying and hoping (emotion-oriented coping) in PwH (n=209), in comparison with CLBP and sickle cell disease.

Factors associated with pain coping behavior in PwH

Two studies (n=61)[32] and (n=68)[30] with moderate risk of bias used the Haemophilia-adapted CSQ and one study (n=101)[30] with low risk of bias used the HPCQ and CPAQ to investigate factors associated with pain coping behavior in PwH. They found negative thoughts about pain to be associated with beliefs about pain being controlled by chance[32], a lower annual income[32, 35], lower mental QoL[30], lower pain acceptance[30], more passive adherence[30] and concerns about pain medication.[32, 35] Passive adherence seemed associated with lower pain acceptance[30], lower activity engagement and pain willingness[30], more visits to healthcare institutions[32, 35], higher use of pain medication[32], more beliefs about pain being controlled by doctors[32] and dependence of income related benefits (passive coping).[32, 35] Emotion-oriented pain coping in PwH (n=86) was strongly associated with poor psychosocial health and weakly associated with less participation in daily life (autonomy indoor/outdoor, family role, social relations, etc.) and lack of social interaction.[36] Being married and employed increased the use of problem solving in PwH (n=63).[33]

Adherence to prophylactic treatment predicted better HR-QoL in PwH (n=82).[31] PwH ≥20 years old treated in haemophilia care centers (n=192) showed better adherence to prophylactic treatment.[29] Clotting factors consumption positively intercorrelated with haemophilia severity and pain intensity (n=209).[37] The VERITAS-Pro showed better adherence in PwH ≥60 years than PwH between 20-59 years, with a significant positive correlation between increasing age and VERITAS-Pro score up to 59 years.[29]

Non-validated questionnaires

Pain coping behavior in PwH

Two studies used a comprehensive list or open questions[35] and found PwH (n=68)[35] and (n=764)[34] to use alcohol[34, 35], smoking[35] and illicit drugs[34, 35] as pain coping strategies. Conflicting results regarding the ratio between alcohol and illicit drugs were reported. One study assumed that illicit drugs were more used than alcohol[35], while another study found the opposite ratio.[34]

Witkop et al.[34] found along with factor replacement, RICE method to be used in the majority of patients (n=764), both suffering from acute and persistent pain.

Three studies reported PwH's intake of medication by use of their infusion logs[38] (n=28), open questions[35] (n=68) and comprehensive list of pharmacological pain coping strategies (n=764).[34] Pain medication such as short-acting opioids, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) were most used in both acute and persistent pain.[34] PwH tend faster to over-the-counter analgesics instead of prescribed analgesics.[35] Dominantly PwH with acute pain (associated with a bleeding episode) used additional clotting factor concentrates, but it was also used to control persistent pain (pain that lasted >6 months and did not resolve with current available treatment).[34]

Factors associated with pain coping behavior in PwH

A higher use of pain medication in PwH (n=68) seemed associated with not being employed, a lower income, less income-related benefits, a higher pain frequency and more visits to healthcare.[35] PwH receiving On-Demand treatment (n=28) showed better treatment adherence than those on prophylaxis or immune tolerance.[38]

Discussion

Summary of main findings

The aim of the current systematic review was to identify the range of pain coping behavior strategies used among PwH and the factors associated with pain coping behavior. This in order to obtain an inventory of non-pharmacological strategies (i.e. cognitive-emotional and behavioral) and pharmacological strategies (i.e. intake of pain medication or additional clotting factors in response to pain and adherence to prophylactic treatment to prevent bleedings and control pain). The included studies describe a heterogenous sample of PwH, containing a wide variation in age, different types of disease severity and treatment regimen. In addition, studies had considerable risk of bias and reported heterogenous quality of questionnaires to assess pain coping behavior. Therefore it is difficult to draw general conclusions.

Pain coping behavior in PwH

Only preliminary conclusions could be drawn regarding non-pharmacological pain coping strategies used in PwH. Elander et al.[37] found in a large sample of PwH that PwH used less praying and hoping, but more adaptive pain acceptance in comparison with patients with CLBP and sickle cell disease. This might be explained by the fact that PwH have a more clear physiological basis for pain, initiated by measurable joint bleeds, which is often not the case in other chronic musculoskeletal conditions such as CLBP. In comparison to healthy controls, PwH seemed to predominantly use task-oriented coping, but significantly less emotion-oriented and avoidance coping.[36]

An increased use of emotion-oriented coping was shown in PwH with poor psychological health, lack of social interaction and less participation in daily life.[36] This is in concordance with previous research stating that patients tend to use more emotion-oriented coping in chronic diseases with less controllability.[39] The fact that two studies found that PwH preferred task-oriented coping seems positive, as the disease is indeed controllable with prophylactic therapy to prevent bleeding and control pain[3, 24, 25] and that self-treatment in case of a bleed is made possible.[33, 36] Nonetheless, both studies describe a rather small sample size and moderate[29] and high[32] risk of bias, so we need to interpret results with caution. It was observed that PwH with good illness behavior use better emotional expression and social support, whereas patients with more irritable and hypochondriac behavior showed more maladaptive social withdrawal.[33] Therefore, it can be beneficial that health care workers promote and support adequate coping strategies and identify PwH at risk.[36]

The preliminary findings of intake of pain medication indicate that PwH tend faster to over-the-counter analgesics instead of prescribed analgesics.[35]

More than one-third of PwH expressed concerns about their intake of pain medication, which indicates the importance of addressing patient's concerns about pain medication as well.[35] However, given the small number of participants, further research is needed to confirm these findings.

Non-pharmacological strategies in PwH showed conflicting results concerning the ratio of alcohol versus illicit drug use, which might be explained by the difference in sample size (68 PwH[35] and 764 PwH[34]) and the fact that self-reports may not have been completely truthful.[40] One study investigated smoking behavior in a context of pain coping strategies.[35] As previous literature showed increased smoking behavior in adults with chronic pain[41], future research and haemophilia care should take this behavior into account. Furthermore, along with clotting factors, RICE method was identified as the most frequently applied pain coping strategy used in large samples of PwH both suffering from acute and persistent pain.[6, 34]

Factors associated with pain coping behavior in PwH

Negative thoughts about pain seemed associated with beliefs about pain being controlled by chance happenings[32], lower annual income[32, 35], lower mental QoL[30], lower pain acceptance[30], more concerns about medication[32], lower activity engagement and pain willingness[37]. In contrast, passive adherence was associated with receiving more benefits[32], more visits to health care professionals[32], higher use of pain medication[32], beliefs about pain being controlled by powerful doctors[32] and lower activity engagement and pain willingness[30, 37] .

Other key aspects favouring adaptive coping strategies such as problem solving, seemed being married and employed[33], which is confirmed by the study of Brodin et

al.[42], where better adapted patients still work despite their difficulties. Also disease severity showed that PwH with moderate/mild forms used poorer coping strategies, like problem-avoidance[33] than severe PwH, due to the lack of experiencing symptoms.[43, 44] In contrast to other studies claiming early prophylactic treatment to improve HR-QoL[31, 45, 46], one study with moderate risk of bias showed PwH on prophylactic treatment to use more maladaptive coping strategies as self-criticism, social withdrawal and wishful thinking.[33] However, given the moderate[32, 33, 35] and high[37] risk of bias, we need to interpret these results with caution. So, based on the present study designs it is not possible to draw general conclusions and establish the direction of causation, therefore longitudinal analysis are needed. Nevertheless, whichever direction, these preliminary findings support the importance of promoting employment, education and improving socio-economic circumstances as a part of comprehensive haemophilia care.[35, 37]

Miesbach et al.[29] a study with low risk of bias, found poorer adherence to treatment with increasing age, which is in accordance to other studies utilizing the VERITAS-Pro.[47, 48]

High intensity treatment regimens were more used than On-Demand therapy, which might explain the lower adherence. But these results need to be interpreted carefully as they are based on non-validated patients' infusion logs and a sample of 47 PwH[38] in comparison to 192 PwH.[29]

Previous findings show that people who adhere better to their prophylactic treatment have a significantly decreased risk to experience bleeds and significantly decreased risk to suffer from pain.[3, 24, 25] Based on these results, we see the importance of considering adherence to treatment as an important (preventive) pain coping strategy. Therefore, we should emphasize the importance of adherence to prophylaxis in relation to the reduced risk of bleeding but also the prevention of pain.

Strengths and limitations

The present study has some limitations. First, only eleven articles were identified for this systematic review. As clinical pain experience, especially pain coping behavior, is still a quite new topic in haemophilia research, it was frequently added as a sub-analysis instead of a main research goal. Therefore, further research is needed to gain more insight into pain coping behavior in this specific population in order to evolve towards appropriate pain management.

Second, the risk of bias of the included studies strongly varied, but since they were designed as cross-sectional and comparative studies they were all situated in the lower part of the pyramid of evidence.[49] Third, it was difficult to compare results, due to the wide heterogeneity of study participants, heterogenous data collection methods of the included studies, divergent outcome measures and use of non-validated or non-haemophilia specific questionnaires. Therefore, it is advisable for future studies

to standardize the assessment of pain coping behavior in PwH to improve the generalizability.

This systematic review also has some strengths. To our knowledge, this is the first systematic review collecting the range of pain coping behavior strategies and associated factors used among PwH. Additionally, a comprehensive combination of MeSH-terms, key words and synonyms was used to ensure the inclusion of all available evidence. Moreover, reference lists of included articles were hand searched for additional studies. Finally, screening and risk of bias analysis were performed by independent and blinded reviewers to objectively determine inclusion of the studies.

Recommendations for further research

Based on the results of the present review, a certain literature gap regarding the evaluation of PwH's pain coping behavior became visible. Therefore, recommendations for further research are given to improve the study of pain in these patients. First, the terminology of pain coping behavior is still quite grey, open to interpretation, so a standard definition of pain coping behavior and a list of strategies that fall under this heading is needed. In nine included articles pain coping behavior strategies were evaluated by self-reported questionnaires in a cross-sectional study design.[6, 29-35, 38] However, literature states that cross-sectional studies have not the appropriate design to detect variations in pain coping behavior over time, whereas longitudinal studies do have this ability.[50] Therefore, longitudinal studies are needed to investigate pain coping behavior in PwH, taking into account haemophilia-specific clinical covariables and adherence to prophylactic treatment, to see how one factor might influence the others. In the present review, some studies examined the effects of demographic variables like: age, income[32, 35], marital status[33] and clinical variables such as: treatment modality[33, 38], disease severity[33], acute/persistent pain.[34]

Second, the inventory of pain coping behavior strategies was mainly based on non-validated or non-haemophilia specific questionnaires. So, it is recommended to use haemophilia-specific questionnaires that underwent a psychometric evaluation. It also seems necessary to investigate the effectiveness of the current management of pain guidelines as section of the World Federation of Hemophilia (WFH) Guidelines for the Management of Haemophilia, the role of multidisciplinary care (e.g. physiotherapy) and their effect on pain coping and pain reduction. This in order to move towards the development of haemophilia-specific pain management guidelines, including a pain coping behavior approach. Further research taking these recommendations into account is needed.

Conclusion

Literature describing pain coping behavior strategies and associated factors in PwH is still scarce and results provide inconclusive messages due to heterogenous study samples, divergent outcome measures, considerable risk of bias and the use of non-validated or non-haemophilia specific questionnaires. Therefore, no general conclusions can be drawn. Validated haemophilia-specific instruments are warranted to inventory pain coping behavior in a standardized way in order to move towards appropriate pain management.

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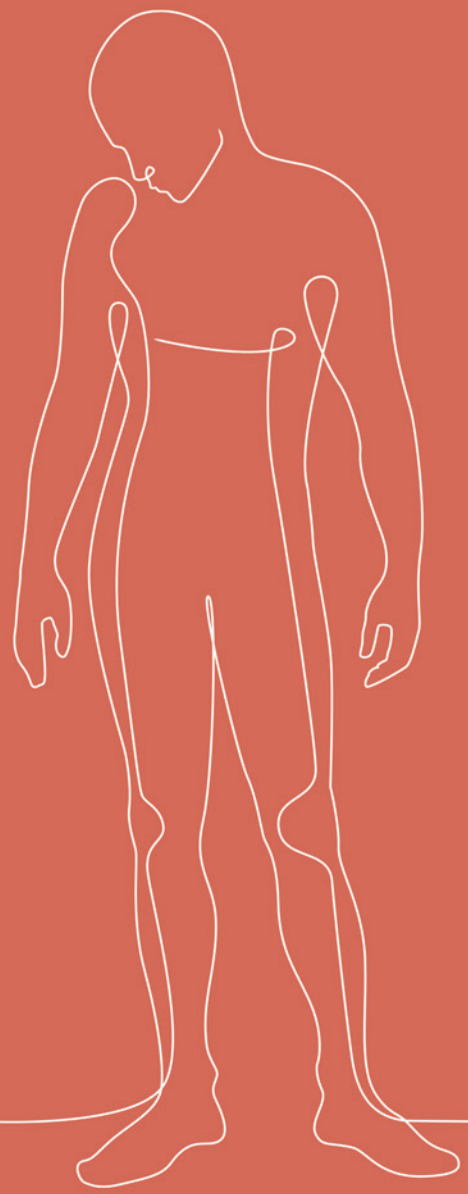
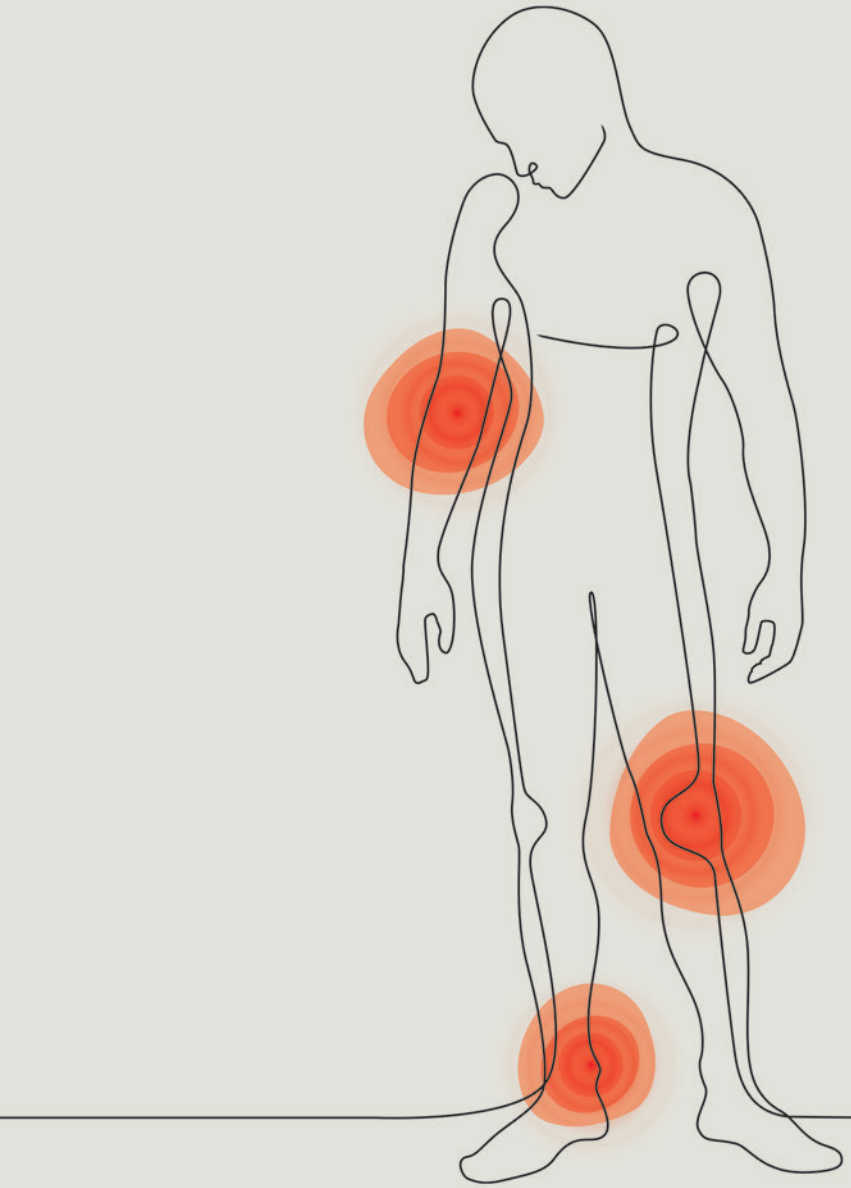


Part 2

LONGITUDINAL INVESTIGATION OF PAIN
IN PEOPLE WITH (SUB)ACUTE LOW BACK PAIN



Chapter 2

Associations between psychological factors, pressure pain thresholds and conditioned pain modulation and disability in (sub)acute low back pain: a three-month follow-up study

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Abstract

Background: The clinical presentation and pain experience of patients with (sub)acute low back pain ((S)ALBP) can strongly vary in clinical practice. However, despite growing evidence that psychological factors are associated with disability in chronic pain conditions including low back pain, studies examining the influence of psychological factors, quantitative sensory testing (QST) (i.e. pressure pain thresholds (PPTs)) and conditioned pain modulation (CPM) on future disability are still lacking in (S)ALBP.

Objective: This prospective cohort study aims to determine associations between baseline psychological factors, PPTs and CPM in (S)ALBP and disability after three months.

Methods: Fifty-two patients with (S)ALBP underwent a baseline PPTs evaluation at rest and during a CPM protocol. Patients were asked to fill in self-report questionnaires: the Visual Analogue Scale (VAS), the Quebec Back Pain Disability Scale (QBPDS), the Pain Catastrophizing Scale (PCS), the Tampa Scale for Kinesiophobia (TSK) and the Illness Perception Questionnaire – Brief version (IPQ-B). At three months follow-up, participants were asked to fill in the QBPDS again. Multiple linear regression analysis was conducted to determine associations between baseline factors and disability at follow-up.

Results: Thirty-eight patients participated at follow-up. Because of the multicollinearity issue, the TSK score was selected for analyses and the PCS and IPQ-B score were excluded from the model. No significant associations between baseline factors and disability at follow-up were found.

Conclusion: Neither baseline psychological factors, nor PPTs or CPM in (S)ALBP were significantly associated with disability after three months. Our multiple linear regression analysis was likely underpowered to detect significant associations.

Introduction

Low back pain (LBP) is one of the most common musculoskeletal disorders, representing a major health problem and an economic burden to society, as the course of LBP is characterized by a recurring pattern of complaints.[1, 2] Despite the magnitude of the problem of LBP, little is known about the precise causes. Degenerative processes and/or impairments in body structures of the lumbar vertebral column and musculoskeletal structures related to sustained postures and movement are regularly seen on medical imaging, but these impairments do not explain the symptoms in all patients with LBP, as they are observed in healthy individuals as well.[3] A cognitive-behavioral framework highlighted the importance of maladaptive interpretations of bodily sensations and the patient's expectations.[4, 5] Therefore, a pure biomedical diagnosis cannot be given for the majority of patients with LBP and a more biopsychosocial approach, taking into account beliefs about pain and illness perceptions, is needed.[6]

Besides the contribution of physical and psychological factors, also pain mechanisms such as an impaired endogenous pain inhibition or central sensitization (CS) might explain the variance in pain and symptoms.[7] Increased responses of the central nervous system to somatosensory input ('CS') has been found to underlie (chronic) pain in patients with a variety of unexplained disorders, including LBP.[8] For example, prolonged or strong activity in the dorsal horn neurons, caused by repeated (peripheral) noxious stimulation, may lead to increased neuronal responsiveness and CS.[9] Quantitative sensory testing (QST) is used to study these sensory function alterations.[10] Several mechanisms, comprising changes in descending and ascending central modulatory mechanisms may be responsible for this altered nociception. Malfunctioning of these inhibitory descending pathways can be assessed by conditioned pain modulation (CPM).[11] CPM is also called the "pain inhibits pain phenomenon" in which the inhibition of a nociceptive stimulus is measured when it is interrupted by a secondary conditioning stimulus.[11] Several reviews revealed growing evidence for CS and altered endogenous pain inhibition, including alterations in both brain structure and brain function at least in a subgroup of patients with chronic non-specific LBP.[12, 13]

However, it still remains unclear why CS is only present in a subgroup of patients with chronic non-specific LBP and studies investigating pain mechanisms in patients with (S)ALBP in clinical settings are extremely limited. Until now, only a few studies have tested whether variations in QST and CPM exist in the acute phase of LBP, but the majority of studies have a cross-sectional design or use samples of patients with chronic LBP.[14]

Since it is suggested that alterations in pain mechanisms are important determinants in the transition from acute to chronic LBP[15], longitudinal prospective studies are

needed to explain the influence of QST and CPM on the chronification of pain. In this way, it will be possible to investigate how prognostic factors work together or influence each other.[16]

Also psychological factors have been reported to influence the clinical pain experience and outcomes in primary care settings.[17] Studies revealed that maladaptive psychological factors such as fear and stress are known to rather facilitate than inhibit pain, this because these factors change the sensitivity of the central nervous system to a state of 'cognitive emotional sensitization'.[18, 19] A systematic review reported that fear avoidance, depression and catastrophizing (an excessively negative orientation towards pain) were even predictive for the transition from acute to chronic LBP.[20] Moreover, findings of a more recent systematic review suggest an association between psychological factors such as kinesiophobia (fear of movement), catastrophizing and self-efficacy and pain and disability outcomes in patients with chronic LBP treated by physiotherapists.[21] However, further studies are needed to confirm the effectiveness of physiotherapy. Again, the bulk of literature mainly exists of studies describing experiments investigating patients with chronic LBP, not specifically focusing on a (S) ALBP population. Prospective studies examining both psychological factors, QST and CPM in patients with (S)ALBP in relation to clinical prognosis are lacking to allow statements about associations. We hypothesize that patients with (S)ALBP presenting signs of CS, impaired efficacy of endogenous pain inhibition and maladaptive psychological factors will have worse outcomes. By unraveling associations, it might be possible to move towards better outcomes, by use of tailored treatment interventions taking pain mechanisms and psychological factors into account.

Therefore, the purpose of the present prospective study was to determine associations between psychological factors, QST (i.e. pressure pain thresholds (PPTs)) and CPM in (S)ALBP seen at baseline and disability after three months follow-up.

Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines for reporting observational studies were used in the present study.[22]

Study design & setting

This study is a prospective cohort study. Patients with (S)ALBP were recruited in private clinical practices and outpatient rehabilitation settings in Flanders (Belgium) and in the Netherlands. Before study participation, all participants received written and verbal

information about the procedure. Baseline assessment included pressure algometry with and without a conditioned pain modulation test at several segmental and widespread locations by one of three researchers during individual appointments at the beginning of care. Next, patients were asked to fill in five questionnaires. Depending on their complaints, participants received routine physiotherapy in the weeks after their baseline assessment. The researcher conducting the assessment was not involved in the participant's process of care. Participants were contacted per e-mail and by phone for the follow-up measurement, three months following the baseline assessment to fill in two questionnaires: Quebec Back Pain Disability Scale (QBPDS) and Visual analogue scale (VAS) which they received by e-mail. The Medical Ethics Committee of the University Hospital (UZ Brussel, Brussels Belgium) approved the study protocol and all participants provided written informed consent prior to study participation.

Participants

Fifty-two participants with non-specific (S)ALBP volunteered for the study. Inclusion criteria were an age between 18 and 65 years and a new episode of LBP, lasting between 2-12 weeks. Participants with recurrent LBP had to be pain free for at least one month preceding the current episode of pain and were not allowed to have had any treatment during the last three months.[23] In order to determine improvement or impairment in disability after three months follow-up, patients with a baseline Quebec Back Pain Disability Scale (QBPDS) score less than 20/100 were excluded, a QBPDS score of '0' indicates 'no disability' and scores from '0-20' indicate 'minimal disability'.[24] Patients were excluded if they had undergone surgery during the past two years, had any serious physical trauma within the past six months, suffered from specific LBP (e.g. LBP with motor or sensory loss due to radicular involvement) or from other musculoskeletal pain syndromes. Patients with comorbidities, such as or central neurologic diseases (Parkinson, Multiple Sclerosis, etc.) or chronic pain syndromes (Fibromyalgia, Chronic Fatigue Syndrome, Irritable Bowel Syndrome, Rheumatoid Arthritis, etc.) were excluded as well.

Baseline assessment

Clinical pain assessment

Pressure pain thresholds (PPTs) were measured with an analogue Fisher algometer (Force Dial model FDK 40 Push Pull Force Gage, Wagner Instruments, Greenwich CT, USA) at 12 locations on the body (Figure 1A). The order of PPTs testing was standardized: (1,2) the paraspinal muscles of C6, (3,4) the paraspinal muscles of L3, (5,6) the paraspinal muscles of L5, (7,8) the muscle belly of the deltoid muscles, (9,10) the middle phalanx of the index fingers and (11,12) the muscle belly of the medial calf muscles. These sites were chosen based on previous research in order to test PPTs on both specific locations at the trunk and non-specific locations on the extremities.[25, 26]

The force was gradually increased at a rate of 1 kg/s by silently counting seconds. PPT was defined as the point at which the patient reported a score of 3 out of 10 on a Numeric Rating Score (NRS).[27] The threshold was determined as the mean of the two last values out of three consecutive (10s in between) measurements, since this procedure has found to be reliable in healthy individuals[28] and efficient in the exploration of physio-pathological mechanisms involved in pain.[29] As patients were assessed by one of three researchers, the inter-observer reliability of PPT assessment was examined.

CPM was used to test the paradigm of heterotopic noxious conditioning stimulation to assess endogenous pain inhibition and has been described elsewhere.[30] In brief, participants sat quietly for three minutes after the completion of the PPT assessment at rest and were then asked to lay down in prone position again. The conditioning stimulus for eliciting CPM was an occlusion cuff (Heine Optotechniek GmbH & Co. KG, Germany) strapped on the left upper arm with the lower edge three cm proximal of the cubital fossa (Figure 1B). The cuff was inflated at approximately 20 mmHg/s until participants reported a NRS score of 3 out of 10. Participants adapted to the stimulus for 30s, at which point the inflation was maintained while the pressure algometry was performed three times again at three locations (the paraspinal muscle of L5 vertebra on both sides and the muscle belly of the deltoid muscle on the heterolateral side of the occlusion cuff) with a time-interval of 10s. Bias was avoided by standardizing the verbal information.

Self-report measures

Pain was measured with a VAS, ranging from 0 (no pain) to 100 mm (worst imaginable pain) to assess current pain intensity (min/max in last 24 hours and current intensity during answering questionnaire), and the QBPDS was used to evaluate **disability** in patients with (S)ALBP, ranging from 0 (no limitation) to 100 (totally limited). High levels of reliability and validity have been described for these questionnaires.[31, 32] In addition, the following questionnaires were used to assess **psychological factors**. The Tampa Scale for Kinesiophobia (TSK) a 17 item questionnaire with a total score ranging from 17 to 68, indicating a high degree of kinesiophobia when the cut-off score of 37 is reached.[33] The Pain Catastrophizing Scale (PCS) scores catastrophizing thoughts on a scale from 0 – 52. Scores above 24 indicate patients as catastrophizers, those with a score below 15 as non-catastrophizers.[34] The Illness Perception Questionnaire – Brief version (IPQ-B) was used to assess cognitive and emotional perceptions of illness. The clinimetric properties of these questionnaires have been well-established in patients with LBP.[35, 36]

The follow-up QBPDS questionnaire was sent by mail to the participants three months after the baseline assessment. Non-responders were first reminded by phone, and if necessary by mail. The non-responding participants were contacted at least

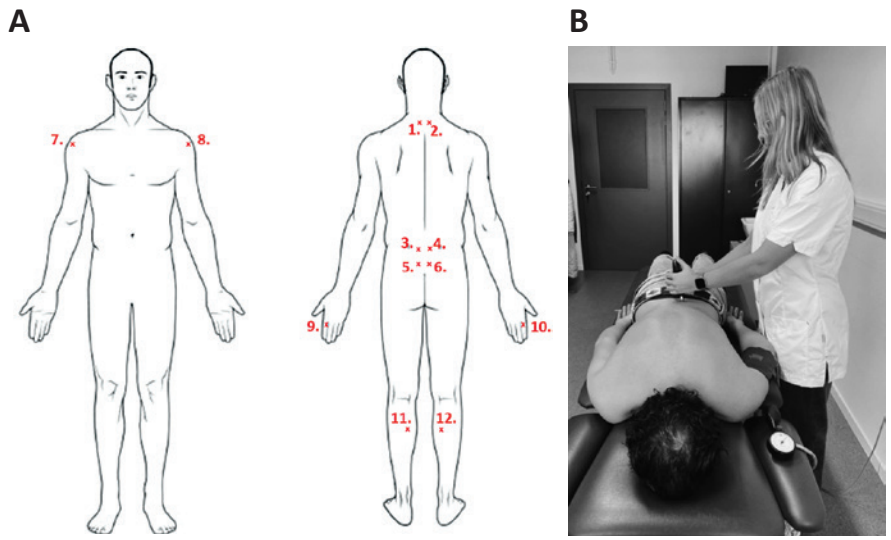

Figure 1. (A) Body chart of PPT regions: (1,2) the paraspinal muscles of C6, (3,4) the paraspinal muscles of L3, (5,6) the paraspinal muscles of L5, (7,8) the muscle belly of the deltoid muscles, (9,10) the middle phalanx of the index fingers and (11,12) the muscle belly of the medial calf muscles. A random sequence was used. (B) Experimental setup for the CPM paradigm. The participant lay down in prone position. An occlusion cuff was strapped on the left upper arm. While the inflation of the cuff was maintained pressure algometry was performed again at the paraspinal muscles of L5 and the deltoid muscle on the heterolateral side.

three times by e-mail or phone. In case the participant did not respond after three times, the participant was classified as loss to follow-up.

Study size

The number of participants who visited a physiotherapist fort their (S)ALBP within the period of the study and who met the inclusion criteria were included. Accordingly, a total of 52 participants determined the total sample size.

Statistical analysis

All data were analyzed using Statistical Package for the Social Science (SPSS) version 27.0 for Windows (SPSS Inc. Headquarters, 233s. Wacker Drive, 11th Floor, Chicago, Illinois 60606, USA). The baseline scores of TSK, PCS, IPQ-B, PPTs at 12 locations and CPM score were considered as predictor variables. Before regression analysis, baseline characteristics between participants who dropped out and those who remained at follow-up and between participants whose disability improved and those whose

disability did not improve at follow-up were compared by use of Students' t-tests (normally distributed data), Mann-Whitney U tests (skewed data) and Chi-squared tests (categorical data). In preparation for regression modeling, associations between predictor variables were explored using scatterplots and Pearson correlations. In case of correlation coefficients >0.3, only one of the correlated predictor variables was included in order to prevent collinearity. The significance level was set at 0.05.

Results

Procedure

Of the 52 participants who indicated to suffer from (S)ALBP at baseline, 38 people participated in the follow-up assessment three months later. A detailed flowchart diagram of the study procedure is presented in Figure 2.

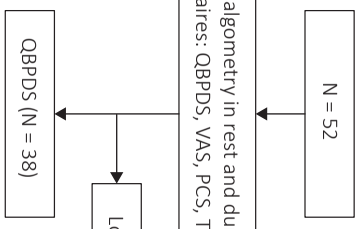

Figure 2. Flowchart of the study procedure.

Baseline characteristics

Baseline characteristics of the 52 participants show a mean age of 41.62 years (SD: 12.27 years), with over 52% being female. At initial contact 1 participant (2%) reported an episode of (S)ALBP with a duration of 2 weeks, 37 (71%) with a duration of <2-6 weeks and 14 (27%) with a duration of <6-12 weeks. The characteristics of the study population and results of the questionnaires are presented in Table 1. Results of QST are presented in Table 2. During CPM patients demonstrated higher mean PPT values in comparison to the pressure algometry at rest (average increase in CPM of 0.84 kg/cm^2, p<.001).

Table 1. Baseline characteristics of the study population.

Variable	Total group (N=52)		Participants completing the whole study (N=38)		Participants who dropped out (N=14)		Comparison p-value
	Mean (range)	SD	Mean (range)	SD	Mean (range)	SD	
Age (years)	41.62 (18-65)	12.27	41.95 (18-65)	12.22	40.71 (20-63)	12.81	0.751[a]
BMI (weight/height^2)	25.39 (18.98-41.52)	4.21	25.49 (18.98-41.52)	4.55	25.10 (19.60-31.46)	3.21	0.901[b]
Sex (% female)	52	-	50	-	57	-	0.647[c]
VAS score	38.15 (13-72.33)	12.73	38.21 (13-72.33)	13.81	38.00 (23-57.33)	9.62	0.958[a]
ΔVAS after 3m follow-up	-	-	-20.43 (-68.67-22.67)	21.35	-	-	-
QBPDS score	36.03 (21-71)	12.40	36.79 (21-71)	12.85	33.96 (21-61)	11.27	0.502[b]
ΔQBPDS after 3m follow-up	-	-	-2.21 (-31-20)	13.27	-	-	-
PCS total score	17.87 (2-43)	8.37	18.74 (4-43)	8.75	15.50 (2-27)	7.00	0.203[b]
PCS Helplessness	6.77 (1-17)	3.78	7.11 (1-17)	3.92	5.86 (1-12)	3.30	0.271[b]
PCS Magnification	3.21 (0-11)	2.47	3.47 (0-11)	2.63	2.50 (0-6)	1.87	0.278[b]
PCS Rumination	7.88 (1-15)	3.31	8.16 (1-15)	3.41	7.14 (1-12)	3.01	0.331[a]
Kinesiophobia score (TSK)	36.81 (21-50)	6.63	37.21 (22-50)	6.36	35.71 (21-47)	7.46	0.476[a]
Patients with score ≥ 37 (%)	46	-	47	-	43	-	0.772[c]
IPQ-B score	47.89 (22-72)	11.09	48.30 (22-72)	11.67	46.79 (30-65)	9.66	0.666[a]

[a]p-values of the Students t-test, [b]p-values of the Mann-Whitney U test, [c]p-values of the Chi-squared test from the comparative analysis between participants completing the whole study and participants who dropped out. ***Abbreviations:*** BMI: Body Mass Index; LBP: Low Back pain; Δ: difference between follow-up and baseline measurement; VAS: Visual Analogue Scale; QBPDS: Quebec Back Pain Disability Scale; PCS: Pain Catastrophizing Scale; TSK: Tampa Scale for Kinesiophobia; IPQ-B: Illness Perception Questionnaire Brief Version.

Table 2. Results of QST (PPTs) and CPM at 12 locations of the participants completing the whole study (N=38) in (kg/cm²).

Test locations of PPTs	Mean (range)	SD
Paraspinal muscle of C6 left	3.36 (2.00-6.63)	1.28
Paraspinal muscle of C6 right	3.39 (2.10-7.88)	1.42
Paraspinal muscle of L3 left	6.28 (2.35-14.05)	2.83
Paraspinal muscle of L3 right	6.22 (2.50-13.30)	2.85
Paraspinal muscle of L5 left	6.05 (2.30-13.20)	3.05
Paraspinal muscle of L5 right	6.12 (2.00-13.65)	2.71
Muscle belly of the Deltoid left	3.58 (2.00-7.75)	1.47
Muscle belly of the Deltoid right	3.84 (2.00-11.38)	1.89
Middle phalanx of digit finger left	6.54 (2.88-12.80)	2.29
Middle phalanx of digit finger right	7.08 (3.40-13.45)	2.56
Muscle belly of the medial calf left	4.08 (2.05-9.40)	1.69
Muscle belly of the medial calf right	4.05 (2.00-8.50)	1.61
Total PPTs (at 12 locations)	5.05 (2.43-10.15)	1.88
Test locations of CPM	**Mean (range)**	**SD**
Paraspinal muscle of L5 left (during CPM)	7.13 (2.50-19.45)	3.82
Paraspinal muscle of L5 right (during CPM)	7.15 (2.50-19.65)	3.53
Muscle belly of the Deltoid right (during CPM)	4.28 (2.00-10.63)	1.89
Total PPTs at 3 locations (pre-CPM)	5.34 (2.10-11.75)	2.38
Total PPTs at 3 locations (during CPM)	6.18 (2.50-16.07)	2.94
CPM change score paraspinal muscle of L5 left	1.07 (-1.06-6.35)	1.38
CPM change score paraspinal muscle of L5 right	1.03 (-2.38-6.00)	1.56
CPM change score muscle belly of the Deltoid right	0.44 (-1.50-1.81)	0.81
Total CPM change score (at 3 locations)	0.84 (-0.96-4.57)	1.07
CPM responders	**N**	**%**
Paraspinal muscle of L5 left	28	73.70
Paraspinal muscle of L5 right	28	73.70
Muscle belly of the Deltoid right	25	65

Abbreviations: PPTs: pressure pain thresholds; CPM: conditioned pain modulation.

Associations with disability at three months follow-up

At three months, 38 participants (73%) attended the follow-up assessment. No significant differences were found between the baseline characteristics of the 38 participants who remained and the 14 who dropped out (Table 1). In 16 participants (42%) the

QBPDS score at follow-up improved, while in 22 participants (58%) the score remained the same or worsened compared to the score at baseline. Comparative analysis between these two groups showed no significant differences in pain scores, demographic characteristics and psychological factors at baseline.

Psychological factors significantly correlated with each other, namely the scores of the TSK with the PCS ($r=0.36$, $p<0.05$), the TSK with the IPQ-B ($r=0.32$, $p<0.05$) and the PCS with the IPQ-B ($r=0.58$, $p<0.05$). Because of the multicollinearity issue, only the TSK was selected to represent the psychological factors in the analyses because this questionnaire is very user-friendly and easy to interpret due to only one total score and clear cut-off value. The PCS and IPQ-B scores were excluded from the model. The results of the multiple linear regression analyses are shown in Table 3 and the scatterplots in Appendix 1.

The TSK score at baseline was not significantly associated with the QBPDS score after three months follow up ($p=0.098$). The estimate ($\beta=0.470$) only suggests that patients with the same QBPDS score but a higher TSK score at baseline, meaning a higher level of kinesiophobia, had a higher level of disability after three months follow-up in our sample. Both the mean PPT at 12 locations and the CPM change score at baseline were not significantly associated with the QBPDS score at three months follow-up ($p=0.534$ and $p=0.188$). Although the results are not significant, the estimate ($\beta=-6.25$) suggests that patients with the same QBPDS score but a higher mean PPT score at baseline, had a lower QBPDS score at follow-up. Patients with the same QBPDS score and the same mean PPT score at baseline, but a higher positive CPM change score, had a higher QBPDS score at three months follow-up ($\beta=0.843$).

Table 3. Multiple linear regression analysis for the association between baseline factors and disability after three months follow-up (N=38).

Dependent	Independent	β	SE	P
QBPDS at 3 months follow-up	QBPDS at baseline	0.319	0.137	0.026
	Psychosocial factors (TSK)	0.470	0.276	0.098
	Total PPTs baseline (at 12 locations)	-0.625	0.995	0.534
	Change score in CPM	0.843	0.627	0.188

Abbreviations: QBPDS: Quebec Back Pain Disability Scale; TSK: Tampa Scale for Kinesiophobia; PPTs: pressure pain thresholds; CPM: conditioned pain modulation.*p≤0.05 (two tailed).

Discussion

The results of the present study could not demonstrate significant associations between baseline psychological factors such as kinesiophobia, baseline PPTs and CPM and future disability status in (S)ALBP.

Previous studies in patients with (S)ALBP showed the prospective influence of kinesiophobia and high levels of pain catastrophizing on future disability both in cross-sectional[37, 38] and longitudinal studies.[39-42] As a result, psychological factors such as kinesiophobia[43-45] and catastrophizing[42] were identified as indicators for chronicity. The current study could not show associations between baseline psychological factors and future disability. The estimate of the multiple regression analysis could only suggest that patients presenting a high TSK score at baseline, by means a higher level of kinesiophobia, had a higher score on LBP disability at three months follow-up. The fact that no significant associations were found is probably due to the small sample size, which underpowered the study to detect significant associations. Future longitudinal prospective studies with a sufficient sample size should be performed to confirm previous findings in (S)ALBP.

In the present study, baseline PPTs and CPM did not seem to be significantly associated with future disability in (S)ALBP. In analogy with previous literature, this is not surprising, since no consensus exists regarding the relation between QST and CPM and future disability in patients with LBP.[46]

Generally no significant differences in baseline PPTs are found between patients suffering from acute LBP and healthy controls.[47-49] However, a decrease in PPTs at the back has been reported in cross-sectional studies in (S)ALBP.[50-52] In people with a longer duration of LBP, decreases in PPTs were more often described.[26, 53, 54] Nonetheless, PPTs changes do not occur uniformly in all patients with chronic LPB and pain-related psychological factors seem to have an important influence too.[53-55]

Literature describing changes in CPM efficacy in acute LBP remains sparse. Literature findings reveal no significant differences in CPM efficacy[56], but a significantly faster decline in CPM effect compared to healthy controls.[14] Even in chronic LPB, the results are conflicting, with some studies presenting reduced CPM efficacy[54, 57] while others reporting no difference in CPM efficacy[14, 58] compared to controls.

There is growing evidence suggesting that CPM might be a biomarker of chronic pain and predictor of treatment outcome[52, 59], but if CPM efficacy can be a precursor already in the (sub)-acute phase of LPB remains unclear. Nevertheless, literature

including CPM in LBP is still contradictory, because of the various CPM-protocols and mainly cross-sectional studies with a clinically heterogenous population, potentially due to different pain phenotypes. Therefore, interpreting findings with caution is emphasized as it is difficult to compare results.

Study limitations and further recommendations

The results of the study should be seen in the light of several methodological limitations. Firstly, all participants were recruited in clinical practices, meaning that they were all treated with physiotherapy in primary care. However, we did not control the treatments given to the patients, which may have influenced the course of LBP as well. Secondly, the study had a small sample size and an important loss to follow-up (27%). An a priori sample size calculation might have reduced the risk of the study being underpowered. Although the follow-up responders were demographically comparable to the participants at baseline, attrition bias may exist, by means that only the motivated participants may have participated again.

Besides limitations, this study provides directions for future research. As, current literature regarding CPM is usually focused on chronic LBP, further research would be recommended to investigate the role of CPM efficacy in (S)ALBP. Furthermore, up to now research concerning QST and CPM has been contradictory due to methodological issues. First, differences in conditioned stimulus intensity are described; we used a rather weak stimulus (NRS 3/10) which may explain an absent CPM effect. Second, the power of most studies is either not calculated, or studies are underpowered. Third, literature describing associations between baseline factors and future disability in a (S) ALBP is still relatively new and mainly makes use of a cross-sectional study design. Whereas more longitudinal prospective studies with a sufficient sample size are needed to investigate how prognostic factors work together or influence each other.[16] In this way, a screening procedure for the identification of plausible risk factors could already take place in the earliest possible phase of pain. Fourth, medication use is often not registered. Fifth, inclusion criteria of patients with LBP strongly differ between studies. This heterogeneity may influence study results and may explain the subgroups observed in patients with LBP. So, future longitudinal prospective studies with well-defined inclusion criteria and adequate power are needed to confirm findings and to investigate associations between psychological factors, QST and CPM and future disability. Preferably, the population studied should be in the (sub)-acute phase of LBP.

Clinical relevance

The identification of plausible risk factors in the earliest possible phase of pain, could support the choice for an appropriate intervention. Since, current literature already showed the clinical importance of informing patients presenting psychological factors

that negatively affect future outcomes, it would be possible to decrease the risk of poor recovery and development of chronic LBP in this way.[60]

Conclusion

Although we did not find significant associations between baseline psychological factors, QST (i.e. PPTs) and CPM with disability at three month follow-up, psychological factors such as kinesiophobia might negatively affect future disability in (S)ALBP. Since these psychological factors can threaten a successful treatment outcome and can contribute to chronicity, it is necessary to clinically recognize these already in a (sub)-acute phase. Future longitudinal prospective studies with a larger sample size are needed to confirm these findings and to investigate associations between QST and CPM and disability in (S)ALBP.

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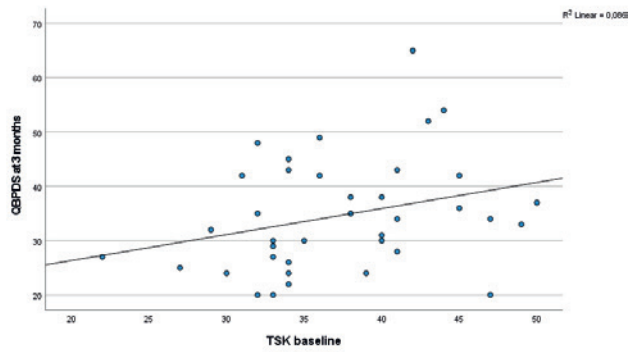
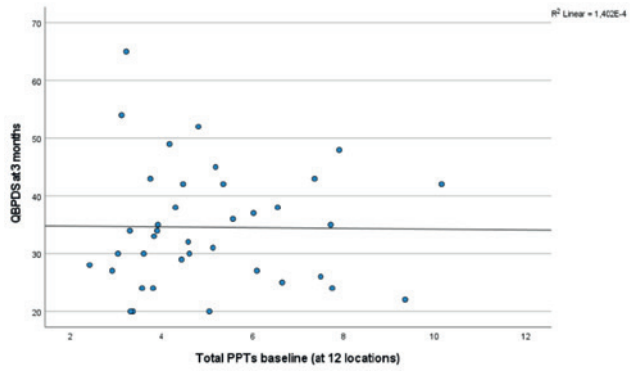
Appendix

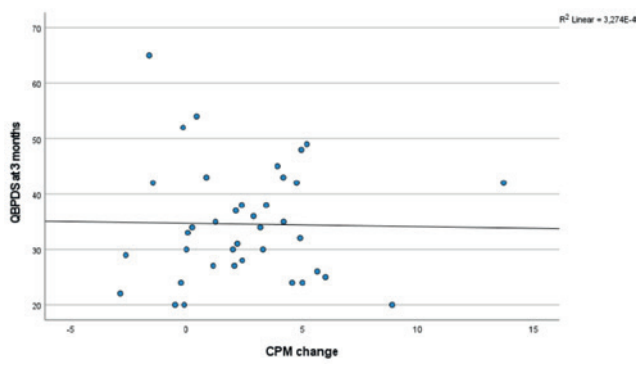
A



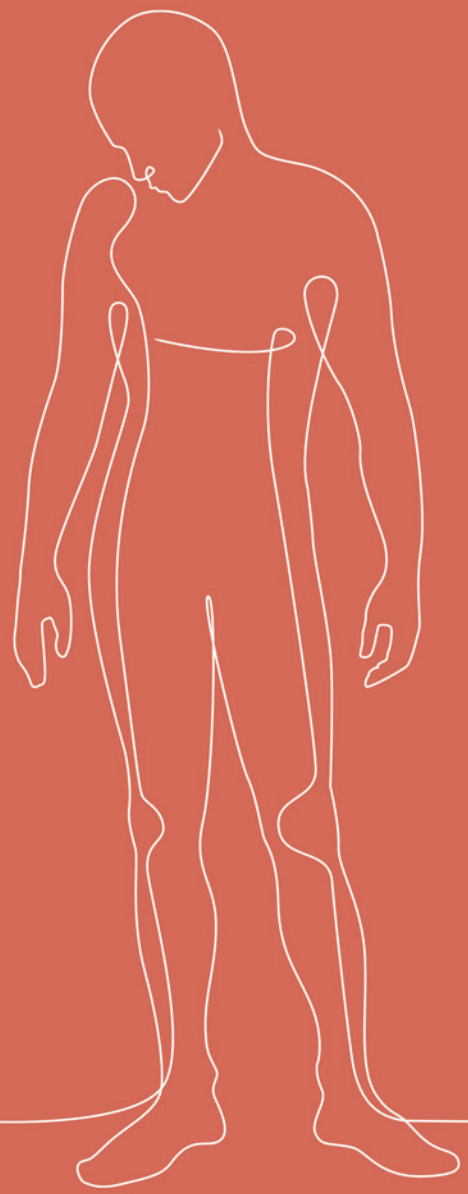
B



C

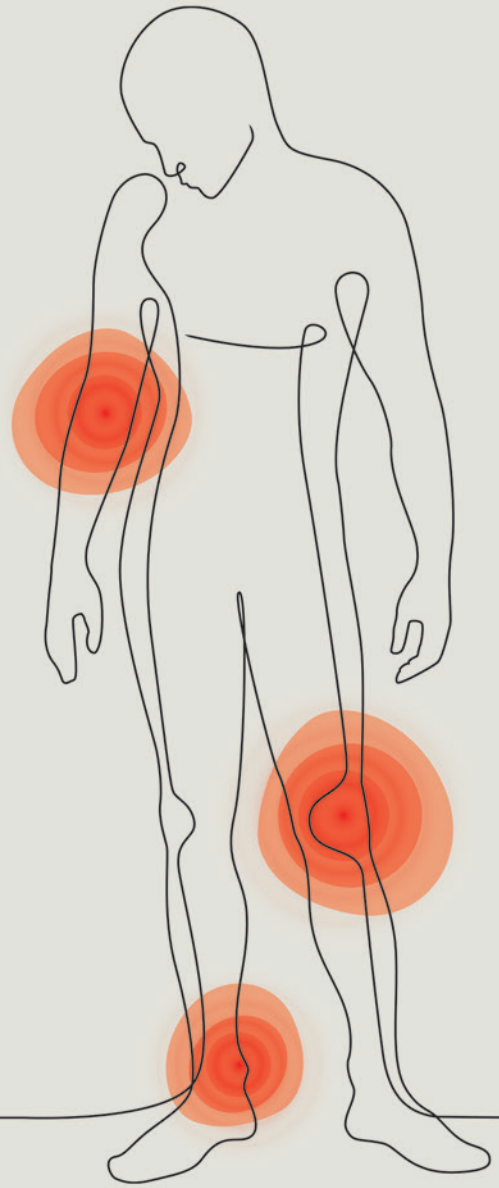


Appendix 1. Scatterplot of (A) the Tampa Scale of Kinesiophobia (TSK) baseline score; (B) the total Pressure Pain Thresholds (PPTs) at 12 locations and (C) the Conditioned Pain Modulation (CPM) change at baseline and the Quebec Back Pain Disability Scale (QBPDS) at 3 months follow-up.



Part 3

LONGITUDINAL INVESTIGATION OF PAIN IN PEOPLE WITH HAEMOPHILIA



Chapter 3

Psychophysical assessment of pain in adults with moderate and severe haemophilia: A cross sectional study

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Abstract

Background: Joint pain is the hallmark of haemophilia, therefore it seems clinically rather a musculoskeletal than a bleeding disorder. Although joint pain in people with haemophilia (PwH) is a complex and multidimensional problem, pain assessment remains primarily focused on the structural evaluation of their joints. Whereas, only few data are available on the potential implication of psychophysical and psychological factors.
Objective: This study aimed to perform a psychophysical pain assessment including quantitative sensory testing (QST) and an evaluation of psychological factors in a large sample of PwH, to get insight into the individuals' pain system.
Methods: Ninety-nine adults (36.9 ± 13.5 years) with moderate/severe haemophilia A/B and 46 healthy controls filled in self-reported pain and psychological questionnaires and underwent a QST evaluation including static and dynamic tests. Static tests focused on the determination of thermal detection and pain thresholds and mechanical pressure pain thresholds. Dynamic tests evaluated pain facilitation and the efficacy of endogenous pain inhibition. Besides comparing PwH and healthy controls, between-subgroup differences were studied in PwH based on their pain distribution.
Results: The study revealed increased thermal and mechanical pain sensitivity and the presence of unhelpful psychological factors such as anxiety/depression in PwH. Among the subgroups, especially PwH with widespread pain showed altered somatosensory functioning. Enhanced pain facilitation and impaired efficacy of endogenous pain inhibition in PwH could not be observed.
Conclusion: Altered somatosensory functioning and unhelpful psychological factors, appear to play an important role in the pathophysiology of pain in PwH, especially in PwH with widespread pain.

Introduction

Recent decades have brought tremendous scientific advances in the treatment of people with haemophilia (PwH), such as the development of prophylactic treatment. Despite this positive evolution which has reduced the number of joint bleedings (haemarthroses) and improved their life expectancy and quality of life, poor joint status still remains the hallmark of haemophilia. Recurrent haemarthroses may lead to progressive destruction of joint cartilage and bone with the final stage being haemophilic arthropathy, characterised by disability and chronic pain.[1]

A German survey in adult PwH revealed that 86% experienced episodes of pain, with joint pain indeed being the most common type of pain (92%).[2] Moreover, 43% of adults with severe haemophilia experienced pain in 3-5 body regions, while 28% reported pain in at least 6 regions, indicating widespread distribution of pain.[3] Despite these high prevalence rates, assessment of pain has received only limited attention in PwH and is often limited to the evaluation of pain intensity.[4]

However, pain is a more complex and multidimensional experience.[5] This was highlighted by studies demonstrating discrepancies between the clinical pain experience and actual structural tissue damage in PwH[6-9], but also in people with chronic joint pain, such as low back pain (LBP)[10] or knee osteoarthritis[11]. Studies emphasized that in case of discrepancy, alterations in peripheral and central pain processing, pain coping strategies and psychological factors might play an important role.[12, 13] Thus, to unravel the complexity of pain and the risk of pain chronification, the evaluation should go beyond the evaluation of the joints.

Psychophysical pain assessment offers the opportunity to create a comprehensive picture of how an individual's pain system functions. Such assessments consists of an evaluation of the functioning of the somatosensory system as well as psychological factors that contribute to it. Quantitative sensory testing (QST) protocols were found to integrate useful methods to assess the functioning of the somatosensory system, such as the determination of detection and pain thresholds for sensory stimuli (i.e. heat, cold or pressure) and methods to assess nociceptive pain facilitation (i.e. temporal summation (TS)) or the efficacy of endogenous pain inhibition (i.e. conditioned pain modulation (CPM)).[14]

Previous studies in PwH showed reduced pressure pain thresholds (PPTs), not only at painful joints but also at remote asymptomatic locations, such as the sternum, indicating altered pain sensitivity.[15] Also indications for reduced efficacy of endogenous pain inhibition were recently observed in PwH[16], which is also commonly

observed in fibromyalgia and osteoarthritis.[17] The latter are populations in which nociplastic pain (pain due to altered nociception and thus altered somatosensory function) is evidenced.[18, 19]

Given these previous findings in relatively small samples[15, 16], we initiated a psychophysical pain assessment in a larger PwH sample, to test the hypothesis for the presence of altered pain sensitivity (i.e. increased pressure and thermal sensitivity), altered pain modulation (i.e. reduced efficacy of endogenous pain inhibition and increased pain facilitation) and the presence of more unhelpful psychological factors such as anxiety and pain catastrophizing in PwH compared to healthy volunteers. Additionally, we wanted to investigate whether these indications were more prevalent in PwH with a widespread pain distribution, since previous studies in non-haemophilia populations highlighted the risk of pain chronification and poor prognosis with widespread pain.[20] Therefore, we conducted a comprehensive psychophysical pain assessment to identify differences in somatosensory functioning and psychological factors between a large sample of PwH, subgroups of PwH based on their pain distribution and healthy controls.

Methods

Participants

Between February 2020 and January 2022, all PwH who met the inclusion criteria and who were scheduled for regular follow-up consultations at the Haemophilia Comprehensive Treatment Centre of the *Cliniques universitaires Saint-Luc* (Brussels, Belgium) and the Antwerp University Hospital (Edegem, Belgium) were contacted to participate in the study. The inclusion and exclusion criteria are presented in Table 1.[21, 22]

After recruitment, PwH were classified into subgroups based on the number of pain sites. In the week prior to the study, they completed the Brief Pain Inventory (BPI) indicating any location where they perceived pain at the time of completion, regardless of intensity. This allowed for the classification of PwH into four subgroups:: 1. PwH with widespread pain (WP; ≥6 pain sites), 2. regional pain (RP; 2-5 pain sites), 3. local pain (LP; 1 pain site) and 4. without pain. This subgroup definition was used in previous studies in chronic musculoskeletal (MSK) conditions.[23, 24]

Methods

The ethical committee of the Antwerp University Hospital approved the multicentre study(B300201942304). Written consent was provided before study onset. Participants were asked to complete a battery of questionnaires in the week prior to the study and

Table 1. Inclusion and exclusion criteria study participants

	Inclusion criteria	Exclusion criteria
PwH	Adult men aged between 18-65 years with moderate (FVIII or FIX activity between 2-5 IU/dL) or severe (FVIII or FIX activity <1 IU/dL) haemophilia A or B with a stable haemophilia treatment regimen (i.e. an unmodified treatment over the last six months, verified by the patients' logbook).	1. PwH suffering from known neuropathies with definite medical causes independent from haemophilia (e.g. diabetic polyneuropathy) were excluded as this might influence pain assessment.[21] 2. PwH with a haemarthrosis in the month preceding study participation were excluded. In case of doubt, point of care ultrasound was used to check the presence of blood in the joint.
Control group	Aged-matched healthy men without haemophilia.	1. Men with known pain diseases or conditions influencing nociceptive processing (e.g. rheumatologic, inflammatory, metabolic, malignant diseases). 2. Men reporting pain/discomfort in >3 body regions with a score of >3 on the 10-point NRS between 0 (no pain) and 10 (worst imaginable pain) for >30 days in the past 12 months and a NRS >3 at the time of assessment[22] 3. Diagnosis of depression or other psychiatric complaints.

Abbreviations: PwH, people with haemophilia; NRS, numeric rating scale.

to avoid any pain medication 24 hours before the consultation. PwH underwent a comprehensive pain assessment after their consultation in the hospital consultation setting, while healthy volunteers were broadly recruited through social media, posters and flyers and were invited to the M^{2}SENS lab (University of Antwerp, Belgium). The whole assessment lasted approximately 90 minutes.

Outcome measures

Pain-related questionnaires

Four items of the BPI-short form were used to evaluate the individual's pain experience within the last 24 hours, resulting in a total pain severity score.[25] The *Douleur Neuropathique en 4 questions* (DN4) was applied as a screening tool for the presence

of a neuropathic pain component, a score of ≥4/10 was used as a cut-off.[15, 26, 27] The Central Sensitisation Inventory (CSI) part A was used to identify signs of central sensitization (CS) i.e. increased sensitivity of nociceptive neurons in the central nervous system.[28] The presence of 25 psychological, cognitive and functional signs are scored from 0 (never) to 4 (always). A total score exceeding ≥40/100 indicated CS.[29]

Psychological questionnaires

The Pain Catastrophizing Scale (PCS) asked participants to reflect on previous painful experiences and to rate their degree of catastrophic thinking in the content domains of rumination, magnification and helplessness.[30, 31] A score of 0 (not at all) to 4 (all the time) was indicated for each of the 13 items, resulting in a total score between 0–52. Higher scores indicated higher levels of pain catastrophizing. The Hospital Anxiety and Depression Scale (HADS) was used to establish symptoms of anxiety and depression.[32, 33] This 14-item questionnaire consists of two subscales each including 7 items, the first to identify anxiety and the second depression. Individual items were scored from 0 to 3, resulting in a total score between 0-21 for each subscale. A score of ≥8/21 was determined as cut-off, indicating anxiety and depression.[33]

Quantitative Sensory Testing (QST)

QST, a validated non-invasive examination of the somatosensory system, was performed based on the protocol of the German Research Network on neuropathic Pain (DFNS).[34] The assessment was conducted by investigator (AF), who was trained by an experienced researcher prior study onset to obtain good interrater reliability (interclass correlation coefficient of .86; two-way model, absolute agreement). QST consisted of 'static' and 'dynamic' tests. Static tests determined the subjects' detection and pain thresholds, while dynamic tests investigated mechanisms in pain processing with specific stimulation that explored central integration such as TS and CPM.[35]

Static QST measures

Thermal detection and pain thresholds

The cold and warm detection threshold (CDT and WDT), cold and heat pain threshold (CPT and HPT) were determined by a 30 x 30 mm thermode of the TSA-2 device (Medoc©, Ramat-Yishai, Israel) attached at the dominant wrist.[16, 36] Starting at 32°C, the temperature increased or decreased with 1°C per second. A maximum was set at 0°C and 50°C to prevent tissue damage. First, participants were instructed to press a button as soon as the temperature change was perceived as cold or warm, to indicate the CDT and WDT. Second, to evaluate the CPT and HPT, participants had to press the button as soon as the temperature became painful. For each parameter the average of three consecutive recordings was used for further analysis.[37]

Pressure pain thresholds (PPTs)

PPTs were assessed with a digital algometer (Wagner Instruments©, Greenwich, CT, USA). With the subject lying supine; a 1-cm^2 algometer probe was applied pressure perpendicular to the skin at seven body locations. The order of PPT testing was randomized: (1) left and (2) right medial knee joint space, (3) left and (4) right lateral knee joint space, (5) left and (6) right talocrural joint space, (7) forehead. Pressure was applied by an increasing rate of 10 Newton/second until participants perceived an 'unpleasant' sensation.[38] An average of two recordings was used for analyses.

Dynamic QST measures

Temporal summation (TS)

TS of pain was assessed by repeatedly applying a weighted 60g von Frey monofilament on the skin both at local (medial joint space of the dominant knee) and remote sites (dorsal side of the dominant wrist) with a frequency of 1 Hz for 30 seconds. After the first and final stimulus, subjects were asked to rate their pain using a NRS. The magnitude of TS was determined by two calculation methods: 1. the absolute difference in NRS score between the last and first stimulus, in which TS was defined by an increase in pain intensity of >2 points.[39] 2. the percentage change in NRS score: (NRS final stimulus – NRS first stimulus)/NRS final stimulus, where a percentage change >33% indicated TS. To avoid a loss of zero values, a constant (0.1) was added to all NRS data.[39] Occurrence of pain after-sensations was measured with a NRS 15 seconds after the final stimulus.

Conditioned pain modulation (CPM)

CPM response was investigated by calculating the difference between the pain intensity of a personalized heat pain stimulus (test stimulus) before and under the influence of a standardized cold pain stimulus (conditioning stimulus).[40] The stimuli were applied to the wrists by 30 x 30 mm thermodes (TSA-2; Medoc©). The CPM protocol is presented in detail in figure 1.[36]

We used the recommendations of Kennedy et al. (2020)[41] to determine a meaningful CPM effect. Therefore, the interclass correlation coefficient (ICC) of the four NRS's during phase A were calculated. To classify participants into three groups (anti-nociceptive = decreased NRS, pain pronociceptive = increased NRS and non-response = no change), the ± 2 SEm (standard errors of measurement) method was used: [1 SEm = (SD NRS phase A)√(1-ICC))].[41, 42] The absolute NRS change was calculated as [mean NRS (phase B) – mean NRS (phase A)] and the percentage NRS change was determined by [(absolute NRS change/mean NRS (phase A))x100].[43] To calculate absolute and percentage NRS changes, the ± 2 SEm method was applied. As a result, we accounted for participants who may have had a small absolute increase in NRS in phase B, but a large percentage change in comparison to their NRS in phase A.[44]

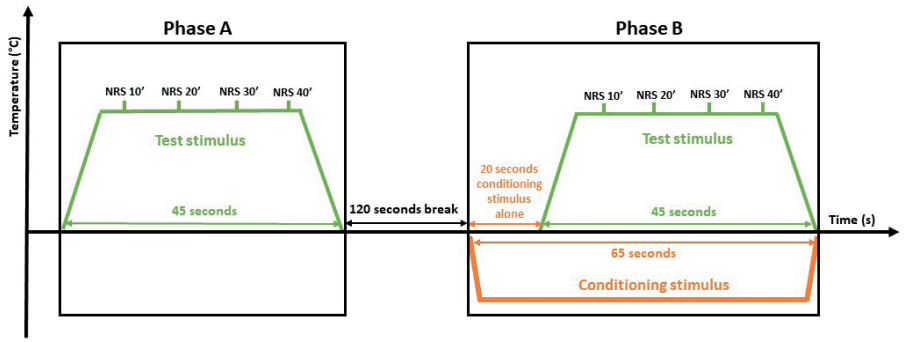

Figure 1. Conditioned pain modulation protocol with TSA-2:

Determination test stimulus: temperature participants verbally scored equal to a NRS score of 4/10. The determination started with an initial stimulation of 43°C at the dominant wrist. For a NRS score above/below 4/10, the temperature of the next stimulation was increased/decreased by 1°C.[36] The maximal temperature was set at 46°C to avoid tissue damage. **Phase A:** test stimulus was applied alone for 45 seconds and the pain intensity was calculated as the mean score of the NRSs at four time points, being after 10, 20, 30 and 40 seconds. **Phase B:** conditioning stimulus was applied by a thermode to the non-dominant wrist for 65 seconds giving a standardized temperature of 10°C. After 20 seconds, the test stimulus was repeated and NRS ratings were investigated again at 4 time points. ***Abbreviations:*** NRS: numeric rating scale.

Participants for which the maximum test stimulus temperature of 46°C did not equal a NRS score of 4/10 were excluded, as well as those for whom the mean NRS in phase A was equal to 0, since a CPM effect could not be assessed if the test stimulus was considered as 'not painful'.

Statistical analyses

Statistical data were analysed using SPSS version 28 (IBM Corporation, Armonk, NY). First, normality and homoskedasticity were visually checked. Before analyses, variables were checked for outliers, extreme outliers (3xIQR) where misinterpretation of the test or questionnaire was suspected were removed. Descriptive data for continuous variables were presented as means and standard deviations, data for categorical variables are presented as percentages.

Second, the Student's t-test was applied to compare PwH and healthy controls. The large number of observations in both groups allowed parametric testing. Frequency differences for categorical variables were tested using the Chi-squared test. Kruskal-Wallis test was used to identify differences between the four PwH subgroups and healthy controls. For this latter analysis, although some variables would allow parametric testing, all variables were analysed using the Kruskal-Wallis test for consistency. P-values from the Kruskal-Wallis test were corrected for multiple testing using the Benjamini-Hochberg procedure.[45] If the corrected p-value reached significance, Bonferroni-corrected post-hoc analysis was carried out.

Results

Out of the 111 eligible PwH, eight PwH (7%) declined to participate in the study due to lack of time (4), moving abroad (1) and being unreachable (3). Consequently, 103 PwH and 50 healthy controls participated in the study. Four healthy controls were excluded based on exclusion criteria and four PwH were excluded because they did not complete the questionnaires, making classification into subgroups impossible. Therefore, results of 99 PwH and 46 healthy controls were used for final evaluation. Demographic, anthropometric and clinical characteristics of PwH (n=99), PwH subgroups (PwH with WP (n=11), PwH with RP (n=49), PwH with LP (n=24) and PwH without pain (n=15)) and healthy controls are presented in Table 2.

Pain-related questionnaires

The total BPI pain severity and CSI score were higher in PwH compared to healthy controls (p<.001, Table 3). Significant more PwH compared to healthy controls exceeded the CSI cut-off score of 40/100 (13% versus 0%; p=.011). Twenty-six (27.1%) PwH achieved the DN4 cut-off score of 4/10, indicating that their pain might be of neuropathic origin. Among the subgroups, PwH with WP showed the highest mean scores on all pain-related questionnaires and highest percentages of individuals exceeding the DN4 and CSI cut-off scores (all p<.001, Table 4). Mean scores and percentages decreased across subgroups as the number of pain sites decreased.

Psychological questionnaires

PwH showed higher levels of anxiety and depression (both p<.001) as well as pain catastrophizing (p<.001, subscales all p<0.006) compared to healthy controls. Between PwH subgroups, PwH with WP showed the highest HADS and PCS (sub)scores (all p<.044). Differences were mainly significant between PwH with WP and PwH without pain or PwH with WP and healthy controls (Table 4).

Static QST measures

Thermal detection thresholds did not differ between PwH and healthy controls. Among the subgroups, CDTs were decreased in PwH with WP (p=.025) and LP (p=.047) compared to PwH without pain. A significant higher CPT (p=.002) and lower HPT (p<.001) was observed in PwH compared to healthy controls, indicating an increased sensitivity to thermal pain (Table 3). Between subgroups, only higher CPT (p=.049) and lower HPTs (p=.003) were observed between PwH with LP and healthy controls (Table 4).

Table 2. Demographic, anthropometric and clinical characteristics

	Total sample	Subgroup 1	Subgroup 2		Subgroup 3	Subgroup 4	Healthy controls (n=46)	PwH versus controls	Between subgroup analysis	Posthoc subgroups[d]	p-value
	PwH (n=99)	PwH with widespread pain (n=11)	PwH with regional pain (n=49)		PwH with local pain (n=24)	PwH without pain (n=15)		p-value[a]	p-value[c]		
Age (years)	36.92 ± 13.45 (18-65)	39.6 ± 14.1 (19-61)	41.2 ± 13.0 (18-61)		30.2 ± 11.7 (18-61)	31.6 ± 11.7 (18-65)	37.4 ± 15.4 (18-64)	0.954	**.016**	2 vs 3	.013
Weight (kg)	79.27 ± 15.81 (48.70-117)	92.1 ± 17.1 (65-117)	77.8 ± 14.1 (48.7-112)		81.0 ± 16.7 (53-115)	72.0 ± 14.2 (59.3-112)	77.2 ± 10.1 (60-105)	0.750	**.010**	1 vs 4	.004
Height (m)	1.77 ± 0.06 (1.62-1.94)	1.75 ± .05 (1.65-1.85)	1.76 ± .06 (1.62-1.87)		1.78 ± .06 (1.65-1.88)	1.81 ± .07 (1.70-1.94)	1.80 ± .07 (1.64-1.93)	0.089	.044	-	-
BMI (kg/m^2)	25.21 ± 4.96 (16.79-37.88)	30.1 ± 5.9 (19.0- 37.9)	25.0 ± 4.3 (16.8- 37.0)		25.5 ± 5.0 (16.9-35.2)	21.9 ± 3.5 (17.3-29.8)	24.0 ± 3.3 (18.6- 34.7)	0.165	**.001**	1 vs 4 1 vs 5	.001 .015
Type of haemophilia- severity									**<.001[b]**	-	-
A/B- severe	73 (73.7%)	10 (90.9%)	35 (71.4%)		21(87.5%)	7 (46.7%)	-		-	-	-
A/B- moderate	26 (26.3%)	1 (9.1%)	14 (28.6%)		3 (12.5%)	8 (53.3%)	-		-	-	-
Treatment regimen									**<.001[b]**	-	-
On-demand	18 (18.2%)	-	9 (18.4%)		2 (8.3%)	7 (46.6%)	-		-	-	-
Prophylaxis	64 (64.6%)	10 (90.9%)	35 (71.4%)		16 (66.7%)	3 (20%)	-		-	-	-
Emicizumab	16 (16.2%)	1 (9.1%)	5 (10.2%)		6 (25%)	4 (26.7%)	-		-	-	-
Gene therapy	1 (1.0%)	-	-			1 (6.7%)	-		-	-	-
Self-reported use of regular pain medication	20 (20.2%)	6 (54.6%)	14 (28.6%)		0 (0%)	0 (0%)	0 (0%)	**0.029[b]**	**<.001[b]**	-	-
Non-opioid analgesics	11 (11.1%)	5 (45.5%)	6 (12.3%)		-	-	-		-	-	-
Non-opioid + weak opioid analgesics	1 (1.0%)	-	1 (2%)		-	-	-		-	-	-
Non-opioid + strong opioid analgesics	1 (1.0%)	-	1 (2%)		-	-	-		-	-	-
Non-opioid analgesics + recombinant factor	7 (7.1%)	1 (9.1%)	6 (12.3%)		-	-	-		-	-	-
Positive HIV	6 (6.1%)	1 (9.1%)	5 (10.2%)		0 (0%)	0 (0%)	-	-	**<.001[b]**	-	-
Hepatitis C											
Negative	54 (54.5%)	4 (36.4%)	18 (36.3%)		20 (83.3%)	12 (80%)	-	-	-	-	-
Succesfully treated for HCV (negative viral load)	45 (45.5%)	7 (63.6%)	31 (63.3%)		4 (16.7%)	3 (20%)	-	-	-	-	-

Data are presented as mean ± SD (range) for continuous variables and as frequency counts (%) for categorical variables. Widespread pain: ≥6 pain locations; regional pain: 2-5 pain locations; local pain: 1 pain location on the Brief Pain Inventory- Body chart. [a]Mann-Whitney U test, P < 0.05. bChi-squared tests, P < 0.05. Bolt p-values reached significance. [b]p-values of the Chi-squared tests. [c]bolt p-values of the Kruskal-Wallis tests remained significant after Benjamini-Hochberg correction for multiple tests. [d]Only statistically significant post hoc results after Bonferroni correction for multiple tests are shown. Abbreviations: PwH, people with haemophilia; SD, standard deviation; kg, kilograms; m, meters; BMI, body mass index; HIV, human immunodeficiency virus; HCV: hepatitis C virus.

Table 3. Data of Quantitative Sensory Testing, pain-related and psychological questionnaires

		PwH (n=99)			Healthy controls (n=46)			p-value[a]
		mean ± SD	*n*	%	mean ± SD	*n*	%	
QST - static tests								
CDT (Δ,°C)	Dominant wrist	-2.50 ± 2.02	91	-	-2.49 ± 1.70	46	-	.977
WDT (Δ,°C)	Dominant wrist	2.39 ± 1.23	92	-	2.21 ± .70	40	-	.298
CPT (°C)	Dominant wrist	12.58 ± 10.05	98	-	7.48 ± 8.27	46	-	**.002**
HPT (°C)	Dominant wrist	44.76 ± 3.25	98	-	46.33 ± 1.98	45	-	**<.001**
PPT (N)								
	Left ankle	45.79 ± 21.30	98	-	68.25 ± 21.47	46	-	**<.001**
	Right ankle	44.19 ± 20.20	98	-	67.13 ± 21.92	46	-	**<.001**
	Left knee medial	41.45 ± 20.87	98	-	64.68 ± 21.48	46	-	**<.001**
	Right knee medial	43.61 ± 21.04	98	-	67.39 ± 23.47	46	-	**<.001**
	Left knee lateral	46.60 ± 23.10	98	-	78.39 ± 30.43	46	-	**<.001**
	Right knee lateral	48.22 ± 23.65	98	-	76.13 ± 29.42	46	-	**<.001**
	Forehead	28.78 **±** 10.56	98	-	38.97 ± 11.80	46	-	**<.001**
QST - dynamic tests								
Temporal summation								
Dominant knee	Absolute NRS change	.32 ± 1.10	92	-	.39 ± 1.00	46	-	.694
	Δ>2 NRS-points	-	10	10.9%	-	4	8.7%	.690[b]
	Percentage NRS change	2.60 ± 57.90	92	-	16.37 ± 47.75	46	-	.166
	Δ>33% NRS-points	-	21	22.8%	-	13	28.3%	.485[b]
	Mean NRS aftersensation (0-10)	.15 ± .51	92	-	.05 ± .22	46	-	.118
Dominant wrist	Absolute NRS change	.41 ± 1.01	95	-	.35 ± .88	46	-	.718
	Δ>2 NRS-points	-	9	9.5%	-	5	10.9%	.795[b]
	Percentage NRS change	21.72 ± 46.00	95	-	22.57 ± 40.94	46	-	.915
	Δ>33% NRS-points	-	30	31.6%	-	12	26.1%	.504[b]
	Mean NRS aftersensation (0-10)	.11 ± .34	95	-	.04 ± .21	46	-	.185
CPM paradigm								
	Mean NRS phase A (0-10)	2.71 ± 1.12	67	-	2.47 ± 1.15	28	-	.356
	Mean NRS phase B (0-10)	2.28 ± 1.32	67	-	1.71 ± 1.22	28	-	.052
	CPM absolute NRS change	-.43 ± 1.25	67	-	-.76 ± 1.30	28	-	.237
	Anti-nociceptive	-	13	19.4%	-	8	28.6%	.326[b]
	Pronociceptive	-	5	7.5%	-	1	3.6%	.477[b]
	Non-response	-	49	73.1%	-	19	67.8%	.603[b]
	CPM percentage NRS change	-7.71 ± 61.89	67		-30.92 ± 51.58	28	-	.084
	Anti-nociceptive	-	15	22.4%	-	10	35.8%	.179[b]
	Pronociceptive	-	7	10.4%	-	2	7.1%	.616[b]
	Non-response	-	45	67.2%	-	16	57.1%	.353[b]
Questionnaires								
BPI	Pain severity	2.06 ± 1.79	99	-	.59 ± 1.03	45	-	**<.001**
DN4	Total sum score	2.26 ± 2.22	96	-	-	-	-	-
	Positive score	-	26	27.1%	-	-	-	-
CSI	Total sum score	26.19 ± 13.02	99	-	17.72 ± 8.25	46	-	**<.001**
	Positive score	-	13	13.1%	-	0	0%	**.011[b]**
PCS	Total sum score	13.62 ± 11.02	99	-	7.62 ± 6.86	45	-	**<.001**
	Rumination	4.87 ± 4.11	99	-	3.07 ± 3.25	44	-	**.006**
	Magnification	2.96 ± 2.50	99	-	1.57 ± 1.67	46	-	**<.001**
	Helplessness	5.79 ± 5.60	99	-	2.82 ± 2.76	45	-	**<.001**
HADS	Anxiety	6.14 ± 3.59	99	-	3.10 ± 1.95	41	-	**<.001**
	Depression	4.13 ± 3.42	98	-	1.84 ± 1.57	43	-	**<.001**

Data are presented as mean ± SD for continuous variables and as frequency counts (%) for categorical variables.
[a]Student's t-test, P < 0.05. [b]Chi-squared tests, P < 0.05. Bolt p-values reached significance.
Abbreviations: PwH, people with haemophilia; SD, standard deviation; CDT: cold detection threshold; WDT: warmth detection threshold; CPT: cold pain threshold; HPT: heat pain threshold; PPT: pressure pain threshold; N: Newton; QST: quantitative sensory testing; NRS: numeric rating scale; CPM: conditioned pain modulation; BPI: brief pain inventory; DN4: douleur neuropathique en 4 questions; CSI: central sensitization inventory; PCS: pain catastrophizing scale; HADS: hosptial anxiety and depression scale.

Table 4. Data of Quantitative Sensory Testing, pain-related and psychosocial questionnaires

		Subgroup 1 PwH with widespread pain (n=11)			Subgroup 2 PwH with regional pain (n=49)			Subgroup 3 PwH with local pain (n=24)				Subgroup 4 PwH without pain (n=15)			Healthy controls (n=46)			p-value Kruskal-Wallis[a]	Posthoc subgroups[c]	p-value
		mean ± SD	n	%	mean ± SD	n	%	mean ± SD	n	%		mean ± SD	n	%	mean ± SD	n	%			
QST - static tests																				
CDT (Δ,°C)		-3.95 ± 3.40	11	-	-2.36 ± 1.54	45	-	-2.78 ± 2.12	23	-		-1.18 ± .38	12	-	-2.49 ± 1.70	46	-	**.024**	1 vs 4	.025
																			3 vs 4	.047
WDT (Δ,°C)		2.38 ± 1.24	10	-	2.41 ± 1.34	44	-	2.48 ± 1.21	24	-		2.17 ± .93	14	-	2.21 ± .70	40	-	.965	-	-
CPT (°C)		10.69 ± 9.85	11	-	11.67 ± 10.32	48	-	14.72 ± 10.22	24	-		13.48 ± 9.32	15	-	7.48 ± 8.27	46	-	**.031**	3 vs 5	.049
HPT (°C)		46.06 ± 2.32	11	-	45.36 ± 3.24	48	-	43.18 ± 3.65	24	-		44.40 ± 2.33	15	-	46.33 ± 1.98	45	-	**.003**	3 vs 5	.003
PPT (N)																				
	Left ankle	42.33 ± 21.24	11	-	41.70 ± 21.37	49	-	53.72 ± 20.53	23	-		49.54 ± 20.17	15	-	68.25 ± 21.47	46	-	**<.001**	1 vs 5	.011
																			2 vs 5	.000
	Right ankle	41.15 ± 16.38	11	-	40.18 ± 19.99	49	-	50.98 ± 21.48	23	-		49.13 ± 19.35	15	-	67.13 ± 21.92	46	-	**<.001**	1 vs 5	.008
																			2 vs 5	.000
																			3 vs 5	.043
	Left knee medial	34.23 ± 14.12	11	-	39.03 ± 22.08	49	-	45.40 ± 17.21	23	-		48.62 ± 24.39	15	-	64.68 ± 21.48	46	-	**<.001**	1 vs 5	.001
																			2 vs 5	.000
																			3 vs 5	.023
	Right knee medial	37.22 ± 18.78	11	-	42.41 ± 23.31	49	-	47.40 ± 17.48	23	-		46.37 ± 20.03	15	-	67.39 ± 23.47	46	-	**<.001**	1 vs 5	.002
																			2 vs 5	.000
																			3 vs 5	.025
																			4 vs 5	.042
	Left knee lateral	41.59 ± 23.10	11	-	43.79 ± 22.81	49	-	51.27 ± 21.17	23	-		52.31 ± 26.63	15	-	78.39 ± 30.43	46	-	**<.001**	1 vs 5	.002
																			2 vs 5	.000
																			3 vs 5	.018
	Right knee lateral	43.56 ± 22.26	11	-	46.88 ± 25.77	49	-	49.59 ± 18.88	23	-		53.89 ± 24.95	15	-	76.13 ± 29.42	46	-	**<.001**	1 vs 5	.008
																			2 vs 5	.000
																			3 vs 5	.013
	Forehead	26.72 ± 8.62	11	-	29.58 ± 11.55	49	-	30.86 ± 10.29	23	-		24.50 ± 7.99	15	-	38.97 ± 11.80	46	-	**<.001**	1 vs 5	.020
																			2 vs 5	.001
																			4 vs 5	.000
QST - dynamic tests																				
Temporal summation																				
Dominant knee	Absolute NRS change	.91 ± 1.45	11	-	.36 ± 1.09	45	-	.19 ± .60	21	-		-.07 ± 1.28	15	-	.39 ± 1.00	46	-	.344	-	-
	Δ>2 NRS-points	-	2	18.2%	-	4	8.9%	-	2	9.5%		-	2	13.3%	-	4	8.7%	.888[b]	-	-
	Relative NRS change	19.18 ± 38.95	11	-	6.97 ± 55.20	45	-	6.14 ± 19.41	21	-		-27.62 ± 95.54	15	-	16.37 ± 47.75	46	-	.423	-	-
	Δ>33% NRS-points	-	2	18.2%	-	13	28.9%	-	2	9.5%		-	4	26.7%	-	13	28.3%	.459[b]	-	-
	Mean NRS aftersensation	.00 ± .00	11	-	.24 ± .57	45	-	.14 ± .65	21	-		.00 ± .00	15	-	.05 ± .22	46	-	.097	-	-

Table 4. Continued

		Subgroup 1 PwH with widespread pain (n=11)			Subgroup 2 PwH with regional pain (n=49)			Subgroup 3 PwH with local pain (n=24)				Subgroup 4 PwH without pain (n=15)			Healthy controls (n=46)			p-value Kruskal-Wallis[a]	Posthoc subgroups[c]	p-value
		mean ± SD	n	%	mean ± SD	n	%	mean ± SD	n	%		mean ± SD	n	%	mean ± SD	n	%			
QST - dynamic tests																				
Temporal summation																				
Dominant wrist	Absolute NRS change	.56 ± .88	9	-	.43 ± 1.02	47	-	.50 ± 1.22	24	-		.13 ± .64	15	-	.35 ± .88	46	-	.726	-	-
	Δ>2 NRS-points	-	2	22.2%	-	4	8.5%	-	3	12.5%		-	2	13.3	-	5	10.9%	.477[b]	-	-
	Relative NRS change	14.77 ± 24.91	9	-	24.08 ± 40.32	47	-	24.39 ± 61.26	24	-		14.21 ± 47.11	15	-	22.57 ± 40.94	46	-	.882	-	-
	Δ>33% NRS-points	-	2	22.2%	-	16	34.0%	-	9	37.5%		-	3	20%	-	12	26.1%	.676[b]	-	-
	Mean NRS aftersensation	.00 ± .00	9	-	.15 ± .42	47	-	.13 ± .34	24	-		.00 ± .00	15	-	.04 ± .21	46	-	.274	-	-
CPM paradigm																				
	Phase A (NRS 0-10)	2.94 ± 1.11	8	-	2.78 ± 1.11	32	-	2.47 ± 1.00	17	-		2.70 ± 1.36	10	-	2.47 ± 1.15	28	-	.669	-	-
	Phase B (NRS 0-10)	2.41 ± 1.77	8	-	2.27 ± 1.22	32	-	1.96 ± 1.15	17	-		2.78 ± 1.57	10	-	1.71 ± 1.22	28	-	.241	-	-
	CPM absolute NRS change	-.53 ± 1.03	8	-	-.51 ± 1.10	32	-	-.51 ± 1.43	17	-		.08 ± 1.58	10	-	-.76 ± 1.30	28	-	.658	-	-
	Anti-nociceptive	-	3	37.5%	-	5	15.6%	-	3	17.6%		-	2	20%	-	8	28.6%	.595[b]	-	-
	Pronociceptive	-	0	0%	-	2	6.3%	-	1	5.9%		-	2	20%	-	1	3.6%	.397[b]	-	-
	Non-response	-	5	62.5%	-	25	78.1%	-	13	76.5%		-	6	60%	-	19	67.8%	.727[b]	-	-
	CPM relative NRS change	-23.16 ± 38.92	8	-	-12.42% ± 52.45	32	-	-12.07% ± 43.76	17	-		27.10% ± 111.18	10	-	-30.92% ± 51.58	28	-	.254	-	-
	Anti-nociceptive	-	3	37.5%	-	8	25%	-	3	17.6%		-	1	10%	-	10	35.8%	.426[b]	-	-
	Pronociceptive	-	0	0%	-	3	9.4%	-	2	11.8%		-	2	20%	-	2	7.1%	.661[b]	-	-
	Non-response	-	5	62.5%	-	21	65.6%	-	12	70.6%		-	7	70%	-	16	57.1%	.895[b]	-	-
Questionnaires																				
BPI	Pain severity	3.95 ± 2.13	11	-	2.64 ± 1.51	49	-	1.10 ± 1.15	24	-		.32 ± .50	15	-	.59 ± 1.03	45	-	**<.001**	1 vs 3	.005
																			1 vs 4	.000
																			1 vs 5	.000
																			2 vs 3	.004
																			2 vs 4	.000
																			2 vs 5	.000
DN4	Total sum score	4.55 ± 2.34	11	-	2.51 ± 2.11	49	-	1.83 ± 1.76	24	-		0 ± 0 (0)	12	-	-	-	-	**<.001**	1 vs 4	.000
																			2 vs 4	.000
																			3 vs 4	.006
	Positive score n(%)	-	8	72.7%	-	13	26.5%	-	5	20.8%		-	0	0%	-	-	-	**<.001[b]**	-	-

Table 4. Continued

		Subgroup 1 PwH with widespread pain (n=11)			Subgroup 2 PwH with regional pain (n=49)			Subgroup 3 PwH with local pain (n=24)				Subgroup 4 PwH without pain (n=15)			Healthy controls (n=46)			p-value Kruskal-Wallis[a]	Posthoc subgroups[c]	p-value
		mean ± SD	n	%	mean ± SD	n	%	mean ± SD	n	%		mean ± SD	n	%	mean ± SD	n	%			
Questionnaires																				
CSI	Total sum score	42.55 ± 12.93	11	-	25.18 ± 10.96	49	-	24.04 ± 13.14	24	-		20.93 ± 11.00	15	-	17.72 ± 8.25	46	-	**<.001**	1 vs 2	.008
																			1 vs 3	.006
																			1 vs 4	.002
																			1 vs 5	.000
																			2 vs 5	.020
	Positive score n(%)	-	5	45.5%	-	5	10.2%	-	2	8.3%		-	1	6.7%	-	0	0%	**<.001[b]**	-	-
PCS	Total sum score	24.09 ± 13.79	11	-	14 ± 10.38	49	-	11.96 ± 10.64	24	-		7.33 ± 5.04	15	-	7.62 ± 6.86	45	-	**<.001**	1 vs 4	.010
																			1 vs 5	.001
																			2 vs 5	.013
	Rumination	7.45 ± 4.95	11	-	4.82 ± 4.31	49	-	4.38 ± 3.77	24	-		3.93 ± 2.69	15	-	3.07 ± 3.25	44	-	**.044**	1 vs 5	.038
	Magnification	4.64 ± 3.33	11	-	3.12 ± 2.41	49	-	2.63 ± 2.22	24	-		1.73 ± 1.94	15	-	1.57 ± 1.67	45	-	**.002**	1 vs 5	.020
																			2 vs 5	.012
	Helplessness	12.00 ± 6.80	11	-	6.06 ± 5.06	49	-	4.96 ± 5.34	24	-		1.67 ± 1.50	15	-	2.82 ± 2.76	45	-	**<.001**	1 vs 3	.032
																			1 vs 4	.000
																			1 vs 5	.000
																			2 vs 4	.008
																			2 vs 5	.010
HADS	Anxiety	10.09 ± 4.25	11	-	5.31 ± 2.95	49	-	5.62 ± 3.12	24	-		6.80 ± 3.97	15	-	3.10 ± 1.95	41	-	**<.001**	1 vs 2	.010
																			1 vs 5	.000
																			2 vs 5	.007
																			3 vs 5	.015
																			4 vs 5	.005
	Depression	8.00 ± 4.41	11	-	3.80 ± 3.03	49	-	4.42 ± 3.15	24	-		1.79 ± 1.42	14	-	1.84 ± 1.57	43	-	**<.001**	1 vs 4	.000
																			1 vs 5	.000
																			2 vs 5	.008
																			3 vs 5	.006

Data are presented as mean ± SD for continuous variables and as frequency counts (%) for categorical variables. Widespread pain: >5 pain locations; regional pain: 2-5 pain locations; local pain: 1 pain location on the Brief Pain Inventory - Body chart. [a]bolt p-values remained significant after Benjamini-Hochberg correction for multiple tests. [b]p-values of the Chi-squared tests.[c]Only statistically significant post hoc results after Bonferroni correction for multiple tests are shown. Abbreviations: PwH, people with haemophilia; SD, standard deviation; CDT: cold detection threshold; WDT: warmth detection threshold; CPT: cold pain threshold; HPT: heat pain threshold; PPT: pressure pain threshold; N: Newton; QST: quantitative sensory testing; NRS: numeric rating scale; CPM: conditioned pain modulation; BPI: brief pain inventory; DN4: douleur neuropathique en 4 questions; CSI: central sensitization inventory; PCS: pain catastrophizing scale; HADS: hosptial anxiety and depression scale.

Lower PPTs at the knees, ankles and forehead were observed in PwH compared to healthy controls (p<.001, Table 3). Significantly decreased PPTs at all locations were found in the subgroups of PwH suffering from at least LP (>1 pain site) compared to healthy controls (Table 4). PwH without pain showed lower PPTs at the right medial knee (p=.042) and the forehead (p=.000) compared to healthy controls.

Dynamic QST measures

The TS absolute and percentage NRS change and NRS aftersensation did not differ between PwH and healthy controls (Table 3). Among the subgroups, PwH with WP showed the highest values of TS absolute and percentage NRS change at the dominant knee and highest TS absolute NRS change at the wrist. However, none of the TS parameters reached significance (Table 4).

For 32 (32.3%) PwH and 18 (39.1%) healthy controls, CPM effect could not be analysed since the test stimulus was not considered painful. The ICC value of the mean NRS in phase A was .68 for PwH and .69 for healthy controls, both can be considered as a good level of reliability.[46] For this study, the 2 SEm was 1.27 NRS (or 46.7%) for PwH and 1.27 NRS (or 51.6%) for healthy controls. Participants with an increase in NRS greater than 1.27 (or +46.7%/51.6% with their mean NRS in phase A) were considered as being pronociceptive, a decrease greater than 1.27 (or -46.7%/51.6% with their mean NRS in phase A) as anti-nociceptive and participants with an NRS score in between as non-responders. Between PwH and healthy controls and between the subgroups, no significant differences in meaningful CPM effects (both absolute or percentage NRS change) were observed (Table 3 and 4).

Discussion

The present study revealed indications of altered somatosensory functioning in PwH, especially in PwH with WP, reflected by increased thermal and mechanical pain sensitivity and the presence of more unhelpful contributing psychological factors. Evidence for enhanced pain facilitation and impaired efficacy of endogenous pain inhibition in PwH could not be observed.

Pain-related and psychological questionnaires

PwH, especially PwH with WP reported significantly higher pain intensity and more comorbidities assessed by the CSI compared to healthy controls. While the CSI has limited ability to directly reflect alterations in QST results[47], its strength lies in identifying psychological factors associated with CS.[48, 49] Despite the CSI has rarely been used in PwH, we believe in its added value as it might offer clinicians insight into symptoms that are particularly prevalent in those with CS. Almost a third of PwH had

a positive DN4 score, which is in line with previous findings.[7, 27] However, a recent study showed that by use of the DN4 it is impossible to distinguish neuropathic from nociplastic pain. Therefore, objective clinical neurological tests are needed to investigate disease or lesion of the nervous system.[50] High levels of unhelpful psychological factors were found in PwH, especially in those with WP, which emphasises the multidimensional and biopsychological construct of pain. In summary, our findings revealed significant differences in self-reported pain and psychological variables between PwH with WP and PwH without pain, suggesting different phenotypes within PwH. These results indicate the need for tailored management approaches.

Static QST measures

Using the same protocol as Kruger et al.[51] , but with a larger sample, we could not confirm their previous findings of reduced thermal detection thresholds (thermal hypoesthesia) in PwH compared to healthy controls. Only PwH with WP and LP showed reduced detection thresholds to cold stimuli in comparison with PwH without pain. However, our study did find hypersensitivity to cold and heat pain stimuli (thermal hyperalgesia) in PwH. Based on the findings of an earlier study in knee osteoarthritis, we can assume that thermal hypoesthesia and hyperalgesia are identified as indicators of altered somatosensory functioning.[52]

Further, our results confirmed previously reported mechanical hyperalgesia in PwH, proven by significantly lower PPTs at the knees and ankles[53] compared to healthy controls.[51, 54] Although previous studies in PwH did not find significantly lower PPTs at remote, seldom painful sites such as the hand[51, 54], forehead[9, 15] or sternum[9], PPTs in this study were lower at the forehead compared to healthy controls.[15]

Therefore, in line with studies in rheumatoid arthritis, we suspect the presence of secondary mechanical hyperalgesia as an indication of altered somatosensory functioning in PwH.[55] Although PwH with WP showed trends of lower PPTs compared to other PwH subgroups, statistical significance was not reached. This may be due to the limited number of participants within each subgroup, which affected statistical power. Therefore, further research with sufficient sample sizes is needed to confirm or refute these findings.

Dynamic QST measures

In line with Kruger et al.[51], TS was not significantly different between PwH and healthy controls. Since both studies allowed the inclusion of PwH with mild or no joint pain, it might be more difficult to show differences with healthy subjects. We expected enhanced TS in PwH compared to healthy controls, as seen in other chronic MSK conditions such as knee osteoarthritis[56] or fibromyalgia[57]. The subgroup analysis, revealed that PwH with WP showed the highest absolute and relative NRS change scores and the most intense aftersensation intensities. These findings suggest an

augmented presence of TS in PwH with WP, particularly when compared to PwH without pain. This highlights the potential utility of pain phenotyping using dynamic QST measures in distinguishing between different pain phenotypes. However, cautious interpretation is needed as significance could not be reached. Future studies should take into account the presence or absence of joint pain, as well as the choice of assessment tool for TS. The application of the monofilament may not generate a sufficiently intense stimuli, since the initial pain ratings and aftersensation intensities were very low in our sample.

We were unable to confirm the presence of impaired endogenous pain inhibition in PwH, as seen in the study of Kruger et al.[16] This might be due to several aspects. First, PwH with mild or no joint pain were included as well. Second, the CPM protocol defined a test stimulus temperature that evoked pain of at least 4/10 instead of 6/10.[16] Third, the test stimulus temperature was limited to 46°C, which for 28.2% PwH and 34.8% healthy controls did not equate to an NRS score of 4/10. Fourth, the conditioning stimulus temperature was fixed at 10°C instead of 7°C.[16] Fourthly, previous research has highlighted the presence of healthy individuals who do not exhibit efficient pain modulation, indicating the heterogeneity within this population.[44] Fifthly, there is no gold standard protocol for assessing dynamic QST measures. For these reasons, it remains difficult to confirm impaired endogenous pain inhibition in PwH.[16] Therefore, further research in large populations is needed to clarify these contradictions.

Clinical implications

To the best of our knowledge, this is the first study performing a comprehensive psychophysical assessment in a large PwH sample, including both QST and psychological evaluation. We are well aware that conducting a complete QST examination is not realistic in everyday practice. And unfortunately, reliable and valid bedside-testing procedures which can help clinicians better understand the somatosensory functioning of an individual's pain system are not yet available.[58]

Nevertheless, our study confirmed the potential usefulness of the pain drawing tool to identify PwH with a widespread pain distribution, since they presented significant more alterations in somatosensory functioning and reported more unhelpful psychological factors. Although, it is important to acknowledge that the pain drawing tool provides a momentary assessment. Further studies in PwH are needed to investigate the long-term stability and reliability of this measure, which will enhance its utility for accurately assessing pain phenotypes based on the number of painful body locations. People with altered somatosensory functioning are probably more likely to present or develop nociplastic pain, therefore a psychophysical assessment could help to get insight in the pain phenotypes in PwH.[59] Currently there is growing evidence

considering the potential prognostic value of QST measures in predicting the response of therapeutic interventions and long-term outcomes.[60-62] Previous studies in knee osteoarthritis showed that QST measures, such as TS, can serve as predictor of poor response to pain treatment with non-steroidal anti-inflammatory drugs (NSAIDS).[61] In these individuals with altered pain modulation, the use of centrally acting tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors (SNRIs) may be more effective. [4] Furthermore, another longitudinal study in people with knee osteoarthritis has revealed that individuals with widespread (pressure and/or thermal) hyperalgesia, are more likely to experience persistent pain one year after total knee arthroplasty.[62] Additionally, previous research has demonstrated a significant association between pain catastrophizing and dynamic QST measures such as TS in both people with chronic LBP[63] and knee osteoarthritis.[64] The presence of unhelpful psychological factors such as pain catastrophizing and anxiety are known to be associated with poor prognosis and treatment outcome, early detection could help in considering the integration of more psychological treatment modalities (i.e. cognitive behavioral therapy).[12, 65] In conclusion, findings of the present exploratory study could open new perspectives for future research to focus beyond the joint evaluation, but also take into account the psychophysical modalities or pain phenotypes.

However, further research is needed to determine whether QST, CSI results or psychological profiles can also be used in PwH to guide the decision for an appropriate pain management approach. It seems plausible that tailoring treatment to QST outcomes may improve individual QST outcomes over time, but addressing factors such as pain intensity, disability and quality of life should remain the primary goal.

Limitations

A limitation of this study was that we allowed the inclusion of PwH with mild or no joint pain, which potentially biased our comparison between PwH and healthy controls. Additionally, based on previous findings in other chronic MSK conditions such as LBP[66] and osteoarthritis[52], it is perfectly reasonable that only a subgroup of PwH would demonstrate alterations in pain sensitivity, pain modulation and psychological factors. To address this, this exploratory study attempted to differentiate based on the number of painful body sites. However, due to the limited number of participants in each subgroup, the statistical power was affected.

Therefore, we recognize the importance of expanding the spectrum of future research by including a wider range of populations for comparison. More specifically, it would be valuable to compare people with haemophilia not only by severity (i.e. moderate, severe haemophilia versus mild haemophilia), but also with healthy volunteers and individuals with other chronic MSK conditions. By making such comparisons, a better

understanding of pain in people with haemophilia can be achieved, allowing a better understanding of the pain phenotypes and psychological profiles associated with the condition and/or pain. In addition, this cross-sectional study design did not allow us to establish causal relationships or prediction models, for example, pain intensity in relation to psychological factors or somatosensory functioning. Therefore longitudinal studies are required.

CONCLUSION

Results of this study suggest altered somatosensory functioning in PwH such as increased thermal and mechanical pain sensitivity and the presence of more unhelpful psychological factors, especially in PwH with WP. Evidence for the presence of enhanced pain facilitation or impaired endogenous pain inhibition could not be confirmed.

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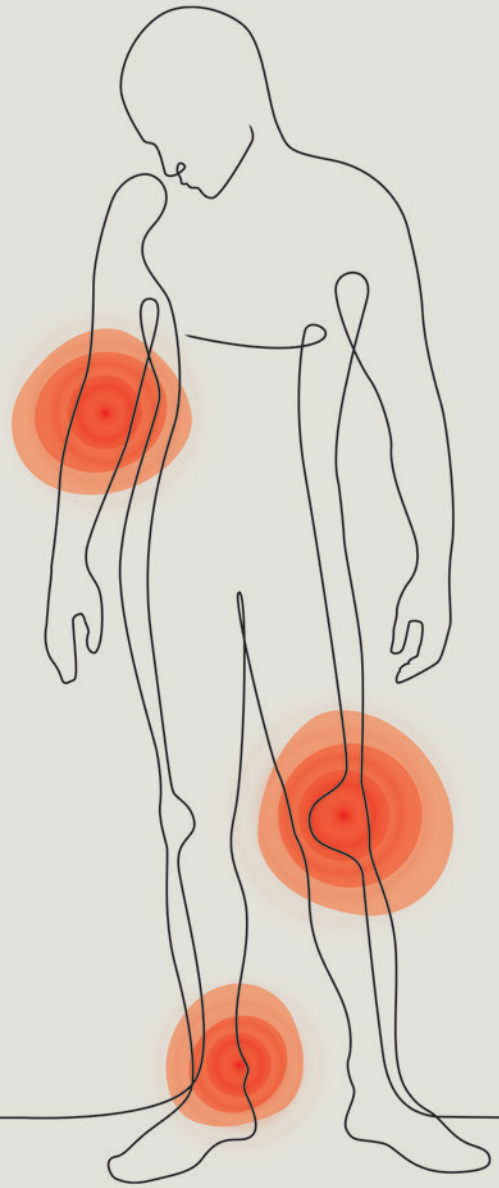

Chapter 4

The classification of suspected predominant nociplastic pain in people with moderate and severe haemophilia: a secondary exploratory study

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Abstract

Background: In people with haemophilia (PwH), joint pain is a major comorbidity that is often overlooked and under-treated. It is believed that, to ensure the most successful outcome, pain management should be tailored to the predominant pain phenotype (i.e., nociceptive, neuropathic and nociplastic). The 2021 clinical criteria and grading system for nociplastic pain, established by the International Association for the Study of Pain (IASP), emphasize the necessity of early-stage identification and predominant pain type classification. Consistent with findings in other chronic musculoskeletal pain conditions, studies suggest that a subgroup of PwH suffers from nociplastic pain, i.e., pain arising from altered nociception rather than structural damage, but this has not yet been explored in PwH.

Purpose: This study aimed to identify PwH with "unlikely", "possible" and "probable" nociplastic pain and investigate differences in anthropometric, demographic, clinical characteristics and psychological factors between subgroups of PwH and healthy individuals.

Materials and methods: The IASP clinical criteria and grading system were used to classify pain types in adult men with moderate and severe haemophilia recruited from two Belgian haemophilia treatment centres. Statistical analyses were applied to study between-subgroup differences.

Results: Of 94 PwH, 80 PwH (85%) were classified with "unlikely" and 14 (15%) with "at least possible" nociplastic pain (including 5 PwH (5%) with "possible" and 9 PwH (10%) with "probable" nociplastic pain). PwH in both the "unlikely" and "at least possible" nociplastic pain groups showed significantly higher levels of unhelpful psychological factors compared to healthy individuals. Additionally, age may partially account for the observed differences in body height and psychological factors. Larger sample sizes may be needed to detect more subtle between-group differences.

Conclusions: This study confirmed the presence of nociplastic pain in haemophilia, categorising a notable subgroup as individuals who experience at least possible nociplastic pain. These exploratory insights may provide a starting point for future studies and the development of more effective and tailored pain management.

Introduction

Pain is recognized as a significant concern in people with haemophilia (PwH), negatively impeding their daily activities and overall quality of life (QoL).[1, 2] This was emphasised by a German survey which showed that 86% of adults and 66% of children and adolescents experienced episodes of pain.[3] In addition to episodes of bleeding-related pain, PwH also experience pain associated with inflammation and multiarticular joint degeneration, with non-reversible end-stage haemophilic arthropathy.[4] Therefore, haemophilia can be considered as a chronic musculoskeletal disorder.

In contrast to chronic joint pain conditions such as osteoarthritis, the development of evidence-based guidelines for the management of pain in PwH faces many challenges. Indeed, the uncertainty about the presence of a bleed as a source of pain remains challenging both for patients as for Health Care Professionals (HCPs).[5] More importantly, HCPs' limited understanding of pain, along with the succinct evaluation of pain during clinical consultations creates obstacles to the development of a comprehensive biopsychosocial management strategy that takes into account biomedical, social and psychological factors contributing to pain and the underlying pain mechanisms.[6] The underassessment of pain and the lack of pain management options tailored to the underlying pain mechanism might explain the reduced QoL, as well as the PwH's low satisfaction rate with their pain treatment.[3, 7]

The importance of assessing the predominant pain mechanism in PwH was established in a review by our research group, and pain management should be adapted accordingly to ensure the most successful outcome.[6] Nowadays, it is assumed that pain in PwH is usually nociceptive in origin, due to the activation of nociceptors by an acute haemarthrosis or haemophilic arthropathy in a normally functioning somatosensory system. However, recent studies[8-10] revealed that a proportion of PwH demonstrated signs of neuropathic pain, i.e. pain caused by injury or lesion of the somatosensory system.[11]

Moreover, in a variety of chronic musculoskeletal conditions, nociceptive and neuropathic pain mechanisms could not explain chronic pain in all patients. Subgroups of people with osteoarthritis[12], rheumatoid arthritis[13] and low back pain[14] demonstrated hypersensitivity in body regions with normal tissues and without signs of neuropathy (i.e. injury or lesion of the somatosensory system). For this phenomenon, the International Association for the Study of Pain (IASP) introduced the term nociplastic pain as a third underlying pain mechanism, in which pain results from altered somatosensory functioning without obvious activation of nociceptors or neuropathy. (IASP Terminology (2017) https://www.iasp-pain.org/resources/terminology/, accessed on 2 April 2022).

Recent findings suggest that a subgroup of PwH is indeed more likely to suffer from nociplastic pain. The low associations between structural joint damage and pain experience[15, 16], a rather widespread pain distribution and reduced pressure pain thresholds (PPTs) at several locations, including asymptomatic locations such as the sternum or forehead[10, 17] suggest that these people present alterations in somatosensoric functioning, which may lead to nociplastic pain.

Diagnosing nociplastic pain is challenging since there is no gold standard methods. Consequently, patients experiencing such pain may feel that their symptoms are not taken seriously.[18] To address this issue, the IASP has developed clinical criteria and a grading system for nociplastic pain to help clinicians classify patients with predominant nociplastic pain.[19] With this grading system, it is possible to differentiate between "unlikely", "possible" and "probable" nociplastic pain (Table 1). In contrast to the neuropathic pain grading system[20], the term "definite" nociplastic pain cannot be applied yet, due to the lack of validated diagnostic tests.

Members of the IASP Terminology Task Force strongly encourage field testing of the IASP grading system.[19] Therefore, the primary objective of this study was to determine the occurrence of nociplastic pain among a substantial sample of adult PwH by utilizing the IASP clinical criteria and grading system for nociplastic pain, categorizing the participants into groups of unlikely, possible, and probable nociplastic pain. Our hypothesis was based on comparable chronic musculoskeletal conditions[18], assuming that there would be a subset of PwH exhibiting predominant nociplastic pain. The secondary aim was to analyse the dissimilarities in patient characteristics and psychological factors among the four groups: PwH with unlikely, possible, and probable nociplastic pain and healthy individuals. These observations could potentially facilitate the development of more targeted treatment approaches specific to the identified pain phenotype.

Methods

The present study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[21]

Study design and setting

This field study is a secondary analysis of data obtained from observational studies aiming to gain insight into the complexity of pain in PwH.[10, 16, 22] The recruitment method has previously been described. [10, 16, 22] Briefly, data were collected between February 2020 and April 2022. PwH regularly followed at the Haemophilia Comprehensive Treatment Centre of the *Cliniques universitaires Saint-Luc* (Brussels, Belgium) and the

Antwerp University Hospital (UZA) (Edegem, Belgium) underwent a comprehensive pain assessment after their consultation in the hospital setting. Healthy individuals were invited to the M²SENS lab (MOVANT, University of Antwerp, Belgium) to undergo identical tests. The ethical committee of the Antwerp University Hospital approved the multicentre study (B300201942304) and all participants provided written informed consent before study participation.

Participants

To be included, PwH had to be adult men above 18 years old with moderate (FVIII or FIX activity between 2-5 IU/dL) or severe (FVIII or FIX activity <1 IU/dL) haemophilia A or B, providing evidence that their haemophilia treatment regimen is stable (i.e. an unmodified treatment during the last six months, verified by the existing patients' logbook). PwH suffering from known neuropathies with definite medical causes independent from the haemophilia (e.g. diabetic polyneuropathy) were excluded as this might influence pain assessment.[23] For the same reason, PwH with acute pain due to a joint bleed occurring in the month preceding study participation were excluded as well. In case of doubt, point of care ultrasound was used to check the presence of blood in the joint. Additional exclusion criteria for this field study were: 1. PwH without pain and 2. PwH who had not completed the questionnaires.

Exclusion criteria for the pain-free individuals were: 1. known pain diseases or conditions influencing nociceptive processing (e.g. rheumatologic, inflammatory, metabolic, malignant diseases), 2. having any pain/discomfort with a score of >0 on the 10-point numeric rating scale (NRS) at the time of assessment[24] 3. diagnosis of depression or other psychiatric complaints.

The IASP clinical criteria and grading system for nociplastic pain applied to pain in PwH

The step-by-step clinical reasoning process below describes how the authors applied the IASP clinical criteria and grading system for nociplastic pain to PwH suffering from chronic pain. [19] For each step, the assessment tools or questionnaires used to evaluate whether PwH met the criterion are explained. In addition, the cut-offs available in the literature that supported the author's decision are stipulated. Table 1 summarises the clinical reasoning process.

Step 1 - A chronic pain duration

Based on the inclusion criteria, no PwH without pain or with acute pain were included.

Step 2 - A regional/multifocal/widespread pain distribution
The Brief Pain Inventory (BPI) body chart pain drawing was used to determine whether PwH had a regional/multifocal/widespread rather than a discrete pain distribution. To objectify the assessment, individuals who indicated four or more painful sites on the body chart were considered as having regional/multifocal/widespread pain.[25]

Step 3 - The pain cannot entirely be explained by nociceptive mechanisms
PwH in which nociceptive mechanisms are considered to be entirely responsible for their pain, should be classified as PwH with nociceptive pain. However, the decision on this criterion is difficult and depends on the clinical judgment of the investigator, this is recognized by the task force as a limitation.[19] Since, the presence of "nociceptive" pain does not exclude the possibility of concurrent nociplastic pain (i.e. mixed pain), when the pain distribution exceeds the identifiable source of nociception (i.e. widespread pain). [19] Therefore we assumed that it would not be possible to reliably identify nociceptive pain as the main driver of pain in PwH with a widespread pain distribution and they will move on to step 4.

Step 4 - The pain cannot entirely be explained by neuropathic mechanisms
Individuals with known neuropathies with definite medical causes independent from the haemophilia were excluded prior to study participation. However, to detect PwH with undiagnosed neuropathic pain, we followed the guideline for the classification of neuropathic pain.[20] Accordingly, PwH with a score of ≥4/10 on the DN4 questionnaire (i.e. indicating signs of neuropathic pain) and a neuroanatomically plausible pain distribution were considered as having possible neuropathic pain for which further confirmatory testing is recommended.[20, 26]. Similar to nociceptive pain, the presence of neuropathic pain does not exclude the possibility of concurrent nociplastic pain (i.e mixed pain). [19]

Therefore, in PwH with only a positive DN4 score without a plausible pain distribution, the neuropathic pain cannot be considered as entirely responsible for the pain and they will move on to step 5.

Step 5 - Evoked hypersensitivity phenomena
The presence of evoked pain hypersensitivity was evaluated according to previous results of three QST outcomes: mechanical pressure pain thresholds (PPT), cold- and heath- pain thresholds (CPT and HPT). PPT were evaluated using a digital algometer (Wagner Instruments©, Greenwich, CT, USA) at the medial joint space of the knees and anterior aspect of the talocrural joint line of the ankles.[10] For each PwH, the mean value of two PPT assessments performed at a self-reported painful joint without a prothesis was used for comparison with pain-free individuals. Hypersensitivity to

mechanical pressure pain was considered when the PPT value exceeded a Z-score of 1.96 compared to healthy individuals in ≥50% of the painful joints. [27, 28]

CPT and HPT were determined by a 30 x 30 mm thermode of the TSA-2 device (Medoc©, Ramati-Yishai, Israel) attached at the dominant wrist.[29, 30] Starting at 32°C, the temperature increased or decreased with 1°C per second. A maximum was set at 0°C and 50°C to prevent tissue damage. Participants had to press the button as soon as the temperature became painful. For both parameters the average of three consecutive recordings was used to determine the threshold.[27] Hypersensitivity to cold or heat was considered when the threshold exceeded the Z-score of 1.96 compared to healthy individuals.[27, 28] PwH presenting at least one of the three evoked pain hypersensitivity phenomena were considered to fulfil step 5. Consequently, PwH who met all five steps of the grading system were classified as having "possible" nociplastic pain, the others as having "unlikely" nociplastic pain.

Step 6 - A history of pain hypersensitivity
A thorough patient interview may suffice to examine a history of pain hypersensitivity to touch, pressure, movement or cold and heat.[19] However, we had the possibility to use the QST results from step 5 to determine whether PwH had a history of pain hypersensitivity.[19] Consequently, PwH who fulfilled step 5 also fulfilled step 6.

Step 7 - The presence of comorbidities
To evaluate the final step, we followed the additional recommendations of Nijs et al.[31] and used the results from the Central Sensitization Inventory (CSI) questionnaire (part A), since it covers the listed comorbidities such as increased sensitivity to sound, light and/or odours, sleep disturbance with frequent nocturnal awakenings, fatigue and cognitive problems. Comorbidities are scored using a numerical rating scale: never (0), rarely (1), sometimes (2), often (3), and always (4) present.[32] Since no recommendations are yet available on what score the item should have to be defined as a comorbidity, we chose a strict cut-off. PwH achieving at least a score of 3 (often present) for "two or more" comorbidities were considered to meet this criterion and therefore classified as having "probable" nociplastic pain. Indeed, this contrasts with having "one" comorbidity in the IASP clinical criteria for nociplastic pain, but as a recent study highlighted, thorough clinical reasoning is needed to decide whether comorbidities can contribute to pain phenotyping.[33] For example sleep disturbances are commonly reported[34] in PwH, including in people with mild haemophilia[35] and in the general population.[36] Besides part A of the CSI questionnaire, part B was used to collect additional information on specific central sensitivity syndromes that have been diagnosed in the past.

Table 1. The IASP clinical criteria and grading system for nociplastic pain applied to pain in PwH

STEP 1.	**The pain is chronic:** PwH with chronic pain will fulfil this step.
STEP 2.	**The pain has a regional/multifocal/widespread distribution:** ≥4 painful body sites on the BPI-Body chart.
STEP 3.	**The pain cannot entirely be explained by nociceptive mechanisms:** All PwH will fulfil this step, since it is impossible to reliably identify nociceptive pain as the main driver of the PwH's experienced pain.
STEP 4.	**The pain cannot entirely be explained by neuropathic mechanisms:** PwH without possible neuropathic pain will fulfil this step. (Possible neuropathic pain: a DN4 score of ≥4/10 and a neuroanatomically plausible pain distribution).
STEP 5.	**Evoked hypersensitivity phenomena:** PwH presenting evoked hypersensitivity evaluated with QST will fulfil this step: - Pressure Pain Threshold at painful knee/ankle joints without prothesis: Hypersensitivity: Z-score >1.96 in ≥50 of painful joints ⇔ healthy individuals - Cold & Heat Pain Threshold at dominant wrist: Hypersensitivity: Z-score >1.96 ⇔ healthy individuals
	Possible nociplastic pain: PwH who fulfil all 5 steps. **Unlikely** nociplastic pain: PwH who fulfil none or some of the steps.
STEP 6.	**A history of pain hypersensitivity:** When QST results are present they can be used to determine whether PwH have a history of pain hypersensitivity. PwH who present pain hypersensitivity in step 5 will automatically fulfil step 6.
STEP 7.	**The presence of comorbidities**: PwH will fulfil step 7 if they achieve at least a score of 3 (often present) for ≥2 comorbidities on the CSI part A: - Increased sensitivity to: (1) bright lights or (2) odours - Sleep disturbances: (3) bad sleep, (4) feeling unrefreshed, (5) restless legs - Fatigue: (6) having low energy, (7) getting tired very easily when physically active - Cognitive problems: (8) having difficulty to concentrate, (9) memory disturbances
	Probable nociplastic pain: PwH who fulfil all 7 steps.

Abbreviations: PwH, People with Haemophilia; BPI, Brief Pain Inventory; DN4, Douleur Neuropathique en 4 questions; QST, Quantitative Sensory Testing ; CSI, Central Sensitization Inventory.

Comparison between groups

After the application of the grading system, PwH were divided into three subgroups: "unlikely"-, "possible"- and "probable" nociplastic pain. Additionally, patient characteristics (i.e. anthropometric, demographic and clinical details) and psychological factors were compared to investigate intergroup differences. Psychological factors were investigated by a battery of validated self-reported questionnaires. The Pain Catastrophizing Scale (PCS) examined the degree of catastrophic thinking in the content domains of rumination, magnification and helplessness. Higher scores indicated higher levels of pain catastrophizing.[37] The Hospital Anxiety and Depression Scale (HADS) was used to investigate symptoms of anxiety and depression. Higher scores indicated more symptoms of anxiety and depression.[38] Fear-avoidance beliefs were measured using the Fear Avoidance and Beliefs Questionnaire (FABQ). Higher scores indicated elevated fear-avoidance beliefs. Health-related quality of life (HR-QoL) was evaluated with the EuroQol-5 Dimensions 5 Levels questionnaire (EQ-5D-5L). A health utility index (EQ-HUI) score was calculated to rate the impact of their disease on mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The visual analogue scale (EQ-VAS) asked participants to rate their health state from 0 "worst imaginable" to 100 "best imaginable".[39]

Statistical analyses

Statistical data analyses were carried out using the IBM Statistical Package for Social Sciences Version 28 (SPSS, IBM Corporation, Armonk, NY). Descriptive data for continuous variables are presented as means and standard deviations (±SD), data for categorical variables are presented as percentages. The Student's t-test was applied to compare PwH and healthy individuals. One-way analysis of variance (ANOVA) was used to compare patient characteristics and psychological factors between the subgroups formed after applying the IASP clinical criteria and grading system of nociplastic pain. Additionally, analysis of covariance (ANCOVA) was used to compare patient characteristics and psychological factors while controlling for age. Post hoc analyses following ANOVA and ANCOVA were adjusted for multiple hypothesis testing using a Bonferroni correction ($\alpha=0.05/3=0.017$). Frequency differences for categorical variables were tested using the Chi-squared test. Significance level was set at 0.05.

Results

Participants

Clinical data from 94 PwH and 41 pain-free healthy individuals, who underwent a comprehensive pain assessment between February 2020 and April 2022, were available to apply to the grading system. Demographic, anthropometric and clinical characteristics are presented in Table 2.

The classification of nociplastic pain

For each step of the grading system, the number and percentage of PwH that fulfilled the criteria are presented below. Figure 1 provides a visual overview of the clinical reasoning process

Step 1 – A chronic pain duration

In total 94 PwH (100%) suffering from chronic pain were included.

Step 2 - A regional/multifocal/widespread pain distribution

According to the BPI body chart, 35 PwH (37%) indicated at least four painful body sites and were therefore considered as having regional/multifocal/widespread pain. The remaining 59 PwH (63%) indicate less than four painful sites and were therefore removed from the grading system, as they were unlikely to have nociplastic pai.

Step 3 - The pain cannot entirely be explained by nociceptive mechanisms

As mentioned in the methods section, we did not exclude participants based on this condition, so the remaining 35 PwH (37%) were considered to move on to the next step.

Step 4 - The pain cannot entirely be explained by neuropathic mechanisms

Of the 35 PwH, 16 scored ≥4/10 on the DN4, but none of them had a positive DN4 score together with a neuroanatomically plausible pain distribution on the BPI body chart. For this reason, the presence of pain entirely explained by neuropathic pain is unlikely, and all 35 PwH (37%) moved further to the next steps.

Step 5 - Evoked hypersensitivity phenomena

Table 3 presents the QST results of the 35 PwH. Fourteen of them (40%) had a cold-, heat- or pressure- pain threshold exceeding the Z-score of 1.96 compared to healthy individuals, indicating clinical signs of evoked pain hypersensitivity. Consequently, these 14 PwH met the requirements of the first five steps and could therefore be classified as PwH having "possible" nociplastic pain.

Table 2. Demographic, anthropometric and clinical characteristics of the participants

	PwH (n=94)		Healthy individuals (n=41)		p-value[a]
	mean ± SD (range)	n (%)	mean ± SD (range)	n (%)	
Age (years)	41.7 ± 16.9 (18-81)	-	38.8 ± 17.2 (18-79)	-	.372
Weight (kg)	80.8 ± 16.1 (48.7-128)	-	77.5 ± 10.9 (60-104)	-	.177
Height (m)	1.77 ± 0.06 (1.60-1.88)	-	1.80 ± 0.07 (1.64-1.93)	-	**.005**
BMI (kg/m^2)	26.0 ± 4.9 (16.9- 40.9)	-	24.1 ± 3.3 (18.6- 31.1)	-	**.008**
Type of haemophilia - severity					
A - severe	-	62 (66.0%)	-	-	
A - moderate		12 (12.8%)			
B - severe		11 (11.7%)			
B - moderate	-	9 (9.6%)	-	-	
Treatment regimen					-
On-demand	-	11 (11.7%)	-	-	
Prophylaxis	-	83 (88.3%)	-	-	
Self-reported use of pain medication		24 (25.5%)		0 (0%)	**<.001[b]**
Non-opioid analgesics	-	14 (14.9%)	-	-	
Non-opioid + weak opioid analgesics	-	1 (1.1%)	-	-	
Non-opioid analgesics + recombinant factor	-	9 (9.6%)	-	-	
Positive HIV	-	6 (6.4%)	-	-	-
Hepatitis C					-
Negative	-	44 (46.8%)	-	-	
Succesfully treated for HCV (negative viral load)	-	50 (53.2%)	-	-	

Data are presented as mean ± SD for continuous variables and as frequency counts (%) for categorical variables. ***Abbreviations:*** PwH, people with haemophilia; SD, standard deviation; kg, kilograms; m, meters; BMI, body mass index; HIV, human immunodeficiency virus; HCV, hepatitis C virus. [a]Student's t-test, P<0.05. [b]Chi-squared tests, P<0.05.

Table 3. Results Quantitative Sensory Testing

QST	Healthy individuals (n=41)		PwH (n=35)			
	n	mean ± SD	n	mean ± SD	n(%) Z-score >1.96	n(%) Z-score PPT >1.96 in ≥50% of painful joints or Z-score CPT/HPT >1.96
CPT wrist (°C)	41	6.67 ± 7.98	33[a]	10.19 ± 9.77	7 (20%)	14 (40%)
HPT wrist (°C)	41	46.36 ± 2.60	33[a]	45.90 ± 3.22	3 (9%)	
PPT knee left (N)	41	67.04 ± 20.18	14[b]	36.72 ± 16.72	6 (17%)	
PPT knee right (N)	41	68.64 ± 22.37	10[b]	43.73 ± 16.25	1 (3%)	
PPT ankle left (N)	41	68.94 ± 19.84	22[b]	41.25 ± 17.14	7 (20%)	
PPT ankle right (N)	41	68.87 ± 22.59	24[b]	43.42 ± 19.77	3 (9%)	

[a]Two missing values for this outcome parameter

[b]Number of PwH reporting the joint as painful (but without prothesis).

Abbreviations: QST, Quantitative Sensory Testing ; CPT, Cold Pain Threshold; HPT, Heat Pain Threshold; PPT, Pressure Pain Threshold; N, Newton.

Step 6 - A history of pain hypersensitivity

As mentioned in the Methods section, all 14 PwH who fulfilled step 5 also fulfilled step 6.

Step 7 – The presence of comorbidities

From the 14 remaining PwH, nine (10%) had at least a score of 3 ('often present') for two or more comorbidities of the CSI (part A). Therefore, these nine PwH (10%) could be classified as having "probable" nociplastic pain. Among those, four PwH (44%) reported having been diagnosed with a central sensitivity syndrome in the past.

Comparison between groups

According to the IASP clinical criteria for nociplastic pain, PwH were classified into three subgroups: PwH with "unlikely" nociplastic pain (n=80), PwH with "possible" nociplastic pain (n=5), and PwH with "probable" nociplastic pain (n=9). Given the small sample size, the "possible" and "probable" nociplastic pain subgroups were merged into one "at least possible" nociplastic pain subgroup (n=14), for analyses of differences between the PwH subgroups and the group of healthy individuals (n=41), in which 3 groups were compared (Table 4).

One-way ANOVA showed significant group differences in height (P=.004), body mass index (BMI, P=.038), use of self-reported pain medication (P<.001) and psychological factors (all P<.012). Pairwise post-hoc comparisons (Bonferroni-corrected) revealed that PwH with "at least possible" nociplastic pain were significantly shorter compared to healthy individuals (P=.005), but could not demonstrate significant between-group differences for BMI. For the psychological factors, both PwH with "unlikely" nociplastic pain and PwH with "at least possible" nociplastic pain showed significantly higher mean scores compared to healthy individuals (all P<.012). There were no significant differences between PwH with "unlikely" and "at least possible" nociplastic pain.

When taking age into account, ANCOVA revealed significant group differences for body height (P=.013) and psychological factors (all P<.013). Pairwise post-hoc comparison revealed that both PwH with "unlikely" and "at least possible" nociplastic pain showed significantly higher mean scores for psychological factors compared to healthy individuals (all P<.016). There were no significant differences between PwH with "unlikely" and "at least possible" nociplastic pain.

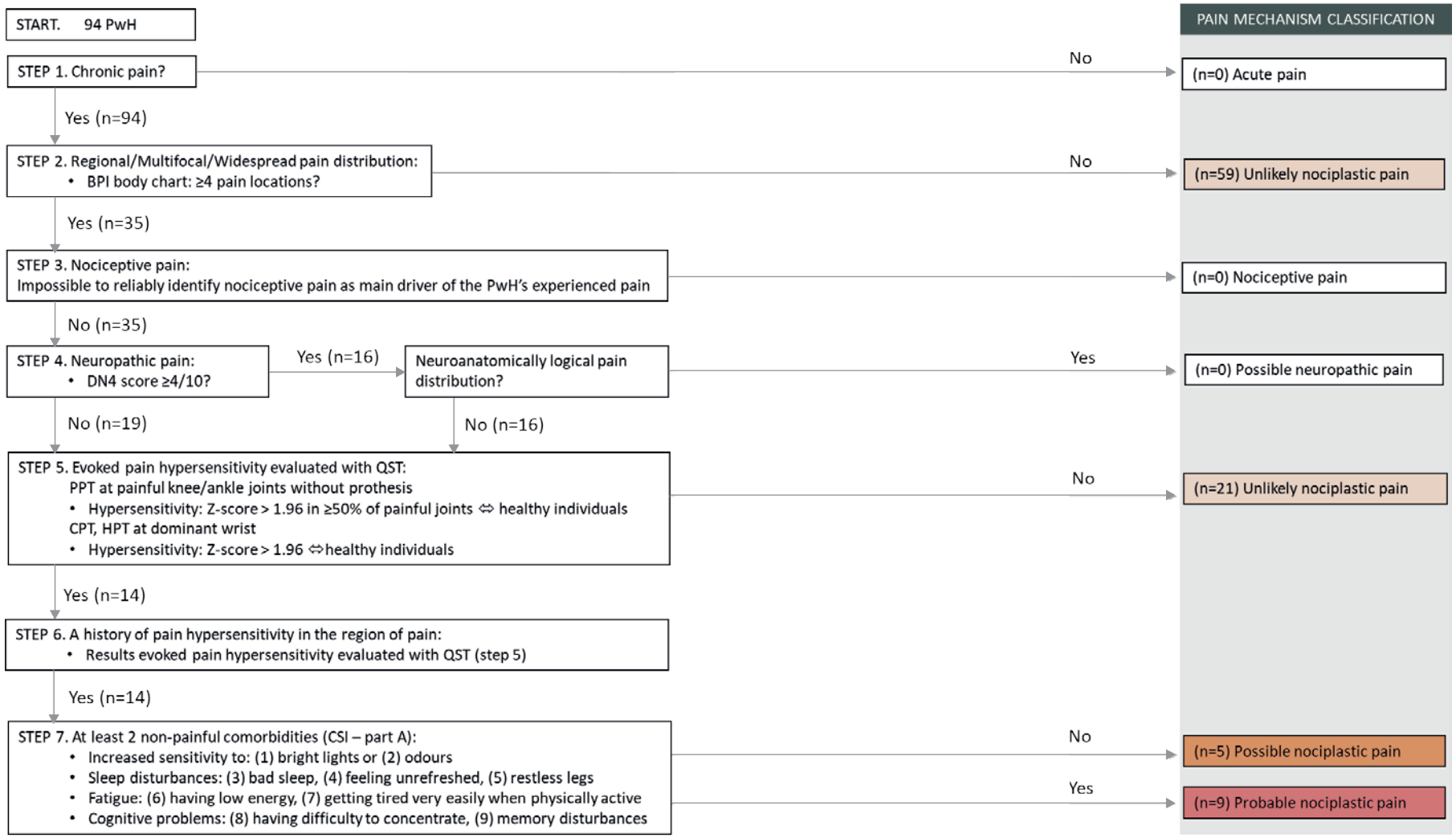

Figure 1. Clinical reasoning process on the application of the IASP clinical criteria and grading system for nociplastic pain in PwH.

Table 4. Subgroup analysis by ANOVA and ANCOVA (adjusted for age)

	PwH with "unlikely" nociplastic pain (n=80)	**PwH with "possible" nociplastic pain (n=14)**		**Healthy individuals (n=41)**	**ANOVA p-value**	**P-value* pairwise comparison subgroups (ANOVA)**	**ANCOVA p-value**	**P-value* pairwise comparison subgroups (ANCOVA)**
	mean ± SD (range) or n(%)	**mean ± SD (range) or n(%)**		**mean ± SD (range) or n(%)**				
Age (years)	40.3 ± 15.9 (18-74)	49.5 ± 21 (19-81)		38.8 ± 17.2 (18-79)	.117	-	-	-
Weight (kg)	80.6 ± 15.1 (48.7-128)	82 ± 21.6 (50-117)		77.5 ± 10.9 (60-104)	.480	-	.526	-
Height (m)	1.77 ± 0.06 (1.62-1.88)	1.73 ± 0.08 (1.60-1.87)		1.80 ± 0.07 (1.64-1.93)	**.004**	**.005** (Possible vs Healthy)	**.013**	-
BMI (kg/m^2)	25.8 ± 4.6 (16.9- 40.9)	27.3 ± 6.7 (18.6- 37.9)		24.1 ± 3.3 (18.6- 31.1)	**.038**	**-**	.069	-
Type of haemophilia- severity					.102[a]	-	-	-
A- severe	53 (66%)	9 (64%)		-				
A- moderate	12 (15%)	-		-				
B- severe	7 (9%)	4 (29%)		-				
B- moderate	8 (10%)	1 (7%)		-				
Treatment regimen					.412[a]	-	-	-
On-demand	11 (14%)	-		-				
Prophylaxis	56 (70%)	11 (79%)		-				
Emicizumab	13 (16%)	3 (21%)		-				
Gene therapy		-		-				
Self-reported use of pain medication	20 (25%)	4 (28%)		0 (0%)	**<.001[a]**	**-**	-	-
Non-opioid analgesics	12 (15%)	2 (14%)		-				
Non-opioid + weak opioid analgesics	1 (1%)	-		-				
Non-opioid + strong opioid analgesics	-	-		-				
Non-opioid analgesics + recombinant factor	7 (9%)	2 (14%)		-				
HADS								
Anxiety (max. 21)	6.0 ± 3.8 (0- 18)	6.3 ± 3.0 (1- 10)		3.6 ± 2.7 (0- 12)	**<.001**	**<.001 '**(Unlikely vs Healthy)	**<.001**	**<.001 '**(Unlikely vs Healthy)
								.016 (Possible vs Healthy)
Depression (max. 21)	4.3 ± 3.5 (0- 15)	5.7 ± 2.6 (0- 9)		2.2 ± 1.9 (0- 7)	**<.001**	**<.001 '**(Unlikely vs Healthy)	**<.001**	**<.001 '**(Unlikely vs Healthy)
						<.001 (Possible vs Healthy)		**<.001** (Possible vs Healthy)
PCS								
Total (max. 52)	14.2 ± 11.1 (0- 47)	20.3 ± 12.6 (0- 37)		7.2 ± 7.1 (0- 23)	**<.001**	**.002** (Unlikely vs Healthy)	**<.001**	**.002** (Unlikely vs Healthy)
						<.001 (Possible vs Healthy)		**<.001** (Possible vs Healthy)
PCS Rumination (max. 16)	4.9 ± 4.4 (0- 16)	7.2 ± 4.5 (0- 13)		3.4 ± 3.7 (0- 14)	**.012**	**.012** (Possible vs Healthy)	**.013**	**.013** (Possible vs Healthy)
PCS Magnification (max. 12)	3.0 ± 2.4 (0- 10)	4.6 ± 3.3 (0- 9)		1.3 ± 1.6 (0- 6)	**<.001**	**<.001 '**(Unlikely vs Healthy)	**<.001**	**<.001 '**(Unlikely vs Healthy)
						<.001 (Possible vs Healthy)		**<.001** (Possible vs Healthy)
PCS Helplessness (max. 24)	6.3 ± 5.4 (0- 23)	8.4 ± 6.4 (0- 21)		2.5 ± 2.6 (0- 10)	**<.001**	**<.001 '**(Unlikely vs Healthy)	**<.001**	**<.001 '**(Unlikely vs Healthy)
						<.001 (Possible vs Healthy)		**<.001** (Possible vs Healthy)

Table 4. Subgroup analysis by ANOVA and ANCOVA (adjusted for age)

	PwH with "unlikely" nociplastic pain (n=80)	PwH with "possible" nociplastic pain (n=14)		Healthy individuals (n=41)	ANOVA p-value	P-value* pairwise comparison subgroups (ANOVA)	ANCOVA p-value	P-value* pairwise comparison subgroups (ANCOVA)
	mean ± SD (range) or n(%)	mean ± SD (range) or n(%)		mean ± SD (range) or n(%)				
FABQ								
Physical activity (max. 24)	13.8 ± 6.2 (0- 24)	16.1 ± 6.4 (7- 24)		9.2 ± 7.5 (0-24)	**<.001**	**.001 '**(Unlikely vs Healthy)	**<.001**	**.001 '**(Unlikely vs Healthy)
						.003 (Possible vs Healthy)		**.006** (Possible vs Healthy)
EQ-5D-5L								
EQ-HUI (max. 1)	.7 ± .2 (0- 1)	.6 ± .2 (.2- .9)		1.0 ± .1 (.7- 1)	**<.001**	**<.001 '**(Unlikely vs Healthy)	**<.001**	**<.001 '**(Unlikely vs Healthy)
						<.001 (Possible vs Healthy)		**<.001** (Possible vs Healthy)
EQ-VAS (max. 100)	70.4 ± 15.3 (27- 80)	69.0 ± 19.8 (30- 100)		84.9 ± 8.5 (67- 100)	**<.001**	**<.001 '**(Unlikely vs Healthy)	**<.001**	**<.001 '**(Unlikely vs Healthy)
						.001 (Possible vs Healthy)		**<.001** (Possible vs Healthy)

Data are presented as mean ± SD for continuous variables and as frequency counts (%) for categorical variables.
Abbreviations: PwH, people with haemophilia; SD, standard deviation; kg, kilograms; m, meters; BMI, body mass index; HIV, human immunodeficiency virus; HCV, hepatitis C virus; HADS, hospital anxiety and depression scale; PCS, pain catastrophizing scale; FABQ, fear-avoidance and beliefs questionnaire; EQ-5D-5L, EuroQol 5 dimensions 5 levels questionnaire; EQ-HUI, EuroQol health utility index; EQ-VAS, EuroQol visual analogue scale.
[a]P-values calculated using Chi-squared tests.
*p-values for posthoc analysis corrected with Bonferroni method (α=.05/3=.017).

Discussion

Application of the IASP clinical criteria and grading system of nociplastic pain revealed that 80/94 PwH (85%) could be classified with "unlikely" nociplastic pain, 5/94 PwH (5%) with "possible" and 9/94 PwH (10%) with "probable" nociplastic pain. When merging the latter two into a group with "at least possible" nociplastic pain, these 14 PwH (15%) were significantly shorter than healthy individuals. Both PwH with "at least possible" and "unlikely" nociplastic pain showed significantly higher levels of unhelpful psychological factors compared to healthy individuals. When controlling for age, again both PwH groups (i.e. "unlikely" and "at least possible" nociplastic pain) showed significantly higher levels of unhelpful psychological factors compared to healthy individuals. These findings suggest that age may partially account for the observed group differences in body height and psychological factors.

Indeed, considering that many conditions clinically show a mixed presentation of pain mechanisms[40], we did not intent to utilize the criteria to identify a single pain mechanism, but rather to investigate the predominant pain mechanism in PwH. Since this is the first field study applying the clinical criteria for nociplastic pain in a haemophilia population, a cautious interpretation is needed. Therefore, we would like to highlight the challenges encountered during the course of this study:

A clear definition of regional/multifocal/widespread pain is needed

Pain drawings have recently been recommended as reliable and valid tools to evaluate an individuals' pain distribution.[31] However, this recommendation does not provide a clear definition or cut-off when a patient presents a regional, multifocal or widespread pain distribution which is indicative for nociplastic pain. [19] Consistent with a previous study, we considered individuals who indicated four or more painful body sites as having regional pain.[25] But a clear definition is needed when this criteria is used for identifying nociplastic pain, to avoid the decision depending entirely on the expertise and clinical reasoning of HCPs.

Clinical criteria or a grading system for nociceptive pain is needed

Currently, no single guidelines or criteria exist for nociceptive pain. Therefore, the IASP Terminology Task Force recognises the reliance on clinical judgement to decide whether nociceptive pain mechanisms can be considered entirely responsible for the person's pain as a major limitation. [19] For this reason we assumed that it would not be possible to reliably identify nociceptive pain as the main driver of pain in PwH. Thus, further research is needed to elaborate this.

The evaluation of evoked pain hypersensitivity needs clarification

Again, no clear definition or cut-off values are provided to define evoked pain hypersensitivity as a clinical criteria for nociplastic pain.[19] Therefore, by analogy with the field study of Schmidt et al. (2022)[28, 41], we defined hypersensitivity as a QST threshold exceeding the Z-score of 1.96 compared to healthy individuals. In addition, information about the exact body location where the QST analysis should be performed is lacking.[19] Since we are convinced that QST in one painful body region might overestimate the presence of pain hypersensitivity, we opted for a stricter cut-off, namely that hypersensitivity had to be present in ≥50% of the painful body regions. QST at remote locations, such as the dominant wrist in our case, seems more reliable because it immediately investigates secondary hyperalgesia.[42] Moreover, we support the suggestion of Schmidt et al.(2022) to switch the sequence of step 4 and step 5, as we agree that clinical pain assessment should follow the patient's history and self-reported questionnaires, by analogy with the grading system for neuropathic pain.[20] Especially, since QST is not mandatory to assess pain hypersensitivity[19], it would make more sense for clinicians who cannot include QST in daily practice.

The impact of assessing comorbidities

Our subgroup analysis revealed that PwH with "at least possible" nociplastic pain were significantly shorter and reported higher levels of unhelpful psychological factors (i.e. pain catastrophizing and anxiety) compared to healthy individuals. Although these differences may be related to the higher age of PwH with "at least possible" nociplastic pain, we should continue to investigate comorbidities (i.e. through the CSI) in PwH. Since studies showed that obesity[43], sleep disturbances[44] and unhelpful psychological factors[45] are risk factors for the development of chronic pain, we should include these risk factors in the biopsychosocial pain management approach.

Strengths and limitations

As mentioned above, this is the first field test application of the IASP clinical criteria for nociplastic pain in a large sample of PwH, which may motivate other researchers investigating chronic musculoskeletal pain conditions (including haemophilia) to explore it further. Secondly, the task force indicated the dependence on clinical judgement of the investigator as a major limitation of the clinical criteria.[19] To overcome this limitation, we assessed the criteria as objectively as possible based on validated QST protocols, existing literature and cut-offs.[27] A limitation of this study is that for the subgroup analysis, we had to combine the subgroups having "possible" and "probable" nociplastic pain into one group with "at least possible" nociplastic pain. A power analysis showed that comparing a group with 14 observations to groups with 80 and 41 observations, offers 80% power to detect an effect size (Cohen's D) of 0.79 and 0.86 standard deviations at a significance level of .05. Since this is the first study ever

investigating this, no reference data are available to judge whether these differences are realistic. With a larger sample size, more subtle differences between the "at least possible" group and the two other groups can be detected.

Clinical implications and implications for future research

The IASP task force has strongly encouraged field tests of the clinical criteria, but to date, clinimetric and psychometric properties have not been investigated. Therefore, validation studies are urgently needed to ensure that future field tests follow validated and reliable procedures. In addition, the present study provides information for future experimental studies. For example, studies investigating pain management strategies tailored to a predominant nociplastic pain mechanism (i.e. interventional studies focussing on psychological treatment modalities[45] or trials of centrally acting pain medications such as antidepressants or serotonin-norepinephrine reuptake inhibitors).[6, 46]

Conclusion

A subgroup of PwH could be classified as having at least possible nociplastic pain. This early identification of PwH with predominant nociplastic pain might be an important step towards more effective and tailored pain management. Since this field study applied the IASP clinical criteria for nociplastic pain in haemophilia for the first time, reference data are not yet available and further studies with a larger sample size may be needed to detect more subtle differences between groups. Moreover, further studies examining the clinimetric and psychometric properties of the IASP clinical criteria are needed, as we believe that sound criteria could help HCPs in steering their pain approach.

Author Contributions

Investigation: A.F. and V.-A.C.; analysis: A.F.; writing original first draft preparation: A.F.; writing-review and editing: N.A.R., V.-A.C., P.M., L.D., S.L., C.L., C.H. and M.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Antwerp University Hospital (B300201942301, approval 2 December 2019).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data available on request from the authors.

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Conflicts of Interest

The authors declare no conflict of interest.

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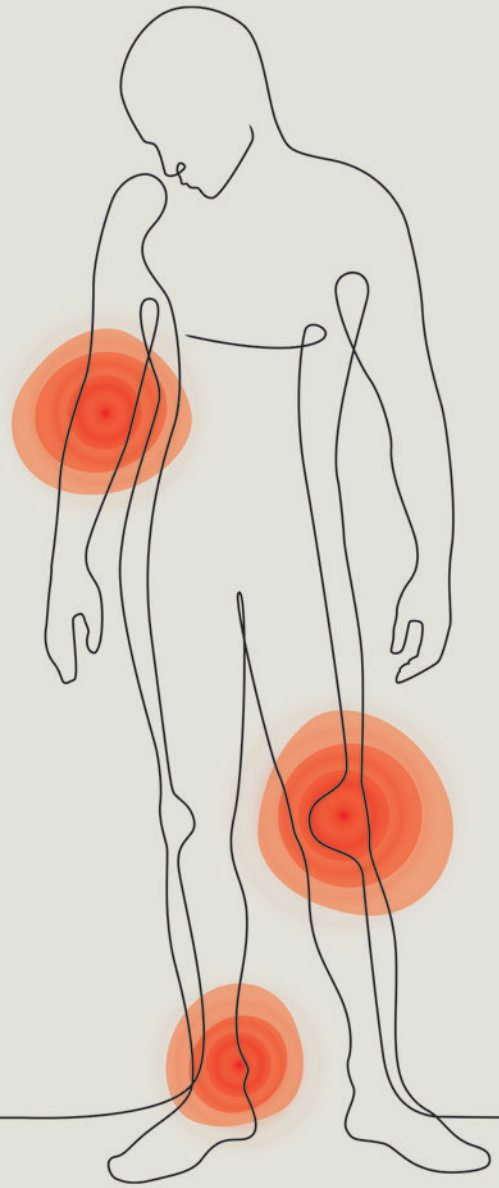

Chapter 5

Determinants of pain interference in adults with moderate and severe haemophilia: a one-year prospective study

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Abstract

Background: In chronic musculoskeletal conditions, a biopsychosocial pain assessment allows to explore interactions between biological and psychological factors, as well as their influence on the experience, impact and chronification of pain. Despite the multidimensional character of pain in people with haemophilia (PwH), evidence is lacking on pain-related and psychological factors influencing the impact of pain on daily functioning (i.e. pain interference).

Objectives: This study aimed to determine associations between pain-related and psychosocial factors at baseline and pain interference at one-year follow-up in adults with moderate/severe haemophilia.

Methods: Ninety-nine PwH completed a battery of questionnaires at baseline: the Brief Pain Inventory (BPI), Central Sensitization Inventory, Hospital Anxiety and Depression Scale, Pain Catastrophizing Scale, Fear Avoidance and Beliefs Questionnaire and Illness Perceptions Questionnaire – Brief Version. Twelve months later the participants were asked to complete the BPI pain interference subscale again. Associations between baseline factors and pain interference at follow-up were determined by stepwise multiple linear regression analysis.

Results: Ninety-one PwH completed follow-up. Pain-related (i.e. pain severity and distribution and self-reported symptoms of central sensitization) and psychological factors (i.e. pain catastrophizing, anxiety and fear-avoidance beliefs) at baseline were significant determinants of pain interference with daily functioning at one-year follow-up. Up to 55% of the variance in pain interference could be explained by baseline pain severity (41%), symptoms of central sensitization (11%) and pain distribution (3%).

Conclusions: These findings highlight the importance of a biopsychosocial pain assessment in PwH to identify individuals at risk for the development of persistent pain interference with daily functioning.

Introduction

Despite improved treatment strategies, it remains widely accepted that joint arthropathy is still highly prevalent in people with haemophilia (PwH). Haemophilic arthropathy not only has a huge impact on daily functioning, but also causes reduced health-related quality of life (HR-QoL) and chronic pain.[1] Recent studies indicated that more than two-thirds of adults with severe haemophilia experience daily joint pain[2] and that 89% of PwH report that pain affects their daily lives.[3]

By analogy with other chronic musculoskeletal (MSK) conditions, such as osteoarthrosis and low back pain, no one-to-one relationship has been found between pain symptoms and the degree of tissue damage demonstrated on medical imaging.[4, 5] These findings do not mean that we should dismiss the search for possible joint pathology, but we should also pay attention to components that interact and determine the individual's pain experience.[6] A biopsychosocial approach allows to examine the interaction between biological (i.e. physical), psychological and social factors, as well as their influence on the experience, impact and chronification of pain.[7]

Currently, there are numerous self-reported questionnaires available that aim to assist healthcare professionals (HCPs) in comprehending the biopsychosocial background of an individual's pain. For example, the Brief Pain Inventory (BPI) is a multidimensional pain assessment tool commonly used for pain assessment in chronic MSK conditions.[8] In both clinical and research settings, it is often applied to obtain information about pain severity, pain distribution and the extent to which pain interferes with daily functioning. Some recent studies have also used the BPI questionnaire in PwH and found that their pain interfered with daily activities, sleep, emotions and HR-QoL.[9, 10] Despite these findings, the use of multidimensional pain questionnaires is not yet implemented in routine consultations.

The same applies to the limited evaluation of pain-related psychological factors (i.e. beliefs and emotions about pain) in haemophilia care. In many chronic MSK conditions it was found that psychological factors have an influence on future pain and disability.[11, 12] Moreover, studies found that negative beliefs and perceptions about pain were associated with unhelpful pain coping behaviour strategies, poor treatment outcome and treatment adherence.[13] Preliminary cross-sectional studies in PwH showed associations between non-helpful psychological factors (i.e. fear and pain catastrophizing) and the number of painful body sites[14] and between illness perceptions and coping behaviour strategies (i.e. treatment adherence).[15, 16] In contrast to the longitudinal results in other MSK populations, prospective studies investigating the prognostic value of pain characteristics and psychological factors in PwH are still lacking.

This study aimed at prospectively determining associations between baseline pain-related and psychological factors and the impact of pain on daily functioning (i.e. pain interference) at one-year follow-up in a large sample of adults with moderate and severe haemophilia. The findings of this study may help in the early identification of PwH at risk of developing persistent pain interference.

We hypothesised that more severe pain characteristics such as a wider pain distribution, higher pain intensity and self-reported symptoms of central sensitization (i.e. hyper-sensitivity to sensory stimuli or senses unrelated to the MSK system) and unhelpful psychological factors (i.e. pain catastrophizing, fear-avoidance beliefs, etc.) observed at baseline would be associated with more pain interference at follow-up.

Methods

Study design and setting

This prospective cohort study included baseline data (that were published/submitted elsewhere)[5, 14] of PwH examined between February 2020 and January 2022. Adult male PwH regularly followed at the Haemophilia Comprehensive Centre of the Cliniques universitaires Saint-Luc (Brussels, Belgium) and the Antwerp University Hospital (UZA) (Edegem, Belgium) were invited to participate. After their regular consultation, a comprehensive evaluation of joint function, structure, psychological outcomes and pain was performed.[5, 14] Baseline parameters of the following questionnaires were included: the Brief Pain Inventory (BPI), the Central Sensitization Inventory (CSI), the Fear Avoidance and Beliefs Questionnaire (FABQ), the Pain Catastrophizing Scale (PCS), the Hospital Anxiety and Depression Scale (HADS) and the Illness Perceptions Questionnaire – Brief version (IPQ-B). One year after the baseline assessment, participants were asked to complete the BPI pain interference subscale again (Figure 1). The ethical committee of both centres approved the study (B300201942304) and all participants provided written informed consent.

Participants

Inclusion criteria were as follows: adult males (18-65 years) with moderate or severe haemophilia A/B on a stable treatment regimen for at least six months. PwH with a haemarthrosis in the month preceding inclusion or those with known neuropathies with definite medical causes independent from haemophilia (e.g. diabetes polyneuropathy) were excluded as this might influence pain assessment.[17]

Dependent outcome variables

Pain interference at one-year follow-up

In The **BPI – Pain interference items (BPI-PI)** the participant is asked to rate the degree to which his pain interfered with seven domains including general activity, mood, walking, normal work, relations with others, sleep and enjoyment of life.[18] For each activity, 11-point numeric rating scales ranging from 0 (“no interference”) to 10 (“interferes completely”) were used to calculate a mean pain interference score (BPI-PI, 0-10). A higher total score represents more severe pain interference, with categories of no (0), mild (1-3), moderate (4-6) and severe pain interference (7-10).[18] The BPI was shown to be a valid and reliable tool to use in PwH.[19]

Independent outcome variables

Baseline pain-related characteristics

The **BPI – Pain severity item (BPI-PS)** evaluated the PwH’s pain severity during the last 24h as worst, least, average and current pain. For these four items, 11-point numeric rating scales ranging from 0 (“no pain”) to 10 (“worst imaginable pain”) were used to calculate one mean pain severity score (BPI-PS, 0-10). A higher score indicates higher pain severity, with categories of no (0), mild (1-3), moderate (4-6) and severe pain (7-10). [18] The **BPI – Body chart (BPI-BC)** was used to count the number of painful body regions to understand the participant’s pain distribution. A higher score indicates a higher number of painful sites.[18] The **CSI – Part A** was used to investigate symptoms of central sensitization (i.e. hypersensitivity to noise, bright light, odours, concentration and sleep difficulties).[20] The presence of 25 symptoms was scored from 0 “never” to 4 “always” present. A total score exceeding ≥40/100 indicates central sensitization.[21]

Baseline psychological factors

Anxiety and depression levels were measured using the **HADS**, consisting of two subscales with seven items each.[22] For these 14 items, 4-point numeric rating scales (0-3) were used to calculate the total score (0-42). A higher total score indicated higher levels of anxiety and depression.[23] Participants who scored ≥8 were considered “probably” anxious or depressed. The 13-item **PCS** was used to assess the degree of catastrophic thinking during previous painful events in the content domains of rumination, magnification and helplessness.[24, 25] Participants scored each item on a 5-point scale ranging from 0 (“not at all”) to 4 (“all the time”), resulting in a total score (0-52). A higher total score indicates a higher level of pain catastrophizing.

The **IPQ-B** questionnaire allows researchers to replace the term “illness” with the condition they are investigating.[26-28] Therefore we replaced “illness” with “haemophilia-related joint pain” to assess participants’ perceptions of it. The questionnaire consists of eight dimensions: identification (i.e. degree of experienced symptoms), timeline

(i.e. beliefs regarding the chronicity), concerns (i.e. concerns about their joint pain), consequences (i.e. impact on daily life), personal control (i.e. self-control over their joint pain), treatment control (i.e. efficacy of treatment modalities), emotional representation (i.e. emotional impact), and coherence (i.e. personal understanding of their joint pain). Each dimension is scored on a 11-point numeric rating scale (0-10). High scores on the identification, timeline, concerns, consequences and emotional representation indicate unhelpful beliefs about their joint pain. High scores on the personal control, treatment control and coherence dimension indicate helpful beliefs and a good understanding of their joint pain.[26] The last item of the IPQ-B asked the participant to rank the three most important factors causing their joint pain.

Only the dimension of personal control (0-10) as an independent variable was considered, since it specifically focusses on the PwH's perception of self-control over their joint pain.

Fear-avoidance beliefs were measured using the **FABQ – Physical activity subscore (FABQ-PA).** The FABQ-PA was originally developed for people with low back pain and showed excellent psychometric properties.[29] A modified version has been used in a population of people with knee pain, where they changed the word "back" to "knee".[30] By analogy with this study, we modified the word "back" to "joint pain", since haemophilia affects multiple joints. The FABQ-PA scale consists of four items (0-6), resulting in a total score (0-24). A score ≥15 is considered as elevated fear-avoidance beliefs.[29]

Sample size

Based on a-priori sample size calculation using Gpower® 3.1.9.2. (Franz Faul, Kiel University, Germany) for linear multiple regression: Fixed model, with $\alpha = .05$, 7 predictors (pain severity, pain distribution, signs of central sensitization, pain catastrophizing, fear-avoidance beliefs, level of anxiety and depression, pain controllability), and medium effect size of .18, a total sample of 88 participants was needed with an actual power of .80.

Statistical analysis

Data were analysed using SPSS 28.0 (IBM software). Baseline characteristics of participants who dropped out and those who remained at follow-up were compared using Mann-Whitney U and Chi-squared tests for categorical data to check for selective loss-to-follow-up. Associations between baseline pain characteristics (pain severity (BPI-PS); distribution (BPI-BC); symptoms of central sensitization (CSI)) and psychological factors (pain catastrophizing (PCS); anxiety and depression (HADS); fear-avoidance beliefs (FABQ-PA) and perception of personal control (IPQ-B)) as potential predictor

variables on the one hand and the dependent variable pain interference with daily functioning at one year follow-up (BPI-PI) were explored using Pearson's correlations. Correlations were considered low, fair, moderate and very strong with coefficient of .10-.29, .30-.59, .60-.79, ≥.80.[31]

A multiple regression model was conducted using stepwise forward elimination, containing all independent variables with a significant association with the dependent variable upon simple linear regression. The linear model only include complete data. To exclude any bias due to working with complete cases, we refitted these models using a linear mixed model, taking the baseline measurements into account.

These models consider the baseline and follow-up values of the dependent variable (BPI-PI) as a repeated measurement, correcting for the non-independence between the two measurements within the same person using a random intercept term. As fixed effects, the linear mixed model includes the predictor of interest, and time as a covariate. The model assumption from all fitted regression models (homoscedasticity and normality of residuals) were checked using diagnostic plots. The significance level was set at .05.

Results

Participants

Of the 99 PwH who participated at baseline, 91 PwH (92%) completed the one-year follow-up questionnaires. A detailed flowchart of the study procedure is presented in figure 1. Demographic, anthropometric and clinical characteristics are presented in Table 1. Eight participants (8%) dropped out because they were unreachable (n=3) or refused to participate in the follow-up study due to lack of time (n=5). Results of the comparative analysis between participants who completed the study and those who dropped out are described in Appendix 1. PwH who dropped out reported significantly lower pain severity, pain interference, pain catastrophizing at baseline and indicated fewer painful body regions compared to PwH who completed the whole study ($p<.05$).

Descriptive analysis of pain characteristics and psychological factors

Results of the pain and psychological questionnaires are detailed in Table 2. Fifty-one PwH (56%) reported mild pain severity (BPI-PS, 1-3/10) and 14 PwH (15%) at least moderate pain severity (BPI-PS, ≥4/10) during the last 24h before baseline assessment. Seventy-nine PwH (87%) reported at least 1 painful joint, while 26 PwH (29%) reported ≥4 painful joints. At baseline, 21 PwH (23%) reported that their pain interfered at least moderately with their daily functioning (BPI-PI, ≥4/10). At follow-up this was 17 PwH (18%). Twelve PwH (13%) reached the cut-off for central sensitization (CSI, ≥40).

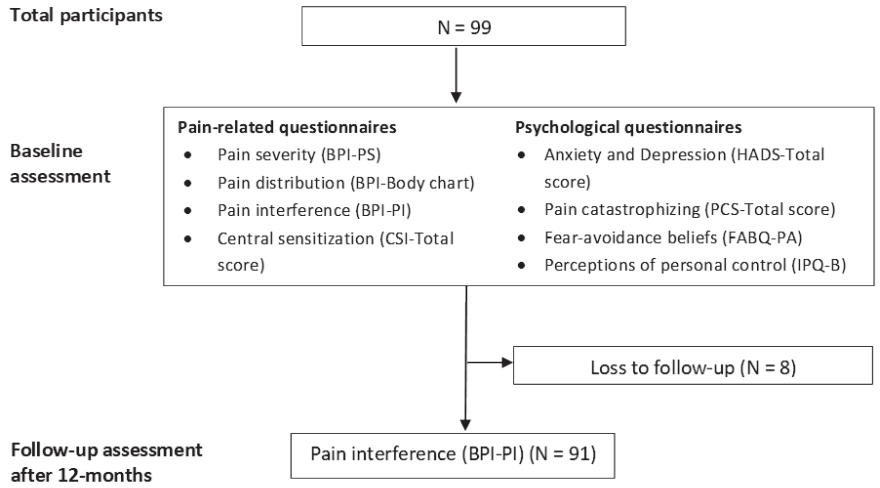

Figure 1. Flowchart of the study procedure

Twenty-six PwH (29%) were likely to suffer from anxiety (HADS-Anxiety, ≥8/21), while 11 PwH (12%) were likely to suffer from depression (HADS-Depression, ≥8/21). Almost half of the PwH (48%) reported elevated fear-avoidance beliefs (FABQ-PA, ≥15/24). PwH reported high levels of helpful beliefs regarding understanding their joint pain (7.9 ± 2.2) and treatment control (7.3 ± 2.7), but lower levels of personal control (5.4 ± 2.5). High levels of unhelpful beliefs about their joint pain were reported for the dimensions of timeline (8.7 ± 2.6) and concern (6.0 ± 3.1), while moderate to low levels were reported for consequences (5.0 ± 2.8), identify (5.0 ± 2.9) and emotional response (4.4 ± 2.9).

Table 3 describes the self-reported causes for their haemophilia-related joint pain. Bleeding was reported in 27 PwH (30%) as main reason, followed by intense physical activity or overuse in 12 PwH (13%) and having no idea in 12 PwH (13%). In total, 10 PwH (11%) filled in "I have no idea" three times or left all boxes blank.

Table 1. Characteristics of PwH completing the whole study (n=91)

	mean ± SD (range)	n (%)
Age (years)	37.4 ± 13.3 (18-61)	-
BMI (kg/m^2)	25.4 ± 4.9 (16.8-37.9)	-
Type of haemophilia- severity		
A severe	-	59 (65%)
B severe	-	9 (10%)
A moderate	-	15 (16%)
B moderate	-	8 (9%)
Treatment regimen		
On-demand	-	16 (18%)
Prophylaxis	-	75 (82%)
Self-reported use of pain medication		19 (21%)
Non-opioid analgesics	-	10 (11%)
Non-opioid + weak opioid analgesics	-	1 (1%)
Non-opioid + strong opioid analgesics	-	1 (1%)
Non-opioid analgesics + recombinant factor	-	7 (8%)
Positive HIV	-	6 (7%)
Hepatitis C		
Negative	-	49 (54%)
Succesfully treated for HCV (negative viral load)	-	42 (46%)
Employment status		
Employed	-	50 (55%)
Self-employed	-	9 (10%)
Employed + self-employed	-	1 (1%)
Unemployed	-	3 (3%)
Student	-	18 (20%)
Retired	-	1 (1%)
Medical insurance	-	9 (10%)

Abbreviations: PwH, People with Haemophilia; HIV, Human Immunodeficiency Virus; kg, kilograms; m, meters.

Table 2. Results self-reported questionnaires of PwH completing the whole study (n=91)

	mean ± SD (range)	n (%)
Brief Pain Inventory (BPI)		
Pain severity (BPI-PS /10)	2.2 ± 1.8 (0-7)	-
No (0)	-	26 (29%)
Mild (1-3)	-	51 (56%)
Moderate (4-6)	-	12 (13%)
Severe (≥7)	-	2 (2%)
Pain interference at baseline (BPI-PI /10)	2.2 ± 2.2 (0-8.1)	-
No (0)	-	34 (37%)
Mild (1-3)	-	36 (40%)
Moderate (4-6)	-	18 (20%)
Severe (≥7)	-	3 (3%)
Pain interference at follow-up (BPI-PI /10)	2.1 ± 2.0 (0-7.3)	-
No (0)	-	37 (41%)
Mild (1-3)	-	37 (41%)
Moderate (4-6)	-	15 (16%)
Severe (≥7)	-	2 (2%)
N painful body locations – Pain distribution (BPI-Body chart)	2.7 ± 2.2 (0-8)	-
Central Sensitization Inventory (CSI)		
Total score part A (/100)	26.9 ± 12.8 (1-69)	-
Symptoms of central sensitization (≥40)	-	12 (13%)
Pain Catastrophizing Scale (PCS)		
Total score (/52)	14.3 ± 11.2 (0-47)	-
Rumination (/16)	5.1 ± 4.2 (0-16)	-
Magnification (/12)	3.1 ± 2.5 (0-10)	-
Helplessness (/24)	6.1 ± 5.7 (0-23)	-
Hospital Anxiety and Depression Scale (HADS)		
Total score (/42)	10.3 ± 6.2 (0-33)	-
Anxiety (/21)	6.1 ± 3.6 (0-18)	-
Probably anxious (≥8)	-	26 (29%)
Depression (/21)	4.1 ± 3.4 (0-15)	-
Probably depressed (≥8)	-	11 (12%)
Fear Avoidance and Beliefs Questionnaire (FABQ)		
Physical activity (FABQ-PA /24)	13.8 ± 6.2 (0-24)	-
Elevated fear-avoidance beliefs (≥15)	-	44 (48%)

Table 2. Continued

	mean ± SD (range)	n (%)
Illness Perceptions Questionnaire Brief version (IPQ-B /10)		
Consequences	5.0 ± 2.8 (0-10)	-
Timeline	8.7 ± 2.6 (1-10)	-
Personal control	5.4 ± 2.5 (0-10)	-
Treatment control	7.3 ± 2.7 (0-10)	-
Identity	5.0 ± 2.9 (0-10)	-
Concern	6.0 ± 3.1 (0-10)	-
Comprehensibility	7.9 ± 2.2 (1-10)	-
Emotional response	4.4 ± 2.9 (0-10)	-

Table 3. Self-reported causes of joint pain in PwH (n=91)

Category	Included responses	Reason 1 n(%)	Reason 2 n(%)	Reason 3 n(%)
Bleeding related	Haemarthrosis, (recurrent) bleeding, large bleeding, spontaneous bleeding, microbleeds, bleeding in the past	27 (30%)	3 (3%)	3 (3%)
Intense physical activity / overuse	Walking too much, carry heavy weights, sports or leisure activities, more intense physical activity than usual, prolonged standing, no warming-up before physical activity, taking the stairs, overuse	12 (13%)	21 (23%)	15 (17%)
No idea	No idea, left blank, illogical, no reason, pain comes randomly or spontaneous	12 (13%)	12 (13%)	10 (11%)
Haemophilia	Haemophilia, inhibitors	9 (10%)	-	2 (2%)
Arthropathy	Joint arthropathy, cartilage or bone degeneration	7 (8%)	6 (7%)	2 (2%)
Trauma/injury/ surgery	Specific trauma, (sports)injury, accident, surgery in the past	8 (9%)	9 (10%)	5 (6%)
Haemostatic treatment related	Lack of prophylaxis, lack of prophylaxis in childhood, late/irregular prophylaxis injection, forgot my treatment, bad treatment compliance, refused my treatment advice, not looking for professional help	8 (9%)	11 (12%)	8 (9%)

Table 3. Self-reported causes of joint pain in PwH (n=91)

Category	Included responses	Reason 1 n(%)	Reason 2 n(%)	Reason 3 n(%)
Hereditary	Hereditary, genetic, genetic disease	3 (3%)	-	-
Psychological factors	Depression, wishing to be like the others, not accepting the disease	-	1 (1%)	2 (2%)
Inactivity	Lack of exercises, sedentary lifestyle, immobility	2 (2%)	1 (1%)	10 (11%)
Poor posture	Body posture, spine posture, how I use my joint, lack of muscles, wrong movements	1 (1%)	8 (9%)	3 (3%)
Overweight	Overweight	1 (1%)	2 (2%)	3 (3%)
Environmental factors	Weather, sports equipment, shoes	1 (1%)	-	1 (1%)
Older age	My age	-	1 (1%)	1 (1%)
Fatigue	Fatigue	-	2 (2%)	1 (1%)

Answers are derived from the text items of the Illness Perceptions Questionnaire Brief version. Identical responses were counted only the first time. 10 PwH (11%) filled in an answer from the "no idea" category 3 times.

Determinants of pain interference at one-year follow-up

Pearson's correlation coefficients between pain-related characteristics and psychosocial factors are presented in Table 4. The simple linear regression analysis (Table 5) showed that the perception of personal control was not significantly associated with the pain interference score at one-year follow-up (p=.201) and was therefore not included in the stepwise model.

Details of the forward stepwise multiple linear regression model are presented in Table 5. Pain severity explained 41% of the variance of pain interference at one-year follow-up. Symptoms of central sensitization and the pain distribution explained each an additional 11% and 3%. The entire model explained 55% of the variance of the pain interference score at one-year follow-up (R^2=.545, p=.023).

A side-by-side evaluation of the simple linear regression and the linear mixed models (Appendix 2) did not show any differences in effect sizes and significance results.

Table 4. Pearson's (r) correlation coefficient between pain-related characteristics and psychological factors (n=91)

	Pain interference at one-year follow-up (BPI-PI)	Pain severity (BPI-PS)	Painful locations (BPI-Body chart)	Central sensitization (CSI-Total score)	Pain catastrophizing (PCS-Total score)	Fear-avoidance beliefs (FABQ-PA)	Anxiety and depression (HADS-Total score)	Perception of personal control (IPQ-B)
Pain interference at one-year follow-up (BPI-PI)	-	.646**	.558**	.522**	.357**	.219*	.434**	-.136
Pain severity (BPI-PS)	.646**	-	.520**	.338**	.311**	.033	.311**	-.054
Painful locations (BPI-Body chart)	.558**	.520**	-	.426**	.330**	-.022	.351**	-.011
Central sensitization (CSI-Total score)	.522**	.338**	.426**	-	.404**	.324**	.731**	-.267*
Pain catastrophizing (PCS-Total score)	.357**	.311**	.330**	.404**	-	.375**	.380**	-.187
Fear-avoidance beliefs (FABQ-PA)	.219*	.033	-.022	.324**	.375**	-	.213*	-.140
Anxiety and depression (HADS-Total score)	.434**	.311**	.351**	.731**	.380**	.213*	-	-.328**
Perception of personal control (IPQ-B)	-.136	-.054	-.011	-.267*	-.187	-.140	-.328**	-

Abbreviations: BPI-PI, Brief Pain Inventory pain interference; BPI-PS, Brief Pain Inventory pain severity; CSI, Central Sensitization Inventory; PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety and Depression Scale; FABQ-PA, Fear Avoidance and Beliefs Questionnaire – Physical Activity; IPQ-B, Illness Perceptions Questionnaire – Brief version; n, number.

*correlation is significant at the .05 level (2-tailed).

**correlation is significant at the .01 level (2-tailed).

Table 5. Simple and stepwise multiple linear regression analysis- Dependent variable: BPI-Pain interference at one-year follow-up (n=91)

Predictor simple linear regression	**R^2**	**p-value**	**β**	**SE**
Pain distribution (BPI-Body chart)	.311	<.001*	.527	.083
Pain severity (BPI-PS)	.417	<.001*	.746	.094
Central sensitization (CSI-Total score)	.272	<.001*	.084	.014
Pain catastrophizing (PCS-Total score)	.128	<.001*	.056	.018
Anxiety and depression (HADS-Total score)	.189	<.001*	.143	.031
Fear-avoidance beliefs (FABQ-PA)	.048	.038*	.073	.035
Perception of personal control (IPQ-B)	.019	.201	-.110	.086
Predictor stepwise multiple linear regression	**R^2 (change)**	**p-value**	**β**	**SE**
1 Pain severity (BPI-PS)	.411	<.001*	.641	1.586
2 Central sensitization (CSI-Total score)	.516 (.106)	.001*	.719	1.445
3 Pain distribution (BPI-Body chart)	.545 (.029)	.023*	.738	1.409

Abbreviations: BPI-(PS), Brief Pain Inventory (pain severity); CSI, Central Sensitization Inventory; PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety and Depression Scale; FABQ-PA, Fear Avoidance and Beliefs Questionnaire – Physical Activity; IPQ-B, Illness Perceptions Questionnaire – Brief version; n, number; SE, non-standardized standard error. *p≤0.05 (2-tailed).

Discussion

Baseline pain-related and psychological factors were found to be significant determinants of pain interference with daily functioning at one-year follow-up in a large sample of people with moderate and severe haemophilia. Since pain is a major problem in haemophilia, these findings highlight the importance of a better understanding and biopsychosocial assessment of pain in PwH.

Pain characteristics

At baseline, 71% of PwH reported some degree of pain (BPI-PS, ≥1/10) in the last 24h, which is consistent with previous studies.[10, 32, 33] Eighty-seven percent of the included PwH reported at least one painful joint, while nearly 30% reported ≥4 painful regions, indicating a more widespread pain distribution. Regarding pain interference with daily functioning, the BPI-PI scores were in line with previous findings from a Belgian study by our research group (median score: 1.6 [0;3.6])[10] and a study from the United States (mean score: 3.2 ± 2.7).[9]

Results of the CSI indicated that 13% of PwH reported symptoms of central sensitization (CSI, ≥40/100). Consistent with previous studies in other chronic MSK

conditions[34-37], we found fair associations between the CSI score and pain characteristics (pain severity and distribution) and fair to moderate associations with psychological factors such as anxiety and depression, fear-avoidance beliefs and pain catastrophizing. These findings suggest that PwH with higher CSI scores exhibit more unhelpful psychological factors (i.e. anxiety) that may influence their pain experience, pain coping behaviour strategies and so its persistence.

Psychological factors

Almost 30% of PwH were likely to suffer from anxiety, 12% of PwH from depression and almost 50% of PwH reported elevated fear-avoidance beliefs. The majority believes that their joint pain will last forever (IPQ-B Timeline, 8.7 ± 2.6), but most patients believe that treatment can help (IPQ-B Treatment control; 7.3 ± 2.7) and that they have less personal control over their pain themselves (IPQ-B Personal control, 5.4 ± 2.5). Since psychological factors strongly contribute to the development of persistent pain[38], the high prevalence of unhelpful psychological factors in our study demonstrates the importance of investigating them.

Bleeding and intense physical activity or overuse were most often attributed as the cause of their joint pain. Interestingly, more than 10% of PwH reported having no idea about the cause of their joint pain. Since illness perceptions will determine the pain coping behavior strategy[39], it is essential to question PwH' perceptions during routine clinical consultations.

Determinants of pain interference at one-year follow-up

The simple linear regression analysis showed that only the perception of personal control was not significantly associated with the pain interference score at one-year follow-up. The stepwise regression analysis revealed that up to 55% of the variance in pain interference with daily functioning at one-year follow-up could be explained by baseline pain severity (41%), symptoms of central sensitization (11%) and pain distribution (3%). Although psychological factors correlated significantly with pain-related characteristics, they may not provide additional unique explanatory power to the pain interference score at one-year follow-up beyond what was already captured by the multidimensional pain-related questionnaires. Indeed they fairly-moderately correlated with the central sensitization score, but to lesser extent with the pain interference score at one-year follow-up.

Strengths and Limitations

The present study has several strengths, including the large sample of PwH, which provided adequate power and increased the generalisability of the findings to the Belgian haemophilia population. To exclude that the results of the linear regression analysis were biased due to non-random drop-out, all analysis were refitted using

linear mixed model as described in the methods. However, for none of the covariates of interest, the conclusion of the linear mixed model differed from the previous conclusion of the linear regression (Appendix 2). Moreover, our study fills an important gap in the literature by investigating symptoms of central sensitization using the CSI and illness perceptions related to their joint pain through the IPQ-B in PwH, which has not been studied before. A potential limitation of the study is that we did not take into account the possible effects of the global COVID-19 pandemic, as the study was conducted during this time period.

Clinical and Research Relevance

The BPI seems an appropriate tool to assess pain multidimensionally. While the CSI and IPQ-B, despite their rare application in haemophilia, also provided valuable insights into the presence of symptoms of central sensitization and perceptions related to their joint pain. Therefore, we encourage further studies to evaluate their use in PwH. Our results call for a comprehensive biopsychosocial pain assessment in routine haemophilia care, where self-reported questionnaires can serve as a starting point for a broader conversation and be used in conjunction with a clinical examination. The identification of PwH at risk (i.e. those with a widespread pain distribution or symptoms of central sensitization), provides opportunities for further research. For example, clinical trials and/cohort studies investigating the efficacy of targeted pain management strategies for patients at risk for the development of prolonged pain interference and possibly unhelpful pain coping behavior strategies and pain chronification.[13]

Conclusion

The present study found that baseline pain-related (i.e. pain severity, pain distribution and symptoms of central sensitization) and psychological factors (i.e. pain catastrophizing, anxiety, fear-avoidance beliefs) were significant determinants of pain interference with daily functioning at one-year follow-up in a large sample of PwH. These findings highlight the importance of a biopsychosocial pain assessment in PwH to identify individuals at risk for the development of persistent pain interference with daily functioning. In addition, they call for the development and evaluation of tailored pain management strategies.

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Appendix 1. Results of pain-related characteristics and psychological factors

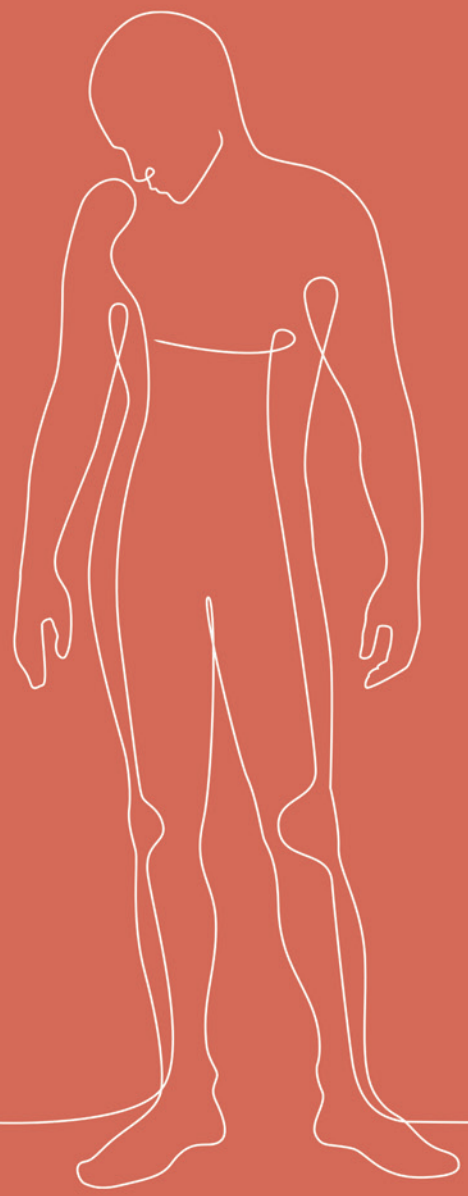
	Total group PwH (n=99)	PwH completing the whole study (n=91)	PwH who dropped out (n=8)	p-value[a]
	mean ± SD (range)	mean ± SD (range)	mean ± SD (range)	
Brief Pain Inventory (BPI)				
Pain severity (BPI-PS /10)	2.1 ± 1.8 (0-7)	2.2 ± 1.8 (0-7)	1.0 ± 1.7 (0-4.8)	.026*
Pain interference at baseline (BPI-PI /10)	2.1 ± 2.2 (0-8.1)	2.2 ± 2.2 (0-8.1)	1.0 ± 2.0 (0-5.9)	.035*
Pain interference at follow-up (BPI-PI /10)	-	2.1 ± 2.0 (0-7.3)	-	-
N painful body locations (BPI-Body chart)	2.5 ± 2.2 (0-8)	2.7 ± 2.2 (0-8)	0.6 ± 1.1 (0-3)	.003*
Central Sensitization Inventory (CSI)				
Total score part A (/100)	26.2 ± 13.0 (1-69)	26.9 ± 12.8 (1-69)	18.1 ± 14.1 (3-42)	.072
Pain Catastrophizing Scale (PCS)				
Total score (/52)	13.6 ± 11.0 (0-47)	14.3 ± 11.2 (0-47)	6.0 ± 4.2 (0-13)	.031*
Rumination (/16)	4.9 ± 4.1 (0-16)	5.1 ± 4.2 (0-16)	2.4 ± 1.8 (0-5)	.099
Magnification (/12)	3.0 ± 2.5 (0-10)	3.1 ± 2.5 (0-10)	1.3 ± 1.3 (0-3)	.039*
Helplessness (/24)	5.8 ± 5.6 (0-23)	6.1 ± 5.7 (0-23)	2.4 ± 2.7 (0-8)	.051
Hospital Anxiety and Depression Scale (HADS)				
Total score (/42)	10.2 ± 6.2 (0-33)	10.3 ± 6.2 (0-33)	9.9 ± 7.1 (4-25)	.607
Anxiety (/21)	6.2 ± 3.6 (0-18)	6.1 ± 3.6 (0-18)	6.3 ± 4.1 (3-14)	.882
Depression (/21)	4.1 ± 3.4 (0-15)	4.1 ± 3.4 (0-15)	3.6 ± 3.9 (0-11)	.535
Fear Avoidance and Beliefs Questionnaire (FABQ)				
Physical activity (FABQ-PA /24)	13.8 ± 6.2 (0-24)	13.8 ± 6.2 (0-24)	13.4 ± 7.5 (0-24)	.800
Illness Perceptions Questionnaire Brief version (IPQ-B /10)				
Consequences	4.8 ± 3.0 (0-10)	5.0 ± 2.8 (0-10)	3.5 ± 4.0 (0-10)	.175
Timeline	8.4 ± 2.8 (0-10)	8.7 ± 2.6 (1-10)	6.0 ± 4.6 (0-10)	.101
Personal control	5.3 ± 2.6 (0-10)	5.4 ± 2.5 (0-10)	3.9 ± 2.9 (0-7)	.114
Treatment control	7.2 ± 2.9 (0-10)	7.3 ± 2.7 (0-10)	5.8 ± 4.4 (0-10)	.464
Identity	4.8 ± 2.9 (0-10)	5.0 ± 2.9 (0-10)	3.3 ± 2.4 (0-6)	.141
Concern	5.7 ± 3.3 (0-10)	6.0 ± 3.1 (0-10)	2.0 ± 3.2 (0-8)	.002*
Comprehensibility	7.8 ± 2.4 (0-10)	7.9 ± 2.2 (1-10)	6.4 ± 4.3 (0-10)	.522
Emotional response	4.2 ± 2.9 (0-10)	4.4 ± 2.9 (0-10)	2.9 ± 3.1 (0-8)	.159

[a]p-values of the Mann-Whitney U test, *p≤0.05 (2-tailed).

Appendix 2. Linear Mixed Model (LMM) with time (baseline or follow-up) as covariate, outcome as repeated measurement and random intercept for participant's ID.

Fixed effects	Estimate	SE	t-value	p-value
Painful locations (BPI-Body chart)	.537	.073	7.403	<.001*
Pain severity (BPI-PS)	.790	.076	10.431	<.001*
Central sensitization (CSI-Total score)	.075	.013	5.772	<.001*
Pain catastrophizing (PCS-Total score)	.083	.016	5.305	<.001*
Anxiety and depression (HADS-Total score)	.134	.028	4.737	<.001*
Fear-avoidance beliefs (FABQ-PA)	.079	.031	2.568	.011*
Perception of personal control (IPQ-B)	-.090	.077	-1.180	.235

Abbreviations: BPI, Brief Pain Inventory; CSI, Central Sensitization Inventory; PCS, Pain Catastrophizing Scale; HADS, Hospital Anxiety and Depression Scale; FABQ-PA, Fear Avoidance and Beliefs Questionnaire – Physical Activity; IPQ-B, Illness Perceptions Questionnaire – Brief version; SE, non-standardized standard error. *p≤0.05 (2-tailed).



GENERAL DISCUSSION

The overall aim of this doctoral thesis was to gain insight into the complexity of pain in people with haemophilia (PwH) from a biopsychosocial perspective. The previous chapters provided the results related to the different research questions. This general discussion serves to provide a comprehensive overview of the different research questions and main findings (as shown in Figure 1), as well as to highlight methodological considerations of the included studies. Additionally, this discussion offers an overview of clinical implications and recommendations for future research. Finally, the overall conclusion summarises the main messages gained by this doctoral thesis.

1. Main findings and discussion

PART 1: Exploring pain in haemophilia literature

Shortly after the initiation of the present PhD dissertation, the global covid-19 pandemic started. Due to restrictions and safety measures from the hospital and university institutions, experimental studies were temporarily forbidden, which strongly delayed the recruitment and assessment of PwH. Therefore, a systematic review (**Chapter 1**) was conducted to delve deeper into the haemophilia literature.

What is the current knowledge about the pain coping behaviour strategies in PwH and the factors associated with pain coping behaviour? (Chapter 1)

A systematic review of the existing literature was performed to answer this first research question. The clinical importance lies in the need to better understand pain coping behaviour in order to evolve towards appropriate pain management. Consequently, the study aimed to identify an inventory of non-pharmacological strategies (i.e. cognitive-emotional and behavioural efforts) and pharmacological strategies (i.e. intake of pain medication or additional clotting factors in response to pain and adherence to prophylactic treatment to prevent bleeding and control pain).

The 11 included studies described a heterogenous sample of PwH, containing a wide variation in age, different types of disease severity and treatment regimen. In addition, studies had considerable risk of bias and reported heterogenous quality of questionnaires to assess pain coping behaviour. Despite these challenges in drawing general conclusions, the preliminary findings of this systematic review serve as an encouragement for HCPs to actively promote and support adequate cognitive-emotional pain coping behaviour strategies (i.e. seeking professional help or taking care of yourself).[1] Additionally, it is crucial for HCPs to gain insight into the PwH's biopsychosocial context of pain to identify PwH who may be at risk, as maladaptive coping strategies can contribute to poorer health outcome and increase the risk for psychopathology.[2-4]

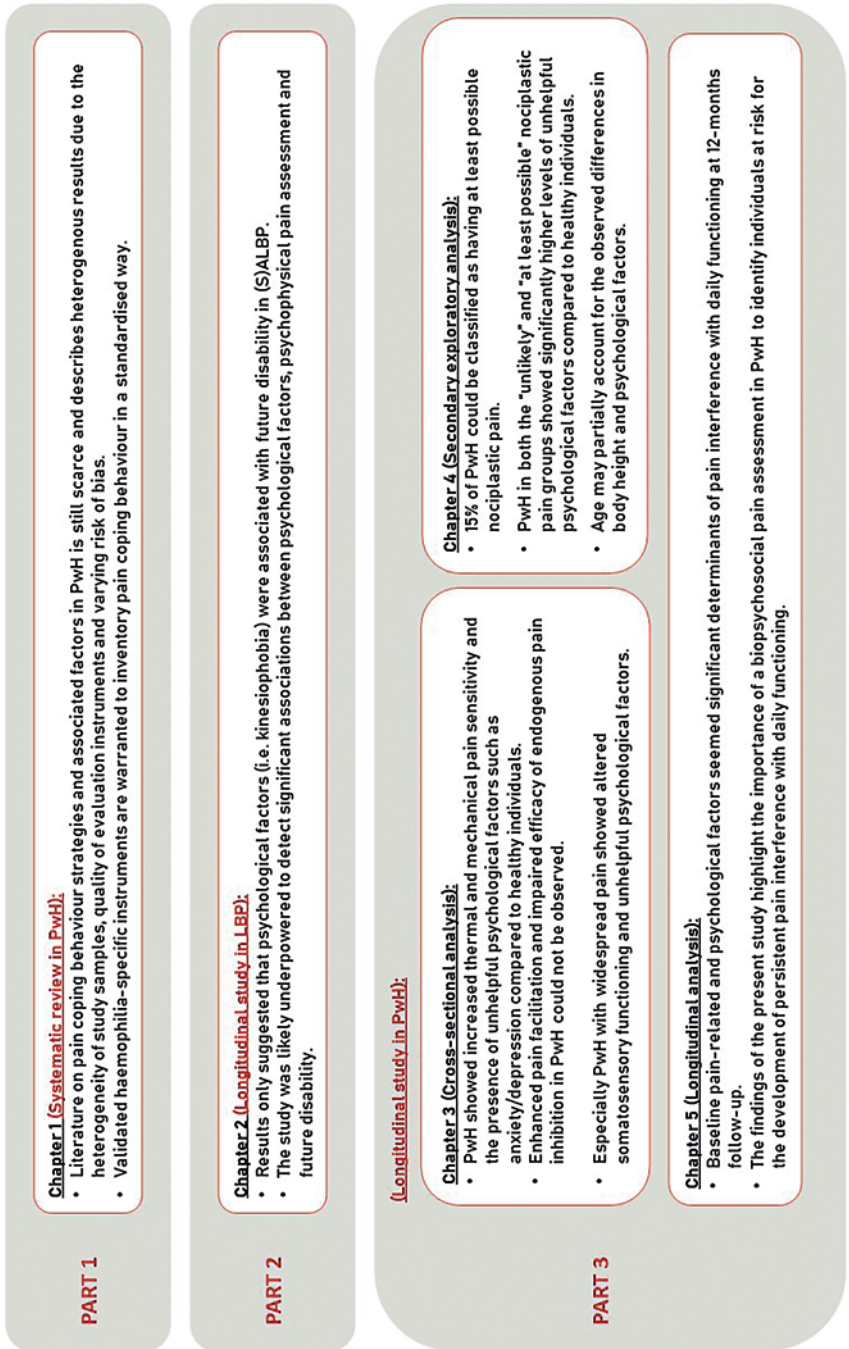


Figure 1. Overview main findings PhD dissertation

One notable study included in the systematic review revealed that more than one-third of PwH expressed concerns regarding their intake of pain medication[5], highlighting the relevance of addressing the use of pharmacological strategies to cope with pain during clinical consultations. Furthermore, it is often overlooked that maintaining a better adherence to prescribed prophylaxis is associated with a significantly lower risk to suffer from chronic pain.[6-8] In line with these previous studies, this systematic review emphasized the importance of considering adherence to prophylactic treatment as an important (preventive) pain coping behaviour strategy in PwH.

PART 2: Longitudinal investigation of pain in people with (sub)acute low back pain

This part includes **Chapter 2** which describes a longitudinal pain study investigating the role of psychological and psychophysical factors on pain-related disability in people with another MSK condition, specifically (S)ALBP. Together with **Chapter 1**, these two chapters were undertaken in preparation of the subsequent longitudinal analysis in PwH (**Part 3**).

Can we determine associations between psychological factors, psychophysical pain assessment in (S)-ALBP at baseline and disability after three months follow-up? (Chapter 2)

To answer this research question**,** a prospective longitudinal study was conducted utilizing data obtained from individuals with (S)ALBP. This choice was particularly relevant since longitudinal studies incorporating psychophysical pain assessment and psychological questionnaires have not previously been conducted in haemophilia. The decision of utilizing the same methodology and study design in the preliminary study with people with (S)ALBP provided valuable practical experience and familiarity with the procedure and analysis, which benefited the conduct of the subsequent longitudinal study in PwH **(Chapter 5)**.

Therefore, in **Chapter 2**, 52 adults with (S)ALBP underwent a baseline psychophysical pain assessment (i.e. static and dynamic QST and CPM) and filled in self-reported pain, disability and psychological questionnaires. At three-months follow-up, 38 participants filled in the disability questionnaire again. Multiple linear regression analysis was conducted to investigate associations between baseline factors and disability after three-months follow-up.

Results of the present study showed no significant associations between baseline QST (i.e. PPTs) and CPM and future disability in (S)ALBP. Based on previous literature, this is not surprising, since no consensus exists regarding the relation between QST and CPM and future disability in LBP.[9] Similar observations can be made regarding CPM, where

the literature on LBP remains contradictory. The main reason for these inconsistencies is probably due to the various CPM-protocols and the predominantly cross-sectional study designs.

Based on previous findings in people with (S)ALBP it was expected that psychological factors (such as kinesiophobia or pain catastrophizing) would prospectively influence future disability.[10-13] However, the results of **Chapter 2** could not confirm significant associations between psychological factors and future disability in (S)ALBP. This was probably due to the small sample size (n=52) and important loss to follow-up (27%), which underpowered the study.

Although no significant associations were found between baseline psychophysical pain assessment and psychological factors and disability at three-months follow-up, which is indeed probably attributed to the study's limited power, a trend was observed suggesting that kinesiophobia may have a negative impact on future disability in (S) ALBP (β=.470, P=.098). While this association did not reach statistical significance, it is worth noting since previous literature already showed that unhelpful psychological factors can threaten a successful health-related outcome and contribute to chronicity.[14, 15] Therefore, it is recommended to identify these factors, including kinesiophobia, already in a (sub-acute) phase of LBP.[16]

PART 3: Longitudinal investigation of pain in PwH

The three chapters included in **Part 3** are based on the study results of the longitudinal pain study to gain insight into the biopsychosocial context of pain in PwH. Therefore, **Chapter 3-5** were included to present the results related to the (patho)physiology of pain, underlying pain mechanisms and longitudinal investigation of pain in PwH. The investigations in these chapters were guided by the following research questions:

Can we identify differences in somatosensory functioning and psychological factors between PwH and age-matched healthy individuals evaluated by psychophysical pain assessment? (Chapter 3)

In **Chapter 3**, a psychophysical pain assessment was conducted to investigate differences between adults with moderate and severe haemophilia A/B (PwH, n=99) and age-matched healthy individuals (n=46). The results of the Student's t tests revealed that PwH exhibited significant differences in static QST measures (i.e. decreased thresholds for thermal pain and mechanical pressure pain) compared with healthy individuals. These findings are consistent with a previous study by Kruger et al.[17] conducted with a smaller sample of PwH (n=30), which also reported hypersensitivity to cold and heat pain (thermal hyperalgesia).

Previous research in people with knee osteoarthritis[18] has indicated that thermal hyperalgesia may serve as an indicator of altered somatosensory functioning. Similarly, a study in people with rheumatoid arthritis[19] has demonstrated this alteration through the presence of lower pain thresholds for mechanical pressure (mechanical hyperalgesia). The present study did not only demonstrate thermal hyperalgesia, but also increased pain sensitivity to mechanical pressure in painful body locations such as the knees and ankles (primary mechanical hyperalgesia). Interestingly, this hypersensitivity to mechanical stimuli was also observed at the forehead, a location which is typically not associated with pain (secondary mechanical hyperalgesia). These findings collectively suggest that PwH exhibit alterations in central somatosensory functioning when compared to age-matched healthy individuals.

In contrast to other chronic MSK conditions such as knee osteoarthritis[20] or fibromyalgia[21], our study did not reveal significant differences in dynamic QST measures (i.e. TS and CPM) between PwH and healthy individuals. Similarly, a previous pain study in PwH(n=30)[17] also failed to report significant differences in TS. Drawing upon previous findings in other chronic MSK conditions such as LBP[22] and osteoarthritis[18], it is plausible that alterations in pain sensitivity and pain modulation may be observed only in a subgroup of PwH. In an attempt to address this, the present exploratory study aimed to differentiate PwH based on their pain distribution (**Chapter 3, research question 2**). However, it is also important to consider methodological factors that could potentially account for these observations, which will be discussed in detail later (see **Methodological Considerations**).

Furthermore, the results of the self-reported questionnaires in this study confirmed our hypothesis that PwH presented significantly more unhelpful psychological factors (i.e. pain catastrophizing and anxiety) compared to healthy individuals, emphasising the biopsychosocial construct of pain.

Can we identify subgroups in PwH based on their pain distribution and do these subgroups show differences in somatosensory functioning and psychological factors evaluated by psychophysical pain assessment? (Chapter 3)

To answer this second research question, the sample of PwH (n=99) described above (**Chapter 3**, **research question 1**) was divided in four subgroups based on their pain distribution, as defined by previous studies in chronic MSK conditions.[23, 24] Among the PwH, 11 PwH (11%) were classified as having widespread pain (≥6 painful body sites), 49 PwH (50%) with regional pain (2-5 painful body sites), 24 PwH (24%) with local pain (1 painful body site) and 15 PwH (15%) without pain. These proportions align with a previous study that also indicated the widespread distribution of pain in PwH.[25] Differences between subgroups were subsequently examined using the Kruskal-Wallis tests with Bonferroni-corrected post-hoc analysis.

The present study revealed that PwH, and especially PwH with widespread pain presented significantly more thermal and mechanical hyperalgesia and reported more unhelpful psychological factors (i.e. pain catastrophizing and anxiety) compared to healthy individuals. Additionally, PwH with widespread pain and local pain showed reduced detection thresholds to cold stimuli (thermal hypoesthesia) in comparison with PwH without pain. These findings are in line with previous findings in PwH (n=30) [17] and people with knee osteoarthritis[18], indicating altered somatosensory functioning. However, again no differences could be unravelled when using the dynamic QST measures.

To conclude, the findings of **Chapter 3** suggest that altered somatosensory functioning and unhelpful psychological factors play an important role in the pathophysiology of pain in PwH, especially in those with widespread pain. This suggests the presence of different phenotypes and psychological profiles within PwH. Additionally, they confirmed the usefulness of the pain drawing tool (i.e. the BPI body chart) to easily identify those PwH with a widespread pain distribution. These findings align with previous research in non-haemophilia populations[26], suggesting that PwH with widespread pain might be at risk of pain chronification and poor prognosis.

Is there a possibility to clinically classify PwH with a suspected predominant nociplastic pain mechanism by applying the IASP grading system for nociplastic pain? (Chapter 4)

Chapter 4 contains innovative, but exploratory, results to answer this research question, as it applied for the first time the IASP grading system for nociplastic pain in haemophilia. Based on a secondary analysis of data from 94 PwH with pain and 41 healthy pain-free individuals from the cross-sectional study (**Chapter 3**), it was possible to classify a subgroup of PwH with suspected predominant nociplastic pain. More specifically 5 PwH (5%) met the criteria for "possible" nociplastic pain and 9 PwH (10%) met the criteria for "probable" nociplastic pain. The majority of PwH was classified with "unlikely" nociplastic pain.

Indeed, we are well aware that many chronic conditions, such as LBP for example, clinically show an overlap between different components, resulting in a mixed presentation of pain mechanisms.[27, 28] Therefore, the intention was not to apply the criteria to identify a single pain mechanisms, but rather to investigate the suspected predominant pain mechanism in PwH.

Can we identify differences in anthropometric, demographic, clinical and psychological characteristics between subgroups and healthy controls? (Chapter 4)

Due to the small sample size of the PwH subgroups with "possible (n=5) and "probable" (n=9) nociplastic pain, as described in **Chapter 4** (**research question 1**), they were combined to form an "at least possible" nociplastic pian subgroup (n=14). In order to gain insight into unique characteristics that may contribute to the predominant nociplastic pain mechanism, participants characteristics (i.e. anthropometric, demographic and clinical features) and psychological factors were compared between the PwH subgroups (i.e. "unlikely" (n=80) and "at least possible" (n=14) nociplastic pain) and the healthy individuals (n=41) using Analysis of Variance (ANOVA). Additionally, Analysis of Covariance (ANCOVA) was used to make comparisons while controlling for age.

The results of the present study showed that both PwH with "at least possible" and "unlikely" nociplastic pain showed significantly higher levels of unhelpful psychological factors compared to healthy individuals. Even after controlling for age, both PwH groups (i.e. "unlikely" and "at least possible" nociplastic pain) continued to demonstrate significantly higher levels of unhelpful psychological factors compared to healthy individuals.

In line with our findings in **Chapter 3 (research question 1)**, the presence of more unhelpful psychological factors might be a risk factor for a successful health-related outcome and the development of chronicity.[14, 15] However, based on our exploratory findings, there were no significant differences in participant characteristics observed between PwH with "unlikely" and "at least possible" nociplastic pain.

Are pain characteristics and pain-related psychological factors associated with pain interference with daily activities over time in adults with moderate and severe haemophilia? (Chapter 5)

Chapter 5 describes the prospective cohort study that answered this research question. Taking into account the insights obtained in the longitudinal study in people with (S)ALBP (**Chapter 2**), an a-priori sample size calculation was conducted. With 99 PwH completing pain-related and psychological questionnaires at baseline and 91 PwH completing the follow-up evaluation again, the study had sufficient statistical power.

The results of the present study showed that pain-related (i.e. pain severity and distribution and self-reported symptoms of central sensitization) and psychological factors (i.e. pain catastrophizing, anxiety and fear-avoidance beliefs) were significantly associated with pain interference with daily functioning at 12-months follow-up. The stepwise multiple linear regression analysis showed that up to 55% of the variance in pain interference could be explained by baseline pain severity (41%), symptoms of central sensitization (11%) and pain distribution (3%). Interestingly, the inclusion of psychological factors did not provide additional explanatory power to the pain

interference score beyond what was already captured by the BPI and CSI. These findings are particularly interesting given the rare application of the latter two questionnaires in haemophilia.

In line with previous findings in other MSK conditions[29-32], the CSI score showed fair associations with pain characteristics and psychological factors, suggesting that PwH who reported more self-reported symptoms of central sensitization (i.e. increased sensitivity to sound, light and/or odours or sleep disturbances) also exhibited more unhelpful psychological factors, such as anxiety.

Besides the CSI, the present study was also the first to use the IPQ-B to investigate the PwH's perceptions regarding their joint pain. Although no significant associations were found between baseline pain perceptions and future pain interference, notable findings were observed. For example, it was found that 10% of PwH reported having no idea about the underlying cause of their joint pain. This lack of understanding may have implications for their pain coping behaviour strategies.

2. Methodological considerations

Each chapter provides an evaluation of the strengths and limitations specifically related to the presented study. However some general methodological considerations related to the enrolment of study participants, assessment tools and longitudinal investigation of pain in PwH were formulated.

Enrolment of study participants

One of the major strengths of this PhD dissertation was the successful inclusion of a **large sample of participants**, which is particularly noteworthy considering the rarity of the condition (approximately 1 in 5000 male births for haemophilia A and 1 in 30,000 for haemophilia B) and the challenges posed by the covid-19 pandemic, which interrupted various research fields. Previous studies investigating pain in PwH have often been limited by relatively small sample sizes.[17, 33, 34] Based on the insights gained from the preliminary longitudinal study in (S)ALBP (**Chapter 2**), where we encountered the issue of being underpowered and experienced a significant loss to follow-up (27%), we applied our knowledge to the 12-months longitudinal study in PwH (**Chapter 5**). As a result, we performed an a-priori sample size calculation in Gpower® 3.1.9.2. (Franz Faul, Kiel University, Germany), including seven pain-related and psychological predictors at baseline and accounted for an anticipated drop-out rate of approximately 20%. With an actual dropout rate of 8%, an appropriate sample size was achieved to obtain statistically significant results with sufficient power, as well as to ensure generalizability to the adult Belgian haemophilia population.

This large sample size allowed us to demonstrate differences between PwH and healthy volunteers with sufficient statistical power, but it also allowed **subgroup analyses** to investigate differences between PwH based on their pain distribution (**Chapter 3**) and their suspected pain mechanism (**Chapter 4**). In **Chapter 4**, however, some subgroups still contained too few participants, requiring an even larger sample size to detect differences between subgroups.

Assessment tools

There are several methodological aspects to consider regarding the **QST methods** included in this doctoral thesis.

The presence of enhanced **TS** and aftersensations was evaluated with a weighted 60g von Frey monofilament on the skin both at local (medial joint space of the dominant knee) and remote sites (dorsal side of the dominant wrist) (**Chapter 3**).[35] However, since initial pain ratings and aftersensation intensities were very low in our sample, it is believed that the application of the monofilament may not generate a sufficiently intense stimuli. Alternatively, previous studies in chronic MSK conditions such as osteoarthritis-related pain[20, 36], have demonstrated enhanced TS when a (force-controlled) pressure algometer provided an intensity equal to the PPT.

To evaluate the efficacy of endogenous pain inhibition, two distinct **CPM protocols** were employed in this thesis. In Chapter 2, where individuals with (S)ALBP were the focus of the study, we utilized PPT assessment in combination with the application of an occlusion cuff. This particular methodological choice was made to align with the practical considerations of conducting assessments within a clinical practice setting. In contrast, Chapter 3 shifted its attention to PwH and took place in a controlled research laboratory setting. In this setting, we employed a novel and specialized tool with 30 x 30 mm thermodes (TSA-2). As a result, the selection of CPM protocols in these chapters was strategically tailored to the research objectives and practical limitations associated with each population and setting. It is important to consider these factors when interpreting the results.

In chapter 3, we used the CPM protocol including the TSA-2 that differed in some aspects from a previous study that investigated this in PwH (n=30).[37] First, we defined a test stimulus temperature that evoked pain with a NRS score of at least 4/10 instead of 6/10.[37] Second, the test stimulus temperature was limited to 46°C, while temperatures of 48.6°C were reported in the study of Kruger et al. [37] For almost one third of PwH and healthy individuals a maximum temperature of 46°C did not equate to an NRS score of 4/10. Third, the conditioning stimulus temperature was fixed at 10°C instead of 7°C, which may not be a sufficiently strong stimulus.[37] Fourth, there is currently no accepted gold standard protocol for assessing dynamic QST measures.

Possibly these methodological differences were the reason why we could not confirm enhanced TS and reduced endogenous pain inhibition in PwH.

For the PPT assessment, we intended to investigate the **inter-observer reliability**. In Chapter 2, the reliability analysis was performed but results were not reported in the results section due to the unavailability of the data. This limitation prompted us to make improvements in our methodology, and in Chapter 3, we thoroughly assessed and reported the inter-observer reliability for PPT assessments.

For this doctoral thesis, a range of **self-reported tools** were selected to evaluate pain in PwH from a biopsychosocial perspective, following existing protocols and validated questionnaires already used in longitudinal studies in other chronic MSK conditions (i.e. LBP and knee osteoarthritis).[14, 38-41] However, it is worth noting that **our selection of instruments was not exhaustive** and there may be questionnaires that could identify additional interesting biopsychosocial factors that we may have missed. For example, the Pittsburgh Sleep Quality Index[42], since the assessment of sleep quality and -disturbances is frequently conducted in various other chronic MSK conditions.[43]

When analysing our data, we discovered that we did not thoroughly explore the **social component of the biopsychosocial framework** for pain assessment. It was only briefly included in a sub-question of the BPI, asking about the relationship with others. Unfortunately, we could not include additional questionnaires to specifically address this aspect, as data collection had already been completed by the time we identified this limitation. Therefore, in the studies included in this research project, we intentionally used the term “psychological factors” and omitted the social aspect.

As previously mentioned, **Chapter 4** includes the **first secondary exploratory analysis** of the **IASP clinical criteria for nociplastic pain** in a large sample of PwH. Considering this innovative aspect, there is currently a lack of reference data available to judge whether our findings are realistic. Therefore a cautious interpretation is needed and certain critical reflections can be drawn. First, the task force of the IASP clinical criteria indicated the **dependence on clinical judgment** of the investigator as a major limitation of the criteria.[44] To overcome this limitation, we assessed the criteria as objectively as possible based on QST protocols, existing literature and cut-offs.[45]

Similarly, there is a criterion that inquires whether individuals experience **regional, multifocal or widespread pain**, however, the criteria do not offer a clear definition or cut-off to ascertain this.[56] In line with previous studies, we regarded those with 2-5 painful body sites as having regional pain and ≥6 painful body sites as having widespread pain in **Chapter 3**.[23, 24] In **Chapter 4**, we tightened the criteria further to 4 painful

body sites[46], as many PwH had bilateral complaints, 2 did not seem sufficiently strict to us. However, it is important to acknowledge that the pain drawing tool used in this thesis provides a momentary assessment. Therefore, further studies in PwH are needed to investigate the long-term stability and reliability of this measure.

Longitudinal investigation of pain in PwH

It is worth noting that the majority of our 12-months prospective study (i.e. recruitment, assessment and follow-up), as described in **Chapter 5,** took place during the **global COVID-19 pandemic**. A potential limitation of this doctoral thesis is that we did not consider the possible effects of the global pandemic.

In addition, not including a **pain coping behaviour questionnaire** (i.e. the Pain-Coping Inventory[47]) in our longitudinal study (**Chapter 5**) may have been a missed opportunity to address the literature gap on this topic highlighted in the systematic review (**Chapter 1**). However, due to the ongoing recruitment and data collection of the study at the time of obtaining the results of the systematic review, introducing an additional questionnaire was deemed inconsistent and therefore not implemented.

Moreover, we noticed that a certain proportion of our participants with haemophilia A switched from their standard haemophilia treatment (i.e. prophylactic infusions of factor VIII (FVIII)) to the novel treatment modality **emicizumab**, a humanized monoclonal bispecific antibody that mimics the function of FVIII. Multiple benefits are attributed to emicizumab such as subcutaneous injections every one, two or four weeks versus intravenous injections several times a week.[48] This has proved to bring a significant change in the individual’s lifestyle and quality of life.[49-51] Additionally, recent studies show promising results in which switching to emicizumab provides a decrease in pain experience.[52, 53] However, we did not specifically ask our participants whether switching to emicizumab during the follow-up period had an effect on their pain experience.

3. Implications for clinical practice

The results of this doctoral thesis provide some implications for incorporating a biopsychosocial pain assessment in routine haemophilia care:

First, we are well aware that conducting a complete **QST examination** is not realistic in everyday practice. Furthermore, there is currently a lack of reliable and valid bedside-testing procedures which can help clinicians better understand the somatosensory functioning of an individual’s pain system. Despite the limited feasibility of QST

examination in clinical practice, our study confirmed the usefulness of the **pain drawing tool** to identify PwH with a widespread pain distribution (**Chapter 2**). Since they presented significant more alterations in somatosensory functioning and reported more unhelpful psychological factors, an early identification might be valuable.

Additionally, **self-reported questionnaires** can serve as a starting point for a broader **conversation** and be used in conjunction with a clinical examination. For example, The BPI seemed an appropriate tool to assess pain multidimensionally.[54, 55] Whereas, the CSI and IPQ-B, despite their rare application in PwH, provided valuable insights into the presence of self-reported symptoms of central sensitization and perceptions related to their joint pain. Furthermore, our results revealed that PwH who reported more symptoms of central sensitization exhibited more unhelpful psychological factors, that may influence their pain experience, pain coping behaviour strategies[56] and so its persistence.[38, 57] Therefore, we should question and identify these risk factors during routine clinical consultations and consider integrating a more biopsychosocial pain management approach.[58, 59]

Finally, it is recommended to adapt the pain management approach to the **predominant underlying pain mechanism** to ensure the most successful outcome.[60] The findings of **Chapter 4** showed that a certain subgroup of PwH had suspected predominant nociplastic pain. This may explain why pain management targeting nociceptive pain does not seem to produce satisfying results for everyone. Based on findings in other chronic MSK conditions, further research is needed to investigate tailored pain management strategies in PwH. Therefore, the following section will outline potential study designs to investigate this.

4. Implication for future research

The findings of the present doctoral thesis could open new perspectives for future research to focus beyond the joint evaluation, but also consider the biopsychosocial context of pain in PwH and the underlying pain mechanisms when establishing an appropriate pain management approach. However, some questions remain partially incomplete, leaving room for further investigation and suggestions for future research.

First, a certain **literature gap** regarding the evaluation of **PwH's pain coping behaviour strategies** became visible in the systematic review (**Chapter 1**). Since pain coping behaviour is still a quite new topic in haemophilia research, it is frequently added as a sub-analysis instead of a main research goal. Moreover, the terminology of pain coping behaviour is still quite grey, open to interpretation, so a standard definition of pain

coping behaviour in PwH and a list of strategies that fall under this heading is needed. In addition, it is advisable for future studies to standardise the assessment of pain coping behaviour in PwH by using validated haemophilia-specific questionnaires that underwent a psychometric evaluation to improve the generalizability. Furthermore, literature states that cross-sectional studies have not the appropriate design to detect variations in pain coping behaviour over time, whereas **longitudinal studies** are needed to investigate pain coping behaviour in PwH, taking into account haemophilia-specific clinical covariables (i.e. treatment modality, disease severity) and adherence to prophylactic treatment, to see how one factor might influence the others.

Next, we acknowledge the importance of broadening the scope of future research by including a more diverse range of populations for comparative analysis (**Chapter 3**). Specifically, it would be valuable to compare PwH not only by severity (i.e. moderate, severe haemophilia versus mild haemophilia) but also with healthy individuals and individuals with other chronic MSK conditions. Through such comparisons, a better understanding of pain in PwH can be achieved, allowing insights into the pain phenotypes and psychological profiles associates with the condition and/or pain.

Moreover, we are the first research group that conducted a **secondary exploratory analysis of the IASP clinical criteria for nociplastic pain** in haemophilia (**Chapter 4**). Therefore **reference data** and further studies examining their **clinimetric and psychometric properties are needed**. In addition, this secondary exploratory analysis provided information for future **experimental studies**. For example, studies investigating pain management strategies tailored to a predominant nociplastic pain mechanism (i.e. interventional studies focussing on psychological treatment modalities[58, 59] or trials of centrally acting pain medications such as antidepressants or serotonin-norepinephrine reuptake inhibitors).[60, 61]

Finally, the **identification of PwH at risk** (i.e. those with a widespread pain distribution, symptoms of central sensitization or suspected predominant nociplastic pain), provides opportunities for further research. For example, clinical trials and/cohort studies investigating the efficacy of targeted pain management strategies for patients at risk for the development of prolonged pain interference and possibly unhelpful pain coping behaviour strategies and pain chronification.

General conclusion

The experience of pain in PwH is a complex and multifactorial phenomenon that requires a biopsychosocial pain assessment that evaluates both psychophysical components and the underlying pain mechanisms. With this doctoral thesis, I aimed not only to contribute to the improvement of PwH's quality of life but also to help HCPs, who daily provide the best possible care to their patients. By presenting findings from a longitudinal observational study on the biopsychosocial pain assessment of PwH, I hope to inspire them to integrate some aspects into their clinical practice. Additionally, I hope my research will motivate other researchers to continue research on pain in this unique population, leading to the development of tailored hemophilia-specific pain management strategies.

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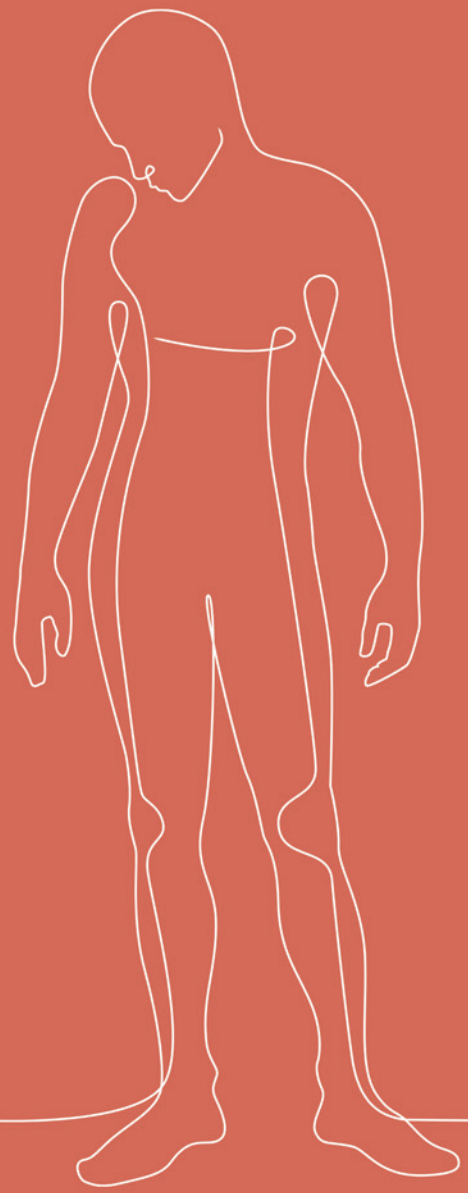

Summary

Joint pain is the hallmark of haemophilia, therefore it seems clinically rather a musculoskeletal (MSK) than a bleeding disorder. Unlike other chronic MSK disorders, pain assessment in people with haemophilia (PwH) remains mainly focused on the structural evaluation of their joints. While there is currently insufficient knowledge about the (patho)physiology, underlying pain mechanisms and biopsychosocial context of pain in PwH. Presumably, this explains the fact that, to date, only a limited number of haemophilia-specific pain management options exist, that PwH suffer from chronic pain and that they report reduced health-related quality of life (HR-QoL). Therefore, the **overall aim** of this thesis was to understand the complexity of pain in PwH from a biopsychosocial perspective.

To contribute to this knowledge, this thesis was divided into **three parts** and focused on 1) reviewing the current scientific literature around pain coping behaviour strategies, 2) a longitudinal pain study in people with (sub)acute low back pain ((S)ALBP) a related chronic MSK condition and 3) a longitudinal pain study in PwH.

In chronic MSK conditions, it has been shown that maladaptive or unhelpful pain coping behaviour strategies (i.e. avoidance behaviour or excessive drug use) can increase the risk of poor health-related outcomes and decrease the individuals' HR-QoL. Therefore, the question arises whether PwH are using helpful strategies to cope with their pain. To answer this question, **Part 1** of this thesis conducted a systematic literature review (**Chapter 1**) to identify PwH's non-pharmacological strategies, pharmacological strategies and factors associated with these pain coping strategies.

After conducting this systematic literature review, it was concluded that the heterogeneity of the study samples, the quality of the evaluation instruments and the varying risk of bias made it difficult to draw conclusions. However, the preliminary findings of this systematic literature review serve as encouragement for healthcare professionals to actively promote and support adequate cognitive-emotional behavioural strategies to cope with pain (i.e. seek professional help, take care of yourself and adhere to prophylactic treatment), as inadequate coping strategies may lead to worse health outcomes.

The second part of this thesis involved a longitudinal pain study in people with (S)ALBP (**Chapter 2**). A study set up during the COVID-19 pandemic to become familiar with the procedure and analyses that would also be used in the longitudinal pain study in PwH (**Part 3**). The aim of this study was to investigate associations between baseline

psychophysical and psychological factors and disability after three-month follow-up. However, no significant associations could be demonstrated, presumably this was due to the small study sample which negatively affected statistical power.

Despite the significance level not being reached, a trend was shown that unhelpful psychological factors such as kinesiophobia can have a negative impact on disability. This is in line with previous studies showing that unhelpful psychological factors can affect successful health-related outcome and contribute to chronicity.

The third and final part of this study involved a longitudinal pain study in individuals with moderate and severe haemophilia and consisted of three different chapters (**Chapter 3-5**).

Chapter 3 described the results of a cross-sectional study conducted in a large sample of PwH to understand their pain sensitivity, pain modulation and pain-related psychological factors. PwH showed significant differences in static QST measurements (lowered thermal and mechanical pain thresholds) and psychological factors (more non-helpful factors such as anxiety or pain catastrophising) compared with age-matched healthy volunteers. However, no significant differences in dynamic QST measurements could be demonstrated. As previous studies in other MSK conditions did find significant differences, there are possibly methodological factors influencing our findings. However, there is also the possibility that by analogy with other MSK conditions, only a subset of PwH show changes in pain sensitivity and pain modulation. Therefore, we subsequently subdivided the large sample (in **Chapter 3 research question 2**) based on their pain distribution. This since previous studies showed that widespread pain distribution is linked to a higher risk of pain chronicity and poor prognosis. The results confirmed our hypothesis that especially PwH with widespread pain showed changes in pain sensitivity and more non-helpful psychological factors, not only compared to healthy volunteers but also to PwH without pain. These findings suggest the presence of different pain phenotypes and psychological profiles within PwH.

Chapter 4 reports the results of a secondary exploratory study using the IASP clinical criteria for nociplastic pain for the first time in PwH. The results showed that small subgroups could be categorised as having suspected nociplastic pain (5%) and probable nociplastic pain (10%), while the vast majority could be categorised as having unlikely nociplastic pain (85%). For clarification, the intention was to use the IASP criteria to indicate a suspected predominant pain mechanism and not to hold only one pain mechanism responsible, since a mixed presentation of pain mechanisms might occur.
Finally, **Chapter 5**, based on the findings from **Chapter 2** in people with (S)ALBP, describes the results of a 12-month prospective study in PwH. This study aimed to

investigate associations between pain-related and psychological factors measured at baseline and pain interference measured after 12-month follow-up.

The results of the present study showed that pain-related (i.e. pain severity and distribution and self-reported symptoms of central sensitisation) and psychological factors (i.e. pain catastrophising, anxiety and fear-avoidance beliefs) were significantly associated with pain interference with daily functioning at 12-months follow-up.

In addition, this study also showed the potential value of using the BPI, CSI and IPQ-B questionnaires during clinical consultations, since the presence of self-reported symptoms of central sensitisation and perceptions related to their joint pain could potentially influence pain experience, pain coping behaviour and pain persistence.

In conclusion, the exploratory findings of the three components (**Part 1-3**) included in this PhD thesis highlight the multidimensional and biopsychosocial context of pain in PwH. Building on these findings, in the **general discussion**, some concrete suggestions for future research are made. For instance, it may be important to broaden the spectrum of future research by including more different populations for comparison (i.e. moderate, severe haemophilia versus mild haemophilia), as well as with healthy individuals and individuals with other chronic MSK disorders. Through such comparisons, a better understanding of pain in PwH can be obtained, providing insights into their pain phenotypes and psychological profiles associated with the condition and/or pain. In addition, this thesis serves to encourage researchers to conduct future experimental studies that can evaluate pain management strategies tailored to these different pain phenotypes and psychological profiles. This with the aim of developing tailored haemophilia-specific pain management strategies to improve their HR-QoL.

Samenvatting

Gewrichtspijn is het kenmerk van hemofilie, daarom lijkt het klinisch eerder een musculoskeletale (MSK) dan een bloedingsstoornis. In tegenstelling tot andere chronische MSK-aandoeningen, blijft pijnonderzoek bij mensen met hemofilie (PwH) voornamelijk gericht op de structurele evaluatie van hun gewrichten. Terwijl er momenteel onvoldoende kennis is over de (patho)fysiologie, onderliggende pijnmechanismen en biopsychosociale context van pijn bij PwH. Vermoedelijk verklaart dit het feit dat er tot op heden slechts een beperkt aantal hemofilie-specifieke pijnbestrijdingsopties bestaan, dat mensen met hemofilie lijden aan chronische pijn en dat zij een verminderde gezondheid-gerelateerde kwaliteit van leven (HR-QoL) rapporteren. Daarom was het **algemene doel** van dit proefschrift om de complexiteit van pijn bij PwH te begrijpen vanuit een biopsychosociaal perspectief.

Om een bijdrage te leveren aan deze kennis, was dit proefschrift opgedeeld in **drie delen** en gericht op 1) een overzicht van de huidige wetenschappelijke literatuur rondom pijn coping gedrag, 2) een longitudinaal pijnonderzoek bij mensen met (sub) acute lage rugklachten ((S)ALBP een gerelateerde chronische MSK-aandoening en 3) een longitudinaal pijnonderzoek bij PwH.

Bij chronische MSK-aandoeningen is aangetoond dat maladaptieve of niet-helpende strategieën om met pijn om te gaan (d.w.z. vermijdingsgedrag of overmatig medicijngebruik) het risico op slechte gezondheid-gerelateerde uitkomsten kunnen verhogen en de HR-QoL van het individu kunnen verminderen. Daarom rijst de vraag of PwH nuttige strategieën gebruiken om met hun pijn om te gaan. Om deze vraag te beantwoorden, werd in deel 1 van dit proefschrift een systematisch literatuuronderzoek uitgevoerd (**hoofdstuk 1**) om de niet-farmacologische strategieën, farmacologische strategieën en factoren die samenhangen met deze strategieën om met pijn om te gaan, te identificeren.

Na het uitvoeren van deze systematische literatuurstudie werd geconcludeerd dat de heterogeniteit van de onderzoekspopulatie, de kwaliteit van de evaluatie-instrumenten en het variërende risico op bias het moeilijk maakten om conclusies te trekken. De voorlopige bevindingen van deze systematische literatuurstudie dienen echter als aanmoediging voor gezondheidsmedewerkers om adequate cognitief-emotionele gedragsstrategieën om met pijn om te gaan (d.w.z. professionele hulp zoeken, voor jezelf zorgen en je houden aan profylactische behandeling) aan te moedigen en te ondersteunen, omdat inadequate coping strategieën kunnen leiden tot slechtere gezondheidsuitkomsten.

Het tweede deel van dit proefschrift betrof een longitudinale pijnstudie bij mensen met (S)ALBP (**Hoofdstuk 2**). Een studie opgezet tijdens de COVID-19 pandemie om vertrouwd te raken met de procedure en analyses die ook gebruikt zouden worden in de longitudinale pijnstudie bij PwH (**Hoofdstuk 3**). Het doel van deze studie was om associaties te onderzoeken tussen psychofysische en psychologische factoren bij baseline en functiebeperking na 3 maanden follow-up. Er konden echter geen significante associaties worden aangetoond, vermoedelijk was dit te wijten aan de kleine steekproef die de statistische power negatief beïnvloedde. Ondanks het feit dat het significantieniveau niet werd bereikt, werd er een trend aangetoond dat niet-helpende psychologische factoren zoals kinesiofobie een negatieve impact kunnen hebben op functiebeperking na 3 maanden. Dit is in lijn met eerdere studies die aantonen dat niet-helpende psychologische factoren een succesvolle gezondheid-gerelateerde uitkomst kunnen beïnvloeden en kunnen bijdragen aan chroniciteit.

Het derde en laatste deel van dit onderzoek betrof een longitudinaal pijnonderzoek bij personen met matige en ernstige hemofilie en bestond uit 3 verschillende hoofdstukken (**Hoofdstuk 3-5**).

Hoofdstuk 3 beschrijft de resultaten van een cross-sectionele studie uitgevoerd bij een grote steekproef PwH om inzicht te krijgen in hun pijngevoeligheid, pijnmodulatie en pijn-gerelateerde psychologische factoren. PwH vertoonden significante verschillen in statische QST metingen (verlaagde thermische en mechanische pijndrempels) en psychologische factoren (meer niet-helpende factoren zoals angst of pijnkatastrofering) in vergelijking met leeftijd gematchte gezonde vrijwilligers. Er konden echter geen significante verschillen in dynamische QST metingen worden aangetoond. Aangezien eerdere onderzoeken bij andere MSK aandoeningen wel significante verschillen vonden, zijn deze bevindingen mogelijk beïnvloed door methodologische factoren. Het is echter ook mogelijk dat, naar analogie van andere MSK aandoeningen, alleen een subset van PwH veranderingen in pijngevoeligheid en pijnmodulatie laat zien. Daarom hebben we vervolgens de grote steekproef (in **hoofdstuk 3 onderzoeksvraag 2**) onderverdeeld op basis van pijnverdeling. Dit omdat eerdere studies aantoonden dat een wijdverspreide pijnverdeling samenhangt met een hoger risico op chronische pijn en een slechte prognose. De resultaten bevestigden onze hypothese dat vooral PwH met wijdverspreide pijn veranderingen in pijngevoeligheid en meer niet-helpende psychologische factoren vertoonden, niet alleen vergeleken met gezonde vrijwilligers maar ook met PwH zonder pijn. Deze bevindingen suggereren de aanwezigheid van verschillende pijnfenotypen en psychologische profielen binnen PwH.

Hoofdstuk 4 rapporteert de resultaten van een secundair exploratief onderzoek waarbij de klinische criteria van de IASP voor nociplastische pijn voor het eerst werden gebruikt bij PwH. De resultaten lieten zien dat kleine subgroepen konden worden gecategoriseerd als personen met vermoedelijke nociplastische pijn (5%) en waarschijnlijke nociplastische pijn (10%), terwijl de overgrote meerderheid kon worden gecategoriseerd als personen met onwaarschijnlijke nociplastische pijn (85%). Ter verduidelijking: het was de bedoeling om de IASP-criteria te gebruiken om een vermoedelijk predominant pijnmechanisme aan te geven en niet om slechts één pijnmechanisme verantwoordelijk te stellen, aangezien een gemengde presentatie van pijnmechanismen kan bestaan.

Tot slot beschrijft **hoofdstuk 5**, gebaseerd op de bevindingen uit **hoofdstuk 2** bij mensen met (S)ALBP, de resultaten van een 12 maanden durende prospectieve studie bij PwH. Deze studie had als doel de associaties te onderzoeken tussen pijngerelateerde en psychologische factoren gemeten op baseline en pijninterferentie gemeten na 12 maanden follow-up. De resultaten van dit onderzoek toonden aan dat pijngerelateerde (d.w.z. de ernst en verdeling van de pijn en zelf-gerapporteerde symptomen van centrale sensitisatie) en psychologische factoren (d.w.z. pijn katastrofiëring, angst en angstvermijdingsovertuigingen) significant geassocieerd waren met pijninterferentie in het dagelijks functioneren na 12 maanden follow-up. Daarnaast toonde dit onderzoek ook de potentiële waarde aan van het gebruik van de BPI, CSI en IPQ-B vragenlijsten tijdens klinische consulten, aangezien de aanwezigheid van zelf-gerapporteerde symptomen van centrale sensitisatie en percepties met betrekking tot hun gewrichtspijn mogelijk van invloed zijn op de pijnervaring, het pijngedrag en de pijnpersistentie.

In conclusie, deze exploratieve bevindingen van de drie onderdelen (**Deel 1-3**) van dit proefschrift benadrukken de multidimensionale en biopsychosociale context van pijn bij PwH. Voortbouwend op deze bevindingen worden in de algemene discussie enkele concrete suggesties gedaan voor **toekomstig onderzoek**. Het kan bijvoorbeeld belangrijk zijn om het spectrum van toekomstig onderzoek te verbreden door meer verschillende populaties ter vergelijking op te nemen (d.w.z. matige, ernstige hemofilie versus milde hemofilie), evenals met gezonde individuen en individuen met andere chronische MSK-aandoeningen. Door dergelijke vergelijkingen kan een beter begrip van pijn bij PwH worden verkregen, wat inzicht geeft in de pijnfenotypes en psychologische profielen die samenhangen met de aandoening en/of pijn. Daarnaast dient dit proefschrift om onderzoekers aan te moedigen om toekomstige experimentele studies uit te voeren die pijnmanagementstrategieën kunnen evalueren die zijn afgestemd op deze verschillende pijnfenotypen en psychologische processen. Dit met het doel om op maat gemaakte hemofilie-specifieke pijnbestrijdingsstrategieën te ontwikkelen om hun HR-QoL te verbeteren.

Résumé

Les douleurs articulaires sont la caractéristique principale de l'hémophilie, c'est pourquoi ce trouble de la coagulation est plutôt considéré comme un trouble musculosquelettique (MSK) sur le plan clinique. Contrairement à d'autres troubles MSK chroniques, l'évaluation de la douleur chez les personnes atteintes d'hémophilie (PwH) reste principalement axée sur l'évaluation de leurs articulations. Les connaissances sur la (patho)physiologie, les mécanismes sous-jacents de la douleur et le contexte biopsychosocial de la douleur chez les PwH sont actuellement insuffisantes. Cela explique qu'à ce jour, seulement un nombre limité d'options de gestion de la douleur spécifiques à l'hémophilie existent, que les PwH souffrent de douleurs chroniques et qu'ils signalent une diminution de la qualité de vie liée à la santé (HR-QoL). Par conséquent, l'objectif global de cette thèse était de comprendre la complexité de la douleur chez les PwH d'un point de vue biopsychosocial.

Afin de contribuer à ces connaissances, cette thèse de doctorat a été divisée en **trois parties** et s'est concentrée sur 1) une–revue systématique de la littérature sur les stratégies de gestion de la douleur en hémophilie, 2) une étude longitudinale sur la douleur chez les personnes souffrant de lombalgie aiguë ou subaiguë ((S)ALBP) une affection MSK chronique connexe et 3) une étude longitudinale sur la douleur chez les PwH.

Dans le cas des affections MSK chroniques, il a été démontré que les stratégies de gestion de la douleur inadaptées ou inefficaces (i.e., les comportements d'évitement ou l'utilisation excessive de médicaments) peuvent augmenter le risque de manque de résultats et réduire la qualité de vie des individus concernés. Par conséquent, la question se pose de savoir si les PwH utilisent des stratégies efficaces pour faire face à leur douleur. Pour répondre à cette question, **la première partie** de cette thèse consistait en une revue systématique de la littérature (**Chapitre 1**) afin d'identifier les stratégies non pharmacologiques et pharmacologiques utilisées par les PwH, ainsi que les facteurs associés à ces stratégies de gestion de la douleur.

De cette revue systématique de la littérature, nous avons conclu que l'hétérogénéité des personnes étudiés, la qualité des instruments d'évaluation et les risques de biais rendaient difficile la formulation de conclusions. Malgré cela, ces résultats préliminaires encouragent les professionnels de la santé à promouvoir et à soutenir des stratégies cognitivo-émotionnelles comportementales adéquates pour faire face à la douleur, car des stratégies de gestion inadéquates peuvent entraîner de plus mauvais résultats en termes de santé. Il est question de stratégies telles que (i.e., demander l'aide d'un professionnel, prendre soin de soi, respecter le traitement prophylactique).

La deuxième partie de cette thèse a porté sur une étude longitudinale sur la douleur chez les personnes souffrant de (S)ALBP (**Chapitre 2**). Cette étude a été mise en place pendant la pandémie de COVID-19 afin de se familiariser avec les procédures et les analyses qui seraient également utilisées dans notre étude longitudinale en hémophilie (**Partie 3**). Cette étude visait à examiner les liens entre les facteurs psychophysiques et psychologiques initiaux et l'incapacité physique après un suivi de trois mois. Aucune association significative n'a pu être démontrée, probablement en raison de la petite taille de l'échantillon d'étude, ce qui a nui à la puissance statistique. Malgré le fait que le seuil de signification n'ait pas été atteint, une tendance a été observée montrant que des facteurs psychologiques défavorables tels que la kinésiophobie peuvent avoir un impact négatif sur l'incapacité physique. Ceci serait conforme à des études antérieures montrant que des facteurs psychologiques défavorables peuvent influencer les résultats liés à la santé et contribuer à la chronicité de la douleur.

La troisième et dernière partie de cette étude a porté sur une étude longitudinale sur la douleur chez des personnes atteintes d'hémophilie modérée et sévère, et comprenait **trois chapitres** différents (**Chapitres 3 à 5**).

Le chapitre 3 décrit les résultats d'une étude transversale menée sur un échantillon important de PwH afin de comprendre leur sensibilité à la douleur, leur modulation de la douleur et les facteurs psychologiques liés à la douleur. Les PwH présentaient des différences significatives dans les mesures statiques du QST (seuils de douleur thermique et mécanique réduits) et les facteurs psychologiques (plus de facteurs inutiles tels que l'anxiété ou la catastrophisation de la douleur) par rapport à des personnes volontaires en bonne santé du même âge. Cependant, aucune différence significative n'a pu être démontrée dans les mesures dynamiques du QST. Puisque des études antérieures sur d'autres affections MSK ont report des différences significatives, il est possible que des facteurs méthodologiques aient influencé nos-résultats. Cependant, il est également possible que, par analogie avec d'autres affections MSK, seul un sous-ensemble de PwH présente des modifications de la sensibilité à la douleur et de la modulation de la douleur. Par conséquent, nous avons ensuite subdivisé le grand échantillon (dans la **question de recherche 2 du chapitre 3**) en fonction de la répartition de leur douleur. Ceci, parce qu'il a été montré que la répartition généralisée de la douleur est liée à un risque plus élevé de chronicité de la douleur et de mauvais pronostic dans d'autre populations. Nos-résultats ont confirmé notre hypothèse selon laquelle en particulier les PwH présentant une douleur généralisée présentaient des modifications de la sensibilité à la douleur et davantage de facteurs psychologiques maladaptatifs, non seulement par rapport aux personnes contrôles, mais aussi par rapport aux PwH sans douleur. Ces résultats suggèrent la présence de différents phénotypes de douleur et profils psychologiques chez les PwH.

Le chapitre 4 présente les résultats d'une étude exploratoire secondaire utilisant les critères cliniques de l'IASP pour la douleur nociplastique, utilisés pour la première fois chez les PwH. Dans ce chapitre, l'intention était d'utiliser les critères de l'IASP afin d'identifier la présence de d'un mécanisme de douleur nociplastique. Ceci, sans négliger que d'autres mécanismes peuvent avoir lieu indépendamment, puisque plusieurs mécanismes peuvent avoir lieu de manière simultanée chez une même personne (i.e. présentation mixte). Les résultats ont montré que de petits sous-groupes pouvaient être catégorisés comme présentant une douleur nociplastique suspectée (5%) et une douleur nociplastique probable (10%), tandis que la grande majorité pouvait être catégorisée comme présentant une douleur nociplastique improbable (85%).

Enfin, **le chapitre 5**, basé sur les résultats du **chapitre 2** chez les personnes atteintes de (S)ALBP, décrit les résultats d'une étude prospective de 12 mois chez les PwH. Cette étude visait à étudier les liens entre les facteurs liés à la douleur et psychologiques mesurés au départ et l'interférence de la douleur mesurée après 12 mois de suivi. Les résultats de cette étude ont montré que les facteurs liés à la douleur (i.e. sa sévérité et sa répartition, et les symptômes subjectifs de la sensibilisation centrale) et les facteurs psychologiques (i.e. la catastrophisation de la douleur, l'anxiété et les croyances d'évitement) étaient significativement associés à l'interférence de la douleur après 12 mois de suivi. Cette étude a également montré la valeur potentielle de l'utilisation du BPI, du CSI et de l'IPQ-B lors des consultations cliniques, car la présence de symptômes subjectifs de la sensibilisation centrale et les perceptions liées à leur douleur articulaire pourraient potentiellement influencer l'expérience de la douleur, les comportements d'adaptation à la douleur ainsi que sa persistance.

En conclusion, les résultats exploratoires des trois composantes (**Partie 1-3**) incluses dans cette thèse de doctorat mettent en évidence le contexte multidimensionnel et biopsychosocial de la douleur chez les PwH. Sur la base de ces résultats, dans la discussion générale, des suggestions concrètes pour des recherches futures sont formulées. Par exemple, il peut être important d'élargir le spectre des recherches futures en incluant davantage de populations différentes pour les comparer (i.e., hémophilie modérée et sévère versus hémophilie mineure), ainsi qu'avec des individus en bonne santé et des individus atteints d'autres troubles MSK chroniques. Ceci améliorerait la compréhension de la douleur chez les PwH fournissant des informations sur les phénotypes de douleur et les profils psychologiques associés à l'hémophilie et/ou à la douleur. De plus, cette thèse encourage les chercheurs à mener des études afin d'évaluer les stratégies de gestion de la douleur adaptées à ces différents phénotypes de douleur et processus psychologiques. Cela, dans le but de développer des stratégies de gestion de la douleur spécifiques à l'hémophilie et d'améliorer leur qualité de vie.

Biography of Anthe Foubert

Anthe Foubert was born on the 28th of February 1994 in Beveren, Belgium. With a driven and positive mindset, she completed her Rehabilitation Sciences and Physiotherapy education in 2017 at the University of Antwerp.

During her Master in Rehabilitation Sciences and Physiotherapy in Musculoskeletal Conditions, she developed a growing interest in clinical care and pain research, for which she was awarded the Best Master's Thesis prize in 2017.

Anthe began her career as a (sport)physiotherapist in 2019, spending part of her time at the Stedelijk Lyceum topsport school Edegem where she focused on the rehabilitation of sport injuries in young athletes and provided injury prevention training twice a week. The rest of her time she worked at KineMoves, a private practice in Kruibeke, where she managed a variety of musculoskeletal conditions and sport injuries in patients of all ages. As a lifelong learner, Anthe completed a postgraduate Master in Manual Therapy at Ghent University in 2018 while working as a (sport)physiotherapist.

In 2019 Anthe started with the PhD project described in this thesis where she combined her expertise as physiotherapist in musculoskeletal conditions and her passion for pain research. This joint-PhD project between the University of Antwerp and UCLouvain was performed under supervision of Prof. dr. Nathalie Roussel, Prof. dr. Mira Meeus, Prof. dr. Cédric Hermans and dr. Sébastien Lobet. Anthe has currently authored and co-authored ten full-text papers. For her research Anthe received the BPS-YRD Best Poster Presentation Award 2020, the PRESS>SPEAK Award in 2021 and EAHAD Top Scoring Abstract 2023.

Anthe has a passion for sharing knowledge with others, which has led her to become a member of the Pain in Motion international research group. Additionally, she was a member of the scientific organising committee of the Belgian Pain Society Young Researchers Day in 2023, a day where clinicals and young researchers could meet and share their interest in pain research.

As a former (sports)physiotherapist, Anthe continuous to promote an active lifestyle. In her free time, she makes time for activities like running outdoors, learning to play tennis and spending time with family and friends, since she strongly believes in the importance of a healthy work-life balance.

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1. **Foubert A**, Chantrain VA, Meeus M, Maes P, Durnez L, Lobet S, Lambert C, Hermans C, Roussel NA. Determinants of pain interference in adults with moderate and severe haemophilia : a one-year prospective study. *Submitted in Haemophilia.*
2. Chantrain VA, **Foubert A**, Meeus M, Lambert C, Lobet S, Maes P, Durnez L, Hermans C, Roussel NA. Joint status, pain, and quality of life in elderly people with haemophilia: A case-control study. *Submitted in Haemophilia.*
3. Haenen V, Meeus M, Devoogdt N, Morlion B, Dams L, De Groote A, Vande Vyvere T, **Foubert A**, De Groef A. Concurrent validity of conditioned pain modulation and temporal summation paradigms in breast cancer survivors with persistent pain. *Submitted in the The Scandinavian Journal of Pain.*

Presentations at (inter)national congresses

1. **Foubert A**, Chantrain VA, Meeus M, Maes P, Haenen V, Lobet S, Lambert C, Hermans C, Roussel NA. Psychophysical assessment of pain in adults with moderate and severe haemophilia: a cross-sectional study. 16th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD). Manchester (England), February 2023.

Poster presentations at (inter)national congresses

1. **Foubert A**, Chantrain VA, Meeus M, Maes P, Lobet S, Lambert C, Hermans C, Roussel NA. The clinical classification of pain mechanisms in people with moderate and severe haemophilia. 16th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD). Manchester (England), February 2023.
2. **Foubert A**, Chantrain VA, Meeus M, Hermans C, Lambert C, Lobet S, Roussel NA. Pain mechanisms in adults with haemophilia: research protocol of a cross-sectional study. Pain Science in Motion IV, Maastricht (the Netherlands), May 2022.
3. **Foubert A**, Chantrain VA, Meeus M, Hermans C, Lambert C, Lobet S, Roussel NA. Illness perceptions related to joint pain in adults with haemophilia. 12th Congress of the European Pain Federation (EFIC). Dublin (Ireland), April 2022.
4. **Foubert A**, Chantrain VA, Meeus M, Hermans C, Lambert C, Lobet S, Roussel NA. Illness perceptions related to joint pain in adults with haemophilia. 15th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD). Online, February 2022.

5. **Foubert A**, Cleenders E, Sligchers M, Heystee L, Meeus M, Vaes P, Nijs J, Roussel NA. Do psychosocial factors and nociceptive stimuli processing influence pain intensity and disability in (sub)acute low back pain? A prospective cohort study. World Physiotherapy Congress (WPTC). Online, April 2021.
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Website publications

1. **Foubert A**, Blogpost EOS Wetenschap: "Waarom linkshandigen de wetenschap blijven boeien?" (August 2021).https://www.eoswetenschap.eu/gezondheid/hoe-linkshandigen-de-wetenschap-blijven-boeien
2. **Foubert A**, Blogpost Pintra Universiteit Antwerpen: "Hemofilie en de zoektocht naar de optimale pijnbehandeling" (May 2021). https://blog.uantwerpen.be/pintra/hemofilie-en-de-zoektocht-naar-de-optimale-pijnbehandeling/
3. **Foubert A**, Blogpost Pain in Motion website: "Chronic pain as hallmark of haemophilia. Remarkable, but true. (April 2021) http://www.paininmotion.be/blog/detail/chronic-pain-hallmark-haemophilia-remarkable-true
4. **Foubert A**, Blogpost EOS Wetenschap: "Zeldzame ziekten in de spotlight" (February 2021). https://www.eoswetenschap.eu/gezondheid/zeldzame-ziekten-de-spotlight

Awards

1. European Association of Haemophilia and Allied Disorders 2023 – Top Scoring Abstract.
2. PRESS > SPEAK Contest University of Antwerp – Best Blogpost.
3. Belgian Pain Society – 1st Young Researchers Day 2020 – Second Best Poster Presentation.

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